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THESE

Présentée pour obtenir le titre de

DOCTEUR DE L'ECOLE POLYTECHNIQUE

Spécialité

CHIMIE

Par

Andrea-Krisztina BUZAS

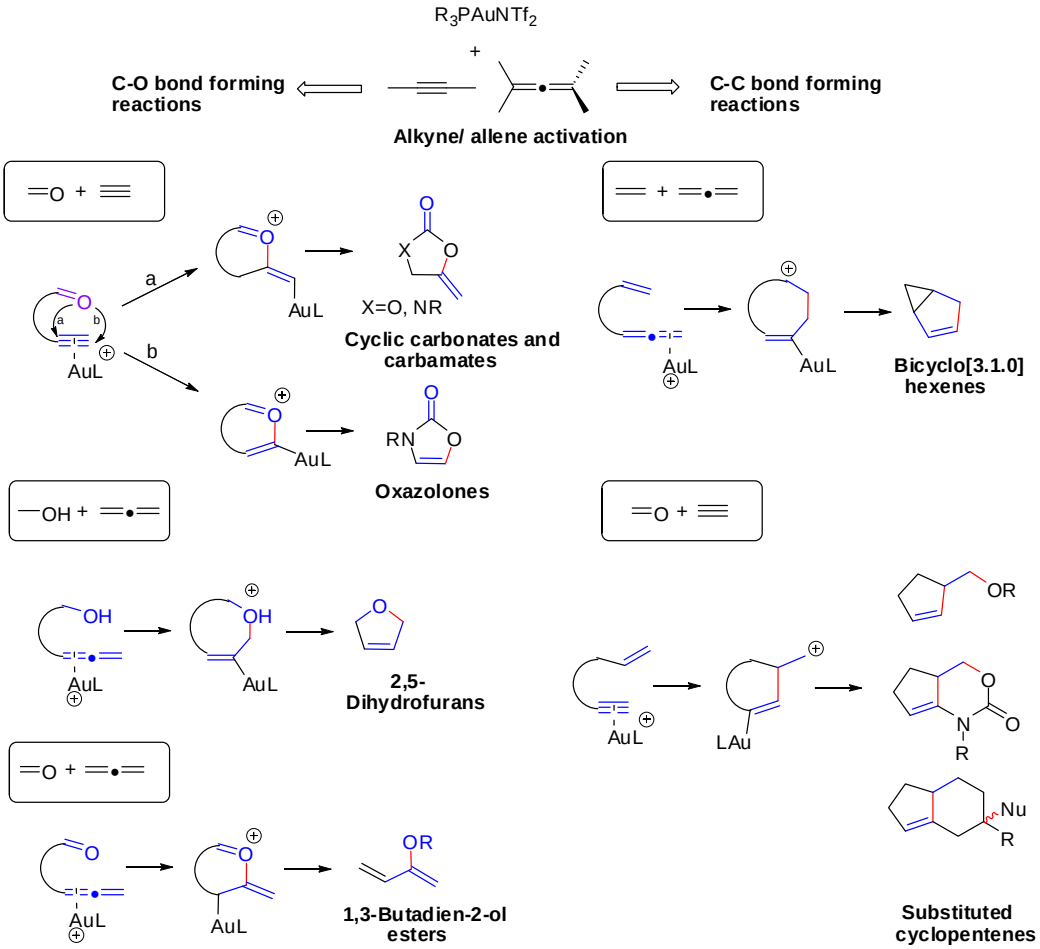
ETUDES DE NOUVELLES TRANSFORMATIONS CATALYSEES PAR DES COMPLEXES D'OR (I)

Soutenue le 30 mars 2009 devant le jury composé de:

Dr. Véronique MICHELET – Présidente
Dr. Charles FEHR – Rapporteur
Pr. Jean-Marc CAMPAGNE – Rapporteur
Pr. Samir ZARD – Examinateur
Dr. Fabien GAGOSZ – Examinateur

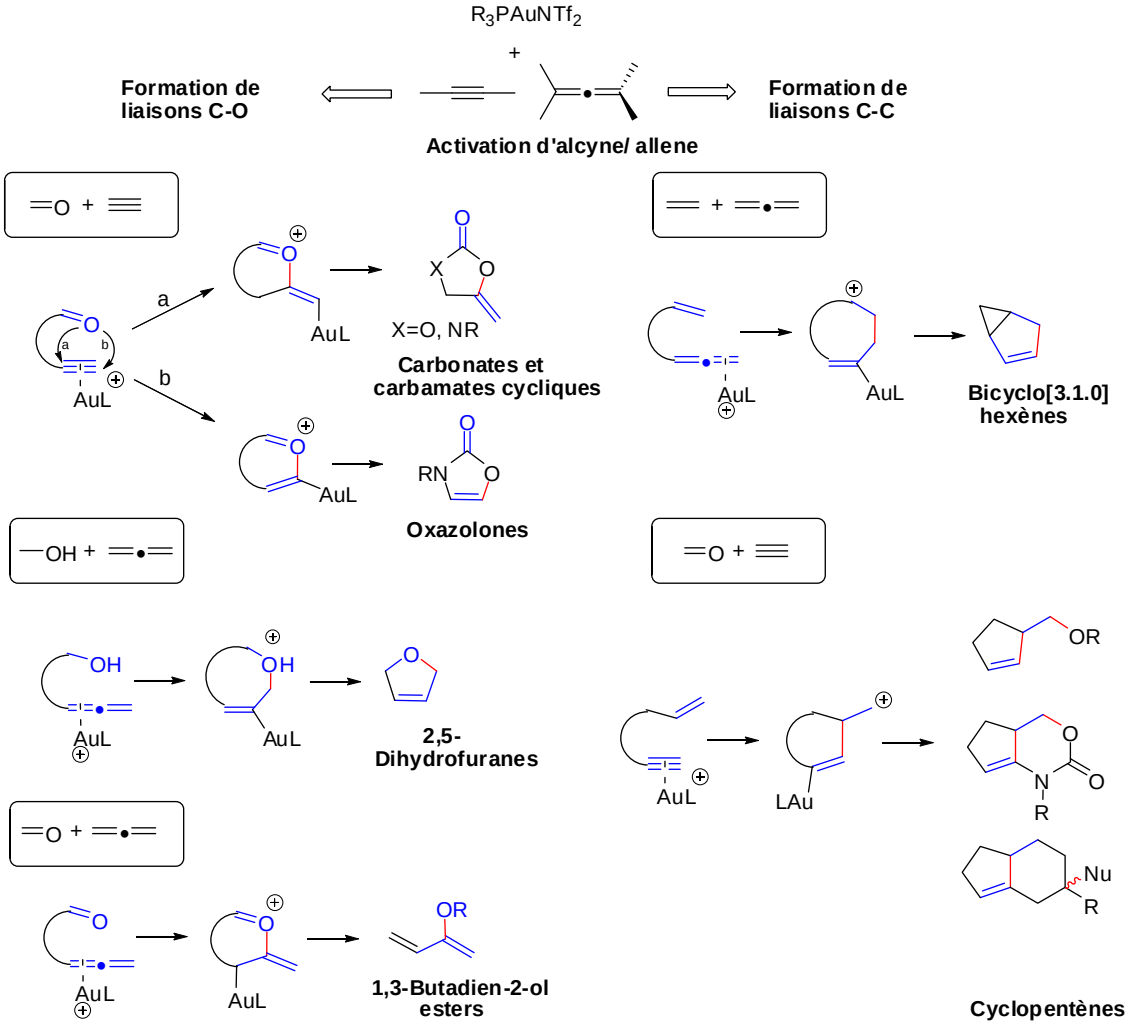
ABSTRACT

The aim of this scientific project carried out at the "Laboratoire de Synthèse Organique" (DCSO) at Ecole Polytechnique under the guidance of Dr. Fabien Gagosz and Prof. Samir Zard was the study of new transformations catalyzed by gold (I) complexes developed in the laboratory. These air-stable, crystallin cationic gold(I) catalysts act as soft carbophilic Lewis acids towards carbon–carbon multiple bonds which, after this activation, undergo a variety of transformations affording new carbon–carbon or carbon–heteroatom bonds. New methods leading to the efficient synthesis of heterocycles such as cyclic carbonates and carbamates (Chapters II and III), oxazolones (Chapter IV), 2,5 dihydrofurans (Chapter V) or carbocycles such as bicyclo[3.1.0]hexenes (Chapter VII) and substituted cyclopentes (Chapters VIII and IX) were developed.



RESUME

L'objectif de ce projet scientifique réalisé dans le Laboratoire de Synthèse Organique (DCSO) de l'Ecole Polytechnique sous la direction du Dr. Fabien Gagosz et Pr. Samir Zard a été l'étude de nouvelles transformations catalysées par des complexes d'or (I) développées au laboratoire. Ces catalyseurs agissent comme des acides de Lewis "soft" vis à vis des liaisons carbone-carbone multiples permettant la formation de nouvelles liaisons carbone-carbone ou carbone-hétéroatome. De nouvelles méthodes permettant la synthèse des hétérocycles: des carbonates et des carbamates cycliques (Chapitres II et III), des oxazolones (Chapitre IV), des 2,5-dihydrofuranes (Chapitre V) ou bien des cycles carbonés: des bicyclo[3.1.0]hexènes (Chapitre VII) et des cyclopentènes (Chapitres VIII and IX) ont été développées.



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« Life is about people »
« Life is about the jouney, not the destination »

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ABREVIATIONS

Units:

°C	Celsius degrees
g, mg	Gram, milligram
h	Hour
Hz, MHz	Hertz, megahertz
L, mL	Liter, milliliter
min	Minute
m/z	Mass units on elementary charge
mol, mmol	Mol, millimol
ppm	Parts per million

Chemical groups:

AIBN	2,2-Azo*bis-iso*-butyronitrile
Ac	Acetyl
Acac	Acetylacetonate
Ad	Adamantyl
AD	Asymmetric dihydroxylation
Ar	Aryl
9-BBN	9-Borabicyclononane
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bipy	Bipyridyl
BMIm	1-Butyl-3-methylimidazolium
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
Bu	Butyl
Bz	Benzoyl
Cbz	Carbobenzyloxy
$CDCl_3$	Deuterated chloroform
COD	1,5-Cyclooctadiene
COT	1,3,5-Cyclooctatriene
Cp	Cyclopentadienyl
18-crown-6	1,4,7,10,13,16-Hexaoxacyclooctadecane
Cy	Cyclohexyl
DEAD	Diethyl azodicarboxylate
Dba	Dibenzylideneacetone
DBAD	*Di-tert*-butylazo-dicarboxylate
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	N,N-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DIBALH	Diisobutylaluminun hydride
DIPA	Diisopropylamine
DMAM-PS	(Dimethylamino)methyl-polystyrene-supported
DMAD	Dimethyl acetylene dicarboxylate
DMAP	*N*,*N*-Dimethyl-4-aminopyridine
DMDO	2,2-Dimethyldioxirane
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide

DPP	1,2,5-Triphenylphosphole
DPPA	Diphenylphosphoryl azide
DPPBA	2-(Diphenylphosphino)benzoic acid
Et	Ethyl
HMPA	Hexamethylphosphoramide
i-Pr	Isopropyl
LDA	Lithium diisopropylamide
LiHMDS	Lithium hexamethyldisilazide
Me	Methyl
m-CPBA	*meta*-Chloroperoxybenzoic acid
MOP	Methoxypropyl
Ms	Mesityl
n-Bu	*n*-Butyl
NBS	*N*-Bromosuccinimide
NHC	*N*-Heterocyclic carbenes
NIS	*N*-Iodosuccinimide
NME	*N*,*N*-Dimetylephedrine
Ns	Nosyl (*o*-nitrobenzensulfonyl)
NSAIDs	Nonsteroidal antiinflammatory drugs
OTMM	Oxatrimethylenemethane
PE	Petroleum ether
PCC	Pyridinium chlorochromate
Ph	Phenyl
PHOX	Phosphinooxazoline
Piv	Pivalyl
PKC	Protein kinase C
PMB	*p*-Methoxybenzyl
PNBSA	*p*-Nitrobenzenesulfonic acid
PPTS	Pyridinium *p*-toluene sulphonate
p-TSA	*p*-Toluensulphonic acid
PTC	Phase transfer catalyst
Py	Pyridine
TBDMS	*tert*-Butyldimethylsilyl
TBHP	*tert*-Butylhydroperoxyde
TBS	*tert*-Butyldimethylsilyl
TEA	Triethylamine
TEAC	Tetraethylammonium carbonate
TEAHC	Tetraethylammonium hydrogen carbonate
TBAF	Tetrabutylammonium fluoride
TIPS	Triisopropylsilyl
TFA	Trifluoroacetic acid
TMANO	Trimethylamine *N*-oxide
TMS	Trimethylsilyl
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
Tf	Trifluoromethansulfonyl
Tol	*p*-Toluyl
o-Tol	*o*-Toluyl
TPPTS	*Tris*(*m*-sulfonatophenyl)phosphine trisodium salt
Ts	Tosyl
Salen	Bis(5-dodecylsalicylidene)ethylenediamino
SOPS	Solid-phase organic synthesis

Other abreviations:

aq.	Aqueous
ax.	Axial
bs	Broad singulet
cat.	Catalytic
CN	Coordination number

conv.	Conversion
d	Doublet
δ	Chemical shift
Δ	Heating
de	Diastereoisomeric excess
dr	Diastereoisomeric ratio
ee	Enantiomerical excess
EI	Electronic ionisation
eq.	Equatorial
equiv.	Equivalent
EWG	Electron withdrawing group
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectroscopy
HUVEC	Human umbilical vein endothelial cell
IR	Infrared
CI	Chemical ionisation
J	Coupling constant in NMR
m	Multiplet
M	Mass
MS	Mass spectroscopy
M.S.	Molecular sieves
NMR	Nuclear magnetic resonance
q	Quadruplet
RCM	Ring closing metathesis
RT	Room temperature
sc	Super critical
s	Singulet
t	Triplet
TLC	Thin layer chromatography
TOF	Turnover frequency
TON	Turnover number

I. Generalities on Gold Catalysis

I.1. Background

Since historical times, gold always fascinated mankind and represented something very valuable. Gold belongs to the metals that have been known since ancient times, its discovery dating back at least to 5000 BC. Gold is unique among the metals because it is resistant to oxidation and corrosion, it is the most malleable and ductile metal known and also it has a good electrical and thermal conductivity. Thanks to its exceptional stability, gold in metallic form has been used for centuries in medicine,[1] jewelery, currency, chinaware, dentistry, electronics, photography etc.

For a long time, ancients believed that gold was the "ultimate" metal and all other base metals could be converted to it by some "magical" process. Alchemy, the forbearer to modern chemistry as we know it today, was concerned with the transmutation of common metals into gold. This process was believed to be mediated by the "philosopher's stone," a mythical substance which was also believed to bestow eternal youth. The concept of the philosopher's stone may have been inspired by the chemical extraction of gold from certain alloys. This remained a long-held philosophical idea that even today has a certain attraction. The early efforts of alchemists to produce gold synthetically largely contributed to the development of chemistry over the decades.[2] Although gold has occupied the minds of alchemists and chemists for centuries, until recently its chemistry was virtually unexplored.

The special interest of gold is connected with its value as a metal. Consequently the development of its chemistry had been mainly concerned with metallurgical processes. Chemical compounds employed for the production of gold film as decoration have been developed, but the chemistry of these substances remained little understood. After silicon, gold is probably the most frequently used element in nanoscale science today, and nanoparticles of gold have a much longer history than those of any other metal. The oldest well documented example is the Lycurgus cup from the 4th century AD, which is now exhibited in the British Museum.[3] The art of handling gold in the form of nanoparticles developed to a science with Faraday's legendary 1857 report in which he described that gold was present in solution in a "finely divided metallic state".[4]

One may consider surprising that gold has taken so long to be applied in catalysis. Gold has traditionally been overlooked in catalysis, possibly because of preconceived notions that it is expensive and chemically inert. The reason for this has nothing to do with cost, as might be expected (many metals commonly used as catalysts such as platinum, rhodium and iridium are much more expensive than gold, see Table I.1).[5]

---

[1] Fricker, S. P. *Gold Bull.* **1996**, *29*, 53

[2] a) Krätz, O. *7000 Jahre Chemie*, Nikol Verlagsgesellschaft, Hamburg, **1999**; b) Schmidtbaur, H. *Chem. Soc. Rev.* **1995**, *24*, 391; c) *Gold-Progress in Chemistry, Biochemistry and Technology* (Ed: Schmidbaur, H.), Wiley, New York **1999**

[3] Hutchings, G. J.; Brust, M.; Schmidbaur, H. *Chem. Soc. Rev.* **2008**, *37*, 1759

[4] Faraday, M.; *Philos. Trans. R. Soc. London*, **1857**, *147*, 145

[5] http://www.taxfreegold.co.uk/preciousmetalpricesusdollars.html

Precious metal	Price/gram
Silver	0.19 $
Ruthenium	1.96 $
Iridium	4.66 $
Palladium	6.17 $
Osmium	12.86 $
Gold	13.66 $
Platinum	27.62 $
Rhenium	39.38 $
Rhodium	50.15 $

Table I.1

The chemical inertness of gold would appear at first sight to render it unsuitable as a catalyst,[6] since heterogeneous catalysis requires the formation of intermediate species of moderate stability at the surface of the metal. Indeed, gold adsorbs neither hydrogen nor oxygen and it cannot therefore act as a hydrogenation or oxidation catalyst in the normal sense.[7] Notwithstanding this unfavorable prognosis, gold has been shown to possess some most interesting properties.

Applications of gold and gold salts in heterogeneous catalysis evolved at the beginning of the last century, when Bond et *al.* reported the hydrogenation of olefins over supported gold catalysts.[8] Later, Haruta and Hutchings simultaneously and independently prognosticated gold to be an extraordinary good catalyst. Haruta et *al.* studied the low-temperature oxidation of CO[9] and Hutchings the hydrochlorination of ethyne to vinyl chloride,[10] both heterogeneous reactions. For the first time these studies showed gold to be the best catalyst for these reactions, despite the previous reports on its poor catalytical activity. Nowadays gold catalysts belong to the most active catalysts for such diverse reactions as selective oxidation reactions, oxidative decomposition of halogen compounds, catalytic combustion of hydrocarbons, hydrogenation of carbon oxides, reduction of nitrogen oxides with propane, carbon monoxide or hydrogen.[11,12,13]

Although the utility of heterogeneous gold catalysis has already been demonstrated in industry, it is only recently, at the end of the 20th century, that the field of homogeneous gold catalysis has come into attention (see Chapter I.3).[11]

The discovery that gold can be synthesized in catalytically active forms has motivated growing interest in investigation of the chemical and catalytic properties of gold.[14] The

[6] "Catalytically dead" was used in the literature. For a discussion, see: Schmidbaur, H. *Naturwiss. Rundsch.* **1995**, *48*, 443

[7] Bond, G. C. *Gold Bull.* **1972**, *5*, 11

[8] Bond, G. C.; Sermon, P. A.; Webb, G.; Buchanan, D. A.; Wells, P. B. *J. Chem. Soc. Chem. Commun.* **1973**, 444

[9] Haruta, M.; Kobayashi, T.; Sano, H.; Yamada, N. *Chem. Lett.* **1987**, *16*, 405

[10] Hutchings, G. J. *J. Catal.* **1985**, *96*, 292

[11] a) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 7896; b) Hutchings, G. J. *Catal. Today* **2005**, *100*, 55; c) Hutchings, G. J. *Catal. Today* **2002**, *72*, 11

[12] a) Bond, G. C. *Catal. Today* **2002**, *72*, 5; b) Haruta, M. *Gold Bull.* **2004**, *37*, 27

[13] a) Thompson, D. *Gold Bull.* **1998**, *31*, 111; b) Thompson, D. *Gold Bull.* **1999**, *32*, 12

[14] For a general treatise, see: Bond, G. C.; Louis, C.; Thompson, D. T. *Catalysis by Gold*; Imperial College Press: London, **2006**

understanding of gold catalysis has been facilitated by the theories of frontier orbitals,[15] relativistic effects,[16] and л-acidity.[15] Because of their unique properties (see Chapter I.2), gold catalysts have become the choice for many chemical transformations in both heterogeneous and homogeneous transformations. Since gold catalysts can carry out processes for which no other catalyst has yet been discovered, the exploitation of gold catalysts for commercial applications is being pursued.[17,18]

From an environmental point of view, gold catalysts show many valuable features.[19] They are in the center of new developments in green chemistry,[20] and their ambient temperature activity, in particular, has opened up new opportunities for waste prevention and for pollution control applications. These compounds are employed as catalysts in the chemical processing of a range of bulk and specialty chemicals, in the emerging "hydrogen economy" for clean hydrogen production and fuel cell systems, as well as for sensors to detect poisonous or flammable gases or substances in solution.[18]

Gold catalyzed reactions often proceed under extremely mild conditions, often at room temperature with reaction times of just minutes, and gold catalysts are active in very small amounts. This contrasts with other metal-catalyzed reactions that require higher temperatures and reaction times of hours or even days.[16b] Likewise other transition metals, gold salts are capable of forming several bonds in one pot, allowing the minimization of waste elements and most importantly the reaction can be performed with high atom economy.

Gold derivatives are robust transition metal catalysts and their catalytic reactions are conveniently performed under experimentally simple reaction conditions, are generally air and moisture tolerant and generate only environmentally benign byproducts.[21] In addition, the apparent redox stability of Au(I) complexes under ambient temperature and pressure allows the development of new modes of reactivity by precluding the traditional oxidative addition/reductive elimination cycles so prevalent in late transition-metal catalysis. Also, as the use of safer solvents and the reduction of solvent waste play a critical role in “greening” synthetic chemistry, gold catalysts can be used with alternative solvents which enable easy catalyst separation and recycling. The impact of catalysis by gold toward sustainable chemistry has been highilighted by Ishida and Haruta.[22]

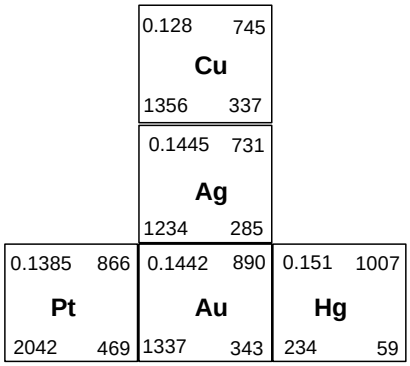
I.2. The Unusual Properties of Gold

Gold (Z=79) has the electronic configuration $[Xe]4f^{14}5d^{10}6s^{1}$. Chemists today are increasingly fascinated by gold's unique position in the family of elements. In the periodic table, gold is placed in Group 11 (IB) with copper and silver and between platinum (Group 10) and mercury (Group 12). It is intriguing why the **unique position of gold** in the family of elements has simply been accepted and not been more of an intellectual challenge to scientists. In contrast, the question of the **fascinating color of gold** metal received much more attention than any other physical or chemical property.

---

[15] Fürstner, A.; Davies, P. W. *Angew. Chem. Int. Ed.* **2007**, *46*, 3410
[16] a) Bartlett, N. *Gold Bull.* **1998**, *31*, 22; b) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395; c) Schwarz, H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4442
[17] Corti, C. W.; Holliday, R. C.; Thompson, D. T. *Top. Catal.* **2007**, *44*, 331
[18] Corti, C. W.; Holliday, R. C.; Thompson, D. *Appl. Catal. A: General* **2005**, *291*, 253
[19] Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266
[20] Hutchings, G. J. *Catal. Today* **2007**, *122*, 196
[21] Sherry, B. D.; Toste, F. D. *Chemtracts Org. Chem.* **2005**, *18*, 14
[22] Ishida, T.; Haruta, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 7154

There are many aspects in which the properties of gold are unexpected compared to those of its neighbors'.[12] Gold has a **high electronegativity** for a metal, as shown by its high first ionisation potential, and it can form compounds such as $Au^{-}Cs^{+}$ where it is anionic. The most common oxidation states for gold are I (aurous compounds) and III (auric compounds); the V state is seen only in $[AuF_6]^{-}$. Its metallic radius is slightly smaller than that of silver (see Fig. I.1 for selected physical properties of gold and its neighbours),[12] but the Au(III) state is more stable than Au(I), while the reverse is true for silver. It doesn't react directly with other electronegative elements, such as sulfur or oxygen, but dissolves in hydrochloric acid when nitrate ion (strongly oxidizing agent) is present (*aqua regia*).



Clockwise from top left: metallic radius (nm); first ionisation potential (kJ/ mol); melting temperature (K); sublimation enthalpy (kJ/ mol).

Figure I.1

These and other puzzling observations associated with gold have been subjected to new scrutiny when new structure determination methods like single crystal X-ray diffraction became available. New oxidation states and coordination numbers were discovered for gold in an unlimited variety of gold compounds and a new phenomena came to light, mainly concerning unprecedented and unexpected gold-gold interactions absent with other elements and lacking a clear-cut theoretical explanation.[23,24] This new phenomena baptized **"aurophilicity"** (the tendency for Au–Au interactions to be stabilizing on the order of hydrogen bonds),[25] appeared not only with gold metal in the zero oxidation state Au(0), but also in gold clusters with mixed valence characteristics, for compounds of the classical oxidation states Au(III) and Au (I), and even for the newly discovered $[Au(II)_2]$ species.[23] Although metallophilicity has been recognized to be a more general effect, it appears to be strongest and most obvious for gold(I) owing not only to its strongest relativistic contraction (see discussion below) but also to the low coordination number (CN 2) and therefore reduced steric hindrance for complexes with the metal in this oxidation state.[3]

The uniqueness of gold and many of its properties can be rationalized in terms of **relativistic effects.**[16] The differences between the 4d and 5d elements and their compounds have been ascribed to the great stability of the $6s^2$ electron pair. This is now thought to originate in an operation of Einstein's Theory of Special Relativity on the energies of electron orbits.[26,13a] As

[23] Schmidbaur, H. *Gold Bull.* **1990**, *23*, 11
[24] Puddephatt, R. J. *"The Chemistry of Gold"* **1978**, Elsevier, Amsterdam
[25] Scherbaum, F., Grohmann, A., Huber, B., Krüger, C.; Schmidbaur, H. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1544
[26] a) Pyykkö , P. *Angew. Chem. Int. Ed.*, **2004**, *43*, 4412; b) Bond, G.C. *J. Molec. Catal. A: Chem.* **2000**, *1*, 156; c) Pyykkö , P. *Chem. Soc. Rev.* **2008**, *37*, 1967

the mass of the nucleus increases, the speed of the innermost $1s^2$ electrons has to increase to maintain their position, and for gold they attain a speed which is about 60% that of light. There is then a relativistic effect on their mass and the 1s orbital contracts: all the outer s orbitals have to contract in sympathy (the actual size of the 6s electron shell for Pt and Au is some 15% smaller than it would be in the absence of the relativistic effect), but p and d electrons are much less affected. In consequence, the $6s^2$ pair is contracted and stabilized and much of the chemistry (including the catalytic properties) of the 5d elements is determined by the high energy and reactivity of the 5d electrons. The second manifestation of relativistic effects is indirect; electrons occupying the d and f orbitals are better shielded by the electrons in the contracted s and p orbitals and therefore see a weaker nuclear attraction. These effects scale roughly with Z^2 and become important for elements heavier than the lanthanides.[16,23]
Gold, because it is also at the end of the 5d orbital filling, (third transition series contraction effect) following on the 4f filling (lanthanide contraction) exhibits maximum impact of this relativistic effects.
Thus theoretical studies of the electronic structure of gold might also provide an important insight into how it might function as a catalyst and what reactive mechanistic pathways might be accessible.[16b] Taken together, the points discussed above mean that valence shell electrons of different orbitals (s, p, d) are brought much closer together in energy, especially with respect to the gap between the 6s and 5d states. Calculations shave shown that through these drastic changes (as compared with the Ag homologue) the block of the $5d^{10}$ "closed shell" can be broken up and mobilized for chemical bonding.[23] Also, the relativistic contraction of the 6s orbital can be translated in greatly strengthened gold-ligand bonds. Additionally, Au(I) predominantly adopts a linear, bicoordinate geometry, in contrast to tricoordinate and tetracoordinate Cu(I) and Ag(I) complexes. This limited coordination number observed in Au(I) chemistry translates into the general need to abstract a ligand from neutral bicoordinate Au(I) species in order to induce catalytic reactivity.[16b]

I.3. Homogeneous Catalysis by Gold

The most interesting domain of application of gold in organic synthesis is the homogeneous catalysis. It must be noted that this domain has been practically unexplored before the 90's but has witnessed a tremendous activity in the recent years.
In comparison with heterogeneous catalysis, homogeneous gold catalysis presents some advantages: the reaction media being homogeneous, the problems arising from substrate absorption-desorption on the catalyst surface are minimized. Difficulties regarding the preparation of the catalyst (choice of coating method of the active species on the surface, particle dimension and surface characteristics) are also eliminated. Typical catalyst loadings are somewhere between 1 and 5 mol%, which corresponds to 20-100 turnovers (turnover number TON). Reaction times are often in the range of hours and the turnover frequencies (TOF) are significantly smaller than 100 h^{-1}.[27] The reaction conditions are simple and robust, and neither dry solvents nor the exclusion of air is needed. While in heterogeneous catalysis very complex catalysts are used in most cases and the substrates are often simple small molecules, in homogeneous catalysis the catalyst can be relatively simple and the substrate

[27] Hashmi, A. S. K. *Gold Bull.* **2007**, *40*, 31

tends to be complex and highly functionalized. This makes the domain of homogeneous gold catalysis very interesting for the synthesis of fine chemicals.[15,11,28,29,31]
The increasing interest for the application of homogeneous gold catalysis in organic synthesis is due to the major virtues and uniqueness of gold compounds. The most representative example is the exceptional ability of gold(I) and gold(III) salts to act as soft carbophilic Lewis acids towards carbon–carbon multiple bonds which, after this activation, undergo a variety of transformations affording new carbon–carbon or carbon–heteroatom bonds (Figure I.2). In addition, they are capable of activating C–H bonds of aromatic and other substrates, opening unprecedented pathways for their functionalization. This unusual property of gold catalysts to activate all type of л-systems including alkenes, allenes, and alkynes towards intermolecular and intramolecular nucleophilic attack leads to the development of methods to efficiently assemble diverse complex structures like those found in natural products.[30]
Occasionally, gold salts of both stable oxidation states – Au(I) and Au(III) – are capable of catalyzing the same transformation, and very often it is not clear what the oxidation state of the catalytically active species might be.[31] Gold compounds are hard to oxidise, but are easily reduced and do not tend to undergo β-hydride eliminations, which complements the classical metals used for transition metal catalysis (palladium, platinum, etc.). Also, gold often reacts faster than other transition metals which can catalyze the same reaction. Gold intermediates undergo fast protodemetallation, and cross-coupling chemistry is difficult with gold. To all this it must be added that gold compounds are non-toxic.[19]
Gold-catalyzed reactions have other several unique features: the high oxidation potential of gold(I) to gold(III) allows most gold(I)-catalyzed reactions to proceed in the presence of air and oxygen. Au(I) and Au(III) ligand exchange reactions are associative, and can occur at extremely high rates. Unlike many Lewis acids, gold catalysts are exceptionally alkynophilic,[31,15] but not oxophilic, so oxygen, water, and alcohols are often well tolerated, in sharp contrast to most air- and moisture-sensitive Lewis acid or transition metal-catalyzed reactions. Furthermore, the non-classical carbocation/carbene nature of intermediates involved in gold-catalyzed transformations frequently results in well-controlled reactivity and selectivity, as demonstrated in several gold-catalyzed cyclization and cycloaddition reactions. Lastly, gold catalysis often demonstrates highly substrate dependent reaction manifolds.[19]

*

In the following resumé, a personal selection among recent examples on the use of gold in homogeneous catalysis is illustrated.
This overview begins with a brief introduction on the different types of reactions catalyzed by gold. This chapter is organized by reactivity patterns and by functional groups in the substrates. An organization by the gold catalyst used or the type of bond(s) formed in the product would have been unsuitable, because in most cases many different gold complexes with different oxidation states of gold have been used as precatalysts for the same reaction, the same principles for several different C-element bond forming reactions, and often, several new bonds are formed in one reaction.[32] A detailed bibliographic section with recent examples will be illustrated in each following chapter.

---

[28] Recent reviews: a) Hoffmann-Röder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387; b) Jimenez-Nuñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, *4*, 333; c) Bongers, N; Krause, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 2178; d) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239; e) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885
[29] a) Hashmi, A. S. K. *Nature* **2007**, *449*, 292; b) Nolan, S. P. *Nature* **2007**, *445*, 496
[30] Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766
[31] a) Hashmi, A. S. K. *Gold Bull.* **2003**, *36*, 3; b) Hashmi, A. S. K. *Gold Bull.* **2004**, *37*, 51
[32] Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180

The last part of this overview is dedicated to the presentation and classification of gold catalysts used in homogeneous transformations, illustrated by some representative examples on their use.

I.3.1. Nucleophilic Additions to C-C Multiple Bonds

Almost all gold-catalyzed nucleophilic heteroatom additions to unsaturated C-C bonds follow the same mechanistic steps depicted in Figure I.2. The precatalyst is transformed into the catalytically active species [Au] which will coordinate to the multiple bond of the substrate activating it towards subsequent nucleophilic attack. Depending on the nature of the nucleophile employed (nitrogenated, oxygenated, sulfur containing, double or triple C-C bond, aromatic or allenic double bond), a new C-N, C-O, C-S or C-C bond is formed. The following step is highly dependent on the nature of the intermediate gold species thus formed: proton loss, protodeauration, hydride ion migration, Wagner-Meerwein rearrangement, cyclization, a second nucleophilic attack etc. The energetic differences between the different intermediate species are often very small, explaining thus the great variety of transformations involving gold compounds and the difficulty of predicting them. The last step is always the regeneration of the active species (as discussed above, gold species present a reduced susceptibility towards *β*-eliminations, but carbon-gold bonds are labile toward protodeauration).

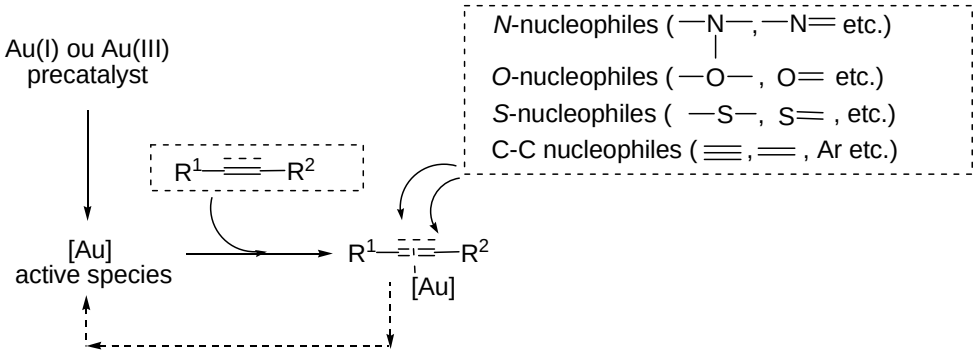
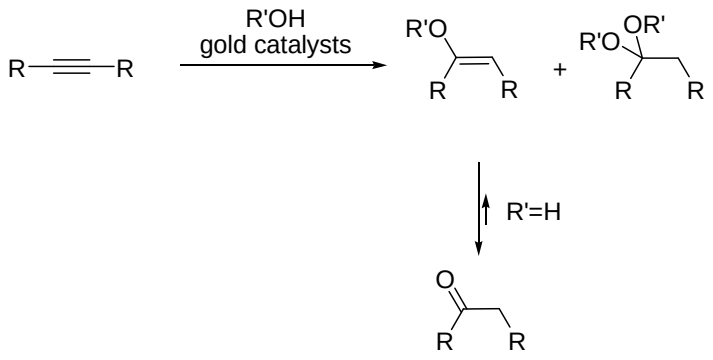


Figure I.2

Addition of Oxygenated Nucleophiles to C-C Multiple Bonds

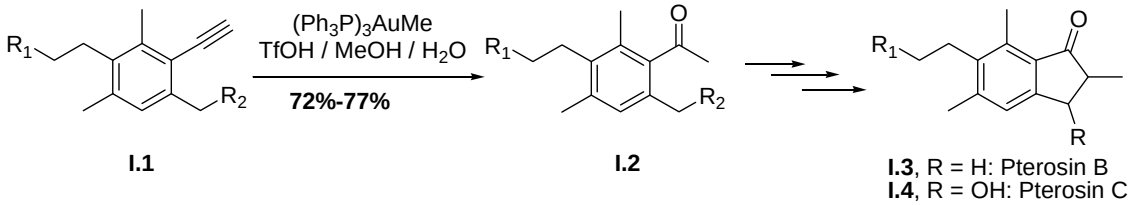
One of the earliest and most representative reaction catalyzed by gold involving the addition of oxygenated nucleophiles to C-C multiple bonds is the hydroalkoxylation, *bis*(hydroalkoxylation), and hydration of alkynes. The first reactions of this type were developed by Utimoto et *al.* who observed that with 2 mol % $Na[AuCl_4]$ as the catalyst, alcohols and water can serve as nucleophiles in the gold-catalyzed reactions of alkynes (Scheme I.1).[33]

[33] a) Fukuda, Y.; Utimoto, K. *J. Org. Chem.* **1991**, *56*, 3729; b) Fukuda, Y.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2013



Scheme I.1

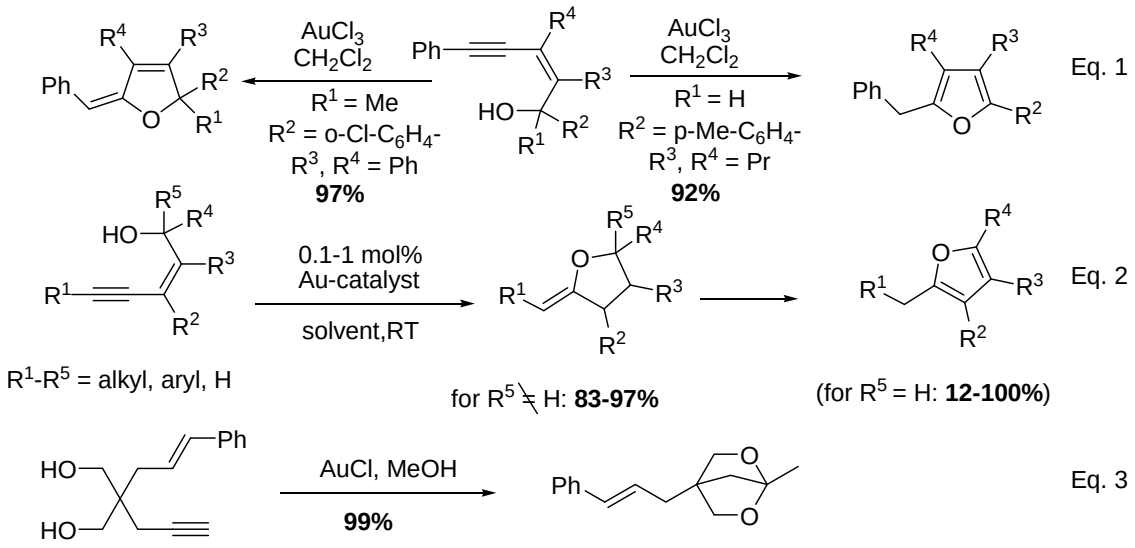
This method was further developed by Teles and colleagues using cationic gold(I)-phosphane complexes which proved to be very active (TON up to 10^5, TOF up to 5400 h^{-1}).[34] This method finds utility in the synthesis of Pterosins B and C, where the selective introduction of the acyl group in I.2 was achieved by the gold catalyzed hydration of ethynylarene I.1 (Scheme I.2.):[30,35]



Scheme I.2.

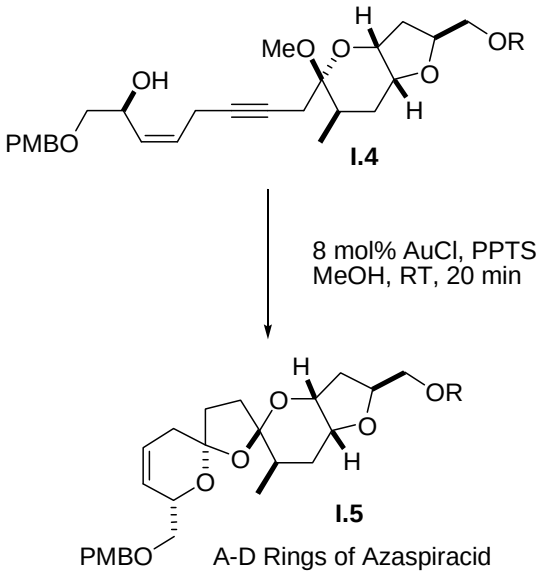
With CO as the coligand, which allowed Hayashi and Tanaka et *al.* to even improve the activity of Teles' catalysts for the hydration of alkynes, a TOF of 15600 s^{-1} was accessible.[36] Intramolecular versions of the alcohol addition were also reported by Liu's[37] and Hashmi's[38] group affording furan derivatives (Scheme I.3, Eq. 1 and 2) and by Michelet et *al.*[39] in the synthesis of bicyclic ketals (Scheme I.3, Eq. 3):

[34] a) Teles, J. H.; Schulz, M. (BASF AG), WO-A1 97/21648, **1998**, [Chem. Abstr. **1997**, *127*, 121499]; b) Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 1415
[35] Wessig, P; Teubner, J. *Synlett* **2006**, 1543
[36] Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M. *Angew. Chem. Int. Ed*. **2002**, *41*, 4563
[37] Liu, Y.; Song, F.; Song, Z.; Liu, M.; Yan, B. *Org. Lett.* **2005**, *7*, 24, 5409
[38] Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem. Int. Ed.* **2000**, *39*, 2285
[39] Antoniotti, S.; Genin, E.; Michelet, V.; Genêt, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 9976



Scheme I.3

Forsyth and colleagues reported the use of gold chloride in the related two-fold additions of one hydroxy group and one methyl ether group as the second nucleophile in the synthesis of a trioxadispiroketal containing the A-D rings of azaspiracid (I.5, Scheme I.4),[40] a member of a family of marine toxins that was found to be the cause of human poisoning in the Netherlands.[29b]

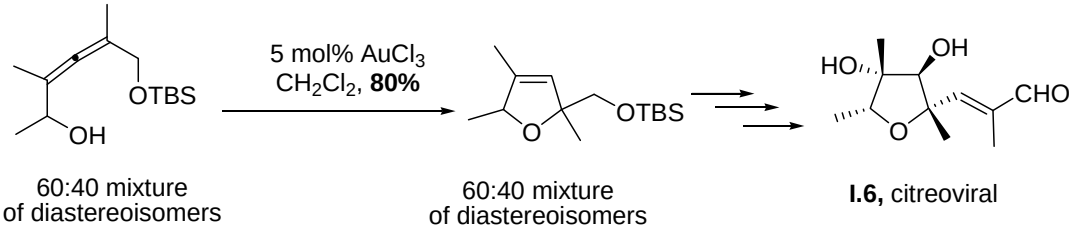


Scheme I.4

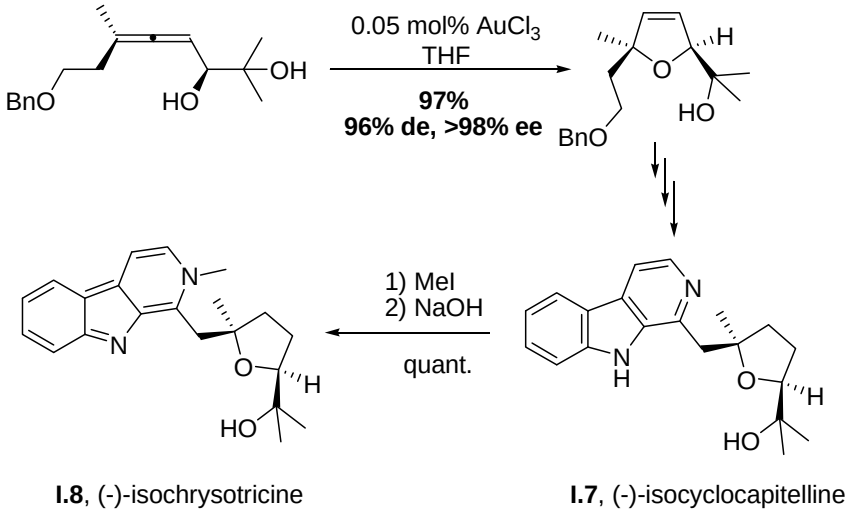
For other examples of gold-catalyzed additions of oxygenated nucleophiles to C-C multiple bonds, see examples illustrated in Chapters II-VI. For a detailed discussion concerning the addition of *O*-nucleophiles to allenes, see Chapter V.3.2. The hydroxy- and alkoxycyclizations of enynes will be illustrated in Chapter VIII.

[40] Li, Y., Zhou, F.; Forsyth, C. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 279

As will be discussed in detail in Chapter V.3.2, gold catalysts activate allenes toward nucleophilic additions. A methodology involving selective cyclisation of allenyl carbinols was used in a formal total synthesis of Citreoviral (I.6, Scheme I.5), a metabolite of the antiparasitic mycotoxin Citreoviridin.[41] Similar allene cyclisations have been applied in key steps in the enantiospecific total syntheses of (-)-isocyclocapitelline (I.7) and (-)-isochrysotricine (I.8) (Scheme I.6).[30,42]



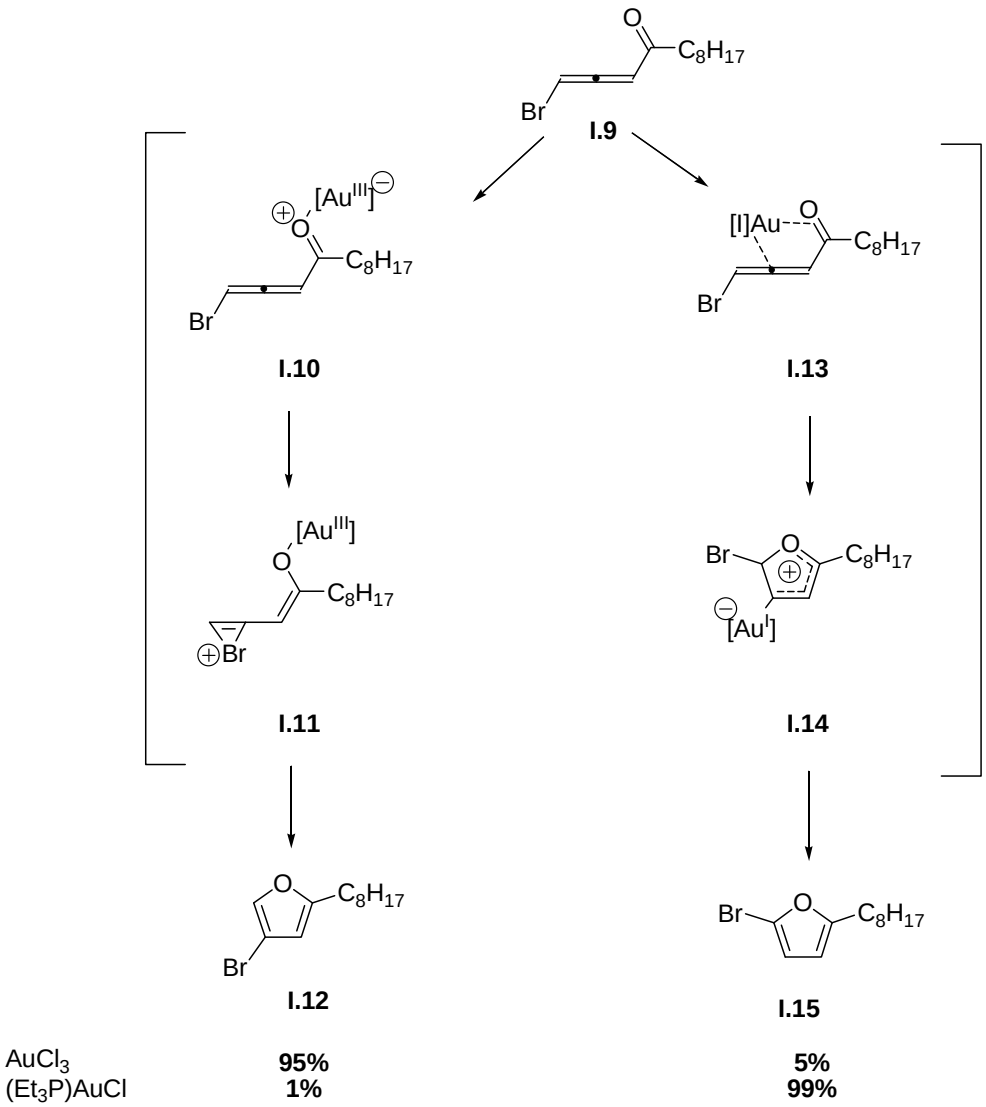
Scheme I.5



Scheme I.6

The carbonyl group can also act as a nucleophile. For example, Gevorgyan et *al.* studied the reactivity of the bromoallenyl ketone I.9 in presence of different gold catalysts (Scheme I.7). Which one of the two different products I.12 or I.15 was obtained depended on the oxidation state of the gold catalyst. This was explained by an enhanced oxophilic behavior of gold(III) (intermediates I.10 and I.11), while gold(I) is more carbophilic (intermediates I.13 and I.14).[43]

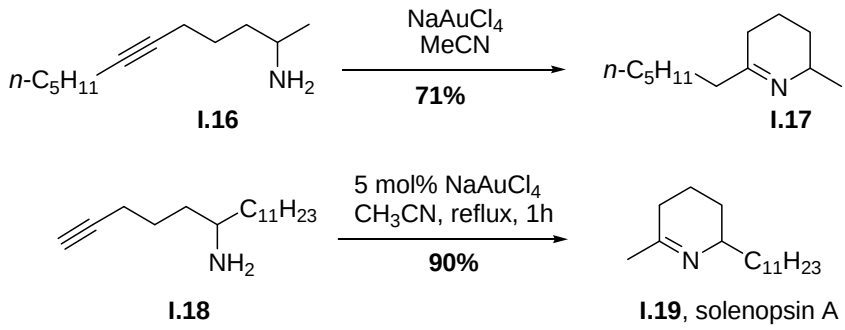
[41] a) Hoffmann-Röder, A.; Krause, N. *Org. Lett.* **2001**, *3*, 2537; b) Krause, N.; Hoffmann-Röder, A.; Cansius, J. *Synthesis* **2002,** 1759; c) Marshall, J. A.; Pinney, K. G. *J. Org. Chem.* **1993**, *58*, 7180
[42] Volz, F.; Krause, N. *Org. Biomol. Chem.* **2007**, *5*, 1519
[43] Sromek, A. W.; Rubina, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2005**, *127*, 10500



Scheme I.7

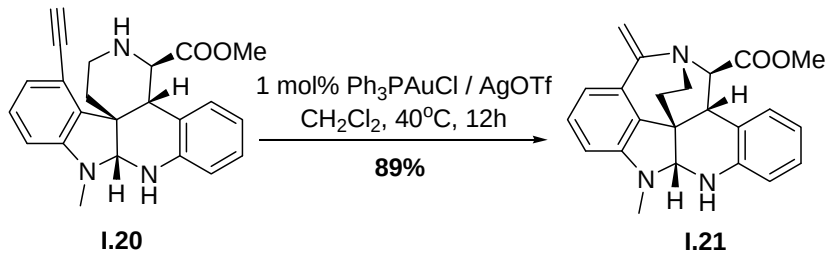
Addition of Nitrogenated Nucleophiles to C-C Multiple Bonds

It was also Utimoto's group who showed for the first time that gold(III) complexes can catalyse the hydroamination of alkynes. Tetrahydropyridines I.17 and I.19 are obtained by a 6-*exo-dig* cyclisation of alkynes I.16 and I.18 bearing a primary amine nucleophile (Scheme I.8). (±)-Solenopsin A (I.19) and related ant venom constituents were prepared employing this methodology.[30,33]



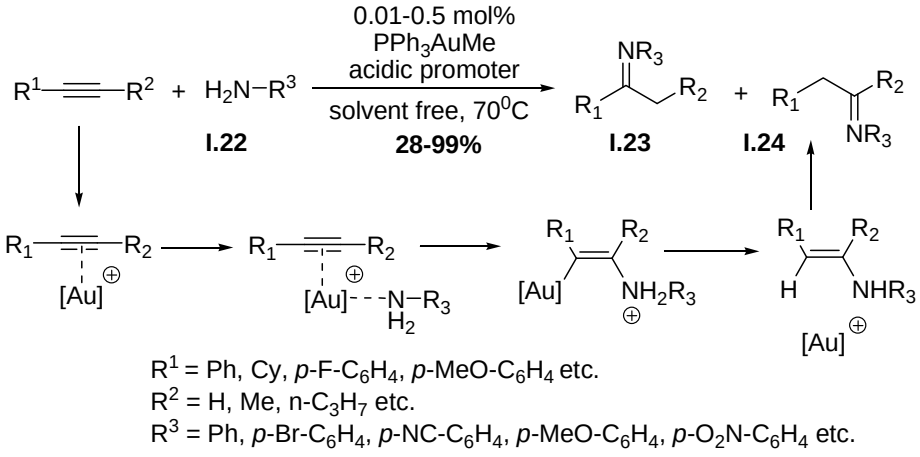
Scheme I.8

An intramolecular hydroamination of I.20 to I.21 was employed in the construction of the hexacyclic core of Communesin B (I.21) by Crawley and Funk (Scheme I.9).[30,44]



Scheme I.9

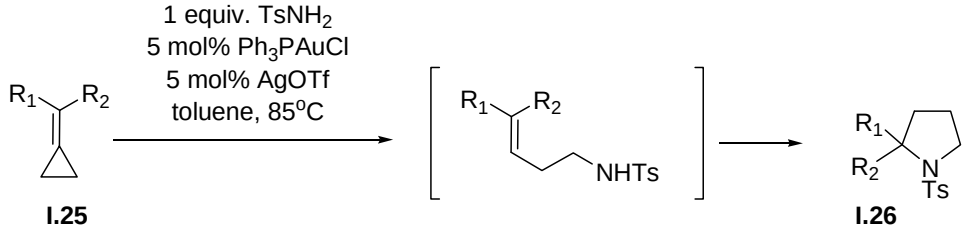
The first intermolecular versions were reported by Tanaka et *al.* for the reaction of alkynes and anilines I.22 to imines I.23/I.24 under solvent-free conditions (Scheme I.10).[45]



Scheme I.10

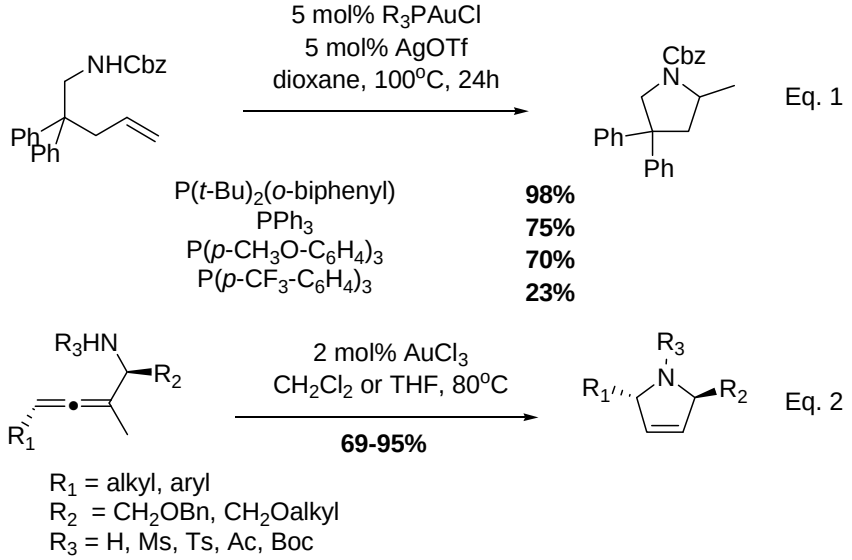
[44] Crawley, S. L.; Funk, R. L. *Org. Lett.* **2006**, *8*, 3995
[45] Mizushima, E.; Hayashi, T.; Tanaka, M. *Org. Lett.* **2003**, *5*, 3349

An interesting reaction involving a domino ring-opening ring-closing hydroamination process afforded pyrrolidine derivatives I.26 starting from methylenecyclopropanes I.25 (Scheme I.11): [46]



Scheme I.11

Electron-rich phosphines such as P(*t*-Bu)$_2$(*o*-biphenyl) were particularly effective ligands for intramolecular hydroamination of unactivated olefins under milder conditions and with broader substrate scope than previously reported with late transition-metal catalyst systems (Scheme I.12, Eq. 1).[47] By analogy with the cyclization of allenyl carbinols, different related amines undergo this transformation in presence of gold catalysts (Scheme I.12, Eq. 2).[48]



Scheme I.12

Addition of Carbon Nucleophiles to C-C Multiple Bonds. Enynes as Substrates

[46] Shi, M.; Liu, L.-P.; Tang, J. *Org. Lett.* **2006**, *8*, 4043
[47] Han, X.; Widenhofer, R. A. *Angew. Chem. Int. Ed.* **2006**, *45*, 1747
[48] a) Morita, N.; Krause, N. *Org. Lett.* **2004**, *6*, 4121; b) Morita, N.; Krause, N. *Eur. J. Org. Chem.* **2006**, 4634

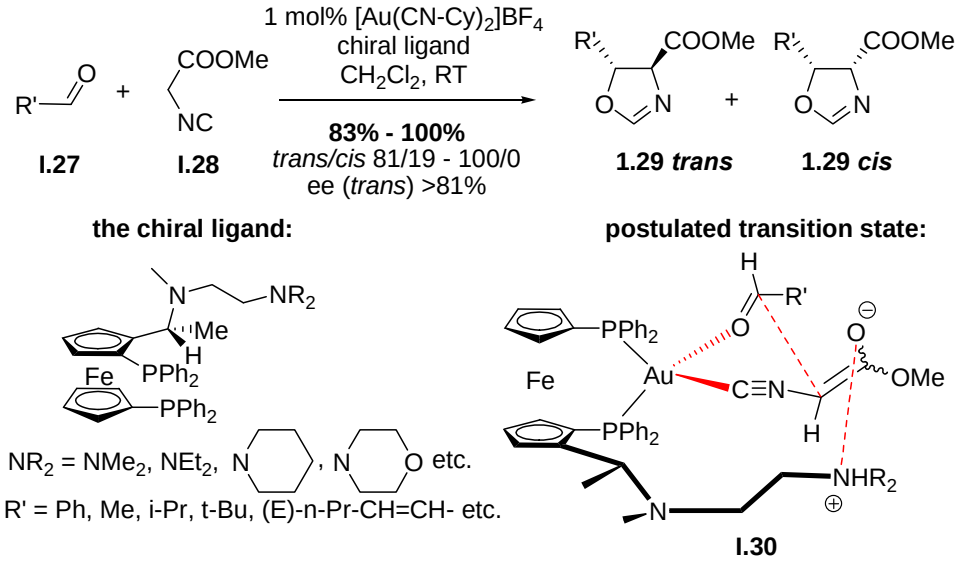
Undoubtedly, the cycloizomerisation of enynes is the most popular and most studied gold-catalyzed reaction.[15,49] This subject will de discussed in detail in Chapters VII and VIII.

I.3.2. Activation of Carbonyl/Imine Groups and Alcohols

Gold salts can operate as bifunctional Lewis acids activating either (or both) carbon-carbon multiple bonds *via* π-binding or make σ-complexes with heteroatoms.[49c]

Aldol Reactions

A first landmark in gold catalysis, which also had an important impact in organic asymmetric synthesis, was made by Ito, Sawamura and Hayashi.[50] They reported the asymmetric reaction of aldehydes I.27 and isocyanoacetates I.28 to deliver oxazolines I.29 using a gold(I)-catalyzed aldol reaction in the presence of chiral ferrocenylamine ligands that possess both planar and central chirality (Scheme I.13).[51] The postulated transition state (I.30) explaining the stereoselectivity observed is depicted in Scheme I.13. The amino group in the sidearm of the ligand deprotonates the isocyanoacetate, which is acidified by coordination to gold. An ion pair bonding keeps the isocyanoacetate on the coordination site of the gold complex, the carbonyl oxygen atom of the aldehyde then coordinates to the other site, and this directs the facial selectivity of the deprotonated isocanoacetate. Overall, both the carbonyl group and the nucleophile are activated by the gold catalyst.



[49] For excellent reviews on transition metal-catalyzed cycloisomerization of enynes, see: a) Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem. Int. Ed.* **2008**, *47*, 4268; b) Bruneau, C. *Angew. Chem. Int. Ed.* **2005**, *44*, 2328; c) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813; For reviews on gold-catalyzed cycloisomerisation, see: d) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271; e) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326; f) Fürstner, A.; Morency, L. *Angew. Chem. Int. Ed.* **2008**, *47*, 5030; g) Shen, H. C. *Tetrahedron* **2008**, *64*, 7847

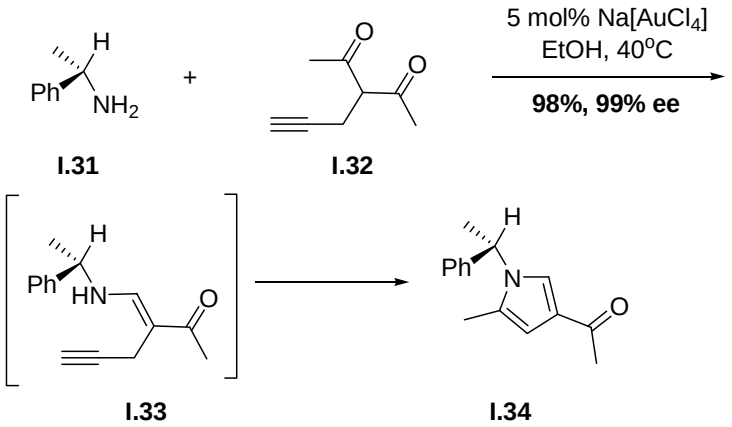
[50] Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405

[51] For a review, see: a) Sawamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 857; For applications, see: b) synthesis of chiral 2,3-diaminoacids: Zhou, X. T.; Lin, Y. R.; Dai, L. X. *Tetrahedron: Asym.* **1999**, *10*, 855; c) synthesis of D-threo-sphingosine: Ito, Y.; Sawamura, M.; Hayashi, T. *Tet. Lett.* **1988**, *29*, 2, 239

Scheme I.13

Condensation Reactions

Gold-catalyzed condensation reactions of carbonyl derivatives with amines, alcohols and thiols have also been reported.[19,32]
For example, Scheme I.14 illustrates the gold-catalyzed condensation reaction between chiral amines I.31 and 1,3-dicarbonyl compounds I.32 and their intramolecular hydroamination/ isomerization to substituted pyrroles I.34:[52]

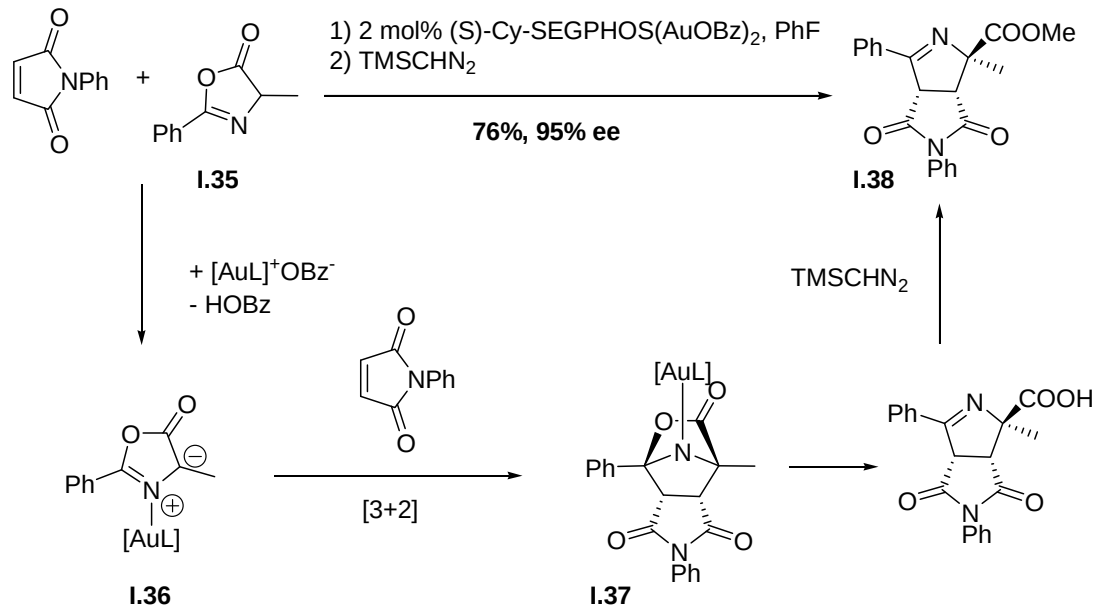


Scheme I.14

Cycloaddition Reactions

An example of [3+2] cycloaddition was disclosed by Toste and colleagues who reported the 1,3-dipolar cycloaddition of münchnone I.35 with electron-deficient alkenes. In this reaction, the chiral gold species *S*-Cy-SEGPHOS(AuOBz)$_2$ dictated the stereochemical outcome of the reaction (Scheme I.15).[53]

[52] a) Arcadi, A.; Di Giuseppe, S.; Marinelli, F.; Rossi, E. *Adv. Synth. Catal.* **2001**, *343*, 443; b) Arcadi, A.; Di Giuseppe, S.; Marinelli, F.; Rossi, E. *Tetrahedron: Asym.* **2001**, *12*, 2715
[53] Melhado, A. D.; Luparia, M.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 12638



Scheme I.15

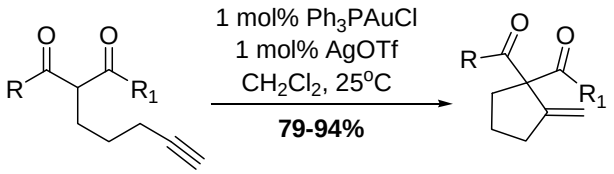
I.3.3. Gold-Catalyzed C-H Bond Functionalization

Catalytic C-H activation and functionalization by metal complexes is a hot topic in organic chemistry.[54] In the past few years, gold has been recognized to be very active in this domain.[19,28f] The reactivity of C–H bonds depends on the hybridization of the carbon atom. In the case of Csp–H bonds, the heterolysis or an insertion of a transition metal is much easier than into Csp^2–H bonds. The most difficult functionalization is noticed in case of compounds with unactivated Csp^3–H bonds. Substrates such as alkynes, alkenes or arenes, *α,β*-unsaturated ketones, *β*-diketones or allenes can be activated by gold(I) or gold(III) salts.

Csp^3-H Bond Functionalization

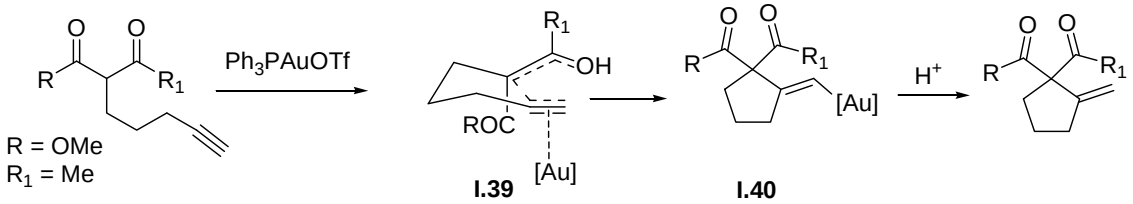
Activated Csp^3-H bonds like methylene bonds in 1,3-dicarbonyl compounds, benzylic or allylic derivatives can be easily functionalized in presence of gold catalysts.[19]
For example, Toste and co-workers applied phosphine-gold(I) complexes in the carbocyclization of *β*-keto esters with alkynes (also called the Conia-ene reaction) under mild and neutral conditions. An intramolecular example of this reaction is illustrated in Scheme I.16:[55]

[54] a) Bergman, R. G. *Nature* **2007**, *446*, 391; b) Dyker, G. *In Handbook of C-H Activation*, 1st ed. **2005**, Wiley-VCH: Weinheim, Germany
[55] a) Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 17168; b) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526; c) Staben, S. T.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem. Int. Ed.* **2004**, *43*, 5350



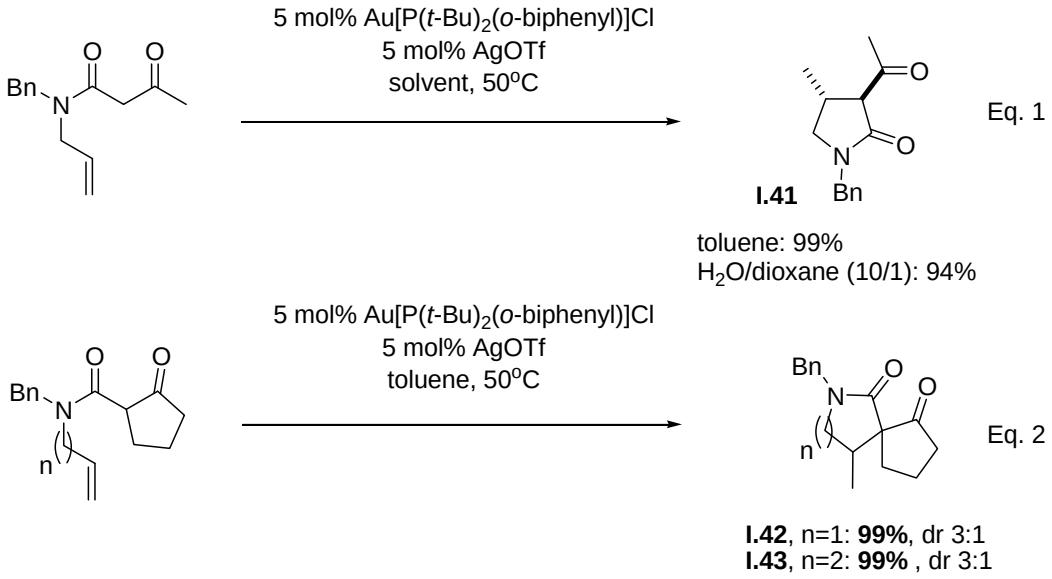
Scheme I.16

In the mechanism proposed in Scheme I.17, the Au(I)–alkyne complex I.39 was attacked by the enol form of the ketoester, resulting in the formation of the vinyl–Au intermediate I.40, which was protonated to form the final product:



Scheme I.17

The preparation of substituted lactams I.41 by an intramolecular addition of *β*-ketoamide to unactivated alkenes using 5 mol % of ClAuP(*t*-Bu)$_2$(*O*-biphenyl)/AgOTf in toluene was described by Che and Zhou (Scheme I.18, Eq. 1). This method allowed also the synthesis of spirolactams I.42-I.43 with modest to high diastereoselectivities (Eq. 2).[56]

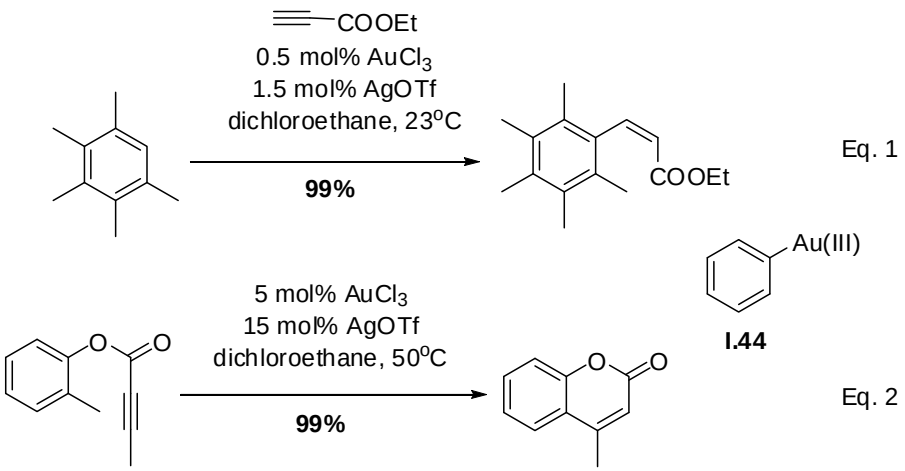


Scheme I.18

[56] Zhou, C.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2007**, *129*, 5828

Csp^2-H Bond Functionalization

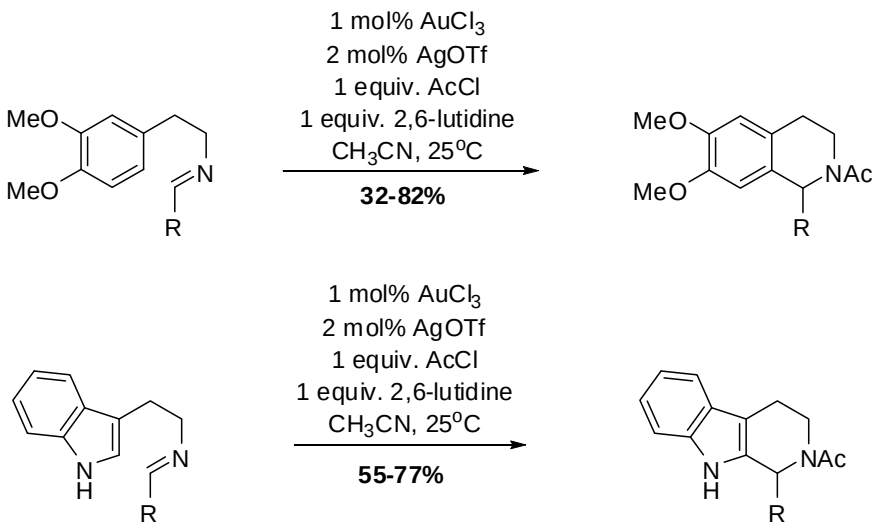
Inter and intramolecular alkenylation of arenes (or hydroarylation of alkynes)[57] is an important method for the formation of new C-C bond. Despite the fact that other transition metals (Pd, Pt, Sc) can also effectuate this transformation, gold can often provide comparable or better results but with a lower catalyst loading. The intermolecular hydroarylation reactions proceed at room temperature and even under solvent-free conditions in the presence of small amounts of $AuCl_3$ and AgOTf (Scheme I.19, Eq. 1), whereas the intramolecular application leading to coumarins requested higher temperature and higher catalyst loading (Scheme I.19, Eq. 2).[58] The intermediacy of arylgold(III) species (I.44) was demonstrated in the case of these reactions.[59]



Scheme I.19

It was shown that gold(III) complexes can be used as catalysts for the Pictet–Spengler reaction. A variety of tetrahydroisoquinolines (Scheme I.20, Eq. 1) and tetrahydro-*β*-carboline derivatives (Eq. 2) can be obtained in good yields by using 1 mol % of $AuCl_3$ and 2 mol % of AgOTf as a combined catalyst system in acetonitrile in the presence of a base.[60] This example can also be regarded as an example of imine activation by coordination with the gold(III) complex.

[57] a) Nevado, C.; Echavarren, A. M. *Synthesis* **2005**, 167; b) Nevado, C.; Echavarren, A. M. *Chem. Eur. J. 2005*, *11*, 3155
[58] a) Shi, Z.; He, C. *J. Org. Chem.* **2004**, *69*, 3669; b) Shi, Z.; He, C. *J. Am. Chem. Soc.* **2004**, *126*, 5964
[59] Porter, K. A.; Schier, A.; Schmidbaur, H. *Organometallics* **2003**, *22*, 4922 and references cited therein
[60] Youn, S. W. *J. Org. Chem.* **2006**, *71*, 2521

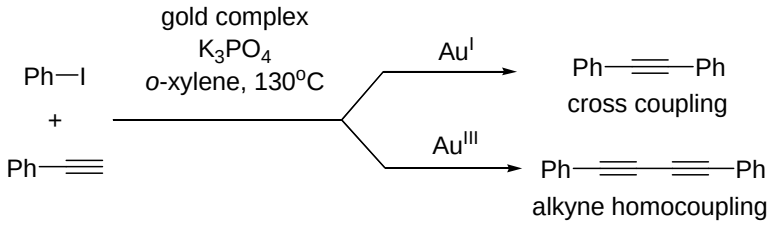


R = COOEt, *p*-NO_2-C_6H_4, *p*-MeO-C_6H_4, 2-(5-methylfuran-2-yl), 2-(6-methylpyridin-2-yl), cinnamyl, *n*-pentyl

Scheme I.20

Csp-H Bond Functionalization

Gold-catalyzed activation of the terminal C-H bond alkynes provided a variety of synthetic applications. For example, Corma's group showed that Au(I) is active and very selective for performing the Sonogashira reaction, whereas Au(III) only catalyzes the homocoupling (Scheme I.21).[61]

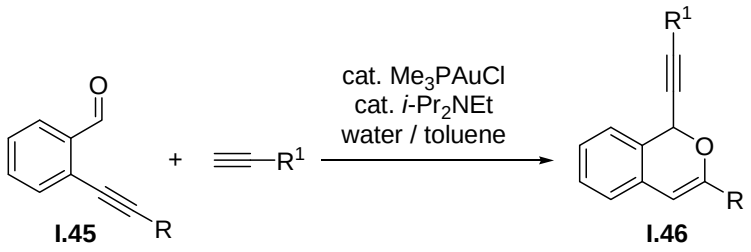


Scheme I.21

Another example is the reaction of *o*-alkynyl benzaldehydes I.45 with terminal alkynes in a mixture of water and toluene and in the presence of catalytic amounts of a tertiary base and a phosphine gold(I) complex (Scheme I.22):[62]

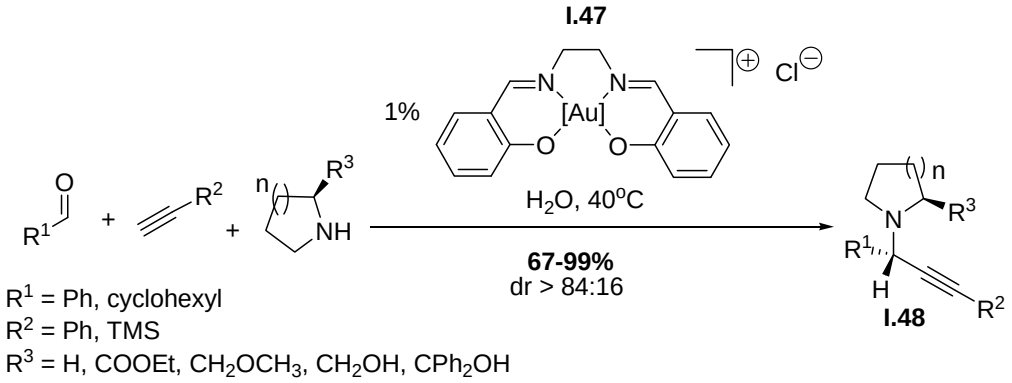
[61] a) Gonzalez-Arellano, C.; Abad, A.; Corma, A.; Garcia, H.; Iglesias, M.; Sanchez, F. *Angew. Chem. Int. Ed.* **2007**, *46*, 1536; b) Corma, A.; Gonzalez-Arellano, C; Iglesias, M; Perez-Ferreras, S; Sanchez, F. *Synlett* **2007**, 1771

[62] Yao, X.; Li, C.-J. *Org. Lett.* **2006**, *8*, 1953



Scheme I.22

Gold also demonstrated its potential in multicomponent reactions which allow increasing molecular complexity in a single step with a clear economical and environmental advantage. The three-component coupling of an aldehyde, an alkyne, and an amine, first reported by Wei and Li[63] is a representative example.
Lo and co-workers used original gold(III)-salen complexes I.47 with chiral amines as substrates to effectuate this reaction and applied it to the synthesis of propargylamine-modified artemisine derivatives of type I.48 (Scheme I.23).[64]



Scheme I.23

I.3.4. Hydrogenation Reactions

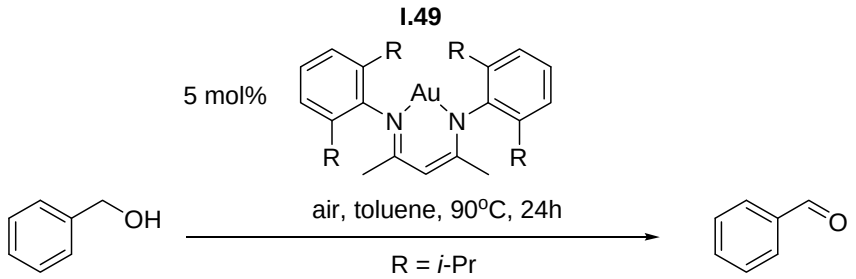
Gold catalysts are effective in the hydrogenation of a large number of substrates including alkenes, dienes, or alkynes,[32] and in the selective reductions of *α,β*-unsaturated carbonyl groups,[65] nitro groups and 1,3-dienes.[19] Most of these procedures involve heterogeneous reactions and therefore do not constitute the topic of this resumé.

I.3.5. Oxidation Reactions

Supported gold catalysts have been found to be particularly effective in the oxidation of alcohols and the epoxidation of alkenes.[32]

[63] Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2003**, *125*, 9584
[64] Lo, V. K.-Y.; Liu, Y.; Wong, M.-K.; Che, C.-M. *Org. Lett.* **2006**, *8*, 1529
[65] Claus, P. *Appl. Catal. A* **2005**, *291*, 222

The homogeneous oxidation of alcohols catalyzed by gold has more rarely been reported. The soluble complex I.49 (which is formed *in situ* from AuCl and β-diketiminate anion) serves as an excellent catalyst for the highly selective aerobic oxidation of alcohols. Benzyl alcohol has been oxidized to benzaldehyde in 99% GC yield with 100% conversion in toluene at 90 °C after 10 h with O_2 as the oxidant (Scheme I.24):[66]



Scheme I.24

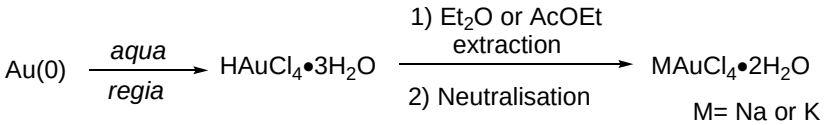
I.4. Gold Complexes Used in Homogeneous Catalysis

I.4.1. Au (III) Complexes

Au(III) is the best known oxidation state of gold. Au(III) complexes are d^8 and prefer to be square planar, four-coordinate. However, Au(III) salts are less-frequently used in cyclizations than gold(I) salts, perhaps due to their propensity for increased byproducts generation as well as their relatively high oxidative potentials.[28f]

Au(III) Halides

Early work in the application of soluble gold complexes as catalysts for organic transformations focused on the use of simple Au(III) halides as catalysts, like $AuCl_3$ which is the commercially available source of Au(III). It exists as a dimer (Au_2Cl_6) with μ-Cl ligands.
$AuCl_3$ was used in a plethora of transformations, the above mentioned Csp^2-H bond functionalization leading to heterocyles[58-60] or the hydroxycyclization and hydroamination of allenes[48] being just a few examples.
Tetrachloric acid and tetrachlorates are the cheapest available source of Au(III) and they are obtained as depicted in Scheme I.25.



Scheme I.25

[66] Guan, B.; Xing, D.; Cai, G.; Wan, X.; Yu, N.; Fang, Z.; Yang, L.; Shi, Z. *J. Am. Chem. Soc.* **2005**, *127*, 18004

Tetrachlorates are used as catalysts in a large variety of transformations like hydration and hydroxyalkylation of alkynes,[33] hydroamination of alkynes, condensation reactions affording nitrogenated heterocycles like pyrroles[52] or pyridines.[67] $NaAuCl_4$ have been reported to act as propargylic alcohol activating agent in propargylic, benzylic, and allylic substitutions.[68]

Pyridine type ligands I.50-I.54[69] illustrated in Figure I.3, were extensively used by Hashmi's and Zhang's groups, for example in the rearrangement of furans to phenol derivatives[27,70] and in the synthesis of tetrahydroisoquinolines.[71]

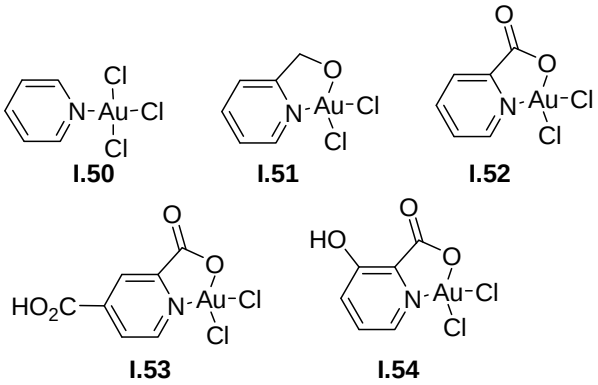
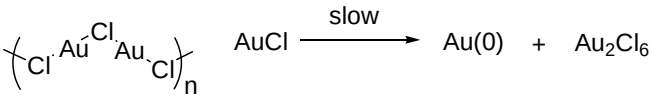


Figure I.3

I.4.2. Au (I) Complexes

Au(I) complexes are d^{10} and prefer to be linear, two-coordinate. AuCl is the commercially available source of Au(I); it exists as a polymeric chain with μ-Cl ligands (Scheme I.26). It is bench stable, but can reduce to Au(0) slowly:



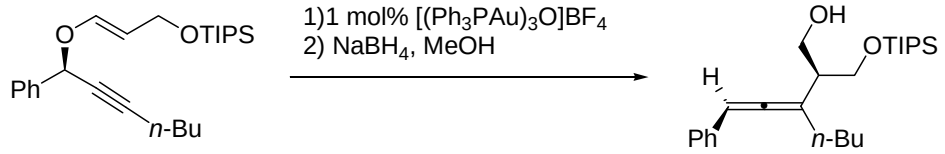
Scheme I.26

The **gold-oxo complex** $[(Ph_3PAu)_3O]BF_4$, used in organometallic synthesis[72] has also been introduced as a catalyst in certain reactions of enynes.[73]

---

[67] Arcadi, A.; Chiarini, M.; Di Giuseppe, S.; Marinelli, F. *Synlett* **2003**, 203
[68] a) Georgy, M.; Boucard, V.; Campagne, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 14180; b) Georgy, M.; Boucard, V.; Debleds, O.; Dal Zotto, C.; Campagne, J. M. *Tetrahedron* **2009** asap
[69] Dar, A.; Moss, K.; Cottrill, S. M.; Parisch, R. V.; McAuliffe, C. A.; Pritchard, R. G.; Beagley, B.; Sandbank, J. *J. Chem. Soc. Dalton Trans.* **1992**, *1*, 1907
[70] Hashmi, A. S. K.; Rudolph, M.; Bats, J. W.; Frey, W.; Rominger, F.; Oeser, T. *Chem. Eur. J.* **2008**
[71] Hashmi, A. S. K.; Weyrauch, J. P.; Rudolph, M.; Kurpejovic, E. *Angew. Chem. Int. Ed.* **2004**, *43*, 6545
[72] a) Yang, Y.; Ramamoorthy, V.; Sharp, P. R. *Inorg. Chem.* **1993**, *32*, 1946; b) Nesmeyanov, A. N.; Perevalova, E. G.; Struchkov, Y. T.; Antipin, M. Y.; Grandberg, K. I.; Dyadchenko, V. P. *J. Organomet. Chem.* **1980**, *201*, 343
[73] Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 15978

This catalyst was employed by Sherry and Toste in the Claisen rearrangement of enantiomerically enriched propargyl vinyl ethers, which leads to *β*-hydroxyallenes with high stereocontrol (Scheme I.27):[73]



95% ee

81%, 94% ee, dr > 20:1

Scheme I.27

Cationic Gold(I)–Phosphine Complexes

Recently, effort has increasingly shifted toward cationic gold(I)–phosphine complexes, generated by chloride abstraction from $[AuCl(PPh_3)]$ or similar phosphine complexes, using a silver salt with a noncoordinating anion to generate the corresponding cationic species $[Au(S)(PPh_3)]X$ (S being the solvent or a substrate molecule) *in situ*.[74] Similar cationic complexes can be obtained *in situ* by cleavage of the Au-Me bond in $[AuMe(PPh_3)]$ using a protic acid (Scheme I.28).[74,75,76]

1) $[AuCl(PPh_3)] + AgX \longrightarrow [Au(PPh_3)]X + AgCl\downarrow$

X= non-coordinating anion SbF_6^-, BF_4^-, NTf_2^-

2) $LAuCH_3 + HY \longrightarrow [Au(PPh_3)]Y + CH_4\uparrow$

HY = strong protic acid H_2SO_4, MsOH, HBF_4

3) LAuX or $[(LAu)_3O]BF_4 + F_3B{\bullet}OEt_2$

Scheme I.28

The 14-electron $[Au(PR_3)]^+$, which is isolobal to H^+,[77] is a highly electrophilic, soft Lewis acid that renders gold(I) highly carbophilic but relatively nonoxophilic. As a consequence, gold(I) displays good chemoselectivity and good functional group compatibility. Importantly, weak 5d→л* metal-to-ligand back bonding further predisposes a gold(I)–л-alkene/alkyne complex toward outersphere nucleophilic attack.[78] Although both Au(I) and Au(III) oxidation states are stable, gold(I) is not prone to air oxidation and does not readily participate in potentially deleterious redox-based processes.

---

[74] a) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cardenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2402; b) Nieto-Oberhuber, C.; Muñoz, M. P.; Lopez, S.; Jimenez-Nuñez, E.; Nevado, C.; Herrero-Gomez, E.; Raducan, M.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 1677; c) Ferrer, C.; Raducan, M.; Nevado, C.; Claverie, C. K.; Echavarren, A. M. *Tetrahedron* **2007**, *63*, 6306

[75] Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 1415

[76] Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 4563; b) Mizushima, E.; Hayashi, T.; Tanaka, M. *Org. Lett.* **2003**, *5*, 3349

[77] a) Hoffmann, R. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 711; b) Schmidbaur, H. *Chem. Soc. Rev.* **1995**, *24*, 391

[78] a) Hertwig, R. H.; Koch, W.; Schröder, D.; Schwarz, H.; Hruak, J.; Schwerdtfeger, P. *J. Phys. Chem.* **1996**, *100*, 12253; b) Nechaev, M. S.; Rayon, V. M.;. Frenking, G *J. Phys. Chem. A* **2004**, *108*, 3134

Although a diverse range of transformations have been reported, cationic gold(I) complexes have demonstrated particular utility as catalysts for the metathesis and/or cycloisomerization of enynes and related substrates, for the hydrofunctionalization of alkenes, allenes, and alkynes with carbon or heteroatom nucleophiles.[28,32,79]

For example, the cationic gold complex obtained *in situ* by cleavage of the Au-Me bond in [AuMe(PPh_3)] using a protic acid, was described by Teles et *al.* as a non-toxic, kinetically highly active catalyst for the hydratation of alkynes (see also Scheme I.2, Chapter I.3.1).[75]

Figure I.4 shows a number of gold(I) complexes that act as catalysts or precatalysts in a variety of transformations.[80] The gold(I) complexes I.55-I.60 (Figure I.4) bearing bulky, biphenyl-based phosphine ligands, developed by Echavarren's group, afford very active catalysts when mixed with Ag(I) salts.[81] Crystalline solids I.61-I.61bis are very reactive as catalysts in a variety of transformations.[82,83] Gold(I) complex I.61bis bearing *tris*(2,4-di-*tert*-butylphenyl)phosphite as a bulky ligand leads to a highly electrophilic cationic Au(I) catalyst *in situ* upon chloride abstraction with $AgSbF_6$.[84]

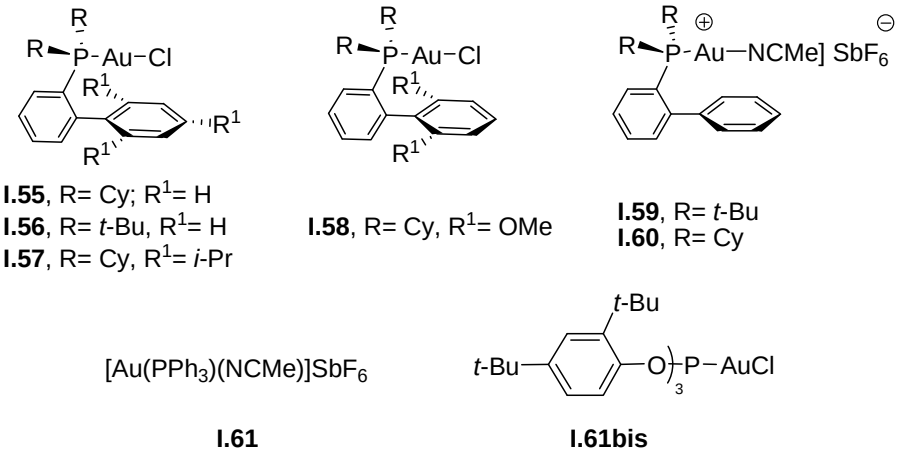


Figure I.4

Recently, *N*-heterocyclic carbenes (NHCs) have become serious alternatives to the ubiquitous tertiary phosphines and a number of NHC–gold(I) complexes, mainly Au(I) species of formulae [(NHC)AuCl] I.62a-j (Figure I.5) were used in synthesis.[85] The use of strongly σ-

[79] a) Widenhoefer, R. A.; Han, X. *Eur. J. Org. Chem.* **2006**, 4555; b) Wiedenhoefer, R. A. *Chem. Eur. J.* **2008**, *14*, 5382
[80] Jimenez-Nuñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326
[81] Nieto-Oberhuber, C.; Lopez, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178
[82] a) Nieto-Oberhuber, C.; Lopez, S.; Muñoz, M. P.; Jimenez-Nuñez, E.; Buñuel, E.; Cardenas, D. J.; Echavarren, A. M. *Chem.-Eur. J.* **2006**, *12*, 1694; b) Jimenez-Nuñez, E.; Claverie, C. K.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5452
[83] a) Ferrer, C.; Echavarren, A. M. Angew. Chem. Int. Ed. 2006, 45, 1105; b) Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. *Chem. Eur. J.* **2007**, *13*, 1358
[84] a) Lopez, S.; Herrero-Gomez, E.; Perez-Galan, P.; Nieto-Oberhuber, C.; Echavarren, A. M. A*ngew. Chem. Int. Ed.* **2006**, *45*, 6029; b) Nieto-Oberhuber, C.; Perez-Galan, P.; Herrero-Gomez, E.; Lauterbach, T.; Rodriguez, C.; Lopez, S.; Bour, C.; Rosellon, A.; Cardenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 269
[85] Marion, N.; Nolan, S. P. *Chem. Soc. Rev.* **2008**, *37*, 1776

donating *N*-heterocyclic carbene (NHC) ligands could be beneficial in cases where the use of phosphine led to a poor or moderate catalytic activity of the gold(I) complexes. These complexes are gaining popularity, taking advantage of straightforward synthetic routes developed recently.[86]

Besides having permitted to uncover important general features regarding the nature of the NHC–metal bond,[87] NHC–gold complexes have also encountered successes as potential drugs.[86b]

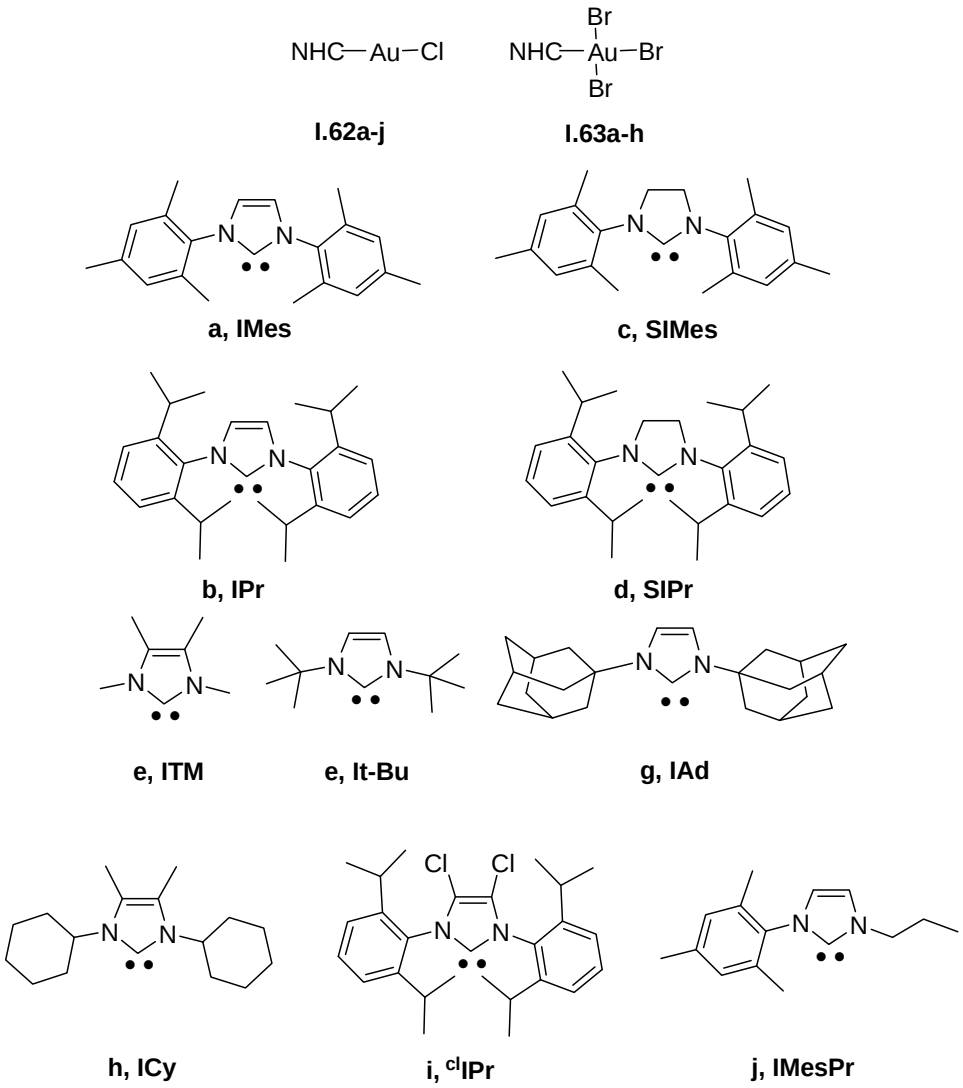
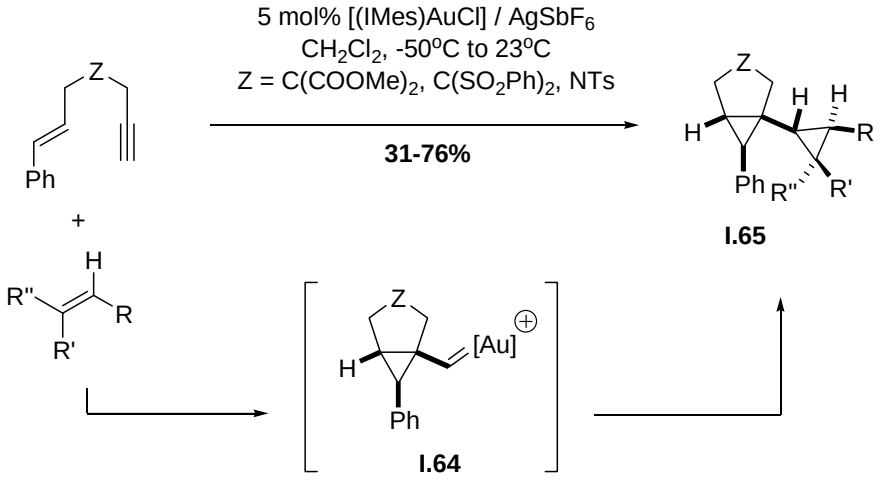


Figure I.5

NHC–gold(I) complexes have been succesfully used in enyne cycloisomerizations (Scheme I.29),[84a] in rearrangements of propargylic esters (Schemes I.30-I.33), in alkene and allene activation and in alkyne hydratation.[85]

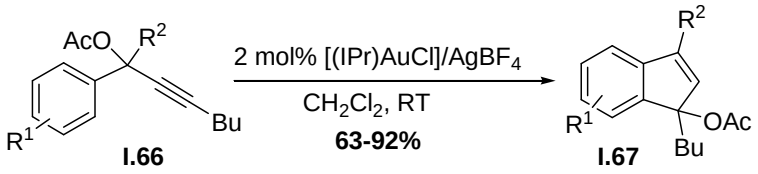
[86] For a review on NHC–gold complexes, see: a) Lin, I. J. B.; Vasam, C. S. *Can. J. Chem.* **2005**, *83*, 812; b) Raubenheimer, H. G.; Cronje, S. *Chem. Soc. Rev.* **2008**, *37*, 1998

[87] a) Hu, X.; Castro-Rodriguez, I.; Olsen K.; Meyer, K. *Organometallics* **2004**, *23*, 755; b) Nemcsok, D.; Wichmann, K.; Frenking, G. *Organometallics* **2004**, *23*, 3640 and references cited therein



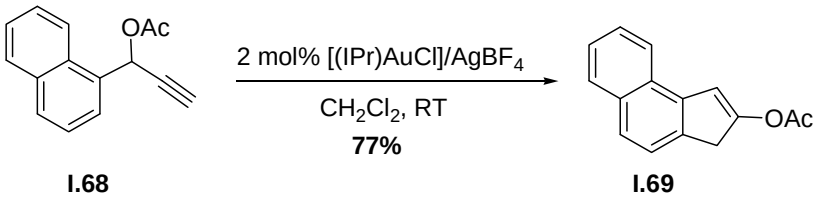
Scheme I.29

Recently, Nolan and co-workers reported an interesting example of NHC–gold(I) complex-catalyzed cycloisomerization of a propargyl acetate containing an adjacent aryl fragment I.66 (Scheme I.30). Propargylic acetates I.66 undergo a rearrangement to allenes with tandem hydroarylation to furnish substituted indenes I.67:[88]



Scheme I.30

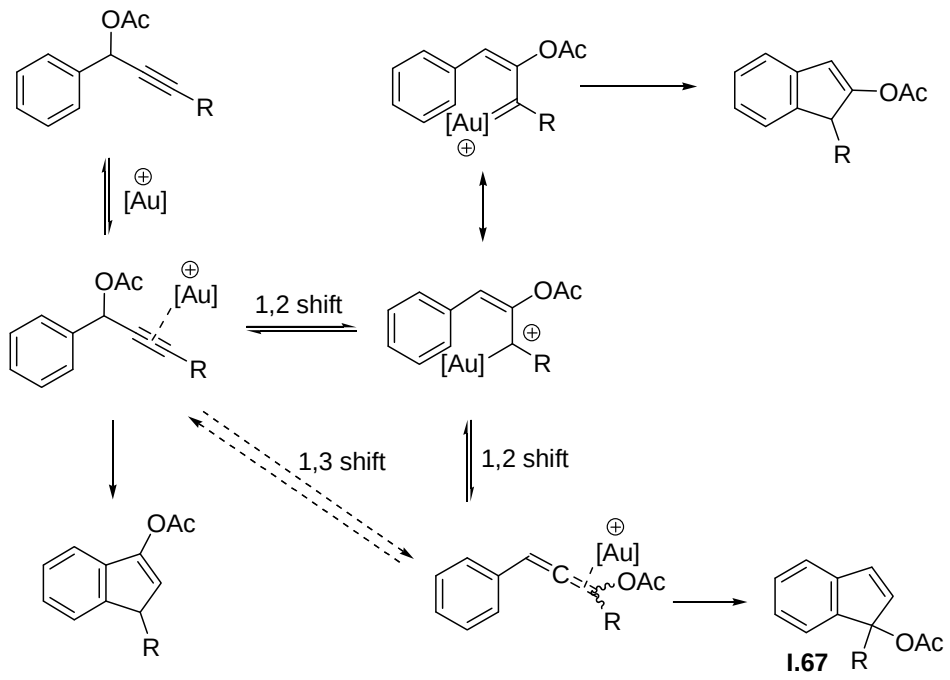
It appears that the behavior of the $[(IPr)Au]^+$ catalyst and, subsequently, the outcome of the reaction are highly dependent on the substitution pattern at the acetylenic position. With a proton at the acetylenic position, the formation of I.69 was observed, resulting primarily from a 1,2-migration of the propargylic acetate group in I.68 (Scheme I.31):



Scheme I.31

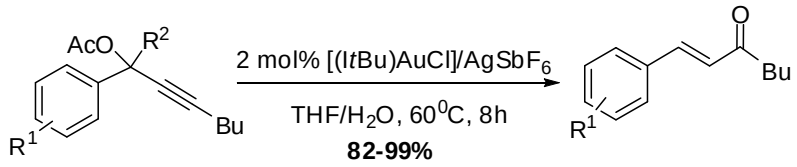
A plausible mechanism proposed by the authors is depicted in Scheme I.32:

[88] Nicolas Marion, N.; Diez-Gonzalez, S.; de Fremont, P.; Noble, A. R.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2006**, *45*, 3647



Scheme I.32

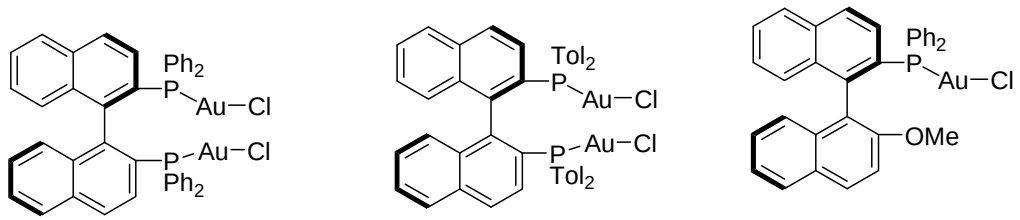
Notably, this reaction requires strictly anhydrous conditions; if water is present, the same substrates give conjugated enone and enal products.[89] Higher temperatures or microwave assistance are required in the latter case (Scheme I.33).



Scheme I.33

Gold catalysts bearing chiral mono- or bidentate phosphane ligands were used in enantioselective transformations by Echavarren's and Toste's groups.[90]
Moderate stereoselectivity was obtained by Echavarren et *al.* in the first example of an enantioselective transformation involving prochiral substrates and a chiral gold catalyst (after the aldol reaction shown in Scheme I.13) (up to 53% ee; 94% ee in a single case) in the alkoxycyclization of enynes in the presence of gold catalysts bearing chiral phosphane ligands (Figure I.6).[91]

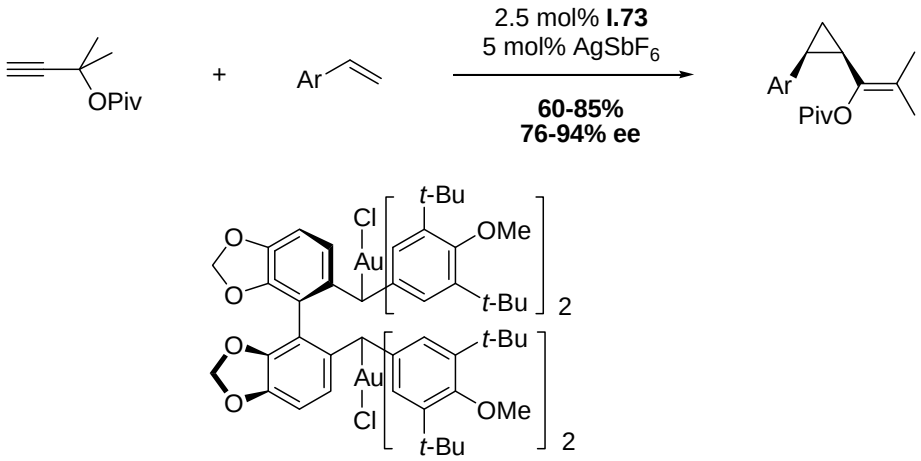
[89] Marion, N.; Carlqvist, P.; Gealageas, R.; de Fremont, P.; Maseras, F.; Nolan, S. P. *Chem. Eur. J.* **2007**, *13*, 6437
[90] Bongers, N; Krause, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 217 and references cited therein
[91] Muñoz, M. P.; Adrio, J.; Carretero, J. C.; Echavarren, A. M. *Organometallics* **2005**, *24*, 1293



I.70 **I.71** **I.72**

Figure I.6

The catalytic system *R*-DTBM-segphos-gold(I) complex I.73 and silver hexafluoroantimonate (Scheme I.34, DTBM-segphos=(4,4'-bi-1,3-benzodioxol)-5,5'-diylbis[di-(3,5-di-tert-butyl-4-methoxyphenyl)-phosphane]) was used by Toste and colleagues in the cyclopropanation of styrene derivatives, with selectivities reaching up to 94% ee.[92]



I.73

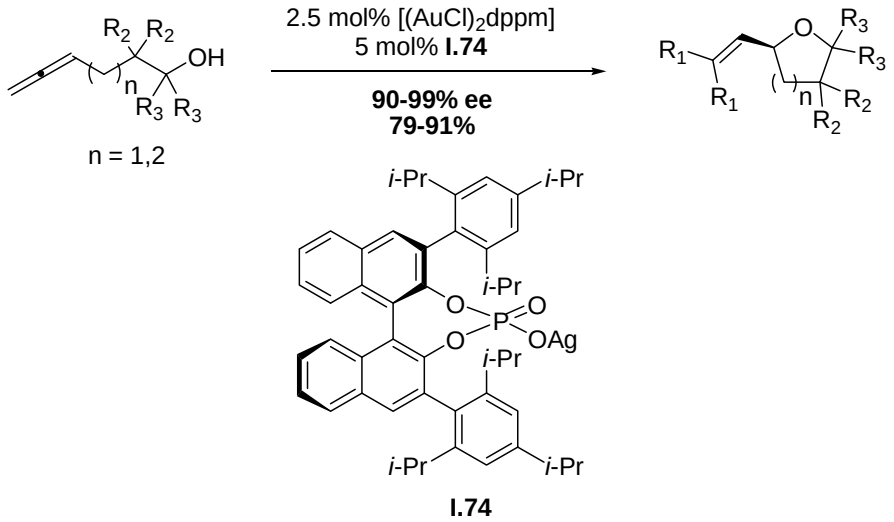
Scheme I.34

An overview on the cationic gold catalysts used in homogeneous catalysis wouldn't be complete without highlighting the catalysts with chiral counterions developed by Toste's group.[93] In spite of the recent upsurge of reports documenting reactions catalyzed by homogeneous gold complexes,[19,28,32] relatively few enantioselective transformations have been revealed.[50,73,91,92,94] Au(I) complexes incorporating chiral phosphines (see discussion above) have proven very successful for certain processes but inadequate for others. The linear coordination geometry of gold, which places the chiral components distant from the substrate, can be probably hold responsible for this fact.[95]

Taking advantage of the fact that most of the *in situ* formed gold(I)-phosphine complexes (see Scheme I.26) bear a positive charge, Toste tried an alternative approach for the induction

[92] Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002
[93] Hamilton, G. L.; Kang, E. J.; Mba, M.; F. Dean Toste, F. D. *Science* **2007**, *317*, 496
[94] a) González-Arellano, C.; Corma, A.; Iglesias, M.; Sanchez, F. *Chem. Commun.* **2005**, 3451; b) Zhang, Z.; Widenhoefer, R. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 283; c) Liu, C.; Widenhoefer, R. A. *Org. Lett.* **2007**, *9*, 1935
[95] a) Hashmi, A. S. K. *Nature* **2007**, *449*, 292; b) Lacour, J.; Linder, D. *Science* **2007**, *317*, 462

of asymmetry, e.g. by interaction of the cationic catalyst with a chiral counteranion associated with the metal in an ion pair. The use of chiral binaphthol–derived phosphate anions I.74 as counterions in the gold(I)-phosphine complexes generated products in 90 to 99% enantiomeric excess. Particularly high enantioselectivities were achieved in the cycloisomerization of various γ- and δ-hydroxyallenes using a mixture of the achiral gold complex [$(AuCl)_2$dppm] and the chiral silver phosphate I.74 (Scheme I.35):



Scheme I.35

Cationic Gold(I) Complexes Developed by our Group

As discussed above, cationic phosphine gold(I) complexes have recently emerged as highly active catalysts for the conversion of a plethora of substrates into a range of useful structural motifs.[19,28,32] Nevertheless, despite their efficiency, the catalytic system commonly used in these transformations, which corresponds to the combined use of a phosphine gold(I) chloride complex and a silver salt as a cocatalyst (Scheme I.36, see also Scheme I.26), suffers some limitations.

Scheme I.36

Another extensively used procedure to generate the cationic gold species is by protonation of an alkylgold(I) complex with a strong acid (see Scheme I.26). However, these conditions are not always compatible with the substrates.

One limitation of the first mentioned method is the fact that silver salts are all very hygroscopic, causing difficulties in properly weighing the reagent and in keeping the reaction

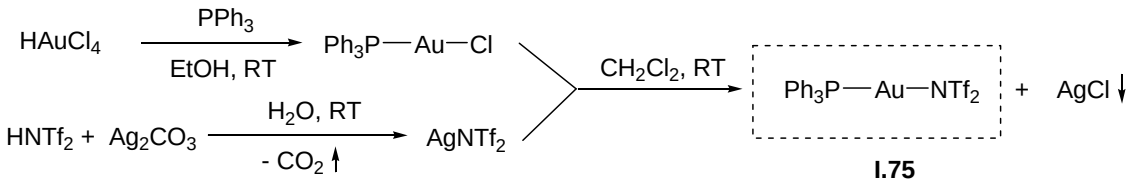
medium nonacidic.[96] Additionally they are also light-sensitive. Another drawback is due to the instability of the active gold(I) species generated *in situ*, especially when a fluorine-based counteranion is used.[97]
It is known that weakly coordinating anions such as BF_4^-, PF_6^-, and SbF_6^- are Lewis acid/base conjugates of a superior nucleophile, for example in the case of fluoride based counterions:

$$MF_{n+1} \longrightarrow MFn + F^-$$

Scheme I.37

In consequence their ability to act as inert counterions is always limited by a competition reaction for that nucleophile (e.g., F^-), and the free Lewis acid MF_n can act as an oxidizing agent causing unwanted side reactions.[98]

Taking into account these limitations, it is of particular interest to develop efficient catalysts that would not require the use of a cocatalyst and would hence be more convenient to use.
By analogy with the plentiful studies documenting the use of the *bis*(trifluoromethanesulfonyl)imidate moiety (Tf_2N^-) for the synthesis of highly electrodeficient cationic complexes,[99] Gagosz et *al.*[100] envisaged this weakly coordinating counterion[101] as a potentially valuable candidate for the synthesis of stable gold(I) catalysts. Moreover, it was reported that NTf_2^- is a weaker coordinating anion than OTf^- and ClO_4^-.[99b] The desired $(Ph_3P)AuNTf_2$ complex (I.75) was obtained by treatment of $(Ph_3P)AuCl$ with 1 equiv. of $AgNTf_2$ (Scheme I.38):



Scheme I.38

[96] The use of a glovebox is required to properly weigh the silver salt
[97] Echavarren and co-workers have reported the isolation of the two air-stable cationic complexes $(Ph_3P)Au(NCMe)SbF_6$ and (2-(di-*tert*-butylphosphino)biphenyl)$Au(NCMe)SbF_6$ as active catalysts for cycloisomerization reactions: a) Nieto-Oberhuber, C.; Lopez, S.; Muñoz, M. P.; Cardenas, D. J.; Bunuel, E.; Nevado, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6146; b) Ferrer, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 1105; c) Nieto-Oberhuber, C.; Muñoz, M. P.; Lopez, S.; Jimenez-Nuñez, E.; Nevado, C.; Herrero-Gomez, E.; Raducan, M.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 1677
[98] a) Raabe, I.; Krossing, I. *Angew. Chem. Int. Ed.* **2004**, *43*, 2066; b) Raabe, I.; Krossing, I. *Chem. Eur. J.* **2004**, *10*, 5017
[99] Numerous metal triflimides are known as strong Lewis acid catalysts: For lanthanides, see: a) Ishihara, K., Kubota, M.; Yamamoto, H. *Synlett* **1996**, 265 and 839; For silicium, see: b) Mathieu, B.; Ghosez, L. *Tetrahedron* **2002**, *58*, 8219; For tin, see: c) Vij, A.; Wilson, W. W.; Vij, V.; Corley, C. R.; Tham, F. S.; Gerken, M.; Haiges, R.; Schneider, S.; Schroer, T.; Wagner, R. I. *Inorg. Chem.* **2004**, *43*, 3189; For other metals, see: d) Sibi, M. P.; Petrovic, G. *Tetrahedron: Asymmetry* **2003**, *14*, 2879
[100] a) Mezailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133; b) Ricard, L.; Gagosz, F. *Organometallics* **2007**, *26*, 4704
[101] By analogy with the stability of $AgNTf_2$ compared to the hygroscopic salts AgOTf, $AgBF_4$, $AgPF_6$, or $AgSbF_6$

This new complex (Figure I.7)[102] was isolated as a crystalline compound and proved to be stable toward air and moisture and with time. Furthermore, its synthesis can easily be performed on a multi-gram scale and it is soluble in the majority of usual organic solvents (CH_2Cl_2, THF, Et_2O, toluene, CH_3CN, MeOH…).

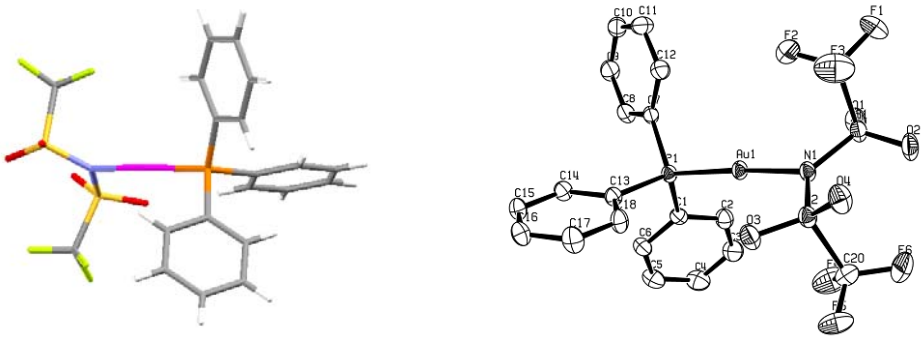


Figure I.7

In solution, the catalyst can be dissociated leading to $Ph_3P–Au^+$ and NTf_2^-.
The counter anion NTf_2^- is a poor ligand and presents a very reduced nucleophilic character due to the steric, electronic and lipophilic effects of the two triflate moieties.
In contrast, the cationic species $Ph_3P–Au^+$ is electrophilic and possesses a strong Lewis acid character, easily modulable changing the properties of the phosphine ligand. A phosphine richer or poorer in electrons will render the cationic species less or more electrophilic. Similarly, a more or a less sterically encumbered phosphine will reduce or increase its electrophilicity (see Figure I.10).
The alkynophilicity of $(Ph_3P)AuNTf_2$ is a function of the solvent used as illustrated in Figure I.9, being less reactive and less acidic in weakly coordinating solvents like dichloromethane and more reactive in coordinating solvents like methanol (Figure I.8 and I.9):

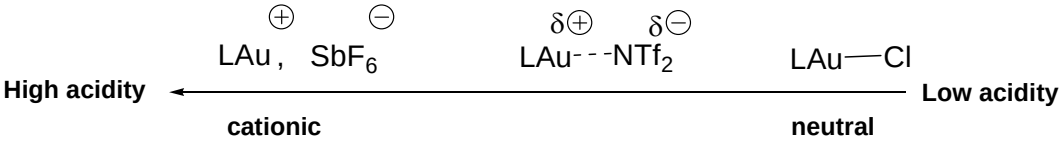


Figure I.8

[102] The crystal structure of I.75 was established by X-ray diffraction (CCDC 273834)

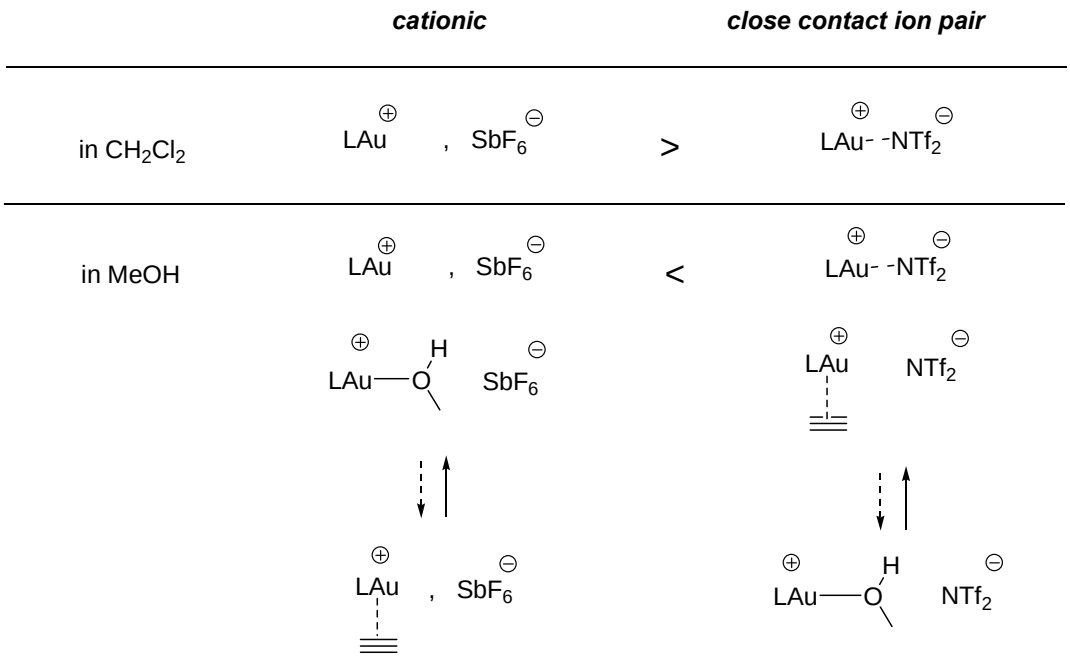


Figure I.9

These results led to the discovery of a new class of highly active and air-stable phosphine gold(I) complexes (Figure I.10). Their evaluation in various catalytic transformations like the Conia-ene,[55] the Rautenstrauch,[103] and the propargyl Claisen rearrangements[104] reported by Toste and co-workers, revealed that they were, most of the time, at least as active as other catalytic systems generally employed for such transformations.
By analogy with Nolan's work on the synthesis of NHC-gold(I)complexes,[85,105] a family of gold(I) complexes with *bis*(trifluoromethanesulfonyl)imidate moiety as a weakly coordinating counteranion, bearing the most commonly used IPr, IMes, IAd, SIPr, and SIMes NHC ligands was synthesized (Figure I.10).[100b]

[103] Shi, X.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802
[104] Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 15978
[105] De Fremont, P.; Stevens, E. D.; Fructos, M. R.; Diaz-Requejo, M. M.; Perez, P. J.; Nolan, S. P. *Chem. Commun.* **2006**, 2045

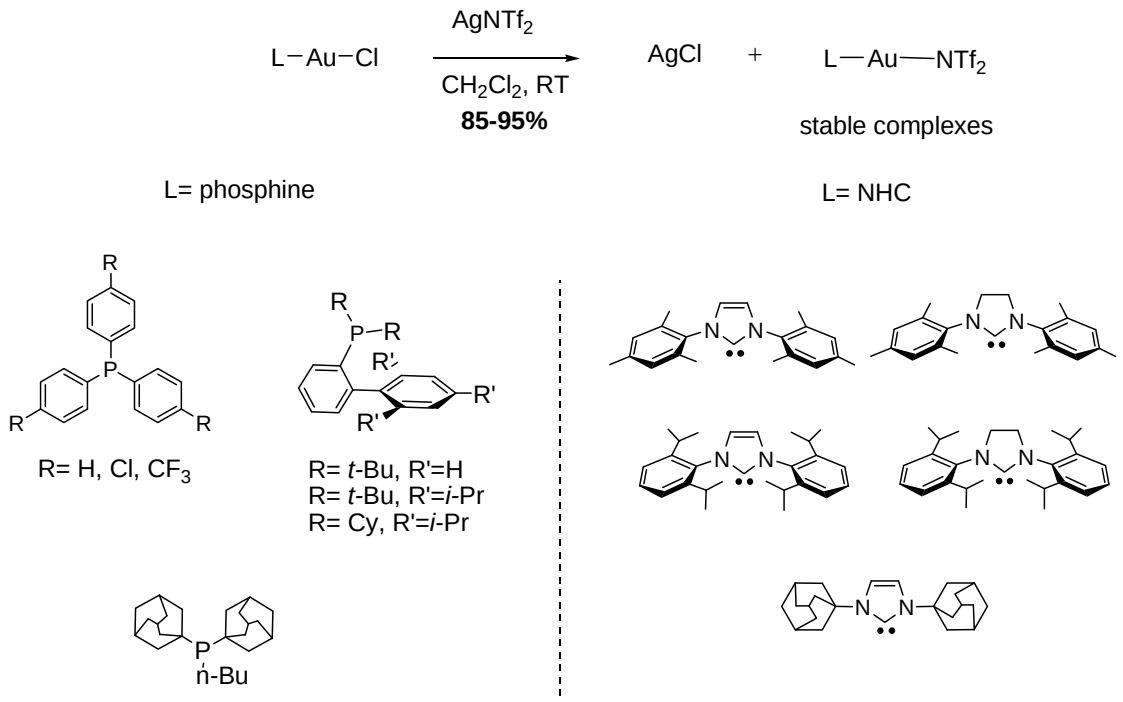


Figure I.10

The interest of these very convenient complexes in the development of numerous gold(I)-catalyzed transformations was documented by reports by ourselves and others (see the next chapters).

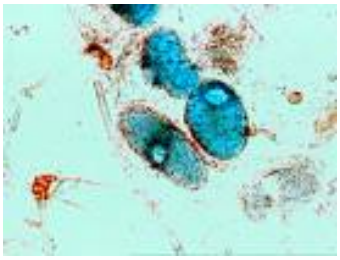
II. Gold(I)-Catalyzed Formation of 4-Methylene-1,3-dioxolan-2-ones

This work, done in collaboration with Dr. Fabien Gagosz and Florin-Marian Istrate, made the object of two publications.[106] The part dealing with the synthesis of 4-*Z*- and 4-*E*-halomethylene-1,3-dioxolan-2-ones and their valorisation in palladium-catalyzed cross coupling reactions was done by Florin-Marian Istrate.

II.1. Introduction

II.1.1. Natural Products Containing the Dioxolan-2-one Ring

The dioxolan-2-one ring is a cyclic carbonate skeleton quite rare in natural product chemistry, but found however in the structure of some biologically active or naturally occurring compounds. For example, Fenical et *al.* reported the isolation of a new metabolite, phomoxin (II.1, Figure II.1) from the fermentation broth of a marine-derived fungus of the genus *Phoma* (strain CNC-651), collected in the Bahamas.[107] Phomoxin contains an unusual, naturally occurring, cyclic carbonate functionality reminiscent of a similar structure in the aldgarose sugar moiety of the glycoside antibiotic swalpamycin.[108]



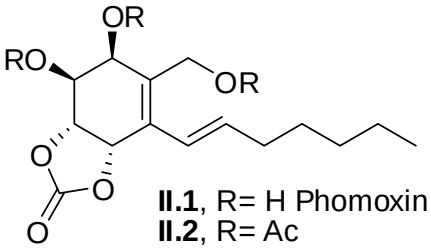
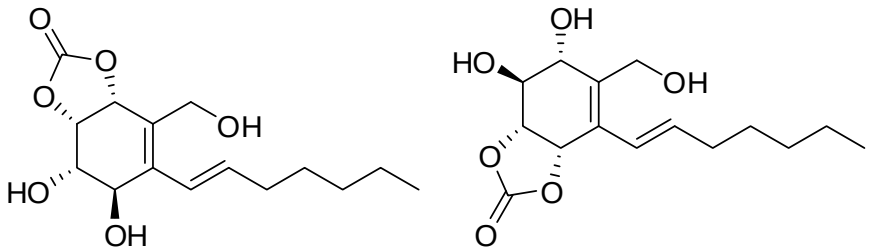


Figure II.1: *Phoma* sp. and phomoxin

Later, two new polyketides, phomoxins B and C (Figure II.2) were isolated from the culture broth from an endophytic fungus *Eupenicillium* sp. These compounds both contain a cyclic carbonate moiety that is rare among natural products.[109]

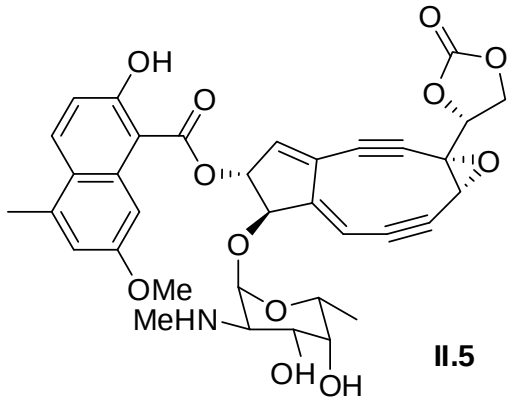
[106] a) Buzas, A.; Gagosz, F. Org. Lett. 2006, 8, 515; b) Buzas, A.; Istrate, F. M; Gagosz, F. *Tetrahedron* **2009**, *65*, 1889
[107] Liu, Z; Jensen, P. R.; Fenical, W. *Phytochemistry* **2003**, *64*, 571
[108] Chatterjee, S.; Reddy, G.C.S.; Franco, C.M.M.; Rupp, R.H.; Ganguli, B.N.; Fehlhaber, H.W.; Kogler, H. *J. Antibiotics* **1987**, *40*, 1368
[109] Davis, R. A.; Andjic, V.; Kotiw, M.; Shivas, R. G. *Phytochemistry* **2005**, *66*, 2771



II.3, Phomoxin B **II.4**, Phomoxin C

Figure II.2: *Eupenicillium* sp. and Phomoxins

Neocarzinostatin (II.5, Figure II.3), the first enediyne antibiotic,[110] isolated from a culture of *Streptomyces carzinostaticus* var. F-41 in 1965,[111] also contains the cyclic carbonate functionality.



II.5

Figure II.3: Neocarzinostatine chromophore

Cyclic carbonates are a versatile class of compounds used as solvents,[112] as monomers for the preparation of polycarbonates *via* ring-opening polymerization[113] and they have been widely used for the preparation and the protection of polyhydroxylated compounds[114,115] and carbohydrates.[116]

Derivatives of 4-methylene-1,3-dioxolan-2-ones represent interesting building blocks for organic synthesis since they can be regarded as a source of masked hydroxyketones, which can be further transformed into a range of more elaborated structures like dihydrofuranones, cyclic carbamates etc.

---

[110] Reviews on enediyne antibiotics: a) Nicolaou, K. C.; Dai, W.-M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1387; b) Grissom, J. W.; Gunawardena, G. U.; Klingberg, D.; Huang, D. *Tetrahedron* **1996**, *52*, 6453

[111] Ishida, N.; Mizugaki, K.; Kumagai, K.; Rikimaru, M. *J. Antibiot.* **1965**, *18*, 68

[112] Roush, W. R.; Lesur, B. M. *Tet. Lett.* **1983**, *24*, 2231

[113] a) Shibasaki, Y.; Sanda, H; Yokoi, M.; Sanada, F. *Macromolecules* **2000**, *33*, 4316; b) Sanado, F; Fucki, T.; Endo, T. *Macromolecules* **1999**, *32*, 4220; c) Takata, T.; Kanamaru, M.; Endo, T. *Macromolecules* **1996**, *29*, 2315

[114] a) Notz, W.; Hartel, C.; Waldscheck, B.; Schmidt, R. R. *J. Org. Chem.* **2001**, *66*, 4250; b) Kim, H.; Kim, I.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 35

[115] a) Corey, E. J.; Hopkins, P. B.; Munroe, J. E.; Marfat, A.; Hashimoto, S. *J. Am. Chem. Soc.* **1980**, *102*, 7086; b) Bongini, A.; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Org. Chem.* **1982**, *47*, 4626

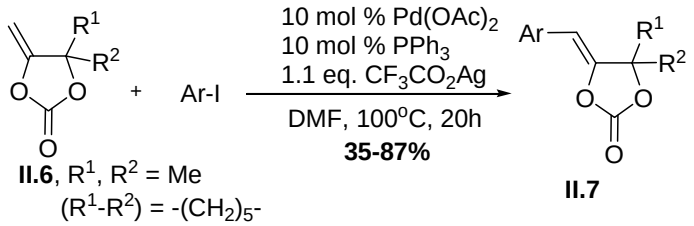
[116] Roush, W. R.; Brown, R. J.; Dimare, M. *J. Org. Chem.* **1983**, *48*, 5033

II.1.2. Uses of 4-Methylene-1,3-dioxolan-2-ones

Pd-Catalyzed Transformations

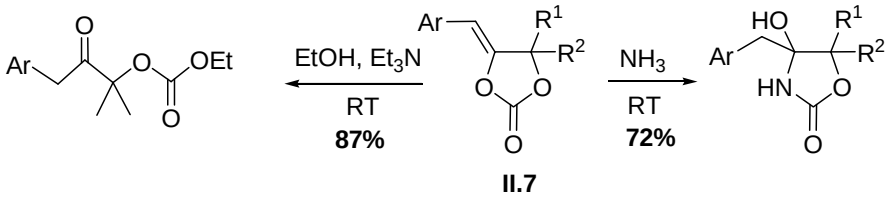
Derivatives of 4-methylene-1,3-dioxolan-2-ones can undergo a variety of palladium-catalyzed transformations, which make up an important class of palladium-catalyzed reactions.

For instance, Dixneuf and co-workers reported the first stereoselective synthesis of *Z*-trisubstituted alkylidene cyclic carbonates applying a modified Heck reaction protocol. *Z*-4-phenylmethylene-1,3-dioxolan-2-ones II.7 can be obtained in good yields from the methylene carbonates II.6, resistant to the classical Heck conditions, and aryl iodides in presence of palladium catalyst and CF_3CO_2Ag according to Scheme II.1:[117]



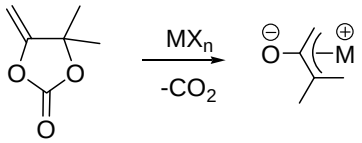
Scheme II.1

The *Z*-trisubstituted alkylidene cyclic carbonates II.7 obtained this way can be further transformed into acyclic ketocarbonates and hydroxyoxazolidinones upon reaction with a nucleophile in the presence of a base (Scheme II.2):



Scheme II.2

Five-membered methylene carbonates can serve as potential precursors for conjunctive reagents (Scheme II.3):[118]



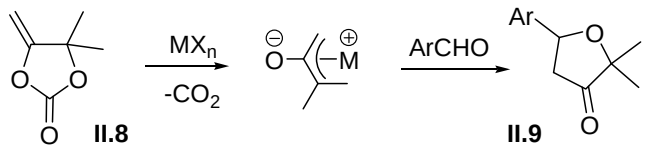
Scheme II.3

[117] Toullec, C.; Martin, A. C.; Gio-Batta, M.; Bruneau, C. Dixneuf, P. H. *Tet. Lett.* **2000**, *41*, 5527

[118] a) Trost, B. M.; Chan, D. M. T. *J. Org. Chem.* **1983**, *48*, 3346; b) Trost, B. M.; Schneider, S. *J. Am. Chem. Soc.* **1989**, *111*, 4430; c) Ohe, K.; Ishihara, T.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **1990**, *112*, 9646

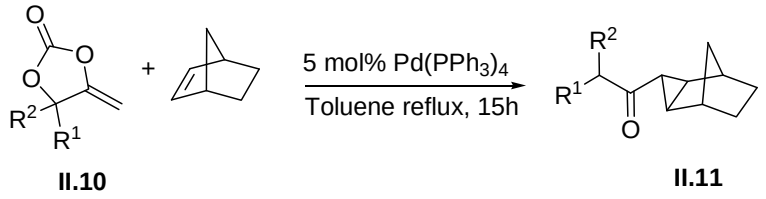
The oxidative addition of 4-methylene-1,3-dioxolan-2-one to a low valent palladium complex and the subsequent decarboxylation gives access to oxatrimethylenemethane-palladium (OTMM-Pd) intermediates with zwitterionic character. This activation by palladium or platinum catalysts makes possible the synthesis of a variety of heterocycles upon reaction with aromatic aldehydes,[119] isonitriles and heterocumulenes, as well as ketonic cyclopropanes on reaction with norbornene.[120]

A decarboxylative cycloaddition reaction of 5,5-dimethyl-4-methylene-1,3-dioxolan-2-one II.8 to aromatic aldehydes takes place in the presence of a dicationic palladium complex $[Pd(CH_3CN)_4](BF_4)_2$ to produce dihydrofuranone derivatives II.9, as illustrated in Scheme II.4:[119]



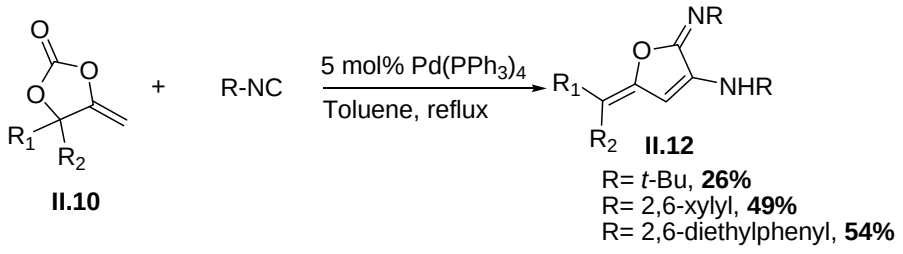
Scheme II.4

The reaction of 5,5-disubstituted 4-methylene-1,3-dioxolan-2-ones II.10 with norbornene in the presence of $Pd(PPh_3)_4$ gives the [2+1] cycloaddition product II.11:[120a]



Scheme II.5

On treatment of 5,5-disubstituted 4-methylene-1,3-dioxolan-2-one with isonitriles in the presence of $Pd(PPh_3)_4$, the incorporation of two isonitrile molecules was observed to afford an iminofuran derivative II.12:[120a]

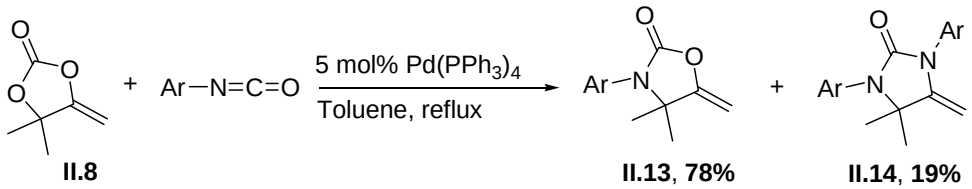


Scheme II.6

[119] Inoue, Y.; Matsushita, K.; Yen, I-F.; Imaizumi, S. *Chem. Lett.* **1991**, 1377

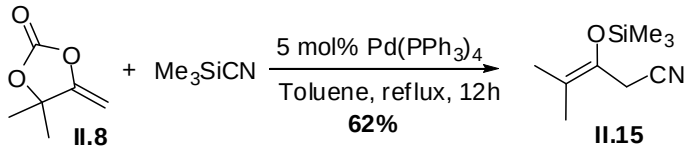
[120] a) Ohe, K.; Matsuda, H.; Ishihara, T.; Ogoshi, S.; Chatani, N.; Murai, S. *J. Org. Chem.* **1993**, *58*, 1173; b) Ohe, K.; Matsuda, H.; Morimoto, T.; Ogoshi, S.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **1994**, *116*, 4125

The palladium catalyzed reaction of II.8 with aromatic isocyanates underwent cycloaddition to give the corresponding carbamates II.13 and II.14, as depicted in Scheme II.7:[120b]



Scheme II.7

The reaction of II.8 with trimethylsilyl cyanide in the presence of the palladium catalyst resulted in the formation of II.15:[120a]

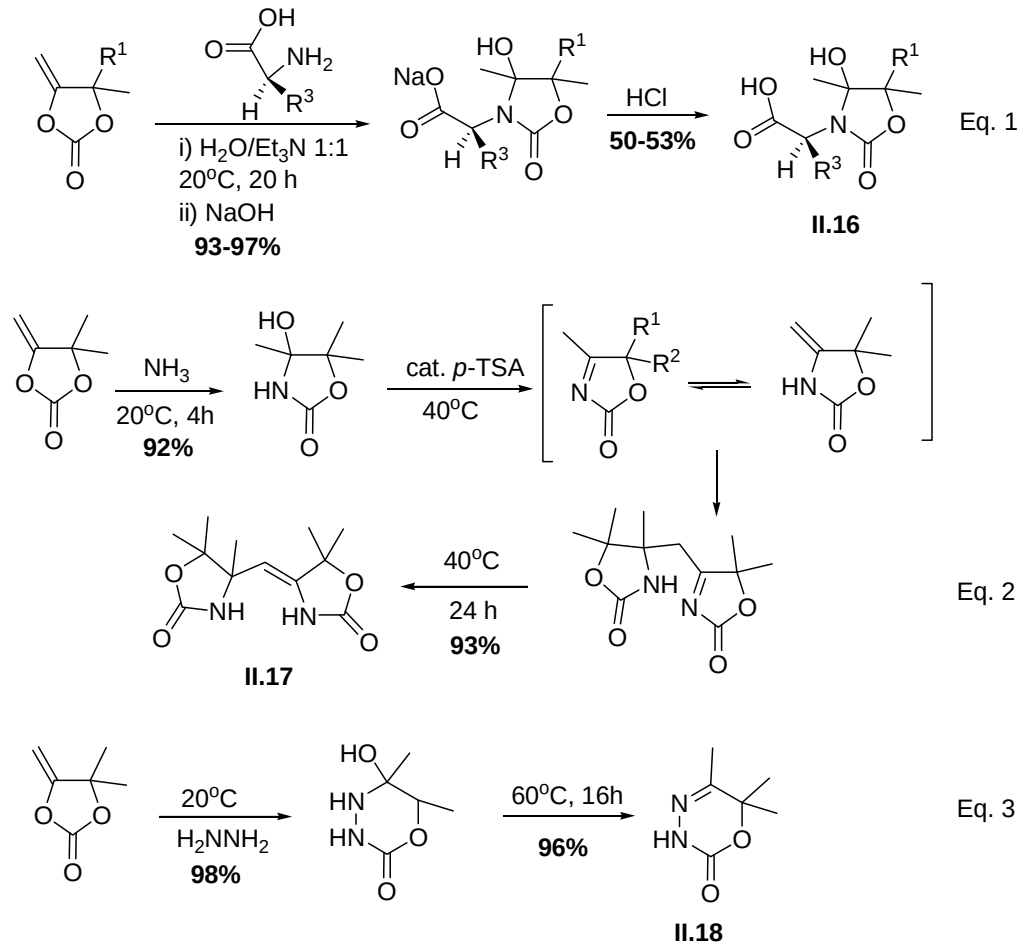


Scheme II.8

Reaction of Alkylidene Cyclic Carbonates with Amines[121]

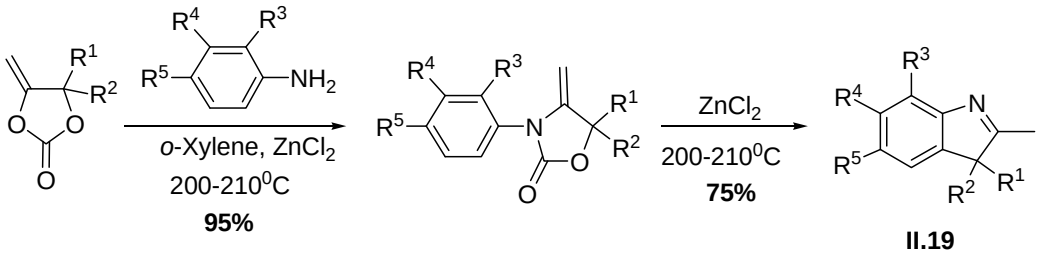
Alkylidene cyclic carbonates are useful intermediates for the easy access to oxazolidinones, *bis*-oxazolidinones, oxadiazinones and derivatives. For example, cyclic *α*-methylene carbonates allow the access to functional 4-hydroxy oxazolidin-2-ones II.16 by reaction with unprotected amino acids (Scheme II.9, Eq. 1), to *bis*-oxazolidin-2-ones II.17 with ammonia (Eq. 2), and to oxadiazin-2-ones II.18 with hydrazine (Eq. 3):[121a]

[121] a) Joumier, J.-M.; Grainger, R.; Bruneau, C.; Dixneuf, P.H. *Synlett* **1993**, 423; b) Laas, H.; Nissen, A.; Nürrenbach, A. *Synthesis* **1981**, 958



Scheme II.9

The reaction with substituted anilines allows the synthesis of 3*H*-indoles II.19 according to Scheme II.10:[121b]

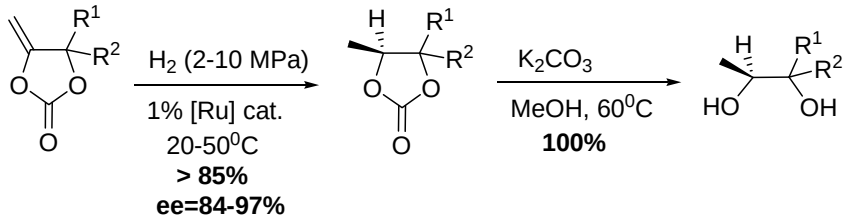


Scheme II.10

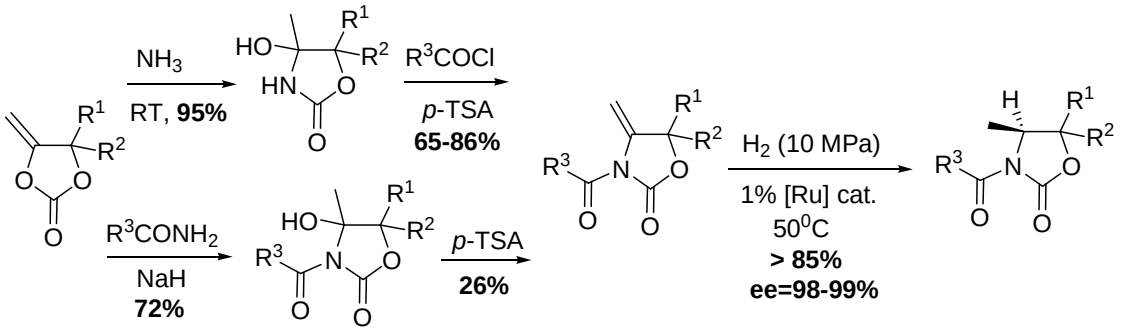
Enantioselective Hydrogenation

Enantioselective hydrogenation of α-methylene cyclic carbonates in the presence of chiral (diphosphine)ruthenium complexes has led to the synthesis of optically active bicyclic

carbonates, 1,2-diols[122] (Scheme II.11) and *N*-acyloxazolidinones[123] (Scheme II.12) with very high enantioselectivities. The excellent enantioselectivities might be due to the fact that the exocyclic double bond and the adjacent oxygen atom in cyclic carbonates allow the double chelation to the ruthenium center, thus leading to high enantioface differentiation.



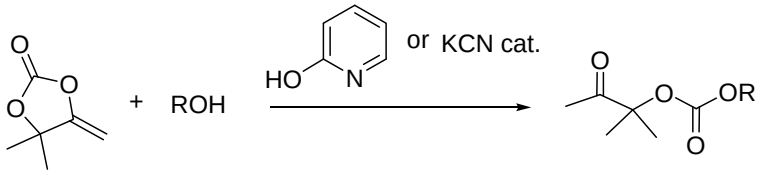
Scheme II.11



Scheme II.12

Acces to *β*-Oxopropyl Carbonates and Enol Ethers

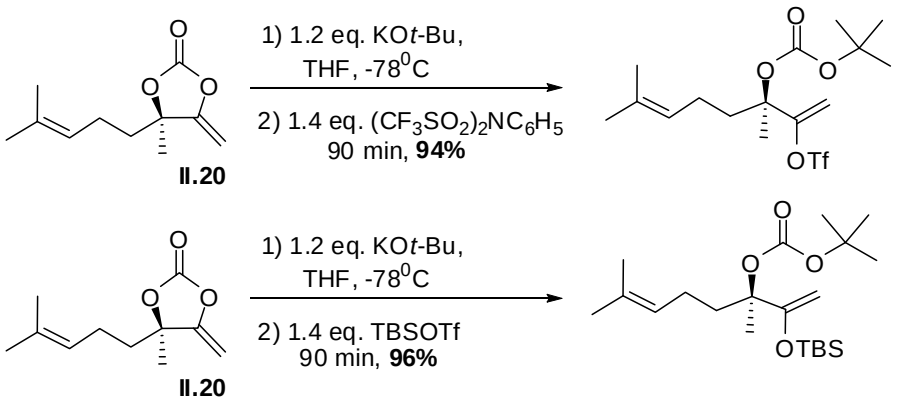
Cyclic *α*-methylene carbonates react with bulky alcohols in the presence of catalytic amounts of either 2-hydroxypyridine, potassium cyanide or DBU to give *β*-oxopropyl carbonates (Scheme II.13):[124]



Scheme II.13

Maddess and Lautens demonstrated that the reaction of 4-methylene-1,3-dioxolan-2-ones II.20 with potassium *tert*-butoxide results in the *in situ* formation of potassium enolates which can be trapped with silylating or triflating agents (Scheme II.14):[125]

[122] Le Gendre, P.; Thominot, P.; Bruneau, C.; Dixneuf, P. H. *J. Org. Chem.* **1998**, *63*, 1806
[123] a) Le Gendre, P.; Thominot, P.; Bruneau, C.; Dixneuf, P. H. *J. Org. Chem.* **1996**, *61*, 8453; b) Le Gendre, P.; Jérôme, F.; Bruneau, C.; Dixneuf, P. H. *Chem. Comunn.* **1998**, 533
[124] Joumier, J.-M.; Bruneau, C.; Dixneuf, P. H. *J. Chem. Soc. Perkin Trans.1* **1993**, 1749
[125] Maddess, M. L.; Lautens, M. *Synthesis* **2004**, 1399



Scheme II.14

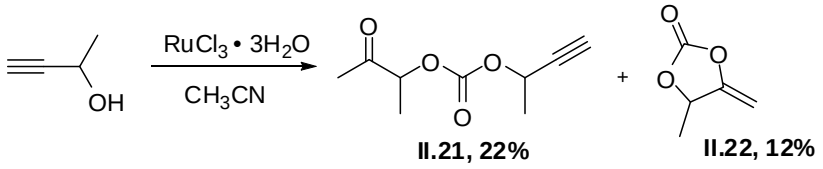
II.2. Synthetic Methods

Despite the fact that derivatives of 4-methylene-1,3-dioxolan-2-ones are attractive building blocks for organic synthesis, their use in synthesis remains largely unexplored due to a lack of efficient and general methods to access them. 4-Methylene-1,3-dioxolan-2-ones are typically synthesized using propargylic alcohols under CO_2 pressure and in the presence of a catalyst. The great majority of these methods are generally limited to the use of tertiary propargylic alcohols.

II.2.1. Synthesis from Propargylic Alcohols and CO_2

Reaction of Propargylic Alcohols with CO_2 Catalyzed by Ruthenium

Sasaki showed that 1-butyn-3-ol reacted with CO_2 in the presence of ruthenium catalysts to give 1-methyl-2-oxo-propyl-1'-methyl-2'-propynyl carbonate II.22 and 2,3-dioxycarbonyl-1-butene II.21 (Scheme II.15):[126]

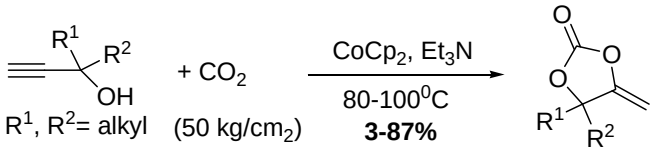


Scheme II.15

Reaction of Propargylic Alcohols with CO_2 Catalyzed by Cobalt

[126] Sasaki, Y. *Tet. Lett.* **1986**, *27*, 1573

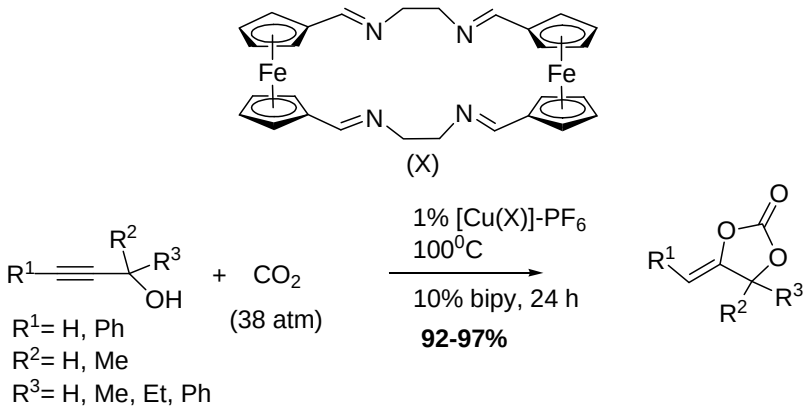
The cobalt mediated reaction of α-ethynyl tertiary alcohols was performed in an autoclave under pressure of CO_2, generally without employing a solvent as illustrated in Scheme II.16:[127]



Scheme II.16

Reaction of Propargylic Alcohols with CO_2 Catalyzed by Copper

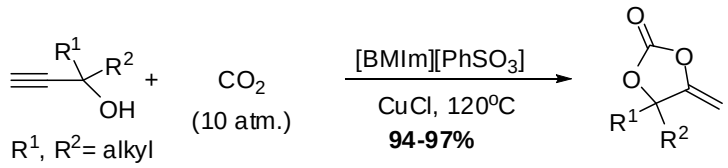
Cyclic carbonates are known to be obtained catalytically from propargylic carbonates using various copper salts such as CuCl, Cu(acetate)$_2$, $CuCl_2$.[128]
Kim et *al.* demonstrated that $[Cu(X)]PF_6$ complex can also be an excellent choice for the same purposes (Scheme II.17):[129]



Scheme II.17

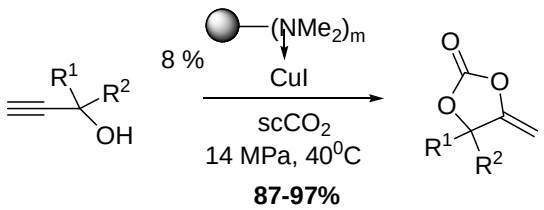
Deng et *al.* reported an efficient and environmentally benign method for the synthesis of α-methylene cyclic carbonates from CO_2 and propargyl alcohols catalyzed by copper salts (CuCl, CuBr, CuI) in recyclable ionic liquids like 1-butyl-3-methylimidazolium benzene sulfonate ([BMIm][$PhSO_3$]) without any other cocatalysts and organic solvents (Scheme II.18). The copper catalyst immobilized in ionic liquids could be reused 3 times without losing activity. Unfortunately, this method seems to be limited to the use of tertiary propargylic alcohols.[130]

[127] Inoue, Y.; Ishikawa, J.; Taniguchi, M.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1204
[128] a) Dimroth, P.; Pasedach, H.; Bruneau, C.; Schefezik, E. *Ger. Pat.* **1964**, *1(151)*, 507; b) Dimroth, P.; Pasedach, H. *Ger. Pat.* **1961**, *1(098)*, 953; c) Dimroth, P.; Pasedach, H. *Ger. Pat.* **1964**, *1(164)*, 411
[129] Kwon, S.-C.; Cho, C.-S.; Shim, S.-C.; Kim, T.-J. *Bull. Korean Chem. Soc.* **1999**, *20*, 103
[130] Gu, Y.; Shi, F.; Deng, Y. *J. Org. Chem.* **2004**, *69*, 391



Scheme II.18

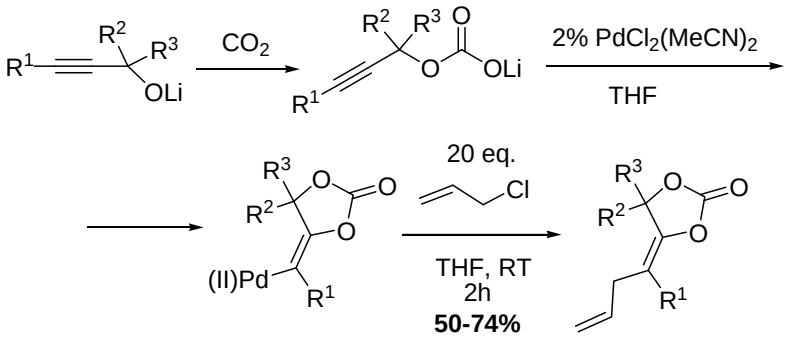
Recently, the use of (dimethylamino)methyl-polystyrene-supported copper(I) iodide (DMAM-PS-CuI) as an efficient and environmentally benign heterogeneous catalyst for the cyclization of CO_2 and propargyl alcohols under supercritical conditions (Scheme II.19) was disclosed by Jiang et *al.*[131] DMAM-PS-CuI can be recovered easily by simple filtration and reused after minimal treatment. The reused DMAM-PS-CuI still retained its catalytic activity after multiple trials, but its catalytic capacity decreased with increasing reuse.



Scheme II.19

Reaction of Propargylic Alcohols with CO_2 Catalyzed by Palladium

Utimoto et *al.* reported the regio and stereoselective formation of methylene carbonates by palladium(II)-catalyzed allylative cyclization of lithium 2-alkynyl carbonates, synthesized by the reaction of lithium 2-alkyn-1-olates with carbon dioxide (Scheme II.20):[132]

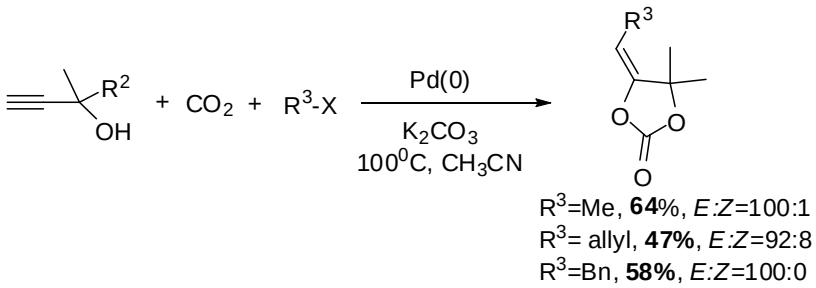


Scheme II.20

Inoue et *al.* described the palladium-mediated preparation of alkylidene cyclic carbonates and the incorporation of an alkyl group onto the double bond of the product during cyclization

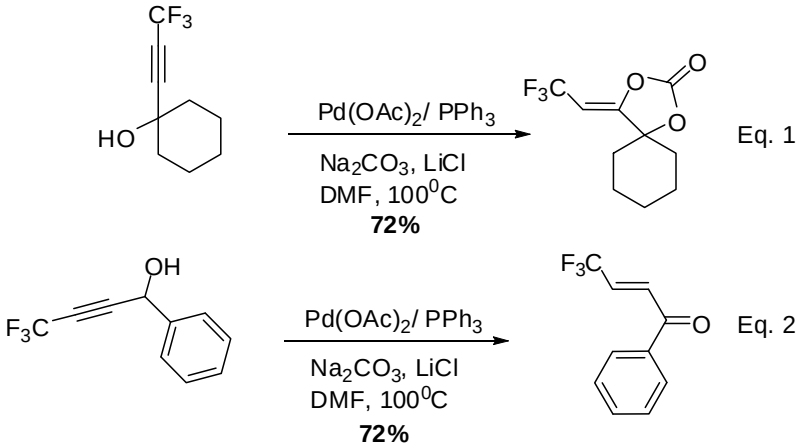
[131] Jiang, H-F.; Wang, A-Z.; Liu, H.-L.; Qi, C-R. *Eur. J. Org. Chem.* **2008**, *13*, 2309
[132] Iritani, K.; Yanagihara, N.; Utimoto, K. *J. Org. Chem.* **1986**, *51*, 5499

when a mixture of propargylic alcohol, methyl iodide and K_2CO_3 were heated at 100°C in the presence of catalytic quantities of $Pd(OAc)_2$ and PPh_3 under CO_2 pressure (Scheme II.21):[133]



Scheme II.21

The synthesis of cyclic carbonates containing a trifluoromethyl group by the palladium-promoted reaction of trifluoromethylated propargylic alcohols with sodium carbonate used as a source of carbon dioxide, was reported by Quing and Jiang (Scheme II.22, Eq. 1).[134] The method seems to be limited to tertiary trifluoromethylated propargylic alcohols, the secondary trifluoromethylated propargylic alcohol underwent rearrangement to an unsaturated ketone (Scheme II.22, Eq. 2). In the case of non-fluorinated propargyl alcohol, there was no reaction under the same reaction conditions.



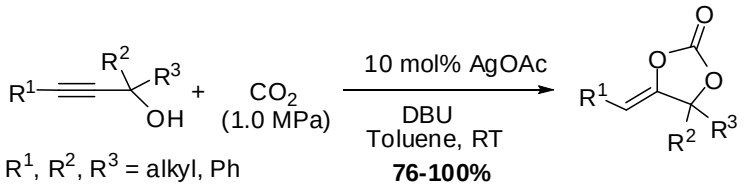
Scheme II.22

Reaction of Propargylic Alcohols with CO_2 Catalyzed by Silver

The combined use of a catalytic amount of silver acetate and a stoichiometric amount of DBU efficiently catalyzed the incorporation of CO_2 under mild reaction conditions into a wide range of propargylic alcohols bearing a terminal or an internal triple bond to afford

[133] Uemura, K., Kawaguchi, T.; Takayama, H. Nakamura, A. Inoue, Y. *J. Mol. Catal. A: Chem.* **1999**, *139*, 1
[134] Jiang, Z-X.; Qing, F-L. *J. Fluorine Chem.* **2003**, *123*, 57

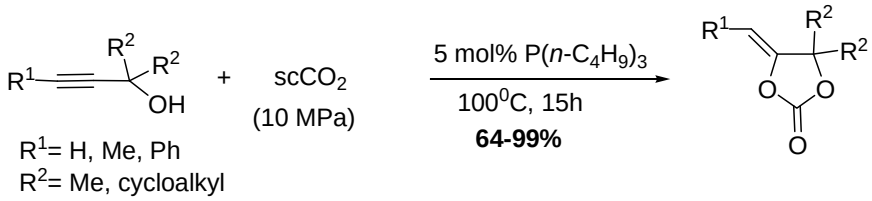
stereoselectively the corresponding *Z*-cyclic carbonates in high-to-excellent yields (Scheme II.23):[135]



Scheme II.23

Reaction of Propargylic Alcohols with CO_2 Catalyzed by Tertiary Phospines

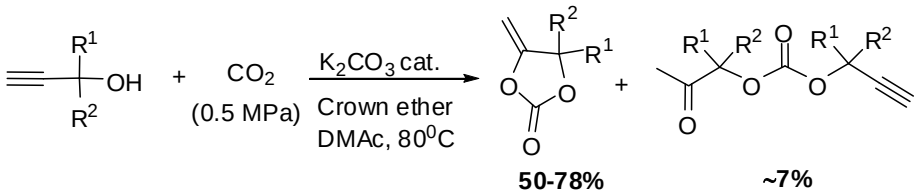
Dixneuf et *al.* have shown that *α*-methylene carbonates are very conveniently obtained in one step from propargyl alcohol derivatives and CO_2 in the presence of catalytic amounts of a tertiary phospine.[136] Ikariya et *al.* extended this method to internal propargyl alcohols in supercritical CO_2 which afforded *Z*-alkylidene cyclic carbonates exclusively in presence of tri-*n*-butylphosphine (Scheme II.24):[137]



Scheme II.24

Reaction of Propargylic Alcohol with CO_2 Catalyzed by Inorganic Bases

Inoue et *al.* reported that K_2CO_3-crown ether (dibenzo-18-crown-6 ether) is another effective catalyst for the preparation of alkylidene cyclic carbonate starting from propargylic alcohols and CO_2 (Scheme II.25).[133]

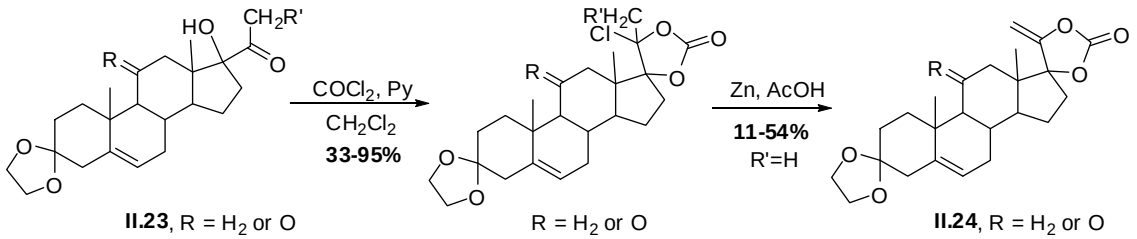


[135] Yamada, W.; Sugawara, Y.; Cheng, H. M.; Ikeno, T.; Yamada, T. *Eur. J. Org. Chem.* **2007**, *16*, 2604
[136] a) Fournier, J.; Bruneau, C.; Dixneuf, P. H. *Tet. Lett.* **1989**, *30*, 3981; b) Joumier, J.-M.; Fournier, J.; Bruneau, C.; Dixneuf, P. H. *J. Chem. Soc. Perkin Trans.1* **1991**, 3271; c) Joumier, J. M.; Bruneau, C.; Dixneuf, P. H. *Synlett* **1992**, 453
[137] Kayaki, Y.; Yamamoto, M.; Ikariya, T. *J. Org. Chem.* **2007**, *72*, 647

Scheme II.25

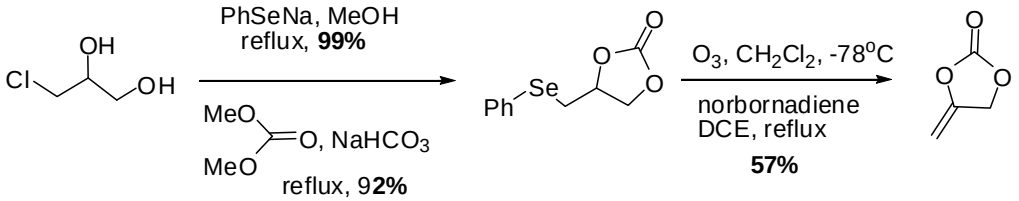
II.2.2. Synthesis from *α*-Difunctional Substrates

Lewbart prepared carbonate II.24 by phosgenation of 11-deoxycortisol acetate 3-ethyleneketal II.23 (Scheme II.26) followed by a dehydrohalogenation step:[138]



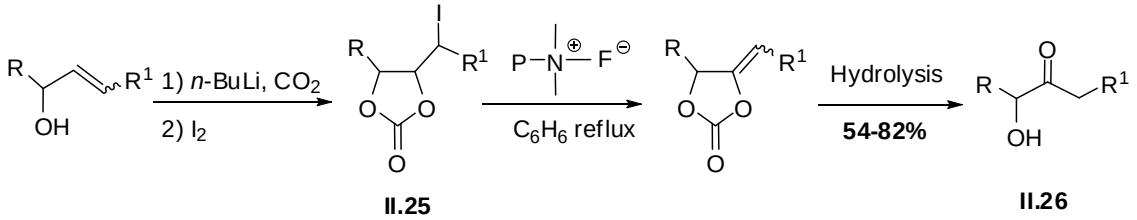
Scheme II.26

Trost et *al.* described the synthesis of 4-methylene-1,3-dioxolan-2-one by a sequence of 3 steps involving the ozonolysis of a phenylselenyl carbonate intermediate (Scheme II.27):[139]



Scheme II.27

Cardillo et *al.* reported a short, regioselective synthesis of hydroxy ketones II.26 starting from allylic alcohols by treatment of iodo carbonates with fluoride anion on polymeric support *via* cyclic iodo carbonates II.25 (Scheme II.28):[140]

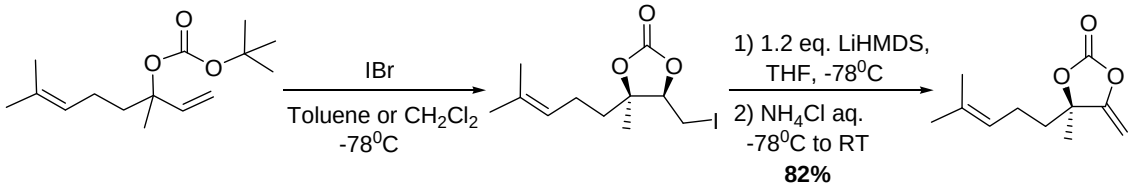


Scheme II.28

Maddess and Lautens have shown that the iodocarbonates, obtained from allyl carbonates and IBr,[141] are versatile intermediates providing facile access to enol cyclic carbonates (Scheme II.29):[125]

---

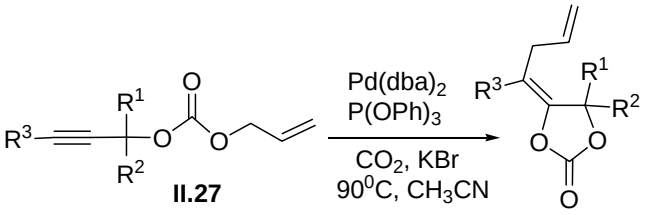
[138] Lewbart, M. L. *J. Org. Chem.* **1976**, *41*, 78
[139] Trost, B. M.; Chan, D. M. T. *J. Org. Chem.* **1983**, *48*, 3346
[140] Cardillo, G.; Orena, M.; Porzi, G.; Sergio Sandri, S.; Tomasini, C. *J. Org. Chem.* **1984**, *49*, 701



Scheme II.29

II.2.3. Synthesis from Allylic or Propargylic Carbonates

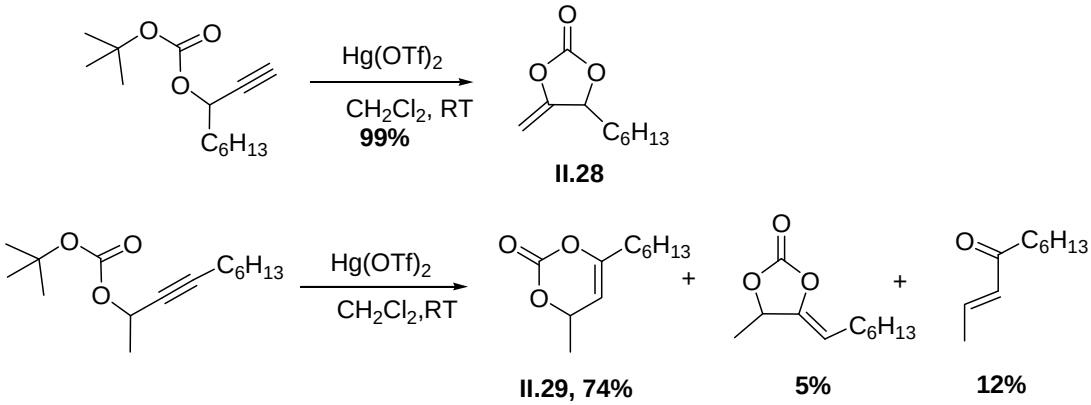
Another approach to alkylidene cyclic carbonates is the utilization of allylic propargylic carbonates as substrates. For example, treatment of allyl 1,1-dialkyl-2-ynyl carbonates II.27 with a catalytic amount of $Pd(dba)_2$ and $P(OPh)_3$ in the presence of KBr at 90°C in acetonitrile under high pressure of CO_2 afforded the expected cyclized product:[133]



R^1, R^2=Me, R^3=H, **79%**, *E:Z*=91:9
R^1=H, R^2= Me, R^3=H, **54%**, *E:Z*=97:3
R^1, R^2=Me, R^3=Ph, **37%**, *E:Z*=100:0

Scheme II.30

Nishizawa et *al.* showed that mercuric triflate is a powerful catalyst for the cyclization of alkynyl *tert*-butylcarbonates giving rise to cyclic enol carbonates under mild conditions. Internal alkynyl carbonate affords *endo* cyclization product II.28 selectively, while terminal alkynyl carbonate provides only *exo* cyclization product II.29 (Scheme II.31).[142]



[141] Smith, A. B.; Duan, J. J.-W. *J. Org. Chem.* **1993**, *58*, 3703
[142] Yamamoto, H.; Nishiyama, M.; Imagawa, H.; Nishizawa, M. *Tet. Lett.* **2006**, *47*, 8369

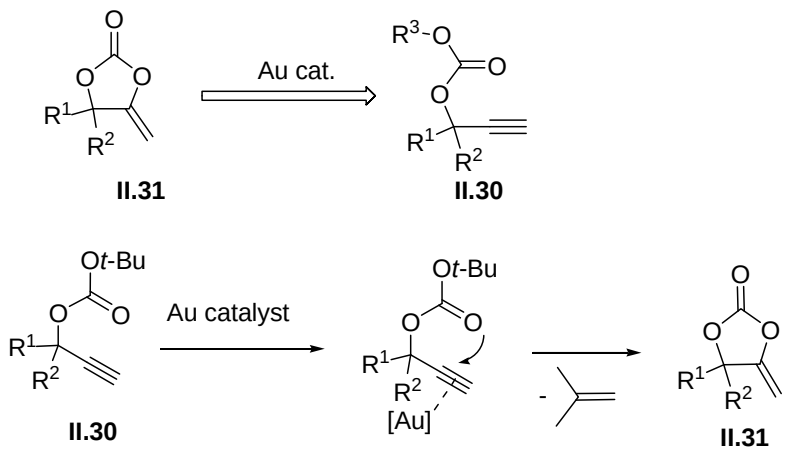
Scheme II.31

II.3. Preliminary Work in the Literature. Our Synthetic Approach

As presented earlier, 4-alkylidene-1,3-dioxolan-2-ones are mainly prepared by the reaction of propargylic alcohols with carbon dioxide in the presence of a catalyst which can be a metallic species,[126-135] a phosphine[136-137]or an inorganic base.[133] However, the scope of these reactions remains limited due to the fact that these transformations are generally narrowed to the use of tertiary alcohols and require a high carbon dioxide pressure (until 14MPa) and/or a high temperature of reaction (80-120°C). Given the lack of efficient and general methods to access this type of structures, we decided to devise a new synthetic route which would permit the easy obtention of 4-alkylidene-1,3-dioxolan-2-ones under mild conditions.

As discussed in Chapter I, the use of gold in homogeneous catalysis has witnessed tremenduous activity in recent years, as illustrated by the high number of publications and reviews appeared in the literature (see Chapter I and references cited therein). Moreover, in the last eight years, the benefits of gold as a homogeneous catalyst for the synthesis of fine chemicals have emerged in a spectacular fashion. This is mainly due to the exceptional ability of gold(I) and gold(III) salts to act as soft carbophilic Lewis acids towards carbon–carbon multiple bonds which, after activation, undergo a variety of transformations that lead to new carbon–carbon or carbon–heteroatom bonds.
Gold-catalyzed sequential or tandem reactions involving the addition of oxygenated nucleophiles to alkynes constitute efficient strategies to assemble oxygen-containing heterocycles.[143,144]
Following the recent developments in the field of gold catalyzed synthesis of heterocycles by nucleophilic additions onto alkynes,[143-144] we surmised that a suitably selected propargylic carbonate II.30 could be rearranged in the presence of gold(I) catalyst into the desired 4-alkylidene-1,3-dioxolan-2-one II.31 (Scheme II.32):

[143] For recent reviews, see: a) Patil, N. T.; Yamamoto, Y. *Arkivoc* **2007** (v), 6; b) Muzard, J. *Tetrahedron* **2008**, *64*, 5815; c) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395
[144] For selected examples, see: *furans*: a) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem. Int. Ed.* **2000**, *39*, 2285; b) Yao, T.; Zhang, X.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 7679; c) Hashmi, A. S. K.; Sinha, P. *Adv. Synth. Catal.* **2004**, *346*, 432; d) Liu, Y.; Song, F.; Song, Z.; Liu, M.; Yan, B. *Org. Lett.* **2005**, *7*, 5409; lactones and furanones: e) Genin, E.; Toullec, P. Y.; Antoniotti, S.; Brancour, C.; Genêt, J.-P.; Michelet, V. *J. Am. Chem. Soc.* **2006**, *128*, 3112; f) Liu, Y.; Liu, M.; Guo, S.; Tu, H.; Zhou, Y.; Gao, H. *Org. Lett.* **2006**, *8*, 3445; butenolides: g) Kang, J. E.; Lee, E.-S.; Park, S.-I.; Shin, S. *Tet. Lett.* **2005**, *46*, 7431

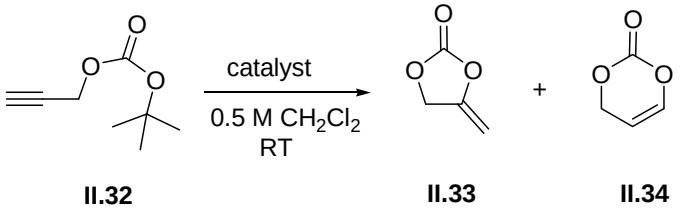


Scheme II.32

This approach could be regarded as a formal internal deprotection of a *tert*-butylcarbonyl group using a gold-alkyne complex as the acidic species by analogy to the iodine-mediated cyclization of allylic and homoallylic *tert*-butyl carbonates (see Scheme II.29).[125,141]

II.4. First Results and Optimisation of the Catalytic System

Compound II.32 was first chosen as a model substrate to validate the synthetic approach illustrated in Scheme II.32. We were pleased to observe a rapid and clean conversion of II.32 when the reaction was performed in dichloromethane, on a 1 mmol scale, with 1 mol% of the bench stable $(PPh_3)AuNTf_2$[100] affording *exo*-methylene cyclic carbonate II.33 in 83% yield. It is worth to mention that no trace of *endo* cyclisation product II.34 was observed, proving that the reaction was regiospecific.[142]



Entry	Catalyst	Substrate	Time	Yield (II.33/II.34)
1	1 mol% Ph_3AuNTf_2	1 mmol	10 min	**83% / 0%**
2	5 mol% $AgNTf_2$	1 mmol	1h	**0% / 0%**
3	5 mol% $HNTf_2$	1 mmol	1h	**0% / 0%**
4	0.1 mol % $Ph_3PAuNTf_2$	12 mmol	5h	**81% / 0%**

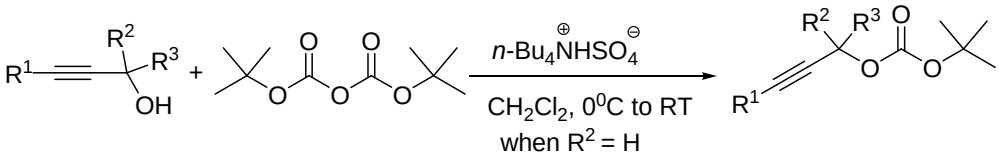
Table II.1

In order to check the nature of the active species, control experiments were performed which led to the conclusion that $HNTf_2$ and $AgNTf_2$ were not suitable catalysts for this reaction. When the reaction was carried out on a larger scale (12 mmol, see Entry 4, Table II.1), catalyst loading could be reduced to 0.1 mol% without noticeable loss of efficiency.
Encouraged by these results (it is worth mentioning that Trost's synthesis afforded the same compound in 57% yield over 3 steps),[139] we proceeded to the investigation of the scope of the reaction. To this end, a wide range of diversely substituted propargylic *ter*t-butylcarbonates were prepared.

II.5. Synthesis of the Precursor Propargylic tert-Butylcarbonates

Propargylic *tert*-butylcarbonates were generally synthesized from the corresponding alcohol and di-*tert*-butyl dicarbonate following classical methods described in the literature (see the experimental section).

For example, primary and secondary propargylic alcohols were reacted with di-*tert*-butyl dicarbonate in dichloromethane in the presence of a phase transfer catalyst to afford the desired propargylic *tert*-butylcarbonates in good yields as illustrated in Table II.2:[145a]

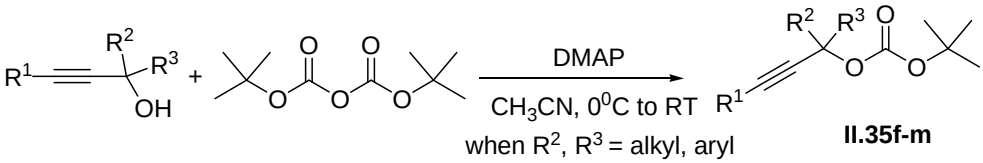


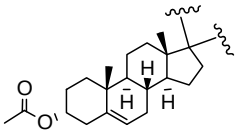
R^1	R^2	R^3	Compound	Yield
H	H	H	**II.32**	**80%**
H	Me	H	**II.35a**	**86%**
CH_2OBoc	H	H	**II.37b**	**70%**

Table II.2

The other substrates were prepared in the presence of a catalytic quantity of DMAP in acetonitrile as depicted in Table II.3:[145b]

[145] a) Houlihan, F.; Bouchard, F.; Fréchet, J. M. J.; Willson, C. G. *Can. J. Chem.* **1985**, *63*, 153; b) Parker, K. A.; Coburn, C. A.; Johnson, P.D.; Aristoff, P. *J. Org. Chem.* **1992**, *57*, 5547; c) Eren, D.; Keinan, E. *J. Am. Chem. Soc.* **1988**, *110*, 4356

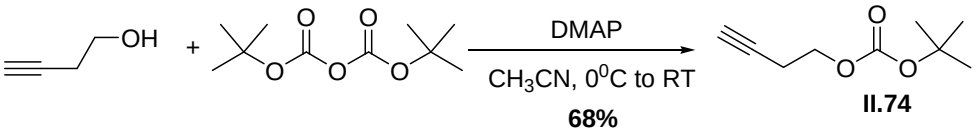


R^1	R^2	R^3	Compound	Yield
H	Me	Me	**II.35h**	**49%**
H	—$(CH_2)_5$—		**II.35j**	**88%**
H	Me	Et	**II.35i**	**83%**
H	Ph	H	**II.35f**	**97%**
H	Ph	Me	**II.35l**	**96%**
H	CH_2=CH	Me	**II.35m**	**80%**
H			**II.35k**	**46%**
$CH_3CHOBoc$	Me	Me	**II.37c**	**68%**[a]
CH_2OBoc	Me	H	**II.37d**	**51%**[a]

[a]: global yield obtained after a sequence of 3 steps illustrated in Scheme II.36

Table II.3

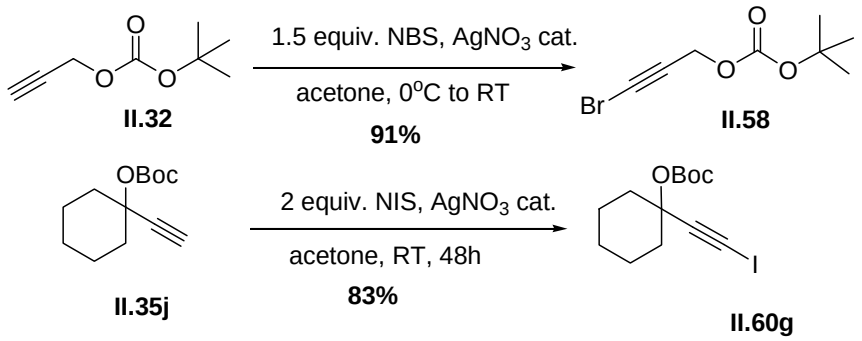
Homopropargylic derivative **II.74** was prepared by the same method (Scheme II.33):



Scheme II.33

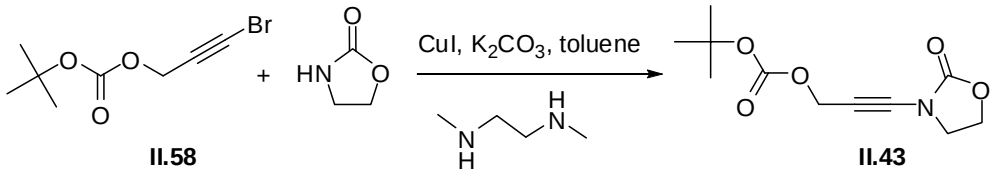
Bromoalkynes and iodoalkynes were synthesized by bromination or iodination of the corresponding alkynes with NBS or NIS (Scheme II.34).[146]

[146] Nishiwaka, T.; Shibuya, S.; Hosokawa, S.; Isobe, M. *Synlett* **1994**, 485



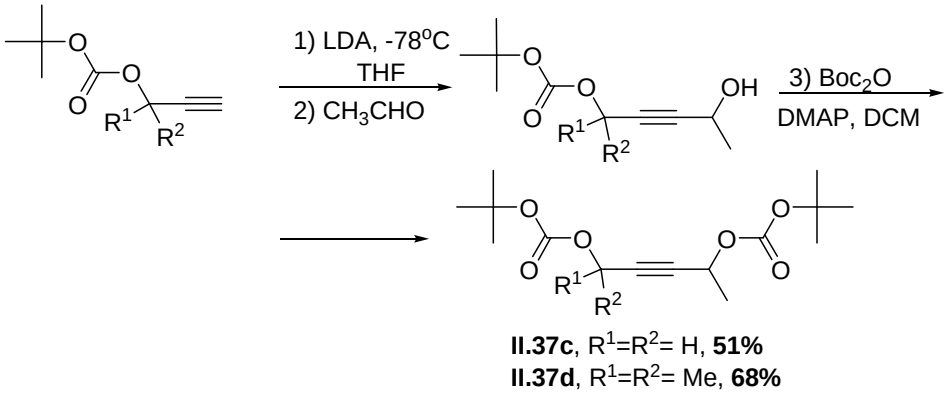
Scheme II.34

Substrate II.43 was synthesized by Dr. Fabien Gagosz by copper(I) catalyzed coupling of bromoalkyne II.58 and oxazolidinone:[147]



Scheme II.35

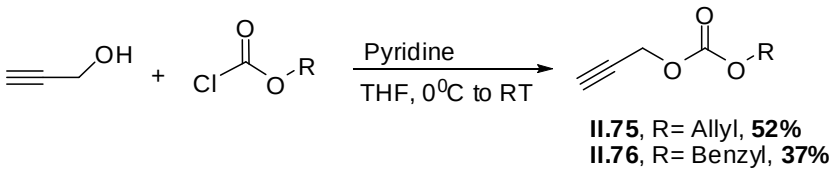
Unsymmetrical substrates II.37c-d were synthesized by a sequence of 3 steps according to Scheme II.36:



Scheme II.36

Allyl and benzyl carbonates II.75 and II.76 were made as follows:

[147] Frederick, M. O.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P.; Huang, J.; Kurtz, K. C. M.; Shen, L.; Douglas, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 2368



Scheme II.37

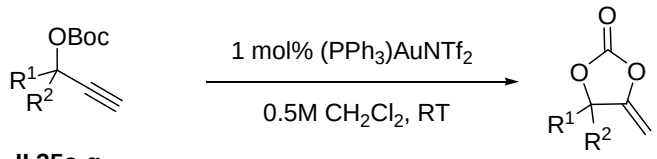
II.6. Au(I)-Catalyzed Formation of 4-Alkylidene-1,3-dioxolan-2-ones

In order to test the scope of the reaction, different types of propargylic carbonates with terminal or internal triple bonds and with different substituents were subjected to the optimized reaction conditions.

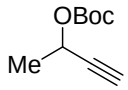
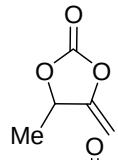
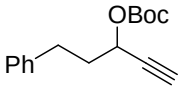
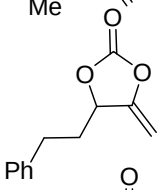
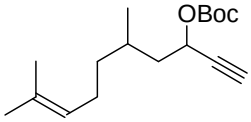
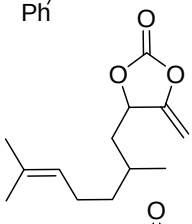
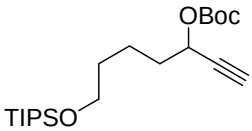
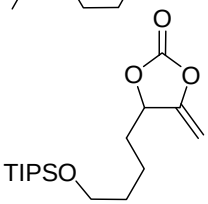
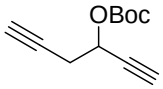
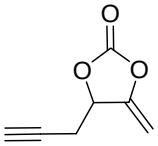
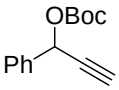
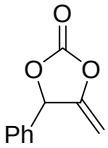
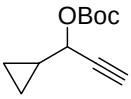
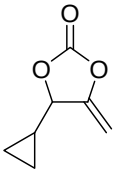
II.6.1. Reactivity of Propargyl Carbonates Derived from Terminal Alkynes

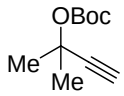
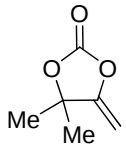
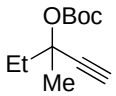
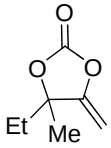
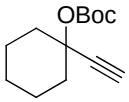
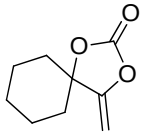
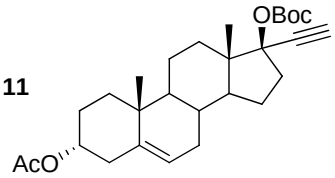
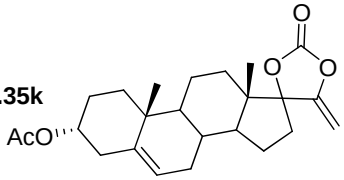
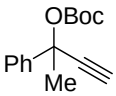
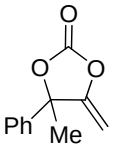
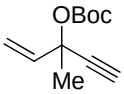
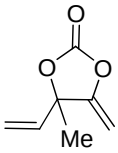
The reaction proved to be quite general and various substituted terminal alkynes reacted under the optimized reaction conditions to afford the corresponding cyclic carbonates in yields ranging from 40% to 100% (Table II.4). Secondary and tertiary *tert*-butylcarbonates II.35f (Entry 6), II.35g (Entry 7), II.35l (Entry 12) and II.35m (Entry 13) needed longer reaction times due to their lower reactivity, but otherwise the transformation was fast and a complete conversion of the substrate was generally observed after one hour. A competitive formation of side-products was observed in the case of the afore-mentioned secondary and tertiary substrates, probably due to the presence of a carbocation stabilizing group at the propargylic position of II.35f, g, l and m (phenyl, vinyl, cyclopropyl groups). It is worth mentioning that these side-products were not detected in the case of tertiary *tert*-butylcarbonates bearing simple alkyl groups at the propargylic position (Entries 8-11). Despite the mildness of the reaction conditions, it seems that the gold catalyst proved to be acidic enough to provoke a competitive fragmentation of the C-O propargylic bond leading to undesired products. The cyclopropyl derivative II.35g was transformed into the desired cyclic carbonate II.36g in the presence of a higher catalyst loading (3%) or employing the more electrophilic gold complex $[Ph_3PAu(NC\text{-}CH_3)]SbF_6$ (1 mol%) (Table II.4, Entry 7). Also, the moderate yield obtained in the case of substrate II.35m (40%, Entry 13) may be attributed to its poor stability in acidic medium.
Various functionalities such as a phenyl group (Entries 2, 6 and 12), an alkene moiety (Entries 3, 11 and 13), a silyl ether (Entry 4) or an ester group (Entry 11) were tolerated. The rearrangement proved to be regioselective since diyne derivative II.35e exclusively afforded II.36e, without formation of the 6-membered cyclic carbonate resulting from a 6-*exo* cyclization[148] (Entry 5).
The reaction of the androstene derivative II.35k was exceptionally efficient and gave the corresponding pure spirocyclic carbonate II.36k in 90% yield after a simple filtration of the crude reaction mixture (Entry 11).

[148] a) Shin, S. *Bull. Korean Chem. Soc.* **2005**, *26*, 1925; b) Kang, J.-E.; Shin, S. *Synlett* **2006**, 717



II.35a-g **II.36a-g**

Entry	Substrate		Product		Time	Yield[a]
1		**II.35a**		**II.36a**	15 min	**94%**
2		**II.35b**		**II.36b**	5 min	**100%**
3		**II.35c**		**II.36c**	10 min	**91%**
4		**II.35d**		**II.36d**	5 min	**96%**
5		**II.35e**		**II.36e**	5 min	**95%**
6		**II.35f**		**II.36f**	10 h	**74%**
7		**II.35g**		**II.36g**	1h 5 h	**49%**[b] **49%**[c]

Entry	Substrate		Product		Time	Yield[a]
8		**II.35h**		**II.36h**	5 min	**85%**
9		**II.35i**		**II.36i**	5 min	**98%**
10		**II.35j**		**II.36j**	30 min	**96%**
11		**II.35k**		**II.36k**	10 min	**90%**
12		**II.35l**		**II.36l**	17 h	**76%**
13		**II.35m**		**II.36m**	18 h	**40%**

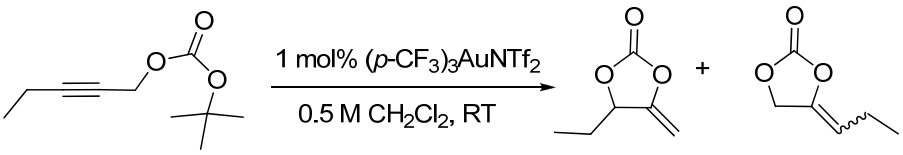
[a] Isolated yield; [b] with 3 mol% of $(PPh_3)AuNTf_2$; [c] with 1 mol% of $[Ph_3PAu(NC\text{-}CH_3)]SbF_6$

Table II.4

II.6.2. Reactivity of Propargyl Carbonates Derived from Internal Alkynes

We next decided to study the reactivity of internal alkynes in the $(PPh_3)AuNTf_2$ catalyzed transformation. As depictet in Table II.5, internal substrates II.37a-k reacted as well when subjected to the optimized reaction conditions, but longer reaction times were required to reach completion and the yields were lower (60-87%) than for the rearrangement of the corresponding terminal alkynes. Methylene dioxolanones II.38a-c formed by cyclization of substrates II.37a-c were exclusively obtained as the *Z*-isomers (Table II.5, Entries 1-3). The reaction of the ester derivative II.37a can be regarded as a Michael type addition of the Boc group onto the gold(I) activated alkyne. As expected, the Thorpe-Ingold effect favoured a faster cyclization of the more substituted *tert*-butylcarbonate in the case of the unsymmetrically substituted substrates II.37c-d, furnishing stereoselectively II.38c-d (Entries 3 and 4). The second Boc group remained intact under the reaction conditions in the case of

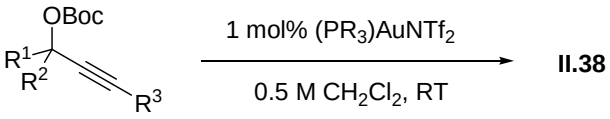
substrates II.37b and d (Entries 2 and 4). The substrate II.37c gave allene derivative II.38c (Entry 4). Oddly, *tert*-butylcarbonates II.37e-g did not react in the presence of $(Ph_3P)AuNTf_2$ (Entries 5-8). Gratifyingly, these substrates were rearranged in the presence of the more electrophilic gold complex $[(pCF_3Ph)_3P]AuNTf_2$ furnishing *exo*-methylene compounds II.37e (Entry 5) and II.37f-g (Entries 6-8) in moderate yields (60-68%). Unpredictably, in the case of these substrates, the cyclic carbonate moiety was shifted by one carbon in comparison with the structures of the previously obtained products, attesting an unexpected reaction pathway. Substrate II.37f represented a frontier case, affording the expected product II.39 and the shifted product II.38f in a 1:6 ratio (Scheme II.38).



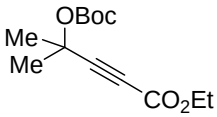
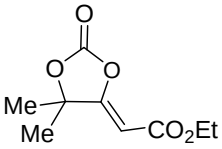
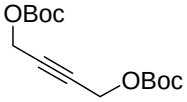
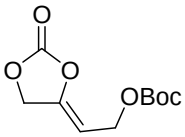
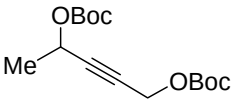
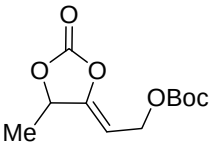
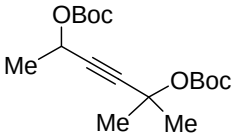
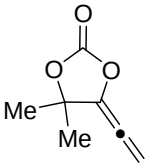
II.37 f **II.38f, 60%** **II.39, 10%**

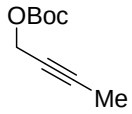
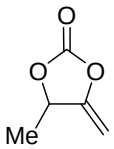
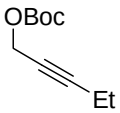
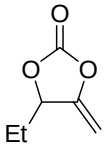
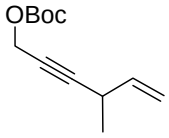
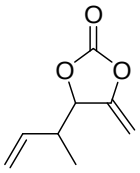
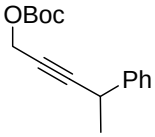
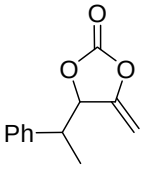
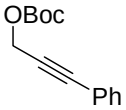
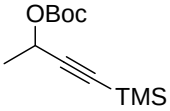
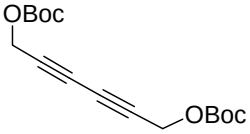
Scheme II.38

Diasteroisomeric mixtures of cylic carbonates were obtained when substrates II.37g and h (Entries 7 and 8), possessing an asymmetric center at the propargylic position, underwent the gold-catalyzed cyclization. The selectivity observed, albeit modest, increased as a function of the steric hindrance induced by the group located at the propargylic position, the diastereoisomeric ratio reaching 1:3.9 in the case of phenyl-substituted substrate II.37h (Entry 8).



II.37

Entry	Substrate		Product		Time	Yield[a]
1[b]		**II.37a**		**II.38a**	2 h	**87%**
2[b]		**II.37b**		**II.38b**	50 min	**62%**
3[b]		**II.37c**		**II.38c**	30 min	**77%**
4[b]		**II.37d**		**II.38d**	2 h	**50%**

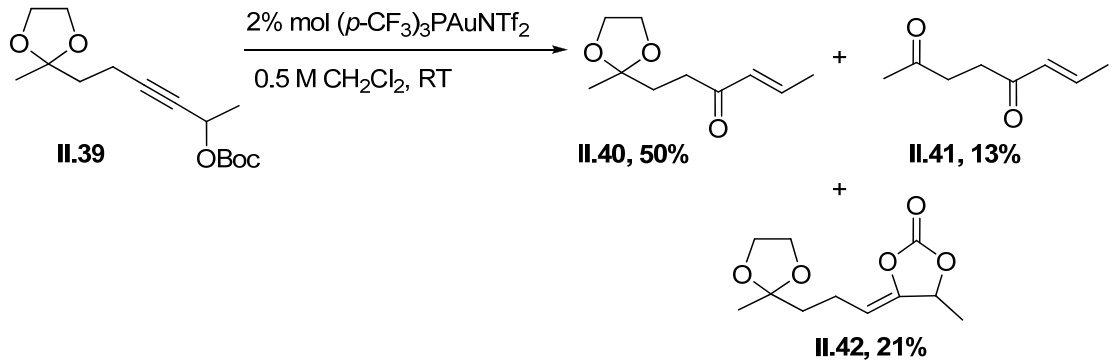
5[c]		**II.37e**		**II.38e**	24 h	**62%**
6[c]		**II.37f**		**II.38f**	24 h	**60%**[d]
7[c]		**II.37g**		**II.38g**	20 h	**68%** dr=1:1.6
8[c]		**II.37h**		**II.38h**	20 h	**66%** dr=1:3.9
9[b,c]		**II.37i**	—	**II.38i**	20 h	—
10[b,c]		**II.37j**	—	**II.38j**	3 h	—
11[b,c]		**II.37k**	—	**II.38k**	24 h	—

[a] Isolated yield; [b] with $(PPh_3)AuNTf_2$; [c] with $[(pCF_3Ph)_3P]AuNTf_2$; [d] isolated along with 10% **II.39** (see Scheme II.38)

Table II.5

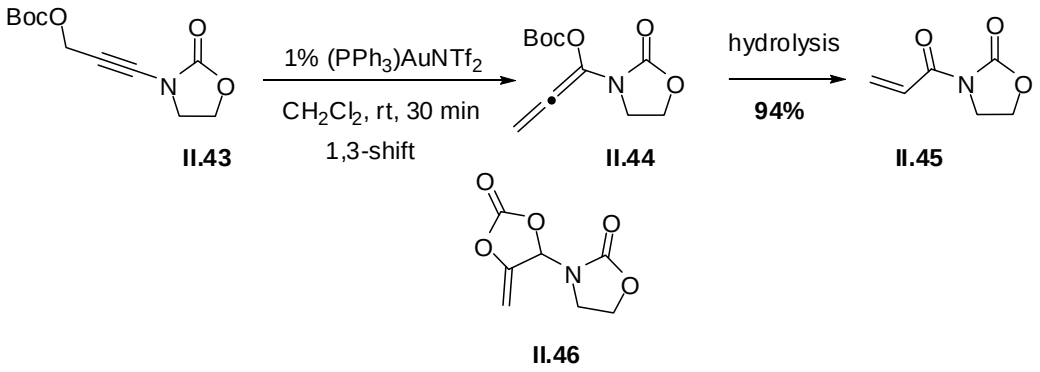
Disappointing results were obtained in the case of internal alkynes II.37i-k (Entries 9-11), whatever the catalyst used. In the cases of derivatives II.37i and II.37k, the substrates were inert in presence of the catalyst, while numerous products derived from the degradation of the Boc group were formed when TMS derivative II.38j was subjected to the cyclisation conditions.

It is worth to mention that acetal derivative II.39 afforded a mixture of 3 products in presence of $[(pCF_3Ph)_3P]AuNTf_2$ as the catalyst (Scheme II.39):[149]



Scheme II.39

Also, reexamination of the NMR spectra of the rearrangement product of substrate II.43 led to the conclusion that the structure of the product had been initially misassigned in our preliminary communication (II.46, Scheme II.40). Rearrangement of II.43, in the presence of 1 mol% of $(PPh_3)AuNTf_2$ actually afforded compound II.45 (instead of compound II.46) as the result of a 1,3-*tert*-butoxycarbonyl migration followed by the hydrolysis of the resulting *tert*-butoxycarbonyloxyallene II.44 by traces of water.[149]



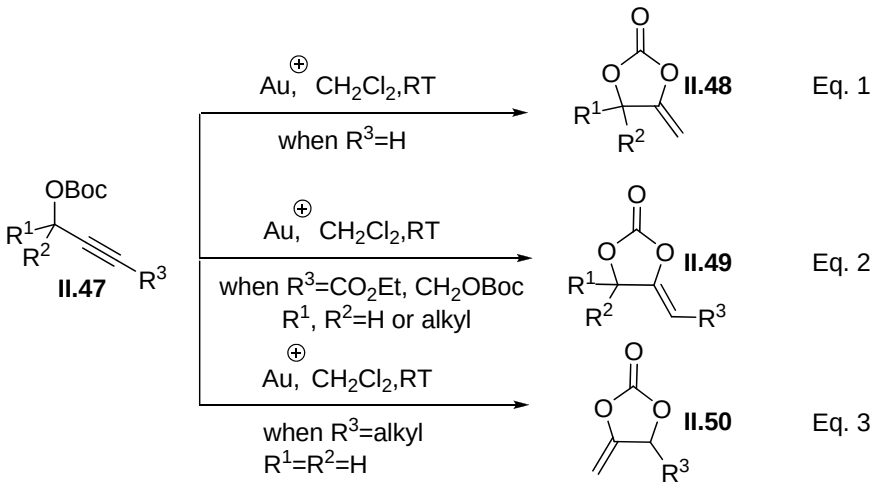
Scheme II.40

II.6.3. Reaction Mechanism

The results obtained led to the conclusion that the structure of the cyclic carbonates (II.48, II.49 or II.50) obtained was significantly dependant on the nature of the substituent attached at the alkyne terminus (Scheme II.41).[150]

[149] This transformation is analogous to the rearrangement of propargylic ester to α,β-unsaturated ketones, see: Yu, M.; Li, G.; Wang, S.; Zhang, L. *Adv. Syn. Catal.* **2007,** *349*, 871

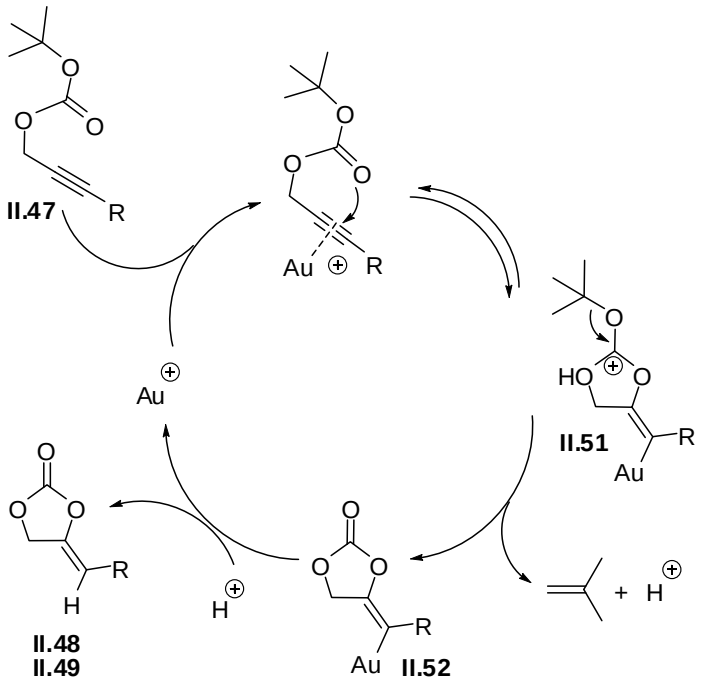
[150] For a computation study on gold-catalyzed rearrangement of propargylic esters, see: Correa, A.; Marion, N.; Fensterbank, L.; Malacria, M.; Nolan, S. P.; Cavallo, L. *Angew. Chem. Int. Ed.* **2008**, *47*, 613



Scheme II.41

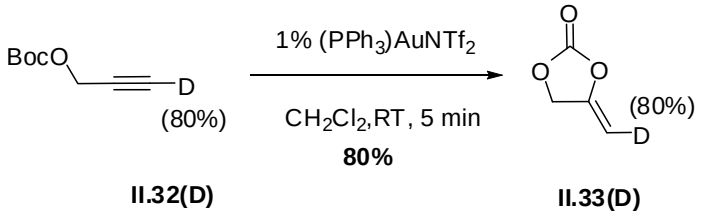
In order to account for these observations, two distinct mechanistic manifolds explaining the formation of the cyclic carbonates II.48-II.50 are proposed in Schemes II.42 and II.43.[151]
A mechanistic proposal accounting for the formation of cyclic carbonates of type II.48 and II.49 is depicted in Scheme II.42. Stabilized cationic species of type II.51 are obtained by the nucleophilic attack of the *tert*-butyloxycarbonyl group on the gold(I) activated triple bond in substrate II.47.
Fragmentation of the C-O bond of the *tert*-butyloxy group in II.51 leads to the formation of the neutral vinyl-gold species II.52 which is subsequently protodemetallated to finally furnish cyclic carbonate II.48 or II.49. This mechanistic pathway appears to be favored in the case of terminal alkynes (see Table II.4 and Scheme 41, Eq. 1), alkynes possessing electron-withdrawing groups (see Table II.5, Entry 1) or substrates possessing a second propargylic BocO group (see Table II.5, Entries 2-4, Scheme 41, Eq. 2).

[151] For related Pt(II) catalyzed cyclisation-fragmentation processes, see: a) Davies, P. W.; Fürstner, A. *J. Am. Chem. Soc.* **2005**, *127*, 15024; b) Nakamura, I.; Mizushima, Y.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15022



Scheme II.42

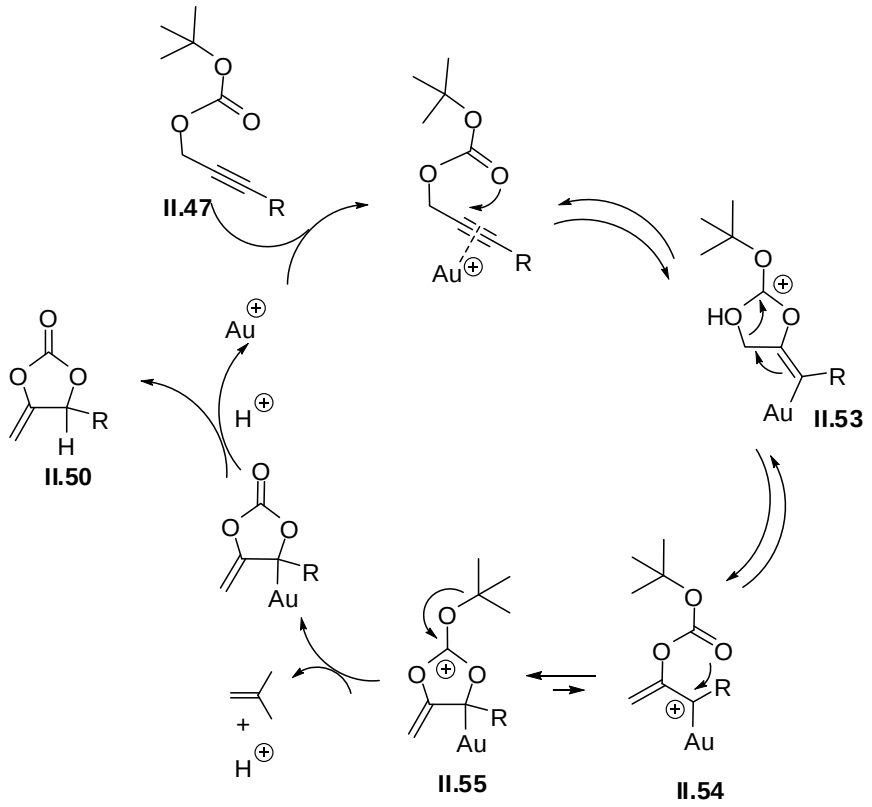
The exclusive formation of compound II.33(D) during the rearrangement of 80% deuterated alkyne II.32(D) is in agreement with this mechanistic proposal (Scheme II.43).



Scheme II.43

The stereospecific formation of compounds II.38a-c (see Table II.5, Entries 1-3) also brings further evidence for the *anti* addition of the *tert*-butyloxycarbonyl group onto the activated alkyne followed by the stereoselective protodemetallation step.

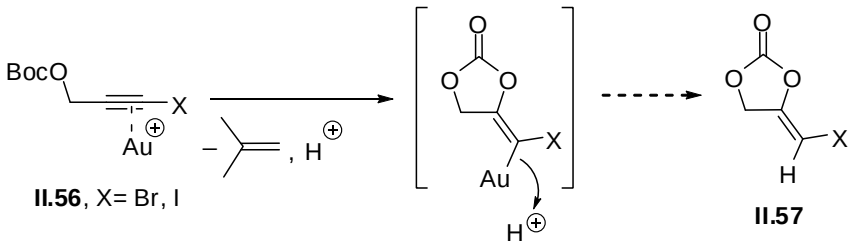
Scheme II.44 illustrates a reasonable mechanistic pathway that may elucidate the formation of cyclic carbonates of type II.50. After the formation of the carbocationic intermediate II.53 in the same way as depicted in Scheme II.42, the internal allylic C-O bond in this intermediate can fragment in a different manner to afford the stabilized allylic cation II.54. Cyclic carbonate II.55 is obtained by a subsequent cyclization of the Boc group, followed by a sequence of fragmentation and protodemetallation. This pathway seems to be operational in the case of internal alkynes ($R^3 \neq H$, Scheme 41, Eq. 3) and more especially in the presence of electron rich groups (R^3=alkyl). Again, this mechanistic proposal can account for the selectivity observed in the case of substrates II.37f and g (see Table II.5, Entries 6 and 7).



Scheme II.44

II.6.4. Synthesis of 4-(*Z*-Halomethylene)-1,3-dioxolan-2-ones

To further highlight the potential of this new gold-catalyzed transformation, we wondered if propargylated haloalkynes of type II.56 could be feasible substrates for the synthesis of haloalkenes II.57 (Scheme II.45). Vinyl bromides and iodides obtained this way could be further functionalized, notably by transition metal-catalyzed cross coupling reactions.

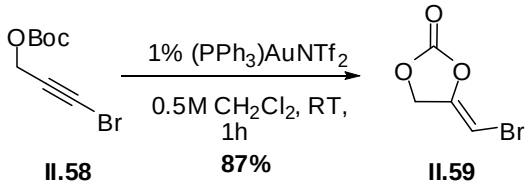


Scheme II.45

It is important to note that this procedure would allow the *stereoselective* formation of *Z*-haloalkenes, if the reaction follows the same pathway as in the case of terminal alkynes (Scheme II.41). Moreover, since the use of a source of electrophilic iodine exclusively affords the opposite *E*-isomers, these isomers could not be obtained following the previously

reported methods involving the direct iodocyclization of similar homopropargylic *tert*-butyl carbonates.[152] Also, these haloalkenes could not be obtained using the mercury-catalyzed rearrangement developed by Nishizawa (see Scheme II.31).[142]

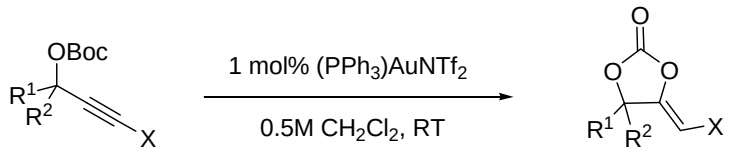
Bromoalkyne II.58 was first chosen as a model substrate to validate this approach. Gratifyingly, bromoalkene II.59 was formed with complete *Z*-selectivity in 87% yield with 1 mol% of $(PPh_3)AuNTf_2$ and dichloromethane as the solvent.



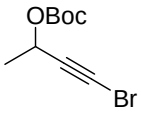
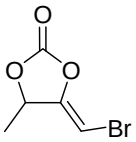
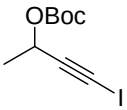
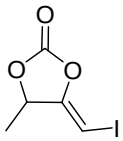
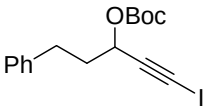
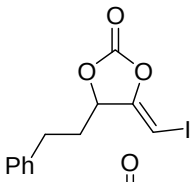
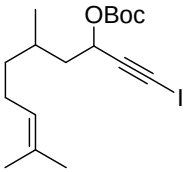
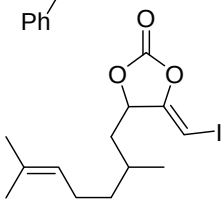
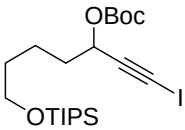
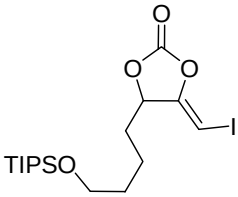
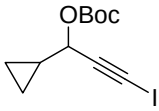
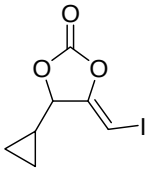
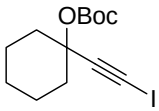
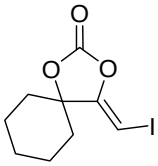
Scheme II.46

A series of diversely substituted haloalkynes were synthesized in order to test the scope of this transformation. As illustrated in Table II.6, the reaction was fast in all cases, proving that the presence of a halogen atom at the alkyne terminus did not significantly change the kinetics of the cyclization.
The reaction time was even shorter in the case of bromoalkyne II.60a, having an extra methyl substituent at the propargylic position, affording *Z*-bromoalkyne II.61a in 87% yield.
We decided to turn our attention to the transformation of iodoalkyne derivatives, since iodoalkenes are more suitable substrates for the transition metal-catalyzed cross coupling reactions. A range of secondary and tertiary iodoalkynes possessing a variety of substituents were subjected to the reaction conditions furnishing the corresponding *Z*-iodoalkenes II.61b-g in yields ranging from 32% to 99% (Table II.6, Entries 2-7). Other functionalities, such as a phenyl group (Entry 3), an alkene moiety (Entry 4) or a silyl ether (Entry 5) were tolerated. However, only traces of the corresponding iodoalkene II.61f were obtained when alkyne II.60f, possessing a cyclopropyl group at the propargylic position, was treated with 1 mol% $(PPh_3)AuNTf_2$. A modest yield of 32 % was obtained employing the more electrophilic $[Ph_3PAu(NC\text{-}CH_3)]SbF_6$. As previously discussed, this difference may be due to the fact that $(PPh_3)AuNTf_2$ might be acidic enough to activate the OBoc group and cause the degradation of the substrate by formation of a positive charge at the propargylic position, especially favored by the presence of the carbocation stabilizing cyclopropyl ring.

[152] Marshall, J. A.; Yanik, M. M. *J. Org. Chem. Soc.* **1999**, *64*, 3798



II.60 **II.61**

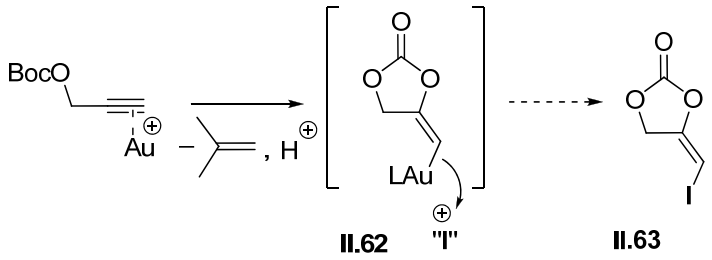
Entry	Substrate		Product		Time	Yield[a]
1		**II.60a**		**II.61a**	20 min	**87%**
2		**II.60b**		**II.61b**	10 min	**95%**
3		**II.60c**		**II.61c**	5 min	**99%**
4		**II.60d**		**II.61d**	5 min	**97%**
5		**II.60e**		**II.61e**	5 min	**69%**
6[b]		**II.60f**		**II.61f**	1 h	**32%**
7		**II.60g**		**II.61g**	5 min	**83%**

[a] Isolated yield; [b] with 1mol% of $[Ph_3PAu(NC\text{-}CH_3)]SbF_6$

Table II.6

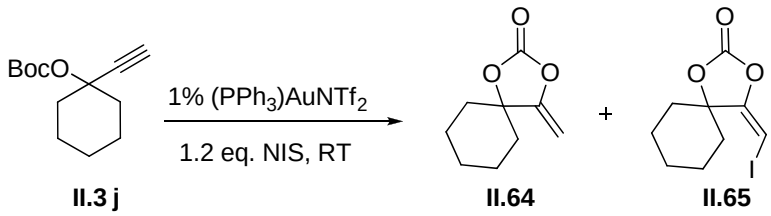
II.6.5. Synthesis of 4-(*E*-Iodomethylene)-1,3-dioxolan-2-ones

To further highlight the potential of this new gold catalyzed process, we wondered if it would be possible to trap the intermediate vinyl-gold species II.62 by a source of electrophilic iodine prior to protonation,[153] allowing thus the stereoselective synthesis of the *E*-isomers of 4-iodomethylene-1,3-dioxolan-2-ones II.63 (Scheme II.47). One should note that these isomers cannot be obtained by the rearrangement of iodoalkynes derivatives, due the stereospecificity of the transformation.
The obtention of the *E*-isomers by gold catalysis would represent a synthetically useful variation allowing the selective synthesis of either one or the other isomer starting from the same propargylic *tert*-butyl carbonate precursor.



Scheme II.47

NIS was selected as the source of electrophilic iodine[153] and the reactivity of alkyne II.35j as the substrate was tested using the conditions previously optimized for the simple rearrangement of propargylic *tert*-butyl carbonates (1 mol% of $(PPh_3)AuNTf_2$, dichloromethane as the solvent) with a slight excess of NIS (1.2 equiv.). To our delight, the reaction was fast allowing the formation of a 1:1 mixture of the desired *E*-iodinated product II.65 and the protodemetallated product II.64. Supposing that the protonation is slowed down in a polar solvent, thus favoring the trapping of the vinyl-gold intermediate by NIS, the reaction of substrate II.35j was attempted using acetone as the solvent. Pleasantly, under these conditions, compound II.65 was exclusively and stereoselectively formed and isolated in 95% yield. It seems that the use of acetone as the solvent had a dramatic effect on the selectivity of the reaction, while the rate remains the same (Scheme II.48).

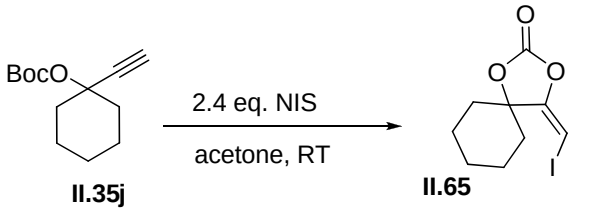


Solvent	Time	Yield II.64/II.65
dichloromethane	5 min	**48% / 48%**
acetone	5 min	**0% / 95%**

[153] For selected other examples of vinyl-gold species trapping with NIS, a) Kirsch, S. F.; Binder, J. T.; Crone, B.; Duschek, A.; Haug, T. T.; Liebert, C.; Menz, H. *Angew. Chem. Int. Ed.* **2007**, *46*, 2310; b) Yu, M.; Zhang, G.; Zhang, L. *Org. Lett.* **2007**, *9*, 2147; c) Crone, B.; Kirsch, S. F. *J. Org. Chem.* **2007**, *72*, 5435

Scheme II.48

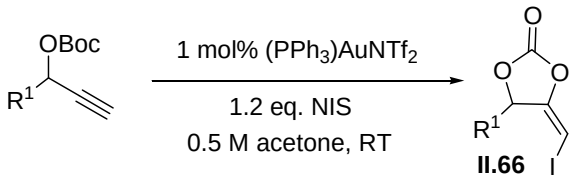
While the iodine-mediated cyclization of allylic and homoallylic *tert*-butyl carbonates is well documented,[125,141] no example of the same transformation applied to propargylic derivatives has been reported.
In order to elucidate the nature of the catalytic species and the role of the gold catalyst in this transformation, a control experiment was carried out subjecting substrate II.35j to a two-fold excess of NIS, with and without $(PPh_3)AuNTf_2$. The formation of iodoalkene II.65 was slow, being however isolated in 82% yield after 48h.



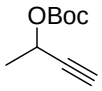
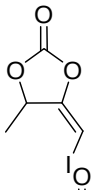
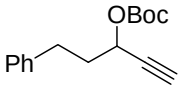
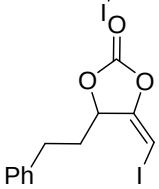
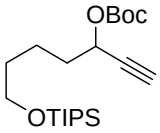
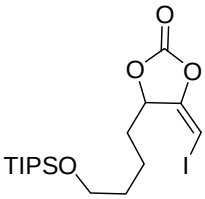
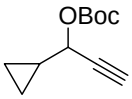
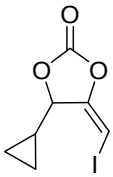
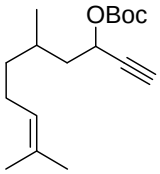
Time	Yield II.65
3 h	**5%**
48 h	**83%**

Scheme II.49

The difference observed in the reaction kinetics demonstrates the decisive role played by the gold complex in the transformation, even if the results do not prove the formation of the iodoalkene after a iododemetallation step as implied in Scheme II.48.
Diversely substituted secondary propargylic alcohol derivatives were synthesized to perform an exploration of the scope of this reaction. As depicted in Table II.7, iodoalkenes II.66a-f were obtained in low to moderate yields (35 to 76%), but with a complete stereoselectivity. Comparing the results showed in Table II.7 with those in Table II.4, one can notice that in most cases, the iodocyclization was slower than the simple cyclization. This fact may be due to the lower activity of the gold complex in acetone than in dichloromethane. Alkynes II.35b and d (Entries 2 and 3), bearing a longer side chain gave the expected products II.66b and d with improved yields (66% and 64%), while the reaction times were longer. The fact that only limited desilylation occurred in the case of substrate II.35d is due to the mildness of the reaction conditions used. Cyclopropyl derivative II.35g also furnished the desired iodoalkene II.66d in a good 76% yield (Entry 4) employing the more electrophilic $[Ph_3PAu(NC\text{-}CH_3)]SbF_6$ gold complex, as in the case of the simple rearrangement (Table II.1, Entry 7). In the cases of substrates II.35c and II.32 (Entries 5 and 6), the corresponding iodoalkenes could not be isolated and only degradation products were obtained. This contrasting reactivity remains unclear even if the occurrence of competitive side reactions initiated by the attack of NIS on the alkene moiety might be invoked for substrate II.35c.



II.66

Entry	Substrate		Product		Time	Yield[a]
1		**II.35a**		**II.66a**	5 min	**35%**
2		**II.35b**		**II.66b**	45 min	**66%**
3		**II.35d**		**II.66c**	15 min	**64%**
4[b]		**II.35g**		**II.66d**	1 h	**76%**
5		**II.35c**	—	**II.66e**	5 min	—
6		**II.32**	—	**II.66f**	15 min	—

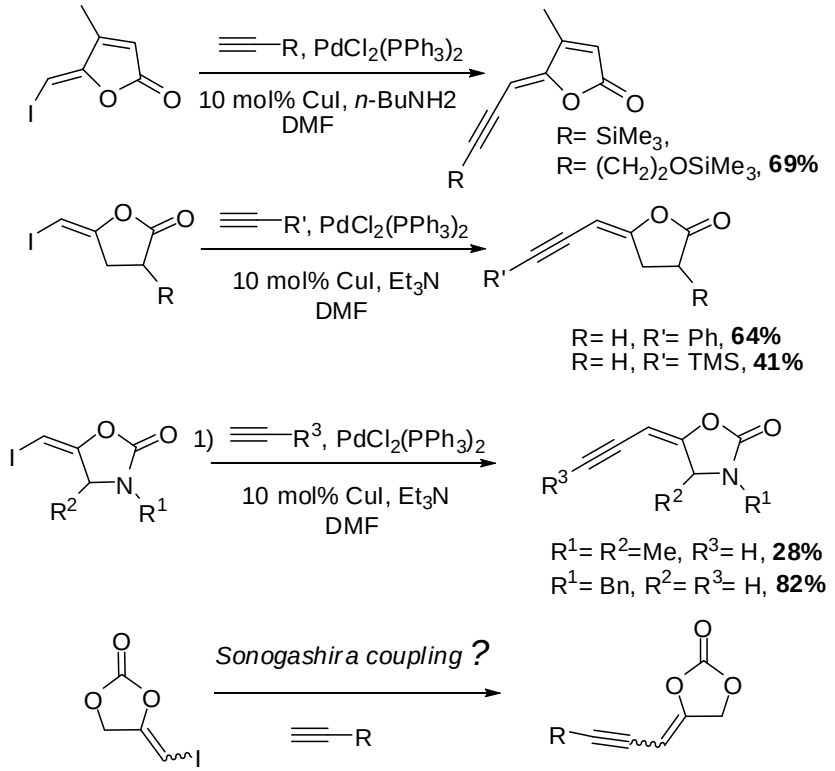
[a] Isolated yield; [b] with 1 mol% of $[Ph_3PAu(NC\text{-}CH_3)]SbF_6$

Table II.7

II.7. Transformation of the Adducts

Having in hand a series of 4-halogenomethylene-1,3-dioxolan-2-ones, we attempted to test their reactivity in palladium catalyzed cross-coupling reactions.

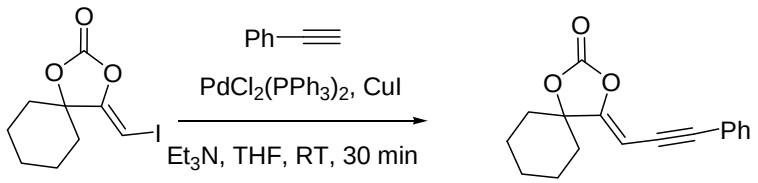
The Sonogashira coupling has already been successfully applied to the coupling reaction of various alkynes with cyclic derivatives as furanones,[154] dihydrofuranones, [155] tetrahydropyranones[155,156] or oxazolidinones[157]. Encouraged by these previous reports, we decided to first study the Sonogashira coupling reaction of dioxolanones with alkynes (Scheme II.50).



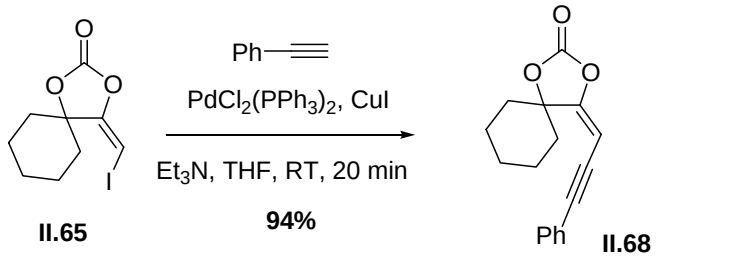
Scheme II.50

As illustrated in Scheme II.51, the reaction of *Z*-iodoalkene II.61g with phenylacetylene under the classical Sonogashira reaction conditions led to the formation of enyne II.67 which was isolated in a moderate 61% yield. Surprisingly, the reaction of the isomeric *E*-iodoalkene II.65 was more efficient and furnished the corresponding enyne II.68 in an excellent 94% yield. Various alkynes could be employed as partners in the Sonogashira coupling as attested by the transformation of iodoalkene II.61b into enynes II.69-II.71 (67 to 72% yield).[158]

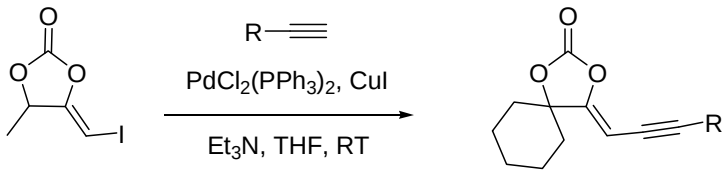
[154] Duchene, A.; Thibonnet, J.; Parrain, J.-L.; Anselmi, E.; Abarbri, M. S*ynthesis* **2007**, 597
[155] Spencer, R. W.; Tam, T. F.; Thomas, E.; Robinson, V. J.; Krantz, A. *J. Am. Chem. Soc.* **1986**, *108*, 5589
[156] a) Zupan, L. A.; Weiss, R. H.; Hazen, S. L.; Parnas, B. L.; Aston, K. W.; Lennon, P. J.; Getman, D. P.; Gross R. W. *J. Med. Chem.* **1993**, *36*, 95; b) Tam, T. F.; Spencer, R. W.; Thomas, E. M.; Copp, L. J.; Krantz, A. *J. Am. Chem. Soc.* **1984**, *106*, 6849
[157] a) Tam, T. F.; Thomas, E.; Krantz, A. *Tet. Lett.* **1987**, *28*, 1127; b) Pinto, I. L.; Boyd, H. F.; Hickey, D. M. B. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2015
[158] Bromoalkenes II.59 and II.61a were not suitable substrates under the same reaction conditions. The reactions only led to degradation products in these cases.



II.61g **61%** **II.67**

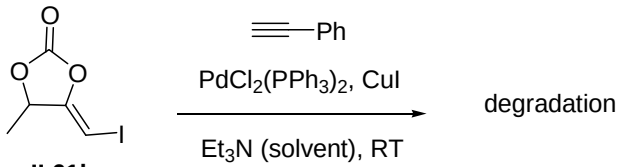


II.65 **94%** **II.68**

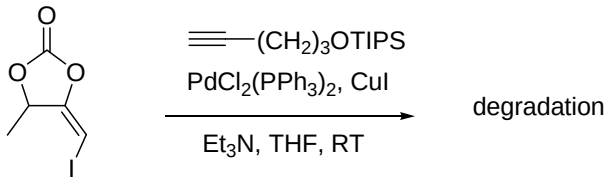


II.61b

R	Time	Product	Yield
n-C_5H_{11}	1.5 h	**II.69**	**67%**
Ph	20 min	**II.70**	**72%**
$(CH_2)_3OTIPS$	18 h	**II.71**	**67%**



II.61b

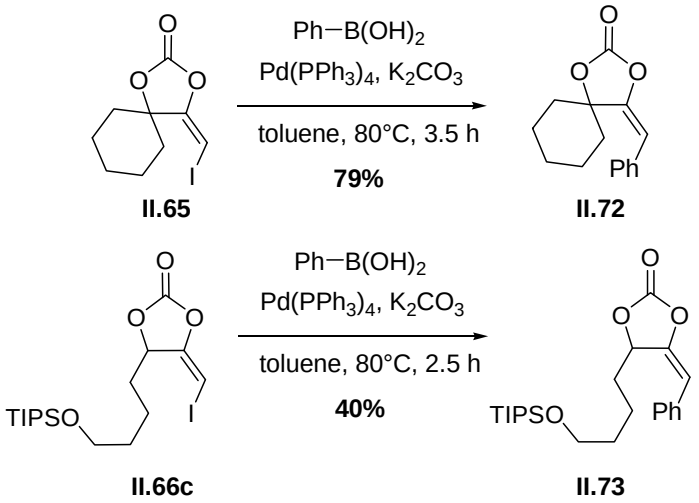


II.66a

Scheme II.51

It is worth mentioning that the quantity of triethylamine used for the Sonogashira cross-coupling played a crucial role on the outcome of the reaction. As depicted in Scheme II.51, when only 10 equivalents of triethylamine were used the reaction between *Z*-iodoalkene II.61b and phenylacetylene was relatively efficient, but when the base was used as the solvent, it only gave degradation products. *E*-iodoalkene II.66a gave also disappointing results. While *Z* isomer II.61b reacted with triisopropyl-pent-4-ynyloxy-silane to give enyne

II.71 in 67% yield, the reaction with *E* isomer II.66 only led to degradation products under the same reaction conditions.
We next turned our attention to the Suzuki coupling reaction. Dioxolanones II.72 and II.73 were isolated in respectively 79% and 40% yield when substrates II.65 and II.66c reacted with phenylboronic acid in the presence of *tetrakis*(triphenylphosphine)palladium(0) and potassium carbonate in toluene at 80°C. However, the reaction proved to be more sluggish for this coupling, probably due to the higher temperature and the instability of the vinylcarbonate functionality under the basic conditions used.



Scheme II.52

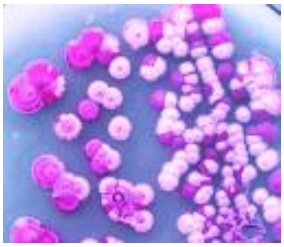
II.8. Conclusion and Perspectives

In summary, we have shown that gold(I) complexes efficiently catalyze the formation of a variety of 4-(alkylidene)-1,3-dioxolan-2-ones from readily available propargylic *tert*-butyl carbonates. The mildness of the reaction conditions insures a compatibility with diversely substituted substrates and functional groups. The loading of the catalyst is low (1 mol%) and can be reduced to 0.1 mol% on a larger scale without noticeable loss of efficiency. It seems to exist a strong dependence of the structure of the cyclic carbonates obtained and the nature of the substituent attached at the alkyne terminus. An extension of the procedure to the stereoselective formation of *E*- or *Z*-4-(halomethylene)-1,3-dioxolan-2-ones has also been developed, using respectively haloalkynes or terminal alkynes as the substrates. The haloalkenes thus obtained proved to be suitable substrates for Sonogashira and Suzuki cross-coupling reactions.

III. Gold(I)-Catalyzed Formation of 5-Methylene-oxazolidin-2-ones

III.1. Introduction

The 1,3-oxazolidin-2-one ring is a cyclic carbamate skeleton quite rare in natural product chemistry but a popular heterocycle framework in the Synthetic Organic Chemistry since Evans' report[159] in 1981 on the use of enantiomerically pure 4- substituted oxazolidin-2-ones as chiral auxiliaries in asymmetric synthesis.[160] They also represent a useful source of protected 1,2-amino alcohols.[161]
However, the oxazolidinone moiety is found in some biologically active naturally occurring compounds.
One of them, (-)-cytoxazone, (4*R*, 5*R*)-5-(hydroxymethyl)-4-(4-methoxyphenyl)-2-oxazolidinone (Figure III.1), a microbial metabolite isolated from a soil sample of *Streptomyces* sp., was shown to have some cytokinemodulating activity.[162]



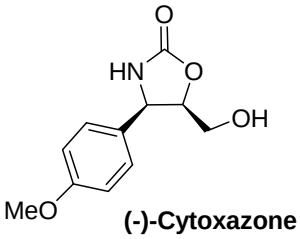


Figure III.1: *Streptomyces* sp. strain and (-)-Cytoxazone

(+)-Streptazolin (III.1, Figure III.2), a lipophilic neutral tricyclic compound, was first isolated by Drautz et *al.* in 1981 from a culture of *Streptomyces viridochromogenes*.[163] Variation of the culture conditions of *Streptomyces* sp. strain A1, which produced streptazolin III.1, resulted in the isolation of three new co-metabolites: 5-*O*-(*β*-D-xylopyranosyl)streptazolin III.2, 9-hydroxystreptazolin III.3 and 13-hydroxystreptazolin III.4 (Figure III.2).[164]

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[159] For earlier reviews see: a) Evans, D.A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, *J. Pure Appl. Chem.* **1981**, *53*, 1109; b) Evans, D. A. *Aldrichim. Acta* **1982**, *15*, 23
[160] Chung, C. W. Y.; Toy, P. H. *Tetrahedron: Asymmetry* **2004**, *15*, 387
[161] For the use of oxazolidinone as a source of protected 1,2-amino alcohols, see: a) Bhaket, P.; Morris, K.; Stauffer, C. S.; Datta, A. *Org. Lett.* **2005**, *7*, 875; b) Ayad, T.; Faugeroux, V.; Genisson, Y.; Andre, C.; Baltas, M.; Gorrichon, L. *J. Org. Chem.* **2004**, *69*, 8775
[162] a) Kakeya, H.; Morishita, M.; Kobinata, K.; Osono, M.; Ishizuka, M.; Osada, H. *J. Antibiot.* **1998**, *51*, 1126; b) Kakeya, H.; Morishita, M.; Koshino, H.; Morita, T.; Kobayashi, K.; Osada, H. *J. Org. Chem.* **1999**, *64*, 1052
[163] Drautz, H.; Zahner, H.; Kupfer, E.; Keller-Schierlein, W. *Helv. Chim. Acta* **1981**, *64*, 1752
[164] Puder, C.; Loya, S.; Hizi, A.; Zeeck, A. *J. Nat. Prod.* **2001**, *64*, 42

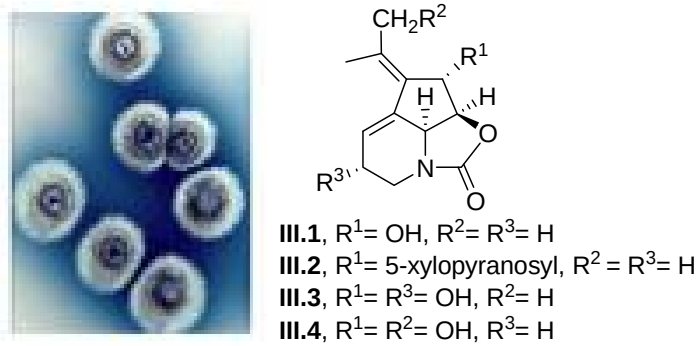


Figure III.2: *Streptomyces viridochromogenes* and Streptazolins

Two new modified novel peptides containing unique amino acids, banyaside A and banyaside B were isolated from the hydrophilic extract of a natural bloom of the cyanobacterium *Nostoc* sp. (Figure III.3).[165]

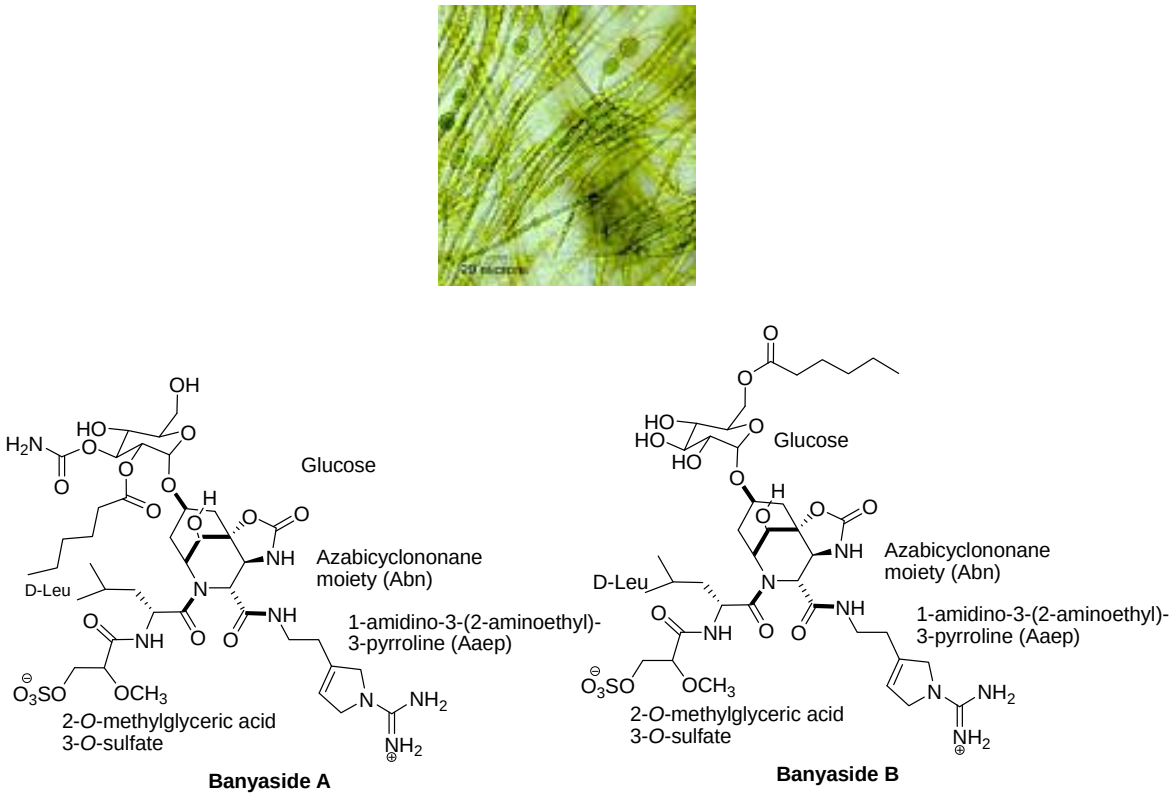


Figure III.3: *Nostoc* sp. and Banyasides

A new oxazoloaporphine, artabonatine E (Figure III.4) was isolated from *Artabotrys uncinatus*, a plant used for treatment of human nasopharyngeal carcinoma as a traditional folk medicine in Taiwan.[166]

[165] Pluotno, A.; Carmeli, S. *Tetrahedron* **2005**, *61*, 575
[166] Hsieh, T.-J.; Chang, F.-R.; Chia, Y.-C.; Chen, C.-Y.; Lin, H.-C.; Chiu, H.-F.; Wu, Y.-C. *J. Nat. Prod.* **2001**, *64*, 1157

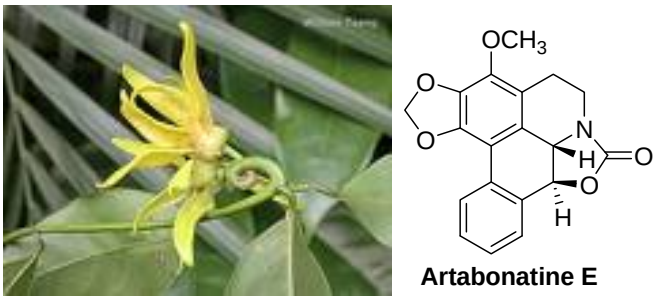


Figure III.4: *Artabotrys uncinatus* and Artabonatine E

Two new classes of inhibitors of lipoprotein-associated phospholipase A_2 ($LpPLA_2$) have been identified in the culture broths of *Pseudomonas fluorescens* strain DSM11579.[167] SB-253514 (Figure III.5) represents the major component of this metabolite family.[168]

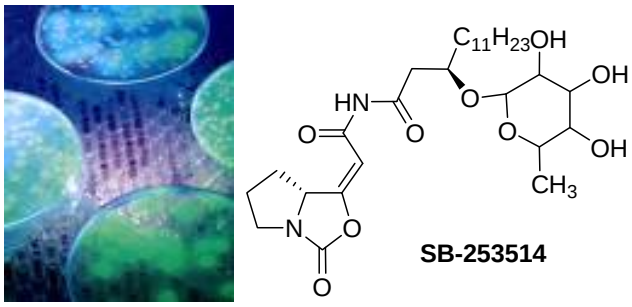


Figure III.5: *Pseudomonas fluorescens* and SB-253514

Finally, the introduction in the pharmaceutical market of Linezolid (Figure III.6), an oxazolidin-2-one-based antibacterial drug, attracted the interest of the scientists and resulted in the apparition of several publications.[169]

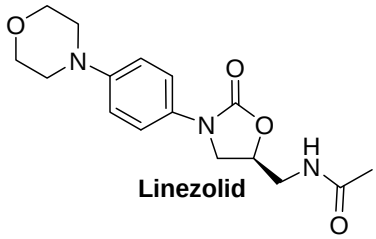


Figure III.6

III.2. Synthetic Methods

Organic chemists addressed considerable synthetic efforts to the construction of the oxazolidinone framework. Different pathways have been reported for the building of this

[167] a) Thirkettle, J.; Alvarez, E.; Boyd, H.; Brown, M.; Diez, E.; Hueso, J.; Elson, S.; Fuslton, M.; Gershater, C.; Morata, M. L.; Perez, P. *J. Antibiot.* **2000**, *53*, 664; b) Busby, D. J.; Copley, R. C. B.; Hueso, J. A.; Readshaw S. A.; Rivera, A. *J. Antibiot.* **2000**, *53*, 670

[168] Pinto, I. L.; Boyd, H. F.; Hickey, D. M. B. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2015

[169] For a review on Linezolid see: Barbachyn, M. R.; Ford, C.W. *Angew. Chem. Int. Ed.* **2003**, *42*, 2010

cottage-like molecule. For example, in the approach starting from 1,2-aminoalcohols, the future carbons C-4 and C-5 are the basement (Figure III.7), the oxygen and nitrogen atoms are supported by the walls, and the carbonyl group closes the building as a roof. In other approaches the five elements are already present and the ring closure is promoted by different catalysts.

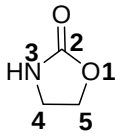


Figure III.7

Another method is the opening of smaller (three membered) heterocyclic rings, such as those of epoxides and aziridines which may occur by intervention of isocyanate for the first ones, and CO_2 or its surrogates in the second case.[170]

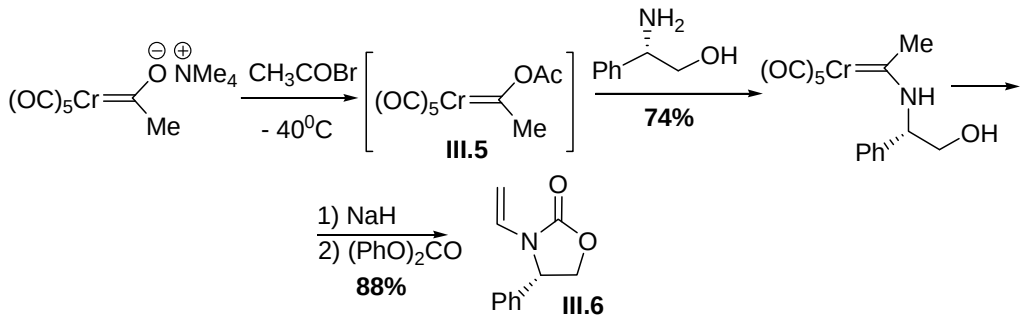
III.2.1. Synthesis of Oxazolidinones by Carbonyl Ring Closure

The origin of the carbonyl roof-closing may come from an outside reactant or can be present inside the starting molecule, *e.g.* in *N*-Boc derivatives or in isocyanate intermediates.

Synthesis from 1,2-Aminoalcohols

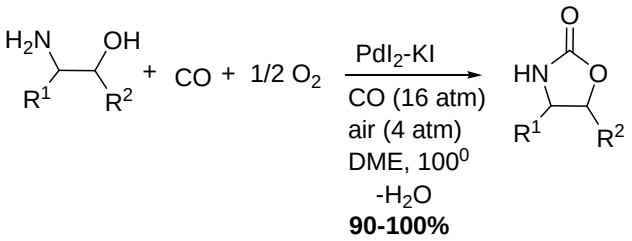
1,2-Aminoalcohols can be converted into cyclic carbamates using phosgene[171] or safer synthetic equivalent reactants, such as diphosgene,[172] triphosgene,[173] and urea.[174]
Diphenyl carbonate has been used to improve the conversion of 1,2-aminoalcohols into oxazolidin-2-ones. For example, Hegedus et *al.* disclosed a simple procedure for the preparation of ene carbamates III.6 by treatment of the amino chromium-carbene complex III.5 with NaH, followed by addition of diphenylcarbonate (Scheme III.1):[175]

[170] Zappia, G.; Gacs-Baitz, E.; Delle Monache, G.; Misiti, D.; Nevola, L.; Botta, B. *Curr. Org. Synthesis* **2007**, *4*, 81
[171] See for example a) Makoto, S.; Tetsuya, S. *Chem. Lett.* **2002**, 808; b) Seki, M.; Shimizu, T.; Matsumoto, K. *J. Org. Chem.* **2000**, *65*, 1298
[172] See for example Bunnage, M. E.; Burke, A. J.; Davies, S. G.; Millican, N. L.; Nicholson, R. L.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2003**, *1*, 3708
[173] See for example Pojarliev, P., Biller,W. T.; Martin, H. J.; List, B. *Synlett* **2003**, *12*, 1903
[174] Huebner, C. F.; Donoghue, E. M.; Novak, C. J.; Dorfman, L.; Wenkert E. *J. Org. Chem.* **1970**, *35*, 1149
[175] Montgomery, J.; Wieber, G. M.; Hegedus, L. S. *J. Am. Chem. Soc.* **1990**, *112*, 6255



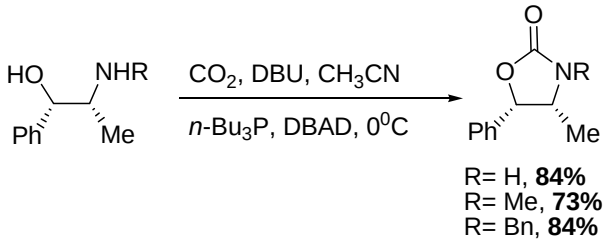
Scheme III.1

β-Aminoalcohols can be converted to 1,3-oxazolidin-2-ones also by palladium-catalyzed oxidative carbonylation. In particular, Gabriele and co-workers used PdI_2-KI as a catalytic system under 20 atm of a CO/air 4:1 mixture, as resumed in Scheme III.2.[176]



Scheme III.2

A mild method for the synthesis of enantiopure oxazolidin-2-ones from *β*-aminoalcohols, previously reported by Kodaka,[177] involving carboxylation followed by an intramolecular Mitsunobu reaction[178] was extended to various substrates (Scheme III.3):[179]

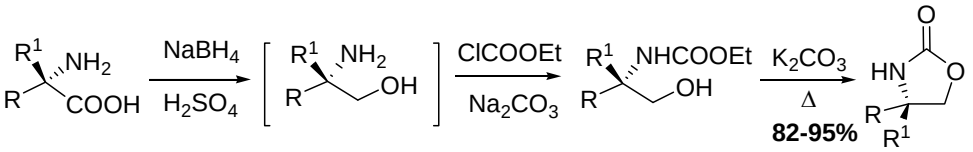


Scheme III.3

Synthesis from *α*-Aminoacids

[176] a) Gabriele, B.; Mancuso, R.; Salerno, G.; Costa, M. *J. Org. Chem.* **2003**, *68*, 601; b) Gabriele, B.; Salerno, G.; Costa, M.; Chiusoli, G. P. *J. Organomet. Chem.* **2003**, *687*, 219; c) Gabriele, B.; Salerno, G.; Brindisi, D.; Costa, M.; Chiusoli, G. P. *Org. Lett.* **2000**, *2*, 625
[177] Kodaka, M.; Tohomiro, T.; Okuno, H. *J. Chem. Soc. Chem. Commun.* **1993**, 81
[178] Mitsunobu, O. *Synthesis* **1981**, 1
[179] Dinsimore, C. J.; Mercer, S. *Org. Lett.* **2004**, *6*, 2885

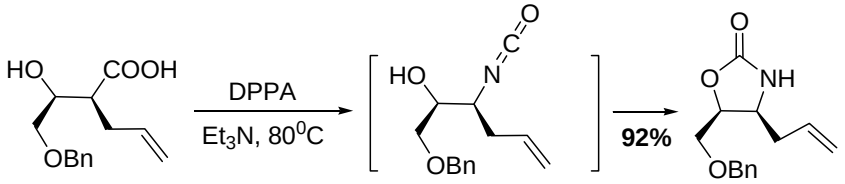
Generally, the synthetic approach to obtain the oxazolidin-2-one ring from *α*-aminoacids involves 3 steps: reduction of the carboxylic function, conversion of the free amino group into a carbamate and base promoted cyclization.
For example, in the low-cost, high yield synthesis of Wu and Shen,[180] the *α*-aminoacid is reduced to the corresponding *β*-aminoalcohol and immediately reacted with ethylchloroformate. The crude alkoxycarbonylated carbamate is then heated with catalytic K_2CO_3 at 100-130°C to give enantiomerically pure oxazolidin-2-ones (82-95%), which are suitable to be used as chiral auxiliaries without any further purification (Scheme III.4):



Scheme III.4

Synthesis from *β*-Hydroxyacids and Amides

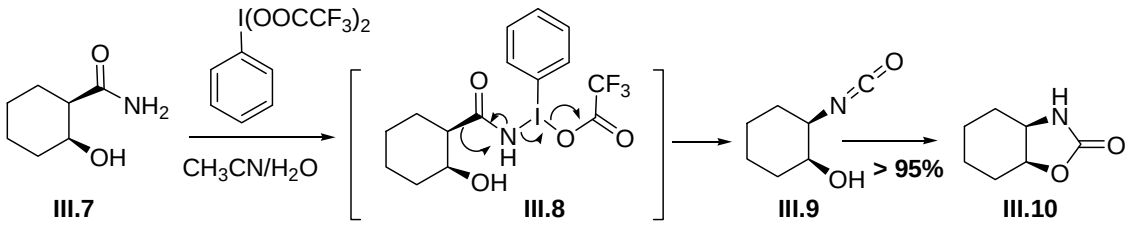
Mono- or disubstituted oxazolidin-2-ones are obtained starting from *β*-hydroxy acids by an intramolecular Curtius degradation-cyclization reaction.[181] For instance, treatment of *β*-hydroxy acid with diphenylphosphoryl azide (DPPA) and Et_3N at 80°C afforded the corresponding *β*-hydroxyisocyanate, which directly cyclized into the expected carbamate (Scheme III.5).[182]



Scheme III.5

An isocyanate intermediate III.9 which evolves into the corresponding carbamate III.10 is generated by the Hofmann rearrangement of *β*-hydroxy amides (Scheme III.6). [183] A mild and efficient protocol, using *bis*(trifluoroacetoxy) iodobenzene (BTI) in acetonitrile at room temperature, was described by Yu et *al.*[184]

[180] Wu, Y.; Shen, X. *Tetrahedron: Asymm.* **2000**, *11*, 4359
[181] For a review on organic azides: Brase, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem. Int. Ed.* **2005**, *44*, 5188
[182] a) Ghosh, A.K.; Bischoff, A.; Cappiello, *J. Org. Lett.* **2001**, *3*, 2677; b) Roers, R.; Verdine, G. L. *Tet. Lett.* **2001**, *42*, 3562
[183] a) Hofmann, A. W. *Ber.* **1881**, *14*, 2725; b) Wallis, E. S.; Lane, *J. Org. React.* **1946**, *3*, 267
[184] Yu, C.; Jiang, Y.; Liu, B.; Hu, L. *Tet. Lett.* **2001**, *42*, 1449



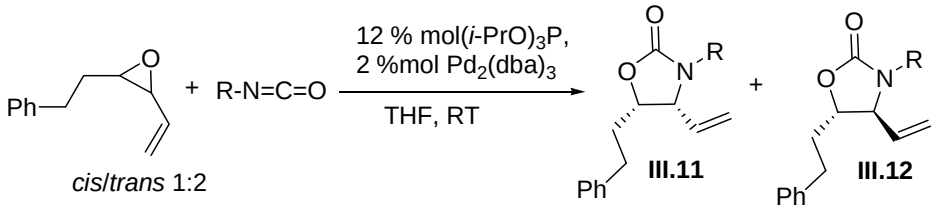
Scheme III.6

III.2.2. Carbonyl Ring Enlargement

Another important method for the construction of the oxazolidin-2-one nucleus consists in the cycloaddition of substituted three-membered rings, notably oxiranes and aziridines, with heterocumulenes.

Synthesis from Epoxides

Low yields and, for unsymmetrical oxiranes, low regioselectivity are observed in the reaction of epoxides with isocyanates. Moreover, the reaction usually requires severe conditions (temperatures over 150 °C) and polymerization of isocyanate may occur as a side reaction during the cycloaddition.
An efficient stereoselective conversion of substituted vinyloxiranes to *cis*-oxazolidin-2-ones III.11, catalyzed by $Pd_2(dba)_3$ and trialkyl phosphite, has been reported by Trost (Scheme III.7).[185] The reaction afforded mainly *cis*-oxazolidin-2-one with all the isocyanates investigated, independent of the *cis/trans*-ratio of the starting epoxides, except for TsN=C=O, when the oxazolidin-2-one reproduced the *cis/trans* ratio of the starting epoxide.



R= Ts, **III.11/III.12**= 1:2, **92%**
R= Ph, **III.11/III.12**= 3.1:1, **88%**
R= *p*-OMePh, **III.11/III.12**= 3.7:1, **81%**
R= $C_{10}H_7$, **III.11/III.12**= 10:1, **75%**

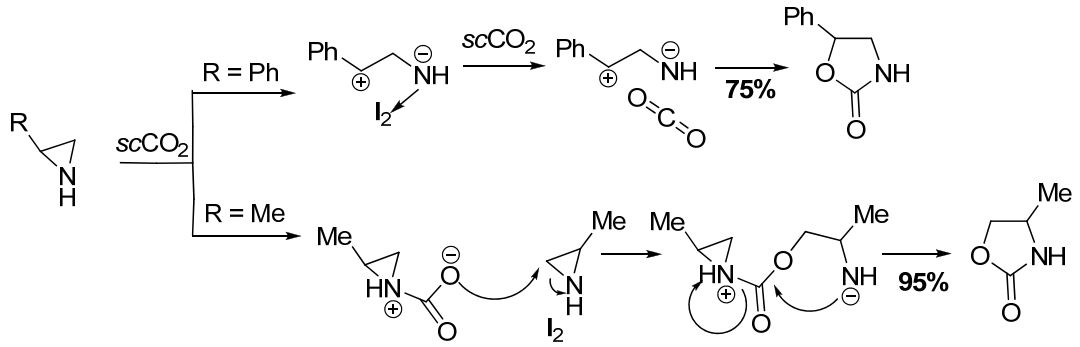
Scheme III.7

Synthesis from Aziridines

[185] a) Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1987**, *109*, 3792; b) Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1988**, *110*, 7933

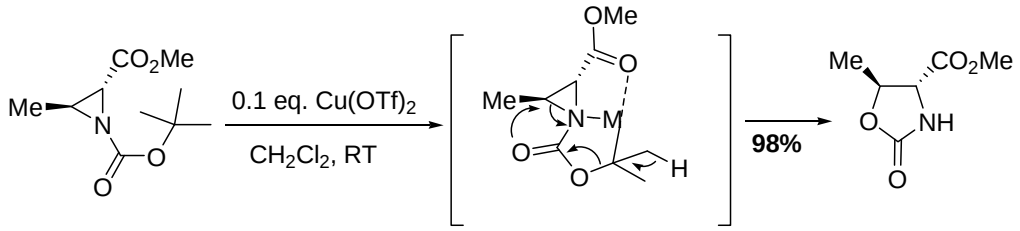
The main problem with the conversion of aziridines by reaction with CO_2 into the expected oxazolidin-2-ones was the low reactivity of CO_2, a shortcoming which was overcome by high pressure conditions or by electrochemical processes in the presence of nickel complex as a catalyst.[186]

For instance, Kawanami and Ikushima converted 2-phenyl aziridine into 5-phenyl oxazolidinone under supercritical conditions ($scCO_2$) in the presence of catalytic iodine (Scheme III.8, Eq. 1).[187] By contrast, the reaction with 2-methyl aziridine afforded only 4-methyl oxazolidinone (Scheme III.8, Eq. 2).



Scheme III.8

The Lewis acid-catalyzed ring expansion of chiral aziridines into oxazolidin-2-ones has been explored by Tomasini et *al*.[188] *N*-Boc-aziridines rearrange in the presence of $Cu(OTf)_2$ with total regioselectivity, affording exclusively 4-carboxymethyl oxazolidin-2-ones, and with whole stereoselectivity, giving *cis* and *trans*-oxazolidin-2-ones from *cis* and *trans* disubstituted *N*-Boc aziridines, respectively (Scheme III.9):



Scheme III.9

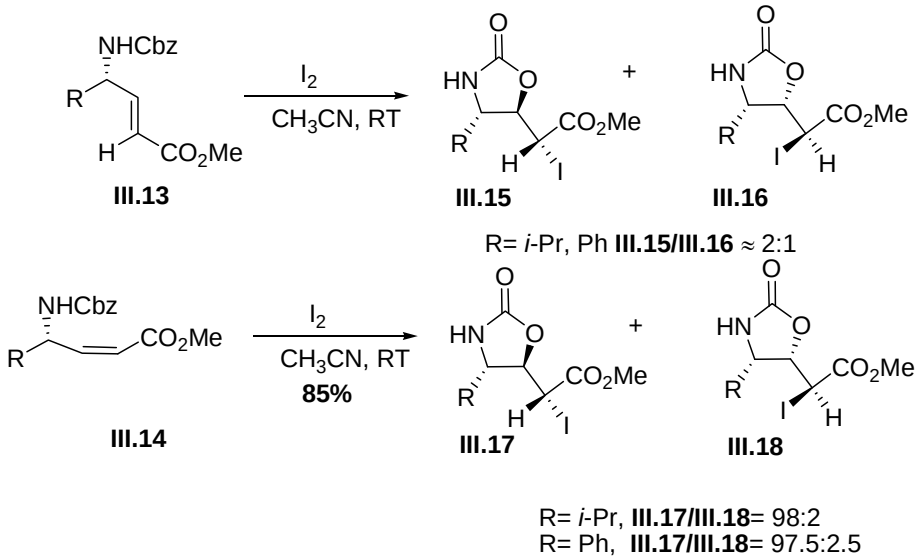
III.2.3. Cyclocarbamation

Iodocyclization

Another possible approach to obtain oxazolidin-2-ones is the halo-cyclofunctionalization of allyl carbamates, a reaction resulting very often in high regio- and stereocontrol.

[186] Tascedda, P.; Dunach, E. *Chem. Commun.* **2000**, 449
[187] Kawanami, H.; Ikushima, Y. *Tet. Lett.* **2002**, *43*, 3841
[188] a) Tomasini, C.; Vecchione, A. *Org. Lett.* **1999**, *1*, 2153; b) Luppi, G.; Tomasini, C. *Synlett* **2003**, 797

Zappia et *al.* studied the iodocyclocarbamation of chiral allylic carbamates derived from the corresponding *α*-aminoacids. *E*-isomers (III.13) gave mainly a mixture of *trans*- and *cis*-oxazolidin-2-ones III.15 and III.16, but *Z* isomers (III.14) afforded almost exclusively *trans* derivatives III.17 (Scheme III.10):[189]

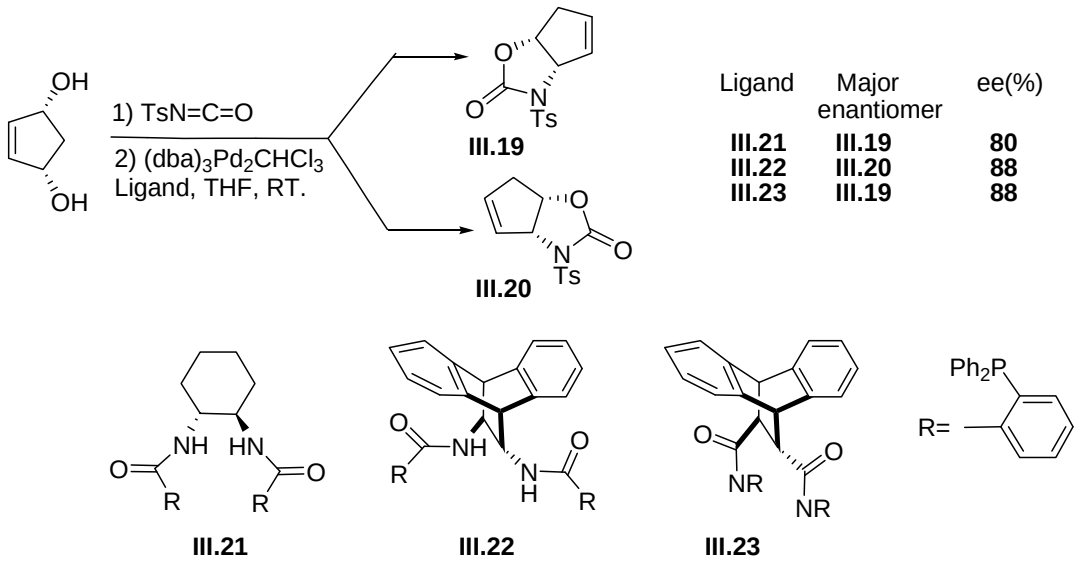


Scheme III.10

Pd-Catalyzed Cyclisations

Trost et *al.* described the synthesis of the two enantiomers of 5-vinyl oxazolidin-2-one derivatives III.19 and III.20 by palladium-catalyzed desymmetrization of cyclic *meso*-2-ene-1,4-diol biscarbamates (Scheme III.11). A series of ligands, based mainly upon 2-(diphenylphosphino)benzoic acid (DPPBA) frame, with chiral diol or 1,2-diamino groups and a C_2 symmetry, have been prepared and tested in the intramolecular allylic substitution reaction, giving rise to products with enantiomeric excesses up to 88%.[190]

[189] Misiti, D.; Zappia, G. *Tet. Lett.* **1990**, *31*, 7359
[190] a) Trost, B.M. *J. Org. Chem.* **2004**, *69*, 5813; b) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395

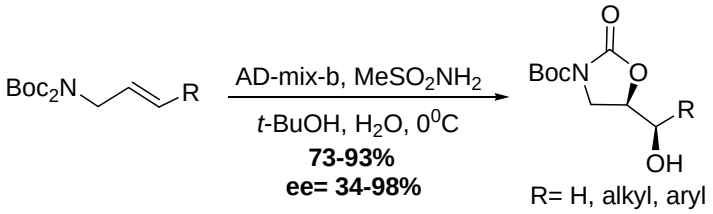


Scheme III.11

III.2.4. Additions to Double Bonds

Asymmetric Dihydroxylation

The asymmetric dihydroxylation (AD) of *N*-diBoc allylic amines (Scheme III.12), to give directly 5-substituted oxazolidin-2-ones, was first reported by Sharpless et *al*.[191]

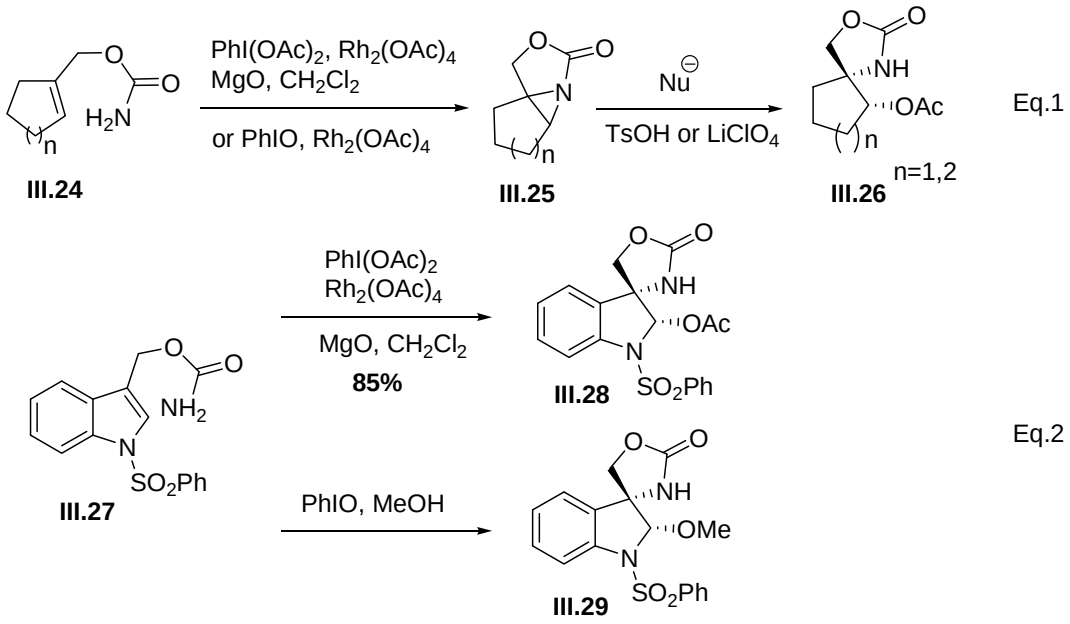


Scheme III.12

Acilnitrene Insertion

For example, the intramolecular Rh(II)-catalyzed aziridination of cycloalkenyl derivatives III.24 to generate tricyclic products III.25 (Scheme III.13, Eq. 1) has been reported by Padwa.[192] By contrast, the reaction of the protected 3-indolyl-carbamate III.27 provided the oxazolidin-2-one III.28 as a single diastereoisomer (Eq. 2).

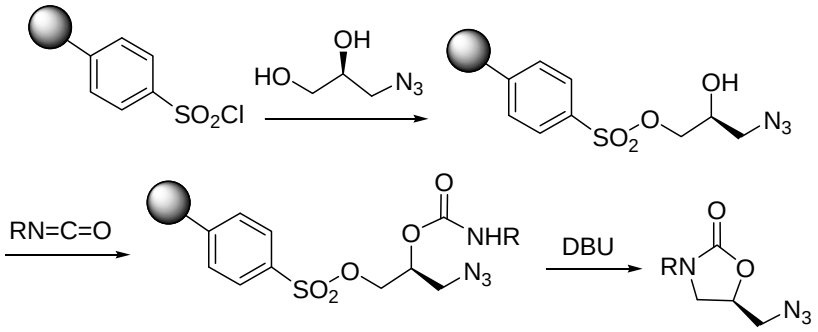
[191] Walsh, P. J.; Bennani, Y. L., Sharpless, K. B. *Tet. Lett.* **1993**, *34*, 5545
[192] a) Padwa, A.; Stengel, T. *Org. Lett.* **2002**, *4*, 2137; b) Padwa, A.; Flick, A. C.; Leverett, C.A.; Stengel, T. *J. Org. Chem.* **2004**, *69*, 6377



Scheme III.13

III.2.5. Solid Phase Preparation

The solid-phase organic synthesis (SOPS) of substituted 1,3-oxazolidin-2-ones was investigated by different research groups.
For example, Zwanenburg et *al.* disclosed the solid-phase synthesis of 3,5-disubstituted oxazolidin-2-ones by treatment of 1,2-diols with a polymer-supported sulphonyl chloride (Scheme III.14):[193]



Scheme III.14

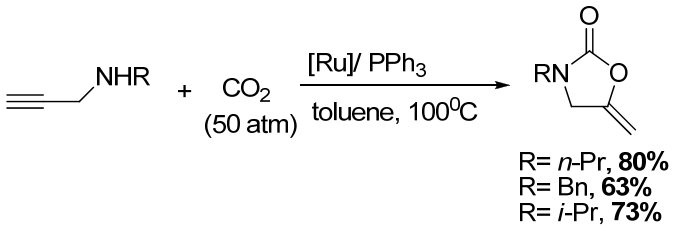
III.2.6. Specific Synthesis of 5-Methylene-oxazolidin-2-ones

[193] a) ten Holte, P.; van Esseveldt, B. C. J.; Thjis, L.; Zwanenburg, B. *Eur. J. Org. Chem.* **2001**, 965; b) ten Holte, P.; Thjis, L.; Zwanenburg, B. *Org. Lett.* **2001**, *3*, 1093

From Acetylenic Amines

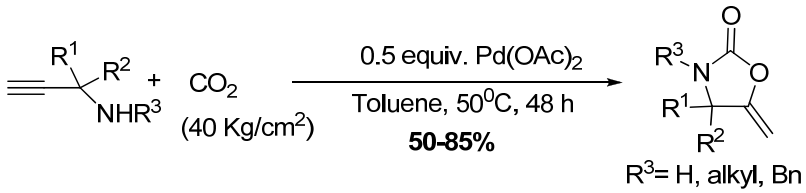
One of the most widely used synthetic method to access 5-methylene-oxazolidin-2-ones is starting from the corresponding acetylenic amine and a carbonyl source like CO_2 or CO.
For example, 5-methylene-1,3-oxazolidin-2-ones have been obtained starting from acetylenic amines and carbon dioxide in the presence of copper salts,[128] Ru catalysts,[194] Pd complexes,[198] tertiary phosphines[195,136] or of strong organic bases.[196] 5-Methylene-1,3-oxazolidin-2-ones have also been synthesized from acetylenic amines and a tetraalkylammonium carbonate or hydrogen carbonate.[197]

N-substituted propargylamines were found to react with CO_2 to give oxazolidinones in moderate yields in the presence of a (η^4-1,5-cyclooctadiene)(η^6-1,3,5-cyclooctatriene)ruthenium [Ru(COD)(COT)] catalyst and tertiary phosphine or in the presence of a base (Scheme III.15):[194]



Scheme III.15

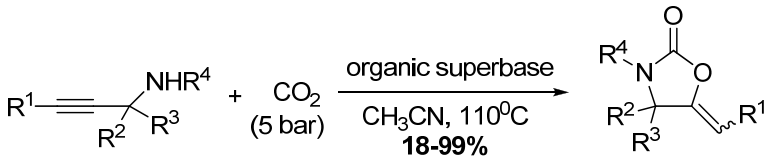
Shi et *al.* described the Pd(0)-catalyzed reaction of *N*-unsubstituted and *N*-substituted propargylamines with carbon dioxide. Pd(OAc) was found to be the best catalyst for the formation of oxazolidinones (Scheme III.16):[198]



Scheme III.16

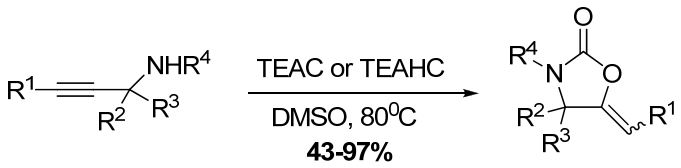
Costa et *al.* reported the use of superbases to catalyse the direct introduction of carbon dioxide into acetylenic amines under mild conditions to give methylene-oxazolidinones by 5-*exo-dig* ring closure (Scheme III.17):[196]

[194] Mitsudo, T.; Hori, Y.; Yamakawa, Y.; Watanabe, Y. *Tet. Lett.* **1987**, *28*, 4417
[195] Fournier, J.; Bruneau, C.; Dixneuf, P. H. *Tet. Lett.* **1990**, *31*, 1721
[196] a) Costa, M.; Chiusoli, G. P.; Rizzardi, M. *Chem. Commun.* **1996**, 1699 ; b) Costa, M.; Chiusoli, G. P.; Taffurelli, D.; Dalmonego, G. *J. Chem. Soc., Perkin Trans*. 1 **1998**, 1541
[197] Arcadi, A.; Inesi, A.; Marinelli, F.; Rossi, L.; Verdecchia, M. *Synlett* **2005**, 67
[198] Min Shi, M.; Shen, Y-M. *J. Org. Chem.* **2002**, *67*, 16



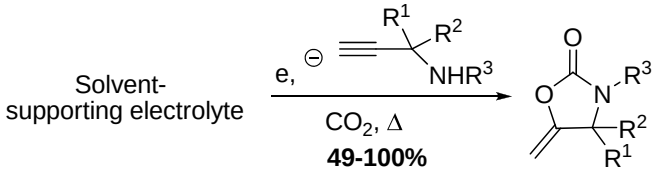
Scheme III.17

The reaction of acetylenic amines with electrochemically generated tetraethylammonium carbonate (TEAC) or chemically generated tetraethylammonium hydrogen carbonate (TEAHC) as carbonyl source was disclosed by Arcadi's group (Scheme III.18):[197]



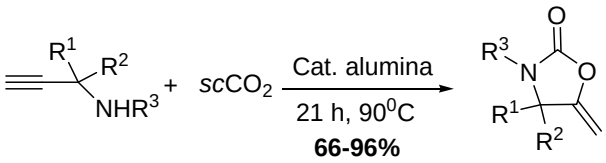
Scheme III.18

An efficient electrochemical synthesis of 5-methylene-1,3-oxazolidin-2-ones from acetylenic amines and carbon dioxide has been described by Inesi and co-workers by direct electrolysis of a solution of MeCN and Et_4NPF_6 containing the amine, with subsequent CO_2 bubbling and heating (Scheme III.19):[199]



Scheme III.19

The use of commercial basic alumina as an efficient catalyst for the reaction of propargylamines with CO_2 under supercritical conditions ($scCO_2$), was disclosed by Maggi's group (Scheme III.20):[200]

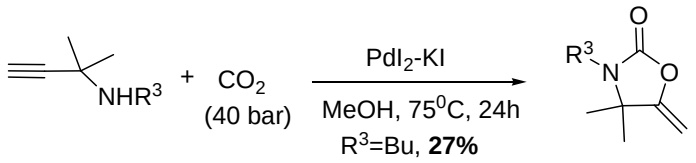


Scheme III.20

Salerno et *al.* reported the formation of disubstituted 5-methylene-oxazolidin-2-ones in 27% yield when carbon dioxide (40 bar) reacted with the acetylenic amine in MeOH in the

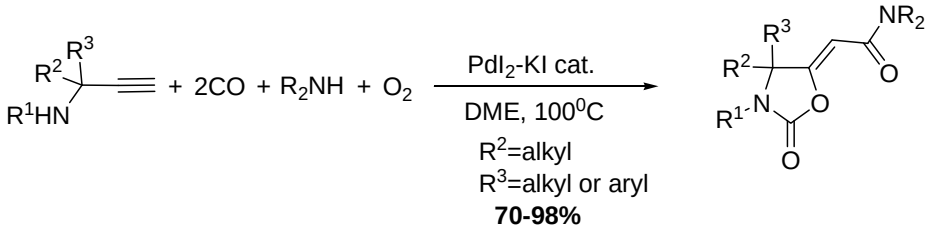
[199] Feroci, M.; Orsini, M.; Sotgiu, G.; Rossi, L.; Inesi, A. *J. Org. Chem.* **2005**, *70*, 7795
[200] Maggi, R.; Bertolotti, C.; Orlandini, E.; Oro, C.; Sartoria G.; Selvab, M. *Tet. Lett.* **2007**, *48*, 2131

presence of PdI_2 (100:1 molar ratio to the substrate) and KI (15:1 molar ratio to Pd) in the absence of carbon monoxide and oxygen at 75 °C for 24 h:[201]



Scheme III.21

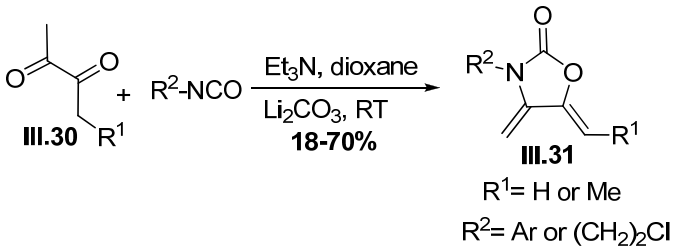
Later, a novel synthesis of 2-oxazolidinones was described, starting from readily available 2-ynylamines and dialkyl-amines through the concatenation of two catalytic cycles, both promoted by PdI_2, corresponding to oxidative aminocarbonylation of the triple bond followed by cyclocarbonylation (Scheme III.22):[202]



Scheme III.22

Synthesis from Propargylic Alcohols or Diketones

Tamariz et *al.* described a one-pot synthesis of the *N*-substituted 4,5-dimethylene 2-oxazolidinones III.31 from diacetyl derivative III.30 and the corresponding isocyanate (Scheme III.23):[203]

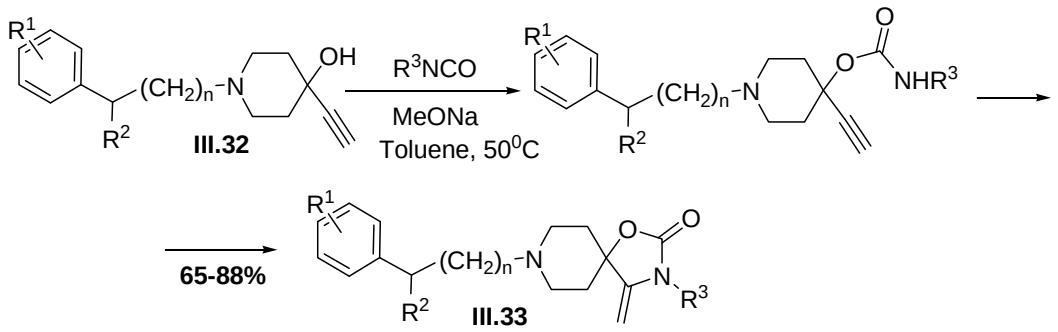


Scheme III.23

Kiss et *al.* synthesized a series of novel 1-oxa-3,8-diazaspiro[4.5]decan-2-one derivatives III.33 starting from 4-ethynyl-4-piperidinol III.32 and the appropriate isocyanates (Scheme III.24):[204]

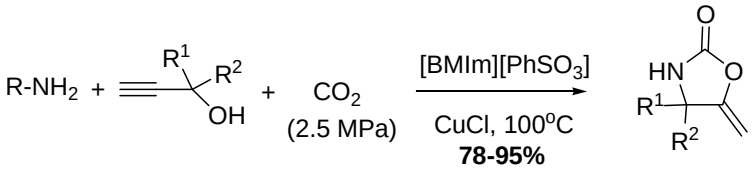
---

[201] Bacchi, A.; Chiusoli, G. P; Costa, M.; Gabriele, B.; Righib, C.; Salerno, G. *Chem. Commun.* **1997**, *13*, 1209
[202] Gabriele, B.; Plastina, P.; Giuseppe Salerno, Mancuso, R.; Costa, M. *Org. Lett.* **2007**, *9*, 3319
[203] Hernandez, R.; Sanchez, J. M.; Gomez, A.; Trujillo, G.; Aboytes, R.; Zepeda, G.; Bates, R. W.; Tamariz, J. *Heterocycles* **1993**, *36*, 1951



Scheme III.24

Deng et *al.* reported an efficient and environmentally benign method for the synthesis of *α*-methylene cyclic carbamates from CO_2 and propargyl alcohols and aliphatic primary amines catalyzed by CuCl in recyclable ionic liquids like 1-butyl-3-methylimidazolium benzene sulfonate ([BMIm][$PhSO_3$]) without any other co-catalysts and organic solvents (Scheme III.25). The copper catalyst immobilized in ionic liquids could be reused 3 times without losing activity. Unfortunately, this method seems to be limited to the use of tertiary propargylic alcohols.[205]



Scheme III.25

From 5-Methylene-1,3-dioxolan-2-one

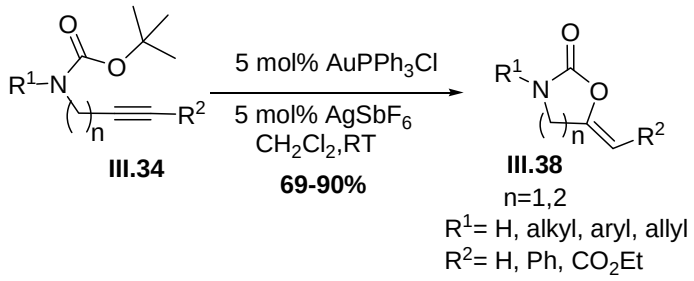
Alkylidene cyclic carbonates are useful intermediates for the easy access to *α*-methylene-oxazolidinones as discussed in Chapter II.

From *N*-Boc Propargylamines

During the preparation of our manuscript,[206] Carretero et *al.* published the conversion of *N*-Boc-protected alkynylamines III.34 into the corresponding alkylidene 2-oxazolidinones or 2-oxazinones III.38 in the presence of a cationic Au(I) complex (Scheme III.26).[207] A wide variety of substrates reacted in the presence of $Au(PPh_3)SbF_6$ in short reaction times and with complete *Z*-stereoselectivity regardless of the electronic character of the alkyne substitution. *N*-Unsubstituted oxazolidinones (R^1=H) and *N*-ferrocenyl carbamates can be prepared in

[204] Toth, E.; Kiss, B.; Gere, A.; Karpati, E.; Torley, J.; Palosi, E.; Kis-Varga, A.; Paroczai, M.; Szabo, S.; Groo, D.; Laszlovszky, I.; Lapis, E.; Csomor, K.; Szporny, L. *Eur. J. Med. Chem.* **1997**, *32*, 27
[205] Gu, Y.; Zhang, Q.; Duan, Z.; Zhang, J.; Zhang, S.; Deng, Y. *J. Org. Chem.* **2005**, *70*, 7376
[206] Buzas, A.; Gagosz, F. *Synlett* **2006**, 2727
[207] Robles-Machin, R.; Adrio, J.; Carretero, J. C. *J. Org. Chem.* **2006**, *71*, 5023

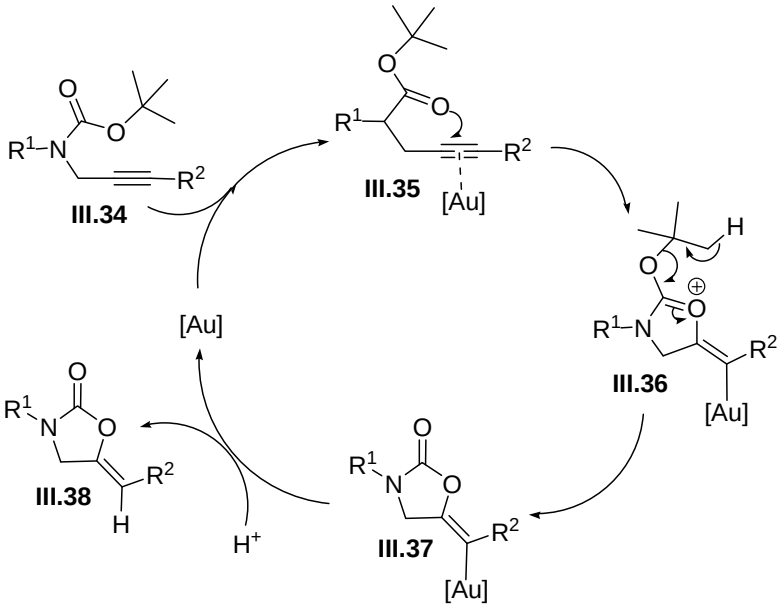
good yields by the cyclization of the Boc derivatives of primary propargylamines (Scheme III.26).



Scheme III.26

This procedure also tolerates the presence of functional groups at the nitrogen chain, such as silyl ethers or alcohols.

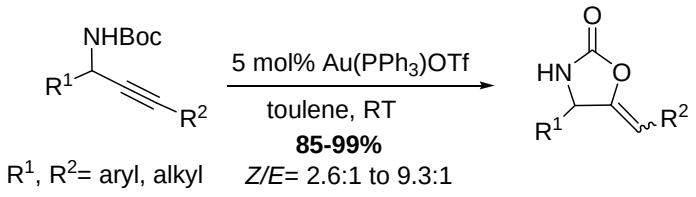
The mechanism suggested by the authors is illustrated in Scheme III.27. The nucleophilic attack of the carbamate carbonyl group on the activated Au(I)-alkyne complex III.35 affords the cationic vinyl-gold intermediate III.36. Subsequent *tert*-butyl fragmentation, by releasing isobutene and a proton, furnishes the oxazolidinone-Au complex III.37, which after protonation would provide the observed oxazolidinone III.38:



Scheme III.27

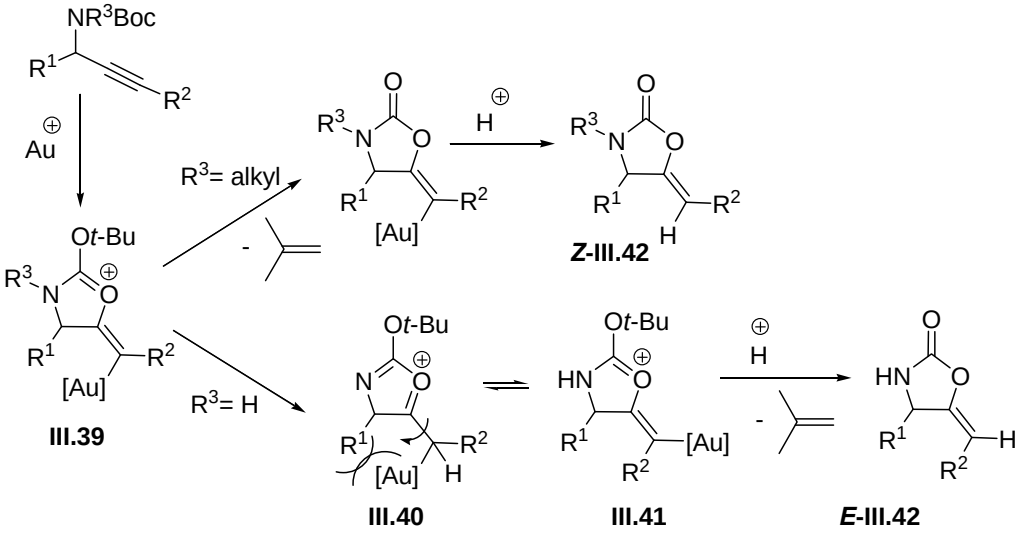
One year after the publication of our work,[206] Shin and co-workers published their own results on the gold-catalyzed cyclisation of *N*-Boc propargylamines into 4-alkylidene oxazolidin-2-ones.[208] This method allows the cyclisation of substrates with an internal acetylenic bond giving a mixture of geometric isomers of the expected oxazolidinone (Scheme III.28):

[208] Lee, E.-S.; Yeom, H.-S.; Hwang, J.-H.; Shin, S. *Eur. J. Org. Chem.* **2007**, 3503



Scheme III.28

A mechanistic pathway accounting for these observations was proposed by the authors (Scheme III.29). Apparently in the case of substrates without an *N*-substituent (R^3 = H), cationic vinyl–Au intermediate III.39 partly undergoes proton shift to form imine form III.40, which isomerizes into III.41 to relieve the allylic strain.

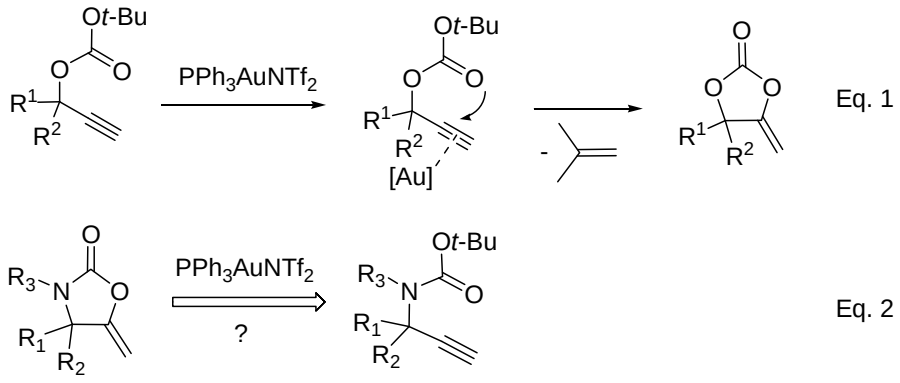


Scheme III.29

III.3. Preliminary Work in the Literature and First Experiments

As we seen in Chapter III.1, 5-methylene-1,3-oxazolidin-2-ones are useful substrates in organic synthesis. As resumed in Chapter III.2, a number of synthetic procedures have been developed, but regarding the availability and the economic viability, the most attractive method for the synthesis of 5-methylene-1,3-oxazolidin-2-ones remains the three-component reactions of propargylic alcohols, primary amines, and carbon dioxide, which are usually catalyzed by copper salts[128] or tributylphosphine.[136,195] However, most of the synthetic protocols for 5-methylene-1,3-oxazolidin-2-ones reported thus far suffer from harsh conditions (5.0 MPa of CO_2 pressure and 110-140°C), poor yields (38-72%), prolonged time periods (20 h), and use of hazardous and often expensive catalysts. Moreover, the reactions have been usually carried out in polar solvents such as acetonitrile, DMF, and DMSO, leading to complex isolation and recovery procedures. These processes also generate waste-containing solvent and catalyst, which have to be recovered, treated, and disposed of. This leads to the conclusion that the development of practical and efficient routes to synthesize functionalized oxazolidinones under mild and "environment friendly" conditions remains of high interest.

Following our recent results in using the air stable crystalline PPh_3AuNTf_2 catalyst[100] for the rearrangement of propargylic *tert*-butyl carbonates into 4-alkylidene-1,3-dioxolones (see Chapter II and Scheme III.30, Eq. 1),[106] we surmised that analogous *tert*-butyl carbamates might have the same reactivity and would afford the corresponding 5-methylene-oxazolidin-2-ones (Scheme III.30, Eq. 2).



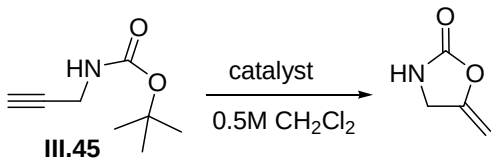
Scheme III.30

In this case, the catalytic process would allow an easy and efficient access to a variety of oxazolidinones bearing an interesting *exo* methylene bond that could be used for the elaboration of more functionalized structures.

During the preparation of this manuscript, Carretero and co-workers reported that such a transformation could be achieved by the combined use of 5 mol% of Ph_3AuCl and 5 mol% of $AgSbF_6$ (Scheme III.26).[207] This work is restricted to the synthesis of oxazolidinones substituted at the nitrogen and alkyne terminus. Our approach would permit the efficient synthesis of a variety of 5-methylene-oxazolidin-2-ones substituted either on the nitrogen atom or at the α-position relative to the triple bond.

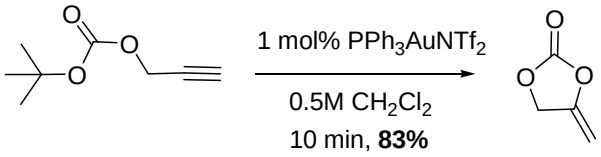
To test our assumption outlined in Scheme III.30, Eq. 2, we selected the simple *N*Boc-protected propargylamine III.45 as the model substrate.

We were pleased to notice that substrate III.45 afforded the desired oxazolidinone when reacted with 1 mol% of PPh_3AuNTf_2 in dichloromethane, albeit in only 37% yield after one hour. A longer reaction time (24 h) did not significantly improve the yield (38%). The yields were similar in the cases when the reaction mixture was refluxed (55%) or when the catalyst loading was increased to 3 mol% (44%). The results obtained in these cases are in contradiction with those obtained in the rearrangement of *tert*-butyl carbonates, where the desired dioxolanone was obtained in 83% yield after only 10 min of reaction (Scheme III.30, Eq. 2).



Eq. 1

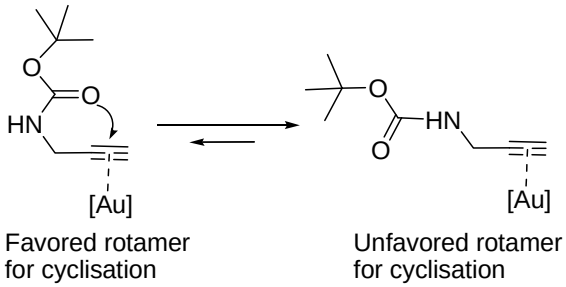
Entry	Catalyst	Conditions	Time	Yield
1	1 mol% Ph_3AuNTf_2	RT	1h	**37%**
2	1 mol% Ph_3AuNTf_2	RT	24h	**38%**
3	1 mol% Ph_3AuNTf_2	reflux	2h	**55%**
4	3 mol % $Ph_3PAuNTf_2$	RT	72h	**44%**



Eq. 2

Table III.1

The observed constrast between the reactivity of carbonates and carbamates might be due to the existence of an equilibrium between the two possible rotamers of *tert*-butylcarbamate III.45, thus disfavoring the formation of the intermediate cyclizing conformer (Scheme III.31):

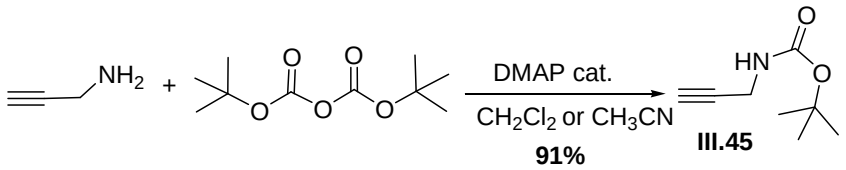


Scheme III.31

Thus reducing the population of the unfavored rotamer, this problem was overcome by simply substituting the nitrogen atom, for example with a benzyl group. Gratifyingly, the corresponding oxazolidinone III.44a was obtained in 98% yield when substrate III.43a was treated with 1% of the catalyst (Table III.3, Entry 1).
With the optimized reaction conditions in hand, we wanted to examine the scope of this gold-catalyzed rearrangement. To this end, various propargylic *tert*-butylcarbamates were synthesized.

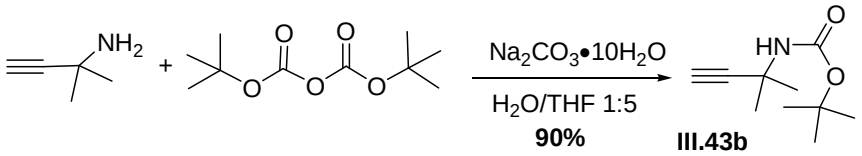
III.4. Synthesis of the Precursors

Simple propargylic *tert*-butylcarbamates were generally synthesized from the corresponding propargylic amines and di-*tert*-butyl dicarbonate in dichloromethane or acetonitrile in presence of catalytic quantities of DMAP following the general methods described in the literature (Scheme III.32):[209]



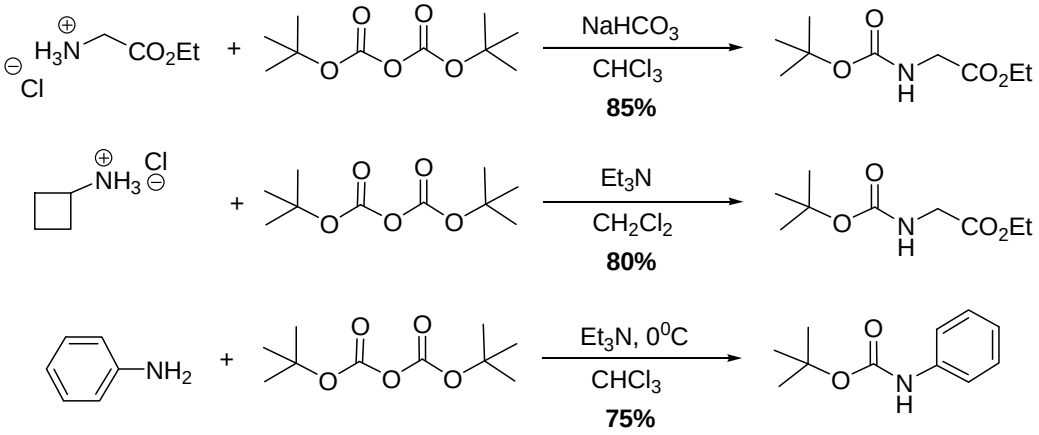
Scheme III.32

The disubstituted propargylic *tert*-butylcarbamate III.43b was prepared according to the method described by Avenoza:[210]



Scheme III.33

The less nucleophilic amines like aniline[211] ot the amino acid hydrochlorides[212] were reacted with di-*tert*-butyl dicarbonate in the presence of a base (Scheme III.34):

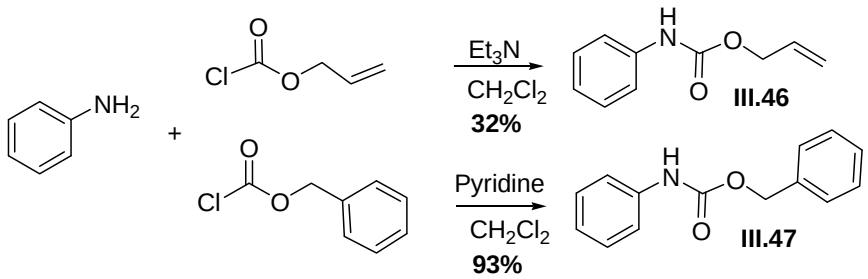


Scheme III.34

The allylcarbamate III.46 and the benzylcarbamate III.47 were prepared by similar manner (Scheme III.35):[213]

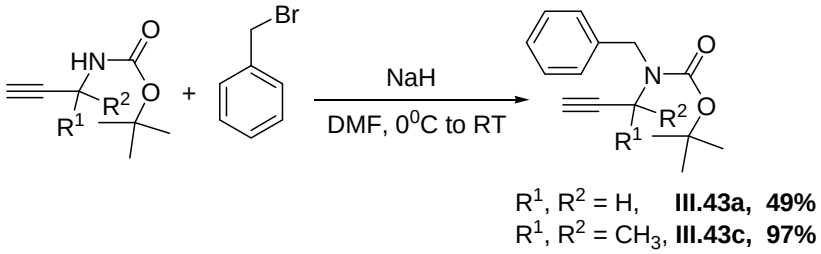
---

[209] a) Denton, T. T.; Zhang, X.; Cashman, J. R. *J. Med. Chem.* **2005**, *48*, 224; b) Parker, K. A.; Coburn, C. A. *J. Org. Chem.* **1992**, *57*, 5547
[210] Avenoza, A.; Cativiela, C.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Tet.: Asymm.* **1999**, *10*, 4653
[211] Xiong, Y.; Moore, H. W. *J. Org. Chem.* **1996**, *61*, 9168
[212] Hayashida, O.; Sebo, L.; Rebek Jr., J. *J. Org. Chem.* **2002**, *67*, 8291
[213] Chong, P. Y.; Janicki, S. Z.; Petillo, P. A. *J. Org. Chem.* **1998**, *63*, 8515



Scheme III.35

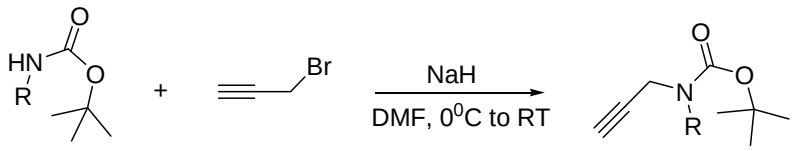
The tertiary *N*-benzyl substituted amines III.43a-III.43c were obtained by the method reported by Boger et *al.* (Scheme III.36):[214]



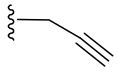
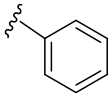
Scheme III.36

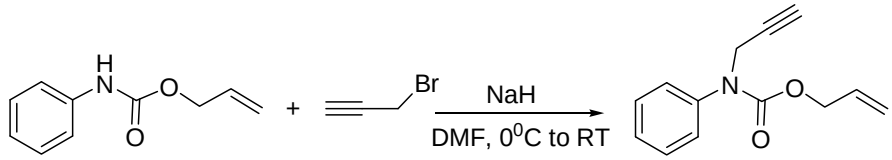
A similar synthetic method was used to substitute *O*-*tert*-butyl (Eq. 1), *O*-allyl (Eq.2) and *O*-benzyl (Eq. 3) carbamates with propargyl bromide (Scheme III.37):[215]

[214] Boger, D. L.; Christine M. Tarby, C. M.; Peter L. Myers, P. L.; Caporale, L. H. *J. Am. Chem. Soc.* **1996**, *118*, 2109
[215] Metcalf, B. W.; Casara, P. *J. Chem. Soc. Chem. Commun.* **1979**, 119



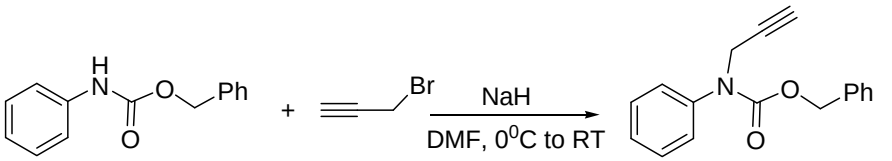
Eq. 1

R	Compound	Yield
	**III.43g**	**97%**
	III.43f	**27%**
	III.43e	**56%**
	**III.43d**	**93%**



III.46 **III.48**

Eq. 2

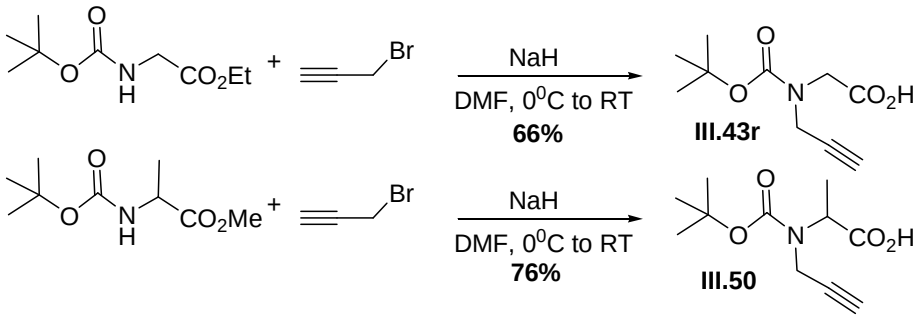


III.47 **III.49**

Eq. 3

Scheme III.37

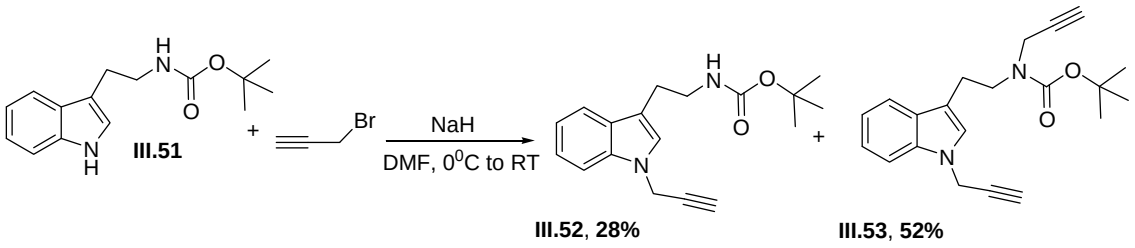
Unfortunately, the amino ester derivatives were hydrolyzed when subjected to these conditions (Scheme III.38):



III.43r **III.50**

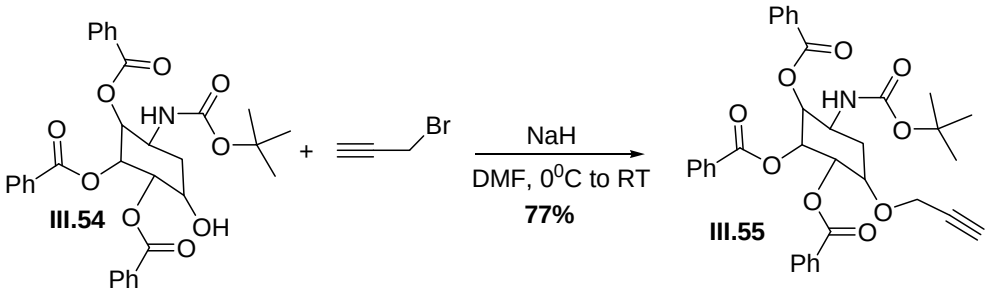
Scheme III.38

Tryptamine derivative III.51 was also propargylated at the indolic position:



Scheme III.39

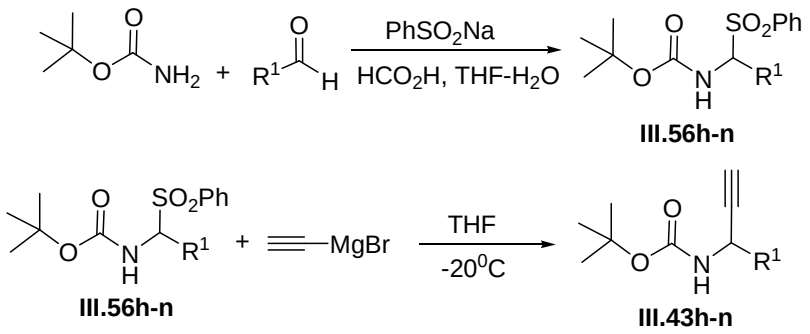
Inositol derivative III.54 was propargylated only at the undesired position on the oxygen giving compound III.55. The desired *N*-propragylated derivative was not obtained, even in the presence of 2 equivalents of base and 2 equivalents of propargyl bromide (Scheme III.40):



Scheme III.40

The substrates substituted at the propargylic position were synthesized according to the method developed by Petrini and co-workers.[216] *α*-Amidoalkyl sulfones III.56 (easily prepared by reaction of a carbamate with a suitable aldehyde and sodium benzenesulfinate, in the presence of formic acid, Table III.2) can be utilized as *N*-acyl imine equivalents. *α*-Amidoalkyl sulfones III.56 are known to react with stabilized carbanions, giving a product that arises from a formal substitution of the phenylsulfonyl anion with the nucleophile used. Ethynylmagnesium bromide is able to react with these at -20 °C in THF affording in good yields the corresponding *N*-protected propargylamines III.43h-n (Table III.2):

[216] Mecozzi, T.; Petrini, M. *J. Org. Chem.* **1999**, *64*, 8970



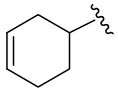
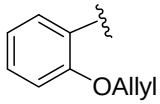
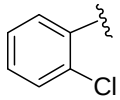
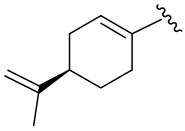
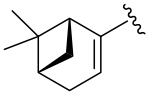
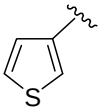
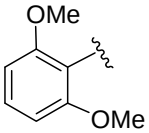
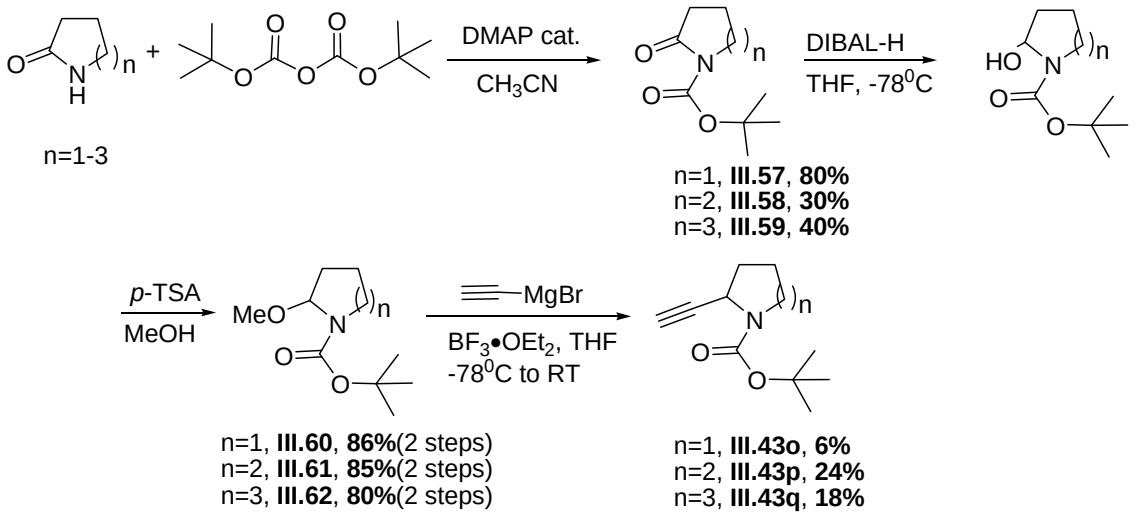
R^1	Compound	Yield
	**III.43h**	**92%**
	**III.43m**	**28%**
	**III.43k**	**74%**
	**III.43i**	**42%**
	**III.43j**	**18%**
	**III.43n**	**18%**
	**III.43l**	**12%**

Table III.2

Cyclic precursors III.43o-q were prepared starting from the commercially available lactames. Protection of these lactams with di-*tert*-butyl dicarbonate (Boc_2O) in the presence of DMAP, followed by reduction of *N*-Boc-lactams with diisobutylaluminium hydride (DIBALH) in THF and etherification in methanol in the presence of *p*-TSA afforded the corresponding aminols.[217] These methoxylactams afforded the corresponding propargyl carbamates when subjected to ethynylmagnesium bromide in presence of a Lewis acid[218] (Scheme III.41):

[217] Hara, O.; Sugimoto, K.; Kazuis; Makino, K.; Hamada, Y. *Synlett* **2004**, 1625
[218] Karstens, W. F. J.; Klomp, D.; Rutjes, F. P. J.; Hiemstra, H. *Tetratehron* **2001**, *57*, 5123



Scheme III.41

III.5. Cyclization by Gold

The various propargylic *tert*-butylcarbamates thus prepared were subjected to the optimized reaction conditions (1 mol% of PPh_3AuNTf_2 in dichloromethane at room temperature). Gratifyingly, as illustrated in Table III.3, the reaction proved to be quite general and the substrates were converted into the corresponding 5-methylene-oxazolidin-2-ones III.44a-q with generally high yields, ranging from 70% to 99%.

As an alternative to the substitution at the nitrogen, substitution of the propargylic position by two methyl groups induced a Thorpe-Ingold effect which led to the rapid and nearly quantitative formation of the corresponding oxazolidinone III.44b (Table III.3, Entry 2). Oxazolidinone III.44c (isolated in 99% yield) was formed in 5 minutes (Table III.3, Entry 3), showing the syncron action of the two effects, nitrogen atom substitution and propargylic substitution.

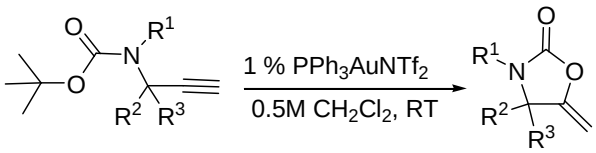
The reaction occurred even when the nitrogen atom was substituted with a phenyl group, as in the case of substrate III.43d, affording α-methylene-oxazolidinone III.44d in 95 % yield (Entry 4). Various alkyl substituents were tolerated on the nitrogen atom of the substrates, such as acid-sensitive cyclobutyl or cyclopropyl rings (Table III.3, Entries 1, 3, 5-7). The rearrangement proved to be regioselective since diyne derivative III.43g exclusively afforded III.44g, without formation of the 6-membered cyclic carbamate resulting from a 6-*exo* cyclization[208] (Entry 7).

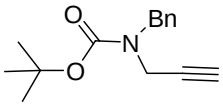
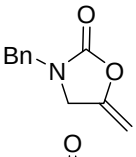
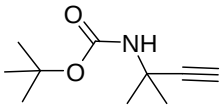
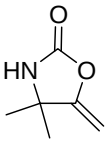
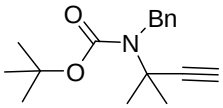
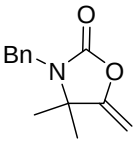
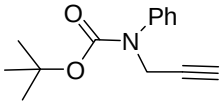
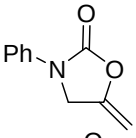
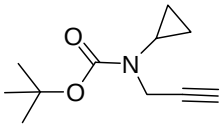
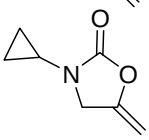
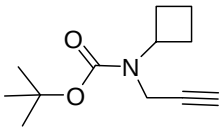
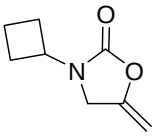
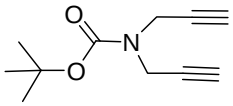
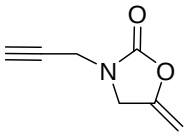
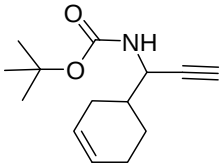
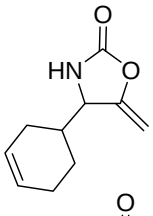
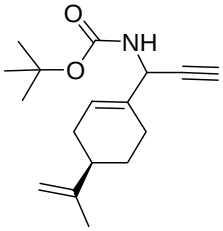
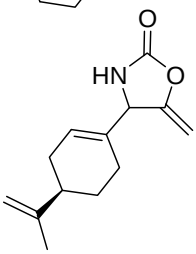
Secondary propargylic carbamates III.43h-m reacted equally, but in these cases the reaction times needed for completion were longer (Table III.3, Entries 8-13).

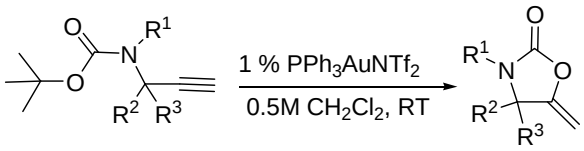
Substrates possessing alkyl groups at the propargylic position such as the cyclohexyl, perillyl or pinenyl derivatives III.43h-j were rearranged providing the corresponding oxazolidinones in high yields (Table III.3, Entries 8-10). The mildness of the reaction conditions employed prevented epimerization or degradation of the substrates. Indeed, acid sensitive substrates III.43h-j were smoothly converted into the corresponding oxazolidinones III.44h-j with the same diastereoisomeric ratio as the precursors (Table III.3, Entris 8-10).

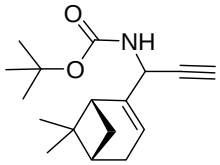
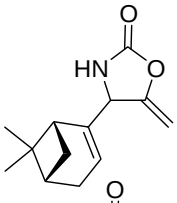
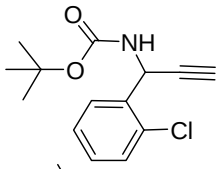
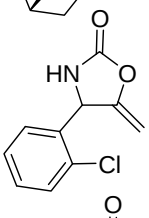
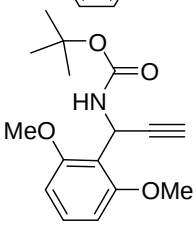
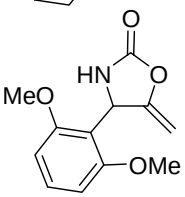
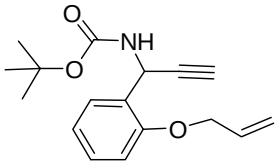
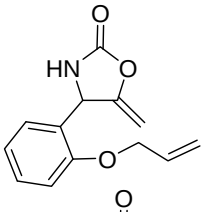
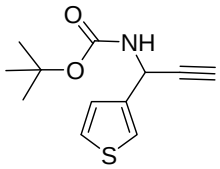
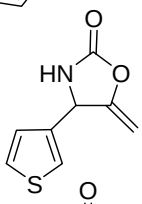
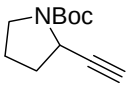
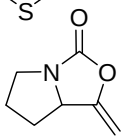
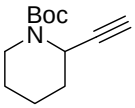
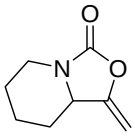
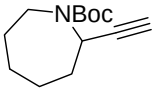
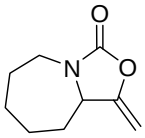
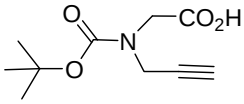
It is interesting to note that the propargylic position could also be substituted with aryl groups possessing electron withdrawing groups (Entry 11) or electron donating groups (Entries 12-13).

The thiophene derivative III.43n reacted normally giving the corresponding oxazolidinone III.44n which, in contrast, decomposed when purified on silica gel (Entry 14).
It was also possible to synthesize the valuable bicyclic oxazolidinones III.44o-q derived from pyrrolidine, piperidine or azepine rings with yields ranging from 65% to 99% (Table III.3, Entries 15-17).
In contrast, no evolution at all was observed in case of the amino acid derivative III.43r, likely as a result of the competitive coordination of the electrophilic gold atom to the basic carboxylic oxygen (Entry 18). It is also worth mentioning that allyl and benzyl derivatives III.48 and III.49 (Scheme III.37) were recovered mainly unchanged when these substrates were subjected to the optimized reaction conditions.



Entry	Substrate		Product		Time	Yield[a]
1		**III.43a**		**III.44a**	30 min	**98%**
2		**III.43b**		**III.44b**	30 min	**99%**
3		**III.43c**		**III.44c**	5 min	**99%**
4		**III.43d**		**III.44d**	5 min	**95%**
5		**III.43e**		**III.44e**	1h	**97%**
6		**III.43f**		**III.44f**	1.5h	**99%**
7		**III.43g**		**III.44g**	10 min	**100%**
8		**III.43h** dr= 1:1[b]		**III.44h**	20 h	**82%** dr= 1:1[b]
9		**III.43i** dr= 1:1[b]		**III.44i**	16h	**91%** dr= 1:1[b]

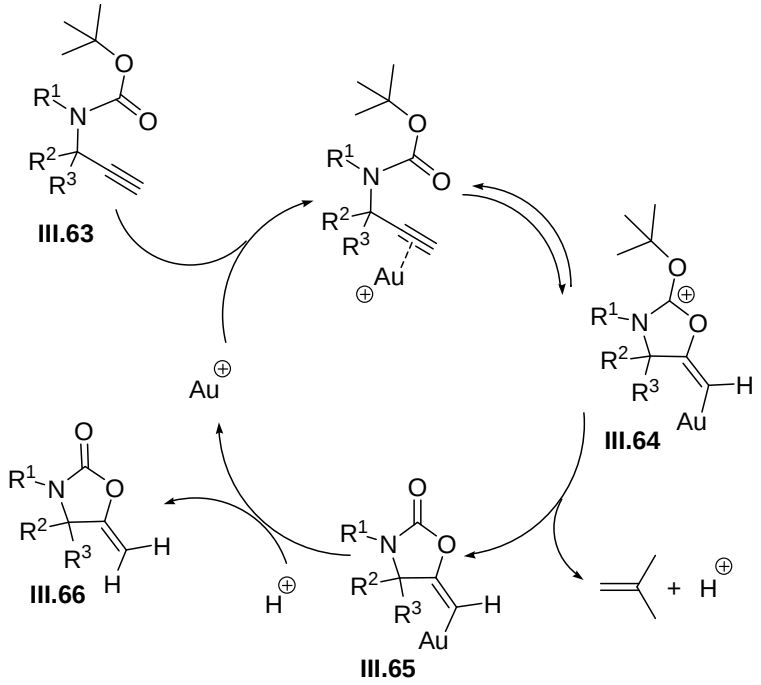


Entry	Substrate		Product		Time	Yield[a]
10		**III.43j** dr= 1:4.8[b]		**III.44j**	6h	**96%** dr= 1:4.8[b]
11		**III.43k**		**III.44k**	2h	**83%**
12		**III.43l**		**III.44l**	4h	**70%**
13		**III.43m**		**III.44m**	20h	**86%**
14		**III.43n**		**III.44n**	18h	**Degradation on silica**
15		**III.43o**		**III.44o**	3.5h	**74%**
16		**III.43p**		**III.44p**	1h	**65%**
17		**III.43q**		**III.44q**	5 min	**99%**
18		**III.43r**	—	—	—	—

[a] isolated yields; [b] ratios determined by ^{1}H-NMR

Table III.3

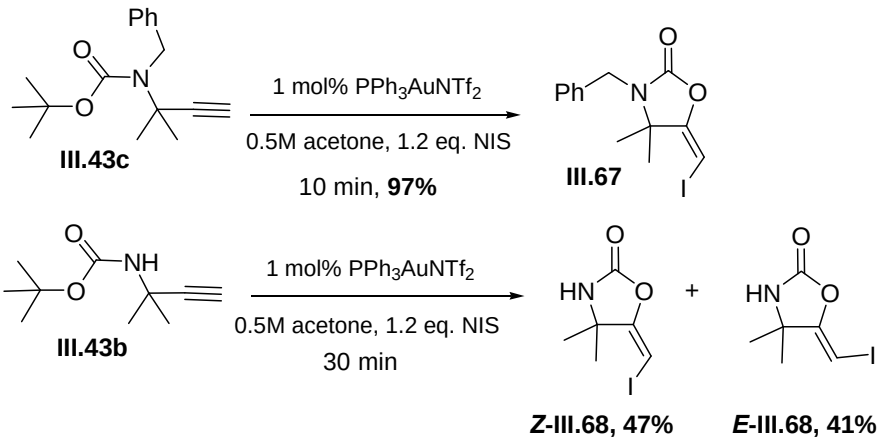
A mechanistic manifold accounting for the experimental results is proposed in Scheme III.42. This mechanism is similar to that previously described for the rearrangement of propargylic *tert*-butyl carbonates with formation of 4-alkylidene-1,3-dioxolones (see Chapter II). Gold(I) promoted activation of the triple bond in propargylic *tert*-butyl carbamate III.63 and subsequent nucleophilic attack of the carbonyl group leads to the formation of the stabilized cationic species III.64. The neutral vinyl-gold species III.65 is formed by fragmentation of the C-O bond of the *tert*-butyloxy group in III.64 and then is protodemetallated to finally afford 5-methylene-oxazolidin-2-one III.66 with the concomitant regeneration of the gold(I) catalyst (Scheme III.42):



Scheme III.42

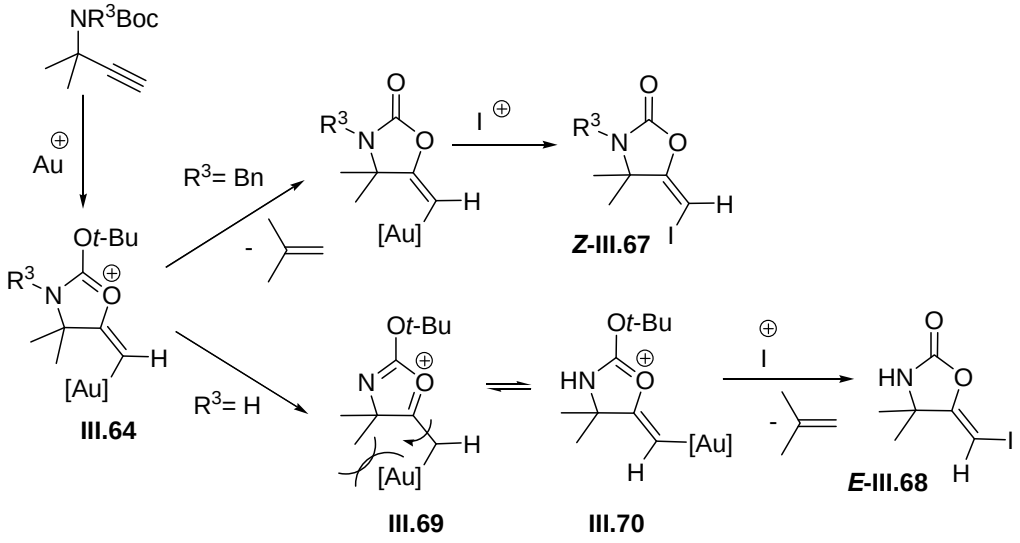
III.6. Transformation of the Adducts

As previously shown for the reaction of propargylic *tert*-butyl carbonates (see Chapter II), we also envisioned the possibility of trapping the intermediate vinyl-gold species III.65 by a source of electrophilic iodine prior to protodemetallation. To this end, carbamate III.43c possessing two methyl groups at the propargylic position was reacted with a light excess of *N*-iodosuccinimide in the presence of 1 mol% of the gold(I) catalyst. This transformation afforded a 1:1 mixture of *Z* and *E*-vinyliodides III.67 (Scheme III.43, Eq. 1). In the case of the *N*-substituted precursor III.43b, the rearrangement was rapid and stereoselective leading to the valuable *Z*-vinyliodide III.68 after only 10 minutes (Scheme III.43, Eq. 2).



Scheme III.43

These observations are in accord with the results obtained later by Shin and co-workers (Scheme III.29):[208] in the case of substrates without an *N*-substituent, cationic vinyl–Au intermediate III.64 partly undergoes proton shift to form the imine form III.69, which isomerizes into III.70 to relieve the allylic strain. This mechanism outlined in Scheme III.44 could explain the formation of the *E*-isomer, along with the expected *Z*-isomer in the case of the *N*-unsubstituted precursor III43b:



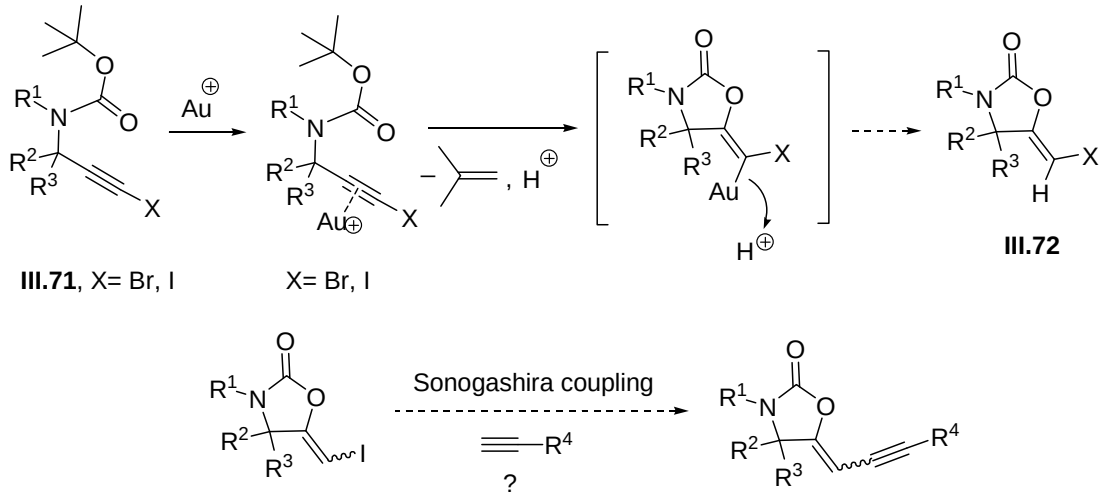
Scheme III.44

III.7. Conclusion and Perspectives

In summary, we have developed an efficient gold(I) catalyzed cyclization / fragmentation process for the synthesis of functionalized 5-methylene-oxazolidin-2-ones from readily available propargylic *tert*-butyl carbamates.

As in the case of *α*-methylene-dioxolanones (see Chapter II), propargylated haloalkynes of type III.71 could be feasible substrates for the synthesis of haloalkenes III.72 (Scheme

III.45). It is important to note that this procedure would allow the *stereoselective* formation of *Z*-haloalkenes, if the reaction occurs as in the case of terminal alkynes. The development of this method would allow the synthesis of the *Z*-isomer, in contrast to the use of a source of electrophilic iodine which exclusively affords the opposite *E*-isomers (see Scheme III.43). Vinyl bromides and iodides obtained this way could be further functionalized, notably by transition metal-catalyzed cross coupling reactions.



Scheme III.45

IV. Synthesis of Functionalized Oxazolones by a Sequence of Cu(II)- and Au(I)-Catalyzed Transformations

This work was done in collaboration with Florin-Marian Istrate, Igor Dias Jurberg and Yann Obadachian and made the object of a publication.[219]

IV.1. Introduction

Oxazolones and their derivatives are interesting heterocyclic compounds that have been used occasionally in organic synthesis. Keeping in mind that the oxazolone moiety incorporates dense functionality that finds great synthetic utility, their derivatives represent attractive building blocks in organic synthesis. This feature has indeed been exploited by additions to the olefinic function of oxazolones, by [4+2] cycloadditions and by catalytic hydrogenations of oxazolones.[220] They also have been sucessfully employed in a range of transformations like intramolecular Pauson-Khand reactions, palladium-catalyzed coupling reactions,[221] radical additions or cyclizations.[222] Oxazolone derivatives serve as intermediates in the synthesis of amino alcohols,[223] as potential protecting groups for vicinal amino alcohols,[224] and as precursors for the synthesis of cyclobutane derivatives.[225] The oxazolone motif is also found in a variety of synthetic substances exhibiting a wide range of pharmacological activities, which will be mentioned along the synthetic methods to access them. (For some examples of biologically active or naturally occurring compounds containing the oxazolidinone moiety, see Chapter III.1).

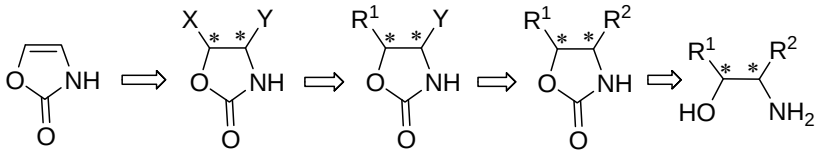
IV.2. Uses of Oxazolones

IV.2.1. Oxazolones as Building Blocks for *vic*-Amino Alcohol Structures. Radical Additions and Cyclizations Involving Oxazolones

Vicinal amino alcohol functions are structural units contained in a substantial number of bioactive compounds as well as in chiral sources which are widely used for asymmetric synthesis.[226] The oxazolone ring can be considered as a synthon for 2-amino alcohols, since the ring can be cleaved easily under mild conditions at the two heteroatoms.
For example, the synthetic strategy developed by Kunieda and co-workers offers versatile routes to a wide variety of *vic*-amino alcohols. The key step is the functionalization of the

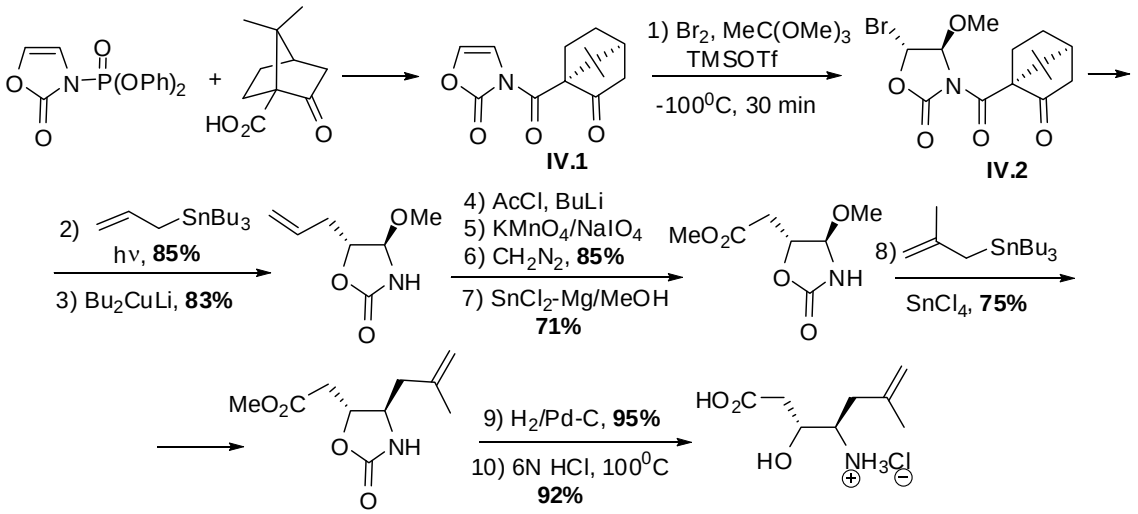
[219] Buzas, A.; Istrate, F.; Dias Jurberg, I.; Odabachian, Y.; Gagosz, F. *Org. Lett*. **2008**, *10*, 925
[220] a) Singh, B. U.S. Patent 4,150,030, 1979; *Chem Abstr.* **1979**, *91*, 74598b, b) Shono,T.; Matsumura, Y.; Kanazawa, T. *Tet. Lett.* **1983**, *24*, 4577; c) Yonezawa, Y.; Shin, C.; Ohtsu, A.; Yoshimura, J. *Chem. Lett.* **1982**, 1171
[221] Choshi, T.; Fujimoto, H.; Sugino, E.; Hibino, S. *Heterocycles* **1996**, *43*, 1847
[222] a) Butora, G.; Hudlicky, T.; Fearnley, S. P.; Gum, A. G.; Stabile, M. R.; Abboud, K. *Tetrahedron Lett.* **1996**; *37*, 8155; b) Butora, G.; Hudlicky, T.; Fearnley, S. P.; Stabile, M. R.; Gum, A. G.; Gonzales, D. *Synthesis* **1998**, 665
[223] Katz, S. J.; Bergmeier, S. C. *Tet. Lett.* **2002**, *43*, 557 and references cited therein
[224] Ishizuka, T.; Kunieda, T. *Tet. Lett.* **1987**, *28*, 4185
[225] Scholz, K. H.; Heine, H. G.; Hartmann, W. *Tet. Lett.* **1978**, 1467
[226] Ager D. J.; Prakash I.; Schaad D. R. *Chem. Rev.* **199**6, *96*, 835

olefinic moiety of the 2-oxazolone ring by regio- and stereodefined introductions of easily replaceable groups (bromo and methoxy), followed by stereospecific and stepwise substitutions with appropriate groups (R^1 and R^2):[227]



Scheme IV.1

The (4*R*, 5*R*)-5-bromo-4-methoxyadduct IV.2, obtained as a major isomer in optically pure form by single recrystallization of the products arising from (+)-3-ketopinyl-2-oxazolone IV.1, was successfully utilized as common synthon for the synthesis of some *vic*-amino alcohols of biological interest (Scheme IV.2):

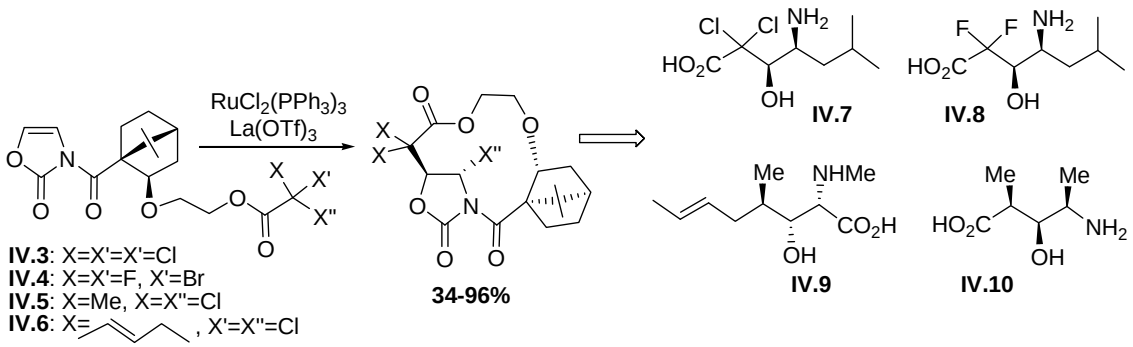


Scheme IV.2

The intramolecular $RuCl_2$-catalyzed radical addition of α-chloroacyl pendant groups as in compounds IV.3-6 to the 2-oxazolone skeleton proceeds with perfect regio- and diastereo-selectivity to give 12-membered macrolide derivatives, which, in turn, represent good precursors for the versatile synthesis of chiral 2-amino alcohols.[228] This methodology was successfully applied to the synthesis of 2,2-dichloro IV.7 and 2,2-difluorostatine derivatives IV.8 and the unusual amino hydroxy acids IV.9 and IV.10 with three contiguous chiral centers, key components of cyclosporins and bleomycins (Scheme IV.3):

[227] a) Kunieda, T.; Ishizuka, T.; Higuchi, T.; Hirobe, M. *J. Org. Chem.* **1988**, *53*, 3381; b) Matsunaga, H.; Ishizuka, T.; Kunieda, T. *Tetrahedron* **1997**, *53*, 1275

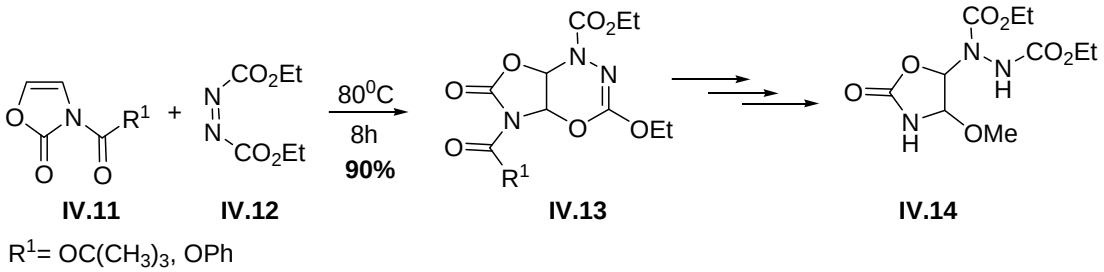
[228] Hoshimoto, S.; Matsunaga, H.; Wada, M.; Kunieda, T. *Chem. Pharm. Bull.* **2002**, *50*, 435



Scheme IV.3

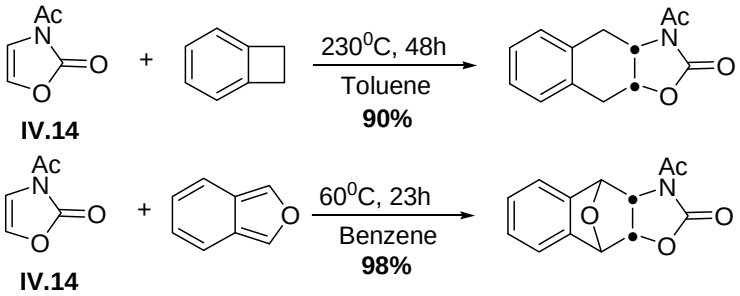
IV.2.2. [4+2] Reactions Involving Oxazolones

Kunieda et *al.* disclosed the synthetic potential of synthons accessible from chiral *N*-acyl-2-oxazolones such as IV.11 and azodicarboxylates IV.12 which serve as α-aminoaldehyde templates, for the synthesis of a wide variety of optically active α-amino acids as well as 4-alkyl and 4-aryl-2-oxazolidinones (Scheme IV.4):[227b]



Scheme IV.4

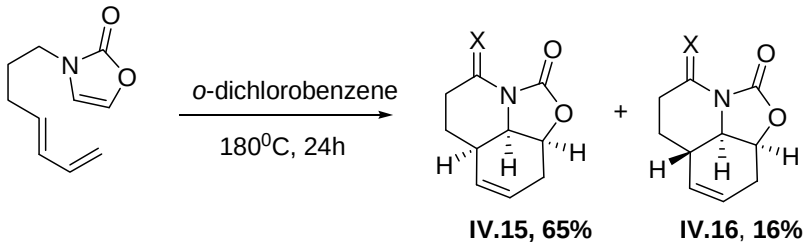
N-acetyl-oxazolin-2-one derivative IV.14 have been shown to undergo Diels-Alder cycloadditions with substrates such as isobenzofuran and *o*-quinodimethane, although high temperatures (60-230^{0}C) and long reaction time were often required (Scheme IV.5):[229]



Scheme IV.5

[229] D'Andrea, S. V.; Freeman, J. P.; Szmuszkovicz, J. *J. Org. Chem.* **1990**, *55*, 4356

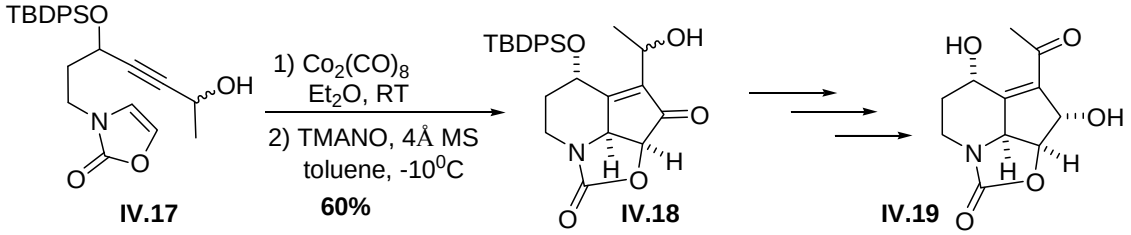
An example of intramolecular Diels-Alder reaction featuring an *N*-substituted oxazolone as the dienophile was reported by Fearnley and Market (Scheme IV.6):[230]



Scheme IV.6

IV.2.3. Pauson-Khand Reactions Involving Oxazolones

Mukai and Nomura developed a novel and efficient procedure for constructing 7-hydroxy-6-substituted-9-oxa-1-azatricyclo-[6.2.1.0^{5,11}]undec-5-en-7,10-dione IV.18 by the intramolecular Pauson-Khand reaction of 2-oxazolone species IV.17 with the proper alkyne appendages. Based on this newly developed Pauson-Khand reaction of 2-oxazolone-alkyne derivatives, the first total synthesis of (±)-8*α*-hydroxystreptazolone IV.19 was accomplished in a highly stereoselective manner (Scheme IV.7):[231]



Scheme IV.7

IV.3. Synthesis of Substituted Oxazolones

Surprisingly, despite their great synthetic utility, there are only a few methods to synthesize polysubstituted oxazolones. Most use 1,2-aminoketone derivatives as starting materials and involve either high temperature,[232] strong basic[233] or acidic conditions,[234] or toxic carbonylating reagents which are not always compatible with the substitution pattern of the substrates.

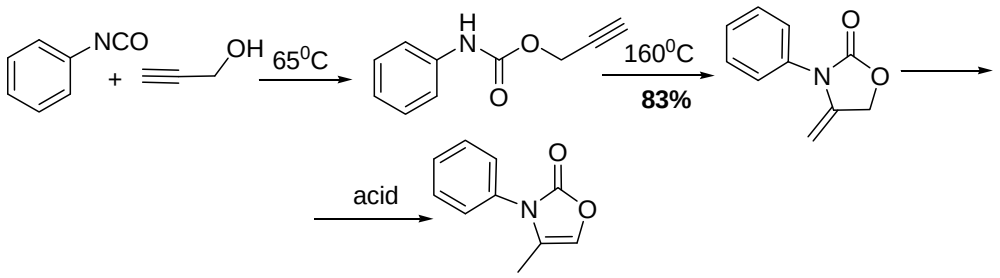
Some selected synthetic methods for the preparation of substituted 4-oxazolin-2-ones by condensation reactions, using carbonylating reagents or by electrochemical methods will de shortly presented in the next chapter.

---

[230] Fearnley, S. P.; Market, E. *Chem. Comm.* **2002**, 438
[231] a) Nomura, I.; Mukai, C. *J. Org. Chem.* **2004**, *69*, 1803; b) Nomura, I.; Mukai, C. *Org. Lett.* **2002**, *4*, 4301
[232] Krieg, B.; Lautenschlaeger, H. *Justus Liebigs Ann. Chem.* **1976**, 788
[233] Lenz, G. R.; Costanza, C. *J. Org. Chem.* **1988**, *53*, 1176
[234] Aichaoui, H.; Poupaert, J. H.; Lesieur, D.; Henichart, J.-P. *Tetrahedron* **1991**, *47*, 6649

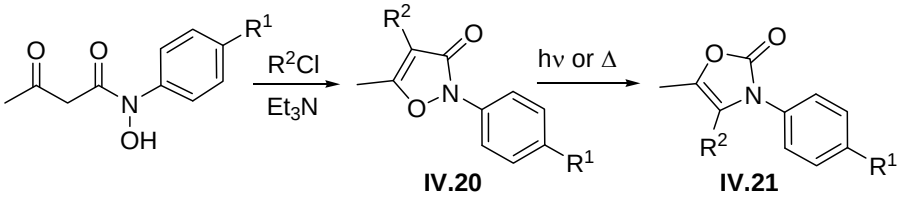
IV.3.1. Synthesis of Oxazolones by Condensation Reactions

4-Oxazolin-2-ones have been widely studied[235] since Maselli reported the first synthesis in 1905 by condensation of fenacilaniline with chloroethers.[236]
McCombie and co-workers reported the synthesis of 4-oxazolin-2-ones from α-aminoketones and ethyl chloroformate.[237]
Stoffel and Dixon showed that 4-methylene-2-oxazolidinone, prepared by heating propargyl alcohol with phenyl isocyanate (see also Chapter III), undergoes facile isomerization to 4-methyl-4-oxazolin-2-one in strongly acidic conditions (Scheme IV.8):[238]



Scheme IV.8

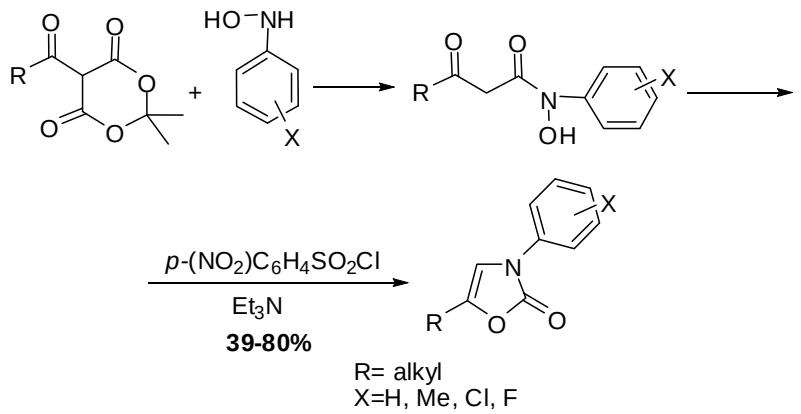
4-Oxazolin-2-ones IV.21 have been synthesized by thermal[239] or photolytic[240] rearrangement of the corresponding 4-isoxalin-3-ones IV.20 (Scheme IV.9):



Scheme IV.9

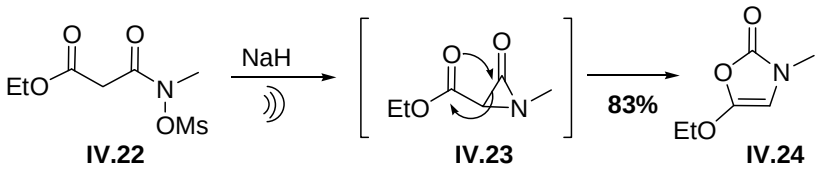
Sato et *al.* described the reaction of (*N*-aryl-*N*-hydroxy)acylacetamides (obtained from acylated Meldrum's acids) with *p*-nitrobenzensulphonylchloride in the presence of triethylamine. The corresponding 4-oxazolin-2-ones were obtained with yields ranging from 39% to 80% (Scheme IV.10):

[235] Hartner, Jr., F. W. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, U.K., **1996**, *3*, 306
[236] Maselli, C. *Gazz. Chim. Ital.* **1905**, *35*, 86
[237] McCombie, H.; Parkes, J. W. *J. Chem. Soc.* **1912**, 1991
[238] Stoffel, P. J.; Dixon, W. D. *J. Org. Chem.* **1964**, *29*, 978
[239] Gagneux, A. R.; Goschke, R. *Tet. Lett.* **1966**, 5451
[240] Nakagawa, M.; Nakamura, T.; Tomita, K. *Agric. Biol. Chem.* **1974**, *38*, 2205



Scheme IV.10

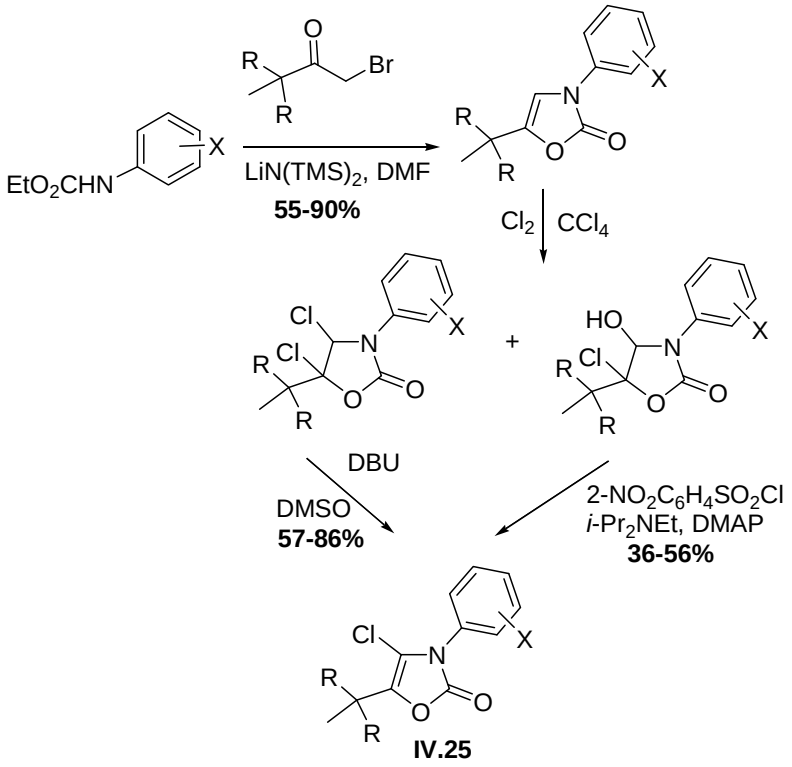
The same approach was used by Hoffman's group to obtain oxazolone IV.24 by ultrasonication, most likely by a vinylcyclopropane-like rearrangement of the intermediate *α*-lactam IV.23 (Scheme IV.11):[241]



Scheme IV.11

An efficient synthetic method for the preparation of 4-oxazolin-2-ones substituted with bulky groups was devised by Kudo's group (Scheme IV.12). These novel 3-aryl-5-*tert*-butyl-4-chloro-4-oxazolin-2-ones IV.25 were found to show significant herbicidal activity in the grams per are range against broadleaf and narrowleaf weeds.[242]

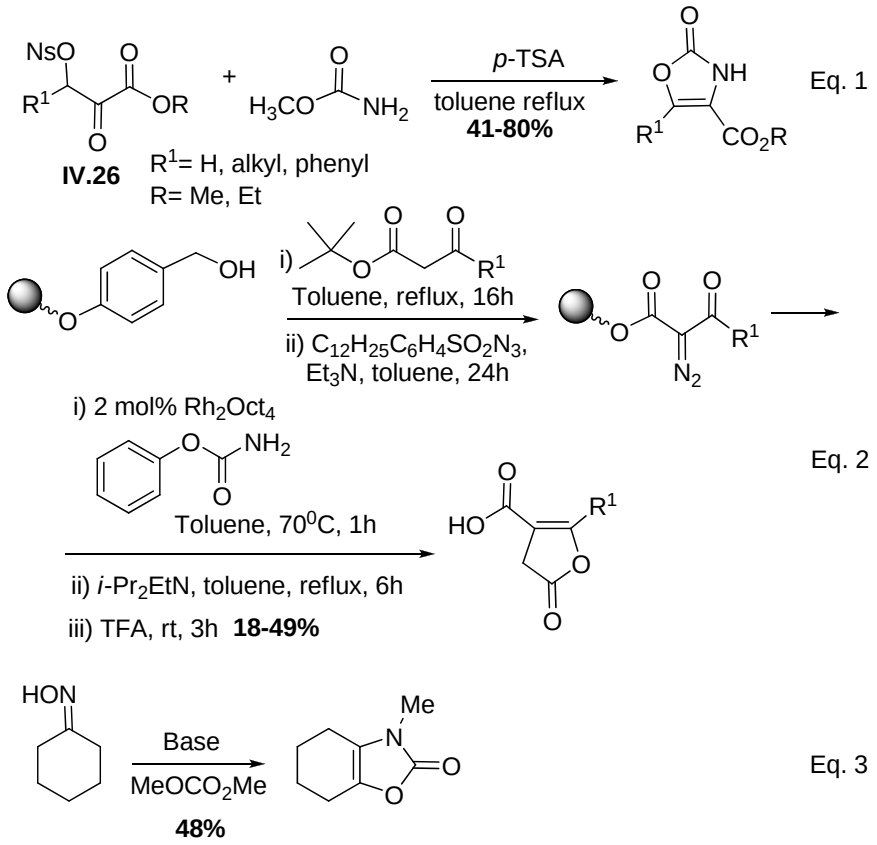
[241] Hoffman, R. V.; Reddy, M. M.; Cervantes-Lee, F. *J. Org. Chem.* **2000**, *65*, 2591
[242] a) Kudo, N.; Taniguchi, M.; Sato, K. *Chem. Pharm. Bull.* **1996**, *44*, 699; b) Kudo, N.; Taniguchi, M.; Furuta, S.; Sato, K.; Endo, T.; Toyokuni Honma, T. *J. Agric. Food Chem.* **1998**, *46*, 5305



Scheme IV.12

Other syntheses providing an efficient access to substituted 4-oxazolin-2-ones, for example the reaction of 3-nosyloxy-2-ketoesters IV.26 with methyl carbamate under acidic conditions (Scheme IV.13, Eq. 1),[243] solid-phase synthesis of oxazolones *via* Wang resin-bound diazocarbonyls (Eq. 2)[244] or reaction of ketone oximes with dimethyl carbonate (Eq. 3)[245] are summarized in Scheme IV.13:

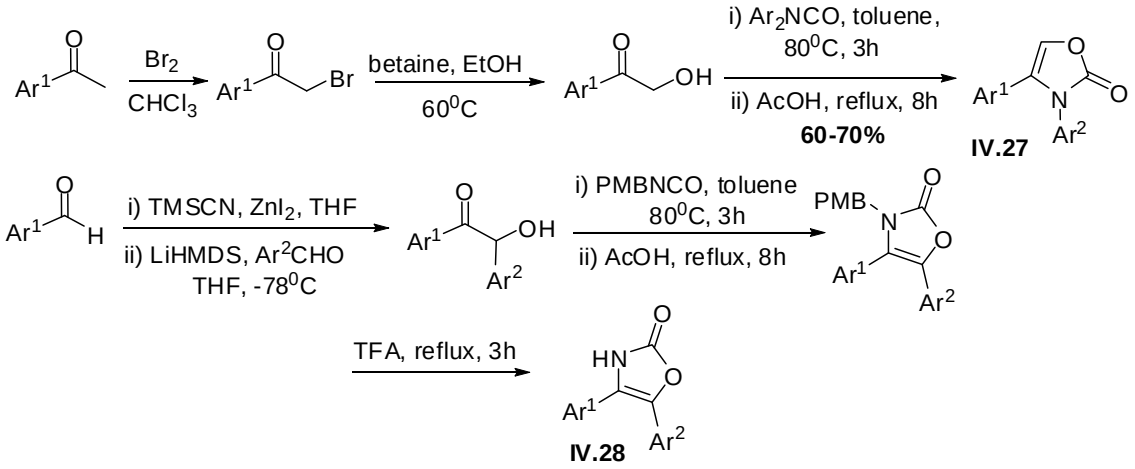
[243] a) Hoffman, R. V.; Johnson, M. C.; Okonya, J. F. *Tet. Lett.* **1998**, *39*, 1283; b) Okonya, J. F.; Hoffman, R. V.; Johnson, M. C. *J. Org. Chem.* **2002**, *67*, 1102
[244] Yamashita, M.; Lee, S.-H.; Koch, G.; Zimmermann, J.; Clapham, B.; Janda, K. D. *Tet. Lett.* **2005**, *46*, 5495
[245] Marques, C. A.; Selva, M.; Tundo, P.; Montanari, F. *J. Org. Chem.* **1993**, *58*, 5765



Scheme IV.13

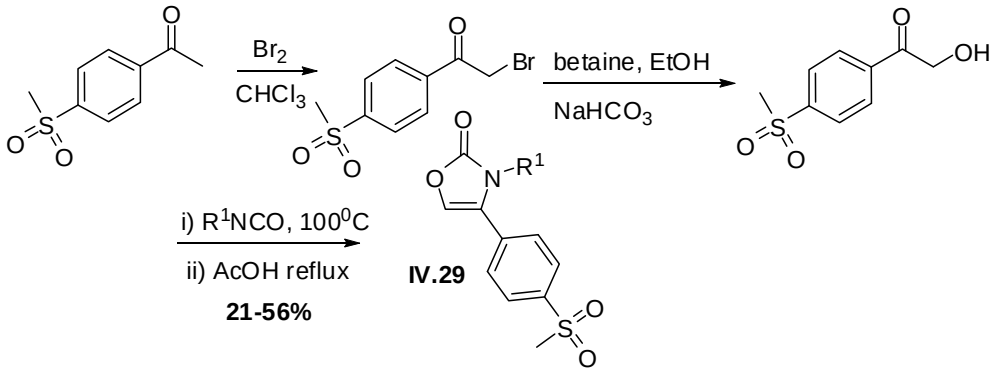
The synthesis and evaluation of the cytotoxic activity of two series of *cis*-restricted five-membered heterocyclic analogues of combretastatin A-4, hereafter given the trivial names of combretoxazolones, was reported by Ahn and colleagues.[246] These series including 3,4-diaryloxazolones IV.27 and 4,5-diaryloxazolones IV.28 were synthesized as outlined in Scheme IV.14 and both series showed strong cytotoxicities against a variety of tumor cell lines.

[246] Nam, N.-H.; Kim, Y.; You, Y.-J.; Hong, D.-H.; Kim, H.-M.; Ahn, B.-Z. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 3073



Scheme IV.14

Crespo et *al.* used a similar method for the synthesis of a new class of nonsteroidal antiinflammatory drugs (NSAIDs), the 3,4-diaryloxazolones of type IV.29,[247] a family of orally active, potent, and selective COX-2 inhibitors (COX-2 is the isoform of cyclooxygenase 1,[248] COX-1, the enzyme that catalyzes the conversion of arachidonic acid into prostaglandins and thromboxane involved in inflammatory processes).

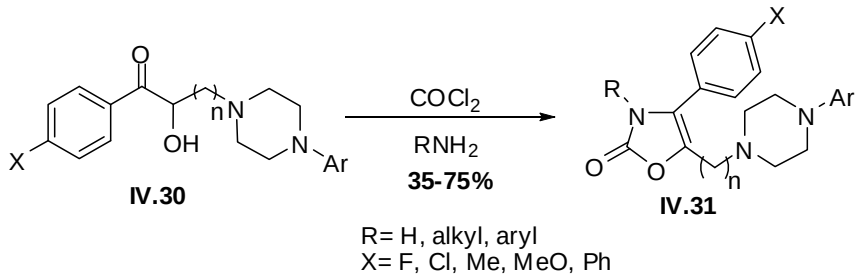


Scheme IV.15

IV.3.2. Synthesis of Oxazolones Involving Carbonylating Agents

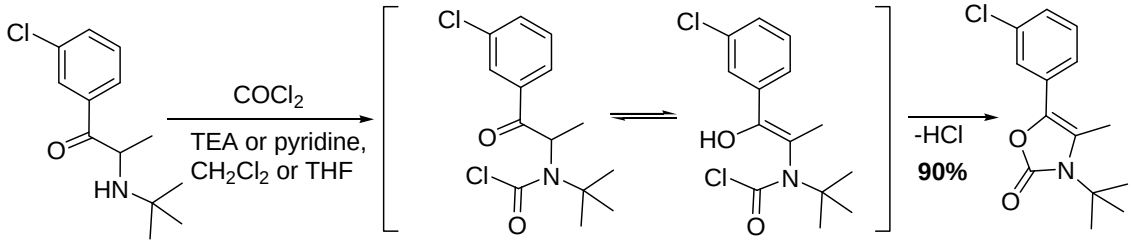
A series of new 4-aryl-5-[*ω*-(4-aryl-l-piperazinyl)alkyl]-2(3*H*)-oxazolones IV.31 were synthesized from the corresponding ketols IV.30 with phosgene and ammonia by Cascio et *al.* (Scheme IV.16):[249]

[247] Puig, C.; Crespo, M. I.; Godessart, N.; Feixas, J.; Ibarzo, J.; Jimenez, J.-M.; Soca, L.; Cardelus, I.; Heredia, A.; Miraplex, M.; Puig, J. *J. Med. Chem.* **2000**, *43*, 214
[248] Dubois, R. N.; Abramson, S. B.; Crofford, L.; Gupta, R. A.; Simon, L. S.; Van de Putte L. B. A.; Lipsky, P. E. *FASEB J.* **1998**, *12*, 1063
[249] Cascio, G.; Manghisi, E.; Fregnan, G. *J. Med. Chem.* **1989**, *32*, 2241



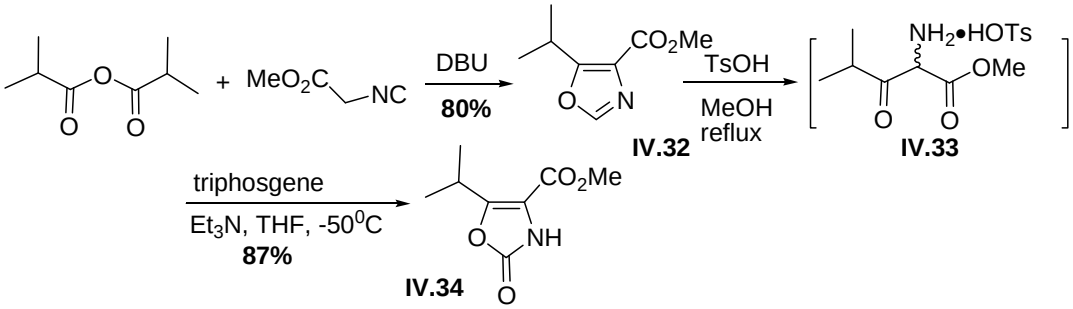
Scheme IV.16

Crooks and co-workers used a similar approach starting from aminoketones (Scheme IV.17):[250]



Scheme IV.17

Acid-catalyzed cleavage of oxazole IV.32 with *p*-toluenesulfonic acid gave the *β*-keto-*α*-amino acid ester IV.33 in quantitative yield, which, in turn, was transformed into the oxazolone IV.34 by reaction with triphosgene in the presence of triethylamine (Scheme IV.18):[251]



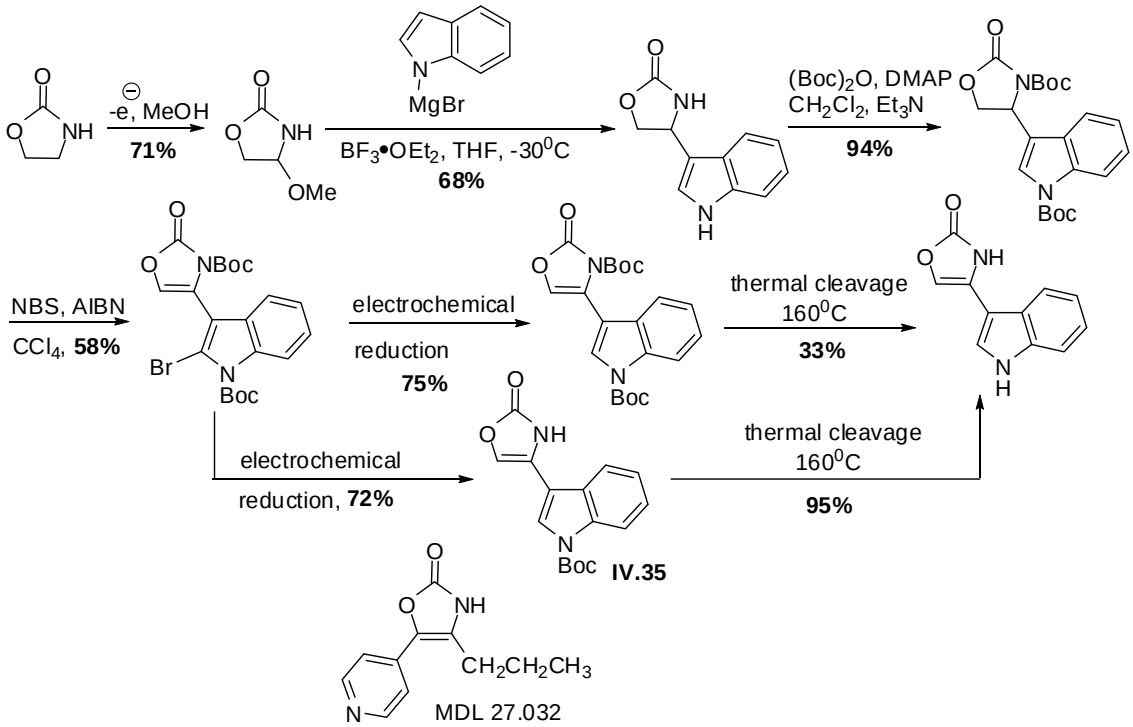
Scheme IV.18

IV.3.3.Synthesis of Oxazolones by Electrochemical Methods

In the course of their search for new protein kinase C (PKC)[252] inhibitors, structurally related to MDL 27.0324 (Scheme IV.19), Prudhomme's group investigated the syntheses and

[250] Hamad, M. O.; Kiptoo, P. K.; Stinchcomb, A. L.; Crooks, P. *Bioorg. Med. Chem.* **2006**, *14*, 7051
[251] Makino, K.; Okamoto, N.; Hara, O.; Hamada, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 1757
[252] Protein kinase C (PKC) belongs to a group of serine/threonine-specific protein kinases which plays an important role in cell surface signal transduction and controls a wide number of physiological processes among which are gene expression, cell proliferation and muscle contraction, see Nishizuka, Y., *Science*, **1986**, *233*, 305

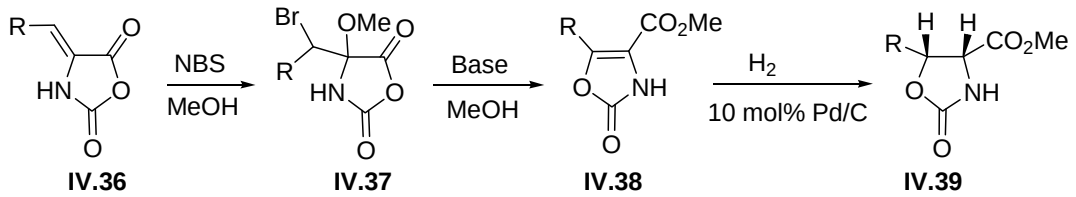
biological activities of new heterocyclic compounds possessing a five-membered ring system that includes a carbamate function. Oxazolone derivative IV.35 was synthesized from commercially available oxazolidin-2-one *via* elecrochemical processes as outlined in Scheme IV.19. This compound strongly inhibited the growth and sporulation of different *Streptomyces* species but it wasn't active as PKC inhibitor.[253]



Scheme IV.19

IV.3.4. Miscellaneous Synthetic Methods of Oxazolones

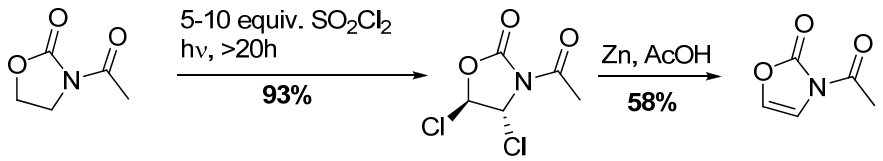
Shin and co-workers described the synthesis of 2-oxazolinone-4-carboxylates IV.38 by addition of methanol to *N*-carboxy-*α*-dehydroamino acid anhydride IV.36 in the presence of NBS, followed by the treatment of the resulting intermediary IV.37 with a base (Scheme IV.20):[220c]



Scheme IV.20

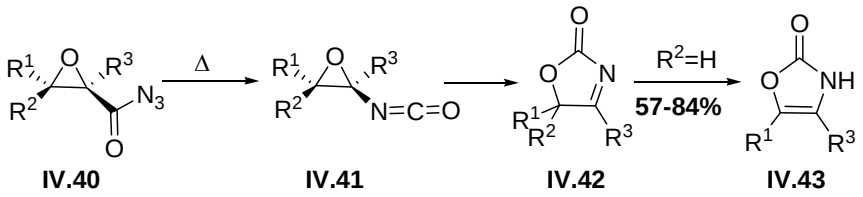
[253] a) Rodrigues Pereira, E.; Sancelme, M.; Towa, J. J.; Prudhomme, M.; Martre, A. M.; Mousset, G.; Rapp, M., J. Antibiotics 1996, 49, 380; b) Rodrigues Pereira, E.; Spessel, V.; Prudhomme, M. *Tet. Lett.* **1995**, *36*, 2749; c) Pereira, E. R.; Sancelme, M.; Voldoire, A.; Prudhomme, M. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2503

Catalytic hydrogenation in methanol at room temperature for 20 h gave the expected 5-methyl-oxazolidione-4-carboxylate IV.39.
Smith and Gaenzler have shown that sulfuryl chloride is an efficient reagent for the conversion of 2-oxazolidinone into the dichloro derivative, *N*-acetyl-4,5-dichloro-2-oxazolidinone. Subsequent Zn/AcOH reductive dehalogenation of this *trans*-dichloride gives *N*-acetyl-2-oxazolone (Scheme IV.21). This route avoids the use of chlorine gas, and is more amenable to smaller scale chlorination reactions where the use of chlorine gas is problematic.[254]



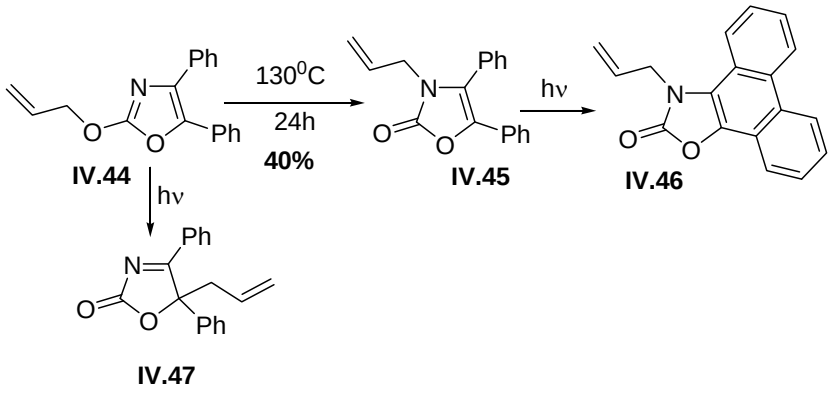
Scheme IV.21

Zwanenburg et *al.* showed that azides IV.40 undergo a smooth thermal Curtius rearrangement to give 3-oxazolin-2-ones IV.42 that tautomerize to the 4-isomers IV.43 (Scheme IV.22):[255]



Scheme IV.22

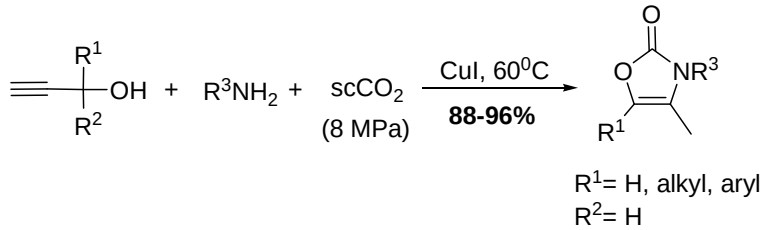
2-Allyloxy-substituted 4,5-diphenyloxazoles IV.44 undergo a facile *aza*-Claisen rearrangement to give 3-allyl-substituted 4,5-diphenyl-4-oxazolin-2-ones IV.46 (Scheme IV.23):[256]



Scheme IV.23

[254] Corbo Gaenzler, F.; Smith, M. B. *Synlett* **200**7, *8*, 1299
[255] Lemmens, J. M.; Blommerde, W. J. M.; Thijs, L.; Zwanenburg, B. *J. Org. Chem.* **1984**, *49*, 2231
[256] Padwa, A.; Cohen, L. A. *J. Org. Chem.* **1984**, *49*, 399

Very recently, Jiang and co-workers reported the synthesis of 4-methyloxazol-2-ones by cycloaddition reactions of carbon dioxide with propargylic alcohols and amines under supercritical conditions (Scheme IV.24):[257]



Scheme IV.24

IV.4. Preliminary Work in the Literature. Our Synthetic Approach

As illustrated in Chapter IV.3, there are only a few synthetic methods leading to substituted oxazolones. Most of these methods use 1,2-aminoketone derivatives, toxic carbonylating reagents or strong acidic or basic conditions not always suitable for the synthesis of highly functionalized oxazolones.

Various oxygen- and nitrogen-containing heterocycles[258] were synthesized by gold catalyzed intramolecular addition of nucleophiles onto multiple bonds (see also Chapters II and III). In this respect, a special attention has been paid to the *tert*-butyloxycarbonyl group which was used as the nucleophilic partner in the gold-catalyzed formation of butenolides,[259] dioxanones,[260] dioxolanones (see Chapter II)[106, 261] and oxazolidinones (see Chapter III and Scheme IV.25, Eq. 1).[206]

By analogy with our work on the synthesis of heterocycles catalyzed by gold (I) complexes (Scheme IV.25, Eq. 1),[106, 206] we hypothesized that it would be possible to rearrange a suitably substituted carbamate IV.48 in a 5-*endo* manner in order to obtain oxazolones such as IV.49 (Scheme IV.26):

---

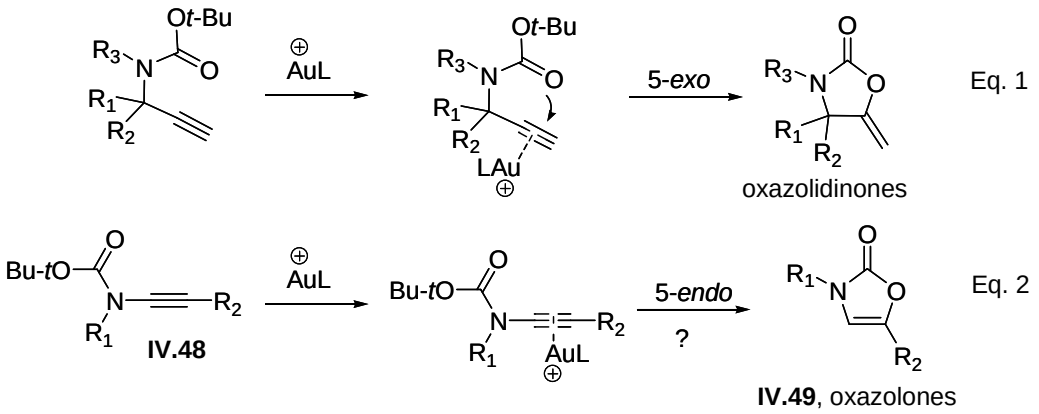
[257] Jiang, H.; Zhao, J.; Wang, A. *Synthesis* **2008**, 763

[258] For selected examples, see: *furans*: a) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem. Int. Ed.* **2000**, *39*, 2285; b) Yao, T.; Zhang, X.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 7679; c) Hashmi, A. S. K.; Sinha, P. *Adv. Synth. Catal.* **2004**, *346*, 432; d) Liu, Y.; Song, F.; Song, Z.; Liu, M.; Yan, B. *Org. Lett.* **2005**, *7*, 5409; *oxazoles and oxazolines*: f) Hashmi, A. S. K.; Rudolph, M.; Shymura, S.; Visus, J.; Frey, W. *Eur. J. Org. Chem.* **2006**, 4905; g) Hashmi, A. S. K.; Weyrauch, J. P.; Frey, W.; Bats, J. W. *Org. Lett.* **2004**, *6*, 4391; h) Milton, M. D.; Inada, Y.; Nishibayashi, Y.; Uemura, S. *Chem. Commun.* **2004**, 2712; i) Kang, J. E.; Kim, H.-B.; Lee, J.-W.; Shin, S. *Org. Lett.* **2006**, *8*, 3537; *lactones and furanones*: j) Genin, E.; Toullec, P. Y.; Antoniotti, S.; Brancour, C.; Genêt, J.-P.; Michelet, V. *J. Am. Chem. Soc.* **2006**, *128*, 3112; k) Liu, Y.; Liu, M.; Guo, S.; Tu, H.; Zhou, Y.; Gao, H. *Org. Lett.* **2006**, *8*, 3445

[259] Kang, J. E.; Lee, E.-S.; Park, S.-I.; Shin, S. *Tetrahedron Lett.* **2005**, *46*, 7431

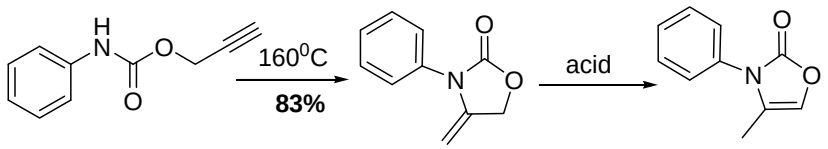
[260] Kang, J.-E.; Shin, S. *Synlett* **2006**, 717

[261] Lim, C.; Kang, J.-E.; Lee, J.-E.; Shin, S. *Org. Lett.* **2007**, *9*, 3539



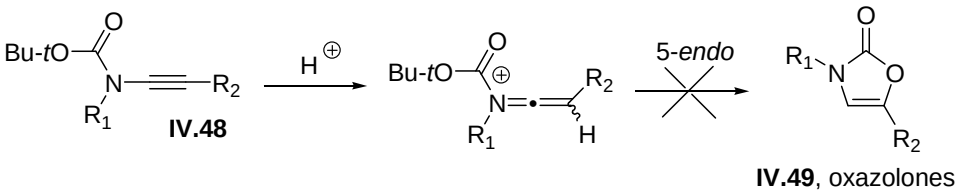
Scheme IV.25

It is known in the literature that 5-*endo* cyclisations of carbamates are less favorable then 5-*exo* cyclisations. For example, oxazolones are obtained from the corresponding 5-*exo* cyclisation products by acid catalysis (Scheme IV.26):[238]



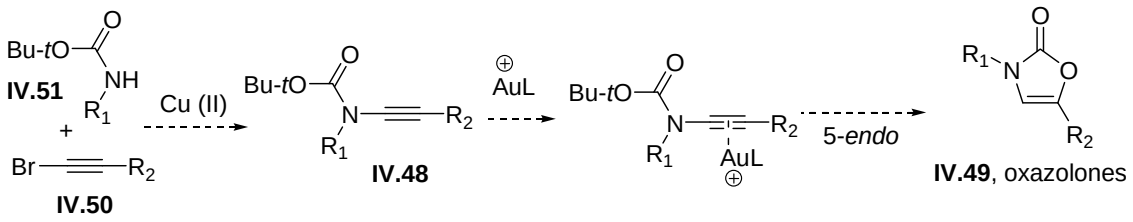
Scheme IV.26

In this respect, Hsung and co-workers have shown that *tert*-butyloxyynamides of type IV.48 do not undergo 5-*endo* cyclisation in the presence of acid, but react preferentially with another nucleophile present in the reaction media (See also Scheme IV.49, Ficini-Claisen rearrangement):



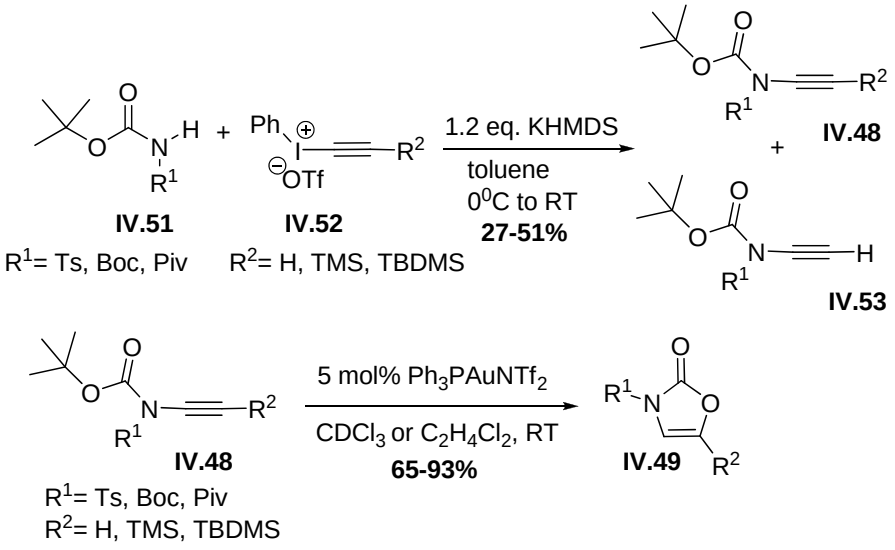
Scheme IV.27

We surmised that due to the special ability of gold (I) to activate triple bonds (see Chapter I and references cited therein), *N*-alkynyl *tert*-butylcarbamates could be rearranged to oxazolones in their presence. Scheme IV.28 illustrates our synthetic approach which relies on a two-step sequence. The *N*-alkynyl *tert*-butylcarbamate IV.48 substrate could be obtained by a Cu(II)-catalyzed coupling of a bromoalkynes IV.50 with *tert*-butylcarbamate IV.51 and would lead to the desired oxazolones IV.49 by a subsequent gold-catalyzed 5-*endo* cyclisation:



Scheme IV.28

Indeed, while this work was in progress, Hashmi and co-workers[262] reported that carbamates IV.48 could actually be rearranged to oxazolones IV.49 (Scheme IV.29), using the catalyst developed in our laboratory ($Ph_3PAuNTf_2$).[100]
Even if this method proved to be mild (0^0C or room temperature) and efficient affording substituted oxazolones in good yields (65-93%), we believed that our approach could present some advantages. Hashmi's group prepared the *N*-alkynyl *tert*-butylcarbamates starting from the *N*-Boc-protected amines IV.51 using phenyliodonium salts IV.52. This procedure was limited to the synthesis of substrates bearing hydrogen or a silyl group on the alkyne and an electron-withdrawing group (Ts, Boc, Piv) on the nitrogen, given the restricted access to functionalized iodonium salts IV.52 and their inefficient coupling with IV.51 (27-51%), (Scheme IV.29). Considering these drawbacks, it appeared to us that the Cu(II)-catalyzed coupling of IV.50 with IV.51 (Scheme IV.28) might advantageously broaden the scope of the transformation.



Scheme IV.29

IV.5. The Precursor tert-Butoxy-ynamides Substrates

In order to validate our approach illustrated in Scheme IV.28 and to test the scope of the envisaged transformation, we needed an efficient procedure for the Cu(II)-catalyzed formation of *N*-alkynyl *tert*-butylcarbamates IV.48.

[262] Hashmi, A. S. K.; Salathé, R.; Frey, W. *Synlett*, **2007**, 1763

Although numerous examples of direct copper-catalyzed cross-coupling reactions of an alkynyl bromide with a carbamate, a sulfonamide or an amide are described in the literature (see Chapter IV.5.2),[263] only a few examples of such a reaction were previously reported using a *tert*-butylcarbamate such as IV.51 as the reactant.[264]

IV.5.1. Introduction to the Chemistry of Ynamides

During the past ten years, numerous organic synthetic chemists have become attracted to the chemistry of electron-deficient ynamines and ynamides. Such an interest may be explained by the fact that these reactive species are easily accessible and possess a high synthetic potential.[265]

Ynamines are highly reactive and sensitive chemical compounds due to the ability of the nitrogen to donate its lone pair to the alkynyl moiety. Therefore, synthetic efforts were made aiming at improving the stability of ynamines without significantly diminishing their reactivity.

Towards the purpose of balancing reactivity and stability, some advances have been made recently in exploring a class of electron-deficient ynamines, namely the ynamides. In these compounds, the nitrogen atom is substituted with an electron-withdrawing group such as sulfonamide, an imidazolidinone, an oxazolidinone or an ester group (Figure IV.1):

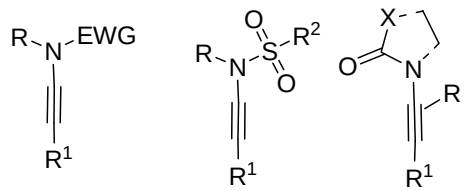


Figure IV.1

Considerably more robust than simple ynamines, ynamides are more easily stored and handled and tolerate a variety of conditions destructive to typical ynamines.

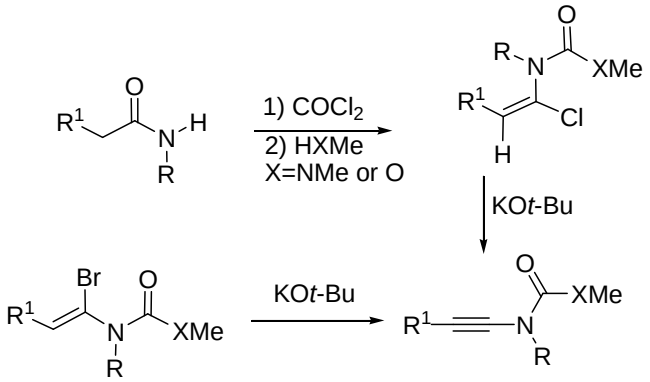
IV.5.2. Synthetic Methods Leading to Ynamides

[263] For leading references dealing with the Cu(II) catalyzed coupling of bromoalkynes with carbamates, see: a) Zhang, Y.; Hsung, R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. *Org. Lett.* **2004**, *6*, 1151; b) Frederick, M. O.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P.; Huang, J.; Kurtz, K. C. M.; Shen, L.; Douglas, C. J. *J. Am. Chem. Soc* **2003**, *125*, 2368

[264] a) Dunetz J. R.; Danheiser, R. L. *Org. Lett.* **2003**, *5*, 4011; b) Dunetz, J. R.; Danheiser, R. L. *J. Am. Chem. Soc.* **2005**, *127*, 5776; c) Zhang, X.; Zhang, Y.; Huang, J.; Hsung, R. P.; Kurtz, K. C. M.; Oppenheimer, J.; Petersen, M. E.; Sagamanove, I. K.; Shen, L.; Tracey, M. R. *J. Org. Chem.* **2006**, *71*, 4170; d) Kohnen, A. L.; Mak, X. Y.; Lam, T. Y.; Dunetz, J. R.; Danheiser, R. L. *Tetrahedron* **2006**, *62*, 3815; e) Villeneuve, K.; Riddell, N.; Tam, W. *Tetrahedron* **2006**, *62,* 3823; f) Danheiser, R. L.; Kohnen, A. L.; Dunetz, J. R. *Org. Synth.* **2007**, *84*, 88

[265] For recent reviews on ynamines and ynamides chemistry, see: a) Hsung, R. P.; Zificsak, C. A.; Mulder, J. A.; Rameshkumar, C.; Wei, L.-L. *Tetrahedron* **2001**, *57*, 7575; b) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P. *Synlett* **2003**, 1379

The concept of improving ynamines' thermal stability and stability toward hydrolytic conditions should be credited to Viehe who in 1972 reported the synthesis of the first ynamides (Scheme IV.30):[266]

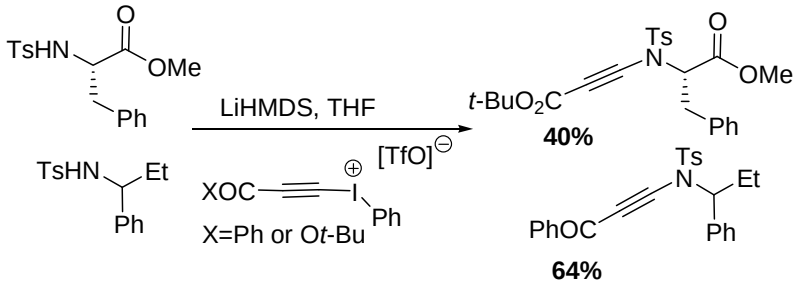


Scheme IV.30

As Witulski pointed it out, in order to truly revitalize the interest of the synthetic community in ynamides, one would need to address issues not only related to stability, but more importantly, synthetic accessibility in the most atom-economical manner. Some recent synthetic approaches towards ester-group substituted ynamides using iodonium salts or involving metal catalyzed coupling reactions are summarized in the next part.

Synthesis of Ynamides Using Iodonium Salts

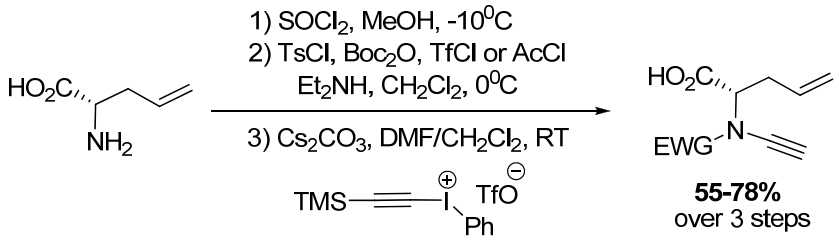
In their attempt to synthesize pyrrole and indole targets, Feldman and co-workers accomplished the synthesis of ynamides using iodonium triflate salts (Scheme IV.31):[267]



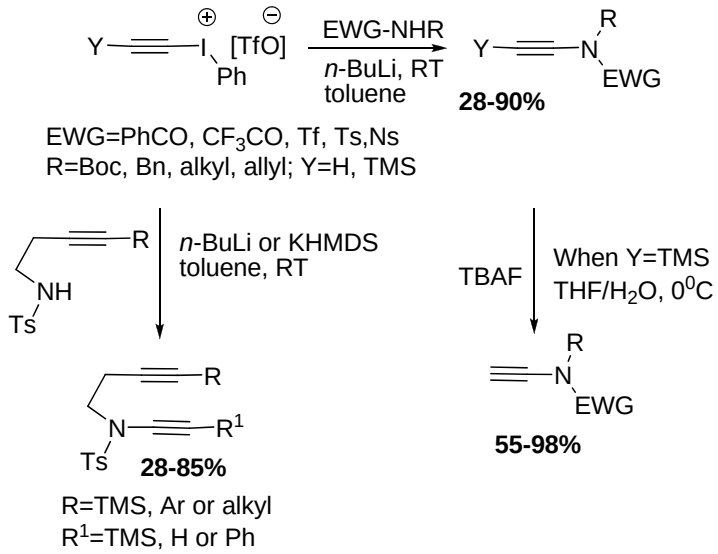
Scheme IV.31

More recently, Witulski[268] and Rainier[269] have extended this chemistry to the preparation of ynamides (Schemes IV.32-IV.33):

[266] Janousek, Z.; Collard, J.; Viehe, H. G. *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 917
[267] Feldman, K. S.; Bruendl, M. M.; Schildknegt, K.; Bohnstedt, A. C. *J. Org. Chem.* **1996**, *61*, 5440
[268] a) Witulski, B.; Gößmann, M. *Chem. Comunn.* **1999**, 1879; b) Witulski, B.; Stengel, T. *Angew. Chem. Int. Ed.* **1998**, *37*, 489 & **1999**, *38*, 2426; c) Witulski, B.; Gößmann, M. *Synlett* **2000**, 1793
[269] a) Rainier, J. D.; Imbriglio, J. E. *Org. Lett.* **1999**, *1*, 2037; b) Rainier, J. D.; Imbriglio, J. E. *J. Org. Chem.* **2000**, *65*, 7272

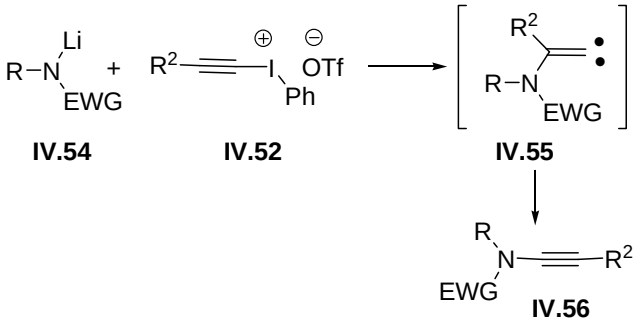


Scheme IV.32



Scheme IV.33

The addition of soft nucleophiles to alkynyl(phenyl)iodonium salts IV.52 is believed to proceed *via* the rearrangement of alkylidenecarbene intermediates of type IV.55, and the requisite 1,2-shift only is a facile process when R^2 is a hydrogen atom or trialkylsilyl or aryl group (Scheme IV.34):[270]



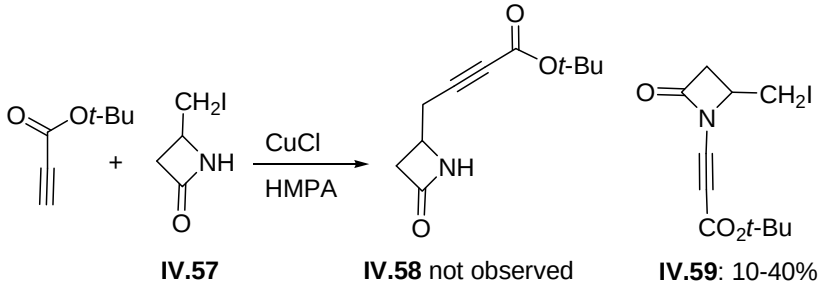
Scheme IV.34

[270] In the case where R^2 is an acyl or sulfonyl group, it is not clear if a 1,2-shift is involved or whether the mechanism proceeds via an addition/elimination pathway.

Unfortunately, this approach using phenyliodonium salts is not applicable to the synthesis of ynamides in which R^2 is a simple alkyl group.

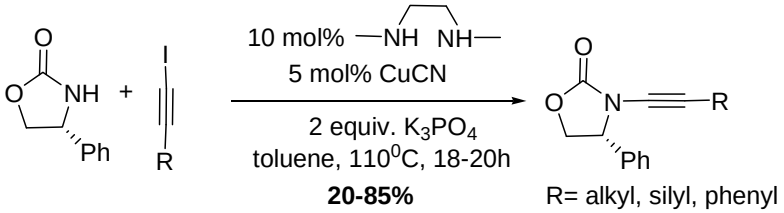
Synthesis of Ynamides by Cu-Catalyzed Coupling Reactions

One noteworthy earlier account related to the transition metal mediated access to ynamides involved a CuCl mediated oxidative process that was intended to couple *tert*-butyl propiolate to the alkyl halide IV.57 to prepare IV.58 (Scheme IV.35). Instead, the ynamide IV.59 was isolated in 10% yield which was improved up to 40% when the reaction was carried out at low temperature.[271]



Scheme IV.35

Hsung and co-workers reported the successful application of Buchwald's catalyst system[272] to the *N*-alkynylation of oxazolidinones and lactams (Scheme IV.36).[273] Unfortunately, these conditions proved to be less effective (24-42%) when applied to other amide derivatives, including acyclic carbamates and sulfonamides.



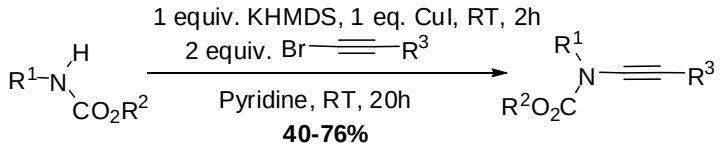
Scheme IV.36

Dunetz and Danheiser reported a convenient and general method for the synthesis of a wide range of ynamides *via* the stoichiometric copper-promoted coupling of amides with alkynyl bromides (Scheme IV.37):

[271] Balsamo, A.; Macchia, B.; Macchia, F.; Rossello, A.; Domiano, P. *Tet. Lett.* **1985**, *26*, 4141

[272] Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421. The Buchwald procedure for amidation of aryl bromides involves reaction with 0.01-0.1 equiv of CuI, 2 equiv of K_3PO_4, and 0.1 equiv of a diamine ligand in toluene or dioxane at 110 °C for 15-24 h

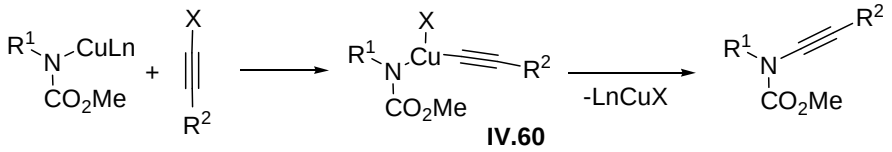
[273] Frederick, M. O.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P.; Huang, J.; Kurtz, K. C. M.; Shen, L.; Douglas, C. *J. Am. Chem. Soc.* **2003**, *125*, 2368



R^1=alkyl, benzyl; R^2= Me, *t*-Bu
R^3=Ph, silyl, alkyl, propargyl, vinyl

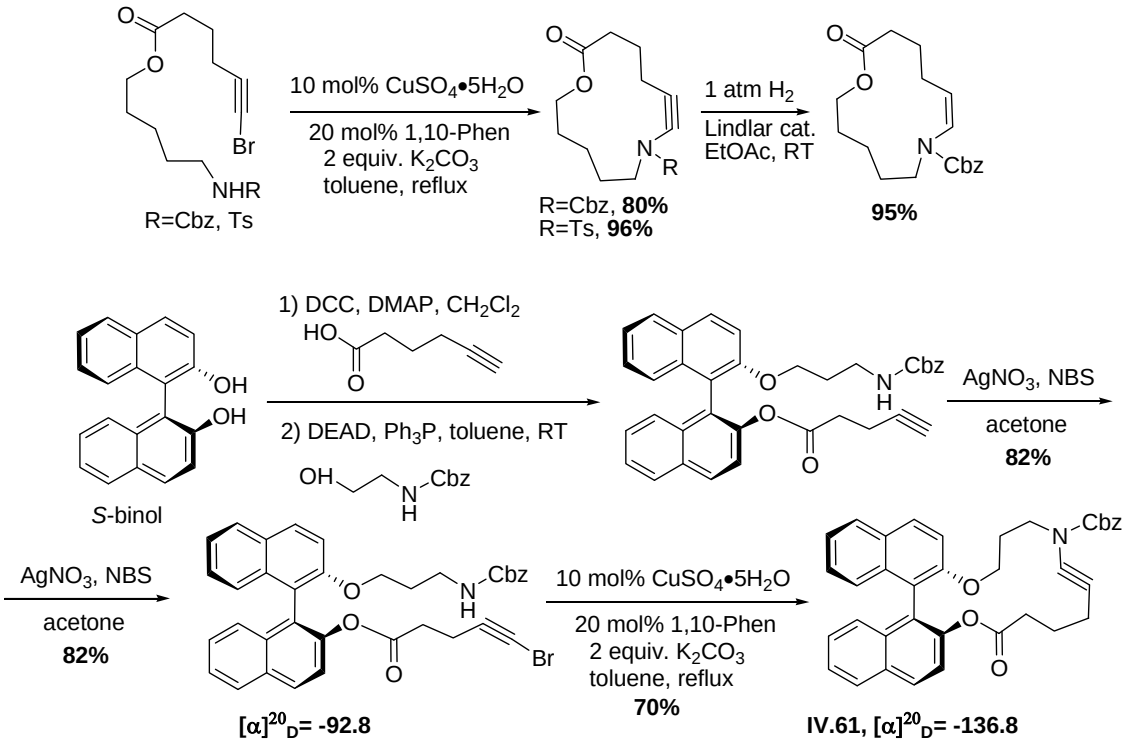
Scheme IV.37

In their work, a stronger base, KHMDS, was employed to generate the desired copper amide species IV.60 (Scheme IV.38). A distinctly attractive feature of this coupling reaction is that it can proceed at room temperature, thereby allowing the preparation of thermally sensitive ynamides.[264a, b, d-f]



Scheme IV.38

Hsung's group disclosed a novel amidation reaction involving a catalytic protocol using copper(II) sulfate and 1,10-phenanthroline to direct the *sp*-C-N bond formation, providing a general entry to a diverse array of ynamides including macrocyclic ynamides (C_9 to C_{19}) and even a chiral amide IV.61 *via* an intramolecular amidation (Scheme IV.39).[264c]



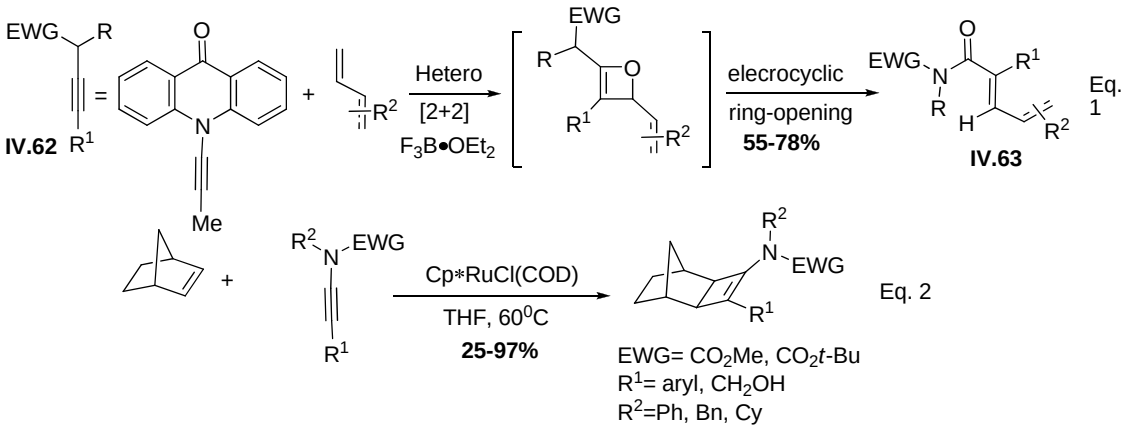
Scheme IV.39

IV.5.3. Reactions of Ynamides

Despite the precedent of electron-deficient ynamines, or ynamides, and their improved stability, only recently have these functionally rich organic building blocks caught the attention of organic chemists.
A large number of new methodologies have been developed employing ynamides as versatile organic building blocks, leading to the synthesis of a structurally diverse array of useful functional groups and carbocycles as well as heterocycles. Depending on the reactivity involved, these transformations can be classified into two major categories: (1) those involving ynamides with reactivity similar to simple alkynes, such as metal-catalyzed cycloadditions, RCM, addition reactions, cross-coupling reactions, radical cyclizations, and other tandem reactions, and (2) those with reactivity based on the *in situ* generated ketene iminium intermediates such as sigmatropic rearrangements, Pictet-Spengler reactions, and enyne cyclizations.

Triple Bond Based Reactivity of Ynamides

Hsung and co-workers reported the reactivity of ynamides in [2+2] cycloaddition reactions.[274] As depicted in Scheme IV.40, Eq. 1, hetero [2+2] cycloaddition reactions of ynamide IV.62 with aldehydes can lead to an oxetane intermediate that would undergo an electrocyclic ring opening to give alkene IV.63. Tam's group investigated the ruthenium-catalyzed [2+2] cycloadditions between norbornene derivatives and ynamides (Scheme IV.40, Eq. 2).[275]



Scheme IV.40

Several groups (Witulski,[268] Rainier[269] and Hsung[276]) explored the efficiency of tosyl ynamides in inter- and intramolecular Pauson-Khand reactions.

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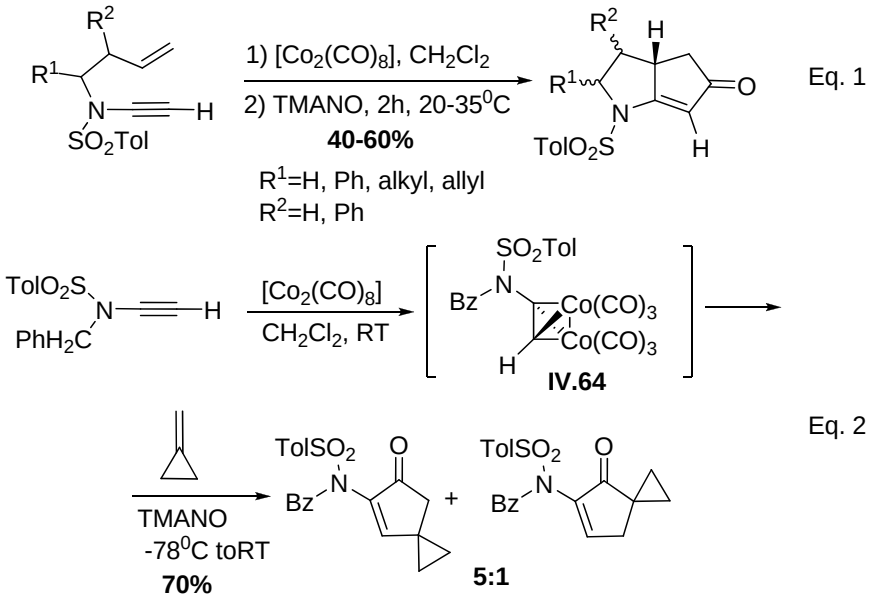
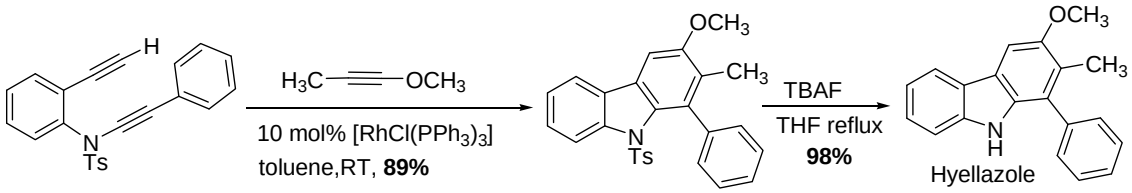
[274] Hsung, R. P.; Zificsak, C. A.; Wei, L.-L.; Douglas, C. J. Xiong, H.; Mulder, J. A. *Org. Lett.* **1999**, *1*, 1237
[275] a) Riddell, N.; Villeneuve, K.; Tam, W. *Org. Lett.* **2005**, *7*, 3681; b) Riddell, N.; Villeneuve, K.; Tam, W. *Tetrahedron* **2006**, *62*, 3823
[276] Shen, L.; Hsung, R. P. *Tet. Lett.* **2003**, *44*, 9353

For example, in the case of $[Co_2(CO)_8]$-mediated [2+2+1] cycloadditions, the $[Co_2(CO)_6]$-alkynylamides IV.64 are transformed immediately into [2+2+1] cycloaddition products by intramolecular[268a,b] (Scheme IV.41, Eq.1) or intermolecular reactions[268c] (Eq. 2). Pauson–Khand cycloadditions using chiral ynamides are achieved in modest to good yields with excellent regioselectivity and modest stereoselectivity.[276]



Scheme IV.41

Witulski et *al.* reported the use of ynamides in [2+2+2] cycloaddition reactions to achieve the synthesis of 2,3 dihydroindoles,[268b] 4,5- and 4,6-indolines[277] and substituted carbazoles.[278] For example, a method based on inter- and intramolecular alkyne cyclotrimerizations was developed and used as a key step in the synthesis of hyellazole, a marine carbazole alkaloid isolated from the blue-green algae *Hyella caespitosa* (Scheme IV.42).[279]

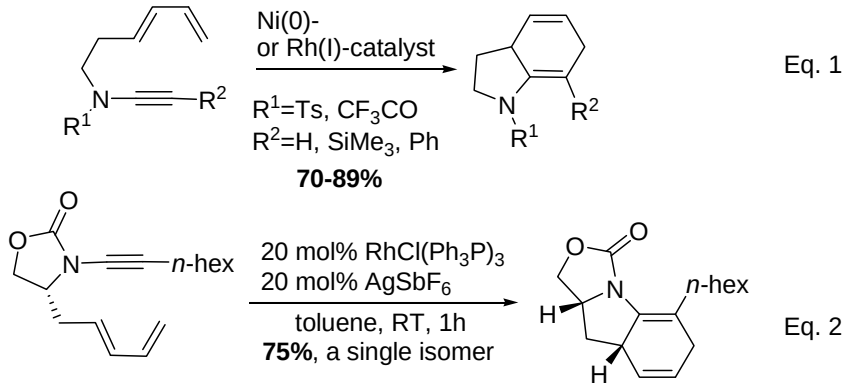


Scheme IV.42

Several groups (Witulski,[280] Saà[281] and Hsung[264c]) reported the reactivity of ynamides in Diels-Alder reactions.

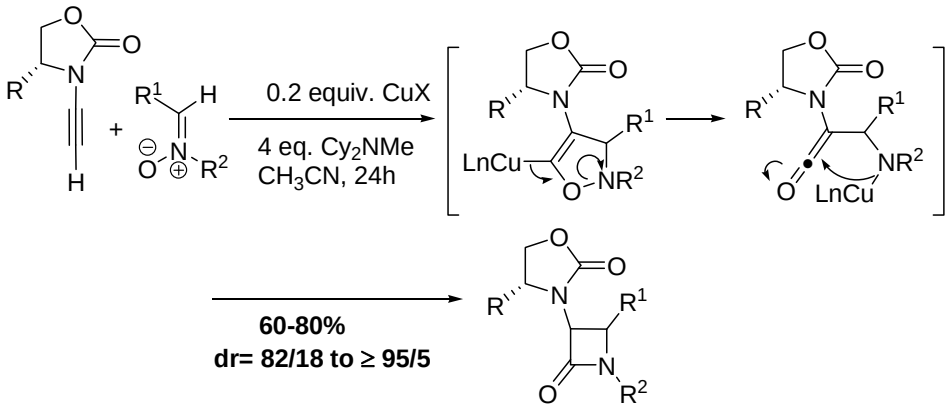
[277] Witulski, B.; Stengel, T.; Fernández-Hernández, J. M. *Chem. Commun.*, **2000**, 1965
[278] Witulski, B.; Alayrac, C. *Angew. Chem. Int. Ed.* **2002**, *41*, 3281
[279] Cardellina II, J. H.; Kirkup, M. P.; Moore, R. E.; Mynderse, J. S.; Seff, K.; Simmons, C. J. *Tet. Lett.* **1979**, 4915
[280] Witulski, B; Lumtscher, J.; Bergsträßer, U. *Synlett* **2003**, 708

Cationic rhodium(I)-complexes generated from $[RhCl(PPh_3)_3]$ and $AgSbF_6$ catalyze at room temperature the intramolecular [4+2] cycloaddition reactions with *N*-tethered ynamides and provide an efficient access to synthetically versatile tetrahydroindoles (Scheme IV.43, Eq. 1). Hsung et *al.* demonstrated that Witulski's elegant intramolecular ynamide- Diels-Alder cycloaddition method could be rendered stereoselective using chiral ynamides (Scheme IV.43, Eq. 2).[264c]



Scheme IV.43

[3+2] cycloaddition reactions leading to chiral *α*-amino-*β*-lactams through an ynamide-Kinugasa reaction[282] was disclosed by Hsung et *al.* (Scheme IV.44):[283]

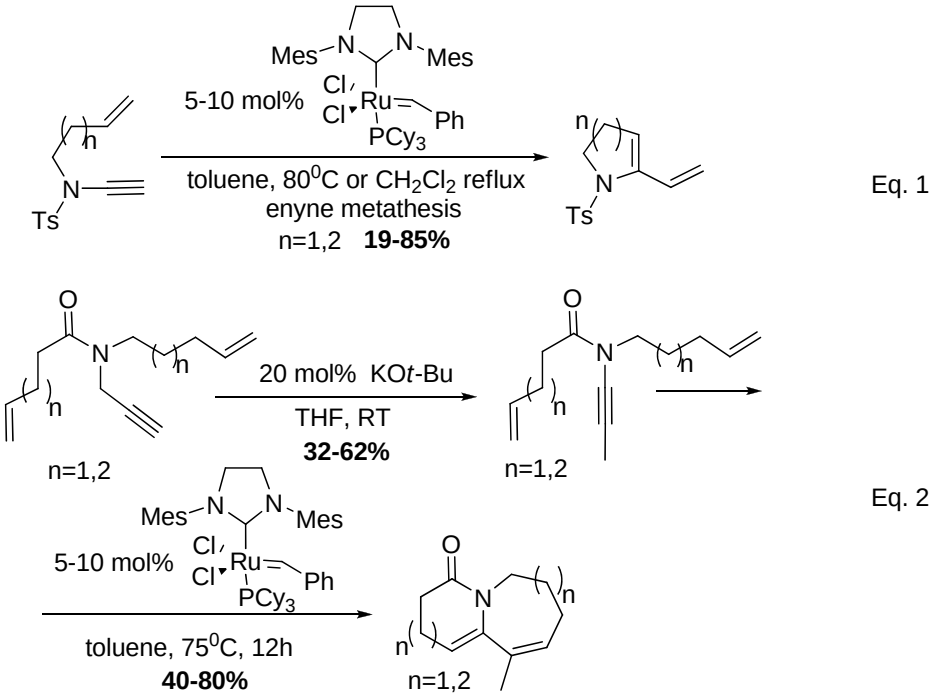


Scheme IV.44

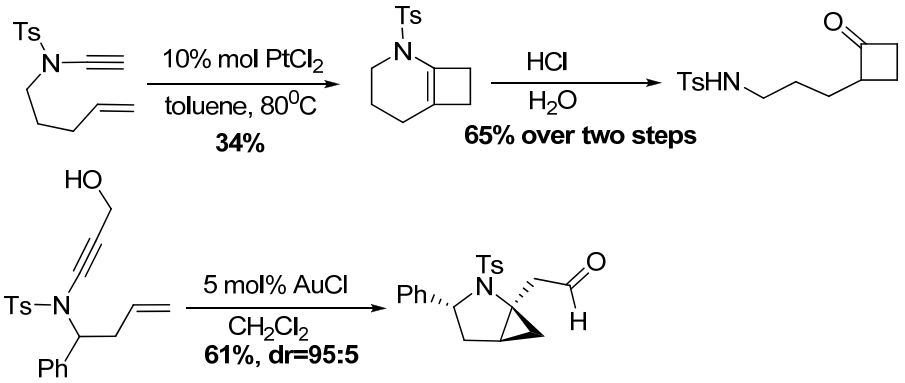
Ynamides substituted with electron-withdrawing groups such as tosyl or acyl were successfully employed in ring closing metathesis reactions using the second-generation

[281] a) Martínez-Esperón, M. F.; Rodríguez, D.; Castedo, L.; Saà, C. *Org. Lett.* **2005**, *7*, 2213; b) Martínez-Esperón, M. F.; Rodríguez, D.; Castedo, L.; Saà, *Tetrahedron* **2006**, *62*, 3843
[282] Kinugasa, M.; Hashimoto, S. *J. Chem. Soc., Chem. Commun. 1972*, 466
[283] Zhang, X.; Hsung, R. P.; Li, H.; Zhang, Y.; Johnson, W. L.; Figueroa, R. *Org. Lett.* **2008**, *10*, 3477

Grubbs catalyst[284] (Scheme IV.45) and in platinum[285] or gold-catalyzed cycloisomerisations[286] (Scheme IV.46).



Scheme IV.45

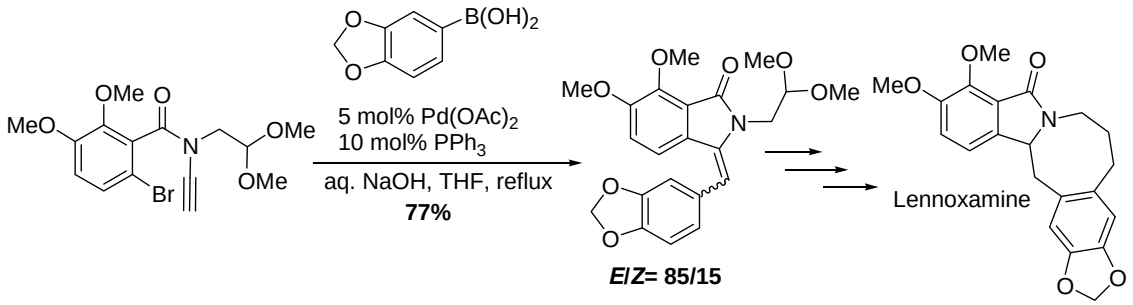


Scheme IV.46

Ynamides can participate in several other transformations usually carried out with alkynes such as nickel(0)[287] or titanium(II)-mediated[288] coupling reactions, carbocupration,[289]

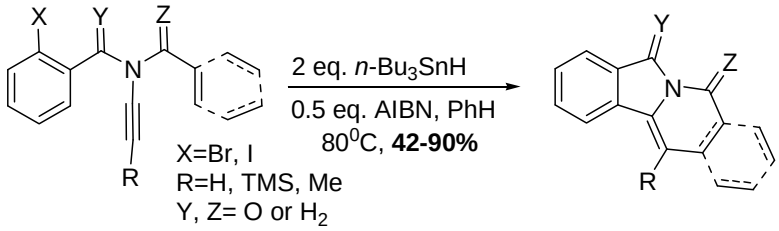
[284] a) Saito, N.; Sato, Y.; Mori, M. *Org. Lett.* **2002**, *4*, 803; b) Huang, J.; Xiong, H.; Hsung, R. P.; Rameshkumar, C.; Mulder, J. A.; Grebe, T. P. *Org. Lett.* **2002**, *4*, 2417
[285] Marion, F.; Coulomb, J.; Courillon, C.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2004**, *6*, 1509
[286] Couty, S.; Meyer, C.; Cossy, J *Angew. Chem. Int. Ed.* **2006**, *45*, 6726
[287] Saito, N.; Katayama, T.; Sato, Y. *Org. Lett.* **2008**, *10*, 3829
[288] a) Hirano, S.; Tanaka, R.; Urabe, H.; Sato, F. *Org. Lett.* **2004**, *6*, 727; b) Tanaka, R.; Hirano, S.; Urabe, H.; Sato, F. *Org. Lett.* **2003**, *5*, 67
[289] Chechik-Lankin, H.; Livshin, S.; Marek, I. *Synlett* **2005**, 2098

hydroboration[290] and hydrohalogenation[291] followed by cross-coupling reactions, as well as palladium-catalyzed Sonogashira[292] or Negishi[281] couplings and Heck–Suzuki–Miyaura domino reactions.[293] The latter domino transformation allows the efficient synthesis of substituted 3-(arylmethylene)isoindolin-1-ones and has been successfully applied to the total synthesis of lennoxamine (Scheme IV.47), an isoindolobenzazepine alkaloid extracted from the Chilean plant *Berberis darwinii*.



Scheme IV.47

Some radical cyclization cascades involving ynamides as substrates have also been reported as a route to various nitrogen heterocycles, such as isoindoles, isoindolinones, and pyridoisoindolones (Scheme IV.48):[294]



Scheme IV.48

Ketene-Iminium Based Reactivity

Hsung et *al.* described the first asymmetric Ficini-Claisen rearrangement (Scheme IV.49)[295] and a highly stereoselective Saucy-Marbet rearrangement (Scheme IV.50)[296] using chiral ynamides. These rearrangements proceeding with high diastereoselectivity at relatively low temperatures were efficiently promoted by using catalytic *p*-nitrobenzenesulfonic acid.

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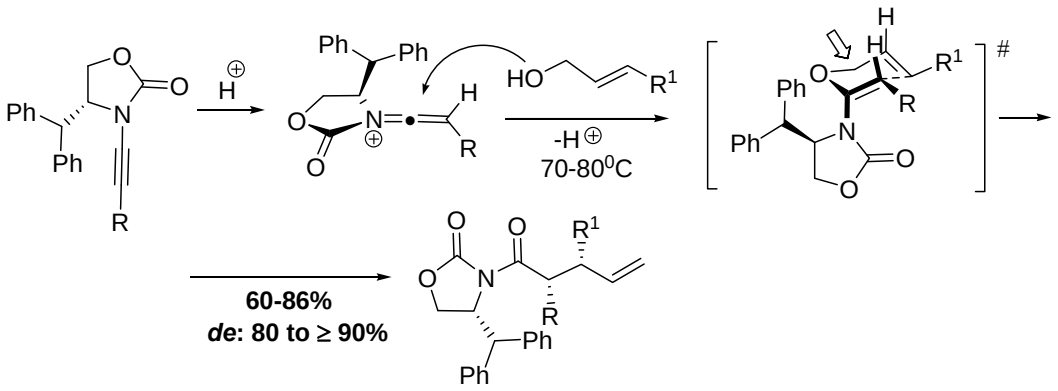
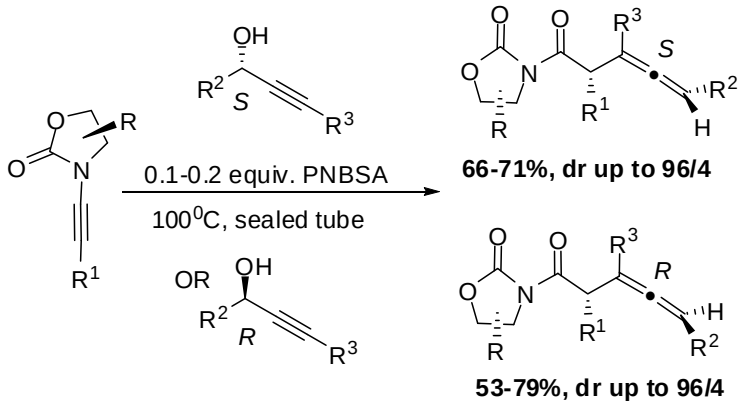
[290] Witulski, B.; Buschmann, N.; Bergsträßer, U. *Tetrahedron* **2000**, *56*, 8473
[291] Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P.; Coverdale, H.; Frederick, M. O.; Shen, L.; Zificsak, C. A. *Org. Lett.* **2003**, *5*, 1547
[292] Tracey, M. R.; Zhang, Y.; Frederick, M. O.; Mulder, J. A.; Hsung, R. P. *Org. Lett.* **2004**, *6*, 2209
[293] Couty, S.; Liegault, B.; Meyer, C.; Cossy, J. *Tetrahedron* **2006**, *62*, 3882
[294] a) Marion, F.; Courillon, C.; Malacria, M. *Org. Lett.* **2003**, *5*, 5095; b) Marion, F.; Coulomb, J.; Servais, A.; Courillon, C.; Fensterbank, L.; Malacria, M. *Tetrahedron* **2006**, *62*, 3856
[295] Mulder, J. A.; Hsung, R. P.; Frederick, M. O.; Tracey, M. R.; Zificsak, C. A. *Org. Lett.* **2002**, *4*, 1383
[296] a) Frederick, M. O.; Hsung, R. P.; Lambeth, R. H.; Mulder, J. A.; Tracey, M. R. *Org. Lett.* **2003**, *5*, 2663; b) Kurtz, K. C. M.; Frederick, M. O.; Lambeth, R. H.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P. *Tetrahedron* **2006**, *62*, 3928



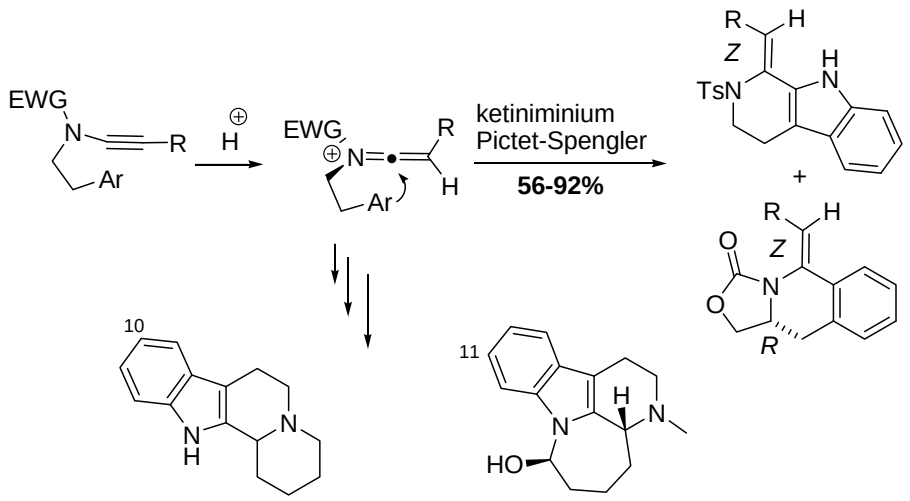
Scheme IV.49



Scheme IV.50

The same group (Hsung) published a Brønsted acid-catalyzed highly stereoselective keteniminium variant of the Pictet-Spengler cyclization. This methodology was successfully applied to the synthesis of nitrogenated heterocycles and related alkaloids such as desbromoarborescidines A and C (Scheme IV.51):[297]

[297] Zhang, Y.; Hsung, R. P.; Zhang, X.; Huang, J.; Slafer, B. W.; Davis, A. *Org. Lett.* **2005**, *7*, 1047

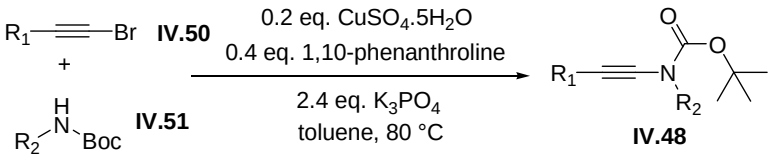


Scheme IV.51

IV.5.4. Our Synthesis of the Precursors

In order to obtain the precursors needed for the gold(I)-catalyzed cyclisation, we decided to study the cross-coupling between a series of functionalized bromoalkynes IV.50 and *tert*-butylcarbamates IV.51 (Table IV.1).

Using slightly modified reaction conditions[263a] (20 mol % of $CuSO_4$▪$5H_2O$ and 40 mol % of 1,10-phenanthroline as the ligand with K_3PO_4 as the base in toluene at 80°C), we were delighted to see that the cross-coupling reaction was generally more efficient than previously reported (Table IV.1). The desired *N*-alkynyl *tert*-butylcarbamates IV.48 containing various functionalities were thus synthesized and isolated in yields ranging from 22% to 88%. It should be noted that the poor yields obtained in the case of substrates IV.48h and IV.48i (Entries 8 and 9) may be attributed to a greater steric hindrance around the nitrogen center.



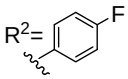
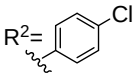
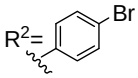
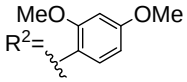
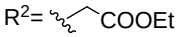
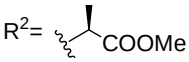
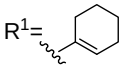
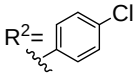
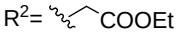
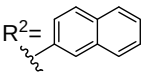
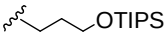
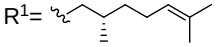
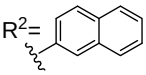
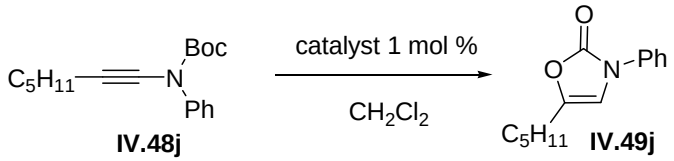
Entry	R^1, Alkyne		R^2, Amine		Product		Time	Yield
1	R^1=Ph	IV.50a	R^2=Ph	IV.51a	IV.48a		40 h	80%
2	R^1=Ph	IV.50a	R^2= 	IV.51b	IV.48b		16 h	65%
3	R^1=Ph	IV.50a	R^2= 	IV.51c	IV.48c		18 h	68%
4	R^1=Ph	IV.50a	R^2= 	IV.51d	IV.48d		16 h	48%
5	R^1=Ph	IV.50a	R^2= 	IV.51e	IV.48e		48 h	22%
6	R^1=Ph	IV.50a	R^2=Bn	IV.51f	IV.48f		48 h	62%
7	R^1=Ph	IV.50a	R^2= 	IV.51g	IV.48g		36 h	70%
8	R^1=Ph	IV.50a	R^2= 	IV.51h	IV.48h		48 h	23%
9	R^1=*t*-Bu	IV.50b	R^2=Ph	IV.51a	IV.48i		38 h	24%
10	R^1=*n*-C_5H_{11}	IV.50c	R^2=Ph	IV.51a	IV.48j		52 h	75%
11	R^1=*n*-C_5H_{11}	IV.50c	R^2=Bn	IV.51f	IV.48k		48 h	69%
12		IV.50d	R^2=Ph	IV.51a	IV.48l		67 h	72%
13	R^1= 	IV.50d	R^2= 	IV.51c	IV.48m		67 h	80%
14		IV.50d	R^2= 	IV.51g	IV.48n		67 h	50%
15	R^1=CH_2OAc	IV.50e	R^2=Ph	IV.51a	IV.48o		65 h	55%
16	R^1=CH_2OAc	IV.50e	R^2= 	IV.51i	IV.48p		45 h	49%
17	R^1=CH_2OAc	IV.50e	R^2=Bn	IV.51f	IV.48q		72 h	49%
18	R^1=CH_2OAc	IV.50e	R^2=	IV.51g	IV.48r		62 h	48%
19	R^1= 	IV.50f	R^2=Ph	IV.51a	IV.48s		45 h	88%
20		IV.50f	R^2=Bn	IV.51f	IV.48t		62 h	72%
21	R^1= 	IV.50g	R^2=Ph	IV.51a	IV.48u		48 h	74%
22		IV.50g	R^2= 	IV.51i	IV.48v		48 h	65%

Table IV.1

IV.6. Optimization of the Catalytic System

Having in hand an efficient procedure for the synthesis of *N*-alkynyl *tert*-butylcarbamates IV.48, we next focused our attention on the second step of the sequence, choosing carbamate IV.48j as a model substrate (Table IV.2). Despite the fact that $Ph_3PAuNTf_2$ proved to be efficient in the procedure reported by Hashmi and co-workers,[262] poor results were obtained in our case with 1 mol% of this catalyst (Table IV.2, Entry 1).



Entry	Catalyst	Temperature	Time	Conversion	Yield[b]
1	PPh_3AuNTf_2	20 °C	7 h	**63%**	**28%**[c]
2	$(pCF_3Ph)_3PAuNTf_2$	20 °C	72 h	**85%**	**52%**[d]
3	$(pCF_3Ph)_3PAuNTf_2$	40 °C	2.5 h	**100%**	**40%**[d]
4	$[Ph_3P\text{-}Au\text{-}(NCCH_3)]^+SbF_6^-$	20 °C	4.5 h	**100%**	**69%**[d]
5	$[Ph_3P\text{-}Au\text{-}(NCCH_3)]^+SbF_6^-$	40 °C	30 min	**100%**	**74%**[c]

[a] Reaction conditions: 0.5 M substrate in CH_2Cl_2. [b] Estimated by ^1H NMR. [c] Isolated yield. [d] Estimated by ^1H NMR on the crude reaction mixture.

Table IV.2

The conversion of the model substrate IV.48j to the desired oxazolone IV.49j was improved when the more electrophilic catalyst $(p\text{-}CF_3Ph)_3PAuNTf_2$[100] was employed, but the yields remained modest (40-52%, Entries 2-3). Finally, the cationic $[Ph_3P\text{-}Au\text{-}(NCCH_3)]^+SbF_6^-$ complex, developed by Echavarren and co-workers,[298] proved to be the catalyst of choice to put in practice this transformation (Entries 4-5). Oxazolone IV.49j could be isolated in 74% yield under optimal conditions (1 mol % of $[Ph_3P\text{-}Au\text{-}(NCCH_3)]^+SbF_6^-$ in dichloromethane at 40°C). In the light of these preliminary results, these experimental conditions were retained for the study of the scope of the transformation.[299]

IV.7. Au(I)-Catalyzed Formation of Oxazolones

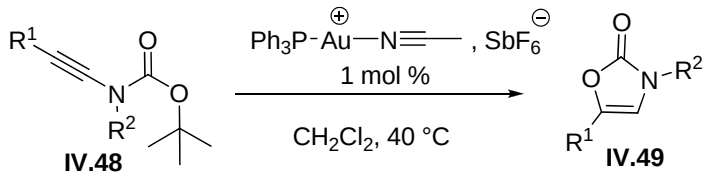
The various *N*-alkynyl *tert*-butylcarbamates IV.49 synthesized by the Cu(I)-catalyzed coupling reaction were subjected to the optimized reaction conditions (1 mol % of $[Ph_3P\text{-}Au\text{-}(NCCH_3)]^+SbF_6^-$ in dichloromethane at 40°C). We were delighted to note that the reaction

[298] Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *11*, 5916

[299] Brønsted acid ($HNTf_2$) did not promote the reaction and led to extensive decomposition of the substrate. Silver salts ($AgNTf_2$, $AgSbF_6$) did promote the reaction (53%, 64%) but their efficiency proved limited to a few substrates

proved to be quite general and various oxazolones IV.49 were obtained in generally good yields (38-94%) (Table IV.3) and short reaction times (the time required to reach completion was in most cases shorter than 2 h). A presence of a wide range of functional groups on the nitrogen was tolerated (aryl, benzyl, acetyl). It is also worth to mention that in the case of substituted aryl groups (Entries 2-5, 13) substituents bearing electron-withdrawing groups or electron-donating groups reacted equally well. The experimental conditions were also compatible with a variety of commonly used functional groups such as a propargylic acetate (Entries 15-18), a silyl ether (Entries 19-20), or an alkene (Entries 12-14 and 21-22). The desired oxazolones were obtained in moderate yields (38 to 50%)[300] in the case of *N*-benzyl-substituted substrates IV.49k, IV.49q and IV.49t but, surprisingly, these products proved to be instable and could not be isolated (Entries 11, 17, 20).

[300] The yield was determined by ^{1}H NMR on the crude reaction mixture

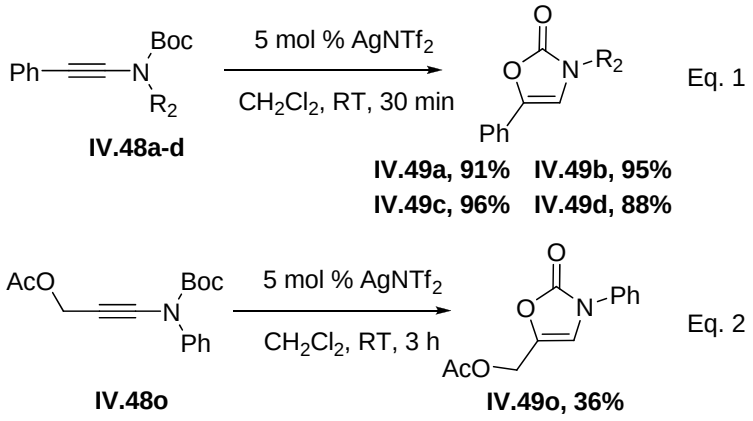


Entry	Substrate	R^1	R^2	Time	Product	Yield[b]
1	**IV.48a**	Ph	Ph	25 min	**IV.49a**	**83%**
2	**IV.48b**		*p*-FPh	10 min	**IV.49b**	**88%**
3	**IV.48c**		*p*-ClPh	10 min	**IV.49c**	**88%**
4	**IV.48d**		*p*-BrPh	10 min	**IV.49d**	**83%**
5	**IV.48e**		2,4(OMe)$_2$Ph	16 h	**IV.49e**	**85%**
6	**IV.48f**		Bn	16 h	**IV.49f**	**78%**
7	**IV.48g**		CH_2CO_2Et	12 h	**IV.49g**	**93%**
8	**IV.48h**		CO_2Me	8 h	**IV.49h**	**94%**
9	**IV.48i**	*t*-Bu	Ph	2 h	**IV.49i**	**58%**
10	**IV.48j**	*n*-C_5H_{11}	Ph	30 min	**IV.49j**	**74%**
11	**IV.48k**		Bn	40 min	**IV.49k**	**50%**[c]
12	**IV.48l**		Ph	30 min	**IV.49l**	**78%**
13	**IV.48m**		*p*-ClPh	10 min	**IV.49m**	**94%**
14	**IV.48n**		CH_2CO_2Et	5 h	**IV.49n**	**70%**
15	**IV.48o**	OAc	Ph	40 min	**IV.49o**	**71%**
16	**IV.48p**		2-Napht	45 min	**IV.49p**	**88%**
17	**IV.48q**		Bn	20 min	**IV.49q**	**50%**[c]
18	**IV.48r**		CH_2CO_2Et	20 min	**IV.49r**	**49%**
19	**IV.48s**	OTIPS	Ph	1 h	**IV.49s**	**69%**
20	**IV.48t**		Bn	40 min	**IV.49t**	**38%**[c]
21	**IV.48u**		Ph	30 min	**IV.49u**	**71%**
22	**IV.48v**		2-Napht	3 h	**IV.49v**	**80%**

[a] Reaction conditions: IV.48 (1 equiv), [(Ph$_3$P)Au(NCMe)]SbF$_6$ (0.01 equiv) in refluxing CH_2Cl_2 (0.5 M); [b] Isolated yield; [c] Yield determined by ^{1}H NMR on the crude reaction mixture using 1,3,5-trimethoxy-benzene as an internal standard.

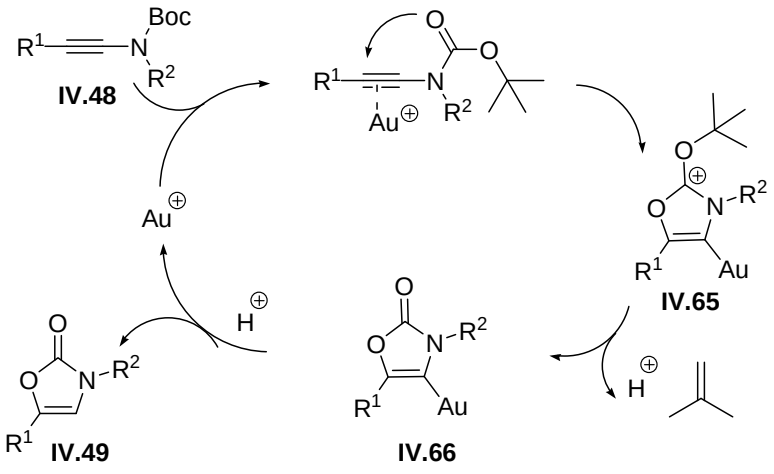
Table IV.3

Next we attempted to run the reaction using 5 mol % of $AgNTf_2$ as the catalyst (Scheme IV.52) in cases of the substrates where the formation of the oxazolone was rapid enough (substrates IV.48a-d). We were delighted to see that these substrates afforded the corresponding oxazolones IV.49a-d in excellent yields (88-96%). However, these conditions proved to be much less general. Substrate IV.48o led for instance to a poor 36% yield of oxazolone IV.49o (Scheme IV.52, Eq. 2).



Scheme IV.52

A mechanistic manifold accounting for the formation of the oxazolones is outlined in Scheme IV.53. After the coordination of the gold(I) catalyst to the triple bond in *N*-alkynyl *tert*-butylcarbamate IV.48 and the subsequent nuclephilic attack of the Boc group, the stabilized cationic species IV.65 is formed. Fragmentation of the C-O bond of the *tert*-butyloxy group in IV.65 leads to the formation of the neutral vinyl-gold species IV.66, which is subsequently protonated to finally afford oxazolone IV.49.

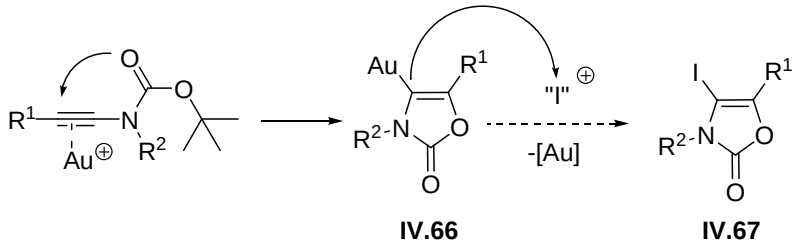


Scheme IV.53

IV.8.Conclusion and Perspectives

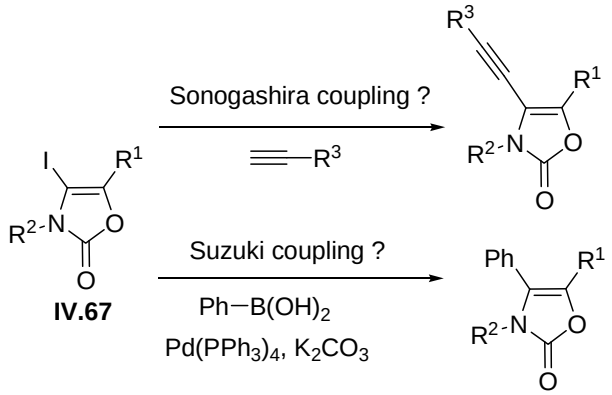
In summary, we have developed an efficient two-step sequence for the synthesis of oxazolones from readily available bromoalkynes and *tert*-butylcarbamates. Various *N*-alkynyl *tert*-butylcarbamates were prepared by the Cu(II)-catalyzed cross-coupling reaction which proved to be a general and efficient method for the synthesis of this kind of substrates. These were converted under mild conditions into a range of diversely substituted oxazolones by using a low loading of gold(I) catalyst.

To further highlight the potential of this new transformation, it would be of interest to study the trapping of the intermediate vinyl-gold species IV.66 by a source of electrophilic iodine prior to protonation (Scheme IV.54):[106, 153, 206]



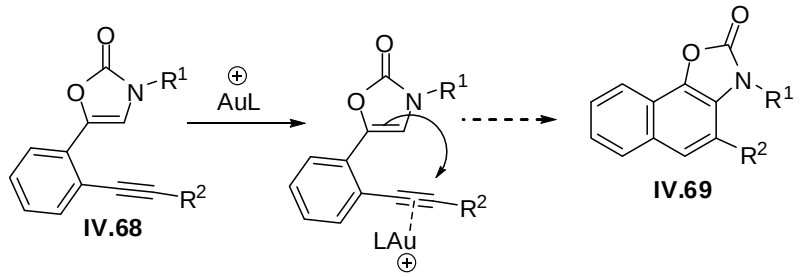
Scheme IV.54

This vinyliodide IV.67 could be an interesting substrate for palladium catalyzed coupling reactions like Sonogashira, Heck or Suzuki (see also Chapter II and III). This transformation would allow the synthesis of oxazolones substituted with alkyl, vinyl or aryl groups (Scheme IV.55):



Scheme IV.55

It would be of interest to examine the cyclisation of phenyl substituted oxazolones of type IV.68 in the presence of gold(I) complexes. They would represent potential substrates for the synthesis of 1-hydroxy, 2-aminonaphtalenes IV.69 (Scheme IV.56):



Scheme IV.56

V. Gold(I) Catalyzed Stereoselective Formation of Functionalized 2,5-Dihydrofurans

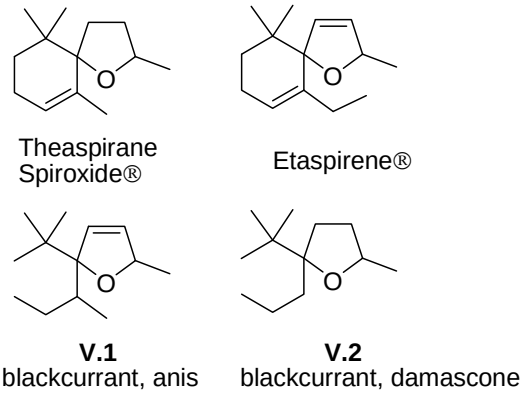
This work was done in collaboration with Dr. Fabien Gagosz and Florin-Marian Istrate.

V.1. Introduction

2,5-Dihydrofurans and their derivatives are structural motifs that are frequent in a wide variety of natural products exhibiting interesting properties with applications in pharmacy, flavor and fragrance industry.[301] They can be found in mycotoxins,[302] polyether antibiotics,[303] spiroketals,[304] and even amino acids.[305]

V.1.1. Fragrance Molecules Possessing the Dihydrofuran Motif

Several fragrance molecules from the theaspirane family possess the dihydro- and tetrahydrofuran motif. Theaspirane (Figure V.1), the parent compound of this family was first identified in raspberry and passion fruit, but occurs also in a variety of other fruits. It has a fresh, fruity odor with a strong blackcurrant impact and an additional camphoraceous tonality. Etaspirene®, commercialized by Givaudan, is used for instance in the female fine fragrance "Pleasures" (E. Lauder, 1995).[306] Structure-activity relationship studies led to the discovery of two powerful new blackcurrant odorants, seco-derivatives V.1 and V.2 (Figure V.1).[307]



[301] a) Heaney, H.; Ahn, J. S. in: *Comprehensive Heterocyclic Chemistry II*, (Eds.: Katritzky, A. R.; Rees, C.W.; Scriven, E. F. V.), Pergamon Press, Oxford, **1996**, *Vol. 2*, pp 297 – 436; b) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles: Structure, Reactions, Syntheses, and Applications*, Wiley-VCH, Weinheim, **2003**; c) Lipshutz, B.H. *Chem. Rev.* **1986**, *86*, 795; d) Aksin, O. ; Krause, N. *Adv. Synth. Catal.* **2008**, *350*, 1106

[302] a) Franck, B.; H.-P. Gehrken *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 461; b) Ganguli, M.; Burka, L. T.; Harris, T. M. *J. Org. Chem.* **1984**, *49*, 3762

[303] a) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309; b) Koert, U.; Stein, M.; Wagner, H. *Chem. Eur. J.* **1997**, *3*, 1170

[304] Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617

[305] Erdsack, J.; Krause, N. *Synthesis* **2007**, 3741, and references cited therein.

[306] Kraft, P.; Bajgrowicz, J. A.; Denis, C.; Fráter, G. *Angew. Chem. Int. Ed.* **2000**, *39*, 2980

[307] Kraft, P.; Popaj, K.; Abate, A. *Synthesis* **2005**, 2798

Figure V.1

V.1.2. Natural Products from Marine Organisms Possessing the Dihydrofuran Motif

Marine microorganisms and phytoplankton are becoming a focal point for research and rising numbers of novel compounds continue to be identified.[308]
As an example, peribysins V.3-V.5 (Figure V.2), from a strain of *Periconia byssoides,* are sesquiterpenoids with important inhibitory activity of the adhesion of HL-60 cells to HUVEC.[309] Another example of a newly discovered molecule is the hexacyclic diterpene, bielschowskysin V.6, isolated from a Caribbean sea plume *Pseudopterogorgia kallos*.[310] Modest biological activity towards *Plasmodium falciparum* and human tumour cell lines was observed (Figure V.3).

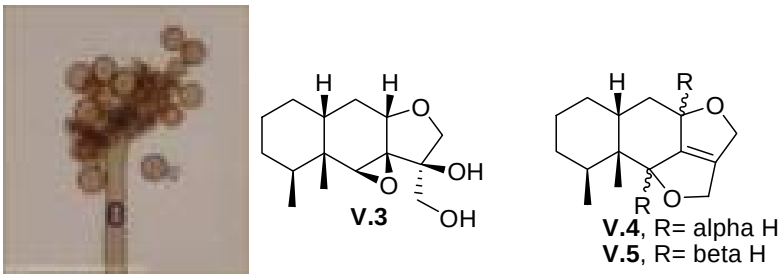


Figure V.2: *Periconia byssoides* and Peribysins V.3-V.5

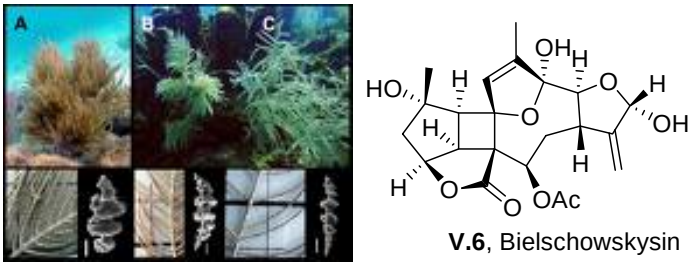
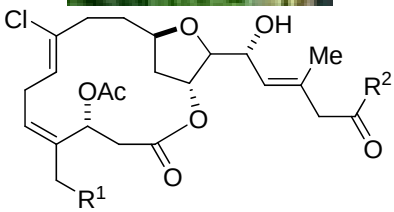


Figure V.3: *Pseudopterogorgia kallos* and bielschowskysin V.6

Five new polyketides, biselides A, B, C, D, and E (Figure V.4), were isolated from the Okinawan ascidian *Didemnidae* sp. The first three compounds showed cytotoxicity against human cancer cells.[311]

[308] Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2006**, *23*, 26
[309] Yamada, T.; Iritani, M.; Minoura, K.; Kawai, K.; Numata, A. *Org. Biomol. Chem.* **2004**, *2*, 2131
[310] Marrero, J.; Rodriguez, A. D.; Baran, P.; Raptis, R. G.; Sanchez, J. A.; Ortega-Barria, E. Capson, T. L. *Org. Lett.* **2004**, *6*, 1661
[311] a) Teruya, T.; Shimogawa, H.; Suenaga, K.; Kigoshi, H. *Chem. Lett.* **2004**, *33*, 1184; b) Teruya, T.; Suenaga, K.; Maruyama, S.; Kurotaki, M.; Kigoshi, H. *Tetrahedron* **2005**, *61*, 6561



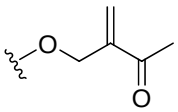
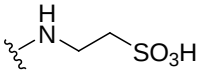
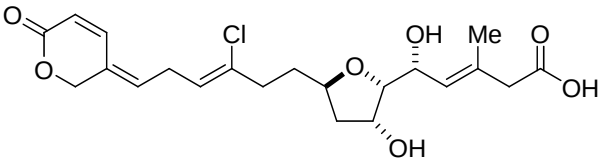
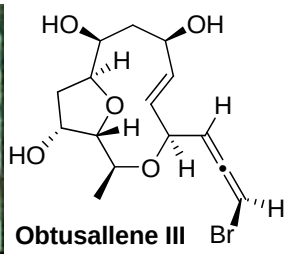
Biselide	R^1	R^2
A	OAc	OH
B	OAc	
C	OH	OH
D	H	
E		

Figure V.4

Obtusallene III (Figure V.5) belongs to a wider family of halogenated C_{15}-acetogenins (obtusallenes) isolated from red algae and seaweeds of the species *Laurencia.* Obtusallenes show potent biological activity, including cytotoxicity towards tumor cells.[312]



Obtusallene III

Figure V.5: *Laurencia* sp. and obtusallene III

[312] a) Guella, G.; Chiasera, G.; Mancini, I.; Öztunç, A.; Pietra, F. *Chem. Eur. J.* **1997**, *3*, 1223 ; b) Braddock, D. C. *Org. Lett.* **2006**, *8*, 6055

V.1.3. Polyether Antibiotics Possessing the Dihydrofuran Motif

Other examples of natural products containing the hydrofuranic ring are the ionophore polyether antibiotics, a class of compounds isolated from fermentation cultures of *Streptomyces*. The framework of these molecules, dominated by the presence of substituted tetrahydrofurans, tetrahydropyrans, and spiroketal systems, is primarily derived from polypropionate and polyacetate fragments and their structural complexity and diversity continue to challenge synthetic organic chemists. For example, Lasalocid A and Isolasalocid A were the first polyether ionophores prepared by total synthesis (Figure V.6).[313]

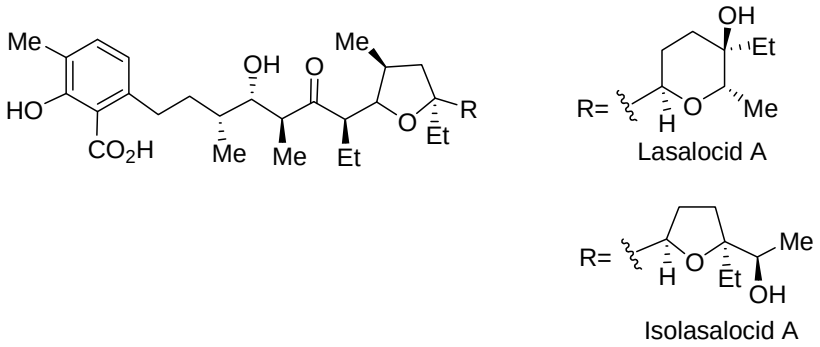


Figure V.6

V.1.4. Acetogenins Possessing the Dihydrofuran Motif

Acetogenins constitute a broad family of compounds with remarkable biological properties. A large number of natural acetogenins have been isolated from the plant family *Annonaceae*. These compounds have attracted the attention of many research groups as a result of their interesting structural complexity and the important biological activities (anticancer, pesticidal, immunosuppressive, and antifeedant) they exert.[314] The four main classes of annonaceous acetogenins are mono-tetrahydrofuran, adjacent bis-tetrahydrofuran, nonadjacent bis-tetrahydrofuran, and nonclassical acetogenins.
One representative example is (+)-Muconin (Figure V.7), a nonclassical acetogenin, which showed a potent *in vitro* cytotoxicity against human pancreatic and breast tumor cells.

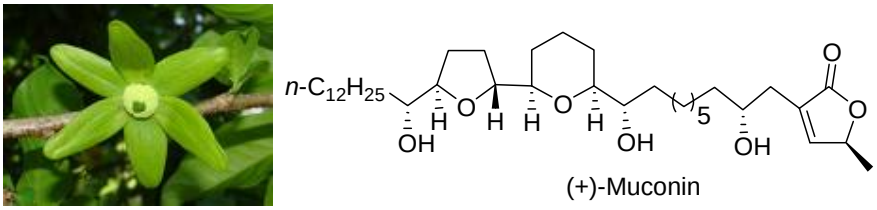


Figure V.7: *Annonaceae* and (+)-Muconin

[313] Nakata, T.; Schmid, G.; Vranesic, B.; Okigawa, M.; Smith-Palmer, T.; Kishi, Y. *J. Am. Chem. Soc.* **1978**, *100*, 2933
[314] a) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504; b) Bermejo, A.; Figadere, B.; Zafra-Polo, M.-C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, *22*, 269

A novel *Annonaceous* acetogenin bearing a hydroxylated tetrahydrofuran ring, Donnaienin (Figure V.8), was isolated from the roots of Goniothalamus donnaiensis.[315]

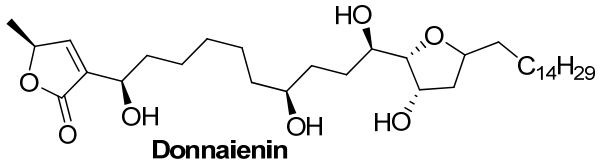


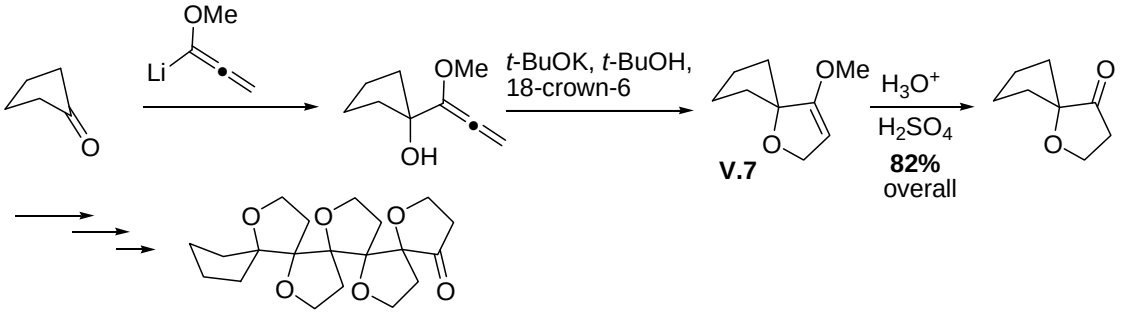
Figure V.8

V.2. Synthesis of the 2,5-Dihydrofuran Ring

In addition to traditional methods (e.g., dehydration of diols,[316] ring derivatization,[317] addition of nucleophiles to carbonyl bonds) numerous transition-metal-catalyzed heteroannulation reactions have been developed with remarkable improvements in terms of efficiency and wide scope of application.[318] This part will cover a personal selection of synthetic methods leading to the 2,5-dihydrofuran ring.

V.2.1. Addition of Nucleophiles to C=O Bonds

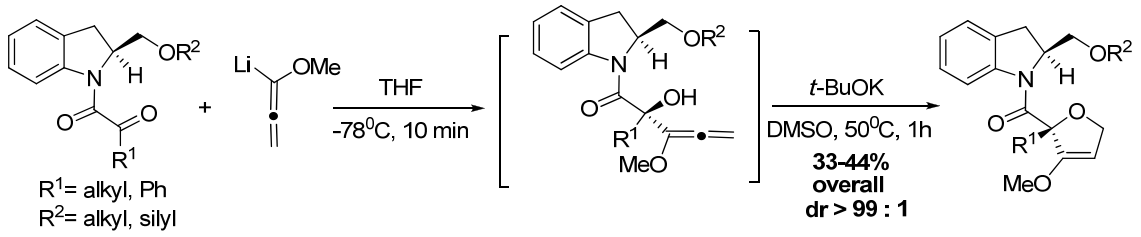
Clardy et *al*. reported a rational synthesis of the first primary helical molecules, based upon the shape (bond angles and bond lengths) of the tetrahydrofuran ring system by a spiroannulation sequence starting from cyclopentanone by the intermediacy of a 2,5-dihydrofuran derivative V.7 (Scheme V.1).[319]



Scheme V.1

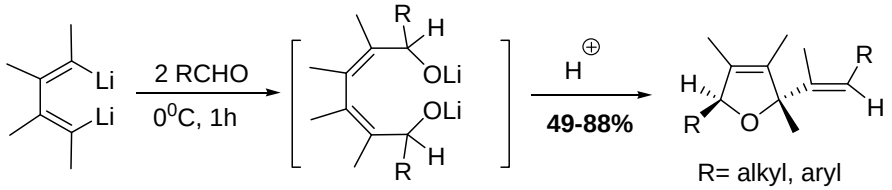
[315] a) Jiang, Z.; Yu, D.-Q. *J. Nat. Prod.* **1997**, *60*, 122; b) Jiang, Z.; Chen, R.-Y.; Chen, Y.; Yu, D.-Q. *J. Nat. Prod.* **1998**, *61*, 86
[316] a) Inoue, Y.; Deguchi, S.; Hakushi, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3031; b) Werner, R. E.; Reynolds, W. B. *J. Am. Chem. Soc.* **1947**, *69*, 633
[317] Daves Jr., G. D.; Hallberg, A. *Chem. Rev.* **1989**, *89*, 1433
[318] For a review on the synthesis of 2-substituted dihydrofurans see Kilroy, T. G.; O'Sullivan, T. P.; Guiry, P. J. *Eur. J. Org. Chem.* **2005**, 4929
[319] Cange, D.; Magnus, P.; Bass, L.; Arnold, E. V.; Clardy, J. *J. Am. Chem. Soc.* **1980**, *102*, 2134

The group of Kim and Do developed a highly diastereoselective version (up to > 99% dr) of this reaction using *α*-keto amides bearing *S*-indoline chiral auxiliaries as shown in Scheme V.2:[320]



Scheme V.2

Polysubstituted 2,5-dihydrofurans were obtained in good to high yields with perfect regio- and stereoselectivities by treatment of 1,4-dilithio-1,3-diene derivatives with 2 equiv. of aldehydes (Scheme V.3):[321]

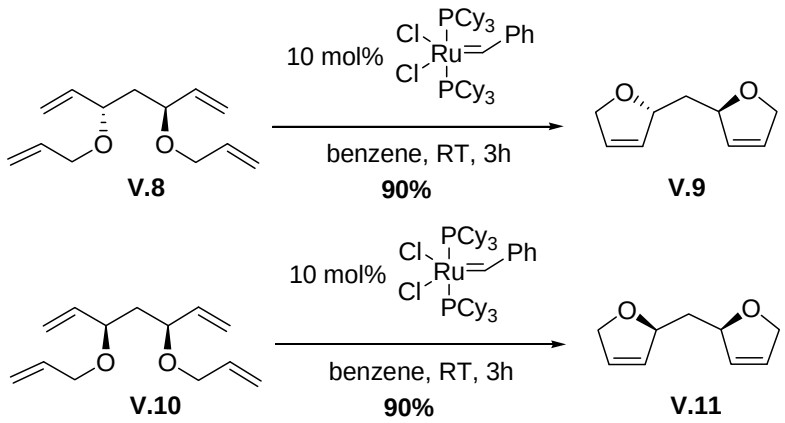


Scheme V.3

V.2.2. Metathesis Reactions

In their efforts toward the synthesis of natural and non-natural acetogenins and polyether antibiotics, Heck et *al*. developed an efficient application of the catalytic intramolecular olefin metathesis of acyclic tetraenes. This method allows the generation of a variety of polyunsaturated oxygen heterocycles (Scheme V.4):[322]

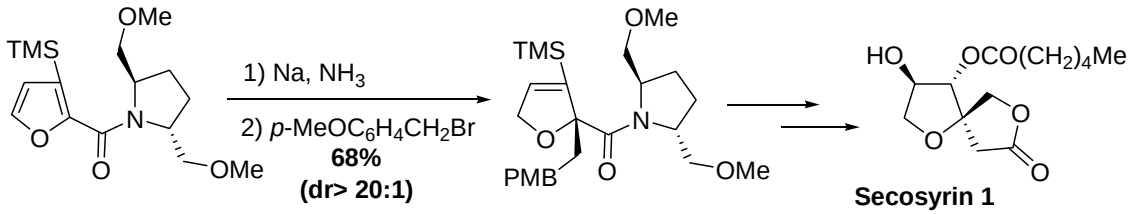
[320] Youn, S. W.; Kim, Y. H.; Hwang, J.-W.; Do, Y. *Chem. Commun.* **2001**, 996
[321] Chen, J.; Song, Q.; Li, P.; Guan, H.; Jin, X.; Xi, Z. *Org. Lett.* **2002**, *4*, 2269
[322] a) Baylon, C.; Heck, M. P.; Mioskowski, C. *J. Org. Chem.* **1999**, *64*, 3354; b) Heck, M. P.; Baylon, C.; Nolan, S. P.; Mioskowski, C. *Org. Lett.* **2001**, *13*, 1989



Scheme V.4

V.2.3. From Furan Derivatives

Donohoe and co-workers applied the Birch reduction using *C2* symmetrical amines as chiral auxiliaries of furan derivatives to the formal synthesis of (–)-Secosyrin 1 (Scheme V.5), a natural product isolated from *Pseudomonas syringae* pv. *tomato*.[323]



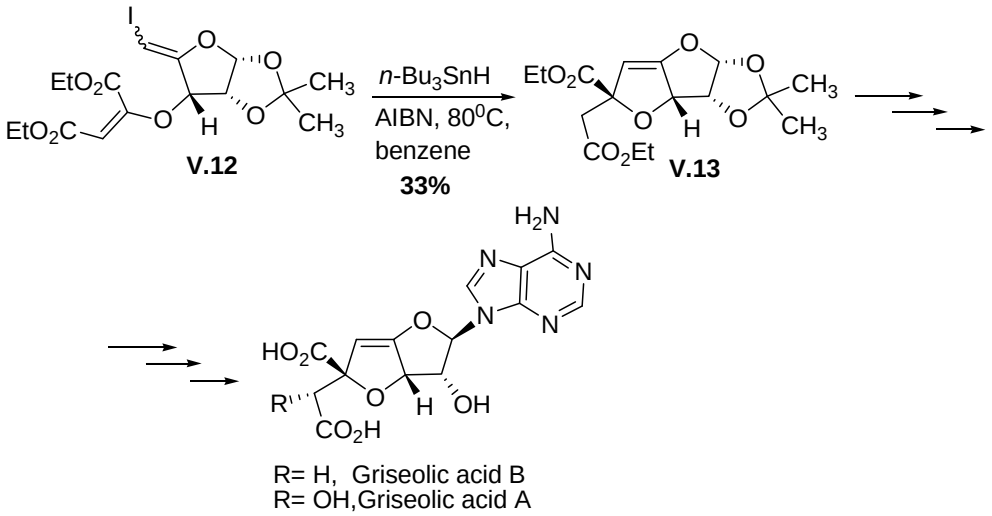
Scheme V.5

V.2.4. Radical Cyclisations

Knapp's group reported a novel vinyl radical cyclization reaction which affords the bicyclic vinyl ether V.13 with the appropriate stereochemistry for elaboration (seven steps) to griseolic acid B (Scheme V.6).[324]

[323] a) Donohoe, T. J.; Guillermin, J.-B.; Calabrese, A. A.; Walter, D. S. *Tet. Lett.* **2001**, *42*, 5841; b) Donohoe, T. J.; Fisher, J. W.; Edwards, P. J. *Org. Lett.* **2004**, *6*, 465

[324] Knapp, S.; Madduru, M. R.; Lu, Z.; Morriello, G. J.; Emge, T. J.; Doss, G. A. *Org. Lett.* **2001**, *3*, 3583

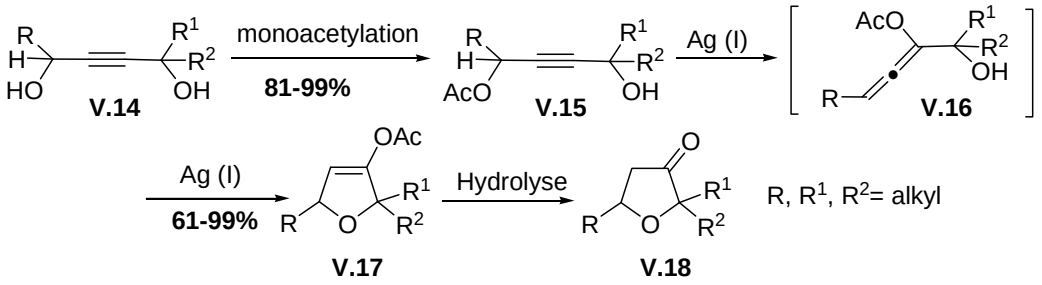


Scheme V.6

V.2.5. Addition of Oxygenated Nucleophiles to C=C Multiple Bonds

Silver Catalysis Leading to the Dihydrofuran Motif

A synthesis of dihydro-3(2*H*)-furanone enol acetates V.17 was found by Hiyama's group in their efforts to obtain 4,5-dihydro-3(2*H*)-furanones V.18 by regiocontrolled hydratation of 2-butyne-1,4-diols.[325] In order to introduce the oxygen function at one position of the triple bond with complete regioselectivity, selective monoacetylation of unsymmetrical 2-butyne-l,4-diols V.14 was carried out. Ag(I)-catalyzed cyclisation with acetoxyl migration to give V.16, and finally hydrolysis are involved to furnish product V.18. According to the authors, the transformation can be explained by a Ag(I)-catalyzed isomerization of the monoacetate V.15 to an allenyl acetate V.16, followed by Ag(I)-assisted cyclization.

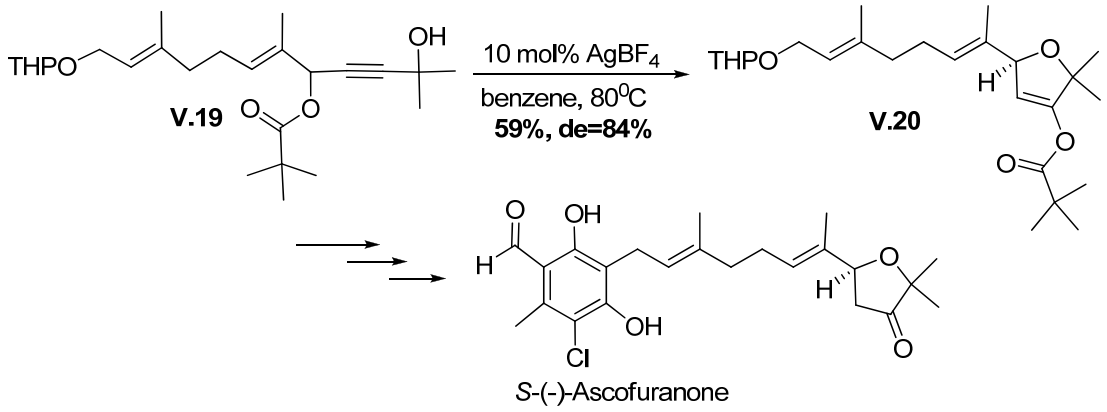


Scheme V.7

The transformation of enantiomerically enriched propargyl esters V.19 into dihydrofurans V.20 with complete enantiospecificity is achieved by Ag(I)-catalyzed rearrangement and cyclization. This sequence is successfully applied to the synthesis of an antitumor protective

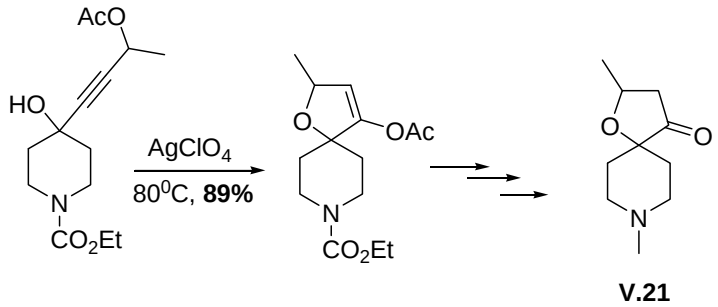
[325] Saimoto, H.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1981**, *103*, 4975

and hypolipidemic antibiotic, *S*-(-)-ascofuranone by Shigemasa and co-workers (Scheme V.8):[326]



Scheme V.8

The same approach was used by Wu et *al.* for the synthesis of spiromuscar-3-one derivatives of type V.21, potential therapeutical agents acting as muscarinic agonists (Scheme V.9):[327]

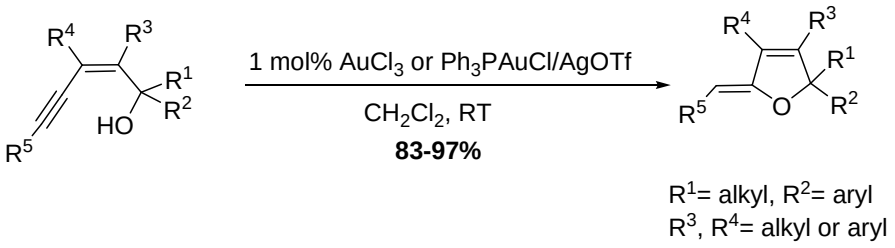


Scheme V.9

Gold Catalysis Leading to the Dihydrofuran Motif

Liu and co-workers reported the utilization of gold-(I) and gold-(III) catalysts for the cyclization of *Z*-enynols, offering an efficient and straightforward route to highly substituted dihydrofurans under extremely mild reaction conditions (Scheme V.10):[328]

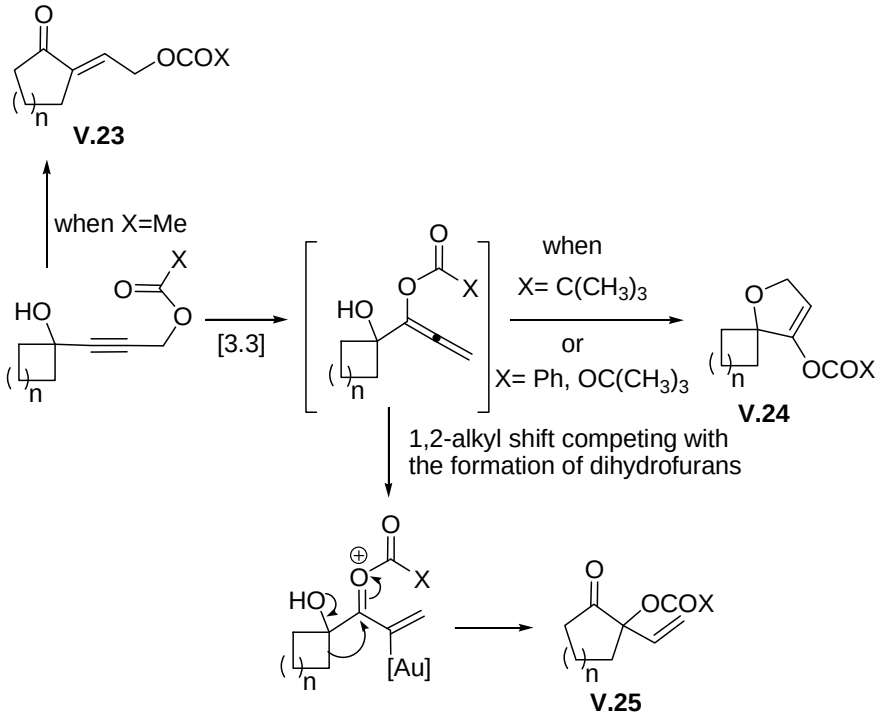
[326] Shigemasa, Y.; Yasui, M; Ohrai, S.-i.; Sasaki, M.; Sashiwa, H.; Saimoto, H. *J. Org. Chem.* **1991**, *56*, 910
[327] Wu, E. S. C.; Griffith, R. C.; Loch, J. T.; Kover, A.; Murray, R. J.; Mullen, G. B.; Blosser, J. C.; Machulskis, A. C.; McCreedy, S. A. *J. Med. Chem.* **1995**, *38*, 1558
[328] Liu, Y.; Song, F.; Song, Z.; Liu, M.; Yan, B. *Org. Lett.* **2005**, *7*, 5409



Scheme V.10

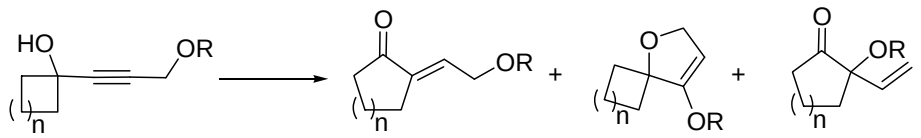
By analogy with our work (see Chapter V.6),[329] an efficient route to spirocyclic dihydrofurans *via* gold-catalyzed tandem [3,3]-sigmatropic rearrangement-cycloisomerization of 1-(3-hydroxypropynyl)cycloalkanol derivatives V.22 was reported by Shin's group.[330] The reaction profile proved to be highly dependent on the ring size, migrating group, as well as reaction conditions (Scheme V.11 and Table V.1).

The pivalate, *tert*-butoxycarbonyl and benzyl substituted alcohols reacted following the mechanistical pathway described by our group (i.e faster [3,3]-rearrangement followed by cycloisomerization, Scheme V.11) giving the corresponding spirocycles V.24 in moderate to excellent yields (Table V.1). Interestingly, changing the ligand to Au[*t*-Bu_2P(o-biphenyl)]OTf further increased the yield of V.24 and delivered the spirocycles in yields ranging from 61% to 98% (Entries 2, 4, 6-10 in Table V.1).



Scheme V.11

[329] Buzas, A.; Istrate, F.; Gagosz, F. *Org. Lett.* **2006**, *8*, 1957
[330] Yeom, H.-S.; Yoon, S.-J.; Shin, S. *Tet. Lett.* **2007**, *48*, 4817



V.22 **V.23** **V.24** **V.25**

Entry	Substrate	Condition	Product
1	**V.22a**, n=0, R=Piv	A	**V.24a, 60%**
2	**V.22b**, n=0, R=Piv	B	**V.24b, 73%**
3	**V.22c**, n=0, R=Boc	A	**V.24c, 68%**
4	**V.22d**, n=0, R=Boc	B	**V.24d, 75%**
5	**V.22e**, n=0, R=Bz	A	**V.24e, 66%**
6	**V.22f**, n=1, R=Ac	B	**V.24f, 61%**
7	**V.22g**, n=1, R=Piv	B	**V.24g, 81%**
8	**V.22h**, n=1, R=Bz	B	**V.24h, 98%**
9	**V.22i**, n=2, R=Ac	B	**V.24i, 92%**
10	**V.22j**, n=2, R=Bz	B	**V.24j, 93%**

Condition A: 5 mol% *in situ* formed Au(PPh_3)OTf
Condition B: 5 mol% Au[*t*-Bu_2P(*o*-biphenyl)]OTf

Table V.1

Another efficient method for the preparation of 2,5-dihyrofurans consists in the cyclization of hydroxyallenes, as it will de discussed in more detail in Chapter V.3.2.

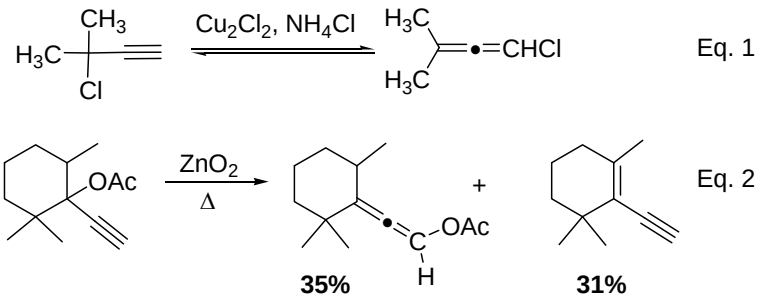
V.3. Preliminary Work in the Literature

V.3.1. Metal-Catalyzed [3,3] Ester Group Rearrangements

The transformation of propargylic esters into allenyl esters is an example of a [3,3] sigmatropic rearrangement.
In 1950, Hennion and co-workers observed the catalytic influence of cuprous chloride on the equilibrium of a chloroacetylene with its isomeric allene (Scheme V.12, Eq. 1).[331] This conversion was described as an 1,3-shift (Meyer-Schuster rearrangement)[332] and according to the authors it may be due to the intervention of a chelate-type intermediate. In 1956, Landor demonstrated the influence of zinc salts on acetylenic esters to give a modest yield of the corresponding rearranged acetoxyallene (Scheme V.12, Eq. 2).[333] Saucy and co-workers at

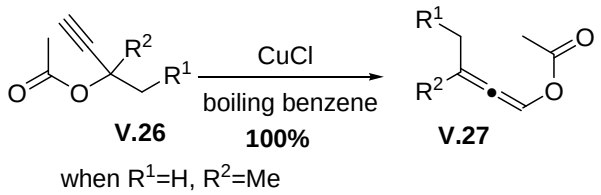
[331] Hennion, G. F.; Sheehan, J. T.; Maloney, D. E. *J. Am. Chem. Soc.* **1950**, *72*, 3542
[332] a) Meyer and Schuster, *Bcr.* **1922**, *66B*, 819; b) Hennion, G. F.; Maloney, D. E. *J. Am. Chem. Soc.* **1949**, *71*, 2813
[333] Landor, P. D.; Landor, S. R. *J. Chem. Soc.* **1956**, 1015

Hoffmann-La Roche found that silver salts were superior to copper and gold salts in catalyzing this latter type of transformation.[334]



Scheme V.12

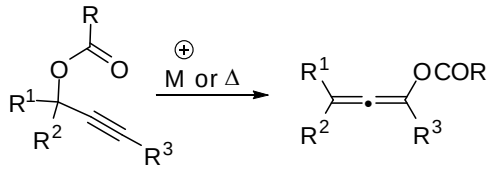
Allenyl acetate V.27 was formed quantitatively when heating tertiary propargyl acetate V.26 in benzene in the presence of copper (I) chloride (Scheme V.13):[335]



Scheme V.13

Silver Catalyzed [3,3] Rearrangements

A variety of methods has been utilized to effect the silver ion catalyzed rearrangement of tertiary propargyl acetates and substituted nitrobenzoates (Scheme V.14).[336] Reported yields vary from 40 to 65% depending upon the degree of substitution and the steric nature of the substituents R^1, R^2 and R^3. Terminal alkynes generally give better yields than internal alkynes. Tertiary esters generally rearrange with higher yields and shorter reaction times than secondary esters.



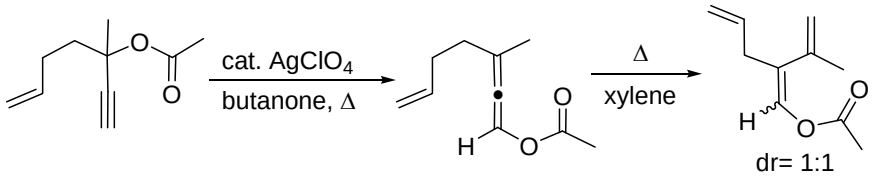
Scheme V.14

[334] a) Saucy, G. R.; Marbet, R.; Lindlar, H.; Isler, O. *Helv. Chim. Acta.* **1959**, *42*, 1945; b) Marbet, R. et *al.*, U. S. Patent **1986**, 3.211.780

[335] Cookson, R. C.; Cramp, M. C.; Parsons, P. J. *J. Chem. Soc. Chem. Comm.* **1980**, 197

[336] a) Hoffmann-La Roche, 7 and Co., Akt.-Ges. Belgian Patent 617 174 *Chem. Abstr.* **1963**, *59*, 1540; b) Day, A. C.; Whiting, M. C. *J. Chem. Soc. C.* **1966**, 464; c) Benn, W. R. *J. Org. Chem.* **1968**, *33*, 3113; d) Schlossarczyk. H.; Sieber, W.; Hesse, M.; Hanson, H.-J.; Schmid, H. *Helv. Chim. Acta.* **1973**, *58*, 875 and numerous references cited therein

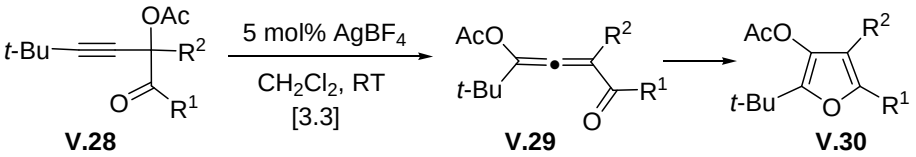
The rearrangement does not tolerate the presence of an aromatic substituent at R^1, R^2 or R^3. Mixtures of products are often obtained. The reported procedures normally employ chlorobenzene or aqueous dioxane as the solvent and utilize up to 10 mol % amounts of $AgNO_3$, Ag_2CO_3, $AgClO_4$, $AgBF_4$, or AgOAc as the catalyst.[336d]
Schiavelli's group reported a more convenient method for the preparation of 3,3-disubstituted terminal allenyl acetates, nitrobenzoates, and diethyl phosphates in dichloromethane at 35°C using reaction times of 2-3 h and 2.5 mol % $AgC1O_4$ or $AgBF_4$.[337]
Cookson et *al.* observed a clean conversion to the corresponding allenyl ester intermediate when the acetate (Scheme V.15) was treated with catalytic quantities $AgClO_4$. This intermediate underwent an additional [3,3] rearrangement when further heated in boiling xylene (Scheme V.15):[338]



Scheme V.15

As described in detail in Chapter V.2.5, the silver salt catalyzed rearrangement of tertiary propargyl acetates into allenyl acetates (Scheme V.14) was largely employed by the groups of Hiyama,[325] Shigemasa[326] and Wu[327] for the synthesis of different 4,5-dihydro-3(2*H*)-furanone derivatives. However, these transformations required 10% of $AgBF_4$ in refluxing benzene and furnished the dihydrofurans in moderate yields (≈ 60%). Moreover, the cyclisation was generally limited to the use of tertiary alcohols.

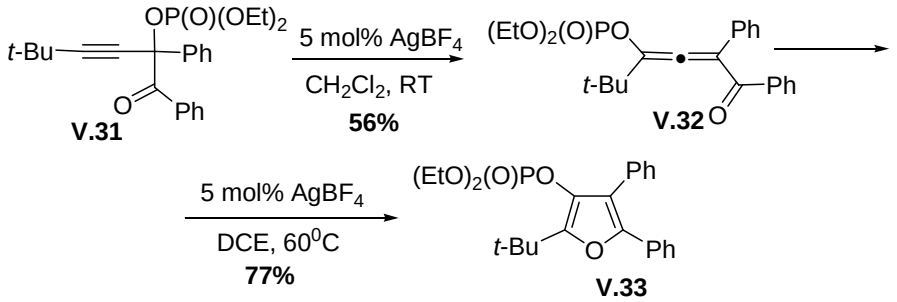
Recently, Gevorgyan et *al.* reported a cascade involving a [3,3] shift/1,2-acyloxy, phosphatyloxy, and sulfonyloxy migration/cycloisomerization sequence to directly afford tri- and tetrasubstituted furans.[339]
For example, in the presence of $AgBF_4$, ketones V.28 smoothly underwent a [3,3] shift/1,2-migration/cycloisomerization sequence to directly afford tetrasubstituted furans V.30 in excellent yields of 73% for R^1=Me and R^2=Ph and of 99% for R^1=R^2=Ph (Scheme V.16):



Scheme V.16

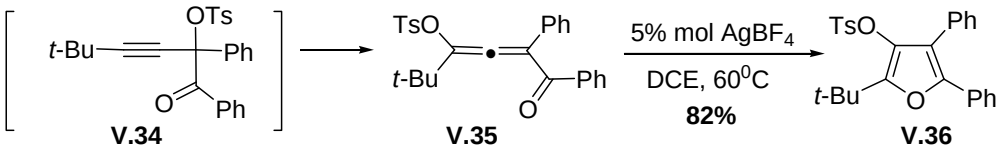
Furthermore, incorporation of hetero migrating groups into the [3,3] shift/1,2-migration/ cycloisomerization cascade was possible when phosphatyloxy analogue of V.28, ketone V.31, underwent cycloisomerization at 60°C in the presence of 5% $AgBF_4$ to afford furanyl phosphate V.33 in 77% yield (Scheme V.17):

[337] Oelberg, D. G.; Schiavelli, M. D. *J. Org. Chem.* **1977**, *42*, 1804
[338] Bowden, B.; Cookson, R. C.; Davis, H. A. *J. Chem. Soc. Perkin Trans. 1* **1973**, 2634
[339] Sromek, A. W.; Kel'in, A. V.; Gevorgyan, V. *Angew. Chem. Int. Ed.* **2004**, *43*, 2280



Scheme V.17

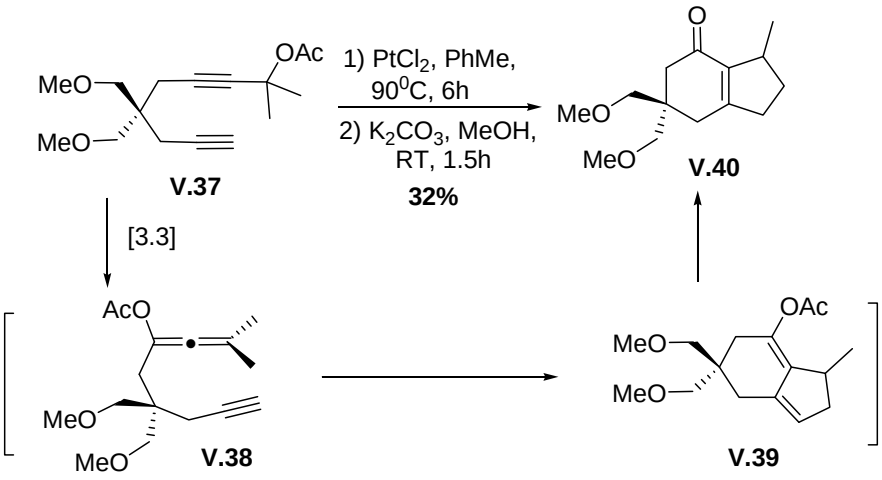
The analogous transformation with propargyl tosylates V.34 gave the expected tosyl allene V.35, apparently through a thermal [3,3] tosyloxy shift. Allene V.35 underwent smooth cycloisomerization at 60°C in the presence of 5% $AgBF_4$ to produce tosyl furan V.36 in 82% yield (Scheme V.18).



Scheme V.18

Platinum Catalyzed [3,3] Rearrangements

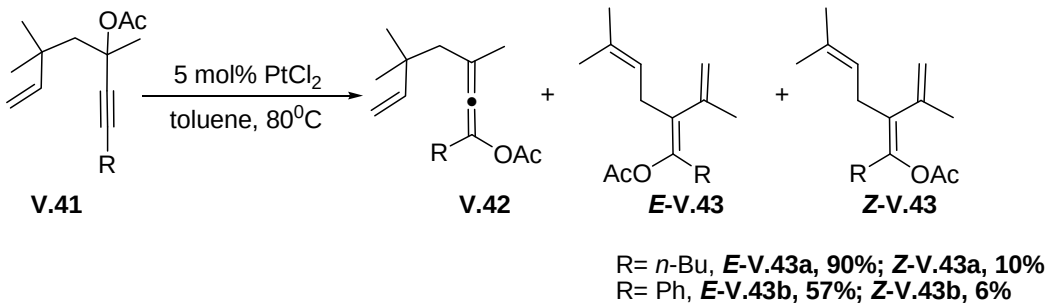
Malacria et *al.* have designed a $PtCl_2$-catalyzed [3,3] rearrangement/cycloisomerization tandem reaction from a diyne acetate V.37. Initial 1,3-migration of the acetate group affords intermediate allenylester V.38 that undergoes cycloisomerization to provide dienyl acetate V.39 (Scheme V.19).[340]



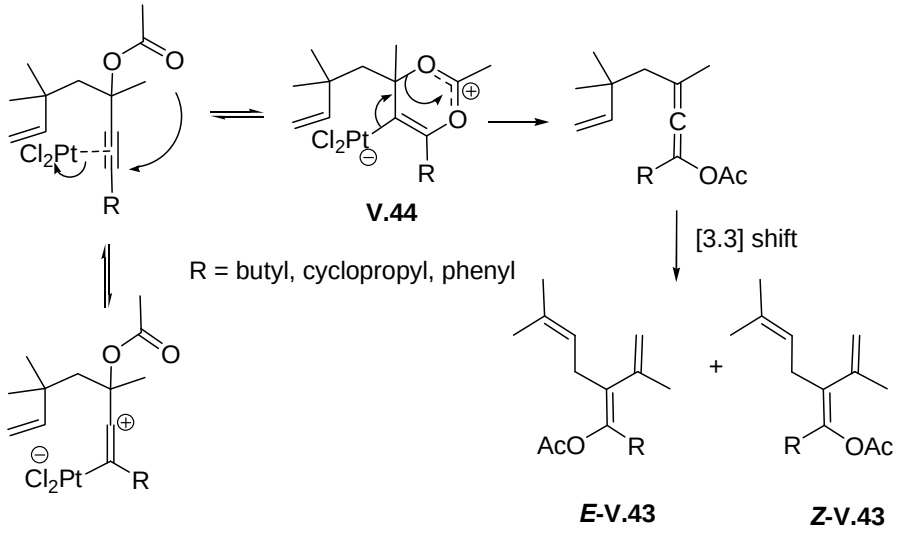
[340] Cadran, N.; Cariou, K.; Hervé, G.; Aubert, C.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. *J. Am. Chem. Soc.* **2004**, *126*, 3408

Scheme V.19

The same group found that 1,6-enyne systems possessing an acetate group at the propargyl position (V.41 in Scheme V.20) undergo tandem $PtCl_2$-catalyzed thermal [3,3] rearrangements leading to trienes V.43.[341] The mechanism outlined in Scheme V.21 is operational when R= *n*-butyl, cyclopropyl or phenyl due to the ability of these groups to stabilise a positively charged center as in intermediate V.44:



Scheme V.20



Scheme V.21

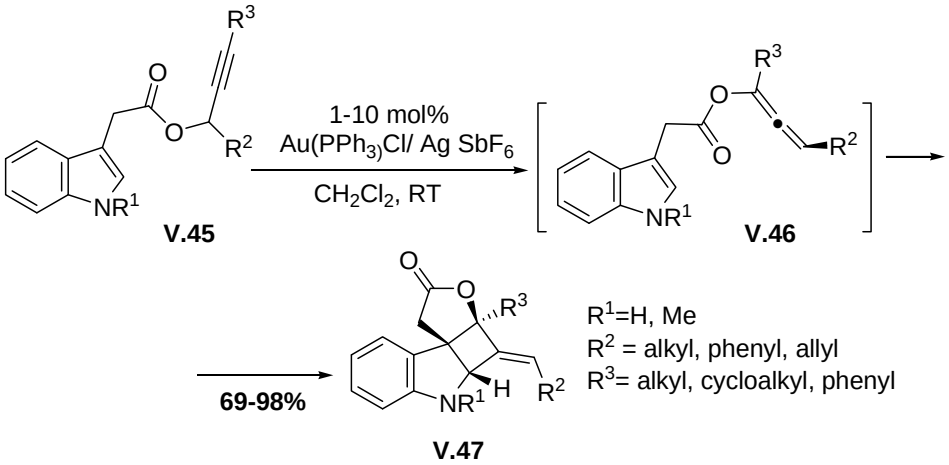
Marco-Contelles and Anjum also observed the formation of intermediate acetoxy-allenes when propargyl acetates derived from geranyl and neryl ketones were treated with $PtCl_2$ in toluene.[342]

Gold Catalyzed [3,3] Rearrangements

[341] Cariou, K.; Mainetti, E., Fensterbank, L.; Malacria, M. *Tetrahedron* **2004**, *60*, 9745
[342] Anjum, S.; Marco-Contelles, J. *Tetrahedron* **2005**, *43*, 4793

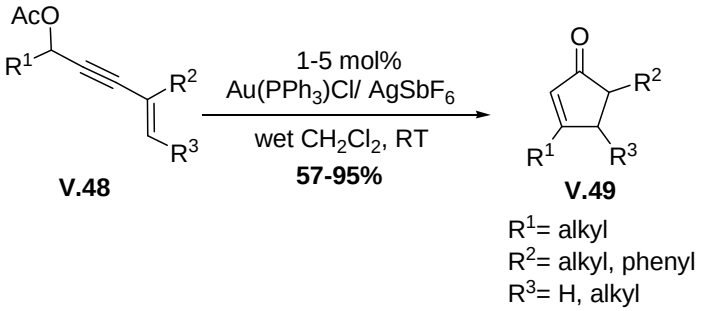
Capitalizing on early work conducted with $PtCl_2$[340,341] and silver salts (see the chapter before), propargylic acetates have played a special role in the field of gold-catalyzed activation of alkynes because of the ability of the ester function to migrate. The particularity of gold catalysts is that in addition to mediating the [3,3] rearrangement, they mildly activate the allene moiety for subsequent reactivity.[343]
For example, Gevorgyan and *al.* found that $AuCl_3$ is as efficient as $AgBF_4$ in catalyzing the [3,3] shift/1,2-migration/cycloisomerization sequence of ketones V.28 to directly afford tetrasubstituted furans V.30 (Scheme V.16) as discussed in the previous chapter.[339]

In 2005, Zhang reported the tandem cationic Au(I)-catalyzed activations of both propargylic esters V.45 and the *in situ* generated allenylic esters V.46, leading to the synthesis of highly functionalized 2,3-indoline-fused cyclobutanes V.47 *via* sequential 3,3-rearrangement and [2 + 2] cycloaddition (Scheme V.22):[344]



Scheme V.22

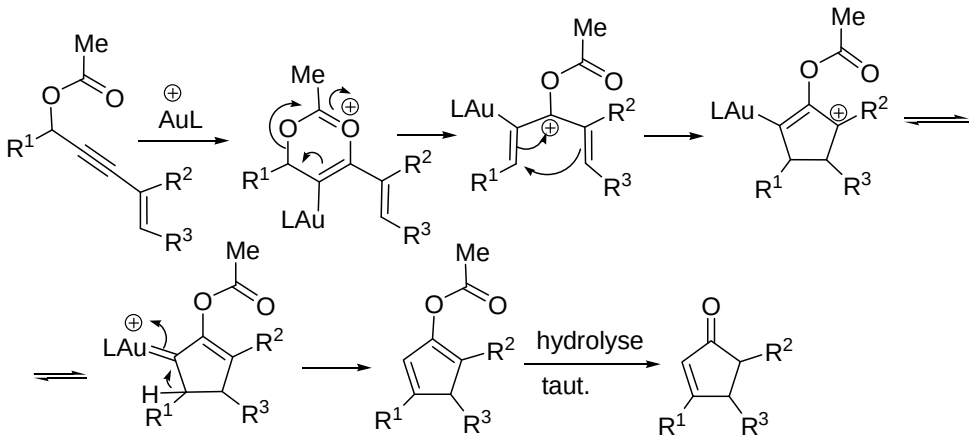
In 2006, Zhang and Wang published the Au(I) catalyzed cycloisomerization of 1,3-enynes, *via* a cascade of sigmatropic [3,3] rearrangement and Nazarov cyclization reactions to afford substituted cyclopentenones V.49.[345] This method enabled an efficient access to a range of 3,5-disubstituted and 3,4,5-trisubstituted cyclopentenones, as well as several bicyclic enones.



[343] For a recent review on propragylic esters in gold catalysis, see: Marion, N.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2007**, *46*, 2750
[344] Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804
[345] Zhang, L.; Wang, S. *J. Am. Chem. Soc.* **2006**, *128*, 1442
a); b); c) Zhang, L; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271

Scheme V.23

This transformation can be rationalized by the series of individual mechanistic steps depicted in Scheme V.24:



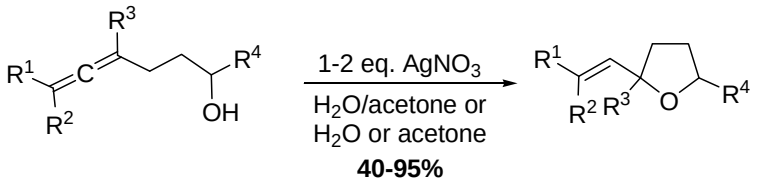
Scheme V.24

V.3.2. Cyclization of Hydroxyallenes

Transition metals coordinate to allenes, allowing the attack of tethered nucleophiles, leading to the formation of various heterocycles.[346]

Silver Promoted Cyclisations

Cyclisation of allenic alcohols was among the first examples of metal-catalyzed heterocyclization reactions. Indeed, while trying to isolate and separate a mixture of isomeric alkynyl and allenic alcohols with ammoniacal silver nitrate, Goré and Balme observed the quantitative formation of cyclisation products (dihydropyrans).[347] Exploring this reaction, Goré's group showed that, in the presence of silver nitrate, γ-allenic alcohols were indeed efficiently converted into tetrahydrofurans bearing a vinyl group at the position adjacent to the oxygen atom (Scheme V.25):

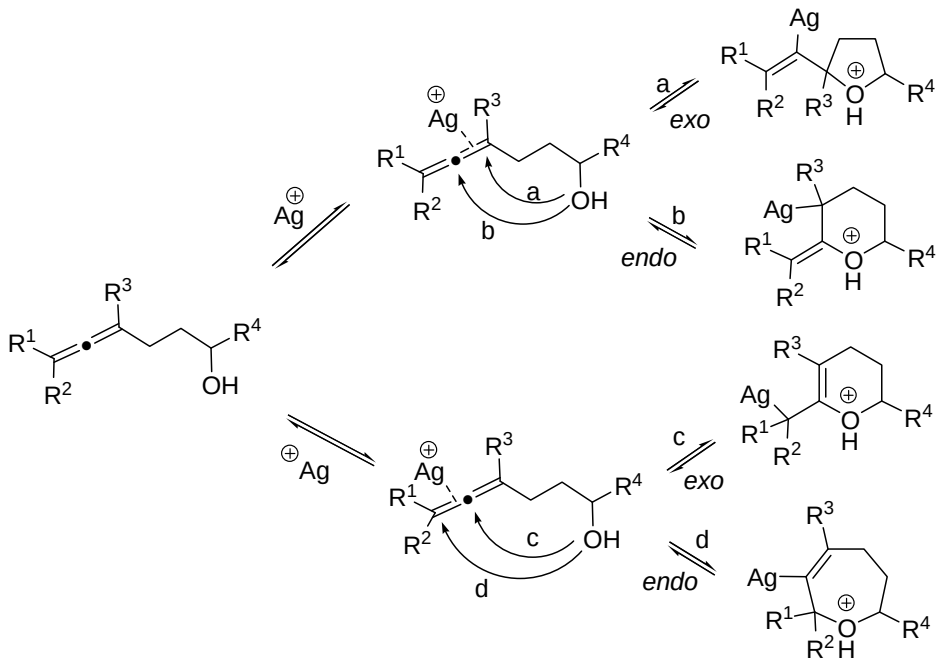


Scheme V.25

[346] For a general review on the activation of allenes by metal catalysts, see: a) Zimmer, R.; Dinesh, C.; Nandanan, E.; Khan, F. *Chem. Rev.* **2000**, *100*, 3067. b) Ma, S. *Chem. Rev.* **2005**, *105*, 2829

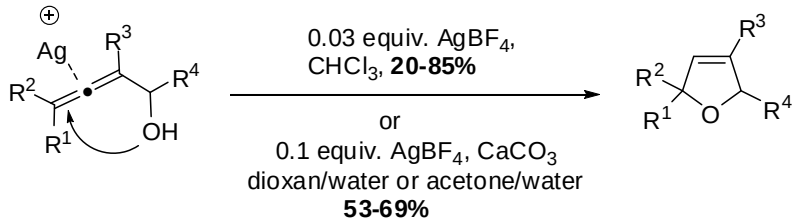
[347] Balme, G. Ph.D. Thesis, University Claude Bernard, Lyon, 1**979**

The mechanism clearly involved the coordination of the double bond closer to the hydroxyl group and then an intramolecular addition of the hydroxyl group to this π-complex (Scheme V.26). Among the four possible cyclization pathways, only the route leading to the smallest cycle (pathway a in Scheme V.26) is operating whatever the substitution, in agreement with the Baldwin rules.[348]



Scheme V.26

In parallel, Claesson and Olsson found that silver tetrafluoroborate was the catalyst of choice for the ring closure of *α*-allenic alcohols (Scheme V.27).[349]

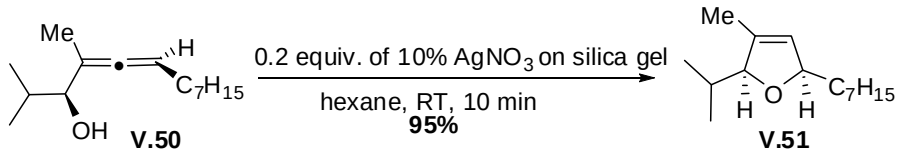


Scheme V.27

From a mechanistic point of view, and as expected from Baldwin rules with such a short chain between the allenic and hydroxy reactive parts, it is no longer the internal double bond of the allenic system, which is activated by Ag coordination but the terminal one. The cyclisation is no longer following an *exo-trig* pathway but an *endo-trig* pathway, leading to the formation of 2,5-dihydrofurans.

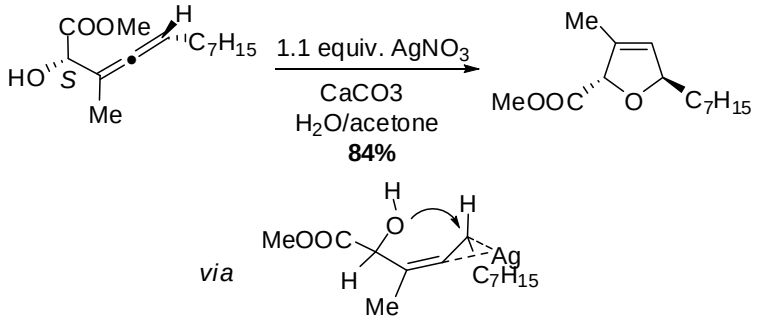
[348] Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734
[349] Olsson, L. I.; Claesson, A. *Synthesis* **1979**, 743

An interesting stereospecific version of this reaction was proposed by Marshall et *al.* As shown in Scheme V.28, the use of optically pure allenylcarbinol V.50 gave *cis*-2,5-dihydrofuran V.51 in high yield.[350]



Scheme V.28

With a stereodefined allene, the chirality at the hydroxyl group was preserved and thus induced the stereospecific formation of a *trans*- or *cis*-2,5-dihydrofuran: the *S* stereochemistry at the hydroxylated carbon gave the *trans* isomer, while the *R* gave the *cis* (Scheme V.29).

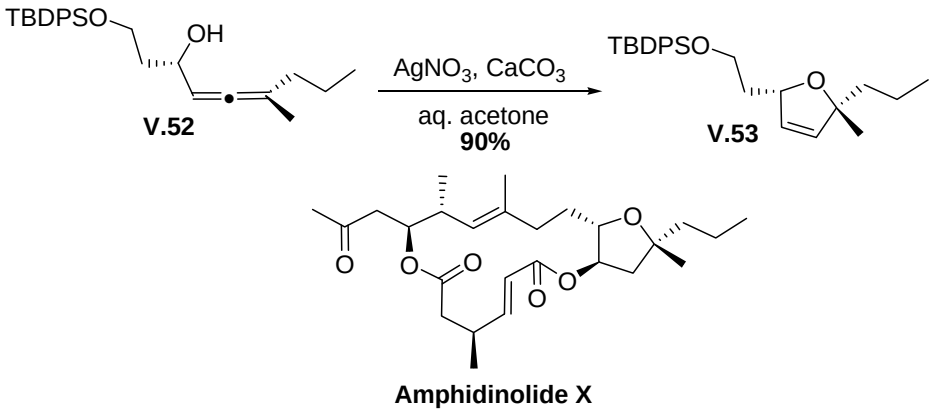


Scheme V.29

Fürstner et *al.* also reported that allenyl alcohol V.52 cyclized in the presence of $AgNO_3$ to afford dihydrofuran V.53 with complete chirality transfer; however, a stoichiometric amount of the silver salt was needed in this case (Scheme V.30).[351] This step was used in the total synthesis of Amphidinolide X, a secondary metabolite isolated from the marine dinoflagellate *Amphidinium* sp. endowed with promising cytotoxicity against murine lymphoma and human epidermoid carcinoma.

[350] a) Marshall, J. A.; Bartley, G. S. *J. Org. Chem.* **1995**, *60*, 5966; b) Marshall, J. A.; Wang, X. J. *J. Org. Chem.* **1991**, *56*, 4913

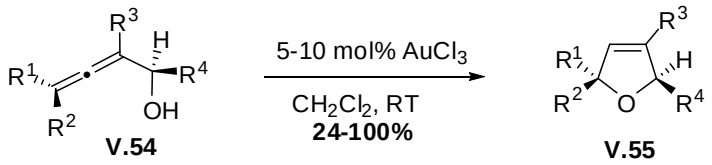
[351] Lepage, O.; Kattnig, E.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 15970



Scheme V.30

Gold Promoted Cyclisations

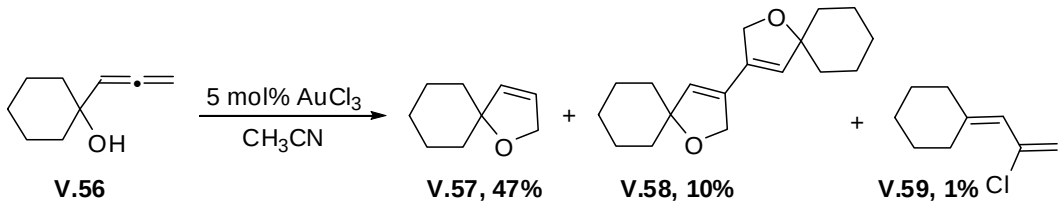
Krause and Hoffmann-Röder showed that gold(III) chloride smoothly converted functionalized α-hydroxyallenes V.54 into the corresponding 2,5-dihydrofurans V.55. This cyclization method was applied to alkyl- and alkenyl-substituted allenes, which furnished tri- and tetrasubstituted dihydrofurans in good to excellent yields and with complete axis-to-center chirality transfer (Scheme V.31).[352]



R^1= *t*-Bu, H, $H_2C{=}CH(CH_2)_2$; R^2= Me, *n*-Bu, *n*-Hex, H;
R^3= H, Me; R^4= CO_2Et, CO_2Me, CH_2OH, CH_2OTBS, CH_2OMe

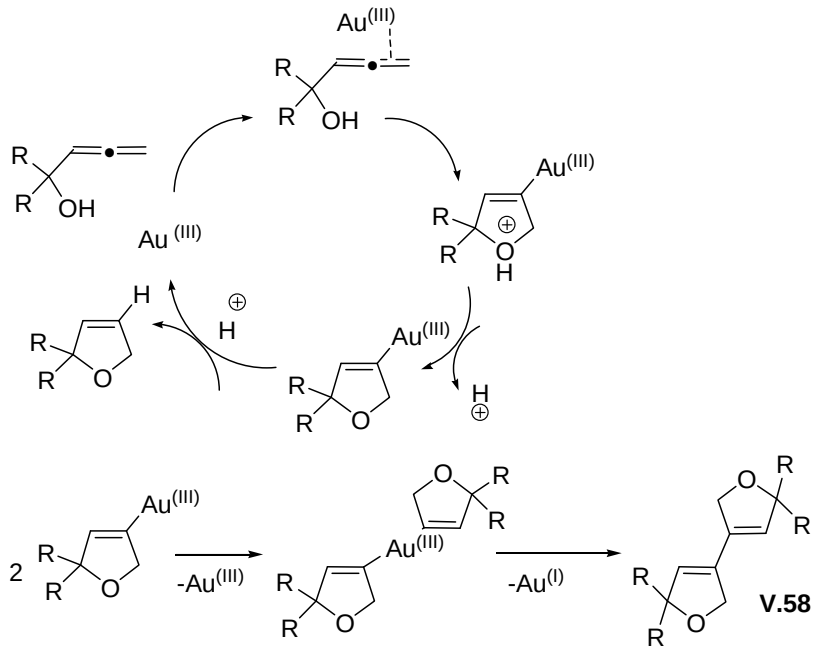
Scheme V.31

Evidence for the *in situ* reduction of gold (III) to gold (I) during the cyclization of allenyl carbinols was reported recently by Hashmi's group.[353] The authors also suggest a possible mechanism accounting for the observed side-product V.58 (Scheme V.32).



Scheme V.32

[352] a) Hoffmann-Röder, A.; Krause, N. *Org. Lett.* **2001**, *3*, 2537; see also: b) Morita, N.; Krause, N. *Org. Lett.* **2004**, *6*, 4121
[353] Hashmi, A. K. S.; Blanco, M. C.; Fischer, D.; Bats, J. W. *Eur. J. Org. Chem.* **2006**, 1387



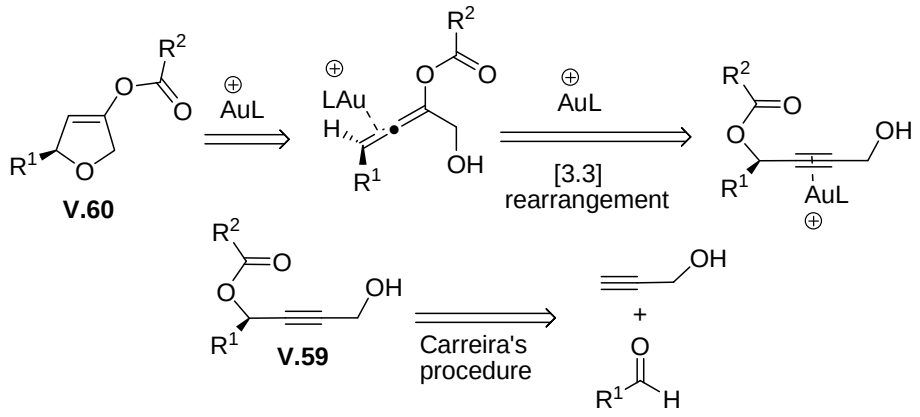
Scheme V.33

Compared to the well established Ag (I)-promoted method,[349, 351] the use of gold(III) chloride not only increases the reaction rate but also allows the transformation of notoriously difficult substrates, e.g., alcohols and silyl ethers.

V.4. Our Synthetic Approach and First Experiments

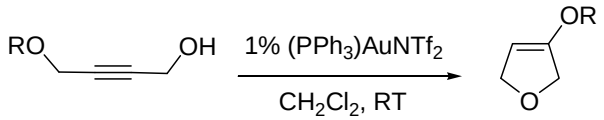
By analogy with the recently reported gold(III) chloride catalyzed cyclisation of hydroxyallenes to polysubstituted 2,5-dihydrofurans,[352] and considering the ability of gold(I) catalyst to promote acyloxy group migrations, we surmised that a suitable propargylic ester V.59 might be a valuable precursor for the synthesis of 2,5-dihydrofuran V.60 through a gold catalyzed sequence of allene formation and cycloisomerisation (Scheme V.34, Eq. 1). This approach would present numerous advantages because the corresponding chiral substrates are easily accessible by Carreira's procedure[354] and would allow a stereoselective synthesis of 2,5-dihydrofurans.

[354] a) Boyall, D.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605; b) El-Sayed, E.; Anand, N. K.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 3017; c) Anand, N. K.; Carreira, E. M. J. *Am. Chem. Soc.* **2001**, *123*, 9687; d) Sans Diez, R.; Adger, B.; Carreira, E. M. *Tetrahedron* **2002**, *58*, 8341



Scheme V.34

Different esters of 2-butyn-1,4-diol like the monoacetate, monobenzoate and monopivalate V.61a-c were first chosen as model substrates to validate our synthetic approach (Table V.2). These compounds, synthesized according to the procedure described by Holt and co-workers (see Table V.3),[355] were subjected to 1 mol% of the gold catalyst (PPh_3AuNTf_2). Among the esters tested, the benzoate derivative proved to be the most suitable precursor. To our delight, the desired 2,5-dihydrofuran V.62 was obtained in 85% yield by rearrangement of the monobenzoate V.61 in the presence of 1% $(Ph_3P)AuNTf_2$ in dichloromethane at room temperature. In contrast, the acetate and pivalate derivatives gave very poor results (Table V.2).



Entry	R, Product	Time	Yield[a]
1	Acetate, **V.62a**	90 min	**< 10%**
2	Pivalate, **V.62b**	60 min	**23 %**
3	Benzoate, **V.62c**	80 min	**85 %**

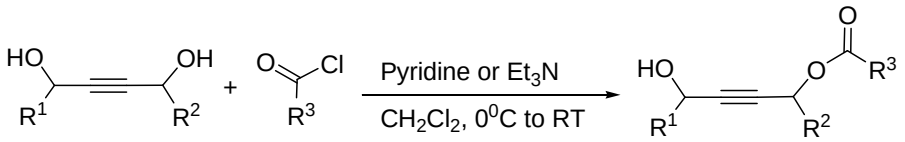
[a] The yields correspond to isolated product.

Table V.2

V.5. Synthesis of the Precursors

In order to test the scope of the reaction, various substituted butynediol monobenzoates were synthesized.
The synthesis of monoprotected butynediols was carried out following the procedure described by Holt's group (Table V.3):

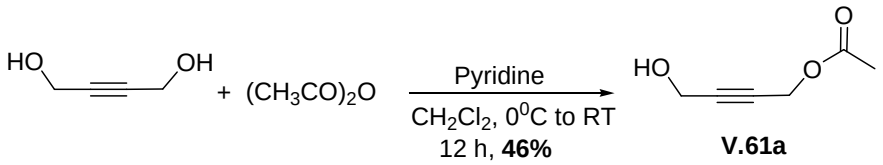
[355] Holt, K. E.; Swift, J. P.; Smith, M. E. B.; Taylor, S. J. C.; McCague, R. *Tet. Lett.* **2002**, *43*, 1545



Entry	Precursor	Time	Yield
1	**V.63a**, R^1=R^2= Me; R^3=Ph	12 h	**49%**
2	**V.68**, R^1=R^2= Me; R^3=$C(CH_3)_3$	20 h	**25%**

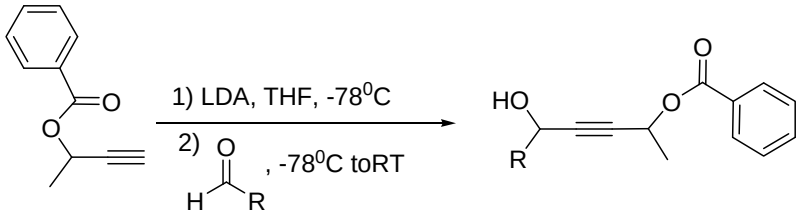
Table V.3

The acetate was prepared according to the known methods in the literature (Scheme V.35):[356]



Scheme V.35

The asymmetrically disubstituted butynediol monobenzoates were synthesized according to Table V.4:

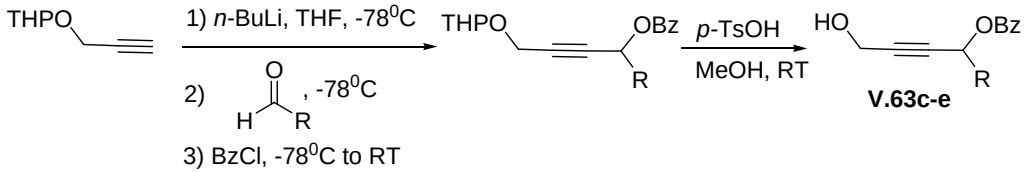


Entry	Precursor	Time	Yield
1	**V.63b**, R= *i*-Pr	4 h	**93%**

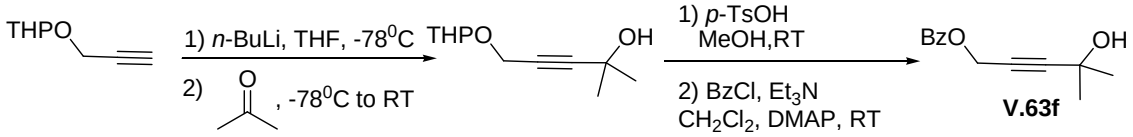
Table V.4

The benzoates V.63c-f were prepared starting from the tetrahydropyranyl protected propargylic alcohol:

[356] Pacheco, M. C.; Gouverneur, V. *Org. Lett.* **2005**, *7*, 1267

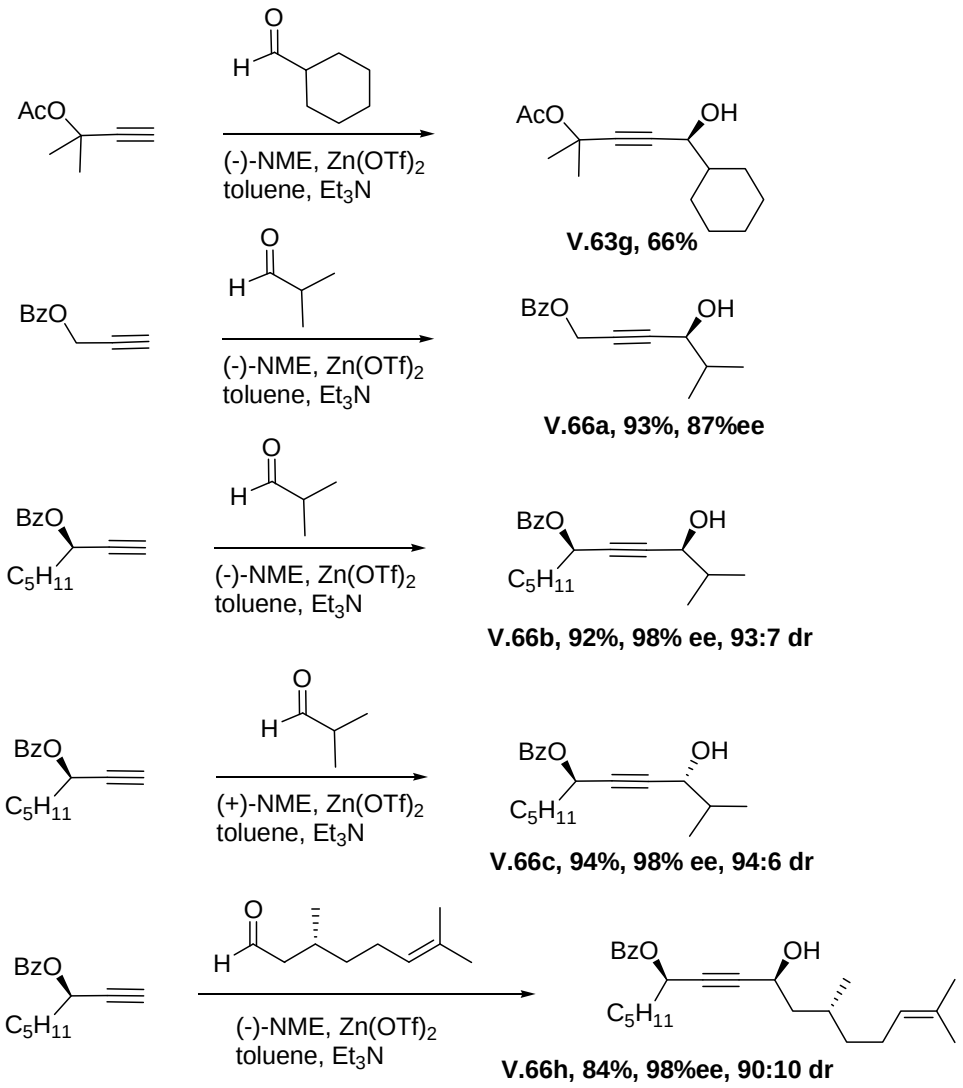


Entry	Substrate	Yield
1	**V.63c**, R= CH_2CH_2Ph	**63%**
2	**V.63d**, R= CH_2OCH_2Ph	**86%**
3	**V.63e**, R= $(CH_2)_4OBz$	**76%**

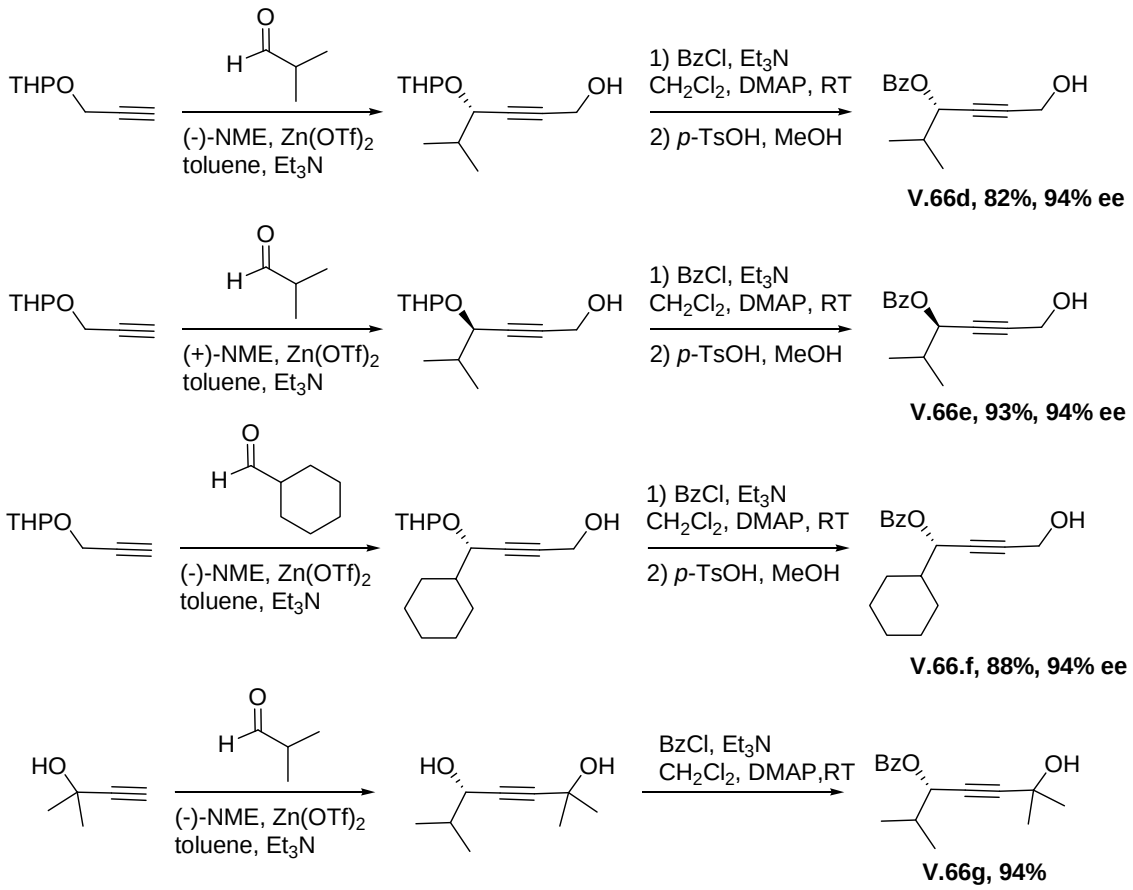


Scheme V.36

Substrates V.63g and V.66a-h were synthesized according to Carreira's procedures[354] (Schemes V.37 and V.38):


AcO
O
H
(-)-NME, Zn(OTf)2
toluene, Et3N
AcO
OH
V.63g, 66%
BzO
O
H
(-)-NME, Zn(OTf)2
toluene, Et3N
BzO
OH
V.66a, 93%, 87%ee
BzO
C5H11
O
H
(-)-NME, Zn(OTf)2
toluene, Et3N
BzO
OH
C5H11
V.66b, 92%, 98% ee, 93:7 dr
BzO
C5H11
O
H
(+)-NME, Zn(OTf)2
toluene, Et3N
BzO
OH
C5H11
V.66c, 94%, 98% ee, 94:6 dr
BzO
C5H11
O
H
(-)-NME, Zn(OTf)2
toluene, Et3N
BzO
OH
C5H11
V.66h, 84%, 98%ee, 90:10 dr

Scheme V.37



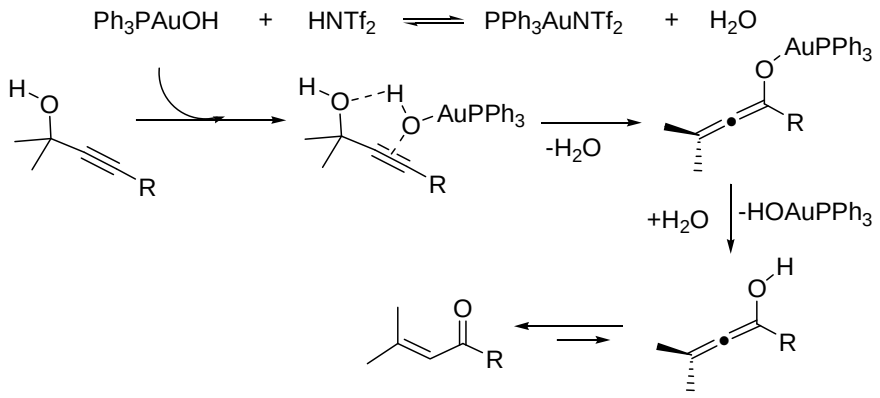
Scheme V.38

V.6. Au(I)-Catalyzed Formation of 2,5-Dihydrofurans

The substrates synthesized according to Schemes V.36-38 were submitted to the optimized reaction conditions (1 % $(Ph_3P)AuNTf_2$ in dichloromethane). To our delight, the transformation proved to be quite general and the reaction times were generally shorter than 1 hour, varying from 5 to 60 minutes. Various substituted butynediol monobenzoates V.63 were rearranged in presence of 2% of $(Ph_3P)AuNTf_2$ as the catalyst to afford the corresponding 2,5 dihydrofurans V.64 in generally high yields varying from 69% to 99% (Table V.5).

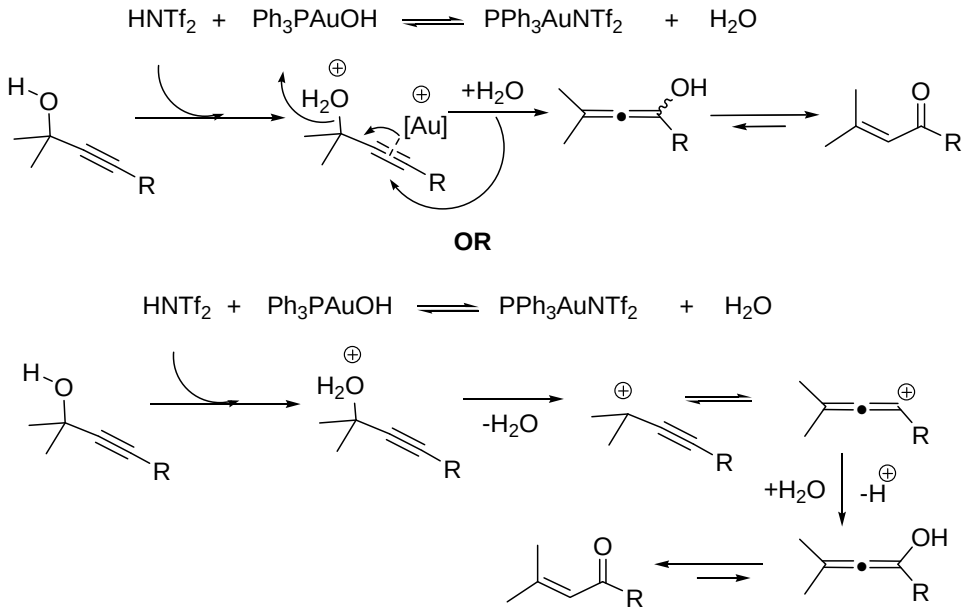
The presence of more sterically encumbered groups like isopropyl or cyclohexyl in the α position relative to the hydroxyl group was also tolerated (Table V.5, Entries 2 and 7). The reaction occurred with the same efficiency in the case of mono- (Entry 6), di- (Entries 1-5) and trisubstituted (Entry 7) propargylic esters. Moreover, no noticeable difference in reactivity was observed when primary or secondary alcohols were used. The presence of extra protected alcohols as in the case of benzyl- (Entry 4) and benzoyl derivatives (Entry 5) was also tolerated. The formation of enone V.65 was observed in case of substrate V.63f, probably arising from a competitive gold (I) catalyzed Meyer-Schuster

rearrangement.[68a,149,357] The adventitious water present in dichloromethane could participate in an equilibrium with $Ph_3PAuNTf_2$ furnishing Ph_3PAuOH which may lead to the formation of intermediate Ph_3PAu-allenolate species (Scheme V.39):[358]



Scheme V.39

Another possible mechanism explaining the formartion of enone V.65 would be the competitive acid ($HNTf_2$) catalyzed Meyer-Schuster rearrangement, with or without the involvement of the gold catalyst (Scheme V.40).[359]

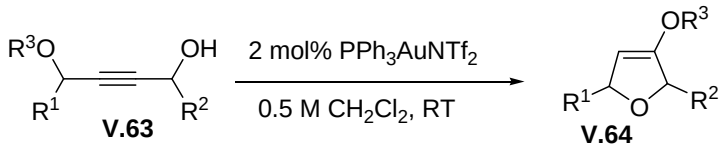


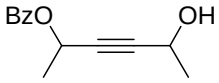
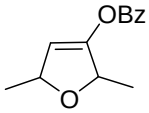
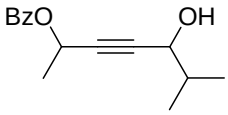
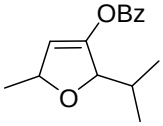
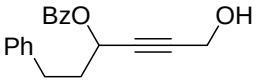
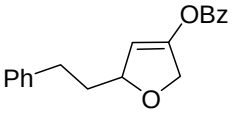
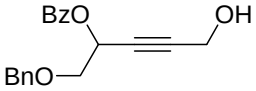
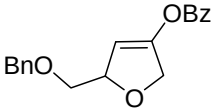
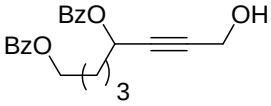
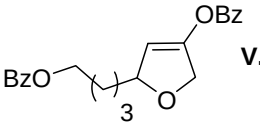
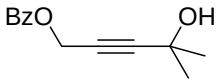
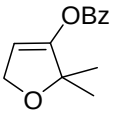
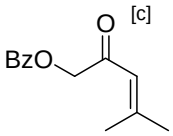
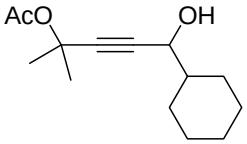
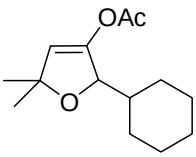
Scheme V.40

The competitive formation of enone V.65 may explain the moderate yield of dihydrofuran V.64f obtained in this case and the longer reaction time (60 minutes).

[357] Swaminathan, S.; Narayanan, K. V. *Chem Rev.* **1971**, *71*, 429
[358] Yu, M; Zhang, G.; Zhang, L Tetrahedron 2009, 65, in press doi: 10.1016/j.tet.2008.11.107
[359] Marion, N.; Carlqvist, P.; Gealageas, R.; de Frémont, P.; Maseras, F.; Nolan, S. P. *Chem. Eur. J.* **2007**, *13*, 6437

The acetate derivative V.63g was used for convenience reasons since the corresponding 3-acetoxy-3-methyl-but-1-yne was commercially available (Entry 7).



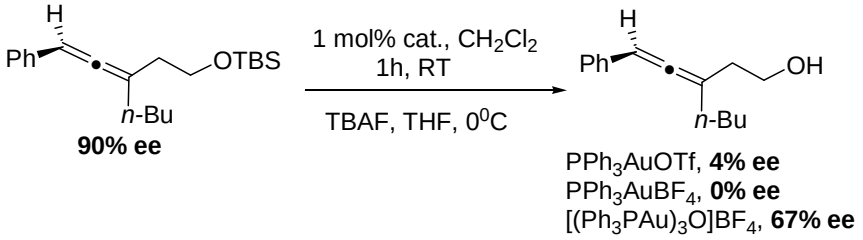
Entry	Substrate		Product		Time	Yield[b]
1		V.63a		V.64a	15 min	95%
2		V.63b		V.64b	20 min	92%
3		V.63c		V.64c	5 min	95%
4		V.63d		V.64d	20 min	99%
5		V.63e		V.64e	10 min	99%
6		V.63f	 V.64f	 V.65	60 min	69%
7		V.63g		V.64g	5 min	82%

[a] Reaction conditions: 0.5 M substrate in CH_2Cl_2, 2% of $(Ph_3P)AuNTf_2$, RT; [b] Isolated yields.
[c] **23%** of enone **V.65** was also isolated.

Table V.5

With these results in hand, we decided to turn our attention to the transformation of enantioenriched substrates. The procedure developed by Carreira and co-workers (Schemes V.37 and V.38)[354] was employed to prepare the enantioenriched butynediol monobenzoates. These substrates were subjected to the gold(I)-catalyzed rearrangement using the same experimental conditions (2% of $Ph_3PAuNTf_2$ in dichloromethane at room temperature). As outlined in Table V.6, the corresponding 2,5-dihydrofurans V.67a-h were obtained in good yields varying from 83 to 99%. In most cases excellent chirality transfer occurred from substrates to products. For example, in the case of enantioenriched alcohol V.66a, compound V.67a was obtained without loss of optical purity (Table V.6, Entry 1). The rearrangement of substrate V.66b possessing two asymmetric centers also took place with complete transfer of chirality and afforded *trans*-2,5-disubstituted dihydrofuran V.67b in 97% yield.[360] The *cis*-isomer V.67c was obtained in 99% yield by the rearangement of the parent diastereoisomer V.66c. This transformation proved to be very practical, allowing the synthesis of *cis* or *trans* 2,5-disubstituted dihydrofurans, depending on the diastereoisomer employed.

In the case of primary alcohols V.66d and V.66e, partial loss of optical purity was noticed under the same reaction conditions (Entries 4 and 5a). This effect was much more pronounced when the reaction was carried out on substrate V.66f bearing a bulkier cyclohexyl group (Entry 6a). A possible competition between a gold (I)-catalyzed isomerisation of the intermediate allene and the nucleophilic attack of the alcohol onto the gold-activated allene may explain this racemisation (see Scheme V.42). Additionally, the reduced Thorpe-Ingold effect in the case of primary alcohol substrates V.66d-f results in diminished reaction kinetics, allowing the isomerisation of the intermediate allene.
Some cases of poor chirality transfer were also reported by Toste's group, most likely as a result of rapid (5 min) racemization of the allene catalyzed by the gold (I) complex (Scheme V.41):[361]



Scheme V.41

Results depicted in Table V.6, Entries 5b-e prove that a proper choice of the gold catalyst and the experimental conditions could eliminate in a large extent the erosion of optical purity. Indeed, carrying out the cycloisomerization reaction of V.66e at 0°C with 2% of (Ad_2*n*-BuP)$AuNTf_2$ gave rise to V.67e in nearly quantitative yield and 90% ee. This observation could be explained by the fact that (Ad_2*n*-BuP)$AuNTf_2$ is a less electrophilic catalyst (due to the donor abilities of the phosphine employed) than (Ph_3P)$AuNTf_2$. The use of this less electrophilic catalyst and conducting the reaction at 0^0C might slow down the isomerization

[360] Structure and stereochemistry determined by full NMR analysis, see the experimental part
[361] Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 15978

of the intermediate allene without disfavoring the cyclisation. It is also interesting to note that the use of the more electrophilic catalyst [(*p*-$CF_3Ph)_3P$]$AuNTf_2$ whose reactivity was similar to (Ph_3P)$AuNTf_2$, had the opposite effect leading to the 2,5-dihydrofuran derivative V.67e only with 66% ee (Entry 5b). The transfer of optical information was improved also in the case of primary alcohol substrate V.66f when (Ad_2*n*-BuP)$AuNTf_2$ was used as catalyst at 0^0C (Entry 6b).

Tertiary alcohol V.66g bearing two methyl groups at the α position relative to the alcohol afforded 2,5-dihydrofuran V.67g in 95% yield with a complete transfer of chirality under the general reaction conditions (Entry 7). A Thorpe-Ingold effect approaching the nucleophilic alcohol to the gold (I)-activated allene may be responsible for the reactivity observed in this case (Figure V.9):

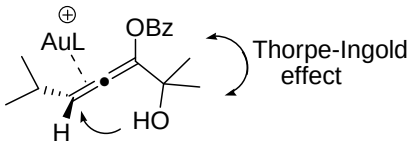
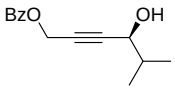
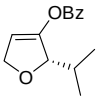
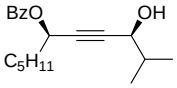
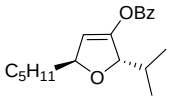
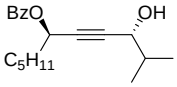
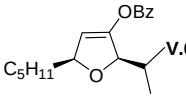
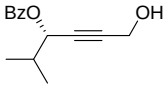
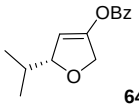
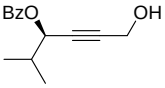
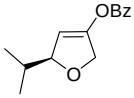
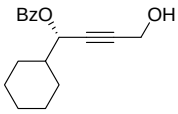
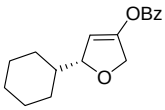
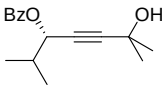
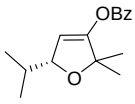
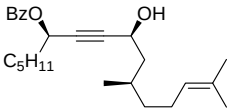
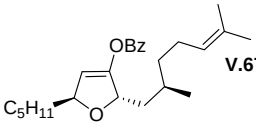


Figure V.9

The gold catalyzed rearrangement of the functionalized alkyne bearing three asymmetric centers V.66h was exceptionally efficient and furnished the corresponding *trans*-2,5-disubstituted dihydrofuran V.67h in 99% yield and complete transfer of the stereochemical information (Entry 8).[360]

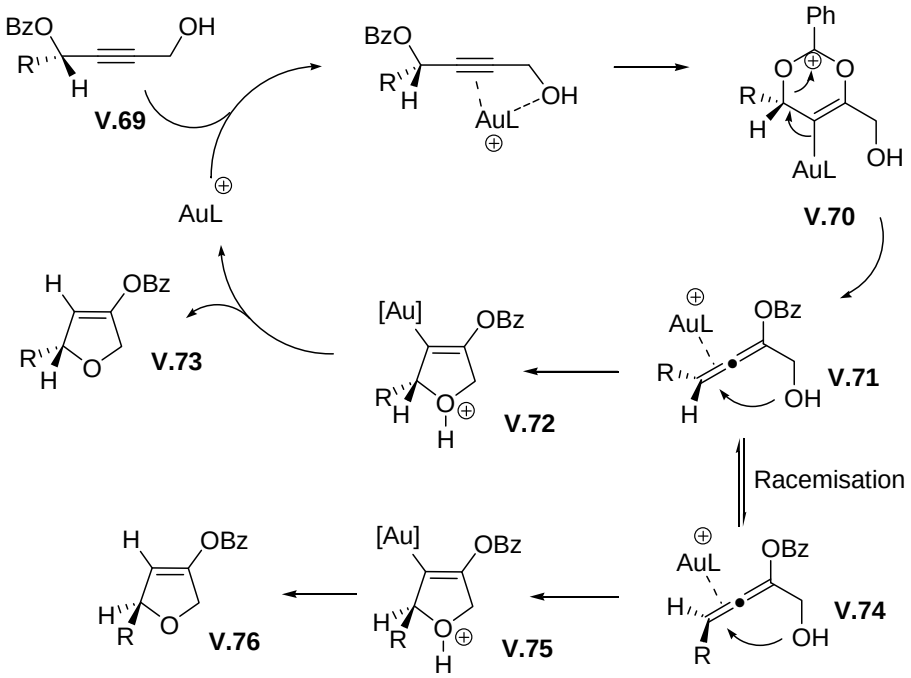
Entry	Substrate	Product	Time	Yield[b]
1	 **V.66a** **87% ee**	 **V.67a** **86% ee**	3 h	**83%**
2	 **V.66b** **93:7 dr** **> 98% ee**	 **V.67b** **93:7 dr** **> 98% ee**	40 min	**97%**
3	 **V.66c** **94:6 dr** **> 98% ee**	 **V.67c** **92:8 dr** **> 98% ee**	35 min	**99%**
4	 **V.66d** **94% ee**	 **V.67d** **64% ee**	10 min	**99%**
5	 **V.66e** **96% ee**	 **V.67e**		
	a- 2% $(Ph_3P)AuNTf_2$, RT	**64% ee**	15 min	**99%**
	b- 2% $[(pCF_3Ph)_3P]AuNTf_2$, RT	**66% ee**	15 min	**99%**
	c- 2% $(Ad_2nBuP)AuNTf_2$, RT	**74% ee**	20 min	**99%**
	d- 2% $(Ph_3P)AuNTf_2$, 0°C	**84% ee**	65 min	**99%**
	e- 2% $(Ad_2nBuP)AuNTf_2$, 0°C	**90% ee**	120 min	**99%**
6	 **V.66f** **94% ee**	 **V.67f**		
	a- 2% $(Ph_3P)AuNTf_2$, RT	**42% ee**	10 min	**89%**
	b- 2% $(Ad_2nBuP)AuNTf_2$, 0°C	**77% ee**	145 min	**91%**
7	 **V.66g** **81% ee**	 **V.67g** **80% ee**	50 min	**95%**
8	 **V.66h** **90:10 dr** **>98% ee**	 **V.67h** **90:10 dr** **>98% ee**	15 min	**99%**

[a] Reaction conditions: 0.5 M substrate in CH_2Cl_2, 2% of $(Ph_3P)AuNTf_2$, RT;
[b] Isolated yields, dr and ee determined by chiral HPLC.

Table V.6

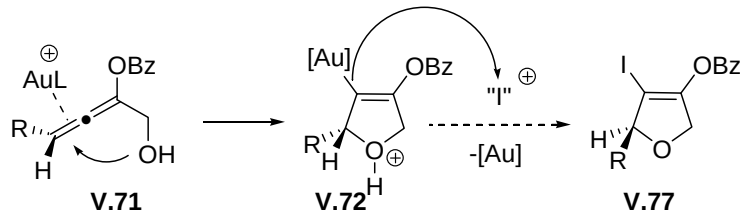
A mechanistic manifold accounting for the formation of the 2,5-dihydrofurans is proposed in Scheme V.42. The stabilized cationic intermediate V.70 is formed by the nucleophilic attack of the benzoate moiety onto the gold (I) activated triple bond in alkyne V.69. Subsequent fragmentation of the allylic C-O bond in V.70 can lead to the 1,3-shift of the benzoate group affording the intermediate allene V.71 in a stereoselective manner.[339, 344, 345] These steps can be regarded as a formal [3.3] sigmatropic transposition leading to the formation of allenyl benzoates V.71. A further gold(I) activation of the allene promotes the nucleophilic attack of the alcohol resulting in the stereoselective formation of the vinyl-gold species V.72.[339, 345, 352] 2,5-Dihydrofuran V.73 is obtained by final protonation of the vinyl-gold intermediate V.72 with catalyst regeneration. This mechanism may account for the regioselective 1,3-shift of the benzoate moiety and for the inversion of configuration at the carbon center initially bearing this benzoate group.

As discussed above, in the case of unsubstituted free propargylic alcohols cyclizing onto sterically hindered carbon centers (Table V.6, Entries 4-6), a competitive gold(I) isomerization of the intermediate allene V.71, prior to the attack of the alcohol, may be responsible for the partial loss of the stereochemical information.[361]



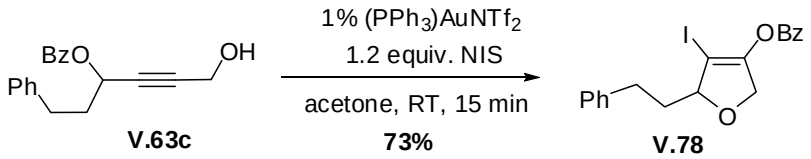
Scheme V.42

To further highlight the potential of this new transformation, we hypothesized that it would be possible to trap the intermediate vinyl-gold species V.72 by a source of electrophilic iodine prior to protonation (Scheme V.43):[106, 153, 206]



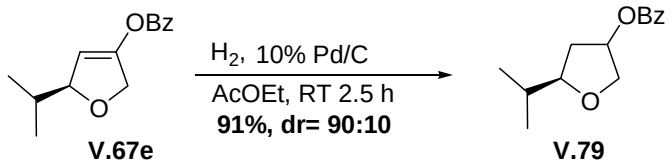
Scheme V.43

To this end, alkyne V.63c was reacted with 1% of $(Ph_3P)AuNTf_2$ and a slight excess of NIS in acetone (Scheme V.44). We were pleased to notice the formation of vinyliodide V.78, which was isolated in 73% yield.



Scheme V.44

Moreover, the functionalized 2,5-dihydrofurans can participate in a number of useful transformations. For example, hydrogenation of compound V.67e with 10% of Pd/C in EtOAc resulted in the diastereoselective formation of tetrahydrofuran V.79 in 91% yield (Scheme V.45):

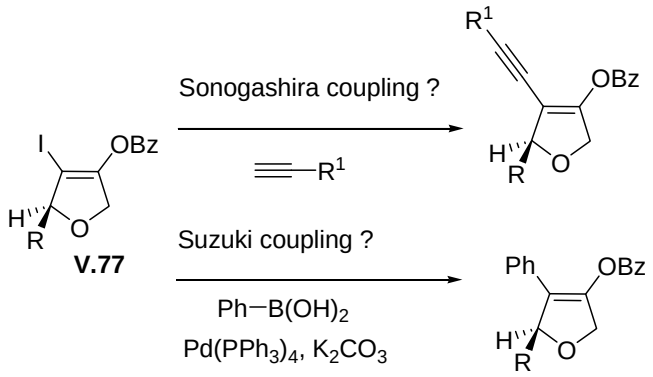


Scheme V.45

V.7. Conclusion and Perspectives

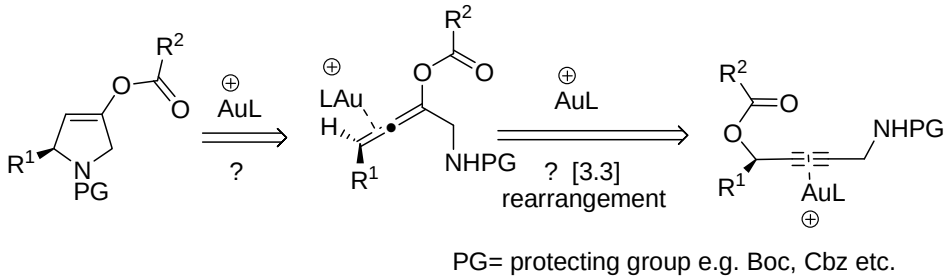
In summary, we have shown that various functionalized 2,5-dihydrofurans are obtained by the gold(I)-catalyzed stereoselective rearrangement of readily available butynediol monobenzoates. A mechanism involving two gold(I)-catalyzed isomerization steps accounts for the observed regio- and stereoselectivities.

The vinyliodide V.77, obtained by trapping of the intermediate vinyl-gold species V.72 by an elecrophilic iodine source like NIS prior to protonation (Scheme V.43) could be an interesting substrate for palladium catalyzed coupling reactions like Sonogashira, Heck or Suzuki (see also Chapter II and III). This transformation would allow the synthesis of dihydrofurans substituted with alkyl, vinyl or aryl groups at the cyclic double bond (Scheme V.46):



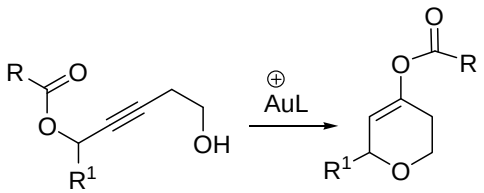
Scheme V.46

It would be also of interest to attempt the analoguos gold (I)-catalyzed rearrangement of amino derivatives (Scheme V.47):[352b]



Scheme V.47

Also an homologation to yield dihydropyranes could be envisioned (Scheme V.48):



Scheme V.48

VI. Gold(I)-Catalyzed Isomerization of Allenyl Carbinol Esters: an Efficient Access to Functionalized 1,3-Butadien-2-ol Esters

This work was done in collaboration with Dr. Fabien Gagosz and Florin-Marian Istrate.[362]

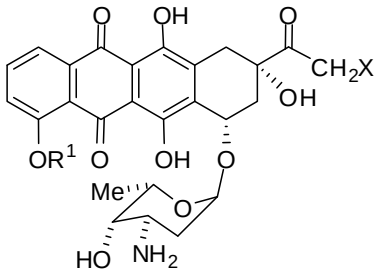
VI.1. Introduction

As olefins and dienes are often key starting materials for the construction of a wide variety of complex molecules, methods for synthesizing them as pure geometric isomers are especially important.
Functionalized 1,3-butadien-2-ol esters are attractive building blocks in organic synthesis, being sucessfully employed in a range of transformations like inter- or intramolecular Diels-Alder reactions but also in [4+1] cycloadditions, metal-catalyzed addition reactions and in stereoselective hydrogenation reactions for the synthesis of chiral allylic esters.
Surprisingly, there are only a few methods to access such dienes. Most methods use enones as starting material and involve either high temperature or strong basic or acidic conditions, thus raising the issue of functional group compatibility.

VI.2. Synthesis and Reactions of 1,3-Butadien-2-ol Esters

VI.2.1. Synthesis and Reactions of 1,3-Butadien-2-ol Esters Obtained from Enones

The great research activity addressed to the preparation of anthracycline antitumor antibiotics like daunorubicin (VI.1), adriamycin (VI.2), and carminomycin (VI.3, Figure VI.1) has intensified the interest in cycloadditions of 1,3-butadien-2-ol esters to quinones.[363]

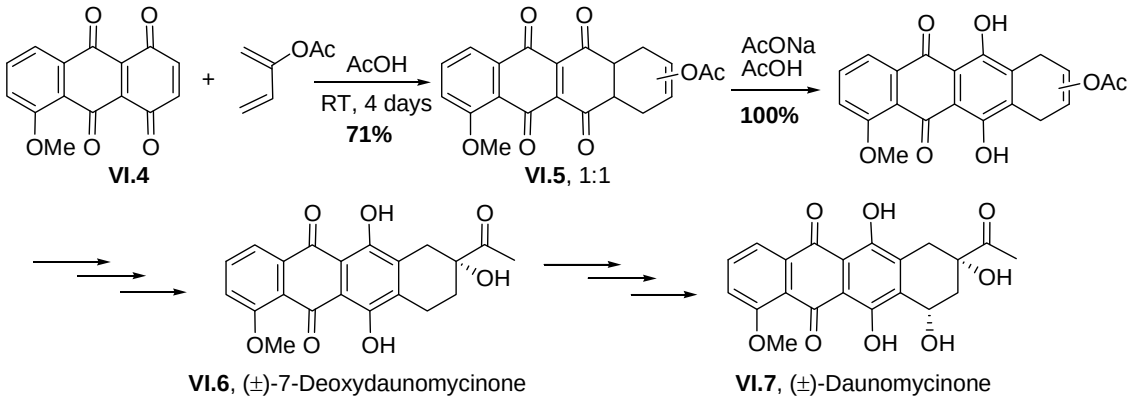


VI.1, R^1= CH_3, X= H
VI.2, R^1= CH_3, X= OH
VI.3, R^1= H, X= H

Figure VI.1

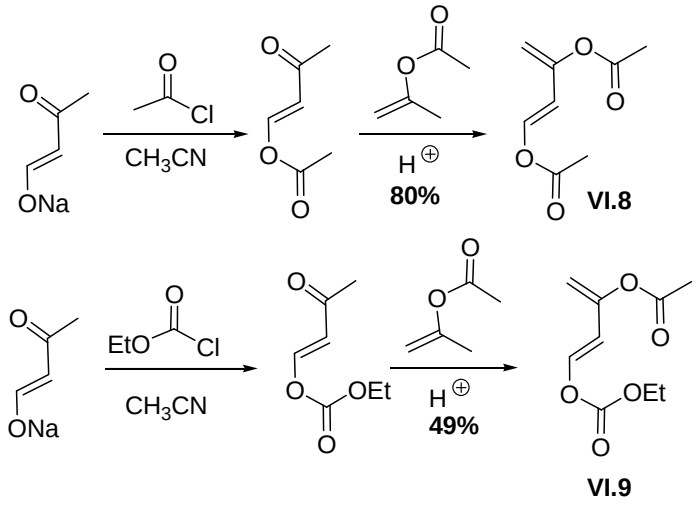
[362] Buzas, A.; Istrate, F.; Gagosz, F. *Org. Lett.* **2007**, *9,* 985
[363] Kende, A. S.; Tsay, Y.-G.; Mills, J. E. *J. Am. Chem. Soc.* **1976**, *98*, 1967

In the first Diels-Alder synthesis of daunomycinone VI.7 by Kende et *al.*, quinizarinquinone VI.4 and 2-acetoxybutadiene was used for the preparation of the tetracyclic compound VI.5, precursor for the synthesis of deoxydaunomycinone VI.6 (Scheme VI.1).[363]



Scheme VI.1

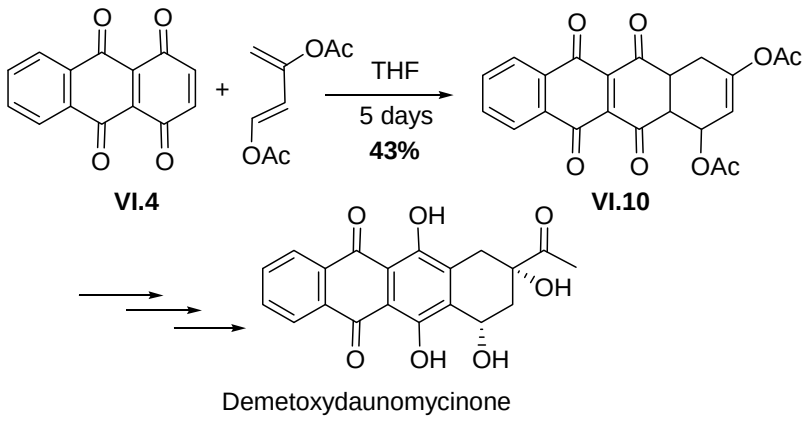
Sheeren and co-workers described the synthesis of two new 1,3-dioxybuta-1,3-dienes, namely, 1,3-diacetoxybuta-l,3-diene VI.8 and 1-[(ethoxycarbonyl)oxy]-3-acetoxybuta-l,3-diene VI.9 (Scheme VI.2).[364]



Scheme VI.2

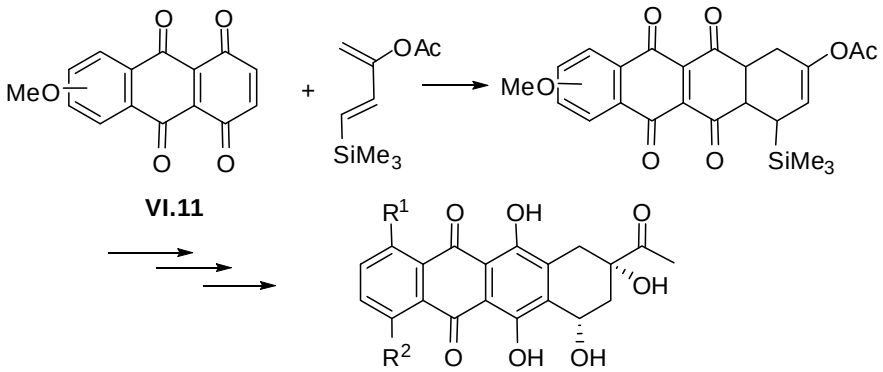
These compounds underwent regioselective cycloaddition reactions with quinizarinquinone VI.4 and other unsymmetrically substituted quinones, leading to promising synthons like VI.10 for the preparation of demethoxydaunomycinone (Scheme VI.3):

[364] Potman, R. P.; Kleef, F. J.; Scheeren, H. W. *J. Org. Chem.* **1985**, *50*, 1955



Scheme VI.3

The complete synthesis of the anthracyclinones (±)-daunomycinone and (±)-isodaunomycinone (VI.7 and VI.12, Scheme VI.4) was disclosed by Hansen et *al.*[365] The construction of the fourth 6-membered ring was accomplished through a Diels-Alder cycloaddition using *trans*-4-(trimethylsilyl)-2-acetoxy-l,3-butadiene as the diene partner and 5-methoxy-1,4,9,10-anthracenetetrone VI.11 as the dienophile.

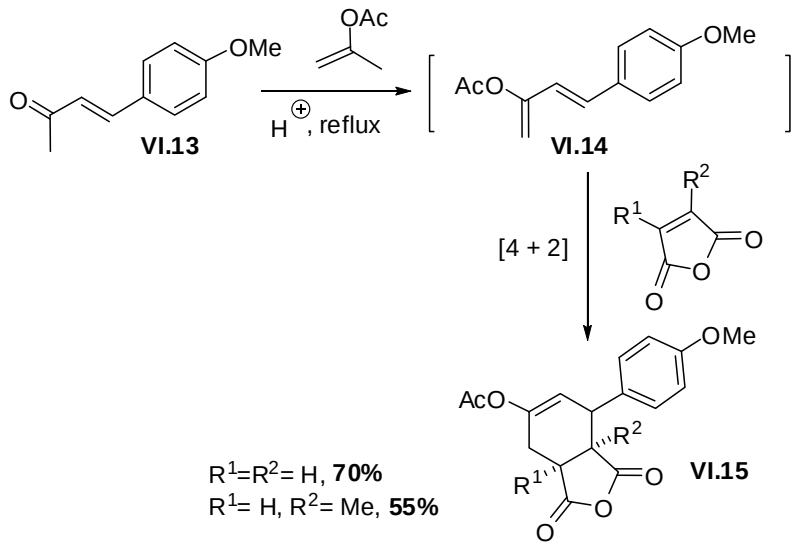


VI.7, R^1= H, R^2= OMe, (±)-Daunomycinone
VI.12, R^1=OMe, R^2= H, (±)-Isodaunomycinone

Scheme VI.4

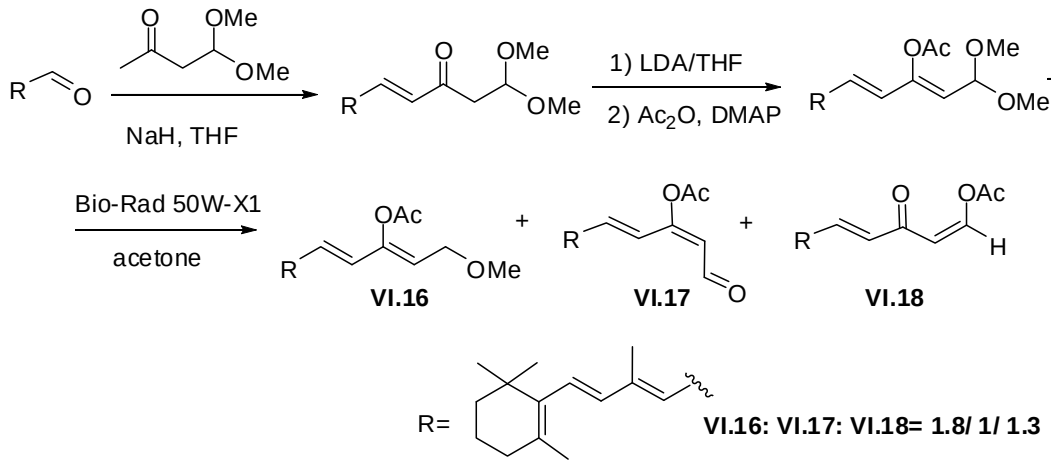
Baylouny's group reported the *in situ* formation of reactive 2-acetoxy 1,3-dienes, such as VI.14, from aromatic enones VI.13 and Diels-Alder trapping of these derivatives offering a relatively simple procedure for the formation of 2-arylcyclohexene-*cis*-and-*trans*-1,2-dicarboxylic anhydrides VI.15 (Scheme VI.5):[366]

[365] Hansen, D. W.; Pappo, R.; Garland, R. B. *J. Org. Chem.* **1988**, *53*, 4244
[366] Baylouny, R. A.; Danna, R. P.; Toth, K. H. *J. Org. Chem.* **1979**, *44*, 204



Scheme VI.5

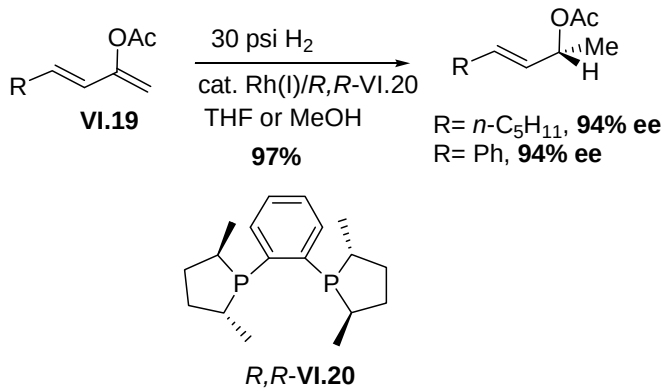
13-*Cis*- and all-*trans*-l3-acetoxy-l3-desmethylretinals VI.16- VI.18 were prepared according to Scheme VI.6 in order to test the involvement of nucleophilic catalysis, presumably by an aspartate moiety in the protein, in the dark *cis-trans* isomerizations of retinal in bacteriorhodopsin.[367]



Scheme VI.6

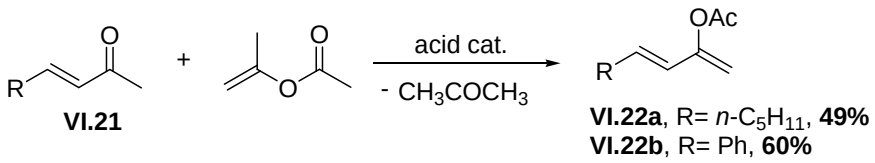
Enantioselective asymmetric hydrogenations of *E*-dienyl acetate substrates VI.19 were reported by Boaz. The catalyst used was a rhodium(I) species prepared *in situ* from *bis*(l,5-cyclooctadiene)-rhodium(I) tetrafluoroborate and the methyl DuPHOS ligand *R,R*- VI.20 (Scheme VI.7).[368]

[367] Seltzer, S. *J. Org. Chem.* **1995**, 60, 1189
[368] Boaz, N. W. *Tet. Lett.* **1998**, *39*, 5505



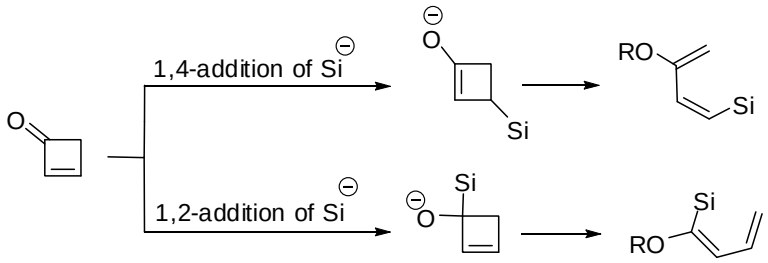
Scheme VI.7

The preparation of these dienyl acetate substrates VI.22, although in moderate yield, involved acid-catalyzed enolization of the corresponding enone VI.21 and capture of the enol with isopropenyl acetate.[369]



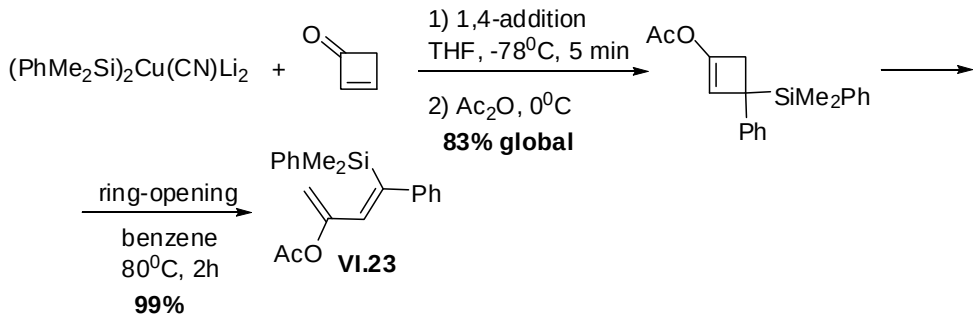
Scheme VI.8

Another method for the synthesis of highly functionalized 1,3-dienes as single isomers *via* the ring-opening of cyclobutenes was published by Ito and co-workers.[370] The success of the synthetic scheme arises from the silyl substituents located at the 3-position, which accelerate the ring-opening reaction and provide complete control over the torquoselectivity.[371] As shown in Scheme VI.9, the starting silyl-substituted cyclobutenes required for this strategy can be conveniently prepared from cyclobutenones. Addition of a silyl nucleophile, either in a 1,4- or 1,2-fashion, provides an efficient route to 3-silyl-1-cyclobutene, which opens up to isomeric functionalized 1,3-dienes (Scheme VI.9). One example leading to the efficient synthesis of functionalized 2-acetoxy1,3-diene VI.23 in 99% yield is illustrated in Scheme VI.10.



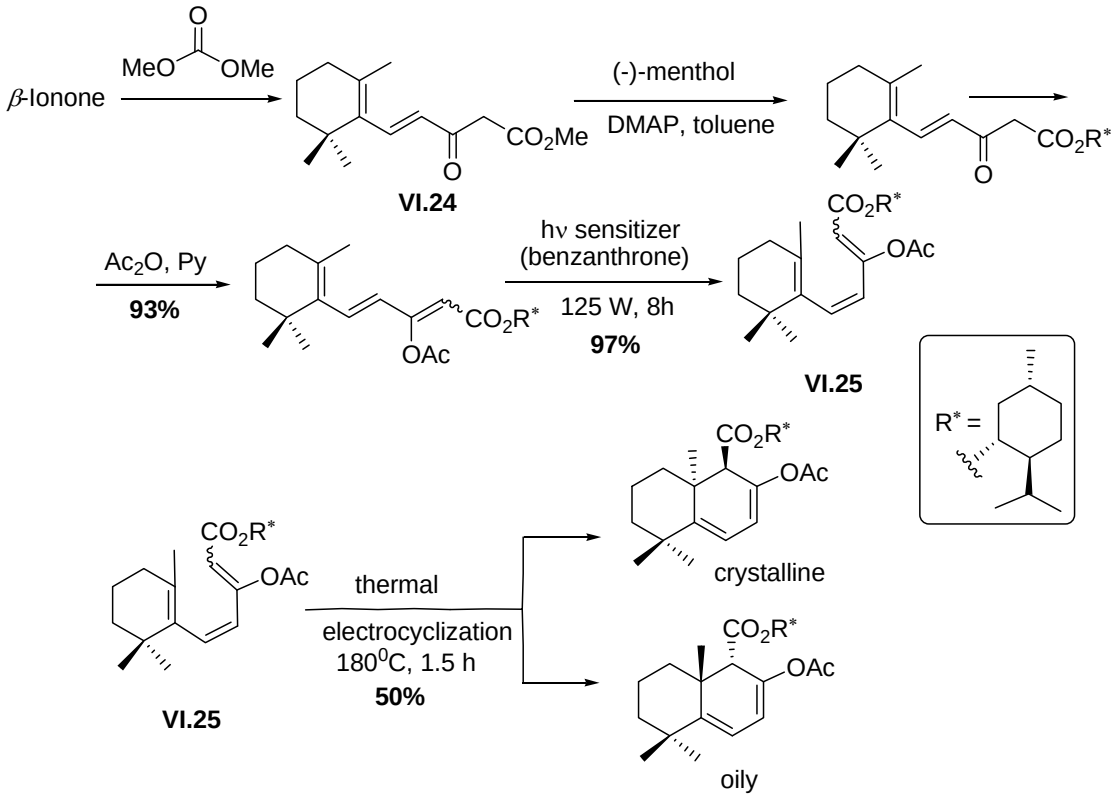
[369] Karlsson, J. O.; Frejd, T. *J. Org. Chem.* **1983**, *48*, 1921
[370] Murakami, M.; Miyamoto, Y.; Ito, Y. *J. Am. Chem. Soc.* **2001**, *123*, 6441
[371] For a review on torquoselective ring-opening reactions of cyclobutenes, see: Dolbier, W. R., Jr.; Koroniak, H.; Houk, K. N.; Sheu, C. *Acc. Chem. Res.* **1996**, *29*, 471

Scheme VI.9



Scheme VI.10

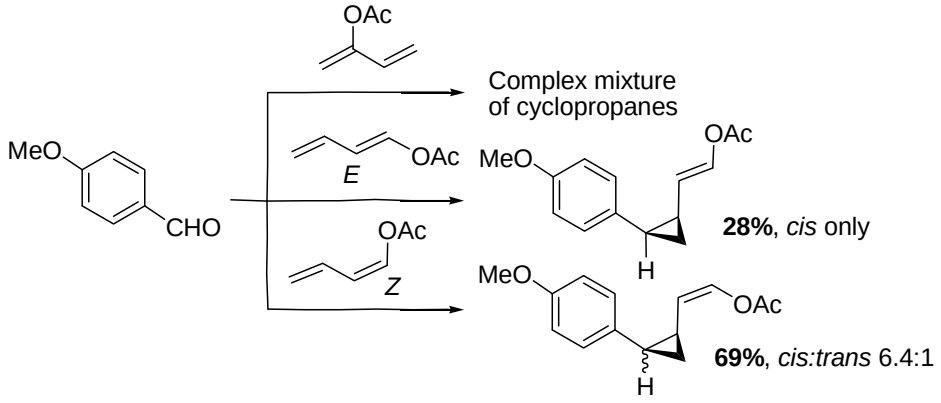
The original route developed by Isoe and co-workers for the synthesis of racemic decalin intermediates starting from *β*-ionone,[372] has been extended by Pollini et *al.*[373] to the synthesis of both optically active *trans*- and *cis*-decalin synthons, which represent useful starting chiral materials for the synthesis of biologically active terpenes families like those of drimane and labdane sesquiterpenes. The chiral auxiliary (-)-menthol allowed a clean separation of the diastereomers obtained in the key electrocyclization step of the corresponding 2-acetoxydiene VI.25 prepared from enone VI.24 (Scheme VI.11):



Scheme VI.11

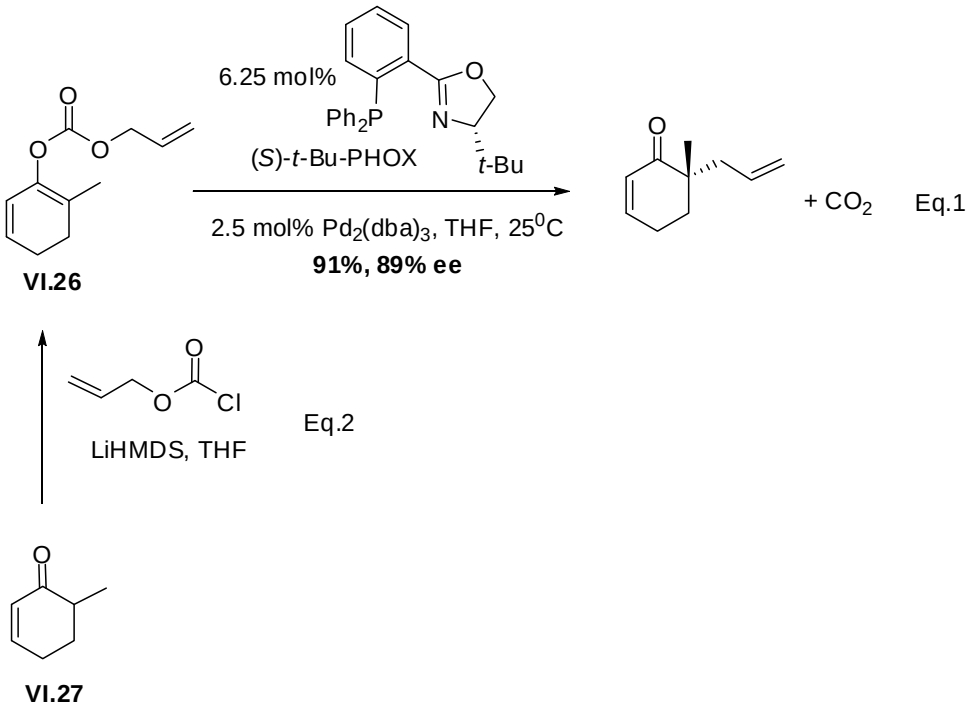
[372] Katsumura, S.; Kimura, A.; Isoe, S. *Tetrahedron* **1989**, *45*, 1337
[373] Pollini, G. P.; Bianchi, A.; Casolari, A.; Risi, C.; Zanirato, V.; Bertolasi, V. *Tetrahedron: Asymmetry* **2004**, *15*, 3223

Motherwell et *al.* studied the regio- and stereoselectivity of the reaction of organozinc carbenoids with acetoxybutadienes derived from enones (Scheme VI.12):[374]



Scheme VI.12

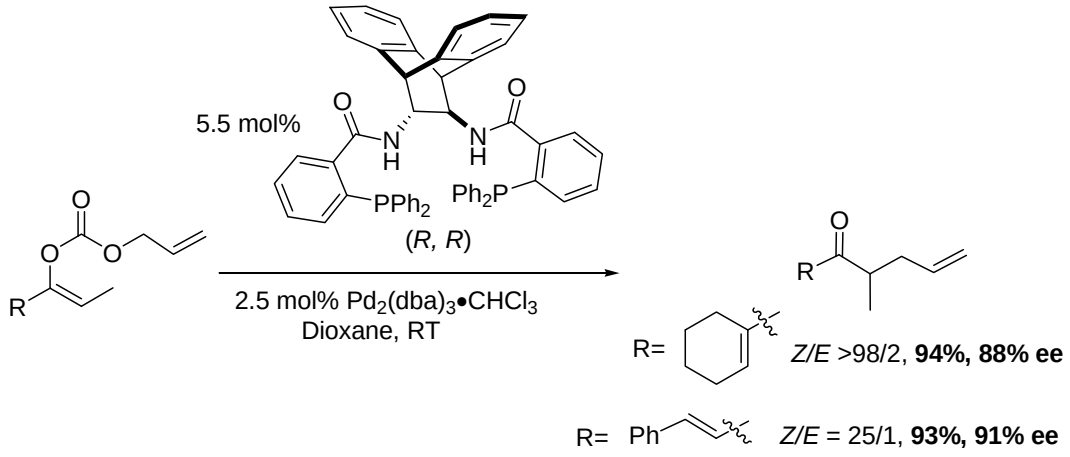
Behenna and Stoltz reported one example of Pd-catalyzed enantioselective allylation using the dienic substrate VI.26, prepared from enone VI.27 as depicted in Scheme VI.13:[375]



Scheme VI.13

Trost and Xu used a similar approach for the palladium-catalyzed asymmetric allylic α-alkylation of acyclic ketone derivatives (Scheme VI.14):[376]

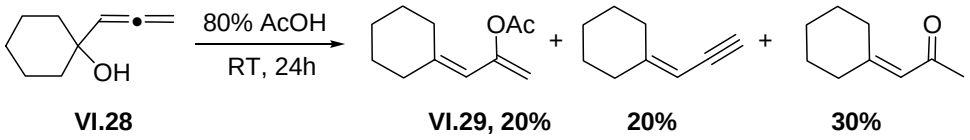
[374] Aqil, R.; Motherwell, W. B.; Roberts, L. R.; Russell, C. A. *Tet. Lett.* **2002**, *43*, 9671
[375] Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044
[376] Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 17180



Scheme VI.14

VI.2.2. Synthesis of 1,3-Butadien-2-ol Esters starting from Allenyl or Propargyl Derivatives

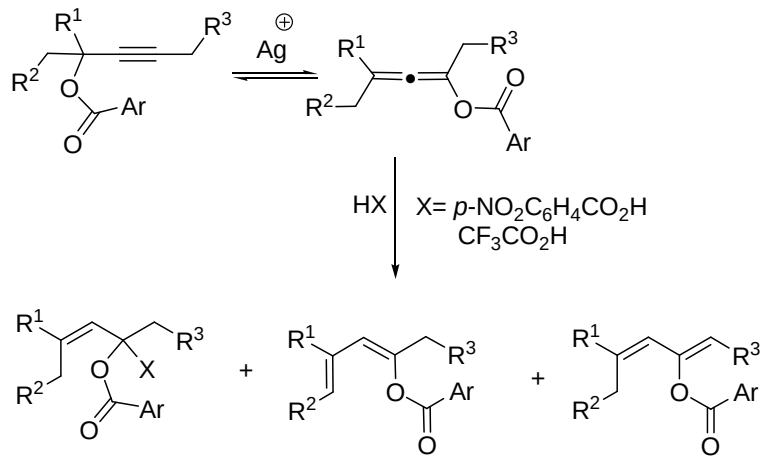
During their investigation on the acid catalyzed rearrangement of different types of α-allenic alcohols, Olsson et *al.* found that allenic alcohol VI.28 gave dienol acetate VI.29 in presence of acetic acid (Scheme VI.15):[377]



Scheme VI.15

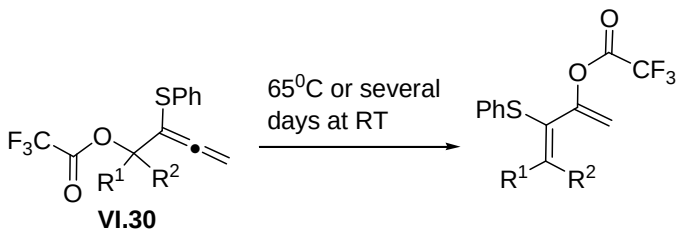
Isomerization of propargyl acetates into 1,3-dienes in the presence of Ag-catalysts at elevated temperatures has been reported (Scheme VI.16).[334a,335,336d] The cascade reaction was hypothesized to proceed *via* an allene intermediate, though, the mechanism of this transformation remained unclear.

[377] Olsson, L. I.; Claesson, A.; Bogentof, C. *Acta Chem. Scand.* **1973**, *27*, 1629



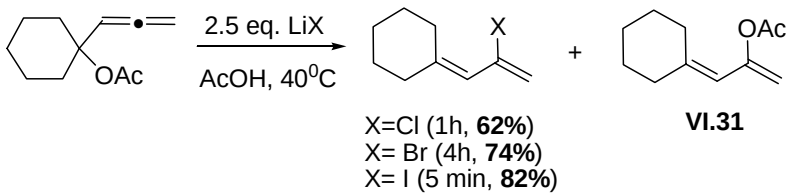
Scheme VI.16

Bridges and colleagues observed that trifluoroacetates VI.30 underwent [3.3] sigmatropic rearrangement to yield the dienol trifluoroacetates when kept several days at room temperature (Scheme VI.17):[378]



Scheme VI.17

2-Acetoxy 1,3 diene VI.31 is obtained as a side-product in the reaction of acetylated α-allenic alcohols with LiX in the presence of 1.5 mol % of $Pd(OAc)_2$ along with the corresponding substituted 2-halo-1,3-diene derivatives (Scheme VI.18):[379]

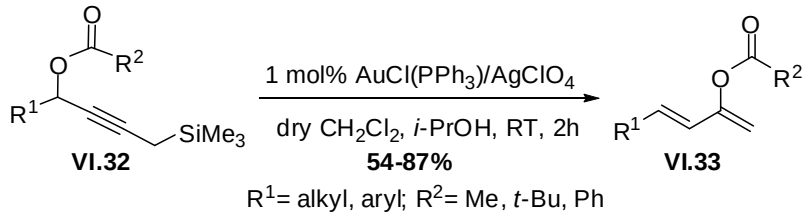


Scheme VI.18

Gold Catalyzed Synthesis of 1,3-butadien-2-ol Esters from Allenyl or Propargyl Derivatives

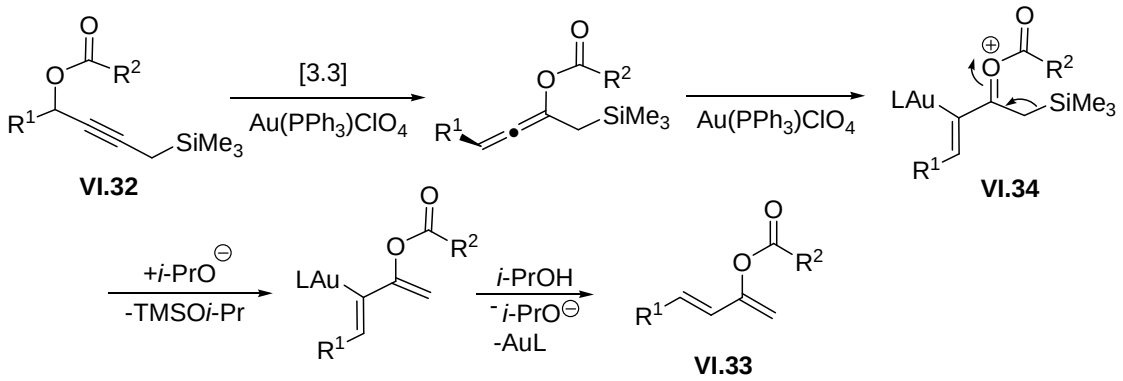
[378] Bridges, A. J.; Thomas, R. D. *Chem. Commun.* **1983**, 485
[379] Horvath, A.; Bäckvall, J.-E. *J. Org. Chem.* **2001**, *66*, 8120

A gold-catalyzed efficient method for the preparation of alkenyl enol esters VI.33 from trimethylsilylmethyl-substituted propargylic esters VI.32 was developed by Wang and Zhang (Scheme VI.19). High *E*-selectivities are observed in the nonenolic C-C double bond of the products.[380]



Scheme VI.19

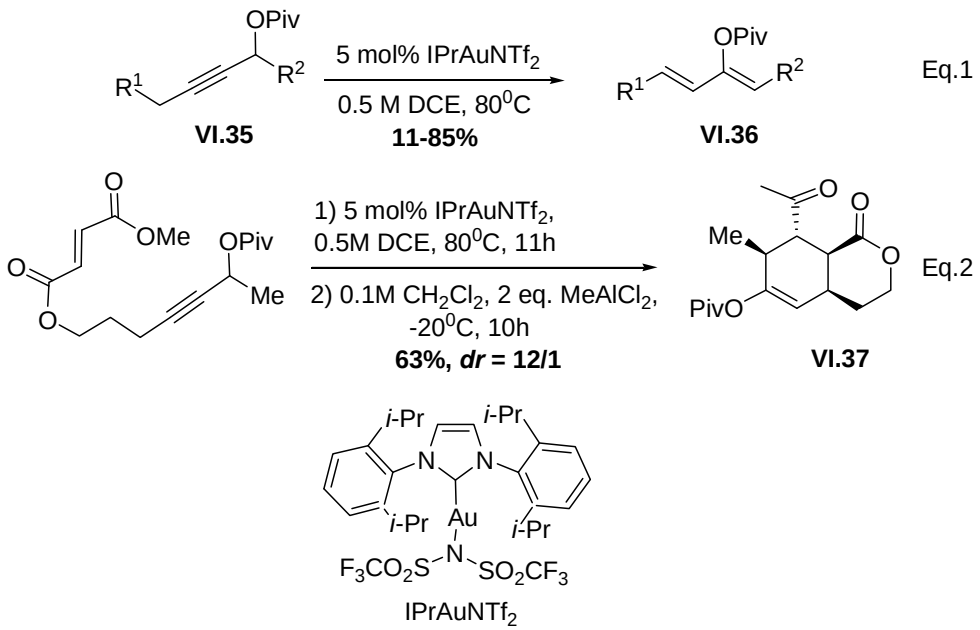
This tandem transformation proceeds through the initial generation of the oxocarbenium intermediate VI.34 followed by desilylation and subsequent protodemetallation of the vinyl gold species (Scheme VI.20).



Scheme VI.20

After the publication of our results,[362] a stereoselective Au(I)-catalyzed isomerization of propargylic esters VI.35 into 2-oxy-1,3-diene esters VI.36 proceeding *via* a double 1,2-migration was reported by Zhang's group (Scheme VI.21, Eq. 1).[381] A one-pot, sequential Au-catalyzed diene formation and Lewis acid-catalyzed intramolecular Diels-Alder reaction was described, offering rapid access to bicyclic lactone VI.37 in 63% yield (Scheme VI.21, Eq. 2).

[380] Wang, S. Zhang, L. *Org. Lett.* **2006**, *8*, 4585
[381] Li, G.; Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 3740



Scheme VI.21

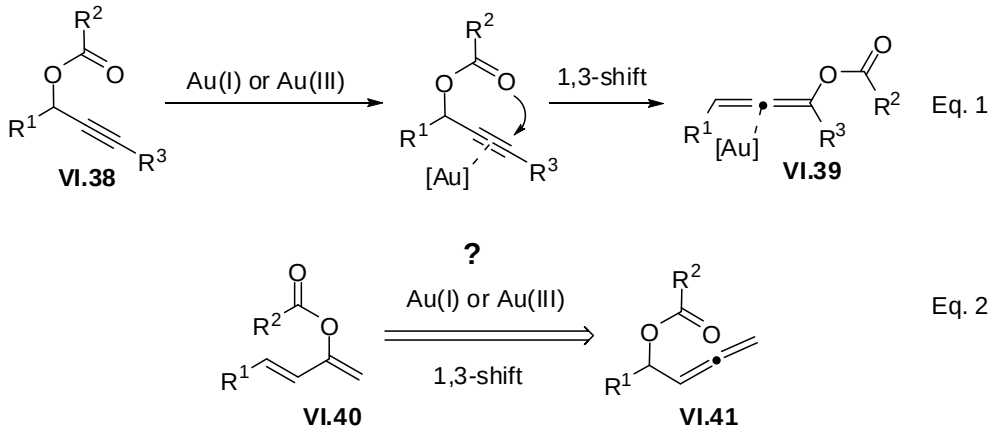
VI.3. Preliminary Work in the Literature

Allenes have extraordinary properties such as an axial chirality of the elongated tetrahedron and a higher reactivity than alkenes, hence, these have been paid attention not only as an attractive building block for organic synthesis but also as a potent functional group for improvement of the biological and pharmacological active compounds.[382] Transition metals coordinate to allenes, allowing the intra- or intermolecular attack of tethered nucleophiles, leading to the formation of various heterocycles.[346] Activation of allenes by silver and gold catalysis was already discussed in Chapter I and V.

VI.4. Our Synthetic Approach. Optimisation of the Catalytic System

As presented in detail in Chapter V, the gold catalyzed isomerization of propargylic esters VI.38 to carboxyallenes VI.39 by an 1,3 acyl shift has been recently used in various tandem processes leading to a range of synthetically useful products (Scheme VI.22, Eq. 1).[383] The particularity of gold catalysts is that in addition to mediating the sigmatropic [3,3] rearrangement, they mildly activate the allene moiety for subsequent reactivity. By analogy with these transformations and given this special property of gold complexes to activate allenes,[346] we hypothesized that allenyl carbinol esters such as VI.41 could be rearranged to afford 1,3-butadien-2-ol esters VI.40 after an analogous gold catalyzed 1,3 acyl group migration (Eq. 2):

[382] a) Krause, N.; Hashmi, A. S. K. Eds. *Modern Allene Chemistry*; Wiley-VCH: Weinheim, **2004**; b) Hoffmann-Röder, A.; Krause, N. *Angew. Chem. Int. Ed.* **2002**, *41*, 2933 and references cited therein.
[383] a) Marion, N.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2007**, *46*, 2750; b) Correa, A.; Marion, N.; Fensterbank, L.; Malacria, M.; Nolan, S. P.; Cavallo, L. *Angew. Chem. Int. Ed.* **2008**, *47*, 718

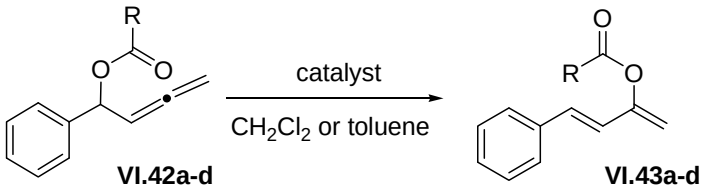


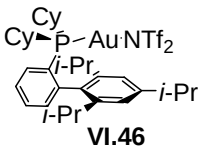
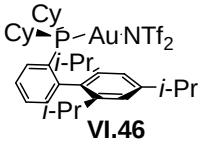
Scheme VI.22

As presented earlier, Zhang and Whang have recently reported a new gold(I) catalyzed reaction for the formation of such 1,3-butadien-2-ol esters from trimethylsilylmethyl-substituted propargyl esters (Scheme VI.20).[380] As depicted in the Scheme VI.20 above, this tandem transformation proceeds through the initial generation of the oxocarbenium intermediate VI.34 followed by desilylation and subsequent protodemetallation of the vinyl gold species. Even if this reaction proved to be efficient and afforded the corresponding 1,3-butadien-2-ol esters VI.33 in good yields (54-87%) and excellent *E*-selectivity, we believed that our approach could present some advantages.

First advantage would be the preparation of the required allenic substrates VI.41, easily accessible by a Crabbé homologation of acetylenes to the desired allenes using inexpensive starting materials. Besides, the reaction would not be water sensitive since no intermediate acyloxocarbenium species VI.34 (Scheme VI.20) would be involved, thus the use of dry dichloromethane can be avoided.

In order to validate our synthetic approach, allenol acetate VI.42a was first synthesized (see Chapter VI.5) to play the role of a model substrate (Table VI.1). Subjecting this substrate to 2 mol% of $AuBr_3$ at room temperature in dichloromethane led to a poor conversion with no formation of the desired diene VI.43a (Table VI.1, Entry 1). Employing a silver salt ($AgNTf_2$) as the catalyst did not substantially improve the conversion but 1,3-butadien-2-ol ester VI.43a could however be isolated in a poor 6% yield (Entry 2).



Entry	R	Substrate	Catalyst	Time	Conversion[a]		Yield
1	Me	**VI.42a**	2 mol % $AuBr_3$	24 h	**< 5%**	**VI.43a**	**0%**
2	Me	**VI.42a**	10 mol % $AgNTf_2$	24 h	**15%**	**VI.43a**	**6%**[a]
3	Me	**VI.42a**	1 mol % PPh_3AuNTf_2	24 h	**15%**	**VI.43a**	**14%**[a]
4	Me	**VI.42a**	1 mol %  **VI.46**	3 h	**100%**	**VI.43a**	**98%**[b]
5	Bz	**VI.42b**	10 mol% $HNTf_2$	24 h	—		—
6	Bz	**VI.42b**	toluene reflux	24 h	**< 5 %**		**< 5 %**
7	Bz	**VI.42b**	1 mol %	75 min	**100%**	**VI.43b**	**100%**[b]
8	$C(Me)_3$	**VI.42c**	 **VI.46**	45 min	**100%**	**VI.43c**	**100%**[b]
9	O*t*-Bu	**VI.42d**		20 h	**75%**	**VI.43d**	**69%**[b]

[a] Estimated by ^{1}H NMR; [b] Isolated yield.

Table VI.1

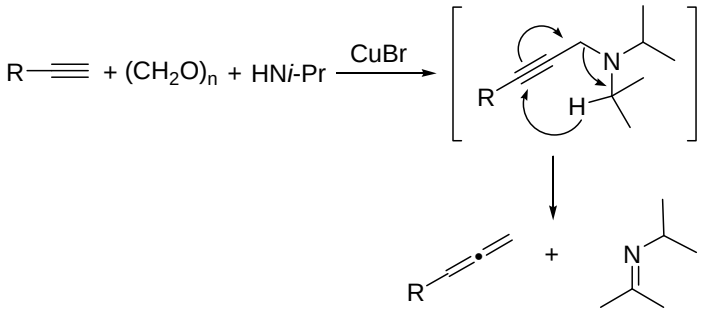
Following our recent success in using the crystalline, air stable PPh_3AuNTf_2 catalyst for the formation of C-O and C-N bonds,[106,206,329] we next attempted to use this catalyst in order to improve the yield of VI.43. Disappointingly, only a very modest yield (14%) of the desired compound could be obtained in the presence of 1 mol% of PPh_3AuNTf_2 (Entry 3). We next focused on the use of biphenylphosphine ligands (Entries 4, 7-9), previously used with success in the formation of C-C bonds by Echavarren's[81,384] and our group (see also Chapters I, VII and VIII).[385,386] Remarkably, the use of 1 mol% of catalyst VI.46[100] dramatically improved the transformation and diene VI.43a was isolated in an excellent 98% yield as a single *E*-isomer (Entry 4). It is also worth to mention that enol acetate VI.43a bearing an unsubstituted phenyl group at the α-allenic position could not be obtained using the procedure developped by Wang and Zhang.[380] Next we turned our attention to the ester group of the substrate. To this end, different allenyl esters (benzoate, pivalate, *t*-butylcarbonate) were prepared (see next Table VI.2). We were delighted to observe that the reaction proved to be more general and besides acetates, other ester groups underwent this gold-catalyzed 1,3-acyl group migration. Benzoate VI.42b and pivalate VI.42c quantitatively afforded the

[384] Munoz, M.; Adrio, J.; Carretero, J. C.; Echavarren, A. M. *Organometalics* **2005**, *24*, 1293
[385] Buzas, A.; Gagosz, F. *J. Am. Chem. Soc.* **2006**, *128*, 12614
[386] Buzas, A.; Istrate, F.; Gagosz, F. *Angew. Chem. Int. Ed.* **2006**, *46*, 1141

corresponding dienes VI.43b and VI.43c in a short reaction time (Entries 5 and 6). *Tert*-butyl carbonate VI.42b reacted more slowly (20 h) and furnished diene VI.43d in a more modest 65% yield (Entry 7). It is interesting to note that no fragmentation of the Boc group, which would lead to an *exo*-methylene dioxolanone,[106] was observed. In the light of the results illustrated in Table VI.1, VI.46 was found to be the catalyst of choice to effect this isomerisation and thus it was retained to examine the scope of this transformation.

VI.5. Synthesis of the Allenic Substrates

In order to study the scope of the gold(I)-catalyzed isomerisation of allenyl carbinol esters into 1,3-butadien-2-ol esters, a variety of diversely substituted allenic substrates VI.44a-o were synthesized in a two steps sequence starting from the corresponding propargylic alcohols in yields ranging from 12% to 77% (Table VI.2). The propargylic alcohol was first homologated to the corresponding allenol using the Crabbé reaction (Scheme VI.23).[387] Crabbé and co-workers developed a simple method for CuBr-catalyzed homologation of alk-1-ynes to terminal allenes with paraformaldehyde and *N*,*N*-diisopropylamine in refluxing dioxane.[388] The mechanistic manifold proposed by the authors involved two-steps: the first one is a CuBr-catalyzed Mannich-type reaction and the second a 1,5-sigmatropic rearrangement of hydrogen (Scheme VI.23).

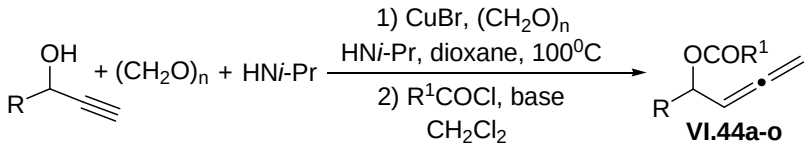


Scheme VI.23

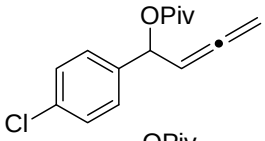
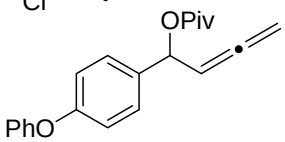
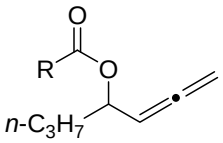
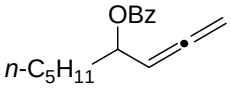
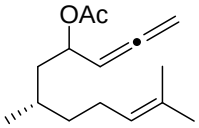
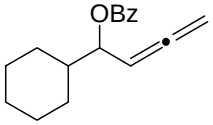
The resulting allenol was next converted into the corresponding acetate, benzoate or *tert*-butylcarbonate using standard procedures (see the experimental section).

[387] a) *Organic Syntheses* **1990**, *7*, 276; b) *Organic Syntheses* **1985**, *63*, 203; c) Kumareswaran, R.; Shin, S.; Gallou, I.; RajanBabu, T. V. *J. Org. Chem.* **2004**, *69*, 7157; d) Nakamura, H.; Sugiishi, T.; Tanaka, Y. *Tet. Lett.* **2008**, *49*, 7230

[388] a) Rona, P.; Crabbé, P. *J. Am. Chem. Soc.* **1968**, *90*, 4733; b) Rona, P.; Crabbé, P. *J. Am. Chem. Soc.* **1969**, *91*, 3289



VI.44a-o

Entry	Substrate		Yield
1		**VI.44a**	**12%**
2		**VI.44b**	**18%**
3		R= Me **VI.44c** R= CMe_3 **VI.44d** R= Bz **VI.44e**	**40%** **44%** **43%**
4		**VI.44f**	**30%**
5		**VI.44g**	**50%**
6		**VI.44h**	**46%**

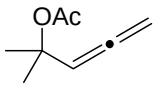
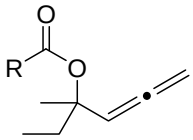
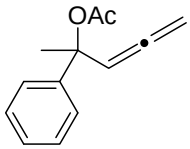
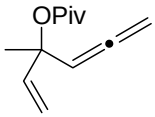
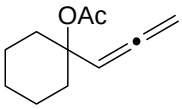
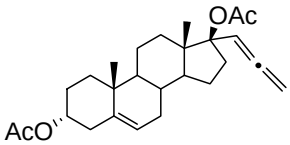
8		**VI.44i**	**13%**
9		R= Me **VI.44j** R= CMe_3 **VI.44k**	**11%** **5%**
10		**VI.44l**	**46%**
11		**VI.44m**	**8%**
12		**VI.44n**	**40%**
13		**VI.44o**	**52%**

Table VI.2

VI.6. Gold(I)-Catalyzed Isomerization of Allenyl Carbinol Esters

The gold-catalyzed isomerization of allenyl carbinol esters proved to be quite general. Various dienes VI.45a-o were obtained in generally good yields (53-100%) and *E*-selectivities (Table VI.3) starting from the corresponding allenyl carbinol esters VI.44a-o in the presence of 1 mol% of VI.46 as the catalyst. The reaction times were in general shorter than 2 h.

Other aryl substituted substrates reacted equally well, although a slight decrease in yield was observed in the case of the *p*-phenoxy substituted allene VI.44b (Table VI.2, Entries 1 and 2). Gratifyingly, the transformation was not limited to the use of aryl substituted allenes, aliphatic 1,3-butadien-2-ol esters being obtained in good yields (67-100%), as depicted in Table VI.2, Entries 3-8 and 11. Even a sterically demanding substituent at the α-allenic position was tolerated furnishing enol benzoate VI.45h in quantitative yield (Entry 6).

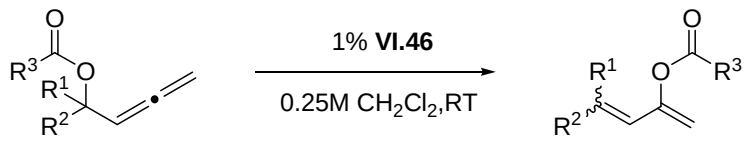
It is worth to mention that a peculiar effect of the nature of the migrating ester group on the stereoselectivity of the reaction was observed in the cases of allenes VI.45c-e (Entry 3). Although such an effect is difficult to rationalize at this stage of the study, the formation of the *E*-isomer seems to be favored by the use of a benzoate as the migrating acyl group. While the use of an acetate or a pivalate generally leads to an *Z*:*E* ratio of around 1:8, this ratio increases up to 1:19 in the case of a benzoate (Entries 3, 4 and 6). Performing the isomerization for a longer time or resubmitting the isolated dienes to the same reaction

conditions did not change the *Z:E* ratios, thus prooving that gold catalyst VI.46 did not isomerize the final dienes.

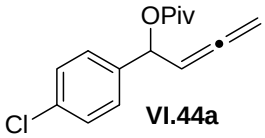
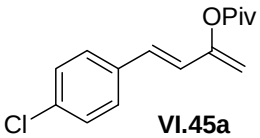
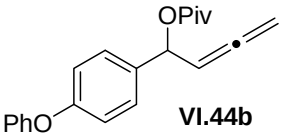
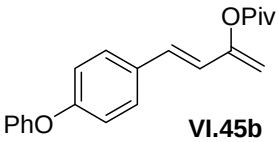
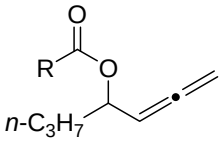
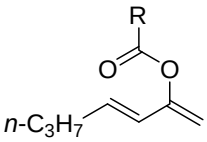
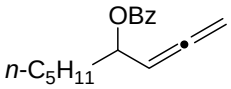
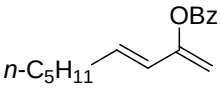
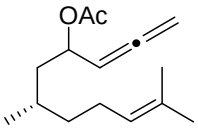
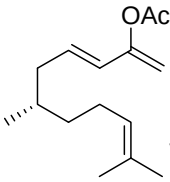
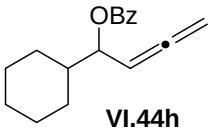
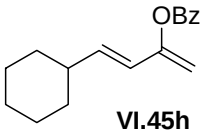
Next we turned our attention on the reaction of substrates bearing two substituents at the allenic position. Delightfully, the isomerization was not limited to the use of *α*-monosubstituted allenols. Tertiary substrates VI.44i-o reacted equally well, even if the reaction was accompanied by a decrease in selectivity (Entries 7-12). Substrates VI.44i-j needed a very short reaction time to reach completion (5 min), probably due to an important Thorpe-Ingold effect of the two alkyl substituents in the *α*-position relative to the allenic bond (Entries 7-8).

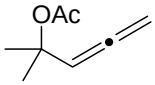
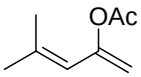
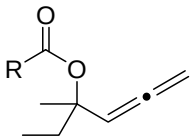
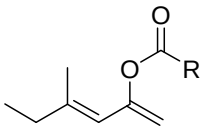
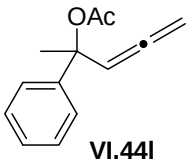
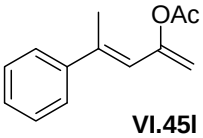
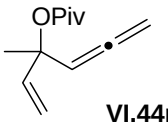
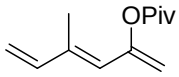
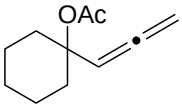
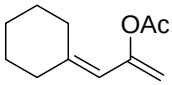
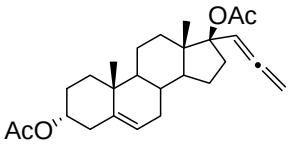
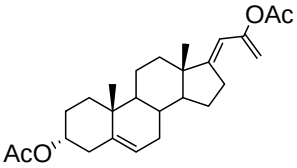
Surprisingly, the isomerization of allene VI.44l did not occur in the classical optimized conditions in dichloromethane. However, diene VI.45l could be isolated in a modest 59% yield along with unreacted subtrate VI.44l when the reaction was performed in refluxing 1,2-dichloroethane. It is worth noting that besides dienes, trienes could also be prepared using this method as demonstrated by the example presented in Entry 10.

Finally, the reaction of androstene derivative VI.44o was exceptionally efficient and gave the correponding enol acetate VI.45o in 97% yield after a simple filtration of the crude reaction mixture (Entry 12).



VI.44a-n **VI.45a-o**

Entry	Substrate	Product	Time	Yield (*Z*:*E*)[a]
1	 **VI.44a**	 **VI.45a**	2 h	**100%** (1:18)
2	 **VI.44b**	 **VI.45b**	8 h	**78%** (1:8)
3	 **VI.44c-e**	 **VI.45c-e**	R= Me **VI.45c**	**100%** (1:7)
			R= CMe_3 **VI.45d** 1 h	**100%** (1:9)
			R= Bz **VI.45e** 5 min	**100%** (1:19)
4	 **VI.44f**	 **VI.45f**	40 min	**100%** (1:15)
5	 **VI.44g**	 **VI.45g**	2 h	**99%** (1:8)
6	 **VI.44h**	 **VI.45h**	9 h	**100%** (0:1)

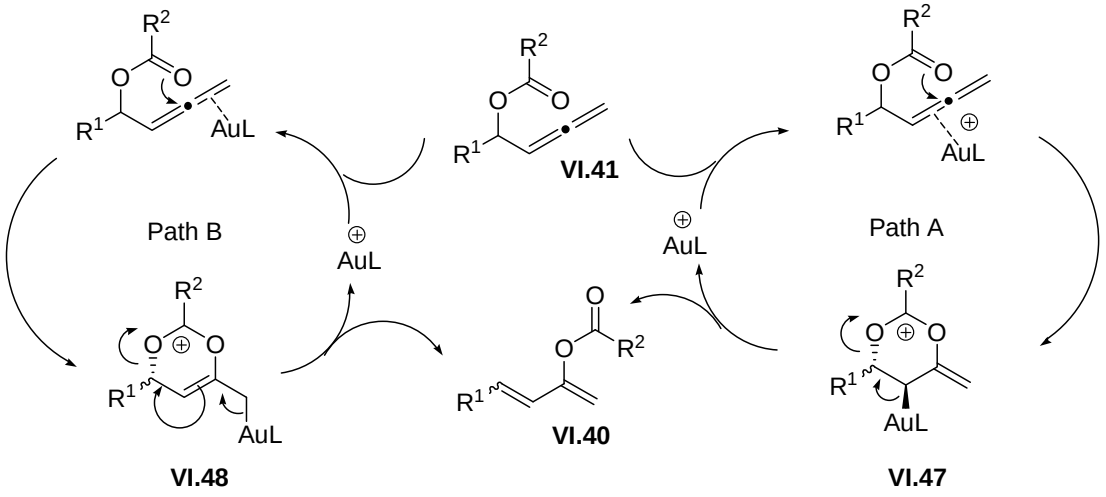
Entry	Substrate	Product	Time	Yield (*Z*:*E*)[a]
7	 **VI.44i**	 **VI.45i**	5 min	**100%**[d]
8	 **VI.44j-k**	 **VI.45j-k**	R= Me **VI.45j**	5 min	**79% (100%)**[c] (1:1.7)
			R= CMe_3 **VI.45k**	5 min	**67% (89%)**[c,e] (1:1.4)
9	 **VI.44l**	 **VI.45l**	3 h	**59%** (1:1) [b]
10	 **VI.44m**	 **VI.45m**	10 min	**53% (93%)**[c] (1:2)
11	 **VI.44n**	 **VI.44n**	5 min	**100%**
12	 **VI.44o**	 **VI.45o**	1 h	**97%** (1:10)

[a] Ratio determined by ^{1}H-NMR; [b] Reaction performed in refluxing 1,2-dichloroethane. Diene **VI.45l** was isolated in mixture with the unreacted allene**VI.44l**; [c] Yield determined by ^{1}H-NMR on the crude reaction mixture; [d] Reaction performed in an NMR tube. Yield determined by ^{1}H-NMR on the crude reaction mixture; [e] Reaction performed at 0 °C.

Table VI.3

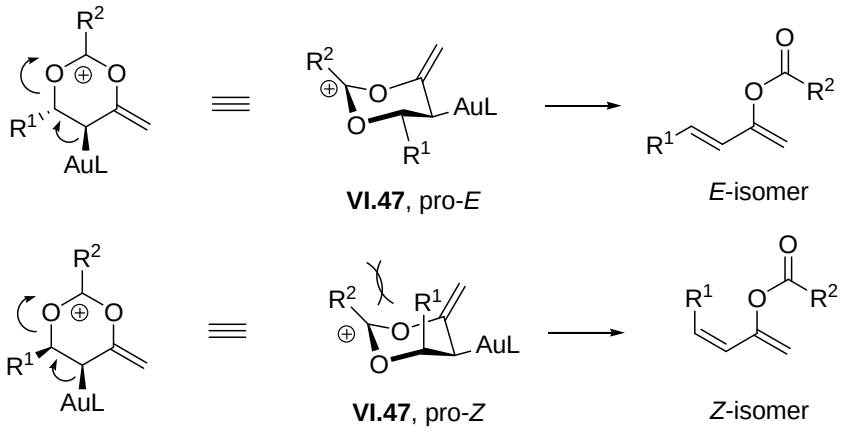
A mechanistic manifold accounting for the formation of 1,3-butadien-2-ol esters VI.40 is presented in Scheme VI.24. The stabilized cationic species VI.47 is formed by regioselective gold(I) activation of the allene in VI.41 followed by the nucleophilic attack of the carbonyl function of the ester moiety. Simultaneous fragmentation of the homoallylic C-O bond and the allylic Au-C in VI.47 leads to the 1,3-acyl migration with formation of diene VI.40 and regeneration of the gold catalyst (Scheme VI.27, path A). An alternative mechanism

involving the activation of the terminal double bond of the allene moiety can be envisaged (Path B).



Scheme VI.24

An explanation accounting for the stereoselectivity observed in the reaction is proposed by considering the two possible half-chair transition states VI.47pro-*E* and pro-*Z* leading respectively to the formation of the *E* and *Z* isomers. In the pro-*E* transition state VI.47, the R^1 substituent and the gold atom adopt a preferential *pseudo*-equatorial position with the requisite antiperiplanar relationship between the homoallylic C-O bond and the allylic Au-C bond. On the contrary, in the pro-*Z* transition state, the R^1 group adopts an energetically less favored *pseudo*-axial position leading to possible 1,3 diaxial interactions while the gold atom remains in a *pseudo*-equatorial position (Scheme VI.25):

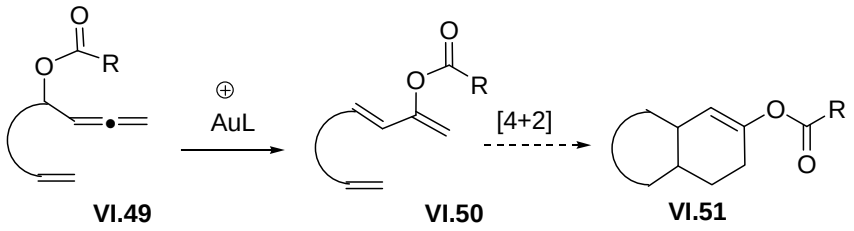


Scheme VI.25

VI.7. Conclusion and Perspectives

In summary, we have developed a new efficient gold(I)-catalyzed isomerisation of readily available allenyl carbinol esters into functionalized 1,3-butadien-2-ol esters. The reaction

conditions employed are mild thus tolerating the presence of a wide range of functional groups. The catalyst loading is low (1 mol%) and generally good *E*-selectivity is obtained.
As a perspective, it would be of interest to study the reactivity of the synthesized 1,3-butadien-2-ol esters as a dienic partner in inter-and intramolecular Diels-Alder reactions. Another synthetic approach illustrated in Scheme VI.26 would involve the gold(I)-catalyzed isomerisation of allenyl-ene substrate VI.49 to afford triene VI.50 which would undergo subsequent [4+2] cycloaddition leading to substituted bicyclic molecules VI.51:



Scheme VI.26

VII. Gold(I) Catalyzed Isomerization of 5-En-2-yn-1-yl Acetates: an Efficient Access to Acetoxy Bicyclo[3.1.0]hexenes and 2-Cycloalken-1-ones

VII.1. Introduction

VII.1.1. Natural Products with Bicyclo[3.1.0]hexene Core

The bicyclo[3.1.0]hexene skeleton can be found in a variety of natural products and biologically active compounds produced by a series of marine organisms (mollusks and algae) and a wide variety of plants.

Natural Products from Marine Organisms

The bicyclo[3.1.0]hexene core occurs in several natural products produced by sacoglossan mollusks, animals which lack a protective shell and thus rely on chemical defense against predators (Figure VII.2).[389] In addition, they harvest functional chloroplasts from algae and use these organelles to live autotrophically through photosynthesis. Not surprisingly, they have yielded a range of interesting biologically active natural products.[390] Architecturally, these metabolites which appear to derive from the condensation of propionate units fall into two categories. Whereas 9,10-deoxytridachione and tridachione are cyclohexadiene derivatives, photodeoxytridachione, tridachiapyrone E, and crispatene (Figure VII.2) feature a bicyclo[3.1.0]hexene core. The isomeric nature of these ring systems raises questions about their mutual biogenetic relationship (see Chapter VII.2.1.).

Figure VII.1: *Placobranchus ocellatus*

[389] Davies-Coleman, M. T.; Garson, M. *J. Nat. Prod. Rep.* **1998**, *15*, 477
[390] a) Ireland, C.; Faulkner, D. J. *Tetrahedron* **1981**, *37*, 233; b) Ksebati, M. B.; Schmitz, F. J. *J. Org. Chem.* **1985**, *50*, 5637

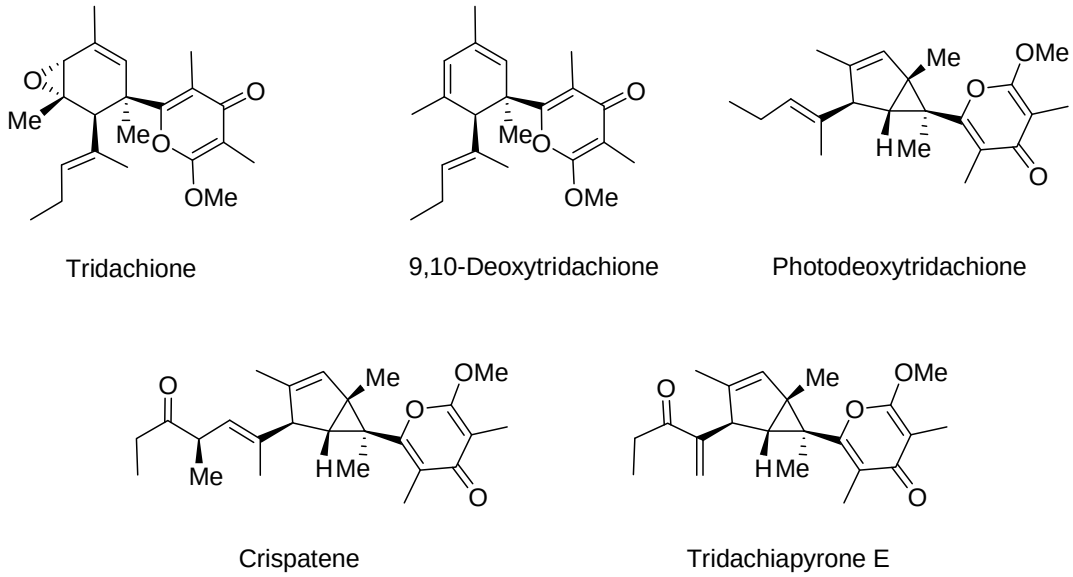


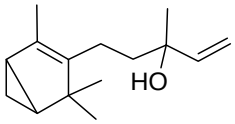
Figure VII.2

Photodeoxytridachione (Figure VII.2), found in the Pacific mollusk *Placobranchus ocellatus*[391] (Figure VII.1) and later identified in the Mediterranean *Elysia timida*,[392] has shown activity in an ichthyotoxicity assay. Crispatene and tridachiapyrone E (Figure VII.2) were isolated from *Elysia crispata* (Figure VII.3). Crispatene was moderately active in a lymphocytic leukemia assay. The total syntheses of photodeoxytridachione[393] and of (-)-crispatene[394] were achieved by Trauner's group by the Lewis acid catalyzed cyclization of hexatrienes or tetraenes to bicyclo[3.1.0]hexenes (see Chapter VII.2.2.).

Figure VII.3: *E. crispata*, the "lettuce slug"

Cardellina et *al.* reported the isolation and characterization of a new sesquiterpene alcohol from the red alga *Laurencia intricata*, collected in Bermuda. This compound called bicyclolaurencenol (Figure VII.4), possesses a novel bicyclic skeleton and seems to represent a biogenetic link between two groups of sesquiterpenes previously found in various *Laurencia* species.[395]

[391] Ireland, C.; Scheuer, P. J. *Science* **1979**, *205*, 922
[392] Gavagnin, M.; Spinella, A.; Castelluccio, F.; Cimino, G. *J. Nat. Prod.* **1994**, *57*, 298
[393] Miller, A. K.; Banghart, M. R.; Beaudry, C. M.; Suh, J. M.; Trauner, D. *Tetrahedron* **2003**, *59*, 8919
[394] K. Miller, A. K.; Byun, D. H.; Beaudry, C. M.; Trauner, D. *PNAS* **2004**, *101*, 12019
[395] Horsley, S. B.; Cardellina, J. H.; Meinwald, J. *J. Am. Chem. Soc.* **1981**, *46*, 5033



Bicyclolaurencenol

Figure VII.4: *Laurencia intricata*

Natural Products from Plants

Bicyclic terpenes are present in many plants.[396] One example of the monoterpene family are thujanes,[397] which are found in the essential oils of a variety of plants like *Angelica*, basil (*Ocimum basilicum*), bergamot (*Citrus aurantium ssp. bergamia*), cedar (*Cedrus*), *Eucalyptus*, lavenders (*Lavandula*) etc. (Figure VII.5).

Figure VII.5: *Angelica*, basil (*Ocimum basilicum*), bergamot (*Citrus aurantium ssp. bergamia*), *Eucalyptus*

α-Thujene also contributes pungency to the flavor of some herbs such as summer savory (*Satureja hortensis*). The term thujene usually refers to α-thujene. A less commonly occurring isomer, β-thujene, is an olefin isomer of α-thujene and is emitted by some plants. It may also have pheromonal properties and is found in essential oils derived from coniferous trees. Another double-bond isomer known as sabinene, found in various *Artemisia*,

[396] Breitmeier, E. *Terpene*; Teuber: Leipzig, **1999**
[397] Newman, A. A. *Chemistry of Terpenes and Terpenoids*, Ed. Academic Press: London and New York, **1972**, 48

Juniperus, and *Thuja* species,[397]is an important intermediate in the perfumery industry (Figure VII.6).

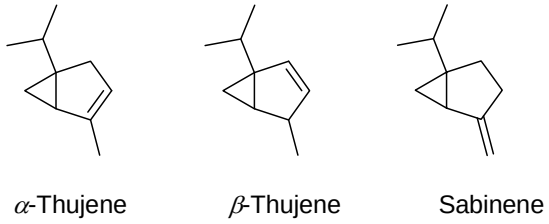


Figure VII.6

Figure VII.7: *Artemisia*, *Lavandula*, *Satureja hortensis*, *Angelica*

Since the isolation of sesquisabinene (Figure VII.8) from pepper (*Piper nigrum*)[398] and of sesquithujene (Figure VII.9) from ginger (*Zingiber officinale*), several relatives have been isolated which differ in the periphery, the chain composition and stereochemistry.[399] However, in many cases, the stereochemistry of these congeners remains uncertain or even completely unknown.

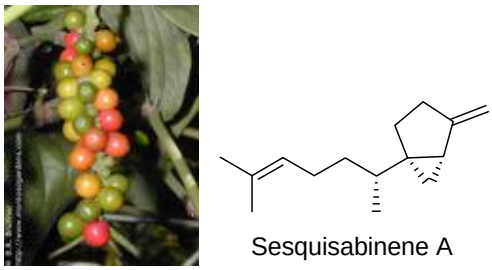


Figure VII.8: *Piper nigrum* and sesquisabinene

[398] Terhune, S. J.; Hogg, J. W.; Bromstein, A. C.; Lawrence, B. M. *Can. J. Chem.* **1975**, *53*, 3285
[399] Joulain, D.; König, W. A. *The Atlas of Spectral Data of Sesquiterpene Hydrocarbons*, EB Verlag, Hamburg, **1998**

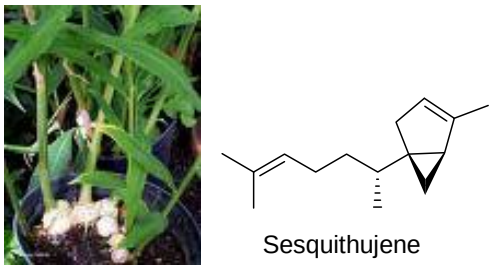


Figure VII.9: *Zingiber officinale* and Sesquithujene

Other interesting terpenes possessing the bicyclo[3.1.0]hexene skeleton are the isomeric (-)-*α*-cubebene and (-)-*β*-cubebene, together with the tertiary alcohols (-)-cubebol or cubebanol and 4-*epi*-cubebol (Figure VII.10). These naturally occurring sesquiterpenes are important components of the essential oil of *Piper cubeba L* (Figure VII.11) from which they were originally isolated.[400] Whereas *epi* has a very bitter taste, the almost odorless (-)-cubebol has a pronounced cooling effect and lends itself to diverse applications in the field of flavors.[401]

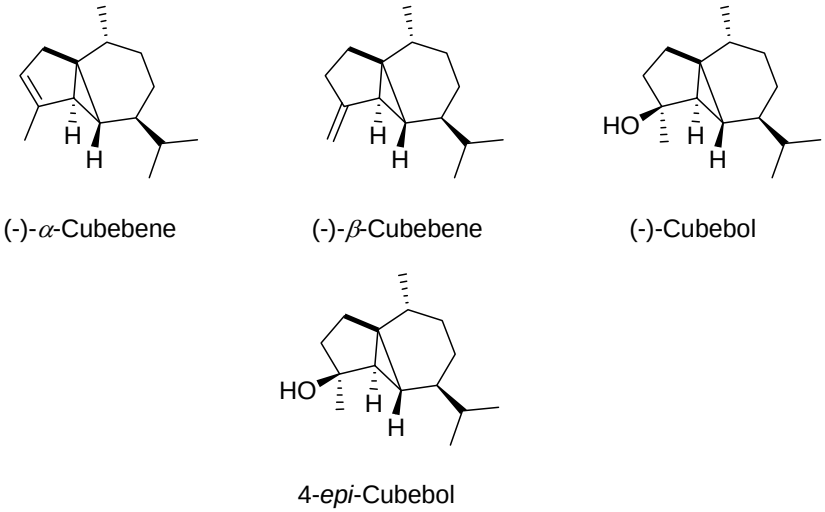


Figure VII.10

Figure VII.11: *Piper cubeba L.*

[400] a) Vonasek, F.; Herout, V.; Sorm, F. *Collect. Czech. Chem. Commun.* **1960**, *25*, 919; b) Ohta, Y.; Sakai, T.; Hirose, Y. *Tet. Lett.* **1966**, *7*, 6365; c) Ohta, Y.; Ohara, K.; Hirose, Y. *Tet. Lett.* **1968**, *9*, 4181

[401] Velazco, M. I.; Wuensche, L.; Deladoey, P. (Firmenich SA), US 6214788 (prior. 31.03.1999), **1999**; [*Chem. Abstr.* **2000**, *133*, 265959]

Mizutani's group disclosed the isolation and structural elucidation of a novel sesquiterpene lactone containg the bicyclo[3.1.0]hexene unit, named shizukanolide and its dehydroderivative, chloranthalactone A (Figure VII.12) from the roots of *Chloranthus japonicus* (Figure VII.13), a perennial herb in chloranthaceae plants that grow in the southern part of Korea, Japan and China.[402] It has been used as a folk remedy for the treatment of dermatopathia and enteric fever in Korea.

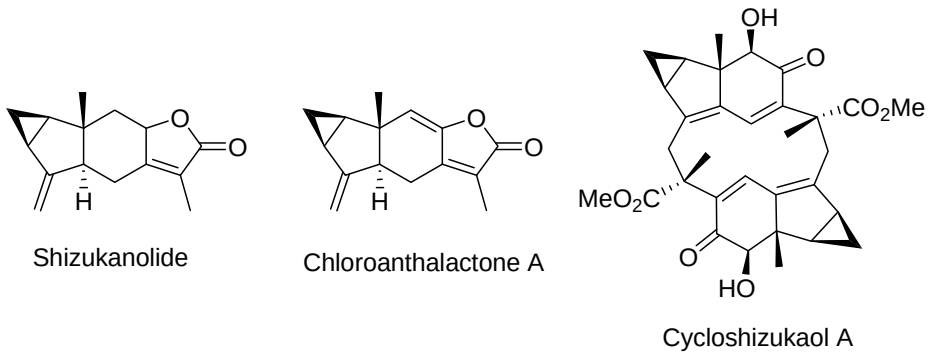


Figure VII.12

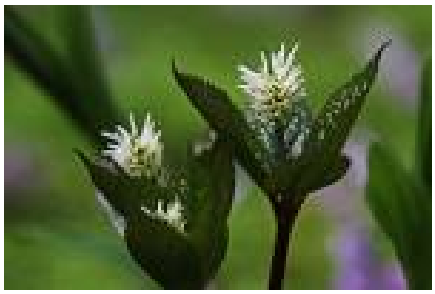


Figure VII.13: *Chloranthus japonicus*

VII.2. Synthesis and Biosynthesis of the Bicyclo[3.1.0]hexane Skeleton

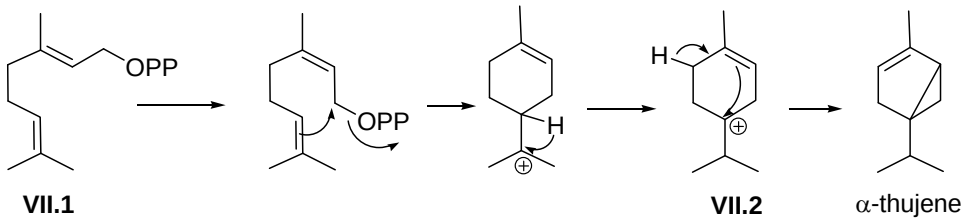
VII.2.1. Biosynthesis of the Bicyclo[3.1.0]hexane Skeleton [403]

Biosynthesis Involving the Rearrangement of Carbon Skeletons *via* Cationic Intermediates

The basic principle of the cyclopropane ring formations *via* cationic intermediates is the electrophilic attack of a carbenium ion on a homoconjugated double bond, an allylic double bond, a double bond, or a methyl group. Most cyclopropanations involving cationic intermediates take place with isoprenoids as substrates, like terpenoids or steroids.

[402] Kawabata, J.; Tahara, S.; Mizutani, J. *J. Agric. Biol. Chem.*, **1981**, *45*, 1447
[403] Wessjohann, L. A.; Brandt, W.; Thiemann, T. *Chem. Rev.* **2003**, *103*, 1625

Cyclizations of homoallylic cations to bicyclic cyclopropanes are commonly observed in isoprenoid rearrangements.
Bicyclic monoterpenes are present in many plants. Among the members of this family are thujanes, such as *α*-thujene, *β*-thujene and *α*-sabinene (see Figure VII.6). The formation of the cyclopropyl group in *α*-thujene and other members of this family is thought to originate from the cyclization of the acyclic C_{10} isoprenyl precursor geranyl diphosphate (VII.1, Scheme VII.1). The cleavage of the diphosphate group is accompanied by cyclization and the formation of the *α*-terpinyl cation VII.2. A subsequent 1,2-hydride shift and subsequent attack of the double bond on the cation results in the formation of a cyclopropane ring. After loss of the proton situated in *α* relative to the double bond, *α*-thujene is obtained (Scheme VII.1):



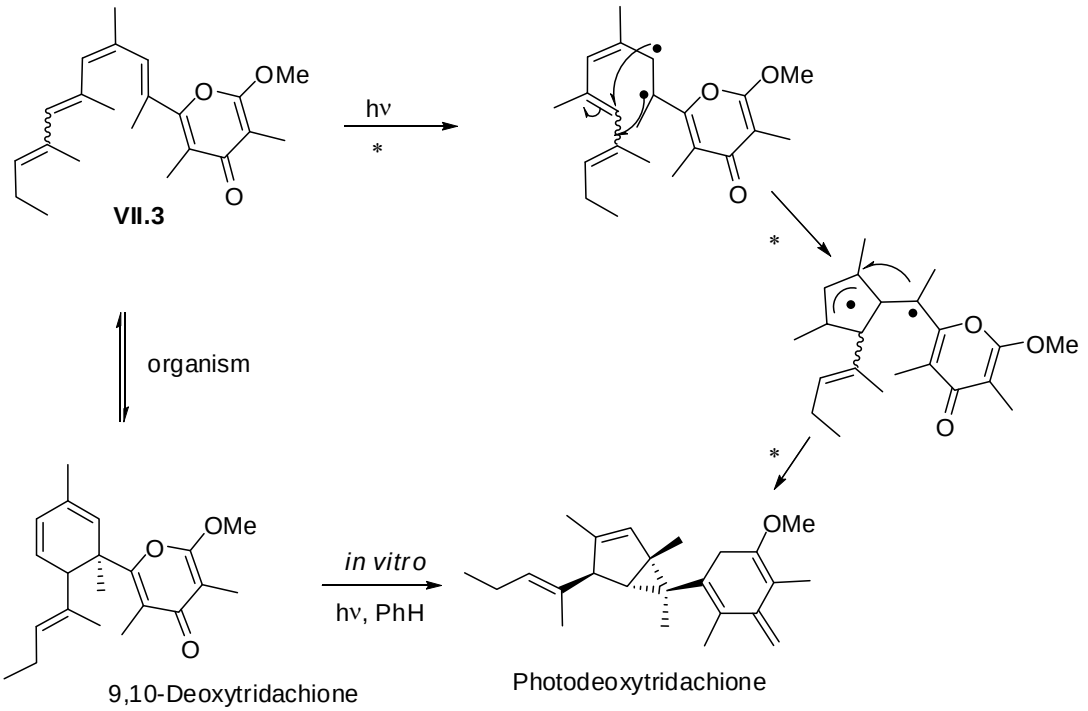
Scheme VII.1

This principal mechanism is supported by labeling studies *in vivo* of 3-thujone, sabinene, and other terpenoids derived from mevalonic acid.[404]

Biosynthesis Involving Photoinduced Cyclopropane Formation

The isomeric nature of the ring systems found in the mollusk metabolites described in Chapter VII.1.1 (Figure VII.2) raised questions about their mutual biogenetic relationship.[390]
Crispatene and erispatene (Figure VII.2) are two metabolites isolated from *Tridachia crispate*, a mollusk species assimilating chloroplasts from siphonous algae.[392]
In 1979, Ireland and Scheuer demonstrated that 9,10-deoxytridachione can be photochemically converted *in vivo* and *in vitro* into photodeoxytridachione (Scheme VII.2).[391] These results support the hypothesis that these compounds are formed through a photochemical cyclization mechanism starting from hexatriene VII.3. It was suggested that the photoreaction proceeds *via* a [σ2a + σ2a] mechanism or by direct photocyclization of the triene moiety VII.3, as depicted in Scheme VII.2:

[404] Banthorpe, D. V.; Mann, J.; Poots, I. *Phytochemistry* **1977**, *16*, 547 and references cited therein



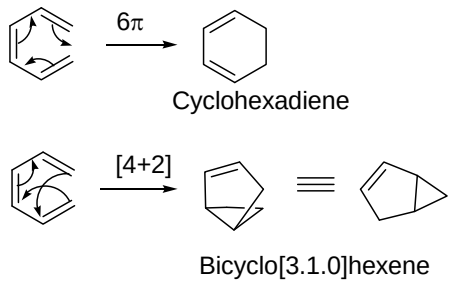
Scheme VII.2

VI.2.2. Chemical Synthesis

Electrocyclisations Leading to the Bicyclo[3.1.0]hexene Skeleton

Thermal 6л and photochemical electrocyclizations are ubiquitous within the chemical literature (Scheme VII.3).[405] Their development as a powerful synthetic tool has been greatly aided by advances in theory, culminating in the Woodward–Hoffmann principle of conservation of orbital symmetry.[406]

In contrast, the thermal isomerization of hexatrienes to bicyclo[3.1.0]hexenes has received relatively little attention (Scheme VII.3).

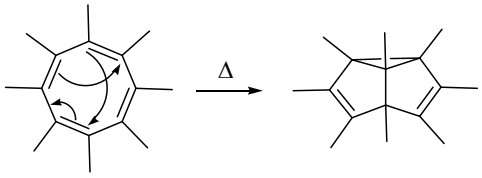


Scheme VII.3

[405] Okamura, W. H.; De Lera, A. R. *Comprehensive Organic Synthesis*; Trost, B., Ed.; Pergamon: Oxford, **1991**, *5*, 699

[406] Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry* **1970**, VCH: Weinheim

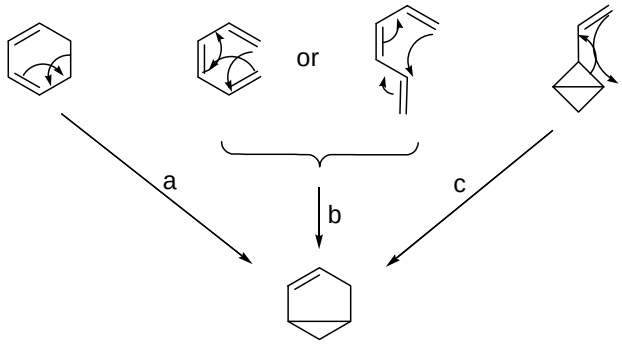
These isomerizations could be considered as intramolecular [4+2] cycloadditions with a tether consisting of a single bond. Hence, they have been dubbed the "photochemical Diels–Alder reaction". In accordance with the Woodward–Hoffmann rules, they proceed as [л4s+л2a] or [л4a+л2s] cycloadditions—antarafacial with respect to one component and suprafacial with respect to the other. Very few thermal isomerizations of this type, which, if concerted, necessarily proceed as [л4a+л2a] cycloadditions, have been reported. Most of these involve cyclooctatetraenes as substrates (Scheme VII.14).



Scheme VII.4

Steric constraints usually favor the [л4s+л2s] pathway found in a "normal" Diels–Alder reaction and preclude the diene and dienophile from approaching each other in such a fashion as to allow concerted twofold antarafacial bond formation.

Nevertheless, photochemical versions of the isomerization of hexatrienes to bicyclo[3.1.0]hexenes are well documented. The photochemistry of 1,3-cyclohexadienes has been the subject of extensive investigation, and, largely because of its importance in vitamin D syntheses from steroidal 5,7-dienes, it has had the benefit of intense examination long before the current renaissance of organic photochemistry.
In 1958 Dauben and co-workers reported the first observations dealing with the photorearrangement of 1,3,5-hexatrienes to bicyclo[3.1.0]hex-2-enes.[407] This reaction has been discussed in terms of at least three mechanistic pathways (Scheme VII.5):[408](1) a vinylcyclopropane- cyclopentene rearrangement of a hypothetical 2-vinylbicyclo[1.1.0]butane intermediate (path a); (2) a prior photoisomerization to a 1,3-cyclohexadiene followed by a bond-switching process (path b); and (3) an electrocyclic, intramolecular photo-Diels-Alder reaction (path c).



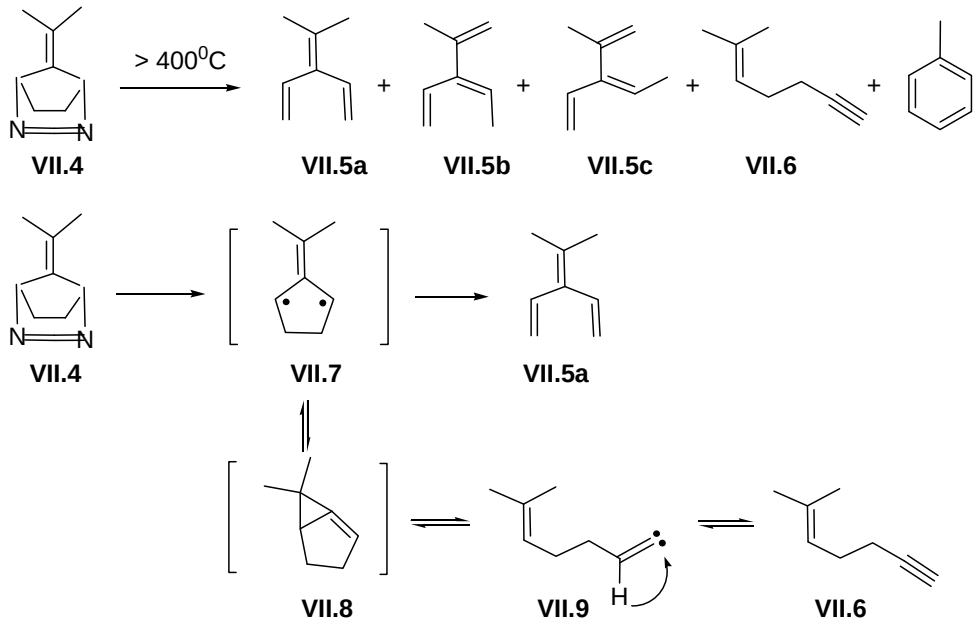
Scheme VII.5

[407] Dauben, W. G.; Bell, I.; Hutton, T. W.; Laws, F. G.; Rheiner, A. *J. Am. Chem. Soc.* **1958**, *80*, 4116
[408] Meinwald, J.; Mazzocchi, P. H. *J. Amer. Chem. Soc.* **1967**, *89*, 1755

Meinwald and Mazzocchi[408] have shown, by deuteration experiments, that 1,1-dimethylhexatriene is photoisomerized to 6,6-dimethylbicyclo[3.1.0]hex-2-ene without passing through a vinylbicyclobutane intermediate. Consequently, pathway (a) can be discounted for this system and probably for closely related systems. In most cases it has been assumed that the corresponding 1,3-cyclohexadienes were not involved in the cyclization of 1,3,5-hexatrienes to bicyclo[3.1.0]hexenes, despite the fact that cyclohexadiene formation is a common and general photoreaction of hexatrienes. There are some additional studies, however, which indicate that the bond switching process (i.e., path b) is not the principal pathway involved in the isomerization of 1,3,5-hexatrienes to bicyclo[3.1.0]hexenes.[409] Orbital symmetry considerations and an acute sense of stereochemical requirements led Woodward and Hoffmann to view these rearrangements as examples of photochemical Diels-Alder reactions.[410]
One application of this reaction is the photolysis of vitamin D_2 to afford a mixture of suprasterol I and II.[411]

Radical Reactions Leading to the Bicyclo[3.1.0]hexene Skeleton

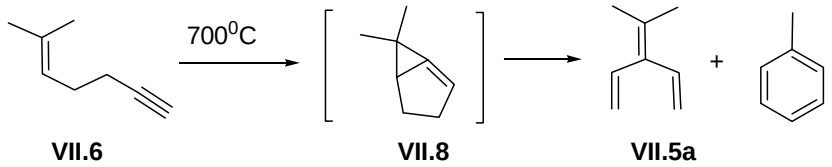
Berson and co-workers showed that flash vacuum pyrolysis of the diazene VII.4 at temperatures above 400°C and pressures of 10^{-3}-10^{-4} Torr gave a complex mixture where trienes VII.5a-c and toluene where the major constituents. The enyne VII.6 apparently arises by a route beginning with cyclization of diradical VII.7 to the bicyclo[3.1.0]hex-1-ene VII.8. This compound suffers thermal vinylidene cycloreversion to the carbene VII.9, which then undergoes a hydrogen shift (Scheme VII.6).



Scheme VII.6

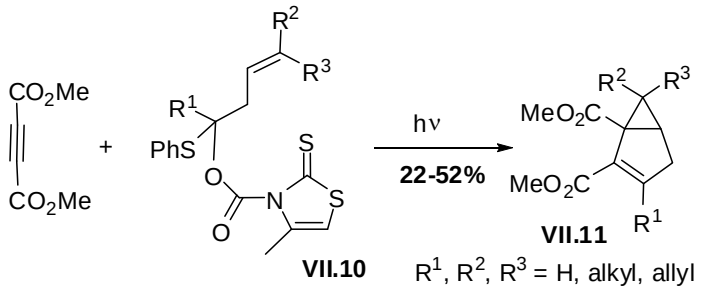
[409] Crowley, K. J. *J. Amer. Chem. Soc.* **1964**, *86*, 5692
[410] Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 781
[411] Okamura, W. H.; De Lera, A. R. *Comprehensive Organic Synthesis*; Trost, B., Ed. Pergamon: Oxford, **1991**, *5*, 79

Reversal of the entire cyclization sequence was observed in the pyrolysis of the enyne VII.6 (Scheme VII.7), which gave the same group of trienes VII.5a-c and toluene obtained from diazene VII.4. From these results the authors conjectured that the thermal rearrangement of 1,5-enyne VII.6 proceeds *via* bicyclo[3.1.0]hexene VII.8.[412]



Scheme VII.7

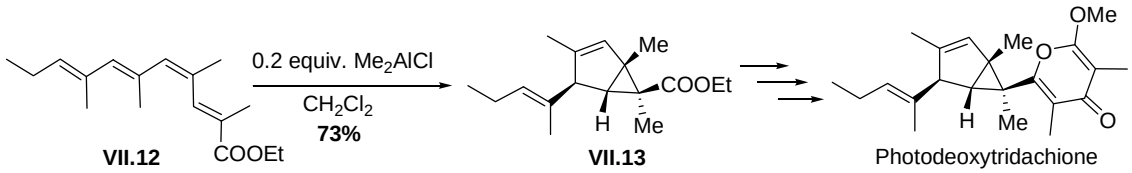
Saicic and colleagues obtained bicyclo[3.1.0]hex-2-enes VII.11 in moderate yields by homolytic decomposition of thiohydroxamic esters VII.10 in the presence of dimethyl acetylenedicarboxylate (Scheme VII.8):[413]



Scheme VII.8

Lewis Acid Catalyzed Reactions Leading to the Bicyclo[3.1.0]hexene Skeleton

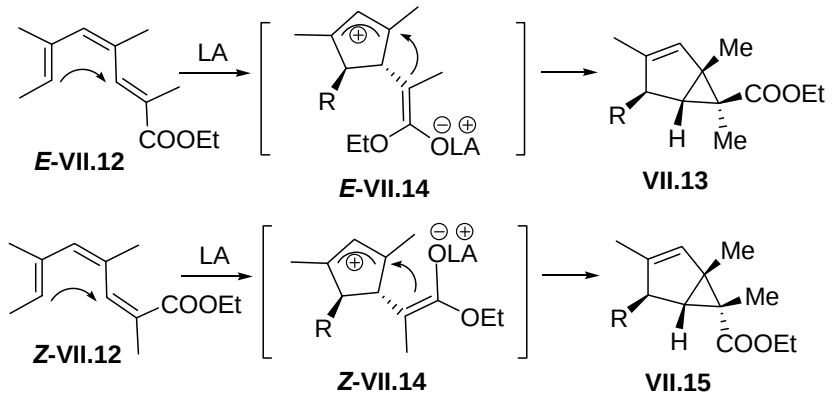
Inspired by the biosyntheses of the mollusk metabolites 9,10-deoxytridachione and photodeoxytridachione, Trauner's group suggested that both compounds could be directly derived from a common acyclic precursor VII.12 (Scheme VII.9). They designed a unified synthetic approach toward both classes: the Lewis acid catalyzed cyclization of hexatrienes to bicyclo[3.1.0]hexenes. The application of this reaction to the total synthesis of photodeoxytridachione is illustrated in Scheme VII.9:[414]



[412] Mazur, M. R.; Potter, S. E.; Pinhas, A. R.; Berson, J. A. *J. Am. Chem. Soc.* **1982**, *104*, 6823
[413] Ferjancic, Z.; Saicic, R. N.; Cekovic, Z. *Tet. Lett.* **1997**, *38*, 4165
[414] Miller, A. K.; Trauner, D. *Angew. Chem. Int. Ed.* **2003**, *42*, 549

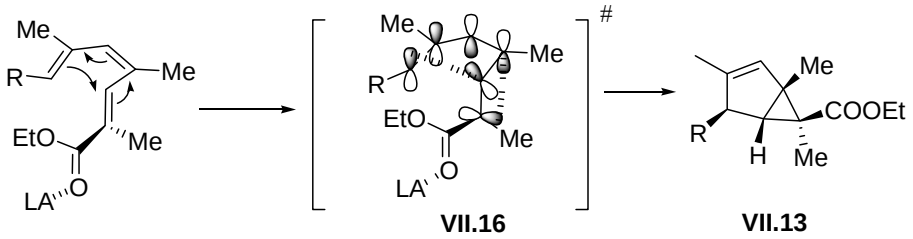
Scheme VII.9

Mechanistically, the Lewis acid catalyzed cyclization could either proceed in a stepwise fashion or as a concerted cycloaddition.
In the stepwise mechanism, coordination of the Lewis acid (LA) to the carbonyl group of trienoic ester *E*-VII.12 or its isomer *Z*-VII.12 triggers a stereoselective ring formation, placing the two substituents *anti* with respect to each other (Scheme VII.10). The resulting zwitterionic intermediates *E*-VII.14/*Z*-VII.14 stabilize themselves by C-C bond formation to yield bicyclo[3.1.0]hexenes VII.13 or VII.15.



Scheme VII.10

Alternatively, in the concerted cycloaddition mechanism, only one transition state VII.16 could be formulated (Scheme VII.11):



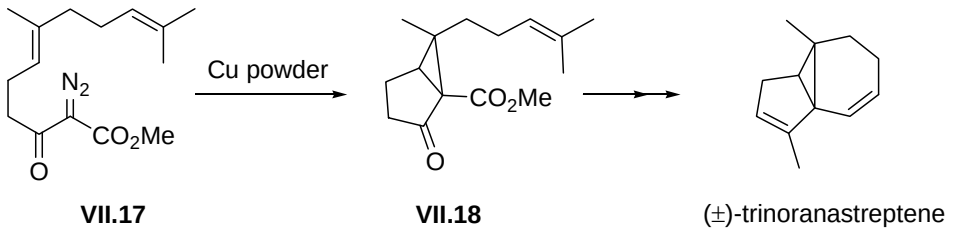
Scheme VII.11

Decomposition Reactions of Diazocompounds

α-Diazocarbonyl compounds have a long history of useful applications in organic chemistry. They are prepared from readily accessible precursors and can be induced to undergo a wide variety of chemical transformations under very mild conditions.[415]
Transition metal catalyzed decomposition of diazocarbonyl compounds in the presence of pendant alkenes or alkynes provides a facile and powerful means of constructing fused cyclopropanes.

[415] Tao Ye, T.; McKervey, A. *Chem. Rev.* **1994**, *94*, 1091

For example, bicyclo[3.1.0]hexane derivative VII.18 was synthesized from the corresponding diazocarbonyl precursor VII.17 *via* the copper catalyzed decomposition method and was converted into (±)-trinoranastreptene (Scheme VII.12).[416]



Scheme VII.12

VII.3. Transition Metal Catalyzed 1,5-Enyne Cycloisomerizations Leading to the Bicyclo[3.1.0]hexene Skeleton. Preliminary Work in the Literature

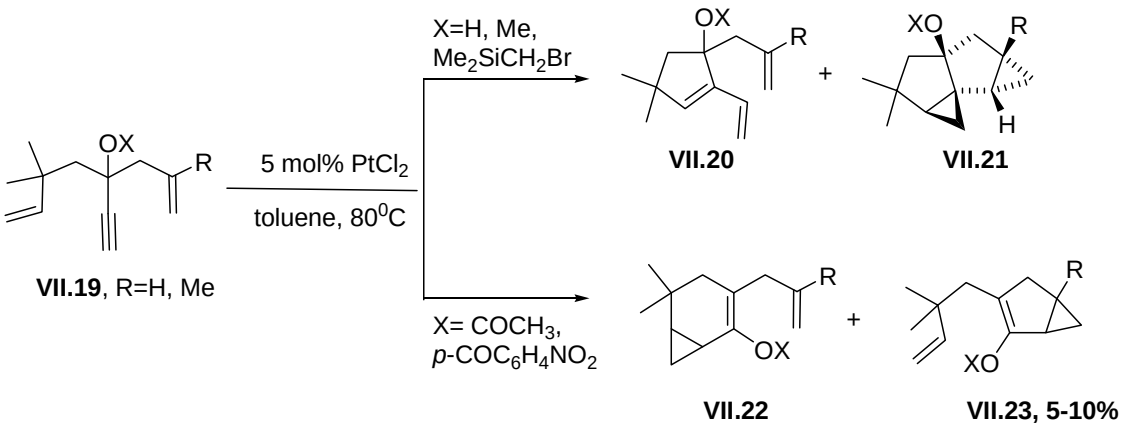
Transition metal-catalyzed isomerization and rearrangement reactions of unsaturated systems provide access to structural motifs not accessible through their thermal counterparts. Metal-induced cycloisomerizations of 1,5-enynes emerged as extremely attractive and unique tools for the synthesis of various types of cyclic compounds in a very easy one-pot process. The significance of this process stems from the rapid increase in structural complexity starting with relatively simple acyclic subunits containing olefinic and acetyl fragments.[49]

VII.3.1. Pt-Catalyzed 1,5-Enyne Cycloisomerizations

Among a range of transition metal complexes capable of catalyzing enyne cycloisomerizations, gold and platinum complexes are particularly powerful as they allow the synthesis of a diverse array of cyclic products that are produced under mild conditions, with excellent chemoselectivity and high synthetic efficiency.[49]

In 2002, Malacria et *al.* studied the reactivity of enyne precursors of type VII.19 in the presence of $PtCl_2$ catalyst (Scheme VII.13):[417]

[416] Kang, S. H.; Kim, W. J.; Chae, Y. B. *Tet. Lett.* **1988**, *29*, 5169
[417] Mainetti, E.; Mouries, V.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. *Angew. Chem. Int. Ed.* **2002**, *41*, 2132



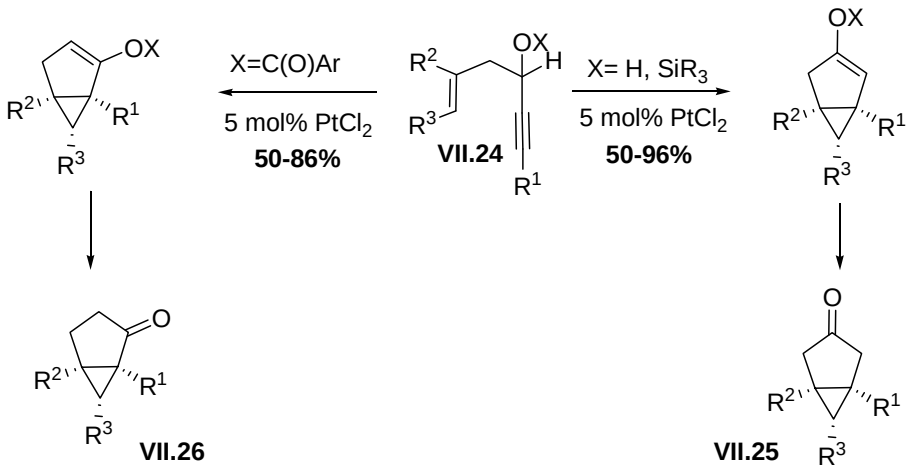
Scheme VII.13

With a free or silylated hydroxy group or the corresponding ethers, a new tetracyclo[4.4.0.0 ^{1,3}0 ^{8,10}]decane skeleton VII.21 was obtained diastereoselectively, along with traces of the expected methatesis type product VII.20. Protecting the alcohol with an acyl group completely shifted the reaction towards a previously undescribed rearrangement, which afforded bicyclic enolesters with a fused cyclopropane ring. These were then methanolyzed to versatile [n.1.0]bicylic ketones as single diastereomers. It should be noted that this combined two-steps protocol can be considered as an equivalent of the well-known cycloisomerization of unsaturated *α*-diazocarbonyl compounds discussed earlier (Scheme VII.12).

In 2004, Fürstner and Malacria published their independent studies of Pt-catalyzed 1,5-enyne cycloisomerizations to bicyclo[3.1.0]hexenes.

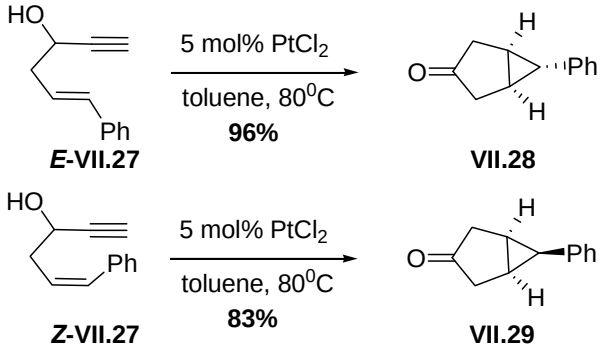
Malacria's group tested the reactivity of secondary 5-en-1-yn-3-ol systems VII.24 in the presence of $PtCl_2$ catalyst. They showed that depending on the nature of the X substituent on the substrate VII.24 (Scheme VII.14), electrophilic activation of the alkyne moiety triggers hydride shift or *O*-acyl migration yielding regioisomeric keto-derivatives VII.25 and VII.26:[418]

[418] Harrak, Y.; Blaszykowski, C.; Bernard, M.; Cariou, K.; Mainetty, E.; Mouries, V.; Dhimane, A.-L.; Fensterbank L.; Malacria, M. *J. Am. Chem. Soc.* **2004**, *126*, 8656



Scheme VII.14

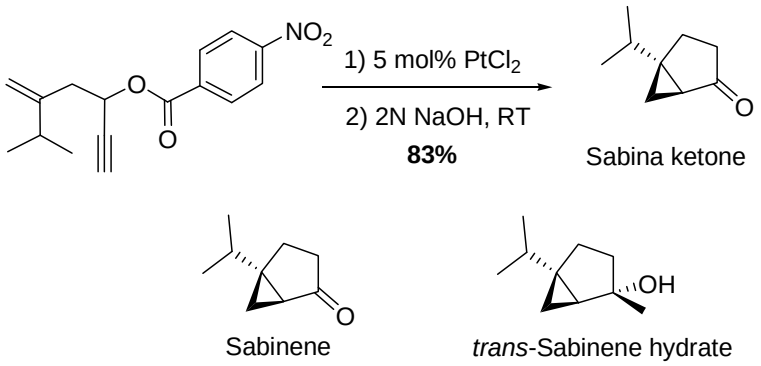
In addition, the authors established that the formation of bicyclo[3.1.0]hexenes was stereospecific. Subjection of enyne VII.27 containing an *E*-alkene to the reaction conditions afforded ketone VII.28, while a similar reaction using *Z*-alkene furnished the diastereoisomeric product VII.29 (Scheme VII.15):



Scheme VII.15

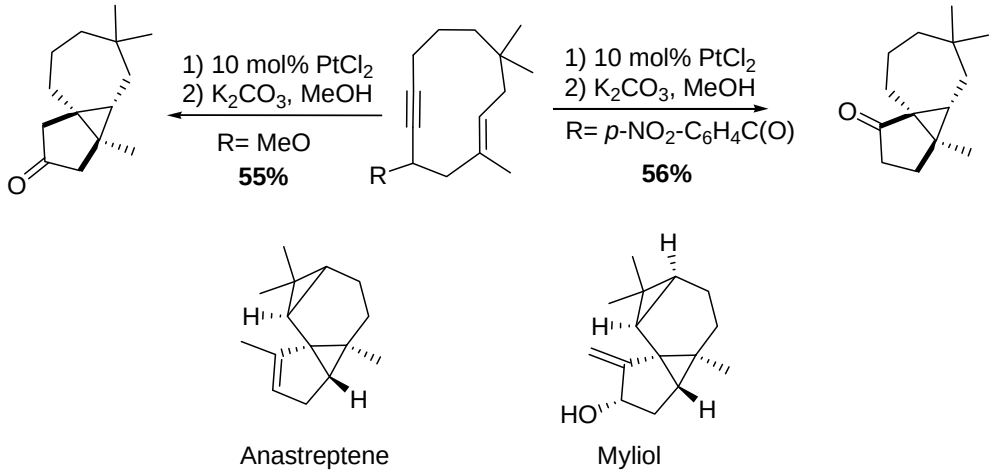
One application of this methodology is the synthesis of sabina ketone, a natural product that is a key intermediate for the synthesis of important monoterpenes such as sabinene and sabinene hydrates (Scheme VII.16).[419]

[419] a) Barberis, M.; Perez-Prieto, J. *Tet. Lett*. **2003**, *44*, 6683; b) Galopin, C. C. *Tet. Lett*. **2001**, *42*, 5589



Scheme VII.16

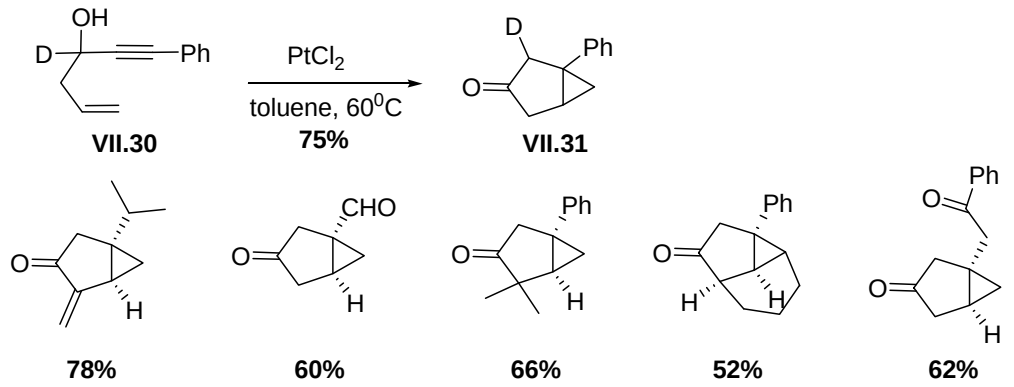
In 2004, the same group reported a transannular version of this reaction,[420] which allowed the assembly of a series of cyclopropanic tricyclic systems like those found in the natural products anastreptene[421] or myliol,[422] isolated from liverwort plants (Scheme VII.17):



Scheme VII.17

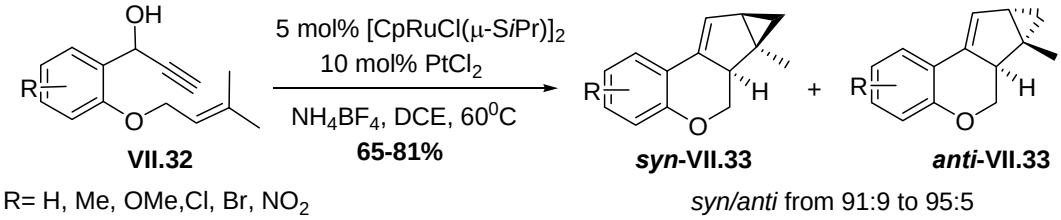
Independently, Fürstner et *al.* found that subjection of enyne VII.30 to a catalytic amount of $PtCl_2$ in toluene at 60°C afforded bicyclic ketone VII.31 in 75% yield by a mechanism involving a 1,2-hydrogen shift. The deuterium label in the product appeared exclusively at the C(2) position of VII.31. Representative examples of the scope of this cycloisomerization reaction are illustrated in Scheme VII.18. In addition to $PtCl_2$ catalysis, the authors reported that the combination of $Au(PPh_3)Cl$ and $AgSbF_6$ was effective in conversion of the acetate derivative of VII.30 to bicyclic ketone VII.31 (see next section).[423]

[420] a) Blaszykowski, C.; Harrak, Y.; Gonçalves, M.-H.; Cloarec, J.-M.; Dhimane, A. L.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2004**, *6*, 3771; b) Blaszykowski, C.; Harrak, Y.; Brancour, C.; Nakama, K.; Dhimane, A. L.; Fensterbank, L.; Malacria, M. *Synthesis* **2007**, *13*, 2037
[421] Warmers, U.; Konig, W. A. *Phytochemistry* **1999**, *52*, 1519
[422] Hayashi, K.-I.; Asano, K.-I.; Tanaka, M.; Takaoka, D.; Nozaki, H. *Phytochemistry* **1998**, *48*, 461
[423] Victor Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654



Scheme VII.18

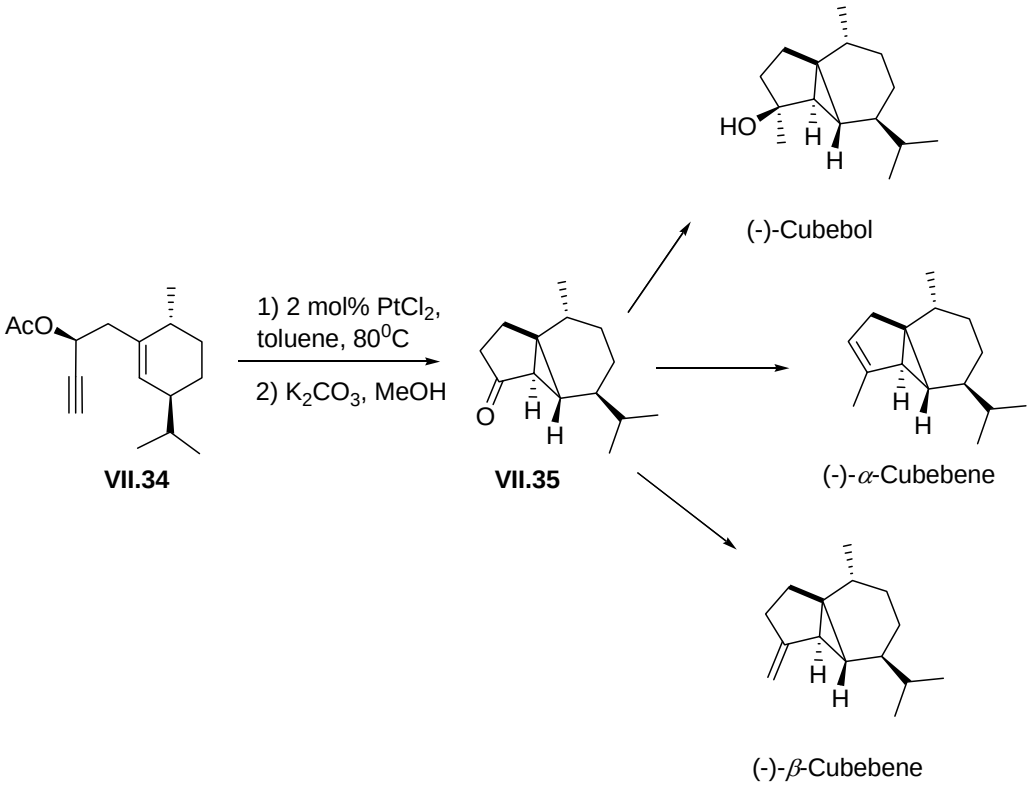
In 2004, Nishibayashi and colleagues also published a sequential reaction transforming 1,5-enyne, which was generated *in situ* from propargyl alcohols of type VII.32, to a bicyclo[3.1.0]hexene skeleton VII.33 by tandem Ru and Pt catalysis (Scheme VII.19).[424]



Scheme VII.19

In 2006, Fürstner and Hannen reported the application of $PtCl_2$-catalyzed cycloisomerization of 1,5-enyne VII.34 (a modified "Rautenstrauch-Ohloff" rearrangement)[425] as the key step for the efficient syntheses of (-)-cubebol , (-)-α-cubebene, and (-)-β-cubebene (Scheme VII.20), which were efficiently accessed from a common intermediate VII.35.[426]

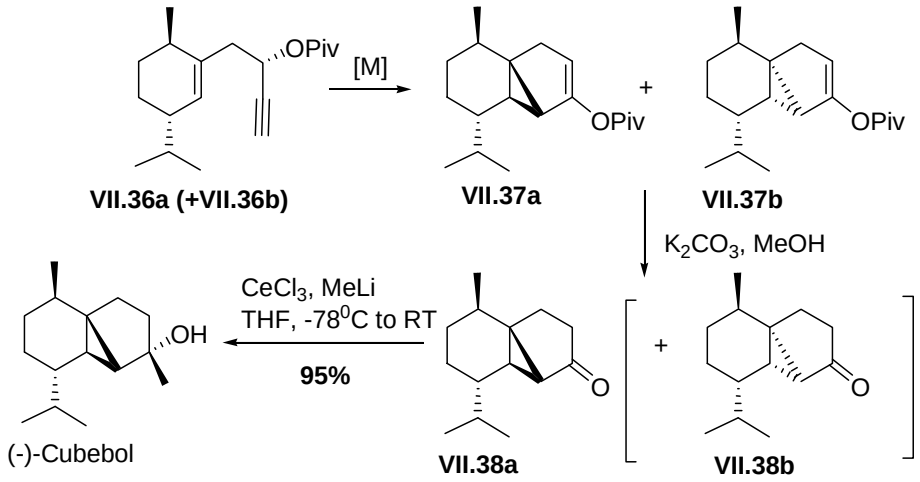
[424] Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2004**, *126*, 16066
[425] Rautenstrauch, V. *J. Org. Chem.* **1984**, *49*, 950
[426] Fürstner, A.; Hannen, P. *Chem.–Eur. J.* **2006**, *12*, 3006



Scheme VII.20

A very elegant synthesis of (-)-cubebol was described by Fehr and Galindo using a cycloisomerization catalyzed by Pt(II), Au(I), or Cu(I) (Scheme VII.21).[427]

[427] Fehr, C.; Galindo, J. *Angew. Chem., Int. Ed.*, **2006**, *45*, 2901

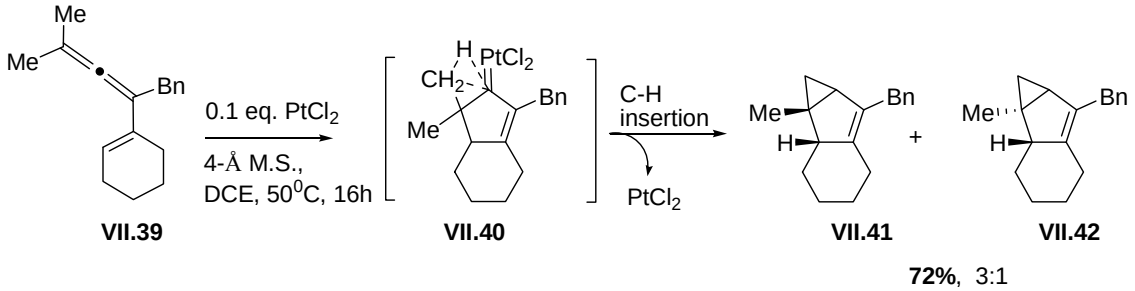


VII.36a: VII.36b	[M]	Conditions	VII.37a: VII.37b	Yield
88:12	2 mol% $PtCl_2$	DCE, 70^0C, 5h	94:6	**81%**
10:90	2 mol% $AgSbF_6$/ PPh_3AuCl	DCM, 20^0C, 40 min	47:53	**65%**
98:2	2 mol% $[Cu(MeCN)_4]BF_4$	DCE, 60^0C, 9h	99:1	**77%**[a]

[a] 90% conversion

Scheme VII.21

Very recently, direct evidence of the presence of a carbene intermediate VII.40 was obtained by Iwasawa et *al.* in the reaction of 1,1-dimethyl-1,2,4-triene VII.39 (Scheme VII.22) with $PtCl_2$ by a tandem cyclization/C-H insertion reaction.[428]



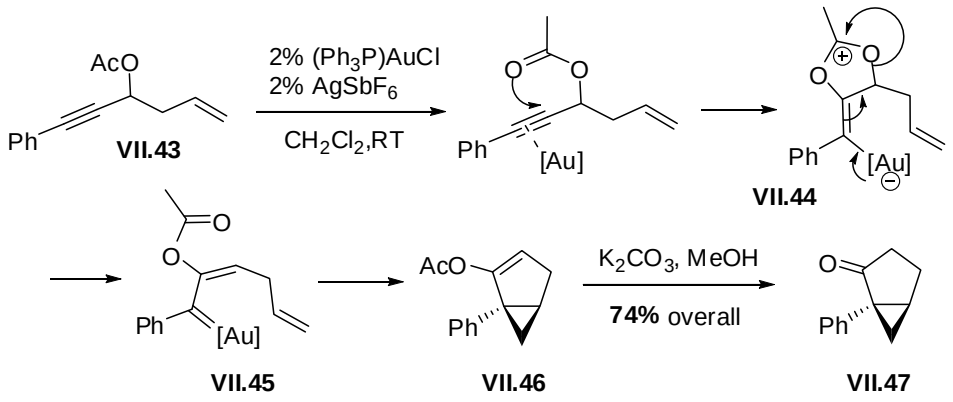
Scheme VII.22

VII.3.2. Au-Catalyzed 1,5-Enyne Cycloisomerizations

Apart from the conventional cyclopropanation methods[429] employing ylides, diazo compounds, or Simmons–Smith reaction, the gold-catalyzed 1,5-enyne cyclization pioneered by the Toste and Fürstner groups has offered yet another avenue to cyclopropanes.
As mentioned earlier in Chapter VII.3.1, Fürstner's group found that $PtCl_2$ can be replaced by $(PPh_3)AuCl/AgSbF_6$[430] as the catalyst in the transformation of acetate VII.43 into the

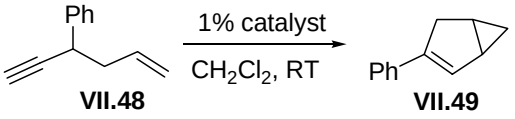
[428] Funami, H.; Kusama, H.; Iwasawa, N. *Angew. Chem. Int. Ed.* **2007**, *46*, 909
[429] Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977

bicyclo[3.1.0]hexanone derivative VII.46 (Scheme VII.23); the *in situ* formed cationic gold complex is particularly reactive and induces the isomerization even at ambient temperature. The ester participates in the rearrangement process by attacking the metal activated triple bond. Interception of the emerging intermediate VII.45 by the terminal double bond results in the formation of compound VII.46 in which the acetate has migrated, masking a ketone group as the corresponding enol ester (Scheme VII.23).[423]



Scheme VII.23

Inspired by the thermal rearrangement of 1,5-enynes (see Scheme VII.7), Toste et *al.* studied the transition metal-catalyzed transformation of VII.48 to bicyclo[3.1.0]hexene VII.49,[431] an olefin isomer of the proposed intermediate in the thermal isomerization (Table VII.1):



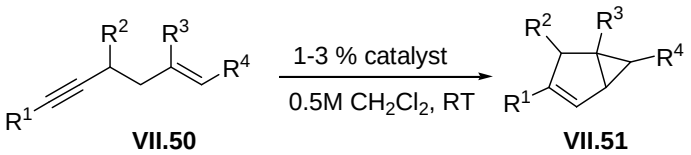
Catalyst	Conversion
$(CH_3CN)_2PdCl_2$, 24 h	**~4%**
$PtCl_2$, 24h	**~4%**
$PtCl_2$, $AgBF_4$, 24 h	**~5%**
$AgBF_4$, 24 h	**trace**
$(PPh_3)AuCl$, $AgBF_4$, 5 min	**100%**
$(PPh_3)AuCl$, 24 h	**0%**
$AuCl_3$, 3 h	**50%**

Table VII.1

Unlike the two previous reports of 1,5-enyne cycloisomerisations using Pt catalysts,[417,418] which used exclusively C(3)-acyloxy- and hydroxy-substituted enynes, Toste and co-workers found that gold catalysis enabled also efficient cycloisomerization of 1,5-enynes bearing aryl and alkyl groups at the C(3) position (Table VII.2).

[430] Nieto-Oberhuber, C.; Munoz, M. P.; Bunuel, E.; Nevado, C.; Cardenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2402
[431] Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858

A range of 1,5-enynes underwent the triphenylphosphinegold(I)-catalyzed rearrangement (Table VII.2). The propargylic and the allylic positions can be unsubstituted (Entry 1) or substituted with aryl (Entry 2) or alkyl substituents (Entry 3). Additionally, enantioenriched 1,5-enyne VII.50d is isomerized to VII.51d with excellent chirality transfer (Entry 4).



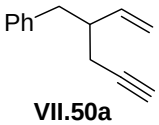
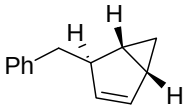
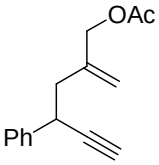
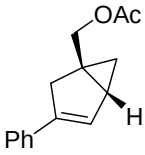
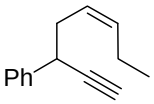
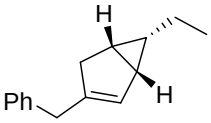
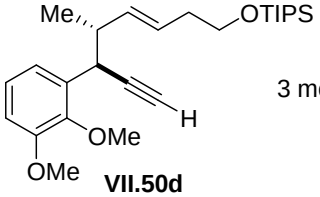
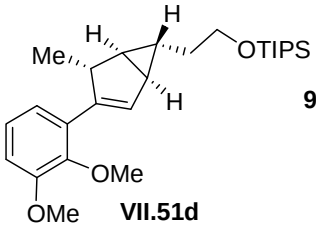
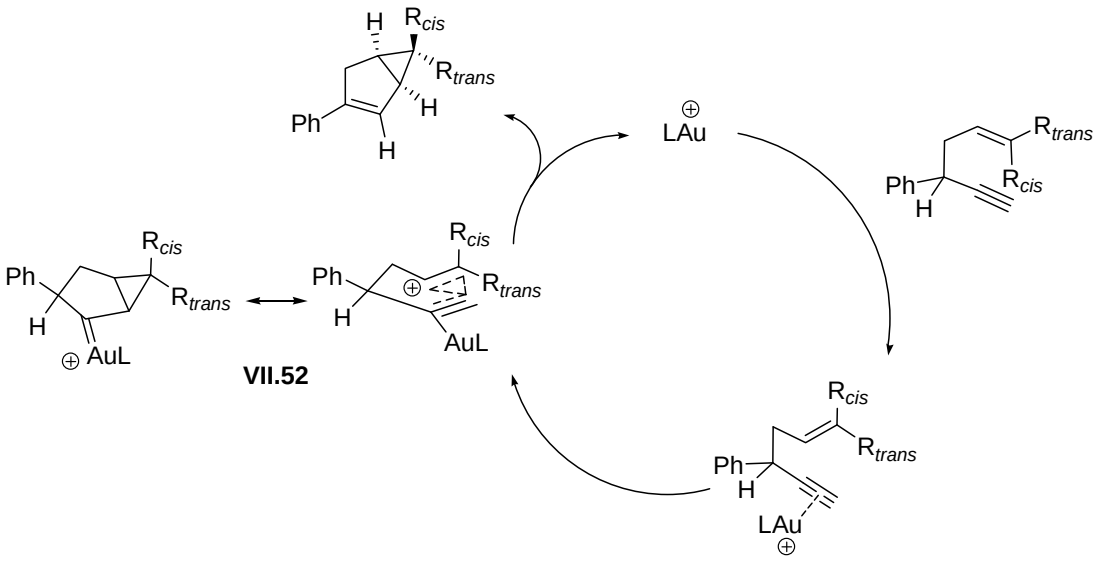
Entry	Substrate	Conditions	Product	Yield
1	 VII.50a	3 mol% $(Ph_3P)AuSbF_6$	 VII.51a	**82%**, dr=10:1
2	 VII.50b	3 mol% $(Ph_3P)AuSbF_6$	 VII.51b	**96%**
3	 VII.50c	1 mol% $(Ph_3P)AuSbF_6$	 VII.51c	**96%**, dr= 97:3
4	 VII.50d	3 mol% $(Ph_3P)AuPF_6$	 VII.51d	**99%**, 91% ee, dr> 99:1

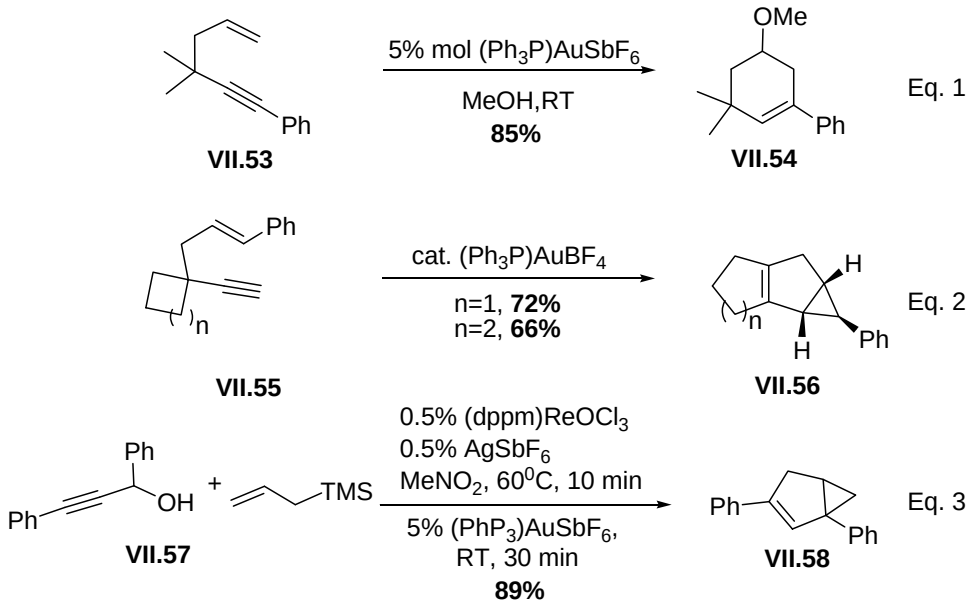
Table VII.2

The mechanistic manifold proposed by the authors is illustrated in Scheme VII.24. Coordination of cationic gold(I) to the alkyne followed by nucleophilic attack of the pendant olefin produces cyclopropylcarbinyl cation VII.52. The bicyclo[3.1.0]hexene product is generated by a 1,2-hydrogen shift onto a cation or a gold(I) carbene:



Scheme VII.24

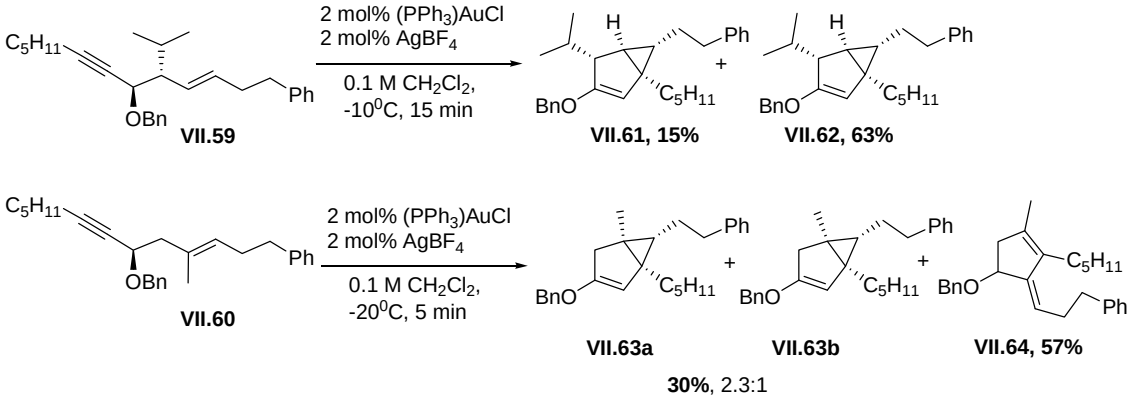
Cationic intermediate VII.52 was trapped in the presence of a nucleophile, forming the cyclohexene derivative VII.54 (Scheme VII.25, Eq. 1). However, in the absence of a nucleophile, a 1,2-alkyl shift is observed as in the tandem cycloisomerization-ring enlargement process of compound VII.55 (Scheme VII.25, Eq. 2). This method can also be combined with the rhenium-catalyzed propargylic allylation[432] to provide a one-pot synthesis of bicyclo[3.1.0]hexenes VII.58 from propargyl alcohols VII.57 (Scheme VII.25, Eq. 3).



Scheme VII.25

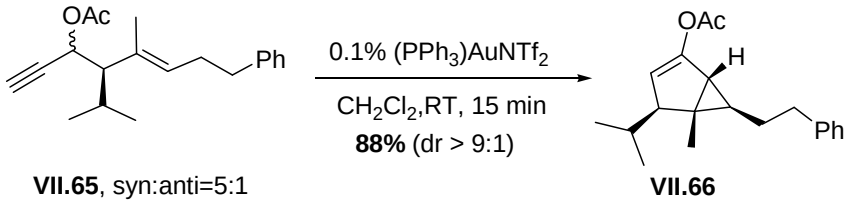
[432] Luzung, M. R.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 15760

Our group studied the isomerisation of diversely substituted 3-hydroxylated 1,5-enynes in the presence of cationic gold(I) complexes.[433] Bicyclo[3.1.0]hexenes VII.63a-b are obtained as minor products when enyne VII.60 was treated with 2 mol % $(PPh_3)AuBF_4$ or as major products in the case of enynol VII.59 (Scheme VII.26):



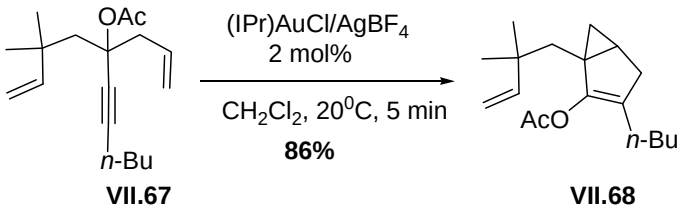
Scheme VII.26

The new phosphine gold(I) complex with *bis*(trifluoromethanesulfonyl)imidate as counterion developed in our laboratory (see Chapter I)[100a] proved to be also effective in catalyzing the cycloisomerization of 1,5-enyne VII.65 to bicyclo[3.1.0]hexene VII.66 isolated in 88% yield using only 0.1 % catalyst (Scheme VII.27):

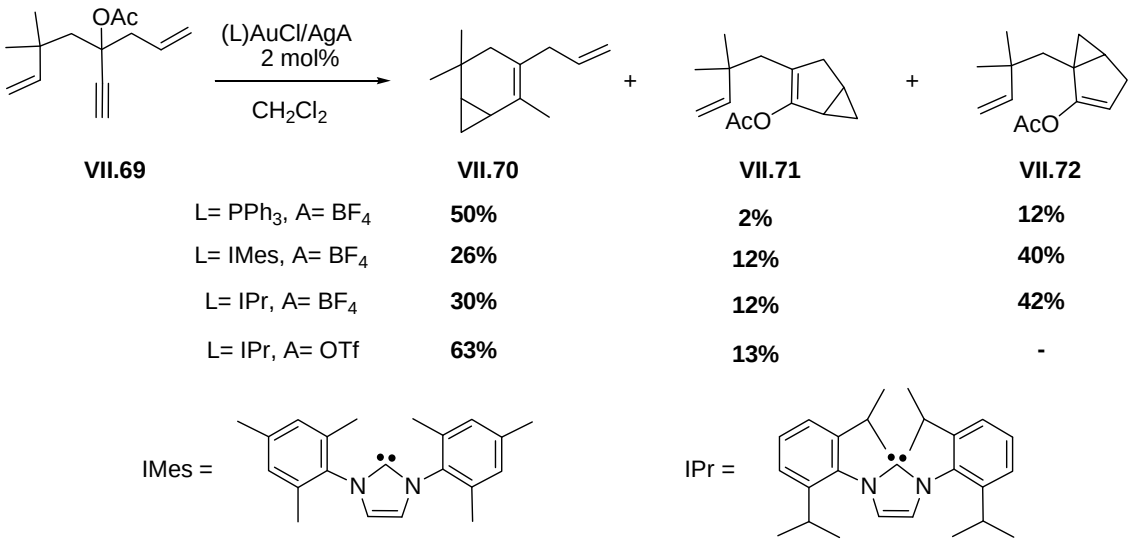


Scheme VII.27

Recently, Nolan and co-workers reported the use of the *N*-heterocyclic carbene ligands to enable an Au(I)-catalyzed cycloisomerization of 1,5-enyne VII.67, which resulted in the formation of a new bicyclo[3.1.0]hexene skeleton VII.68 (Scheme VII.28).[434] They found that the nature of the ligand on gold and the counterion both played a significant role on the reaction outcome.

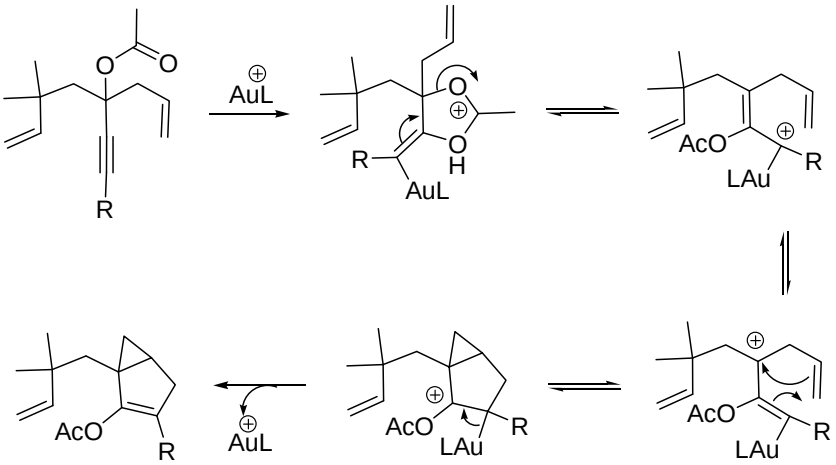


[433] Gagosz, F. *Org. Lett.* **2005**, *7*, 4129
[434] Marion, N.; de Fremont, P.; Lemiere, G.; Stevens, E. D.; Fensterbank, L.; Malacria, M.; Nolan, S. P. *Chem. Commun.* **2006**, 2048



Scheme VII.28

The mechanism aiming to explain the formation of isomeric bicyclo[3.1.0]hexenes VII 68 and VII.72 is depicted in Scheme VII.29:



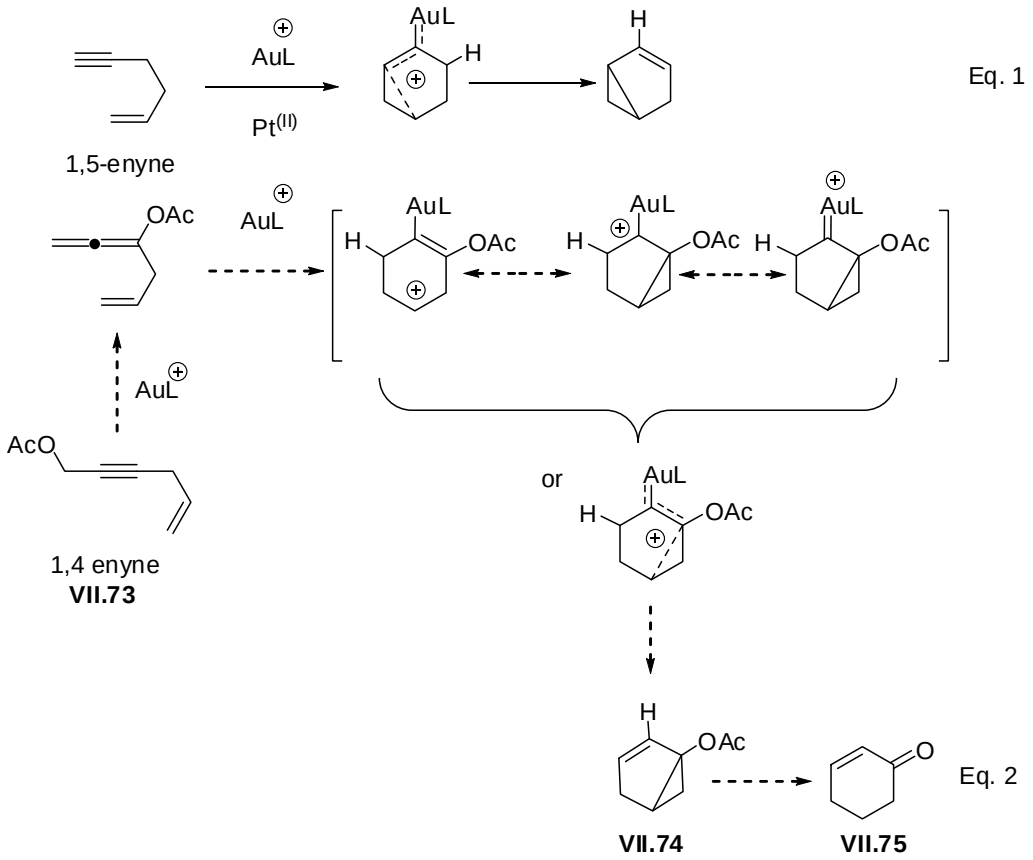
Scheme VII.29

VII.4. First Results on Gold(I) Catalyzed Isomerization of 5-en-2-yn-1-yl Acetates. Optimisation of the Catalytic System

As reviewed in Chapter VII.3.2, gold(I) complexes usually surpass the reactivity shown by Pt(II) and other electrophilic metal salts and complexes for the activation of enynes toward a variety of nucleophiles under homogeneous conditions. They are highly reactive yet uniquely selective Lewis acids that have a high affinity for π bonds. This high π-acidity is linked to relativistic effects, which reach a maximum in the periodic table with gold (see Chapter I and references cited therein).

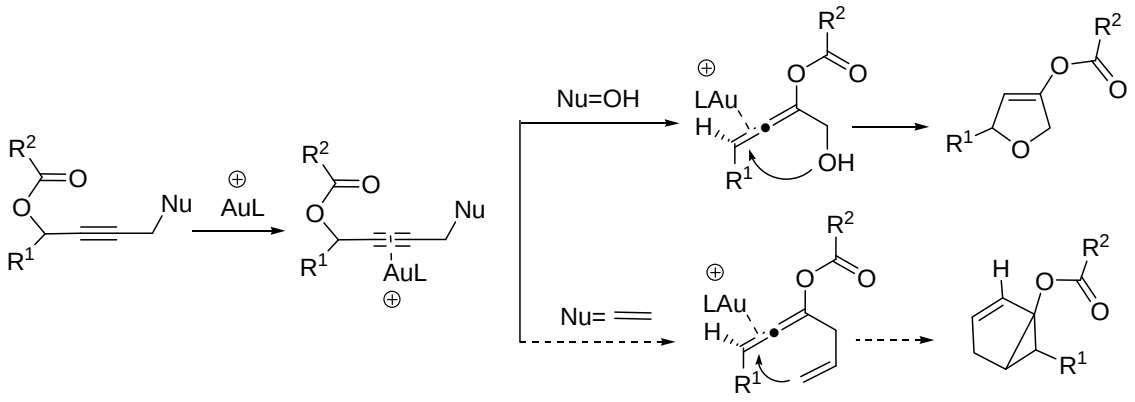
By analogy with the work on Pt or Au(I) catalyzed isomerization of 1,5-enynes to bicyclo[3.1.0]hexenes (Chapter VII.3 and Scheme VII.30) and with the 1,3 acyl shift leading

to allene formation (Chapter V.3.1), we wanted to combine these two concepts to allow the synthesis of highly functionalized bicyclo[3.1.0]hexenes (Scheme VII.30). In this respect, we hypothesized that 5-en-2-yn-1-yl acetates such as VII.73 might be valuable precursors for the synthesis of acetoxy bicyclo[3.1.0]hexene VII.74 after a gold catalyzed sequence of allene formation and cycloisomerization (Scheme VII.30, Eq. 2). The presence of the acetoxy functionality at the ring junction in the resulting product VII.74 might allow the synthesis of more elaborate structures such as 2-cyclohexen-1-ones VII.75.



Scheme VII.30

This procedure could also be considered as an extension of our previously reported dihydrofuran synthesis (see Chapter V),[329] but in this case the intramolecular nucleophile is the pendant double bond (Scheme VII.31):



Scheme VII.31

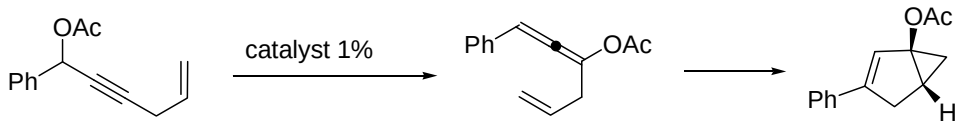
We chose the use of air stable crystalline catalyst $Ph_3PAuNTf_2$ developed and succesfully used by our group[100,106,206] to validate this approach (Table VII.3).

Simple propargylic acetate VII.76a with a pendant alkene group was chosen as a model substrate to test this approach and for the optimisation of the catalytic system. Bicyclo[3.1.0]hexene VII.78a and the postulated intermediate allene VII.77a were obtained in 49% respectively 41% yield when substrate VII.76a was treated with 1% of $Ph_3PAuNTf_2$ in CH_2Cl_2 at room temperature (Table VII.3, Entry 1). Heating the reaction mixture at 40°C did not give better results (Entry 2). VII.78a was obtained in better yield and the transformation was faster (82%, Entry 3) when the reaction mixture was heated at 60°C in 1,2-dichloroethane.

Next we turned our attention to the phosphine ligands linked to gold and decided to study their effect on the outcome of the cyclisation. It turned out that changing the electronic properties of the phosphine had a significant effect on the course of the transformation (Entries 4 and 5). The use of the bulkier and more electron rich Ad_2n-$BuPAuNTf_2$ furnished VII.78a in 78% yield, while the electron deficient $(p\text{-}CF_3Ph)_3PAuNTf_2$ catalyst gave VII.78a in a modest 32% yield. The yield could even be improved to 94% by using 1% of Ad_2n-$BuPAuNTf_2$ and heating the reaction mixture at 60°C in 1,2-dichloroethane for 0.5 hour (Entry 6).

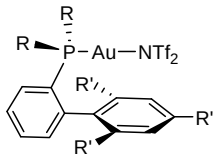
We next tested the biphenylphosphine ligands (Entries 7 and 8), previously used by Echavarren's[81,91] and our group.[362] Astoundingly, the use of VII.79 and VI.46 provided VII.78a in excellent yields (98% and 96%) in CH_2Cl_2 at room temperature. Furthermore, VII.78a was obtained in 98% yield by treatement of allene VII.77a with 1% of VII.79 in CH_2Cl_2 at room temperature, thus validating the intermediacy of the allene pathway and our approach. It is worth notice that the use of Au(III), Pt(II) or Ag(I) catalysts did not furnish the desired bicyclo[3.1.0]hexene VII.78a, albeit allene VII.77a was obtained in 89% yield by reaction of VII.76a with 10% of $AgNTf_2$ in CH_2Cl_2 at room temperature for 30 min (Entry 9).

In the light of these results, catalyst VII.79 was retained to study further the scope of this transformation (Table VII.3).



VII.76a **VII.77a** **VII.78a**

Entry	Catalyst	Conditions	Time	Yield (VII.76a/ VII.77a / VII.78a) [a]
1	Ph_3AuNTf_2	CH_2Cl_2,RT	6h	0% / 41% / 49%
2	Ph_3AuNTf_2	CH_2Cl_2, reflux	6h	0% / 37% / 48%
3	Ph_3AuNTf_2	1,2-DCE, 60°C	2h	0% / 4% / 82%
4	$(pCF_3Ph)_3PAuNTf_2$	CH_2Cl_2, RT	6h	0% / 53% / 32%
5	Ad_2n-$BuPAuNTf_2$	CH_2Cl_2, RT	6h	0% / 21% / 78%
6	Ad_2n-$BuPAuNTf_2$	1,2-DCE, 60°C	0.5h	0% / 0% / 94%
7	**VII.79**	**CH_2Cl_2, RT**	**1h**	**0% / 0% / 98%**
8	**VI.46**	CH_2Cl_2, RT	5h	0% / 0% / 96%
9	10 mol% $AgNTf_2$	CH_2Cl_2, RT	0.5h	0% / 89% / 0%
10	5 mol% $AuBr_3$	CH_2Cl_2,RT	6h	0% / 0% / 0%
11	5 mol% $PtCl_2$	CH_2Cl_2, RT	6h	80% / 17% / 0%



[a] isolated yields

VII.79 R= *t*-Bu, R'= H

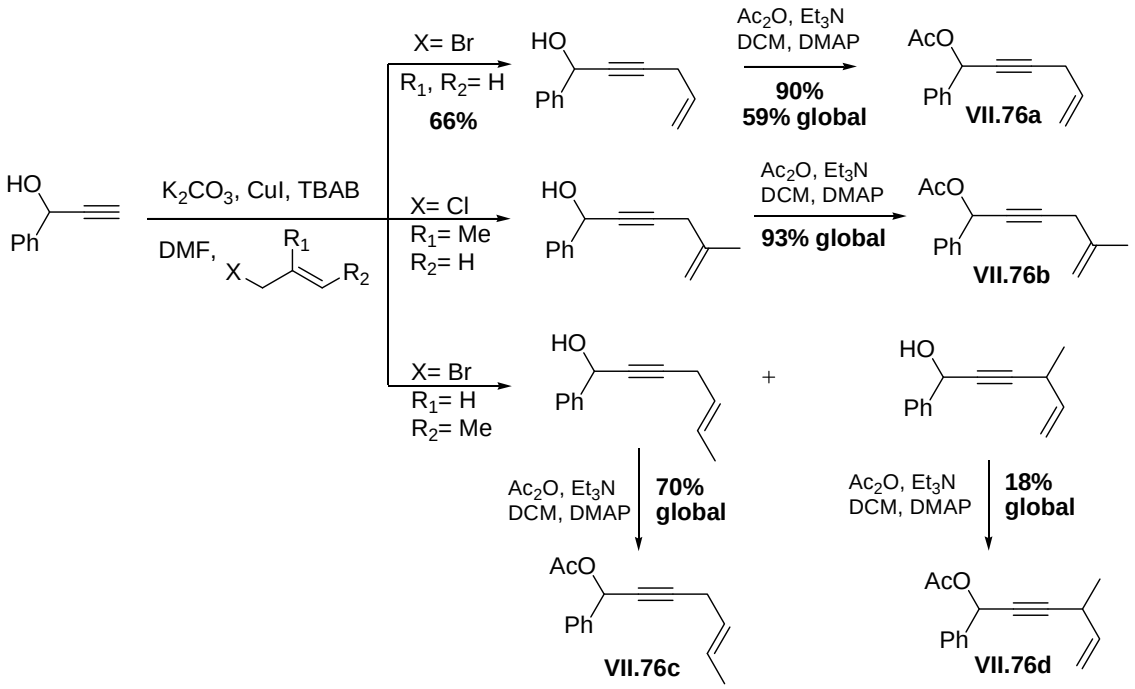
VI.46 R=Cy, R'= *i*-Pr

Table VII.3

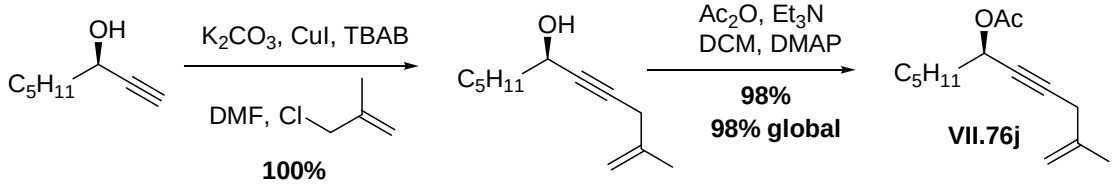
VII.5. Synthesis of the Precursors

In order to study the scope of the reaction, various diversely substituted enynes were synthesized.
Substrates VII.76a-d and VII.76j were synthesized according to a two step sequence:
1) copper(I) mediated allylation[435] of the readily available propargyl alcohols followed by
2) acetylation of the resulted enynols in the classical conditions (Scheme VII.32):

[435] Betancort, J. M.; Martin, T.; Palazon, J. M.; Martin, V. S. *J. Org. Chem*. **2003**, *68*, 3216



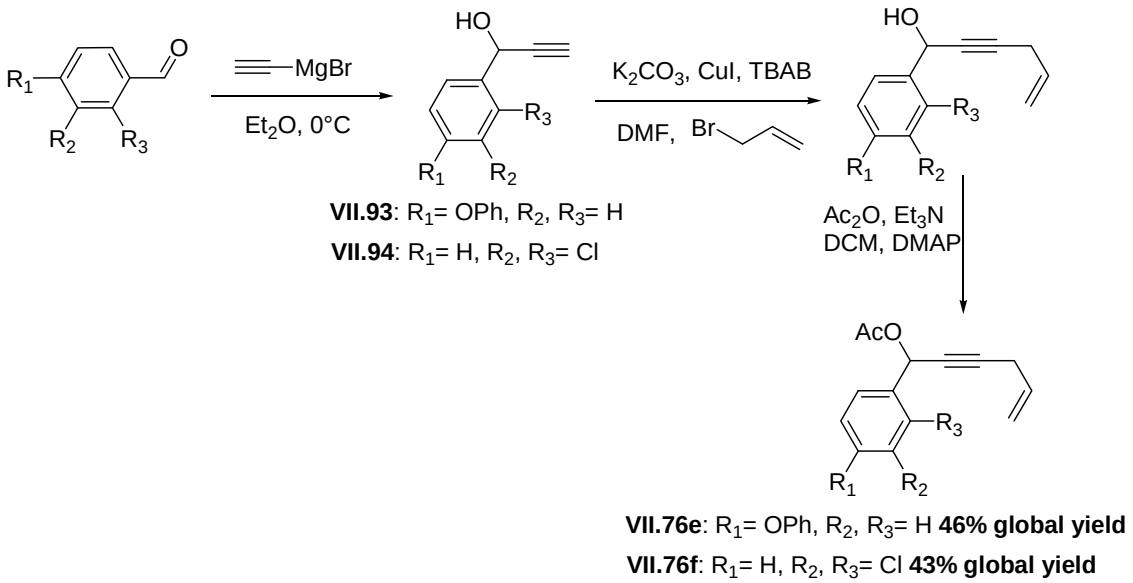
Scheme VII.32



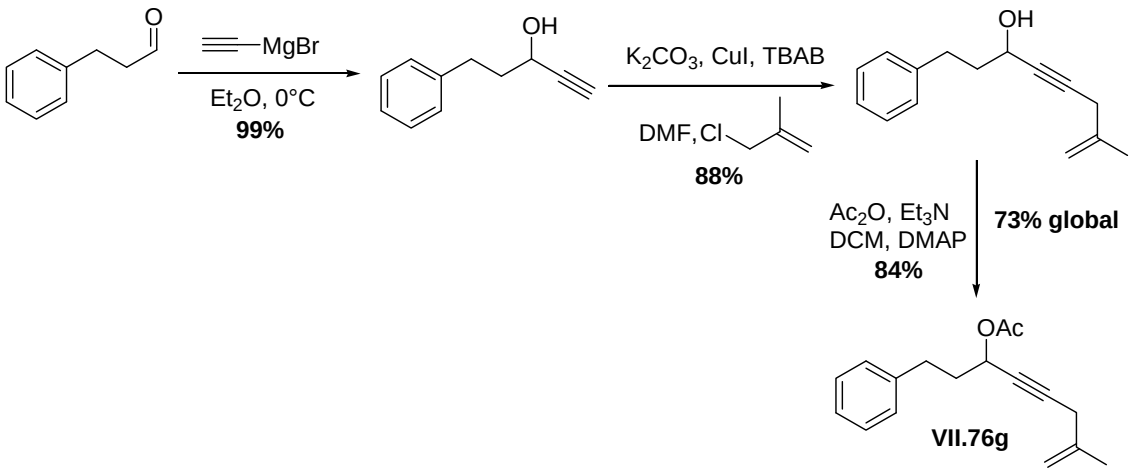
Scheme VII.33

Enynes VII.76e-f and VII.76g were synthesized in a three step sequence as illustrated in Schemes VII.34 and VII.35:
1) addition of ethynylmagnesium bromide on the readily available aldehydes;
2) copper(I) mediated allylation[436]
3) acetylation of the resulted alcohols in the classical conditions.

[436] For a recent example, see: Taber, D. F.; Reddy, P.; Ganapati; A. Kyle O. *J. Org. Chem.* **2008**, *73*, 3467

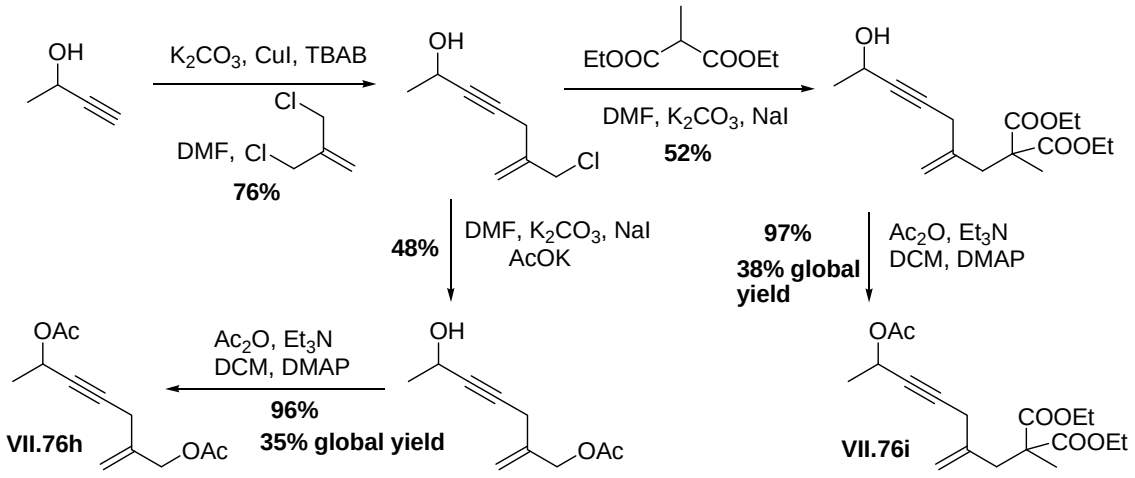


Scheme VII.34



Scheme VII.35

Substrates VII.76h-i were prepared according to a two step procedure starting with a copper (I) catalyzed allylation with dichloro-2-propene and subsequent substitution of the second chloride by methylmalonic ester or potassium acetate (Scheme VII.36):



Scheme VII.36

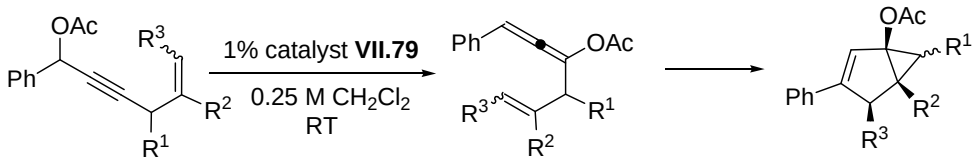
VII.6. Gold(I) Catalyzed Cyclisation of 5-en-2-yn-1-yl Acetates

To our delight, the transformation proved to be quite general and various substituted 5-en-2-yn-1-yl acetates VII.76b-j reacted under the optimized conditions (1% of VII.79 as the catalyst in CH_2Cl_2 at room temperature) to furnish the corresponding bicyclo[3.1.0]hexenes VII.78b-j in generally good yields (38%-99%) (Tables VII.4-6).

VII.6.1. Substitution around the Pendant Alkene Moiety

We examined first the substitution at the alkene moiety. The reaction was remarkably fast with methallyl derivative VII.76b furnishing bicyclo[3.1.0]hexene VII.78b in 97% yield (Entry 1, Table VII.4). This can be explained by the fact that the substituted alkene in substrate VII.76b is more nucleophilic and the tertiary carbocationic intermediate formed (see Scheme VII.39) is more stable in this case.
Crotyl derivative VII.76c reacted more slowly due mainly to the steric hindrance at the alkene terminus. VII.78c was obtained as the only product in 93% yield despite the fact that a 85:15 *E:Z* mixture of substrate was used (Entry 2).
Substrate VII.76d bearing a methyl group at the allylic position reacted equally well, producing bicyclo[3.1.0]hexene VII.78d as a 1:2.8 mixture of diastereoisomers (Entry 3, Table VII.4).[437,438] In this case a Thorpe Ingold effect may be responsible for the similar reaction kinetics like in the case of the more nucleophilic alkene VII.76b.

[437] The stereochemistry of the major endo isomer was assigned on the basis of NMR experiments
[438] The enantiomeric excess was determined by chiral HPLC analysis. However, the configuration of the major enantiomer was not determined



VII.76b-d **VII.77b-d** **VII.78b-d**

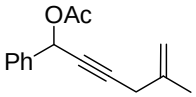
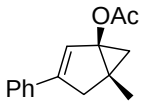
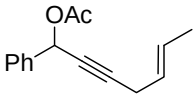
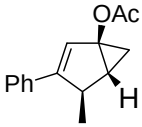
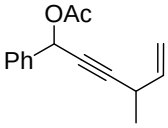
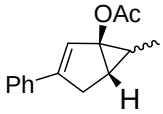
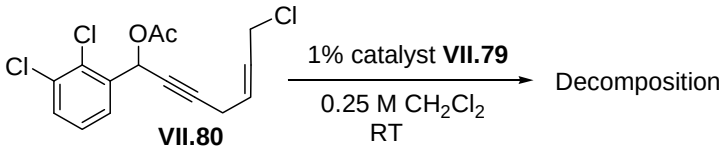
Entry	Substrate		Product		Time	Yield
1		**VII.76b**		**VII.78b**	5 min	**97%**
2		**VII.76c** (*E*:*Z*=85:15)		**VII.78c**	5 h	**93%**
3		**VII.76d** (dr=1:1)		**VII.78d**	30 min	**98%** (*exo*:*endo* =1:2.8)

Table VII.4

Chloroderivative VII.80 gave disappointing results leading to decomposition when subjected to the reaction conditions (Scheme VII.37):

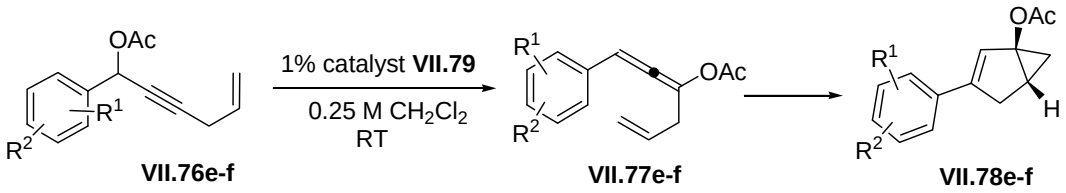


VII.80

Scheme VII.37

VII.6.2. Substitution at the Phenyl Group

A substitution at the aromatic ring is also tolerated, the reaction working exceptionally well in case of electron-donating groups such as phenoxy (Entry 1, Table VII.5). A decrease in efficiency was observed when the 2,3-dichlorophenyl derivative VII.76f was used as the substrate (Entry 2, Table VII.5).



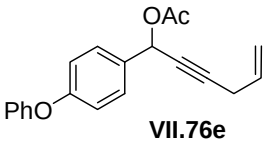
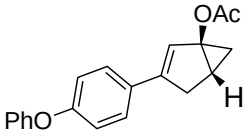
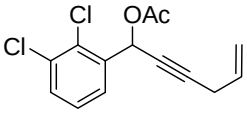
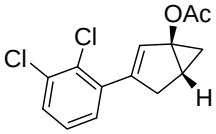
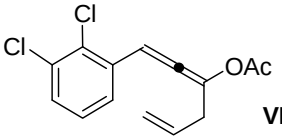
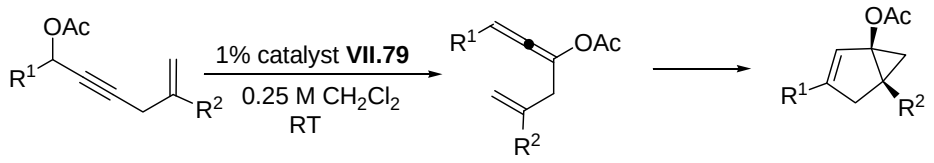
Entry	Substrate	Product	Time	Yield
4	 VII.76e	 VII.78e	2 h	99%
5	 VII.76f	 VII.78f	2 h	38%
		 VII.77f	2 h	44%

Table VII.5

VII.6.3. Replacement of the Phenyl Ring with an Alkyl Chain

Delightfully, the rearrangement occured as well when the propargylic position of the enyne was substituted with an alkyl chain instead of the aryl group (Entries 6-9, Table VII.6). Various substituted bicyclo[3.1.0]hexenes VII.78g-j possessing two adjacent quaternary centers at the ring junction were therefore synthesized starting from the corresponding -en-2-yn-1-yl acetates VII.76g-j in yields ranging from 72% to 99%. The rapid formation of bicyclo[3.1.0]hexene VII.78j, isolated in 92% yield was observed when enantioenriched substrate VII.76j was subjected to the cycloisomerization conditions. Remarkably, the stereochemical information of the substrate was nearly completely transferred to the final product.[438]



VII.76g-j **VII.77g-j** **VII.78g-j**

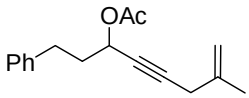
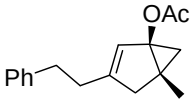
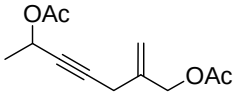
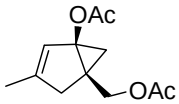
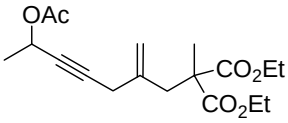
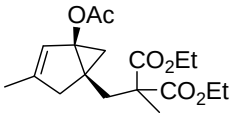
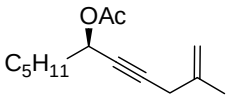
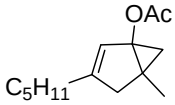
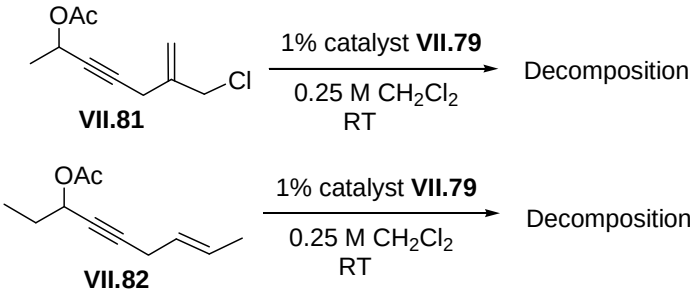
Entry	Substrate		Product		Time	Yield
6		**VII.76g**		**VII.78g**	20 min	**99%**
7		**VII.76h**		**VII.78h**	2.5 h	**72%**
8		**VII.76i**		**VII.78i**	15 min	**96%**
9		**VII.76j** **99% ee**		**VII.78j**	15 min	**92%** **90% ee**

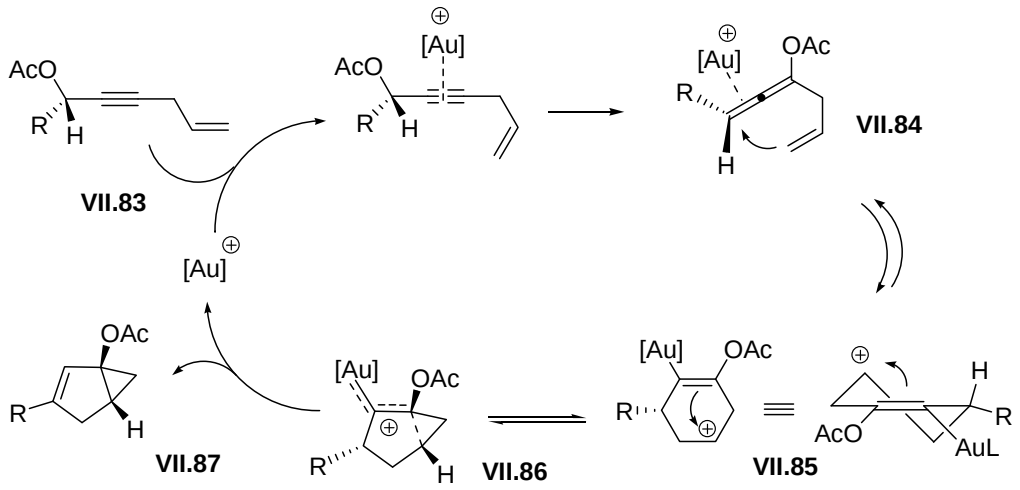
Table VII.6

Chloroderivative VII.81 and substrate VII.82 bearing a methyl group at the alkene terminus gave dissapointing results leading to decomposition (Scheme VII.38):



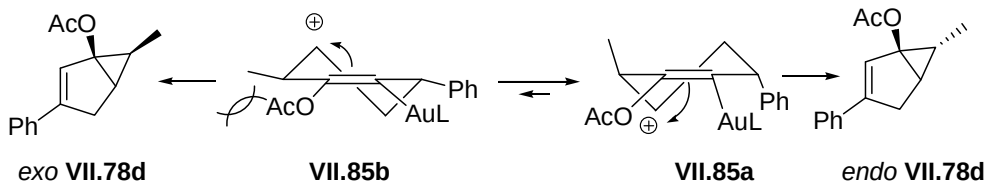
Scheme VII.38

The mechanism illustrated in Scheme VII.39 is proposed to account for these experimental observations. Gold(I) activation of the triple bond in alkyne VII.83 triggers a [3,3]-sigmatropic rearrangement leading to the formation of allene VII.84. Cationic vinyl-gold species VII.85 is formed by the nucleophilic attack of the pendant alkene on the gold activated allenic bond. Subsequent formation of the cyclopropyl ring assisted by electron donation from gold(I) affords gold(I) species VII.86. The desired bicyclo[3.1.0]hexene VII.87 is obtained by a final 1,2-hydride shift which occurs with regeneration of the gold(I) catalyst.



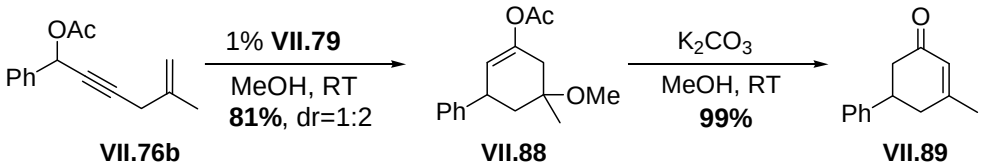
Scheme VII.39

It should be noted that an equilibrium between the two conformers VII.85a and VII.85b may explain the stereochemistry observed for VII.78d:



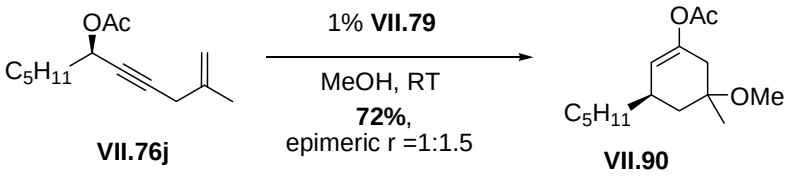
Scheme VII.40

As also suggested by mechanistic manifold illustrated in Scheme VII.39, we raised the question of the possibility of trapping intermediate VII.85 by a nucleophile. To this end, the rearrangement of VII.76b was performed in MeOH and the expected cyclohexene VII.88 was isolated in 81% yield as a 1:2 mixture of diastereoisomers (Scheme VII.41). This fact demonstrates that surprisingly, the nucleophilic addition of the alkene onto the gold(I) activated allene seems to be faster than the addition of methanol. Subsequent basic treatment of VII.88 afforded 2-cyclohexen-1-one VII.89 in 99% yield by deprotection of the enol acetate and tautomerisation:



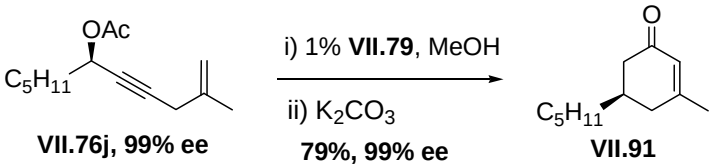
Scheme VII.41

Enol-acetate VII.90 was obtained in 72% yield as a 1:1.5 mixture of epimers by reacting enantioenriched propargylic acetate VII.76j under the same experimental conditions (Scheme VII.42):



Scheme VII.42

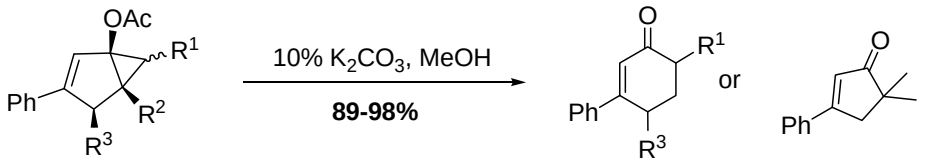
A one-pot deprotection sequence was also attempted and led to the formation of the corresponding 2-cyclohexen-1-one VII.91 with a complete retention of the chiral information (Scheme VII.43):



Scheme VII.43

VII.7. Transformation of the Cyclized Products

The functionalized acetoxy bicyclo[3.1.0]hexenes obtained by the gold(I)-catalyzed cycloisomerization can be further functionalized therefore highlighting the general utility of this transformation. For example, they can be efficiently transformed into 2-cycloalken-1-ones by simple treatment with K_2CO_3 in methanol (Table VII.7).



VII.78a-d R^2=H, **VII92a,c-d** R^2=Me, **VII.93**

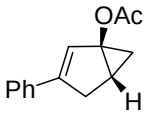
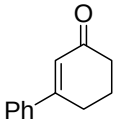
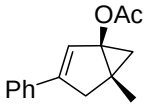
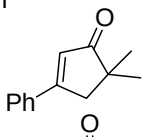
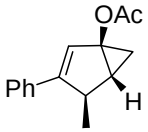
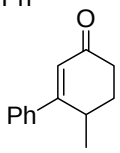
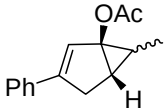
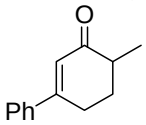
Entry	Substrate		Product		Yield
1		**VII.78a**		**VII.92a**	**94%**
2		**VII.78b**		**VII.93**	**89%**
3		**VII.78c**		**VII.92c**	**96%**
4		**VII.78d**		**VII.92d**	**98%**

Table VII.7

The substitution pattern of the cylopropyl ring seems to direct which cyclopropanic bond will be broken. Bicyclo[3.1.0]hexenes VII.78a, VII.78c and VII.78d afforded the corresponding 2-cyclohexen-1-ones VII.92a, VII.92c and VII.92d, while bicyclo[3.1.0]hexene VII.78c bearing a methyl group at the ring junction gave 2-cyclopenten-1-one VII.93.
It should be noted that the cyclohexenones obtained by this pathway are regioisomeric with those generated by the one-pot cycloisomerization deprotection sequence as in Scheme VII.43.

VII.8. Conclusion and Perspectives

In summary, an efficient access to acetoxy bicyclo[3.1.0]hexenes which can be further transformed into 2-cycloalken-1-ones have been developed by an efficient gold(I) catalyzed cycloisomerization of 5-en-2-yn-1-yl acetates.
It would be of interest to test the trapping of intermediate VII.85 by other nucleophiles like other alcohols, phenols amines or carboxilic acids. Another perspective is to use another intramolecular nucleophile like an allene moiety instead of the pendant alkene (Scheme VII.31)

VIII. Gold(I)-Catalyzed 5-*endo* Hydroxy- and Alkoxy-Cyclization of 1,5-Enynes: an Efficient Access to Functionalized Cyclopentenes

This work was done in collaboration with Dr. Fabien Gagosz and Florin-Marian Istrate.[386]

VIII.1. Introduction

VIII.1.1. Natural Products Containing the Cyclopentyl Unit

The cyclopentyl unit is found in a wide variety of natural products exhibiting biological activity, such as the sesquiterpene lactones, dictamnoside derivatives and marine natural products. As a consequence, the development of practical synthetic routes to access it remains of interest.

Sesquiterpene Lactones

Sesquiterpene lactones constitute a large and diverse group of biologically active chemicals that have been identified in several plant families. They are a class of naturally occurring plant terpenoids that are formed by condensation of three isoprene units and subsequent cyclization and oxidative transformation to produce a *cis* or *trans*-fused lactone. A diverse range of biological properties have been attributed to these compounds such as anti-malarial,[439] allergenic, neurotoxic, antimicrobial, anti-inflammatory and anticarcinogenic effects.[440] The families of Guaianolides, Pseudoguaianolides, and Hypocretenolides contain the substituted cyclopentyl unit as illustrated in Figure VIII.1:

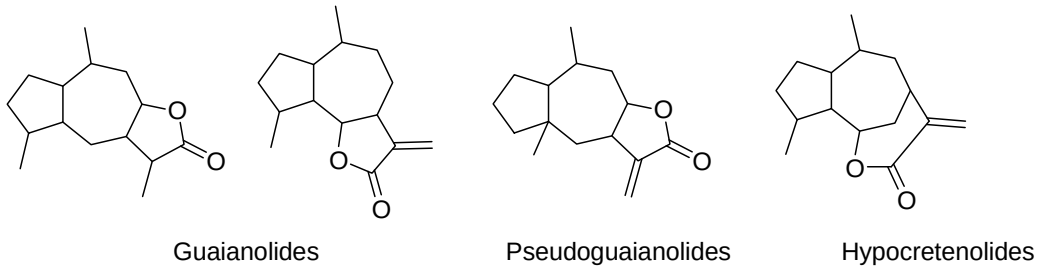


Figure VIII.1

Guaianolides, which consist of a tricyclic 5,7,5-ring system, represent a large subgroup of naturally occurring sesquiterpene lactones exhibiting significant biological activity.[441] Plants

[439] Chea, A.; Hout, S.; Long, C.; Marcourt, L.; Faure, R.; Azas, N.; Elias, R. *Chem.& Pharm. Bull.* **2006**, *54*, 1437
[440] a) Li-Weber, M.; Giaisi, M.; Baumann, S.; Treiber, M. K.; Krammer, P. H. *Nature* **2002**, *9*, 1256; b) Yang, M. C.; Choi, S. U.; Choi, W. S.; Kim, S. Y.; Lee, K. R. *J. Nat. Prod.* **2008,** *71,* 678
[441] Andreas Schall, A.; Reiser, O. *Eur. J. Org. Chem.* **2008**, 2353 and referenced cited therein

containing such compounds as the active principles have been used in traditional medicine throughout history for treating conditions ranging from rheumatic pain and increase of bile production to pulmonary disorders.
Thapsigargin (Figure VIII.2) is the most prominent and intensely studied member of the family of 17 structurally-related guaianolides, collectively termed as thapsigargins, which were isolated from seeds and roots of the umbelliferous plant, *Thapsia garganica L.*[442]

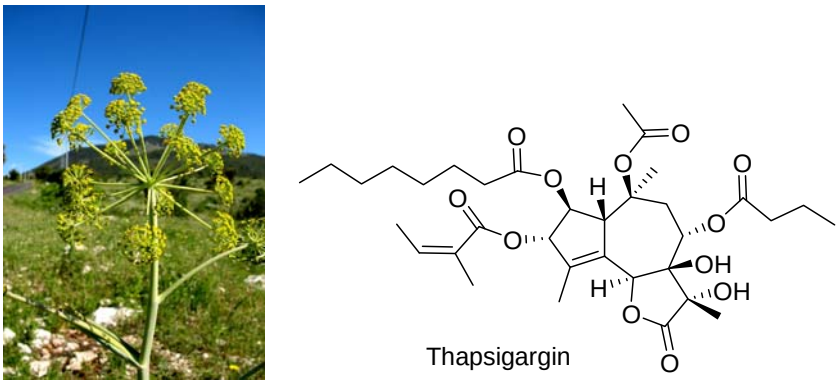


Figure VIII.2: *Thapsia garganica L.* and Thapsigargin

Initially, thapsigargin was found to be a histamine liberator,[443] but the subsequent discovery of its potent inhibitory action on sarco/endoplasmic reticulum ATPases (SERCAs)[444] earned its widespread and increasing recognition as a powerful molecular tool for studying cell physiology and might offer a new type of chemotherapeutics for treatment of prostate cancer.[445]

Dictamnosides

Three natural products possessing the fused bicyclo[4.3.0]decenyl ring termed dictamnosides E,[446] N[447] and dictamnol[448] (Figure VIII.4) were isolated from the root bark extract of *Dictamnus dasycarpus* Turcz. (Figure VIII.3).

[442] a) Christensen, S. B.; Andersen, A.; Smitt, U. W. *Prog. Chem. Natl. Prod.* **1997**, *71*, 129; b) S. B. Christensen, U. Rasmussen, and C. Christophersen, *Tet. Lett.* **1980**, *21*, 3829
[443] Christensen, S. B.; Rasmussen, U.; Sandberg, F. *Acta Pharm. Suec.* **1978**, *15*, 133
[444] a) Sorensen, T. L. M.; Olesen, C.; Jensen, A. M. L.; Moller, J. V.; Nissen, P. *J. Biotechnol.* **2006**, *124*, 704 and referenced cited therein
[445] Andrews, S. P.; Ball, M.; Wierschem, F.; Cleator, E.; Oliver, S.; Hogenauer, K.; Simic, O.; Antonello, A.; Hunger, U.; Smith, M. D.; Ley, S. V. *Chem. Eur. J.* **2007**, *13*, 5688
[446] Zhao, W.; Wolfender, J.-L.; Hostettmann, K.; Lin, H.-Y.; Stoeckli-Evans, H.; Xu, R.; Quin, G. *Phytochemistry* **1998**, *47*, 63
[447] Chang, J.; Xuan, L.-J.; Xu, Y.-M.; Zhang, J.-S. *J. Nat. Prod.* **2001**, *64*, 935
[448] Lange, G. L.; Merica, A.; Chimanikire, M. *Tet. Lett.* **1997**, *38*, 6371

Figure VIII.3: *Dictamnus dasycarpus* Turcz.

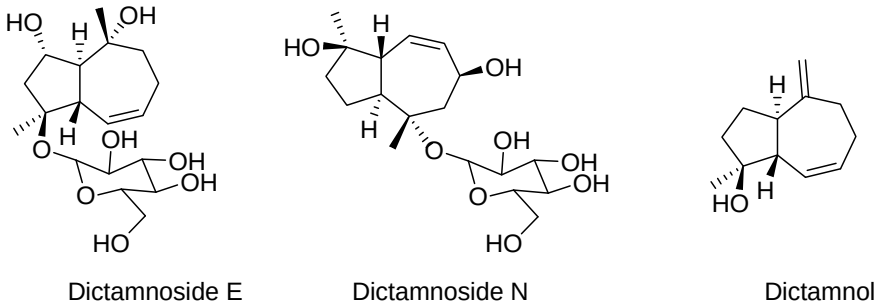


Figure VIII.4

Marine Natural Products

The Okinawan soft corals of the genus *Clavularia* comprise a number of structurally unique natural products with various bioactivities. Recently, neodolabellanskeleton diterpenes VIII.1 and the modestly cytotoxic VIII.2 were isolated from an Okinawan soft coral *Clavularia koellikeri* (Figure VIII.5).[449]

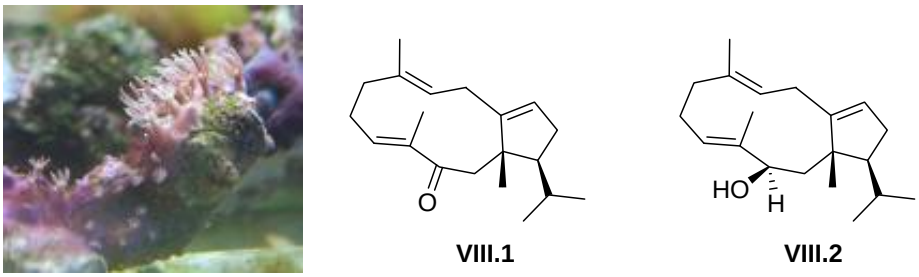


Figure VIII.5: *Clavularia* and diterpenes VIII.1 and VIII.2

Four hydroazulene diterpenes, dictyone acetate, dictyol F monoacetate, isodictytriol monoacetate and cystoseirol monoacetate (Figure VIII.7) were isolated from the brown alga *Cystoseira myrica* (Figure VIII.6) collected in the Gulf of Suez. All four compounds exhibited moderate cytotoxicity.[450]

[449] Iguchi, K.; Fukaya, T.; Yasumoto, A.; Watanabe, K. *J. Nat. Prod.* **2004**, *67*, 577
[450] Ayyad, S.-E. N.; Abdel-Halim, O. B.; Shier, W. T.; Hoye, T. R. *Z. Naturforsch., C: Biosci.* **2003**, *58*, 33

Figure VIII.6: *Cystoseira myrica*

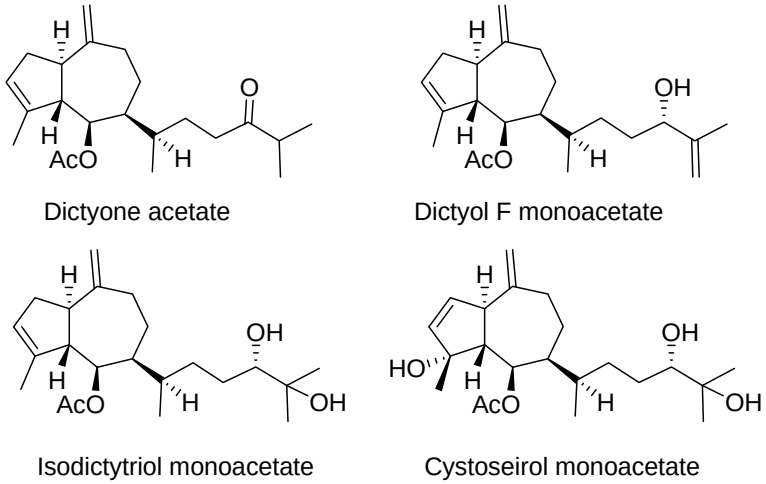


Figure VIII.7

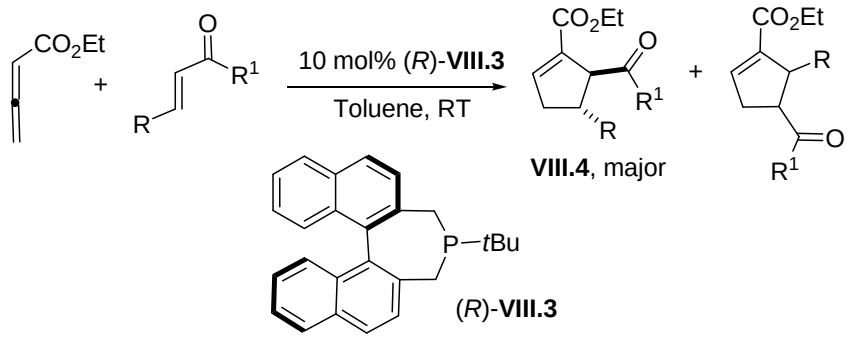
VIII.2. Synthesis of Substituted Cyclopentenyl Rings

As it has been discussed earlier in this chapter, five-membered carbocycles are a common substructure in a wide array of natural products. Among this family of compounds, cyclopentenes are particularly important targets, in part because derivatization of the olefin often occurs with good diastereoselectivity, thereby providing access to highly functionalized, stereochemically complex cyclopentanes. Some recent selected examples of catalytic synthesis of highly substituted cyclopentenes are described in the following chapter.

VIII.2.1.Synthesis of Substituted Cyclopentenyl Rings Catalyzed by Nuclephiles (Phosphines)

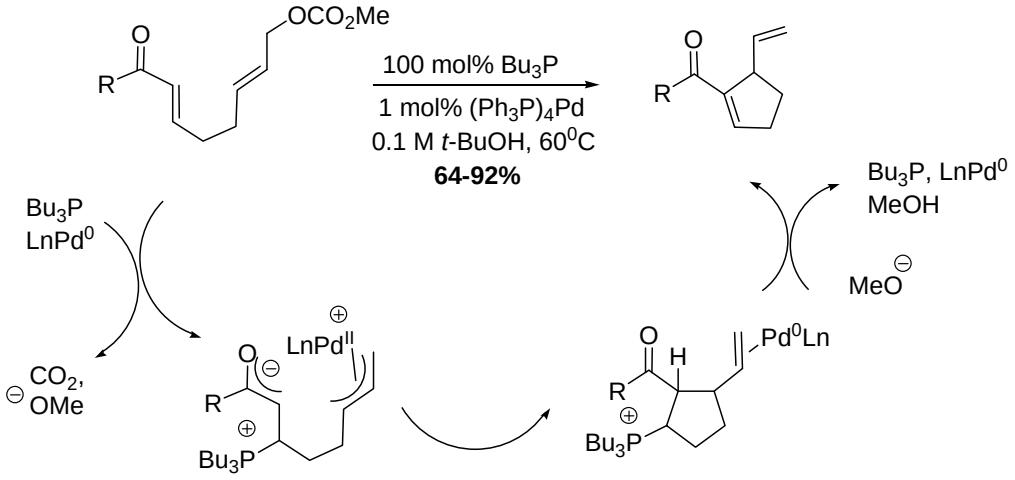
Tertiary phosphines catalyze a variety of annulation reactions, including the [3+2] cycloaddition of allenes with olefins to generate cyclopentenes.[451]
Recently, Fu et *al.* described the phosphine-catalyzed asymmetric [3+2] cycloadditions of allenes with a variety of *β*-substituted *α*,*β*-unsaturated enones to produce highly functionalized cyclopentenes that contain two contiguous stereocenters with yields ranging from 39-76% and enantiomeric excesses from 75 to 90% (Scheme VIII.1):[452]

[451] Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535
[452] Wilson, J. E.; Fu, G. C. *Angew. Chem. Int. Ed.* **2006**, *45*, 1426



Scheme VIII.1

The group of Krische disclosed a catalytic cycloallylation *via* concommitant activation of latent nucleophilic (enone) and electrophilic (allyl carbonate) partners through the use of a two-component catalyst system that unites the nucleophilic features of the Morita-Baylis Hillman reaction[453] with the electrophilic features of the Trost-Tsuji allylation.[454]



Scheme VIII.2

VIII.2.2. Synthesis of Substituted Cyclopentenyl Rings Catalyzed by Transition Metals

Enyne Cycloisomerisations and Metathesis Reactions

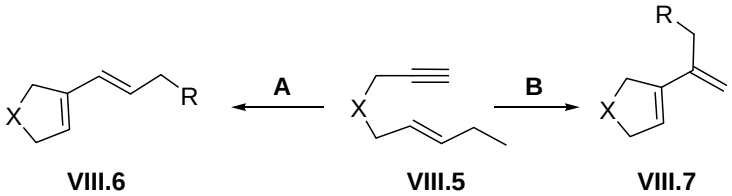
Transition metal catalyzed enyne cycloisomerizations and rearrangements represent a very useful synthetic tool for the preparation of highly functionalized cyclopentenes. Such metal-catalyzed processes are atom economical, more ecological and result in a significant increase

[453] Deevi Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811
[454] Jellerichs, B. G.; Kong, J. -R.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 7758

in structural complexity. In addition, they are operationally simple, safe, and convenient to perform on a large scale.[49]

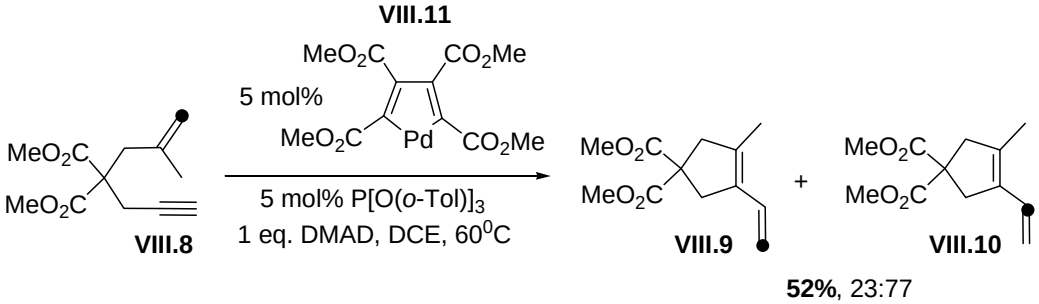
Pd-Catalyzed Transformations Leading to Substituted Cyclopentenes

The type of palladium-catalyzed transformations illustrated in Scheme VIII.3, which lead to the formation of cyclopentenes, has often been referred to as "metathesis". However, the metathesis mechanism only explains the formation of products resulting from path A. Palladium catalysis that leads to diene products in this reaction manifold are best described as "skeletal rearrangements".[455]



Scheme VIII.3

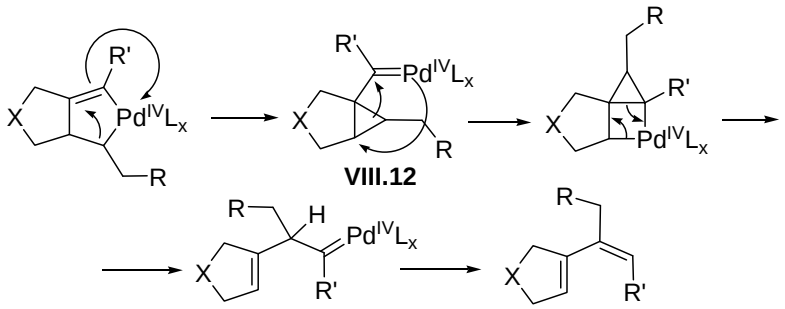
Nevertheless, ^{2}H- and ^{13}C-labeling experiments[456] have shown that two different kinds of rearranged dienes are obtained. Treatment of labeled enyne VIII.5 in the presence of Pd catalyst VIII.11 led to a mixture of 1,3-dienes VIII.6 and VIII.7, which were designated as "single cleavage" and "double cleavage" products, respectively (Scheme VIII.4):



Scheme VIII.4

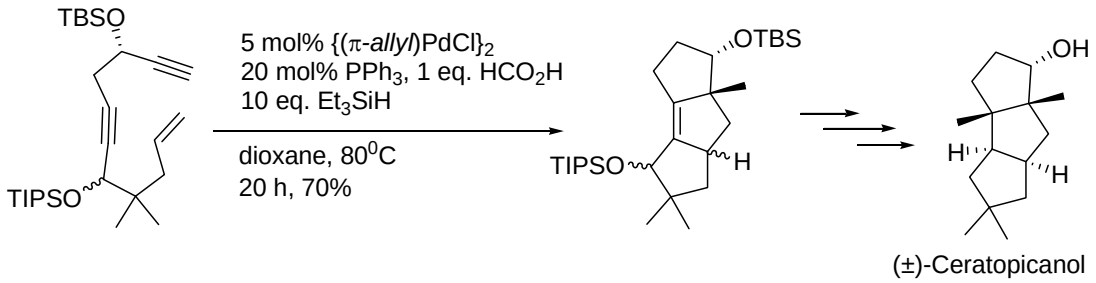
To explain the formation of products of type VIII.7 (Path B, Scheme VIII.3), a mechanism has been proposed which relies on the generation of a cyclopropylcarbene-palladium intermediate VIII.12 (Scheme VIII.5).

[455] Lloyd-Jones, G. C. *Org. Biomol. Chem.* **2003**, *1*, 215
[456] Trost, B. M.; Czeskis, B. A. *Tet. Lett.* **1994**, *35*, 211



Scheme VIII.4

A respresentative example of Pd-catalyzed reductive cyclization has recently been applied to the total synthesis of (±)-ceratopicanol:[457]

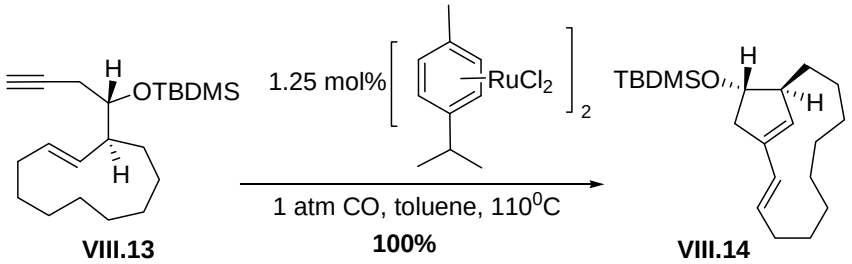


Scheme VIII.6

Ru-Catalyzed Transformations Leading to Substituted Cyclopentenes

The formal metathesis of enynes catalyzed by ruthenium complexes is extremely well described.[458]

One example reported by Trost and colleagues is the reaction of 1,6-enyne VIII.13 in presence of 1.25 mol % of cymene-ruthenium chloride dimer which afforded vinyl cyclopentene VIII.14 in quantitative yield as shown in Scheme VIII.7:[459]



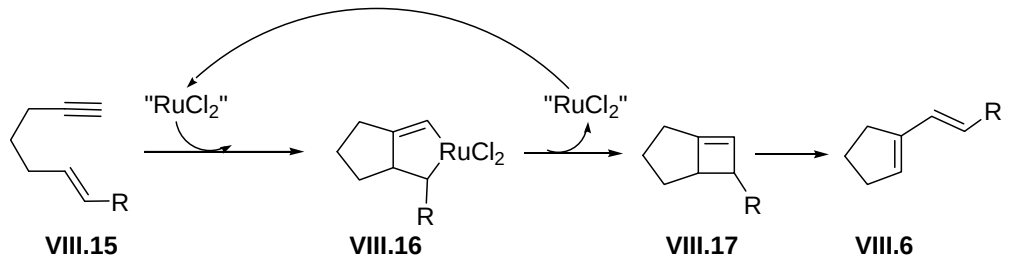
Scheme VIII.7

[457] Tong, X.; Beller, M.; Tse, M. K. *J. Am. Chem. Soc.* **2007**, *129*, 4906

[458] a) Trost, B. M.; Toste, D. F.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067; b) Trost, B. M.; Frederiksen, M. U.; Rudd, M. T. *Angew. Chem. Int. Ed.* **2005**, *44*, 6630

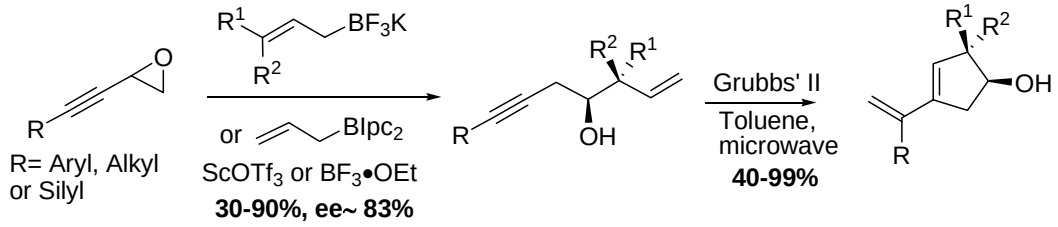
[459] Trost, B. M.; Doherty, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 3801

From a mechanistic point of view, reaction of ruthenium (II) with an enyne VIII.15 generates ruthenacycle VIII.16. This latter undergoes a reductive elimination, in preference to *β*-hydrogen elimination, to furnish cyclobutene VIII.17 and regenerate the ruthenium catalyst. A conrotatory cycloreversion of cyclobutene VIII.17 affords the vinylcyclopentene product VIII.6.



Scheme VIII.8

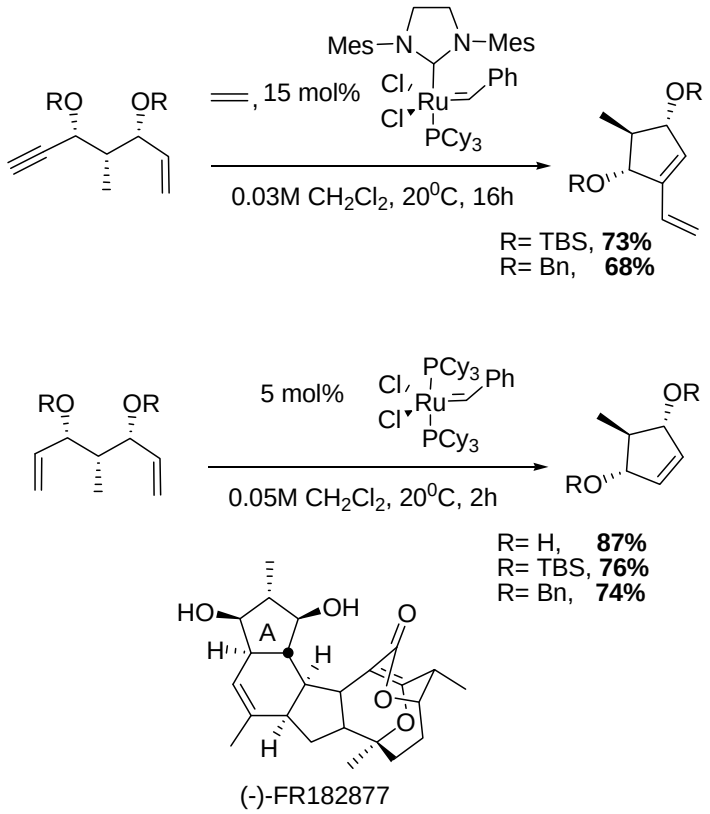
A two-step method to prepare functionalized cyclopentanols starting from alkynyloxiranes and using an enyne metathesis as a key step was disclosed by Lautens' group (Scheme VIII.9):[460]



Scheme VIII.9

Prunet's group published a study where a systematic comparison of enyne *vs* diene RCM for the formation of highly substituted cyclopentene derivatives showed that the latter metathesis proceeds much more easily even for this ring size. This methodology was used for the synthesis of the A ring of FR182877, isolated from *Streptomyces sp*. no. 9885 (Scheme VIII.10):[461]

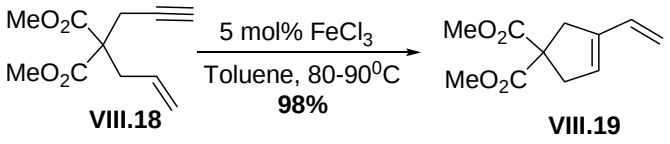
[460] Wang, L.; Maddess, M. L.; Lautens, M. *J. Org. Chem.* **2007**, *72*, 1822
[461] Jacques-Alexis Funel, J.-A.; Prunet, J. *J. Org. Chem*. **2004**, *69*, 4555



Scheme VIII.10

Fe-Catalyzed Transformations Leading to Substituted Cyclopentenes

Iron trichloride was recently found to promote skeletal rearrangements of enynes.[49,462] As depicted in Scheme VIII.11, the reaction of VIII.18 was carried out in toluene at 80–90°C and afforded the *exo*-adduct VIII.19 as the major product. The authors observed that the reaction scope was limited compared to the analogous gold-catalyzed reaction.



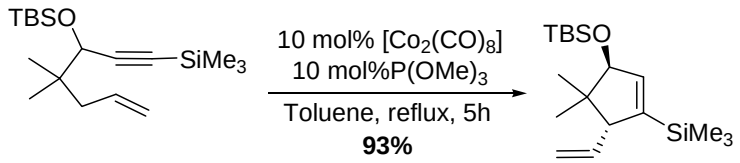
Scheme VIII.11

Co-Catalyzed Transformations Leading to Substituted Cyclopentenes

The transformations of enynes in the presence of cobalt complexes are directly linked to studies carried out on the Pauson–Khand reaction[463] and [2+2+2] cyclotrimerizations.

[462] Nieto-Oberhuber, C.; Paz Munoz, M.; Lopez, S.; Jimenez-Nunez, E.; Nevado, C.; Herrero-Gomez, E.; Raducan, M.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 1677
[463] Shibata, T. *Adv. Synth. Catal.* **2006**, *348*, 2328

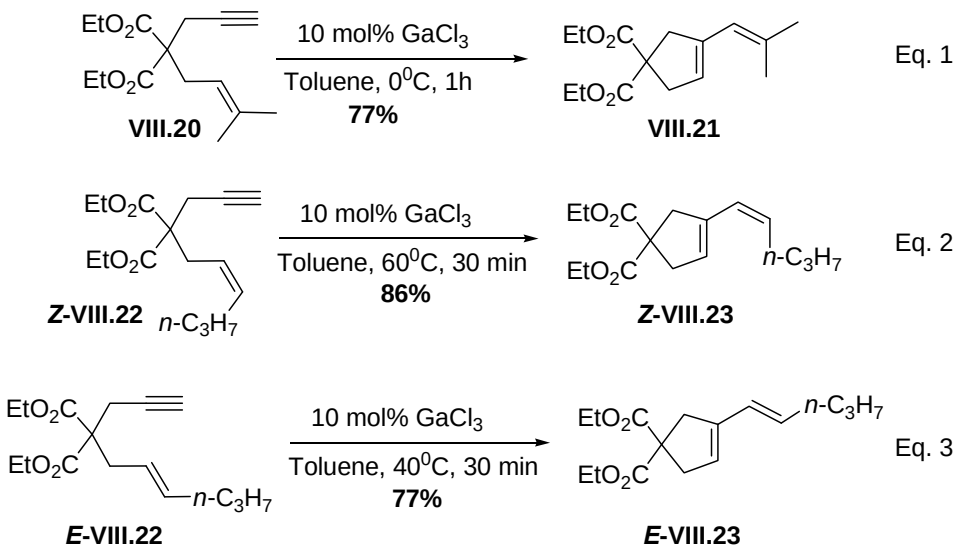
Ajamian and Gleason reported the first catalytic cycloisomerization of 1,6-enynes in the presence of a combination of $[Co_2(CO)_8]$ and $P(OMe)_3$ (Scheme VIII.12):[464]



Scheme VIII.12

Ga-Catalyzed Transformations Leading to Substituted Cyclopentenes

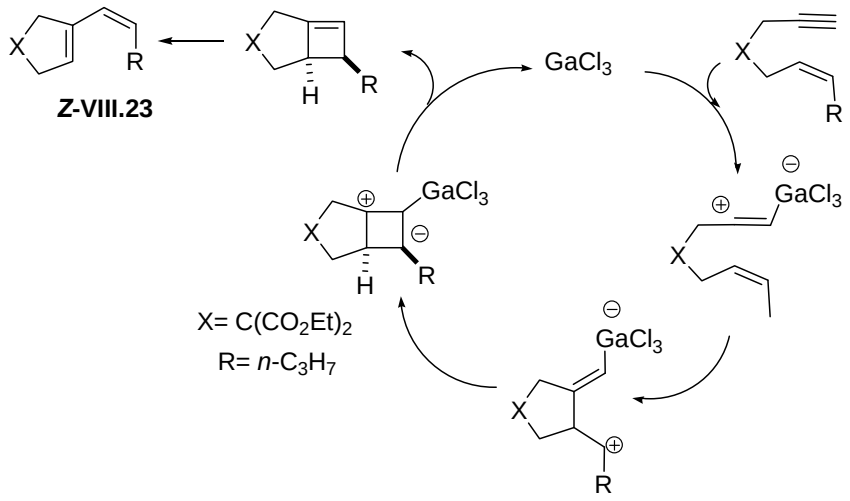
The first documented report dealing with applications of Ga catalysts in enyne cycloisomerizations appeared in 2002 when Chatani et *al.* presented their study on the use of $GaCl_3$ for the skeletal rearrangement of 1,6-enynes.[465] As illustrated in Scheme VIII.13, treatment of enyne VIII.20 with 10 mol% $GaCl_3$ in toluene at 0°C afforded 1,3-diene VIII.21 in 77% yield by skeletal rearrangement and the cleavage of one bond (Scheme VIII.13, Eq. 1). In contrast with the use of Ru and Pt catalysts, the reaction with the Ga catalyst is completely stereospecific: enyne *Z*-VIII.22 leads to product *Z*- VIII.23 (Eq. 2), while enyne *E*-VIII.22 afforded the *E* product (Scheme VIII.13, Eq. 3):



Scheme VIII.13

To explain the selectivity observed, the authors proposed a mechanistic rationale involving the intermediacy of cyclobutenes (Scheme VIII.14):

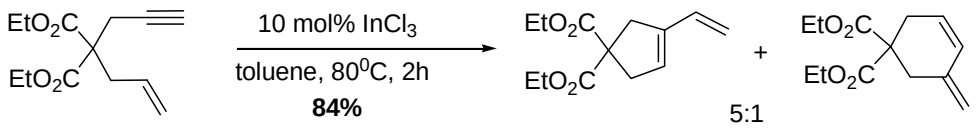
[464]Ajamian, A.; Gleason, J. L. *Org. Lett.* **2003**, *5*, 2409
[465] Chatani, N; Inoue, H.; Kotsuma, T.; Murai, S. *J. Am. Chem. Soc.* **2002**, *124*, 10294



Scheme VIII.14

In-Catalyzed Transformations Leading to Substituted Cyclopentenes

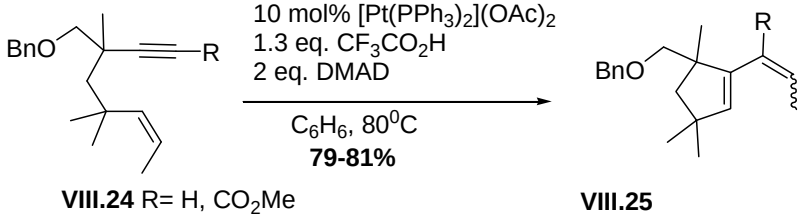
Recently, Miyanohana and Chatani presented the first example of indium salts in cycloisomerization transformations (Scheme VIII.15):[466]



Scheme VIII.15

Pt-Catalyzed Transformations Leading to Substituted Cyclopentenes

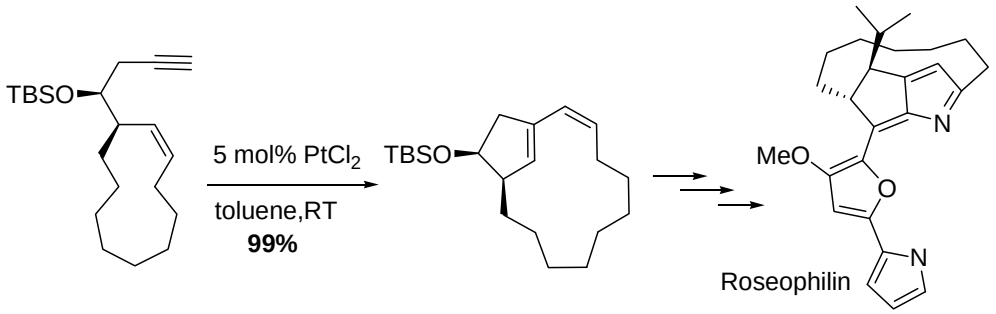
Trost and Chang disclosed the first platinum-catalyzed skeletal rearrangement of an enyne VIII.24 to the 1,3-diene VIII.25 in the presence of a catalytic system consisting of $[Pt(PPh_3)_2](OAc)_2$, dimethyl acetylene dicarboxylate (DMAD), and trifluoroacetic acid:[467]



Scheme VIII.16

[466] Miyanohana, Y.; Chatani, N. *Org. Lett.* **2006**, *8*, 2155
[467] Trost, B. M; Chang, V. K. *Synthesis* **1993**, 824

Murai and co-workers reported that $PtCl_2$ can promote skeletal rearrangements.[468] This versatile methodology has most notably found applications in the synthesis of macrocycles, for example in the assembly of the bicyclic unit of roseophilin (Scheme VIII.17):[469]



Scheme VIII.17

Au-Catalyzed Transformations Leading to Substituted Cyclopentenes

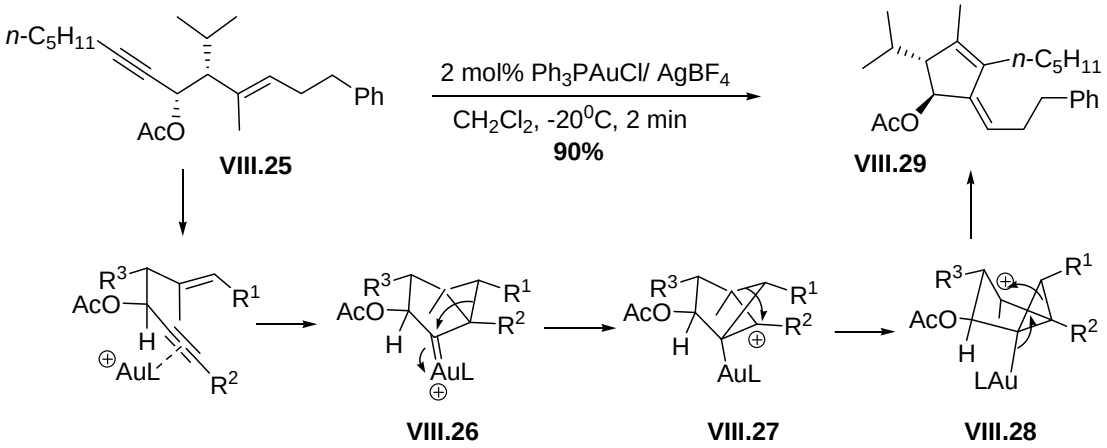
As discussed also in Chapter VII, among the range of transition metal complexes capable of catalyzing enyne cycloisomerizations, gold complexes are particularly powerful as they are capable of delivering a diverse array of cyclic products that are produced under mild conditions, with excellent chemoselectivity and high synthetic efficiency.[49]
Distinct from the enyne cyclizations catalyzed by Pd, Rh, Ru, and Co complexes,[49,470]the gold activated electrophilic alkynes lead to non-classical carbocation and/or carbenoid formation, which often triggers skeletal rearrangements. In addition, there have been no observations of β-hydride elimination in gold-catalyzed reactions (see also Chapter I for a discussion). Moreover, a remarkable impact of alkene/alkyne substitution and/or choice of ligands on the reaction outcome have been commonly observed. The gold-catalyzed reactions of enynes have recently attracted significant interest because of their immense substrate scope, diverse product portfolio, and intriguing mechanistic pathways.
Among enyne substrates, gold-catalyzed isomerization reactions of 1,5- and 1,6-enyne have been most extensively studied and have been highlighted and summarized.[49e-h]

Au-Catalyzed Cycloisomerisation of 1,5-Enynes Leading to Substituted Cyclopentenes

As discussed in Chapter VII, 1,5-enynes are special substrates, which upon addition of a gold catalyst are sufficiently reactive to promote facile access to bicyclo[3.1.0]hexenes. Nevertheless, a high substrate-dependance was observed in the case of 1,5-enyne cycloisomerization reactions. Therefore, other 1,5-enynes may undergo different rearrangements and give mixtures of cyclopropanes and alkylidenecyclopentenes (Scheme VIII.18).[49e-h, 433]

[468] Chatani, N.; Morimoto, T.; Muto, T.; Murai, S. *Organometallics* **1996**, *15*, 901
[469] Trost, B. M.; Doherty, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 3801
[470] a) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1; b) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067; c) Lloyd-Jones, G. C. *Org. Biomol. Chem.* **2003**, *1*, 215

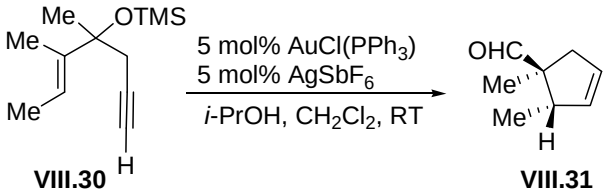
Gagosz discovered an intriguing cyclization of 1,5-enyne VIII.26, which generated novel alkylidene-cyclopentene VIII.29 through a sequential carbocation rearrangement (Scheme VIII.18):[433]
This reaction is also noteworthy for its remarkable efficiency, high yield, and good selectivity.



Scheme VIII.18

The formation of rearrangement products VIII.29 from 1,5-enyne VIII.25 can be rationalized as shown in Scheme VIII.18. The complexation of Au(I) to the alkyne triggers an *endo*-cyclization leading to cyclopropyl gold carbene VIII.26, which may suffer a skeletal rearrangement *via* VIII.28 to afford VIII.29. This is an example of a single-cleavage rearrangement occurring in 1,5-enynes.

An interesting method based on the cyclization of 3-silyloxy-1,5-enynes VIII.30 under mild conditions with gold(I) catalysts in a process that involves a pinacol rearrangement has been reported for the synthesis of cyclopentenyl carbonyl compounds (Scheme VIII.19).[471]



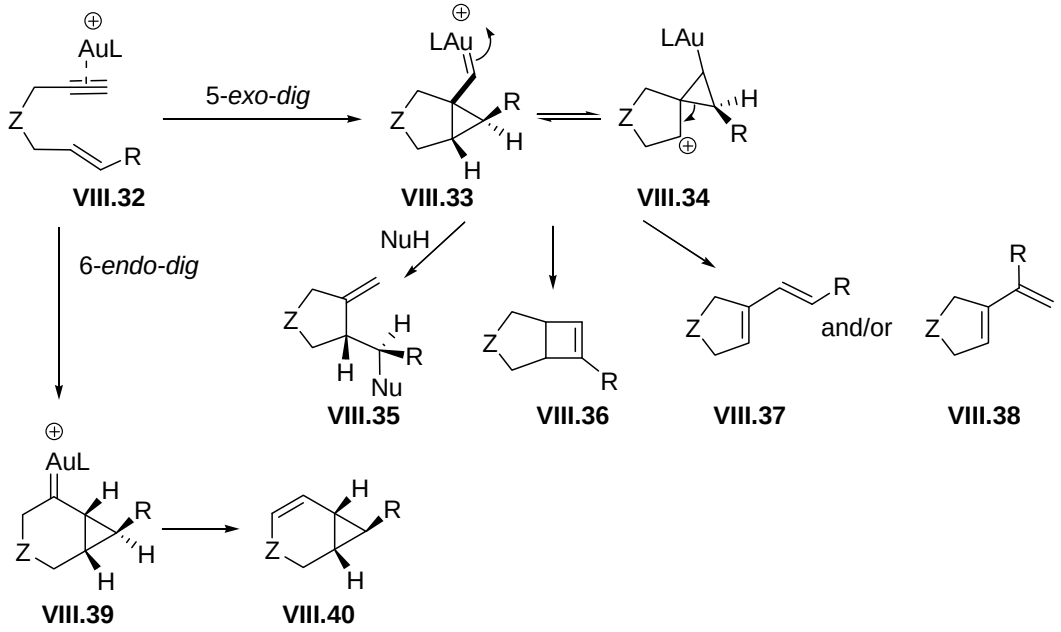
Scheme VIII.19

Au-Catalyzed Cycloisomerisation of 1,6-Enynes Leading to Substituted Cyclopentenes

Pioneering work by Echavarren and co-workers has shown that gold-based catalysts were very effective in a series of 1,6-enyne cycloisomerizations (Scheme VIII.20).[472,47] The

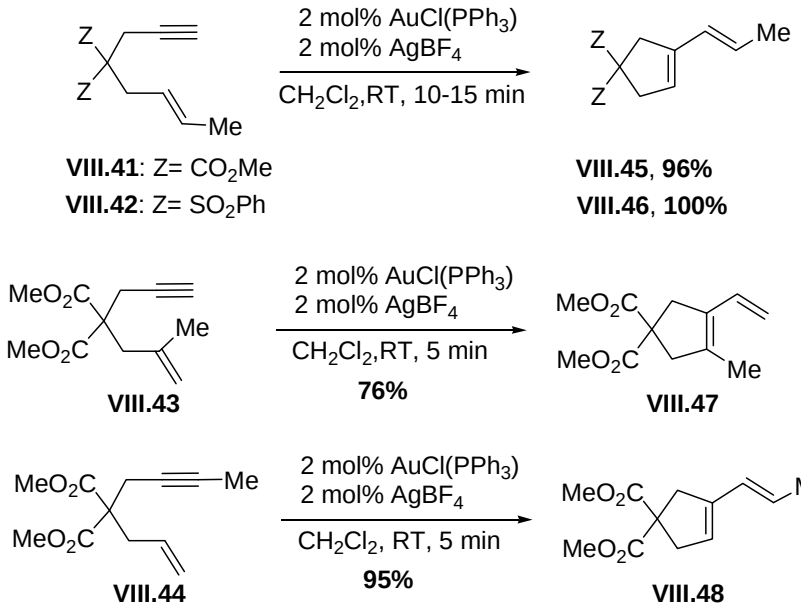
[471] Kirsch, S. F.; Binder, J. T.; Crone, B.; Duschek, A.; Haug, T. T.; Liébert, C.; Menz, H. *Angew. Chem. Int. Ed.* **2007**, *46*, 2310
[472] Nieto-Oberhuber, C.; Munoz, M. P.; Bunuel, E.; Nevado, C.; Cardenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2402

cycloisomerization reactions of classical 1,6-enynes are highly substrate dependent leading to dienes by an *exo* or *endo* process.
Coordination of the gold complex to the alkyne forms a (η^2-alkyne)metal complex VIII.32, which evolves to form the metal cyclopropyl carbene complexes VIII.33 (5-*exo-dig*) or VIII.39 (6-*endo-dig*) (Scheme VIII.20). Skeletal rearrangement of 1,6-enynes may proceed *via* intermediates VIII.34 to afford conjugated dienes VIII.37 and VIII.38 depending on which bond of the cyclopropane is cleaved. Alternatively, attack of nucleophiles NuH (alcohols or water) onto VIII.33 gives alkoxy- or hydroxycyclization products VIII.35 (for a discussion, see next chapter, VIII.3).



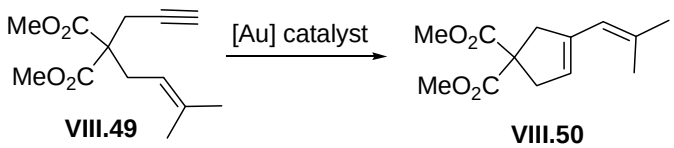
Scheme VIII.20

For example, differently substituted enynes VIII.41-44 afforded cyclopentenes VIII.45-48 when subjected to the *in situ* formed gold(I) catalyst (Scheme VIII.21):[472]



Scheme VIII.21

Different catalyst systems have been described for the transformation of VIII.49, with diene VIII.50 being isolated in all cases in high yield (Table VIII.1):[49a]



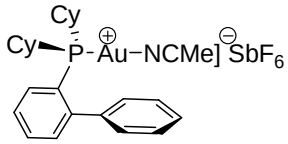
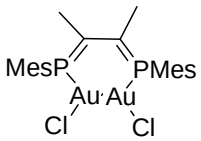
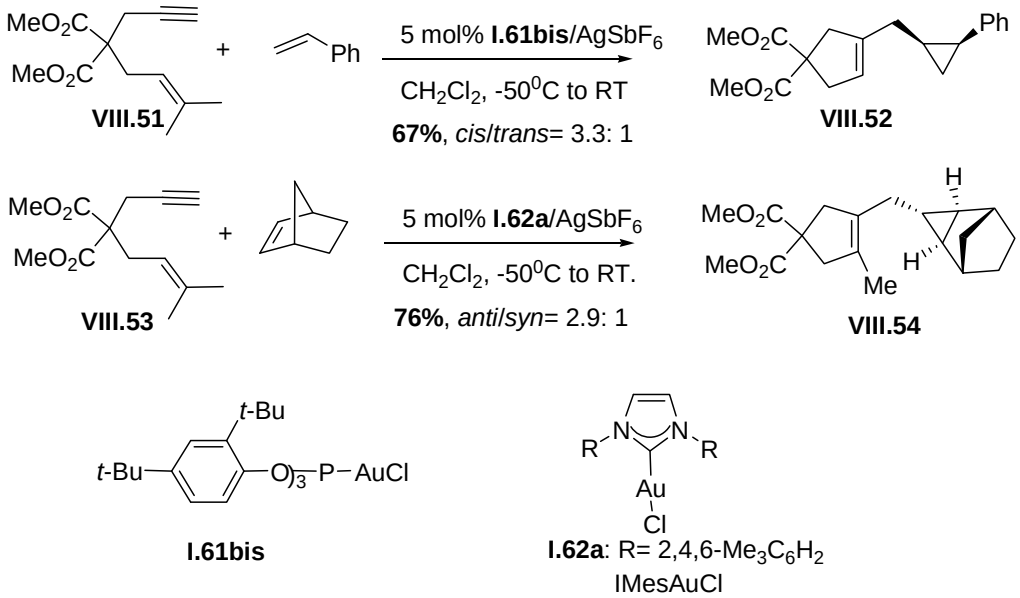
Entry	Catalyst	Conditions	Yield
1	0.01 mol% Ph_3AuNTf_2	CH_2Cl_2,RT	**97%**
2	2 mol%  I.59	CH_2Cl_2, -63^{0}C to -26^{0}C	**99%**
3	2.5 mol% 	CH_2Cl_2, RT	**100%**

Table VIII.1

The use of $Ph_3PAuNTf_2$ developed in our laboratory was particularly interesting as this catalyst was found to be highly stable and efficient for many other enyne rearrangements.[100] The replacement of PPh_3 by a bulkier and more electron-rich phosphane increased the

activity of the gold catalyst.[97c] A digold(I) complex was also recently prepared and showed a good activity for the cycloisomerization of enyne VIII.49.[473]

The intermolecular reaction between 1,6-enynes and alkenes leading to cyclopentenes proceeds with *in situ* formed catalysts from complexes I.61bis or I.62a and a silver salt (Scheme VIII.22).[474]



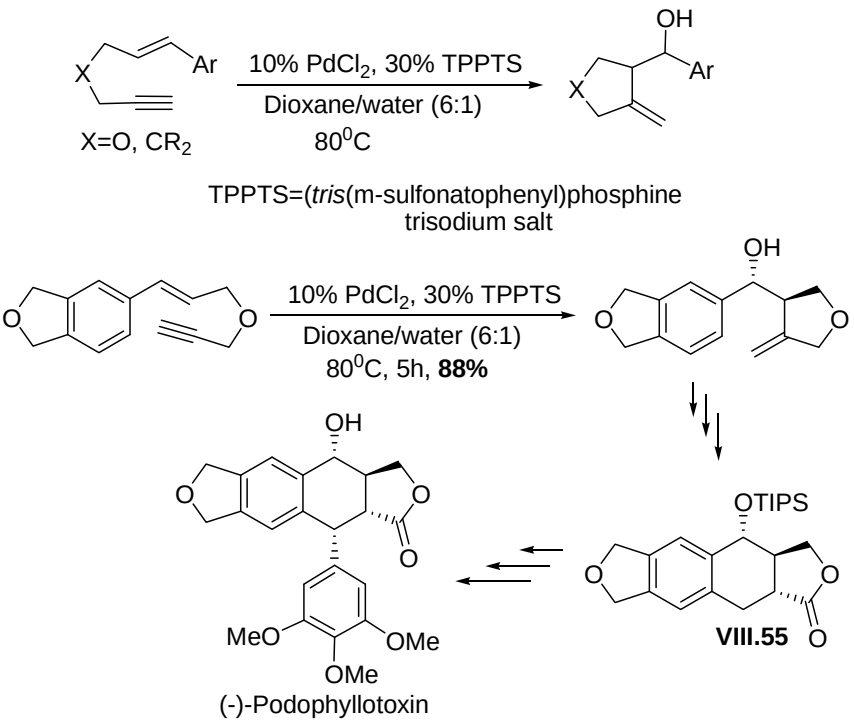
Scheme VIII.22

VIII.3. Preliminary Work in the Literature. Hydroxy- and Alkoxycyclizations Catalyzed by Transition Metals

VIII.3.1. Pd-Catalyzed Hydroxy- and Alkoxycyclizations Leading to Substituted Cyclopentene Derivatives

In the course of their study on palladium catalysis in aqueous medium, Genêt, Michelet and co-workers disclosed an unprecedented carbohydroxypalladation reaction allowing cyclization and hydroxyfunctionalization of 1,6-enynes.[475] This new reaction has been applied to the synthesis of (±)-podophyllotoxin precursor VIII.55 as shown in Scheme VIII.23:[476]

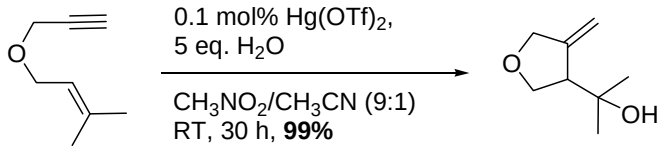
[473] Freytag, M.; Ito, S.; Yoshifuji, M. *Chem. Asian J.* **2006**, *1*, 693
[474] Lopez, S.; Herrero-Gomez, E.; Perez-Galan, P.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 6029
[475] Galland, J.-C.; Savignac, M.; Genêt, J.-P. *Tet. Lett.* **1997**, *38*, 8695
[476] Lise Charruault, L.; Michelet, V.; Genêt, J.-P. *Tet. Lett.* **2002**, *43*, 4757



Scheme VIII.23

VIII.3.2. Hg-Catalyzed Hydroxy- and Alkoxycyclizations Leading to Substituted Cyclopentene Derivatives

By exploiting the alkynophilic nature of $Hg(OTf)_2$, Nishizawa et *al.* developed a highly effective protocol for the hydroxycyclization of 1,6-enynes possessing oxygen or carbon tethers (Scheme VIII.24):[477]

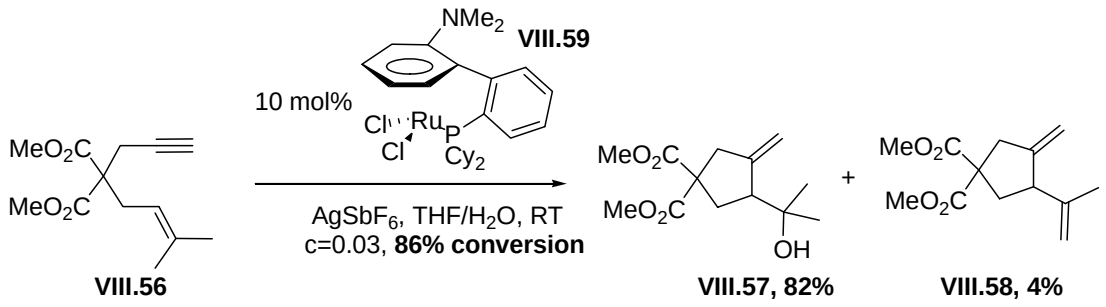


Scheme VIII.24

VIII.3.3. Ru-Catalyzed Hydroxy- and Alkoxycyclizations Leading to Substituted Cyclopentene Derivatives

Hydroxycyclizations of 1,6-enynes were found to be promoted also by ruthenium catalysts such as the arene-tethered ruthenium complex VIII.59 (Scheme VIII.25):[478]

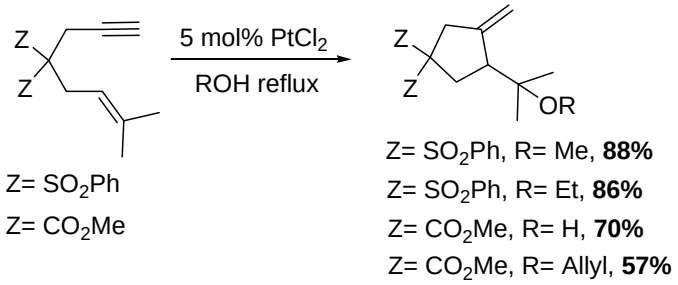
[477] Nishizawa, M.; Yadav, V. K.; Skwarczynski, M.; Takao, H.; Imagawa, H.; Sugihara, T. *Org. Lett.* **2003**, *5*, 1609
[478] Faller, J. W.; Fontaine, P. P. *J. Organomet. Chem.* **2006**, *691*, 1912



Scheme VIII.25

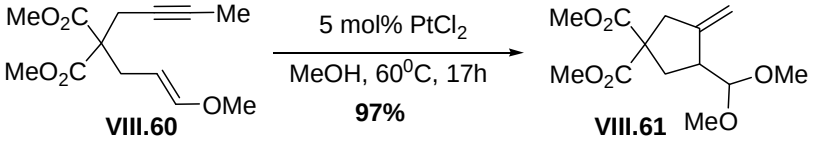
VIII.3.4. Pt-Catalyzed Hydroxy- and Alkoxycyclizations Leading to Substituted Cyclopentene Derivatives

Echavarren and colleagues reported a highly versatile platinum-catalyzed hydroxy-, alkoxy, and acyloxycyclization of 1,6-enynes. A large variety of carbon- and oxygen-bridged enynes bearing disubstituted or trisubstituted double bonds have been efficiently cyclized to the corresponding alcohols, ethers, and esters (Scheme VIII.26):[479]



Scheme VIII.26

The same research group extended this transformation to enynes possessing an enol ether function (VIII.60 in Scheme VIII.27), which allowed the synthesis of acetals of type VIII.61:[480]

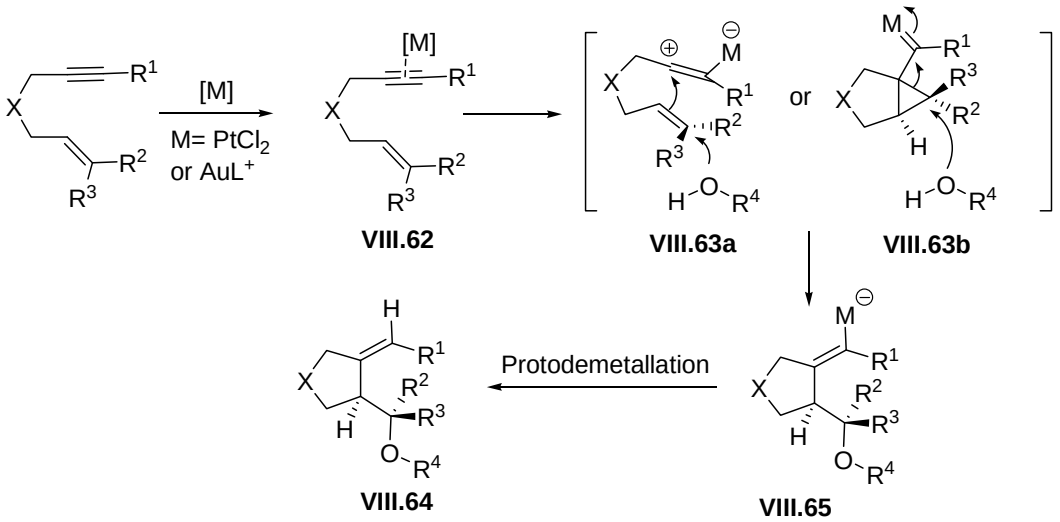


Scheme VIII.27

On the basis of deuterium labeling experiments[479,481] and DFT calculations[482] the authors invoked the initial formation of an electrophilic л-alkyne–platinum complex VIII.62. The

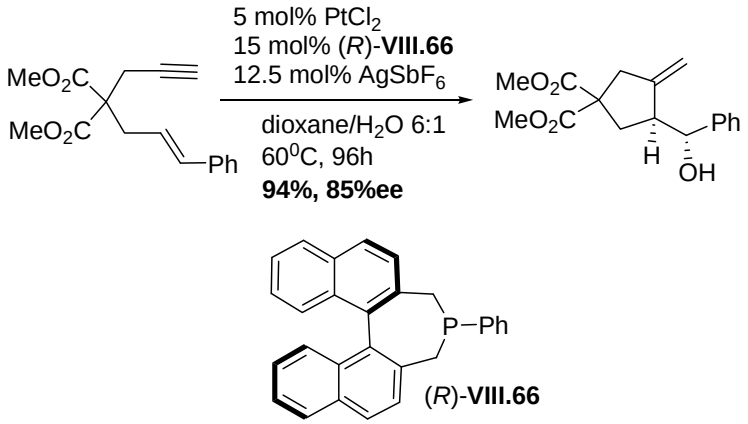
[479] Mendez, M.; Munoz, M. P.; Echavarren, A. M. *J. Am. Chem. Soc.* **2000**, *122*, 11549
[480] Nevado, C.; Cardenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2003**, *9*, 2627
[481] Nevado, C.; Charruault, L.; Michelet, V.; Nieto-Oberhuber, C.; Munoz, M. P.; Mendez, M.; Rager, M.-N.; Genêt, J.-P.; Echavarren, A. M. *Eur. J. Org. Chem.* **2003**, 706

mechanism of alkoxycarbocyclizations was described to proceed in a highly concerted manner involving simultaneous attack of the activated alkyne by the alkene with a concomitant addition of the alcohol nucleophile. Alternatively, the process may involve a stepwise formation and opening of cyclopropane intermediate VIII.63b. The final step involves protodemetallation of an alkenyl metal complex VIII.65 (Scheme VIII.28):



Scheme VIII.28

Genêt and Michelet's group published an enantioselective version of this transformation where a dicationic platinum complex synthesized from $PtCl_2$, (*R*)-binepine ((*R*)-VIII.66), and $AgSbF_6$ was employed as a catalyst.[483]



Scheme VIII.29

[482] Mendez, M.; Munoz, M. P.; Nevado, C.; Cardenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2001**, *123*, 10511

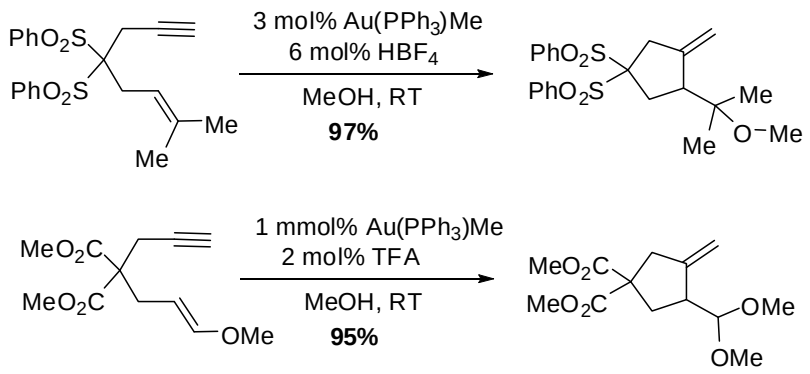
[483] a) Charruault, L.; Michelet, V.; Taras, R.; Gladiali, S.; Genêt, J.-P. *Chem. Commun.* **2004**, 850; b) Michelet, V.; Charruault, L.; Gladiali, S.; J Genêt, J.-P. *Pure Appl. Chem.* **2006**, *78*, 397

VIII.3.5. Au-Catalyzed Hydroxy- and Alkoxycyclizations Leading to Substituted Cyclopentene Derivatives

As previously reported in the presence of palladium and platinum catalysts (see Chapter VIII.3.4), the efficient trapping of the transient cyclopropylcarbene VIII.63b intermediate (Scheme VIII.28) by an oxygen nucleophile, such as water or an alcohol, was found to occur also in presence of gold catalysts. The main advantage of using electrophilic gold catalysts is the possibility of accessing a large variety of alcohols and ethers under extremely mild conditions.[49a, e-h]

Several catalyst systems were reported to effect the alkoxycyclisation of 1,6-enynes leading to cyclized products at room temperature, based either on gold(I) or gold(III) precursors.

In 2004, as a part of their comprehensive study of gold-based catalysis of enyne cycloisomerizations, Echavarren et *al.* reported that cationic gold complexes were exceedingly effective in promoting alkoxycarbocyclizations of a wide range of 1,6-enynes.[49,484] Some representative examples of this methodology, as well as the typical reaction conditions, are illustrated in Scheme VIII.30:

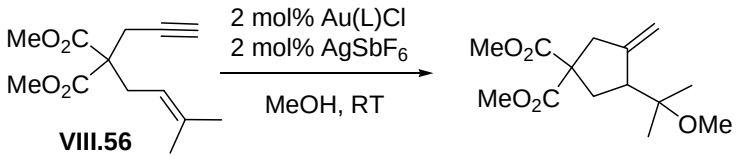


Scheme VIII.30

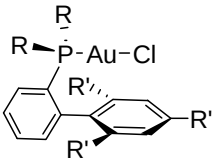
Biphenylphosphine based catalysts were reported to be superior for the methoxycyclization of 1,6-enynes (Table VIII.2):[485]

[484] Nieto-Oberhuber, C.; Paz Muñoz, M.; Bunuel, E.; Nevado, C.; Cardenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2402

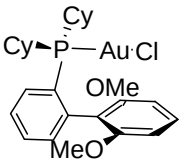
[485] Lopez, S.; Nieto-Oberhuber, C.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178



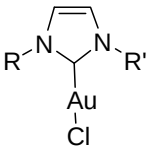
Entry	Catalyst	Time	Yield
1	PPh_3AuCl	3 h	**84%**
2	(*o*-Tol)$_3$PAuCl	24 h	**90%**
3	(1-Naph)$_3$PAuCl	18 h	**76%**
4	**I.55**	0.5 h	**97%**
5	**I.56-I.58**	0.25 h	**89-92%**
6	**I.62a**	1.5 h	**71%**
7	**VIII.57**	5 h	**87%**
8	**VIII.58**	24 h	**34%**



I.55: R= Cy, R'= H
I.56: R= *t*-Bu, R'=H
I.57: R= Cy, R'= *i*-Pr



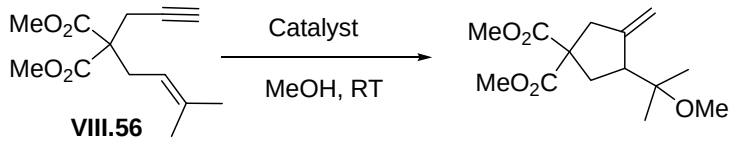
I.58



I.62a: R= R'= Mes
VIII.57: R= Mes, R'= Me
VIII.58: R= R'=Me

Table VIII.2

The catalytic activity of the gold (I) complexes developed in our group,[100] was once again extremely high, as only 0.1 mol% $Au(PPh_3)NTf_2$ was needed to afford 77% yield (Table VIII.3):



Entry	Catalyst	Time	Yield
1	1 mol% PPh_3AuNTf_2	2 h	94%
2	0.1 mol% PPh_3AuNTf_2	24 h	77%
3	2 mol% PPh_3AuSbF_6	3 h	84%
4	1 mol% **VIII.59a**	2 h	94%
5	1 mol% **VIII.59b**	75 min	97%
6	1 mol% **VIII.59c**	75 min	96%
7	1 mol% **VIII.59d**	20 min	97%
8	2 mol% **VIII.60**	15 min	89%

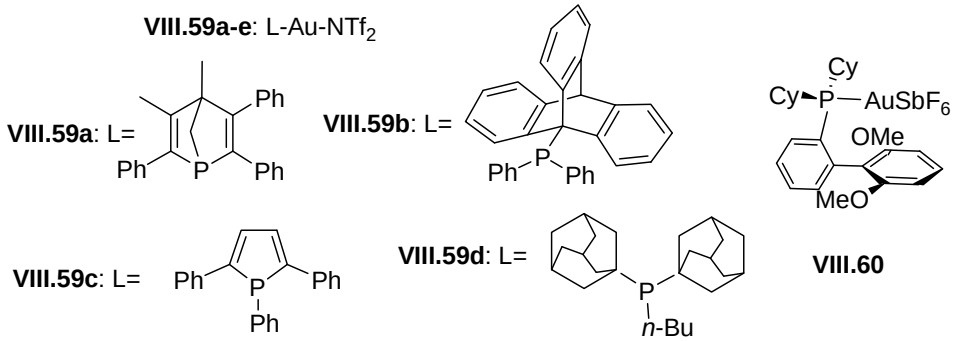
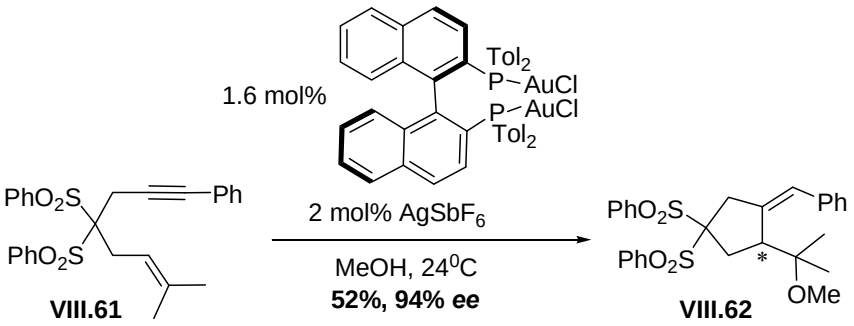


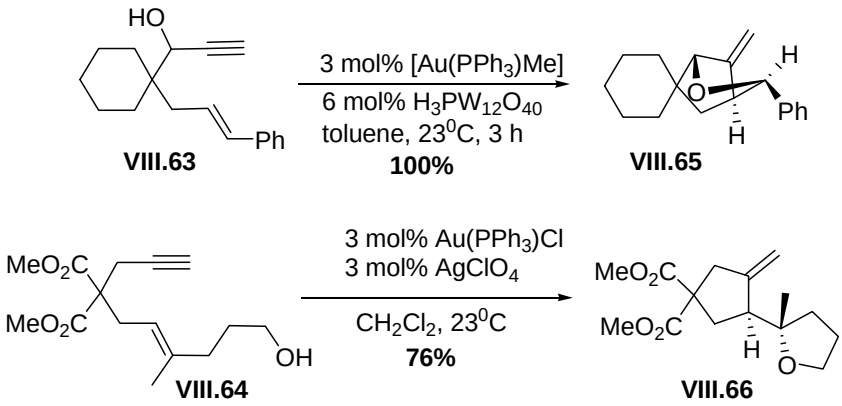
Table VIII.3

In 2005, Echavarren and co-workers reported the results of their studies aimed at the development of catalytic enantioselective alkoxycarbocyclizations. While the cyclization products were produced generally with only moderate enantioselectivity, a promising enantiomeric excess was obtained in the case of derivative VIII.61, which bears two sulfone moieties and a substituted triple bond (Scheme VIII.31):[91]



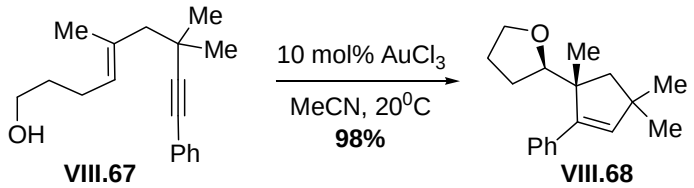
Scheme VIII.31

Intramolecular hydroxycyclization reactions were reported by the same group giving rise to an easy access to oxygenated heterocyclic compounds VIII.65-66:[97c]



Scheme VIII.32

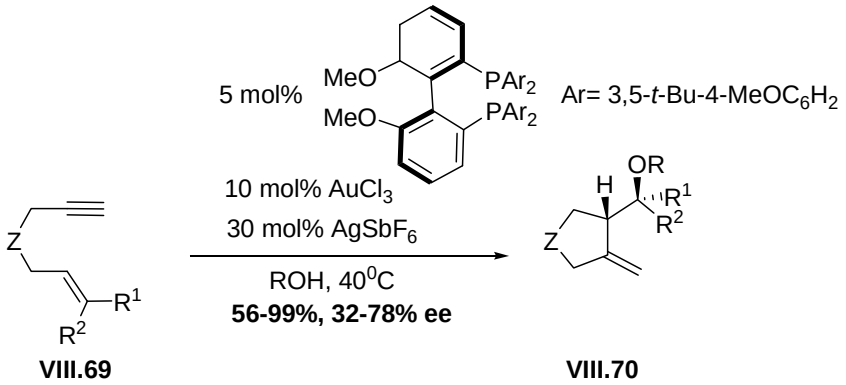
Zhang and Kozmin demonstrated that hydroxycyclizations are not only limited to 1,6-enynes. In the course of their investigation of gold-catalyzed cycloisomerization of 1,5-enynes, they discovered that treatment of trisubstituted *E*-alkene VIII.67 with $AuCl_3$ unexpectedly furnished tetrahydrofuran VIII.68 as an exclusive *anti*-Markovnikov reaction product (dr > 97:3, Scheme VIII.33).[486]



Scheme VIII.33

Michelet and co-workers reported the synthesis of enantiomerically enriched functionalized alcohols and ethers *via* hydroxy- and alkoxycyclization reactions using of $AuCl_3$ associated with a chiral ligand (*R*-4-MeO-3,5-(*t*- Bu)$_2$-MeOBIPHEP) in the presence of silver salts.[487]

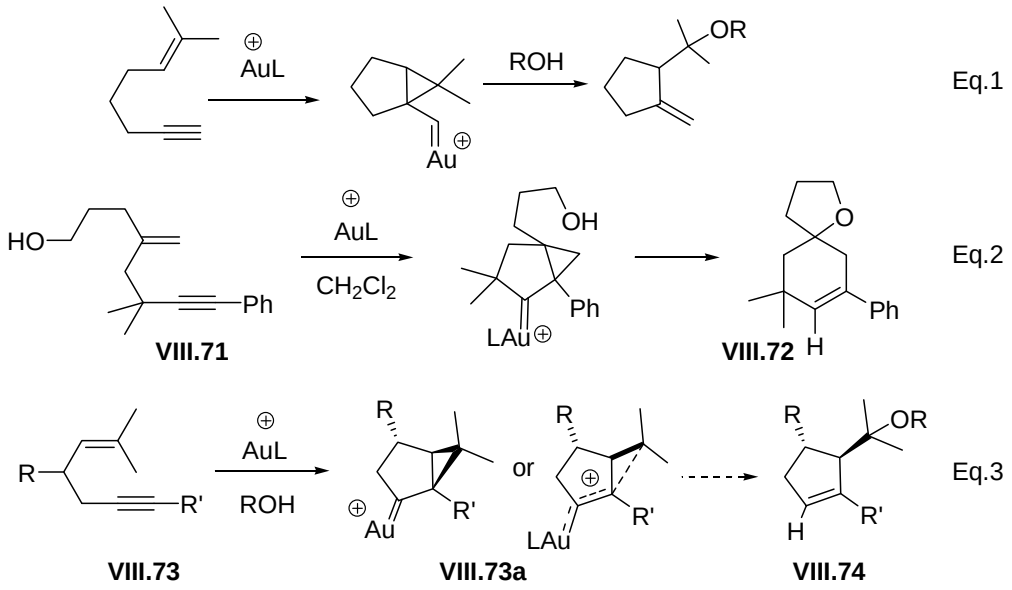
[486] Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6962
[487] Chao, C.-M.; Genin, E.; Toullec, P. Y.; Genêt, J.-P.; Michelet, V. *J. Organomet. Chem.* **2008**, doi:10.1016/j.jorganchem.2008.08.008



Scheme VIII.34

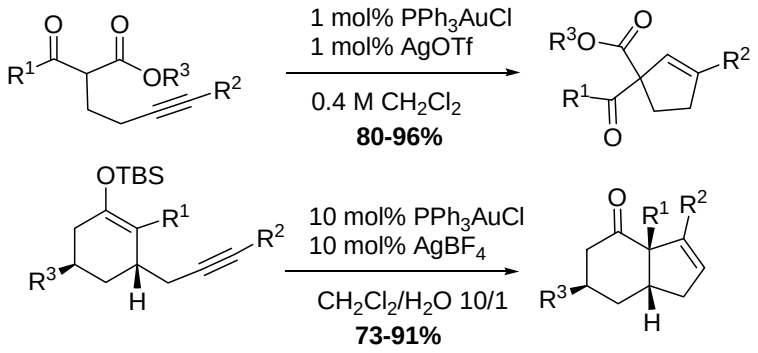
VIII.4. Our Synthetic Approach. First Results and Optimization of the Catalytic System

As highlighted in Chapter VIII.3, the transition metal catalyzed enyne hydroxy- and alkoxycyclizations were subject to extensive study by a large number of research groups.
By analogy with these recent studies, especially by analogy with the gold (I) catalyzed 5-*exo* alkoxycyclization of 1,6-enynes described by Echavarren et *al.* (Scheme VIII.35, Eq. 1),[97c] and the study concerning the 6-*endo*-intramolecular nucleophile trapping,[486] we hypothesized that 1,5-enynes such as VIII.73 might be valuable precursors for the synthesis of functionalized cyclopentenes VIII.74 after a gold catalyzed 5-*endo* alkoxycyclization step (Scheme VIII.35, Eq. 3):



Scheme VIII.35

Two 5-*endo-dig* gold(I)-catalyzed carbocyclisation processes were previously reported in the literature by Toste and *al.* (Scheme VIII.36):[488]

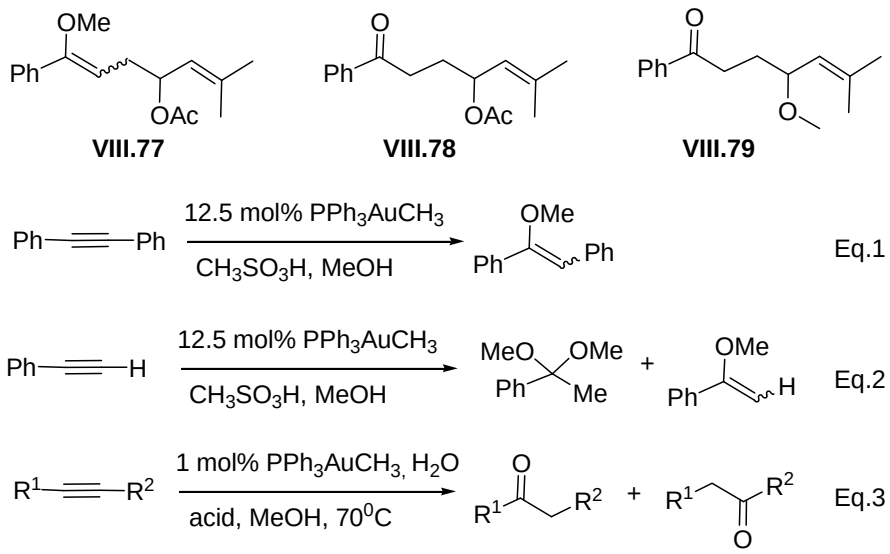


Scheme VIII.36

We estimated that the reverse substitution pattern of the alkene in substrate VIII.73 would favor a 5-*endo-dig* process and that the presence of the R group might allow to the stereoselective formation of VIII.74 (Scheme VIII.35, Eq. 3), in contrast to the work of Zhang and Kozmin[486] (Scheme VIII.35, Eq. 2), where the intramolecular 6-*endo* alkocyclization of enyne VIII.71 led to the exclusive formation of cyclohexene VIII.72. We also believed that this transformation would be favoured with internal alkynes, while the 5-*exo* alkoxycyclization of 1,6-enynes is generally limited to the use of terminal alkynes.[489] This approach would be synthetically useful since the cyclopentenes obtained by this transformation could lend for the elaboration of more complex structures, like those described in Chapter VIII.1.

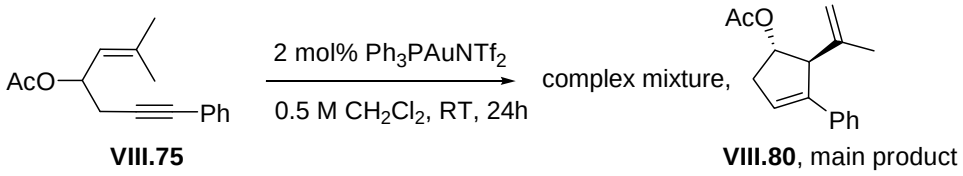
Model substrate VIII.75 was chosen to validate our synthetic approach (Table VIII.4). In a first attempt, this substrate was treated with 1% of the air stable cristalline $Ph_3PAuNTf_2$ catalyst in methanol at room temperature.[100] Delightfully, the stereoselective formation of the desired cyclopentene VIII.76 was observed, which was isolated in 58% yield along with by-products derived from the direct methoxylation of the alkyne (Scheme VIII.37 and Table VIII.4, Entry 1).
The formation of compounds of type VIII.77-79 is in agreement with the results obtained by Teles (Scheme VIII.37, Eq.1-2)[34] and Tanaka (Scheme VIII.37, Eq. 3)[76] in their study on gold(I)-catalyzed addition of methanol to alkynes:

[488] a) Staben, S. T.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem. Int. Ed.* **2004**, *43*, 5350; b) Staben, S. T.; Kennedy-Smith, J. J.; Huang, D.; Corkey, B. K.; LaLonde, R. L.; Toste, F. D. *Angew. Chem. Int. Ed.* **2006**, *45*, 5991
[489] A single example of methoxycyclization of an aryl substituted 1,6-enyne has been reported: see reference 97c



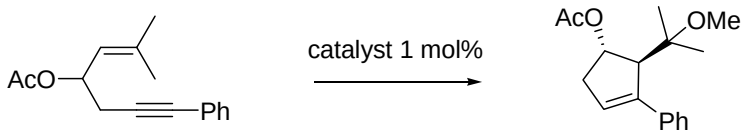
Scheme VIII.37

It should be noted that a complex mixture of products is obtained when substrate VIII.75 is treated with 2 % $Ph_3PAuNTf_2$ in dichloromethane, cyclized product VIII.80 (Scheme VIII.38) and the starting material being the main components (isolated together in 36% yield).

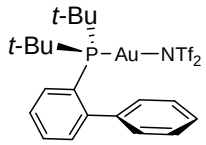
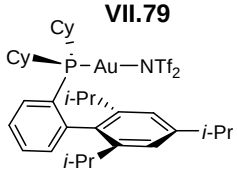


Scheme VIII.38

The use of the bulkier and more electron rich Ad_2n-$BuPAuNTf_2$[100] did not significantly improve the yield. It is worth mentioning that product VIII.79 (Scheme VIII.37) arising from the direct methoxylation of the double bond and substitution of the acetate is obtained in 25% yield along with the desired cyclopentene derivative VIII.76 (Table VIII.4, Entry 2). Biphenylphosphine based catalysts were reported to be superior for the methoxycyclization of 1,6-enynes (see Chapter VII).[81] Outstandingly, the use of biphenylphosphine based catalysts VI.46 and VII.79 cleanly and rapidly furnished VIII.76 in 98% yield (Entry 3-4). Moreover, conducting the reaction in a 10:1 CH_2Cl_2: MeOH mixture led to an even faster transformation without loss of efficiency (Table VIII.4, Entry 5).



VIII.75 **VIII.76**

Entry	Catalyst	Conditions	Time	Yield [a]
1	$Ph_3PAuNTf_2$	MeOH, 0.5M, RT	24 h	**58%**
2	Ad_2*n*-BuPAuNTf$_2$	MeOH, 0.5M, RT	24 h	**64%**[b]
3	 **VII.79**	MeOH, 0.5M, RT	1 h	**98%**
4	 **VI.46**	MeOH, 0.5M, RT	40 min	**98%**
5		CH_2Cl_2:MeOH 10:1, 0.5M,RT	20 min	**99%**

[a] Isolated yields. [b] Obtained along with 25% isolated yield of compound **VIII.79.**

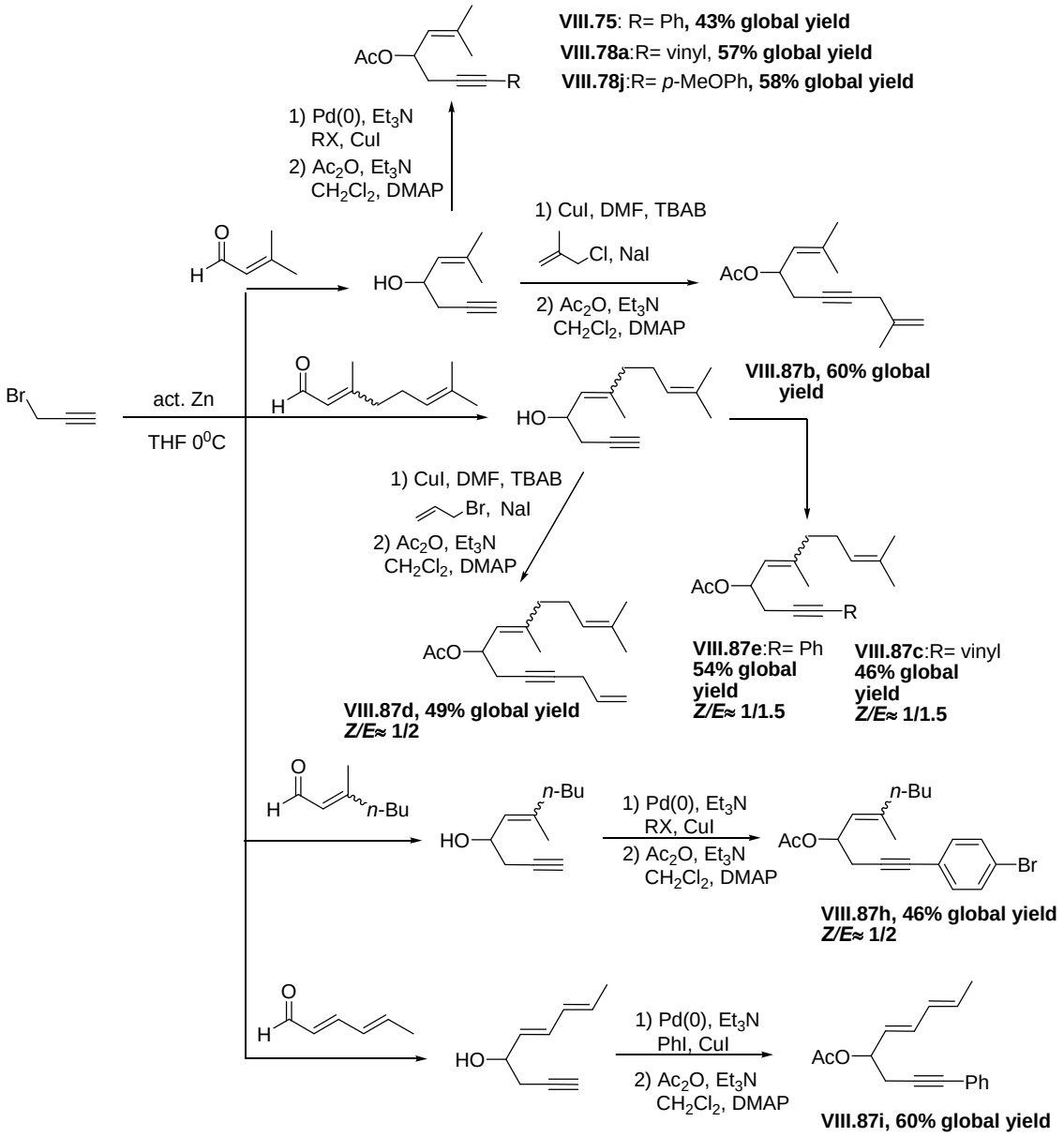
Table VIII.4

In the light of these preliminary results, the experimental conditions in Entry 5, Table VIII.4 were retained for the study of this transformation.

VIII.5. Synthesis of the Substrates

In order to examine the scope of the reaction, a variety of diversely substituted enynes were synthesized according to the classical procedures described in the literature.
The three-step sequence is illustrated in Scheme VIII.39:
1) Zinc mediated propargylation of an *α,β*-unsaturated aldehyde (3-methyl-2- buten-1-al, neral or sorbal) following the procedure described by Danishefski and co-workers.[490]
2) Pd(0) mediated Sonogashira type coupling reaction in the conditions described by Hiyama and co-workers[491] or copper(I) mediated allylation.[492]
3) Acetylation of the secondary alcohol under classical conditions.

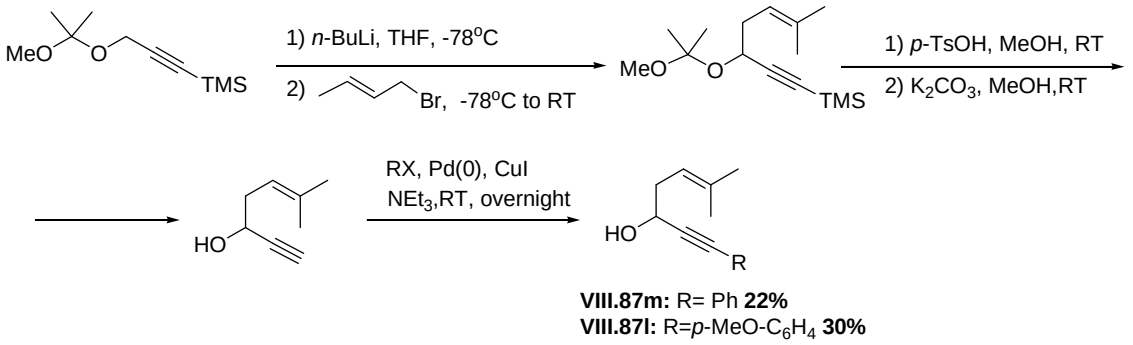
[490] Yang, Z.Q.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 9602
[491] Nakao, Y.; Hirata, Y.; Ishihara, S.; Oda, S.; Yukawa, T.; Shirakawa, E.; Hiyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 15650 b) Chinchilla, R; Carmen Najera, C. *Chem. Rev.* **2007**, *107*, 874
[492] Betancort, J. M.; Martin, T.; Palazon, J. M.; Martin, V. S. *J. Org. Chem.* **2003**, *68*, 3216



Scheme VIII.39

4-Hydroxy-1,5-enynes VIII.87m and VIII.87l were synthesized according to the procedure developed by Malacria and co-workers (Scheme VIII.40).[493]

[493] Harrak, Y.; Blaszykowski, C.; Bernard, M.; Cariou, K.; Mouries, V.; Dhimane, A-L. ; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2004**, *126*, 8656



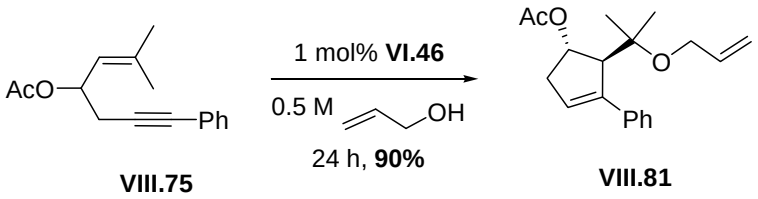
Scheme VIII.40

VIII.6. Gold(I)-Catalyzed Alkoxycyclization of 1,5-Enynes

With these variously substituted enynes in hands, we examined the scope of the gold-catalyzed cycloisomerisation.

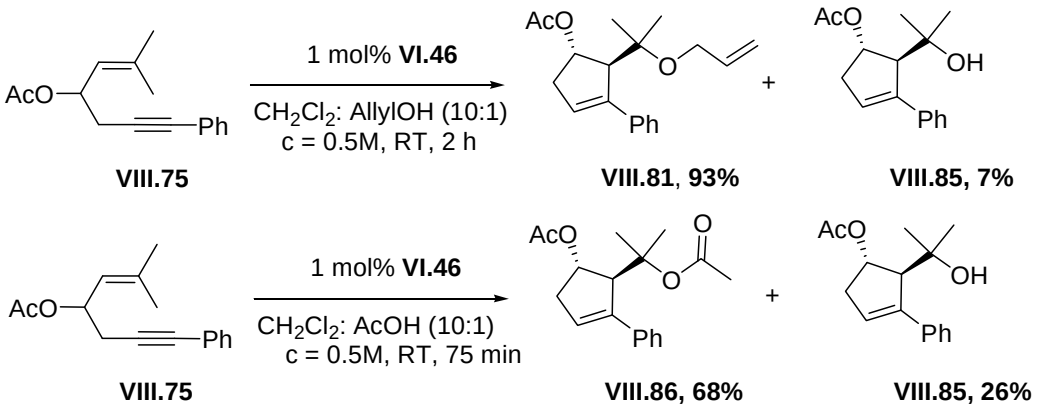
VIII.6.1. Variation of the Nucleophile

We first focused our attention on the variation of the nucleophile which intercepts the intermediate cationic gold species VIII.73a (Schemes VIII.35, Eq. 3 and Scheme VIII.47).
First, enyne VIII.75 was subjected to alkoxycyclization in the presence of VI.46 as catalyst using allylic alcohol as the solvent. We were delighted to observe the formation of the desired cyclopentene VIII.81 in 90% yield. The reaction was completed in 24 hours according to TLC analysis.



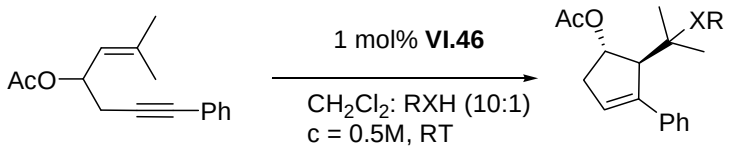
Scheme VIII.41

When the reaction was carried out in a mixture of alcohol and dichloromethane 1:10, the transformation was faster (2 h) and the desired product was obtained in higher yield (Table VIII.5, Entry 1). This time, the presence of a more polar compound on the TLC plate caught our attention. This compound proved to be the hydroxyderivative VIII.85 isolated in 7% yield, formed by the hydroxycyclization reaction of the enyne VIII.75, probably due to adventitious water present in the allylic alcohol (Scheme VIII.42, Eq. 1). The same side-product VIII.85 was isolated in 26% yield when acetic acid was tested as the nucleophile (Table VIII.5, Entry 6 and Scheme VIII.42, Eq. 2).

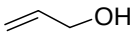
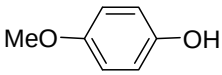
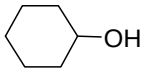
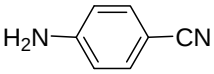


Scheme VIII.42

To our delight, the reaction proved to be quite general and enyne VIII.75 reacted with various nucleophiles using 1% of VI.46 as the catalyst in a mixture alcohol: dichloromethane 1: 10 to furnish cyclopentenes VIII.81-86 in generally high yields (54%-100%) (Table VIII.5):



VIII.75 **VIII.81-86**

Entry	RXH	Time	Product	Yield[a]
1		2 h	**VIII.81**	**93%**[d]
2[b]		10 min	**VIII.82**	**95%**
3		45 min	**VIII.83**	**98%**
4		24 h	**VIII.84**	**54%**
5[c]	H_2O	4.5 h	**VIII.85**	**100%**
6		75 min	**VIII.86**	**68%**[d]
7		24 h	No reaction	–
8		24 h	No reaction	–

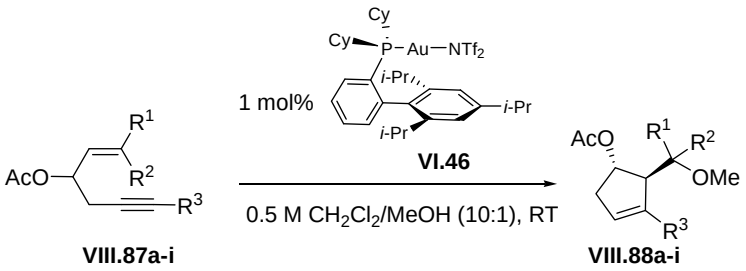
[a] Isolated yields. [b] With 2 equiv. of *p*-MeOPhOH. [c] In a CH_2Cl_2: acetone: H_2O mixture (8:2:1). [d] Obtained along with compound **VIII.85**.

Table VIII.5

Primary and secondary alcohols as well as phenols reacted equally well (Table VIII.5, Entries 1-4). Water was also successfully employed in this transformation. Quantitative formation of tertiary alcohol VIII.86 was observed when the reaction was carried out in a ternary mixture of 8:2:1 CH_2Cl_2: acetone: H_2O (Entry 5) (for the optimisation of the hydroxycyclization conditions, see Table VIII.8). Interestingly, acetic acid was also compatible with the catalytic system, affording the formation of acetoxycyclopentene VIII.86 (Entry 6).
Unfortunately, tertiary alcohols like *tert*-butanol were less nucleophilic and/or sterically too encumbered to give the reaction. Substrate VIII.75 was recovered unchanged when *p*-cyanoaniline was used as a nucleophile, most likely due to the incompatibility of the gold catalyst with free basic amino groups.

VIII.6.2. Substitution at the Triple and/or Double Bond of the Enyne Substrate

Next we focused our attention to the substitution pattern of the triple and double bond of the enyne substrate. We were pleased to notice that the alkoxycyclization was not limited to aryl substituted alkynes or trisubstituted alkenes. Vinylic, allylic and methallylic substituents were compatible with the reaction conditions used: synthetically valuable 1,3-dienes VIII.88a and VIII.88d were obtained in 77% and 78% yield respectively *via* methoxycyclization of enynes VIII.87a and VIII.87d (Table VIII.6, Entries 1, 4), while cyclopentenes VIII.88b and VIII.88e were furnished in good yields starting from enynes VIII.87b and VIII.87e (Entries 2, 5).



Entry	Substrate	Time	Product	Yield[a]
1	**VIII.87a**: R^3= vinyl	80 min	**VIII.88a**	**77% (54%)**[c]
2	**VIII.87b**: R^3= methallyl	24 h	**VIII.88b**	**87% (75%)**[c]
3	**VIII.87c**: R^3= vinyl (1:1.5)[b]	6 h	**VIII.88c**	**78% (1:1.5)**[d]
4	**VIII.87d**: R^3= allyl (1:2)[b]	6 h	**VIII.88d**	**64%** (1:2)[d]
5	**VIII.87e**: R^3= Ph (1:1.5)[b]	1 h	**VIII.88e**	**90%** (1:1.5)[d]
6	**VIII.87f**: R^3= Ph	1 h	**VIII.88f**	**98%**
7[e]	**VIII.87g**: R^3= ≡—Ph	1h	**VIII.88g**	**72%**
8	**VIII.87h**: R^3= *p*-BrC_6H_4 (1:2)[b]	24 h	**VIII.88h**	**65%** (1:2)[d]
9	**VIII.87i**	1 h	**VIII.88i**	**87%**

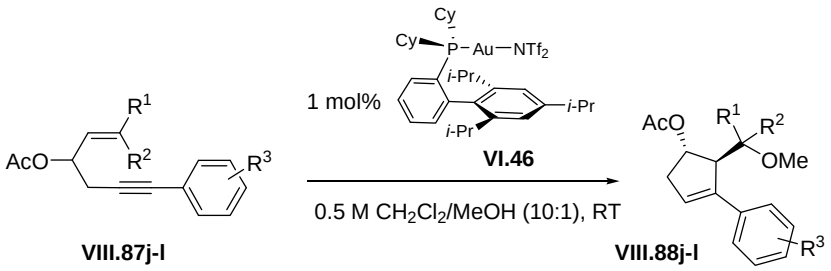
[a] Isolated yields. [b] *Z:E* ratio. [c] Yield obtained when methanol was used as the solvent. [d] Diastereoisomeric ratio. [e] The reaction mixture was heated at reflux.

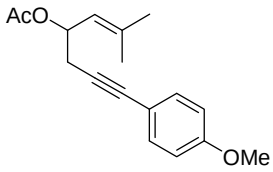
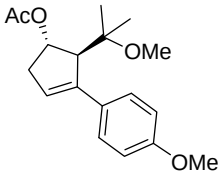
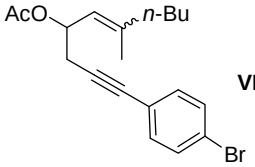
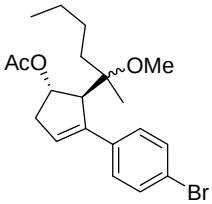
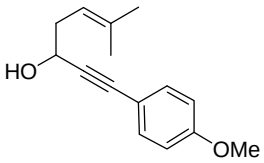
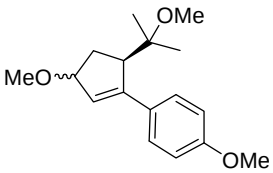
Table VIII.6

Methoxycyclization of the 1:1.5 *E:Z* diastereoisomeric mixture of enyne VIII.87c led to the formation of cyclopentene VIII.88c in the same diastereoisomeric ratio (Entry 5), proving the stereoselectivity of the transformation. Identical results were obtained when enynes VIII.87d, VIII.87e and VIII.87h were used as substrates. The stereospecificity of the reaction was demonstrated by the methoxycyclization of the pure *E*-isomer VIII.87f which afforded cyclopentene VIII.88f as single isomer (Entry 6). It is also worth to mention that no isomerization of the second alkene functionality was observed in the case of enyne VIII.87h which was also converted into derivative VIII.88h in good yields (Entry 8).

VIII.6.3. Substitution on the Aromatic Ring

The reaction was also efficient when functionalized aryl substituted alkynes were employed (Table VIII.7):



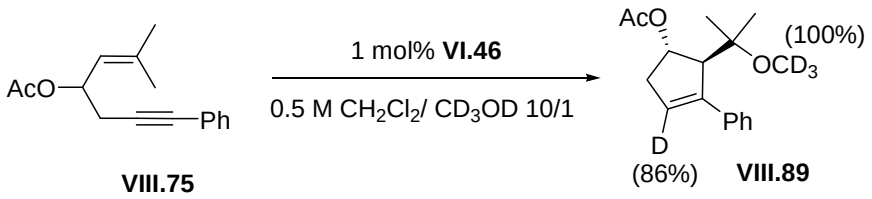
Entry	Substrate		Time	Product		Yield[a]
1		**VIII.87j**	20 min		**VIII.88j**	**93% (95%)**[c]
2		**VIII.87k,** (1:2)[b]	24 h		**VIII.88k**	**65%** (1:2)[d]
3		**VIII.87l**	15 min		**VIII.88l**	**87%** (2:1)[d]

[a] Isolated yields. [b] *Z:E* ratio. [c] Yield obtained when methanol was used as the solvent.
[d] Diastereoisomeric ratio.

Table VIII.7

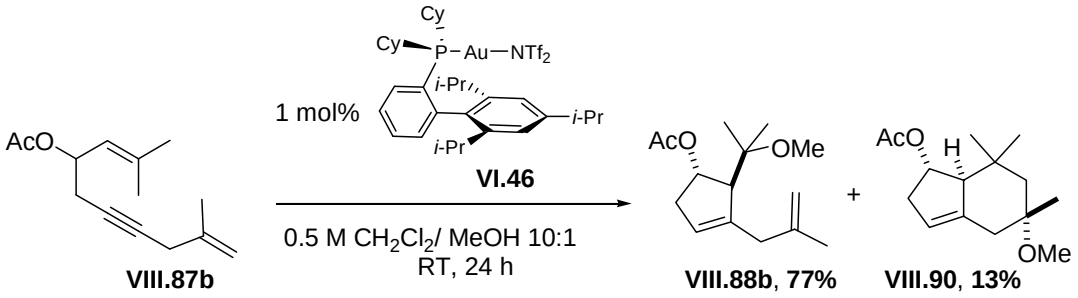
A non selective gold catalyzed substitution of the intermediate acid sensitive allylic alcohol by methanol might explain the incorporation of an additional methoxy group in the case of

product VIII.88l. This mechanism is supported by deuterium-labelling experiments (Scheme VIII.43):



Scheme VIII.43

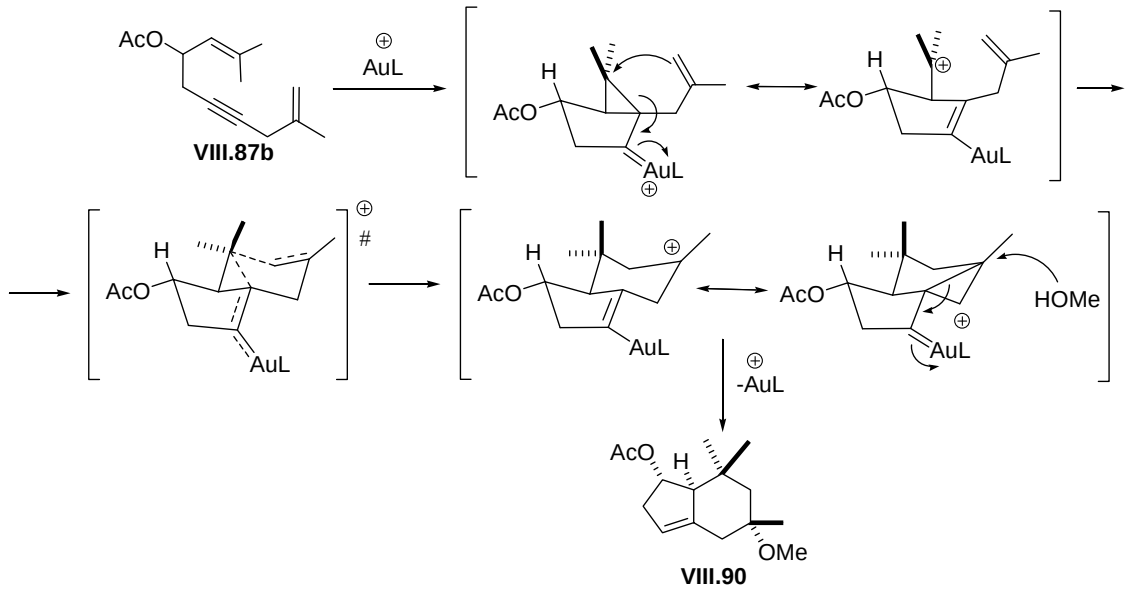
It is worth to mention that methallyl substrate VIII.87b furnished two structurally different products under the same reaction conditions (2 mol% of gold(I) complex VI.46 in a 10:1 CH_2Cl_2/MeOH mixture at c=0.5 M) (Scheme VIII.44). While the expected cyclopentene VIII.88b was mainly produced, a small amount of bicyclo[4.3.0]nonene VIII.90, derived from a formal sequence of [4+2] annelation/nucleophilic addition, was also isolated (13%).[494]



Scheme VIII.44

Despite the fact that bicycle VIII.90 was isolated in only 13% yield, its formation was remarkable since two cycles, three new bonds and two quaternary centers were assembled in a stereospecific manner. A mechanistic manifold for its formation is proposed in Scheme VIII.45:[494]

[494] The structure of VIII.90 was determined by NMR analysis and the stereochemistry later confirmed by analogy with other bicyclo[4.3.0]nonenes whose structure was obtained by X-Ray crystallography: Böhringer, S.; Gagosz, F. *Adv. Synth. Catal.* **2008**, *350*

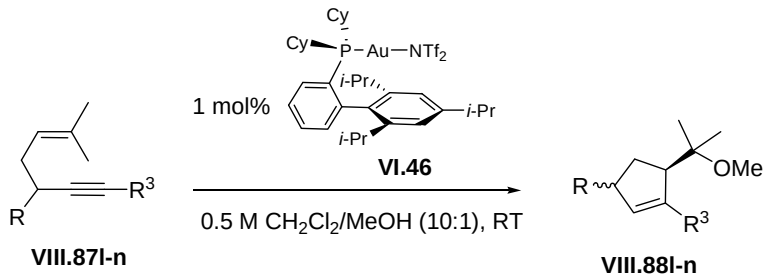


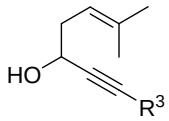
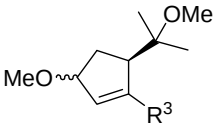
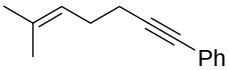
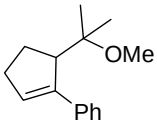
Scheme VIII.45

VIII.6.4. Variation of the Tether

We were curious to see if the reaction takes place with substrates where the position of the oxygenated tether group was changed from position at C-4 to C-3 (Table VIII.7, Entry 1-2) or with substrates bearing no oxygenated group at all in these positions (Entry 3). Therefore, the methoxycyclization was applied to alcohols VIII.87l and VIII.87m, which gave respectively cyclopentenes VIII.88l and VIII.88m as mixtures of diastereoisomers (Entries 1-2). No competitive formation of bicyclo[3.1.0]hexanone was observed hence confirming the rapid nucleophilic attack of methanol.[495] In this case also, the introduction of an additional methoxy unit in VIII.88l-m might result from a non selective gold catalyzed substitution of the intermediate acid sensitive allylic alcohol by methanol.

[495] An alternative gold-catalyzed propargylic substitution could be envisaged: see reference 68a



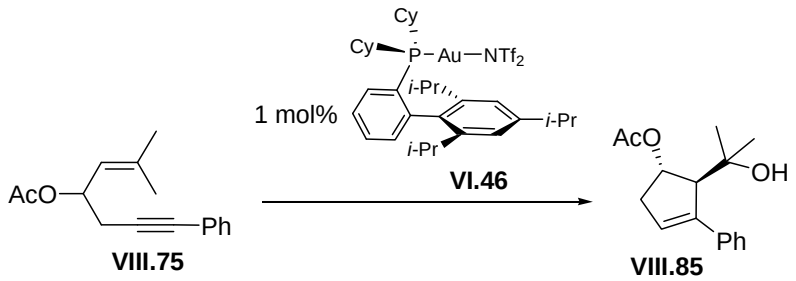
Entry	Substrate		Time	Product		Yield[a]
1		**VIII.87m**: R^3= Ph	2 h		**VIII.88m**	**77%** (1:1)[d]
2		**VIII.87l**: R^3= *p*-(MeO)C_6H_4	15 min		**VIII.88l**	**87%** (2:1)[d]
3		**VIII.87n**	1 h		**VIII.88n**	**92%**

[a] Isolated yields. [b] *Z:E* ratio. [c] Yield obtained when methanol was used as the solvent. [d] Diastereoisomeric ratio. [f] The reaction mixture was heated at reflux.

Table VIII.7

VIII.7. Gold(I)-Catalyzed Hydroxycyclization of 1,5-Enynes

In order to explore the scope of the hydroxycyclisation reaction observed in case of substrate VIII.75 (Table VIII.5), we next focused on the optimisation of the conditions needed to increase the yield of the expected hydroxycyclopentene VIII.85. The use of 8:2:1 CH_2Cl_2: acetone: H_2O ternary mixture gave the best results with the quantitative formation of tertiary alcohol VIII.85 (Table VIII.8, Entry 3):

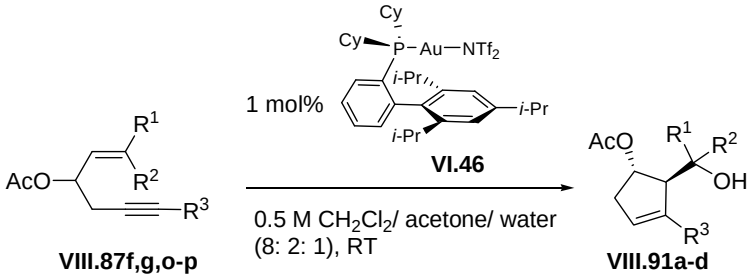


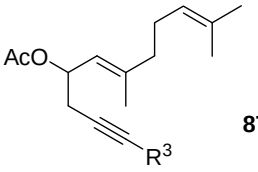
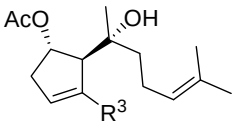
Entry	Conditions	Time	Yield [a]
1	0.5 M "wet"[b] CH_2Cl_2, RT	24 h	complex mixture
2	0.5M, acetone: water 10:1, RT	24 h	**99%**
3	0.5 M, CH_2Cl_2: acetone: water 8: 2: 1, RT	4.5 h	**100%**

[a] Isolated yields. [b] Obtained by extraction of CH_2Cl_2 from a binary CH_2Cl_2/H_2O mixture using a separatory funnel.

Table VIII.8

Enynes VIII.87f,g,o-p, previously prepared to test the scope of the methoxycylisation reaction, were subjected to these optimized reaction conditions. The results obtained are illustrated in Table VIII.9.

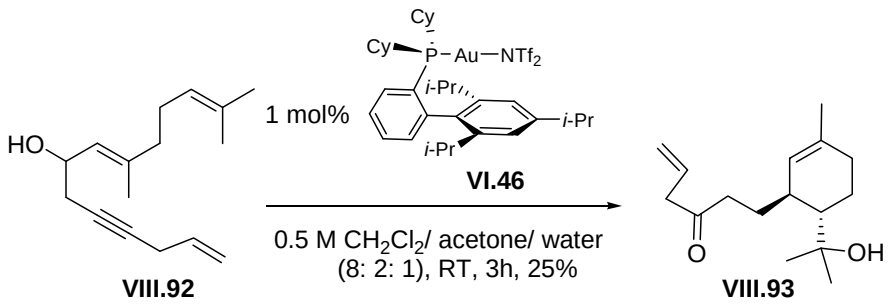


Entry	Substrate		Time	Product		Yield[a]
1		**87f**: R^3= Ph	1 h		**VIII.91a**	**94%**
2[b]		**87o**: R^3= vinyl	2 h		**VIII.91b**	**91%**
3		**87g**: R^3= ≡—Ph	2.5 h		**VIII.91c**	**97%**
4[b,c]		**87p**: R^3= allyl	>24 h		**VIII.91d**	**92%**

[a] Isolated yields. [b] Reaction carried out with 2 mol% catalyst. [c] The reaction mixture was heated at reflux.

Table VIII.9

The six-membered ring derivative VIII.93 was obtained in 25% yield when unprotected alcohol VIII.92 was subjected to the normal hydroxycyclisation conditions:

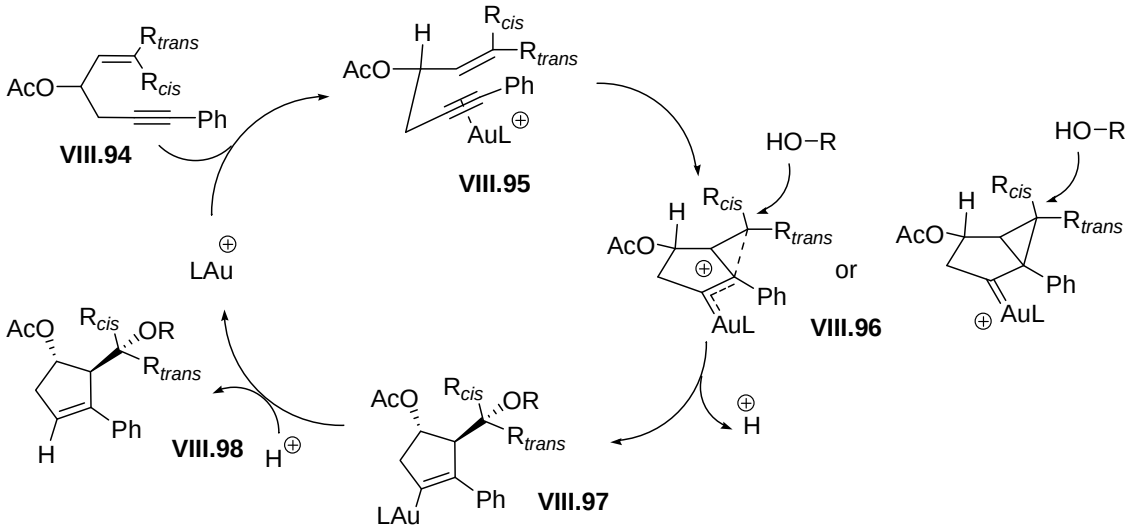


Scheme VIII.46

The formation of this product could be explained by an initial 5-*endo-dig* cyclization leading to the formation of a dihydrofuran ring. Subsequent gold-catalyzed opening of this ring and attack of the terminal dimethyl-substituted double bond on the resulting carbocation furnished the six-membered derivative.

VIII.8. Reaction Mechanism

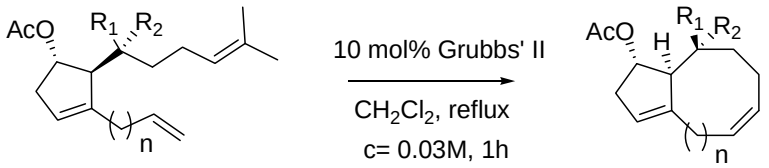
Based on deuterium-labelling experiments (Scheme VIII.43), a mechanistic manifold accounting for the formation of the cyclopentenes is proposed in Scheme VIII.47. Upon complexation of the gold(I) catalyst to the triple bond in enyne VIII.94, nucleophilic attack of the pendant olefin occurs and leads to the formation of a stabilized carbocationic gold intermediate VIII.96. A subsequent stereoselective attack of the oxygenated nucleophile onto this intermediate triggers the formation of the vinyl-gold species VIII.97 which affords cyclopentene VIII.98 by protodeauration. The exclusive formation of cyclopentenes could be attributed to the substitution pattern of the alkene moiety in VIII.94 which ultimately results in the regioselective cleavage of the weakest bond of the cyclopropyl ring in intermediate VIII.96 upon attack by the oxygenated nucleophile.



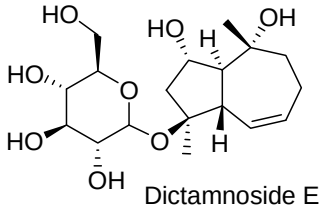
Scheme VIII.47

VIII.9. Transformation of the Functionalized Cyclopentenes Obtained by Gold Catalysis. Towards the Synthesis of Dictamnoside E

Taking advantage of the pendant alkenes functionalities present in compounds VIII.88c and VIII.88d, these functionalized cyclopentenes obtained by the gold-catalyzed hydroxy- and alkoxycyclization of 1,5-enynes were then submitted to the ring closing metathesis conditions: 10 mol% of Grubbs' II catalyst in refluxing dichloromethane (Scheme VIII.48). We were pleased to observe the rapid consumption of the substrates and the quantitative formation of the corresponding fused (5-7) and (5-8) bicyclic products VIII.99-101. Such bicyclic motifs are found in many terpenes, dictamnoside E being an example as discussed in Chapter VIII.1

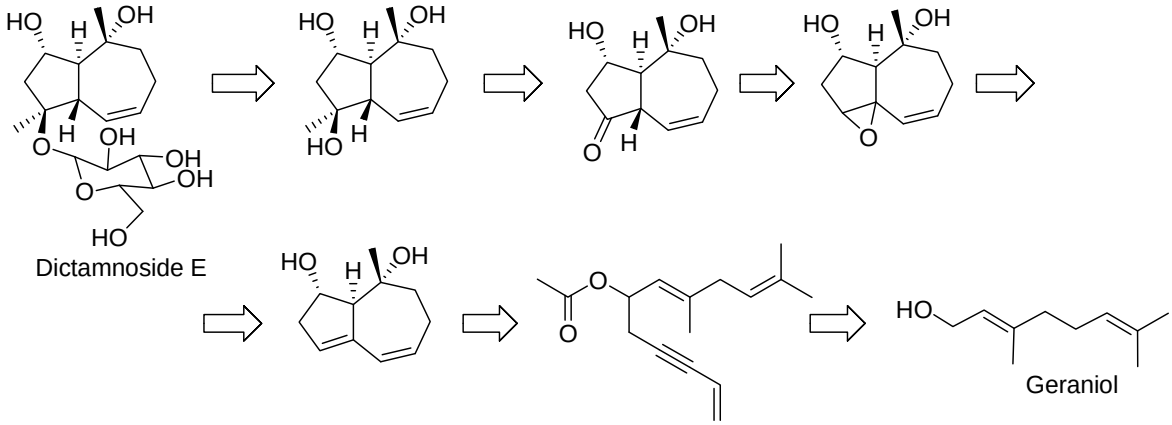


major **VIII.88c** (R_1=Me, R_2=OMe, n=0)	**VIII.99** (R_1=Me, R_2=OMe, n=0)	**100%**
minor **VIII.88c** (R_1=OMe, R_2=Me, n=0)	**VIII.100** (R_1=OMe, R_2=Me, n=0)	**100%**
major **VIII.88d** (R_1=Me, R_2=OMe, n=1)	**VIII.101** (R_1=Me, R_2=OMe, n=1)	**100%**



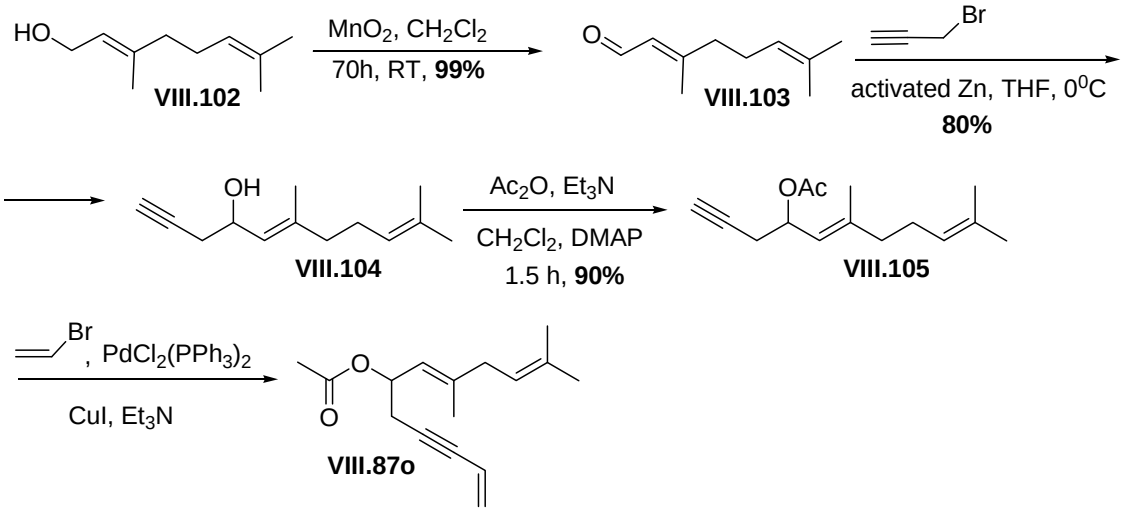
Scheme VIII.48

With an efficient method to prepare the fused (5-7) bicycle in hand, we turned our attention to the adaptation of this method to a synthetic approach towards dictamnoside E. The retrosynthetic analysis envisioned is depicted in Scheme VIII.49:



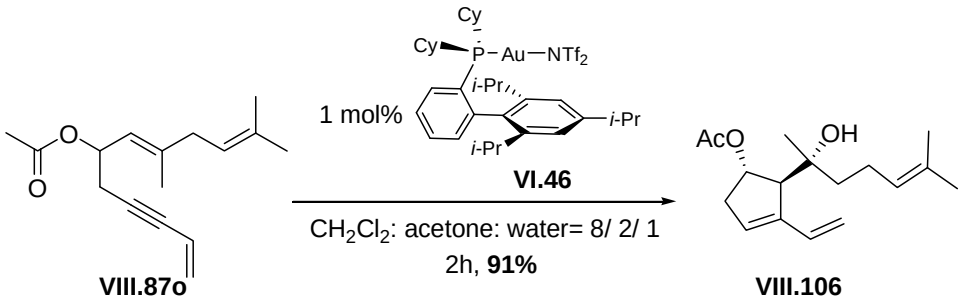
Scheme VIII.49

The preparation of the required substrate for the envisaged noble metal catalyzed cycloisomerization reaction started with the large scale adaptable oxidation of geraniol (Scheme VIII.50). The resulting aldehyde VIII.103 (geranial) was reacted with propargyl bromide in the presence of activated zinc in THF at 0^0C and the alcohol thus obtained was acetylated with acetic anhydride. Palladium mediated coupling with vinyl bromide afforded the enyne substrate VIII.106:



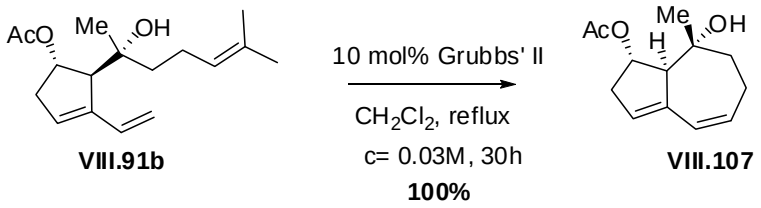
Scheme VIII.50

Gold-(I) catalyzed cyclization of this enyne derivative (VIII.106, Scheme VIII.51) was carried out according to the method developed for the hydroxycyclization reaction described earlier (see Table VIII.9):



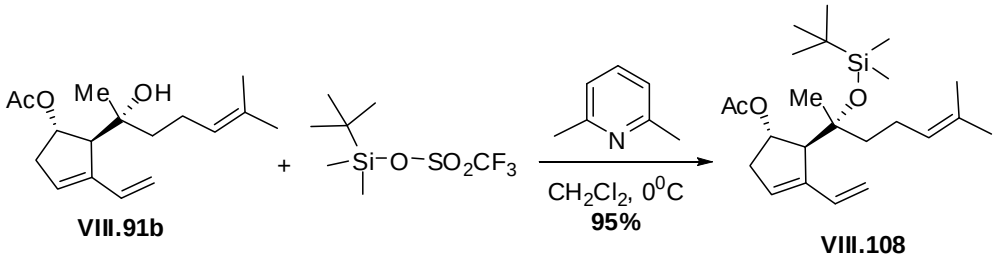
Scheme VIII.51

Triene VIII.91b was subjected to the ring closing metathesis and furnished bicyclic alcohol VIII.107 in quantitative yield (Scheme VIII.52):



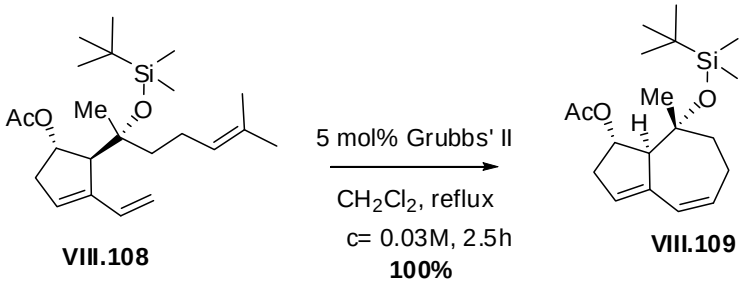
Scheme VIII.52

The long reaction time and the high catalyst loading needed for reaction completion can be due to the presence of the free hydroxyl group on the substrate. In order to use a smaller catalyst loading, the metathesis reaction was carried out on the protected alcohol, prepared according to Scheme VIII.53:



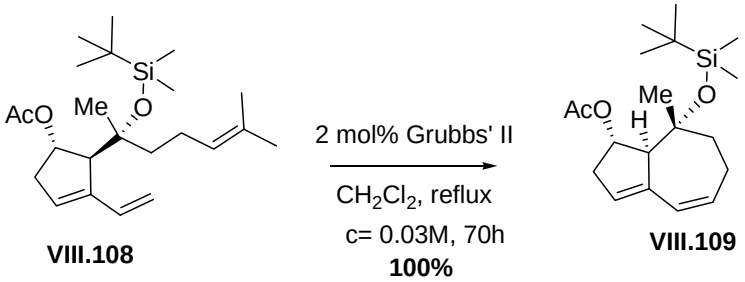
Scheme VIII.53

To our delight, silylated derivative VIII.108 underwent the ring closing metathesis with 5 mol% of Grubbs' II catalyst in refluxing dichloromethane in 2.5h (Scheme VIII.54):



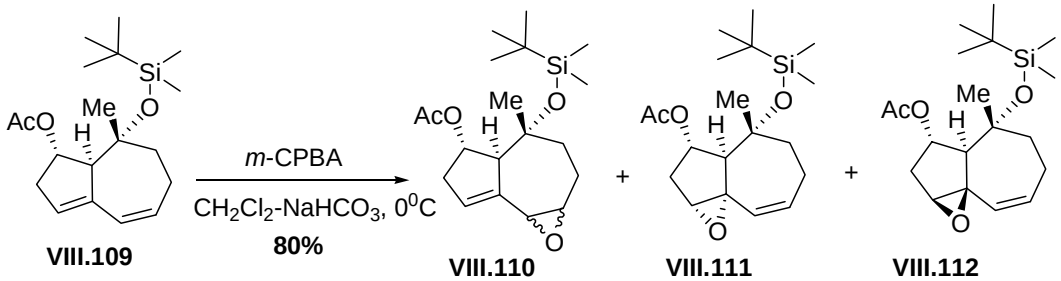
Scheme VIII.54

The same reaction was conducted successfully even with 2% catalyst, but in this case the reaction took longer to complete (Scheme VIII.55):



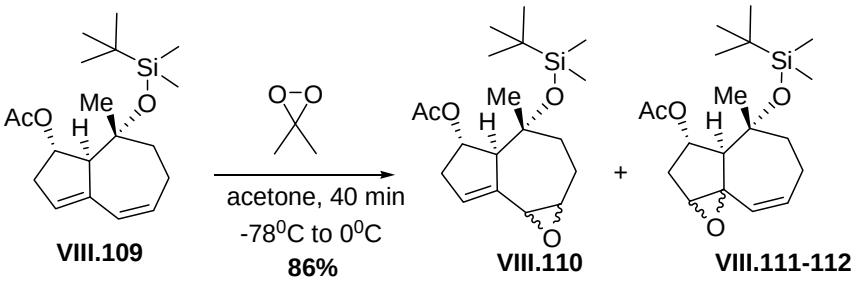
Scheme VIII.55

With the desired bicyclic frame in hand, we next undertook the introduction of the oxygen functionality on the five-membered ring.
By analogy with the results obtained by Hanna and Boyer during the formal synthesis of guanacastepene A,[496] protected bicyclic diol was subjected to epoxidation with *meta*-chloroperbenzoic acid in dichloromethane and saturated aqueous $NaHCO_3$ at 0^0C. We wanted to take advantage of the homoallylic acetate functionality to direct regioselectively the epoxidation to the cyclopentenyl ring.[497] Unfortunately, the epoxidation took place at both double bonds (Scheme VIII.56):[498]



Scheme VIII.56

The epoxidation reaction wasn't regioselective either when dimethyldioxirane was used as reagent in the conditions described by Murray et *al.*[499] affording an inseparable mixture of isomers (Scheme VIII.57):

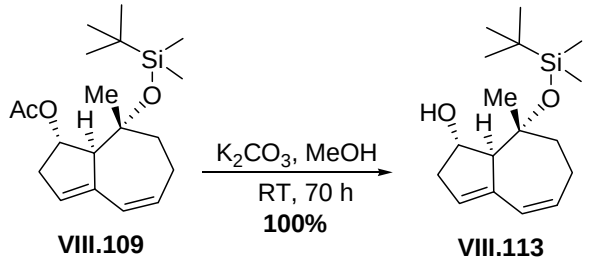


Scheme VIII.57

We next turned our attention to the hydroxyl-directed metal catalyzed epoxidation of homoallylic alcohols.[500] Olefinic alcohols are epoxidized with regio- and stereocontrol by

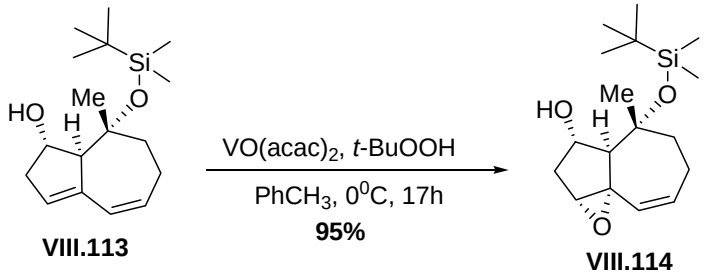
[496] a) Boyer, F.-D.; Hanna, I.; Ricard, L. *Org. Lett.* **2004**, *6*, 1817; b) Boyer, F.-D.; Hanna *J. Org. Chem*. **2005**, *70*, 1077
[497] a) For a review on substrate-directed reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307; b) Mousseron-Canet, M.; Labeeuw, B.; Lanet, J.-C. *Bull. Soc. Chim. Fr.* **1968**, 2125
[498] Product ratio determined by ^{1}H-RMN of the crude reaction mixture
[499] Murray, R. W.; Pillay, M. K.; Jeyaraman, R. *J. Org. Chem*. **1988**, *53*, 3007
[500] For a review on substrate-directed reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307

TBHP in the presence of either $MoO(CO)_6$ or $VO(acac)_2$.[501] Allylic, homoallylic, and even bishomoallylic alcohols are substantially more reactive toward epoxidation by $VO(acac)_2$/TBHP than are the analogues lacking a hydroxyl group. In cyclic systems, high levels of *syn* stereoselectivity are observed, consistent with oxygen atom transfer within an intramolecular complex.[502]
In order to favour the epoxidation at the cyclopentenyl ring taking advantage of the directing effect of a free hydroxyl group, the acetate group was hydrolyzed to afford alcohol VIII.113 (Scheme VIII.58):



Scheme VIII.58

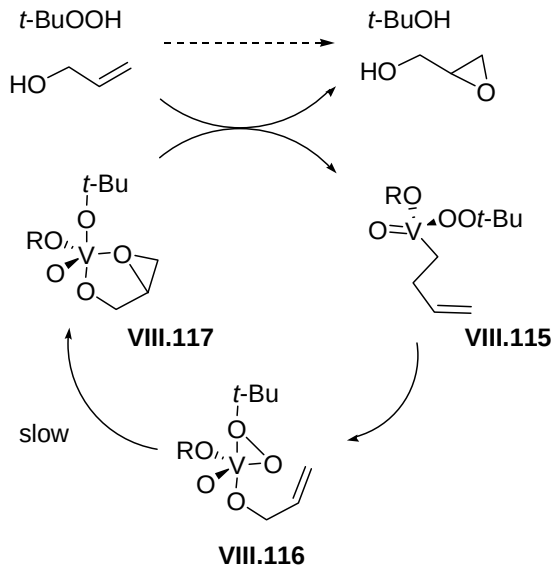
To our delight, alcohol VIII.13 underwent selective epoxidation at the double bond of the 5-membered cycle in the presence of a catalytic quantity of vanadyl acetylacetonate and *tert*-butyl hydroperoxide in toluene at 0^0C (Scheme VIII.59):[503]



Scheme VIII.59

Although a detailed mechanistic pathway for these metal-catalyzed epoxidations has not been elucidated, based on the available data, Sharpless et *al.* has proposed that the vanadium-catalyzed reaction proceeds through the cycle depicted in Scheme VIII.60 in the case of allylic alcohols.[500]

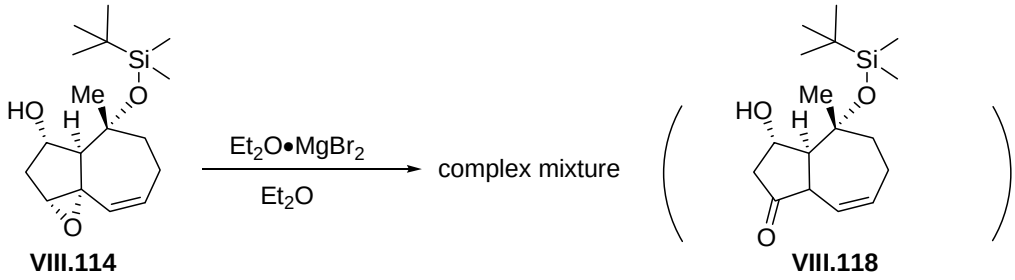
[501] Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136
[502] Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63
[503] Kato, T.; Aoki, M.; Uyehara, T. *J. Org. Chem.* **1987**, *52*, 1803



Scheme VIII.60

The lower-valent $VO(acac)_2$ complex is oxidized by TBHP to a catalytically active d^0 vanadate ester ($VO(OR)_3$),[504] which undergoes rapid ligand exchange[505] to provide VIII.15. Following activation of the alkylperoxide by bidentate coordination (VIII.116, Scheme VIII.60), nucleophilic attack by the alkene in the rate- and stereochemistry-determining step yields the epoxy alcohol complex VIII.117.

The next envisaged step consisting of the epoxide opening reaction to afford the desired ketone VIII.118. (Scheme VIII.61) in the presence of a Lewis acid gave a complex mixture of products:



Scheme VIII.61

Unfortunately we couldn't find the appropriate conditions to run efficiently the opening of the epoxide to ketone VIII.118.

[504] For kinetic and spectroscopic evidence for rapid formation of vanadateesters, $VO(OR)_3$, upon treatment of $VO(acac)_2$ withTBHP in alcoholic solvents, see: Cenci, S.; Di Furia, F.; Modena, G.; Curci, R.; Edwards, J. O. *J. Chem. Soc., Perkin Trans. 2* **1978**, 979

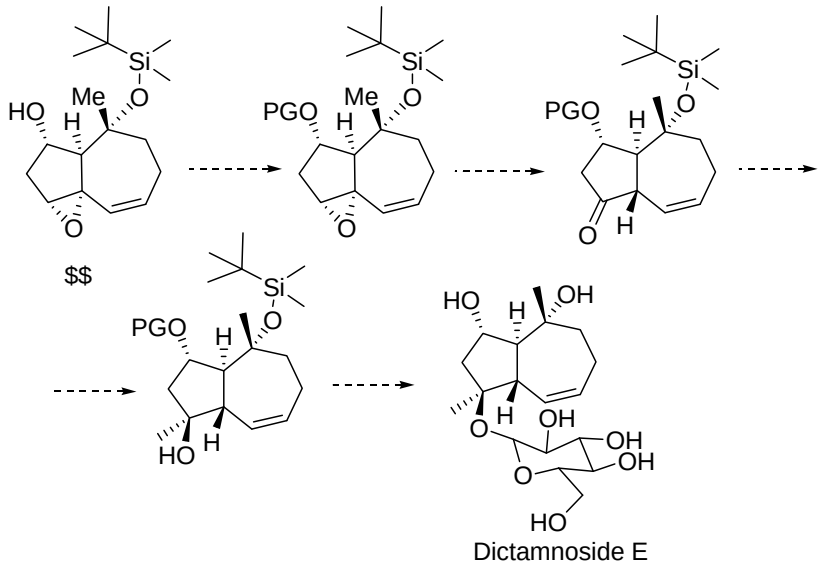
[505] White, P. J.; Kaus, M. J.; Edwards, J. O.; Rieger, P. H. *J. Chem. Soc., Chem. Commun.* **1976**, 429

VIII.10. Conclusion and Perspectives

In conclusion, we have developed an efficient stereoselective gold(I) catalyzed 5-*endo* hydroxy- and alkoxycyclization of 1,5-enynes that provides access to functionalized cyclopentenes. Combination with the powerful RCM reaction furnishes even more complex structures.

An interesting perspective would be the use of other type nucleophiles in this transformation, for example nitrogenated ones like amines or carbonated ones.

It would be also of synthetic interest to find the appropriate experimental conditions to conduct the last 3 steps in the synthesis of Dictamnoside E: to find the appropriate conditions to the epoxide ring opening in order to obtain ketone VIII.118, which afterwards could be subjected to methylation with methyl lithium and etherification with the sugar moiety (Scheme VIII.62):



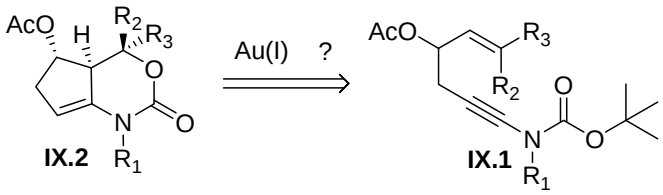
Scheme VIII.62

IX. Gold(I)-catalyzed [4+2] Cycloaddition of *N*-(Hex-5-enynyl) *tert*-butyloxycarbamates

This work was done in collaboration with Florin-Marian Istrate, Xavier F. Le Goff, Yann Odabachian and Dr. Fabien Gagosz.[506]

IX.1. Introduction

As discussed in detail in Chapter IV, the chemistry of electron-deficient ynamines and ynamides received considerable attention during the past ten years. Such a growing interest may be explained by the fact that these reactive species are easily accessible and possess a high synthetic potential (see Chapter IV for synthetic methods and reactivity). As a consequence, a wide variety of methodologies have been developed involving ynamines, and ynamides, affording a wide range of cyclic and acyclic nitrogen containing structures.
Following our recent success in the chemistry of ynamides,[219] we became interested in the gold(I)-catalyzed synthesis of bicyclic oxazinones of type IX.2 by cyclisation of the *N*-Boc protected ynamines such as IX.1 (Scheme IX.1). This isomerisation could be regarded as a synthetically useful extension of one of our previously reported transformations concerning the alkoxycylisation of 1,5-enynes (see Chapter VIII).[386] Oxazinones of this type can be considered as precursors of protected 1,3 amino-alcohols or 1,3 amino-acids (Scheme IX.4).



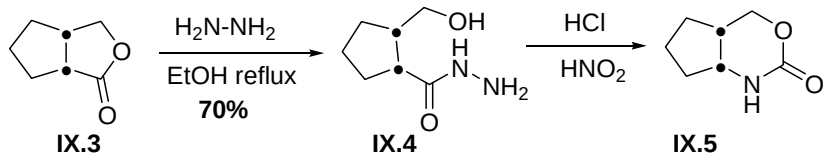
Scheme IX.1

Surprisingly, there are only a few documented synthetic methods in the literature to access this type of bicyclic oxazinones.

IX.2. Synthetic Methods Leading to the Bicyclic Oxazinone Skeleton

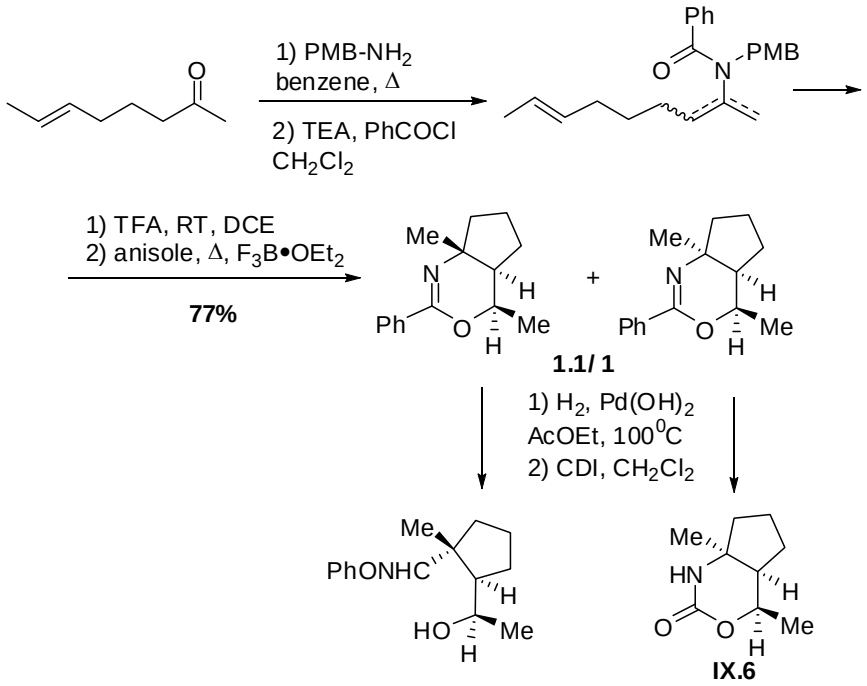
The first synthesis of 2-oxa-4-azabicyclo[4.3.0]nonan-3-one was reported by Cope and LeBel. This method started from the cyclopentane-*cis*-1,2-dicarboxylic anhydride IX.3, which was converted *via* the hydrazide IX.4 and a Curtius degradation to the cyclic urethane IX.5 (Scheme IX.2):[507]

[506] Buzas A.; Istrate, F.; Le Goff, X. F.; Odabachian, Y.; Gagosz, F. *J. Organomet. Chem.* **2008**, asap
[507] Cope, A. C.; LeBel, N. A. *J. Am. Chem. Soc.* **1960**, *82*, 465



Scheme IX.2

Weinreb et *al.* prepared bicyclic carbamide IX.6 by hetero-Diels-Alder cycloaddition of *N*-acylimines derived from acyclic ketones and hydrogenolysis followed by treatment of the resulting amino alcohol with 1,1'-carbonyldiimidazole (Scheme IX.3):[508]

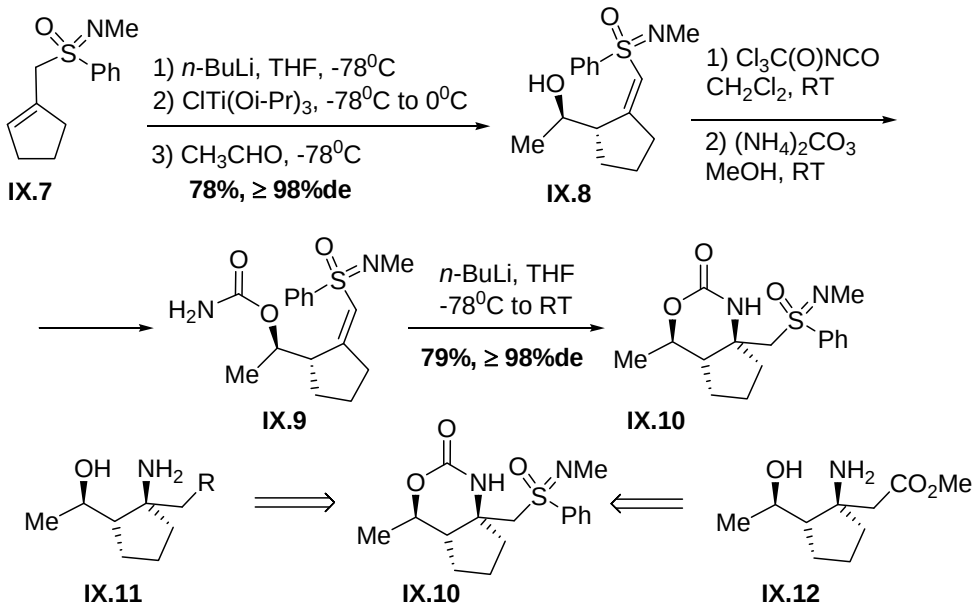


Scheme IX.3

Gais and co-workers described the synthesis of bicyclic derivative IX.10 by lithiation of the *S*-phenylsulfoximine derivative followed by the treatment of the lithiated allyl sulfoximines with 2.1 equiv of ClTi(O*i*-Pr)$_3$. This reaction furnished the corresponding *bis*(allyl)-titanium complexes admixed with ClTi(O*i*-Pr)$_3$. This complex reacted with acetaldehyde with high regioselectivities and good diastereoselectivities at the *γ*-position and afforded the homoallylic alcohol IX.8. This alcohol furnished carbamate IX.9 by reaction with trichloroacetyl isocyanate and subsequent hydrolysis (Scheme IX.4).[509] It is important to note that the obtained bicyclic carbamates are precursors for the synthesis of *β*-aminoalcohols IX.11 or disubstituted *β*-aminoacids IX.12.

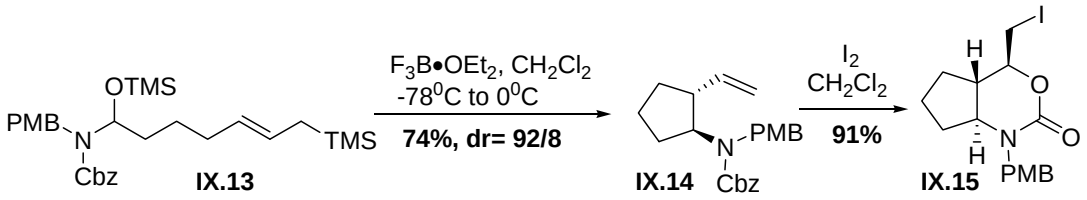
[508] Chao, W.; Waldman, J. H.; Weinreb, S. M. *Org. Lett.* **2003**, *5*, 2915

[509] a) Gais, H.-J.; Loo, R.; Roder, D.; Das, P.; Gerhard Raabe, G. *Eur. J. Org. Chem.* **2003**, 1500; b) Adrien, A.; Gais, H.-J.; Köhler, F.; Runsink, J.; Raabe, G. *Org. Lett.* **2007**, *9*, 2155; c) Köhler, F.; Gais, H.-J.; Runsink, J.; Raabe, G. *Org. Lett.* **2007**, *9*, 1231



Scheme IX.4

Iodocarbamate IX.15 was synthesized by stereoselective halolactonisation of cyclopentylamine IX.14, obtained by a reaction of intramolecular amidoalkylation of the *N*,*O*-acetal TMS ether IX.13 (Scheme IX.5):[510]



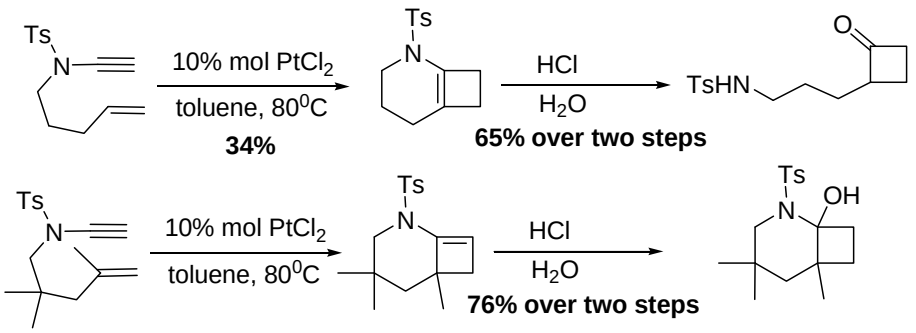
Scheme IX.5

IX.3. Preliminary Work in the Literature. Our Synthetic Approach

As also discussed briefly in Chapter IV, ynamides substituted with electron-withdrawing groups were successfully employed in platinum[285] (Scheme IX.6) or gold-catalyzed cycloisomerisations.

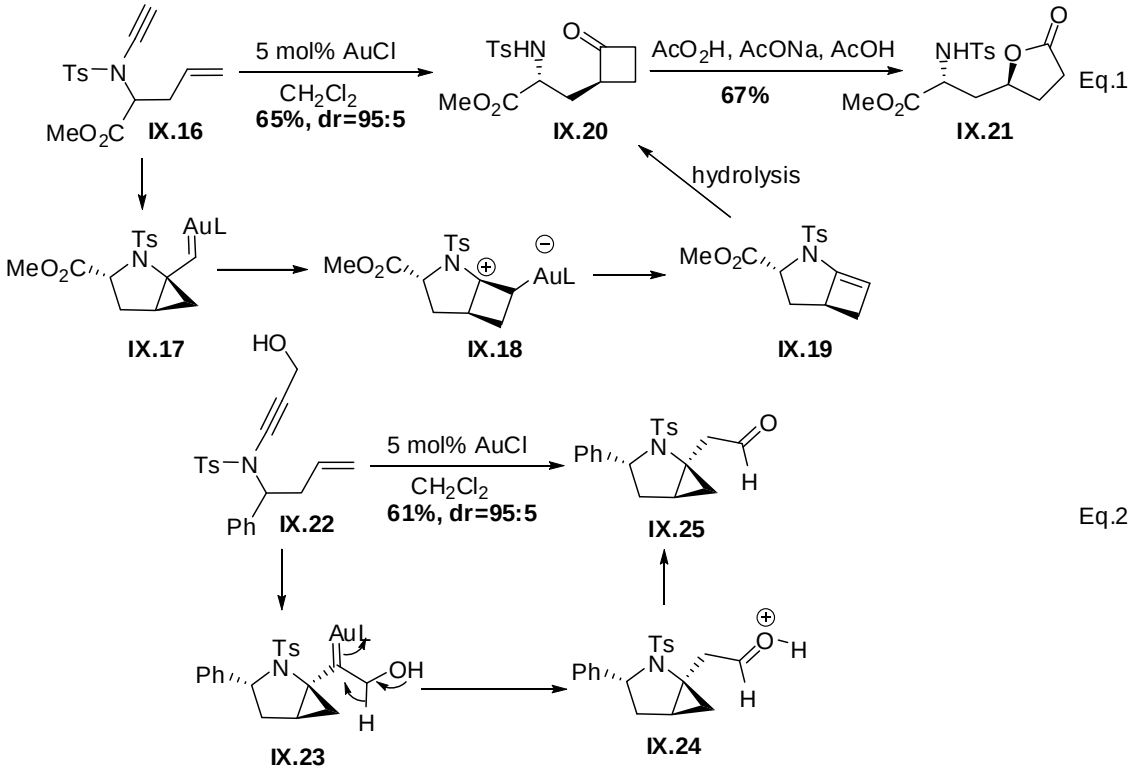
Malacria and co-workers found that tosylynamides underwent cycloisomerisation in the presence of $PtCl_2$ leading to bicyclic nitrogenated heterocycles which can be hydrolyzed to give various cyclobutanone derivatives (Scheme IX.6):[285]

[510] Jung, J.-W.; Shin, D.-Y.; Seo, S.-Y.; Kim, S.-H.; Paek, S.-M.; Jung, J.-K.; Suh, Y.-G. *Tet. Lett.* **2005**, *46*, 573



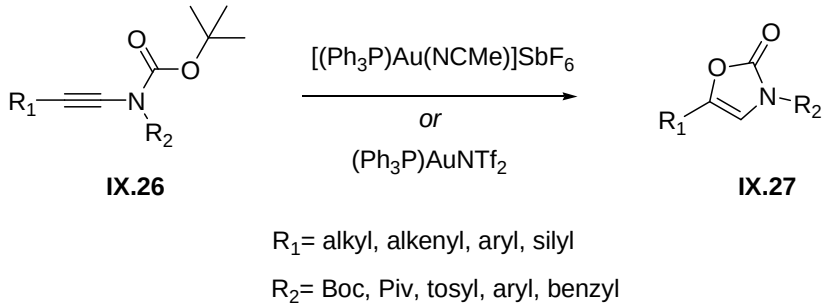
Scheme IX.6

The first study in the field of gold catalyzed transformations involving ynamides was made by Cossy and colleagues who described the diastereoselective gold(I)-catalyzed cycloisomerization of ene-ynamides into substituted cyclobutanones or 2-azabicylco[3.1.0]hexanes depending on the substitution pattern.[286] The authors suggested that ynamides underwent a diastereoselective formal [2+2] cycloaddition through cyclopropyl gold carbenoid IX.17 to give cyclobutene intermediate IX.19. Upon exposure to atmospheric moisture, cyclobutene IX.19 was hydrolyzed to cyclobutanone IX.20, a precursor of a functionalized γ-lactone IX.21 *via* a Baeyer–Villiger oxidation (Scheme IX.7, Eq. 1). With a propargylic alcohol in substrate IX.22, the 1,2-hydride shift is more facile than the cyclopropyl ring expansion, thereby affording cyclopropyl aldehyde IX.25 with a 95:5 diastereoselectivity (Scheme IX.7, Eq. 2).



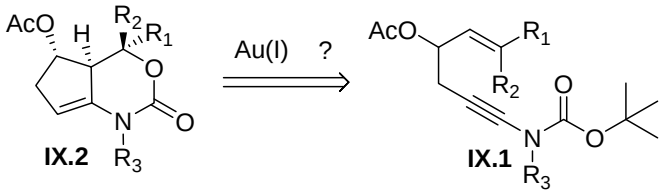
Scheme IX.7

More recently, the group of Hashmi[262]and our group[219] independently reported that *N*-alkynyl *tert*-butylcarbamates IX.26 could be converted in the presence of a gold(I) complex into a range of functionalized oxazolones IX.27 (Scheme IX.8 and see also chapter IV).



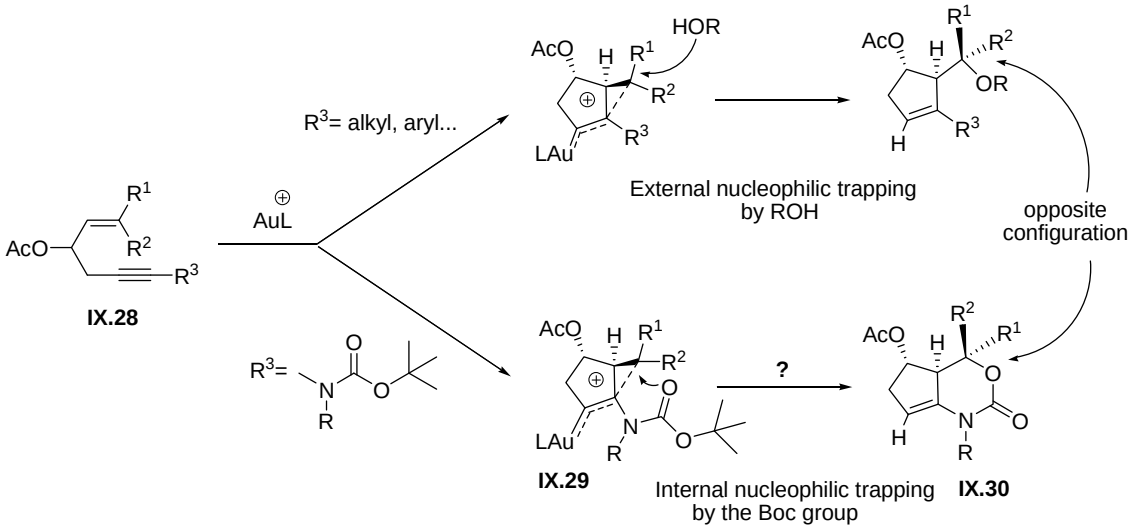
Scheme IX.8

Following our recent success in the chemistry of ynamides,[219] we became interested in the gold(I)-catalyzed synthesis of bicyclic oxazinones of type IX.2 by taking advantage of the Boc functionality in *N*-hex-5-enynyl *tert*-butylcarbamates IX.1 (Scheme IX.9).



Scheme IX.9

We indeed recently reported the cycloisomerisation of enynes of type IX.28 in the presence of an oxygenated nucleophile to stereoselectively furnish cyclopentenes (Scheme IX.10, upper equation). The formation of an intermediate cyclopropyl gold(I) species which is regio- and stereoselectively opened by an external nucleophile was postulated (see Chapter VIII).[386]

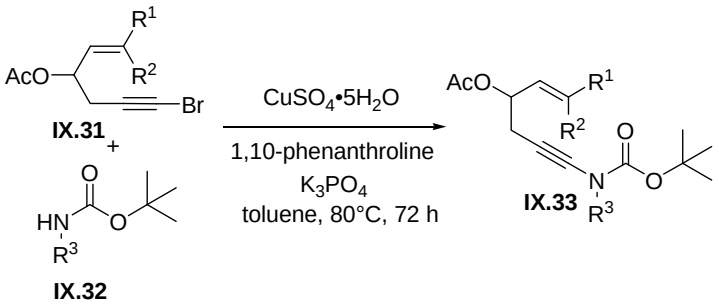


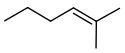
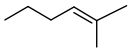
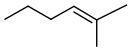
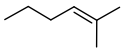
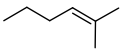
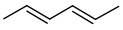
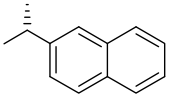
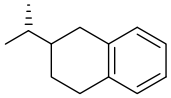
Scheme IX.10

By analogy with this transformation, we surmised that substrates of type IX.28 possessing an ynamide functionality could generate an analogous cyclopropyl gold species IX.29 in the presence of a gold(I) complex (Scheme IX.10). The *tert*-butylcarbonate moiety could act as an internal nucleophile to stereoselectively open the cyclopropyl ring. This would lead to the formation of the bicyclic compound IX.30 in which the stereochemistry of one of the new stereocentres would have been inverted by comparison with the previously reported transformation. Furthermore, the enamide functionality still present in the cycloisomerized products would be particularly useful to effect further transformations such as reduction, hydration or oxidation.

IX.4. Synthesis of the Precursors

Starting materials for the gold-catalyzed cycloisomerisation were prepared in two steps following the procedure previously reported by our group for the synthesis of ynamides (see also Chapter IV).[219] Treatment of bromoalkynes IX.31 and *tert*-butylcarbonate IX.32 (1.2 equiv.) with $CuSO_4 \cdot 5H_2O$ (20 mol%), 1,10-phenanthroline (40 mol%) and K_3PO_4 (1.2 equiv.) in toluene at 80°C for 72 hours led to the formation of the desired *N*-alkynyl *tert*-butylcarbamates IX.33 (Table IX.1):



Entry	R^1, R^2 Alkyne		R^3, Amine		Product	Yield[a]
1	R^1=Me, R^2= Me	IX.31a	R^3=Bn	IX.32a	IX.33a	69%
2	R^1=Me, R^2= Me	IX.31b	R^3=Me	IX.32b	IX.33b	16%
3	R^1=Me, R^2= Me	IX.31c	R^3=CH_2CO_2Et	IX.32c	IX.33c	31%
4	R^1= Me, R^2= 	IX.31d	R^3=Bn	IX.32d	IX.33d	45%
5	R^1= Me, R^2= 	IX.31e	R^3=Me	IX.32e	IX.33e	37%
6	R^1= Me, R^2= 	IX.31f	R^3=CH_2CO_2Et	IX.32f	IX.33f	63%
7	R^1=  , R^2= Me	IX.31g	R^3=Bn	IX.32g	IX.33g	61%
8	R^1=  , R^2=Me	IX.31h	R^3=Me	IX.32h	IX.33h	38%
9	R^1=  , R^2= Me	IX.31i	R^3=Me	IX.32i	IX.33i	43%
10	R^1=Ph, R^2=H	IX.31j	R^3=Bn	IX.32j	IX.33j	31%
11	R^1=Me, R^2= Me	IX.31k	R^3=	IX.32k	IX.33k	25%
12	R^1=Me, R^2= Me	IX.31l	R^3=	IX.32l	IX.33l	29%
13	R^1=Me, R^2= Me	IX.31m	R^3= 	IX.32m	IX.33m	68%
14	R^1=Me, R^2= Me	IX.31n	R^3= 	IX.32n	IX.33n	19%

[a] Isolated yields

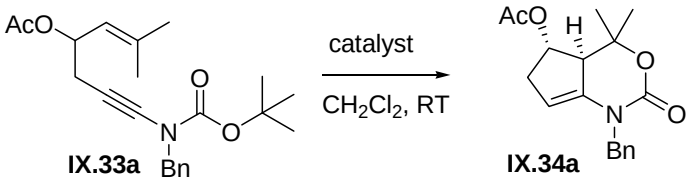
Table IX.1

IX.5. Gold(I)-Catalyzed [4+2] Cycloaddition of N-(Hex-5-enynyl) tert-butylcarbamates

With *tert*-butyl 4-acetoxy-6-methylhept-5-en-1-ynylbenzylcarbamate IX.33a as model substrate in hands, we proceeded to the cycloisomerisation step. To this end, substrate IX.33a was treated with 1 mol% of the crystalline and air stable $Ph_3PAuNTf_2$ gold complex[100] in dichloromethane at room temperature. Delighfully, the desired bicyclic compound IX.34a was isolated in 68% yield.

IX.5.1. Optimisation of the Catalytic System

The use of biphenylphosphine based gold complex VII.79 as catalyst enabled to increase the yield to 78%, although the reaction time was longer in this case:



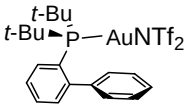
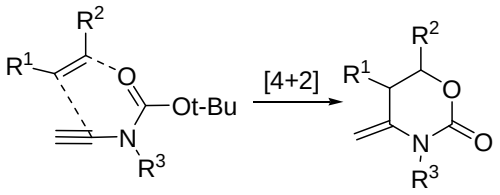
Catalyst		Time	Yield
1 mol%	$Ph_3PAuNTf_2$	30 min	**68%**
1 mol%	 **VII.79**	1 h	**78%**

Table IX.2

IX.5.2. Scope of the Transformation

This new cycloisomerisation can be considered as a formal [4+2] cycloaddition of an *N*-alkynyl *tert*-butylcarbamate with an alkene (Scheme IX.11).[511] Hence it presents a great potential from a synthetic point of view, two cycles and one new stereocentre being assembled from linear substrates under mild reaction conditions.

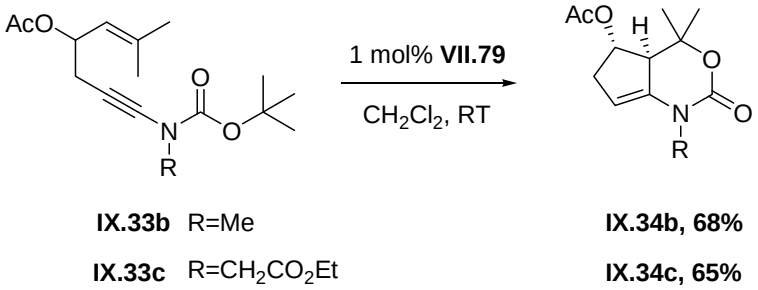
[511] For gold catalyzed [4+2] cycloadditions of polyenynes, see: a) Nieto-Oberhuber, C.; Péres-Galan, P.; Herreo-Gomez, E.; Lautenbach, T.; Rodriguez, C.; Lopez, S.; Bour, C.; Rosellon, A.; Cardenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 269; b) Nieto-Oberhuber, C.; Lopez, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178; c) Fürstner, A.; Stimson, C. C. *Angew. Chem. Int. Ed.* **2007**, *46*, 8845; For [4+2] cycloadditions involving furans, see: d) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 11553; e) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *Org. Lett.* **2002**, *4*, 3769; f) Hashmi, A. S. K.; Rudolph, M.; Weyrauch, J. P.; Wölfle, M.; Frey, W.; Bats, J. W. *Angew. Chem. Int. Ed.* **2005**, *44*, 2798



Scheme IX.11

Interestingly, it is worth to mention that the previously reported 5-*endo* cyclization of the *tert*-butylcarbamate on the alkyne (Scheme IX.8) [219, 262]did not significantly compete with this new transformation. The nucleophilic addition of the alkene moiety on the activated gold-alkyne complex seems to be a more favored process and only traces of oxazolones of type IX.27 could be observed.

First we focused on the variation of the substituents on the nitrogen atom. To this end, *N*-alkynyl *tert*-butylcarbamates possessing a methyl or an ester group were prepared according to the procedure described (Table IX.1). The cycloisomerisation proved to be compatible with these substrates: enynes IX.33b and IX.33c bearing either a methyl group or an ester group reacted comparably under the same reaction conditions to afford bicyclic compounds IX.34b and IX.34c in respectively 68% and 65% yield (Scheme IX.12):



Scheme IX.12

As also documented in our previous report,[386] the reactions were highly stereoselective, leading to the formation of single isomers. NMR analysis and X-ray crystallography of compound IX.34b confirmed the *cis* relationship between the acetoxy group and the hydrogen at the ring junction (Figure IX.1):[512]

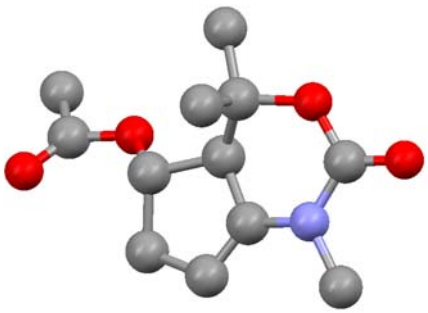
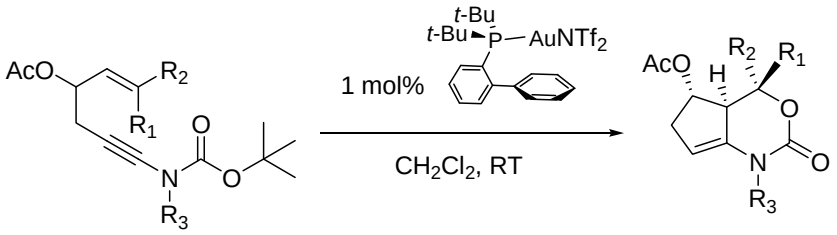
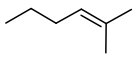
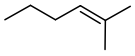


Figure IX.1

[512] Hydrogen atoms are omitted for clarity

Next, we turned our attention to the substituents on the double bond. Gratifyingly, the reaction could also be applied to substrates possessing diversely substituted alkenes. A complete transfer of the chiral information from the *cis* or *trans* alkene to the final product was observed in the case of enynes *Z*-IX.33g-h and *E*-IX.33d-e with the stereoselective formation of two new contiguous stereocenters (Scheme IX.13). Nitrogenated bicycles IX.34d-e, g-h were thus obtained as single isomers in yields ranging from 56 to 63%.



R_1= Me, R_2= 	R_3=Bn	***E*-IX.33d**	**IX.34d**	**63%**
	R_3=Me	***E*-IX.33e**	**IX.34e**	**61%**
R_1=  , R_2= Me	R_3=Bn	***Z*-IX.33g**	**IX.34g**	**57%**
	R_3=Me	***Z*-IX.33h**	**IX.34h**	**56%**

Scheme IX.13

The relative configuration of the new stereocentres were determined by NMR analysis and confirmed by X-ray crystallography of compound IX.34d and IX.34g (Figures IX.2 and IX.3):[513]

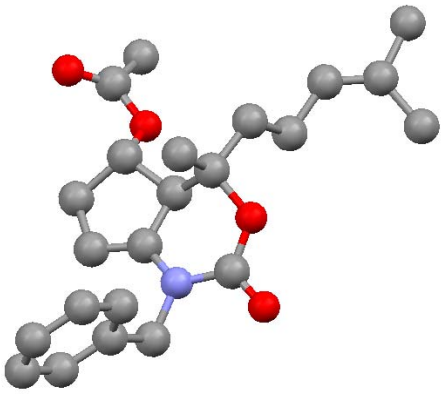


Figure IX.2

[513] Hydrogen atoms are omitted for clarity

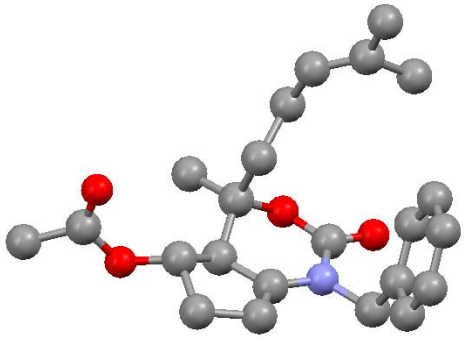
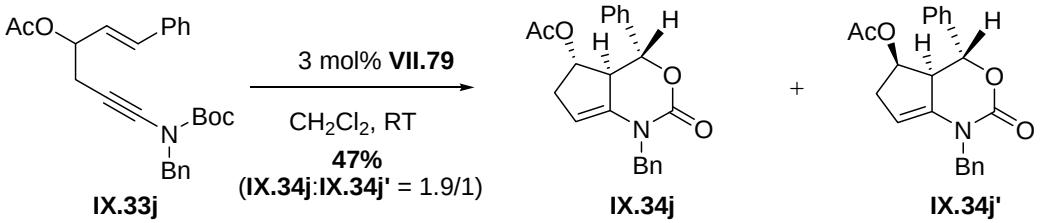


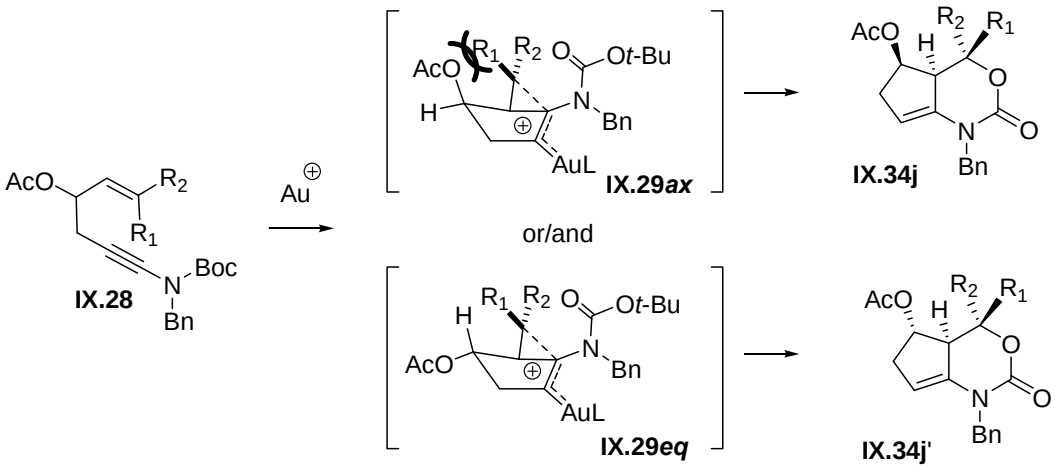
Figure IX.3

This formal [4+2] cycloaddition could also be equally well performed with monosubstituted alkenes, as attested by the reaction of cinnamaldehyde derivative IX.33j (Scheme IX.14). A diastereoisomeric mixture of compounds IX.34j and IX.34j' was obtained, the reaction being less stereoselective in this case.



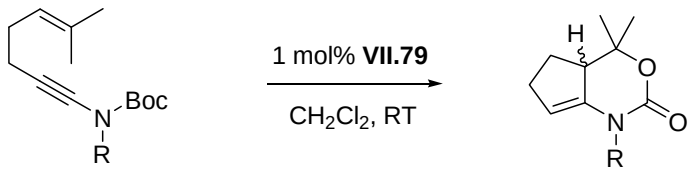
Scheme IX.14

When the trisubstituted alkene (R^1, $R^2 \neq H$) was employed as substrate, the transformation was stereospecific due to a strong steric interaction between the acetoxy group and R^1 which disfavored the formation of an intermediate such as IX.29*ax*. The diminished selectivity observed in the monosubstituted case (R^1=H) can be explained by the lack of a similar interaction since it allows the competitive formation of two intermediate cyclopropyl gold carbenes of types IX.29*ax* and IX.29*eq* (Scheme IX.15):

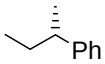
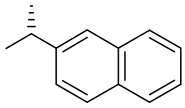
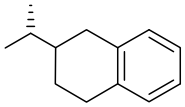


Scheme IX.15

Finally, an attempt to develop an asymmetric version of this gold-catalyzed cycloisomerisation was made. We envisaged an induction of stereoselectivity by the presence of a chiral fragment on the nitrogen atom of substrates IX.33k-m. Nevertheless, the results were highly disappointing since bicyclic compounds IX.34k-m were obtained in moderate yields (41-53%) with a very poor selectivity (Scheme IX.16):



IX.33k-m **IX.34k-m**

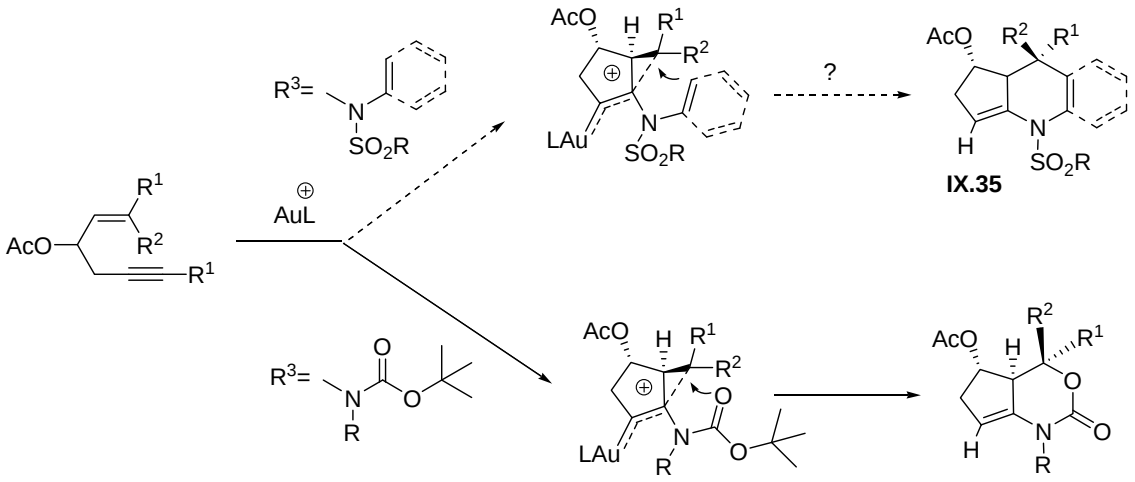
R=		
	IX.33k	**IX.34k**, **43%** (dr= 1:1.3)
	**IX.33l**	**IX.34l**, **41%** (dr= 1:1.2)
	**IX.33m**	**IX.34m, 41%** (dr= 1:1.4)
	**IX.33m**	**IX.34m, 53%** (dr= 1:1.25)

Scheme IX.16

IX.6. Conclusion and Perspectives

In summary, we have shown that functionalized bicyclic carbamates can be obtained by the cycloisomerisation of *N*-(hex-5-enynyl) *tert*-butylcarbamates under mild conditions by using a gold(I) complex as the catalyst. This transformation can be regarded as a formal [4+2] cycloaddition between an *N*-alkynyl *tert*-butylcarbamate and an alkene. The transformation is generally strereoselective and allows a rapid increase in structural complexity with the formation of two cycles and up to two new asymmetric centers, even if the yields are moderate (41-78%).

An interesting extension would be the trapping of intermediate cyclopropyl gold species IX.29 by another internal nucleophile like an enamine or aromatic double bond. This approach would anable the synthesis of polycyclic heterocycles such as IX.35 (Scheme IX.17):


AcO
R1
R2
R1
AuL
R3=
N
SO2R
AcO
H
R1
R2
LAu
N
SO2R
?
AcO
R2
R1
H
N
SO2R
IX.35
R3=
N
R
O
O
AcO
H
R1
R2
O
LAu
N
R
O
AcO
H
R2
R1
O
H
N
R
O

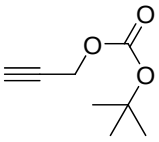
Scheme IX.17

EXPERIMENTAL SECTION

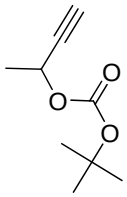
LIST OF COMPOUNDS DESCRIBED IN THE EXPERIMENTAL PART

II. Gold(I)-Catalyzed Formation of 5-Methylene-dioxolan-2-ones

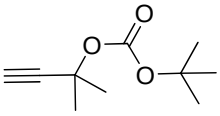
This work was done in collaboration with Florin-Marian Istrate and Dr. Fabien L. Gagosz. For the sake of clarity and in order to preserve the coherence of the subject, the totality of the work was discussed in the theoretical part (see Chapter II, page 49), but here only the experiments performed by the author of this manuscript will be presented.



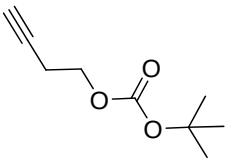
II.32, p. 313



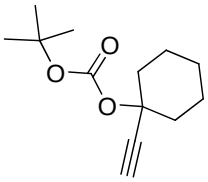
II.35a, p. 314



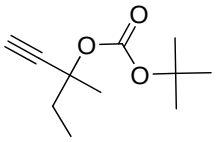
II.35h, p.314



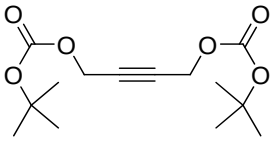
II.74, p. 314



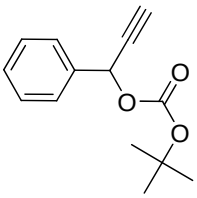
II.35.j, p. 315



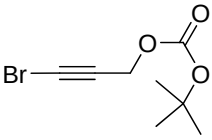
II.35i, p. 315



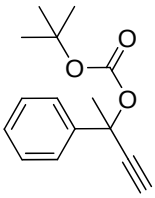
II.37b, p. 316



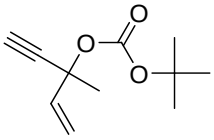
II.35f, p. 316



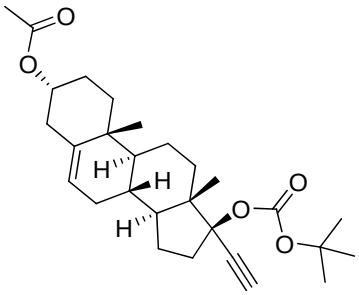
II.58, p. 317



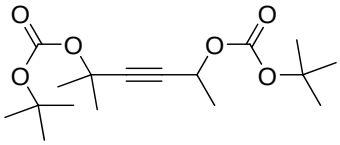
II.35l, p. 317



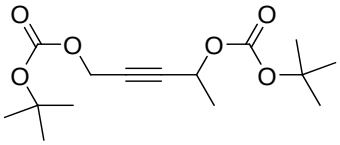
II.35m, p. 318



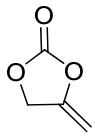
II.35k, p. 319



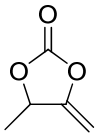
II.37d, p.319



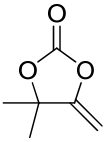
II.37c, p.320



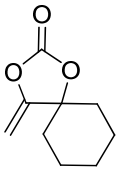
II.33, p. 321



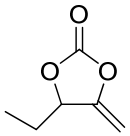
II.36a, p. 321



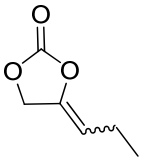
II.36h, p. 322



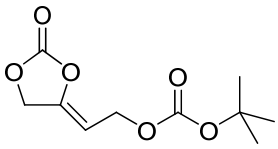
II.36j, p. 322



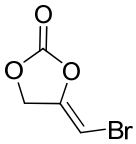
II.38f, p. 323



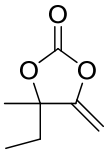
II.39, p. 323



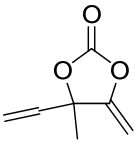
II.38c, p. 324



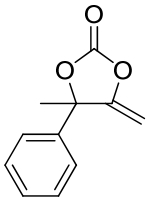
II.59, p. 324



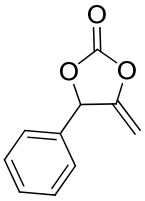
II.36i, p. 325



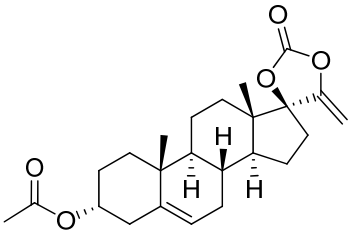
II.36m, p. 325



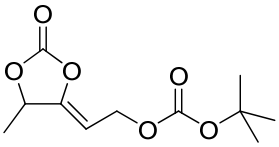
II.36l, p. 326



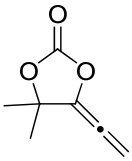
II.36f, p. 326



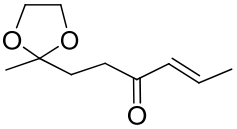
II.36k, p. 327



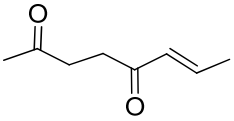
II.38c, p. 328



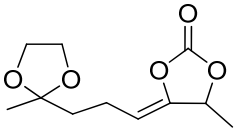
II.38d, p. 328



II.40, p. 329

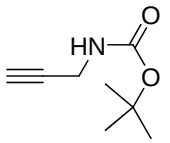


II.41, p. 329

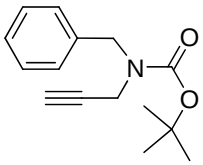


II.42, p. 330

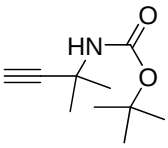
III.Gold(I)-Catalyzed Formation of 5-Methylene-oxazolidin-2-ones



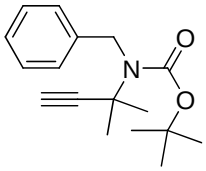
III.45, p. 331



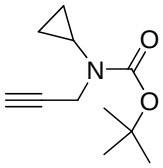
III.43a, p. 332



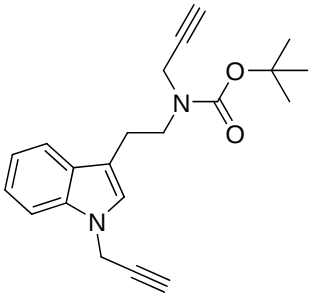
III.43b, p. 332



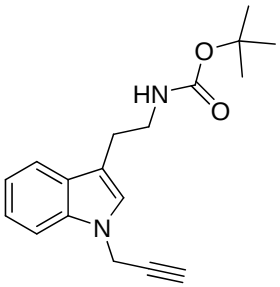
III.43c, p. 333



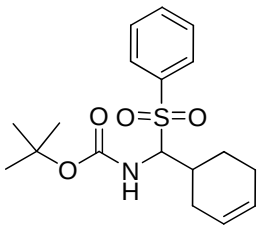
III.43e, p. 333



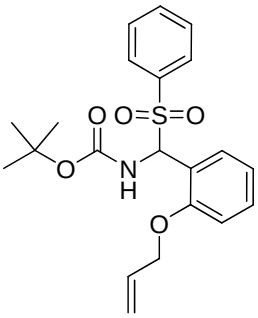
III.53, p. 334



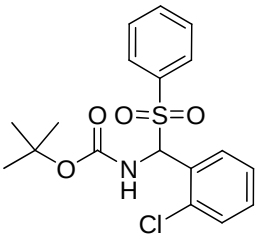
III.52, p. 335



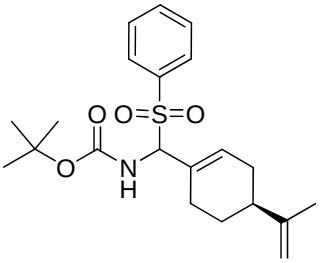
III.56h, p. 335



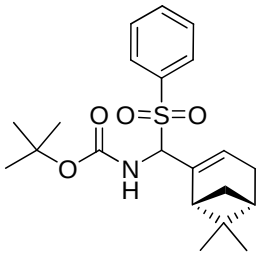
III.56m, p. 336



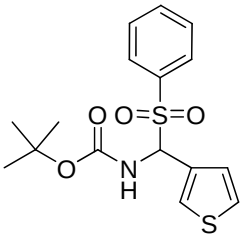
III.56k, p. 337



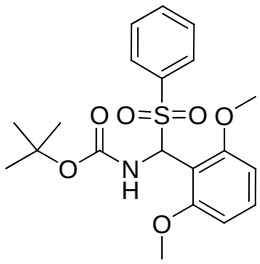
III.56i, p. 337



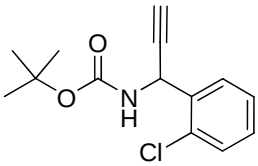
III.56j, p. 338



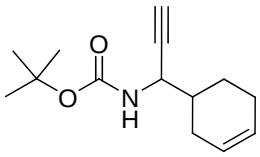
III.56n, p. 338



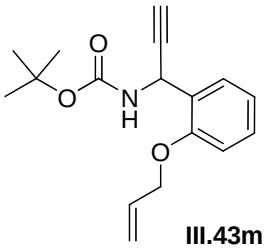
III.56l, p. 339



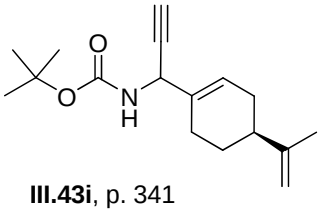
III.43k, p. 340



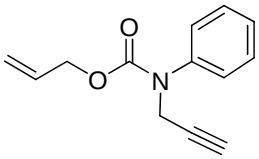
III.43h, p. 340



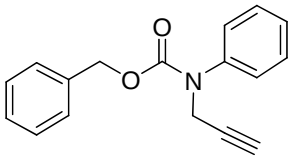
III.43m, p. 341



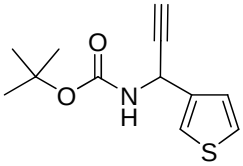
III.43i, p. 341



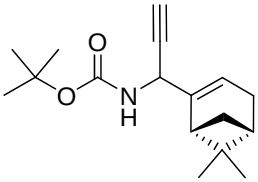
III.48, p. 342



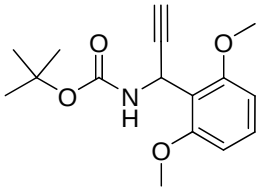
III.49, p. 342



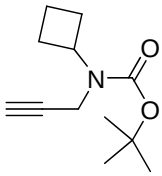
III.43n, p. 343



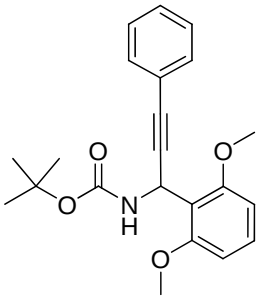
III.43j, p. 344



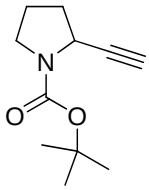
III.43l, p. 344



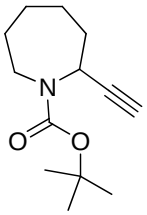
III.43f, p. 345



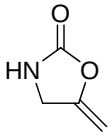
III.43lbis, p. 346



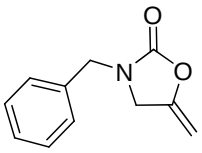
III.43o, p. 346



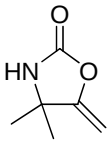
III.43q, p. 347



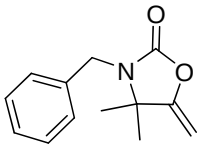
III.45bis, p. 348



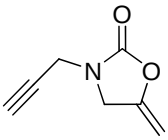
III.44a, p. 349



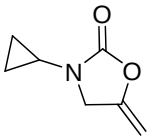
III.44b, p. 350



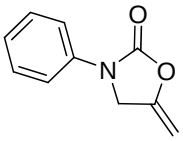
III.44c, p. 350



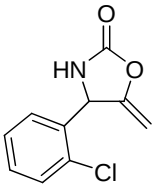
III.44g, p. 350



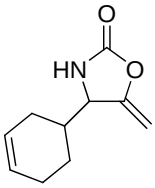
III.44e, p. 351



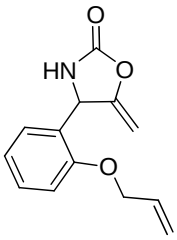
III.44d, p. 351



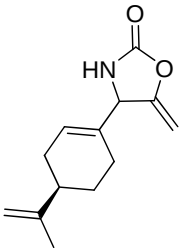
III.44k, p. 352



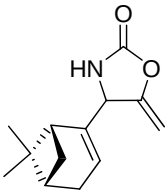
III.44h, p. 352



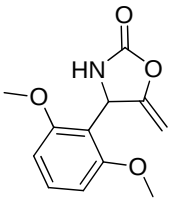
III.44m, p. 353



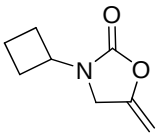
III.44i, p. 354



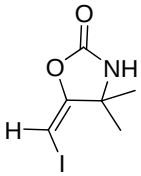
III.44j, p. 354



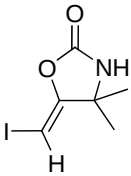
III.44l, p. 355



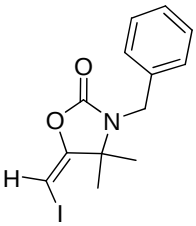
III.44f, p. 355



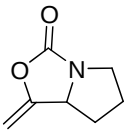
***Z*-III.68**, p. 356



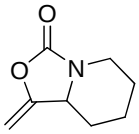
***E*-III.68**, p. 356



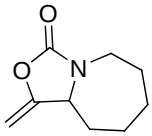
III.67, p. 357



III.44o, p. 358



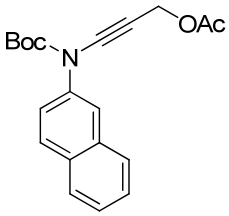
III.44p, p. 358



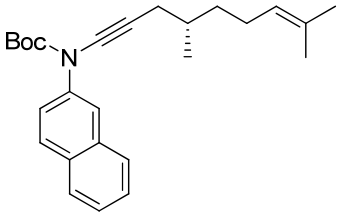
III.44q, p. 358

IV. Synthesis of Functionalized Oxazolones by a Sequence of Cu(II)- and Au(I)-Catalyzed Transformations

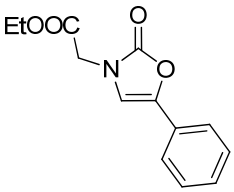
This work was done in collaboration with Florin-Marian Istrate, Igor Dias Jürberg, Yann Obadachian and Dr. Fabien L. Gagosz. For the sake of clarity and in order to preserve the coherence of the subject, the totality of the work was discussed in the theoretical part (see Chapter IV, page 116), but here only the experiments performed by the author of this manuscript will be presented.



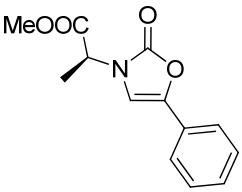
IV.48p, p. 360



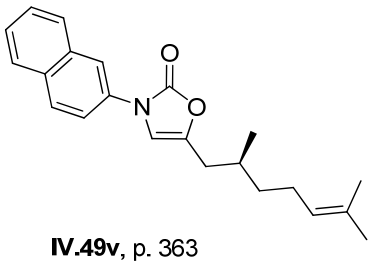
IV.48v, p. 360



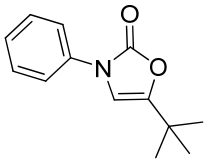
IV.49g, p. 362



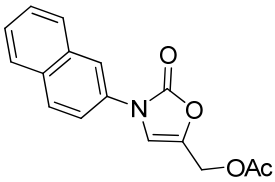
IV.49h, p. 362



IV.49v, p. 363



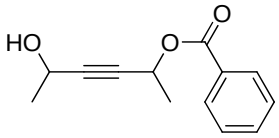
IV.49i, p. 363



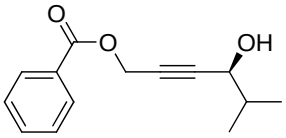
IV.49p, p. 364

V. Gold(I) Catalyzed Stereoselective Formation of Functionalized 2,5-Dihydrofurans

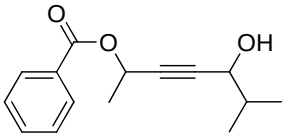
This work was done in collaboration with Florin-Marian Istrate and Dr. Fabien L. Gagosz. For the sake of clarity and in order to preserve the coherence of the subject, the totality of the work was discussed in the theoretical part (see Chapter V, page 149), but here only the experiments performed by the author of this manuscript will be presented.



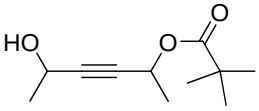
V.63a, p. 365



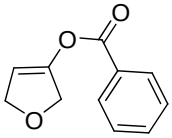
V.66a, p. 366



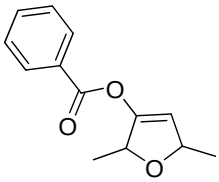
V.63b, p. 366



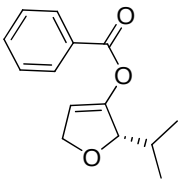
V.68, p. 367



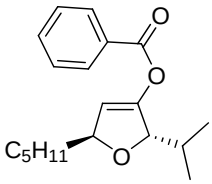
V.62c, p. 368



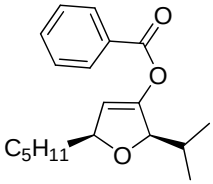
V.64a, p. 368



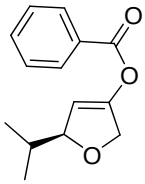
V.67a, p. 369



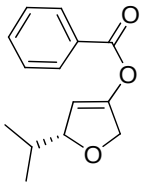
V.67b, p. 369



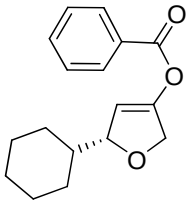
V.67c, p. 370



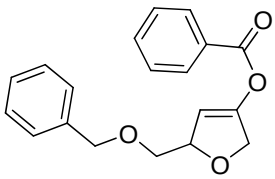
V.67e, p. 370



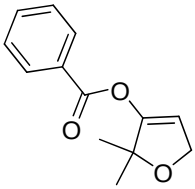
V.67d, p. 371



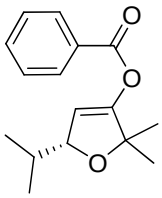
V.67f, p. 371



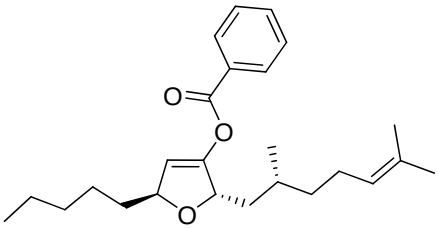
V.64d, p. 372



V.64f, p. 373



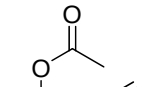
V.67g, p. 373



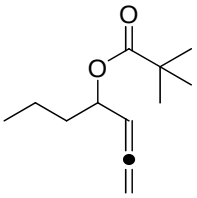
V.67h, p. 374

VI. Gold(I)-Catalyzed Isomerization of Allenyl Carbinol Esters: an Efficient Access to Functionalized 1,3-Butadien-2-ol Esters

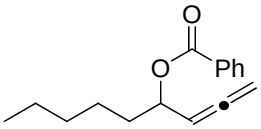
This work was done in collaboration with Florin-Marian Istrate and Dr. Fabien L. Gagosz. For the sake of clarity and in order to preserve the coherence of the subject, the totality of the work was discussed in the theoretical part (see Chapter VI, page 183), but here only the experiments performed by the author of this manuscript will be presented.



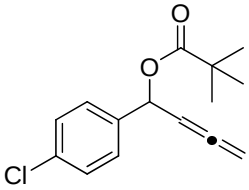
VI.44i, p. 375



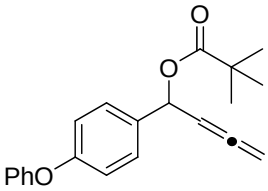
VI.44d, p. 376



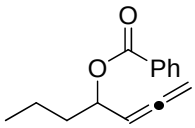
VI.44f, p. 376



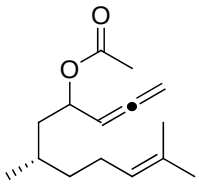
VI.44a, p. 377



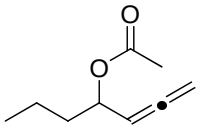
VI.44b, p. 377



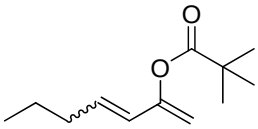
VI.44e, p. 378



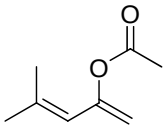
VI.44g, p. 378



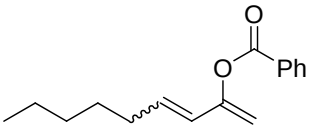
VI.44c, p. 379



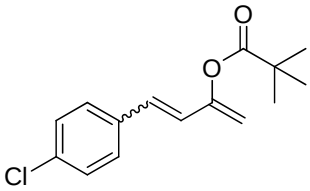
VI.45d, p. 380



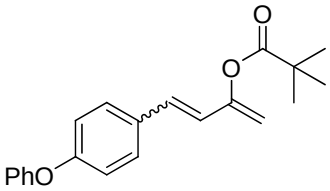
VI.45i, p. 380



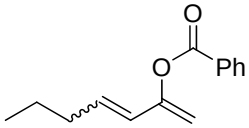
VI.45f, p. 381



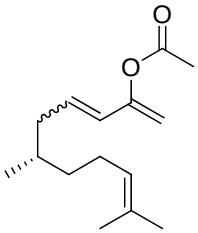
VI.45a, p. 381



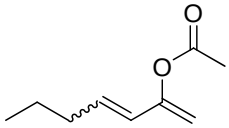
VI.45b, p. 382



VI.45e, p. 382



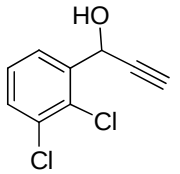
VI.45g, p. 383



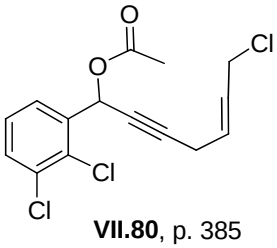
VI.45c, p. 383

VII. Gold(I) Catalyzed Isomerization of 5-en-2-yn-1-yl Acetates: an Efficient Access to Acetoxy Bicyclo[3.1.0]hexenes and 2-Cycloalken-1-ones

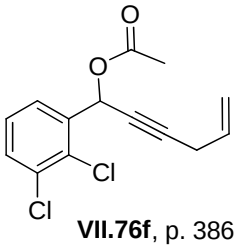
This work was done in collaboration with Dr. Fabien L. Gagosz. For the sake of clarity and in order to preserve the coherence of the subject, the totality of the work was discussed in the theoretical part (see Chapter VII, page 204), but here only the experiments performed by the author of this manuscript will be presented.



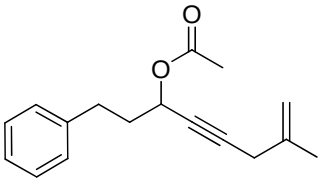
VII.94, p. 385



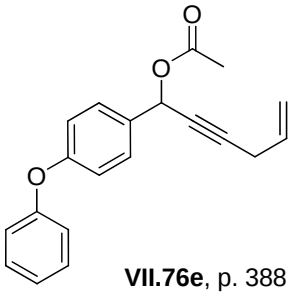
VII.80, p. 385



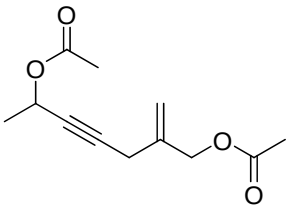
VII.76f, p. 386



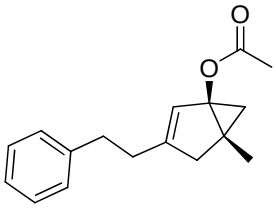
VII.76g, p. 387



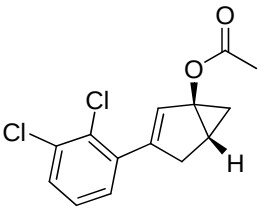
VII.76e, p. 388



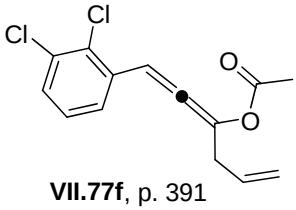
VII.76h, p. 389



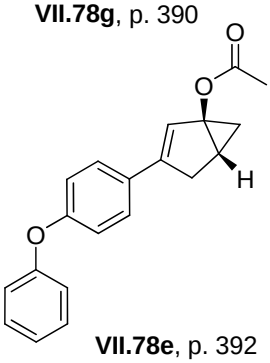
VII.78g, p. 390



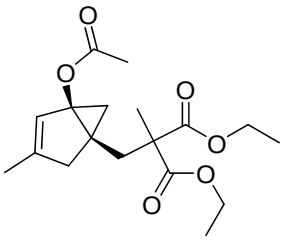
VII.78f, p. 391



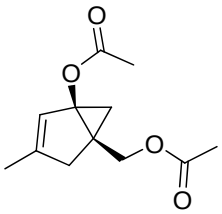
VII.77f, p. 391



VII.78e, p. 392



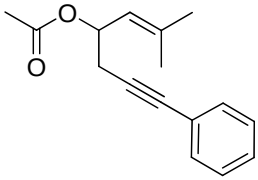
VII.78i, p. 392



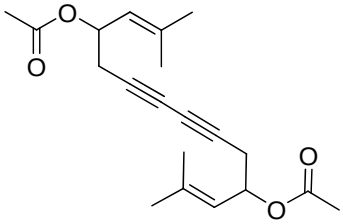
VII.78h, p. 393

VIII. Gold(I)-Catalyzed 5-endo Hydroxy- and Alkoxy-Cyclization of 1,5-enynes: an Efficient Access to Functionalized Cyclopentenes

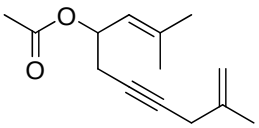
This work was done in collaboration with Florin-Marian Istrate and Dr. Fabien L. Gagosz. For the sake of clarity and in order to preserve the coherence of the subject, the totality of the work was discussed in the theoretical part (see Chapter VIII, page 240), but here only the experiments performed by the author of this manuscript will be presented.



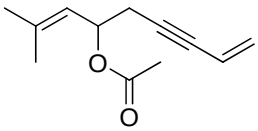
VIII.75, p. 395



VIII.75bis, p. 396



VIII.87b, p. 397



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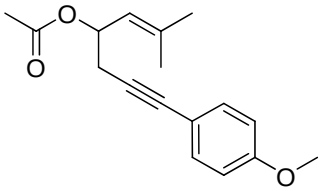
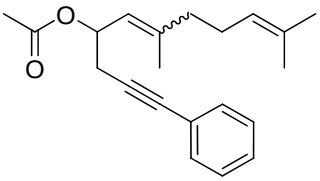


VIII.87j, p. 398



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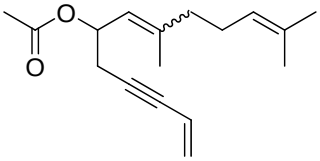

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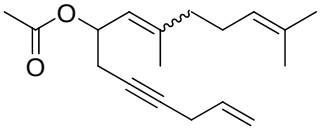

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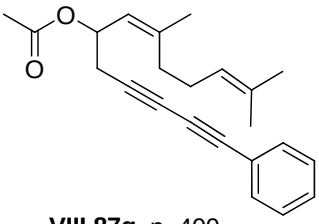

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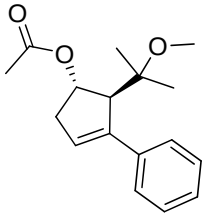

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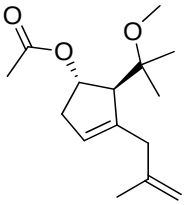

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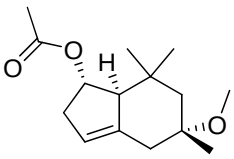

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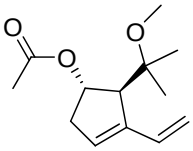

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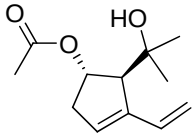

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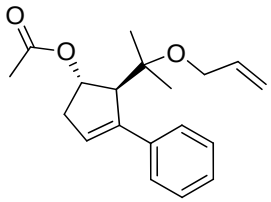

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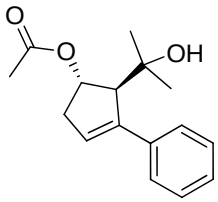

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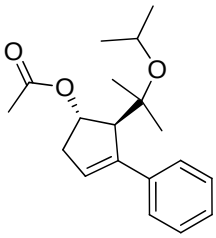

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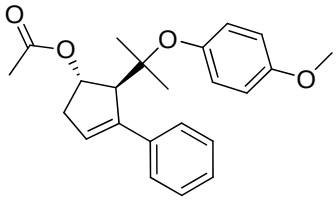

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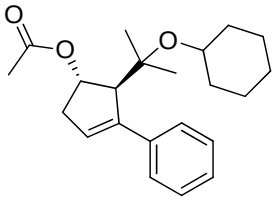

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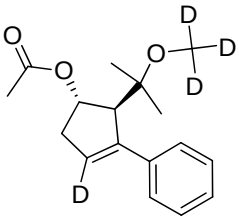

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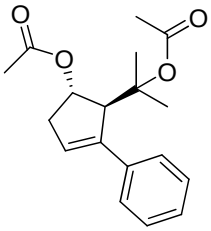

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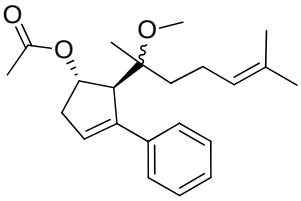

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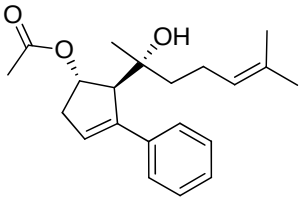

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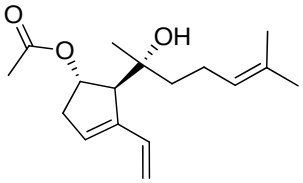

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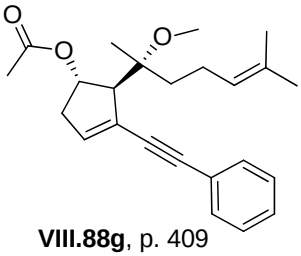

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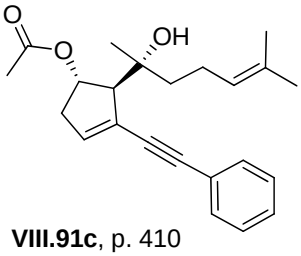

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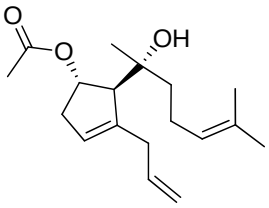

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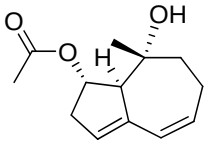

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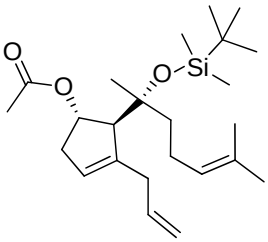

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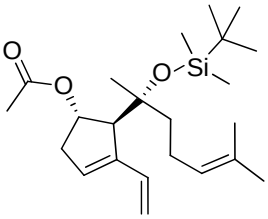

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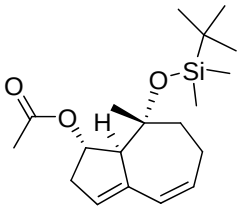
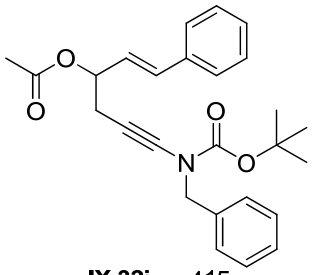


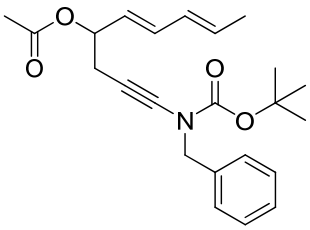
VIII.109, p. 413

IX. Gold(I)-Catalyzed [4+2] Cycloaddition of *N*-(Hex-5-enynyl) *tert*-butyloxycarbamates

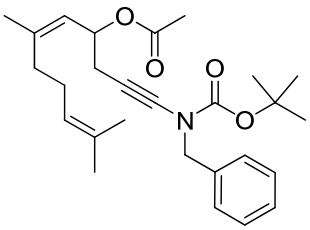
This work was done in collaboration with Florin-Marian Istrate, Yann Obadachian, Xavier Le Goff and Dr. Fabien L. Gagosz. For the sake of clarity and in order to preserve the coherence of the subject, the totality of the work was discussed in the theoretical part (see Chapter IX, page 285), but here only the experiments performed by the author of this manuscript will be presented.



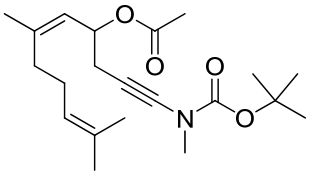
IX.33j, p. 415



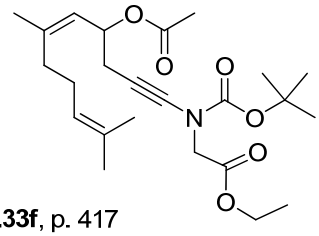
IX.36, p. 415



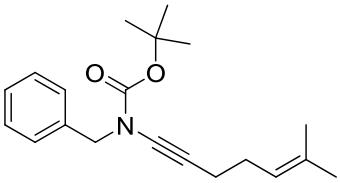
IX.33d, p. 416



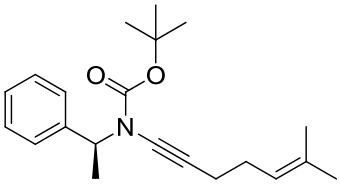
IX.33e, p. 417



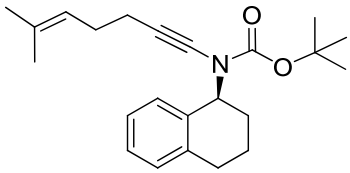
IX.33f, p. 417



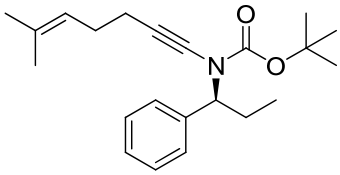
IX.37, p. 418



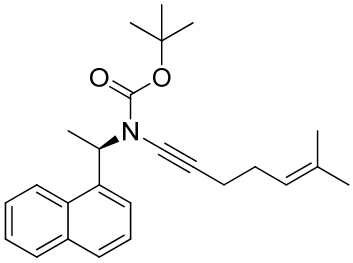
IX.33k, p. 418



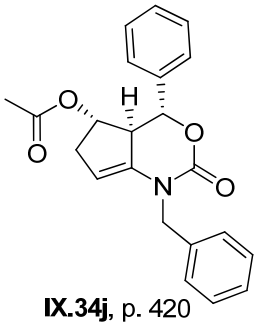
IX.33n, p. 419



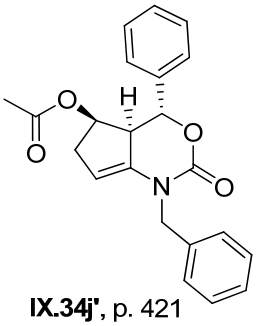
IX.33l, p. 419



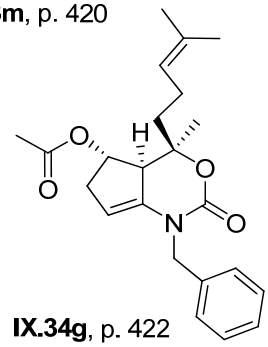
IX.33m, p. 420



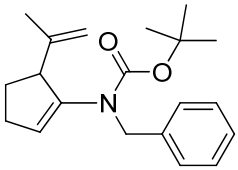
IX.34j, p. 420



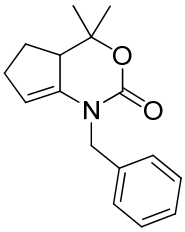
IX.34j', p. 421



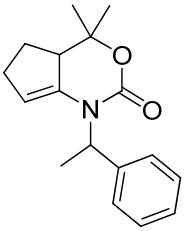
IX.34g, p. 422



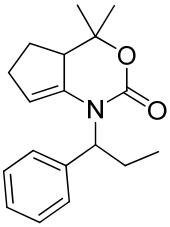
IX.34gbis, p. 422



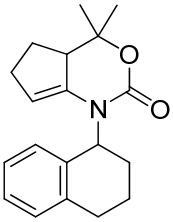
IX.37bis, p. 423



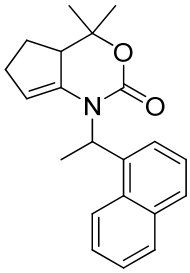
IX.34k, p. 423



IX.34l, p. 424



IX.34n, p. 425



IX.34m, p. 425

General Methods

Commercially available **reagents** were used as purchased without further purification.

All **reaction solvents** correspond to SDS "pure for analysis" solvents and were used as purchased, with the exception of dry Et_2O and THF, which were obtained by distillation from Na/benzophenone and of dry CH_2Cl_2 and toluene from CaH_2. **Solvents for flash chromatographies** correspond to the SDS "pure for synthesis" solvents and were used as purchased. The same goes for **HPLC solvents**, which correspond to the SDS HPLC grade.

All non-aqueous reactions were performed under dry Ar or N_2 atmosphere using standard syringe-cannula/septa techniques, unless specified otherwise.

Concentration under reduced pressure was performed by rotary evaporation at room temperature using a water jet pump. Purified compounds were further dried on a high vacuum pump. Finally, the name of the synthesized compounds was determined according to the CAS nomenclature using the Beilstein AutoNom 2000, version 4.01.305.

Thin-layer chromatographies (**TLC**) were performed on Merck Silica Gel 60 F_{254} plates (aluminium plates coated with silica gel 60). They were visualized under UV light at 254 or 366 nm, then stained using $KMnO_4$ or anisaldehyde solution. **$KMnO_4$ solution** was prepared from 600 mL of water, 6 g $KMnO_4$, 40 g K_2CO_3 and 0.5 mL concentrated acetic acid. **Anisaldehyde solution** was prepared from 26 mL p-anisaldehyde, 950 mL ethanol 95%, 35 mL concentrated sulfuric acid and 10.5 mL concentrated acetic acid.

Flash chromatographies were done on SDS 60 CC 40-63 silica gel (pore size 60 Å, particle size 40-63 μm) using a forced flow of eluent at 0.1–0.5 bar pressure.

High pressure liquid chromatography (HPLC) analyses were performed on a Waters LC Module I Plus fitted with a chiral analytical column Chiralcel OD-H (amylose tris (3,5-dimethylphenyl carbamate) on a substrate of silica gel (5μm), lenght 150 mm, interior diameter 4.6 mm).

NMR spectra were recorded on a Bruker Avance 400 operating at 400 MHz for ^1H and at 100 MHz for ^{13}C.

In **^1H NMR** chemical shifts (δ) are expressed in ppm using tetramethylsilane (δ=0 ppm) or the residual peak of the solvent (δ=7.27 ppm in the case of chloroform). Coupling constants (J) are given in Hertz (Hz).

En **^{13}C NMR**, chemical shifts (δ) are expressed in ppm taking the solvent peak (δ=77 ppm in the case of the middle peak of the chloroform) as an internal reference.

IR spectra were recorded with a Perkin Elmer FT-1600 spectrophotometer. Oil or solid samples were dissolved in carbon tetrachloride, and then placed in a sodium chloride cell. The spectra values are reported as absorption maxima and expressed in cm^{-1}.

Mass spectra (**MS**) were recorded on a Hewlett Packard HP-5890 B using electron ionization (EI^+) or chemical ionization with ammonia (CI^+, NH_3) methods. Fragment signals are given as a mass-to-charge ratio (m/z).

High resolution mass spectra (**HRMS**) were recorded on a Jeol GCmate II spectrometer using electron ionization (EI^+) method.

All analyses were performed at the DCSO Laboratory (Laboratoire de Synthèse Organique) of Ecole Polytechnique.

II. Gold(I)-Catalyzed Formation of 5-Methylene-dioxolan-2-ones

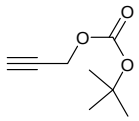
II.1. Synthesis and Characterisation of Propargylic tert-butylcarbonates

Propargylic *tert*-butylcarbonates were generally synthesized from the corresponding propargylic alcohol and *di-tert*-butyl dicarbonate following the two general methods Method II.1.a.[145a] and Method II.1.b[145b] described in the literature.
Bromoalkyne was synthesized by bromination of the corresponding alkyne with NBS.[146]

Method II.1.a. In a typical reaction, the propargylic alcohol (1 equiv.) was dissolved in dichloromethane (3.725 M concentration) containing *di-tert*-butyl dicarbonate (1.2 equiv.) and a catalytic amount of tetrabutyl ammonium hydrogen sulfate (0.03 equiv.). After cooling to 0°C, ice-cold 30 % aqueous sodium hydroxide was added with vigorous stirring. After consumption of all propargylic alcohol (reaction monitored by TLC), the organic phase was diluted with dichloromethane, washed with a saturated brine solution, then dried over anhydrous magnesium sulfate. After evaporation of the solvent, the product was purified over a silica gel column using ethyl acetate or diethyl ether and petroleum ether as eluting solvents.

Method II.1.b. To a solution of propargylic alcohol (1 equiv.) in acetonitrile, *di-tert*-butyl dicarbonate (2.5 equiv.) and a catalytic amount of DMAP (0.122 equiv.) were added. The resulted solution was stirred at room temperature under N_2 until the consumption of all propargylic alcohol (reaction monitored by TLC). The resulted crude was concentrated *in vacuo* then extracted with diethyl ether, washed with a 1M solution of hydrochloric acid, water and saturated brine solution, then dried over anhydrous magnesium sulfate. After evaporation of the solvent, the crude was purified over a silica gel column using ethyl acetate or diethyl ether and petroleum ether as eluting solvents.

***tert*-Butyl prop-2-ynyl carbonate**	**II.32**

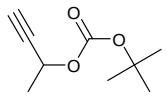


MF: $C_8H_{12}O_3$

MW = 156.17 g.mol^{-1}

Reaction:	Prepared according to **Method II.1.a.**
Purification :	Flash column chromatography (silica gel, PE/AcOEt 90/10 to 80/20).
Product :	Emulsion.
Yield :	80 %
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	4.66 (d, J = 2.45 Hz, 2H, C***H***$_2$), 2.49 (t, J = 2.47 Hz, 1H, ***H***C≡), 1.50 (s, 9H, C(C***H***$_3$)$_3$).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	152.5, 82.4, 77.2, 75.0, 53.9, 27.3.
IR (ν, cm^{-1}) (CCl_4)	3293, 2982, 2938, 1809, 1745.
MS (CI, NH_3, m/z)	157 (MH^+).
HRMS (EI+, m/z) **:**	Calculated for $C_8H_{12}O_3$: 156.0787. Found for $C_8H_{12}O_3$: 156.0783.

***tert*-Butyl but-3-yn-2-yl carbonate**	**II.35a**



MF: $C_9H_{14}O_3$

MW = 170.20 g.mol^{-1}

Reaction: Prepared according to **Method II.1.a.**

Purification : Flash column chromatography (silica gel, PE/Et_2O 95/5).

Product : Pale yellow oil.

Yield : 86 %

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.15 (m, 1H, C***H***), 2.42 (m, 1H, ***H***C≡), 1.42 (m, 12H, C(C***H***$_3$)$_3$ and C***H***$_3$).

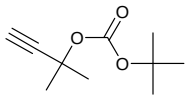
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 152.2 (***C***=O), 82.4 (HC≡***C***$_q$), 81.6 (H***C***≡), 73.2 (***C***H), 62.5 (***C***$_q$), 27.5 (C(***C***H$_3$)$_3$), 21.0 (***C***H$_3$).

IR (ν, cm^{-1}) (CCl_4): 3312, 2984, 2937, 1744 (C=O), 1154, 1313, 1271, 1168, 1101, 1020.

MS (CI, NH_3, m/z): 188, 186, 178, 169, 156 (MH^+).

HRMS (EI+, m/z) **:** Calculated for $C_9H_{14}O_3$: 170.0943.
Found for $C_9H_{14}O_3$: 170.0934.

***tert*-Butyl 2-methylbut-3-yn-2-yl carbonate**	**II.35h**



MF: $C_{10}H_{16}O_3$

MW = 184.23 g.mol^{-1}

Reaction: The reaction was carried out according to **Method II.1.b.**

Purification : Flash column chromatography (silica gel, PE/Et_2O 95/5).

Product : Pale yellow oil.

Yield : 49 %

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 2.55 (s, 1H, ***H***C≡), 1.70 (s, 6H, 2 x C***H***$_3$), 1.50 (s, 9H, C(C***H***$_3$)$_3$).

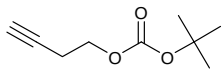
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 151.1 (***C***=O), 99.8 (HC≡***C***$_q$), 84,2 (H***C***≡), 81.8 (***C***$_q$),72.5 (***C***$_q$), 28.6 (C(***C***H$_3$)$_3$), 27.5 (***C***H$_3$).

IR (ν, cm^{-1}) (CCl_4): 3310, 2983, 2937, 1749 (C=O), 1466, 1368, 1282, 1255, 1176, 1128.

MS (CI, NH_3, m/z): 202 (MNH_4^+), 185 (MH^+), 147.

HRMS (EI+, m/z) **:** Calculated for $C_{10}H_{16}O_3$: 184.1100.
Found for $C_{10}H_{16}O_3$: 184.1098.

***tert*-Butyl but-3-ynyl carbonate**	**II.74**



MF: $C_9H_{14}O_3$

MW = 170.20 g.mol^{-1}

Reaction: The reaction was carried out according to **Method II.1.b.**

Purification : Flash column chromatography (silica gel, PE/Et_2O 95/5).

Product : Colourless oil.

Yield : 68 %

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 3.80 (m, 2H, C***H***$_2$), 2.19 (m, 2H, C***H***$_2$), 1.67 (m, 1H, ***H***C≡), 1.12 (m, 9H, C(C***H***$_3$)$_3$).

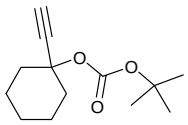
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 152.9 (***C***=O), 81.9 (HC≡***C***$_q$), 81.8 (H***C***≡), 64.2 (***C***H$_2$), 27.4 (C(***C***H$_3$)$_3$), 18.8 (***C***H$_2$).

IR (ν, cm^{-1}) (CCl_4): 3313, 2980, 2933, 1807, 1744 (C=O), 1459, 1390, 1370, 1277, 1167, 1113, 1072.

MS (CI, NH_3, m/z): 188 (MNH_4^+), 171 (MH^+).

HRMS (EI+, m/z) **:** Calculated for $C_9H_{14}O_3$: 170.0943.
Found for $C_9H_{14}O_3$: 170.0946.

tert-Butyl 1-ethynylcyclohexyl carbonate — II.35j



MF: $C_{13}H_{20}O_3$

MW = 224.29 g.mol^{-1}

Reaction: The reaction was carried out according to **Method II.1.b.**

Purification : Flash column chromatography (silica gel, PE/Et_2O 95/5).

Product : White crystalline solid.

Yield : 88 %

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 2.60 (s, 1H, ***H***C≡), 2.16 (m, 2H, C***H***$_2$), 1.81 (m, 2H, C***H***$_2$), 1.70-1.50 (m, 6H, 3 x C***H***$_2$), 1.47 (s, 9H, C(C***H***$_3$)$_3$).

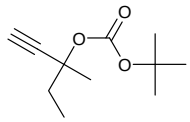
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 151.2 (***C***=O), 83.2 (H***C***≡), 82.0 (HC≡***C***$_q$), 76.5 (***C***(CH$_3$)$_3$), 74.4 (***C***$_q$), 36.8 (***C***H$_2$), 27.8 (C(***C***H$_3$)$_3$), 25.0 (***C***H$_2$), 22.5 (***C***H$_2$).

IR (ν, cm^{-1}) (CCl_4): 3311, 2979, 2938, 2861, 1748 (C=O), 1450, 1367, 1283, 1246, 1163, 1085, 1013.

MS (CI, NH_3, m/z): 242 (MNH_4^+), 225 (MH^+), 186, 181, 163, 143, 126.

HRMS (EI+, m/z) **:** Calculated for $C_{13}H_{20}O_3$: 224.1413.
Found for $C_{13}H_{20}O_3$: 224.1406.

tert-Butyl 3-methylpent-1-yn-3-yl carbonate — II.35i



MF: $C_{11}H_{18}O_3$

MW = 198.25 g.mol^{-1}

Reaction: The reaction was carried out according to **Method II.1.b.**

Purification : Flash column chromatography (silica gel, PE/Et_2O 95/5).

Product : Pale yellow oil.

Yield : 83 %

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 2.56 (s, 1H, ***H***C≡), 2.01 (m, 1H, C***H***$_2$), 1.87 (m, 1H, C***H***$_2$), 1.67 (s, 3H, C***H***$_3$), 1.50 (s, 9H, C(C***H***$_3$)$_3$), 1.04 (t, J = 7.4 Hz, 3H, C***H***$_3$).

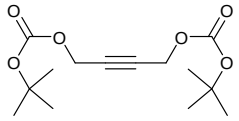
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 151.2 (***C***=O), 83.2 (H***C***≡), 81.7 (HC≡***C***$_q$), 76.3 (***C***(CH$_3$)$_3$), 73.3 (***C***$_q$), 34.0 (***C***H$_2$), 27.6 (C(***C***H$_3$)$_3$), 25.6 (***C***H$_3$), 8.3 (***C***H$_3$).

IR (ν, cm^{-1}) (CCl_4): 3310, 2980, 2937, 2883, 1748 (C=O), 1459, 1370, 1272, 1167, 1147, 1126, 995.

MS (CI, NH_3, m/z): 216 (MNH_4^+), 208, 199 (MH^+), 160, 156, 136.

HRMS (EI+, m/z) **:** Calculated for $C_{11}H_{18}O_3$: 198.1256.
Found for $C_{11}H_{18}O_3$: 198.1262.

Carbonic acid 4-*tert*-butoxycarbonyloxy-but-2-ynyl ester *tert*-butyl ester — II.37b



MF: $C_{14}H_{22}O_6$

MW = 286.32 g.mol^{-1}

Reaction: The reaction was carried out according to **Method II.1.a.**

Purification : Flash column chromatography (silica gel, PE/Et_2O 95/5).

Product : Colourless oil.

Yield : 70 %

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 4.71 (s, 4H, 2 x C***H***$_2$), 1.49 (s, 18H, 2 x C(C***H***$_3$)$_3$).

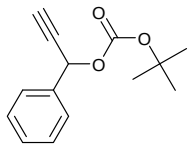
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 152.5 (***C***=O), 82.7 (C≡***C***$_q$), 80.7 (***C***$_q$), 54.2 (***C***H$_2$), 27.5 (C(***C***H$_3$)$_3$).

IR (ν, cm^{-1}) (CCl_4): 2981, 2939, 1747 (C=O),1476, 1454, 1372, 1272, 1153, 1088.

MS (CI, NH_3, m/z): 304 (MNH_4^+), 248, 231, 192.

HRMS (EI+, m/z) **:** Calculated for $C_{14}H_{22}O_6$: 286.1416.
Found for $C_{14}H_{22}O_6$: 286.1426.

tert-Butyl 1-phenylprop-2-ynyl carbonate — II.35f



MF: $C_{14}H_{16}O_3$

MW = 232.10 g.mol^{-1}

Reaction: The reaction was carried out according to **Method II.1.b.**

Purification : Flash column chromatography (silica gel, PE/Et_2O 95/5).

Product : Pale yellow oil.

Yield : 97 %

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.58-7.55 (m, 2H, 2 x C***H***$_{Ar}$), 7.42-7.33 (m, 3H, 3 x C***H***$_{Ar}$), 6.27 (d, J = 2.2 Hz, 1H, ***H***C), 2.71(d, J = 2.3 Hz, 1H, ***H***C≡), 1.51 (m, 9H, C(C***H***$_3$)$_3$).

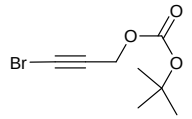
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 152.3 (***C***=O), 136.1 (***C***$_{qAr}$), 128.9 (***C***H$_{Ar}$), 128.5 (***C***H$_{Ar}$), 127.5 (***C***H$_{Ar}$), 82.9 (HC≡***C***$_q$), 79.9 (H***C***≡), 75.9 (***C***H), 27.6 (C(***C***H$_3$)$_3$).

IR (ν, cm^{-1}) (CCl_4): 3311, 2981, 2935, 1744 (C=O), 1456, 1392, 1368, 1321, 1256, 1163, 1081, 1032.

MS (CI, NH_3, m/z): 304, 250 (MNH_4^+), 192, 132.

HRMS (EI+, m/z) **:** Calculated for $C_{14}H_{16}O_3$: 232.1100.
Found for $C_{14}H_{16}O_3$: 232.1105.

tert-Butyl 3-bromoprop-2-ynyl carbonate — II.58



MF: $C_8H_{11}BrO_3$

MW = 235.07 g.mol^{-1}

Reaction: To a solution of **II.32** (325 mg, 2.08 mmol) in acetone (12 ml), *N*-bromosuccinimide (450 mg, 2.4 mmol) and a catalytic quantity of silver nitrate (22 mg, 0.13 mmol) were added at 0°C and the resulted mixture was stirred for 1 hour. The reaction crude was extracted with petroleum ether and the combined organic phases were washed with a saturated brine solution, then dried over magnesium sulfate and concentrated *in vacuo*.

Purification : Work-up.

Product : Colourless oil.

Yield : 91 %

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 4.69 (s, 2H, C***H***$_2$), 1.50 (s, 9H, C(C***H***$_3$)$_3$).

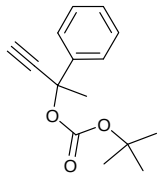
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 152.5 (***C***=O), 83.1 (BrC≡***C***$_q$), 73.7 (Br***C***≡C$_q$), 55.1 (***C***H$_2$), 47.6 (***C***$_q$), 27.7 (C(***C***H$_3$)$_3$).

IR (ν, cm^{-1}) (CCl_4): 2981, 2936, 1748 (C=O),1430, 1370, 1271, 1163, 1092.

MS (CI, NH_3, m/z): 328, 272, 216.

HRMS (EI+, m/z) **:** Calculated for $C_8H_{11}BrO_3$: 233.9892.
Found for $C_8H_{11}BrO_3$: 233.9898.

tert-Butyl 2-phenylbut-3-yn-2-yl carbonate — II.35l



MF: $C_{15}H_{18}O_3$

MW = 246.30 g.mol^{-1}

Reaction: The reaction was carried out according to **Method II.1.b.**

Purification : Flash column chromatography (silica gel, PE/Et_2O 95/5).

Product : Yellow oil.

Yield : 96 %

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.62-7.59 (m, 2H, 2 x C***H***$_{Ar}$), 7.39-7.30 (m, 3H, 3 x C***H***$_{Ar}$), 2.83 (s, 1H, ≡C***H***), 1.89 (s, 3H, C***H***$_3$), 1.41 (s, 9H, C(C***H***$_3$)$_3$).

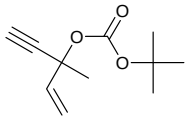
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 150.7 (***C***=O), 142.0 (***C***$_{qAr}$), 128.2 (***C***H$_{Ar}$), 127.8 (***C***H$_{Ar}$), 124.5 (***C***H$_{Ar}$), 82.6 (***C***$_q$O), 82.4 (HC≡***C***$_q$), 76.6 (***C***$_q$O), 75.6 (H***C***≡), 32.4 (***C***H$_3$), 27.6 (C(***C***H$_3$)$_3$).

IR (ν, cm^{-1}) (CCl_4): 3310, 3064, 2982, 2934, 1756 (C=O), 1369, 1273, 1160, 1080, 1055.

MS (CI, NH_3, m/z): 307, 264 (MNH_4^+), 149, 130.

HRMS (EI+, m/z) **:** Calculated for $C_{15}H_{18}O_3$: 246.1256.
Found for $C_{15}H_{18}O_3$: 246.1252

tert-Butyl 3-methylpent-4-en-1-yn-3-yl carbonate — II.35m



MF: $C_{11}H_{16}O_3$

MW = 196.24 g.mol^{-1}

Reaction: The reaction was carried out according to **Method II.1.b.**

Purification : Flash column chromatography (silica gel, PE/Et_2O 95/5).

Product : Pale yellow oil.

Yield : 80 %

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.99 (dd, J = 17.1, 10.3 Hz, 1H, ***H***C=), 5.62 (dd, J = 17.1, 0.6 Hz, 1H, ***H***$_2$C=), 5.27 (dd, J = 10.3, 0.6 Hz, 1H, ***H***$_2$C=), 2.70 (s, 1H, ≡C***H***), 1.71 (s, 3H, C***H***$_3$), 1.49 (s, 9H, C(C***H***$_3$)$_3$).

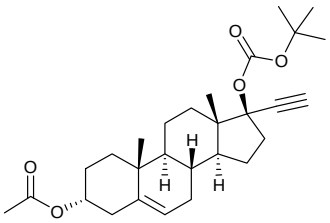
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 150.8 (***C***=O), 137.9 (H***C***=), 115.8 (H$_2$***C***=), 82.1 (***C***$_q$O), 81.5 (***C***$_q$O), 75.0 (HC≡***C***$_q$), 69.7 (H***C***≡), 28.5 (***C***H$_3$), 27.5 (C(***C***H$_3$)$_3$).

IR (ν, cm^{-1}) (CCl_4): 3310, 2982, 2935, 1753 (C=O), 1454, 1397, 1358, 1276, 1165, 1083.

MS (CI, NH_3, m/z): 214 (MNH_4^+), 205, 158, 136.

HRMS (EI+, m/z) **:** Calculated for $C_{11}H_{16}O_3$: 196.1100.
Found for $C_{11}H_{16}O_3$: 196.1105.

***tert*-Butyl (3*R*,8*R*,9*S*,10*R*,13*S*,14*S*,17*S*)-3-acetoxy-17-ethynyl 2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-10,13-dimethyl-1*H*-cyclopenta[a]phenanthren-17-yl carbonate**	**II.35k**



MF: $C_{28}H_{40}O_5$

MW = 456.61 g.mol^{-1}

Reaction: Prepared in two steps starting from 17-*α*-ethynyl androsten-5-diol(3*β*, 17*β*):
Step 1: To a solution of androstene derivative (1.57 g, 5.0 mmol) in dichloromethane (20 ml), triethylamine (1.4 ml, 10 mmol), acetic anhydride (0.71 ml, 7.5 mmol) and a catalytic quantity of DMAP (30 mg, 0.25 mmol) were added and the resulted mixture was stirred for 15 hours. The reaction crude was diluted with diethyl ether (20 ml), washed with a saturated ammonium chloride solution, then with a saturated brine solution, dried over magnesium sulfate, concentrated *in vacuo* and used in the second step without further purification.
Step 2: The *tert*-butoxycarbonylation reaction was carried out according to **Method II.1.b.**

Purification : Flash column chromatography (silica gel, PE/Et_2O 80/20 to 70/30).

Product : White crystals.

Yield : 46 %

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.37 (m, 1H, ***H***C=), 4.60 (quintuplet, J = 10.4, 6.2, 4.2 Hz, 1H, ***H***COAc), 2.67 (m, 1H, C***H***), 2.63 (s, 1H, ≡C***H***), 2.31 (m, 2H, C***H***$_2$), 2.13 (dddd, J = 15.3, 11.7, 3.4 Hz, 1H, ***H***C), 2.03 (s, 3H, COC***H***$_3$), 1.99 (m, 1H, ***H***C), 1.92-1.81 (m, 4H, 2 x C***H***$_2$), 1.75 (m, 1H, ***H***C), 1.67-1.50 (m, 6H, 3 x C***H***$_2$), 1.49 (s, 9H, C(C***H***$_3$)$_3$), 1.46-1.29 (m, 2H, C***H***$_2$), 1.14 (m, 1H, ***H***C), 1.03 (s, 3H, C***H***$_3$), 0.9 (s, 3H, C***H***$_3$).

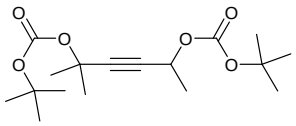
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 170.5 (O***C***OCH$_3$), 152.2 (***C***=O), 139.7 (***C***$_q$=), 122.2 (H***C***=), 85.8 (***C***$_q$O), 83.3 (***C***HOAc), 82.1 (***C***$_q$OBoc), 75.1 (HC≡***C***$_q$), 73.8 (H***C***≡), 49.5 (***C***H), 49.4 (***C***H), 47.5 (***C***$_q$), 38.0 (***C***H$_2$), 37.7 (***C***H$_2$), 36.9 (***C***H$_2$), 36.5 (***C***$_q$), 33.0 (***C***H$_2$), 32.2 (***C***H), 31.4 (***C***H$_2$), 27.8 (C(***C***H$_3$)$_3$), 27.7 (***C***H$_2$), 23.5 (***C***H$_2$), 21.4 (***C***H$_3$), 20.6 (***C***H$_2$), 19.3 (***C***H$_3$), 13.3 (***C***H$_3$).

IR (ν, cm^{-1}) (CCl_4): 3309, 2949, 2906, 2873, 1748 (C=O), 1461, 1368, 1281, 1245, 1164, 1088.

MS (CI, NH_3, m/z): 474 (MNH_4^+),443, 354, 312, 277.

HRMS (EI+, m/z) **:** Calculated for $C_{28}H_{40}O_5$: 456.2876.
Found for $C_{28}H_{40}O_5$: 456.2854.

Carbonic acid 4-*tert*-butoxycarbonyloxy-1,1,4-trimethyl-but-2-ynyl ester *tert*-butyl ester	**II.37d**



MF: $C_{17}H_{28}O_6$

MW = 328.40 g.mol^{-1}

Reaction: Prepared in two steps starting from *tert*-butyl 2-methylbut-3-yn-2-yl carbonate:
Step 1: To a solution of diisopropylamine (0.167 ml, 1.2 mmol) in tetrahydrofurane (2.5 ml) at -20°C, a 1.5 M solution of butyllithium (0.733 ml, 1.1 mmol) was added and the resulted mixture was stirred at -20°C for 20 min and 5 min at 0°C. To this mixture cooled at -78°C, a solution of *tert*-butyl 2-methylbut-3-yn-2-yl carbonate (184 mg, 1 mmol) in tetrahydrofuran (2 ml) was added and the crude was stirred for 30 min. Acetaldehyde (0.067 ml, 1.2 mmol) was added at -78°C and the crude was stirred for 30 min. The reaction was quenched with a saturated ammonium chloride solution and extracted with diethyl ether. The organic phase was washed with a saturated brine solution, dried over magnesium sulfate, concentrated *in vacuo* and purified by chromatography over a silica gel column using diethyl ether and petroleum ether 40/60 as eluting solvents to give the alcohol in 78% as a yellow oil.
Step 2: The *tert*-butoxycarbonylation reaction was carried out according to **Method II.1.b.**

Purification : Flash column chromatography (silica gel, PE/Et_2O 95/5).

Product : Yellow oil.

Yield : 68 % global.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.21 (q, J = 6.6 Hz, 1H, C***H***), 1.58 (s, 3H, C***H***$_3$), 1.57 (s, 3H, C***H***$_3$), 1.42-1.40 (m, 21H, 2 x C(C***H***$_3$)$_3$) and C***H***$_3$).

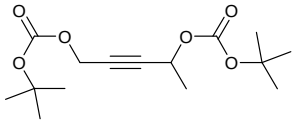
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 152.3 (***C***=O), 151.1 (***C***=O), 85.9 (***C***$_q$O), 82.3 (***C***$_q$O), 82.2 (C≡***C***$_q$), 81.8 (C≡***C***$_q$), 72.9 (***C***$_q$), 63.0 (***C***H), 28.7 (***C***H$_3$), 28.6 (***C***H$_3$), 27.7 (C(***C***H$_3$)$_3$), 27.6 (C(***C***H$_3$)$_3$), 21.2 (***C***H$_3$).

IR (ν, cm^{-1}) (CCl_4): 2983, 2935, 1746 (C=O), 1457, 1368, 1279, 1253, 1171, 1129, 1041.

MS (CI, NH_3, m/z): 346 (MNH_4^+), 290, 214, 172, 155, 103.

HRMS (EI+, m/z) **:** Calculated for $C_{17}H_{28}O_6$: 328.1886.
Found for $C_{17}H_{28}O_6$: 328.1883.

Carbonic acid 4-*tert*-butoxycarbonyloxy-1-methyl-but-2-ynyl ester *tert*-butyl ester — II.37c



MF: $C_{15}H_{24}O_6$

MW = 300.34 $g.mol^{-1}$

Reaction: Prepared in two steps starting from *tert*-butyl but-3-yn-2-yl carbonate:
Step 1: To a solution of diisopropylamine (0.5 ml, 3.6 mmol) in tetrahydrofurane (5 ml) at -20°C, a 1.5 M solution of butyllithium (2.2 ml, 3.3 mmol) was added and the resulted mixture was stirred at -20°C for 20 min and 5 min at room temperature. To this mixture cooled at -78°C, a solution of *tert*-butyl but-3-yn-2-yl carbonate (468 mg, 3 mmol) in tetrahydrofuran (2.5 ml) was added and the crude was stirred for 30 min. Acetaldehyde (0.2 ml, 3.6 mmol) was added at -78°C and the crude was stirred for 30 min. The reaction was quenched with a saturated ammonium chloride solution and extracted with diethyl ether. The organic phase was washed with a saturated brine solution, dried over magnesium sulfate, concentrated *in vacuo* and purified by passing over a silica gel column using diethyl ether and petroleum ether 20/80 as eluting solvents to give the alcohol in 57% as a yellow oil.
Step 2: The *tert*-butoxycarbonylation reaction was carried out according to **Method II.1.b.**

Purification : Flash column chromatography (silica gel, PE/Et_2O 95/5).

Product : Yellow oil.

Yield : 51 % global.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.16 (qt, J = 6.7, 1.5 Hz, 1H, C***H***), 4.56 (d, J = 1.6 Hz, 2H, C$\boldsymbol{H}_2$), 1.41-1.36 (m, 21H, 2 x C(C$\boldsymbol{H}_3$)$_3$) and C$\boldsymbol{H}_3$).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 152.3 (***C***=O), 152.0 (***C***=O), 84.7 (***C***$_q$≡C), 82.3 (***C***$_q$O), 82.1 (***C***$_q$O), 78.7 (C≡***C***$_q$), 62.5 (***C***H), 54.1 (***C***H$_2$), 27.4 (C(***C***H$_3$)$_3$), 27.3 (C(***C***H$_3$)$_3$), 20.8 (***C***H$_3$).

IR (ν, cm^{-1}) (CCl_4): 2982, 2937, 1745 (C=O), 1475, 1453, 1371, 1271, 1160, 1086, 1055, 993.

MS (CI, NH_3, m/z): 318 (MNH_4^+), 262, 245, 206.

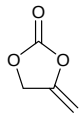
HRMS (EI+, m/z) **:** Calculated for $C_{15}H_{24}O_6$: 300.1573.
Found for $C_{15}H_{24}O_6$: 300.1573.

II.2. Gold(I)-Catalyzed Formation of 4-Alkylidene-1,3-dioxolan-2-ones

Method II.2. General procedure for the cyclization of propargylic *tert*-butylcarbonates:

To a solution of propargylic *tert*-butyl carbonate (1 equiv.) in dichloromethane (0.5 M) at room temperature, the corresponding amount of catalyst $(Ph_3P)AuNTf_2$ was added (generally 1 mol%). The reaction was stirred until full consumption of the starting material (as attested by TLC analysis). Upon completion, the mixture was either directly filtered through a silica pad pre-impregnated with dichloromethane and then evaporated under reduced pressure or evaporated and then purified by flash column chromatography (silica gel, petroleum ether/diethyl ether) to give the expected product.

4-Methylene-1,3-dioxolan-2-one	**II.33**



MF: $C_4H_4O_3$

MW = 100.07 g.mol^{-1}

Reaction: The reaction was carried out following the general procedure described above.

Purification : Flash column chromatography (silica gel, PE/Et_2O 80/20).

Product : Pale yellow solid.

Yield : 83 %

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.01 (t, J = 2.3 Hz, 2H, C$\boldsymbol{H}_2$), 4.92 (dt, J = 3.9, 2.6 Hz, 1H, =C***H***), 4.92 (dt, J = 4.0, 2.1 Hz, 1H, =C***H***).

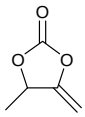
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 152.7 (***C***=O), 148.9 (***C***$_q$=), 87.4 (=***C***H), 67.6 (***C***H$_2$O).

IR (ν, cm^{-1}) (CCl_4): 2925, 1855 (C=O), 1708, 1681, 1349, 1283, 1118, 1067.

MS (CI, NH_3, m/z): 118 (MNH_4^+), 102, 92, 85, 64.

HRMS (EI+, m/z) **:** Calculated for $C_4H_4O_3$: 100.0160.
Found for $C_4H_4O_3$: 100.0159.

4-Methyl-5-methylene-1,3-dioxolan-2-one	**II.36a**



MF: $C_5H_6O_3$

MW = 114.09 g.mol^{-1}

Reaction: The reaction was carried out following the general procedure described above.

Purification : Filtration on silica gel.

Product : Pale yellow oil.

Yield : 94 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.27 (m, 1H, C***H***), 4.86 (dd, J = 3.9, 2.2 Hz, 1H, =C***H***), 4.36 (dd, J = 3.9, 2.1 Hz, 1H, =C***H***), 1.59 (d, J = 6.4 Hz, 3H, C***H***$_3$).

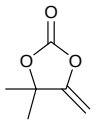
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 154.5 (***C***=O), 151.8 (***C***$_q$=), 86.5 (=***C***H), 76.2 (***C***HO), 20.3 (***C***H$_3$).

IR (ν, cm^{-1}) (CCl_4): 2989, 2934, 1844, 1707, 1682, 1449, 1317, 1279, 1145, 1085, 1003.

MS (CI, NH_3, m/z): 132 (MNH_4^+), 117, 106, 102, 85.

HRMS (EI+, m/z) **:** Calculated for $C_5H_6O_3$: 114.0317.
Found for $C_5H_6O_3$: 114.0313.

4,4-Dimethyl-5-methylene-1,3-dioxolan-2-one — II.36h



MF: $C_6H_8O_3$

MW = 128.12 g.mol^{-1}

Reaction: The reaction was carried out following the general procedure described above.

Purification : Filtration on silica gel.

Product : White solid.

Yield : 85 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 4.74 (d, J = 3.9 Hz, 1H, =C***H***), 4.31 (d, J = 3.9 Hz, 1H, =C***H***), 1.60 (s, 6H, 2 x C***H***$_3$).

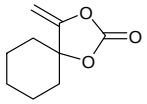
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 158.6 (***C***=O), 151.2 (***C***$_q$=), 85.2 (=***C***H), 84.6 (***C***$_q$O), 27.4 (***C***H$_3$).

IR (ν, cm^{-1}) (CCl_4): 2988, 1906, 1838, 1708, 1678, 1258, 1173, 1080, 1025.

MS (CI, NH_3, m/z): 146 (MNH_4^+).

HRMS (EI+, m/z) **:** Calculated for C_6H_8O: 128.0473.
Found for C_6H_8O: 128.0474.

4-Methylene-1,3-dioxa-spiro[4.5]decan-2-one — II.36j



MF: $C_9H_{12}O_3$

MW = 168.18 g.mol^{-1}

Reaction: The reaction was carried out following the general procedure described above.

Purification : Filtration on silica gel.

Product : Heavy colourless oil.

Yield : 96 %.

^{1}H NMR (δ, ppm) (CDCl$_3$, 400 MHz): 4.81 (d, J = 3.8 Hz, 1H, =C***H***), 4.33 (d, J = 3.8 Hz, 1H, =C***H***), 2.07-2.03 (m, 2H, C***H***$_2$), 1.84-1.58 (m, 8H, 4 x C***H***$_2$).

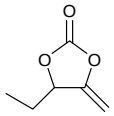
^{13}C NMR (δ, ppm) (CDCl$_3$, 100 MHz): 158.5 (***C***=O), 151.2 (***C***$_q$=), 86.2 (***C***$_q$O), 85.3 (=***C***H$_2$), 36.3 (***C***H$_2$), 24.1 (***C***H$_2$), 21.4 (***C***H$_2$).

IR (ν, cm^{-1}) (CCl$_4$): 2942, 2862, 1842, 1703, 1676, 1264, 1196, 1128, 1059, 1022.

MS (CI, NH$_3$, m/z): 186 (MNH$_4^+$).

HRMS (EI+, m/z) **:** Calculated for $C_9H_{12}O_3$: 168.0786.
Found for $C_9H_{12}O_3$: 168.0791.

4-Ethyl-5-methylene-1,3-dioxolan-2-one — II.38f



MF: $C_6H_8O_3$

MW = 128.12 g.mol^{-1}

Reaction: The reaction was carried out following the general procedure described above.

Purification : Flash column chromatography (silica gel, PE/Et$_2$O 80/20).

Product : Yellow oil.

Yield : 60 %.

^{1}H NMR (δ, ppm) (CDCl$_3$, 400 MHz): 5.17-5.13 (m, 1H, C***H***), 4.86 (dd, J = 3.9, 2.4 Hz, 1H, =C***H***), 4.35 (dd, J = 3.9, 2.4 Hz, 1H, =C***H***), 2.00-1.74 (m, 2H, C***H***$_2$), 1.04 (t, J = 7.3 Hz, 3H, C***H***$_3$).

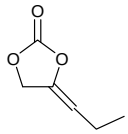
^{13}C NMR (δ, ppm) (CDCl$_3$, 100 MHz): 153.0 (***C***=O), 152.1 (***C***$_q$=), 86.7 (=***C***H), 80.6 (***C***HO), 27.6 (***C***H$_2$), 7.8 (***C***H$_3$).

IR (ν, cm^{-1}) (CCl$_4$): 2976, 2937, 1843, 1705, 1681, 1334, 1282, 1139, 1091.

MS (CI, NH$_3$, m/z): 146 (MNH$_4^+$), 139, 117, 102.

HRMS (EI+, m/z) **:** Calculated for $C_6H_8O_3$: 128.0473.
Found for $C_6H_8O_3$: 128.0478.

4-Propylidene-1,3-dioxolan-2-one — II.39



MF: $C_6H_8O_3$

MW = 128.12 g.mol^{-1}

Reaction: Obtained as a secondary product in the reaction described above, together with compound II.38f.

Purification : Flash column chromatography (silica gel, PE/Et_2O 80/20).

Product : Yellow oil.

Yield : 10 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.07-5.05 (m, 1H, =C***H***), 4.84 (dt, J = 3.1, 1.8 Hz, 2H, =C***H***$_2$), 2.26-2.19 (m, 2H, C***H***$_2$), 1.12 (t, J = 7.4 Hz, 3H, C***H***$_3$).

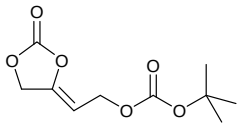
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 154.2 (***C***=O), 152.1 (***C***$_q$=), 94.6 (=***C***H), 66.7 (O***C***H$_2$), 24.9 (***C***H$_2$), 10.1 (***C***H$_3$).

IR (ν, cm^{-1}) (CCl_4): 2975, 2938, 2888, 1794, 1716, 1464, 1399, 1322, 1195, 1145, 1105.

MS (CI, NH_3, m/z): 146 (MNH_4^+), 139, 117, 102, 85.

HRMS (EI+, m/z) **:** Calculated for $C_6H_8O_3$: 128.0473.
Found for $C_6H_8O_3$: 128.0478.

tert-Butyl (*Z*)-2-(2-oxo-1,3-dioxolan-4-ylidene)ethyl carbonate — II.38c



MF: $C_{10}H_{14}O_6$

MW = 230.21 g.mol^{-1}

Reaction: The reaction was carried out following the general procedure described above.

Purification : Flash column chromatography (silica gel, PE/AcOEt 80/20).

Product : Yellow oil.

Yield : 62 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 4.97 (dd, J = 3.4, 1.4 Hz, 2H, =C***H***$_2$), 4.96-4.91 (m, 1H, =C***H***), 4.63 (dt, J = 7.2, 1.4 Hz, 2H, OC***H***$_2$), 1.41 (s, 9H, C(C***H***$_3$)$_3$).

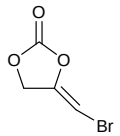
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 153.0 (***C***=O), 151.9 (***C***=O), 145, 6 (***C***$_q$=), 97.4 (=***C***H), 82.5 (***C***$_q$O), 67.4 (O***C***H$_2$), 59.9 (O***C***H$_2$), 24.9 (***C***H$_2$), 27.7 (***C***H$_3$).

IR (ν, cm^{-1}) (CCl_4): 2980, 1855, 1724, 1391, 1366, 1269, 1167, 1094, 1052.

MS (CI, NH_3, m/z): 248 (MNH_4^+), 192.

HRMS (EI+, m/z) **:** Calculated for $C_{10}H_{14}O_6$: 230.0790.
Found for $C_{10}H_{14}O_6$: 230.0795.

(*Z*)-4-(Bromomethylene)-1,3-dioxolan-2-one — II.59



MF: $C_4H_3BrO_3$

MW = 178.96 g.mol^{-1}

Reaction: The reaction was carried out following the general procedure described above.

Purification : Flash column chromatography (silica gel, PE/AcOEt 80/20).

Product : Colourless crystals.

Yield : 87 %

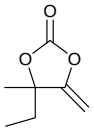
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.50 (t, J = 2.3 Hz, 1H, =C***H***), 5.02 (d, J = 2.1 Hz, 2H, C***H***$_2$).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 151.1 (***C***=O), 145.0 (***C***$_q$=), 78.9 (=***C***H), 67.5 (***C***H$_2$O).

MS (CI, NH_3, m/z): 196 (MNH_4^+), 192, 188, 178, 169, 156.

HRMS (EI+, m/z) **:** Calculated for $C_4H_3BrO_3$: 177.9266.
Found for $C_4H_3BrO_3$: 177.9262.

4-Ethyl-4-methyl-5-methylene-1,3-dioxolan-2-one — II.36i



MF: $C_7H_{10}O_3$

MW = 142.15 g.mol^{-1}

Reaction: The reaction was carried out following the general procedure described above.

Purification : Filtration on silica gel.

Product : Colourless oil.

Yield : 98 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 4.82 (d, J = 3.9 Hz, 1H, =C***H***), 4.27 (d, J = 3.9 Hz, 1H, =C***H***), 1.92 (m, J = 14.7, 7.4 Hz, 1H, C***H***$_2$), 1.76 (m, J = 14.7, 7.4 Hz, 1H, C***H***$_2$), 1.59 (s, 3H, C***H***$_3$), 0.99 (t, J = 7.4 Hz, 3H, C***H***$_3$).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 157.2 (***C***=O), 151.4 (***C***$_q$=), 87.5 (=***C***H), 85.5 (***C***$_q$O), 25.9 (***C***H$_2$), 7.1 (***C***H$_3$).

IR (ν, cm^{-1}) (CCl_4): 2980, 2935, 2839, 1703, 1677, 1291, 1229, 1151, 1090, 104.

MS (CI, NH_3, m/z): 160 (MNH_4^+), 139, 117, 102, 85.

HRMS (EI+, m/z) **:** Calculated for $C_7H_{10}O_3$: 142.0630.
Found for $C_7H_{10}O_3$: 142.0624.

4-Methyl-5-methylene-4-vinyl-1,3-dioxolan-2-one — II.36m

MF: $C_7H_8O_3$

MW = 140.13 g.mol^{-1}

Reaction: The reaction was carried out following the general procedure described above.

Purification : Flash column chromatography (silica gel, PE/Et_2O 90/10 to 70/30).

Product : Yellow oil.

Yield : 40 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.94 (dd, J = 17.1, 10.6 Hz, 1H, =C***H***), 5.49 (d, J = 17.1 Hz, 1H, =C***H***), 5.33 (d, J = 10.6 Hz, 1H, =C***H***), 4.88 (d, J = 3.9 Hz, 1H, =C***H***), 4.34 (d, J = 3.9 Hz, 1H, =C***H***), 1.69 (s, 3H, C$\boldsymbol{H}_3$).

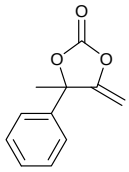
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 156.1 (***C***=O), 151.0 (***C***$_q$=), 136.1 (=***C***H), 116.6 (=***C***H_2), 87.2 (=***C***H_2), 85.7 (***C***$_q$O), 25.9 (***C***H_3).

IR (ν, cm^{-1}) (CCl_4): 3671, 3097, 2988, 2931, 2864, 1843, 1754, 1679, 1291, 1227, 1125, 1023.

MS (CI, NH_3, m/z): 158 (MNH_4^+).

HRMS (EI+, m/z) **:** Calculated for $C_7H_8O_3$: 140.047.
Found for $C_7H_8O_3$: 140.0476.

4-Methyl-5-methylene-4-phenyl-1,3-dioxolan-2-one	**II.36l**



MF: $C_{11}H_{10}O_3$

MW = 190.19 g.mol^{-1}

Reaction: The reaction was carried out following the general procedure described above.

Purification : Flash column chromatography (silica gel, PE/Et_2O 90/10).

Product : Yellow oil.

Yield : 76 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.41-7.27 (m, 5H, C$\boldsymbol{H}_{Ar}$), 4.86 (d, J = 4.0 Hz, 1H, =C***H***), 4.38 (d, J = 4.0 Hz, 1H, =C***H***), 1.88 (s, 3H, C$\boldsymbol{H}_3$).

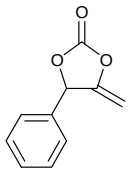
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 157.5 (***C***$_q$=), 151.2 (***C***=O), 139.3 (***C***$_{qAr}$), 129.2 (H***C***$_{Ar}$), 128.9 (H***C***$_{Ar}$), 124.8 (H***C***$_{Ar}$), 88.2 (=***C***H_2), 87.2 (***C***$_q$O), 27.6 (***C***H_3).

IR (ν, cm^{-1}) (CCl_4): 3660, 3065, 2991, 2935, 1843, 1680, 1294, 1222, 1071.

MS (CI, NH_3, m/z): 208 (MNH_4^+), 157, 140.

HRMS (EI+, m/z) **:** Calculated for $C_{11}H_{10}O_3$: 190.0630.
Found for $C_{11}H_{10}O_3$: 190.0622.

4-Methylene-5-phenyl-1,3-dioxolan-2-one	**II.36f**



MF: $C_{10}H_8O_3$

MW = 176.16 g.mol^{-1}

Reaction: The reaction was carried out following the general procedure described above.

Purification : Flash column chromatography (silica gel, PE/Et_2O 95/5).

Product : Yellow oil.

Yield : 74 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.52-7.48 (m, 3H, C***H$_{Ar}$***), 7.47-7.44 (m, 2H, C***H$_{Ar}$***), 6.13 (dd, J = 2.5, 2.1 Hz, 1H, C***H***), 5.03 (dd, J = 4.0, 2.5 Hz, 1H, =C***H***), 4.35 (dd, J = 4.0, 2.1 Hz, 1H, =C***H***).

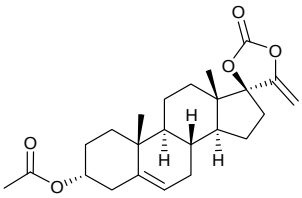
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 153.1 (***C$_q$***=), 151.9 (***C***=O), 134.9 (***C$_{qAr}$***), 130.3 (H***C$_{Ar}$***), 129.3 (H***C$_{Ar}$***), 127.4 (H***C$_{Ar}$***), 89.3 (=***C***H_2), 81.4 (***C$_q$***O).

IR (ν, cm^{-1}) (CCl_4): 1845, 1711, 1684, 1301, 1261, 1127, 1040.

MS (CI, NH_3, m/z): 194 (MNH_4^+).

HRMS (EI+, m/z) **:** Calculated for $C_{10}H_8O_3$: 176.0473.
Found for $C_{10}H_8O_3$: 176.0480.

Androstene derivative	**II.36k**



MF: $C_{24}H_{32}O_5$

MW = 400.50 g.mol^{-1}

Reaction: The reaction was carried out following the general procedure described above.

Purification : Filtration on silica gel.

Product : White crystals.

Yield : 90 %

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.28 (d, J = 4.8 Hz, 1H, ***H***C=), 4.83 (d, J = 3.8 Hz, 1H, ***H***C=), 4.48 (m, 1H, C***H***OAc), 4.31 (d, J = 3.8 Hz, 1H, ***H***C=), 2.43-2.14 (m, 3H, C***H*** and C***H***$_2$), 2.10-1.94 (m, 2H, C***H***$_2$), 1.94 (s, 3H, C***H***$_3$), 1.93 (bd, J = 10.5 Hz, 2H, C***H***$_2$), 1.71-1.60 (m, 1H, C***H***), 1.54-1.26 (m, 8H), 1.29-1.17 (m, 1H, C***H***), 1.07-1.01 (m, 1H, C***H***), 0.95 (s, 3H, C***H***$_3$), 0.90 (s, 3H, C***H***$_3$), 0.85 (m, 1H, C***H***).

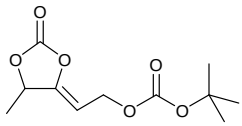
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 170.2 (O***C***OCH_3), 157.6 (***C$_q$***=), 151.3 (***C***=O), 139.6 (***C$_q$***=), 121.6 (H***C***=), 96.8 (***C$_q$***O), 88.8 (H_2***C***=), 73.4 (***C***HOAc), 49.2 (***C***H), 49.0 (***C***H), 47.1 (***C$_q$***), 37.9 (***C***H_2), 36.7 (***C***H_2), 36.4 (***C***H_2), 34.1 (***C***H_2), 31.8 (***C***H), 31.2 (***C***H_2), 30.9 (***C***H_2), 27.5 (***C***H_2), 22.9(***C***H_2), 21.2 (***C***H_3), 20.0 (***C***H_2), 19.1 (***C***H_3), 14.1 (***C***H_3).

IR (ν, cm^{-1}) (CCl_4): 2949, 2907, 1835, 1735, 1674, 1369, 1245, 1137, 1080, 1030.

MS (CI, NH_3, m/z): 419 (MNH_4^+), 355, 339.

HRMS (EI+, m/z) **:** Calculated for $C_{24}H_{32}O_{52}$: 400.2250.
Found for $C_{24}H_{32}O_5$: 400.2257.

***tert*-Butyl (*Z*)-2-(5-methyl-2-oxo-1,3-dioxolan-4-ylidene)ethyl carbonate**	**II.38c**



MF: $C_{11}H_{16}O_6$

MW = 244.24 g.mol^{-1}

Reaction: The reaction was carried out following the general procedure described above.

Purification : Filtration on silica gel.

Product : Pale yellow oil.

Yield : 77 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.24 (m, 1H, =C***H***), 4.87 (td, J = 7.3, 1.9 Hz, 1H, C***H***), 4.63 (dd, J = 7.3, 1.2 Hz, 2H, C***H***$_2$O), 1.53 (d, J = 6.5 Hz, 3H, C***H***$_3$), 1.42 (s, 9H, C(C***H***$_3$)$_3$).

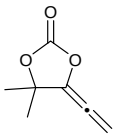
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 153.0 (***C***=O), 151.2 (***C***=O), 151.1 (***C***$_q$=), 96. 8 (=***C***H), 82.5 (***C***$_q$O), 76.1 (***C***H), 59.9 (O***C***H$_2$), 27.6 (***C***H$_3$), 20.2 (***C***H$_3$).

IR (ν, cm^{-1}) (CCl_4): 3683, 2981, 2933, 1847, 1742, 1271, 1144, 1099, 1029.

MS (CI, NH_3, m/z): 262 (MNH_4^+), 218, 206.

HRMS (EI+, m/z) **:** Calculated for $C_{11}H_{16}O_6$: 244.0947.
Found for $C_{11}H_{16}O_6$: 244.0944.

4,4-Dimethyl-5-(prop-1-enylidene)-1,3-dioxolan-2-one	**II.38d**



MF: $C_8H_{10}O_3$

MW = 154.16 g.mol^{-1}

Reaction: The reaction was carried out following the general procedure described above.

Purification : Flash column chromatography (silica gel, PE/Et_2O 97/3 to 96/4).

Product : Pale yellow oil.

Yield : 50 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 6.15 (q, J = 7.1 Hz, 1H, =C***H***), 1.85 (d, J = 7.1 Hz, 3H, C***H***$_3$), 1.57 (s, 3H, C***H***$_3$), 1.55 (s, 3H, C***H***$_3$).

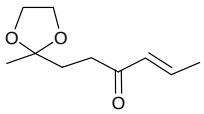
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 182.1 (=***C***=), 150.4 (***C***=O), 128.7 (***C***$_q$=), 108.2 (=***C***H), 82.3 (***C***$_q$O), 26.3 (***C***H$_3$), 25.9 (***C***H$_3$), 15.7 (***C***H$_3$).

IR (ν, cm^{-1}) (CCl_4): 2986, 2929, 1996, 1828, 1465, 1374, 1279, 1245, 1212, 1146, 1048.

MS (CI, NH_3, m/z): 172 (MNH_4^+), 155.

HRMS (EI+, m/z) **:** Calculated for $C_8H_{10}O_3$: 154.0629.
Found for $C_8H_{10}O_3$: 154.0630.

(*E*)-1-(2-Methyl-1,3-dioxolan-2-yl)hex-4-en-3-one **II.40**



MF: $C_{10}H_{16}O_3$

MW = 184.23 g.mol^{-1}

Reaction: Main compound obtained when the reaction was carried out following the general procedure described above using 2 mol% of (*p*-CF_3Ph_3P)$AuNTf_2$ as the catalyst, together with secondary products II.41 and II.42.

Purification : Flash column chromatography (silica gel, PE/Et_2O 70/30).

Product : Pale yellow oil.

Yield : 50 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 6.83 (dq, J = 15.7, 6.8 Hz, 1H, =C***H***CH_3), 6.10 (dq, J = 15.7, 1.6 Hz, 1H, =C***H***CO), 3.95-3.87 (m, 4H, 2 x C***H***$_2$), 2.62-2.58 (m, 2H, C***H***$_2$), 1.99-1.95(m, 2H, C***H***$_2$), 1.87 (dd, J = 6.8, 1.6 Hz, 3H, C***H***$_3$), 1.30 (s, 3H, C***H***$_3$).

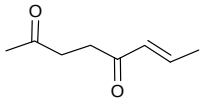
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 199.8 (H***C***=), 142.3 (H***C***=), 131.9 (H***C***=), 109.4 (O***C***$_q$O), 64.7 (***C***H_2),34.5 (***C***H_2), 33.0 (***C***H_2), 24.0 (***C***H_3), 18.2 (***C***H_3).

IR (ν, cm^{-1}) (CCl_4): 3035, 2981, 2943, 2881, 1827, 1695, 1677, 1635, 1442, 1376, 1295, 1254, 1217, 1130, 1052, 970.

MS (CI, NH_3, m/z): 185 (MH^+).

HRMS (EI+, m/z) **:** Calculated for $C_{10}H_{16}O_3$: 184.1099.
Found for $C_{10}H_{16}O_3$: 184.1098.

(*E*)-oct-6-ene-2,5-dione **II.41**



MF: $C_8H_{12}O_2$

MW = 140.17 g.mol^{-1}

Reaction: Obtained as a side-product in the reaction described above, together with compounds II.40 and II.42.

Purification : Flash column chromatography (silica gel, PE/Et_2O 70/30).

Product : Pale yellow oil.

Yield : 13 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 6.90 (dq, J = 15.7, 6.8 Hz, 1H, =C***H***CH_3), 6.14 (dq, J = 15.8, 1.6 Hz, 1H, =C***H***CO), 2.85-2.73 (m, 4H, 2 x C***H***$_2$), 2.20 (s, 3H, C***H***$_3$), 1.91 (dd, J = 6.8, 1.6 Hz, 3H, C***H***$_3$).

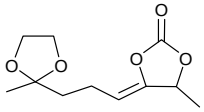
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 207.4 (***C***=O), 198.5 (***C***=O), 143.0 (H***C***=), 142.3 (H***C***=), 131.7 (H***C***=), 37.0 (***C***H_2), 33.5 (***C***H_2), 30.1 (CO***C***H_3), 18.4 (***C***H_3).

IR (ν, cm^{-1}) (CCl_4): 2925, 2856, 1721, 1678, 1635, 1444, 1360, 1261, 1159, 1124, 1086, 1043, 971.

MS (CI, NH_3, m/z): 158 (MNH_4^+), 141, 102, 85.

HRMS (EI+, m/z) **:** Calculated for $C_8H_{12}O$: 140.0837.
Found for $C_8H_{12}O$: 140.0835.

(*E*)-1-(2-methyl-1,3-dioxolan-2-yl)hex-4-en-3-one	**II.42**



MF: $C_{11}H_{16}O_5$

MW = 228.24 g.mol^{-1}

Reaction: Obtained as a side-product in the reaction described above, together with compounds II.40 and II.41.

Purification : Flash column chromatography (silica gel, PE/Et_2O 70/30).

Product : Yellow oil.

Yield : 21 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.21 (m, 1H, =C***H***), 4.65 (ddd, J = 7.4, 1.9 Hz, 1H, C***H***), 3.98-3.90 (m, 4H, 2 x C***H***$_2$), 2.30-2.24 (m, 2H, C***H***$_2$), 1.74 (q, J = 9.0, 6.9 Hz, 2H, C***H***$_2$), 1.53 (d, J = 6.4 Hz, 3H, C***H***$_3$), 1.32 (s, 3H, C***H***$_3$).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 152.4 (***C***=O), 147.0 (***C***$_q$=), 109.6 (O***C***$_q$O), 102.8 (H***C***=), 76.1 (***C***H), 64.8 (***C***H_2), 64.7 (***C***H_2), 38.4 (***C***H_2), 23.9 (***C***H_3), 20.7 (***C***H_3), 19.8 (***C***H_2).

IR (ν, cm^{-1}) (CCl_4): 2983, 2929, 2879, 1839, 1720, 1449, 1374, 1304, 1211, 1145, 1105, 1074, 1052.

MS (CI, NH_3, m/z): 246 (MNH_4^+), 229 (MH^+).

HRMS (EI+, m/z) **:** Calculated for $C_{11}H_{16}O_5$: 228.0997.
Found for $C_{11}H_{16}O_5$: 228.0994.

III. Gold(I)-Catalyzed Formation of 5-Methylene-oxazolidin-2-ones

III.1. Synthesis of Propargylic tert-butylcarbamates

Propargylic *tert*-butylcarbamates were generally synthesized from the corresponding propargylic amines and *di-tert*-butyl dicarbonate following the general methods described in the literature.[209,211, 212]

Method III.1.a. In a typical reaction, the propargylic amine was dissolved in dichloromethane or acetonitrile. *Di-tert*-butyl dicarbonate (1.05 equiv.) and a catalytic amount of DMAP (0.1 equiv.) were added at 0°C. After consumption of all propargylic amine (reaction monitored by TLC), the organic phase was diluted with dichloromethane, washed with a saturated brine solution, then dried over magnesium sulfate. After evaporation of the solvent, the product was purified by passing over a silica gel column using ethyl acetate diethyl ether and petroleum ether as eluting solvents.

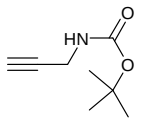
Bromoalkynes were synthesized by bromination of the corresponding alkyne with NBS.[146]

The substrates substituted at the propargylic position were synthesized in two steps according to the method developed by Petrini and co-workers:[216]

Method III.1.b. Preparation of α-amidoalkyl sulfones:
The carbamate derivative (1 equiv.) was dissolved in THF, and then water, sodium phenylsulfinate (1 equiv.), and the appropriate aldehyde (1.08 equiv.) were sequentially added at room temperature. Formic acid was added and the resulted mixture was stirred overnight. The resulting white precipitate was filtered and purified by recrystallization from petroleum ether.

Method III.1.c. Preparation of substituted propargylamides:
A solution of the corresponding sulfone obtained by **Method III.1.c.** (1 equiv.) in dry THF was cooled at -20°C. Ethynylmagnesium bromide (0.5 M in THF, 2 equiv.) was then added dropwise over 15 min, and after 30 min at -20°C the temperature was slowly raised to 0 °C. The reaction mixture was then quenched with saturated aqueous NH_4Cl, and after exctraction with dichloromethane the organic phase was dried over anhydrous magnesium sulfate and filtered. Removal of the solvent afforded the crude *N*-protected propargylamines, which were purified by column chromatography.

***tert*-Butyl prop-2-ynylcarbamate**	**III.45**



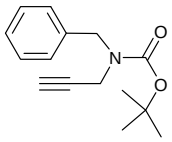
MF: $C_8H_{13}NO_2$

MW = 155.19 g.mol^{-1}

Reaction:	Prepared according to **Method III.1.a.**
Purification :	Flash column chromatography (silica gel, PE/Et_2O 90/10).
Product :	White crystals.
Yield :	91 %.
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	4.71 (bs, 1H, N***H***), 3.93 (d, J = 2.9 Hz, 2H, C$\boldsymbol{H}_2$), 2.22 (t, J = 2.5 Hz, 1H, ***H***C≡), 1.46 (s, 9H, C(C$\boldsymbol{H}_3$)$_3$).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	155.2 (NH***C***=O), 80.0 (HC≡$\boldsymbol{C_q}$), 79.8 (O$\boldsymbol{C_q}$), 71.0 (H***C***≡), 30.2 (***C***H$_2$), 28.2 (C(***C***H$_3$)$_3$).

MS (CI, NH_3, m/z) 156 (MH^+)

***tert*-Butyl benzylprop-2-ynylcarbamate**	**III.43a**



MF: $C_{15}H_{19}NO_2$

MW = 245.31 g.mol^{-1}

Reaction: A suspension of NaH (60 % in mineral oil, 220 mg, 5.50 mmol) in DMF (20 ml) was treated with compound III.45 (775 mg, 5.00 mmol) at 0°C. The reaction mixture was stirred for 30 minutes, cooled to 0°C and benzyl bromide (0.71 ml, 6.00 mmol) was added dropwise. The solution was stirred at 0°C for 1 hour before being allowed to warm at room temperature and stirred overnight. Water (10 ml) was added and the aqueous phase was extracted with Et_2O (3 x 30 ml). The combined organic phases were washed with a saturated brine solution, dried over magnesium sulfate, filtered and concentrated *in vacuo.*

Purification : Flash column chromatography (silica gel, PE/Et_2O 99/1 to 95/5).

Product : Yellow oil.

Yield : 49 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.37-7.09 (m, 5H, 5 x C***H***$_{Ar}$), 4.54 (s, 2H, PhC***H***$_2$), 4.13-3.88 (bd, 2H, C***H***$_2$), 2.21 (s, 1H, ***H***C≡), 1.48 (m, 9H, C(C***H***$_3$)$_3$).

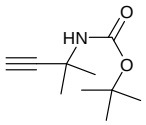
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) 155.0 (NH***C***=O), 137.4 (***C***$_{qAr}$), 128.5 (H***C***$_{Ar}$), 128.2 (H***C***$_{Ar}$), 128.1 (H***C***$_{Ar}$), 127.5 (H***C***$_{Ar}$), 127.3 (H***C***$_{Ar}$), 80.5 (O***C***$_q$), 79.2 (HC≡***C***$_q$), 65.8 (H***C***≡), 49.2 (***C***H$_2$), 35.1 (***C***H$_2$), 28.3 (C(***C***H$_3$)$_3$).

IR (ν, cm^{-1}) (CCl_4) 3310, 3031, 2977, 2929, 1700, 1450, 1408, 1365, 1244, 1167, 1117, 1027.

MS (CI, NH_3, m/z) 246 (MH^+), 218, 207, 190, 174.

HRMS (EI+, m/z) **:** Calculated for $C_{15}H_{19}NO_2$: 245.1415.
Found for $C_{15}H_{19}NO_2$: 245.1416.

***tert*-Butyl 2-methylbut-3-yn-2-ylcarbamate**	**III.43b**



MF: $C_{14}H_{21}NO_2$

MW = 235.32 g.mol^{-1}

Reaction: 1,1 Dimethylpropargylamine (0.52 ml, 5.00 mmol) was dissolved in a 1:5 mixture of H_2O:THF (6 mL) and then $Na_2CO_3 \cdot 10H_2O$ (3.575 g, 12.5 mmol) and Boc_2O (1.3 g, 6.00 mmol) were added. The resulted mixture was stirred at RT for 22 h and the reaction was quenched with saturated NH_4Cl (10 mL) and extracted with ethyl acetate (3 x30 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*.

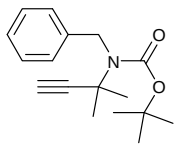
Purification: Flash column chromatography (silica gel, PE/Et_2O 90/10).

Product: White crystals.

Yield: 90 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	4.68 (bs, 1H, N***H***), 2.30 (s, 1H, ***H***C≡), 1.58 (s, 6H, 2 x C***H***$_3$), 1.45 (s, 9H, C(C***H***$_3$)$_3$).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	155.2 (NH***C***=O), 80.0 (HC≡***C$_q$***), 79.8 (O***C$_q$***), 71.0 (H***C***≡), 50.2 (N***C$_q$***), 28.5 (2 x ***C***H$_3$), 28.2 (C(***C***H$_3$)$_3$).

***tert*-Butyl benzyl-2-methylbut-3-yn-2-ylcarbamate**	**III.43c**



MF: $C_{17}H_{23}NO_2$

MW = 273.37 g.mol^{-1}

Reaction: A suspension of NaH (60 % in mineral oil, 132 mg, 3.30 mmol) in DMF (10 ml) was treated with III.43b (549 mg, 3.00 mmol) at 0°C. The reaction mixture was stirred for 30 minutes, cooled to 0°C and benzyl bromide (0.42 ml, 3.60 mmol) was added dropwise. The solution was stirred at 0°C for 1 hour before being allowed to warm at room temperature and stirred overnight. Water (10 ml) was added and the aqueous phase was extracted with Et_2O (3 x 30 ml). The combined organic phases were washed with a saturated brine solution, dried over magnesium sulfate, filtered and concentrated *in vacuo*.

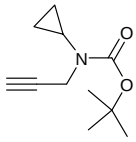
Purification: Flash column chromatography (silica gel, PE/Et_2O 99/1).

Product: Yellow oil.

Yield: 97 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	7.47-7.28 (m, 5H, 5 x C***H***$_{Ar}$), 4.82 (s, 2H, PhC***H***$_2$), 2.47 (s, 1H, ***H***C≡), 1.80 (s, 6H, 2 x C***H***$_3$), 1.54 (m, 9H, C(C***H***$_3$)$_3$).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	155.0 (***C***=O), 140.4 (***C$_{qAr}$***), 128.2 (H***C$_{Ar}$***), 126.6 (H***C$_{Ar}$***), 126.4 (H***C$_{Ar}$***), 88.1 (***C$_q$***), 80.2 (HC≡***C$_q$***), 71.3 (***C$_q$O***), 65.8 (H***C***≡), 49.7 (***C***H$_2$), 29.4 (C(***C***H$_3$)$_3$), 28.4 (***C***H$_3$).
IR (ν, cm^{-1}) (CCl_4)	3309, 2977, 2934, 1697, 1450, 1380, 1248, 1162, 1072, 953.
MS (CI, NH_3, m/z)	274 (MH^+), 235, 218, 174.
HRMS (EI+, m/z) **:**	Calculated for $C_{17}H_{23}NO_2$: 273.1728. Found for $C_{17}H_{23}NO_2$: 273.1730.

***tert*-Butyl cyclopropylprop-2-ynylcarbamate**	**III.43e**



MF: $C_{11}H_{17}NO_2$

MW = 195.25 g.mol^{-1}

Reaction: Prepared in two steps starting from cyclopropylamine:
Step 1: Protected cyclopropylamine was prepared according to **Method III.1.a.** using cyclopropylamine (0.14 ml, 2.00 mmol) in 5 ml dichloromethane. *Di-tert*-butyl dicarbonate (230 mg, 1.05 mmol) in 5 ml dichloromethane and DMAP (55 mg, 0.45 mmol) were then added and the crude mixture was stirred overnight and concentrated *in vacuo*. Flash column chromatography (silica gel, PE/Et_2O 70/30) afforded protected cyclopropylamine in quantitative yield.
Step 2: A suspension of NaH (60 % in mineral oil, 44.0 mg, 1.10 mmol) in DMF (5

ml) was treated with the protected cyclopropylamine prepared in the previous step (157 mg, 1.00 mmol) at 0°C. The reaction mixture was stirred for 30 minutes, cooled to 0°C and propargyl bromide 80% in toluene (0.15 ml, 1.20 mmol) was added dropwise. The solution was stirred at 0°C for 1 hour before being allowed to warm at room temperature and stirred overnight.The reaction was quenched with a saturated solution of NH_4Cl (5 ml) and extracted with Et_2O (3 x 10 ml). The combined organic phases were washed with a saturated brine solution, dried over magnesium sulfate, filtered and concentrated *in vacuo.*

Purification: Flash column chromatography (silica gel, PE/Et_2O 80/20).

Product: Yellow oil.

Yield: 56 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 3.97 (m, 1H, C***H***$_2$), 2.60 (m, 1H, C***H***), 2.16 (m, 1H, ***H***C≡), 1.46 (s, 9H, C(C***H***$_3$)$_3$).

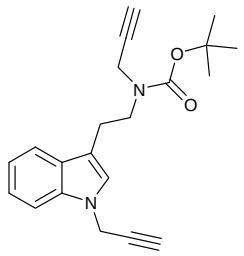
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 156.3 (***C***=O), 80.3 (C≡***C***$_q$), 80.2 (***C***$_q$), 70.8 (H***C***≡), 37.6 (***C***H$_2$), 29.1 (***C***H), 28.4 (C(***C***H$_3$)$_3$), 8.1 (2 x ***C***H$_2$).

IR (ν, cm^{-1}) (CCl_4): 3311, 2977, 2931, 1706, 1427, 1387, 1280, 1244, 1172, 1143, 1063, 1025.

MS (CI, NH_3, m/z): 213 (MNH_4^+).

HRMS (EI+, m/z) **:** Calculated for $C_{11}H_{17}NO_2$: 195.1259.
Found for $C_{11}H_{17}NO_2$:195.1256.

tert-Butyl prop-2-ynyl2-(1-(prop-2-ynyl)-1H-indol-3-yl)ethylcarbamate — III.53



MF: $C_{21}H_{24}N_2O_2$

MW = 336.42 g.mol^{-1}

Reaction: Obtained as the main product starting from tryptamine hydrochloride:
Step 1: III.53 was prepared according to the methods described in the literature[212], using tryptamine hydrochloride (196.7 mg, 1.00 mmol) in 2 ml dichloromethane. Triethylamine (0.15 ml, 1.00 mmol) was added and the mixture stirred for 10 minutes. A solution of *di-tert*-butyl dicarbonate (436.6 mg, 2.00 mmol) in 2 ml dichloromethane was then added and the crude mixture was stirred overnight. Water (10 ml) was added and the aqueous phase was extracted with dichloromethane (3 x 10 ml). The combined organic phases were washed with a saturated brine solution, dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (silica gel, PE/Et_2O 70/30) afforded the desired protected amine in quantitative yield.
Step 2: A suspension of NaH (60 % in mineral oil, 90.0 mg, 2.20 mmol) in DMF (5 ml) was treated with the protected amine previously prepared (260 mg, 1.00 mmol) at 0°C. The reaction mixture was stirred for 40 minutes, cooled to 0°C and propargyl bromide 80% in toluene (0.30 ml, 2.40 mmol) was added dropwise. The solution was stirred at 0°C for 1 hour before being allowed to warm at room temperature and stirred overnight.The reaction was quenched with a saturated solution of NH_4Cl (5 ml) and extracted with Et_2O (3 x 10 ml). The combined organic phases were washed with a saturated brine solution, dried over magnesium sulfate, filtered and concentrated *in vacuo.*

Purification: Flash column chromatography (silica gel, PE/AcOEt 90/10).

Product: Yellow oil.

Yield: 52 %.

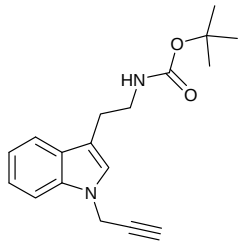
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.71 (d, J = 6.4 Hz, 1H, C***H***$_{Ar}$), 7.43 (d, J = 8.1 Hz, 1H, C***H***$_{Ar}$), 7.31 (t, J = 7.5 Hz, 1H, C***H***$_{Ar}$), 7.21 (t, J = 7.5 Hz, 1H, C***H***$_{Ar}$), 7.09 (s, 1H, NC***H***$_{Ar}$), 4.87 (d, J = 2.4 Hz, 2H, N***H***$_2$C), 4.10 (m, 2H, C***H***$_2$), 3.68 (m, 2H, C***H***$_2$), 3.10 (t, J = 6.9 Hz, 2H, N***H***$_2$C), 2.44 (t, J = 2.4 Hz, 1H, ***H***C≡), 2.29 (m, 1H, ***H***C≡), 1.56-1.46 (m, 9H, C(C***H***$_3$)$_3$).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 155.0 (***C***=O), 136.0 (***C***$_{qAr}$), 128.3 (***C***$_{qAr}$), 125.0 (H***C***$_{Ar}$N), 121.9 (H***C***$_{Ar}$), 119.3 (H***C***$_{Ar}$), 112.8 (***C***$_{qAr}$), 109.2 (H***C***$_{Ar}$), 97.1 (H***C***$_{Ar}$), 87.7 (***C***$_q$O), 80.0 (C≡***C***$_q$), 79.9 (C≡***C***$_q$), 77.7 (H***C***≡), 73.3 (H***C***≡), 47.3 (N***C***H$_2$), 35.5 (2 x ***C***H$_2$), 28.2 (C(***C***H$_3$)$_3$), 24.1 (***C***H$_2$).

IR (ν, cm^{-1}) (CCl_4): 3310, 2976, 2928, 1698, 1463, 1408, 1366, 1249, 1167, 1014.

MS (CI, NH_3, m/z): 337 (MH^+).

tert-Butyl 2-(1-(prop-2-ynyl)-1H-indol-3-yl)ethylcarbamate — III.52



MF: $C_{18}H_{22}N_2O_2$

MW = 298.37 g.mol^{-1}

Reaction: Obtained as a side product in the reaction described above, together with III.53.

Purification: Flash column chromatography (silica gel, PE/AcOEt 90/10).

Product: Yellow oil.

Yield: 28 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.66 (d, J = 7.8 Hz, 1H, C***H***$_{Ar}$), 7.41 (d, J = 8.2 Hz, 1H, C***H***$_{Ar}$), 7.30 (t, J = 7.6 Hz, 1H, C***H***$_{Ar}$), 7.20 (t, J = 7.4 Hz, 1H, C***H***$_{Ar}$), 7.06 (s, 1H, NC***H***$_{Ar}$), 4.84 (d, J = 2.5 Hz, 2H, N***H***$_2$C),4.76 (bs, 1H, N***H***), 3.49 (m, 2H, C***H***$_2$), 2.98 (t, J = 6.7 Hz, 2H, C***H***$_2$), 2.44 (t, J = 2.5 Hz, 1H, ***H***C≡), 1.50 (m, 9H, C(C***H***$_3$)$_3$).

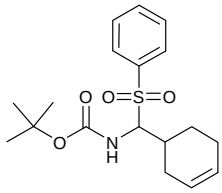
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 155.8 (***C***=O), 136.0 (***C***$_{qAr}$), 128.2 (***C***$_{qAr}$), 125.0 (H***C***$_{Ar}$N), 121.9 (H***C***$_{Ar}$), 119.3 (H***C***$_{Ar}$), 119.0 (H***C***$_{Ar}$),112.6 (***C***$_{qAr}$), 109.2 (H***C***$_{Ar}$), 78.9 (***C***$_q$O), 77.7 (C≡***C***$_q$), 73.3 (H***C***≡), 40.7 (N***C***H$_2$), 35.4 (***C***H$_2$), 28.3 (C(***C***H$_3$)$_3$), 25.6 (***C***H$_2$).

IR (ν, cm^{-1}) (CCl_4): 3459, 3310, 2976, 2930, 1718, 1501, 1466, 1365, 1251, 1171.

MS (CI, NH_3, m/z): 316 (MNH_4^+), 293, 259, 243, 237, 221, 215, 193.

HRMS (EI+, m/z) **:** Calculated for $C_{18}H_{22}N_2O_2$: 298.1681.
Found for $C_{18}H_{22}N_2O_2$: 298.1671.

tert-Butyl (cyclohex-3-enyl)(phenylsulfonyl)methylcarbamate — III.56h



MF: $C_{18}H_{25}NO_4S$

MW = 351.46 g.mol^{-1}

Reaction: The reaction was carried out according to Method **III.1.b**.

Purification: Recrystallization from PE.

Product: White crystals.

Yield: 82 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.90 (d, J = 7.6 Hz, 2H, 2 x C***H***$_{Ar}$), 7.62 (t, J = 7.4 Hz, 1H, C***H***$_{Ar}$), 7.57-7.51 (m, 2H, 2 x C***H***$_{Ar}$), 5.68 (m, 2H, ***H***C=C***H***), 5.19 (d, J = 11.1 Hz, 1H, NC***H***SO_2), 4.82 (dddd, J = 11.2, 4.1 Hz, 1H, C***H***), 2.72 (m, 1H, C***H***), 2.44 (d, J= 16.0 Hz, 1H, C***H***), 2.26-2.05 (m, 2H, C***H***$_2$), 1.99 (m, 1H, C***H***), 1.82 (m, 1H, C***H***), 1.21 (s, 9H, C(C***H***$_3$)$_3$).

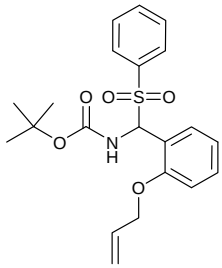
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 153.9 (***C***=O), 137.9 (***C***$_{qAr}$), 133.6 (H***C***$_{Ar}$), 129.0 (H***C***$_{Ar}$), 128.9 (H***C***$_{Ar}$), 126.8 (H***C***$_{Ar}$), 124.9 (H***C***$_{Ar}$), 80.7 (***C***$_q$***O***), 73.8 (N***C***HSO_2), 32.5 (H***C***), 27.9 (C(***C***H$_3$)$_3$), 26.3 (***C***H$_2$), 26.1 (***C***H$_2$), 24.7 (***C***H$_2$).

IR (ν, cm^{-1}) (CCl_4): 3439, 3355, 2976, 2930, 2360, 1727, 1491, 1366, 1319, 1144, 1083, 1055.

MS (CI, NH_3, m/z): 380, 331, 314, 280, 272, 248, 216.

HRMS (EI+, m/z) **:** Calculated for $C_{18}H_{25}NO_4S$: 351.1504.
Found for $C_{18}H_{25}NO_4S$: 351.1508.

tert-Butyl (2-(allyloxy)phenyl)(phenylsulfonyl)methylcarbamate — III.56m



MF: $C_{21}H_{25}NO_5S$

MW = 403.49 g.mol^{-1}

Reaction: The reaction was carried out according to **Method III.1.b.**

Purification: Flash column chromatography (silica gel, PE/AcOEt 80/20).

Product: Yellow solid.

Yield: 37 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.84 (d, J = 7.6 Hz, 2H, 2 x C***H***$_{Ar}$), 7.59 (t, J = 7.3 Hz, 1H, C***H***$_{Ar}$), 7.48 (t, J = 7.6 Hz, 2H, 2 x C***H***$_{Ar}$), 7.43-7.32 (m, 2H, 2 x C***H***$_{Ar}$), 7.01 (t, J = 7.6 Hz, 1H, C***H***$_{Ar}$), 6.86 (d, J = 8.3 Hz, 1H, C***H***$_{Ar}$), 6.41-6.30 (bm, 2H, NC***H***SO_2 and N***H***), 6.12-5.97 (m, 1H, ***H***C=), 5.43 (d, J = 17.2 Hz, 1H, ***H***C=), 5.30 (d, J = 11.9 Hz, 1H, ***H***C=), 4.47 (dddd, J = 12.3, 4.9 Hz, 2H, C***H***$_2$O), 1.46-1.26 (m, 9H, C(C***H***$_3$)$_3$).

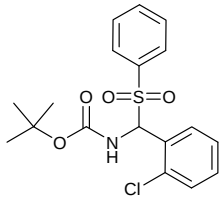
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 156.9 (***C***$_{qAr}$), 153.7 (***C***=O), 137.5 (H***C***$_{Ar}$), 135.7 (***C***H=), 133.5 (H***C***$_{Ar}$), 132.6 (H***C***$_{Ar}$), 130.9 (H***C***$_{Ar}$), 130.1 (H***C***$_{Ar}$), 129.4 (H***C***$_{Ar}$), 128.7 (H***C***$_{Ar}$), 121.0 (H***C***$_{Ar}$), 118.9 (***C***$_{qAr}$), 117.8 (H$_2$***C***=), 112.7 (H***C***$_{Ar}$), 80.7 (***C***$_q$***O***), 70.8 (N***C***HSO_2), 69.4 (***C***H$_2$), 28.1 (C(***C***H$_3$)$_3$).

IR (ν, cm^{-1}) (CCl_4) 3453, 2960, 2927, 1722, 1693, 1601, 1485, 1458, 1293, 1243, 1163, 1016, 928.

MS (CI, NH_3, m/z) 404 (MH^+), 391, 377, 323, 307, 288, 279, 262, 232, 222.

HRMS (EI+, m/z) **:** Calculated for $C_{21}H_{25}NO_5S$: 387.1504.
Found for $C_{21}H_{25}NO_5S$: 387.1495.

tert-Butyl (2-chlorophenyl)(phenylsulfonyl)methylcarbamate — III.56k



MF: $C_{18}H_{20}ClNO_4S$

MW = 381.87 $g.mol^{-1}$

Reaction: The reaction was carried out according to Method III.1.b.

Purification: Recrystallization from PE.

Product: Yellow solid.

Yield: 75 %

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.93 (d, J = 7.5 Hz, 2H, 2 x C***H***$_{Ar}$), 7.66 (t, J = 7.0 Hz, 1H, C***H***$_{Ar}$), 7.56-7.52 (m, 3H, 3 x C***H***$_{Ar}$), 7.42 (m, 1H, C***H***$_{Ar}$), 7.38-7.33 (m, 2H, 2 x C***H***$_{Ar}$), 6.73-5.85 (bm, 2H, NC***H***SO_2 and N***H***), 1.29 (s, 9H, C(C***H***$_3$)$_3$).

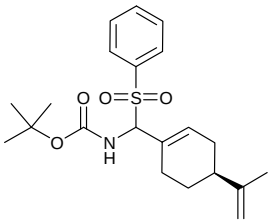
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) 156.3 (***C***=O), 137.1 (***C***$_{qAr}$), 135.3 (***C***$_{qAr}$), 135.0 (***C***$_{qAr}$), 134.0 (H***C***$_{Ar}$), 130.8 (H***C***$_{Ar}$), 129.9 (H***C***$_{Ar}$), 129.4 (H***C***$_{Ar}$), 129.2 (H***C***$_{Ar}$), 129.1 (H***C***$_{Ar}$), 127.3 (H***C***$_{Ar}$), 127.1 (H***C***$_{Ar}$), 124.9 (H***C***$_{Ar}$), 81.3 (***C***$_q$***O***), 70.0 (N***C***HSO_2), 27.9 (C(***C***H_3)$_3$).

IR (ν, cm^{-1}) (CCl_4) 3442, 3228, 2978, 2360, 1731, 1693, 1488, 1365, 1325, 1273, 1148, 1082, 1040, 1003.

MS (CI, NH_3, m/z) 382 (MH^+).

HRMS (EI+, m/z) **:** Calculated for $C_{18}H_{20}ClNO_4S$: 381.0802.
Found for $C_{18}H_{20}ClNO_4S$: 381.0807.

tert-Butyl (phenylsulfonyl)((S)-4-(prop-1-en-2-yl)cyclohex-1-enyl)methylcarbamate — III.56i



MF: $C_{21}H_{29}NO_4S$

MW = 391.52 $g.mol^{-1}$

Reaction: The reaction was carried out according to **Method III.1.b.**

Purification: Recrystallization from PE.

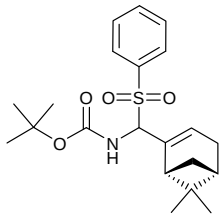
Product: Pale yellow solid.

Yield: 51 %.

^{1}H NMR (δ, ppm) 7.83 (d, J = 7.3 Hz, 2H, 2 x C***H***$_{Ar}$), 7.62 (t, J = 7.4 Hz, 1H, C***H***$_{Ar}$), 7.54 (m, 2H, 2 x

($CDCl_3$, 400 MHz)	C***H***$_{Ar}$), 6.16 (d, J = 11.3 Hz, 1H, NC***H***SO_2), 6.00 (d, J = 10.9 Hz, 1H, ***H***C=), 4.74 (m, 1H, =C***H***), 4.71 (m, 1H, =C***H***), 3.63 (d, J = 5.8 Hz, 1H, C***H***), 2.83 (t, J= 12.3 Hz, 1H, C***H***), 2.56-2.41 (m, 2H, C***H***$_2$), 2.26 (m, 1H, C***H***), 1.73 (s, 3H, C***H***$_3$), 1.63-1.52 (m, 2H, C***H***$_2$), 1.44 (s, 9H, C(C***H***$_3$)$_3$).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	152.2 (***C***=O), 148.6 (=***C***$_q$), 137.6 (***C***$_q$), 133.4 (H***C***), 128.8 (H***C***), 128.6 (H***C***), 124.9 (H***C***), 109.2 (H_2***C***=), 107.6 (***C***$_q$), 80.8 (***C***$_q$***O***), 67.6 (N***C***HSO_2), 38.9 (H***C***), 30.3 (***C***H_2), 30.2 (***C***H_2), 28.1 (C(***C***H_3)$_3$), 23.5 (***C***H_2), 20.8 (***C***H_3).
IR (ν, cm^{-1}) (CCl_4)	3442, 3064, 3030, 2947, 1743, 1599, 1524, 1442, 1311, 1204, 1056, 994.
MS (CI, NH_3, m/z)	392 (MH^+), 239, 195, 178.
HRMS (EI+, m/z) **:**	Calculated for $C_{21}H_{29}NO_4S$: 391.1817. Found for $C_{21}H_{29}NO_4S$: 391.1819.

***tert*-Butyl ((1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)(phenylsulfonyl)methylcarbamate**	**III.56j**

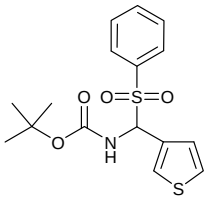


MF: $C_{21}H_{29}NO_4S$

MW = 391.52 $g.mol^{-1}$

Reaction:	The reaction was carried out according to **Method III.1.b.**
Purification:	Recrystallization from PE.
Product:	White solid.
Yield:	36 %.
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	7.88 (d, J = 7.5 Hz, 2H, 2 x C***H***$_{Ar}$), 7.63 (t, J = 6.9 Hz, 1H, C***H***$_{Ar}$), 7.54 (t, J = 7.4 Hz, 2H, 2 x C***H***$_{Ar}$), 6.38 (d, J = 11.1 Hz, 1H, NC***H***SO_2), 6.15 (m, 1H, ***H***C=), 3.99 (d, J = 10.1 Hz, 1H, N***H***), 2.48 (m, 1H, C***H***), 2.45-2.32 (m, 2H, C***H***$_2$), 2.09 (m, 1H, C***H***), 1.94 (m, 1H, C***H***), 1.78 (d, J = 10.1 Hz, 1H, C***H***), 1.42 (s, 9H, C(C***H***$_3$)$_3$), 1.27 (s, 3H, C***H***$_3$), 0.65 (s, 3H, C***H***$_3$).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	152.1 (***C***=O), 138.3 (=***C***$_q$), 133.4 (H***C***$_{Ar}$), 129.3 (***C***$_{qAr}$), 129.2 (H***C***$_{Ar}$), 128.9 (H***C***$_{Ar}$), 125.0 (H***C***=), 80.5 (***C***$_q$***O***), 61.1 (N***C***HSO_2), 42.2 (H***C***), 41.7 (***C***$_q$), 39.2 (***C***H), 28.1 (C(***C***H_3)$_3$), 26.3 (***C***H_2), 25.6 (***C***H_3), 25.3 (***C***H_2), 21.1 (***C***H_3).
IR (ν, cm^{-1}) (CCl_4)	3456, 2977, 2924, 1733, 1670, 1477, 1366, 1313, 1225, 1151, 1081.
MS (CI, NH_3, m/z)	326, 309, 298, 296, 291, 279.
HRMS (EI+, m/z) **:**	Calculated for $C_{21}H_{29}NO_4S$: 391.1817. Found for $C_{21}H_{29}NO_4S$: 391.1835.

***tert*-Butyl (phenylsulfonyl)(thiophen-3-yl)methylcarbamate**	**III.56n**



MF: $C_{16}H_{19}NO_4S_2$

MW = 353.45 g.mol^{-1}

Reaction: The reaction was carried out according to **Method III.1.b.**

Purification: Recrystallization from PE.

Product: Brown solid.

Yield: 85 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.95 (d, J = 7.1 Hz, 2H, 2 x C***H***$_{Ar}$), 7.68 (t, J = 7.4 Hz, 1H, C***H***$_{Ar}$), 7.57 (t, J = 7.6 Hz, 2H, 2 x C***H***$_{Ar}$), 7.50 (m, 1H, C***H***$_{Ar}$), 7.42 (m, 1H, C***H***$_{Ar}$), 7.29 (t, J = 4.9 Hz, 1H, C***H***$_{Ar}$), 6.19-5.71 (m, J = 10.6 Hz, 2H, NC***H***SO_2 and N***H***), 1.30 (s, 9H, C(C***H***$_3$)$_3$).

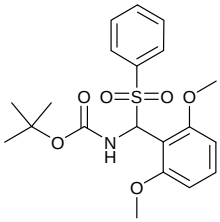
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 153.3 (***C***=O), 136.6 (***C***$_{qAr}$), 133.9 (H***C***$_{Ar}$), 130.2 (***C***$_{qAr}$), 129.4 (H***C***$_{Ar}$), 129.0 (H***C***$_{Ar}$), 127.0 (H***C***$_{Ar}$), 126.6 (H***C***$_{Ar}$), 126.4 (H***C***$_{Ar}$), 81.2 (***C***$_q$***O***), 70.3 (N***C***HSO_2), 27.9 (C(***C***H$_3$)$_3$).

IR (ν, cm^{-1}) (CCl_4): 3441, 2978, 1728, 1491, 1450, 1366, 1326, 1301, 1236, 1148, 1081.

MS (CI, NH_3, m/z): 355 (MH^+), 278, 262, 233, 229.

HRMS (EI+, m/z) **:** Calculated for $C_{16}H_{19}NO_4S_2$: 353.0756.
Found for $C_{16}H_{19}NO_4S_2$: 353.0751.

tert-Butyl (2,6-dimethoxyphenyl)(phenylsulfonyl)methylcarbamate — III.56l



MF: $C_{20}H_{25}NO_6S$

MW = 407.48 g.mol^{-1}

Reaction: The reaction was carried out according to **Method III.1.b.**

Purification: Recrystallization from PE.

Product: Yellow solid.

Yield: 66 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.84 (m, 2H, 2 x C***H***$_{Ar}$), 7.60 (t, J = 7.2 Hz, 1H, C***H***$_{Ar}$), 7.49 (t, J = 7.6 Hz, 2H, 2 x C***H***$_{Ar}$), 6.54 (m, 1H, C***H***$_{Ar}$), 6.40 (m, 1H, NC***H***SO_2), 6.26 (m, 2H, 2 x C***H***$_{Ar}$), 3.80 (s, 3H, C***H***$_3$), 3.70 (s, 3H, C***H***$_3$), 1.32 (m, 9H, C(C***H***$_3$)$_3$).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 162.0 (O***C***$_{qAr}$), 158.9 (O***C***$_{qAr}$), 153.7 (***C***=O), 137.5 (***C***$_{qAr}$), 133.4 (H***C***$_{Ar}$), 131.0 (H***C***$_{Ar}$), 130.6 (H***C***$_{Ar}$), 129.3 (H***C***$_{Ar}$), 128.5 (H***C***$_{Ar}$), 110.9 (***C***$_{qAr}$), 104.9 (H***C***$_{Ar}$), 98.9 (H***C***$_{Ar}$), 80.7 (***C***$_q$***O***), 70.8 (N***C***HSO_2), 55.6 (***C***H$_3$), 55.3 (***C***H$_3$), 28.0 (C(***C***H$_3$)$_3$).

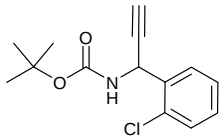
IR (ν, cm^{-1}) (CCl_4): 3441, 2966, 2840, 1727, 1683, 1605, 1489, 1463, 1300, 1262, 1212, 1158, 1037.

MS (CI, NH_3, m/z): 410, 393, 312, 295, 266.

HRMS (EI+, m/z) **:** Calculated for $C_{20}H_{25}NO_6S$: 407.1403.

Found for $C_{20}H_{25}NO_6S$: 407.1396.

***tert*-Butyl 1-(2-chlorophenyl)prop-2-ynylcarbamate**	**III.43k**



MF: $C_{14}H_{16}ClNO_2$

MW = 265.73 g.mol^{-1}

Reaction: The reaction was carried out according to **Method III.1.c.**

Purification: Flash column chromatography (silica gel, PE/Et_2O 80/20).

Product: Pale yellow solid.

Yield: 74 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.62 (dd, J = 7.1, 2.2 Hz, 1H, C***H$_{Ar}$***), 7.40 (m, 1H, C***H$_{Ar}$***), 7.31-7.27 (m, 2H, 2 x C***H$_{Ar}$***), 5.88 (bm, 1H, NC***H***), 5.12 (bs, 1H, N***H***), 2.47 (d, J = 2.4 Hz, 1H, ≡***C***H), 1.44 (s, 9H, C(C***H***$_3$)$_3$).

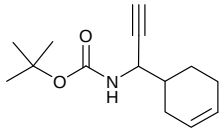
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 156.3 (***C***=O), 138.2 (***C$_{qAr}$***), 132.8 (***C$_{qAr}$***), 130.1 (H***C$_{Ar}$***), 129.5 (H***C$_{Ar}$***), 128.6 (H***C$_{Ar}$***), 127.1 (H***C$_{Ar}$***), 81.2 (≡***C$_q$***), 80.4 (***C$_q$O***), 72.8 (≡***C***H), 44.5 (N***C***H), 28.2 (C(***C***H$_3$)$_3$).

IR (ν, cm^{-1}) (CCl_4): 3455, 3310, 2977, 2930, 1725, 1484, 1365, 1300, 1227, 1167, 1046.

MS (CI, NH_3, m/z): 266 (MH^+), 227, 210.

HRMS (EI+, m/z) **:** Calculated for $C_{14}H_{16}ClNO_2$: 265.0870.
Found for $C_{14}H_{16}ClNO_2$: 265.0878.

***tert*-Butyl 1-(cyclohex-3-enyl)prop-2-ynylcarbamate**	**III.43h**



MF: $C_{14}H_{21}NO_2$

MW = 235.32 g.mol^{-1}

Reaction: The reaction was carried out according to **Method III.1.c.**

Purification: Flash column chromatography (silica gel, PE/AcOEt 95/5).

Product: Pale yellow solid.

Yield: 92 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.63 (m, 2H, ***H***C=C***H***), 4.90 (m, 1H, NC***H***), 4.35 (m, 1H, C***H***), 2.24 (m, 1H, ***H***C≡), 2.10-1.77 (m, 6H, 3 x C***H***$_2$), 1.41 (s, 9H, C(C***H***$_3$)$_3$).

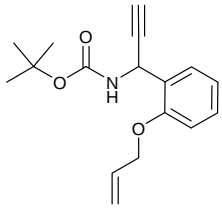
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 154.8 (***C***=O), 126.8 (H***C***=), 125.4 (H***C***=), 82.1 (≡***C$_q$***), 79.6 (***C$_q$O***), 71.8 (≡***C***H), 47.1 (N***C***H), 38.7 (H***C***), 28.2 (C(***C***H$_3$)$_3$), 27.6 (***C***H$_2$), 24.7 (***C***H$_2$), 24.2 (***C***H$_2$).

IR (ν, cm^{-1}) (CCl_4): 3455, 3310, 3024, 2976, 2925, 1778, 1720, 1490, 1365, 1325, 1232, 1168, 1048, 1014.

MS (CI, NH_3, m/z): 267, 236 (MH^+), 211, 197, 180.

HRMS (EI+, m/z) **:** Calculated for $C_{14}H_{21}NO_2$: 234.1494.
Found for $C_{14}H_{21}NO_2$: 234.1499.

***tert*-Butyl 1-(2-(allyloxy)phenyl)prop-2-ynylcarbamate**	**III.43m**



MF: $C_{17}H_{21}NO_3$

MW = 287.35 g.mol^{-1}

Reaction: The reaction was carried out according to **Method III.1.c.**

Purification: Flash column chromatography (silica gel, PE/AcOEt 90/10).

Product: Yellow oil.

Yield: 28 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.48 (d, J = 7.4 Hz, 1H, C***H***$_{Ar}$), 7.31 (t, J = 7.7 Hz, 1H, C***H***$_{Ar}$), 7.03-6.92 (m, 2H, 2 x C***H***$_{Ar}$), 6.11 (dddd, J = 15.6, 10.2, 4.9 Hz, 1H, =C***H***), 5.84 (m, 1H, NC***H***), 5.52 (dd, J = 17.3, 1.1 Hz, 1H, =C***H***), 5.41(bs, 1H, N***H***), 5.33 (dd, J = 10.6, 1.1 Hz, =C***H***), 4.71-4.62 (m, 2H, C***H***$_2$O), 2.41 (d, J = 2.3 Hz, 1H, ≡***C***H), 1.48 (m, 9H, C(C***H***$_3$)$_3$).

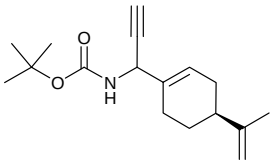
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 155.7 (O***C***$_{qAr}$), 154.4 (***C***=O), 132.8 (***C***H=), 129.4 (H***C***$_{Ar}$), 128.3 (H***C***$_{Ar}$), 127.0 (***C***$_{qAr}$), 120.8 (H***C***$_{Ar}$), 117.3 (H_2***C***=), 112.3 (H***C***$_{Ar}$), 82.7 (≡***C***$_q$), 79.8 (***C***$_q$O), 71.1 (≡***C***H), 68.8 (***C***H_2O), 42.9 (N***C***H), 28.3 (C(***C***H_3)$_3$).

IR (ν, cm^{-1}) (CCl_4): 3455, 3311, 2976, 1721, 1595, 1552, 1488, 1365, 1248, 1168, 1015, 968, 945.

MS (CI, NH_3, m/z): 232, 197, 186, 180, 171, 154.

HRMS (EI+, m/z) **:** Calculated for $C_{17}H_{21}NO_3$: 287.1521.
Found for $C_{17}H_{21}NO_3$: 287.1523.

***tert*-Butyl 1-((*S*)-4-(prop-1-en-2-yl)cyclohex-1-enyl)prop-2-ynylcarbamate**	**III.43i**



MF: $C_{17}H_{25}NO_2$

MW = 275.38 g.mol^{-1}

Reaction: The reaction was carried out according to **Method III.1.c.**

Purification: Flash column chromatography (silica gel, PE/AcOEt 90/10).

Product: Yellow solid.

Yield: 42 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.93 (m, 1H, =C***H***), 4.99-4.71 (m, 2H, C***H*** and N***H***), 4.70 (d, J = 7.2 Hz, 1H, =C***H***$_2$), 2.54-2.32 (m, 1H, C***H***), 2.28-2.11(m, 4H, 2 x C***H***$_2$), 1.95 (m, 1H, C***H***), 1.84 (m, 1H, C***H***), 1.71 (s, 3H, C***H***$_3$), 1.44 (s, 9H, C(C***H***$_3$)$_3$).

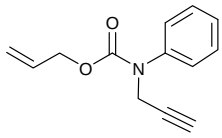
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 154.8 (***C***=O), 150.5 (=***C***$_q$), 141.2 (=***C***$_q$), 124.0 (=***C***H), 108.7 (H_2***C***=), 81.8 (≡***C***$_q$), 79.9 (***C***$_q$***O***), 72.1 (≡***C***H), 47.6 (N***C***H), 40.7 (H***C***), 30.3 (***C***H_2), 28.9 (C(***C***H_3)$_3$), 27.4 (***C***H_2), 25.5 (***C***H_2), 20.6 (***C***H_3).

IR (ν, cm^{-1}) (CCl_4): 3309, 2976, 1724, 1368, 1261, 1159, 1018, 979, 940, 923.

MS (CI, NH_3, m/z) 276 (MH^+), 253, 237, 220, 218.

HRMS (EI+, m/z) **:** Calculated for $C_{17}H_{25}NO_2$: 275.1885.
Found for $C_{17}H_{25}NO_2$: 275.1896.

Allyl phenylprop-2-ynylcarbamate	**III.48**



MF: $C_{13}H_{13}NO_2$

MW = 215.24 g.mol^{-1}

Reaction: Prepared in two steps starting from aniline:
Step 1: To a solution of aniline (0.45 ml, 5.00 mmol) in 10 ml dichloromethane, triethylamine (1.4 ml, 10.00 mmol) and allylchloroformate (0.8 ml, 7.5 mmol) were added at 0°C. The resulted mixture was allowed to warm at room temperature and stirred overnight. Water (10 ml) was added and the aqueous phase was extracted with diethyl ether (3 x 10 ml). The combined organic phases were washed with a saturated brine solution, dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (silica gel, PE/Et_2O 80/20) afforded the allylcarbamate in 32 % yield as a white solid.
Step 2: A suspension of NaH (60 % in mineral oil, 66.0 mg, 1.65 mmol) in DMF (5 ml) was treated with the allylcarcarbamide previously prepared (270 mg, 1.50 mmol) at 0°C. The reaction mixture was stirred for 30 minutes, cooled to 0°C and propargyl bromide 80% in toluene (0.20 ml, 1.80 mmol) was added dropwise. The solution was stirred at 0°C for 1 hour before being allowed to warm at room temperature and stirred overnight.The reaction was quenched with a saturated solution of NH_4Cl (5 ml) and extracted with Et_2O (3 x 10 ml). The combined organic phases were washed with a saturated brine solution, dried over magnesium sulfate, filtered and concentrated *in vacuo*.

Purification: Flash column chromatography (silica gel, PE/AcOEt 80/20).

Product: Orange oil.

Yield: 90 %

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.44-7.38 (m, 4H, 4 x C$\boldsymbol{H_{Ar}}$), 7.34-7.30 (m, 1H, C$\boldsymbol{H_{Ar}}$), 5.94 (m, 1H, =C$\boldsymbol{H}$), 5.37-5.12 (m, 2H, =C$\boldsymbol{H_2}$), 4.68 (d, J = 4.5 Hz, 2H, OC$\boldsymbol{H_2}$), 4.47 (d, J = 2.4 Hz, 2H, NC$\boldsymbol{H_2}$), 2.32 (t, J = 2.4 Hz, 1H, ≡$\boldsymbol{C}$H).

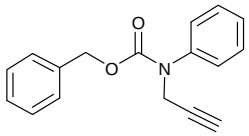
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) 154.7 ($\boldsymbol{C}$=O), 141.3 ($\boldsymbol{C_{qAr}}$), 132.3 ($\boldsymbol{C}$H=), 128.8 (H$\boldsymbol{C_{Ar}}$), 126.9 (H$\boldsymbol{C_{Ar}}$), 126.6 (H$\boldsymbol{C_{Ar}}$), 117.2 ($H_2\boldsymbol{C}$=), 112.3 (H$\boldsymbol{C_{Ar}}$), 79.4 (≡$\boldsymbol{C_q}$), 72.2 (≡$\boldsymbol{C}$H), 66.4 ($\boldsymbol{C}H_2O$), 40.1 (N$\boldsymbol{C}H_2$).

IR (ν, cm^{-1}) (CCl_4) 3311, 3070, 3039, 2942, 1714, 1595, 1498, 1392, 1276, 1229, 1142, 1046, 1018, 988, 929.

MS (CI, NH_3, m/z) 232 (MNH_4^+), 216, 215 (MH^+), 212.

HRMS (EI+, m/z) **:** Calculated for $C_{13}H_{13}NO_2$: 214.0868.
Found for $C_{13}H_{13}NO_2$: 214.0871.

Benzyl phenylprop-2-ynylcarbamate	**III.49**



MF: $C_{17}H_{15}NO_2$

MW = 265.30 g.mol^{-1}

Reaction: Prepared in two steps starting from aniline:
Step 1: III.49 was prepared according to the methods described in the literature[213], using aniline (0.45 ml, 5.00 mmol) in 25 ml dichloromethane to which pyridine (0.45 ml, 5.50 mmol) and benzylchloroformate (0.78 ml, 5.5 mmol) were added at 0°C. The resulted mixture was allowed to warm at room temperature and stirred overnight. Water (10 ml) was added and the organic phase was washed with a 1M solution of HCl (10 ml), a 5% sodium hydroxide solution and with water. The combined organic phases were washed with a saturated brine solution, dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (silica gel, PE/Et_2O 80/20) afforded the benzylcarbamate in 93 % yield as a pale yellow solid.
Step 2: A suspension of NaH (60 % in mineral oil, 204.2 mg, 5.107 mmol) in DMF (15 ml) was treated with the benzylcarbamate previously prepared (1.055 g, 4.64 mmol) at 0°C. The reaction mixture was stirred for 30 minutes, cooled to 0°C and propargyl bromide 80% in toluene (0.62 ml, 5.57 mmol) was added dropwise. The solution was stirred at 0°C for 1 hour before being allowed to warm at room temperature and stirred overnight.The reaction was quenched with a saturated solution of NH_4Cl (15 ml) and extracted with Et_2O (3 x 15 ml). The combined organic phases were washed with a saturated brine solution, dried over magnesium sulfate, filtered and concentrated *in vacuo*.

Purification: Flash column chromatography (silica gel, PE/AcOEt 80/20).

Product: Orange oil.

Yield: 20 % global yield.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.49-7.28 (m, 10H, 10 x C$\boldsymbol{H_{Ar}}$), 5.22 (s, 2H, OC$\boldsymbol{H_2}$), 4.46 (d, J = 2.4 Hz, 2H, NC$\boldsymbol{H_2}$), 2.30 (t, J = 2.4 Hz, 1H, ≡$\boldsymbol{C}$H).

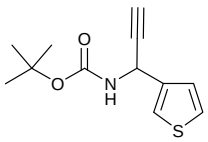
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 154.8 (***C***=O), 141.3 (***C$_{qAr}$***), 136.2 (***C$_{qAr}$***), 128.8 (H***C$_{Ar}$***), 128.3 (H***C$_{Ar}$***), 127.8 (H***C$_{Ar}$***), 127.5 (H***C$_{Ar}$***), 126.9 (H***C$_{Ar}$***), 126.6 (H***C$_{Ar}$***), 79.4 (≡***C$_q$***), 72.2 (≡***C***H), 67.4 (***C***H_2O), 40.1 (N***C***H_2).

IR (ν, cm^{-1}) (CCl_4): 3311, 3066, 3036, 2952, 1713, 1595, 1497, 1396, 1276, 1227, 1138, 1046, 1018, 980.

MS (CI, NH_3, m/z): 318, 283, 266 (MH^+).

HRMS (EI+, m/z) **:** Calculated for $C_{17}H_{15}NO_2$: 265.1103.
Found for $C_{17}H_{15}NO_2$: 265.1104.

tert-Butyl 1-(thiophen-3-yl)prop-2-ynylcarbamate — III.43n



MF: $C_{12}H_{15}NO_2S$

MW = 237.31 g.mol^{-1}

Reaction: The reaction was carried out according to **Method III.1.c.**

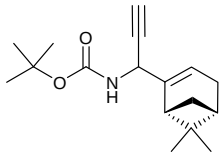
Purification: Flash column chromatography (silica gel, PE/Et_2O 90/10).

Product: White crystals.

Yield: 18 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	7.38 (m, 1H, C***H***$_{Ar}$), 7.30 (dd, J = 5.0, 3.0 Hz, 1H, C***H***$_{Ar}$), 7.13 (dd, J = 5.0, 1.2 Hz, 1H, C***H***$_{Ar}$), 5.69 (d, J = 6.4 Hz, 1H, NC***H***), 5.06 (s, 1H, N***H***), 2.47 (d, J = 2.4 Hz, 1H, ≡***C***H) 1.47 (s, 9H, C(C***H***$_3$)$_3$).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	154.6 (***C***=O), 139.7 (***C***$_{qAr}$), 126.5 (H***C***$_{Ar}$), 126.4 (H***C***$_{Ar}$), 122.5 (H***C***$_{Ar}$), 82.0 (≡***C***$_q$), 80.2 (***C***$_q$***O***), 72.0 (≡***C***H), 42.1 (N***C***H), 28.3 (C(***C***H$_3$)$_3$).
IR (ν, cm^{-1}) (CCl_4)	3649, 3449, 3310, 2978, 1721, 1487, 1367, 1312, 1264, 1171.
MS (CI, NH_3, m/z)	393, 356, 186, 157, 128.
HRMS (EI+, m/z) **:**	Calculated for $C_{12}H_{15}NO_2S$: 237.0823. Found for $C_{12}H_{15}NO_2S$: 237.0830.

tert-Butyl 1-((1*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)prop-2-ynylcarbamate III.43j



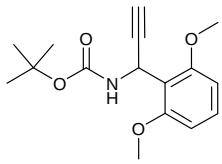
MF: $C_{17}H_{25}NO_2$

MW = 275.38 g.mol^{-1}

Reaction:	The reaction was carried out according to **Method III.1.c.**
Purification:	Flash column chromatography (silica gel, PE/Et_2O 85/15).
Product:	White solid.
Yield:	18 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	5.69 (m, 1H, =C***H***), 4.86 (d, J = 7.7 Hz, 1H, NC***H***), 4.68 (bs, 1H, N***H***), 2.46-2.38 (m, 1H, C***H***), 2.35-2.29 (m, 2H, ***H***C and ≡***C***H), 2.26 (dd, J = 4.2, 2.7 Hz, 1H, C***H***), 2.24-2.19 (m, 1H, C***H***), 2.08 (m, 1H, C***H***), 1.44 (s, 9H, C(C***H***$_3$)$_3$), 1.16 (m, 1H, C***H***), 1.29 (s, 3H, C***H***$_3$), 0.80 (s, 3H, C***H***$_3$).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	154.7 (***C***=O), 143.7 (=***C***$_q$), 119.7 (H***C***=), 81.4 (≡***C***$_q$), 79.9 (***C***$_q$***O***), 71.6 (≡***C***H), 43.0 (N***C***H), 40.6 (H***C***), 40.5 (H***C***), 38.0 (***C***$_q$), 31.7 (***C***H$_2$), 31.0 (***C***H$_2$), 28.3 (C(***C***H$_3$)$_3$), 26.0 (***C***H$_3$), 20.9 (***C***H$_3$).
IR (ν, cm^{-1}) (CCl_4)	3451, 3310, 2978, 2928, 1723, 1483, 1366, 1306, 1251, 1220, 1169, 1045, 956.
MS (CI, NH_3, m/z)	237, 220, 190, 176, 159.
HRMS (EI+, m/z) **:**	Calculated for $C_{17}H_{25}NO_2$: 275.1885. Found for $C_{17}H_{25}NO_2$: 275.1876.

tert-Butyl 1-(2,6-dimethoxyphenyl)prop-2-ynylcarbamate III.43l



MF: $C_{16}H_{21}NO_4$

MW = 291.34 g.mol^{-1}

Reaction:	The reaction was carried out according to **Method III.1.c.**
Purification:	Flash column chromatography (silica gel, PE/AcOEt 75/25).

Product: Yellow oil.

Yield: 12 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.33 (d, J = 8.1 Hz, 1H, C***H***$_{Ar}$), 6.46-6.44 (m, 2H, 2 x C***H***$_{Ar}$), 5.66 (m, 1H, NC***H***), 5.27 (bs, 1H, N***H***), 3.85 (s, 3H, C***H***$_3$), 3.80 (s, 3H, C***H***$_3$), 2.35 (d, J = 2.4 Hz, 1H, ≡***C***H), 1.44 (m, 9H, C(C***H***$_3$)$_3$).

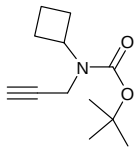
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 160.9 (O***C***$_{qAr}$), 157.8 (O***C***$_{qAr}$), 154.5 (***C***=O), 128.9 (H***C***$_{Ar}$), 119.5 (***C***$_{qAr}$), 104.0 (H***C***$_{Ar}$), 99.1 (H***C***$_{Ar}$), 83.0 (≡***C***$_q$), 79.8 (***C***$_q$***O***), 70.7 (≡***C***H), 55.5 (N***C***H), 28.3 (C(***C***H$_3$)$_3$).

IR (ν, cm^{-1}) (CCl_4): 3456, 3311, 2975, 2935, 2836, 1721, 1612, 1589, 1484, 1365, 1299, 1211, 1163, 1043.

MS (CI, NH_3, m/z): 292, 294 (MH^+); 253, 255; 175, 177.

HRMS (EI+, m/z) **:** Calculated for $C_{16}H_{21}NO_4$: 291.1471.
Found for $C_{16}H_{21}NO_4$: 291.1472.

tert-Butyl cyclobutylprop-2-ynylcarbamate — III.43f



MF: $C_{12}H_{19}NO_2$

MW = 209.28 g.mol^{-1}

Reaction: Prepared in two steps starting from cyclobutylamine hydrochloride:
Step 1: To a solution of cyclobutylamine hydrochloride (215 mg, 2.00 mmol) in 5 ml dichloromethane, triethylamine (0.30 ml, 2.00 mmol) was added and the mixture stirred for 15 minutes. A solution of di-*tert*-butyl dicarbonate (872 mg, 2.00 mmol) in 5 ml dichloromethane was then added and the mixture was stirred overnight. The organic phase was separated, washed with a 1M solution of hydrochloric acid and a saturated brine solution, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (silica gel, PE/Et_2O 90/10) afforded the protected amine in 80% yield.
Step 2: A suspension of NaH (60 % in mineral oil, 66.0 mg, 1.65 mmol) in DMF (5 ml) was treated with the protected amine previously prepared (256.5 mg, 1.50 mmol) at 0°C. The reaction mixture was stirred for 30 minutes, cooled to 0°C and propargyl bromide 80% in toluene (0.20 ml, 1.80 mmol) was added dropwise. The solution was stirred at 0°C for 1 hour before being allowed to warm at room temperature and stirred overnight.The reaction was quenched with a saturated solution of NH_4Cl (5 ml) and extracted with Et_2O (3 x 10 ml). The combined organic phases were washed with a saturated brine solution, dried over magnesium sulfate, filtered and concentrated *in vacuo.*

Purification: Flash column chromatography (silica gel, PE/Et_2O 95/5).

Product: Yellow oil.

Yield: 27 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 4.30 (m, 1H, NC***H***), 3.97 (m, 2H, NC***H***$_2$), 2.18-2.12 (m, 5H, 2 x C***H***$_2$ and ≡***C***H), 1.69-1.53 (m, 1H, ***H***C), 1.44 (s, 9H, C(C***H***$_3$)$_3$).

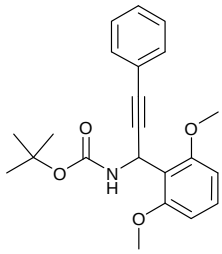
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 154.8 (***C***=O), 81.0 (≡***C***$_q$), 80.0 (***C***$_q$), 70.2 (H***C***≡), 50.6 (N***C***H), 32.7 (***C***H$_2$), 28.8 (2 x ***C***H$_2$), 28.3 (C(***C***H$_3$)$_3$), 14.6 (***C***H$_2$).

IR (ν, cm^{-1}) (CCl_4): 3707, 3375, 2926, 2855, 2360, 1649, 1513, 1457, 1261, 1113, 1004, 918.

MS (CI, NH_3, m/z): 210 (MH^+).

HRMS (EI+, m/z) **:** Calculated for $C_{12}H_{19}NO_2$: 209.1415.
Found for $C_{12}H_{19}NO_2$: 209.1421.

***tert*-Butyl 1-(2,6-dimethoxyphenyl)-3-phenylprop-2-ynylcarbamate**	**III.43lbis**



MF: $C_{22}H_{25}NO_4$

MW = 367.43 g.mol^{-1}

Reaction: Phenylacetylene (0.4 ml, 3.6 mmol) was dissolved in dry THF (14 mL), and the solution was cooled to -20 °C. BuLi (2.7 mL, 3.7 mmol, 1.6 M in hexane) was added dropwise, and after 30 min at -20°C the temperature was lowered to -78 °C. Sulfone III.56l (744 mg, 1.80 mmol) in dry THF (5 mL) was added, and the temperature was kept at -78 °C for 1 h. Quenching was made at -78 °C by rapid addition of saturated aqueous NH_4Cl (4 mL), and the mixture was allowed to reach room temperature. The mixture was extracted with CH_2Cl_2 (3 x 20 ml) and the organic phase dried over magnesium sulfate, filtered and concentrated *in vacuo.*

Purification: Flash column chromatography (silica gel, PE/AcOEt 80/20).

Product: Yellow solid.

Yield: 31 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.44-7.40 (m, 3H, 3 x C***H***$_{Ar}$), 7.29-7.27 (m, 3H, 3 x C***H***$_{Ar}$), 6.50-6.46 (m, 2H, 2 x C***H***$_{Ar}$), 5.92 (m, 1H, NC***H***), 5.38 (bs, 1H, N***H***), 3.88 (s, 3H, C***H***$_3$), 3.81 (s, 3H, C***H***$_3$), 1.47 (m, 9H, C(C***H***$_3$)$_3$).

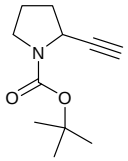
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) 160.8 (O***C***$_{qAr}$), 157.9 (O***C***$_{qAr}$), 154.5 (***C***=O), 131.6 (H***C***$_{Ar}$), 129.0 (H***C***$_{Ar}$), 128.0 (H***C***$_{Ar}$), 127.9 (H***C***$_{Ar}$), 123.0 (***C***$_{qAr}$), 120.2 (***C***$_{qAr}$), 104.0 (H***C***$_{Ar}$), 99.1 (H***C***$_{Ar}$), 88.5 (≡***C***$_q$), 82.6 (≡***C***$_q$), 79.6 (***C***$_q$***O***), 55.5 (O***C***H$_3$), 55.3 (O***C***H$_3$), 28.3 (C(***C***H$_3$)$_3$).

IR (ν, cm^{-1}) (CCl_4) 3456, 3059, 2974, 2935, 2836, 1720, 1611, 1590, 1484, 1364, 1296, 1211, 1164, 1041, 926.

MS (CI, NH_3, m/z) 368 (MH^+); 311, 266, 251, 230.

HRMS (EI+, m/z) **:** Calculated for $C_{22}H_{25}NO_4$: 367.1783.
Found for $C_{22}H_{25}NO_4$: 367.1786.

***tert*-Butyl 2-ethynylpyrrolidine-1-carboxylate**	**III.43o**



MF: $C_{11}H_{17}NO_2$

MW = 195.25 g.mol^{-1}

Reaction: Prepared in 3 steps starting from 2-pyrrolidone:
Step 1: To a solution of 2-pyrrolidone (340 mg, 4.00 mmol) and *di-tert*-butyl dicarbonate (960 g, 4.4 mmol) in acetonitrile (5 ml), *N*,*N*-(dimethylamino) pyridine (50 mg, 0.4 mmol) was added and the mixture was stirred at room temperature over the

weekend. Removal of the solvent and purification by column chromatography (silica gel, PE/AcOEt 70/30) afforded the *N*-protected amide III.57 in 80 % yield as a colourless oil.
Step 2: [217]To a solution of the *N*-protected amide III.57 (590 mg, 3.18 mmol) in dry THF (15 mL) at -78°C, DIBAL-H (3.8 mL, 3.82 mmol, 1 M solution in hexanes) was added and the resulted mixture was stirred at that temperature for 2 h. The reaction mixture was quenched with ethyl acetate (4ml) and a 10 % Rochelle salt solution (10 ml), stirred until the mixture was clear and extracted with diethyl ether (3 x 20 ml). The organic extracts were combined, dried over anhydrous magnesium sulfate, and filtered. The solvent was removed under reduced pressure to give the hemiaminal as a yellow oil which was dissolved in dry methanol (6.0 ml), a catalytic quantity of *p*TSA (55.7 mg, 0.293 mmol) was added, and the mixture was stirred overnight. A saturated solution of sodium bicarbonate was added, and the mixture was stirred for 20 min before being extracted with DCM (3 x 5 ml). The organic extracts were combined, dried over anhydrous magnesium sulfate, and filtered. The solvent was removed under vacuum and purification by column chromatography (silica gel, PE/AcOEt 80/20) afforded the aminal III.60 in 86 % yield over the 2 steps as a pale yellow oil.
Step 3:[218] To a suspension of trifluoroborate etherate complex (1.3 ml, 10.40 mmol) in anhydrous THF (4 mL) at -78 °C, ethynylmagnesium bromide 0.5 M in THF (20.80 mL, 10.40 mmol) was added and the reaction mixture was stirred at -78°C for 15 min.
The prevously synthesized aminal III.60 (496 mg, 2.6 mmol) was then added, and the reaction mixture was stirred at -78 °C for 1 h and then slowly warmed to room temperature. The reaction mixture was quenched with a saturated solution of NH_4Cl (10 ml) and extracted with Et_2O (3 x 10 ml). The combined organic extracts were washed with brine, dried overanhydrous sodium sulfate, filtered and concentrated *in vacuo*.

Purification: Flash column chromatography (silica gel, PE/AcOEt 85/15).

Product: Pale yellow oil.

Yield: 6 % global yield over 3 steps.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 4.47 (m, 1H, NC***H***), 3.47 (m, 1H, NC***H***), 3.31 (m, 1H, NC***H***), 2.22 (m, 1H, ≡***C***H), 2.13-1.98 (m, 3H, C***H*** and C***H***$_2$), 1.96-1.82 (m, 1H, ***H***C), 1.48 (s, 9H, C(C***H***$_3$)$_3$).

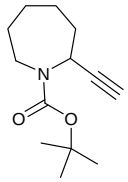
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 153.9 (***C***=O), 88.6 (≡***C***$_q$), 79.7 (***C***$_q$), 69.4 (H***C***≡), 47.8 (N***C***H), 45.5 (N***C***H), 33.6 (***C***H$_2$), 28.4 (C(***C***H$_3$)$_3$), 23.5 (***C***H$_2$).

IR (ν, cm^{-1}) (CCl_4): 2955, 2926, 2858, 1787, 1698, 1458, 1389, 1255, 1163, 1117, 974, 918.

MS (CI, NH_3, m/z): 196 (MH^+).

HRMS (EI+, m/z) **:** Calculated for $C_{11}H_{17}NO_2$: 195.1259.
Found for $C_{11}H_{17}NO_2$: 195.1261.

tert-Butyl 2-ethynylazepane-1-carboxylate — III.43q



MF: $C_{13}H_{21}NO_2$

MW = 223.31 g.mol^{-1}

Reaction: Prepared in 3 steps starting from ε-caprolactame:
Step 1: To a solution of ε-caprolactame (452 mg, 4.00 mmol) and *di-tert*-butyl dicarbonate (960 g, 4.4 mmol) in acetonitrile (5 ml), *N*,*N*-(dimethylamino) pyridine (50 mg, 0.4 mmol) was added and the resulted mixture was stirred at room temperature over the weekend. Removal of the solvent and purification by column chromatography

(silica gel, PE/AcOEt 80/20) afforded the *N*-protected amide III.59 in 40 % yield as a colourless oil.
Step 2:[217] To a solution of the previously prepared *N*-protected amide III.59 (341 mg, 1.60 mmol) in dry THF (8 mL) at -78°C, DIBAL-H (2.0 mL, 1.92 mmol, 1 M solution in hexanes) was added and the mixture was stirred at that temperature for 2 h. The reaction mixture was quenched with ethyl acetate (4ml) and a 10 % Rochelle salt solution (10 ml), stirred until the mixture was clear and extracted with diethyl ether (3 x 20 ml). The organic extracts were combined, dried over anhydrous magnesium sulfate, and filtered. The solvent was removed under reduced pressure to give the hemiaminal as a yellow oil which was dissolved in dry methanol (3.5 ml), a catalytic quantity of *p*TSA (30.4 mg, 0.16 mmol) was added, and the mixture was stirred overnight. A saturated solution of sodium bicarbonate was added, and the mixture was stirred for 20 min before being extracted with DCM (3 x 5 ml). The organic extracts were combined, dried over anhydrous magnesium sulfate, and filtered. The solvent was removed under vacuum and purification by column chromatography (silica gel, PE/AcOEt 85/15) afforded the aminal III.62 in 80 % yield over the 2 steps as a colourless oil.
Step 3:[218] To a suspension of trifluoroborate etherate complex (0.65 ml, 5.08 mmol) in anhydrous THF (2.5 mL) at -78 °C was added ethynylmagnesium bromide 0.5 M in THF (10.2 mL, 5.08 mmol), and and the reaction mixture was stirred at -78°C for 15 min. The prevously synthesized aminal III.62 (292 mg, 1.27 mmol) was then added, and the reaction mixture was stirred at -78 °C for 1 h and then slowly warmed to room temperature. The reaction mixture was quenched with a saturated solution of NH_4Cl (10 ml) and extracted with Et_2O (3 x 10 ml). The combined organic extracts were washed with brine, dried overanhydrous sodium sulfate, filtered and concentrated *in vacuo*.

Purification: Flash column chromatography (silica gel, PE/AcOEt 90/10).

Product: Pale yellow oil.

Yield: 18 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 4.85 (td, J =14.5, 8.1 Hz, 1H, NC***H***), 3.78 (tttt, J = 14.5, 3.4 Hz, 1H, NC***H***$_2$), 3.09-2.87 (m, 1H, NC***H***$_2$), 2.23 (d, J = 2.2 Hz, 1H, ≡***C***H), 2.20-2.10 (m, 1H, C***H***), 1.84-1.54 (m, 5H, ***H***C and 2 x C***H***$_2$), 1.47 (s, 9H, C(C***H***$_3$)$_3$), 1.41-1.25 (m, 2H, C***H***$_2$).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 155.2 (***C***=O), 84.16 (≡***C***$_q$), 79.6 (***C***$_q$), 70.2 (H***C***≡), 46.1 (N***C***H$_2$), 42.5 (N***C***H), 35.5 (***C***H$_2$), 28.7 (***C***H$_2$), 28.4 (C(***C***H$_3$)$_3$), 28.3 (***C***H$_2$), 24.2 (***C***H$_2$).

IR (ν, cm^{-1}) (CCl_4): 2956, 2925, 2858, 1787, 1698, 1460, 1390, 1260, 1163, 1118, 964.

MS (CI, NH_3, m/z): 124 (MH^+), 168.

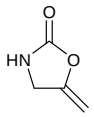
HRMS (EI+, m/z) **:** Calculated for $C_{13}H_{21}NO_2$: 223.1572.
Found for $C_{13}H_{21}NO_2$: 223.1575.

III.2. Cyclisation of propargylic tert-butylcarbamate

Method III.2. Representative experimental procedure for the cyclisation of propargylic *tert*-butylcarbamates:

To a solution of propargylic *tert*-butylcarbamate (1 equiv.) in dichloromethane (0.5 M) was added a catalytic quantity of PPh_3AuNTf_2 (generally 1 mol %). The reaction mixture was stirred at room temperature until the consumption of the starting material (reaction monitored by TLC), then filtered through a small pad of silica and the solvent was removed under reduced pressure. The residue was then purified by flash column chromatography to give the corresponding oxazolidinones.

5-Methyleneoxazolidin-2-one	**III.45bis**



MF: $C_4H_5NO_2$

MW = 99.08 g.mol^{-1}

Reaction: The reaction was carried out according to **Method III.2.**

Purification: Flash column chromatography (silica gel, PE/AcOEt 40/60).

Product: White crystals.

Yield: 55 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 6.71 (bs, 1H, N***H***), 4.75 (d, J = 2.6 Hz, 1H, =C***H***), 4.30 (d, J = 2.4 Hz, 1H, =C***H***), 4.25 (t, J = 2.2 Hz, 2H, NC$\boldsymbol{H}_2$).

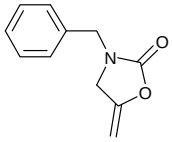
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 157.8 (***C***$_q$=), 151.3 (***C***=O), 86.2 (=***C***H_2), 44.3 (***C***H_2N).

IR (ν, cm^{-1}) (CCl_4): 3482, 3262, 3191, 2884, 2360, 1791, 1724, 1693, 1666, 1472, 1358, 1275, 1187, 1083, 983.

MS (CI, NH_3, m/z): 100 (MH^+).

HRMS (EI+, m/z) **:** Calculated for $C_4H_5NO_2$: 99.0320.
Found for $C_4H_5NO_2$: 99.0320.

3-Benzyl-5-methyleneoxazolidin-2-one — III.44a



MF: $C_{11}H_{11}NO_2$

MW = 189.21 g.mol^{-1}

Reaction: The reaction was carried out according to **Method III.2.**

Purification: Filtration on silica gel.

Product: Pale yellow oil.

Yield: 98 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.39-7.30 (m, 3H, 3 x C$\boldsymbol{H}_{Ar}$), 7.29-7.27 (m, 2H, 2 x C$\boldsymbol{H}_{Ar}$), 4.74 (dd, J = 2.8 Hz, 1H, =C***H***), 4.47 (s, 2H, NC$\boldsymbol{H}_2$Ph), 4.24 (dt, J = 2.9, 2.2 Hz, 1H, =C***H***), 4.02 (t, J = 2.4 Hz, 2H, NC$\boldsymbol{H}_2$).

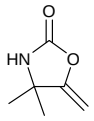
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 155.3 (***C***$_q$=), 148.7 (***C***=O), 134.7 (***C***$_{qAr}$), 128.7 (H***C***$_{Ar}$), 128.0 (H***C***$_{Ar}$), 127.9 (H***C***$_{Ar}$), 86.4 (=***C***H_2), 47.5 (Ph***C***H_2N), 46.9 (***C***H_2N).

IR (ν, cm^{-1}) (CCl_4): 3067, 3032, 2918, 2867, 1793, 1694, 1666, 1474, 1419, 1377, 1328, 1281, 1238, 1171, 1058, 970.

MS (CI, NH_3, m/z): 207 (MNH_4^+), 190 (MH^+).

HRMS (EI+, m/z) **:** Calculated for $C_{11}H_{11}NO_2$: 189.0790.
Found for $C_{11}H_{11}NO_2$: 189.0790.

4,4-Dimethyl-5-methyleneoxazolidin-2-one **III.44b**



MF: $C_6H_9NO_2$

MW = 127.14 g.mol^{-1}

Reaction: The reaction was carried out according to **Method III.2.**

Purification: Flash column chromatography (silica gel, PE/AcOEt 40/60).

Product: White solid.

Yield: 99 %.

^{1}H NMR (δ, ppm) (CDCl$_3$, 400 MHz) 4.63 (dd, J = 3.3, 0.9 Hz, 1H, =C***H***), 4.22 (d, J = 3.3 Hz, 1H, =C***H***), 1.45 (s, 6H, 2 x C***H***$_3$).

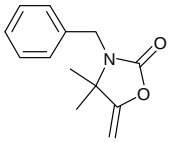
^{13}C NMR (δ, ppm) (CDCl$_3$, 100 MHz) 162.1 (***C***$_q$=), 155.7 (***C***=O), 84.1 (=***C***H$_2$), 58.3 (N***C***$_q$), 29.2 (2 x ***C***H$_3$).

IR (ν, cm^{-1}) (CCl$_4$) 3276, 3167, 2979, 2931, 1925, 1787, 1694, 1666, 1378, 1341, 1261, 1209, 1136, 1008.

MS (CI, NH$_3$, m/z) 145 (MNH$_4^+$), 128 (MH$^+$).

HRMS (EI+, m/z) **:** Calculated for $C_6H_9NO_2$: 127.0633.
Found for $C_6H_9NO_2$: 127.0633.

3-Benzyl-4,4-dimethyl-5-methyleneoxazolidin-2-one **III.44c**



MF: $C_{13}H_{15}NO_2$

MW = 217.26 g.mol^{-1}

Reaction: The reaction was carried out according to **Method III.2.**

Purification: Filtration on silica gel.

Product: Pale yellow crystals.

Yield: 100 %.

^{1}H NMR (δ, ppm) (CDCl$_3$, 400 MHz) 7.39-7.25 (m, 5H, 5 x C***H***$_{Ar}$), 4.67 (d, J = 3.3 Hz, 1H, =C***H***), 4.46 (s, 2H, NC***H***$_2$), 4.24 (d, J = 3.3 Hz, 1H, =C***H***), 1.31 (s, 6H, 2 x C***H***$_3$).

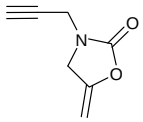
^{13}C NMR (δ, ppm) (CDCl$_3$, 100 MHz) 160.5 (***C***$_q$=), 154.6 (***C***=O), 137.4 (***C***$_{qAr}$), 128.4 (H***C***$_{Ar}$), 127.6 (H***C***$_{Ar}$), 127.5 (H***C***$_{Ar}$), 84.0 (=***C***H$_2$), 61.4 (N***C***$_q$), 43.8 (***C***H$_2$), 27.4 (2 x ***C***H$_3$).

IR (ν, cm^{-1}) (CCl$_4$) 3066, 3031, 2979, 2930, 1786, 1692, 1663, 1393, 1326, 1293, 1206, 1118, 1054, 971.

MS (CI, NH$_3$, m/z) 235 (MNH$_4^+$), 218 (MH$^+$).

HRMS (EI+, m/z) **:** Calculated for $C_{13}H_{15}NO_{22}$: 217.1103.
Found for $C_{13}H_{15}NO_2$: 217.1103.

5-methylene-3-(prop-2-ynyl)oxazolidin-2-one **III.44g**



MF: $C_7H_7NO_2$

MW = 137.13 g.mol^{-1}

Reaction: The reaction was carried out according to **Method III.2.**

Purification: Filtration on silica gel.

Product: Colourless oil.

Yield: 100 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 4.77 (dd, J = 5.6, 2.6 Hz, 1H, =C***H***), 4.35 (dt, J = 5.3, 2.3 Hz, 1H, =C***H***), 4.26 (t, J = 2.4 Hz, 2H, C***H***$_2$), 4.12 (d, J = 2.5 Hz, 2H, NC***H***$_2$), 2.35 (t, J = 2.5 Hz, 1H, ≡***C***H).

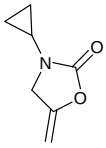
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 154.8 (***C***$_q$=), 148.5 (***C***=O), 87.1 (=***C***H$_2$), 76.0 (≡***C***$_q$), 73.8 (H***C***≡), 46.9 (N***C***H$_2$C=CH$_2$), 33.3 (N***C***H$_2$).

IR (ν, cm^{-1}) (CCl_4): 3309, 2959, 2914, 2873, 1799, 1697, 1670, 1474, 1420, 1378, 1356, 1280, 1239, 1182, 1074, 973.

MS (CI, NH_3, m/z): 155 (MNH_4^+), 138 (MH^+).

HRMS (EI+, m/z) **:** Calculated for C_7H_7NO: 137.0477.
Found for C_7H_7NO: 137.0477.

3-Cyclopropyl-5-methyleneoxazolidin-2-one — III.44e



MF: $C_7H_9NO_2$

MW = 139.15 g.mol^{-1}

Reaction: The reaction was carried out according to **Method III.2.**

Purification: Flash column chromatography (silica gel, PE/Et_2O 60/40).

Product: White solid.

Yield: 97 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 4.69 (dd, J = 5.5, 2.7 Hz, 1H, =C***H***), 4.25 (dt, J = 5.3, 2.2 Hz, 1H, =C***H***), 4.14 (t, J = 2.4 Hz, 2H, NC***H***$_2$), 2.57 (dddd, J = 7.9, 6.8, 3.9 Hz, 1H, NC***H***), 0.83-0.75 (m, 4H, 2 x C***H***$_2$).

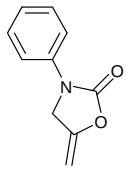
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 155.4 (***C***$_q$=), 148.9 (***C***=O), 86.3 (=***C***H$_2$), 48.9 (N***C***H$_2$), 25.2 (N***C***H), 5.75 (2 x ***C***H$_2$).

IR (ν, cm^{-1}) (CCl_4): 3096, 3004, 2922, 2869, 2359, 1800, 1694, 1665, 1471, 1411, 1280, 1109, 1025, 967.

MS (CI, NH_3, m/z): 157 (MNH_4^+), 140 (MH^+).

HRMS (EI+, m/z) **:** Calculated for $C_7H_7NO_2$: 137.0477.
Found for $C_7H_7NO_2$: 137.0477.

5-Methylene-3-phenyloxazolidin-2-one — III.44d



MF: $C_{10}H_9NO_2$

MW = 175.18 g.mol^{-1}

Reaction: The reaction was carried out according to **Method III.2.**

Purification: Flash column chromatography (silica gel, PE/Et_2O 60/40).

Product: White solid.

Yield: 95 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.54 (dd, J = 8.6, 0.8 Hz, 2H, 2 x C***H$_{Ar}$***), 7.39 (td, J =8.6, 7.4, 2.0 Hz, 2H, 2 x C***H$_{Ar}$***), 7.17 (td, J = 7.4, 0.9 Hz, 1H, C***H$_{Ar}$***), 4.85 (dd, J = 5.8, 2.6 Hz, 1H, =C***H***), 4.63 (t, J = 2.3 Hz, 2H, NC***H***$_2$), 4.43 (dt, J = 3.2, 2.2 Hz, 1H, =C***H***).

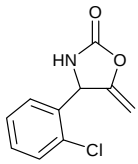
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 152.2 (***C***=O), 147.6 (***C$_q$***=), 137.1 (***C$_{qAr}$***), 129.1 (H***C$_{Ar}$***), 124.4 (H***C$_{Ar}$***), 118.0 (H***C$_{Ar}$***), 87.0 (=***C***H$_2$), 48.3 (N***C***H$_2$).

IR (ν, cm^{-1}) (CCl_4): 3046, 1796, 1698, 1670, 1597, 1504, 1472, 1398, 1374, 1290, 1205, 1116, 993.

MS (CI, NH_3, m/z): 193 (MNH_4^+), 176 (MH^+).

HRMS (EI+, m/z) **:** Calculated for $C_{10}H_9NO_2$: 175.0633.
Found for $C_{10}H_9NO_2$: 175.0633.

4-(2-Chlorophenyl)-5-methyleneoxazolidin-2-one — III.44k



MF: $C_{10}H_8ClNO_2$

MW = 209.62 g.mol^{-1}

Reaction: The reaction was carried out according to **Method III.2.**

Purification: Flash column chromatography (silica gel, PE/AcOEt 80/20).

Product: White solid.

Yield: 83 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.45-7.41 (m, 2H, 2 x C***H$_{Ar}$***), 7.35-7.28 (m, 2H, 2 x C***H$_{Ar}$***), 6.75 (bs, 1H, N***H***), 5.93 (s, 1H, NC***H***), 4.80 (m, 1H, =C***H***), 4.33 (dd, J = 3.0, 2.0 Hz, 1H, =C***H***).

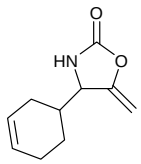
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 156.5 (***C***=O), 154.2 (***C$_q$***=), 136.6 (***C$_{qAr}$***), 132.9 (Cl***C$_{qAr}$***), 130.1 (H***C$_{Ar}$***), 130.0 (H***C$_{Ar}$***), 127.9 (H***C$_{Ar}$***), 127.6 (H***C$_{Ar}$***), 88.5 (=***C***H$_2$), 56.4 (N***C***H).

IR (ν, cm^{-1}) (CCl_4): 3468, 1809, 1674, 1473, 1445, 1393, 1355, 1315, 1250, 1173, 1043, 989.

MS (CI, NH_3, m/z): 229,227 (MNH_4^+); 212, 210 (MH^+), 197, 187.

HRMS (EI+, m/z) **:** Calculated for $C_{10}H_8ClNO_2$: 209.0244.
Found for $C_{10}H_8ClNO_2$: 209.0243.

4-(Cyclohex-3-enyl)-5-methyleneoxazolidin-2-one — III.44h



MF: $C_{10}H_{13}NO_2$

MW = 179.21 g.mol^{-1}

Reaction: The reaction was carried out according to **Method III.2.**

Purification: Flash column chromatography (silica gel, PE/AcOEt 90/10).

Product: White solid.

Yield: 82 % (obtained as a 1:1.7 mixture of diastereisomers).

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.23 (bd, 1H, N***H***), 5.66-5.62 (m, 2H, C***H***=C***H***), 4.78 (dd, J = 5.4, 2.2 Hz, 1H, =C***H***), 4.38-4.34 (m, 1H, NC***H***), 4.28 (dd, J = 3.0, 1.9 Hz, 1H, =C***H***), 2.20-2.01 (m, 3H, C***H*** and C$\boldsymbol{H_2}$), 1.92-1.71 (m, 3H, C***H*** and C$\boldsymbol{H_2}$).

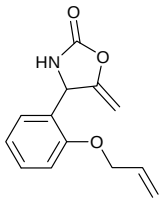
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 157.5, 157.4 (***C***$_q$=), 154.6, 154.5 (***C***=O), 127.1, 126.6 (=***C***H), 125.3, 125.2 (=***C***H), 87.2, 87.0 (=***C***H$_2$), 60.3, 60.2 (N***C***H), 39.1, 38.6 (***C***H), 27.5, 25.1 (***C***H$_2$), 25.0, 24.9 (***C***H$_2$), 24.2, 22.4 (***C***H$_2$).

IR (ν, cm^{-1}) (CCl_4): 3476, 3246, 2921, 2843, 1784, 1695, 1667, 1437, 1353, 1297, 1252, 1189, 1115, 979.

MS (CI, NH_3, m/z): 197 (MNH_4^+), 180 (MH^+).

HRMS (EI+, m/z) **:** Calculated for $C_{10}H_{13}NO_2$: 178.0868.
Found for $C_{10}H_{13}NO_2$: 178.0868.

4-(2-(Allyloxy)phenyl)-5-methyleneoxazolidin-2-one — III.44m



MF: $C_{13}H_{13}NO_3$

MW = 231.24 g.mol^{-1}

Reaction: The reaction was carried out according to **Method III.2.**

Purification: Flash column chromatography (silica gel, PE/AcOEt 70/30).

Product: White solid.

Yield: 86 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.35-7.31 (m, 2H, 2 x C$\boldsymbol{H_{Ar}}$), 6.98 (ddd, J = 7.5, 0.8 Hz, 1H, C$\boldsymbol{H_{Ar}}$), 6.92 (d, J = 8.1 Hz, 1H, C$\boldsymbol{H_{Ar}}$), 6.13 (bs, 1H, N***H***), 6.07 (ddddd, J = 17.1, 10.5, 5.2 Hz, 1H, =C***H***CH$_2$O), 5.75 (s, 1H, NC***H***), 5.41 (dddd, J = 17.2, 2.9, 1.4 Hz, 1H, =C$\boldsymbol{H_{Allyl}}$), 5.31 (dd, J = 10.5, 1.3 Hz, 1H, =C$\boldsymbol{H_{Allyl}}$), 4.79 (m, 1H, =C***H***), 4.60 (dd, J =5.2, 1.4 Hz, 2H, C$\boldsymbol{H_2}$O), 4.29 (dd, J = 2.8, 2.1 Hz, 1H, =C***H***).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 156.4 (O$\boldsymbol{C_{qAr}}$), 156.0 (***C***=O), 154.9 (***C***$_q$=), 132.6 (=***C***H), 129.9 (H$\boldsymbol{C_{Ar}}$), 127.3 (H$\boldsymbol{C_{Ar}}$), 126.7 ($\boldsymbol{C_{qAr}}$), 120.9 (H$\boldsymbol{C_{Ar}}$), 117.9 (=H$_2$$\boldsymbol{C_{Allyl}}$), 112.1 (H$\boldsymbol{C_{Ar}}$), 87.7 (=***C***H$_2$), 69.0 (O***C***H$_2$), 55.0 (N***C***H).

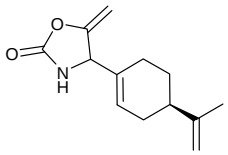
IR (ν, cm^{-1}) (CCl_4): 3473, 1798, 1671, 1597, 1490, 1456, 1358, 1323, 1247, 1174, 1110, 988.

MS (CI, NH_3, m/z): 249 (MNH_4^+), 232 (MH^+), 178.

HRMS (EI+, m/z) **:** Calculated for $C_{13}H_{13}NO_3$: 231.0895.

Found for $C_{13}H_{13}NO_3$: 231.0909.

5-Methylene-4-((R)-4-(prop-1-en-2-yl)cyclohex-1-enyl)oxazolidin-2-one **III.44i**



MF: $C_{13}H_{17}NO_2$

MW = 219.27 g.mol^{-1}

Reaction: The reaction was carried out according to **Method III.2.**

Purification: Flash column chromatography (silica gel, PE/AcOEt 70/30).

Product: Pale yellow solid.

Yield: 91 % (obtained as a 1:1.2 mixture of diastereisomers).

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 6.37 (bd, 1H, N***H***), 5.79 (m, 1H, =C***H***), 4.84 (m, 1H, =C***H***), 4.76-4.73 (m, 2H, 2 x =C***H***), 4.69 (m, 1H, =C***H***), 4.25 (m, 1H, C***H***), 2.22-1.95 (m, 5H, C***H*** and 2 x C$\boldsymbol{H}_2$), 1.87 (m, 1H, C***H***), 1.73 (s, 3H, C$\boldsymbol{H}_3$), 1.46 (m, 1H, C***H***).

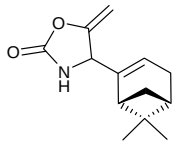
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 156.7 (***C***=O), 154.8, 154.5 (***C***$_q$=), 149.0, 148.9 (***C***$_q$=), 134.3, 134.2 (***C***$_q$=), 127.8, 127.4 (=***C***H), 109.0, 108.9 (=***C***H_2), 86.93, 86.90 (=***C***H_2), 62.4, 62.1 (N***C***H), 40.8, 40.5 (***C***H), 30.5, 30.4 (***C***H_2), 27.1, 26.9 (***C***H_2), 22.7, 22.0 (***C***H_2), 20.7, 20.6 (***C***H_3).

IR (ν, cm^{-1}) (CCl_4): 3473, 3248, 2922, 1792, 1696, 1668, 1436, 1387, 1348, 1320, 1277, 1249, 1181, 1155, 1069, 986.

MS (CI, NH_3, m/z): 253, 237 (MNH_4^+), 220 (MH^+), 166.

HRMS (EI+, m/z) **:** Calculated for $C_{13}H_{17}NO_2$: 219.1259.
Found for $C_{13}H_{17}NO_2$: 219.1254.

4-(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)-5-methyleneoxazolidin-2-one **III.44j**



MF: $C_{13}H_{17}NO_2$

MW = 219.27 g.mol^{-1}

Reaction: The reaction was carried out according to **Method III.2.**

Purification: Flash column chromatography (silica gel, PE/AcOEt 80/20).

Product: White solid.

Yield: 96 % (obtained as a 1:4.8 mixture of diastereisomers).

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.82 (bd, 1H, N***H***), 5.68-5.57 (m, 1H, =C***H***), 4.92-4.86 (m, 1H, =C***H***), 4.73 (m, 1H, =C***H***), 4.23 (m, 1H, NC***H***), 2.455 (m, 1H, C***H***), 2.38-2.22 (m, 2H, C$\boldsymbol{H}_2$), 2.17 (ddd, J = 5.5, 1.4 Hz, 1H, C***H***), 2.12 (m, 1H, C***H***), 1.29 (s, 3H, C$\boldsymbol{H}_3$), 1.11(d, J = 8.7 Hz, 1H, C***H***), 0.81 (s, 3H, C$\boldsymbol{H}_3$).

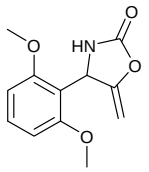
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 156.4 (***C***=O), 154.0, 153.9 (***C***$_q$=), 143.8, 143.7 (***C***$_q$=), 123.8, 123.3 (=***C***H), 87.7, 87.2 (=***C***H_2), 60.7, 60.6 (N***C***H), 41.2, 41.1 (***C***H), 40.4, 40.3 (***C***H), 37.7, 37.6 (***C***$_q$), 32.3, 31.7 (***C***H_2), 31.3, 31.1 (***C***H_2), 25.9, 25.8 (***C***H_3), 21.2, 21.1 (***C***H_3).

IR (ν, cm^{-1}) (CCl_4) 3472, 3269, 2931, 1805, 1696, 1669, 1366, 1334, 1250, 1179, 1087, 986.

MS (CI, NH_3, m/z) 237 (MNH_4^+), 220 (MH^+).

HRMS (EI+, m/z) **:** Calculated for $C_{13}H_{17}NO_2$: 219.1259.
Found for $C_{13}H_{17}NO_2$: 219.1253.

4-(2,6-Dimethoxyphenyl)-5-methyleneoxazolidin-2-one **III.44l**



MF: $C_{12}H_{13}NO_4$

MW = 235.23 $g.mol^{-1}$

Reaction: The reaction was carried out according to **Method III.2.**

Purification: Flash column chromatography (silica gel, PE/AcOEt 60/40).

Product: Pale yellow solid.

Yield: 70 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.22 (dd, J = 9.0, 2.0 Hz, 1H, C***H***$_{Ar}$), 6.49-6.46 (m, 2H, 2 x C***H***$_{Ar}$), 5.73 (bs, 1H, N***H***), 5.62 (s, 1H, NC***H***), 4.78 (m, 1H, =C***H***), 4.22 (dd, J = 2.7, 2.2 Hz, 1H, =C***H***), 3.84 (s, 3H, C***H***$_3$), 3.81 (s, 3H, C***H***$_3$).

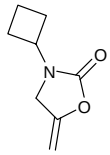
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) 161.3 (O***C***$_{qAr}$), 158.2 (O***C***$_{qAr}$), 156.2 (***C***=O), 155.3 (***C***$_q$=), 128.2 (H***C***$_{Ar}$), 119.0 (***C***$_{qAr}$), 104.2 (H***C***$_{Ar}$), 99.0 (H***C***$_{Ar}$), 87.4 (=***C***H_2), 55.5, 55.4 (O***C***H_3), 54.8 (N***C***H).

IR (ν, cm^{-1}) (CCl_4) 3473, 2956, 1796, 1671, 1612, 1588, 1506, 1462, 1291, 1257, 1210, 1162, 1120, 1039, 986, 902.

MS (CI, NH_3, m/z) 253 (MNH_4^+), 236 (MH^+), 208, 193.

HRMS (EI+, m/z) **:** Calculated for $C_{12}H_{13}NO_4$: 235.0845.
Found for $C_{12}H_{13}NO_4$: 235.0851.

3-Cyclobutyl-5-methyleneoxazolidin-2-one **III.44f**



MF: $C_8H_{11}NO_2$

MW = 153.17 $g.mol^{-1}$

Reaction: The reaction was carried out according to **Method III.2.**

Purification: Flash column chromatography (silica gel, PE/Et_2O 75/25).

Product: Orange oil.

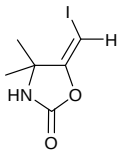
Yield: 99 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 4.70 (dd, J = 5.4, 2.6 Hz, 1H, =C***H***), 4.39 (quintuplet, J = 8.7 Hz, 1H, NC***H***), 4.28 (dd, J = 4.8, 2.4 Hz, 1H, =C***H***), 4.22 (t, J = 2.3 Hz, 2H, NC***H***$_2$), 2.18-2.09 (m, 4H, 2 x CH_2), 1.72-1.64 (m, 2H, C***H***$_2$).

^{13}C NMR (δ, ppm) 154.5 (***C***$_q$=), 149.2 (***C***=O), 86.5 (=***C***H_2), 47.8 (N***C***H), 44.8 (N***C***H_2), 27.3 (2 x ***C***H_2),

($CDCl_3$, 100 MHz)	14.8 (***C***H_2).
IR (ν, cm^{-1}) (CCl_4)	2983, 2950, 2870, 1792, 1693, 1664, 1472, 1417, 1361, 1279, 1228, 1198, 1115, 1067, 993.
MS (CI, NH_3, m/z)	171 (MNH_4^+), 154 (MH^+), 152, 128, 125.
HRMS (EI+, m/z) **:**	Calculated for $C_8H_{11}NO_2$: 153.0789. Found for $C_8H_{11}NO_2$: 153.07991.

(*Z*)-5-(Iodomethylene)-4,4-dimethyloxazolidin-2-one ***Z*-III.68**



MF: $C_6H_8INO_2$

MW = 253.03 $g.mol^{-1}$

Reaction: Obtained as the main product (together with side-product *E*-III.68) in the following reaction: to a solution of propargylic *tert*-butylcarbamate (27.45 mg, 0.15 mmol) in acetone (0.3 ml), *N*-iodosuccinimide (50.62 mg, 0.225 mmol) and a catalytic quantity of PPh_3AuNTf_2 (1.10 mg, 0.0015 mmol) were added. The reaction mixture was stirred at room temperature for 30 minutes, and then the solvent was removed under reduced pressure. The crude was washed with water, extracted with diethyl ether (3 x 5 ml), dried on anhydrous magnesium sulfate, filtered, evaporated.

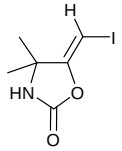
Purification : Flash column chromatography (silica gel, PE/AcOEt 60/40).

Product : Yellow solid.

Yield : 47 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	6.21 (bs, 1H, N***H***), 5.71 (s, 1H, =C***H***), 1.71 (s, 6H, 2 x C***H***$_3$).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	156.4 (***C***$_q$=), 153.5 (***C***=O), 59.9 (N***C***$_q$), 46.5 (=***C***H), 26.3 (2 x ***C***H_3).
IR (ν, cm^{-1}) (CCl_4)	3250, 3162, 1789, 1653, 1375, 1330, 1264, 1173, 1080, 1005, 955.
MS (CI, NH_3, m/z)	271 (MNH_4^+), 254 (MH^+).
HRMS (EI+, m/z) **:**	Calculated for $C_6H_8INO_2$: 252.9600. Found for $C_6H_8INO_2$: 252.9605.

(*E*)-5-(Iodomethylene)-4,4-dimethyloxazolidin-2-one ***E*-III.68**



MF: $C_6H_8INO_2$

MW = 253.03 $g.mol^{-1}$

Reaction: Obtained as a secondary product in the reaction described above, together with the other isomer *Z*-III.68.

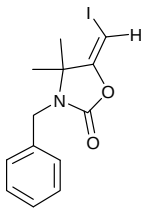
Purification : Flash column chromatography (silica gel, PE/AcOEt 60/40).

Product : Yellow solid.

Yield : 41 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	6.19 (bs, 1H, N***H***), 5.21 (s, 1H, =C***H***), 1.50 (s, 6H, 2 x C$\boldsymbol{H}_3$).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	161.8 ($\boldsymbol{C_q}$=), 153.5 (***C***=O), 59.6 (N$\boldsymbol{C_q}$), 44.5 (=***C***H), 29.3 (2 x ***C***H_3).
IR (ν, cm^{-1}) (CCl_4)	3251, 2975, 2927, 1814, 1792, 1661, 1376, 1334, 1257, 1183, 1065, 987, 919.
MS (CI, NH_3, m/z)	271 (MNH_4^+), 254 (MH^+).
HRMS (EI+, m/z) **:**	Calculated for $C_6H_8INO_2$: 252.9600. Found for $C_6H_8INO_2$: 252.9604.

(*E*)-3-Benzyl-5-(iodomethylene)-4,4-dimethyloxazolidin-2-one — III.67



MF: $C_{13}H_{14}INO_2$

MW = 343.16 $g.mol^{-1}$

Reaction: To a solution of propargylic *tert*-butylcarbamate (271 mg, 1.00 mmol) in acetone (2 ml), *N*-iodosuccinimide (337.5 mg, 1.50 mmol) and a catalytic quantity of PPh_3AuNTf_2 (7.39 mg, 0.01 mmol) were added. The reaction mixture was stirred at room temperature for 10 minutes, and then the solvent was removed under reduced pressure. The crude was washed with water, extracted with diethyl ether (3 x 5 ml), dried on anhydrous magnesium sulfate, filtered, evaporated.

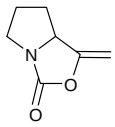
Purification : Flash column chromatography (silica gel, PE/AcOEt 85/15).

Product : White crystals.

Yield : 97 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	7.40-7.23 (m, 5H, 5 x C$\boldsymbol{H_{Ar}}$), 5.70 (s, 1H, =C***H***), 1.56 (s, 6H, 2 x C$\boldsymbol{H}_3$).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	154.8 ($\boldsymbol{C_q}$=), 153.1 (***C***=O), 137.0 ($\boldsymbol{C_{qAr}}$), 128.4 (H$\boldsymbol{C_{Ar}}$), 127.5 (H$\boldsymbol{C_{Ar}}$), 127.3 (H$\boldsymbol{C_{Ar}}$), 62.9 (N$\boldsymbol{C_q}$), 46.0 (=***C***H), 43.7 (N***C***H_2), 23.8 (2 x ***C***H_3).
IR (ν, cm^{-1}) (CCl_4)	3072, 2983, 2934, 1788, 1650, 1431, 1392, 1321, 1201, 1164, 1080, 1054, 948.
MS (CI, NH_3, m/z)	361 (MNH_4^+), 344 (MH^+), 328.
HRMS (EI+, m/z) **:**	Calculated for $C_{13}H_{14}INO_2$: 343.0069. Found for $C_{13}H_{14}INO_2$: 343.0070.

Tetrahydro-1-methylenepyrrolo[1,2-c]oxazol-3(1*H*)-one — III.44o



MF: $C_7H_9NO_2$

MW = 139.15 $g.mol^{-1}$

Reaction: The reaction was carried out according to **Method III.2.**

Purification : Flash column chromatography (silica gel, PE/AcOEt 70/30).

Product : Colorless oil

Yield : 74 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 4.73 (dd, J = 5.0, 2.2 Hz, 1H, =C***H***), 4.38 (dd, J = 8.8, 6.9 Hz, 1H, NC***H***), 4.31 (dd, J = 2.9, 1.7 Hz, 1H, =C***H***), 3.65 (dt, J = 11.1, 7.7 Hz, 1H, NC***H***), 3.23 (dt, J = 11.2, 8.8, 4.3 Hz, 1H, NC***H***), 2.24-1.90 (m, 4H, 2 x CH_2).

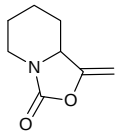
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 154.9 (***C***=O), 134.3(***C***$_q$=), 86.9 (=***C***H_2), 62.5 (N***C***H), 46.0 (N***C***H_2), 32.0 (***C***H_2), 26.3 (***C***H_2).

IR (ν, cm^{-1}) (CCl_4): 2975, 2908, 1795, 1698, 1669, 1355, 1266, 1205, 1046, 956.

MS (CI, NH_3, m/z): 157 (MNH_4^+), 140 (MH^+).

HRMS (EI+, m/z) **:** Calculated for $C_7H_9NO_2$: 139.0633.
Found for $C_7H_9NO_2$: 139.0635.

Tetrahydro-1-methylene-1*H*-oxazolo[3,4-a]pyridin-3(5*H*)-one — III.44p



MF: $C_8H_{11}NO_2$

MW = 153.17 $g.mol^{-1}$

Reaction: The reaction was carried out according to **Method III.2.**

Purification : Flash column chromatography (silica gel, PE/AcOEt 85/15).

Product : White crystals.

Yield : 65 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 4.69 (t, J = 2.7 Hz, 1H, =C***H***), 4.22 (dd, J = 2.8, 2.1 Hz, 1H, =C***H***), 4.131 (m, 1H, C***H***), 3.95 (m, 1H, C***H***), 2.86 (m, 1H, C***H***), 2.03-1.89 (m, 2H, CH_2), 1.77-1.57 (m, 2H, CH_2), 1.54-1.35 (m, 2H, CH_2).

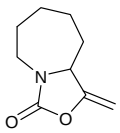
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 154.7 (***C***$_q$=), 153.5 (***C***=O), 85.4 (=***C***H_2), 56.6 (N***C***H), 40.7 (N***C***H_2), 31.5 (***C***H_2), 22.5 (***C***H_2).

IR (ν, cm^{-1}) (CCl_4): 2945, 2861, 1793, 1694, 1664, 1419, 1290, 1065, 1016, 926.

MS (CI, NH_3, m/z): 171 (MNH_4^+), 154 (MH^+).

HRMS (EI+, m/z) **:** Calculated for $C_8H_{11}NO_2$: 153.0790.
Found for $C_8H_{11}NO_2$: 153.0790.

Hexahydro-1-methyleneoxazolo[3,4-a]azepin-3(1*H*)-one — III.44q



MF: $C_9H_{13}NO_2$

MW = 167.20 $g.mol^{-1}$

Reaction: The reaction was carried out according to **Method III.2.**

Purification : Filtration on silica gel.

Product :	White crystals.
Yield :	100 %.
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	4.70 (t, J = 2.8 Hz, 1H, =C***H***), 4.44 (dddd, J = 6.4, 4.3, 2.3 Hz, 1H, NC***H***), 4.22 (dd, J = 2.7, 2.3 Hz, 1H, =C***H***), 3.63 (dddd, J = 13.1, 8.1, 3.5 Hz, 1H, C***H***), 3.17 (dddd, J = 13.9, 8.1, 2.3 Hz, 1H, C***H***), 2.00-1.92 (m, 1H, C***H***), 1.88-1.76 (m, 2H, CH_2), 1.74-1.52 (m, 5H, 2 x C$\boldsymbol{H}_2$ and C***H***).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	155.5 ($\boldsymbol{C_q}$=), 154.9 (***C***=O), 85.5 (=***C***H_2), 59.6 (N***C***H), 44.0 (N***C***H_2), 36.8 (***C***H_2), 28.9 (***C***H_2), 26.9 (***C***H_2), 25.5 (***C***H_2).
IR (ν, cm^{-1}) (CCl_4)	2933, 2858, 2360, 1787, 1691, 1662, 1446, 1407, 1298, 1238, 1100, 1046, 979.
MS (CI, NH_3, m/z)	185 (MNH_4^+), 168 (MH^+).
HRMS (EI+, m/z) **:**	Calculated for $C_9H_{13}NO_2$: 167.07946. Found for $C_9H_{13}NO_2$: 167.07947.

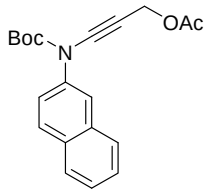
IV. Synthesis of Functionalized Oxazolones by a Sequence of Cu(II)- and Au(I)-Catalyzed Transformations

IV.1. Synthesis of Carbamate Substrates

Substrates were synthesized by a copper(II)-catalyzed coupling between bromoalkynes and *tert*-butyloxycarbamates following a slightly modified version of a procedure previously reported by Hsung and co-workers.

Method IV.1. To a solution of a bromoalkyne (1 equiv.) in dry toluene (0.33 M) were sequentially added the carbamate (1.2 equiv.), K_3PO_4 (2.4 equiv.), $CuSO_4 \cdot 5H_2O$ (0.2 equiv.) and 1,10-phenanthroline (0.4 equiv.). The reaction mixture was capped and heated at 80°C for 16 to 72 h while beeing monitored by TLC analysis. Upon completion, the reaction mixture was cooled to room temperature, diluted with ethyl acetate and filtered through celite, and the filtrate was concentrated *in vacuo*. The crude products were purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to afford the desired carbamate.

Acetic acid 3-(*tert*-butoxycarbonyl-naphthalen-2-yl-amino)-prop-2-ynyl ester	**IV.48p**



MF: $C_{20}H_{21}NO_4$

MW = 339.39 g.mol^{-1}

Reaction: Prepared according to **Method IV.1.**

Purification : Flash column chromatography (silica gel, PE/Et_2O 70/30).

Product : Yellow oil.

Yield : 49%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.92 (s, 1H, C***H***$_{Ar}$), 7.83-7.79 (m, 3H, 3 x C***H***$_{Ar}$), 7.57 (dd, J = 1.6, 8.8 Hz, 1H, C***H***$_{Ar}$), 7.45 (m, 2H, 2 x C***H***$_{Ar}$), 4.91 (s, 2H, C***H***$_2$), 2.07 (s, 3H, COC***H***$_3$), 1.55 (s, 9H, C(C***H***$_3$)$_3$).

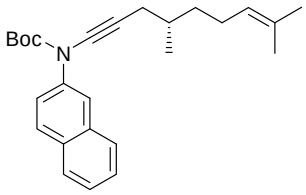
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 170.0 (C=O), 152.8 (N***C***O), 136.6 (***C***$_{qAr}$), 133.0 (***C***$_{qAr}$), 131.7 (***C***$_{qAr}$), 128.4 (***C***H$_{Ar}$), 127.7 (***C***H$_{Ar}$), 127.4 (***C***H$_{Ar}$), 126.3 (***C***H$_{Ar}$), 126.0 (***C***H$_{Ar}$), 123.1 (***C***H$_{Ar}$), 122.6 (***C***H$_{Ar}$), 83.6 (C$_q$≡***C***$_q$), 80.9 (***C***$_q$≡C$_q$), 64.7 (***C***(C***H***$_3$)$_3$), 52.6 (O***C***H$_2$), 27.7 (C(***CH***$_3$)$_3$), 20.6 (CO***C***H$_3$).

IR (ν, cm^{-1}) (CCl_4): 3464, 2061, 2980, 2936, 2260, 1741, 1597, 1512, 1468, 1368, 1289, 1223, 1156, 1020.

MS (EI+, m/z): 339 (MH$^+$), 319, 316, 305.

HRMS (EI+, m/z) **:** Calculated for $C_{20}H_{21}NO_4$: 339.1471.
Found for $C_{20}H_{21}NO_4$: 339.1471.

((*S*)-4,8-Dimethyl-non-7-en-1-ynyl)-naphthalen-2-yl-carbamic acid *tert*-butyl ester	**IV.48v**



MF: $C_{26}H_{33}NO_2$

MW = 391.55 g.mol^{-1}

Reaction: Prepared according to **Method IV.1.**
The corresponding bromoalkyne was prepared by the Corey-Fuchs method[514] starting from (*S*)-(-)-citronellal: To a solution of PPh_3 (4 equiv.) in DCM (2 M) at 0°C was added a solution of CBr_4 (2 equiv.) in DCM (2 M). The mixture was stirred at 0°C for 5', then a solution of (*S*)-(-)-citronellal (1 equiv.) in DCM (1 M) was added dropwise. The mixture was allowed to react at 0°C for 1h. Upon completion, the reaction was quenched with saturated $NaHCO_3$ aqueous solution and extracted 2 times with DCM. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Petroleum ether was added to the residue, which was then filtered and reevaporated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether) to give the dibromoalkene. The resulting dibromoalkene (1 equiv.) was dissolved in THF (0.1 M) and cooled at -78°C. LiHMDS (2 equiv., 1 M in THF solution) was added and the mixture was stirred at -78°C for 3h30'. Upon completion, the reaction was quenched with saturated NH_4Cl aqueous solution and extracted 2 times with petroleum ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether) to give the expected bromoalkyne.

Purification : Flash column chromatography (silica gel, PE/Et_2O 90/10).

Product : Yellow oil.

Yield : 65%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.96 (d, J = 2.0 Hz, 1H, C***H***$_{Ar}$), 7.83 (m, 3H, 3 x C***H***$_{Ar}$), 7.64 (dd, J = 8.8, 2.1 Hz, 1H, C***H***$_{Ar}$), 7.49 (m, 2H, 2 x C***H***$_{Ar}$), 5.13 (tm, J = 7.1 Hz, 1H, =C***H***), 2.38 (dd, J = 16.4, 5.6 Hz, 1H, C***H***$_2$), 2.29 (dd, J = 6.8, 16.4 Hz, 1H, C***H***$_2$), 2.03 (m, 2H, C***H***$_2$), 1.74 (m, 1H, C***H***), 1.70 (s, 3H, C***H***$_3$), 1.61 (s, 3H, C***H***$_3$), 1.58 (s, 9H, C(C***H***$_3$)$_3$), 1.52 (m, 1H, C***H***), 1.30 (m, 1H, C***H***), 1.06 (d, J= 6.7 Hz, 3H, C***H***$_3$).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 153.7 (N***C***O), 137.9 (N***C***$_{qAr}$), 133.3 (***C***$_{qAr}$), 131.7 (***C***$_{qAr}$), 131.3 (***C***$_{qAr}$), 128.3 (***C***H$_{Ar}$), 127.9 (***C***H$_{Ar}$), 127.6 (***C***H$_{Ar}$), 126.4 (=***C***H), 125.9 (***C***H$_{Ar}$), 124.6 (***C***H$_{Ar}$), 123.4 (***C***H$_{Ar}$), 122.3 (***C***H$_{Ar}$), 83.1 (C$_q$≡***C***$_q$), 75.3 (***C***$_q$≡C$_q$), 68.3 (***C***(C***H***$_3$)$_3$), 36.2 (***C***H$_2$), 32.5 (***C***H), 28.1 (C(***CH***$_3$)$_3$), 25.9 (***C***H$_2$), 25.8 (***C***H$_2$), 25.7 (C***H***$_3$), 19.6 (CO***C***H$_3$), 17.7 (C***H***$_3$).

IR (ν, cm^{-1}) (CCl_4): 3439, 3060, 2971, 2919, 2727, 2262, 1943, 1899, 1731, 1512, 1460, 1369, 1294, 1159, 1047.

MS (CI+, NH_3, m/z): 409 (MNH_4^+), 392 (MH^+), 353, 348, 336, 309, 292.

HRMS (EI+, m/z) **:** Calculated for $C_{26}H_{33}NO_2$: 391.2511.
Found for $C_{26}H_{33}NO_2$: 391.2512.

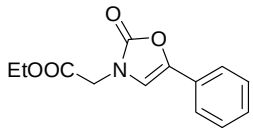
IV.2. Gold(I)-Catalyzed Formation of Oxazolones

Method IV.2.: To a solution of the substrate (1 equiv.) in dry dichloromethane (0.5 M) was added $[Ph_3P\text{-}Au\text{-}(NC\text{-}CH_3)]^+SbF_6^-$ (0.01 equiv.). The mixture was heated at 40°C and monitored periodically by TLC. Upon completion, the mixture was evaporated and the crude mixture purified either by flash column chromatography

[514] a) Charrette, A. B.;Giroux, A. *J. Org. Chem.* **1996**, *61*, 8718; b) Gung, B. W.; Dickson, H. *Org. Lett.* **2002**, *4*, 2517; c) Simpkins, S. M. E., Kariuki, B. M.; Aric, C.S.; Cox, L. R. *Org. Lett.* **2003**, *5*, 3971

(silica gel, petroleum ether / diethyl ether) or by recrystallization in petroleum ether to afford the desired oxazolones.

(2-Oxo-5-phenyl-2,3-dihydro-oxazol-4-yl)-acetic acid ethyl ester **IV.49g**



MF: $C_{13}H_{13}NO_4$

MW = 247.25 g.mol^{-1}

Reaction: Prepared according to **Method IV.2.**

Purification : Recrystallization in PE.

Product : Yellow solid.

Yield : 93%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.48 (d, J = 7.3 Hz, 2H, 2 x C$\boldsymbol{H_{Ar}}$), 7.37 (t, J = 7.3 Hz, 2H, 2 x C$\boldsymbol{H_{Ar}}$), 7.29 (t, J = 7.3 Hz, 1H, C$\boldsymbol{H_{Ar}}$), 6.85 (s, 1H, =C$\boldsymbol{H}$), 4.40 (s, 2H, C$\boldsymbol{H}_2$), 4.25 (q, J = 7.1 Hz, 2H, C$\boldsymbol{H}_2$), 1.3 (t, J = 7.1 Hz, 3H, C$\boldsymbol{H}_3$).

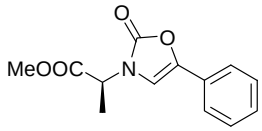
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 167.4 (***C***OOEt), 154.9 (N***C***O), 139.4 (***C$_{qAr}$***), 128.8 (***C***H$_{Ar}$), 128.3 (***C***H$_{Ar}$), 127.2 (=***C$_q$***), 123.0 (***C***H$_{Ar}$), 109.8 (=***C***H), 62.1 (O***C***H$_2$), 45.0 (***C***H$_2$), 14.1 (***C***H$_3$).

IR (ν, cm^{-1}) (CCl_4): 3063, 2981, 2937, 2360, 2336, 1775, 1759, 1419, 1260, 1199, 1096, 1021.

MS (CI+, NH_3, m/z): 265 (MNH_4^+), 248 (MH^+), 236, 225, 208, 149, 139, 132.

HRMS (EI+, m/z) **:** Calculated for $C_{13}H_{13}NO_4$: 247.0845.
Found for $C_{13}H_{13}NO_4$: 247.0843.

(*S*)-2-(2-Oxo-5-phenyl-2,3-dihydro-oxazol-4-yl)-propionic acid methyl ester **IV.49h**



MF: $C_{13}H_{13}NO_4$

MW = 247.25 g.mol^{-1}

MO : Prepared according to **Method IV.2.**

Purification : Recristallization in PE.

Product : Orange solid.

Yield : 94%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.49 (d, J = 7.5 Hz, 2H, 2 x C$\boldsymbol{H_{Ar}}$), 7.37 (t, J = 7.4 Hz, 2H, 2 x C$\boldsymbol{H_{Ar}}$), 7.29 (t, J = 7.3 Hz, 1H, C$\boldsymbol{H_{Ar}}$), 6.95 (s, 1H, =C$\boldsymbol{H}$), 4.89 (q, J = 7.4 Hz, 1H, C$\boldsymbol{H}$), 3.77 (s, 3H, COOC$\boldsymbol{H}_3$), 1.63 (d, J = 7.4 Hz, 3H, C$\boldsymbol{H}_3$).

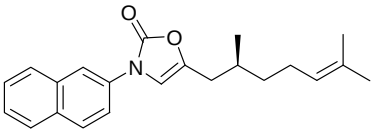
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 170.8 (***C***OOMe), 154.4 (N***C***O), 139.5 (***C$_{qAr}$***), 128.8 (***C***H$_{Ar}$), 128.2 (***C***H$_{Ar}$), 127.2 (=***C$_q$***), 123.0 (***C***H$_{Ar}$), 107.1 (=***C***H), 52.9 (O***C***H$_3$), 51.4 (***C***H), 17.1 (***C***H$_3$).

IR (ν, cm^{-1}) (CCl_4): 3156, 3063, 2991, 2953, 2850, 1766, 1599, 1451, 1395, 1201, 1182, 1055.

MS (CI+, NH_3, m/z): 265 (MNH_4^+), 248 (MH^+), 240, 220, 208, 149.

HRMS (EI+, m/z) **:** Calculated for $C_{13}H_{13}NO_4$: 247.0845.
Found for $C_{13}H_{13}NO_4$: 247.0845.

5-((*S*)-2,6-Dimethyl-hept-5-enyl)-3-naphthalen-2-yl-3*H*-oxazol-2-one **IV.49v**



MF: $C_{22}H_{25}NO_2$

MW = 335.44 g.mol^{-1}

MO : Prepared according to **Method IV.2.**

Purification : Flash column chromatography (silica gel, PE/Et_2O 70/30).

Product : White solid.

Yield : 80%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 8.01 (d, J = 1.8 Hz, 1H, C***H***$_{Ar}$), 7.90 (d, J = 8.9 Hz, 1H, C***H***$_{Ar}$), 7.84 (d, J = 8.0 Hz, 2H, 2 x C***H***$_{Ar}$), 7.73 (dd, J = 8.9, 2.1 Hz, 1H, C***H***$_{Ar}$), 7.50 (m, 2H, 2 x C***H***$_{Ar}$), 6.73 (s, 1H, =C***H***), 5.13 (t, J = 7.0 Hz, 1H, =C***H***), 2.50 (dd, J = 15.1, 5.8 Hz, 1H, C***H***), 2.30 (dd, J = 15.2, 7.8 Hz, 1H, C***H***), 2.06 (m, 2H, C***H***$_2$), 1.88 (m, 1H, C***H***), 1.71 (s, 3H, C***H***$_3$), 1.64 (s, 3H, C***H***$_3$), 1.47 (m, 2H, C***H***$_2$), 1.00 (d, J = 6.7 Hz, 3H, C***H***$_3$).

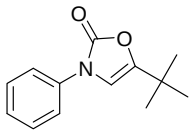
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 153.4 (N***C***O), 141.0 (***C***$_{qAr}$), 133.4 (***C***$_{qAr}$), 133.2 (=***C***$_q$), 131.7 (=***C***$_q$O), 131.3 (***C***H$_{Ar}$), 129.4 (***C***H$_{Ar}$), 127.8 (***C***H$_{Ar}$), 127.7 (***C***H$_{Ar}$), 127.0 (***C***H$_{Ar}$), 126.0 (=***C***H), 124.2 (***C***H$_{Ar}$), 119.4 (***C***H$_{Ar}$), 118.2 (***C***H$_{Ar}$), 110.0 (=***C***H), 36.6 (***C***H$_2$), 33.5 (***C***H$_2$), 30.8 (***C***H), 25.8 (***C***H$_3$), 25.5 (***C***H$_2$), 19.4 (***C***H$_3$), 17.7 (***C***H$_3$).

IR (ν, cm^{-1}) (CCl_4): 3650, 3154, 3059, 2964, 2922, 2856, 1768, 1634, 1599, 1513, 1474, 1397, 1298, 1102.

MS (CI+, NH_3, m/z): 353 (MNH_4^+), 336 (MH^+), 322, 310, 292, 224.

HRMS (EI+, m/z) **:** Calculated for $C_{22}H_{25}NO_2$: 335.1885.
Found for $C_{22}H_{25}NO_2$: 335.1888.

5-*tert*-Butyl-3-phenyl-3*H*-oxazol-2-one **IV.49i**



MF: $C_{13}H_{15}NO_2$

MW = 217.26 g.mol^{-1}

MO : Prepared according to **Method IV.2**.

Purification : Flash column chromatography (silica gel, PE/Et_2O 80/20).

Product : Yellow solid.

Yield : 58%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.57 (d, J = 7.7 Hz, 2H, 2 x C***H***$_{Ar}$), 7.43 (t, J = 7.6 Hz, 2H, 2 x C***H***$_{Ar}$), 7.26 (t, J = 7.4 Hz, 1H, C***H***$_{Ar}$), 6.50 (s, 1H, =C***H***), 1.27 (s, 9H, C(C***H***$_3$)$_3$).

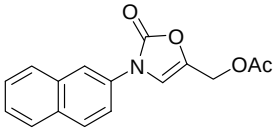
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 153.4 (N***C***O), 149.7 (=***C***$_q$O), 135.9 (***C***$_{qAr}$), 129.4 (***C***H$_{Ar}$), 126.2 (***C***H$_{Ar}$), 120.8 (***C***H$_{Ar}$), 106.6 (=***C***H), 31.3 (***C***(C***H***$_3$)$_3$), 27.7 (C(***C***H$_3$)$_3$).

IR (ν, cm^{-1}) (CCl_4): 3651, 3160, 2968, 2872, 1768, 1597, 1505, 1390, 1301, 1250, 1223, 11111

MS (CI+, NH_3, m/z): 235 (MNH_4^+), 218 (MH^+), 202.

HRMS (EI+, m/z) **:** Calculated for $C_{13}H_{15}NO_2$: 217.1103.
Found $C_{13}H_{15}NO_2$: 217.1103.

Acetic acid 3-naphthalen-2-yl-2-oxo-2,3-dihydro-oxazol-5-ylmethyl ester	**IV.49p**



MF: $C_{16}H_{13}NO_4$

MW = 283.28 g.mol^{-1}

MO : Prepared according to **Method IV.2.**

Purification : Recristallization in PE.

Product : Orange solid.

Yield : 88%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.99 (d, J = 1.6 Hz, 1H, C***H$_{Ar}$***), 7.90 (d, J = 8.8 Hz, 1H, C***H$_{Ar}$***), 7.84 (d, J = 8.4 Hz, 2H, 2 x C***H$_{Ar}$***), 7.65 (dd, J = 2.1, 8.8 Hz, 1H, C***H$_{Ar}$***), 7.51 (m, 2H, 2 x C***H$_{Ar}$***), 7.10 (s, 1H, =C***H***), 4.93 (s, 2H, C***H***$_2$), 2.13 (s, 3H, COC***H***$_3$).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 170.5 (C=O), 152.8 (N***C***O), 135.6 (***C$_{qAr}$***), 133.3 (***C$_{qAr}$***), 132.6 (***C$_{qAr}$***), 131.6 (=***C$_q$***O), 129.6 (***C***H$_{Ar}$), 127.9 (***C***H$_{Ar}$), 127.7 (***C***H$_{Ar}$), 127.1 (***C***H$_{Ar}$), 126.4 (***C***H$_{Ar}$), 119.4 (***C***H$_{Ar}$), 118.9 (***C***H$_{Ar}$), 114.9 (=***C***H), 56.1 (O***C***H$_2$), 20.8 (CO***C***H$_3$).

IR (ν, cm^{-1}) (CCl_4): 3671, 3154, 3060, 2962, 2081, 1776, 1748, 1633, 1599, 1513, 1401, 1218, 1098, 1021.

MS (EI+, m/z): 283 (M^+), 267, 232.

HRMS (EI+, m/z) **:** Calculated for $C_{16}H_{13}NO_4$: 283.0845.
Found for $C_{16}H_{13}NO_4$: 283.0843.

V. Gold(I) Catalyzed Stereoselective Formation of Functionalized 2,5-Dihydrofurans

V.1. Synthesis of Substrates

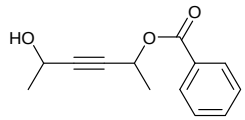
Method V.1.a. General procedure for the synthesis of monoprotected butynediols:[355]

3-Hexyne-2,5-diol (1 equiv.) in dichloromethane was treated with the corresponding acyl chloride (1 equiv.) and pyridine (1.5 equiv.) at 0°C. The resulted mixture is stirred at room temperature overnight and then washed with a 1M solution of HCl (3 x 10 ml), water (2 x 10 ml) and a saturated brine solution, then dried over anhydrous magnesium sulfate, filtered and evaporated.

Method V.1.b. Substrates were synthesized according to Carreira's procedures:[354]

A flask was charged with $Zn(OTf)_2$ (400 mg, 1.1 mmol, 1.1 equiv.) and heated under *vacuum* using a heat gun for 5 minutes. (+) or (-)-*N*-methyl ephedrine (216 mg, 1.2 mmol, 1.2 equiv.) was added and the flask was purged with nitrogen for 15 min. Toluene (3 mL) and triethylamine (0.170 mL, 1.2 mmol, 1.2 equiv.) were added. The resulting mixture was stirred at room temperature for 2h before the corresponding alkyne (1 equiv.) diluted in 1 mL of toluene was added. After 30 min of stirring, the aldehyde (1.1 equiv.) was added in one portion by syringe. The reaction was stirred and heated at 60°C for 1h to 2h depending on the alkyne substrate. The mixture was quenched with a saturated aqueous ammonium chloride solution and extracted with ether. The combined organic layers were dried over anhydrous magnesium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography (Silica gel, petroleum ether-diethyl ether).
The resulted diol was dissolved in dichloromethane (0.5 M, 10 mL) and triethylamine (1.2 equiv., 6 mmol, 0.835 mL), acyl chloride (1.1 equiv., 5.5 mmol, 0.640 mL) and a catalytic amount of DMAP were successively added. After 1 hour, water (10 mL) was added and the mixture was then extracted with diethyl ether. The combined organic layers were washed with a saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulphate, filtered and the solvents were removed under reduced pressure. The residue was finally purified by flash column chromatography (silica gel, petroleum ether – diethyl ether) to give the corresponding propargylic alcohol.

5-Hydroxyhex-3-yn-2-yl benzoate	**V.63a**



MF: $C_{13}H_{14}O_3$

MW = 218.24 g.mol^{-1}

Reaction: Prepared according to **Method V.1.a.**

Purification: Flash column chromatography (silica gel, PE/Et_2O 60/40).

Product: Pale yellow oil.

Yield: 63 % (obtained as a 1:1 mixture of diastereoisomers).

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): For the 1:1 mixture of diastereoisomers: 8.12-8.10 (m, 4H, 4 x C$\boldsymbol{H_{Ar}}$), 7.64-7.60 (m, 2H, 2 x C$\boldsymbol{H_{Ar}}$), 7.51-7.47 (m, 4H, 4 x C$\boldsymbol{H_{Ar}}$), 5.77 (qd, J = 6.7, 1.3 Hz, 2H, 2 x ***H***COBz), 5.65-4.58 (m, 2H, 2 x ***H***COH), 2.07 (bs, 2H, 2 x O***H***), 1.65 (d, J = 6.7 Hz, 6H, 2 x C$\boldsymbol{H_3}$), 1.50 (d, J = 6.7 Hz, 6H, 2 x C$\boldsymbol{H_3}$).

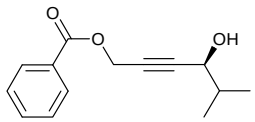
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): For the 1:1 mixture of diastereoisomers: 2 x 165.6 (***C***=O), 2 x 133.7 (H$\boldsymbol{C_{Ar}}$), 2 x 130.0 ($\boldsymbol{C_{qAr}}$), 2 x 129.9 (H$\boldsymbol{C_{Ar}}$), 2 x 128.5 (H$\boldsymbol{C_{Ar}}$), 2 x 86.8 (C≡$\boldsymbol{C_q}$), 2 x 82.5 ($\boldsymbol{C_q}$≡C), 2 x 61.0 (H***C***OBz), 2 x 58.4 (***C***HOH), 2 x 24.2 (***C***H_3), 2 x 21.6 (***C***H_3).

IR (ν, cm^{-1}) (CCl_4) 3614, 2988, 1724, 1449, 1316, 1262, 1170, 1103,1059.

MS (CI, NH_3, m/z) 236 (MNH_4^+), 219 (MH^+), 202.

HRMS (EI+, m/z) **:** Calculated for $C_{13}H_{14}O_3$: 218.0943.
Found for $C_{13}H_{14}O_3$: 218.0942.

(*S*)-4-hydroxy-5-methylhex-2-ynyl benzoate	**V.66a**



MF: $C_{14}H_{16}O_3$

MW = 232.27 $g.mol^{-1}$

Reaction: Prepared according to **Method V.1.b.**

Purification: Flash column chromatography (silica gel, PE/Et_2O 75/25).

Product: Colourless oil.

Yield : 93 %, 87% ee.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 8.11 (d, J = 8.1 Hz, 2H, 2 x C***H***$_{Ar}$), 7.64 (t, J = 8.1 Hz, 1H, C***H***$_{Ar}$), 7.50 (t, J = 8.1 Hz, 2H, 2 x C***H***$_{Ar}$), 5.02 (d, J = 1.7 Hz, 2H, C***H***$_2$), 4.28 (dt, J = 5.7, 1.7 Hz, 1H, ***H***COH), 2.01-1.89 (m, 1H, C***H***), 1.80 (bs, 1H, O***H***), 1.06 (d, J = 6.4 Hz, 3H, C***H***$_3$), 1.05 (d, J = 6.4 Hz, 3H, C***H***$_3$).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) 166.1 (***C***=O), 133.4 (H***C***$_{Ar}$), 129.8 (***C***$_{qAr}$), 129.4 (H***C***$_{Ar}$), 128.5 (H***C***$_{Ar}$), 87.1 (C≡***C***$_q$), 79.3 (***C***$_q$≡C), 67.7 (H***C***OBz), 53.0 (***C***HOH), 34.4 (***C***H), 18.2 (***C***H_3), 17.6 (***C***H_3).

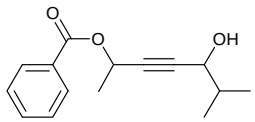
IR (ν, cm^{-1}) (CCl_4) 3618, 2964, 2874, 1728, 1452, 1268, 1263, 1101, 1022.

MS (CI, NH_3, m/z) 250 (MNH_4^+), 215.

HRMS (EI+, m/z) **:** Calculated for $C_{14}H_{16}O_3$: 232.1099.
Found for $C_{14}H_{16}O_3$: 232.1093.

HPLC (15 cm ChiracelOD-H column, hν= 254 nm)**:** Heptane/ isopropanol : 98/2, 1 mL / min
Major V.66a: 20.52 min
Minor ent-V.66a: 16.26 min

5-Hydroxy-6-methylhept-3-yn-2-yl benzoate	**V.63b**



MF: $C_{15}H_{18}O_3$

MW = 246.30 $g.mol^{-1}$

Reaction: A lithium diisopropylamide solution (LDA) was prepared by adding *n*-butylithium (1.43 mL, 1.6 M in hexanes, 2.3 mmol) to 5 mL of THF containing diisopropylamine (0.335 mL, 2.4 mmol) at -20°C. After 30 min, the LDA solution was cooled to -78°C and benzoic acid 1-methyl-prop-2-ynyl ester (348 mg, 2 mmol) dissolved in 2 mL of THF was added. After 30 min, the aldehyde (3 mmol) was added and the mixture was stirred for a further 30 min. Saturated aqueous ammonium chloride was then added and the cooling bath was removed to reach room temperature. The mixture was extracted with diethyl ether. The combined organic layers were washed with a saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered and the solvents were removed under reduced pressure.

Purification: Flash column chromatography (silica gel, PE/Et_2O 80/20).

Product: Pale yellow oil.

Yield: 67 % (obtained as a 1:1 mixture of diastereoisomers).

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): For the 1:1 mixture of diastereoisomers: 8.12-8.10 (m, 4H, 4 x C***H$_{Ar}$***), 7.64-7.59 (m, 2H, 2 x C***H$_{Ar}$***), 7.51-7.47 (m, 4H, 4 x C***H$_{Ar}$***), 5.81-5.75 (m, 2H, 2 x ***H***COBz), 4.26 (bt, J = 5.4 Hz, 2H, 2 x ***H***COH), 1.99-1.89 (m, 4H), 1.06 (d, J = 6.7 Hz, 3H, C***H***$_3$), 1.05 (d, J = 6.7 Hz, 3H, C***H***$_3$), 1.03 (d, J = 6.7 Hz, 6H, 2 x C***H***$_3$).

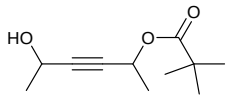
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): For the 1:1 mixture of diastereoisomers: 2 x 165.5 (***C***=O), 2 x 133.2 (H***C$_{Ar}$***), 2 x 130.0 (***C$_{qAr}$***), 2 x 129.8 (H***C$_{Ar}$***), 2 x 128.4 (H***C$_{Ar}$***), 84.8 (C≡***C$_q$***), 84.7 (C≡***C$_q$***), 84.5 (***C$_q$***≡C), 84.0 (***C$_q$***≡C), 2 x 67.8 (H***C***OBz), 2 x 60.9 (***C***HOH), 2 x 34.8 (***C***H), 2 x 21.6 (***C***H$_3$), 18.1 (***C***H$_3$), 18.0 (***C***H$_3$), 17.5 (***C***H$_3$), 17.4 (***C***H$_3$).

IR (ν, cm^{-1}) (CCl_4): 3618, 2964, 1724, 1600, 1451, 1315, 1262, 1166, 1105, 1023.

MS (CI, NH_3, m/z): 264 (MNH_4^+), 247 (MH^+), 229.

HRMS (EI+, m/z) **:** Calculated for $C_{15}H_{18}O_3$: 246.1256.
Found for $C_{15}H_{18}O_3$: 246.1249.

5-Hydroxyhex-3-yn-2-yl pivalate **V.68**



MF: $C_{11}H_{18}O_3$

MW = 198.25 $g.mol^{-1}$

Reaction: Prepared according to **Method V.1.a.**

Purification: Flash column chromatography (silica gel, PE/Et_2O 65/35).

Product: Pale yellow oil.

Yield: 25 % (obtained as a 1:1 mixture of diastereoisomers).

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): For the 1:1 mixture of diastereoisomers: 5.41 (dq, J = 6.6, 1.3 Hz, 1H, ***H***COPiv), 4.52 (dq, J = 6.6, 1.4 Hz, 1H, ***H***COH), 2.75 (bs, 1H, O***H***), 1.44 (d, J = 6.7 Hz, 3H, C***H***$_3$), 1.41 (d, J = 6.6 Hz, 3H, C***H***$_3$), 1.18 (s, 9H, C(C***H***$_3$)$_3$).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): For the 1:1 mixture of diastereoisomers: 177.6 (***C***=O), 86.5 (C≡***C$_q$***), 82.4 (***C$_q$***≡C), 60.2 (H***C***OPiv), 58.2 (***C***HOH), 38.7 (***C***(CH$_3$)$_3$), 27.0 (C(***C***H$_3$)$_3$), 24.1 (***C***H$_3$), 21.2 (***C***H$_3$).

IR (ν, cm^{-1}) (CCl_4): 3615, 2980, 2935, 2872, 1732, 1479, 1370, 1276, 1146, 1052, 965.

MS (CI, NH_3, m/z): 216 (MNH_4^+), 182.

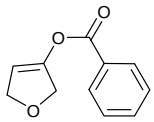
HRMS (EI+, m/z) **:** Calculated for $C_{11}H_{18}O_3$: 198.1255.
Found for $C_{11}H_{18}O_3$: 198.1257.

V.2. Au(I) Catalyzed Formation of 2,5-Dihydrofurans

Method V.2.: To a solution of the substrate (0.25 mmol, 1 equiv.) in 0.5 mL (0.5 M) of dry dichloromethane at the stated conditions of temperature was added 2 mol% of the gold catalyst (3.7 mg of $(Ph_3P)AuNTf_2$, 4.2 mg of $(Ad_2nBuP)AuNTf_2$, 4.7 mg of $[(pCF_3Ph)P]AuNTf_2$ respectively). The reaction was stirred until full consumption of the starting material (as attested by TLC analysis). The resulting mixture was then filtered through a small

pad of silica pre-impregnated with dichloromethane. The pad was washed with ether and the filtrate evaporated. The residue was purified by flash chromatography (silica gel, petroleum ether – diethyl ether).

2,5-Dihydrofuran-3-yl benzoate	**V.62c**



MF: $C_{11}H_{10}O_3$

MW = 190.19 g.mol^{-1}

Reaction: The reaction was carried out according to **Method V.2.**

Purification: Flash column chromatography (silica gel, PE/Et_2O 70/30).

Product: Colorless crystals.

Yield: 85 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 8.12 (d, J = 8.2 Hz, 2H, 2 x C***H$_{Ar}$***), 7.66 (t, J = 8.2 Hz, 1H, C***H$_{Ar}$***), 7.52 (t, J = 8.2 Hz, 2H, 2 x C***H$_{Ar}$***), 5.91-5.89 (m, 1H, ***H***C=), 4.84-4.77 (m, 4H, 2 x OC***H***$_2$).

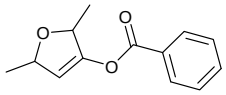
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 163.4 (***C***=O), 145.7 (=***C$_q$***O), 133.9 (H***C$_{Ar}$***), 130.1 (***C$_{qAr}$***), 128.9 (H***C$_{Ar}$***), 128.7 (H***C$_{Ar}$***), 2 x 107.5 (=H***C***), 73.7 (***C***H$_2$), 71.1 (***C***H$_2$).

IR (ν, cm^{-1}) (CCl_4): 2855, 1748, 1662, 1255, 1197, 1090, 1054.

MS (CI, NH_3, m/z): 208 (MNH_4^+), 191 (MH^+).

HRMS (EI+, m/z) **:** Calculated for $C_{11}H_{10}O_3$: 190.0630.
Found for $C_{11}H_{10}O_3$: 190.0621.

2,5-Dihydro-2,5-dimethylfuran-3-yl benzoate	**V.64a**



MF: $C_{13}H_{14}O_3$

MW = 218.24 g.mol^{-1}

Reaction: The reaction was carried out according to **Method V.2.**

Purification: Flash column chromatography (silica gel, PE/Et_2O 65/35).

Product: Pale yellow oil.

Yield: 95 % (obtained as a 1:1 mixture of diastereoisomers).

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): For the 1:1 mixture of diastereoisomers: 8.09-8.07 (m, 4H, 4 x C***H$_{Ar}$***), 7.63 (t, J = 8.0 Hz, 2H, 2 x C***H$_{Ar}$***), 7.49 (t, J = 8.0 Hz, 4H, 4 x C***H$_{Ar}$***), 5.91-5.89 (m, 2H, 2 x ***H***C=), 5.12-5.06 (m, 1H, OC***H***), 5.05-4.98 (m, 2H, 2 x OC***H***), 4.97-4.90 (m, 1H, OC***H***), 1.41 (d, J = 6.3 Hz, 3H, C***H***$_3$), 1.38 (d, J = 6.3 Hz, 3H, C***H***$_3$), 1.37 (d, J = 6.3 Hz, 3H, C***H***$_3$), 1.36 (d, J = 6.3 Hz, 3H, C***H***$_3$).

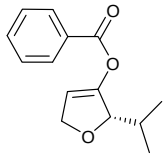
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): For the 1:1 mixture of diastereoisomers: 163.5, 163.4 (***C***=O), 148.5, 148.4 (=***C$_q$***O), 2 x 133.7 (H***C$_{Ar}$***), 2 x 129.9 (***C$_{qAr}$***), 2 x 129.1 (H***C$_{Ar}$***), 2 x 128.7 (H***C$_{Ar}$***), 111.9, 111.5 (=H***C***), 79.3 (***C***H$_2$), 79.2 (***C***H$_2$), 23.7 (***C***H$_3$), 22.4 (***C***H$_3$), 21.4 (***C***H$_3$), 20.0 (***C***H$_3$).

IR (ν, cm^{-1}) (CCl_4): 2975, 2859, 1749, 1658, 1449, 1253, 1196, 1104, 1064.

MS (CI, NH_3, m/z): 236 (MNH_4^+), 219 (MH^+).

HRMS (EI+, m/z) **:** Calculated for $C_{13}H_{14}O_3$: 218.0943.
Found for $C_{13}H_{14}O_3$: 218.0942.

(*S*)-2,5-Dihydro-2-isopropylfuran-3-yl benzoate	**V.67a**



MF: $C_{14}H_{16}O_3$

MW = 232.27 g.mol^{-1}

Reaction: The reaction was carried out according to **Method V.2.**

Purification: Flash column chromatography (silica gel, PE/Et_2O 90/10 to 80/20).

Product: Colourless oil.

Yield: 83 %, 86% ee.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 8.07 (d, J = 8.1 Hz, 2H, 2 x C***H***$_{Ar}$), 7.67 (t, J = 8.1 Hz, 1H, C***H***$_{Ar}$), 7.49 (t, J = 8.1 Hz, 2H, 2 x C***H***$_{Ar}$), 6.03 (t, J = 1.5 Hz, 1H, ***H***C=), 4.79-4.70 (m, 3H, OC***H***$_2$ and OC***H***), 1.98 (septd, J = 6.9, 2.5 Hz, 1H, ((CH$_3$)$_2$C***H***), 1.06 (d, J = 6.9 Hz, 3H, C***H***$_3$), 0.94 (d, J = 6.9 Hz, 3H, C***H***$_3$).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 163.5 (***C***=O), 146.1 (=***C***$_q$O), 133.8 (H***C***$_{Ar}$), 130.0 (***C***$_{qAr}$), 129.1 (H***C***$_{Ar}$), 128.7 (H***C***$_{Ar}$), 108.3 (=H***C***), 85.8 (O***C***H$_2$), 73.4 (O***C***H), 31.5 (CH$_3$)$_2$***C***H), 18.7 (***C***H$_3$), 15.7 (***C***H$_3$).

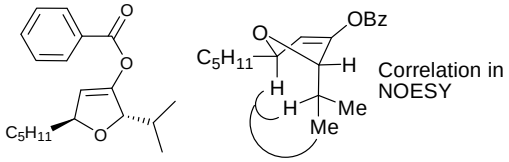
IR (ν, cm^{-1}) (CCl_4): 2964, 2873, 1749, 1658, 1454, 1253, 1193, 1056, 1021.

MS (CI, NH_3, m/z): 250 (MNH$_4^+$), 233 (MH$^+$).

HRMS (EI+, m/z) **:** Calculated for $C_{14}H_{16}O_3$: 232.1099.
Found for $C_{14}H_{16}O_3$: 232.1097.

HPLC (15 cm ChiracelOD-H column, hν= 254 nm): Heptane/ isopropanol : 99.5/0.5, 1 mL / min
Major V.67a: 6.13 min
Minor ent-V.67a: 6.88 min.

(2*S*,5*S*)-2,5-Dihydro-2-isopropyl-5-pentylfuran-3-yl benzoate	**V.67b**



MF: $C_{19}H_{26}O_3$

MW = 302.40 g.mol^{-1}

Reaction: The reaction was carried out according to **Method V.2.**

Purification: Flash column chromatography (silica gel, PE/Et_2O 97.5/2.5).

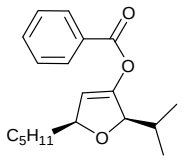
Product: Pale yellow oil.

Yield: 97 %, 98 % ee, 93:7 dr.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 8.10 (d, J = 8.0 Hz, 2H, 2 x C***H***$_{Ar}$), 7.65 (t, J = 8.0 Hz, 1H, C***H***$_{Ar}$), 7.52 (t, J = 8.0 Hz, 2H, 2 x C***H***$_{Ar}$), 6.03 (bs, 1H, ***H***C=), 4.94 (qd, J = 5.8, 1.2 Hz, 1H, ***H***CO), 4.84-4.81 (m, 1H, ***H***CO), 2.01 (septd, J = 6.9, 2.8 Hz, 1H, ((CH$_3$)$_2$C***H***), 1.76-1.62 (m, 2H, C***H***$_2$), 1.53-1.30 (m, 6H, 3 x C***H***$_2$), 1.11 (d, J = 6.9 Hz, 3H, C***H***$_3$), 0.99 (d, J = 6.9 Hz, 3H, C***H***$_3$), 0.94 (t, J = 6.8 Hz, 3H, C***H***$_3$).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	163.4 (***C***=O), 146.3 (=***C***$_q$O), 133.7 (H***C***$_{Ar}$), 129.9 (***C***$_{qAr}$), 129.2 (H***C***$_{Ar}$), 128.7 (H***C***$_{Ar}$), 111.8 (=H***C***), 85.7 (O***C***H), 84.2 (O***C***H), 36.9 (***C***H_2), 32.0 (***C***H_2), 31.8 $(CH_3)_2$***C***H), 24.7 (***C***H_2), 22.7 (***C***H_2), 18.7 (***C***H_3), 16.0 (***C***H_3), 14.1 (***C***H_3).
IR (ν, cm^{-1}) (CCl_4)	2960, 2930, 2862, 1748, 1657, 1458, 1253, 1193, 1078.
MS (CI, NH_3, m/z)	320 (MNH_4^+), 303 (MH^+).
HRMS (EI+, m/z) **:**	Calculated for $C_{19}H_{26}O_3$: 302.1882. Found for $C_{19}H_{26}O_3$: 302.1880.
HPLC (15 cm ChiracelOD-H column, hν= 254 nm):	Heptane/ isopropanol : 99.5/0.5, 0.5 mL / min Major V.67b: 4.55 min Minor ent-V.67b: 5.20 min.

(2*R*,5*S*)-2,5-dihydro-2-isopropyl-5-pentylfuran-3-yl benzoate — V.67c

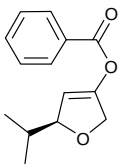


MF: $C_{19}H_{26}O_3$

MW = 302.40 $g.mol^{-1}$

Reaction:	The reaction was carried out according to **Method V.2.**
Purification:	Flash column chromatography (silica gel, PE/Et_2O 95.5/4.5).
Product:	Pale yellow oil.
Yield:	99 %, 98 % ee, 92:8 dr.
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	8.10 (d, J = 8.0 Hz, 2H, 2 x C***H***$_{Ar}$), 7.66 (t, J = 8.0 Hz, 1H, C***H***$_{Ar}$), 7.53 (t, J = 8.0 Hz, 2H, 2 x C***H***$_{Ar}$), 6.01 (bt, J = 1.7 Hz, 1H, ***H***C=), 4.92-4.87 (m, 1H, ***H***CO), 4.82-4.79 (m, 1H, ***H***CO), 1.99 (septd, J = 6.9, 2.8 Hz, 1H, $((CH_3)_2$C***H***), 1.75-1.56 (m, 2H, C***H***$_2$), 1.55-1.30 (m, 6H, 3 x C***H***$_2$), 1.11 (d, J = 6.9 Hz, 3H, C***H***$_3$), 0.97 (d, J = 6.9 Hz, 3H, C***H***$_3$), 0.95 (t, J = 6.8 Hz, 3H, C***H***$_3$).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	163.5 (***C***=O), 146.6 (=***C***$_q$O), 133.7 (H***C***$_{Ar}$), 129.9 (***C***$_{qAr}$), 129.2 (H***C***$_{Ar}$), 128.7 (H***C***$_{Ar}$), 112.2 (=H***C***), 85.6 (O***C***H), 83.1 (O***C***H), 36.9 (***C***H_2), 31.9 (***C***H_2), 30.7 $(CH_3)_2$***C***H), 25.2 (***C***H_2), 22.7 (***C***H_2), 18.9 (***C***H_3), 16.4 (***C***H_3), 14.1 (***C***H_3).
IR (ν, cm^{-1}) (CCl_4)	2961, 2871, 1750, 1698, 1601, 1256.
MS (CI, NH_3, m/z)	320 (MNH_4^+), 303 (MH^+).
HRMS (EI+, m/z) **:**	Calculated for $C_{19}H_{26}O_3$: 302.1882. Found for $C_{19}H_{26}O_3$: 302.1883.
HPLC (15 cm ChiracelOD-H column, hν= 254 nm)**:**	Heptane/ isopropanol : 99.5/0.5, 0.5 mL / min Major V.67c: 5.23 min Minor ent-V.67c: 4.59 min

(*S*)-2,5-Dihydro-5-isopropylfuran-3-yl benzoate — V.67e



MF: $C_{14}H_{16}O_3$

MW = 232.27 $g.mol^{-1}$

Reaction: The reaction was carried out according to **Method V.2** with $(Ad_2nBuP)AuNTf_2$ as catalyst**.**

Purification: Flash column chromatography (silica gel, PE/Et_2O 90/10).

Product: Colourless oil.

Yield: 99%, up to 90% ee (see Table V.6, Chapter V)

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 8.08 (d, J = 7.9 Hz, 2H, 2 x C$\boldsymbol{H_{Ar}}$), 7.62 (t, J = 7.9 Hz, 1H, C$\boldsymbol{H_{Ar}}$), 7.48 (t, J = 7.9 Hz, 2H, 2 x C$\boldsymbol{H_{Ar}}$), 5.81 (bs, 1H, ***H***C=), 4.75 (m, 3H, OC$\boldsymbol{H_2}$ and OC***H***), 1.90-1.91 (m, 1H, $(CH_3)_2$C***H***), 0.97 (d, J = 7.0 Hz, 3H, C$\boldsymbol{H_3}$), 0.96 (d, J = 7.0 Hz, 3H, C$\boldsymbol{H_3}$).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 163.4 (***C***=O), 146.4 (=$\boldsymbol{C_q}$O), 133.8 (H$\boldsymbol{C_{Ar}}$), 130.1 ($\boldsymbol{C_{qAr}}$), 128.9 (H$\boldsymbol{C_{Ar}}$), 128.7 (H$\boldsymbol{C_{Ar}}$), 109.2 (=H***C***), 89.7 (O***C***H), 71.4 (O***C***H_2), 33.8 ($(CH_3)_2$***C***H), 17.9 (***C***H_3), 17.8 (***C***H_3).

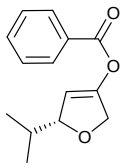
IR (ν, cm^{-1}) (CCl_4): 2970, 1746, 1697, 1598, 1253, 1090.

MS (CI, NH_3, m/z): 250 (MNH_4^+), 233 (MH^+).

HRMS (EI+, m/z) **:** Calculated for $C_{14}H_{16}O_3$: 232.1099.
Found for $C_{14}H_{16}O_3$: 232.1106.

HPLC (15 cm ChiracelOD-H column, hν= 254 nm): Heptane/ isopropanol : 99.75/0.25, 0.25 mL / min
Major V.67e: 20.48 min
Minor ent-V.67e: 19.30 min

(*R*)-2,5-Dihydro-5-isopropylfuran-3-yl benzoate — V.67d



MF: $C_{14}H_{16}O_3$

MW = 232.27 $g.mol^{-1}$

Reaction: The reaction was carried out according to **Method V.2.**

Purification: Flash column chromatography (silica gel, PE/Et_2O 90/10).

Product: Colourless oil.

Yield: 99%, 64% ee.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 8.08 (d, J = 7.9 Hz, 2H, 2 x C$\boldsymbol{H_{Ar}}$), 7.62 (t, J = 7.9 Hz, 1H, C$\boldsymbol{H_{Ar}}$), 7.48 (t, J = 7.9 Hz, 2H, 2 x C$\boldsymbol{H_{Ar}}$), 5.81 (bs, 1H, ***H***C=), 4.75 (m, 3H, OC$\boldsymbol{H_2}$ and OC***H***), 1.90-1.91 (m, 1H, $(CH_3)_2$C***H***), 0.97 (d, J = 7.0 Hz, 3H, C$\boldsymbol{H_3}$), 0.96 (d, J = 7.0 Hz, 3H, C$\boldsymbol{H_3}$).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 163.4 (***C***=O), 146.4 (=$\boldsymbol{C_q}$O), 133.8 (H$\boldsymbol{C_{Ar}}$), 130.1 ($\boldsymbol{C_{qAr}}$), 128.9 (H$\boldsymbol{C_{Ar}}$), 128.7 (H$\boldsymbol{C_{Ar}}$), 109.2 (=H***C***), 89.7 (O***C***H), 71.4 (O***C***H_2), 33.8 ($(CH_3)_2$***C***H), 17.9 (***C***H_3), 17.8 (***C***H_3).

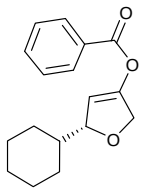
IR (ν, cm^{-1}) (CCl_4): 2967, 2875, 1747, 1697, 1598, 1254, 1087.

MS (CI, NH_3, m/z): 250 (MNH_4^+), 233 (MH^+).

HRMS (EI+, m/z) **:** Calculated for $C_{14}H_{16}O_3$: 232.1099.
Found for $C_{14}H_{16}O_3$: 232.1101.

HPLC (15 cm ChiracelOD-H column, hν= 254 nm): Heptane/ isopropanol : 99.75/0.25, 0.25 mL / min
Major V.67d: 14.10 min
Minor ent-V.67d: 15.07 min

(*R*)-5-Cyclohexyl-2,5-dihydrofuran-3-yl benzoate — V.67f



MF: $C_{17}H_{20}O_3$

MW = 272.33 g.mol^{-1}

Reaction: The reaction was carried out according to **Method V.2** with $(Ad_2nBuP)AuNTf_2$ as catalyst**.**

Purification: Flash column chromatography (silica gel, PE/Et_2O 90/10).

Product: Pale yellow oil.

Yield: 91 %, 77 % ee.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 8.07 (d, J = 8.0 Hz, 2H, 2 x C***H***$_{Ar}$), 7.62 (t, J = 8.0 Hz, 1H, C***H***$_{Ar}$), 7.48 (t, J = 8.0 Hz, 2H, 2 x C***H***$_{Ar}$), 5.81 (m, 1H, ***H***C=), 4.77-4.71 (m, 3H, OC***H***$_2$ and OC***H***), 1.87-1.67 (m, 5H, 2 x C***H***$_2$ and C***H***), 1.60-1.51 (m, 1H, C***H***), 1.32-0.98 (m, 5H, 2 x C***H***$_2$ and C***H***).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 163.5 (***C***=O), 146.1 (=***C***$_q$O), 133.8 (H***C***$_{Ar}$), 130.1 (***C***$_{qAr}$), 128.9 (H***C***$_{Ar}$), 128.7 (H***C***$_{Ar}$), 109.5 (=H***C***), 89.0 (O***C***H), 71.2 (O***C***H_2), 43.9 (***C***H), 28.4 (***C***H_2), 28.3 (***C***H_2), 26.6 (***C***H_2), 26.2 (***C***H_2), 26.1 (***C***H_2).

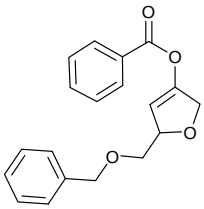
IR (ν, cm^{-1}) (CCl_4): 2927, 2853, 1747, 1659, 1450, 1254, 1199, 1089, 1054.

MS (CI, NH_3, m/z): 290 (MNH_4^+), 273 (MH^+).

HRMS (EI+, m/z) **:** Calculated for $C_{17}H_{20}O_3$: 272.1412.
Found for $C_{17}H_{20}O_3$: 272.1422.

HPLC (15 cm ChiracelOD-H column, hν= 254 nm): Heptane/ isopropanol : 99.25/0.75, 0.5 mL / min
Major V.67f: 9.03 min
Minor ent-V.67f: 9.83 min

5-((Benzyloxy)methyl)-2,5-dihydrofuran-3-yl benzoate — V.64d



MF: $C_{19}H_{18}O_4$

MW = 310.34 g.mol^{-1}

Reaction: The reaction was carried out according to **Method V.2.**

Purification: Filtration on silica gel.

Product: Yellow oil.

Yield: 99 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 8.12 (d, J = 7.9 Hz, 2H, 2 x C***H***$_{Ar}$), 7.67 (t, J = 7.9 Hz, 1H, C***H***$_{Ar}$), 7.53 (t, J = 7.9 Hz, 2H, 2 x C***H***$_{Ar}$), 7.44-7.31 (m, 5H, 5 x C***H***$_{Ar}$), 5.90-5.88 (m, 1H, ***H***C=), 5.20-5.14 (m, 1H, OC***H***), 4.91-4.81 (m, 2H, OC***H***$_2$), 4.68 (d, J = 12.2 Hz, 1H, PhC***H***O), 4.65 (d, J = 12.2 Hz, 1H, PhC***H***O), 3.68-3.64 (m, 2H, OC***H***$_2$CH).

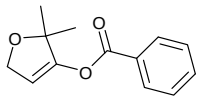
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 163.2 (***C***=O), 147.2 (=***C***$_q$O), 138.2 (***C***$_{qAr}$), 133.9 (H***C***$_{Ar}$), 130.1 (H***C***$_{Ar}$), 128.8 (***C***$_{qAr}$), 128.7 (H***C***$_{Ar}$), 128.4 (H***C***$_{Ar}$), 127.8 (H***C***$_{Ar}$), 127.74 (H***C***$_{Ar}$), 108.0 (=H***C***), 83.8 (O***C***H), 73.5 (O***C***H_2), 73.0 (O***C***H_2), 71.3 (O***C***H_2).

IR (ν, cm^{-1}) (CCl_4) 2971, 1750, 1698, 1254, 2085.

MS (CI, NH_3, m/z) 328 (MNH_4^+).

HRMS (EI+, m/z) **:** Calculated for $C_{19}H_{18}O_4$: 310.1205.
Found for $C_{19}H_{18}O_4$: 310.1210.

2,5-Dihydro-2,2-dimethylfuran-3-yl benzoate	**V.64f**



MF: $C_{13}H_{14}O_3$

MW = 218.24 $g.mol^{-1}$

Reaction: The reaction was carried out according to **Method V.2.**

Purification: Flash column chromatography (silica gel, PE/Et_2O 90/10).

Product: Colourless oil.

Yield: 69 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 8.12 (d, J = 8.0 Hz, 2H, 2 x C***H***$_{Ar}$), 7.67 (t, J = 8.0 Hz, 1H, C***H***$_{Ar}$), 7.54 (t, J = 8.0 Hz, 2H, 2 x C***H***$_{Ar}$), 6.01 (t, J = 1.7 Hz, 1H, ***H***C=), 4.76 (d, J = 1.7 Hz, 2H, OC***H***$_2$), 1.47 (s, 6H, 2 x C***H***$_3$).

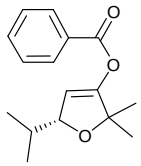
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) 163.6 (***C***=O), 150.0 (=***C***$_q$O), 133.7 (H***C***$_{Ar}$), 129.9 (***C***$_{qAr}$), 129.3 (H***C***$_{Ar}$), 128.7 (H***C***$_{Ar}$), 104.9 (=H***C***), 83.4 (O***C***$_q$), 70.8 (O***C***H_2), 26.1 (2 x ***C***H_3).

IR (ν, cm^{-1}) (CCl_4) 2975, 1852, 1750, 1659, 1255, 1149, 1049.

MS (CI, NH_3, m/z) 236 (MNH_4^+), 219 (MH^+).

HRMS (EI+, m/z) **:** Calculated for $C_{13}H_{14}O_3$: 218.0943.
Found for $C_{13}H_{14}O_3$: 218.0947.

(*R*)-2,5-dihydro-5-isopropyl-2,2-dimethylfuran-3-yl benzoate	**V.67g**



MF: $C_{16}H_{20}O_3$

MW = 260.32 $g.mol^{-1}$

Reaction: The reaction was carried out according to **Method V.2.**

Purification: Flash column chromatography (silica gel, PE/Et_2O 99/1 to 97/3).

Product: Yellow oil.

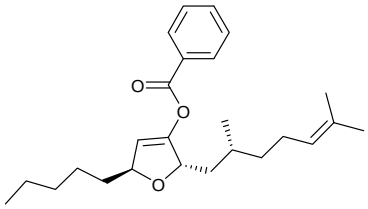
Yield: 95%, 80% ee.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 8.12 (d, J = 8.0 Hz, 2H, 2 x C***H***$_{Ar}$), 7.66 (t, J = 8.0 Hz, 1H, C***H***$_{Ar}$), 7.54 (t, J = 8.0 Hz, 2H, 2 x C***H***$_{Ar}$), 5.94 (d, J = 1.3 Hz, 1H, ***H***C=), 4.73 (dd, J = 5.5, 1.3 Hz, 1H, OC***H***), 1.84 (septd, J = 6.7, 5.5 Hz, 1H, $(CH_3)_2$C***H***), 1.49 (s, 3H, C***H***$_3$), 1.47 (s, 3H, C***H***$_3$), 1.01 (d, J = 6.7 Hz, 3H, C***H***$_3$), 0.99 (d, J = 6.7 Hz, 3H, C***H***$_3$).

^{13}C NMR (δ, ppm) 163.6 (=***C***$_q$O), 150.7 (***C***=O), 133.7 (H***C***$_{Ar}$), 129.9 (***C***$_{qAr}$), 129.4 (H***C***$_{Ar}$), 128.7 (H***C***$_{Ar}$), 106.9 (=H***C***), 86.9 (O***C***H), 83.0 (O***C***$_q$), 33.6 ($(CH_3)_2$***C***H), 27.0 (***C***H_3), 26.4 (***C***H_3), 18.3

($CDCl_3$, 100 MHz)	(***C***H_3), 17.9 (***C***H_3).
IR (ν, cm^{-1}) (CCl_4)	2970, 1749, 1658, 1459, 1254, 1152, 1057.
MS (CI, NH_3, m/z)	278 (MNH_4^+), 261 (MH^+).
HRMS (EI+, m/z) **:**	Calculated for $C_{16}H_{20}O_3$: 260.1412. Found for $C_{16}H_{20}O_3$: 260.1404.
HPLC (15 cm ChiracelOD-H column, hν= 254 nm):	Heptane/ isopropanol : 99.25/0.75, 0.3 mL / min Major V.67g: 11.22 min Minor ent-V.67g: 12.10 min.

(2*S*,5*S*)-2,5-Dihydro-2-((*R*)-2,6-dimethylhept-5-enyl)-5-pentylfuran-3-yl benzoate **V.67h**



MF: $C_{25}H_{36}O_3$

MW = 384.55 $g.mol^{-1}$

Reaction:	The reaction was carried out according to **Method V.2.**
Purification:	Flash column chromatography (silica gel, PE/Et_2O 85/15).
Product:	Yellow oil.
Yield:	99%, >98% ee, 90:10 dr.
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	8.10 (d, J = 8.0 Hz, 2H, 2 x C***H***$_{Ar}$), 7.66 (t, J = 8.1 Hz, 1H, C***H***$_{Ar}$), 7.53 (t, J = 8.1 Hz, 2H, 2 x C***H***$_{Ar}$), 5.96 (bs, 1H, ***H***C=), 5.15 (t, J = 7.1 Hz, 1H, ***H***C=), 5.00-4.94 (m, 2H, 2 x OC***H***), 2.13-1.95 (m, 2H, C***H***$_2$), 1.86-1.63 (m, 3H, C***H***$_2$ and C***H***), 1.70 (s, 3H, C***H***$_3$), 1.63 (s, 3H, C***H***$_3$), 1.57-1.31 (m, 9H), 1.27-1.17 (m, 1H, C***H***), 1.03 (d, J = 6.6 Hz, 3H, C***H***$_3$), 0.94 (t, J = 6.9 Hz, 3H, C***H***$_3$).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	163.5 (***C***=O), 148.1 (=***C***$_q$O), 133.7 (***C***$_{qAr}$), 131.1 (H***C***$_{Ar}$), 129.9 (H***C***$_{Ar}$), 129.2 (H***C***$_{Ar}$), 128.7 (H***C***$_{Ar}$), 124.9 (H***C***$_{Ar}$), 110.7 (=H***C***), 83.2 (O***C***H), 79.8 (O***C***H), 41.7 (***C***H_2), 36.9 (***C***H_2), 36.6 (***C***H_2), 32.0 (***C***H_2), 29.4 (***C***H), 25.7 (***C***H_3), 25.4 (***C***H_2), 24.7 (***C***H_2), 22.7 (***C***H_2), 20.5 (***C***H_3), 17.7 (***C***H_3), 14.1 (***C***H_3).
IR (ν, cm^{-1}) (CCl_4)	3066, 2926, 2859, 2360, 1748, 1656, 1453, 1254, 1192, 1081, 1021.
MS (CI, NH_3, m/z)	402 (MNH_4^+), 385 (MH^+), 367, 259.
HRMS (EI+, m/z) **:**	Calculated for $C_{25}H_{36}O_3$: 384.2665. Found for $C_{25}H_{36}O_3$: 384.2662.
HPLC (15 cm ChiracelOD-H column, hν= 254 nm):	Heptane/ isopropanol : 99.75/0.25, 0.25 mL / min Major V.67h: 12.47 min Minor ent-V.67h: 13.26 min.

VI. Gold(I)-Catalyzed Isomerization of Allenyl Carbinol Esters: an Efficient Access to Functionalized 1,3-Butadien-2-ol Esters

VI.1. Synthesis of the Allenic Substrates

The precursors were all synthesized in a 2 step sequence starting from the corresponding propargylic alcohols *via* a Crabbé homologation, followed by the protection of the resulting allenols using standard procedures described in the literature.[388]

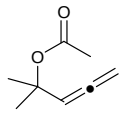
Method VI.1.a.

Step 1: To a solution of propargylic alcohol (1 equiv.) in THF (0.5 M), paraformaldehyde (2 equiv.), cuprous bromide (0.5 equiv.), and diisopropylamine (1.5 equiv.) were sequentially added. The resulting mixture was refluxed and upon completion, it was allowed to cool to room temperature and filtered through a Celite plug. The filtrate was concentrated under reduced pressure and the resulting residue was diluted with diethyl ether and HCl 1N solution. The etheric phase was separated, and the aqueous solution was extracted with diethyl ether. The combined organic phases were then washed with saturated sodium chloride solution, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The crude is purified by flash column chromathography (silica gel, petroleum ether/diethyl ether).
Step 2: To a solution of the previously prepared secondary alcohol (1 equiv.) in DCM (0.4 M) at 0^oC, NEt_3 (2 equiv.), the corresponding acylating agent (1.5 equiv. of Ac_2O or 1.1 equiv. of BzCl or PivCl or 1.0 equiv. of Boc_2O respectively) and a catalytical amount of DMAP (0.05 equiv.) were added. The resulted mixture was stirred at RT before being quenched with saturated aqueous NH_4Cl solution and extracted with diethyl ether. The combined organic phases were washed with brine, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether/diethyl ether).

Method VI.1.b.

Step 1: To a solution of propargylic alcohol (1 equiv.) in THF (0.5 M), paraformaldehyde (2 equiv.), cuprous bromide (0.5 equiv.), and diisopropylamine (1.5 equiv.) were sequentially added. The resulting mixture was refluxed and when completed it was allowed to cool to room temperature and filtered through a Celite plug. The filtrate was concentrated under reduced pressure and the resulting residue was diluted with diethyl ether and HCl 1N solution. The etheric phase was separated and the aqueous solution was extracted diethyl ether. The combined organic phases were then washed with saturated sodium chloride solution, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The crude is purified by flash column chromathography (silica gel, petroleum ether/diethyl ether).
Step 2: To a solution containing the tertiary alcohol prepared in the previous step (1 equiv.) in pyridine (0.5 M), the corresponding acylating agent (2 equiv. of Ac_2O or 1.5 equiv. of PivCl respectively) and a catalytical amount of DMAP (0.1 equiv.) were sequentially added. The mixture was heated at 60^oC, quenched with saturated aqueous HCl 1N solution and then extracted with diethyl ether. The combined organic phases were washed with water and then brine, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether/diethyl ether).

Acetic acid 1,1-dimethyl-buta-2,3-dienyl ester	**VI.44i**

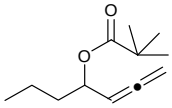


MF: $C_8H_{12}O_2$

MW = 140.18 $g.mol^{-1}$

EP :	Prepared according to Method **VI.1.b.**
Purification :	Flash column chromatography (silica gel, PE/Et_2O 90/10).
Product :	Colourless oil
Yield :	60 %
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	5.60 (t, J = 6.7, 6.7 Hz, 1H, =C***H***), 4.81 (d, J = 6.7 Hz, 2H, =C$\boldsymbol{H}_2$), 1.91 (s, 3H, COC$\boldsymbol{H}_3$), 1.47 (s, 6H, 2 x C$\boldsymbol{H}_3$).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	206.9 (=***C***=), 170.1 (***C***=O), 96.6 (=***C***H), 78.9 ($\boldsymbol{C_q}$), 77.9 (=***C***H_2), 27.1 (2 x ***C***H_3), 22.2 (CO***C***H_3).
IR (ν, cm^{-1}) (CCl_4)	3647, 2982, 2935, 1956, 1736, 1435, 1367, 1251, 1125, 1012, 918.
MS (CI, NH_3, m/z)	203, 180, 169, 145, 127, 113.
HRMS (EI+, m/z) **:**	Calculated for $C_8H_{12}O_2$: 140.0837. Found for $C_8H_{12}O_2$: 140.0835.

2,2-Dimethyl-propionic acid 1-propyl-buta-2,3-dienyl ester — VI.44d

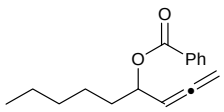


MF: $C_{12}H_{20}O_2$

MW = 196.29 $g.mol^{-1}$

Reaction:	Prepared according to **Method VI.1.a.**
Purification :	Flash column chromatography (silica gel, PE/Et_2O 90/10).
Product :	Pale yellow oil.
Yield :	99 %
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	5.23-5.07 (m, 2H, 2 x =C***H***), 4.81-4.72 (m, 2H, =C***H*** and =C***H***O), 1.69-1.51 (m, 2H, C$\boldsymbol{H}_2$), 1.42-1.27 (m, 2H, C$\boldsymbol{H}_2$), 1.15 (s, 9H, C(C$\boldsymbol{H}_3$)$_3$), 0.9 (t, J = 7.4 Hz, 3H, C$\boldsymbol{H}_3$).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	208.1 (=***C***=), 177.7 (***C***=O), 91.1 (=***C***H), 77.1 (=***C***H_2), 70.7 (O***C***H), 38.7 (***C***(CH_3)$_3$), 36.2 (***C***H_2), 27.1 (C(***C***H_3)$_3$), 18.5 (***C***H_2), 13.7 (***C***H_3).
IR (ν, cm^{-1}) (CCl_4)	2965, 2935, 2873, 1958, 1811, 1727, 1478, 1395, 1366, 1280, 1156, 1037, 1004, 938.
MS (CI, NH_3, m/z)	214 (MNH_4^+), 204, 197 (MH^+).
HRMS (EI+, m/z) **:**	Calculated for $C_{12}H_{20}O_2$: 196.1463. Found for $C_{12}H_{20}O_2$: 196.1469.

Benzoic acid 1-propa-1,2-dienyl-hexyl ester — VI.44f



MF: $C_{16}H_{20}O_2$

MW= 244.33 $g.mol^{-1}$

Reaction:	Prepared according to **Method VI.1.a**.
Purification :	Flash column chromatography (silica gel, PE/Et_2O 90/10).

Product : Pale yellow oil

Yield : 99 %

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 8.07 (d, J = 7.1 Hz, 2H, 2 x C***H***$_{Ar}$), 7.53 (t, J = 7.4 Hz, 1H, C***H***$_{Ar}$), 7.42 (t, J = 7.2 Hz, 2H, 2 x C***H***$_{Ar}$), 5.54 (m, 1H, =C***H***), 5.35 (q, J = 6.6 Hz, 1H, =C***H***), 4.94-4.80 (m, J = 6.6 Hz, 2H, =C***H***$_2$), 1.90-1.73 (m, 2H, C***H***$_2$), 1.45 (m, 2H, C***H***$_2$), 1.37-1.32 (m, 4H, 2 x C***H***$_2$), 0.90 (t, J = 7.0 Hz, 3H, C***H***$_3$).

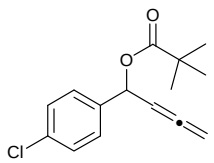
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 208.4 (=***C***=), 165.8 (***C***=O), 132.7 (***C***H$_{Ar}$), 130.5 (***C***$_{qAr}$), 129.5 (***C***H$_{Ar}$), 128.2 (***C***H$_{Ar}$), 90.9 (=***C***H), 77.2 (=***C***H$_2$), 72.3 (O***C***H), 34.2 (***C***H$_2$), 31.5 (***C***H$_2$), 24.9 (***C***H$_2$), 22.5 (***C***H$_2$), 13.9 (***C***H$_3$).

IR (ν, cm^{-1}) (CCl_4): 3660, 3418, 3066, 2954, 2932, 2862, 1958, 1721, 1601, 1453, 1314, 1267, 1175, 1106, 1067, 1024, 988, 928.

MS (CI, NH_3, m/z): 262, 253, 249, 246, 245 (MH^+), 243.

HRMS (EI+, m/z) **:** Calculated for $C_{16}H_{20}O_2$: 244.1463.
Found for $C_{16}H_{20}O_2$: 244.1459.

2,2-Dimethyl-propionic acid 1-(4-chloro-phenyl)-buta-2,3-dienyl ester — VI.44a



MF: $C_{15}H_{17}O_2Cl$

MW = 264.75 g.mol^{-1}

Reaction: Prepared according to **Method VI.1.a.**

Purification : Flash column chromatography (silica gel, PE/Et_2O 99/01).

Product : Pale yellow oil

Yield : 25 %

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.32 (s, 4H, 4 x C***H***$_{Ar}$), 6.24 (dt, J = 6.3, 2.5 Hz, 1H, =C***H***), 5.40 (q, J = 6.5 Hz, 1H, =C***H***), 4.85 (m, 2H, =C***H***$_2$), 1.23 (s, 9H, C(C***H***$_3$)$_3$).

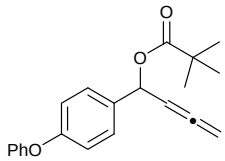
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 208.4 (=***C***=), 177.1 (***C***=O), 138.1 (***C***$_{qAr}$), 133.8 (Cl***C***$_{Ar}$), 128.6 (***C***H$_{Ar}$), 128.0 (***C***H$_{Ar}$), 91.6 (=***C***H), 78.1 (=***C***H$_2$), 72.2 (O***C***H), 38.8 (***C***(CH$_3$)$_3$), 27.1 (C(***C***H$_3$)$_3$).

IR (ν, cm^{-1}) (CCl_4): 2974, 2873, 1958, 1734, 1597, 1488, 1398, 1275, 1145, 1093, 1012, 964, 918.

MS (CI, NH_3, m/z): 282 (MNH_4^+), 269, 267, 265 (MH^+).

HRMS (EI+, m/z) **:** Calculated for $C_{15}H_{17}O_2Cl$: 264.0917.
Found for $C_{15}H_{17}O_2Cl$: 264.0914.

2,2-Dimethyl-propionic acid 1-(4-phenoxy-phenyl)-buta-2,3-dienyl ester — VI.44b



MF: $C_{21}H_{22}O_3$

MW = 322.40 g.mol^{-1}

Reaction: Prepared according to **Method VI.1.a.**

Purification : Flash column chromatography (silica gel, PE/Et_2O 95/05).

Product : Yellow oil

Yield : 40 %

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.38-7.32 (m, 4H, 4 x C***H***$_{Ar}$), 7.14 (tt, J = 7.4, 0.9 Hz, 1H, C***H***$_{Ar}$), 7.06-6.98 (m, 4H, 4 x C***H***$_{Ar}$), 6.28 (td, J = 6.4, 2.3 Hz, 1H, =C***H***), 5.43 (q, J = 6.5 Hz, 1H, =C***H***), 4.90 (m, 2H, =C***H***$_2$), 1.26 (s, 9H, C(C***H***$_3$)$_3$).

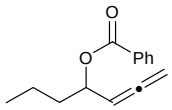
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 208.4 (=***C***=), 177.3 (***C***=O), 157.2 (O***C***$_{qAr}$), 156.9 (O***C***$_{qAr}$), 134.3 (***C***$_{qAr}$), 129.8 (***C***H$_{Ar}$), 128.3 (***C***H$_{Ar}$), 123.5 (***C***H$_{Ar}$), 119.2 (***C***H$_{Ar}$), 118.6 (***C***H$_{Ar}$), 92.0 (=***C***H), 78.0 (=***C***H$_2$), 72.5 (O***C***H), 38.9 (***C***(CH$_3$)$_3$), 27.2 (C(***C***H$_3$)$_3$).

IR (ν, cm^{-1}) (CCl_4): 3039, 2974, 2872, 1958, 1732, 1589, 1489, 1396, 1275, 1242, 1146, 1026.

MS (CI, NH_3, m/z): 323 (MH^+), 233, 221, 169.

HRMS (EI+, m/z) **:** Calculated for $C_{21}H_{22}O_3$: 322.1569
Found for $C_{21}H_{22}O_3$: 322.1573.

Benzoic acid 1-propyl-buta-2,3-dienyl ester — VI.44e



MF: $C_{14}H_{16}O_2$

MW = 216.28 $g.mol^{-1}$

Reaction: Prepared according to **Method VI.1.a.**

Purification : Flash column chromatography (silica gel, PE/Et_2O 99/01).

Product : Yellow oil

Yield : 98 %

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 8.09-8.06 (m, 2H, 2 x C***H***$_{Ar}$), 7.55 (tt, J = 7.4, 1.9, 1.3 Hz, 1H, C***H***$_{Ar}$), 7.44 (tt, J = 7.8, 7.5 Hz, 2H, 2 x C***H***$_{Ar}$), 5.55 (m, 1H, =C***H***), 5.40 (q, J = 6.6 Hz, 1H, =C***H***), 4.92-4.82 (m, 2H, =C***H***$_2$), 1.90-1.70 (m, 2H, C***H***$_2$), 1.58-1.40 (m, 2H, C***H***$_2$), 0.98 (t, J = 7.4 Hz, 3H, C***H***$_3$).

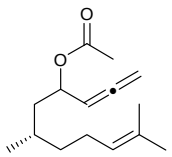
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 208.5 (=***C***=), 165.9 (***C***=O), 132.8 (***C***H$_{Ar}$), 130.6 (***C***$_{qAr}$), 129.6 (***C***H$_{Ar}$), 128.3 (***C***H$_{Ar}$), 91.0 (=***C***H), 77.3 (=***C***H$_2$), 72.1 (O***C***H), 36.4 (***C***H$_2$), 18.6 (***C***H$_2$), 13.9 (***C***H$_3$).

IR (ν, cm^{-1}) (CCl_4): 3066, 3036, 2961, 2872, 1958, 1721, 1601, 1453, 1315, 1267, 1175, 1105, 1066, 940.

MS (CI, NH_3, m/z): 234 (MNH_4^+), 217 (MH^+).

HRMS (EI+, m/z) **:** Calculated for $C_{14}H_{16}O_2$: 216.1150.
Found for $C_{14}H_{16}O_2$: 216.1152.

Acetic acid (*S*)-3,7-dimethyl-1-propa-1,2-dienyl-oct-6-enyl ester — VI.44g



MF: $C_{15}H_{24}O_2$

M = 236.35 $g.mol^{-1}$

Reaction: Prepared according to **Method VI.1.a.**

Purification : Flash column chromatography (silica gel, PE/Et_2O 95/05).

Product : Pale yellow oil (obtained as a ~1:1 mixture of 2 diastereoisomers).

Yield : 88%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): For the mixture of 2 diastereoisomers ~1/1: 5.30 (m, 1H, =C***H***), 5.13 (ddd, J = 6.7, 2.7 Hz, 1H, =C***H***), 5.02 (m, J = 2.7 Hz, 1H, =C***H***O), 4.84-4.73 (m, 2H, =C***H***$_2$), 1.98 (s, 3H, COC***H***$_3$), 1.97-1.90 (m, 2H, C***H***$_2$), 1.72-1.65 (m, 1H, C***H***), 1.62 (s, 3H, C***H***$_3$), 1.55 (s, 3H, C***H***$_3$), 1.51-1.25 (m, 3H, C***H***$_2$ and C***H***), 1.12 (m, 1H, C***H***), 0.9 (t, J = 6.5, 3H, C***H***$_3$).

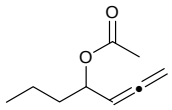
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): For the mixture of 2 diasereoisomers ~1/1: 208.4, 208.2 (=***C***=), 170.2, 170.0 (***C***=O), 131.1, 131.0 (=***C***$_q$), 124.6, 124.5 (=H***C***), 91.3, 90.9 (=***C***H), 77.0 (=***C***H$_2$), 70.3, 69.8 (O***C***H), 41.3, 41.1 (***C***H$_2$), 37.1, 36.8 (***C***H$_2$), 29.0, 28.8 (***C***H), 25.6 (***C***H$_3$), 25.3, 25.2 (***C***H$_2$), 21.1, 21.0 (CO***C***H$_3$), 19.6, 19.3 (***C***H$_3$), 17.5 (***C***H$_3$).

IR (ν, cm^{-1}) (CCl_4): 3458, 2963, 2921, 2856, 1957, 1739, 1448, 1372, 1238, 1114, 1051, 1016, 952.

MS (CI, NH_3, m/z): 254 (MNH_4^+), 249, 239, 237 (MH^+).

HRMS (EI+, m/z) **:** Calculated for $C_{15}H_{24}O_2$: 236.1776.
Found for $C_{15}H_{24}O_2$: 236.1781.

Acetic acid 1-propyl-buta-2,3-dienyl ester **VI.44c**



MF: $C_9H_{14}O_2$

MW = 154.21 $g.mol^{-1}$

Reaction: Prepared according to **Method VI.1.a.**

Purification : Flash column chromatography (silica gel, PE/Et_2O 99/01).

Product : Yellow oil.

Yield : 89 %

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.20-5.12 (m, 1H, =C***H***), 5.10 (q, J = 6.5 Hz, 1H, OC***H***), 4.78-4.69 (m, 2H, =C***H***$_2$), 1.94 (s, 3H, COC***H***$_3$), 1.62-1.45 (m, 2H, ***C***H$_2$), 1.35-1.20 (m, 2H, ***C***H$_2$), 0.83 (t, J = 7.4 Hz, 3H, ***C***H$_3$).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 208.2 (=***C***=), 170.1 (***C***=O), 90.8 (=***C***H), 76.9 (=***C***H$_2$), 36.1 (***C***H$_2$), 21.0 (CO***C***H$_3$), 18.4 (***C***H$_2$), 13.6 (***C***H$_3$).

IR (ν, cm^{-1}) (CCl_4): 3686, 3460, 2961, 2872, 2251, 1958, 1739, 1460, 1435, 1370, 1238, 1104, 1059, 1016.

MS (CI, NH_3, m/z): 155 (MH^+), 145, 128, 113.

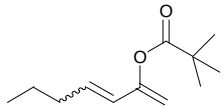
HRMS (EI+, m/z) **:** Calculated for $C_9H_{14}O_2$: 154.0994.
Found for $C_9H_{14}O_2$: 154.0997.

VI.2. Gold(I)-Catalyzed Isomerization of Allenyl Carbinol Esters

Method VI.2. To a solution of substrate (1 equiv., 0.25 mmol) in dry dichloromethane (0.25 M, 1 mL) was added the corresponding amount of catalyst. The reaction was stirred at RT until full consumption of the starting material (as attested by TLC analysis). The resulting mixture was then filtered through a small pad of silica pre-

impregnated with dichloromethane. The pad was washed with ether and the filtrate evaporated. If necessary, the residue was purified by flash column chromatography.

2,2-Dimethyl-propionic acid-1-methylene-hex-2-enyl ester	**VI.45d**



MF: $C_{12}H_{20}O_2$

MW = 196.29 g.mol^{-1}

Reaction: Reaction carried out according to **Method VI.2.**

Purification : Flash column chromatography (silica gel, PE/Et_2O 98/2).

Product : Pale yellow oil (obtained as 1:9 mixture of *Z:E* isomers).

Yield : 100 %

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): For the 1:9 mixture of *Z:E* isomers: 5.97 (dt, J = 15.5, 1.3 Hz, 1H, =C***H*** *Z* + *E* isomers), 5.74 (td, J = 15.4, 6.9 Hz, 1H, =C***H*** *E* isomer), 5.58 (td, J = 11.9, 7.2 Hz, 1H, =C***H*** *Z* isomer), 4.89 (s, 1H, =C***H*** *Z* isomer), 4.87 (s, 1H, =C***H*** *E* isomer), 4.84 (s, 1H, =C***H*** *Z* isomer), 4.71 (s, 1H, =C***H*** *E* isomer), 2.27 (m, 2H, C$\boldsymbol{H}_2$ *Z* isomer), 2.08 (q, J = 6.9 Hz, 2H, C$\boldsymbol{H}_2$ *E* isomer), 1.46-1.36 (m, J = 14.7, 7.3 Hz, 2H, C$\boldsymbol{H}_2$ *Z* + *E* isomer), 1.31 (s, 9H, C(C$\boldsymbol{H}_3$)$_3$ *Z* + *E* isomers), 0.93 (t, J = 7.4 Hz, 3H, C$\boldsymbol{H}_3$ *Z* isomer), 0.90 (t, J = 7.4 Hz, 3H, C$\boldsymbol{H}_3$ *E* isomer).

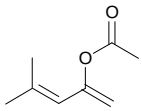
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): For the major (*E*) isomer: 176.4 (***C***=O), 152.2 (=$\boldsymbol{C_q}$), 132.4 (=***C***H), 124.5 (=***C***H), 103.2 (=***C***H_2), 39.2 (***C***$(CH_3)_3$), 34.3 (***C***H_2), 27.3 (C(***C***H_3)$_3$), 22.2 (***C***H_2), 13.7 (***C***H_3).
For the Z isomer: 174.1 (***C***=O), 152.2 (=$\boldsymbol{C_q}$), 135.5 (=***C***H), 123.1 (=***C***H), 105.2 (=***C***H_2), 40.3 (***C***$(CH_3)_3$), 31.0 (***C***H_2), 27.2 (C(***C***H_3)$_3$), 22.9 (***C***H_2), 13.9 (***C***H_3).

IR (ν, cm^{-1}) (CCl_4): 3118, 2965, 2931, 2871, 1811, 1751, 1658, 1612, 1478, 1461, 1395, 1367, 1259, 1126, 1037, 1005, 962.

MS (CI, NH_3, m/z): 214 (MNH_4^+), 204, 197 (MH^+), 183, 169, 145.

HRMS (EI+, m/z) **:** Calculated for $C_{12}H_{20}O_2$: 196.1463.
Found for $C_{12}H_{20}O_2$: 196.1460.

Acetic acid 3-methyl-1-methylene-but-2-enyl ester	**VI.45i**



MF: $C_8H_{12}O_2$

MW = 140.18 g.mol^{-1}

Reaction: Reaction carried out according to **Method VI.2.**

Purification : Flash column chromatography (silica gel, PE/Et_2O 98/2).

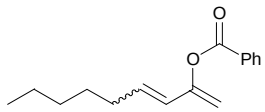
Product : Yellow oil

Yield : 100 %

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.60 (s, 1H, =C***H***), 4.76 (d, J = 7.1 Hz, 2H, =C$\boldsymbol{H}_2$), 2.08 (s, 3H, COC$\boldsymbol{H}_3$), 1.8 (s, 3H, C$\boldsymbol{H}_3$), 1.7 (s, 3H, C$\boldsymbol{H}_3$).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	192.5 (***C***=O), 175.9 (=C_q), 162.8 (=C_q), 143.0 (=***C***H), 127.7 (=***C***H_2), 50.4 (CO***C***H_3), 44.5 (***C***H_3), 43.0 (***C***H_3).
IR (ν, cm^{-1}) (CCl_4)	3647, 2930, 2860, 1760, 1655, 1447, 1370, 1238, 1205, 1162, 1065, 1016, 932.
MS (CI, NH_3, m/z)	184, 180, 169, 155, 141 (MH^+).
HRMS (EI+, m/z) **:**	Calculated for $C_8H_{12}O_2$: 140.0837. Found for $C_8H_{12}O_2$: 140.0834.

Benzoic acid-1-methylene-oct-2-enyl ester — VI.45f

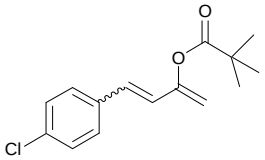


MF: $C_{16}H_{20}O_2$

MW = 244.33 $g.mol^{-1}$

Reaction:	Reaction carried out according to **Method VI.2.**
Purification :	Flash column chromatography (silica gel, PE/Et_2O 98/2).
Product :	Colourless oil (obtained as a 1:15 mixture of *Z: E*).
Yield :	100 %
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	For the major isomer (*E*): 8.18-8.16 (m, 2H, 2 x CH_{Ar}), 7.63 (tt, J= 7.4, 1.6, 1.2 Hz, 1H, CH_{Ar}), 7.51 (t, J = 7.7 Hz, 2H, 2 x CH_{Ar}), 6.07 (dt, J = 15.6, 1.2 Hz, 1H, =C***H***), 5.85 (td, J = 15.6, 6.9 Hz, 1H, =C***H***), 5.01 (s, 1H, =C***H***), 4.91 (s, 1H, =C***H***), 2.10 (q, J = 6.9 Hz, 2H, CH_2), 1.4 (m, 2H, CH_2), 1.33-1.15 (m, 4H, 2 x CH_2), 0.88 (t, J = 6.9 Hz, 3H, CH_3).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	For the major isomer (*E*): 164.6 (***C***=O), 152.2 (=C_q), 133.5 (=***C***H), 133.2 (***C***H_{Ar}), 130.1 (***C***H_{Ar}), 129.6 (C_{qAr}), 128.6 (***C***H_{Ar}), 124.0 (=***C***H), 103.7 (=***C***H_2), 32.3 (***C***H_2), 31.5 (***C***H_2), 28.6 (***C***H_2), 22.5 (***C***H_2), 14.1 (***C***H_3).
IR (ν, cm^{-1}) (CCl_4)	3035, 2958, 2928, 2858, 1742, 1658, 1608, 1453, 1239, 1176, 1090, 1023, 961.
MS (CI, NH_3, m/z)	262 (MNH_4^+), 249, 246, 245 (MH^+), 235, 232.
HRMS (EI+, m/z) **:**	Calculated for $C_{16}H_{20}O_2$: 244.1463 Found for $C_{16}H_{20}O_2$: 244.1464.

2,2-Dimethyl-propionic acid-3-(4-chloro-phenyl)-1-methylene-allyl ester — VI.45a



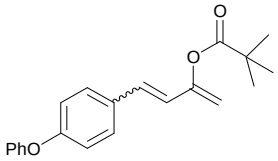
MF: $C_{15}H_{17}O_2Cl$

MW = 264.75 $g.mol^{-1}$

Reaction:	Reaction carried out according to **Method VI.2.**
Purification :	Flash column chromatography (silica gel, PE/Et_2O 90/10).
Product :	Yellow oil (obtained as a 1:18 mixture of *Z: E*)
Yield :	100 %
^{1}H NMR (δ, ppm)	Major isomer (*E*): 7.38-7.20 (m, 4H, 4 x CH_{Ar}), 6.64 (d, J = 16.0 Hz, 1H, =C***H***), 6.52

($CDCl_3$, 400 MHz)	(d, J =16 Hz, 1H, =C***H***), 5.14 (d, J = 1.4 Hz, 1H, =C***H***), 4.96 (d, J = 1.4 Hz, 1H, =C***H***), 1.38 (s, 9H, C(C***H***$_3$)$_3$).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	Major isomer (*E*): 176.3 (***C***=O), 151.9 (=$\boldsymbol{C_q}$), 134.6 (Cl$\boldsymbol{C_{qAr}}$), 133.9 (Cl$\boldsymbol{C_{qAr}}$), 128.9 (***C***H$_{Ar}$), 128.4 (***C***H$_{Ar}$), 128.1 (***C***H$_{Ar}$), 123.6 (=***C***H), 106.5 (=***C***H$_2$), 39.3 (***C***(CH$_3$)$_3$), 27.3 (C(***C***H$_3$)$_3$).
IR (ν, cm^{-1}) (CCl_4)	3040, 2973, 2929, 2871, 1754, 1640, 1605, 1488, 1399, 1260, 1119, 1027, 959.
MS (CI, NH_3, m/z)	284, 282 (MNH_4^+), 267, 265 (MH^+), 256, 252.
HRMS (EI+, m/z) **:**	Calculated for $C_{15}H_{17}O_2Cl$: 264.0917. Found for $C_{15}H_{17}O_2cl$: 264.0919.

2,2-Dimethyl-propionic acid-1-methylene-3-(4-phenoxy-phenyl)-allyl ester — VI.45b

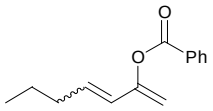


MF: $C_{21}H_{22}O_3$

MW = 322.40 g.mol^{-1}

Reaction:	Reaction carried out according to **Method VI.2.**
Purification :	Flash column chromatography (silica gel, PE/Et_2O 90/10).
Product :	White crystals (obtained as a 1:8 mixture of *Z: E*)
Yield :	78 %
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	For the major isomer (*E*): 7.42-7.32 (m, 4H, 4 x C***H***$_{Ar}$), 7.13 (tt, J = 7.4, 0.9 Hz, 1H, C***H***$_{Ar}$), 7.06-6.92 (m, 4H, 4 x C***H***$_{Ar}$), 6.60 (d, J = 16 Hz, 1H, =C***H***), 6.55 (d, J = 16 Hz, 1H, =C***H***), 5.10 (d, J = 1.4 Hz, 1H, =C***H***), 4.91 (d, J = 1.4 Hz, 1H, =C***H***), 1.40 (s, 9H, C(C***H***$_3$)$_3$).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	For the major isomer (*E*): 176.5 (***C***=O), 157.5 (O$\boldsymbol{C_{qAr}}$), 152.2 (O$\boldsymbol{C_{qAr}}$), 131.3 (=$\boldsymbol{C_q}$), 130.7 ($\boldsymbol{C_{qAr}}$), 130.0 (=***C***H), 129.0 (***C***H$_{Ar}$), 128.4 (***C***H$_{Ar}$), 123.6 (***C***H$_{Ar}$), 122.1 (***C***H$_{Ar}$), 119.2 (=***C***H), 118.9 (***C***H$_{Ar}$), 105.6 (=***C***H$_2$), 39.4 (***C***(CH$_3$)$_3$), 27.4 (C(***C***H$_3$)$_3$).
IR (ν, cm^{-1}) (CCl_4)	3039, 2975, 2873, 1753, 1640, 1588, 1490, 1242, 1165, 1121, 1026, 951.
MS (CI, NH_3, m/z)	340, 323 (MH^+), 249, 238.
HRMS (EI+, m/z) **:**	Calculated for $C_{21}H_{22}O_3$: 322.1569. Found for $C_{21}H_{22}O_3$: 322.1567.

Benzoic acid-1-methylene-hex-2-enyl ester — VI.45e



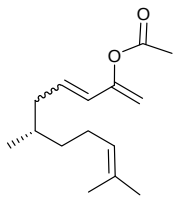
MF: $C_{14}H_{16}O_2$

MW = 216.28 g.mol^{-1}

Reaction:	Reaction carried out according to **Method VI.2.**
Purification :	Flash column chromatography (silica gel, PE/Et_2O 90/10).
Product :	Colorless oil (obtained as a 1:19 mixture of *Z: E*).
Yield :	100 %

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	For the major isomer (*E*): 8.17 (d, J = 7.1 Hz, 2H, 2 x C$\boldsymbol{H_{Ar}}$), 7.63 (tt, J = 7.4, 1.2 Hz, 1H, C$\boldsymbol{H_{Ar}}$), 7.50 (t, J = 7.6 Hz, 2H, 2 x C$\boldsymbol{H_{Ar}}$), 6.08 (dt, J = 15.6, 1.2 Hz, 1H, =C$\boldsymbol{H}$), 5.84 (dt, J = 15.6, 6.9 Hz, 1H, =C$\boldsymbol{H}$), 5.01 (s, 1H, =C$\boldsymbol{H}$), 4.91 (s, 1H, =C$\boldsymbol{H}$), 2.10 (q, J = 7.4 Hz, 2H, C$\boldsymbol{H_2}$), 1.42 (hext., J = 7.4 Hz, 2H, C$\boldsymbol{H_2}$), 0.90 (t, J = 7.4 Hz, 3H, $\boldsymbol{C}H_3$).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	For the major isomer (*E*): 164.6 ($\boldsymbol{C}$=O), 152.2 (=$\boldsymbol{C_q}$), 133.5 ($\boldsymbol{C}H_{Ar}$), 132.9 (=$\boldsymbol{C}$H), 130.1 ($\boldsymbol{C}H_{Ar}$), 129.6 ($\boldsymbol{C_{qAr}}$), 128.6 (=$\boldsymbol{C}$H), 124.2 (=$\boldsymbol{C}$H), 103.8 (=$\boldsymbol{C}H_2$), 34.3 ($\boldsymbol{C}H_2$), 22.1 ($\boldsymbol{C}H_2$), 13.8 ($\boldsymbol{C}H_3$).
IR (ν, cm^{-1}) (CCl_4)	3065, 2960, 2929, 2870, 1742, 1658, 1608, 1453, 1239, 1176, 1090, 1023, 961.
MS (CI, NH_3, m/z)	239, 235, 234 (MNH_4^+), 217 (MH^+), 195.
HRMS (EI+, m/z) **:**	Calculated for $C_{14}H_{16}O_2$: 216.1150. Found for $C_{14}H_{16}O_2$: 250.1153.

Acetic acid-5,9-dimethyl-1-methylene-deca-2,8-dienyl ester	**VI.45g**



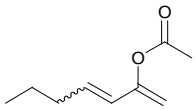
MF: $C_{15}H_{24}O_2$

MW = 236.35 $g.mol^{-1}$

Reaction:	Reaction carried out according to **Method VI.2.**
Purification :	Flash column chromatography (silica gel, PE/Et_2O 90/10).
Product :	Colourless oil (obtained as a 1:8 mixture of *Z: E*).
Yield :	100 %

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	For the mixture of 1:8 mixture of *Z: E*: 5.95 (dt, J = 15.5 Hz, 1H, =C$\boldsymbol{H}$ *E* isomer), 5.82 (dt, J = 12.1, 1.7 Hz, 1H, =C$\boldsymbol{H}$ *Z* isomer), 5.72 (m, J =15.5, 7.4 Hz, 1H, =C$\boldsymbol{H}$ *E* isomer), 5.56 (td, J = 12.1, 7.3 Hz, 1H, =C$\boldsymbol{H}$ *Z* isomer), 5.24-5.16 (m, 1H, =C$\boldsymbol{H}$ *Z* isomer), 5.09 (tt, J = 7.0, 4.1, 1.3 Hz, 1H, =C$\boldsymbol{H}$ *Z* isomer), 4.90 (s, 1H, =C$\boldsymbol{H}$ *E* + Z isomers), 4.80 (s, 1H, =C$\boldsymbol{H}$ *E* + *Z* isomers), 2.22 (s, 3H, CO$\boldsymbol{C}H_3$ *E* isomer), 2.17 (s, 3H, CO$\boldsymbol{C}H_3$ *Z* isomer), 2.05-1.87 (m, 3H, C$\boldsymbol{H}$ and C$\boldsymbol{H_2}$ *E* + *Z* isomers), 1.70 (s, 3H, C$\boldsymbol{H_3}$ *E* + *Z* isomers), 1.60 (s, 3H, C$\boldsymbol{H_3}$ *E* + *Z* isomers), 1.53 (m, 1H, C$\boldsymbol{H}$ *E* + *Z* isomers), 1.42-1.10 (m, 3H, C$\boldsymbol{H}$ and C$\boldsymbol{H_2}$ *E* + *Z* isomers), 0.87 (d, J = 6.7 Hz, 3H, $\boldsymbol{C}H_3$ *E* isomer), 0.90 (d, J = 6.8 Hz, 3H, $\boldsymbol{C}H_3$ *Z* isomer).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	For the major isomer: 168.8 ($\boldsymbol{C}$=O), 151.9 (=$\boldsymbol{C_q}$), 131.5 (=$\boldsymbol{C_q}$), 131.3 (=$\boldsymbol{C}$H), 125.2 (=$\boldsymbol{C}$H), 124.7 (=$\boldsymbol{C}$H), 103.5 (=$\boldsymbol{C}H_2$), 39.8 ($\boldsymbol{C}H_2$), 36.8 ($\boldsymbol{C}H_2$), 32.7 ($\boldsymbol{C}$H), 25.8 ($\boldsymbol{C}H_3$), 25.6 ($\boldsymbol{C}H_2$), 20.9 (CO$\boldsymbol{C}H_3$), 19.5 ($\boldsymbol{C}H_3$), 17.7 ($\boldsymbol{C}H_3$).
IR (ν, cm^{-1}) (CCl_4)	3118, 2961, 2920, 2867, 1765, 1659, 1612, 1451, 1371, 1203, 1017, 962, 902.
MS (CI, NH_3, m/z)	254 (MNH_4^+), 249, 237 (MH^+), 219, 195, 177.
HRMS (EI+, m/z) **:**	Calculated for $C_{15}H_{24}O_2$: 236.1776. Found for $C_{15}H_{24}O_2$: 236.1778.

Acetic acid-1-methylene-hex-2-enyl ester	**VI.45c**



MF: $C_9H_{14}O_2$

MW = 154.21 g.mol^{-1}

Reaction: Reaction carried out according to **Method VI.2.**

Purification : Flash column chromatography (silica gel, PE/Et_2O 90/10).

Product : Colourless oil (obtained as a 1:7 mixture of *Z: E*).

Yield : 100 %

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): For the mixture of 1:7 mixture of *Z: E*: 5.96 (dt, J = 15.6, 1.3 Hz, 1H, =C***H*** *E* isomer), 5.80 (t, J = 1.7 Hz, 1H, =C***H*** *Z* isomer), 5.74 (dt, J =15.5, 7.0 Hz, 1H, =C***H*** *E* isomer), 5.55 (td, J = 11.7, 7.2 Hz, 1H, =C***H*** *Z* isomer), 4.90 (s, 1H, =C***H*** *E* + *Z* isomers), 4.80 (s, 1H, =C***H*** *E* + *Z* isomers), 2.22 (s, 3H, CO***C***H_3 *E* isomer), 2.17 (s, 3H, CO***C***H_3 *Z* isomer), 2.08 (q, J = 14.1, 7.1 Hz, 2H, C***H***$_2$ *E* + *Z* isomers), 1.43 (hext., J = 14.7, 7.4 Hz, 2H, C***H***$_2$ *E* + *Z* isomers), 0.87 (d, J = 7.5 Hz, 3H, ***C***H_3 *E* isomer), 0.90 (t, J = 7.4 Hz, 3H, ***C***H_3 *Z* isomer).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): For the major isomer: 168.9 (***C***=O), 151.9 (=***C***$_q$), 132.7 (=***C***H), 124.7 (=***C***H), 103.6 (=***C***H_2), 34.3 (***C***H_2), 22.1 (***C***H_2), 20.9 (CO***C***H_3), 13.8 (***C***H_3).

IR (ν, cm^{-1}) (CCl_4): 3020, 2961, 2870, 1765, 1659, 1612, 1458, 1369, 1285, 1203, 1129, 1017, 961, 933.

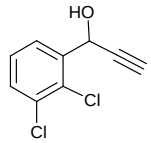
MS (CI, NH_3, m/z): 171 (NH_4^+), 169, 166, 162, 155 (MH^+).

HRMS (EI+, m/z) **:** Calculated for $C_9H_{14}O_2$: 154.0994.
Found for $C_{15}H_{24}O_2$: 154.0997.

VII. Gold(I) Catalyzed Isomerization of 5-en-2-yn-1-yl Acetates: an Efficient Access to Acetoxy Bicyclo[3.1.0]hexenes and 2-Cycloalken-1-ones

VII.1. Synthesis of 5-en-2-yn-1-yl acetate substrates

1-(2,3-Dichlorophenyl)prop-2-yn-1-ol	**VII.94**



MF: $C_9H_6Cl_2O$

MW = 201.04 g.mol^{-1}

Reaction: To a solution of 3,4 dichlorobenzaldehyde (528 mg, 3.00 mmol) in dry diethyl ether (15 ml) at 0°C and under argon was added a solution ethynylmagnesium bromide 0.5M in THF (7.8 mL, 3.90 mmol). After 30 min, the cooling bath was removed to allow the reaction mixture to reach room temperature and the mixture was stirred for further 2 hours. Saturated aqueous ammonium chloride was then added and the mixture was extracted with diethyl ether (3 x 15 ml). The combined organic layers were washed with a saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered and the solvents were removed under reduced pressure.

Purification: Flash column chromatography (silica gel, PE/Et_2O 75/25).

Product: Pale yellow oil.

Yield: 93 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.61 (s, 1H, C***H***$_{Ar}$), 7.42 (d, J = 8.3 Hz, 1H, C***H***$_{Ar}$), 7.33 (d, J = 8.3 Hz, 1H, C***H***$_{Ar}$), 5.38 (s, 1H, C***H***OH), 3.22 (bs, 1H, O***H***), 2.70 (d, J = 2.2 Hz, 3H, C***H***$_3$).

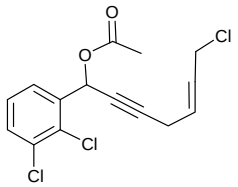
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 139.8 (***C***$_{qAr}$), 132.5 (Cl***C***$_{qAr}$), 132.4 (Cl***C***$_{qAr}$), 130.4 (H***C***$_{Ar}$), 128.5 (H***C***$_{Ar}$), 125.8 (H***C***$_{Ar}$), 82.4 (HC≡***C***$_q$), 75.5 (≡***C***H), 62.9 (***C***HOH).

IR (ν, cm^{-1}) (CCl_4): 3605, 3304, 2102, 1662, 1583, 1467, 1386, 1261, 1225, 1133, 1031.

MS (CI, NH_3, m/z): 202 (MH^+).

HRMS (EI+, m/z) **:** Calculated for $C_9H_6Cl_2O$: 199.9796.
Found for $C_9H_6Cl_2O$: 199.9797.

Trichloroderivative	**VII.80**



MF: $C_{15}H_{13}Cl_3O_2$

MW = 331.62 g.mol^{-1}

Reaction: **Step 1:** To a stirred solution of the propargylic alcohol VII.94 (402 mg, 2.00 mmol) in dry DMF (2 mL) under argon were sequentially added K_2CO_3 (386 mg, 2.80 mmol),

tetrabutylammonium bromide (97 mg, 0.30 mmol), and copper (I) iodide (19 mg, 0.10 mmol) at room temperature. After 15 min, 1,4-dichlorobut-2-ene (1.05 mL, 10.00 mmol) was added. The reaction mixture was stirred for 24h, then it was poured into water and extracted with diethyl ether (3 x 20 ml). The combined organic layers were washed with a saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, petroleum ether/ether 80/20) to give the corresponding allylated propargylic alcohol (187 mg, 34%) as an orange oil.

Step 2: The obtained alcohol (187 mg, 0.68 mmol) was then dissolved in dry dichloromethane (2 mL) under argon and triethylamine (0.2 mL, 1.36 mmol), acetic anhydride (0.1 mL, 1.02 mmol) and DMAP (12 mg, 0.1 mmol) were sequentially added. The reaction was stirred until full consumption of the starting material (as attested by TLC analysis). Then it was poured into water and extracted with diethyl ether (3 x 20 ml). The combined organic layers were washed with a saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered and the solvents were removed under reduced pressure.

Purification: Flash column chromatography (silica gel, PE/Et_2O 95/5).

Product: Pale yellow oil.

Yield: 71 % (24% global).

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.63 (d, J = 9.4 Hz, 1H, C***H***$_{Ar}$), 7.46 (d, J = 8.2 Hz, 1H, C***H***$_{Ar}$), 7.36 (m, 1H, C***H***$_{Ar}$), 6.81 (dt, J = 16.6, 10.6 Hz, 1H, C***H***OAc), 6.69-6.32 (m, 2H, 2 x =C***H***), 5.68-5.51 (m, 2H, C***H***$_2$), 5.44-5.22 (m, 2H, C***H***$_2$), 2.13 (s, 3H, COC***H***$_3$).

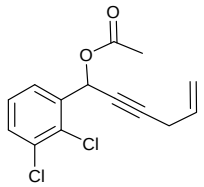
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 169.5 (***C***=O), 142.4 (***C***$_{qAr}$), 137.3 (Cl***C***$_{qAr}$), 132.8 (Cl***C***$_{qAr}$), 130.7 (H***C***$_{Ar}$), 129.7 (H***C***$_{Ar}$), 127.0 (H***C***$_{Ar}$), 125.3 (=***C***H), 121.7 (=***C***H), 87.0 (C≡***C***$_q$), 84.6 (***C***$_q$≡C), 64.9 (***C***HOAc), 46.3 (***C***H_2), 24.5 (***C***H_2), 21.0 (CO***C***H_3).

IR (ν, cm^{-1}) (CCl_4): 3527, 2929, 1748, 1469, 1369, 1222, 1134, 1026.

MS (CI, NH_3, m/z): 332 (MH^+).

HRMS (EI+, m/z) **:** Calculated for $C_{15}H_{13}Cl_3O_2$: 331.6215.
Found for $C_{15}H_{13}Cl_3O_2$: 331.6218.

1-(2,3-Dichlorophenyl)hex-5-en-2-ynyl acetate — VII.76f



MF: $C_{14}H_{12}Cl_2O_2$

MW = 283.14 $g.mol^{-1}$

Reaction: **Step 1:** To a stirred solution of the propargylic alcohol VII.94 (160 mg, 0.8 mmol) in dry DMF (1 mL) under argon, K_2CO_3 (310 mg, 2.24 mmol), tetrabutylammonium bromide (40 mg, 0.12 mmol), and copper (I) iodide (15 mg, 0.08 mmol) were sequentially added at room temperature. After 15 min, allyl bromide (0.14 mL, 1.6 mmol) and sodium iodide (60 mg, 0.4 mL) were added. The reaction mixture was stirred for 24h and then it was poured into water and extracted with ether. The combined organic layers were washed with a saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, petroleum ether/ether 90/10) to give the corresponding allylated propargylic alcohol (95 mg, 50%) as pale yellow oil.

Step 2: The obtained alcohol (95 mg, 0.38 mmol) was then dissolved in dry

dichloromethane (1 mL) under argon and triethylamine (0.1 mL, 0.76 mmol), acetic anhydride (0.06 mL, 0.57 mmol) and DMAP (5 mg, 0.038 mmol) were sequentially added. The reaction was stirred until full consumption of the starting material (as attested by TLC analysis). Then it was poured into water and extracted with ether. The combined organic layers were washed with a saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered and the solvents were removed under reduced pressure.

Purification: Flash column chromatography (silica gel, PE/Et_2O 85/15).

Product: Pale yellow oil.

Yield: 93 % (43 % global).

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.62 (d, J = 2.0 Hz, 1H, C***H***$_{Ar}$), 7.44 (d, J = 8.3 Hz, 1H, C***H***$_{Ar}$), 7.36 (dd, J = 8.3, 2.0 Hz, 1H, C***H***$_{Ar}$), 6.42 (t, J = 1.9 Hz, 1H, C***H***OAc), 5.85-5.75 (m, 1H, CH_2=C***H***), 5.30 (ddd, J = 17.0, 3.1, 1.5 Hz, 1H, =C***H***), 5.14 (ddd, J = 10.0, 3.0, 1.5 Hz, 1H, =C***H***), 3.07-3.04 (m, 2H, C***H***$_2$), 2.11 (s, 3H, COC***H***$_3$).

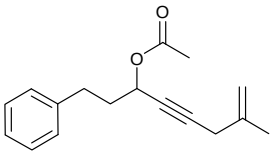
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 169.6 (***C***=O), 137.7 (***C***$_{qAr}$), 133.0 (Cl***C***$_{qAr}$), 132.7 (Cl***C***$_{qAr}$), 131.5 (H***C***$_{Ar}$), 130.6 (H***C***$_{Ar}$), 129.7 (H***C***$_{Ar}$), 127.0 (=***C***H), 116.7 (=***C***H_2), 85.6 (C≡***C***$_q$), 78.3 (***C***$_q$≡C), 64.6 (***C***HOAc), 23.1 (***C***H_2), 21.0 (***C***H_3).

IR (ν, cm^{-1}) (CCl_4): 2985, 1749, 1469, 1369, 1222, 1014, 962.

MS (CI, NH_3, m/z): 240, 223 (M-OAc$^+$).

HRMS (EI+, m/z) **:** Calculated for $C_{14}H_{12}Cl_2O_2$: 282.0214.
Found for $C_{14}H_{12}Cl_2O_2$: 282.0220.

7-Methyl-1-phenyloct-7-en-4-yn-3-yl acetate — VII.76g



MF: $C_{17}H_{20}O_2$

MW = 256.33 g.mol^{-1}

Reaction: **Step 1:** To a solution of hydrocinnamaldehyde (0.65 mL, 5.00 mmol) in dry ether (20 ml) at 0°C and under argon, a solution ethynylmagnesium bromide 0.5M in THF (13 mL, 6.50 mmol) was added. After 30 min, the mixture was allowed to reach room temperature and it was stirred for further 2 hours. Saturated aqueous ammonium chloride was then added and the mixture was extracted with diethyl ether (3 x 20 ml). The combined organic layers were washed with a saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, petroleum ether/ether 70/30) to give the corresponding propargylic alcohol as a yellow oil (790 mg, 99%).
Step 2: To a stirred solution of the resulted propargylic alcohol (400 mg, 2.50 mmol) in dry DMF (2.5 mL) under argon, K_2CO_3 (966 mg, 7.00 mmol), tetrabutylammonium bromide (121 mg, 0.375 mmol), and copper (I) iodide (95 mg, 0.5 mmol) were sequentially added at room temperature. After 15 min, methallyl chloride (1.16 mL, 12.5 mmol) and sodium iodide (75 mg, 0.50 mmol) were added and the reaction mixture was stirred for 24h. Then it was poured into water and extracted with diethyl ether (3 x 20 ml). The combined organic layers were washed with a saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, petroleum ether/ether 80/20) to give the corresponding methallylated propargylic alcohol (469 mg, 88%) as a yellow oil.
Step 3: The obtained alcohol (468 mg, 2.18 mmol) was then dissolved in dry

dichloromethane (3 mL) under argon and triethylamine (0.6 mL, 4.36 mmol), acetic anhydride (0.31 mL, 3.27 mmol) and DMAP (26 mg, 0.21 mmol) were sequentially added. The reaction was stirred until full consumption of the starting material (as attested by TLC analysis). Then it was poured into water and extracted with diethyl ether (3 x 20 ml). The combined organic layers were washed with a saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered and the solvents were removed under reduced pressure.

Purification: Flash column chromatography (silica gel, PE/Et_2O 95/5).

Product: Pale yellow oil.

Yield: 73 % global.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.38-7.34 (m, 2H, 2 x C***H***$_{Ar}$), 7.28-7.25 (m, 3H, 3 x C***H***$_{Ar}$), 5.49 (t, J = 6.4 Hz, 1H, C***H***OAc), 5.11 (bs, 1H, =C***H***), 4.94 (bs, 1H, =C***H***), 3.02 (bs, 2H, C***H***$_2$), 2.87 (t, J = 7.9 Hz, 2H, C***H***$_2$), 2.24-2.11 (m, 2H, C***H***$_2$), 2.10 (s, 3H, C***H***$_3$), 1.87 (s, 3H, C***H***$_3$).

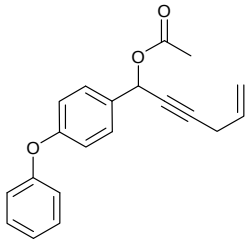
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 169.6 (***C***=O), 140.7 (=***C***$_q$), 139.8 (***C***$_{qAr}$), 128.3 (H***C***$_{Ar}$), 128.2 (H***C***$_{Ar}$), 125.9 (H***C***$_{Ar}$), 111.7 (=***C***H$_2$), 83.3 (C≡***C***$_q$), 79.7 (***C***$_q$≡C), 63.7 (***C***HOAc), 36.4 (***C***H$_2$), 31.2 (***C***H$_2$), 27.2 (***C***H$_2$), 21.9 (***C***H$_3$), 20.7 (***C***H$_3$).

IR (ν, cm^{-1}) (CCl_4): 2935, 1744, 1449, 1370, 1231, 1019, 893.

MS (CI, NH_3, m/z): 274 (MNH_4^+), 257 (MH^+), 197.

HRMS (EI+, m/z) **:** Calculated for $C_{17}H_{20}O_2$: 256.1463.
Found for $C_{17}H_{20}O_2$: 256.1457.

1-(4-Phenoxyphenyl)hex-5-en-2-ynyl acetate — VII.76e



MF: $C_{20}H_{18}O_3$

MW = 306.35 $g.mol^{-1}$

Reaction:

Step 1: To a solution of *para*-phenoxy benzaldehyde (793 mg, 4.00 mmol) in dry diethyl ether at 0°C, under argon, a solution ethynylmagnesium bromide in 0.5M in THF (10.5 mL, 5.20 mmol) was added. After 30 min, the mixture was allowed to reach room temperature and it was stirred for further 2.5 hours. Saturated aqueous ammonium chloride was then added and the mixture was extracted with diethyl ether (3 x 20 ml). The combined organic layers were washed with a saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, petroleum ether/ether 60/40) to give the corresponding propargylic alcohol VII.93 as a yellow solid (895 mg, 100%).

Step 2: To a stirred solution of the resulted propargylic alcohol VII.93 (448 mg, 2.00 mmol) in dry DMF (3 mL), under argon, K_2CO_3 (773 mg, 5.6 mmol), tetrabutylammonium bromide (97 mg, 0.30 mmol), and copper (I) iodide (38 mg, 0.20 mmol) were sequentially added at room temperature. After 15 min, allyl bromide (0.35 mL, 4.00 mmol) and sodium iodide (150 mg, 1.00 mmol) were added. The reaction mixture was stirred for 24h, then it was poured into water and extracted with diethyl ether (3 x 20 ml). The combined organic layers were washed with a saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (Silica gel, Petroleum ether/Ether 90/10) to give the corresponding

allylated propargylic alcohol (264 mg, 50%) as pale yellow oil.
Step 3: The obtained alcohol (264 mg, 1.00 mmol) was then dissolved in dry dichloromethane (1.5 mL) under argon and triethylamine (0.3 mL, 2.00 mmol), acetic anhydride (0.14 mL, 1.50 mmol) and DMAP (12 mg, 0.10 mmol) were sequentially added. The reaction was stirred until full consumption of the starting material (as attested by TLC analysis). Then it was poured into water and extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered and the solvents were removed under reduced pressure.

Purification: Flash column chromatography (silica gel, PE/Et_2O 85/15).

Product: Yellow oil.

Yield: 92 % (46% global).

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.54 (d, J = 8.6 Hz, 2H, 2 x C$\boldsymbol{H_{Ar}}$), 7.35 (t, J = 8.0 Hz, 2H, 2 x C$\boldsymbol{H_{Ar}}$), 7.14 (t, J = 7.4 Hz, 1H, C$\boldsymbol{H_{Ar}}$), 7.06-7.00 (m, 4H, 4 x C$\boldsymbol{H_{Ar}}$), 6.54 (t, J = 1.9 Hz, 1H, C***H***OAc), 5.88-5.79 (m, 1H, CH_2=C***H***), 5.37 (ddd J = 16.9, 3.2, 1.6 Hz, 1H, =C***H***), 5.16 (ddd, J = 9.9, 3.0, 1.5 Hz, 1H, =C***H***), 3.09-3.06 (m, 2H, C$\boldsymbol{H_2}$), 2.10 (s, 3H, COC$\boldsymbol{H_3}$).

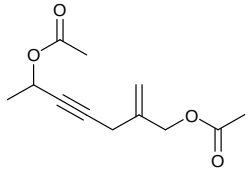
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 169.6 (***C***=O), 157.8 (O$\boldsymbol{C_{qAr}}$), 156.6 (O$\boldsymbol{C_{qAr}}$), 132.0 ($\boldsymbol{C_{qAr}}$), 131.7 (=***C***H), 129.7 (=***C***H), 129.3 (=***C***H), 123.6 (=***C***H), 119.2 (=***C***H), 118.3 (=***C***H), 116.4 (=***C***H_2), 84.5 (C≡$\boldsymbol{C_q}$), 79.3 ($\boldsymbol{C_q}$≡C), 65.4 (***C***HOAc), 23.0 (***C***H_2), 20.9 (***C***H_3).

IR (ν, cm^{-1}) (CCl_4): 3039, 1743, 1588, 1490, 1368, 1227, 1012, 954.

MS (CI, NH_3, m/z): 247 ($M\text{-}OAc^+$).

HRMS (EI+, m/z) **:** Calculated for $C_{20}H_{18}O_3$: 306.1256.
Found for $C_{20}H_{18}O_3$: 306.1262.

Acetic acid 5-acetoxymethyl-1-methyl-hex-5-en-2-ynyl ester	**VII.76h**



MF: $C_{12}H_{16}O_4$

MW = 224.25 $g.mol^{-1}$

Reaction:

Step 1: To a stirred solution of 3-butyn-2-ol (1.56 mL, 20.00 mmol) in dry DMF (20 mL) under argon, K_2CO_3 (5.52 g, 40.00 mmol), tetrabutylammonium bromide (966 mg, 3.00 mmol), and copper (I) iodide (190 mg, 1.00 mmol) were sequentially added at room temperature. After 15 min, 3-chloro-2-chloromethyl-1-propene (7 mL, 60.00 mmol) was added and the reaction mixture was stirred for 24h. Then it was poured into water and extracted with ether. The combined organic layers were washed with a saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, petroleum ether/ether 70/30) to give the corresponding allylated propargylic alcohol (2.4g, 76%) as an oil.
Step 2: The resulted alcohol (400 mg, 2.53 mmol) was then dissolved in dry DMF (4 mL) under argon and potassium acetate (500 mg, 5.06 mmol) and sodium iodide (379 mg, 2.53 mmol) were sequentially added at room temperature. The reaction mixture was stirred for 24h. Then it was poured into water and extracted with diethyl ether. The combined organic layers were washed with a saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, petroleum ether/ether 70/30) to give the corresponding propargylic alcohol (220 mg, 48%) as an oil.
Step 3: The obtained alcohol (220 mg, 1.21 mmol) was then dissolved in dry

dichloromethane (3 mL) under argon and triethylamine (0.336 mL, 2.42 mmol), acetic anhydride (0.171 mL, 1.81 mmol) and DMAP (14 mg, 0.12 mmol) were sequentially added. The reaction was stirred until full consumption of the starting material (as attested by TLC analysis). Then it was poured into water and extracted with ether. The combined organic layers were washed with a saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered and the solvents were removed under reduced pressure.

Purification: Flash column chromatography (silica gel, PE/Et_2O 90/10).

Product: Pale yellow oil.

Yield: 96 % (35 % global).

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.34 (qt, J = 6.6, 1.8 Hz, 1H, C***H***OAc), 5.17 (bs, 1H, =C***H***), 5.06 (bs, 1H, =C***H***), 4.46 (bs, 2H, C***H***$_2$), 2.91 (bs, 2H, C***H***$_2$), 1.98 (s, 3H, COC***H***$_3$), 1.96 (s, 3H, COC***H***$_3$), 1.37 (d, J = 6.6 Hz 3H, C***H***$_3$).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 170.0 (***C***=O), 169.7 (***C***=O), 138.3 (=***C***$_q$), 114.6 (=***C***H$_2$), 81.6 (C≡***C***$_q$), 80.9 (***C***$_q$≡C), 65.9 (O***C***H$_2$), 60.4 (***C***HOAc), 23.1 (***C***H$_2$), 21.4 (***C***H$_3$), 20.8 (CO***C***H$_3$), 20.6 (CO***C***H$_3$).

IR (ν, cm^{-1}) (CCl_4): 2990, 1745, 1446, 1370, 1232, 1168, 1058, 1020.

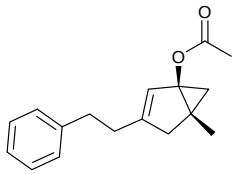
MS (CI, NH_3, m/z): 242 (MNH_4^+), 225 (MH^+), 165 (M-OAc$^+$).

HRMS (EI+, m/z) **:** Calculated for $C_{12}H_{16}O_4$: 224.1049.
Found for $C_{12}H_{16}O_4$: 224.1050.

VII.2. Gold(I) Catalyzed Isomerization of 5-en-2-yn-1-yl Acetates

Method VII.2: To a solution of substrate (1 equiv., 0.25 mmol) in 1 mL of dry dichloromethane (1 ml, 0.25 M) was added 1 mol% of the gold catalyst (1.9 mg). The reaction was stirred until full consumption of the starting material (as attested by TLC analysis). The resulting mixture was then filtered through a small pad of silica pre-impregnated with dichloromethane. The pad was washed with ether and the filtrate evaporated. The residue was purified by flash column chromatography.

(1*R*,5*S*)-5-Methyl-3-phenethylbicyclo[3.1.0]hex-2-en-1-yl acetate	**VII.78g**



MF: $C_{17}H_{20}O_2$

MW = 256.33 g.mol^{-1}

Reaction: Prepared according to **Method VII.2.** described above.

Purification: Filtration on silica gel.

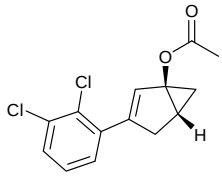
Product: Pale yellow oil.

Yield: 99 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.30-7.27 (m, 2H, 2 x C***H***$_{Ar}$), 7.21-7.16 (m, 3H, 3 x C***H***$_{Ar}$), 5.80 (s, 1H, =C***H***), 2.73 (t, J = 8.1 Hz, 2H, PhC***H***$_2$), 2.49 (d, J = 17.5 Hz, 1H, C***H***$_{cyclopentene}$), 2.40-2.25 (m, 2H, C***H***$_2$), 2.21 (d, J = 17.5 Hz, 1H, C***H***$_{cyclopentene}$), 2.08 (s, 3H, COC***H***$_3$), 1.29 (s, 3H, C***H***$_3$), 0.94 (d, J = 5.1 Hz, 1H, C***H***$_{cyclopropan}$), 0.69 (d, J = 5.1, 1H, C***H***$_{cyclopropan}$).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	171.5 (***C***=O), 142.3 (***C***$_{qAr}$), 141.9 (=***C***$_q$), 128.4 (=***C***H), 128.3 (H***C***$_{Ar}$), 126.4 (H***C***$_{Ar}$), 125.9 (H***C***$_{Ar}$), 72.2 (***C***HOAc), 44.7 (***C***H_2), 34.4 (***C***H_2), 32.7 (***C***H_2), 28.1 (***C***H_2), 21.1 (***C***H_3), 17.5 (CO***C***H_3), 10.6 (***C***$_q$).
IR (ν, cm^{-1}) (CCl_4)	2826, 1752, 1450, 1367, 1228, 1116.
MS (CI, NH_3, m/z)	274 (MNH_4^+), 215.
HRMS (EI+, m/z) **:**	Calculated for $C_{17}H_{20}O_2$: 256.1463. Found for $C_{17}H_{20}O_2$: 256.1463.

(1*S*,5*S*)-3-(2,3-dichlorophenyl)bicyclo[3.1.0]hex-2-en-1-yl acetate **VII.78f**

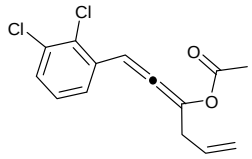


MF: $C_{14}H_{12}Cl_2O_2$

MW = 283.14 $g.mol^{-1}$

Reaction:	Obtained as the main product in the reaction done according to **Method VII.2.** described above, along with side-product VII.77f.
Purification:	Flash column chromatography (silica gel, PE/Et_2O 95/5).
Product:	Pale yellow oil.
Yield:	38 %.
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	7.42 (d, J = 2.0 Hz, 1H, C***H***$_{Ar}$), 7.35 (d, J = 8.4 Hz, 1H, C***H***$_{Ar}$), 7.19 (dd, J = 8.4, 2.1 Hz, 1H, C***H***$_{Ar}$), 6.51 (bs, 1H, =C***H***), 3.13 (ddd, J = 17.3, 6.9, 1.8 Hz, 1H, C***H***$_{cyclopentene}$), 2.50 (d, J = 17.3 Hz, 1H, C***H***$_{cyclopentene}$), 2.08 (s, 3H, COC***H***$_3$), 2.04-1.99 (m, 1H, C***H***), 1.39 (dd, J = 9.4, 5.4 Hz , 1H, C***H***$_{cyclopropan}$), 0.77 (dd, J = 5.3, 5.4 Hz , 1H, C***H***$_{cyclopropan}$).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	171.4 (***C***=O), 137.8 (***C***$_{qAr}$), 135.7 (Cl***C***$_{qAr}$), 132.6 (Cl***C***$_{qAr}$), 131.4 (=***C***$_q$), 130.3 (H***C***$_{Ar}$), 128.7 (H***C***$_{Ar}$), 127.5 (H***C***$_{Ar}$), 124.9 (=***C***H), 70.5 (***C***$_q$OAc), 35.8 (***C***H_2), 23.2 (***C***H_2), 21.2 (CO***C***H_3), 21.1 (***C***$_q$).
IR (ν, cm^{-1}) (CCl_4)	2911, 1755, 1471, 1368, 1225, 1179, 1050, 1029.
MS (CI, NH_3, m/z)	300 (MNH_4^+), 283 (MH^+), 241, 223.
HRMS (EI+, m/z) **:**	Calculated for $C_{14}H_{12}Cl_2O_2$: 282.0214. Found for $C_{14}H_{12}Cl_2O_2$: 282.0218.

1-(2,3-Dichlorophenyl)hexa-1,2,5-trien-3-yl acetate **VII.77f**



MF: $C_{14}H_{12}Cl_2O_2$

MW = 283.14 $g.mol^{-1}$

Reaction:	Obtained as a side product in the reaction described above, along with compound VII.78f.
Purification:	Flash column chromatography (silica gel, PE/Et_2O 95/5).

Product: Pale yellow oil.

Yield : 44 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.50 (d, J = 2.0 Hz, 1H, C***H***$_{Ar}$), 7.39 (d, J = 8.3 Hz, 1H, C***H***$_{Ar}$), 7.27 (dd, J = 8.3, 2.0 Hz, 1H, C***H***$_{Ar}$), 6.50 (t, J = 2.9 Hz, 1H, =C***H***), 5.85-5.75 (m, 1H, CH_2=C***H***), 5.19 (dd, J = 17.0, 1.5 Hz, 1H, =C***H***), 5.12 (dd, J = 10.0, 1.3 Hz, 1H, =C***H***), 3.11-3.09 (m, 2H, C***H***$_2$), 2.17 (s, 3H, C***H***$_3$).

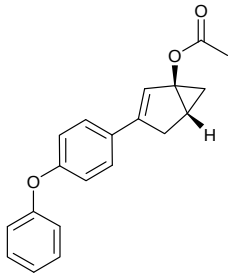
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 198.0 (=***C***=), 168.3 (***C***=O), 134.0 (Cl***C***$_{qAr}$), 132.9 (Cl***C***$_{qAr}$), 132.3 (=***C***H), 131.9 (***C***$_{qAr}$), 130.6 (H***C***$_{Ar}$), 129.5 (H***C***$_{Ar}$), 127.0 (H***C***$_{Ar}$), 125.3 (=***C***$_q$OAc), 118.2 (=***C***H$_2$), 102.7 (=***C***H$_{allene}$), 36.5 (***C***H$_2$), 21.0 (CO***C***H$_3$).

IR (ν, cm^{-1}) (CCl_4): 2925, 1761, 1470, 1367, 1206, 1169, 1132.

MS (CI, NH_3, m/z): 300 (MNH_4^+).

HRMS (EI+, m/z) **:** Calculated for $C_{14}H_{12}Cl_2O_2$: 282.0214.
Found for $C_{14}H_{12}Cl_2O_2$: 282.0214.

(1*S*,5*S*)-3-(4-phenoxyphenyl)bicyclo[3.1.0]hex-2-en-1-yl acetate — VII.78e



MF: $C_{20}H_{18}O_3$

MW = 306.35 g.mol^{-1}

Reaction: Prepared according to **Method VII.2.** described above.

Purification: Filtration on silica gel.

Product: Pale yellow oil.

Yield: 99 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.37-7.33 (m, 4H, 4 x C***H***$_{Ar}$), 7.12 (t, J = 7.4 Hz, 1H, C***H***$_{Ar}$), 7.02 (d, J = 7.6 Hz, 2H, 2 x C***H***$_{Ar}$), 6.95 (d, J = 8.7 Hz, 2H, 2 x C***H***$_{Ar}$), 6.43 (bs, 1H, =C***H***), 3.19 (ddd, J = 17.2, 6.8, 1.6 Hz, 1H, C***H***$_{cyclopentene}$), 2.54 (d, J = 17.2 Hz, 1H, C***H***$_{cyclopentene}$), 2.10 (s, 3H, COC***H***$_3$), 2.02-1.97 (m, 1H, C***H***), 1.39 (dd, J = 9.4, 5.3 Hz , 1H, C***H***$_{cyclopropan}$), 0.80 (dd, J = 5.3, 5.1 Hz, 1H, C***H***$_{cyclopropan}$).

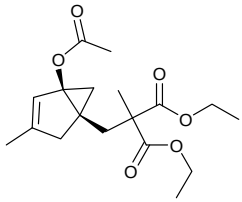
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 171.4 (***C***=O), 157.1 (O***C***$_{qAr}$), 156.9 (O***C***$_{qAr}$), 139.4 (=***C***$_q$), 130.8 (***C***$_{qAr}$), 129.8 (H***C***$_{Ar}$), 127.0 (H***C***$_{Ar}$), 125.5 (H***C***$_{Ar}$), 123.4 (=***C***H), 118.9 (H***C***$_{Ar}$), 118.7 (H***C***$_{Ar}$), 70.8 (***C***$_q$OAc), 35.9 (***C***H$_2$), 23.2 (***C***H$_2$), 21.2 (***C***$_q$), 20.9 (CO***C***H$_3$).

IR (ν, cm^{-1}) (CCl_4): 2993, 1754, 1558, 1490, 1234, 1172.

MS (CI, NH_3, m/z): 324 (MNH_4^+), 307 (MH^+), 265, 247.

HRMS (EI+, m/z) **:** Calculated for $C_{20}H_{18}O_3$: 306.1256.
Found for $C_{20}H_{18}O_3$: 306.1256.

Diethyl 2-(((1*R*,5*R*)-5-acetoxy-3-methylbicyclo[3.1.0]hex-3-en-1-yl)methyl)-2-methylmalonate — VII.78i



MF: $C_{18}H_{26}O_6$

MW = 338.39 g.mol^{-1}

Reaction: Prepared according to **Method VII.2.** described above.

Purification : Flash column chromatography (silica gel, PE/Et_2O 70/30).

Product : Yellow oil.

Yield : 96 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.64 (bs, 1H, =C***H***), 4.23-4.08 (m, 4H, 2 x C***H***$_2$O), 2.44 (d, J = 17.4 Hz, 1H, C***H***$_{cyclopentene}$), 2.38 (d, J = 14.8 Hz, 1H, C***H***), 2.10 (d, J = 17.4 Hz, 1H, C***H***$_{cyclopentene}$), 2.04 (s, 3H, COC***H***$_3$), 1.92 (d, J = 14.8 Hz, 1H, C***H***), 1.60 (s, 3H, C***H***$_3$), 1.51 (s, 3H, C***H***$_3$), 1.24 (t, J = 7.0 Hz, 3H, C***H***$_{3\ ester}$), 1.22 (t, J = 7.0 Hz, 3H, C***H***$_{3\ ester}$), 0.99 (d, J = 5.4 Hz , 1H, C***H***$_{cyclopropan}$), 0.74 (dd, J = 5.4, 1.4, 1H, C***H***$_{cyclopropan}$).

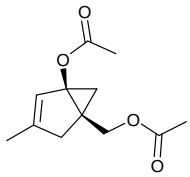
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 172.7 (***C***O_2Et), 172.4 (***C***O_2Et), 171.3 (***C***O_2Me), 138.4 (=***C***$_q$), 126.1 (=***C***H), 71.6 (***C***$_q$OAc), 61.3 (O***C***H_2), 61.2 (O***C***H_2), 53.9 (***C***$_q$), 45.0 (***C***H_2), 37.6 (***C***H_2), 27.9 (***C***H_2), 27.0 (***C***$_q$), 21.0 (***C***H_3), 20.5 (CO***C***H_3), 16.1 (***C***H_{3q}), 2 x 14.1 (***C***H_{3ester}).

IR (ν, cm^{-1}) (CCl_4): 2983, 1736, 1447, 1370, 1290, 1226, 1717, 1113.

MS (CI, NH_3, m/z): 356 (MNH_4^+), 339 (MH^+).

HRMS (EI+, m/z) **:** Calculated for $C_{18}H_{26}O_6$: 338.1729.
Found for $C_{18}H_{26}O_6$: 338.1737.

Acetic acid 5-acetoxymethyl-3-methyl-bicyclo[3.1.0]hex-2-en-1-yl ester — VII.78h



MF: $C_{12}H_{16}O_4$

MW = 224.25 g.mol^{-1}

Reaction: Prepared according to **Method VII.2.** described above.

Purification: Flash column chromatography (silica gel, PE/Et_2O 80/20).

Product: Colourless oil.

Yield: 72 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.68 (bs, 1H, =C***H***), 4.22 (d, J = 11.9 Hz, 1H, C***H***OAc), 4.16 (d, J = 11.9 Hz, 1H, C***H***OAc), 2.70 (d, J = 17.6 Hz, 1H, C***H***$_{cyclopentene}$), 2.20 (d, J = 17.6 Hz, 1H, C***H***$_{cyclopentene}$), 2.08 (s, 3H, COC***H***$_3$), 2.04 (s, 3H, COC***H***$_3$), 1.68 (s, 3H, C***H***$_3$), 1.23 (d, J = 5.6 Hz , 1H, C***H***$_{cyclopropan}$), 0.88 (d, J = 5.6, 1H, C***H***$_{cyclopropan}$).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 171.4 (***C***O_2Me), 171.3 (***C***O_2Me), 138.9 (=***C***$_q$), 126.0 (=***C***H), 72.1 (***C***$_q$OAc), 66.4 (O***C***H_2), 42.8 (***C***H_2), 29.5 (***C***$_q$), 26.9 (***C***H_2), 21.1 (CO***C***H_3), 21.0 (CO***C***H_3), 16.2 (***C***H_3).

IR (ν, cm^{-1}) (CCl_4): 2911, 1747, 1441, 1368, 1228, 1113, 1029.

MS (CI, NH_3, m/z) 242 (MNH_4^+), 225 (MH^+), 181, 165.

HRMS (EI+, m/z) **:** Calculated for $C_{12}H_{16}O_4$: 224.1049.
Found for $C_{12}H_{16}O_4$: 224.1054.

VIII. Gold(I)-Catalyzed 5-endo Hydroxy- and Alkoxy-Cyclization of 1,5-enynes: an Efficient Access to Functionalized Cyclopentenes

VIII.1. Synthesis of 1,5-Enyne Substrates

General procedure for the synthesis of enynes:

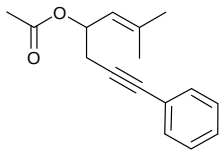
Method VIII.1.a.

Step 1: To a suspension of activated Zn (2 equiv.) in THF (1 M) at 0°C, propargyl bromide (1.5 equiv., 80% wt. toluene solution) was added and the resulted suspension was stirred at 0°C for 1h. *α,β*-Unsaturated aldehyde (1 equiv.) was next added and the mixture was allowed to reach at RT and stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl solution, filtered and the filtrate extracted twice with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether/diethyl ether) to give the desired coupling product.
Step 2: To a solution containing the previously prepared alkynol (1 equiv.) in NEt_3 (0.25 M), the corresponding halide (1.2 equiv.), $PdCl_2(PPh_3)_2$ (0.02 equiv.) and CuI (0.02 equiv.) were added and the resulted mixture was stirred overnight at RT. When completed, the reaction was quenched with saturated aqueous NH_4Cl solution and extracted with diethyl ether. The combined organic phases were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether/diethyl ether) to give the expected coupling product.
Step 3: To a solution of the secondary alcohol prepared in the previous step (1 equiv.) in DCM (0.4 M), NEt_3 (2 equiv.), Ac_2O (1.5 equiv.) and DMAP (0.1 equiv.) were added. When completed, the reaction was treated with saturated aqueous NH_4Cl solution and extracted with diethyl ether. The combined organic phases were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether/diethyl ether) to give the expected acetylated product.

Method VIII.1.b.

Step 1: To a suspension of activated Zn (2 equiv.) in THF (1 M) at 0°C, propargyl bromide (1.5 equiv., 80% wt. toluene solution) was added and the resulted suspension was stirred at 0°C for 1h. *α,β*-Unsaturated aldehyde (1 equiv.) was next added and the mixture was allowed to reach at RT and stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl solution, filtered and the filtrate extracted twice with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether/diethyl ether) to give the desired coupling product.
Step 2: To a solution containing the previously prepared alkynol (1 equiv.) in DMF (1 M), K_2CO_3 (2.8 equiv.), TBAB (0.15 equiv.) and CuI (0.10 equiv.) were sequentially added and the resulted mixture was stirred at RT for 1h. The corresponding allylic halide was then added (5 equiv.) along with NaI (0.2 equiv.). The reaction was allowed to react RT and stirred overnight. When completed, the reaction was quenched with water and extracted with diethyl ether. The combined organic phases were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether/diethyl ether) to give the coupling product.
Step 3: To a solution of the secondary alcohol prepared in the previous step (1 equiv.) in DCM (0.4 M), NEt_3 (2 equiv.), Ac_2O (1.5 equiv.) and DMAP (0.1 equiv.) were added. When completed, the reaction was treated with saturated aqueous NH_4Cl solution and extracted with diethyl ether. The combined organic phases were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether/diethyl ether) to give the expected acetylated product.

6-Methyl-1-phenylhept-5-en-1-yn-4-yl acetate	**VIII.75**



MF: $C_{16}H_{18}O_2$

MW = 242.31 g.mol^{-1}

Reaction: Obtained as the main product according to **Method VIII.1.a.,** along with dimer VIII.75bis.

Purification : Flash column chromatography (silica gel, PE/Et_2O 95/5 to 90/10).

Product : Pale yellow oil.

Yield : 43 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.40-7.37 (m, 2H, 2 x C***H***$_{Ar}$), 7.32-7.27 (m, 3H, 3 x C***H***$_{Ar}$), 6.71 (ddd, J = 9.1, 6.3, 6.3 Hz, 1H, =C***H***), 5.28 (bd, J = 9.1 Hz, 1H, C***H***OAc), 2.73 (dd, J = 16.7, 6.1 Hz, 1H, C*H*), 2.69 (dd, J = 16.7, 6.5 Hz, 1H, C*H*), 2.07 (s, 3H, COC***H***$_3$), 1.79 (d, J = 1.1 Hz, 3H, C***H***$_3$), 1.78 (d, J = 1.1 Hz, 3H, C***H***$_3$).

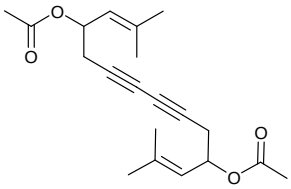
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 170.3 (***C***=O), 138.6 (=***C***$_q$), 131.6 (H***C***$_{Ar}$), 128.3 (H***C***$_{Ar}$), 127.9 (H***C***$_{Ar}$), 123.6 (***C***$_{qAr}$), 122.4 (=***C***H), 85.4 (C≡***C***$_q$), 82.3 (***C***$_q$≡C), 69.5 (***C***HOAc), 26.0 (***C***H$_2$), 25.8 (***C***H$_{3trans}$), 21.3 (CO***C***H$_3$), 18.7 (***C***H$_{3cis}$).

IR (ν, cm^{-1}) (CCl_4): 2974, 2914, 1738, 1371, 1237, 1017.

MS (CI, NH_3, m/z): 260 (MNH_4^+), 243 (MH^+), 200, 183.

HRMS (EI+, m/z) **:** Calculated for $C_{16}H_{18}O_2$: 242.1307.
Found for $C_{16}H_{18}O_2$: 242.1311.

Dimer	**VIII.75bis**



MF: $C_{20}H_{26}O_4$

MW = 330.41 g.mol^{-1}

Reaction: Obtained as a side-product in the previous reaction.

Purification : Flash column chromatography (silica gel, PE/Et_2O 95/5 to 90/10).

Product : Orange oil.

Yield : 20 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.56 (ddd, J = 8.4, 6.0, 6.0 Hz, 1H, =C***H***), 5.19 (bd, J = 9.1, 1.1 Hz, 1H, C***H***OAc), 2.54 (d, J = 5.7 Hz, 2H, C*H*$_2$), 2.03 (s, 3H, COC***H***$_3$), 1.74 (s, 3H, C***H***$_3$), 1.73 (s, 3H, C***H***$_3$).

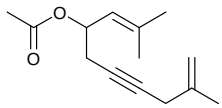
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 170.0 (***C***=O), 138.8 (=***C***$_q$), 121.7 (=***C***H), 72.9 (C≡***C***$_q$), 68.8 (***C***HOAc), 66.7 (***C***$_q$≡C), 25.7 (***C***H$_2$), 25.8 (***C***H$_{3trans}$), 21.1 (CO***C***H$_3$), 18.5 (***C***H$_{3cis}$).

IR (ν, cm^{-1}) (CCl_4): 2974, 2914, 1739, 1442, 1371, 1236, 1017.

MS (CI, NH_3, m/z): 331 (MH^+).

HRMS (EI+, m/z) **:** Calculated for $C_{20}H_{26}O_4$: 330.1831.
Found for $C_{20}H_{26}O_4$: 330.1833.

2,9-Dimethyldeca-2,9-dien-6-yn-4-yl acetate **VIII.87b**



MF: $C_{14}H_{20}O_2$

MW = 220.30 g.mol^{-1}

Reaction: Prepared according to **Method VIII.1.b.**

Purification : Flash column chromatography (silica gel, PE/Et_2O 90/10).

Product : Pale yellow oil.

Yield : 76 % (60% global).

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.58-5.52 (ddd, J = 10.2, 9.9, 6.2 Hz, 1H, C***H***=C(CH_3)$_2$), 5.18 (d, J = 8.3 Hz, 1H, C***H***), 4.94 (s, 1H, C***H***), 4.77 (s, 1H, C***H***), 2.81 (bs, 2H, C*H*$_2$), 2.51-2.36 (m, 2H, C*H*$_2$), 2.00 (s, 3H, COC***H***$_3$), 1.72-1.69 (m, 9H, 3 x C***H***$_3$).

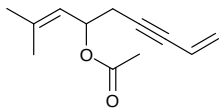
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 170.1 (***C***=O), 140.9 (***C***$_q$=CH_2), 138.3 (CH=***C***$_q$), 122.5 (=***C***H), 111.3 (=***C***H_2), 79.0 (C≡***C***$_q$), 77.8 (***C***$_q$≡C), 69.6 (***C***HOAc), 27.5 (***C***H_2), 25.7 (***C***H_{3trans}), 25.3 (***C***H_2), 21.9 (CO***C***H_3), 21.1 (***C***H_3), 18.5 (***C***H_{3cis}).

IR (ν, cm^{-1}) (CCl_4): 2974, 2916, 1737, 1442, 1371, 1238.

MS (CI, NH_3, m/z): 192, 175, 161.

HRMS (EI+, m/z) **:** Calculated for $C_{14}H_{20}O_2$: 220.1463.
Found for $C_{14}H_{20}O_2$: 220.1474.

2-Methylnona-2,8-dien-6-yn-4-yl acetate **VIII.87a**



MF: $C_{12}H_{16}O_2$

MW = 192.25 g.mol^{-1}

Reaction: Prepared according to **Method VIII.1.b.**

Purification : Flash column chromatography (silica gel, PE/Et_2O 98/2).

Product : Colourless oil.

Yield : 72 % (57 % global).

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.73-5.66 (m, 1H, C***H***=CH_2), 5.56- 5.46 (m, 2H, =C***H***$_2$), 5.34 (d, J = 10.8 Hz, 1H, C***H***=C(CH_3)$_2$), 5.16 (d, J = 8.6 Hz, 1H, C***H***OAc), 2.58-2.49 (m, 2H, C*H*$_2$), 1.98 (s, 3H, COC***H***$_3$), 1.70 (s, 6H, 2 x C***H***$_3$).

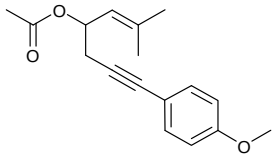
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 169.9 (***C***=O), 138.3 (***C***$_q$=), 126.0 (=***C***H_2), 122.2 (CH=***C***$_q$), 117.2 (=***C***H), 85.9 (C≡***C***$_q$), 80.8 (***C***$_q$≡C), 69.2 (***C***HOAc), 25.7 (***C***H_2), 25.6 (***C***H_{3trans}), 21.0 (CO***C***H_3), 18.5 (***C***H_{3cis}).

IR (ν, cm^{-1}) (CCl_4): 2974, 2914, 1738, 1440, 1371, 1237.

MS (CI, NH_3, m/z): 193 (MH^+), 150, 133.

HRMS (EI+, m/z) **:** Calculated for $C_{12}H_{16}O_2$: 192.1150.
Found for $C_{12}H_{16}O_2$: 192.1147.

1-(4-Methoxyphenyl)-6-methylhept-5-en-1-yn-4-yl acetate	**VIII.87j**



MF: $C_{17}H_{20}O_3$

MW = 272.335 g.mol^{-1}

Reaction: Prepared according to **Method VIII.1.a.**

Purification : Flash column chromatography (silica gel, PE/Et_2O 90/10).

Product : Yellow oil.

Yield : 73 % (58 % global).

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.31 (d, J = 7.9 Hz, 2H, 2 x C***H***$_{Ar}$), 6.80 (d, J = 7.9 Hz, 2H, 2 x C***H***$_{Ar}$), 5.71-5.68 (m, 1H, C***H***OAc), 5.26 (d, J = 8.7 Hz, 1H, =C***H***), 3.78 (s, 3H, OC***H***$_3$), 2.74-2.61 (m, 2H, C*H*$_2$), 2.05 (s, 3H, COC***H***$_3$), 1.76 (s, 6H, 2 x C***H***$_3$).

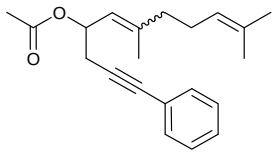
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 170.2 (***C***=O), 159.2 (O***C***$_{qAr}$), 138.5 (***C***$_q$=), 132.9 (H***C***$_{Ar}$), 122.4 (CH=***C***$_q$), 115.7 (***C***$_{qAr}$), 113.8 (H***C***$_{Ar}$), 83.7 (C≡***C***$_q$), 82.0 (***C***$_q$≡C), 69.6 (***C***HOAc), 55.2 (O***C***H$_3$), 26.0 (***C***H$_2$), 25.8 (***C***H$_{3trans}$), 21.2 (CO***C***H$_3$), 18.7 (***C***H$_{3cis}$).

IR (ν, cm^{-1}) (CCl_4): 2931, 1738, 1606, 1511, 1242, 1035.

MS (CI, NH_3, m/z): 273 (MH^+), 230, 213.

HRMS (EI+, m/z) **:** Calculated for $C_{17}H_{20}O_3$: 272.1413.
Found for $C_{17}H_{20}O_3$: 272.1416.

6,10-Dimethyl-1-phenylundeca-5,9-dien-1-yn-4-yl acetate	**VIII.87e**



MF: $C_{21}H_{26}O_2$

MW = 310.42 g.mol^{-1}

Reaction: Prepared according to Method VIII.1.b.

Purification : Flash column chromatography (silica gel, PE/Et_2O 95/5).

Product : Colorless oil.

Yield : 54 % (obtained as a mixture of 1:1.5 *cis: trans* isomers).

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.38 (m, 2H, 2 x C***H***$_{Ar}$), 7.29 (m, 3H, 3 x C***H***$_{Ar}$), 5.73 (dt, J = 6.5, 9.0 Hz, 1H, =C***H***CHOAc), 5.29 (dd, J = 9.1, 1.3 Hz, 1H, C***H***OAc), 5.10 (m, 1H, C***H***=C(CH$_3$)$_2$), 2.70 (dddd, J = 16.7, 16.7, 16.7, 6.3 Hz, 2H, C*H*$_2$), 2.18-2.08 (m, 4H, 2 x C*H*$_2$), 2.08 (s, 3H, COC***H***$_3$), 1.79 (m, 3H, C***H***$_3$), 1.68 (s, 3H, C***H***$_3$ *cis* isomer), 1.66 (s, 3H, C***H***$_3$ *trans* isomer), 1.60 (s, 3H, C***H***$_3$).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): For the *cis* isomer: 170.1 (***C***=O), 142.2 (=***C***$_q$), 132.1 (=***C***$_q$), 131.6 (H***C***$_{Ar}$), 128.2 (H***C***$_{Ar}$), 127.8 (H***C***$_{Ar}$), 123.8 (***C***$_{qAr}$), 123.5 (=***C***H), 122.7 (=***C***H), 85.4 (C≡***C***$_q$), 82.4 (***C***$_q$≡C), 69.0 (***C***HOAc), 39.5 (***C***H$_2$), 26.6 (***C***H$_2$), 26.1 (***C***H$_2$), 25.7 (***C***H$_{3trans}$), 23.4 (***C***H$_3$), 21.3 (CO***C***H$_3$), 17.6 (***C***H$_{3cis}$).
For the *trans* isomer: 170.2 (***C***=O), 141.8 (=***C***$_q$), 131.7 (=***C***$_q$), 131.5 (H***C***$_{Ar}$), 128.1 (H***C***$_{Ar}$), 127.8 (H***C***$_{Ar}$), 123.7 (***C***$_{qAr}$), 123.3 (=***C***H), 122.0 (=***C***H), 85.3 (C≡***C***$_q$), 82.1

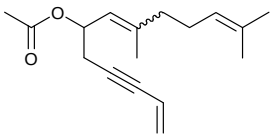
($\boldsymbol{C_q}$≡C), 69.4 (***C***HOAc), 39.5 (***C***H_2), 26.3 (***C***H_2), 26.0 (***C***H_2), 25.6 (***C***H_{3trans}), 21.2 (CO***C***H_3), 17.7 (***C***H_{3cis}), 17.0 (***C***H_3).

IR (ν, cm^{-1}) (CCl_4) 3055, 2969, 2919, 1738, 1669, 1596, 1490, 1442, 1371, 1237, 1017.

MS (CI, NH_3, m/z) 328 (MNH_4^+), 311 (MH^+), 268, 251.

HRMS (EI+, m/z) **:** Calculated for $C_{21}H_{26}O_2$: 310.1933.
Found for $C_{21}H_{26}O_2$: 310.1932.

8,12-Dimethyltrideca-1,7,11-trien-3-yn-6-yl acetate — VIII.87c



MF: $C_{17}H_{24}O_2$

MW = 260.37 $g.mol^{-1}$

EP : Prepared according to **Method VIII.1.a.**

Purification : Flash column chromatography (silica gel, PE/Et_2O 95/5).

Product : Pale yellow oil.

Yield : 70 % (46% global), (obtained as a mixture of 1:1.5 *cis: trans* isomers).

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 5.76 (qt, J = 17.5, 11.0, 2.0 Hz, 1H, C***H***=CH_2), 5.63 (dt, J = 9.0, 6.3 Hz, 1H, =C***H***), 5.57 (dt, J = 17.5, 2.4 Hz, 1H, CH=C***H***$_2$), 5.41 (dd, J = 11.0, 2.3 Hz, 1H, CH=C***H***$_2$), 5.19 (dd, J = 9.0, 0.9 Hz, 1H, C***H***OAc), 5.08 (m, 1H, =C***H***), 2.58 (ddddddd, J = 16.8, 16.8, 6.2, 1.9 Hz, 2H, C*H*$_2$CHOAc), 2.18-2.06 (m, 4H, 2 x C*H*$_2$), 2.06 (s, 3H, COC***H***$_3$ trans isomer), 2.05 (s, 3H, COC***H***$_3$ cis isomer), 1.77 (d, J = 1.4 Hz, C***H***$_3$ cis isomer), 1.76 (d, J = 1.3 Hz, 3H, C***H***$_3$ trans isomer), 1.68 (s, 3H, C***H***$_3$), 1.61 (s, 3H, C***H***$_3$ cis isomer), 1.60 (s, 3H, C***H***$_3$ trans isomer).

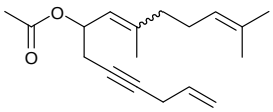
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) For the cis isomer: 170.1 (***C***=O), 142.2 (=$\boldsymbol{C_q}$), 132.1 (=$\boldsymbol{C_q}$), 126.2 (=***C***H_2), 123.8 (=***C***H), 122.6 (=***C***H), 117.3 (***C***H=CH_2), 86.1 (C≡$\boldsymbol{C_q}$), 81.0 ($\boldsymbol{C_q}$≡C), 68.9 (***C***HOAc), 32.6 (***C***H_2), 26.6 (***C***H_2), 26.0 (***C***H_2), 25.7 (***C***H_{3trans}), 23.4 (***C***H_3), 21.2 (CO***C***H_3), 17.6 (***C***H_{3cis}).
For the trans isomer: 170.2 (***C***=O), 142.8 (=$\boldsymbol{C_q}$), 131.8 (=$\boldsymbol{C_q}$), 126.2 (=***C***H_2), 123.7 (=***C***H), 122.0 (=***C***H), 117.3 (***C***H=CH_2), 86.0 (C≡$\boldsymbol{C_q}$), 80.9 ($\boldsymbol{C_q}$≡C), 69.3 (***C***HOAc), 39.5 (***C***H_2), 26.3 (***C***H_2), 25.9 (***C***H_2), 25.7 (***C***H_{3trans}), 21.2 (***C***H_3), 17.7 (CO***C***H_3), 17.0 (***C***H_{3cis}).

IR (ν, cm^{-1}) (CCl_4) 2969, 2919, 2857, 1739, 1669, 1608, 1442, 1371, 1236, 1017.

MS (CI, NH_3, m/z) 261 (MH^+), 233, 218, 201, 161.

HRMS (EI+, m/z) **:** Calculated for $C_{17}H_{24}O_2$: 260.1776.
Found for $C_{17}H_{24}O_2$: 260.1765.

9,13-Dimethyltetradeca-1,8,12-trien-4-yn-7-yl acetate — VIII.87d



MF: $C_{18}H_{26}O_2$

MW = 274.39 $g.mol^{-1}$

Reaction: Prepared according to **Method VIII.1.b.**

Purification : Flash column chromatography (silica gel, PE/Et_2O 98/2 to 95/5).

Product : Pale yellow oil.

Yield : 64 % (49% global), (obtained as a mixture of 1:2 *cis: trans* isomers).

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.81 (qt, J = 16.9, 10.1, 10.1, 5.1 Hz, 1H, C***H***=CH_2), 5.62 (dt, J = 9.1, 6.2 Hz, 1H, =C***H***), 5.31 (dq, J = 16.9, 3.4, 1.7 Hz, 1H, CH=C***H***$_2$), 5.23 (d, J = 9.3 Hz, 1H, =C***H***), 5.13-5.07 (m, 2H, C***H***OAc and CH=C***H***$_2$), 2.93 (m, 2H, C*H*$_2$), 2.17-2.08 (m, 4H, 2 x C*H*$_2$), 2.05 (s, 3H, COC***H***$_3$ *trans* isomer), 2.04 (s, 3H, COC***H***$_3$ *cis* isomer), 1.76 (d, J = 1.3 Hz, C***H***$_3$ *cis* isomer), 1.74 (d, J = 1.3 Hz, 3H, C***H***$_3$ *trans* isomer), 1.68 (s, 3H, C***H***$_3$), 1.61 (s, 3H, C***H***$_3$ *cis* isomer), 1.60 (s, 3H, C***H***$_3$ *trans* isomer).

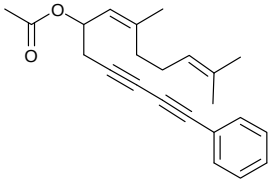
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): For the *cis* isomer: 170.1 (***C***=O), 142.0 (=***C***$_q$), 132.9 (=***C***$_q$), 132.0 (***C***H=CH_2), 123.8 (=***C***H), 122.8 (=***C***H), 115.7 (CH=***C***H_2), 78.5 (C≡***C***$_q$), 78.0 (***C***$_q$≡C), 69.1 (***C***HOAc), 39.5 (***C***H_2), 26.6 (***C***H_2), 25.6 (***C***H_2), 25.4 (***C***H_{3trans}), 23.4 (***C***H_3), 23.1 (***C***H_2), 21.2 (CO***C***H_3), 17.6 (***C***H_{3cis}).
For the *trans* isomer: 170.1 (***C***=O), 141.6 (=***C***$_q$), 132.9 (=***C***$_q$), 131.7 (***C***H=CH_2), 123.7 (=***C***H), 122.1 (=***C***H), 115.7 (CH=***C***H_2), 78.4 (C≡***C***$_q$), 77.9 (***C***$_q$≡C), 69.5 (***C***HOAc), 32.6 (***C***H_2), 26.3 (***C***H_2), 25.6 (***C***H_2), 25.3 (***C***H_{3trans}), 23.0 (***C***H_3), 21.2 (***C***H_2), 17.7 (CO***C***H_3), 17.0 (***C***H_{3cis}).

IR (ν, cm^{-1}) (CCl_4): 2970, 2917, 2857, 1738, 1669, 1643, 1439, 1371, 1237, 1016.

MS (CI, NH_3, m/z): 275 (MH^+), 255, 232, 215, 173.

HRMS (EI+, m/z) **:** Calculated for $C_{18}H_{26}O_2$: 274.1933.
Found for $C_{18}H_{26}O_2$: 274.1925.

(*Z*)-8,12-Dimethyl-1-phenyltrideca-7,11-dien-1,3-diyn-6-yl acetate — VIII.87g



MF: $C_{23}H_{26}O_2$

MW = 334.45 $g.mol^{-1}$

Reaction: Prepared according to **Method VIII.1.a.**

Purification : Flash column chromatography (silica gel, PE/Et_2O 90/10).

Product : Yellow oil.

Yield : 56 % global.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.47 (dd, J = 7.9, 1.5 Hz, 2H, 2 x C***H***$_{Ar}$), 7.36-7.27 (m, 3H, 3 x C***H***$_{Ar}$), 5.65 (dt, J = 9.4, 5.8 Hz, 1H, =C***H***CHOAc), 5.28 (d, J = 9.3 Hz, 1H, C***H***OAc), 5.11 (m, 1H, C***H***=C(CH_3)$_2$), 2.67 (d, J = 5.8 Hz, 2H, C***H***$_2$), 2.34-2.22 (m, 1H, C***H***), 2.18-2.07 (m, 3H, C***H*** and C***H***$_2$), 2.06 (s, 3H, COC***H***$_3$), 1.78 (d, J = 1.2 Hz, 3H, C***H***$_3$), 1.70 (s, 3H, C***H***$_3$), 1.63 (s, 3H, C***H***$_3$).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 170.0 (***C***=O), 142.6 (=***C***$_q$), 132.5 (H***C***$_{Ar}$), 132.2 (=***C***$_q$), 129.0 (H***C***$_{Ar}$), 128.4 (H***C***$_{Ar}$), 123.7 (=***C***H), 122.3 (=***C***H), 121.8 (***C***$_{qAr}$), 79.7 (C≡***C***$_q$), 75.2 (***C***$_q$≡C), 74.2 (***C***$_q$≡C), 68.4 (***C***HOAc), 66.9 (***C***$_q$≡C), 32.6 (***C***H_2), 26.5 (***C***H_2), 26.3 (***C***H_2), 25.7 (***C***H_{3trans}), 23.4 (***C***H_3), 21.2 (CO***C***H_3), 17.7 (***C***H_{3cis}).

IR (ν, cm^{-1}) (CCl_4): 3056, 2969, 2920, 2360, 1739, 1443, 1371, 1235, 1017.

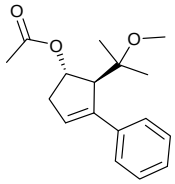
MS (CI, NH_3, m/z): 335 (MH^+).

HRMS (EI+, m/z) **:** Calculated for $C_{23}H_{26}O_2$: 334.1933.
Found for $C_{23}H_{26}O_2$: 334.1930.

VIII.2. Gold(I)-Catalyzed Hydroxy- and Alkoxycyclization of 1,5-Enynes

Method VIII.2. To a solution of the 1,5-enyne substrate (1 equiv., 0.25 mmol) in the apropiate solvent / nucleophile mixture (0.5 M), catalyst **VI.46** (0.01 equiv., 0.0025 mmol, 2.4 mg) was added and the resulted mixture was stirred at RT. When completed, the mixture was evaporated and purified on silicagel (petroleum ether and diethyl ether).

(1*S*,2*S*)-2-(2-Methoxypropan-2-yl)-3-phenylcyclopent-3-enyl acetate	**VIII.76**



MF: $C_{17}H_{22}O_3$

MW = 274.35 g.mol^{-1}

Reaction: Reaction carried out according to **Method VIII.2.**

Purification : Flash column chromatography (silica gel, PE/Et_2O 90/10).

Product : Pale yellow oil.

Yield : 99 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.36 (d, J = 7.1 Hz , 2H, 2 x C***H***$_{Ar}$), 7.31 (t, J = 7.1 Hz , 2H, 2 x C***H***$_{Ar}$), 7.23 (t, J = 7.1 Hz , 1H, C***H***$_{Ar}$), 5.90 (bs, 1H, =C***H***), 5.55 (d, J = 5.8 Hz, 1H, C***H***OAc), 3.42 (s, 1H, C***H***), 3.16 (s, 3H, OC***H***$_3$), 2.90 (dd, J = 18.8, 5.9 Hz, 1H, C***H***$_2$), 2.38 (dd, J = 18.8, 3.0 Hz, 1H, C***H***$_2$), 2.07 (s, 3H, COC***H***$_3$), 1.01 (s, 3H, C***H***$_3$), 0.97 (s, 3H, C***H***$_3$).

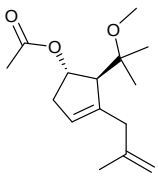
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 170.9 (***C***=O), 144.0 (=***C***$_q$), 138.7 (***C***$_{qAr}$), 128.8 (H***C***$_{Ar}$), 128.3 (H***C***$_{Ar}$), 127.3 (H***C***$_{Ar}$), 126.9 (=***C***H), 77.7 (O***C***$_q$), 77.1 (***C***HOAc), 61.3 (***C***H), 49.4 (O***C***H$_3$), 41.0 (***C***H$_2$), 25.1 (***C***H$_3$), 22.6 (***C***H$_3$), 21.7 (CO***C***H$_3$).

IR (ν, cm^{-1}) (CCl_4): 2977, 2936, 1737, 1244, 1077.

MS (CI, NH_3, m/z): 292 (MNH_4^+), 275 (MH^+), 243, 183.

HRMS (EI+, m/z) **:** Calculated for $C_{17}H_{22}O_3$: 274.1569.
Found for $C_{17}H_{22}O_3$: 274.1564.

(1*S*,2*S*)-2-(2-Methoxypropan-2-yl)-3-(2-methylallyl)cyclopent-3-enyl acetate	**VIII.88b**



MF: $C_{15}H_{24}O_3$

MW = 252.34 g.mol^{-1}

Reaction: Obtained as the main product in the reaction carried out according to **Method VIII.2.,** along with side-product VIII.90.

Purification : Flash column chromatography (silica gel, PE/Et_2O 80/20).

Product : Yellow oil.

Yield : 87 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.49 (s, 1H, =C***H***), 5.20 (bs, 1H, =C***H***$_2$), 4.81 (s, 1H, =C***H***$_2$), 4.73 (s, 1H, C***H***OAc), 3.18 (s, 3H, OC***H***$_3$), 2.94 (d, J = 15.8 Hz, 1H, C***H***$_2$), 2.86 (d, J = 15.8 Hz, 1H, C***H***$_2$), 2.82 (s, 1H, C***H***), 2.72 (dm, J = 17.8, 6.1, 3.2, 1.6 Hz, 1H, C***H***$_2$), 2.16 (d, J = 17.6 Hz, 1H, C***H***$_2$), 2.02 (s, 3H, COC***H***$_3$), 1.71 (s, 3H, C***H***$_3$), 1.18 (s, 3H, C***H***$_3$), 1.08 (s, 3H, C***H***$_3$).

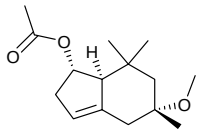
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 170.8 (***C***=O), 143.9 (=***C***$_q$), 141.9 (=***C***$_q$), 126.6 (=***C***H), 111.8 (=***C***H$_2$), 78.0 (***C***HOAc), 76.9 (O***C***$_q$), 60.2 (***C***H), 49.0 (O***C***H$_3$), 39.8 (***C***H$_2$), 39.4 (***C***H$_2$), 23.4 (***C***H$_3$), 22.8 (***C***H$_3$), 22.6 (***C***H$_3$), 21.5 (CO***C***H$_3$).

IR (ν, cm^{-1}) (CCl_4): 2975, 2935, 1736, 1647, 1442, 1371, 1242, 1076, 1025.

MS (CI, NH_3, m/z): 253 (MH^+), 193, 179, 161.

HRMS (EI+, m/z) **:** Calculated for $C_{15}H_{24}O_3$: 252.1726.
Found for $C_{15}H_{24}O_3$: 252.1733.

(1*S*,5*S*,7a*S*)-1,2,4,5,6,7,7a-Heptahydro-5-methoxy-5,7,7-trimethyl-2*H*-inden-1-yl acetate — VIII.90



MF: $C_{15}H_{24}O_3$

MW = 252.34 g.mol^{-1}

Reaction: Obtained as a side-product in the reaction described above, along with main product VIII.88b

Purification : Flash column chromatography (silica gel, PE/Et_2O 80/20).

Product : Yellow oil.

Yield : 13 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.38 (t, J = 1.8 Hz, 1H, =C***H***), 5.19 (dt, J = 6.9 Hz, 1H, C***H***OAc), 3.23 (s, 3H, OC***H***$_3$), 2.70 (dm, J = 18.0, 6.8, 4.7, 1.9 Hz, 1H, C***H***$_2$), 2.47 (dd, J = 12.6, 1.8 Hz, 1H, C***H***), 2.31-2.25 (m, 2H, C***H***$_2$), 2.17 (d, J = 13.2 Hz, 1H, C***H***), 2.04 (s, 3H, COC***H***$_3$), 1.62-1.59 (m, 2H, C***H***$_2$), 1.19 (s, 3H, C***H***$_3$), 1.07 (s, 3H, C***H***$_3$), 0.77 (s, 3H, C***H***$_3$).

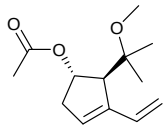
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 170.8 (***C***=O), 140.6 (=***C***$_q$), 121.4 (=***C***H), 75.6 (O***C***$_q$), 74.9 (***C***HOAc), 62.9 (***C***H), 51.4 (***C***H$_2$), 48.8 (O***C***H$_3$), 41.2 (***C***H$_2$), 40.6 (***C***H$_2$), 34.2 (***C***$_q$), 31.8 (***C***H$_3$), 23.5 (***C***H$_3$), 22.0 (***C***H$_3$), 21.6 (CO***C***H$_3$).

IR (ν, cm^{-1}) (CCl_4): 3049, 2935, 1736, 1460, 1436, 1371, 1245, 1153, 1111, 1072, 1027.

MS (CI, NH_3, m/z): 270 (MNH_4^+), 253 (MH^+), 238, 221, 161.

HRMS (EI+, m/z) **:** Calculated for $C_{15}H_{24}O_3$: 252.1725.
Found for $C_{15}H_{24}O_3$: 252.1718.

(1*S*,2*S*)-2-(2-Methoxypropan-2-yl)-3-vinylcyclopent-3-enyl acetate — VIII.88a



MF: $C_{13}H_{20}O_3$

MW = 224.29 g.mol^{-1}

Reaction: Obtained as main product in the reaction carried out according to **Method VIII.2.,** along with side-product VIII.88abis.

Purification : Flash column chromatography (silica gel, PE/Et_2O 80/20).

Product : Colourless oil.

Yield : 77 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 6.42 (dd, J = 17.5, 10.9 Hz, 1H, C***H***=CH_2), 5.87 (s, 1H, C***H***OAc), 5.37 (bd, J = 5.9 Hz, 1H, =C***H***), 5.30 (d, J = 17.6 Hz, 1H, =C***H***$_2$), 5.05 (d, J = 10.9 Hz, 1H, =C***H***$_2$), 3.19 (s, 3H, OC***H***$_3$), 2.98 (s, 1H, C***H***), 2.80 (dd, J = 19.0, 5.7 Hz, 1H, C***H***$_2$), 2.22 (dd, J = 19.0, 2.7 Hz, 1H, C***H***$_2$), 2.02 (s, 3H, COC***H***$_3$), 1.17 (s, 3H, C***H***$_3$), 1.09 (s, 3H, C***H***$_3$).

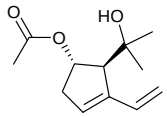
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 170.7 (***C***=O), 142.4 (=***C***$_q$), 134.0 (=***C***H), 128.7 (=***C***H), 114.6 (=***C***H_2), 77.7 (***C***HOAc), 76.9 (O***C***$_q$), 60.2 (***C***H), 49.1 (O***C***H_3), 39.9 (***C***H_2), 24.0 (***C***H_3), 22.8 (***C***H_3), 21.5 (CO***C***H_3).

IR (ν, cm^{-1}) (CCl_4): 2977, 2936, 2828, 1736, 1370, 1243.

MS (CI, NH_3, m/z): 225 (MH^+), 193.

HRMS (EI+, m/z) **:** Calculated for $C_{13}H_{20}O_3$: 224.1413.
Found for $C_{13}H_{20}O_3$: 224.1423.

(1*S*,2*S*)-2-(2-Hydroxypropan-2-yl)-3-vinylcyclopent-3-enyl acetate	**VIII.88abis**



MF: $C_{12}H_{18}O_3$

MW = 210.26 $g.mol^{-1}$

Reaction: Obtained as a side-product in the reaction described above, along with main product VIII.88a

Purification : Flash column chromatography (silica gel, PE/Et_2O 80/20).

Product : Colorless oil.

Yield : 23 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 6.49 (dd, J = 17.6, 11.0 Hz, 1H, C***H***=CH_2), 5.93 (bs, 1H, C***H***OAc), 5.36-5.31 (m, 2H, 2 x =C***H***), 5.13 (d, J = 11.0 Hz, 1H, =C***H***), 2.92 (s, 1H, C***H***), 2.81 (dd, J = 19.2, 5.8 Hz, 1H, C***H***), 2.36-2.30 (m, 2H, 2 x C***H***), 2.04 (s, 3H, COC***H***$_3$), 1.23 (s, 3H, C***H***$_3$), 1.21 (s, 3H, C***H***$_3$).

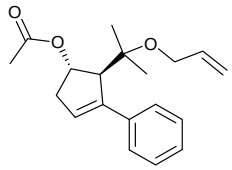
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 171.4 (***C***=O), 142.0 (=***C***$_q$), 134.0 (=***C***H), 129.8 (=***C***H), 115.7 (=***C***H_2), 78.0 (***C***HOAc), 73.2 (HO***C***$_q$), 62.9 (***C***H), 39.3 (***C***H_2), 28.6 (***C***H_3), 27.7 (***C***H_3), 21.5 (CO***C***H_3).

IR (ν, cm^{-1}) (CCl_4): 3518, 2875, 2360, 1735, 1371, 1243, 1179, 1026.

MS (CI, NH_3, m/z): 193, 183, 161, 133.

HRMS (EI+, m/z) **:** Calculated for $C_{12}H_{18}O_3$: 210.1256.
Found for $C_{12}H_{18}O_3$: 210.1259.

(1*S*,2*S*)-2-(2-(Allyloxy)propan-2-yl)-3-phenylcyclopent-3-enyl acetate	**VIII.81**



MF: $C_{19}H_{24}O_3$

MW = 300.39 g.mol^{-1}

Reaction: Reaction carried out according to **Method VIII.2.**

Purification : Flash column chromatography (silica gel, PE/Et_2O 80/20).

Product : White crystals.

Yield : 93 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.36 (d, J = 7.1 Hz, 2H, 2 x CH_{Ar}), 7.30 (t, J = 7.1 Hz , 2H, 2 x CH_{Ar}), 7.23 (t, J = 7.1 Hz , 1H, CH_{Ar}), 5.93 (bs, 1H, =C*H*), 5.78 (dm, J = 17.1, 10.3, 5.1 Hz, 1H, C*H*=CH_2), 5.60 (d, J = 5.7 Hz, 1H, C*H*OAc), 5.18 (ddd, J = 17.2, 1.7 Hz, 1H, =CH_2), 5.05 (ddd, J = 10.4, 3.1, 1.5 Hz, 1H, =CH_2), 3.88 (ddd, J = 5.1, 1.5 Hz, 2H, OCH_2), 3.46 (s, 1H, C*H*), 2.93 (ddd, J = 18.7, 5.8, 1.5 Hz, 1H, CH_2), 2.39 (dd, J = 18.7, 3.0 Hz, 1H, CH_2), 2.06 (s, 3H, COCH_3), 1.06 (s, 3H, CH_3), 1.02 (s, 3H, CH_3).

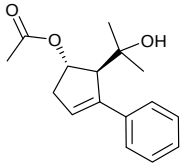
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 170.7 (*C*=O), 143.8 (=C_q), 138.6 (C_{qAr}), 135.8 (=*C*H), 128.6 (HC_{Ar}), 128.2 (HC_{Ar}), 127.1 (HC_{Ar}), 126.8 (=*C*H), 115.3 (=*C*H_2), 77.5 (OC_q), 77.2 (*C*H_2O), 62.6 (*C*HOAc), 61.5 (*C*H), 40.8 (*C*H_2), 25.5 (*C*H_3), 23.2 (*C*H_3), 21.7 (CO*C*H_3).

IR (ν, cm^{-1}) (CCl_4): 2978, 2929, 1737, 1369, 1243, 1142, 1026.

MS (CI, NH_3, m/z): 301 (MNH_4^+), 243, 183.

HRMS (EI+, m/z) **:** Calculated for $C_{19}H_{24}O_3$: 300.1726.
Found for $C_{19}H_{24}O_3$: 300.1724.

(1*S*,2*S*)-2-(2-Hydroxypropan-2-yl)-3-phenylcyclopent-3-enyl acetate — VIII.85



MF: $C_{16}H_{20}O_3$

MW = 260.32 g.mol^{-1}

EP : Reaction carried out according to **Method VIII.2.**

Purification : Flash column chromatography (silica gel, PE/AcOEt 70/30).

Product : Colorless oil.

Yield : 99 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.42 (d, J = 7.1 Hz, 2H, 2 x CH_{Ar}), 7.35 (t, J = 7.4 Hz , 2H, 2 x CH_{Ar}), 7.23 (t, J = 7.2 Hz , 1H, CH_{Ar}), 6.05 (bs, 1H, =C*H*), 5.51 (d, J = 5.9 Hz, 1H, C*H*OAc), 3.35 (s, 1H, C*H*), 2.95 (ddd, J = 18.7, 6.0, 1.7 Hz, 1H, CH_2), 2.52 (dd, J = 18.8, 3.0 Hz, 1H, CH_2), 2.48 (bs, 1H, O*H*), 2.13 (s, 3H, COCH_3), 1.14 (s, 3H, CH_3), 1.11 (s, 3H, CH_3).

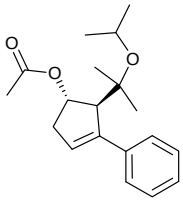
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 171.3 (*C*=O), 142.5 (=C_q), 139.6 (C_{qAr}), 128.6 (HC_{Ar}), 128.2 (HC_{Ar}), 126.6 (HC_{Ar}), 124.8 (=*C*H), 78.0 (*C*HOAc), 77.5 (HOC_q), 63.3 (*C*H), 39.2 (*C*H_2), 28.3 (*C*H_3), 28.0 (*C*H_3), 21.5 (CO*C*H_3).

IR (ν, cm^{-1}) (CCl_4): 3596, 3517, 2976, 1734, 1370, 1247, 1171, 1027.

MS (CI, NH_3, m/z): 278 (MNH_4^+), 268, 261, 243, 211, 183.

HRMS (EI+, m/z) **:** Calculated for $C_{16}H_{20}O_3$: 260.1413.
Found for $C_{16}H_{20}O_3$: 260.1406.

(1*S*,2*S*)-2-(2-isopropoxypropan-2-yl)-3-phenylcyclopent-3-enyl acetate **VIII.83**



MF: $C_{19}H_{26}O_3$

MW = 302.40 g.mol^{-1}

Reaction: Reaction carried out according to **Method VIII.2.**

Purification : Flash column chromatography (silica gel, PE/Et_2O 80/20).

Product : Colorless oil.

Yield : 98 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.37 (d, J = 7.1 Hz, 2H, 2 x C***H$_{Ar}$***), 7.29 (t, J = 7.1 Hz, 2H, 2 x C***H$_{Ar}$***), 7.22 (t, J = 7.1 Hz, 1H, C***H$_{Ar}$***), 5.93 (bs, 1H, =C***H***), 5.53 (d, J = 5.6 Hz, 1H, C***H***OAc), 3.78 (sept, J = 6.1 Hz, 1H, $(CH_3)_2$C***H***), 3.35 (s, 1H, C***H***), 2.90 (ddd, J = 18.7, 5.7, 1.5 Hz, 1H, C***H***$_2$), 2.37 (dd, J = 18.7, 3.0 Hz, 1H, C***H***$_2$), 2.06 (s, 3H, COC***H***$_3$), 1.06 (d, J = 6.1 Hz, 3H, CHC***H***$_3$), 1.01 (s, 3H, C***H***$_3$), 0.97 (s, 3H, C***H***$_3$), 0.96 (d, J = 6.1 Hz, 3H, CHC***H***$_3$).

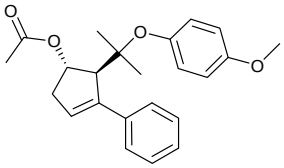
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) 170.8 (***C***=O), 144.0 (=***C$_q$***), 138.8 (***C$_{qAr}$***), 128.8 (H***C$_{Ar}$***), 128.5 (H***C$_{Ar}$***), 128.1 (H***C$_{Ar}$***), 127.5 (H***C$_{Ar}$***), 126.9 (H***C$_{Ar}$***), 126.8 (=***C***H), 77.9 ($(CH_3)_2$***C***HO), 77.4 (O***C$_q$***), 63.2 (***C***HOAc), 62.1 (***C***H), 40.9 (***C***H_2), 26.1 (***C***H_3), 25.2 (***C***H_3), 24.6 (***C***H_3), 23.6 (***C***H_3), 21.5 (CO***C***H_3).

IR (ν, cm^{-1}) (CCl_4) 2974, 2930, 1736, 1370, 1245, 1116, 1019.

MS (CI, NH_3, m/z) 303 (MNH_4^+), 243, 183.

HRMS (EI+, m/z) **:** Calculated for $C_{19}H_{26}O_3$: 302.1882.
Found for $C_{19}H_{26}O_3$: 302.1886.

(1*S*,2*S*)-2-(2-(4-Methoxyphenoxy)propan-2-yl)-3-phenylcyclopent-3-enyl acetate **VIII.82**



MF: $C_{23}H_{26}O_4$

MW = 366.45 g.mol^{-1}

Reaction: Reaction carried out according to **Method VIII.2**.

Purification : Flash column chromatography (silica gel, PE/Et_2O 65/35).

Product : Pale yellow oil.

Yield : 95 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.42 (d, J = 7.1 Hz, 2H, 2 x C***H$_{Ar}$***), 7.31 (t, J = 7.1 Hz, 2H, 2 x C***H$_{Ar}$***), 7.23 (t, J = 7.1 Hz, 1H, C***H$_{Ar}$***), 6.85-6.75 (m, 4H, 4 x C***H$_{Ar}$***), 6.04 (bs, 1H, =C***H***), 5.81 (d, J = 5.6 Hz, 1H, C***H***OAc), 3.77 (s, 3H, OC***H***$_3$), 3.59 (s, 1H, C***H***), 3.07 (dd, J = 18.7, 5.7 Hz, 1H,

C***H***$_2$), 2.47 (dd, J = 18.7, 2.9 Hz, 1H, C***H***$_2$), 2.11 (s, 3H, COC***H***$_3$), 1.11 (s, 3H, C***H***$_3$), 1.08 (s, 3H, C***H***$_3$).

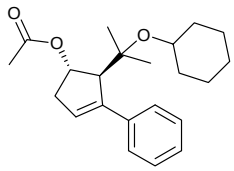
^{13}C NMR (δ, ppm) (CDCl$_3$, 100 MHz): 170.8 (***C***=O), 155.8 (CH$_3$O***C***$_{qAr}$), 148.0 (O***C***$_{qAr}$), 143.6 (=***C***$_q$), 138.6 (***C***$_{qAr}$), 129.0 (H***C***$_{Ar}$), 128.2 (H***C***$_{Ar}$), 127.1 (H***C***$_{Ar}$), 126.8 (H***C***$_{Ar}$), 125.2 (=***C***H), 113.9 (H***C***$_{Ar}$), 82.1 (***C***HOAc), 77.9 (O***C***$_q$), 62.4 (***C***H), 55.5 (O***C***H$_3$), 40.8 (***C***H$_2$), 26.7 (***C***H$_3$), 24.3 (***C***H$_3$), 21.6 (CO***C***H$_3$).

IR (ν, cm^{-1}) (CCl$_4$): 2981, 2910, 1736, 1505, 1370, 1243, 1129, 1037.

MS (CI, NH$_3$, m/z): 232 (MH$^+$), 243, 183.

HRMS (EI+, m/z) **:** Calculated for C$_{23}$H$_{26}$O$_4$: 366.1831.
Found for C$_{23}$H$_{26}$O$_4$: 366.1830.

(1*S*,2*S*)-2-(2-(Cyclohexyloxy)propan-2-yl)-3-phenylcyclopent-3-enyl acetate — VIII.84



MF: C$_{22}$H$_{30}$O$_3$

MW = 342.47 g.mol^{-1}

EP : Reaction carried out according to **Method VIII.2.**

Purification : Flash column chromatography (silica gel, PE/AcOEt 80/20).

Product : Yellow oil.

Yield : 54 %.

^{1}H NMR (δ, ppm) (CDCl$_3$, 400 MHz): 7.39 (d, J = 7.1 Hz, 2H, 2 x C***H***$_{Ar}$), 7.30 (t, J = 7.1 Hz, 2H, 2 x C***H***$_{Ar}$), 7.22 (t, J = 7.1 Hz, 1H, C***H***$_{Ar}$), 5.94 (bs, 1H, =C***H***), 5.56 (d, J = 5.6 Hz, 1H, C***H***OAc), 3.43-3.36 (m, 1H, C***H***), 3.33 (s, 1H, C***H***), 2.92 (dd, J = 18.6, 5.8 Hz, 1H, C***H***$_2$), 2.36 (dd, J = 18.6, 3.0 Hz, 1H, C***H***$_2$), 2.06 (s, 3H, COC***H***$_3$), 1.67-1.54 (m, 4H, 2 x C***H***$_2$), 1.29-1.09 (m, 6H, 3 x C***H***$_2$), 1.01 (s, 3H, C***H***$_3$), 0.99 (s, 3H, C***H***$_3$).

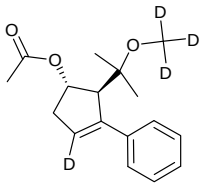
^{13}C NMR (δ, ppm) (CDCl$_3$, 100 MHz): 170.8 (***C***=O), 144.0 (=***C***$_q$), 138.9 (***C***$_{qAr}$), 128.5 (H***C***$_{Ar}$), 128.1 (H***C***$_{Ar}$), 126.9 (H***C***$_{Ar}$), 126.8 (=***C***H), 79.4 (***C***HO), 78.1 (O***C***$_q$), 62.5 (***C***HOAc), 60.1 (***C***H), 40.8 (***C***H$_2$), 35.3 (***C***H$_2$), 34.9 (***C***H$_2$), 26.2 (***C***H$_3$), 25.7 (***C***H$_2$), 24.5 (2 x ***C***H$_2$), 23.7 (***C***H$_3$), 21.6 (CO***C***H$_3$).

IR (ν, cm^{-1}) (CCl$_4$): 2933, 2854, 1736, 1369, 1244, 1025.

MS (CI, NH$_3$, m/z): 343 (MH$^+$), 260, 243, 183.

HRMS (EI+, m/z) **:** Calculated for C$_{22}$H$_{30}$O$_3$: 342.2195.
Found for C$_{22}$H$_{30}$O$_3$: 342.2179.

Deuterated (1*S*,2*S*)-2-(2-Methoxypropan-2-yl)-3-phenylcyclopent-3-enyl acetate — VIII.89



MF: C$_{17}$H$_{18}$D$_4$O$_3$

MW = 278.37 g.mol^{-1}

Reaction: Reaction carried out according to **Method VIII.2.**

Purification : Flash column chromatography (silica gel, PE/Et$_2$O 80/20 to 70/30).

Product : Pale yellow oil.

Yield : 100 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.36 (d, J = 7.1 Hz, 2H, 2 x C$\boldsymbol{H_{Ar}}$), 7.31 (t, J = 7.1 Hz, 2H, 2 x C$\boldsymbol{H_{Ar}}$), 7.23 (t, J = 7.1 Hz, 1H, C$\boldsymbol{H_{Ar}}$), 5.51 (d, J = 5.85 Hz, 1H, C***H***OAc), 3.38 (s, 1H, C***H***), 2.86 (ddd, J = 18.8, 5.9, 1.6 Hz, 1H, C$\boldsymbol{H_2}$), 2.34 (d, J = 18.8 Hz, 1H, C$\boldsymbol{H_2}$), 2.02 (s, 3H, COC$\boldsymbol{H_3}$), 0.97 (s, 3H, C$\boldsymbol{H_3}$), 0.93 (s, 3H, C$\boldsymbol{H_3}$).

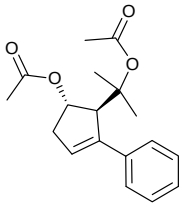
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 170.8 (***C***=O), 143.7 (=$\boldsymbol{C_q}$), 138.5 ($\boldsymbol{C_{qAr}}$), 128.6 (H$\boldsymbol{C_{Ar}}$), 128.2 (H$\boldsymbol{C_{Ar}}$), 127.1 (H$\boldsymbol{C_{Ar}}$), 126.8 (=***C***D), 77.5 (O$\boldsymbol{C_q}$), 76.9 (***C***HOAc), 61.1 (***C***H), 40.7 (***C***H_2), 25.0 (***C***H_3), 22.4 (***C***H_3), 21.6 (CO***C***H_3).

IR (ν, cm^{-1}) (CCl_4): 2977, 2933, 1737, 1368, 1245, 1118, 1025.

MS (CI, NH_3, m/z): 279 (MH^+), 244, 219, 184, 161.

HRMS (EI+, m/z) **:** Calculated for $C_{17}H_{18}D_4O_3$: 278.1820.
Found for $C_{17}H_{18}D_4O_3$: 278.1821.

Acetic acid (1*S*,2*S*)-2-(1-acetoxy-1-methyl-ethyl)-3-phenylcyclopent-3-enyl ester	**VIII.86**



MF: $C_{18}H_{22}O_4$

MW = 302.36 $g.mol^{-1}$

Reaction: Reaction carried out according to **Method VIII.2**.

Purification : Flash column chromatography (silica gel, PE/Et_2O 75/25).

Product : Yellow oil.

Yield : 68 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.36 (d, J = 7.1 Hz, 2H, 2 x C$\boldsymbol{H_{Ar}}$), 7.30 (t, J = 7.1 Hz, 2H, 2 x C$\boldsymbol{H_{Ar}}$), 7.23 (t, J = 7.1 Hz, 1H, C$\boldsymbol{H_{Ar}}$), 5.94 (bs, 1H, =C***H***), 5.45 (d, J = 6.0 Hz, 1H, C***H***OAc), 4.01 (s, 1H, C***H***), 2.89 (dd, J = 18.8, 6.1 Hz, 1H, C$\boldsymbol{H_2}$), 2.42 (dd, J = 18.8, 2.9 Hz, 1H, C$\boldsymbol{H_2}$), 2.07 (s, 3H, COC$\boldsymbol{H_3}$), 1.66 (s, 3H, C$\boldsymbol{H_3}$), 1.41 (s, 3H, C$\boldsymbol{H_3}$), 1.26 (s, 3H, C$\boldsymbol{H_3}$).

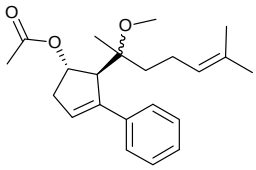
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 170.7 (***C***=O), 170.6 (***C***=O), 143.7 (=$\boldsymbol{C_q}$), 138.3 ($\boldsymbol{C_{qAr}}$), 128.7 (H$\boldsymbol{C_{Ar}}$), 128.2 (H$\boldsymbol{C_{Ar}}$), 127.2 (H$\boldsymbol{C_{Ar}}$), 126.9 (=***C***H), 83.6 (***C***HOAc), 76.5 (O$\boldsymbol{C_q}$), 60.7 (***C***H), 40.6 (***C***H_2), 25.0 (***C***H_3), 24.4 (***C***H_3), 22.3 (CO***C***H_3), 21.7 (CO***C***H_3).

IR (ν, cm^{-1}) (CCl_4): 2984, 2937, 1736, 1368, 1249, 1126, 1023.

MS (CI, NH_3, m/z): 320 (MNH_4^+), 270, 260, 243, 219, 183.

HRMS (EI+, m/z) **:** Calculated for $C_{18}H_{22}O_4$: 302.1518.
Found for $C_{18}H_{22}O_4$: 302.1514.

(1*S*,2*S*)-2-(2-Methoxy-6-methylhept-5-en-2-yl)-3-phenylcyclopent-3-enyl acetate	**VIII.88e**



MF: $C_{22}H_{30}O_3$

MW = 342.47 g.mol^{-1}

Reaction: Reaction carried out according to **Method VIII.2.**

Purification : Flash column chromatography (silica gel, PE/Et_2O 90/10).

Product : Yellow oil.

Yield : 98 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)

For the minor isomer: 7.37 (d, J = 7.1 Hz, 2H, 2 x C***H***$_{Ar}$), 7.30 (d, J = 7.2 Hz, 2H, 2 x C***H***$_{Ar}$), 7.25 (t, J = 7.2 Hz, 1H, C***H***$_{Ar}$), 5.87 (s, 1H, =C***H***), 5.49 (d, J = 6.0 Hz, 1H, C***H***OAc), 5.00 (t, J = 7.1, 1.3 Hz, 1H, =C***H***), 3.57 (d, J = 0.5 Hz, 1H, C***H***), 3.05 (s, 3H, OC***H***$_3$), 2.92 (dd, J = 18.9, 6.2 Hz, 1H, C***H***$_2$), 2.38 (dd, J = 18.9, 2.9 Hz, 1H, C***H***$_2$), 2.08 (s, 3H, COC***H***$_3$), 2.00 (m, 1H, C***H***), 1.89 (m, 1H, C***H***), 1.66 (s, 3H, C***H***$_3$), 1.57 (s, 3H, C***H***$_3$), 1.40 (m, 2H, C***H***$_2$), 0.93 (s, 3H, C***H***$_3$).
For the major isomer: 7.36-7.23 (m, 5H, 5 x C***H***$_{Ar}$), 5.88 (s, 1H, =C***H***), 5.60 (d, J = 5.9 Hz, 1H, C***H***OAc), 4.78 (tt, J = 7.1, 1.4 Hz, 1H, =C***H***), 3.48 (s, 1H, C***H***), 3.16 (s, 3H, OC***H***$_3$), 2.92 (dd, J = 18.8, 5.9 Hz, 1H, C***H***$_2$), 2.38 (dd, J = 18.9, 3.0 Hz, 1H, C***H***$_2$), 2.07 (s, 3H, COC***H***$_3$), 1.91 (m, 2H, C***H***$_2$), 1.61 (s, 3H, C***H***$_3$), 1.53 (s, 3H, C***H***$_3$), 1.32-1.14 (m, 2H, C***H***$_2$), 0.97 (s, 3H, C***H***$_3$).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)

For the minor isomer:170.7 (***C***=O), 144.1 (=***C***$_q$), 138.5 (***C***$_{qAr}$), 131.3 (=***C***$_q$), 128.2 (H***C***$_{Ar}$), 127.9 (H***C***$_{Ar}$), 127.0 (H***C***$_{Ar}$), 126.9 (=***C***H), 124.6 (=***C***H), 78.2 (O***C***$_q$), 77.6 (***C***HOAc), 59.6 (***C***HO), 49.0 (CH_3O), 40.9 (***C***H_2), 35.9 (***C***H_2), 25.7 (***C***H_3), 21.8 (***C***H_2), 21.4 (***C***H_3), 21.3 (CO***C***H_3), 17.6 (***C***H_3).
For the major isomer:170.7 (***C***=O), 144.0 (=***C***$_q$), 138.6 (***C***$_{qAr}$), 131.2 (=***C***$_q$), 129.0 (H***C***$_{Ar}$), 128.2 (H***C***$_{Ar}$), 127.1 (H***C***$_{Ar}$), 126.6 (=***C***H), 124.2 (=***C***H), 78.4 (O***C***$_q$), 77.5 (***C***HOAc), 59.1 (***C***HO), 48.9 (CH_3O), 41.0 (***C***H_2), 36.3 (***C***H_2), 25.6 (***C***H_3), 21.8 (***C***H_2), 21.5 (***C***H_3), 20.0 (CO***C***H_3), 17.6 (***C***H_3).

IR (ν, cm^{-1}) (CCl_4)

For the minor isomer: 2971, 2929, 2857, 1737, 1598, 1493, 1446, 1372, 1244, 1166, 1074, 1025.
For the major isomer: 2973, 2931, 2829, 1736, 1597, 1493, 1445, 1371, 1244, 1176, 1092, 1073, 1024.

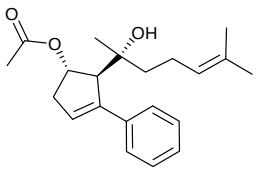
MS (CI, NH_3, m/z)

For the minor isomer: 343 (MH^+), 311, 251, 141.
For the major isomer: 343 (MH^+), 311, 251, 195.

HRMS (EI+, m/z) **:**

For the minor isomer: Calculated for $C_{22}H_{30}O_3$: 342.2195.
Found for $C_{22}H_{30}O_3$: 342.2198.
For the major isomer: Calculated for $C_{22}H_{30}O_3$: 342.2195.
Found for $C_{22}H_{30}O_3$: 342.2187.

(1*S*,2*S*)-2-((*R*)-2-Hydroxy-6-methylhept-5-en-2-yl)-3-phenylcyclopent-3-enyl acetate — VIII.91a



MF: $C_{21}H_{28}O_3$

MW = 328.44 g.mol^{-1}

Reaction: Reaction carried out according to **Method VIII.2.**

Purification : Flash column chromatography (silica gel, PE/Et_2O 65/35).

Product : Yellow oil.

Yield : 94 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.39 (d, J = 7.0 Hz, 2H, 2 x C***H***$_{Ar}$), 7.35 (t, J = 7.0 Hz, 2H, 2 x C***H***$_{Ar}$), 7.29 (t, J = 7.0 Hz , 1H, C***H***$_{Ar}$), 6.01 (bs, 1H, =C***H***), 5.56 (d, J = 6.0 Hz, 1H, C***H***OAc), 4.97 (dd, J = 7.1, 7.1
Hz, 1H, =C***H***), 3.40 (s, 1H, C***H***), 2.97 (dd, J = 18.7, 6.1 Hz, 1H, C***H***$_2$), 2.51 (dd, J = 18.7, 3.0 Hz, 1H, C***H***$_2$), 2.38 (bs, 1H, O***H***), 2.12 (s, 3H, COC***H***$_3$), 2.10-2.03 (m, 2H, C***H***$_2$), 1.67 (s, 3H, C***H***$_3$), 1.59 (s, 3H, C***H***$_3$), 1.40-1.34 (m, 2H, C***H***$_2$), 1.08 (s, 3H, C***H***$_3$).

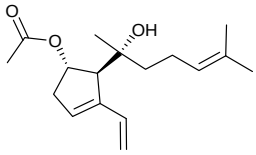
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 171.2 (***C***=O), 143.4 (=***C***$_q$), 138.1 (***C***$_{qAr}$), 131.5 (=***C***$_q$), 128.7 (H***C***$_{Ar}$), 128.4 (H***C***$_{Ar}$), 127.4 (H***C***$_{Ar}$), 126.7 (=***C***H), 124.4 (=***C***H), 77.9 (***C***HOAc), 74.9 (O***C***$_q$), 62.8 (***C***HO), 40.7 (***C***H_2), 40.1 (***C***H_2), 25.7 (***C***H_3), 24.8 (***C***H_3), 22.2 (***C***H_2), 21.5 (CO***C***H_3), 17.7 (***C***H_3).

IR (ν, cm^{-1}) (CCl_4): 3512, 2973, 2918, 1733, 1373, 1247.

MS (CI, NH_3, m/z): 329 (MH^+), 311, 251.

HRMS (EI+, m/z) **:** Calculated for $C_{21}H_{28}O_3$: 328.2039.
Found for $C_{21}H_{28}O_3$: 328.2045.

(1*S*,2*S*)-2-((*R*)-2-Hydroxy-6-methylhept-5-en-2-yl)-3-vinylcyclopent-3-enyl acetate **VIII.91b**



MF: $C_{17}H_{26}O_3$

MW = 278.38 g.mol^{-1}

Reaction: Reaction carried out according to **Method VIII.2.**

Purification : Flash column chromatography (silica gel, PE/AcOEt 80/20).

Product : Pale yellow oil.

Yield : 91 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 6.43 (dd, J = 17.5, 10.9 Hz, 1H, C***H***=CH_2), 5.91 (bs, 1H, =C***H***), 5.40-5.32 (m, 2H, =C***H*** and C***H***OAc), 5.13-5.06 (m, 2H, 2 x =C***H***), 2.94 (s, 1H, C***H***), 2.81 (dd, J = 19.2, 5.8 Hz, 1H, C***H***$_2$), 2.34-2.28 (m, 2H, C***H*** and O***H***), 2.09 (m, 2H, C***H***$_2$), 2.03 (s, 3H, COC***H***$_3$), 1.67 (s, 3H, C***H***$_3$), 1.60 (s, 3H, C***H***$_3$), 1.54-1.47 (m, 2H, C***H***$_2$), 1.13 (s, 3H, C***H***$_3$).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 171.4 (***C***=O), 141.9 (=***C***$_q$), 134.0 (=***C***H), 131.7 (=***C***$_q$), 129.4 (=***C***H), 124.4 (=***C***H), 115.4 (=***C***H_2), 78.0 (***C***HOAc), 74.8 (***C***$_q$O), 62.3 (***C***HO), 40.2 (***C***H_2), 39.5 (***C***H_2), 25.8 (***C***H_3), 24.8 (***C***H_3), 22.3 (***C***H_2), 21.5 (CO***C***H_3), 17.7 (***C***H_3).

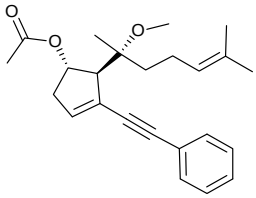
IR (ν, cm^{-1}) (CCl_4): 3507, 2973, 2924, 2361, 1734, 1447, 1373, 1246, 1180, 1098, 1022.

MS (CI, NH_3, m/z): 279 (MH^+).

HRMS (EI+, m/z) **:** Calculated for $C_{17}H_{26}O_3$: 278.1882.
Found for $C_{17}H_{26}O_3$: 278.1887.

(1*S*,2*S*)-2-((*R*)-2-Methoxy-6-methylhept-5-en-2-yl)-3-(2-phenylethynyl)cyclopent-3- **VIII.88g**

enyl acetate



MF: $C_{24}H_{30}O_3$

MW = 366.49 g.mol^{-1}

Reaction: Reaction carried out according to **Method VIII.2.**

Purification : Flash column chromatography (silica gel, PE/Et_2O 90/10).

Product : Yellow oil.

Yield : 72 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.43 (dd, J = 6.6, 3.0 Hz, 2H, 2 x CH_{Ar}), 7.32-7.29 (m, 3H, 3 x CH_{Ar}), 6.22 (bs, 1H, =C*H*), 5.38 (d, J = 6.6 Hz, 1H, C*H*OAc), 5.08 (t, J = 6.9, 6.9 Hz, 1H, =C*H*), 3.26 (s, 3H, OCH_3), 3.20 (s, 1H, C*H*), 2.94 (ddt, J = 19.4, 6.4, 1.9 Hz, 1H, CH_2), 2.32 (d, J = 19.4 Hz, 1H, CH_2), 2.12-2.05 (m, 2H, CH_2), 2.05 (s, 3H, COCH_3), 1.66 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.56-1.44 (m, 2H, CH_2), 1.32 (s, 3H, CH_3).

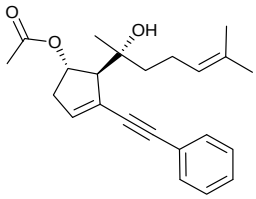
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 170.6 (*C*=O), 138.2 (=*C*H), 131.5 (HC_{Ar}), 131.4 (HC_{Ar}), 128.3 (HC_{Ar}), 128.1 (HC_{Ar}), 124.6 (=*C*H), 124.0 (=C_q), 123.5 (C_{qAr}), 91.1 (C≡C_q), 87.0 (C_q≡C), 77.8 (OC_q), 76.2 (*C*HOAc), 61.2 (*C*HO), 49.4 (O*C*H_3), 40.7 (*C*H_2), 35.7 (*C*H_2), 25.7 (*C*H_3), 22.2 (*C*H_2), 21.3 (CO*C*H_3), 21.0 (*C*H_3), 17.7 (*C*H_3).

IR (ν, cm^{-1}) (CCl_4): 3059, 2973, 2932, 2360, 1738, 1489, 1444, 1373, 1242, 1171, 1025.

MS (CI, NH_3, m/z): 367 (MH^+), 311, 251.

HRMS (EI+, m/z) **:** Calculated for $C_{24}H_{30}O_3$: 352.2039.
Found for $C_{24}H_{30}O_3$: 352.2036.

(1*S*,2*S*)-2-((*R*)-2-Hydroxy-6-methylhept-5-en-2-yl)-3-(2-phenylethynyl)cyclopent-3-enyl acetate **VIII.91c**



MF: $C_{23}H_{28}O_3$

MW = 352.46 g.mol^{-1}

Reaction: Reaction carried out according to **Method VIII.2.**

Purification : Flash column chromatography (silica gel, PE/Et_2O 90/10).

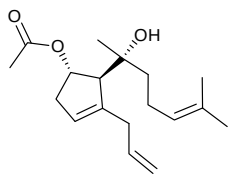
Product : Yellow oil.

Yield : 97 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.43 (dd, J = 6.6, 3.0 Hz, 2H, 2 x CH_{Ar}), 7.32-7.29 (m, 3H, 3 x CH_{Ar}), 6.22 (bs, 1H, =C*H*), 5.38 (d, J = 6.6 Hz, 1H, C*H*OAc), 5.08 (t, J = 6.9, 6.9 Hz, 1H, =C*H*), 3.20 (s, 1H, C*H*), 2.94 (ddt, J = 19.4, 6.4, 1.9 Hz, 1H, CH_2), 2.32 (d, J = 19.4 Hz, 1H, CH_2), 2.12-2.05 (m, 2H, CH_2), 2.05 (s, 3H, COCH_3), 1.66 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.56-1.44 (m, 2H, CH_2), 1.32 (s, 3H, CH_3).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	170.6 (***C***=O), 138.2 (=***C***H), 131.5 (H***C$_{Ar}$***), 131.4 (H***C$_{Ar}$***), 128.3 (H***C$_{Ar}$***), 128.1 (H***C$_{Ar}$***), 124.6 (=***C***H), 124.0 (=***C$_q$***), 123.5 (***C$_{qAr}$***), 91.1 (C≡***C$_q$***), 87.0 (***C$_q$***≡C), 77.8 (O***C$_q$***), 76.2 (***C***HOAc), 61.2 (***C***HO), 40.7 (***C***H$_2$), 35.7 (***C***H$_2$), 25.7 (***C***H$_3$), 22.2 (***C***H$_2$), 21.3 (CO***C***H$_3$), 21.0 (***C***H$_3$), 17.7 (***C***H$_3$).
IR (ν, cm^{-1}) (CCl_4)	3059, 2973, 2932, 2360, 1738, 1489, 1444, 1373, 1242, 1171, 1025.
MS (CI, NH_3, m/z)	353 (MH^+), 311, 251.

(1*S*,2*S*)-3-allyl-2-((*R*)-2-hydroxy-6-methylhept-5-en-2-yl)cyclopent-3-enyl acetate	**VIII.91d**



MF: $C_{18}H_{28}O_3$

MW = 292.41 g.mol^{-1}

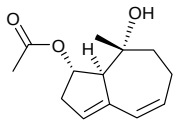
Reaction:	Reaction carried out according to **Method VIII.2.**
Purification :	Flash column chromatography (silica gel, PE/AcOEt 80/20).
Product :	Pale yellow oil.
Yield :	92 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	5.87 (dddd, J = 16.9, 10.1, 6.7, 6.7 Hz, 1H, C***H***=CH$_2$), 5.52 (bs, 1H, =C***H$_{cycle}$***), 5.19 (d, J = 6.5 Hz, 1H, C***H***OAc), 5.12-5.04 (m, 3H, 3 x =C***H***), 3.04 (dd, J = 16.5, 5.5 Hz, 1H, C***H***$_2$), 2.92 (dd, J = 16.3, 6.0 Hz, 1H, C***H***$_2$), 2.75-2.70 (m, 2H, C***H*** and O***H***), 2.21-2.05 (m, 4H, 2 x C***H***$_2$), 2.03 (s, 3H, COC***H***$_3$), 1.68 (s, 3H, C***H***$_3$), 1.61 (s, 3H, C***H***$_3$), 1.50 (t, J = 8.1, 8.1 Hz, 2H, C***H***$_2$), 1.12 (s, 3H, C***H***$_3$).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	171.3 (***C***=O), 142.1 (=***C$_q$***), 136.5 (=***C***H), 132.0 (=***C$_q$***), 125.8 (=***C***H), 124.4 (=***C***H), 116.1 (=***C***H$_2$), 77.7 (***C$_q$***OH), 74.8 (***C***HOAc), 63.8 (***C***HO), 40.3 (***C***H$_2$), 39.3 (***C***H$_2$), 36.3 (***C***H$_2$), 25.8 (***C***H$_3$), 24.4 (***C***H$_3$), 22.1 (***C***H$_2$), 21.4 (CO***C***H$_3$), 17.8 (***C***H$_3$).
IR (ν, cm^{-1}) (CCl_4)	3607, 3508, 2972, 2924, 2360, 1734, 1436, 1374, 1243, 1022.
MS (CI, NH_3, m/z)	293 (MH^+).
HRMS (EI+, m/z) **:**	Calculated for $C_{18}H_{28}O_3$: 292.2039. Found for $C_{18}H_{28}O_3$: 292.2044.

VIII.3. Transformation of the Cyclized Products

Method VIII.3.a. Grubbs II catalyst (0.1 equiv.) was added under argon atmosphere to a solution of the substrate (1 equiv.) in degassed DCM (0.03 M or 0.0015 M). The resulted mixture was stirred at reflux temperature until the complete comsumption of the starting material, before being evaporated and purified by chromatography.

(1*S*,4*Z*,8*R*,8a*S*)-1,2,6,7,8,8a-Hexahydro-8-hydroxy-8-methylazulen-1-yl acetate	**VIII.107**



MF: $C_{13}H_{18}O_3$

MW = 222.28 g.mol^{-1}

Reaction:	Prepared according to **Method VIII.3.**

Purification : Flash column chromatography (silica gel, PE/Et_2O 80/20 to 50/50).

Product : Yellow oil.

Yield : 100 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 6.17 (d, J = 11.2 Hz, 1H, C***H***=), 5.75 (dt, J = 11.0, 5.3 Hz, 1H, C***H***=), 5.57 (s, 1H, C***H***OAc), 5.36 (dt, J = 6.9, 2.1 Hz, 1H, C***H***=), 3.38 (s, 1H, C***H***), 3.01 (s, 1H, C***H***), 2.82 (dd, J = 18.7, 6.8 Hz, 1H, C$\boldsymbol{H}_2$), 2.46 (d, J = 18.7 Hz, 1H, C$\boldsymbol{H}_2$), 2.08 (s, 3H, COC$\boldsymbol{H}_3$), 1.90 (dddd, J = 13.9, 9.4, 2.4 Hz, 1H, C$\boldsymbol{H}_2$), 1.77 (dddd, J = 14.0, 8.2, 2.9 Hz, 1H, C$\boldsymbol{H}_2$), 1.63 (bs, 1H, O***H***), 1.43 (s, 1H, C***H***), 1.11 (s, 3H, C$\boldsymbol{H}_3$).

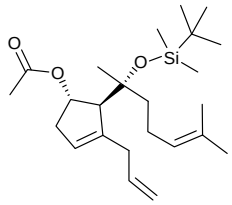
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 172.4 (***C***=O), 140.1 (=$\boldsymbol{C_q}$), 132.7 (=***C***H), 126.7 (=***C***H), 126.1 (=***C***H), 77.4 (***C***HOAc), 73.9 (O$\boldsymbol{C_q}$), 65.1 (***C***H), 43.8 (***C***H_2), 38.4 (***C***H_2), 24.7 (***C***H_2), 23.1 (***C***H_3), 21.5 (CO***C***H_3).

IR (ν, cm^{-1}) (CCl_4): 3508, 2967, 2927, 1722, 1435, 1372, 1253, 1101, 1027.

MS (CI, NH_3, m/z): 223 (MH^+).

HRMS (EI+, m/z) **:** Calculated for $C_{13}H_{18}O_3$: 222.1256.
Found for $C_{13}H_{18}O_3$: 222.1254.

Silylated acetate	**(1*S*,2*S*)-3-allyl-2-((*R*)-2-hydroxy-6-methylhept-5-en-2-yl)cyclopent-3-enyl**	**VIII.91dbis**



MF: $C_{24}H_{42}O_3Si$

MW = 406.67 $g.mol^{-1}$

Reaction: To a solution of alcohol VIII.91d (1 equiv.) in dichloromethane at 0^0C, 2,6-lutidine (2 equiv.) and dimethyl*tert*-butylsilyltriflate (1.5 equiv.) were sequentially added. The resulted mixture was stirred at 0^0C for 2 hours, then poured onto a saturated ammonium chloride solution and extracted with diethyl ether (3x 10 ml). The combined organic phases were washed with water and brine before being dried on anhydrous $MgSO_4$, filtered and concentrated under reduced pressure.

Purification : Flash column chromatography (silica gel, PE/Et_2O 95/5).

Product : Yellow oil.

Yield : 67 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.89 (dddd, J = 16.0, 11.0, 6.7, 6.7 Hz, 1H, C***H***=CH_2), 5.45 (bs, 1H, =C$\boldsymbol{H_{cycle}}$), 5.26 (d, J = 6.4 Hz, 1H, C***H***OAc), 5.07 (d, J = 4.8 Hz, 1H, =C***H***), 5.04-5.01 (m, 2H, 2 x =C***H***), 3.01 (dd, J = 16.9, 6.0 Hz, 1H, C$\boldsymbol{H}_2$), 2.90-2.82 (m, 2H, C$\boldsymbol{H}_2$), 2.74 (d, J = 16.8 Hz, 1H, C$\boldsymbol{H}_2$), 2.14-2.03 (m, 3H, C***H*** and C$\boldsymbol{H}_2$), 2.01 (s, 3H, COC$\boldsymbol{H}_3$), 1.67 (s, 3H, C$\boldsymbol{H}_3$), 1.59 (s, 3H, C$\boldsymbol{H}_3$), 1.46-1.42 (m, 2H, C$\boldsymbol{H}_2$), 1.24 (s, 3H, C$\boldsymbol{H}_3$), 0.88 (s, 9H, SiC(C$\boldsymbol{H}_3$)$_3$), 0.13 (s, 3H, SiC$\boldsymbol{H}_3$), 0.09 (s, 3H, SiC$\boldsymbol{H}_3$).

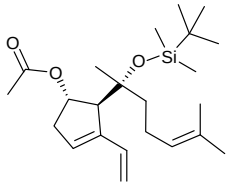
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 170.8 (***C***=O), 142.3 (=$\boldsymbol{C_q}$), 136.3 (=***C***H), 131.4 (=$\boldsymbol{C_q}$), 125.7 (=***C***H), 124.5 (=***C***H), 115.8 (=***C***H_2), 78.0 ($\boldsymbol{C_q}$OH), 77.8 (***C***HOAc), 63.5 (***C***HO), 40.2 (***C***H_2), 39.9 (***C***H_2), 36.3 (***C***H_2), 26.5 (***C***H_3), 26.2 (***C***H_3), 25.8 (***C***H_3), 22.4 (***C***H_2), 21.4 (CO***C***H_3), 18.5 (Si***C***(C$\boldsymbol{H}_3$)$_3$), 17.7 (***C***H_3), -1.47 (***C***H_3), -1.69 (***C***H_3).

IR (ν, cm^{-1}) (CCl_4): 3075, 2958, 2930, 2856, 2360, 1735, 1462, 1373, 1246, 1112, 1027.

MS (CI, NH_3, m/z) 407 (MH^+).

HRMS (EI+, m/z) **:** Calculated for $C_{24}H_{42}O_3Si$: 406.2903.
Found for $C_{24}H_{42}O_3Si$: 406.2889.

Silylated (1*S*,2*S*)-2-((*R*)-2-Hydroxy-6-methylhept-5-en-2-yl)-3-vinylcyclopent-3-enyl acetate	**VIII.108**



MF: $C_{23}H_{40}O_3Si$

MW = 392.64 g.mol^{-1}

Reaction: To a solution of alcohol VIII.106 (1 equiv.) in dichloromethane at 0^0C, 2,6-lutidine (2 equiv.) and dimethyl*tert*-butylsilyltriflate (1.5 equiv.) were sequentially added. The resulted mixture was stirred at 0^0C for 2 hours, then poured onto a saturated ammonium chloride solution and extracted with diethyl ether (3x 10 ml). The combined organic phases were washed with water and brine before being dried on anhydrous $MgSO_4$, filtered and concentrated under reduced pressure.

Purification : Flash column chromatography (silica gel, PE/AcOEt 95/5).

Product : Yellow oil.

Yield : 72 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 6.38 (dd, J = 17.5, 10.9 Hz, 1H, C***H***=CH_2), 5.86 (bs, 1H, =C***H***), 5.41 (d, J = 6.0 Hz, 1H, C***H***OAc), 5.29 (d, J = 17.5 Hz, 1H, =C***H***), 5.08-5.01 (m, 2H, 2 x =C***H***), 2.95 (s, 1H, C***H***), 2.86 (dd, J = 19.0, 5.8 Hz, 1H, C***H***$_2$), 2.19 (dd, J = 19.1, 2.4 Hz, 1H, C***H***$_2$), 2.14-2.01 (m, 2H, C***H***$_2$), 2.01 (s, 3H, COC***H***$_3$), 1.69 (s, 3H, C***H***$_3$), 1.65-1.62 (m, 2H, C***H***$_2$), 1.62 (s, 3H, C***H***$_3$), 1.15 (s, 3H, C***H***$_3$), 0.85 (s, 9H, SiC(C***H***$_3$)$_3$), 0.09 (s, 3H, SiC***H***$_3$), 0.07 (s, 3H, SiC***H***$_3$).

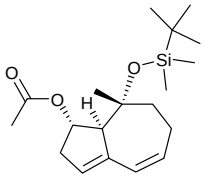
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) 170.7 (***C***=O), 142.1 (=***C***$_q$), 134.3 (=***C***H), 131.4 (=***C***$_q$), 128.7 (=***C***H), 124.3 (=***C***H), 114.2 (=***C***H_2), 78.2 (***C***HOAc), 78.0 (***C***$_q$O), 60.5 (***C***HO), 42.5 (***C***H_2), 40.3 (***C***H_2), 26.2 (***C***H_3), 26.1 (***C***H_3), 25.8 (***C***H_3), 23.3 (***C***H_2), 21.5 (CO***C***H_3), 18.5 (Si***C***(C***H***$_3$)$_3$), 17.8 (***C***H_3), -1.65 (***C***H_3), -1.70 (***C***H_3).

IR (ν, cm^{-1}) (CCl_4) 3087, 2956, 2930, 2856, 1735, 1463, 1372, 1246, 1176, 1107, 1036.

MS (CI, NH_3, m/z) 393 (MH^+).

HRMS (EI+, m/z) **:** Calculated for $C_{23}H_{40}O_3Si$: 392.2747.
Found for $C_{23}H_{40}O_3Si$: 392.2752.

Silylated (1*S*,4*Z*,8*R*,8a*S*)-1,2,6,7,8,8a-Hexahydro-8-hydroxy-8-methylazulen-1-yl acetate	**VIII.109**



MF: $C_{19}H_{32}O_3Si$

MW = 336.54 g.mol^{-1}

Reaction: Prepared according to **Method VIII.3.**

Purification :	Flash column chromatography (silica gel, PE/AcOEt 70/30).
Product :	Yellow oil.
Yield :	100 %.
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	6.19 (d, J = 11.4 Hz, 1H, C***H***=), 5.70 (dt, J = 11.0, 5.3 Hz, 1H, C***H***=), 5.54 (s, 1H, C***H***OAc), 5.39 (dt, J = 6.9, 2.1 Hz, 1H, C***H***=), 3.10 (s, 1H, C***H***), 2.89 (dd, J = 19.3, 7.0 Hz, 1H, C$\boldsymbol{H}_2$), 2.44 (m, 1H, C***H***), 2.22 (d, J = 19.3 Hz, 1H, C$\boldsymbol{H}_2$), 2.13-2.03 (m, 1H, C***H***), 2.01 (s, 3H, COC$\boldsymbol{H}_3$), 1.92-1.85 (m, 2H, C$\boldsymbol{H}_2$), 1.08 (s, 3H, C$\boldsymbol{H}_3$), 0.85 (s, 9H, SiC(C$\boldsymbol{H}_3$)$_3$), 0.11 (s, 6H, 2 x SiC$\boldsymbol{H}_3$).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	172.7 (***C***=O), 141.8 (=$\boldsymbol{C_q}$), 133.4 (=***C***H), 129.7 (=***C***H), 128.5 (=***C***H), 79.3 (***C***HOAc), 67.0 (***C***H), 64.3 (O$\boldsymbol{C_q}$), 46.1 (***C***H_2), 42.2 (***C***H_2), 27.6 (***C***H_3), 26.9 (***C***H_2), 24.5 (***C***H_3), 23.3 (***C***H_3), 20.1 (CO***C***H_3), 18.5 (Si***C***(C$\boldsymbol{H}_3$)$_3$), 17.8 (***C***H_3), 0.02 (***C***H_3), -0.09 (***C***H_3).
IR (ν, cm^{-1}) (CCl_4)	3647, 2928, 2856, 1735, 1463, 1370, 1247, 1110, 1022.
MS (CI, NH_3, m/z)	337 (MH^+).
HRMS (EI+, m/z) **:**	Calculated for $C_{19}H_{32}O_3Si$: 336.2121. Found for $C_{19}H_{32}O_3Si$: 336.2118.

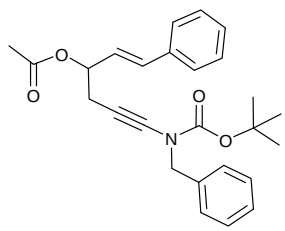
IX. Gold(I)-Catalyzed [4+2] Cycloaddition of *N*-(Hex-5-enynyl) *tert*-butyloxycarbamates

IX.1. Synthesis of the Precursor N-(Hex-5-enynyl) tert-butyloxycarbamates

Substrates were prepared by a copper(II)-catalyzed coupling between bromoalkynes and *tert*-butylcarbamates following a slightly modified version of a procedure previously reported by Hsung and co-workers.

Method IX.1. To a solution of a bromoalkyne (1 equiv.) in dry toluene (0.33 M), carbamate (1.2 equiv.), K_3PO_4 (2.4 equiv.), $CuSO_4 \cdot 5H_2O$ (0.2 equiv.) and 1,10-phenanthroline (0.4 equiv.) were sequentially added. The resulted reaction mixture was heated at 80°C for 16 to 72 h. When completed, it was allowed to cool to RT, diluted with ethyl acetate and filtered through celite, then the filtrate was concentrated *in vacuo* and purified over silica gel.

***tert*-Butyl (*E*)-4-acetoxy-6-phenylhex-5-en-1-ynylbenzylcarbamate**	**IX.33j**



MF: $C_{26}H_{29}NO_4$

MW = 419.51 g.mol^{-1}

Reaction: Synthesized according to **Method IX.1.** decribed above.

Purification : Flash column chromatography (silica gel, Toluene/Et_2O 90/10).

Product : Yellow oil.

Yield : 31 %

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.45-7.27 (m, 10H, C$\boldsymbol{H_{Ar}}$), 6.67 (d, J = 16.2 Hz, 1H, ***H***C=), 6.23 (m, 1H, ***H***C=), 5.53 (m, 1H, ***H***C), 4.57 (s, 2H, C$\boldsymbol{H_2}$), 2.74 (s, 2H, C$\boldsymbol{H_2}$), 2.08 (s, 3H, , C$\boldsymbol{H_3}$), 1.50 (s, 9H, C(C$\boldsymbol{H_3}$)$_3$).

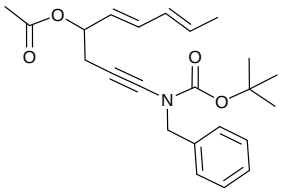
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 169.9 (CH_3***C***=O), 154.2 (NH***C***=O), 136.5 (***C$_{qAr}$***), 136.0 (***C$_{qAr}$***), 133.6 (H***C***), 133.0 (H***C***), 128.5 (H***C***), 128.4 (H***C***), 128.3 (H***C***), 127.9 (H***C***), 127.8 (H***C***), 127.5 (H***C***), 126.6 (H***C***), 126.5 (H***C***), 126.1 (H***C***), 125.4 (H***C***), 82.2 (C≡***C$_q$***), 76.3 (***C$_q$*** ≡C), 72.5 (H***C***), 53.4 (***C***H_2), 27.9 (***C***H_3), 24.9 (***C***H_2), 21.1 (***C***H_3).

IR (ν, cm^{-1}) (CCl_4): 3063, 3031, 2979, 2933, 2263, 1722 (C=O),1497, 1450, 1368, 1296, 1233, 1162, 1019.

MS (CI, NH_3, m/z): 376, 359, 316, 299.

HRMS (EI+, m/z) **:** Calculated for $C_{26}H_{29}NO_4$: 419.2097.
Found for $C_{26}H_{29}NO_4$: 419.2095.

***tert*-Butyl (5*E*,7*E*)-4-acetoxynona-5,7-dien-1-ynylbenzylcarbamate**	**IX.36**



MF: $C_{23}H_{29}NO_4$

MW = 383.48 g.mol^{-1}

Reaction: Synthesized according to **Method IX.1.** described above.

Purification : Flash column chromatography (silica gel, EP/Et_2O 90/10).

Product : Yellow oil.

Yield : 43 %

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.31-7.23 (m, 5H, C***H***$_{Ar}$), 6.21 (q, J = 10.5, 15.1 Hz, 1H, ***H***C=), 5.97 (m, 1H, ***H***C=), 5.70 (sextuplet, J = 6.6, 13.6 Hz, 1H, ***H***C), 5.50 (q, J = 7.1, 15.2 Hz, 1H, ***H***C), 5.30 (m, 1H, C***H***), 4.51 (s, 2H, C***H***$_2$), 2.59 (s, 2H, C***H***$_2$), 1.98 (s, 3H, , C***H***$_3$), 1.73 (d, J = 6.2 Hz, 3H, C***H***$_3$), 1.46 (s, 9H, C(C***H***$_3$)$_3$).

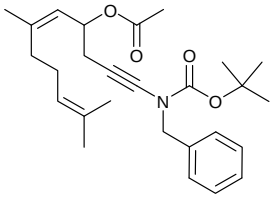
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 169.7 (CH_3***C***=O), 154.1 (NH***C***=O), 136.6 (***C***$_{qAr}$), 133.4 (H***C***), 131.0 (H***C***), 129.0 (H***C***), 128.3 (H***C***), 127.5 (H***C***), 126.8 (H***C***), 82.1 (C≡***C***$_q$), 76.3 (***C***$_q$ ≡C), 72.5 (H***C***), 65.6 (***C***H_2), 64.7 (***C***$_q$), 27.9 (***C***H_3), 24.7 (***C***H_2), 21.0 (***C***H_3), 18.0 (***C***H_3).

IR (ν, cm^{-1}) (CCl_4): 3065, 3027, 2932, 2264, 1722 (C=O), 1498, 1391, 1368, 1296, 1235, 1163, 986.

MS (CI, NH_3, m/z): 345, 285, 268.

HRMS (EI+, m/z) **:** Calculated for $C_{23}H_{29}NO_4$: 383.2097.
Found for $C_{23}H_{29}NO_4$: 383.2084.

tert-Butyl(*Z*)-4-acetoxy-6,10-dimethylundeca-5,9-dien-1-ynylbenzylcarbamate — IX.33d



MF: $C_{27}H_{37}NO_4$

MW = 439.58 g.mol^{-1}

Reaction: Synthesized according to **Method IX.1.** described above.

Purification : Flash column chromatography (silica gel, EP/AcOEt 95/5).

Product : Yellow oil.

Yield : 45 % (57% obtained as an inseparable mixture of product:dimer 4:1)

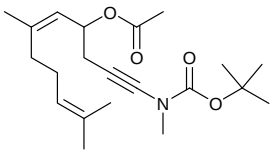
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.34-7.24 (m, 5H, C***H***$_{Ar}$), 5.56 (m, 1H, ***H***C=), 5.27 (d, J = 1.2 Hz, 1H, ***H***C=), 5.21 (t, J = 9.8 Hz, 1H, ***H***C), 5.08 (m, 1H, C***H***), 4.52 (s, 2H, C***H***$_2$), 2.54 (d, J = 5.6 Hz, 2H, C***H***$_2$), 1.97 (s, 3H, C***H***$_3$), 2.1-2.01(m, 3H, C***H***$_2$ and C***H***), 1.71 (s, 3H, C***H***$_3$), 1.66 (s, 3H, C***H***$_3$), 1.58 (s, 3H, C***H***$_3$), 1.47 (s, 9H, C(C***H***$_3$)$_3$).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 170.0 (CH_3***C***=O), 154.3 (NH***C***=O), 141.7 (***C***$_q$), 136.8 (***C***$_q$), 131.9 (***C***$_q$), 128.4 (H***C***), 128.3 (H***C***), 127.6 (H***C***), 123.8 (H***C***), 122.9 (H***C***), 122.3 (H***C***), 82.1 (C≡***C***$_q$), 73.0 (***C***$_q$ ≡C), 66.9 (***C***$_q$), 53.4 (***C***H_2), 32.6 (***C***H_2), 28.0 (***C***H_3), 26.5 (***C***H_2), 25.7 (***C***H_3), 25.2 (***C***H_2), 23.4 (***C***H_3), 21.2 (***C***H_3), 17.6 (***C***H_3).

IR (ν, cm^{-1}) (CCl_4): 3062, 3031, 2973, 2929, 2864, 2263, 1725 (C=O),1446, 1388, 1370, 1296, 1237, 1163, 1071, 904.

MS (CI, NH_3, m/z) 440 (MH^+), 421, 398, 332, 316, 298, 280.

***tert*-Butyl (*Z*)-4-acetoxy-6,10-dimethylundeca-5,9-dien-1-ynylmethylcarbamate**	**IX.33e**



MF: $C_{21}H_{33}NO_4$

MW = 363.49 g.mol^{-1}

Reaction: Synthesized according to **Method IX.1.** described above.

Purification : Flash column chromatography (silica gel, EP/AcOEt 95/5).

Product : Yellow oil.

Yield : 37 % (46% obtained as an inseparable mixture of product:dimer 5:1)

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 5.54 (m, 1H, ***H***CO), 5.17 (m, 1H, ***H***C=), 5.04 (m, 1H, ***H***C=), 2.98 (s, 3H, NC***H***$_3$), 2.50 (m, 2H, C***H***$_2$), 2.25-1.98 (m, 4H, 2 x C***H***$_2$), 1.97 (s, 3H, C***H***$_3$), 1.69 (s, 3H, C***H***$_3$), 1.61 (s, 3H, C***H***$_3$), 1.54 (s, 3H, C***H***$_3$), 1.42 (s, 9H, C(C***H***$_3$)$_3$).

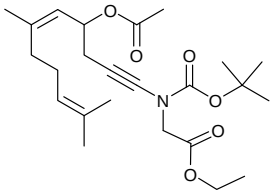
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) 169.9 (CH_3***C***=O), 154.6 (NH***C***=O), 141.7 (***C***$_q$=), 131.9 (***C***$_q$=), 123.7 (H***C***), 122.8 (H***C***), 122.3 (H***C***), 81.7 (C≡***C***$_q$), 72.9 (***C***$_q$ ≡C), 66.9 (***C***$_q$), 32.6 (***C***H_2), 27.9 (***C***H_3), 26.5 (***C***H_2), 25.8 (***C***H_3), 25.1 (***C***H_2), 23.3 (***C***H_3), 21.1 (***C***H_3), 17.5 (***C***H_3).

IR (ν, cm^{-1}) (CCl_4) 2973, 2928, 2263, 1725 (C=O), 1674, 1449, 1370, 1313, 1238, 1158, 1016, 955.

MS (CI, NH_3, m/z) 364 (MH^+), 347, 325, 265, 248.

HRMS (EI+, m/z) **:** Calculated for $C_{21}H_{33}NO_4$:363.2410.
Found for $C_{21}H_{33}NO_4$: 363.2424.

***tert*- Butyl (ethoxycarbonyl)methyl(*Z*)-4-acetoxy-6,10-dimethylundeca-5,9-dien-1-ynylcarbamate**	**IX.33f**



MF: $C_{24}H_{37}NO_6$

MW = 435.55 g.mol^{-1}

Reaction: Synthesized according to **Method IX.1.** described above.

Purification : Flash column chromatography (silica gel, EP/AcOEt 95/5).

Product : Yellow oil.

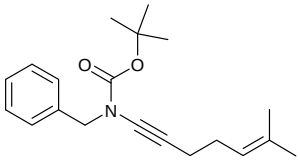
Yield : 63 %.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 5.57 (m, 1H, ***H***CO), 5.13 (d, J = 8.7 Hz, 1H, ***H***C=), 5.07 (m, 1H, ***H***C=), 4.19 (q, J = 7.0 Hz, 2H, C***H***$_2$), 4.05 (s, 2H, C***H***$_2$), 2.52 (d, J = 5.6 Hz, 2H, C***H***$_2$), 2.24-2.02 (m, 4H, 2 x C***H***$_2$), 2.00 (s, 3H, C***H***$_3$), 1.71 (s, 3H, C***H***$_3$), 1.64 (s, 3H, C***H***$_3$), 1.57 (s, 3H, C***H***$_3$), 1.47 (bs, 9H, C(C***H***$_3$)$_3$), 1.25 (t, J = 7.0 Hz, 3H, C***H***$_3$).

^{13}C NMR (δ, ppm) 170.1 (CH_3***C***=O), 168.1 (***C***=OOEt), 154.3 (NH***C***=O), 141.8 (***C***$_q$=), 132.0 (***C***$_q$=), 123.7

($CDCl_3$, 100 MHz)	(H***C***), 122.8 (H***C***), 82.7 (C≡***C$_q$***), 75.7 (***C$_q$*** ≡C), 69.0 (H***C***), 64.5 (***C$_q$***), 61.3 (***C***H_2), 51.0 (***C***H_2), 32.6 (***C***H_2), 27.9 (***C***H_3), 26.5 (***C***H_2), 25.6 (***C***H_3), 25.2 (***C***H_2), 23.3 (***C***H_3), 21.2 (***C***H_3), 17.6 (***C***H_3), 14.2 (***C***H_3).
IR (ν, cm^{-1}) (CCl_4)	2977, 2931, 2871, 2268, 1730 (C=O),1448, 1373, 1320, 1237, 1202, 1161, 1021.
MS (CI, NH_3, m/z)	397, 380, 320, 294, 276.

tert-Butyl benzyl-6-methylhept-5-en-1-ynylcarbamate — IX.37

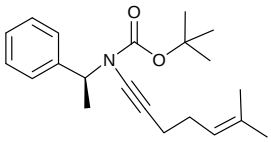


MF: $C_{20}H_{27}NO_2$

MW = 313.43 $g.mol^{-1}$

Reaction:	Synthesized according to **Method IX.1.** described above.
Purification :	Flash column chromatography (silica gel, EP/AcOEt 95/5).
Product :	Yellow oil.
Yield :	56 %
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	7.35-7.27 (m, 5H, C***H$_{Ar}$***), 5.15 (t, J= 6.9 Hz , 1H, ***H***C=), 4.55 (s, 2H, C***H***$_2$), 2.27-2.16 (m, 1H, 2 x C***H***$_2$), 1.69 (s, 3H, C***H***$_3$), 1.60 (s, 3H, C***H***$_3$), 1.50 (s, 9H, C(C***H***$_3$)$_3$).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	154.6 (***C***=O), 137.0 (***C$_{qAr}$***), 132.5 (=***C$_q$***), 128.4 (H***C$_{Ar}$***), 127.6 (H***C$_{Ar}$***), 123.2 (H***C$_{Ar}$***), 82.1 (C≡***C$_q$***), 74.6 (***C$_q$***), 69.6 (***C$_q$*** ≡C), 53.1 (H***C***N), 28.1 (***C***H_3), 27.9 (***C***H_2), 25.7 (***C***H_3), 19.0 (***C***H_2), 17.8 (***C***H_3).
IR (ν, cm^{-1}) (CCl_4)	3066, 2977, 2930, 2259, 1720 (C=O),1451, 1370, 1293, 1249, 1159, 1076.
MS (CI, NH_3, m/z)	274, 258, 244, 230, 214, 169 .
HRMS (EI+, m/z) **:**	Calculated for $C_{20}H_{27}NO_2$: 313.2042. Found for $C_{20}H_{27}NO_2$: 313.2046.

tert-Butyl 6-methylhept-5-en-1-ynyl(*S*)-1-phenylethylcarbamate — IX.33k



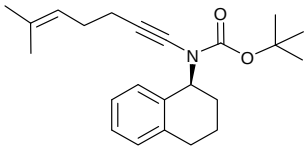
MF: $C_{21}H_{29}NO_2$

MW = 327.46 $g.mol^{-1}$

Reaction:	Synthesized according to **Method IX.1.** described above.
Purification :	Flash column chromatography (silica gel, EP/AcOEt 98/2).
Product :	Yellow oil.
Yield :	25 %
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	7.43 (d, J= 7.2 Hz, 2H, C***H$_{Ar}$***), 7.37 (t, J= 7.3 Hz , 2H, C***H$_{Ar}$***), 7.30 (t, J= 7.01 Hz , 1H, C***H$_{Ar}$***), 5.30 (m, 1H, ***H***C), 5.23 (t, J = 6.9 Hz, 1H, ***H***C=), 2.37 (t, J = 6.8 Hz, 2H, C***H***$_2$), 2.24 (q, J = 6.7, 13.7 Hz, 2H, C***H***$_2$), 1.75 (s, 3H, C***H***$_3$), 1.66-1.63 (m, 6H, 2 x C***H***$_3$), 1.51 (s, 9H, C(C***H***$_3$)$_3$).

^{13}C NMR (δ, ppm) (CDCl$_3$, 100 MHz)	154.5 (***C***=O), 141.9 (***C$_{qAr}$***), 132.4 (=***C$_q$***), 128.3 (H***C$_{Ar}$***), 127.4 (H***C$_{Ar}$***), 126.6 (H***C$_{Ar}$***), 123.4 (H***C***=), 81.9 (C≡***C$_q$***), 71.8 (***C$_q$*** ≡C), 54.4 (H***C***N), 28.1 (***C***H$_3$), 27.9 (***C***H$_2$), 25.7 (***C***H$_3$), 19.2 (***C***H$_2$), 19.1 (***C***H$_3$), 17.8 (***C***H$_3$).
MS (CI, NH$_3$, m/z)	345 (MH$^+$), 288, 272, 262, 244, 232.
HRMS (EI+, m/z) **:**	Calculated for $C_{21}H_{29}O_2$: 327.2198. Found for $C_{21}H_{29}O_2$: 327.2202.

tert- Butyl (*S*)-1,2,3,4-tetrahydronaphthalen-4-yl-6-methylhept-5-en-1-ynylcarbamate — IX.33n

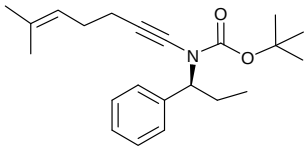


MF: $C_{23}H_{31}NO_2$

MW = 353.49 g.mol^{-1}

Reaction:	Synthesized according to **Method IX.1.** described above.
Purification :	Flash column chromatography (silica gel, EP/AcOEt 98/2).
Product :	Yellow oil.
Yield :	19 %
^{1}H NMR (δ, ppm) (CDCl$_3$, 400 MHz)	7.17-7.13 (m, 3H, C***H$_{Ar}$***), 7.08 (m, 1H, C***H$_{Ar}$***), 5.28 (bm, 1H, C***H***N), 4.96 (t, 1H, ***H***C=), 2.78 (m, 2H, C***H***$_2$), 2.15-2.03 (m, 5H), 1.97 (q, J = 6.8, 13.9 Hz, 2H, C***H***$_2$), 1.80 (m, 1H), 1.63 (s, 3H, C***H***$_3$), 1.55-1.53 (d, 12H, C(C***H***$_3$)$_3$ and C***H***$_3$).
^{13}C NMR (δ, ppm) (CDCl$_3$, 100 MHz)	155.1 (***C***=O), 138.1 (***C$_{qAr}$***), 134.8 (***C$_{qAr}$***), 132.1 (=***C$_q$***), 128.7 (H***C$_{Ar}$***), 127.6 (H***C$_{Ar}$***), 126.8 (H***C$_{Ar}$***), 125.8 (H***C$_{Ar}$***),123.1 (H***C***=), 81.9 (C≡***C$_q$***), 72.4 (***C$_q$*** ≡C), 29.2 (***C***H$_2$), 28.3 (***C***H$_2$), 28.1 (***C***H$_3$), 27.6 (***C***H$_2$), 25.5 (***C***H$_3$), 21.2 (***C***H$_2$), 18.9 (***C***H$_2$), 17.6 (***C***H$_3$).
IR (ν, cm^{-1}) (CCl$_4$)	3062, 2975, 2932, 2865, 2360, 2260, 1710 (C=O),1452, 1392, 1368, 1305, 1255, 1163.
MS (CI, NH$_3$, m/z)	345 (MH$^+$), 298, 254, 168.
HRMS (EI+, m/z) **:**	Calculated for $C_{23}H_{31}NO_2$: 353.2355. Found for $C_{23}H_{31}NO_2$: 353.2348.

tert-Butyl 6-methylhept-5-en-1-ynyl(*S*)-1-phenylpropylcarbamate — IX.33l



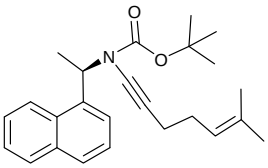
MF: $C_{22}H_{31}NO_2$

MW = 341.48 g.mol^{-1}

Reaction:	Synthesized according to **Method IX.1**. described above.
Purification :	Flash column chromatography (silica gel, EP/AcOEt 95/5).
Product :	Yellow oil.
Yield :	29 %
^{1}H NMR (δ, ppm) (CDCl$_3$, 400 MHz)	7.40 (d, J= 7.2 Hz, 2H, C***H$_{Ar}$***), 7.32 (t, J= 7.2 Hz , 2H, C***H$_{Ar}$***), 7.26 (t, J= 7.10 Hz, 1H, C***H$_{Ar}$***), 5.21 (tt, J = 6.9, 1.2 Hz, 1H, ***H***C=), 4.95 (bm, 1H, C***H***N), 2.35 (t, J = 6.7 Hz, 2H, C***H***$_2$), 2.23 (q, J = 6.7, 13.6 Hz, 2H, C***H***$_2$), 2.11 (m, 1H, C***H***$_2$), 1.89 (m, 1H, C***H***$_2$), 1.72 (s, 3H, C***H***$_3$), 1.63 (s, 3H, C***H***$_3$), 1.47 (s, 9H, C(C***H***$_3$)$_3$), 0.98 (t, J = 7.3 Hz, 3H,

	C***H***$_3$).
^{13}C NMR (δ, ppm) (CDCl$_3$, 100 MHz)	154.9 (***C***=O), 141.0 (***C***$_{qAr}$), 132.4 (=***C***$_q$), 128.2 (H***C***$_{Ar}$), 127.5 (H***C***$_{Ar}$), 127.2 (H***C***$_{Ar}$), 123.4 (H***C***=), 81.8 (C≡***C***$_q$), 71.8 (***C***$_q$ ≡C), 60.1 (***C***$_q$), 53.4 (H***C***N), 28.1 (***C***H$_3$), 27.9 (***C***H$_2$), 25.7 (***C***H$_3$), 19.2 (***C***H$_2$), 17.8 (***C***H$_3$), 11.3 (***C***H$_3$).
IR (ν, cm^{-1}) (CCl$_4$)	3062, 2973, 2929, 2879, 2258, 1713 (C=O),1454, 1391, 1369, 1305, 1254, 1166, 1035.
MS (CI, NH$_3$, m/z)	342 (MH$^+$), 303, 286, 242.
HRMS (EI+, m/z) **:**	Calculated for $C_{22}H_{31}NO_2$: 341.2355. Found for $C_{22}H_{31}NO_2$: 341.2348.

***tert*-Butyl 6-methylhept-5-en-1-ynyl(*R*)-1-(naphthalen-5-yl)ethylcarbamate**	**IX.33m**



MF: $C_{25}H_{31}NO_2$

MW = 377.51 g.mol^{-1}

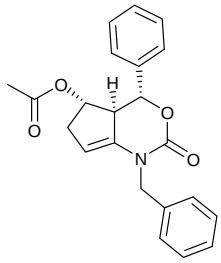
Reaction:	Synthesized according to **Method IX.1.** described above.
Purification :	Flash column chromatography (silica gel, EP/AcOEt 95/5).
Product :	Yellow oil.
Yield :	68 %

^{1}H NMR (δ, ppm) (CDCl$_3$, 400 MHz)	8.24 (bs, 1H, C***H***$_{Ar}$), 7.89 (d, J= 7.9 Hz, 1H, C***H***$_{Ar}$), 7.83 (d, J= 8.1 Hz, 1H, C***H***$_{Ar}$), 7.73 (d, J= 7.1 Hz, 1H, C***H***$_{Ar}$), 7.58 (t, J= 7.0 Hz , 1H, C***H***$_{Ar}$), 7.51 (t, J= 7.6 Hz , 2H, 2 x C***H***$_{Ar}$), 6.15 (bm, 1H, C***H***N), 5.21 (m, 1H, ***H***C=), 2.24 (d, J = 5.5 Hz, 4H, 2 x C***H***$_2$), 1.81 (d, J = 6.9 Hz, 3H, C***H***$_3$), 1.74 (s, 3H, C***H***$_3$), 1.65 (s, 3H, C***H***$_3$), 1.53 (bs, 9H, C(C***H***$_3$)$_3$).
^{13}C NMR (δ, ppm) (CDCl$_3$, 100 MHz)	154.5 (***C***=O), 137.0 (***C***$_{qAr}$), 133.8 (***C***$_{qAr}$), 132.3 (=***C***$_q$), 131.3 (***C***$_{qAr}$), 128.9 (H***C***$_{Ar}$), 128.3 (H***C***$_{Ar}$), 126.4 (H***C***$_{Ar}$), 125.6 (H***C***$_{Ar}$), 125.1 (H***C***$_{Ar}$), 124.2 (H***C***$_{Ar}$), 124.1 (H***C***$_{Ar}$), 123.4 (H***C***=), 82.0 (C≡***C***$_q$), 72.1 (***C***$_q$ ≡C), 53.5 (H***C***N), 28.1 (***C***H$_3$), 28.0 (***C***H$_2$), 25.8 (***C***H$_3$), 19.2 (***C***H$_2$), 17.8 (***C***H$_3$).
IR (ν, cm^{-1}) (CCl$_4$)	3052, 2977, 2926, 2257, 1708 (C=O),1450, 1390, 1370, 1307, 1252, 1166, 1047.
MS (CI, NH$_3$, m/z)	395 (MNH$_4^+$), 339, 322.
HRMS (EI+, m/z) **:**	Calculated for $C_{25}H_{31}NO_2$: 377.2355. Found for $C_{25}H_{31}NO_2$: 377.2355.

IX.2. Gold(I)-Catalyzed [4+2] Cycloaddition

Method IX.2. To a solution of substrate (1 equiv.) in DCM (0.1 M), the corresponding amount of catalyst was added. The reaction was stirred at RT. When completed, the reaction mixture was concentrated under reduced pressure and the crude was purified by chromatography over silica gel.

(4*R*,4a*S*,5*R*)-1-benzyl-1,2,4,4a,5,6-hexahydro-2-oxo-4-phenylcyclopenta[d][1,3]oxazin-5-yl acetate	**IX.34j**



MF: $C_{22}H_{21}NO_4$

MW = 363.40 g.mol^{-1}

Reaction: Obtained as the main diastereoisomer (d.r =1.9:1) in the reaction carried out according to **Method IX.2.,** along with IX.34j'.

Purification : Flash column chromatography (silica gel, EP/AcOEt 70/30).

Product : White-yellow solid.

Yield : 29 %

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.38-7.30 (m, 10H, C***H$_{Ar}$***), 5.23 (q, J = 7.9 Hz, 1H, ***H***C), 5.05 (d, J = 11.1 Hz, 1H, ***H***C), 4.90 (s, 2H, C***H***$_2$), 4.75 (m, 1H, ***H***C), 3.35 (m, 1H, C***H***), 2.80 (dddd, J = 15.2, 8.0, 3.0, 1.2 Hz, 1H, AcO***H***C), 2.27 (tttt, J = 15.3, 7.5, 2.0 Hz, 1H, ***H***C), 1.55 (s, 3H, COC***H***$_3$).

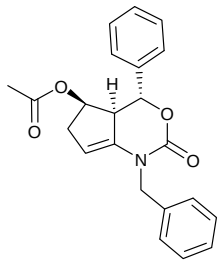
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 169.9 (CH_3***C***=O), 151.7 (N***C***=O), 136.2 (***C$_q$***), 136.0 (***C$_q$***), 135.5 (***C$_q$***), 129.1 (H***C***$_{Ar}$), 128.6 (H***C***$_{Ar}$), 128.4 (H***C***$_{Ar}$), 127.5 (H***C***$_{Ar}$), 127.2 (H***C***$_{Ar}$), 126.8 (H***C***$_{Ar}$), 99.2 (H***C***), 82.4 (H***C***Ph), 73.4 (AcOH***C***), 50.2 (***C***H), 48.8 (***C***H$_2$), 36.0 (***C***H$_2$), 20.1 (***C***H$_3$).

IR (ν, cm^{-1}) (CCl_4): 3063, 3031, 2979, 2933, 2263, 1722 (C=O),1497, 1450, 1368, 1296, 1233, 1162, 1019.

MS (CI, NH_3, m/z): 364 (MH^+), 320, 304.

HRMS (EI+, m/z) **:** Calculated for $C_{22}H_{21}NO_4$: 363.1471.
Found for $C_{22}H_{21}NO_4$: 363.1462.

(4*R*,4a*S*,5*S*)-1-benzyl-1,2,4,4a,5,6-hexahydro-2-oxo-4-phenylcyclopenta[d][1,3]oxazin-5-yl acetate	**IX.34j'**



MF: $C_{22}H_{21}NO_4$

MW = 363.40 g.mol^{-1}

Reaction: Obtained as the minor diastereoisomer (d.r =1.9:1) in the reaction carried out according to **Method IX.2**, along with IX.34j.

Purification : Flash column chromatography (silica gel, EP/AcOEt 70/30).

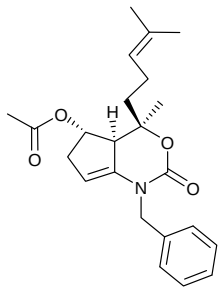
Product : White-yellow solid.

Yield : 18 %

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.42-7.28 (m, 10H, C***H$_{Ar}$***), 5.14 (t, J = 5.3 Hz, 1H, ***H***C), 5.02 (d, J = 15.3 Hz, 1H, ***H***C), 4.87 (m, 2H, C***H***$_2$), 3.38 (m, 1H, ***H***C), 2.75 (tttt, 1H, C***H***), 2.36 (dd, J = 17.4, 2.9 Hz, 1H, AcO***H***C), 2.01 (s, 3H, COC***H***$_3$).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	169.6 (CH_3***C***=O), 151.9 (N***C***=O), 137.5 (***C$_q$***), 136.2 (***C$_q$***), 136.1 (***C$_q$***), 129.3 (H***C$_{Ar}$***), 128.7 (H***C$_{Ar}$***), 128.6 (H***C$_{Ar}$***), 127.5 (H***C$_{Ar}$***), 127.4 (H***C$_{Ar}$***), 126.9 (H***C$_{Ar}$***), 100.3 (H***C***), 78.8 (H***C***Ph), 72.6 (AcO***C***H), 49.4 (***C***H_2), 48.8 (***C***H), 38.7 (***C***H_2), 20.9 (***C***H_3).
IR (ν, cm^{-1}) (CCl_4)	3660, 3035, 2931, 2853, 1726 (C=O), 1656, 1549, 1400, 1370, 1236, 1113, 1032, 964.
MS (CI, NH_3, m/z)	364 (MH^+), 320.
HRMS (EI+, m/z) **:**	Calculated for $C_{22}H_{21}NO_4$: 363.1471. Found for $C_{22}H_{21}NO_4$: 363.1457.

(4*R*,4a*S*,5*S*)-1-benzyl-1,2,4,4a,5,6-hexahydro-4-methyl-4-(4-methylpent-3-enyl)-2-oxocyclopenta[d][1,3]oxazin-5-yl acetate	**IX.34g**



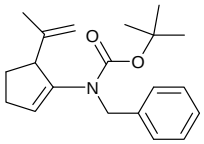
MF: $C_{23}H_{29}NO_4$

MW = 383.48 g.mol^{-1}

Reaction:	Reaction carried out according to **Method IX.2.**
Purification :	Flash column chromatography (silica gel, EP/ Et_2O 85/15).
Product :	White crystals.
Yield :	57 %

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	7.33-7.22 (m, 5H, C***H$_{Ar}$***), 5.20 (q, J = 14.6, 7.8 Hz, 1H, ***H***C), 5.05 (t, J = 7.2 Hz, 1H, ***H***C=), 4.97 (d, J = 15.5 Hz, 1H, NC***H***), 4.68 (t, J = 2.1 Hz, 1H, ***H***C=), 4.67 (d, J = 15.4 Hz, 1H, NC***H***), 3.22 (dq, J = 7.4, 3.5, 1.8 Hz, 1H, ***H***C), 2.75 (qq, J = 15.5, 8.1, 2.9, 1.5 Hz, 1H, C***H***), 2.26 (qt, J = 15.6, 6., 2.0 Hz, 1H, ***H***C), 2.15 (m, 2H, C***H***$_2$), 2.06 (s, 3H, COC***H***$_3$), 1.68 (s, 3H, , C***H***$_3$), 1.58 (s, 3H, C***H***$_3$), 1.51 (m, 2H, C***H***$_2$), 1.39 (s, 3H, C***H***$_3$).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	170.4 (CH_3***C***=O), 151.1 (N***C***=O), 136.4 (***C$_q$***), 135.4 (***C$_q$***), 132.6 (***C$_q$***), 128.6 (H***C***), 127.5 (H***C***), 127.2 (H***C***), 123.1 (H***C***), 100.0 (H***C***=), 82.5 (***C$_q$***), 73.4 (AcO***C***H),54.8 (***C***H), 48.8 (N***C***H_2), 36.8 (***C***H_2), 34.2 (***C***H_2), 25.7 (***C***H_3), 24.2 (***C***H_3), 21.5 (***C***H_2), 21.0 (***C***H_3), 17.6 (***C***H_3).
IR (ν, cm^{-1}) (CCl_4)	3031, 2973, 2929, 2859, 1719 (C=O),1655 (C=O), 1440, 1367, 1233, 1051, 966.
MS (CI, NH_3, m/z)	384 (MH^+), 340, 324, 280.
HRMS (EI+, m/z) **:**	Calculated for $C_{22}H_{21}NO_4$: 383.2097. Found for $C_{22}H_{21}NO_4$: 383.2103.

***tert*-Butyl benzyl5-(prop-1-en-2-yl)cyclopent-1-enylcarbamate**	**IX.34gbis**



MF: $C_{20}H_{27}NO_2$

MW = 313.43 g.mol^{-1}

Procedure: Obtained as a side-product in the above described reaction.

Purification : Flash column chromatography (silica gel, EP/Et_2O 95/5).

Product : Yellow oil.

Yield : 34 %

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.33-7.22 (m, 5H, C***H***$_{Ar}$), 5.39 (s, 1H, ***H***C=), 4.81 (d, J= 16.0 Hz , 1H, C***H***N), 4.74 (m, 2H, 2 x ***H***C=), 4.44 (d, J= 16.0 Hz , 1H, C***H***N), 3.88 (m, 1H, ***H***C), 2.26 (m, 2H, C***H***$_2$), 2.11 (m, 1H, C***H***), 1.73 (m, 1H, C***H***), 1.63 (m, 3H, C***H***$_3$), 1.44 (s, 9H, C(C***H***$_3$)$_3$).

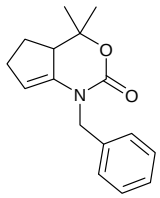
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 153.9 (N***C***=O), 146.9 (***C***$_q$), 144.5 (***C***$_q$), 139.2 (***C***$_q$), 128.3 (H***C***), 126.8 (H***C***), 126.7 (H***C***), 119.1 (H***C***=), 111.2 (H_2***C***=), 80.4 (***C***$_q$), 53.0 (N***C***H_2), 51.9 (***C***H), 29.1 (***C***H_2), 28.5 (***C***H_2), 28.2 (***C***H_3), 19.2 (***C***H_3).

IR (ν, cm^{-1}) (CCl_4): 3069, 2973, 2933, 2854, 1705 (C=O), 1638, 1548, 1450, 1384, 1304, 1241, 1167.

MS (CI, NH_3, m/z): 314 (MH^+),272, 258, 232, 214.

HRMS (EI+, m/z) **:** Calculated for $C_{20}H_{27}NO$: 313.2042.
Found for $C_{20}H_{27}NO$: 313.2050.

1-Benzyl-4,4a,5,6-tetrahydro-4,4-dimethylcyclopenta[d][1,3]oxazin-2(1*H*)-one — IX.37bis



MF: $C_{16}H_{19}NO_2$

MW = 257.32 $g.mol^{-1}$

Reaction: Reaction carried out according to **Method IX.2.**

Purification : Flash column chromatography (silica gel, EP/ Et_2O 95/5).

Product : Pale yellow oil.

Yield : 46 % (88% pure).

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.32-7.23 (m, 5H, C***H***$_{Ar}$), 4.92 (d, J = 16.0 Hz, 1H, N***H***C), 4.84 (q, J = 4.6, 2.3 Hz, 1H, ***H***C=), 4.77 (d, J = 15.5 Hz, 1H, NC***H***), 3.02 (m, 1H, ***H***C), 2.34 (m, 2H, C***H***$_2$), 2.04 (m, 1H, ***H***C), 1.47 (m, 1H, C***H***), 1.40 (s, 3H, , C***H***$_3$), 1.25 (s, 3H, C***H***$_3$).

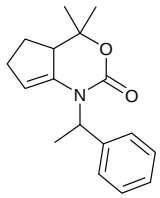
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 151.9 (N***C***=O), 138.5 (***C***$_q$), 136.8 (***C***$_q$), 128.4 (H***C***$_{Ar}$), 127.2 (H***C***$_{Ar}$), 127.1 (H***C***$_{Ar}$), 103.9 (H***C***=), 82.3 (***C***$_q$), 49.7 (***C***H), 49.3 (N***C***H_2), 29.7 (***C***H_2), 27.3 (***C***H_3), 24.9 (***C***H_2), 20.8 (***C***H_3).

IR (ν, cm^{-1}) (CCl_4): 3063, 3032, 2976, 2835, 2858, 1762 (C=O),1654,1442, 1396, 1368, 1297, 1228, 1106.

MS (CI, NH_3, m/z): 258 (MH^+), 228, 214.

HRMS (EI+, m/z) **:** Calculated for $C_{16}H_{19}NO_2$: 257.1416.
Found for $C_{16}H_{19}NO_2$: 257.1417.

4,4a,5,6-Tetrahydro-4,4-dimethyl-1-(1-phenylethyl)cyclopenta[d][1,3]oxazin-2(1*H*)-one — IX.34k



MF: $C_{17}H_{21}NO_2$

MW = 271.35 g.mol^{-1}

Reaction: Reaction carried out according to **Method IX.2**.

Purification : Flash column chromatography (silica gel, EP/AcOEt 80/20).

Product : Pale yellow oil.

Yield : 43 % (obtained as a 1:1.3 diastereoisomeric mixture).

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.35-7.20 (m, 5H, C***H***$_{Ar}$), 5.95, 5.86 (q, J = 7.1 Hz, 1H, ***H***C), 4.63, 4.53 (q, J = 4.5, 2.2 Hz, 1H, ***H***C=), 2.96 (m, 1H, ***H***C), 2.39-2.15 (m, 2H, ***H***$_2$C), 1.96 (m, 1H, C***H***), 1.77 (d, J = 7.1 Hz, 3H, C***H***$_3$), 1.71 (q, J = 7.1, 4.5 Hz, 1H, C***H***), 1.38, 1.36 (s, 3H, C***H***$_3$), 1.26, 1.25 (s, 3H, C***H***$_3$).

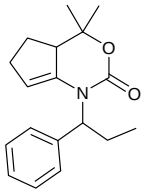
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 152.0, 151.8 (N***C***=O), 140.6, 139.9 (***C***$_q$), 135.9, 135.3 (***C***$_q$), 128.5, 128.4 (H***C***$_{Ar}$), 128.2, 128.0 (H***C***$_{Ar}$), 127.1, 127.0 (H***C***$_{Ar}$), 126.9, 126.6 (H***C***$_{Ar}$), 126.5, 126.4 (H***C***$_{Ar}$), 105.8, 105.1 (H***C***=), 81.8, 81.5 (***C***$_q$), 54.1, 53.4 (***C***H), 50.7, 50.6 (N***C***H), 30.2, 30.0 (***C***H$_2$), 27.4, 27.3 (***C***H$_3$), 24.1, 23.8 (***C***H$_2$), 21.0, 20.7 (***C***H$_3$), 15.7, 14.9 (***C***H$_3$).

IR (ν, cm^{-1}) (CCl_4): 3031, 2977, 2940, 2857, 1706 (C=O),1647, 1499, 1450, 1380, 1295, 1260, 1237, 1161, 1093, 1040, 998, 907.

MS (CI, NH_3, m/z): 272 (MH^+), 228.

HRMS (EI+, m/z) **:** Calculated for $C_{17}H_{21}NO_2$: 271.1572.
Found for $C_{17}H_{21}NO_2$: 271.1575.

4,4a,5,6-Tetrahydro-4,4-dimethyl-1-(1-phenylpropyl)cyclopenta[d][1,3]oxazin-2(1*H*)-one	**IX.34l**



MF: $C_{18}H_{23}NO_2$

MW = 285.38 g.mol^{-1}

Reaction: Reaction carried out according to **Method IX.2.**

Purification : Flash column chromatography (silica gel, EP/AcOEt 96/4 to 90/10).

Product : Pale yellow oil.

Yield : 41 % (obtained as a 1:1.2 diastereoisomeric mixture).

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.35-7.20 (m, 5H, C***H***$_{Ar}$), 5.64, 5.54 (m, 1H, N***H***C), 4.81, 4.68 (q, J = 2.0 Hz, 1H, ***H***C=), 2.99, 2.92 (m, 1H, ***H***C), 2.45-1.90 (m, 4H, 2 x ***H***$_2$C), 1.38, 1.36 (d, J = 5.1 Hz, 3H, C***H***$_3$), 1.25 (s, 6H, 2 x C***H***$_3$), 1.07, 0.98 (q, J = 7.4 Hz, 2H, C***H***$_2$).

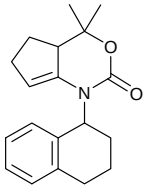
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 152.4, 152.1 (N***C***=O), 140.4, 139.5 (***C***$_q$), 128.3 (H***C***$_{Ar}$), 128.2 (H***C***$_{Ar}$), 127.3 (H***C***$_{Ar}$), 127.1 (H***C***$_{Ar}$), 126.8 (H***C***$_{Ar}$), 105.7, 104.8 (H***C***=), 81.7, 81.5 (***C***$_q$), 60.8, 59.7 (***C***H), 50.6, 50.4 (N***C***H), 30.1, 29.9 (***C***H$_2$), 27.5, 27.4 (***C***H$_3$), 27.2, 271 (***C***H$_3$), 24.0, 23.7 (***C***H$_2$), 21.7, 21.6 (***C***H$_2$), 11.4, 11.0 (***C***H$_3$).

IR (ν, cm^{-1}) (CCl_4) 3031, 2973, 2937, 2859, 1707 (C=O), 1647, 1549, 1453, 1380, 1294, 1239, 1160, 1104, 1065, 958, 917.

MS (CI, NH_3, m/z) 286 (MH^+), 242.

HRMS (EI+, m/z) **:** Calculated for $C_{18}H_{23}NO_2$: 285.1729.
Found for $C_{18}H_{23}NO_2$: 285.1727.

4,4a,5,6-Tetrahydro-1-(1,2,3,4-tetrahydronaphthalen-1-yl)-4,4-dimethylcyclopenta[d][1,3]oxazin-2(1*H*)-one **IX.34n**



MF: $C_{19}H_{23}NO_2$

MW = 297.39 $g.mol^{-1}$

Reaction: Reaction carried out according to **Method IX.2.**

Purification : Flash column chromatography (silica gel, EP/AcOEt 96/4).

Product : Pale yellow oil.

Yield : 53 % (obtained as a 1:1.25 diastereoisomeric mixture).

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.14-6.98 (m, 4H, C***H***$_{Ar}$), 5.97, 5.29 (m, 1H, N***H***C), 4.31, 4.19 (m, 1H, ***H***C=), 2.99-2.80 (m, 1H, ***H***C), 2.35-2.14 (m, 4H, 2 x ***H***$_2$C), 2.09-1.93 (m, 4H, 2 x ***H***$_2$C), 1.81 (m, 2H, ***H***$_2$C), 1.43, 1.40 (s, 3H, C***H***$_3$), 1.33, 1.27 (s, 3H, C***H***$_3$).

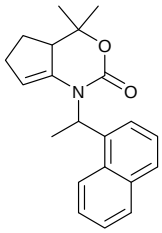
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) 152.5, 152.4 (N***C***=O), 137.5 (***C***$_q$), 137.3 (***C***$_q$), 135.3 (***C***$_q$), 129.2, 128.9 (H***C***$_{Ar}$), 126.6, 126.5 (H***C***$_{Ar}$), 126.2, 126.1 (H***C***$_{Ar}$), 125.5 (H***C***$_{Ar}$), 107.1, 106.7 (H***C***=), 82.0, 81.6 (***C***$_q$), 50.7(***C***H), 50.6 (N***C***H), 30.3, 30.1 (***C***H$_2$), 29.6, 29.5 (***C***H$_2$), 27.5, 27.3 (***C***H$_3$), 25.9, 25.1 (***C***H$_2$), 24.2, 23.8 (***C***H$_2$), 22.7, 22.5 (***C***H$_2$), 21.2, 20.7 (***C***H$_3$).

IR (ν, cm^{-1}) (CCl_4) 3065, 3022, 2938, 2861, 1757 (C=O), 1706, 1647, 1493, 1451, 1380, 1296, 1238, 1159, 1070, 995, 968, 905.

MS (CI, NH_3, m/z) 298 (MH^+), 285, 254, 232, 168.

HRMS (EI+, m/z) **:** Calculated for $C_{19}H_{23}NO_2$: 297.1729.
Found for $C_{19}H_{23}NO_2$: 297.1728.

4,4a,5,6-Tetrahydro-4,4-dimethyl-1-(1-(naphthalen-1 yl)ethyl)cyclopenta[d][1,3]oxazin-2(1*H*)-one **IX.34m**



MF: $C_{21}H_{23}NO_2$

MW = 321.41 $g.mol^{-1}$

Reaction: Reaction carried out according to **Method IX.2.**

Purification : Flash column chromatography (silica gel, EP/AcOEt 80/20).

Product : White solid.

Yield :	41 % (obtained as a 1:1.4 diastereoisomeric mixture).
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	8.05, 7.96 (m, 1H, C***H$_{Ar}$***), 7.89-7.78 (m, 2H, C***H$_{Ar}$***), 7.66, 7.60 (d, J= 7.2 Hz, 1H, C***H$_{Ar}$***), 7.53-7.43 (m, 3H, C***H$_{Ar}$***), 6.5, 6.3 (q, J = 7.2, 7.1 Hz, 1H, ***H***C), 4.80, 4.55 (q, J = 4.6, 2.2 Hz, 1H, ***H***C=), 2.91, 2.75 (m, 1H, ***H***C), 2.22 (m, 2H, ***H***$_2$C), 2.04 (m, 2H, ***H***$_2$C), 1.91, 1.86 (d, J = 7.0 Hz, 3H, C***H***$_3$), 1.32, 1.21 (s, 3H, C***H***$_3$).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	152.1, 151.3 (N***C***=O), 136.4, 135.8 (***C$_q$***), 135.6, 135.5 (***C$_q$***), 133.8, 133.7 (***C$_q$***), 132.0, 131.9 (***C$_q$***), 128.8, 128.7 (H***C$_{Ar}$***), 126.6, 126.5 (H***C$_{Ar}$***), 126.0, 125.9 (H***C$_{Ar}$***), 125.3 (H***C$_{Ar}$***), 124.7, 124.6 (H***C$_{Ar}$***), 123.9, 123.8 (H***C$_{Ar}$***), 123.7 (H***C$_{Ar}$***), 105.7, 105.3 (H***C***=), 81.7, 81.6 (***C$_q$***), 52.4, 51.9 (***C***H), 50.3, 50.3 (N***C***H), 30.2, 30.1 (***C***H$_2$), 27.3, 27.2 (***C***H$_3$), 23.5, 23.4 (***C***H$_2$), 20.8, 20.7 (***C***H$_3$), 16.1, 15.5 (***C***H$_3$).
IR (ν, cm^{-1}) (CCl_4)	3052, 2977, 2940, 2857, 1699 (C=O), 1646, 1515, 1450, 1377, 1297, 1238, 1163, 1107, 1072, 1032, 907.
MS (CI, NH_3, m/z)	322 (MH^+), 278.
HRMS (EI+, m/z) **:**	Calculated for $C_{21}H_{23}NO_2$: 321.1729. Found for $C_{21}H_{23}NO_2$: 321.1731.