Development of new reactions of organic synthesis catalyzed by gold and copper

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Development of New Reactions of Organic Synthesis

Catalyzed by Gold and Copper

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General Introduction

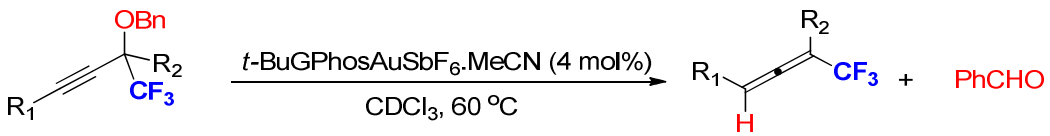
Gold and copper belong to the same family : the coinage metals. However, while copper's rich chemistry has already been known for a long time, gold suffered until recently from a preconception claiming it to be chemically inert. Since its first use in synthetic organic chemistry before 2000, gold has attracted more and more attention and gold(I) and gold(III) complexes are now known to be excellent Lewis-acids with a large range of application in the selective activation of carbon-based insaturations toward the addition of nucleophiles. Notably, gold catalysis is an elegant strategy for the formation of heterocyclic compounds by intramolecular additions of heteroatom-based nucleophiles onto insaturations.

In parallel, the trifluoromethyl moiety has become more and more popular because of its valuable properties in medicinal, agrochemical and material sciences. Therefore, the development of methods for the preparation of trifluoromethyl containing synthetic intermediates or for the direct incorporation of a trifluoromethyl group is of continuous interest.

This manuscript presents the results obtained during this thesis on the development of gold-catalyzed methods for the synthesis of heterocyclic compounds and trifluoromethylated building blocks. The studies of copper-catalyzed hydrotrifluoromethylation and hydroazidation reactions are also summarized.

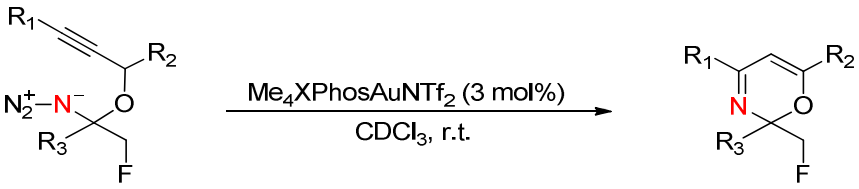
The first chapter is an introduction to homogenous electrophilic gold catalysis. The specificities which makes gold catalysts such useful Lewis-acids will be presented, as well as a selection of examples of their applications in organic synthesis. The following chapters present the methodologies developed during this PhD work.

A gold-catalyzed synthesis of trifluoromethyl allenes is detailed in the chapter 2. The strategy involved relies on a gold(I)-activation of a trifluoromethyl propargyl benzyl ether, which promotes a sequence of 1,5-hydride shift and fragmentation leading to the formation of trifluoromethyl allenes. Enantio-enriched allenes and other perfluoroalkylated allenes could also be obtained by this method and the great potential of these products as trifluoromethylated building blocks is also demonstrated with various derivatizations.



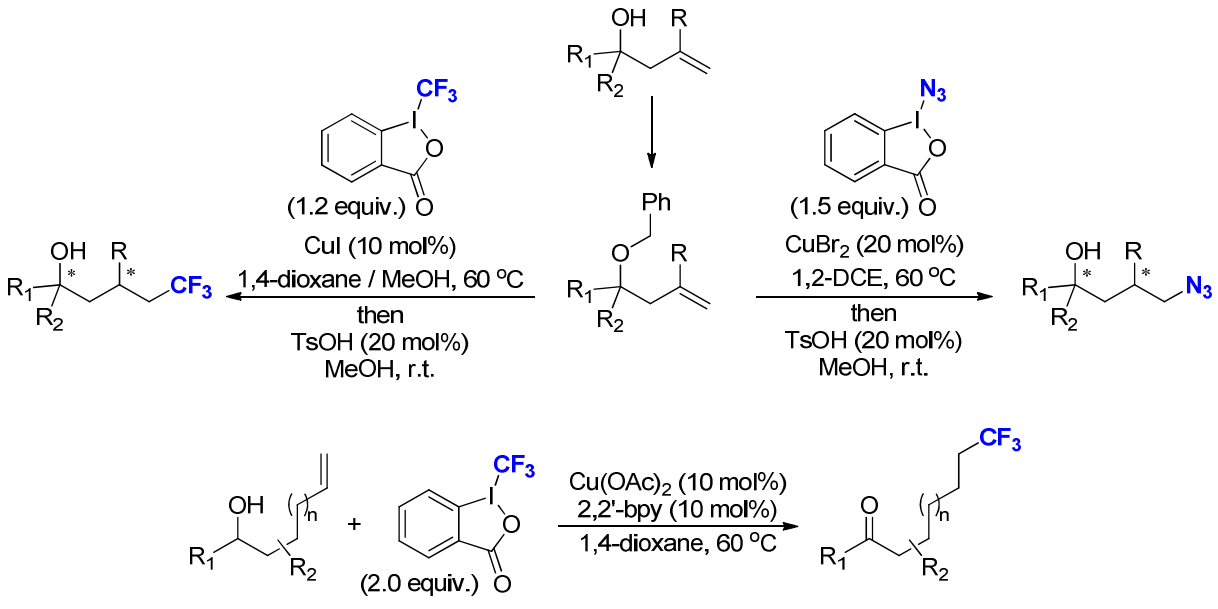
Gold-catalyzed synthesis of trifluoromethylated allenes

Chapter 3 presents a gold-catalyzed synthesis of *2H*-1,3-oxazines. This methodology involves a gold-catalyzed 6-*endo* azide-yne cyclization. The interest of these heterocyclic products as synthetic intermediate was then demonstrated by elegant and unprecedented transformations.



Gold-catalyzed synthesis of *2H*-1,3-oxazines

A copper-catalyzed radical hydrofunctionalization of alkenols is presented in the chapter 4. This methodology relies on a sequence of radical addition to the alkene group and 1,5-hydrogen abstraction using a benzyloxy moiety as the hydrogen donor. In the case of homoallylic substrates, a benzyl moiety is introduced as a traceless hydrogen donor. In the case of 1,5-alkenols, ketone products are obtained. This strategy allows to proceed efficiently to the hydrotrifluoromethylation, as well as the hydroazidation, of alkenes. In the case of 1,1-disubsituted homoallylic alcohols, an interesting diastereoselectivity was obtained.



Copper-catalyzed hydrofunctionalization of alkenols

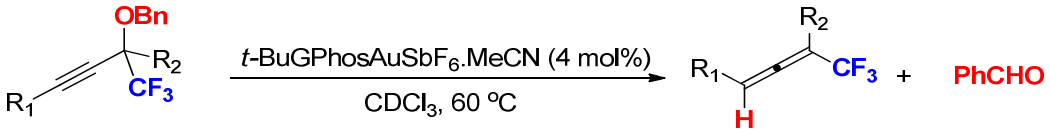
L'or et le cuivre appartiennent la même famille d'éléments chimiques. Cependant, alors que la riche chimie du cuivre est connue depuis longtemps, l'or a pendant longtemps été considéré comme chimiquement inerte. Depuis sa première utilisation en synthèse organique, dans les années 2000, l'or a attiré de plus en plus d'attention, et les complexes d'or(I) et d'or(III) sont maintenant reconnus comme étant d'excellents acides de Lewis, possédant une large gamme d'applications dans l'activation sélective d'insaturations carbonées en vue de l'addition de nucléophiles. En particulier, la catalyse à l'or représente une élégante stratégie pour la formation de composés hétérocycliques par additions intramoléculaires d'hétéroatomes à caractère nucléophile sur des insaturations.

En parallèle, le groupement trifluorométhyl devient de plus en plus populaire en raison de ses avantageuses propriétés dans les domaines médicaux, agrochimiques et dans les sciences des matériaux. Par conséquent, le développement de méthodes pour l'incorporation directe d'un groupement trifluorométhyl ou pour la formation d'intermédiaires de synthèses trifluorométhylés représente un intérêt croissant.

Ce manuscrit présente les résultats obtenus durant cette thèse sur le développement de méthodes catalysées à l'or pour la synthèse de composés hétérocycliques et d'intermédiaires de synthèses trifluorométhylés. Des études sur des réactions d'hydrotrifluorométhylation et d'hydroazidation radicalaires catalysées au cuivre ont également décrites.

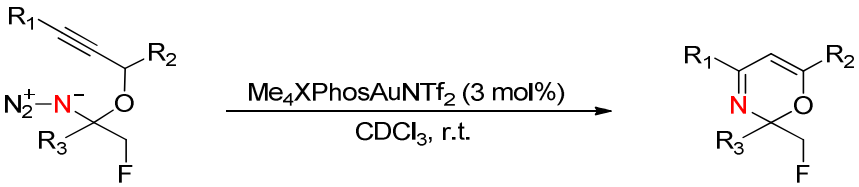
Le premier chapitre est une introduction à la catalyse électrophile homogène à l'or. Il présente tout d'abord les caractéristiques qui font des catalyseurs d'or des acides de Lewis si particuliers, puis expose leurs applications en chimie organique. Les chapitres suivants décrivent les méthodologies développées pendant cette thèse.

Une synthèse d'allènes trifluorométhylés catalysée par l'or est présentée dans le chapitre 2. La stratégie impliquée repose sur une activation par l'or d'éthers benzyliques propargyliques trifluorométhylés, qui promeut une séquence de transfert d'hydrure 1,5, suivi d'une fragmentation conduisant à la formation d'allènes trifluorométhylés. Cette méthode permet également d'accéder à des allènes enrichis énantiomériquement, ainsi qu'à des allènes perfluoroalkylés. L'important potentiel de ces produits en tant qu'intermédiaires de synthèses trifluorométhylés a également été démontré grâce à la formation de divers produits dérivés.



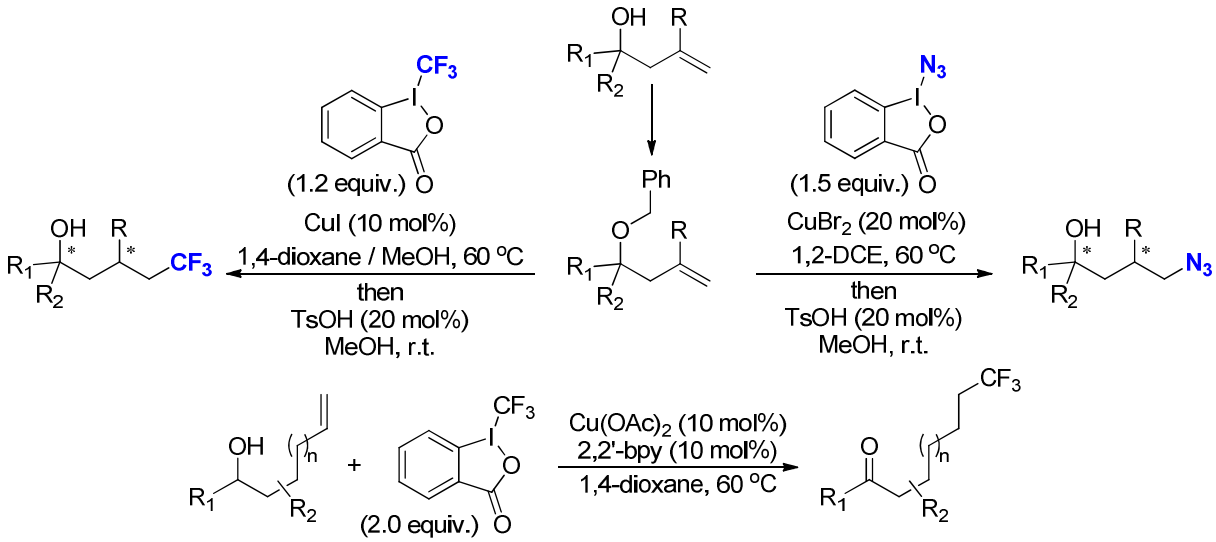
Synthèse d'allènes trifluorométhylés catalysée à l'or

Le chapitre 3 présente une synthèse de *2H*-1,3-oxazines par catalyse à l'or. Cette méthodologie implique une cyclisation de type *6-endo* d'azide-ynes catalysée à l'or. L'intérêt de ces produits hétérocycliques comme intermédiaires de synthèse a aussi été souligné par la découverte d'élégantes transformations.



Synthèse de *2H*-1,3-oxazines catalysée à l'or

Une hydrofonctionnalisation radicalaire d'alcènols catalysée au cuivre est présentée dans le chapitre 4. Cette méthodologie repose sur une séquence d'additio radicalaire sur la partie alcène, suivi d'une abstraction d'hydrogène 1,5 utilisant un motif benzyloxy comme donneur d'hydrogène. Dans le cas d'alcools homoallyliques, un groupement benzyl est introduit comme donneur d'hydrogène. Dans les cas de 1,5-alcènols, des cétones sont obtenues. Cette stratégie permet de procéder efficacement à l'hydrotrifluorométhylation, ainsi qu'à l'hydroazidation, d'alcènes. Dans le cas d'alcools homoallyliques disubstitués en 1,1, une intéressante diastéréosélectivité est obtenue.



Hydrofunctionnalisation d'alkenols catalysée au cuivre

Abbreviations

Alkyl and aryl groups

Ar	aryl
Bu	butyl
Cy	cyclohexyl
Et	ethyl
Hept	heptyl
Hex	hexyl
Me	methyl
Naph	naphtyl
Pent	pentyl
Pr	propyl
Ph	phenyl
Oct	octyl
Und	undecyl

Ligands

IPr	1,3-Diisopropylimidazolium
IMes	1,3-bis(2,4,6-trimethylphenyl)-imidazolium
IAd	1,3-Bis(1-adamantanyl)imidazolium
XPhos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
t-BuXPhos	2-Di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl
Me_4XPhos	2-Di-*tert*-butylphosphino-3,4,5,6-tetramethyl-2′,4′,6′-triisopropyl-1,1′-biphenyl
BrettPhos	2-(Dicyclohexylphosphino)3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl
SPhos	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
JohnPhos	(2-Biphenyl)di-*tert*-butylphosphine, (2-Biphenylyl)di-*tert*-butylphosphine
1,10-phen	1,10-phenanthroline
2,2'bpy	2,2'-bipyridine
18-crown-6	1,4,7,10,13,16-Hexaoxacyclooctadecane
Cat	catechol
CF_3acac	trifluoroacetylacetonate
Dba	dibenzylideneacetone
Dbm	dibenzoylmethane
[dF(CF3)ppy2](dtbpy)	[4,4'-Bis(tert-butyl)-2,2'-bipyridine]bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl]phenyl]
Dppm	Bis(diphenylphosphino)methane
Ppy	2-phenylpyridine
Pin	pinacol
Tc	thiophene-2-carboxylate
Tp	tris(3,5-dimethyl-1-pyrazolyl)borate

Protecting groups

Ac	acetyl
Boc	tert-butyloxycarbonyl
Bn	benzyl
Bz	benzoyl
Cbz	carboxybenzyl
MOM	methoxymethyl
Ms	methanesulfonyl
Piv	pivaloyl
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethylsulfonyl
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TMS	trimethylsilyl
Ts	*para*-toluenesulfonyl

Reagents

CALB	Candida Antartica Lipase B
C. Rugosa	Candida Rugosa
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIPEA	diisopropylethylamine
DMAP	dimethylaminopyridine
DMDO	dimethyldioxirane
Dmpp	N(1)-dimethyl-N(4)-phenylpiperazinium iodide
DTBHN	di-*tert*-butylhyponitrile
m-CPBA	*meta*-chloroperbenzoic acid
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
Selectfluor	1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBCO	2,4,4,6-tetrabromocyclohexa-2,5-dienone

Solvents

1,2-DCE	1,2-dichloroethane
1,1,2,2-TCE	1,1,2,2-tetrachloroethane
DMA	dimethylacetamide
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
Hex	Hexane
HFIP	hexafluoroisopropanol
PE	petroleum ether
THF	tetrahydrofuran

Units

^{o}C	Celcius degree
g	gramm
h	hour
Hz	Hertz
M	molarity
Min	minute

Others

A	acceptor
aq.	aqueous
cat.	Catalytic
δ	chemical shift
D	donor
d	doublet
d.r.	diastereoisomeric ratio
E	electrophile
e.e.	enantiomeric excess
equiv.	equivalent
EWG	electron-withdrawing group
HOMO	Higher Occupied Molecular Orbital
HRMS	High Resolution Mass Spectrometry
IR	infrared
J	coupling constant
LG	leaving group
LUMO	Lower Unoccupied Molecular Orbital
NMR	Nuclear Magnetic Resonance
Nu	nucleophile
p	pentuplet
PG	protecting group
q	quartet
r.t.	room temperature
s	singlet
t	triplet

Chapter 1 :

Introduction to homogeneous electrophilic gold catalysis

1.1 Gold : a carbophilic Lewis-acid

1.1.1 A late gold-rush in organic chemistry

Since its discovery by mankind, gold has always been a center of attention. Its low abundance on earth made it precious and expensive, so it quickly became a tool of monetary exchange. Its color, its malleability and its great resistance to corrosion granted it a place in the world of decoration and jewelry alongside with precious stones. Man's faiths and beliefs even associated it to magical connotations. Later, long after these first considerations, science and industry turned their eyes to it and gold became even more valuable, becoming more than a simple luxury item.

Nowadays, its known properties are numerous and the number of its applications keeps increasing. For instance, its low thermic conductivity made gold a metal of choice in aeronautical and spatial industries, in which it is used as a shield against heat or radiation. On the other hand, its high electric conductivity combined with its known chemical resistance granted a place in the field of electronics, in which it is used for coatings, wires and various types of semiconductors. Even the medical field uses gold and his isotopes for diagnostics and some of its complexes were proven to have curative properties against cancer[1] or arthritis deceases.[2]

Surprisingly, despite the considerable attention it has received from so many different fields, gold has remained ignored by synthetic organic chemists until recently… A sulk that can be explained by various reasons. First of all, gold was long considered to be, on the one hand, too rare and too expensive, and on the other hand, chemically inert. To the first two arguments, one might respond that gold is actually not the scarcest chemical element as some other transition metals currently employed are even less abundant on earth's crust (Figure 1.1), not even talking about the lanthanides and actinides elements.[3]

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[1] Casini, A.; Hartinger, C.; Gabbiani, C.; Mini, E.; Dyson, P.J.; Keppler, B.K.; Messori, L. *J. Inorg. Biochem.* **2008**, *102*, 564.
[2] Messori, L.; Marcon, G. *Metal ions and their complexes in medication,* Sigel, A., Ed.; CRC Press: 2004, p 280.
[3] For a chart including lanthanides elements, see : Fleischer, M. *J. Chem. Educ.*, **1954**, *31*, 446.

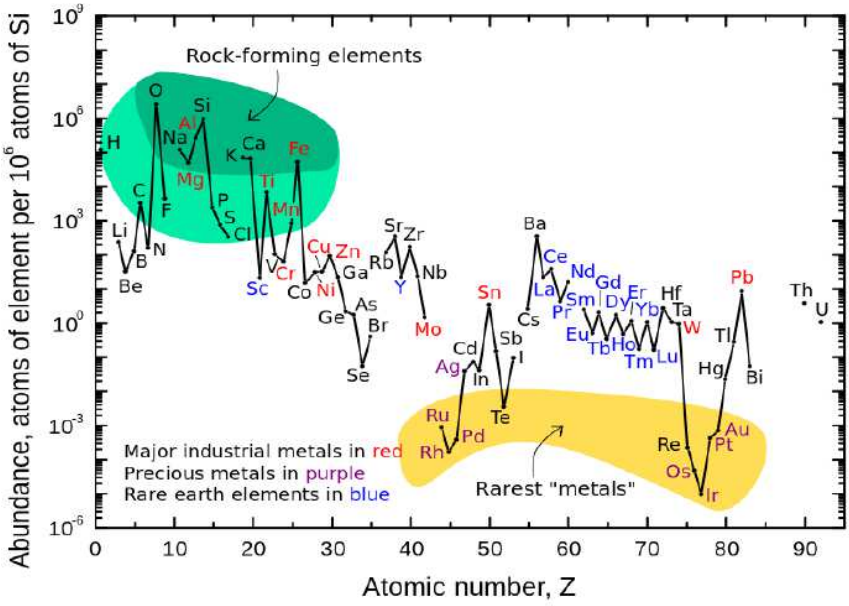

Figure 1.1 - Relative abundance of chemical elements in earth's crust[4]

Moreover, during the last few decades, organic chemists extensively used some transition metals, such as ruthenium, rhodium, palladium, iridium and platinum, of which the prices are relatively close to the price of gold (Figure 1.2). Therefore, expensive metals are commonly used in organometallic chemistry and catalysis.

Figure 1.2 - Prices of several transition metals used in organic chemistry[5]

[4] Source : U.S. Geological Survey – Fact sheet 087-02- Rare Earth Elements – Critical ressources for High Technology - https://pubs.usgs.gov/fs/2002/fs087-02/

[5] Prices found on the website of umicore Precious Metal Management - http://pmm.umicore.com/en/prices/

Additionally, two other financial aspects have to be kept in mind concerning organometallic catalysis. Firstly, the metals used in catalysis are rarely used in their elementary state but as oxides, which can be produced for a cheaper cost than the pure metal. Plus, in organometallic catalysis, the price of the ligand used for the formation of complexes often exceeds the price of the metal itself. So all in all, the price of gold is not such an important factor for organometallic catalysis.

The actual reason for which gold was so despised by organic chemists was the same reason for which it became famous on the first place : its so-called chemical inertness. As a matter of fact, gold was actually known to possess a rich chemistry using stoichiometric amounts of it (clusters, etc.). But gold was thought to be catalytically dead. And it had to wait until the 1970s to see this slander proven wrong with the first development of gold catalyzed heterogeneous processes namely the oxidation of carbon monoxide to carbon dioxide and the hydrochlorination of acetylene to give vinyl chloride (Figure 1.3). These two industrial applications represented an undeniable proof of concept for the use of gold in catalysis and let to further studies in the field of heterogeneous gold catalysis.[6]

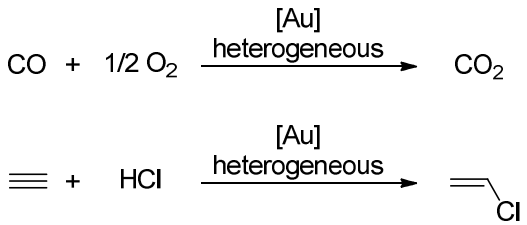

Figure 1.3 – The first two gold catalyzed heterogeneous processes

However, the true gold rush came a few decades later, in the early 2000s, with the event of homogeneous gold catalysis. Indeed, homogeneous catalysis presents many advantages over heterogeneous catalysis. Reactions are more easily reproducible as they don't rely anymore on the properties of the surface of the catalysts (size, contact area, etc.). Besides, all the components are in the same phase, which eliminates the problems of absorption / desorption at the surface of the catalyst. Plus, the reaction conditions are often milder (temperature, pressure, etc.) and the reactions more selective and more tolerant towards functional groups in homogeneous catalysis.

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[6] For a review on heterogeneous gold catalysis, see : Hutchings, G.J. *Chem. Commun.*, **2008**, 1148.

Having said that, these aspects are only general consideration of homogeneous *versus* heterogeneous catalysis and are not sufficient to explain this gold rush. The next section shows how much gold's properties make it an exceptional metal, especially in the field of electrophilic catalysis.

1.1.2 The exceptional properties of gold

The exceptional properties of gold originate in its electronic configuration [Xe] $4f^{14}$ $5d^{10}$ $6s^{1}$. In the same way as the other coinage metals, its d valence shell is completely filled whereas its s valence shell contains only one electron. Therefore, the oxidation state +1 can easily be reached, resulting in a completely empty s valence shell, which makes gold (I) a very good Lewis acid.

So far, gold seems to follow the normal trend of coinage metals but paying more attention to it quickly leads to observe some singularities, the first of which being its size. Indeed, gold possesses thirty two more electrons than silver and is almost twice heavier. In a classical model, gold should be expected to be much bigger than silver. In fact, its atomic radius is slightly smaller. The explanation lies in relativistic effects.[7] Indeed, in the case of gold, the speed of the valence shell electrons is not negligible when compared to the speed of light. This results in a contraction of the 6s and 6p valence orbital. In fact, gold is one of the most affected chemical element by this relativistic effects[8] (Figure 1.4).

[7] For reviews on relativistic effects on gold, see : a) Pyykkö, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 4412 ; b) Gorin, D.J.; Toste, F.D. *Nature*, **2007**, *446*, 395.
[8] Pyykkö, P.; Desclaux, J.P. *Acc. Chem. Res.* **1979**, *12*, 276.

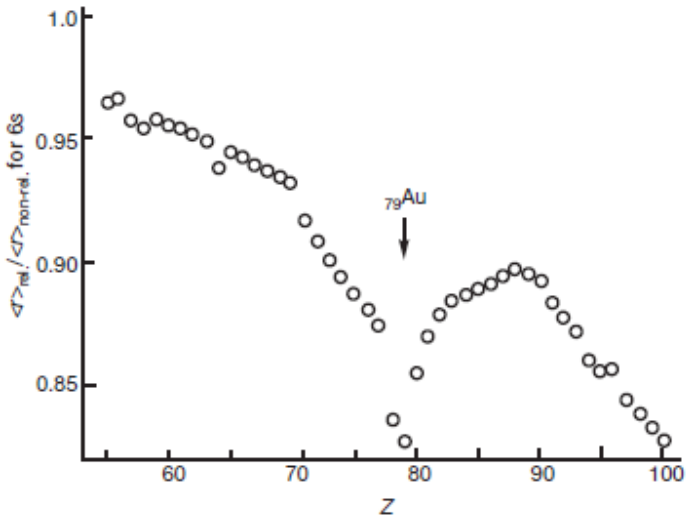


Figure 1.4 - The relativistic contraction of the 6s shell in the elements Cs (Z = 55) to Fm (Z = 100)

From a chemical point of view, this relativistic contraction of the 6s and 6p shells comes with several consequences that make gold such a special Lewis acid.

❖ A powerful Lewis acid :

First of all, the contraction of the 6s orbital, being now closer to the nucleus, stabilizes it. This explains the fact that the ionization energy is higher for gold than for copper and silver. Therefore, after ionization, the LUMO of gold (I) has a lower energy than it would have without taking into account the relativistic effects, making gold (I) a stronger Lewis acid than metals not affected by this effect (Figure 1.5).

❖ A good ability to delocalize electron density :

This relativistic contraction actually concerns all the s and p orbitals which are then closer to the nucleus. This results in a shielding of the 5d orbital electrons which are less attracted by the nucleus. The 5d orbital is then expanded which destabilizes it (Figure 1.5). Therefore, the HOMO of gold (I) has a higher energy than it would have without taking into account the relativistic effects, making gold (I) more inclined to back donation.

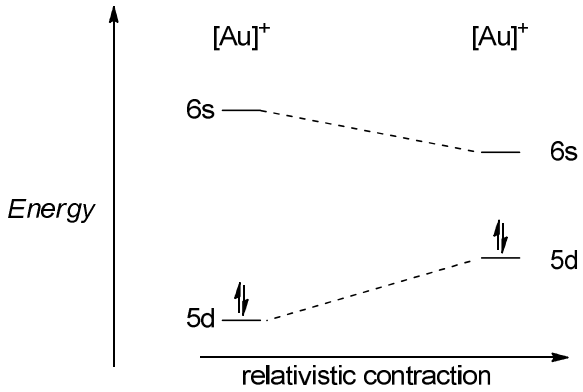


Figure 5. Relativistic effect of the energy of the HOMO and LUMO orbitals of gold (I)

The first evidence of this property was provided by a study of Goddard[9] in which the Au-CH_2^+ moiety is shown to present a marked multiple bond character that results from a back donation of the gold to the non-bonding orbital of the carbocation. However, back donation to *anti*-bonding orbital is still unlikely because of the too important energy gap between the 5d and the *anti*-bonding orbital.

❖ A carbophilic Lewis acid :

Despite the contraction it undergoes, the 6s orbital of gold is still quite diffuse. Diffuse enough for gold to prefer coordination to π systems rather than charge interaction. Moreover, compared to his fellow coinage metals like silver and copper, gold (I) species coordinate selectively to carbon-based insaturations rather than carbonyl compounds. Indeed, Hertwig[10] and Yamamoto[11] provided a calculation study comparing the energies of complexation of different metals to different π systems (Figure 1.6). The following trend was found : copper (I), silver (I) and gold (III) are oxophilic and coordinate more selectively to aldehydes, whereas gold (I) is carbophilic and coordinates more selectively to alkenes and alkynes. However, imines remain far better partners for all four metals.

[9] Irikura, K.K.; Goddard, W.A. *J. Am. Chem. Soc.*, **1994**, *116*, 8733.
[10] Hertwig, R.H. *and al. J. Phys. Chem.* **1996***, 100*, 12253.
[11] Yamamoto, Y. *J. Org. Chem.*, **2007**, *72*, 7817.

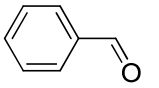
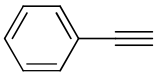
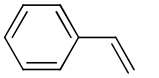
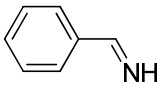
	CuCl	AgCl	AuCl	$AuCl_3$
	-37.4	-26.4	-33.1	-35.9
	-33.1	-22.6	-34.7	-32.5
	-33.6	-22.4	-37.5	-36.8
	-51.8	-39.6	-53.6	-60.3

Figure 1.6 – Computed heats of coordination of coinage oxides with different π systems (B3LYP/SDD, kcal mol-1)

In organometallic catalysis, this carbophilicity of gold entails two advantages. The first is the high functional group tolerance that it involves, allowing for example to perform gold catalysis in oxygenated solvents. For example, some gold-catalyzed reactions can be performed in water or alcohol solvents, which is a strong advantage as the concept of green chemistry becomes more and more fashionable. The second point is the great selectivity of gold towards the activation of carbon-based insaturations, which is presented in the following part.

1.1.3 Reactivity of gold in the activation of insaturations

The strong affinity of gold for carbon-based insaturations can be used for their selective activation towards functionalization by nucleophiles. In the first stage of this process, gold acts as a strong Lewis acid and coordinates to the insaturation, thus promoting an interaction between the LUMO of gold and the HOMO of the insaturation (Figure 1.7). The LUMO of the resulting gold complex is then lower in energy than the LUMO of the uncoordinated insaturation, and also closer to the HOMO of the nucleophile which can then add to the activated insaturation.

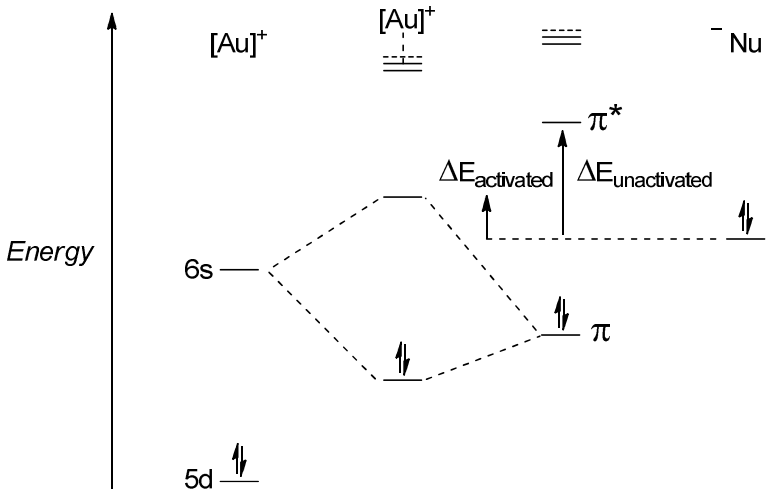
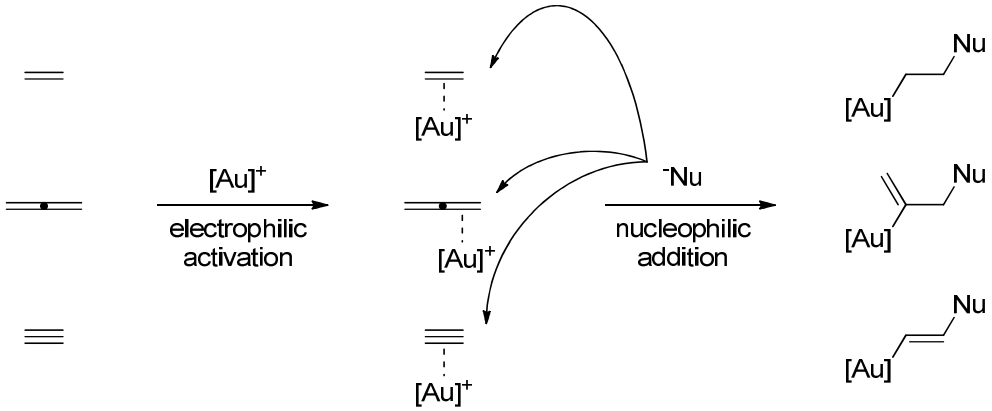


Figure 1.7 – Principle of the activation of carbon-based insaturation by gold (I)

The addition step proceeds in an *anti*-manner regarding the activation of the insaturation by the gold (I) complex[12] (Figure 1.8). From this stage, the resulting aurated intermediates[13] can evolve following various pathways.[14]



[12] For evidence of the *anti*-manner addition see : a) Hashmi, A.S.K.; Weyrauch, J.P.; Frey, W.; Bats, J. *Org. Lett.* **2004**, *6*, 4391 ; b) Buzas, A; Gagosz, F. *Org. Lett.* **2006**, *8*, 515; c) Hashmi, A.S.K.; *Angew. Chem. Int. Ed.* **2010**, *49*, 5232.

[13] For evidence of the existence of the aurate intermediates after addition of the nucleophile, see : a) Liu, L.P.; Xu, B.; Mashuta, M.S.; Hammond, G.B. *J. Am. Chem. Soc.* **2008**, *130*, 17642 ; b) Hashmi, A.S.K.; Schuster, A.; Rominger, F. *Angew. Chem. Int. Ed.* **2009**, *121*, 8396 ; c) Hashmi, A.S.K.; Dondeti Ramamurthi, T.; Rominger, F. *Adv. Synth. Catal.* **2010***, 352*, 971.

[14] Gold intermediates usually do not undergo β-elimination : Baker, R.T.; Nguyen, P.; Marder, T.B.; Westcott, S.A. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1336.
However, a recent study demonstrated the possibility of such a β-elimination with specific gold(III) catalysts : Rekhroukh, F.; Estevez, L.; Mallet-Ladeira, S.; Miqueu, K.; Amgoune, A.; Bourissou, D. *J. Am. Chem. Soc.*, **2016**, *138*, 11920.

Figure 1.8 – Nucleophilic addition on carbon-based insaturations activated by gold (I)

❖ Trapping by an electrophile *via* direct deauration :

A first potential pathway is the case in which the aurated intermediates are directly trapped by an electrophile. A deauration process happens and the carbon – gold bond is replaced by a bond between the carbon atom and the electrophile (Figure 1.9).

If the electrophile is a simple proton, this step is named protodeauration.

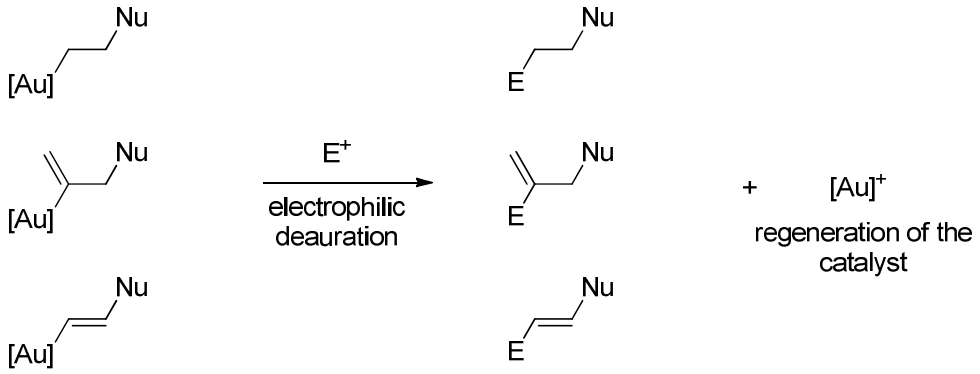


Figure 1.9 – Trapping of the aurated intermediate by an electrophile *via* direct deauration

❖ Trapping by an electrophile *via* back donation of gold :

As stated in section 1.1.2, gold presents the ability to delocalize the electron density of its 5d orbital, especially to the non-bonding orbital of a carbocation, thus stabilizing it. This propensity allows the aurated intermediates to undergo another type of trapping with an external electrophile. In this case, the remaining carbon – carbon double bond proceeds to an electrophilic trapping at the β position to gold, thus generating new aurated intermediates (Figure 1.10). These intermediates can be described by two limit mesomeric forms, namely gold-stabilized carbocations or gold carbenes.[15] In fact, the nature of the intermediates are strongly dependent on the gold catalyst and particularly on its ligand (see 1.1.4). Hereafter, according to its nature, the new aurated intermediate can be trapped following a carbocation or a carbene reactivity.

[15] For evidence of carbene mesomeric form, see : Joost, M.; Estevez, L.; Mallet-Ladeira, S.; Miqueu, K.; Amgoune, A.; Bourissou, D. *Angew. Chem. Int. Ed.* **2014**, *53*, 14512

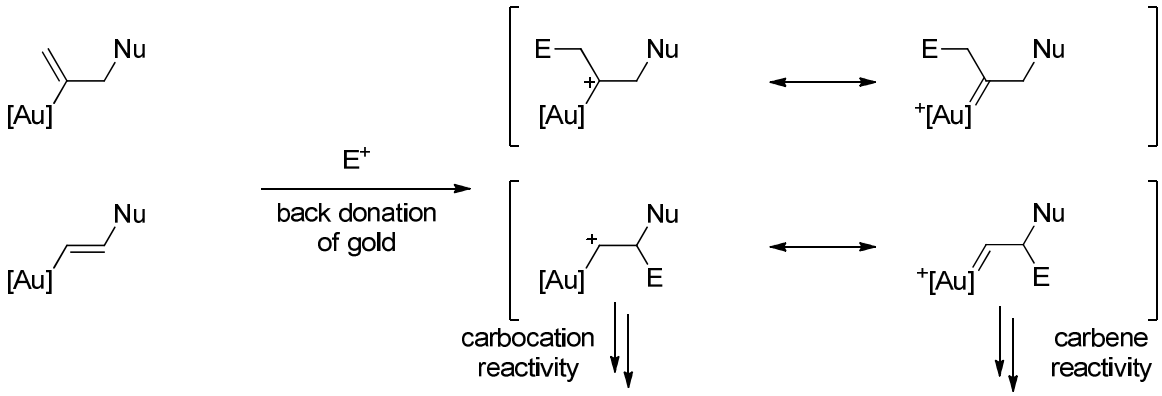


Figure 1.10 – Trapping of an electrophile *via* back donation of gold

❖ Reaction with nucleophiles bearing a leaving group :

Nucleophilic addition of a nucleophile bearing a leaving group to a gold activated alkyne results in the generation of an aurated intermediate which can evolve even differently than in the cases previously described. Indeed, upon back donation from the gold complex, extrusion of the leaving group occurs, thus providing a new gold intermediate that can also be described by two limit mesomeric forms : a gold-stabilized carbocation and a gold carbene (Figure 1.11). Here also, the new gold intermediate can be trapped following a carbocation or a carbene reactivity, according to its nature (see section 1.2.3).

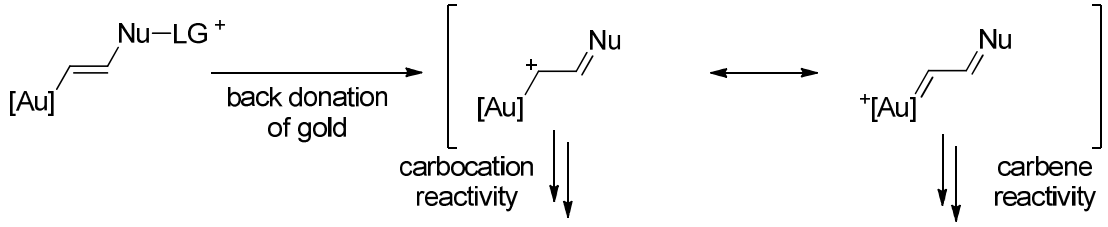


Figure 1.11 – Back donation of gold when the nucleophile bears a leaving group

Obviously, the reactivity of the catalyst, but also the nature of the aurated intermediates, are extremely dependent on the nature of the gold complex. The next section aims at describing the design of the complexes and their general use.

1.1.4 The common gold complexes and their specificities

The complexes commonly used in homogeneous gold catalysis differ widely according to the oxidation state of gold, usually +3 or +1.

- Gold (III) catalysts :

Gold (III) complexes possess the following electronic configuration : [Xe] $4f^{14}$ $5d^{8}$ $6s^{0}$. Their composition is either AuX_3, $MAuX_4$ or $LAuX_3$. Either way, they usually adopt a square plan geometry and most of the time the gold atom is tetracoordinated. The most common gold (III) catalyst is probably the commercially available $AuCl_3$ which has a dimeric composition with two μ-Cl ligands (Figure 1.12). Other salts of the same composition can also be employed such as $AuBr_3$.

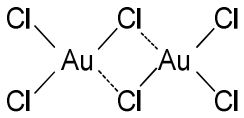


Figure 1.12 – Dimeric form of $AuCl_3$

Other gold (III) salts commonly used are the ones directly resulting from the oxidation of gold (0) by aqua regia and its derivatives : $HAuCl_4$, $NaAuCl_4$ and $[n\text{-}Bu_4]AuCl_4$. Noticeably, they can be reduced to AuCl complexes which is the precursor of the catalysts that will presented in the next section.

Gold (III) complexes can also be coordinated with ligands, which modifies the properties of the catalyst. In most cases, pyridines[16] or NHC[17] carbene ligands are used (Figure 1.13).

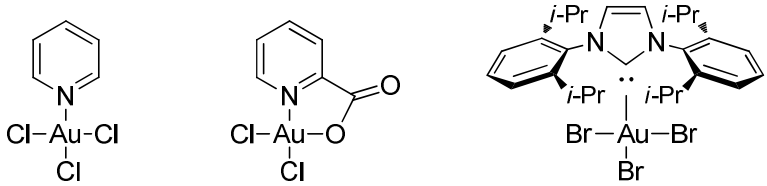


Figure 1.13 – Examples of gold (III) complexes including a ligand

[16] a) Hashmi, A.S.K.; Weyrauch, J.P.; Rudolph, M.; Kurpejovic, E. *Angew. Chem. Int. Ed.* **2004,** *43*, 6545 ; b) Hashmi, A.S.K.; Rudolph, M.; Bats, J.W.; Frey, W.; Rominger, F.; Oeser, T. *Chem. Eur. J.* **2008***, 14*, 6672.

[17] de Fremont, P.; Singh, R.; Stevens, E.D.; Petersen, J.L.; Nolan, S.P. *Organometallics*, **2007**,*26*, 1376.

However, gold (III) catalysts are not often used. Indeed, gold (III) complexes are usually not very selective and their reactions tend to generate many by-products. Indeed, as mentioned previously, gold (III) is more oxophilic than gold (I), which is sometimes problematic for oxygenated substrates. On the contrary, the strong carbophilicity of gold (I) gives a better selectivity, which is the reason why more attention has been paid to their complexes.

- Gold (I) catalysts :

Gold (I) complexes have the electronic configuration [Xe] $4f^{14}$ $5d^{10}$ $6s^0$ and their composition is LAuX, L being a neutral ligand and X a counter anion. They adopt a linear[18], bicoordinated[19] geometry. The simplest gold (I) salt is AuCl, existing as a polymer with μ-Cl ligands bridging the gold atoms (Figure 1.14). Its stability can be greatly enhanced by coordination with a thioether ligand, which is why it is commercially available as $Me_2S{\cdot}AuCl$. However, this complex is not particularly active and is more used as a precursor to synthesize other complexes.

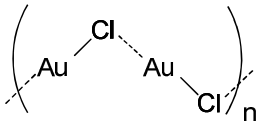


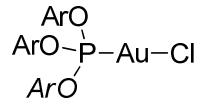
Figure 1.14 – Polymeric form of AuCl

As just mentioned, a ligand L, such as in $Me_2S{\cdot}AuCl$ (L = Me_2S) can improve the stability of the complex. Indeed, gold (I) catalysts usually include a strong σ-donor ligand L to somewhat stabilize the positive charge located on the metal center. Additionally to this σ-donation, the π-donor or π-acceptor properties of the ligand can be used to modulate the reactivity of the catalyst. For this, a large range of ligands are available, among which the most commonly employed are phosphines, NHC carbenes, phosphites and phosphoramidites. These ligands can be classified according to their respective properties.

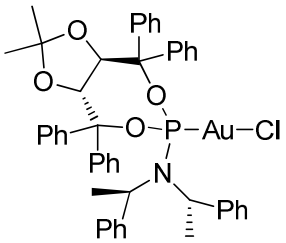
[18] For a calculation of the angles of LAuX complexes, see :Thompson, D. *Chemistry of organic derivatives of gold and silver,* **2000**.
[19] For energies of deformation of the coordination sphere, see : Carjaval, M.A.; Novoa, J.J.; Alvarez, S. *J. Am. Chem. Soc.*, **2004**, *126*, 1465.

- Phosphite and phosphoramidite ligands (Figure 1.15) :

  Because of the three electronegative heteroatoms bonded to the phosphorous atom, these ligands are the weakest σ-donors of the series. As a result, the complexes bearing these ligands provide a strong activation of carbon-based insaturations. They are also the strongest π-acceptors. As a result, the π back donation from the gold atom is not favored and the gold complexes possessing these ligands are not very capable of stabilizing a carbocation or of generating a gold carbene.



Ar = 2,4-t-Bu-Ph



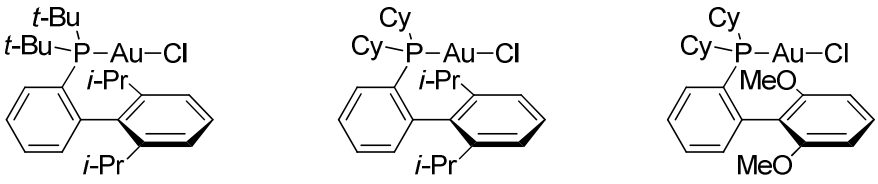
phosphite ligand *phosphoramidite ligand*

Figure 1.15 - Examples of gold (I) pre-catalysts possessing phosphite or phosphoramidite ligands

- Phosphine ligands (Figure 1.16) :

  They are generally good σ-donors and fairly poor π-acceptors, although their properties can be modulated by the groups attached to the phosphorous atom. These groups can be identical or different and can be chosen between alkyl, aryl or even biaryl groups as it is the case in the largely employed Buchwald ligands (JohnPhos, XPhos, SPhos and a series of other commercially available ligands).

Ph_3PAuCl *t*-Bu_3AuCl

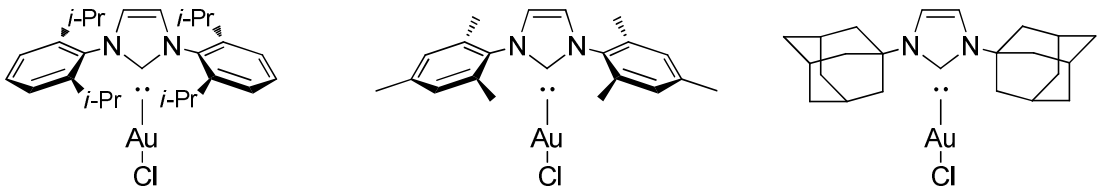


JohnPhosAuCl *XPhosAuCl* *SPhosAuCl*

Figure 1.16 – Examples of gold (I) pre-catalysts possessing phosphine ligands

- NHC carbene ligands (Figure 1.17) :

  They are very good σ-donors and generally weak π-acceptors. As a result, complexes including these ligands activate only moderately the insaturation but are excellent for the stabilization of carbocation intermediates or to generate gold carbenes.



IPrAuCl *IMesAuCl* *IAdAuCl*

Figure 1.17 – Examples of gold (I) pre-catalysts possessing NHC carbene ligands

However, the LAuCl complexes are used as pre-catalysts. They are usually not really catalytically active as the chloride atom is not labile enough (strong Au-Cl bond). It is then necessary to activate the complex by replacing the chloride atom by a less coordinating counter anion. Concretely, weak bases (OTf^-, BF_4^-, NTf_2^-, SbF_6^-) are excellent candidates for this purpose. Practically, the anion exchange in LAuCl type pre-catalysts is performed using the silver salt bearing the desired weakly coordinating counter-anion while the LAuMe type pre-catalysts are activated by addition of the corresponding strong acid (Figure 1.18).

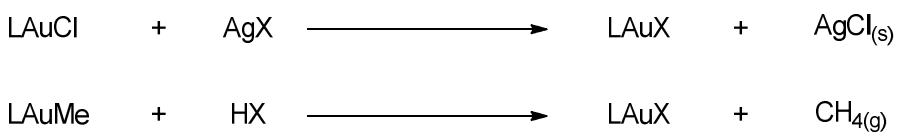


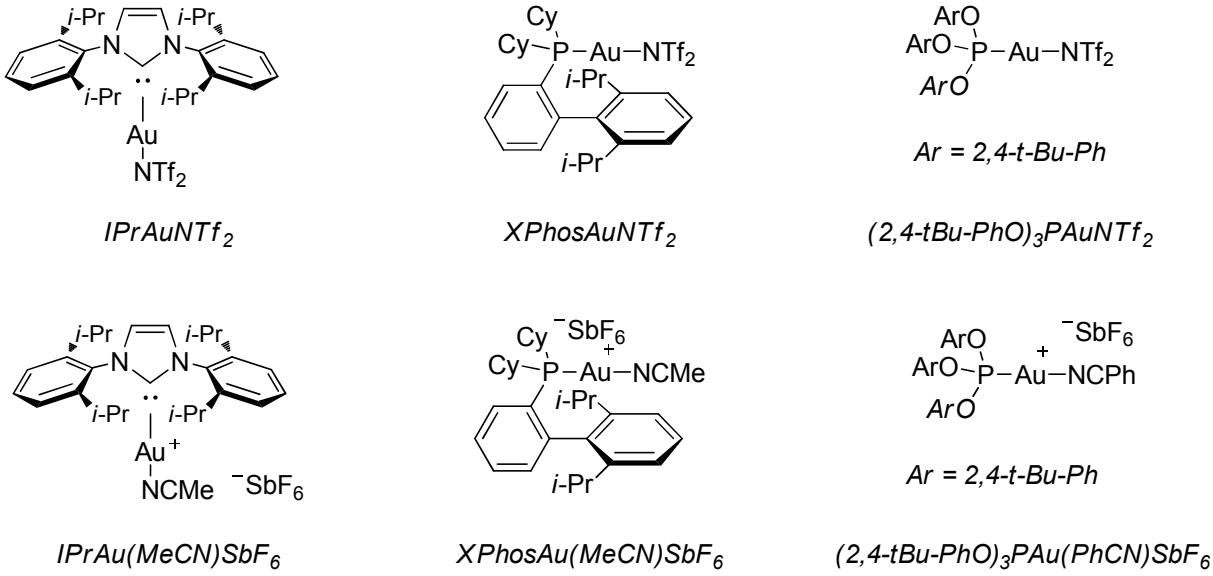
Figure 1.18 – Activation of gold (I) pre-catalysts

Technically, two strategies can be used to prepare the catalysts. The first option consists in proceeding to the *in-situ* activation[20]. However, this method is controversial because of the uncertainty of the active species in the solution. Moreover, the silver salt or the strong acid added for the activation might affect the activity of the catalyst.[21]

[20] For an exemple of *in-situ* generation of the catalyst, see : Gorin, D.J.; Davis, N.R.; Toste, F.D. *J. Am. Chem. Soc.* **2005**, *127*, 11260.

[21] For publications about the silver effect, see : a) Hashmi, A.S.K.; Blanco, M.C.; Fisher, D.; Bats, J.W. *Eur. J. Org. Chem.* **2006**, 1387 ; b) Weber, D.; Gagné, M.R. *Org. Lett.* **2009**, *11*, 4962 ; c) Wang, D.; Cai, R.;

The second option consists in a pre-synthesis of the gold catalyst, which presents the advantage of knowing accurately what is introduced in the reaction mixture. In addition, this approach is made even more attractive by the stability of many gold (I) complexes which can be easily prepared, isolated and stored without much precaution. Factually, most of the bench stable gold (I) catalysts are complexes possessing bis(trifluoromethylsulfonyl)imidate[22] (NTf_2^-) or a hexafluoro*anti*mony[23] (SbF_6^-) counter anions (Figure 1.18). In the case of very weakly coordinating counter anions such as hexafluoro*anti*mony or hexafluorophosphate[24] (PF_6^-), the anion is too remoted from the metal center and a second ligand, usually a nitrile, is necessary to obtain bench stable catalysts (Figure 1.19).



IPrAuNTf$_2$ *XPhosAuNTf$_2$* *(2,4-tBu-PhO)$_3$PAuNTf$_2$*

IPrAu(MeCN)SbF$_6$ *XPhosAu(MeCN)SbF$_6$* *(2,4-tBu-PhO)$_3$PAu(PhCN)SbF$_6$*

Figure 1.19 – Examples of bench stable gold (I) catalysts

Sharma, S.; Jirak, J.; Thumanapelli, S.K.; Akhemedov, N.G.; Zhang, H.; Liu, X.; Peterson, J.L.; Shi, X. *J. Am. Chem. Soc.* **2012**, *134*, 9012.

[22] For literature on the use of the NTf_2^- anion in catalysis, see : a) Mezailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133 ; b) Ricard, L; Gagosz, F. *Organometallics* **2007**, *26*, 4704 ; c) Antoniotti, S.; Dalla, V.; Dunach, E. *Angew. Chem. Int. Ed.* **2010**, *49*, 7860.

[23] a) Nieto-Oberhuber, C.; Lopez, S.; Munoz, M.P.; Cardenas, D.J.; Bunuel, E.; Nevado, C.; Echavarren, A.M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6146 ; b) Herrero-Gomez, E.; Nieto-Oberhuber, C.; Lopez, S.; Benet-Bucholz, J.; Echavarren, A.M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5455.

[24] De Fremont, P.; Stevens, E.D.; Fructos, M.R.; Diaz-Requejo, M.M.; Perez, P.J.; Nolan, S.P. *Chem. Commun.* **2006**, 2045.

Besides, some dinuclear gold (I) catalysts were also designed.[25] An interesting application of dinuclear catalysts is the use of complexes containing chiral diphosphine ligands which promote stereoselective transformations (Figure 1.20).[26] However, because of the linear geometry of gold (I) catalysts, the induction of chirality from the ligand is difficult because of its distance to the reacting site.

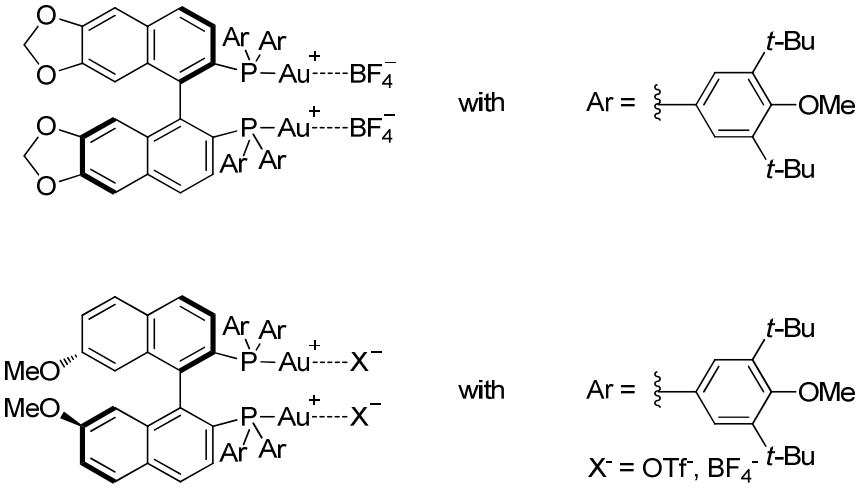


Figure 1.20 – Example of dinuclear gold (I) catalysts containing a chiral ligand

An alternative approach has been reported, in which the chiral information originates from the counter anion and not from the ligand. The very first example of such a strategy involved the use of a chiral phosphate counter anion (Figure 1.21).[27]

[25] Gorin, D.J.; Davis, N.R.; Toste, F.D. *J. Am. Chem. Soc.* **2005**, *127*, 11260
[26] a) Hashmi, A.S.K. *Nature*, **2007**, *449*, 292 ; b) Chao, C.M.; Genin, E.; Toullec, P.Y.; Genet, J.P.; Michelet, V. *J. Organomet. Chem.* **2009**, *694*, 538.
[27] Hamilton, G. L., Kang, E. J., Mba, M. & Toste, F. D. *Science*, **2007**, *317*, 496.

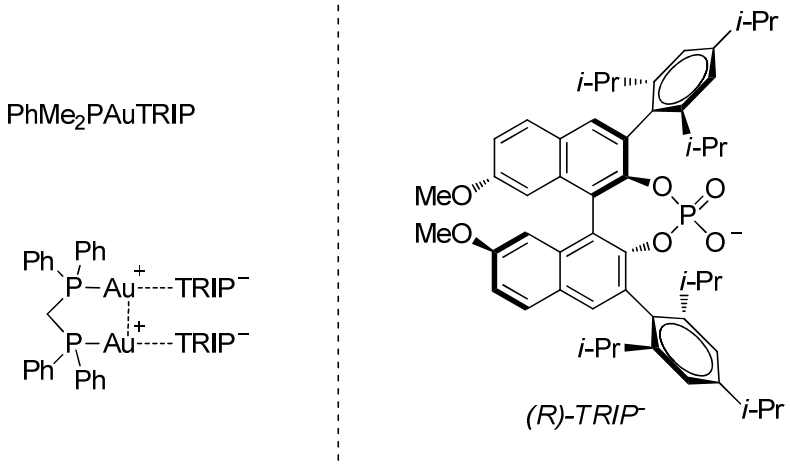


Figure 1.21 – Examples of gold (I) catalysts containing a chiral counter anion

The following section will display some classical examples of reactions involving the use of the catalysts presented above. This list is not exhaustive but only aims at giving a better understanding of the outstanding catalytic potential of gold. The selection is classified according to the nature of the nucleophile and according to the reactivity of the gold catalyst.

1.2 Gold catalyzed addition of heteroatom-based nucleophiles to C-C multiple bonds

From a general point of view, the addition of heteroatom-based nucleophiles onto multiple carbon-carbon bonds starts with the activation of the insaturation by the gold catalyst. This is followed by an *anti*-addition of the nucleophile on the gold-activated insaturation. In the case of a heteroatom-based nucleophile, the resulting aurated intermediate can evolve following different pathways, according to the nature of the nucleophile and the reactivity of the catalyst. Figure 1.22 gives a general view of these routes, which will be presented in more details in the following sections.

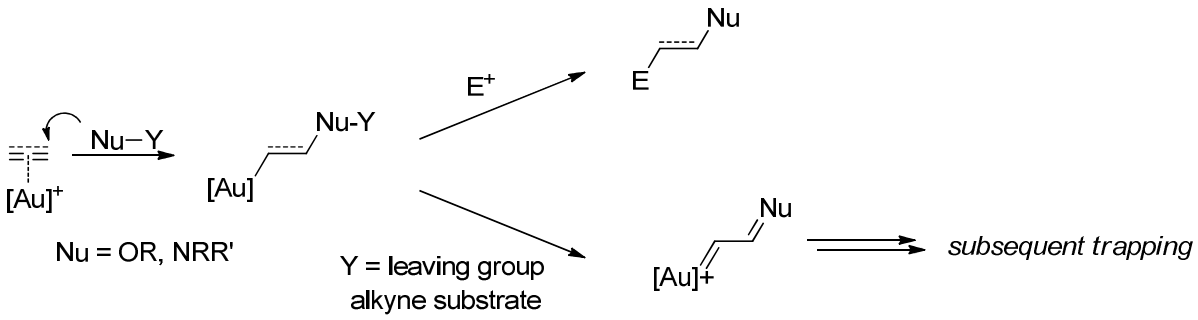


Figure 1.22 – Different evolution pathways after addition of a heteroatom-based nucleophile

The addition of internal nucleophiles usually leads to heterocyclization reactions.

The addition of nucleophiles bearing a leaving group to alkynes usually leads to the generation of gold carbenes which can be subsequently trapped by different methods.

In the special case of propargyl esters, the intramolecular addition of the ester to the gold-activated alkyne leads to acyloxy migrations.

1.2.1 Intermolecular addition of simple heteroatom-based nucleophiles

The general interest for homogeneous electrophilic gold catalysis started with a simple gold catalyzed addition of methanol to an alkyne.[28] A few years later, a gold catalyzed process of hydration of alkynes was developed (Figure 1.23, eq. 1)[29] as well as a hydroamination of alkynes (eq. 2).[30] Examples of intermolecular additions of carboxylic acids (eq. 3)[31] and carbamates (eq. 4)[32] were also demonstrated to be achievable despite their reduced nucleophilicity.

[28] Teles, J.H.; Brode, M.; Chabanas, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 1415.
[29] Mizushima, E.; Sao, K.; Hayashi, T.; Tanaka, M. *Angew. Chem. Int. Ed.*, **2002**, *131*, 4563.
[30] Mizushima, E.; Hayashi, T.; Tanaka, M. *Org. Lett.* **2003**, *5*, 3349.
[31] Chary, B.C.; Kim, S. *J. Org. Chem.* **2010**, *75*, 7928.
[32] Kobayashi, S.; Kakumoto, K.; Sugiura, M. *Org. Lett.* **2002**, *4*, 1319.

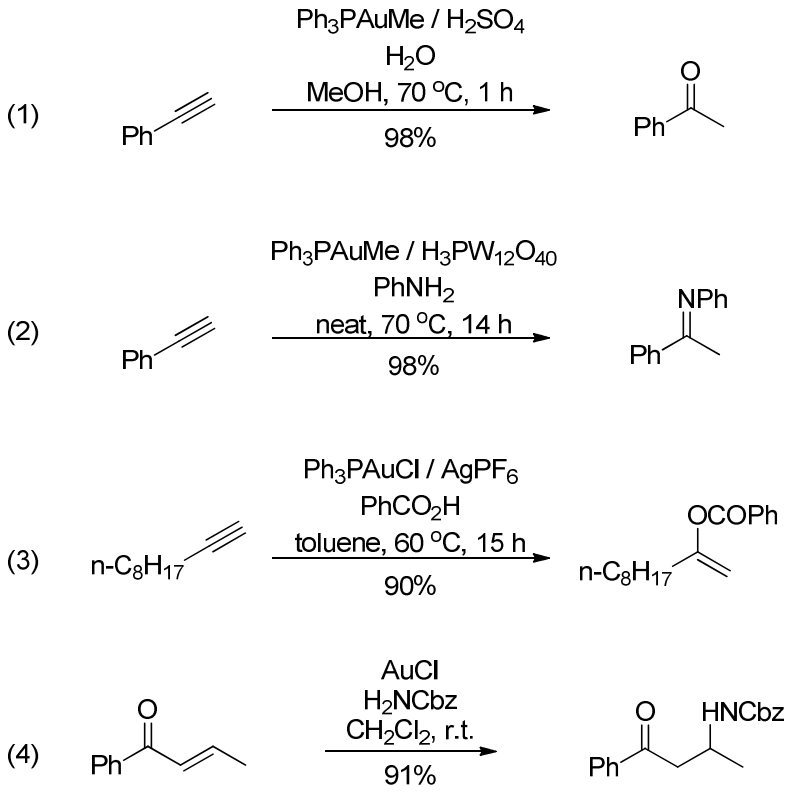


Figure 1.23 – Examples of intermolecular addition of heteroatom-based nucleophiles on π-systems

1.2.2 Heterocyclization reactions

In the case of a nucleophilic addition with an internal nucleophile, the addition leads to a heterocyclization[33]. The simplest version of these intramolecular processes is the case in which the heteroatom bears a hydrogen atom which will directly be used in the following deauration step.

Oxygen nucleophiles can be alcohols[34] (Figure 1.24, eq. 1, 2, 5, 6) or carboxylic acids[35,36] (eq. 3,4).

---

[33] For a review on gold-catalyzed heterocyclization, see : a) Rudolph, M.; Hashmi, A.S.K. *Chem. Commun* **2011**, *47*, 6536 ; b) Debrouwer, W.; Heugebaert, T.S.A.; Roman, B.I; Stevens, C.V. *Adv. Synth. Catal.* **2015**, *357*, 2975.

[34] a) Liu, Y.; Song, F.; Song, Z.; Liu, M.; Yan, B. *Org. Lett.* **2005**, *7*, 5409–5412 ; b) Aponick, A.; Li, C.-Y.; Malinge, J.; Marques, E. F. *Org. Lett.* **2009**, *11*, 4624–4627.

[35] Genin, E.; Toullec, P.Y.; Antoniotti, S.; Brancour, C.; Genet, J.P.; Michelet, V. *J. Am. Chem. Soc.*, **2006**, *128*, 3112.

[36] Salas, C.O.; Roboredo, F.J.; Estevez, J.C., Tapia, R.A.; Estevez, R.J. *Synlett*, **2009**, 3107.

Nitrogen nucleophiles can be free amines[37] (eq. 7) or protected amines[38,39] (eq. 8,9).

Heterocyclization reactions can be performed on alkynes, alkenes and allenes[40,41] in a 5-*exo*, 5-*endo*, 6-*exo* or 6-*endo* manner according to the substrates.

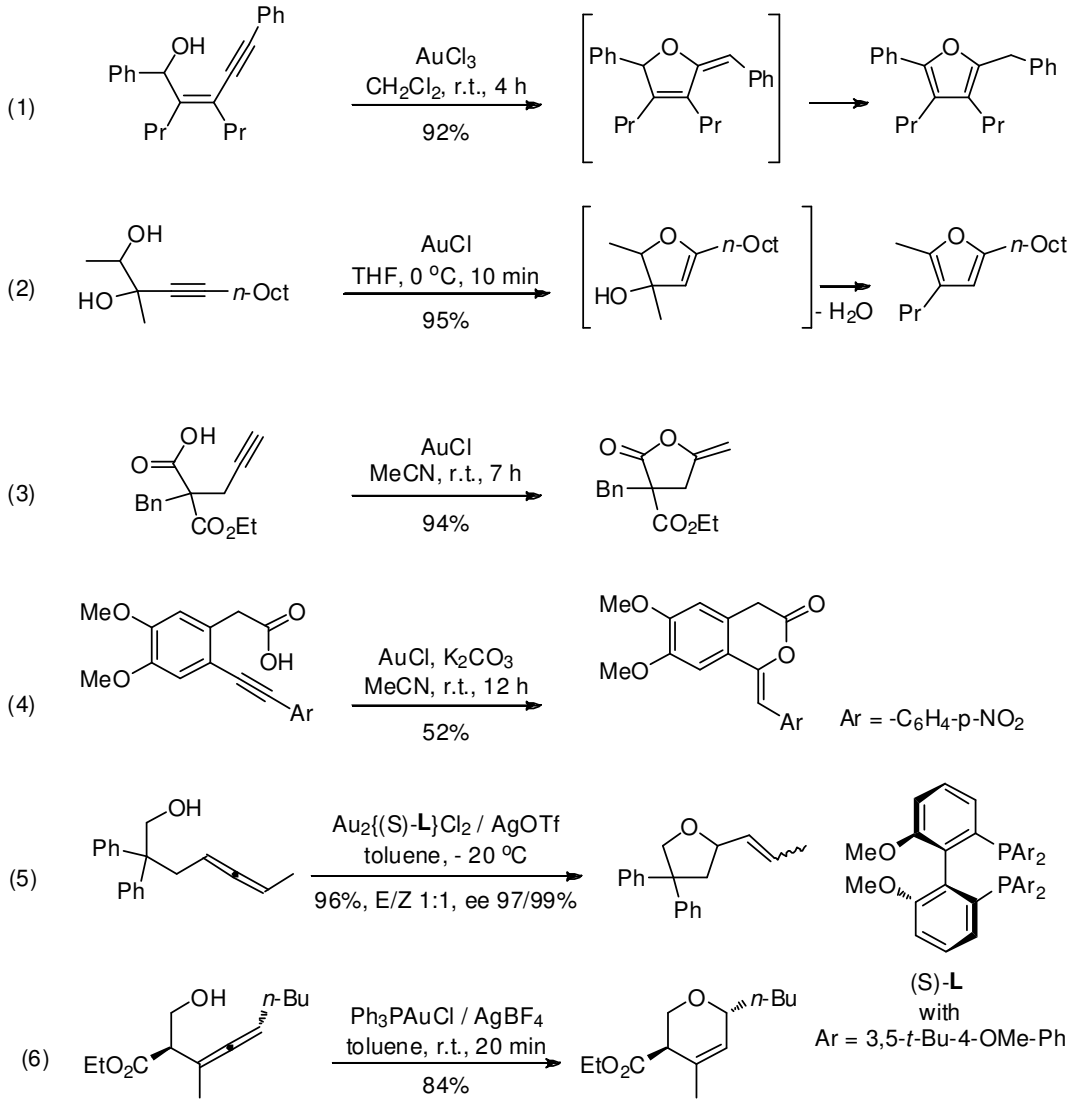


Figure 1.24 – Examples of heterocyclization with direct protodeauration

[37] Fukuda, Y.; Utimoto, K. *Synthesis* **1991**, *1991*, 975.
[38] Li, H.; Widenhoefer, R. A. *Org. Lett.* **2009**, *11*, 2671.
[39] Han, X.; Widenhoefer, R.A. *Angew. Chem. Int. Ed.* **2006**, *45*, 1747.
[40] Zhang, Z.; Widenhoefer, R. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 283
[41] Gockel, B.; Krause, N. *Org. Lett.* **2006**, *8*, 4485.

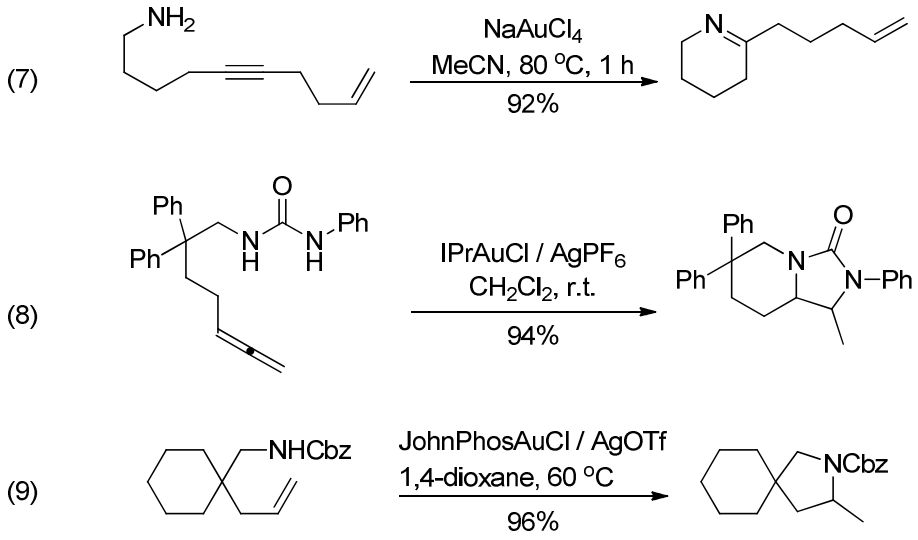


Figure 1.24bis – Examples of heterocyclization with direct protodeauration

In a less simple case, the heteroatom does not bear a hydrogen atom but another hydrogen atom is available on the substrate for the proto-deauration step.

For example, *O-tert*-butyl carbonates[42] (Figure 1.25, eq. 1) or *O-tert*-butyl carbamates[43] (eq. 2) can cyclize onto alkynes. After the addition step, a proto-deauration process occurs with a concomitant extrusion of isobutene.

Addition of the oxygen atom of secondary propargyl amides onto the alkyne provides oxazine products (eq. 3).[44]

Besides, the heterocyclization of propargyl aziridines can lead to the formation of pyrrol compounds (eq. 4).[45]

α-allenic carbonyl substrates can also cyclize to furnish furan products (eq. 5).[46]

[42] Buzas, A.; Gagosz, F. Org. Lett. **2006**, *8*, 515–518.
[43] Robles-Machin, R.; Adrio, J.; Carretero, J. C. *J. Org. Chem*. **2006**, *71*, 5023.
[44] Fustero, S.; Miró, J.; Sánchez-Roselló, M.; del Pozo, C. *Chem. Eur. J*. **2014**, *20*, 14126.
[45] Davies, P. W.; Martin, N. *Org. Lett*. **2009**, *11*, 2293.
[46] Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285.

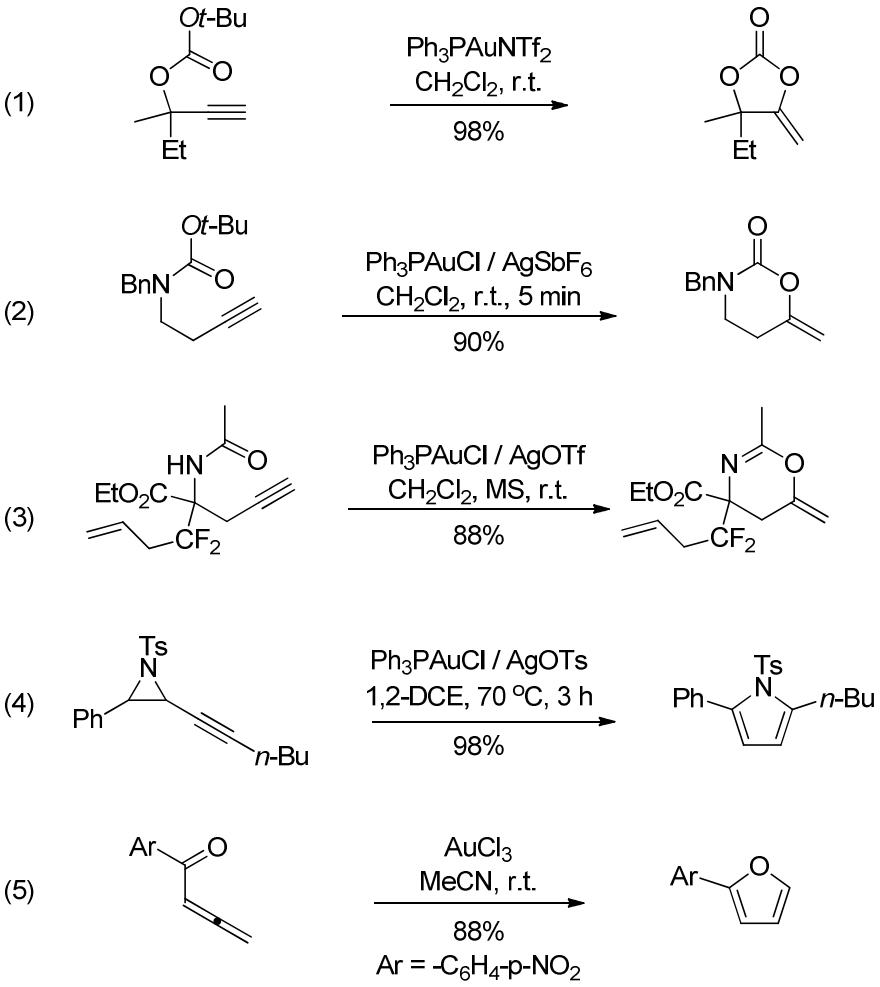


Figure 1.25 – Examples of heterocyclization with indirect protodeauration

However, in the case in which the substrate does not possess a hydrogen atom suitable for proto-deauration, other pathways are conceivable to regenerate the catalytic active specie.

In some cases, a subsequent intramolecular rearrangement such as a 1,2-group shift (Figure 1.26, eq. 1)[47] or a claisen rearrangement can proceed (eq. 2).[48]

When no rearrangement of such a type is possible, an intermolecular trapping can then operate (eq. 3).[49]

[47] Kirsch, S. F.; Binder, J. T.; Liebert, C.; Menz, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 5878.
[48] Istrate, F.M.; Gagosz, F. *Org. Lett.*, **2007**, *9*, 3181.
[49] Liu, Y.; Liu, M.; Guo, S.; Tu, H.; Zhou, Y.; Gao, H. *Org. Lett.* **2006**, *8*, 3445.

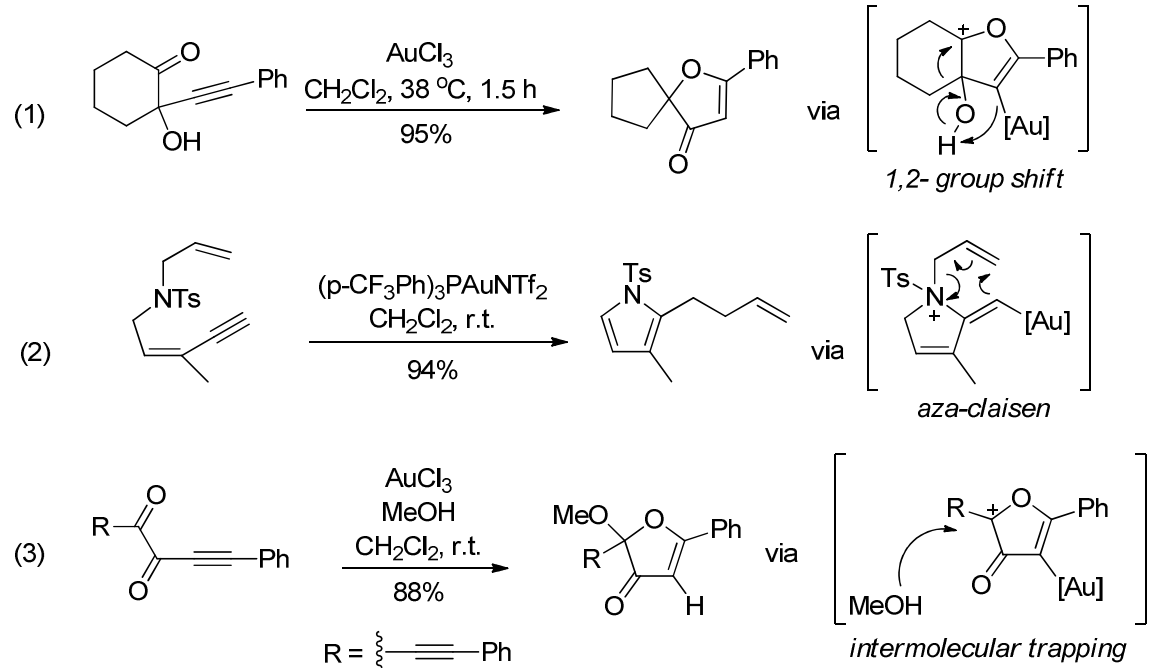


Figure 1.26 – Examples of heterocyclization with no possible protodeauration

In all the previous examples, the gold catalyst is regenerated *via* a proto-deauration step. However, other deauration process can be envisaged.

For example, Selectfluor can be used for gold-catalyzed oxidative cross coupling reactions (Figure 1.27, eq. 1).[50] As a strong oxidant, Selectfluor is used to oxidize gold (I) to a gold (III) complex containing a fluoride ligand. Then, a transmetallation occurs with a boronic acid partner, thus giving a gold (III) complex containing a phenyl ligand. This complex can then activate the C=C bond of the substrate for the heterocyclization step. The resulting aurated intermediate undergoes a reductive elimination to deliver the cross-coupling product along with the regeneration of the catalyst.

Another pathway is to trap the aurated intermediate with an electrophilic source of halogen such as NIS (eq. 2).[51]

[50] Zhang, G.; Cui, L.; Wang, Y.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 1474.
[51] Buzas, A; Gagosz, F. *Org. Lett.* **2006**, *8*, 515.

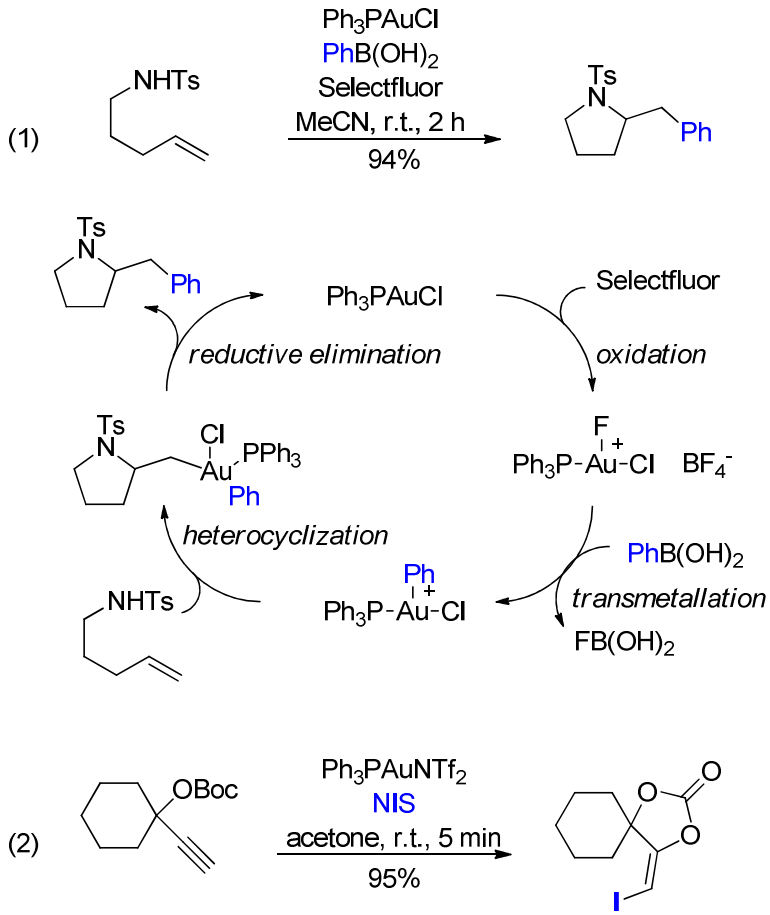


Figure 1.27 – Examples of different deauration processes

1.2.3 Rearrangements of propargyl esters

A particular attention has been granted to the gold-catalyzed rearrangement of propargyl esters.[52] Indeed, upon activation of the alkyne by the gold catalyst, the oxygen of the carbonyl moiety of the ester can proceed to a nucleophilic addition following two different pathways.

On one hand, a 5-*exo-dig* addition provides a 5-membered ring aurated intermediate which, after back donation from the gold complex, generates a gold carbene intermediate which can be subsequently trapped (Figure 1.28, blue pathway). This route is named the 1,2-acyloxy migration.

On the other hand, a 6-*endo-dig* addition provides a 6-membered ring gold intermediate which, after regeneration of the catalyst, evolves to an allenic ester (red pathway). This route is named the 1,3-acyloxy migration.

[52] For reviews on rearrangements of propargyl acetate, see : a) Marion, N.; Nolan, S.P. *Angew. Chem. Int. Ed.* **2007**, *46*, 2750 ; b) Wang, S.; Zhang, G.; Zhang, L. *Synlett* **2010**, 692.

All these steps are reversible and all the different species are in equilibrium, hence the name of golden carrousel of propargyl esters.

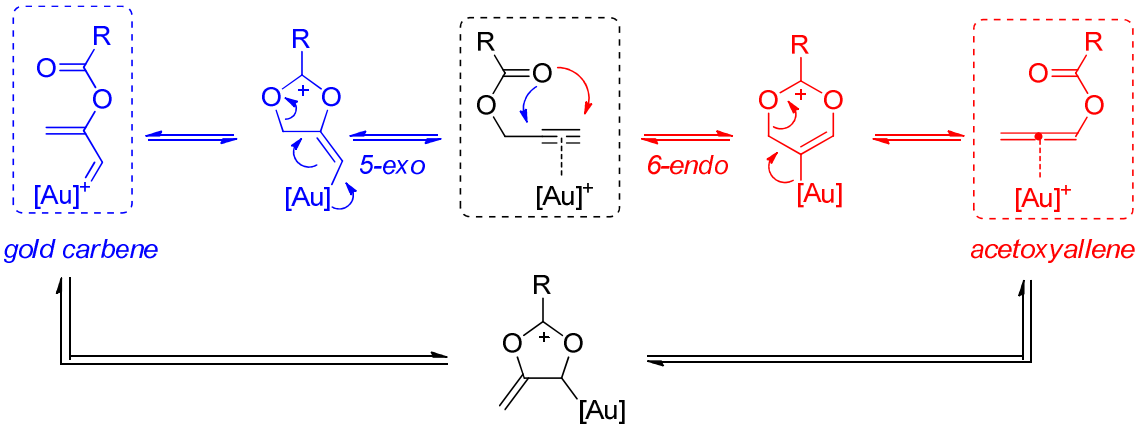


Figure 1.28 – Golden carrousel of propargyl esters

The gold carbenes resulting from the 1,2-acyloxy migration of propargyl esters can be trapped following different methods.

For example, a 1,2-acyloxy migration in the presence of an alkene leads to a cyclopropanation between the gold carbene and the alkene (Figure 1.29, eq. 1).[53]

Another possible evolution of this carbene starts with a 1,2-hydride shift from the α position of the carbene, followed by regeneration of the catalyst to provide a 1,3-diene (eq. 2).[54]

The gold stabilized carbocation can also be trapped by a nucleophilic specie. With an internal nucleophile, this trapping leads to a cyclization and ends, as always, with the regeneration of the catalyst (eq. 3).[55]

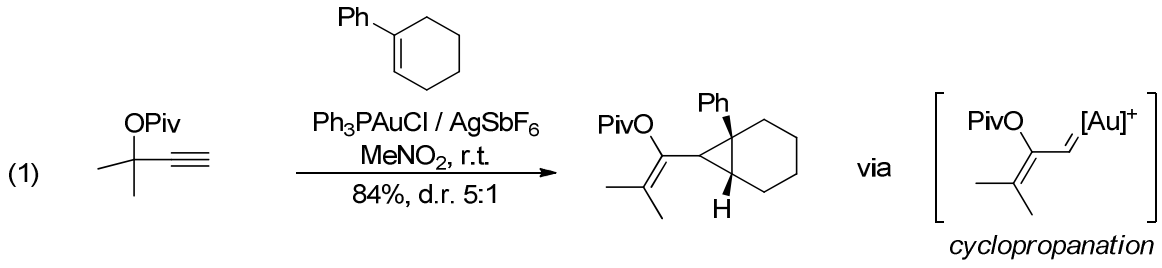


Figure 1.29 – Examples of 1,2-acyloxy migration

[53] Johansson, M.J.; Gorin, D.J.; Staben, S.T.; Toste, F.D. *J. Am. Chem. Soc.*, **2005**, *127*, 18002.
[54] Li, G.; Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 3740.
[55] Uemura, M.; Watson, I. D. G.; Katsukawa, M.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 3464.

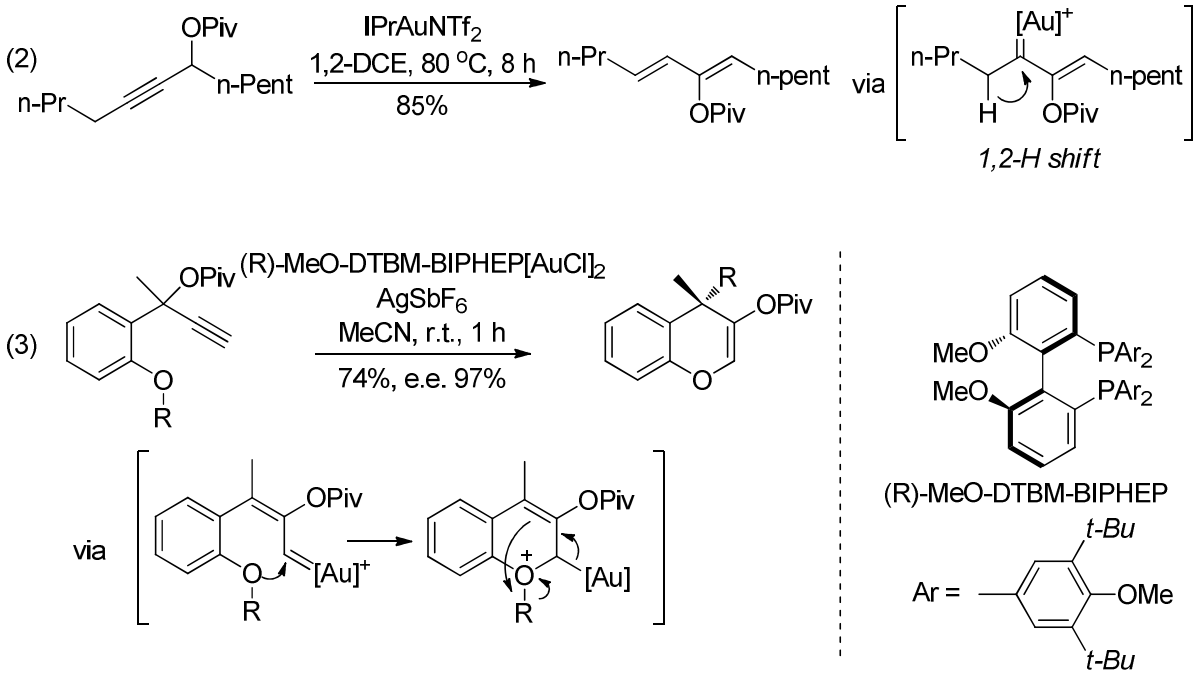


Figure 1.29bis – Examples of 1,2-acyloxy migration

The mechanism ruling the 1,3-acyloxy migration has been clarified after a period of uncertainty. Indeed, two mechanisms can lead to the formation of allenic esters from propargyl esters. The first one, as previously stated, corresponds to the 6-*endo-dig* addition of the ester onto the alkyne (Figure 1.30, eq. 1). The second possible mechanism consists in two consecutive 5-*exo* additions. The first one being the 5-*exo* addition of the ester onto the alkyne. The second one being the addition of the ester onto the resulting carbene (eq. 2).

However, the 6-*endo-dig* addition mechanism was proven to be the most likely one. Indeed, a control experiment using a propargyl ester bearing a ^{18}O isotope on the alcoxy position leads exclusively to the product bearing a ^{18}O isotope on the carbonyl position, which corresponds to the 6-*endo-dig* mechanism. (Figure 1.30).[56]

[56] a) Mauleon, P.; Krinsky, J.L; Toste, F.D. *J. Am. Chem. Soc.* **2009**, *131*, 4513 ; b) Rao, W.; Sally, Berry, S.N.; Chan, P.W.H. *Chem. Eur. J.* **2014**, *20*, 13174.

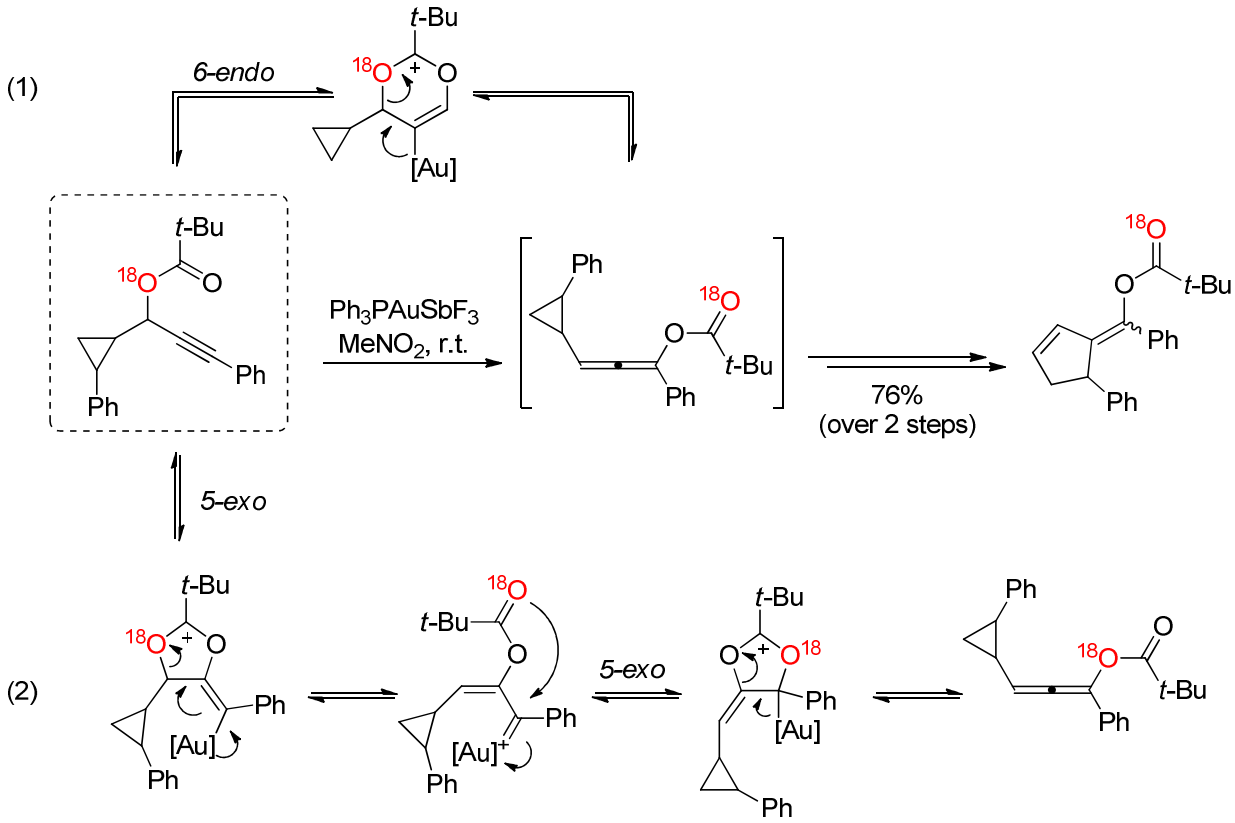


Figure 1.30 – Mechanistic studies on 1,3-acyloxy shift

The allenic ester resulting from a 1,3-acyloxy migration can also be activated by the gold catalyst and then undergo subsequent cascade transformations such as heterocyclizations (Figure 1.31, eq. 1)[57] or formal cycloadditions (eq. 2).[58]

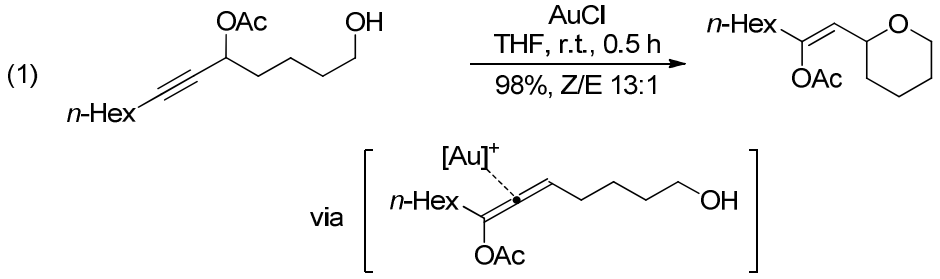


Figure 1.31 – Examples of 1,3-acyloxy migration

[57] De Brabander, J. K.; Liu, B.; Qian, M. *Org. Lett.* **2008**, *10*, 2533.
[58] Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804.

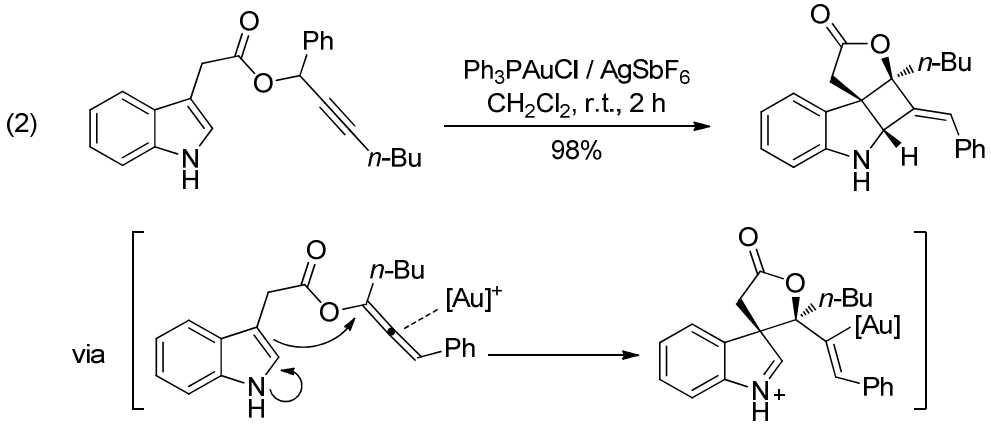


Figure 1.31bis – Examples of 1,3-acyloxy migration

1.2.4 Addition of oxene or nitrene precursors

When the nucleophile bears a leaving group, the gold intermediate resulting from the *anti*-addition can evolve *via* back donation from the gold complex. In this situation, extrusion of the leaving group occurs and a gold carbene is generated (Figure 1.32). As a result, the addition of an oxene precursor leads to the formation of an α-oxo gold carbene while the addition of a nitrene precursor leads to the formation of an α-imino gold carbene. This aspect of gold chemistry will be briefly illustrated in this section but will be presented in more details in section 3.2.

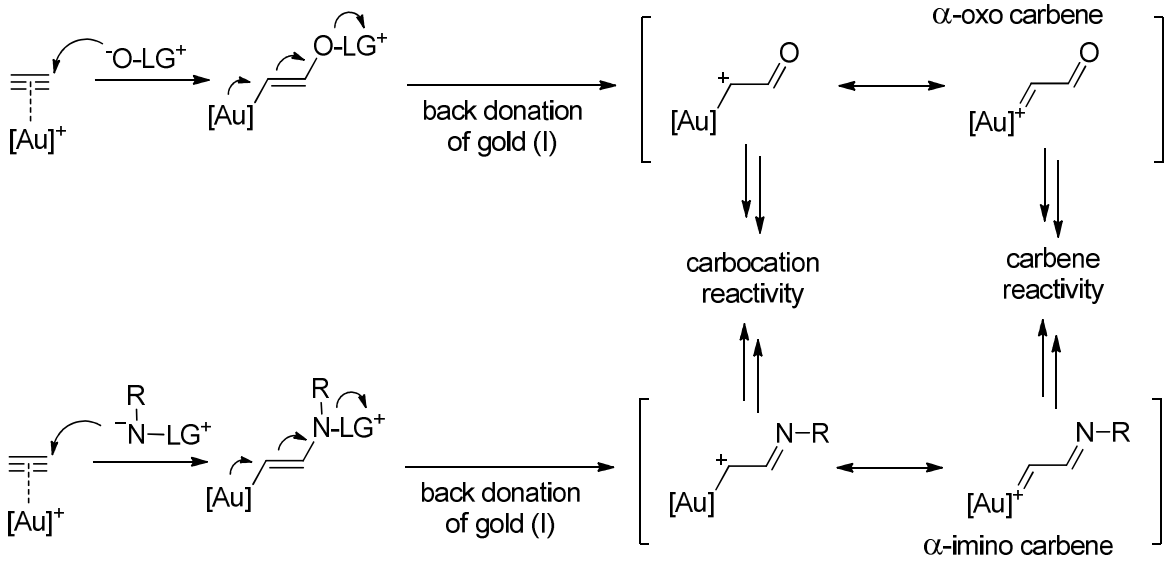


Figure 1.32 – General reactivity of oxene and nitrene precursors in gold catalysis

Oxene precursors can be *N*-oxides such as pyridine N-oxides (Figure 33 – eq. 1,2)[59,60] or nitrones (eq. 3).[61] After the addition of the nucleophile onto the gold-activated insaturation, back donation from gold leads to the formation of the α-oxo carbene and to an easy cleavage of the nitrogen-oxygen bond, thus releasing respectively pyridines, imines or amines.

The resulting α-oxo gold carbene can then evolve following different pathways such as a cyclopropanation (eq. 1), the nucleophilic addition of a heteroatom (eq. 2,), or a group shift (eq. 3).

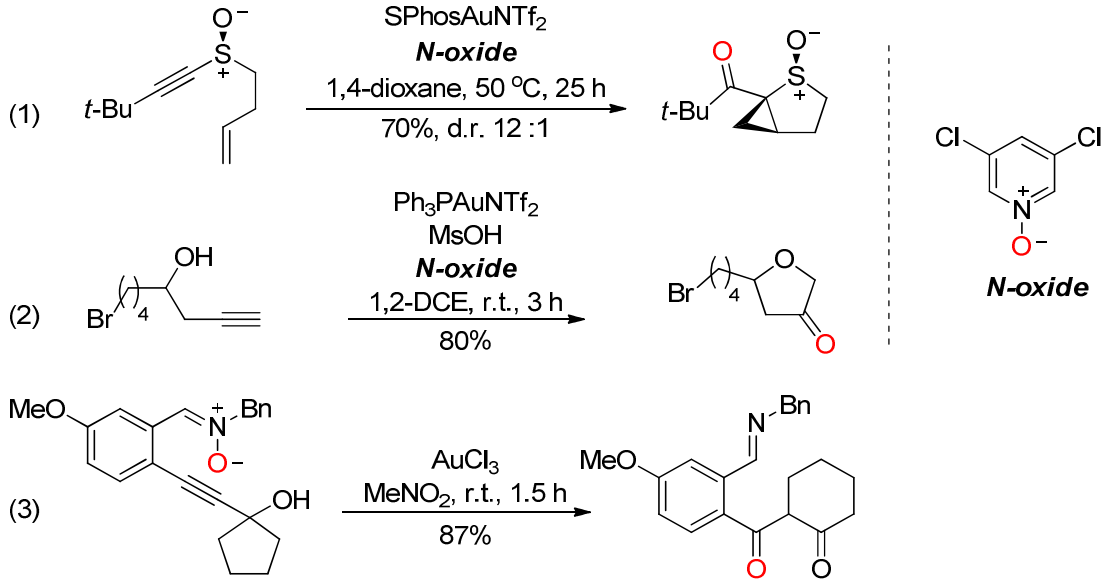


Figure 1.33 - Examples of addition of oxene precursors on alkynes

Azide compounds are known to be viable nitrene precursors. In this case, after the addition of the nucleophile to the activated insaturation, the back donation from the gold atom leads to the formation of a α-imino carbene upon extrusion of molecular nitrogen.

The resulting α-imino gold carbene can then evolve following different pathways such as 1,2-hydride shifts (Figure 1.34, eq. 1) [62] or 1,2-group shifts (eq. 2).[63]

When no intramolecular solution is available, an external nucleophile can be used to trap the carbene (eq. 3).[64]

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[59] Barrett, M.J.; Khan, G.F.; Davies, P.W.; Grainger, R.S. *Chem. Commun.*, **2017**, *53*, 5733.
[60] Ye, L.; Cui, L.; Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 3258.
[61] Yeom, H.-S.; Lee, Y.; Jeong, J.; So, E.; Hwang, S.; Lee, J.-E.; Lee, S. S.; Shin, S. *Angew. Chem. Int. Ed.* **2010**, *49*, 1611.
[62] Gorin, D.J.; Davis, N.R.; and Toste, F.D. *J. Am. Chem. Soc.* **2005**, *127*, 11260.
[63] Gronnier, C.; Boissonnat, G.; Fabien Gagosz, F. *Org. Lett.*, **2013**, *15*, 4234.
[64] Wetzel, A.; Gagosz, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 7354.

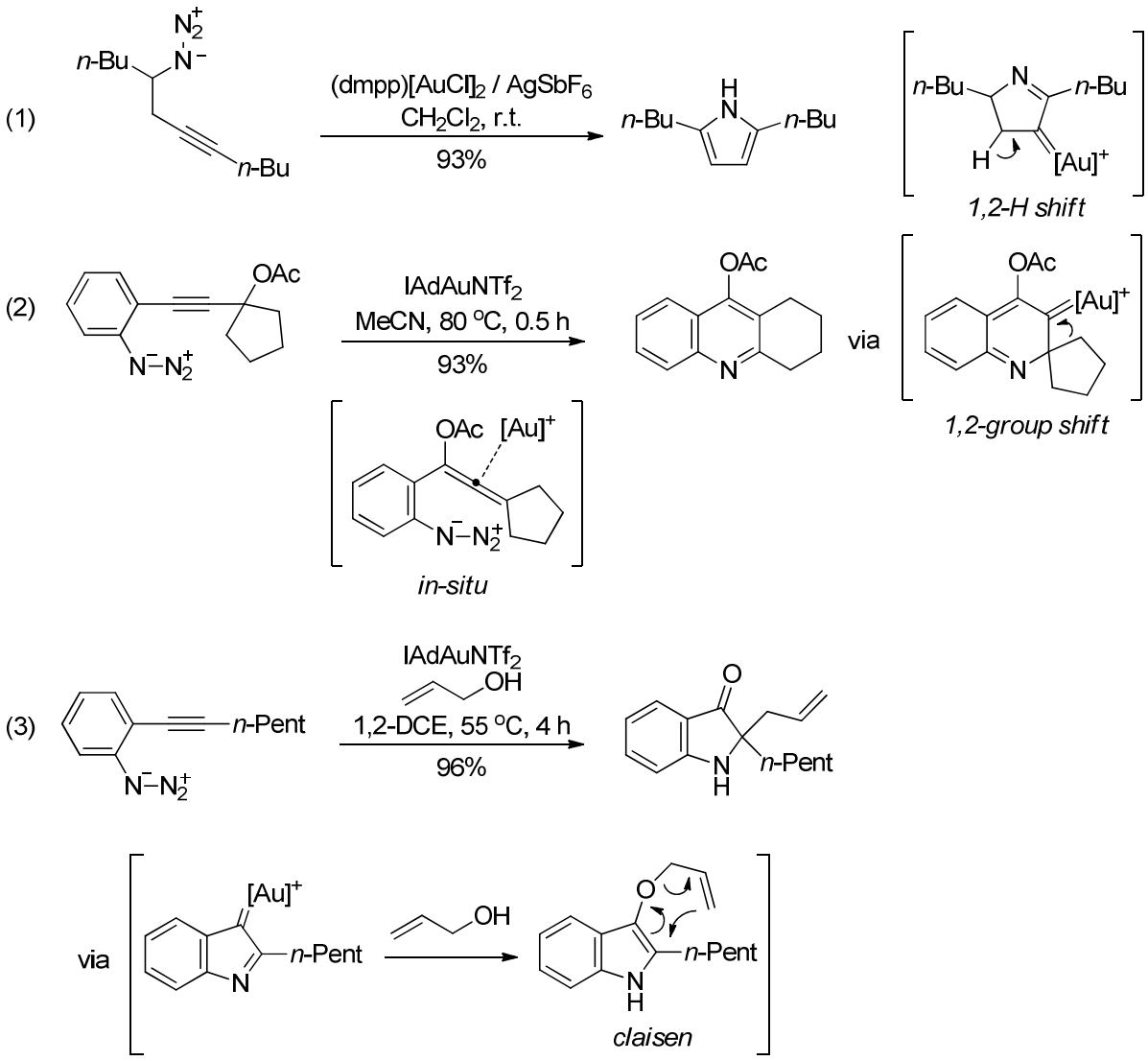


Figure 1.34 - Examples of addition of nitrene precursors on alkynes

1.3 Gold catalyzed addition of carbon nucleophiles to C-C multiple bonds

Following the trend of heteroatom-based nucleophiles, carbon nucleophiles can also be added to gold activated insaturations. The addition step proceeds in an *anti*-manner with regard to the catalyst. Then, in the case of a carbon nucleophile, the resulting gold intermediate can evolve following different pathways, according to the nature of the nucleophile and to the reactivity of the catalyst. Figure 1.35 gives a general view of these routes, which will be presented in more details in the following sections.

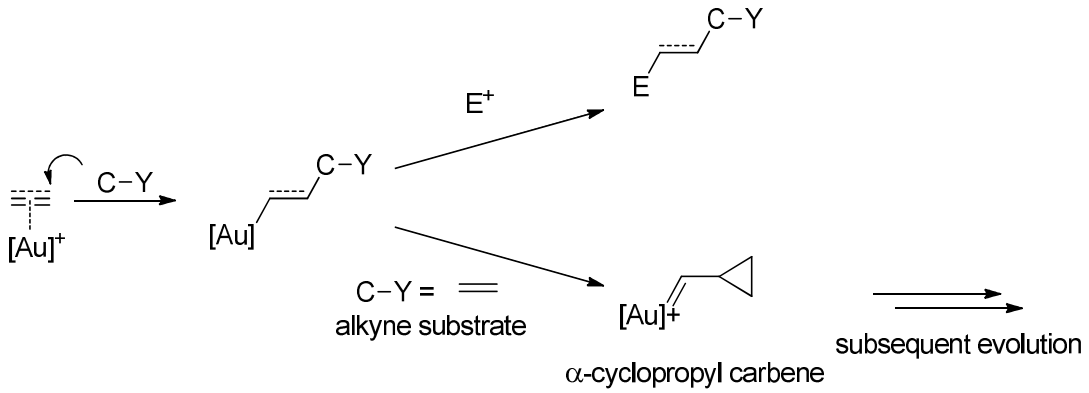


Figure 1.35 - Different evolution pathways after addition of a carbon nucleophile

The addition of internal nucleophiles usually leads to cyclization reactions.

The addition of alkenes to alkynes usually leads to the generation of α-cyclopropyl gold carbenes which can be subsequently trapped following different methods.

1.3.1 Addition of common carbon nucleophiles

A large variety of external or internal carbon nucleophiles can be used for addition to gold activated insaturations.

For examples, aromatic rings are good carbon nucleophiles and can be used for Friedel-Craft type intermolecular hydroarylation (Figure 1.36, eq. 2)[65] or hydroheteroarylation (eq. 1)[66] reactions on alkynes, allenes or alkenes.

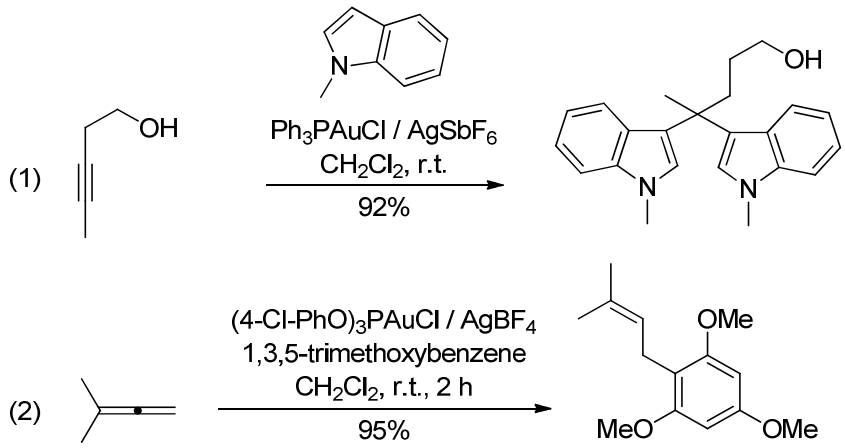


Figure 1.36 – Examples of intermolecular hydroarylation and hydroheteroarylation

Similarly, silyl enol ethers (Figure 1.37, eq. 1),[67] malonates and 1,3-dicarbonyl compounds (eq. 2)[68] are very good carbon nucleophiles for intramolecular reactions.

When an intramolecular addition of a carbon nucleophile ends by a classic direct protodeauration, the reaction leads to a cycloisomerization (eq. 2,3).[69,70]

[65] Tarselli, M.A.; Liu, A.; Gagne, M.R. *Tetrehedron*, **2009**, *65*, 1785.
[66] Barluenga, J.; Fernández, A.; Rodríguez, F.; Fañanás, F. J. *J. Organomet. Chem.* **2009**, *694*, 546.
[67] Lee, K.; Lee, P.H. *Adv. Synth. Catal*. **2007**, *349*, 2092.
[68] Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526.
[69] Z. Li, A. Kumar, D. D. Vachhani, S. K. Sharma, V. S. Parmar, E. V. Van der Eycken, *Eur. J. Org. Chem*. **2014**, 2084.
[70] Mamane, V.; Hannen, P.; Furstner, A. *Chem. Eur. J.* **2004**, *10*, 4556.

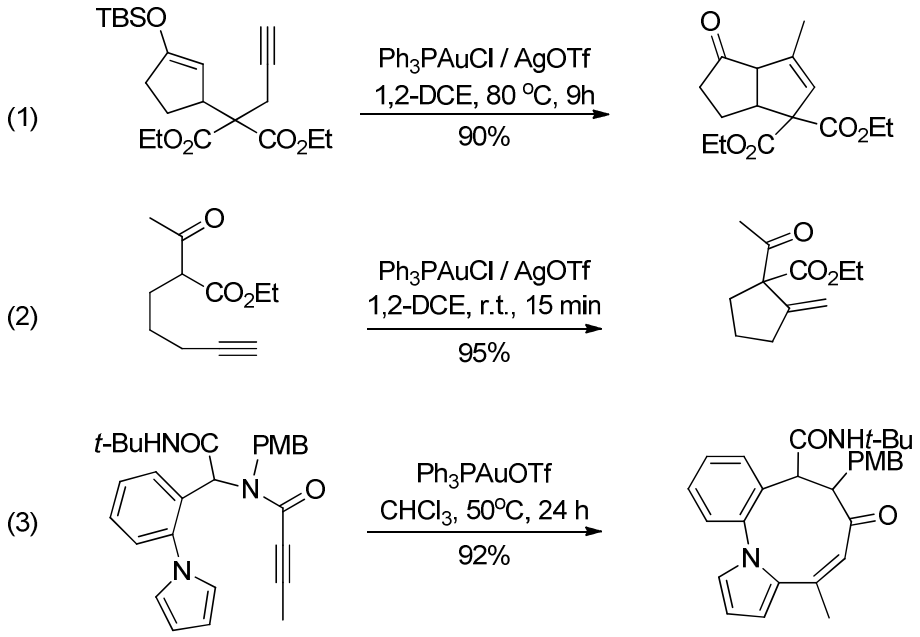


Figure 1.37 – Examples of intermolecular addition of carbon nucleophiles

1.3.2 Cycloisomerization of enynes

In the same way, alkenes are very good carbon nucleophiles in gold catalysis. Indeed, gold complexes can activate selectively alkynes as compared to alkenes. The HOMO of alkenes is indeed higher in energy than the HOMO of alkynes. Thus the LUMO of the alkene gold complex is higher in energy than the LUMO of the alkyne gold complex which is more activated toward a nucleophilic attack (Figure 1.38).

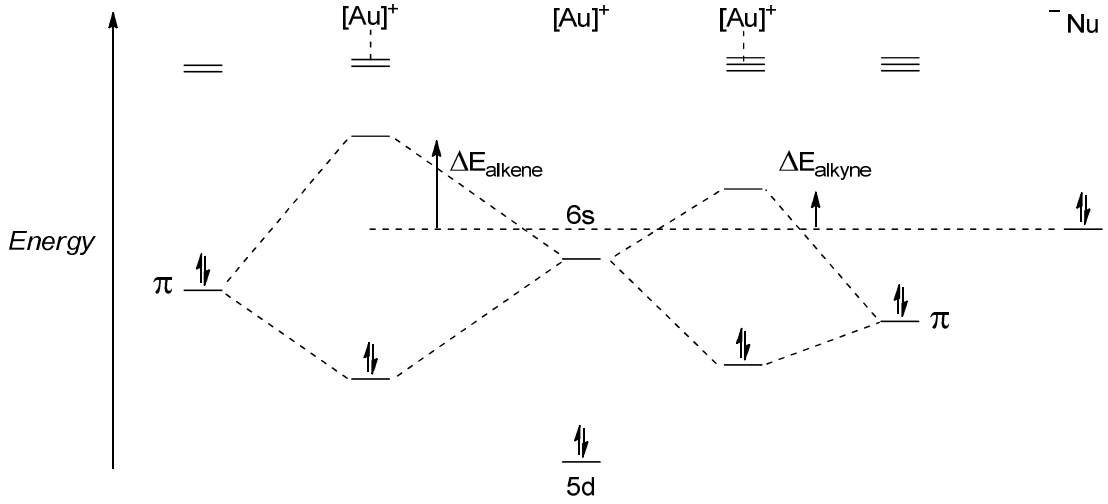


Figure 1.38 Gold selective activation of alkynes rather than alkenes

As a result, under gold catalysis conditions, alkenes can add onto the activated alkynes to generate gold-stabilized homoallylic carbocationic intermediates. This step is usually followed by back donation from the gold complex which ends with the formation of α-cyclopropyl gold carbenes (Figure 1.39).[71]

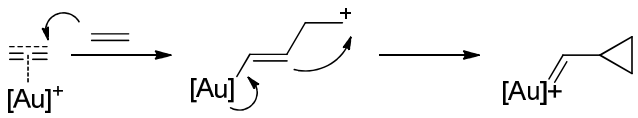


Figure 1.39 – Gold-catalyzed addition of alkenes to alkynes

More particularly, the intramolecular addition of an internal alkene to an alkyne leads to one of the most studied gold catalyzed reactions : the cycloisomerization of enynes.[72] More specifically, in the case of substrates containing both an alkene and an alkyne group, the alkene group can add to the alkyne following two different routes (Figure 1.40).

Exo-dig cyclizations lead to the generation of *exo*cyclic gold carbenes while *endo-dig* cyclizations lead to the generation of *endo*cyclic gold carbenes. Upon cyclopropanation, these intermediates can then evolve following different intramolecular rearrangements or by trapping with nucleophiles.

[71] Michelet, V.; Toullec, P.Y.; Genet, J.P. *Angew. Chem. Int. Ed.* **2008**, *47*, 4268.
[72] a) Jimenez-Nunez, E.; Echavarren, A.M. *Chem. Rev.* **2008**, *108*, 3326 ; b) Gorin, D.J.; Sherry, B.D.; Toste, F.D. *Chem. Rev.* **2008**, *108*, 3351 ; c) Lee, S.I.; Chatani, N. *Chem. Comm.* **2009**, *371* ; Furstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208.

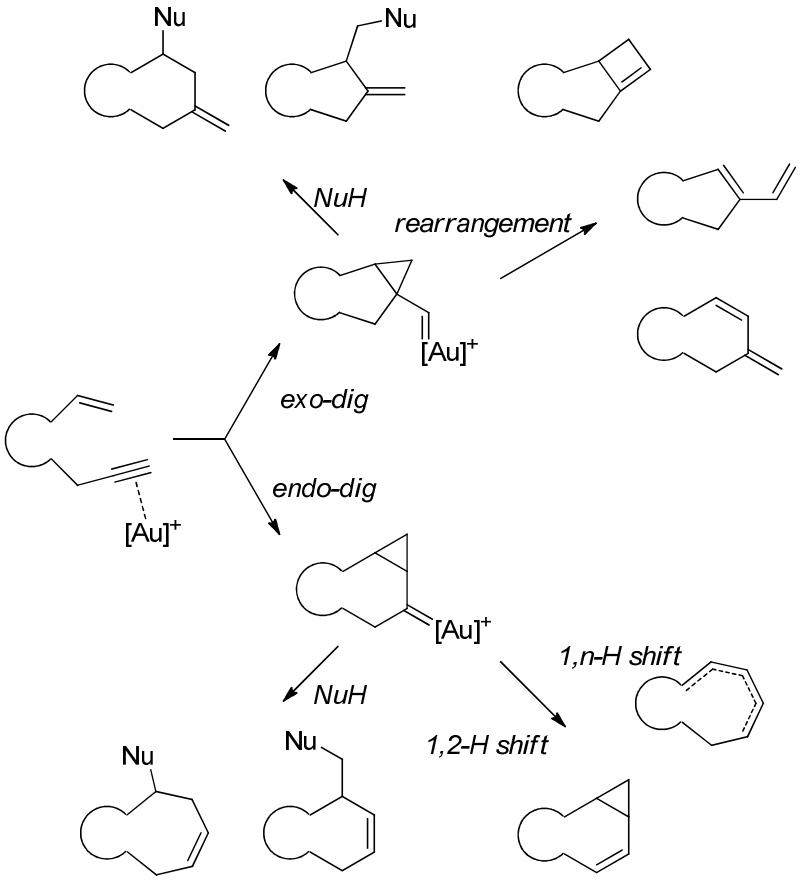


Figure 1.40 – Different pathways for cycloisomerization of enynes

❖ *Endo-dig* cyclization :

Typical substrates undergoing *endo-dig* cyclization are 1,5-enynes. The resulting *endo*cyclic carbenes can be trapped by nucleophiles in an intermolecular (Figure 1.41, eq. 1)[73] or an intramolecular fashion (eq. 2).[74]

Depending on the substrate and the nucleophile, different bonds of the cyclopropyl moiety can be cleaved, which can sometimes lead to ring expansion (eq. 2).

[73] Buzas, A.K.; Istrate, F.M.; Gagosz, F. *Angew. Chem. Int. Ed.* **2007**, *46*, 1141.
[74] Zhang, L.; Kozmin, S.A. *J. Am. Chem. Soc.* **2005**, *127*, 6962.

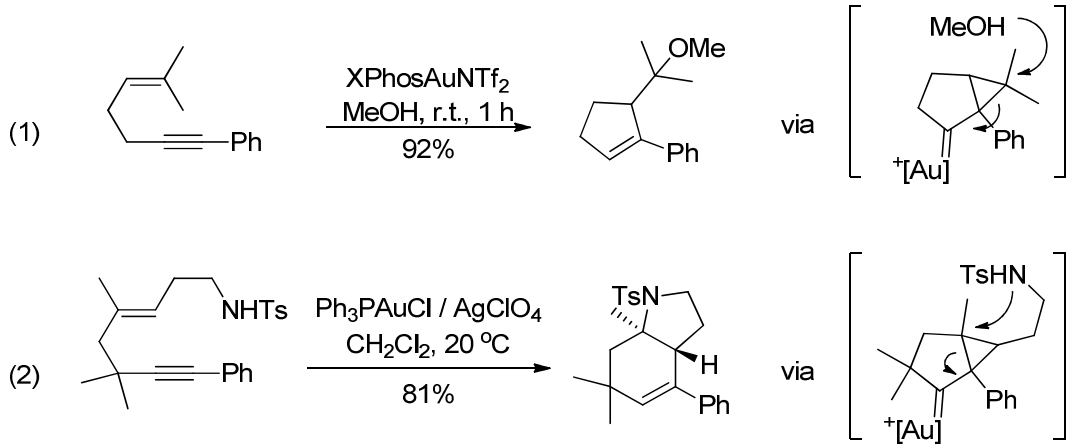


Figure 1.41 – Example of cycloisomerization involving an *endo*cyclic gold carbene in the presence of a nucleophile

In the absence of a nucleophile, the *endo*cyclic carbene intermediate can undergo various rearrangements such as 1,2-group shift (Figure 1.42, eq. 1,2)[75,76] or 1,n-hydride shift (eq. 3).[77]

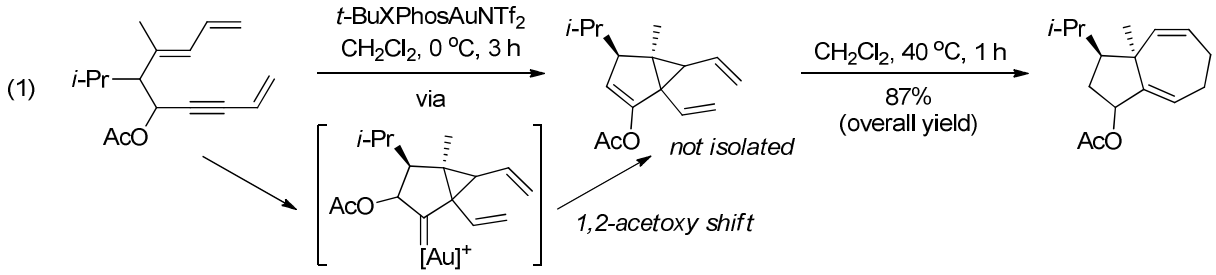


Figure 1.42 – Example of cycloisomerization involving an *endo*cyclic gold carbene in the absence of nucleophile

[75] Cao, Z.; Gagosz, F. *Angew. Chem. Int. Ed.* **2013**, *52*, 1.
[76] Chen, G.Q.; Fang, W.; Wei, Y.; Tang, X.Y.; Shi, M. ***Chem. Sci.*** **2016**, ***7***, 4318.
[77] Comer, E.; Rohan, E.; Deng, L.; Porco, J.A. *Org. Lett.* **2007**, *9*, 2123.

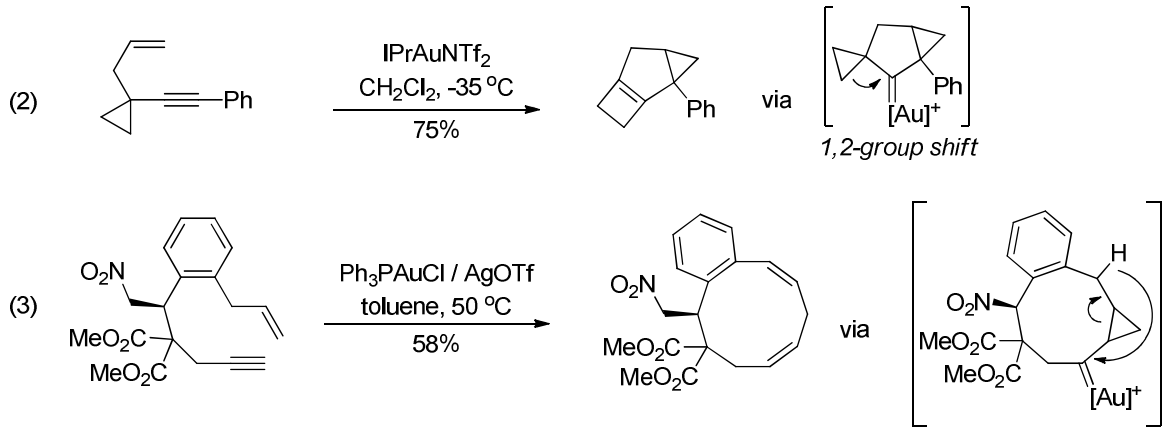


Figure 1.42bis – Example of cycloisomerization involving an *endo*cyclic gold carbene in the absence of nucleophile

❖ *Exo-dig* cyclization :

Typical substrates undergoing *exo-dig* cyclization are 1,6-enynes. The resulting *exo*cyclic carbenes can be trapped by nucleophiles in an intermolecular (Figure 1.43, eq. 1,3,4)[78,79,80] or an intramolecular fashion (eq. 2,5).[81]

Here again, depending on the nature of the substrate and the nucleophile, different bond of the cyclopropyl moiety can be cleaved, which can sometimes lead to ring expansion (eq. 3).

Besides, carbene trapping with reagents such as diphenyl sulfoxide can also be used for oxidative trapping of the carbene intermediates (eq. 4).

Last but not least, the carbene intermediates can be trapped by alkenes and evolve *via* a second cyclopropanation process (eq. 5).

[78] Amjis, C.H.M.; Lopez-Carillo, V.; Raducan, M.; Perez-Galan, P.; Echavarren, A.M. *J. Org. Chem.* **2008**, *73*, 7721.
[79] Leseurre, L.; Toullec, P.Y; Genet, J.P.; Michelet, V. *Org. Lett.* **2007**, *9*, 4049.
[80] Witham, C.A.; Mauleon, P.; Shapiro, N.D.; Sherry, B.D.; Toste, F.D. *J. Am. Chem. Soc.* **2007**, *129*, 5838.
[81] Nieto-Oberhuber, C.; Lopez, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178.

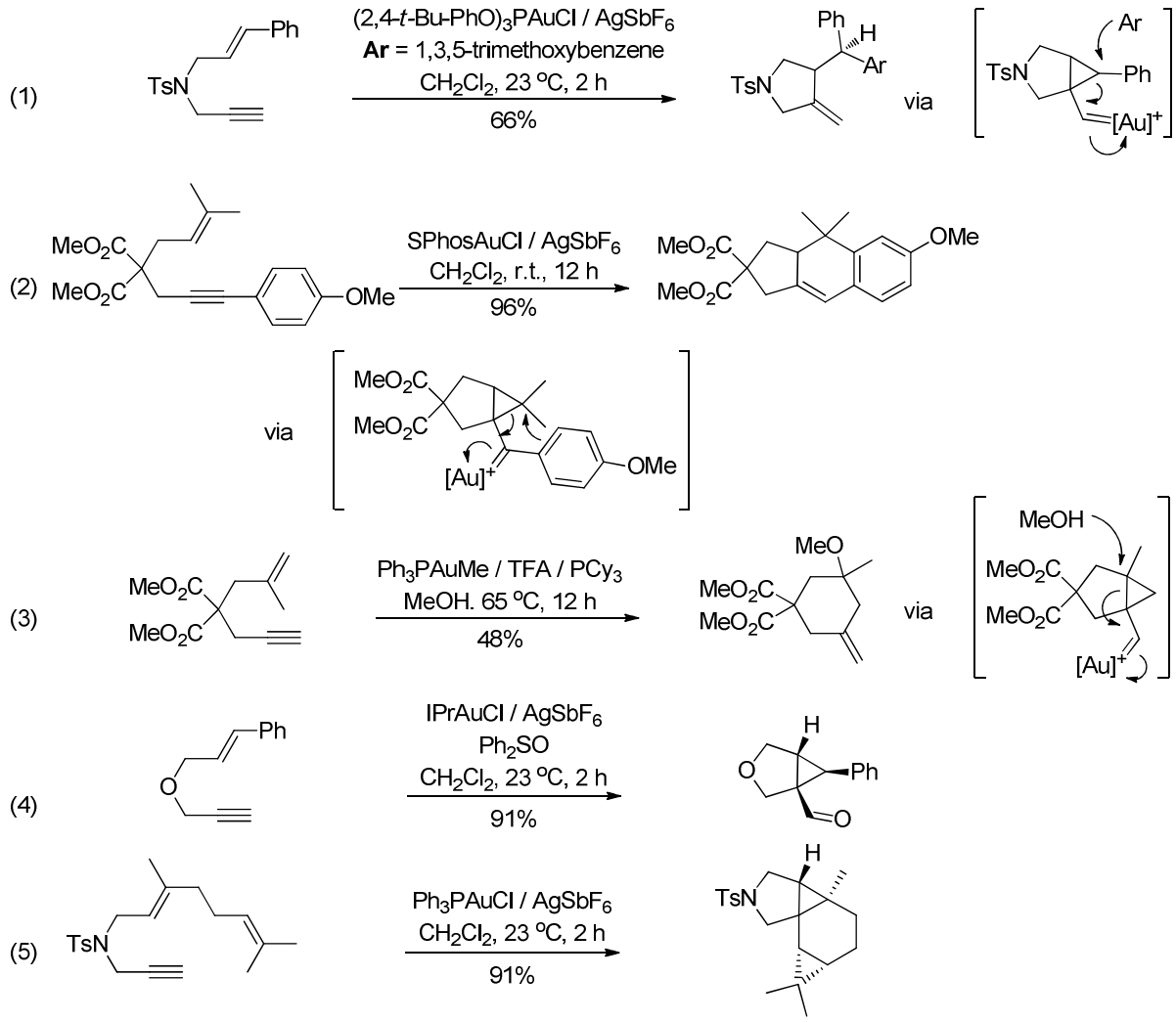


Figure 1.43 – Example of cycloisomerization involving an *exo*cyclic gold carbene in the presence of a nucleophile

In the absence of a nucleophile, the *exo*cyclic carbene intermediate can evolve following different types of rearrangements. Most of the evolution prospects of the carbenes start with a concomitant ring expansion of the cyclopropyl moiety and a 1,2-group shift onto the carbene centers. The resulting gold intermediates can then produce cyclobutenes (Figure 1.44, eq. 1)[82] which can subsequently undergo ring opening to provide 1,3-dienes (eq. 3).[83]

[82] Odabachian, Y.; Gagosz, F. *Adv. Synth. Catal.* **2009**, *351*, 379.
See also : Nieto-Oberhuber, C.; Lopez, S.; Munoz, M.P.; Cardenas, D.J.; Bunuel, E.; Nevado, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6146.
[83] Cabello, N.; Jimenez-Nunez, E.; Bunuel, E.; Cardenas, D.J.; Echavarren, A. M. *Eur. J. Org. Chem.* **2007**, 4217.

Of course other evolution pathways are possible, such as a ring opening of the cyclopropyl ring, thus leading to 1,4-dienes (eq. 2).[84]

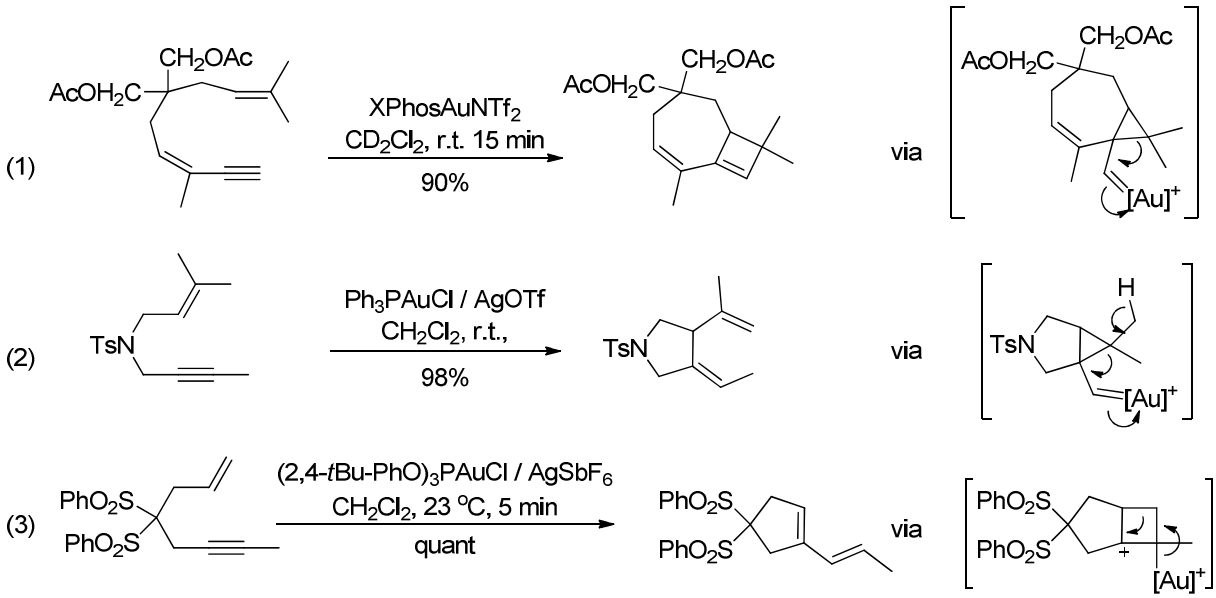


Figure 1.44 – Example of cycloisomerization involving an *endo*cyclic gold carbene in the absence of nucleophile

The general rules previously described for the cycloisomerization of enynes introduced previously are mainly valid for the case of unactivated alkenes and alkynes. In the case of activated insaturations, the reactivity may vary according to the nature of the substrates.

For instance, enynes possessing an activated alkene such as an enol ether may firstly undergo a Claisen rearrangement instead of a cycloisomerization (Figure 1.45, eq. 1).[85]

Enynes possessing an activated alkyne such as a propargyl ester may firstly undergo a 1,2-acyloxy shift instead of a cycloisomerization (eq. 2).[86]

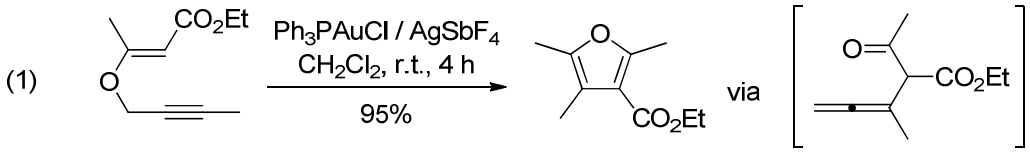


Figure 1.45 – Gold-catalyzed cycloisomerization of activated enynes

[84] Lee, I.; Kim, S. M.; Kim, S. Y.; Chung, Y. K. *Synlett* **2006**, 2256.
[85] Rao, W.; Sally, Berry, S.N.; Chan, P.W.H. *Chem. Eur. J.* **2014**, *20*, 13174.
[86] Suhre, M.H.; Reif, M.; Kirsch, S.F. *Org. Lett.* **2005**, *7*, 3925.

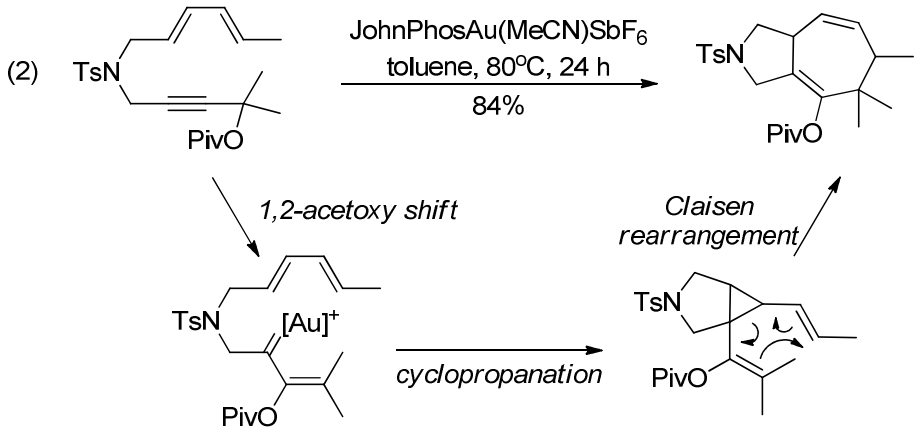


Figure 1.45bis – Gold-catalyzed cycloisomerization of activated enynes

It is also worth noting that gold-catalyzed cycloisomerizations can also be performed on diynes (Figure 1.46, eq. 1),[87] allenenes (eq. 2)[88] or dienes (eq. 3).[89] Representative examples are given below.

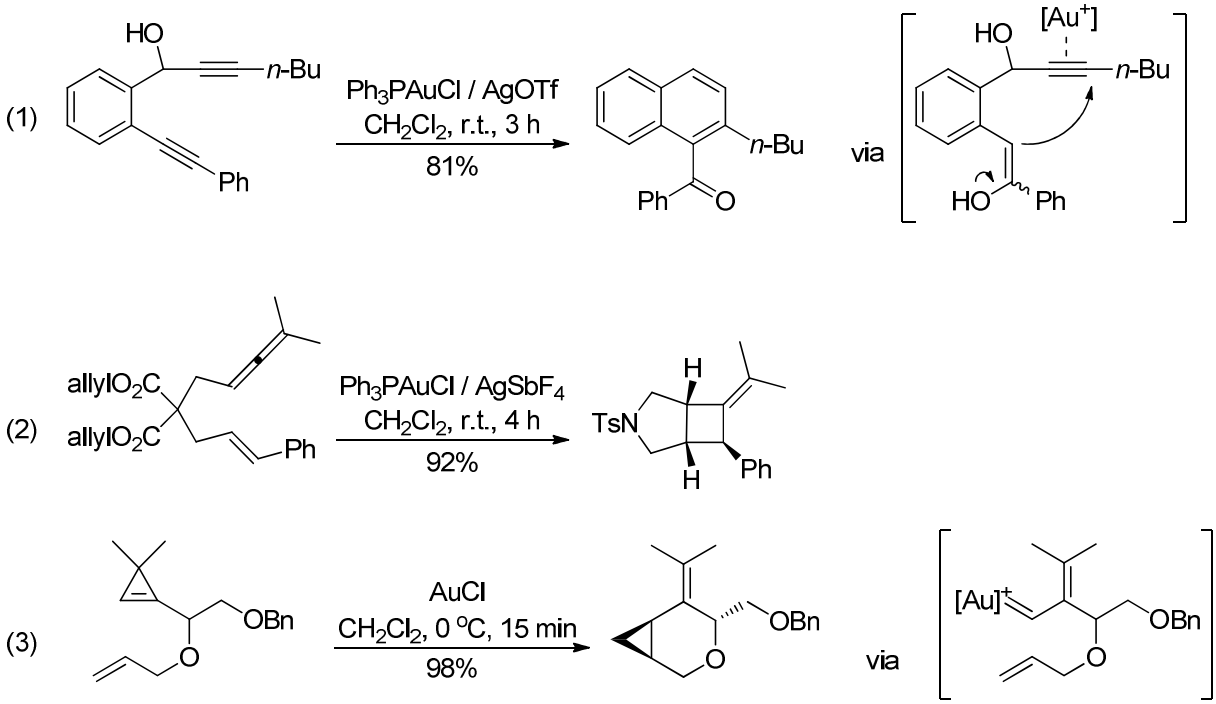


Figure 1.46 – Gold-catalyzed cycloisomerization on other poly unsaturated substrates

[87] Lian, J.L.; Liuchem, R.S. *Chem. Commun*. **2007**, 1337.
[88] Luzung, M.R.; Mauleon, P.; Toste F.D. *J. Am. Chem. Soc.* **2011**, *133*, 5500.
[89] Miege, F.; Meyer, C.; Cossy, J. *Org. Lett.* **2010**, *12*, 4144.

1.4 Gold catalysis in total synthesis

Shortly after the beginning of the gold rush in synthetic organic chemistry, the huge catalytic potential of gold was quickly called upon in total synthesis.[90] This section will display one example of application in total synthesis for each of the main reactions previously introduced.

For instance, an elegant synthesis of (+)-terreusinone was reported by Sperry and coworkers in 2012.[91] The implemented strategy consisted in two simultaneous gold-catalyzed heterocyclizations with the 5-*endo* addition of free amines onto alkynes.

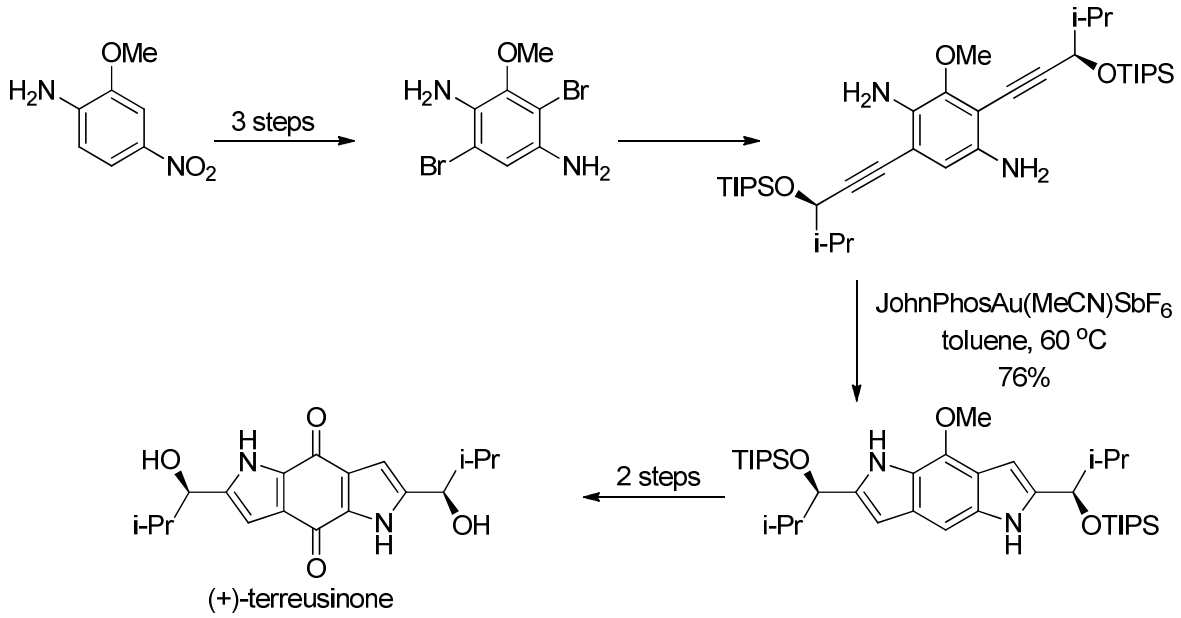


Figure 1.47 – Example of gold-catalyzed heterocyclization
Synthesis of (+)-terreusinone

The synthesis of sesquicarene reported by Furstner *et al.* in 2006 is an other example of gold-catalyzed reaction applied to total synthesis. [92] The key step of this strategy relies on a gold-catalyzed 1,2-acyloxy migration of a propargyl acetate, followed by the cyclopropanation of the resulting carbene with an internal alkene.

[90] Pflasterer, D.; Hashmi, A.S.K. *Chem. Soc. Rev.* **2016**, *45*, 1331.
[91] Wang, C.; Sperry, J. *Synlett*, **2012**, 1824.
[92] Hannen, P.; Furstner, A. *Chem. Eur. J.* **2006**, *12*, 3006.

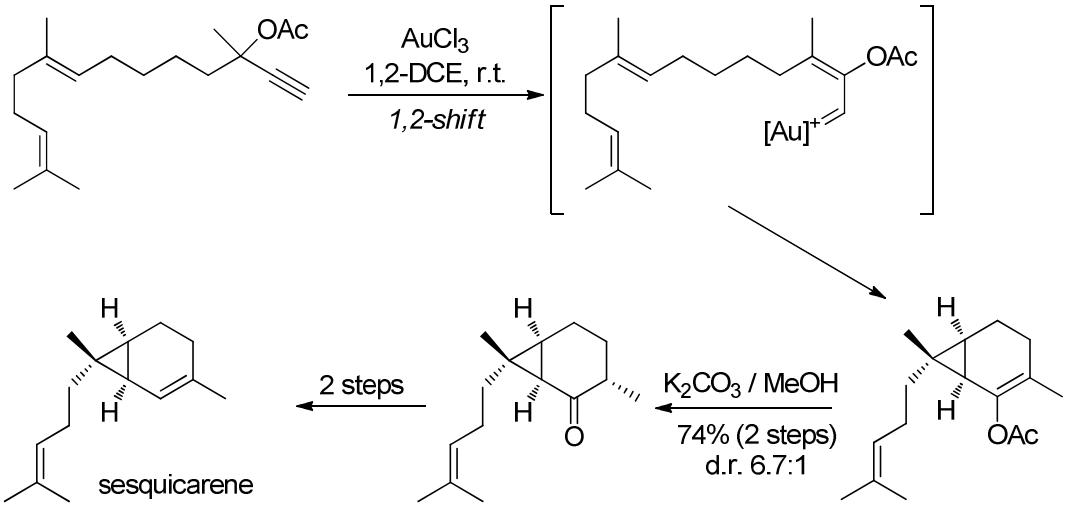


Figure 1.48 - Example of gold-catalyzed acyloxy migration -Synthesis of sesquicarene

The following synthesis of (±)-kumausallene was reported by Tae and coworkers in 2013. [93] In this synthesis, the strategy called upon involves the use of a pyridine *N*-oxide as an oxene precursor for a gold-catalyzed nucleophilic addition onto an alkyne. The resulting gold carbene is then trapped by the intramolecular addition of the oxygen atom of an allylic ether, providing a gold intermediate which spontaneously rearranges.

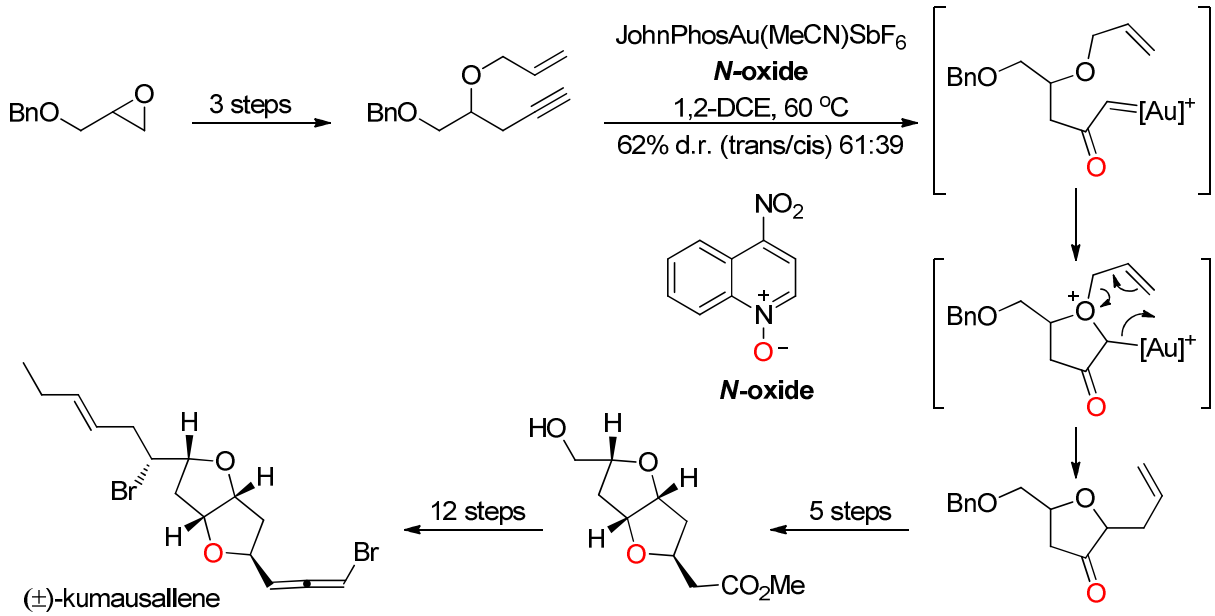


Figure 1.49 - Example of gold-catalyzed addition of oxene precursor
Synthesis of (±)-kumausallene

[93] Han, M.; Bae, J.; Choi, J.; Tae, J. *Synlett*, **2013**, 2077.

The group of Toste reported in 2006 the synthesis of (±)-gemerone C.[94] In this work, a cyclization is performed by a gold-catalyzed intramolecular addition of a silyl enol ether on to an alkyne in a 6-*exo* manner.

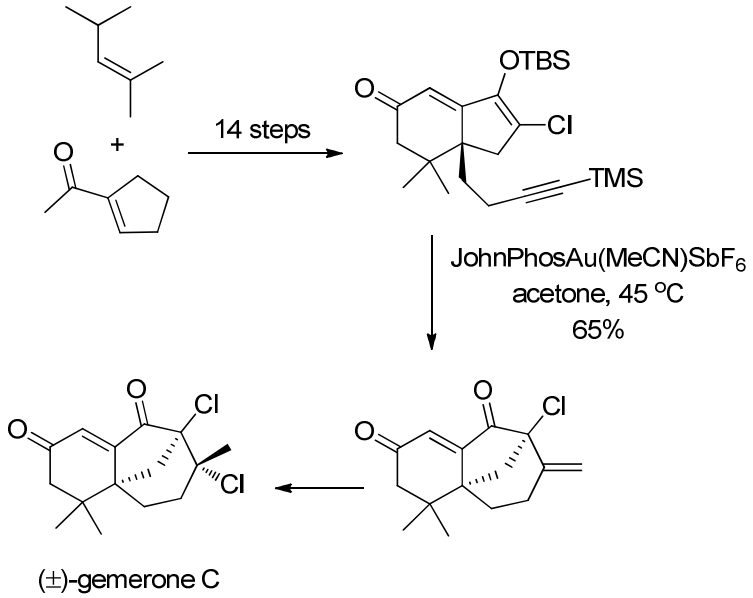
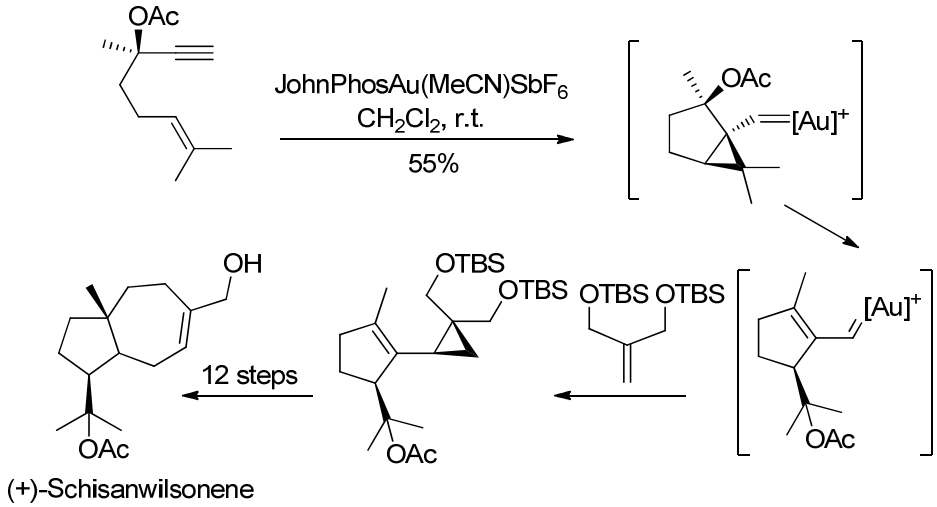


Figure 1.50 - Example of gold-catalyzed addition of carbon nucleophile
Synthesis of (±)-gemerone C

Last but not least, Echavarren *et al.* reported an elegant total synthesis of (+)-Schisanwilsonene.[95] The key step of this sequence is a 5-*exo* cycloisomerization of an enyne. During a first rearrangement, a spontaneous 1,3-acyloxy migration happens with concomitant ring opening of the cyclopropyl moiety. Thereafter, the *exo*cyclic carbene is trapped by an external alkene, thus undergoing cyclopropanation.

[94] 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.
[95] Gaydou, M.; Miller,R. E.; Delpont, N.; Ceccon, J.; Echavarren, A.M. *Angew. Chem., Int. Ed.*, **2013**, *52*, 6396.



(+)-Schisanwilsonene

Figure 1.51 - Example of gold-catalyzed cycloisomerization of enyne
Synthesis of (+)-Schisanwilsonene

1.5 Conclusion

Although being disregarded by the synthetic organic chemist community for decades, gold has finally made its way to the forefront. Gold was proved to have an outstanding catalytic potential, which turns its price into a minor issue. The variety of applications of gold in organic chemistry is now very impressive, with a range going from heterogeneous catalysis, use of gold nanoparticles and clusters, up to homogeneous catalysis.

More particularly, its unique Lewis-acid properties, granted by rare relativistic effects, made gold a metal of choice for homogeneous electrophilic catalysis. Indeed, gold (I) and gold (III) complexes are powerful catalysts which promote transformations allowing the generation of structural complexity with high selectivity. Nowadays, the number of total synthesis strategies involving gold-catalyzed key steps continuously increases, proving gold's potential and usefulness.

However, many aspect of gold chemistry are still subject to improvement, such as better understanding of the mechanisms ruling these transformations. The development of highly stereoselective gold-catalyzed processes is also one of the hottest topic at stake in gold chemistry.

The following two chapters deal with two applications of gold chemistry : the synthesis of trifluoromethyl allenes and the synthesis of *2H*-1,2-oxazines.

Chapter 2 :

Gold-catalyzed synthesis of trifluoromethyl allenes from propargyl benzyl ethers

This project was conducted under the supervision of Dr. Fabien Gagosz and Dr. Olivier Riant in collaboration with Arnaud Boreux who provided part of the results presented hereafter. The results obtained by the author are marked by an asterisk.

These results were published in :

Boreux, A.; Lonca, G.H.; Riant, O.; Gagosz, F. *Org. Lett.* **2016**, *18*, 5162.

2.1 Introduction to CF_3 allenes

2.1.1 Structure and reactivity of allenes

Allenes are the smallest members of the cumulene family. They possess the smallest number of cumulated carbon-carbon double bonds, followed by butatrienes and pentatetraenes (Figure 2.1).

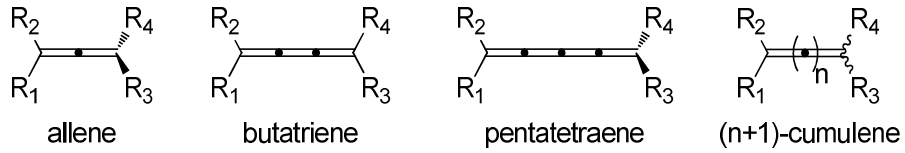


Figure 2.1 – Structures of the different cumulenes

Contrary to alkenes and alkynes, allenes do not possess a planar symmetry. Indeed, the orthogonality of the two consecutive π-systems places the substituents (R_1,R_2) and (R_3,R_4) in perpendicular plans. Therefore, if $R_1 \neq R_2$ and $R_3 \neq R_4$, allenes are chiral compounds (Figure 2.2).

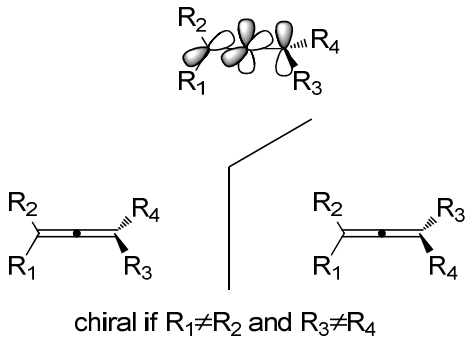


Figure 2.2 – Chirality of allenes

Yet, despite these interesting properties, allenes were ignored for a long period by synthetic organic chemists, mostly because they were presumed to be unstable. But this assumption was proven wrong when allene moieties were found in the structure of natural products. Nowadays, a large range of allenic natural compounds are known, with various type of allenes such as linear allenes, allenic halides, and exocyclic or endocyclic allenes (Figure 2.3).[96]

[96] For a review of allenic natural products, see : Hoffmann-R der, A.; Krause, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 1196.

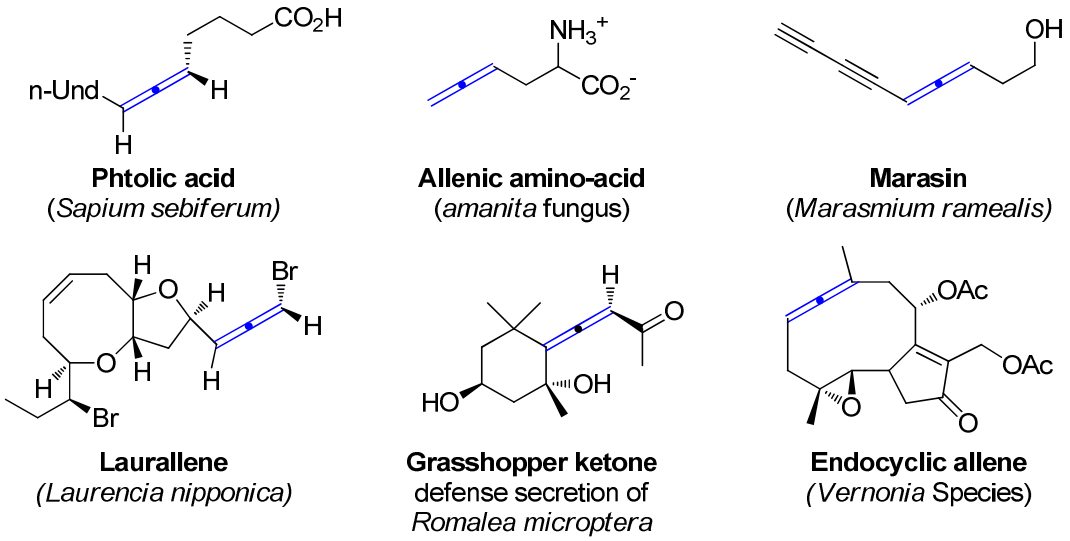


Figure 2.3 – Examples of allenic natural products

With time, a large number of synthetic methods have been developed for the formation of allenes.[97] This infatuation for the chemistry of allenes was motivated partly by their biological activity[98], but above all by their huge synthetic potential. Indeed, allenes are excellent building blocks which can be engaged in a large variety of reactions,[99] including radical reactions, cyclometallations, cycloadditions, epoxidation and palladium-catalyzed difunctionalization (Figure 2.4).

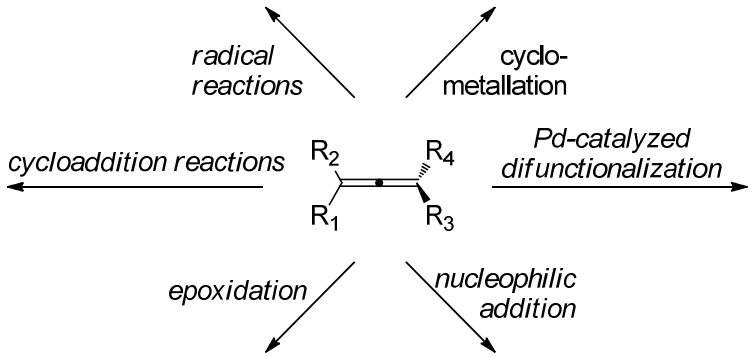


Figure 2.4 – Reactivity of allenes

[97] For reviews on the synthesis of allenes, see : a) Brandsma, L. Synthesis of Acetylenes, Allenes and Cumulenes : Methods and Technics ; b) DeForrest, J.E.; Brummond, K.M. *Synthesis*, **2007**, 795.

[98] a) Landor, S.R. "Naturally Occurring Allenes" in The Chemistry of the Allenes (Ed.: S. R. Landor), Academic Press, London, 1982, 679 ; b) Claesson, A. "Biologically Active Allenes" in The Chemistry of the Allenes (Ed.: S. R. Landor), Academic Press, London, 1982, 709 ; c) Robinson, C.H.; Covey D.F. "Biological Formation and Reactions" in The Chemistry of Ketenes, Allenes and Related Compounds (Ed.: S. Patai), Wiley, Chichester, 1980, 451.

[99] For reviews on the reactivity of allenes, see : a) *Taylor, D.R. Chem. Rev.*, **1967**, *67*, 317 ; b) Ma, S. *Chem. Rev.* **2005,** *105*, 2829.

Although most of these reactions of functionalization involve only one of the C=C bond of the allenes, some reactions involve the three allene carbon atoms, thus marking down a concrete difference between allenes and alkenes. This unique reactivity of allenes is illustrated below with a few applications in total synthesis of natural products.

❖ [3+2] Cycloaddition :

Like alkenes, allenes can be engaged in a large variety of cycloaddition reactions.[100] Among these transformations, phosphine-catalyzed [3+2] cycloadditions are more representative of the unique reactivity of allenes as they stand as the three carbon partner. [101] The other partner can be an aldehyde, an imine or an activated allene. This type of reaction starts with the addition of the phosphine to central carbon atom of the allene, thus generating an allylic anion which can then add onto the partner. The resulting intermediate can then cyclize to produce a phosphine ylide which evolves via a sequence anion transposition and elimination of the phosphine (Figure 2.5).

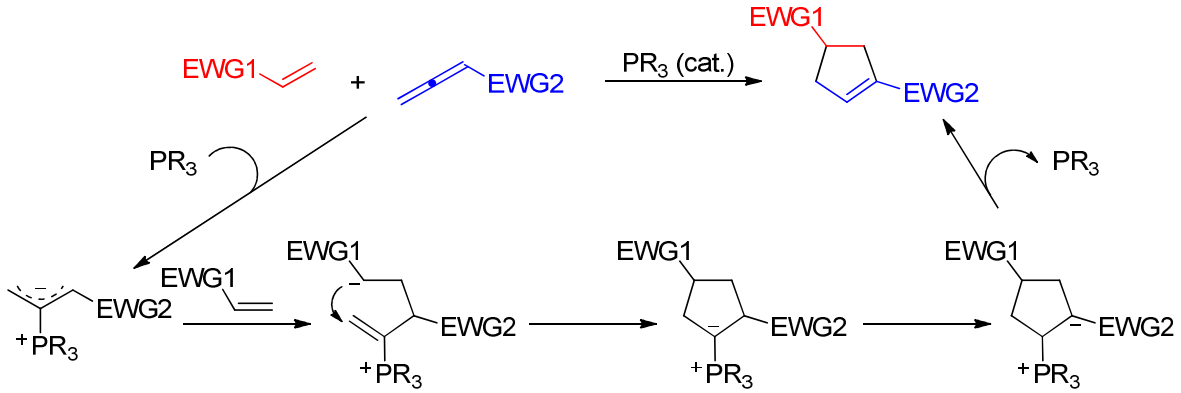


Figure 2.5 – [3+2] cycloadditions of allenes with activated alkenes

[100] For reviews on cycloaddition reactions of allenes, see : a) Kitagaki, S.; Inagaki, F.; Mukai C. *Chem. Soc. Rev.* **2014**, *43*, 2956 ; b) Wang, Z.; Xu, X.; Kwon, O. *Chem. Soc. Rev.* **2014**, *43*, 2927 ; c) Lopez, F.; Mascarenas, J.L. *Chem. Soc. Rev.* **2014**, *43*, 2904.

[101] For examples of [3+2] cycloadditions of allenes, see : a) Du, Y.; Lu, X.; Yu, Y. *J. Org. Chem.* **2002**, *67*, 8901 ; b) Voituriez, A.; Panossian, A.; Fleury,Bregeot, N.; Retailleau, P.; Marinetti, A. *J. Am. Chem. Soc.*, **2008**, *130*, 14030.

This process was ingeniously used by Lu and coworkers in an elegant synthesis of (-)-hinesol (Figure 2.6).[102] In this synthesis, a [3+2] cycloaddition is involved for the generation of the 5-membered spiro cycle moiety of the target with a very efficient 1,2 induction of chirality.

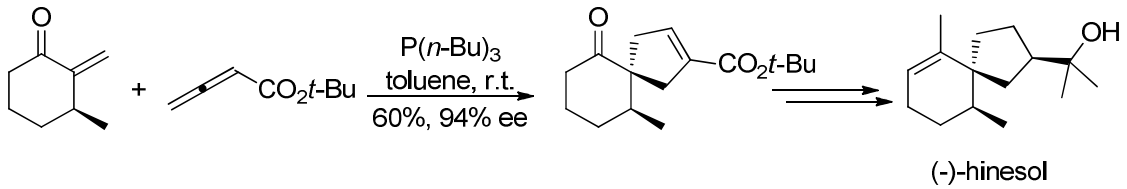


Figure 2.6 – [3+2] cycloadditions of allenes towards the synthesis of (-)-hinesol

❖ Epoxidation :

Like alkenes, allenes can undergo epoxidation (Figure 2.7).[103] A first epoxidation can deliver an allene oxide. This step is usually well controlled and occurs on the more substituted and more electron rich C=C bond with a stereoselectivity controlled by the substituents located on the adjacent C=C bond. Depending on the experimental conditions, epoxidation of the remaining C=C bond can occur to provide a spirodioxide.

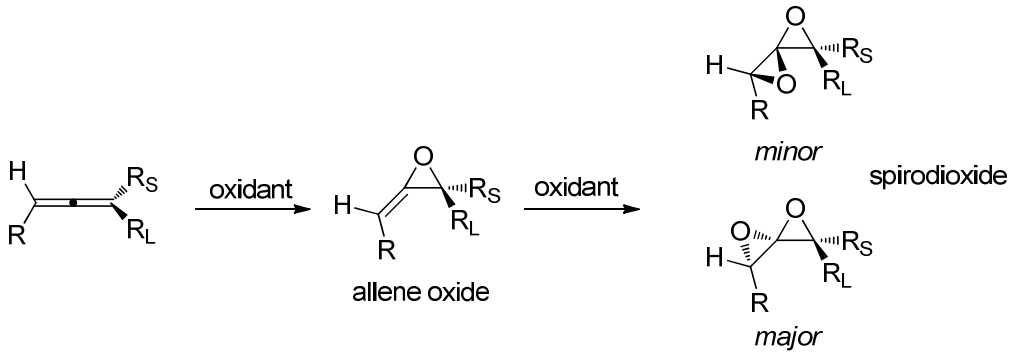


Figure 2.7 – General scheme for epoxidation of allenes

[102] Y. Du, X. Lu, J. Org. Chem. 2003, 68, 6463.
[103] For a review on epoxidation of allenes, see : Adams, C.S.; Weatherly, C.D.; Burke, E.G.; Schomaker, J.M. *Chem. Soc. Rev.* **2014**, *43*, 3136.

Allene oxides and spirodioxides can undergo a subsequent nucleophilic addition to provide ketone derivates (Figure 2.8).[104,105]

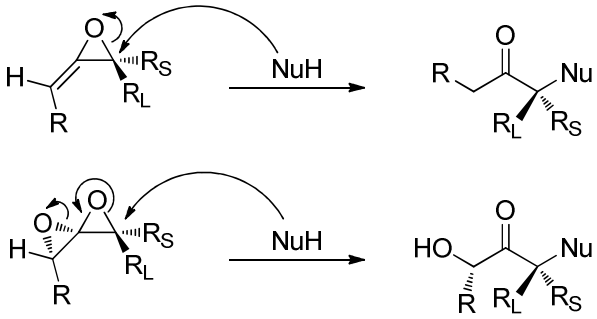


Figure 2.8 – Addition of a nucleophile to allene oxides and spirodioxides

An interesting application of the epoxidation of allenes was reported by Williams and coworkers in 2007 in an elegant synthesis of Psymberin (Figure 2.9).[106] In this synthesis, the key step relies on a di-epoxidation of an optically pure allene substrate. A subsequent intramolecular nucleophilic addition of an alcohol to the resulting spirodioxide provides the 6-member ring motif which is present in the structure of Psymberin.

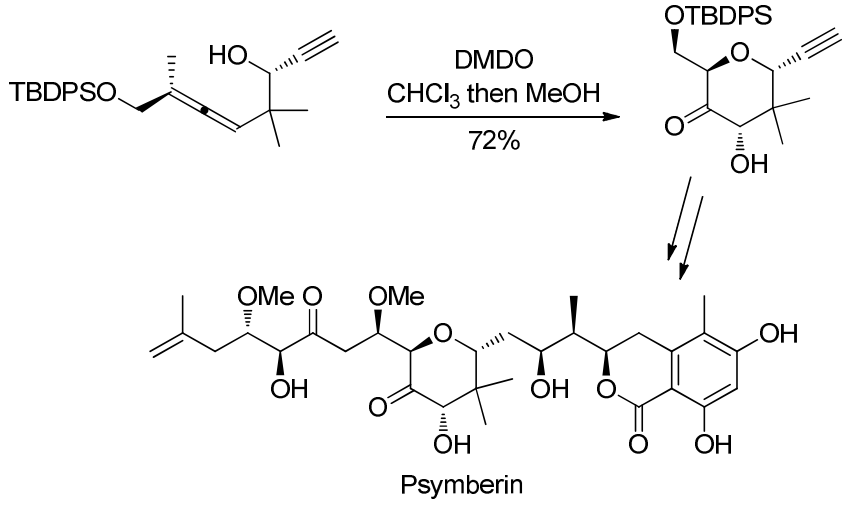


Figure 2.9 – Epoxidation of allenes toward the synthesis of Psymberin

[104] Sakaguchi, S.; Watase, S.; Katayama, Y.; Sakata, Y.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem.* **1994**, *59*, 5681.
[105] Bertrand, M.; Dulcere, J.P.; Gil, G.; Grimaldi, J.; Sylvestre-Panthet, P. *Tetrahedron Lett.*, **1976**, *17*, 3305.
[106] Shangguan, N.; Kiren, S.; Williams, L.J. *Org. Lett.* **2007**, *9*, 1093.

❖ Use of organometallic allenes as propargyl precursors :

Besides, allenic fragments possessing metallic residues are also surrogates of propargylic anions (Figure 2.10).

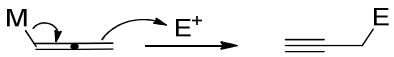


Figure 2.10 – Allenes as surrogates of propargylic anions

An allenic organozinc reagent was used in the synthesis of (+)-6-epi-castanospermine reported by Perez-Luna and coworkers in 2010 (Figure 2.11).[107] In this case, the allenic organozinc reagent adds to an optically pur imine with a 1,2-asymetric induction to provide a homopropargylic amine, which is a precursor to (+)-6-epi-castanospermine.

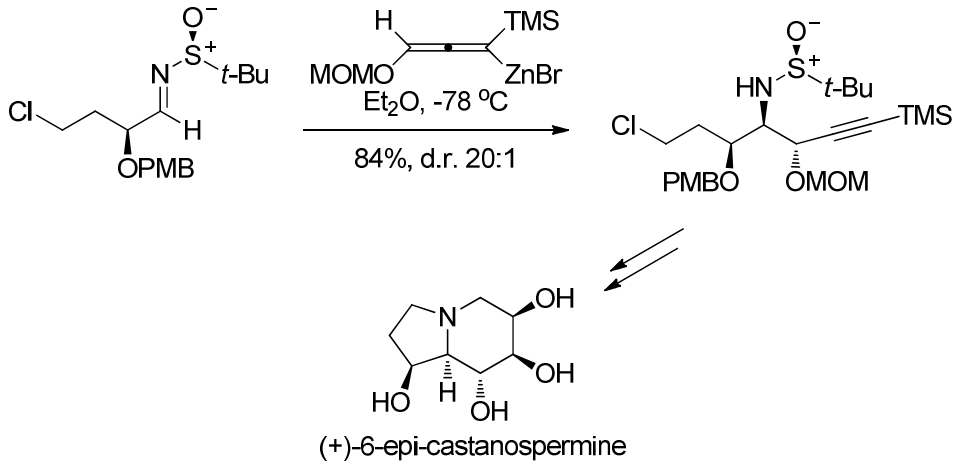


Figure 2.11 – Use of allenic organometallic in total synthesis

All in all, allenes are very powerful building blocks. The potential conversion of the axial chirality of allenes to a central chirality represents a great interest in asymmetric total synthesis. Moreover, additionally to the rich chemistry of alkenes which can be adapted to allenes, the latter also possess unique reactivity and can be used in [3+2] cycloaddition reactions, double epoxidation, an as surrogates of propargylic anions. As a result, allenes are often used to as building blocks to introduce important functional moieties. Among these functional groups, the trifluoromethyl moiety is becoming more and more popular, for reasons that will be introduced in the next section.

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[107] Louvel, J.; Botuha, C.; Chemla, F.; Demont, E.; Ferreira, F.; Perez-Luna, A. *Eur. J. Org. Chem.* **2010**, 2921.

2.1.2 General introduction to fluorine's chemistry and to the CF_3 moiety

Fluorine is the thirteenth most abundant element in Earth's crust, twice more abundant than chlorine and hundreds of time more abundant than bromine and iodine. However, fluorinated compounds are the least abundant of organohalides in nature, with, to date, only twenty-one known biosynthesized natural compounds containing fluorine as compared to the thousands containing chlorine or bromine.[108] The reason of this low abundance originates in the insolubility of most fluorine natural sources, which hampered its assimilation by bioorganisms. Therefore, while nature developed haloperoxidase enzymes to catalyze chlorination or bromination reactions, no fluoroperoxidase is known.

Increasing interest for fluorine started in 1957 with the development of the first fluorine containing drug. Since then, over a hundred fifty more fluorinated drugs have been released on the market, which accounts for about 20% of all pharmaceutical compounds in 2006.[109] The reason of this interest for fluorine in pharmaceutical drugs is its capacity to enhance some essential properties of drugs such as lipophilicity, bioavailability, metabolic stability and binding affinity.[110]

The importance and the occurrence of fluorinated compounds have also boomed in the agrochemical industry. Indeed, many pesticides, fungicides and herbicides contain fluorinated moities.[111] In 2002, 34% of the total amount of agrochemical compounds released on the market were fluorinated.[112]

Additionally, the non-natural isotope ^{18}F is the most commonly used positron-emitting isotope for molecular positron emission tomography[113] (PET) imaging in oncology. For information, millions of PET scans using 2-[^{18}F]-fluoro-2-deoxyglucose are performed every year.

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[108] a) Herz, W.; Kirby, G. W.; Moore, R. E.; Steglich, W.; Tamm, C. *Progress in the Chemistry of Organic Natural Products* **1196***, 68*, 1 ; b) Kinghord, A. D.; Falk, H.; Kobayashi, J. *Progress in the Chemistry of Organic Natural Products* **2009**, *91,* 1.

[109] Diagram borrowed from : Hagmann, W.K. *J. Med. Chem.* **2008***, 51,* 4359.

[110] For reviews on fluorine in medicinal chemistry, see : a) Ismail, F.M.D *Journal of Fluorine Chemistry*, **2002**, *118*, 27 ; b) Kirk, K.L. *Current Topics in Medicinal Chemistry,* **2006***, 6,* 1447 ; c) Muller, K.; Faeh, C.; Diederich, F.*Science*, **2007**, *317*, 1881 ; d) Begue, J.P.; Bonnet-Delpon, D. *Journal of Fluorine Chemistry* **2006**, *127*, 992 ; e) Isanbor, C.; O'Hagan, D. *Journal of Fluorine Chemistry* **2006**, *127*, 303.

[111] Jeschke, P. *ChemBioChem* **2004**, *5*, 570.

[112] Diagram borrowed from : Hall, R.G.; Maienfisch, P. *Chimia*, **2004**, *58*, 93.

[113] For examples on PET imaging, see : a) Ametamey, S. M., Honer, M. & Schubiger, P. A. *Chem. Rev.* **2008**, *108*, 1501 ; b) Patterson, J. C.; Mosley, M. L. *Mol. Imaging Biol.* **2005**, *7*, 197 ; c) Bolton, R. *J. Labelled Compd. Radiopharm.* **2002**, *45*, 485 ; d) Littich, R.; Scott, P.J.H. *Angew. Chem. Int. Ed.* **2012**, *51*, 1106.

The huge potential of fluorine has also been applied in materials sciences. For instance, the incorporation of fluorine in polymers brings a range of unique surface properties such as low surface tension, low electrostatic loading, chemical inertness and low friction coefficient.[114] A daily life example can be found with the polytetrafluoroethylene polymer, also known as Teflon®. The fluorine atoms are responsible for a low coefficient of friction and a low hydrophilicity, which are properties that have made it valuable as a non-sticking coating for cookwares. Besides, very interesting applications were discovered for perfluorinated poly(phenylenevinylene) and perfluorinated poly(phenyleneethynylene) as semiconductors in electronics and optoelectronics.[115]

It is important to underline that the electron withdrawing σ-inductive effect and its impact on the pKa of the neighboring functional groups is the most important aspect of fluorine's application. Therefore, the logical idea is to maximize this effect with the incorporation of several fluorine atoms. As a result, a particular attention has been paid to the trifluoromethyl group (CF_3). In addition to maximizing the σ-inductive effect thanks to its three fluorine atoms, the CF_3 group present a strong advantage. Indeed, while fluorination of a compound lies in the formation of a carbon-fluorine bond, the incorporation of a trifluoromethyl moiety is achieved by the formation of a carbon-carbon bond, which is sometimes easier. Therefore, the trifluoromethyl group has quickly become a very important tool in enhancement of pharmaceuticals and agrochemicals as illustrated by the following selected examples (Figure 2.12).

[114] For examples of fluorine chemistry in polymers, see : a) Schlögl, S.; Kramer, R.; Lenko, D.; Schröttner, H.; Schaller, R.; Holzner, A.; Kern, W. *European Polymer Journal* **2011**, *47*, 2321 ; b) Anton, D. *Adv. Mater.* **1998**, *10*, 1197 ; c) Kassis, C.M.; Steehler, J.K.; Betts, D.E.; Guan, Z.; Romack, T.J.; DeSimone, J.M.; Linton, R.W. *Macromolecules* **1996,** *29,* 3247 ; d) Hung, M. H., Farnham, W. B., Feiring, A. E. & Rozen, S. *Fluoropolymers Synthesis*, **1999**, *1*, 51.

[115] a) Badubri, F.; Farinola, G.M.; Naso, F.; Ragni, R. *Chem. Commun*. **2007**, 1003 ; b) Li, Y. *Acc. Chem. Res.* **2012**, *45*, 723.

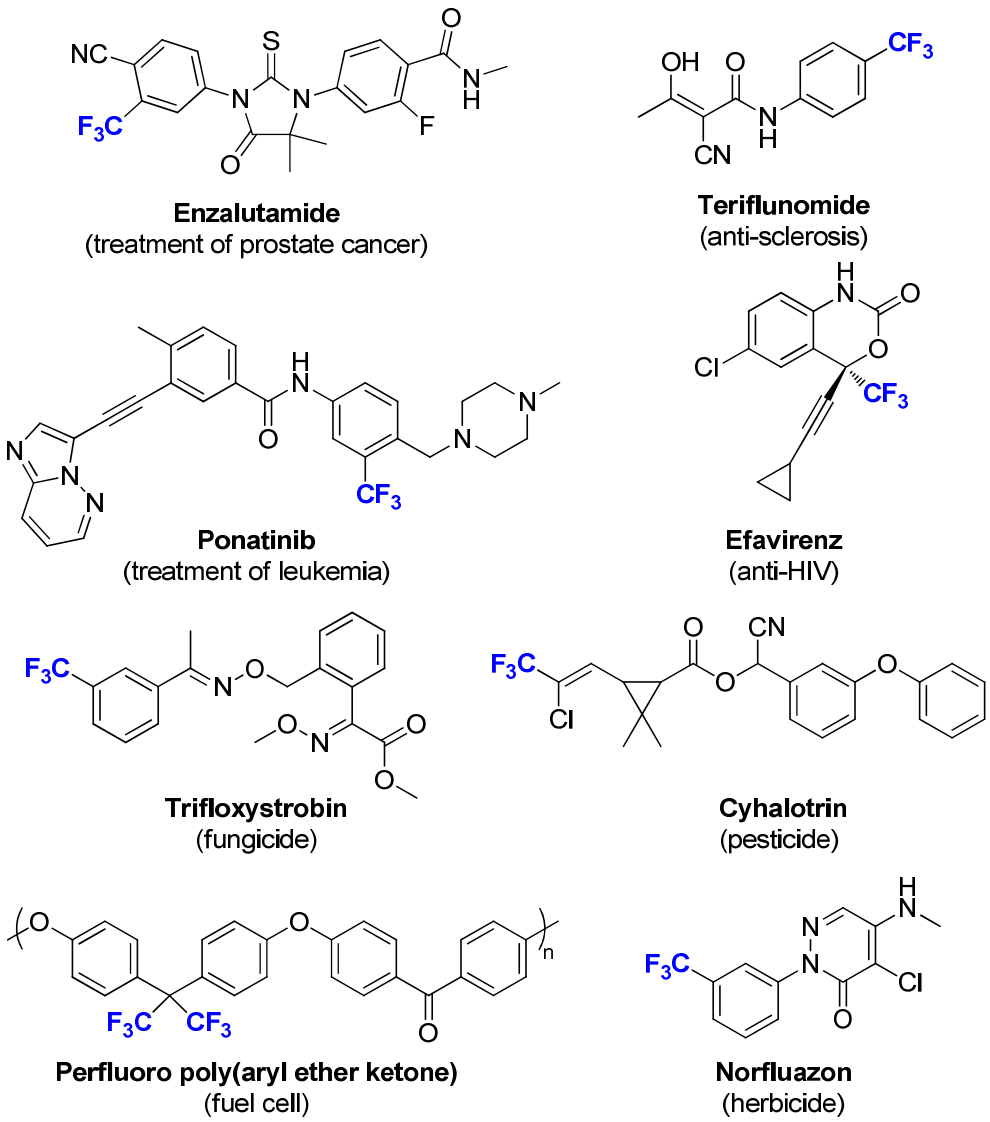


Figure 2.12 – Examples of trifluoromethyl containing pharmaceuticals agrochemicals an materials

2.1.3 Background on the synthesis of trifluoromethyl allenes

Considering the huge synthetic potential of allenes as building blocks and the outstanding properties of the trifluoromethyl group in pharmaceutical, agrochemical and material industries,[116] the synthesis of trifluoromethyl allenes has naturally attracted some attention from synthetic organic chemists (Figure 2.13).

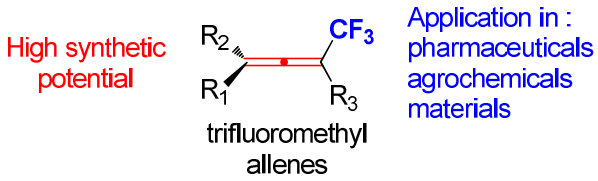


Figure 2.13 – Double interest of trifluoromethyl allenes

Today, an important variety of methods are available to prepare trifluoromethyl allenes, with strategies including elimination on trifluoromethyl alkenes, isomerization of trifluoromethyl alkynes, S_{N2}' substitution on trifluoromethyl alkynes bearing a propargylic leaving group, and nucleophilic trifluoromethylation of alkynes possessing a propargylic leaving group (Figure 2.14).

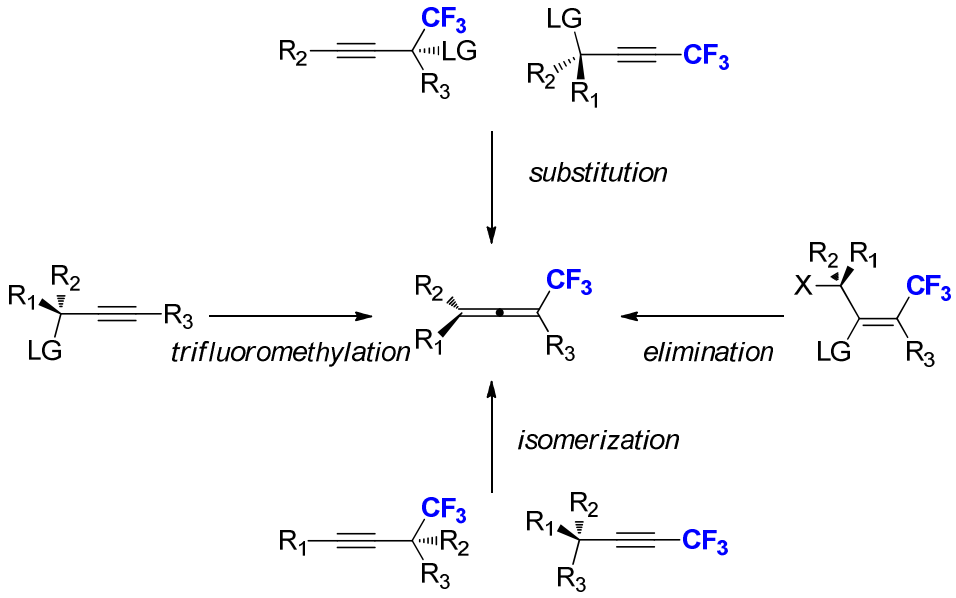


Figure 2.14 – Different strategies for the synthesis of trifluoromethyl allenes

[116] See chapter 2 for a general introduction of the chemistry of fluorine.

❖ Trifluoromethylation of alkynes bearing a propargylic leaving group :

A well-known method to synthesize allenes relies on the use of a S_{N2}' nucleophilic substitution performed on alkyne substrates bearing a propargylic leaving group (Figure 2.15).

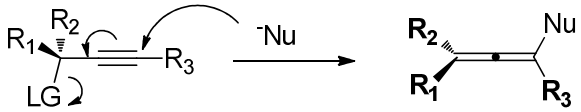


Figure 2.15 – Formation of allenes by S_{N2}' substitution

A first strategy to prepare trifluoromethyl allenes consists of introducing the trifluoromethyl moiety at the last stage of the synthesis by using a nucleophilic trifluoromethyl species as the nucleophile (Nu=CF_3 on Figure 2.15). A series of methods have been developed to generate nucleophilic $CuCF_3$ species. These organometallic compounds are able to perform S_{N2}' type reactions on alkyne substrate bearing a propargylic leaving group, thus generating the corresponding trifluoromethyl allene.

Gu and coworkers developed a method relying on the *in-situ* generation of $CuCF_3$ from trifluoromethyl diaryl sulfonium salts in the presence of copper (Figure 2.16, eq. 1).[117] However, *in-situ* generated $CuCF_3$ species are not well-defined, which raises some selectivity issues.[118]

Thefore, other groups, like Szabo's, preferred to resort to the bench stable and well-defined $(PPh_3)_3CuCF_3$, derived from the Ruppert-Prakash reagent $TMSCF_3$[119] (eq. 2).[120] Additionally to the better selectivity, this method allows for the use of milder reaction conditions.

Another possibility to generate the $CuCF_3$ species relies on the decarboxylation of bromodifluoroacetate species in the presence of a fluoride source (eq. 3).[121] The reaction is initiated by the formation of a nucleophilic $CuCF_3$ complex from sodium bromodifluoroacetate, potassium fluoride and copper (I) iodide. Then, the $CuCF_3$ complex attacks the propargyl bromodifluoroacetate substrate following a S_{N2}' type substitution to give the CF_3 allene product

[117] Ji, Y.L.; Kong, J.J.; Lin, J.H.; Xiao, J.C.; Gu, Y.C. ***Org. Biomol. Chem.*** **2014**, ***12***, 2903.
[118] See section 4.1.1 for more details about the instability of trifluoromethyl organometallic reagents.
[119] Tomashenko, O.A.; Escudero-Adan, E.C.; Martinez Belmonte, M.; Grushin, V.V.; *Angew. Chem. Int. Ed.* **2011**, *50*, 1.
[120] Zhao, T.S.N.; Szabo, K.J. *Org. Lett.* **2012**, *14*, 3966.
[121] Ambler, B.R.; Peddi, S.; Altman, R.A. *Org. Lett.* **2015**, *17*, 2506.

and a copper (I) bromodifluoroacetate complex which, after action of potassium fluoride, regenerate the $CuCF_3$ catalyst.

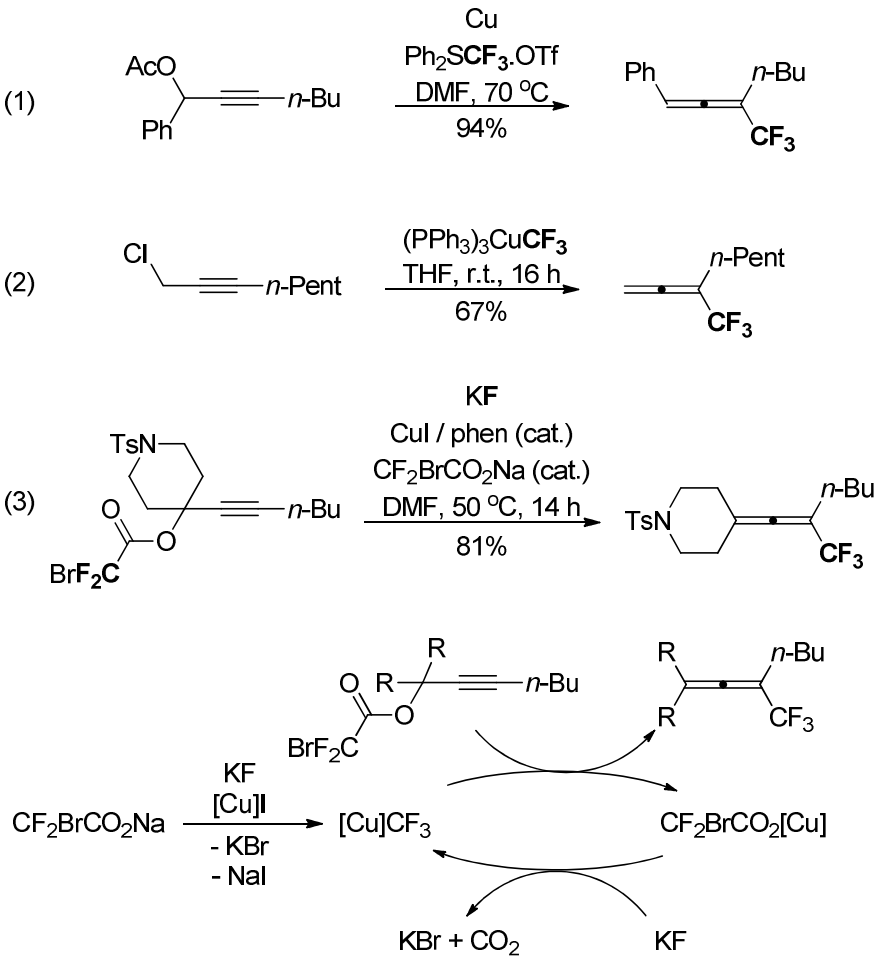


Figure 2.16 – Examples of synthesis of trifluoromethyl allenes by S_{N2}' trifluoromethylation

Yet, introduction of the trifluoromethyl moiety at a late stage is not always preferable. Indeed, the trifluoromethylation reagents are often quite expensive. Plus, these methods present the drawback of having a recurrent trifluoromethyl propargyl byproduct (trifluoromethyl propargyl compounds) which are very difficult to separate from the desired product.

Another alternative approach consists of starting from substrates which already possess a trifluoromethyl group.

❖ Substitution on trifluoromethyl alkynes bearing a propargylic leaving group :

In an analogy with the methods previously described, organometallic reagents can perform S_{N2}' nucleophilic substitutions on trifluoromethylated alkynes bearing a leaving group at the propargyl position.

The trifluoromethyl moiety can be located on the terminal position of the alkyne (Figure 2.17, eq. 1,2)[122,123] or at the propargyl position (eq. 3)[124] and the nucleophiles can be organometallic reagents or simple halide ions as in an Appel type reaction (eq. 2). Several selected examples of this type of transformations are given below.

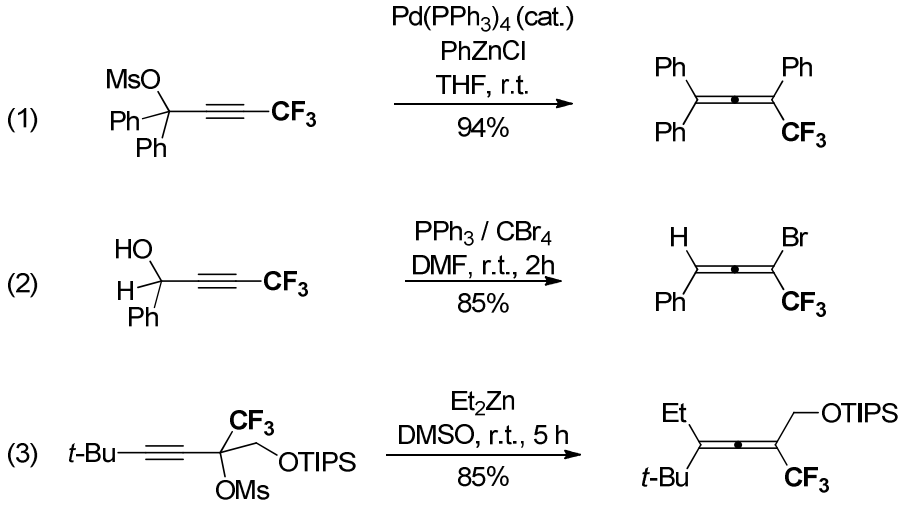


Figure 2.17 – Examples of synthesis of trifluoromethyl allenes by S_{N2}' substitution on trifluoromethyl alkynes

However, here again, the direct substitution of the leaving group by the nucleophile may happen and lead to undesired and hardly separable byproducts.

[122] Shimizu, M.; Higashi, M.; Takeda, Y.; Jiang, G.; Murai, M.; Hiyama, T. *Synlett* **2007**, 1163.
[123] Watanabe, Y.; Yamazaki, T. *Synlett* **2009**, 3352.
[124] Aikawa, K.; Hioki, Y.; Mikami, K. *Org. Lett.* **2010**, *12*, 5716.

❖ Isomerization of trifluoromethyl alkynes :

Another appealing strategy is based on the isomerization of alkynes by migration of a group initially located at the propargyl position to the remote acetylenic position. This group can be a hydrogen atom, which can migrate under basic conditions (Figure 2.18, eq. 1).[125]

More elaborate versions have also been developed, like the method reported by Rodriguez *et al.* for the development of 1-sulfoxido-3-trifluoromethyl allenes (eq. 2). [126] This reaction starts with the *in*-situ generation of a propargyl thioether which undergoes isomerization to give an allene product.

Similarly, Liu and coworkers designed an elegant synthesis of 1-phosphanato-1-trifluoromethyl allenes based on the isomerization of *in-situ* generated propargyl phosphites (eq.3).[127]

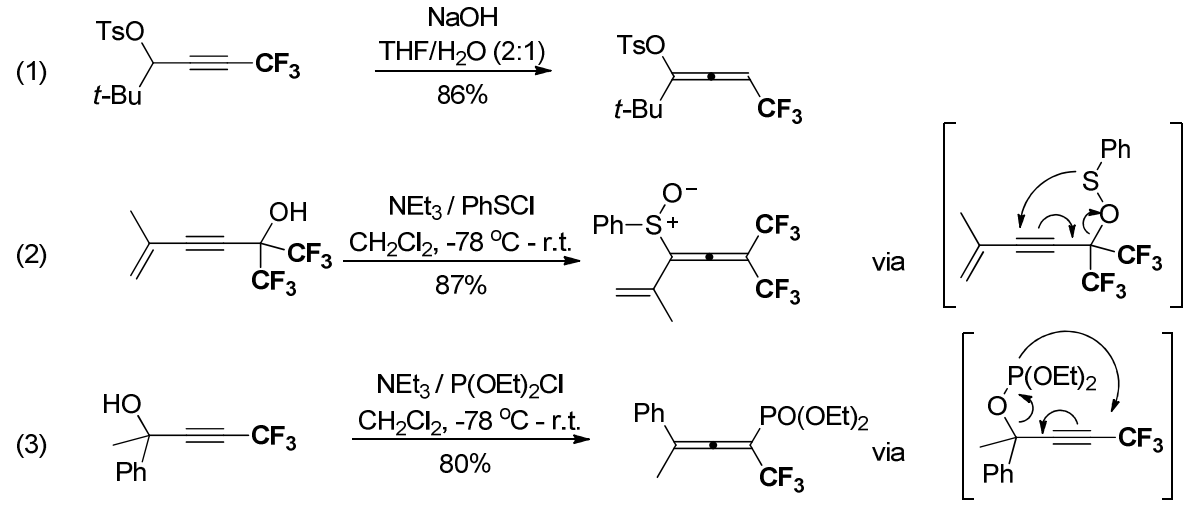


Figure 2.18 – Examples of synthesis of trifluoromethyl allenes by isomerization of trifluoromethyl alkynes

[125] Yamazaki, T.; Watanabe, Y.; Yoshida, N.; Kawasaki-Takasuka, T. *Tetrahedron* **2012**, *68*, 6665.
[126] Wang, X.; Donovalova, J.; Hollis, A.; Johnson, D.; Rodriguez, A. *J. Heterocyclic Chem.* **1994**, *31*, 871.
[127] Li, P.; Liu, Z.J.; Liu, J.T. *Tetrahedron* **2010**, *66,* 9729.

❖ Elimination on trifluoromethyl alkenes :

Trifluoromethyl alkenes can also be used as substrates to generate trifluoromethyl allenes. In this case, the strategy consists of generating a second C=C bond by an elimination process. A large number of olefination methods are available and some of them can be adopted to generate the desired cumulated C=C bond of the allene.

For example, 1,2-dibromides can undergo elimination in the presence of zinc (Figure 2.19, eq. 1)[128] by forming a vinylic organozinc reagent which evolve via elimination of a bromide anion.

Julia-Lythgoe type olefination can also be performed to generate the desired C=C bond (eq. 2).[129] In this case, reduction of the sulfone moeity by SmI_2 allows the formation of a vinylic anion which eliminates the acetate to form the desired allene.

Debromosulfinylation can occur when bromo allyl vinyl thioethers are treated with m-CPBA. The mechanism is thought to be initiated by the oxidation of the sulfide to a sulfoxide. Then, an allylic radical is generated from the bromide, which induces a radical β-elimination of the sulfoxide (eq. 3).[130]

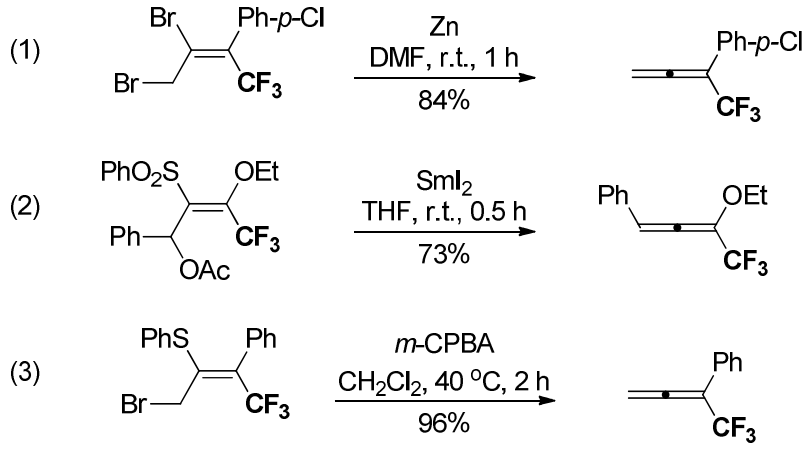


Figure 2.19 – Examples of synthesis of trifluoromethyl allenes by elimination on trifluoromethyl alkenes

[128] Sam, B.; Montgomery, P.; Krische, M.J. *Org. Lett.* **2013**, *15*, 3790.
[129] Hibino, M.; Yoshimatsu, M. *Chem. Pharm. Bull.* **2000**, *48*, 1395.
[130] Han, H.Y.; Kim, M.S.; Son, J.B.; Jeong, I.H. *Tet. Lett.* **2006** *47*, 209.

All in all, although a large variety of strategies have been applied for the synthesis of trifluoromethyl allenes, the reported methods overall suffer from several drawbacks. In most cases, the cost of the trifluoromethylating reagent or trifluoromethyl substrate is a first limitation. Moreover, in the case of methods relying on S_{N2}' type substitutions, the regioselectivity is a critical issue and hardly separable byproducts are often obtained. In other cases, the reaction conditions induce limitation in the diversity of the scope of the reaction. Therefore, the development of an efficient and cheap method with mild conditions still represents an important challenge.

A few years ago, our group has developed an efficient gold-catalyzed synthesis of allenes relying on a 1,5-hydride shift rearrangement of benzyl propargyl ethers. This method uses mild conditions and allows the selective formation of a large range of allenes with benzaldehyde as the sole byproduct which is easily removed. Therefore, we thought that adapting this strategy for the synthesis of trifluoromethyl allenes would be an interesting alternative option.

For a better comprehension of the project, the concept of hydride shift is presented in the next part.

2.2 Intramolecular hydride-shift reactions in C-H functionalization

Turning unactivated C-H bonds into more valuable bonds is now a hot topic in synthetic organic chemistry. Therefore, the development of C-H functionalization methods has attracted a lot of attention, and a large range of strategies including oxidative addition of transition metal into the C-H bond, σ-metathesis, 1,2-insertion of the C-H bond in M=X bonds (where M is a metal and X a heteroatom), or radical activation have been evaluated (Figure 2.20).[131]

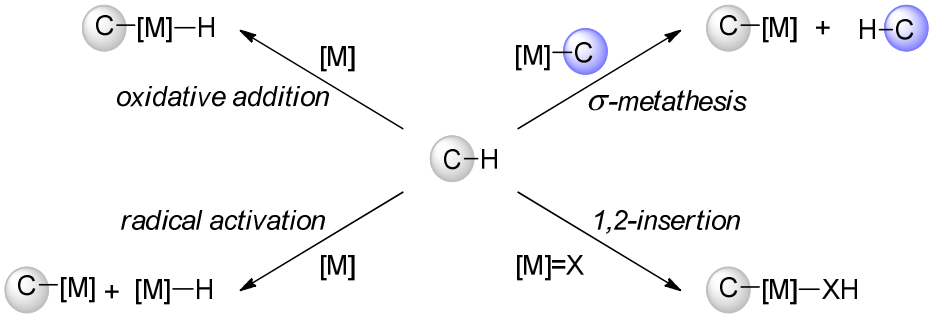


Figure 2.20 – Main strategies C-H bond functionalization

[131] For recent reviews on C-H functionalizations, see : a) Roudesly, F.; Oble, J.; Poli, G. *J. Mol. Cat.* **2017**, *426*, 275 ; (b) Hartwig, J.F. *J. Am. Chem. Soc.* **2016**, *138*, 2 ; (c) Davies, H.M.L.; Morton, D. *J. Org. Chem.* **2016**, *81,* 343 ; (d) Carr, K.T.C.; Macgregor, S.A.; McMullin, C.L. *Top. Organomet. Chem.* **2016**, *55*, 53 ; (e) Jones, W.D. *Top. Organomet. Chem.* **2016**, *56*, 67.

In addition to these strategies, intramolecular hydride shifts to insaturations represent an interesting alternative approach to promote a C-H functionalization via a cyclization (Figure 2.21). Typically after the occurrence of hydride shift between a hydride donor (D) and an acceptor (A), the donor becomes electrophilic in nature while the acceptor becomes nucleophilic. Then, their combination can lead to cyclization products.

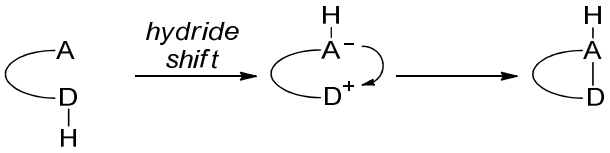


Figure 2.21 – Intramolecular hydride-shift reactions

Practically speaking, the hydride donor should have the capacity to be easily oxidized, meaning that the resulting carbocation must be relatively stable. For this purpose, heteroatom at the α position to the migrating hydride are obviously useful, as they can help in stabilizing the resulting carbocation by mesomeric effect. Therefore, amines, ethers and acetals are excellent hydride donors. Besides, aryl groups and branched alkyl groups can also stabilize carbocations to a lesser extend (Figure 2.22).

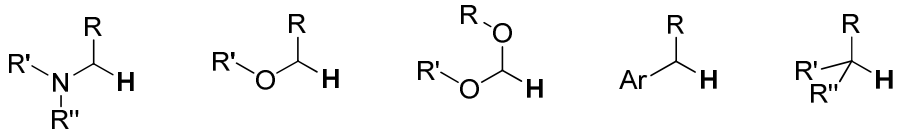


Figure 2.22 – Classical hydride donor

Michael type acceptors, such as activated alkenes, or a 1,2-acceptor, such as carbonyl groups, are also susceptible to hydride transfers and can act as acceptor.

❖ Hydride shifts to activated alkenes

1,5-hydride shifts to 1,4-acceptor can be efficiently performed using heteroatom based hydride donors (Figure 2.23, eq. 1)[132] or activated benzylic moiety (eq. 2).[133]

[132] Pastine, S.J.; McQuaid, K. M.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 12180.
[133] Mahoney, S.J.; Moon, D.T.; Hollinger, J.; Fillion, E. *Tetrahedron Lett.* **2009**, *50*, 4706.

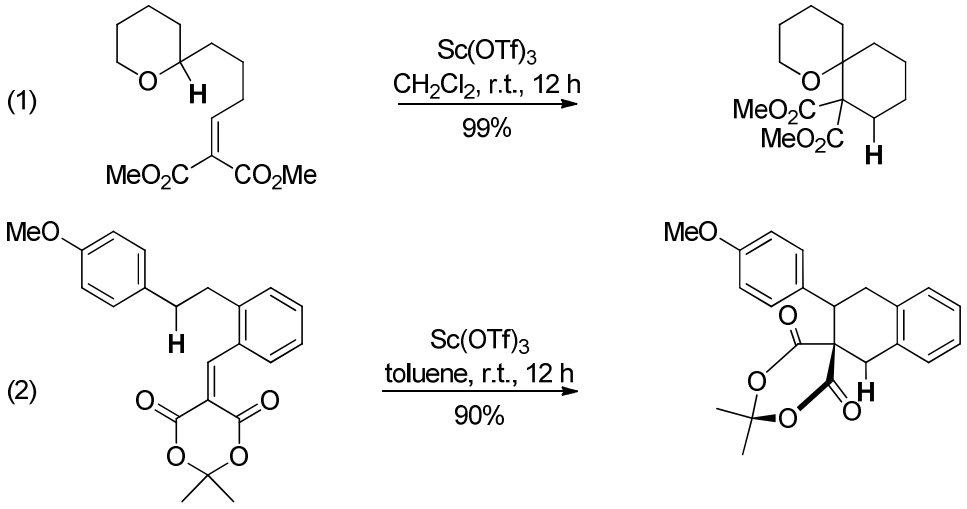


Figure 2.23 – Examples of 1,5-hydride shift to activated alkenes

In the same idea, shorter or longer shifts than a 1,5 are also conceivable, such as 1,4-hydride shift (Figure 2.24, eq. 1)[134] or 1,8-hydride shift (eq. 2).[135]

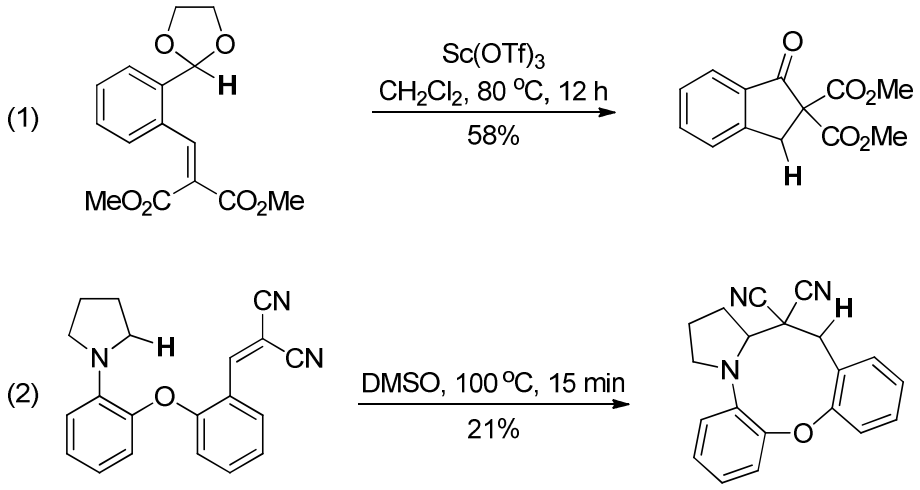


Figure 2.24 – Examples of 1,n-hydride shift to activated alkenes

[134] Alajarin, M.; Marin-Luna, M.; Vidal, A. *Adv. Synth. Catal*. **2011**, *353*, 557.
[135] Bottino, P.; Dunkel, P.; Schlich, M.; Galavotti, L.; Deme, R.; Regdon, G.; Benyei, A.; Pintye-Hodi, K.; Ronsisvalle, G.; Matyus, P. *J. Phys. Org. Chem*. **2012**, *25*, 1033.

❖ Hydride shifts to carbonyls

1,5-hydride shifts to aldehydes and imines is well-document. They can be observed using alkyl groups (Figure 2.25, eq. 1),[136] ethers (eq. 2)[137] or amines (eq. 3)[138] as hydride donors.

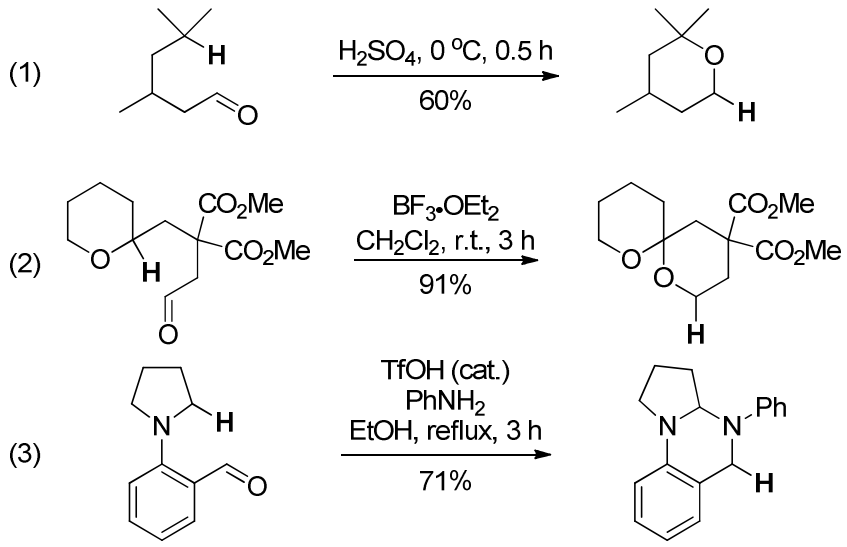


Figure 2.25 – Examples of 1,5-hydride shift to carbonyls

Other atypical hydride sources can also be used, such as aldehydes in the presence of nucleophiles (Figure 2.26).[139] In this example, after addition of the cyanide to the aldehyde, the resulting adduct represents a powerful hydride donor. The transfer of this hydride to the ketone occurs following a formal 1,4-shift. This results in the formation of an alkoxyde which can add to the carbonyl cyanide to produce a benzolactone with concomitant regeneration of the cyanide catalyst.

[136] Schulz, J.G.; Onopchenko, A. *J. Org. Chem.* **1978**, *43*, 339.
[137] Pastine, S.J.; Sames, D. *Org. Lett.* **2005**, *7*, 5429.
[138] Zhang, C.; Murarka, S.; Seidel, D. *J. Org. Chem.* **2009**, *74*, 419.
[139] Gerbino, D.C.; Augner, D.; Slavov, N.; Schmalz, H.G. *Org. Lett.* **2012**, *14*, 2338.

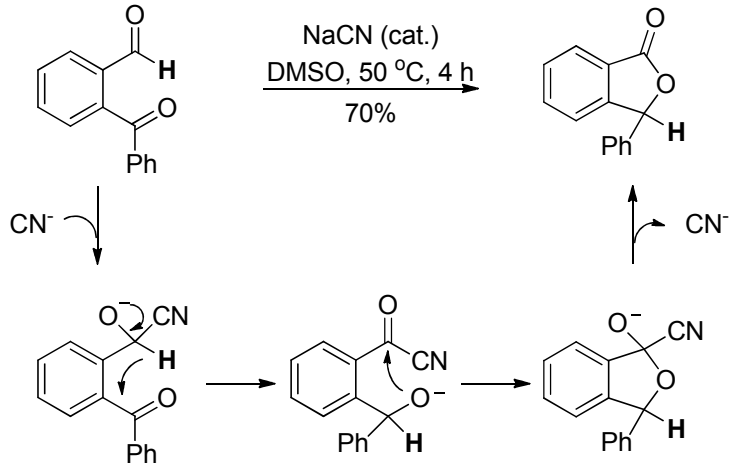


Figure 2.26 – Examples of 1,4-hydride shift to carbonyls with unusual hydride donor

❖ Hydride shifts to alkynes

Metal-activated alkynes can also play the role of hydride acceptors. For example, under platinum or ruthenium catalysis, 2-alkylphenylacetylenes can be efficiently converted to indenes (Figure 2.27).[140]

The mechanism is initiated by the formation of a vinyl carbene. Then, a hydride is transferred from the benzylic position to the carbene following a formal 1,5-shift. The resulting vinylic metal complex attacks the newly generated benzylic carbocation, thus forming a metallocycle which undergoes reductive elimination to give the indene product.

[140] a) Bajracharya, G.B.; Pahadi, N.K.; Gridnev, I.D.; Yamamoto, Y. *J. Org. Chem.* **2006**, *71*, 6204 ; b) Odedra, A.; Datta, S.; Liu, R. S. *J. Org. Chem.* **2007**, *72*, 3289.

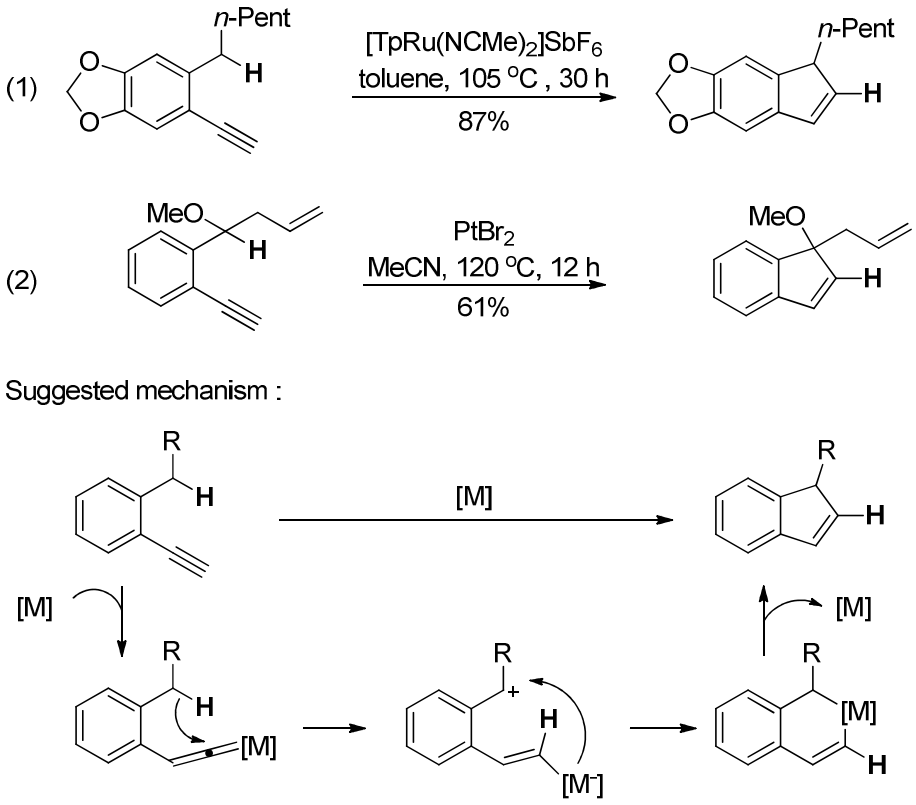


Figure 2.27 – Synthesis of indene from intramolecular 1,5-hydride shifts in phenylacetylene

However, different reactivities can be observed according to the metal complex used for the reaction. For example, the following alkynyl cycloether compound (Figure 2.28) could be converted to a spiro 5-membered cycle under platinum catalysis condition, [141] whereas a spiro 6-membered cycle was obtained under gold catalysis conditions.[142]

[141] Vadola, P.A.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 16525.
[142] Jurberg, I.D.; Odabachian, Y.; Gagosz, F. *J. Am. Chem. Soc.* **2010**, *132*, 3543.

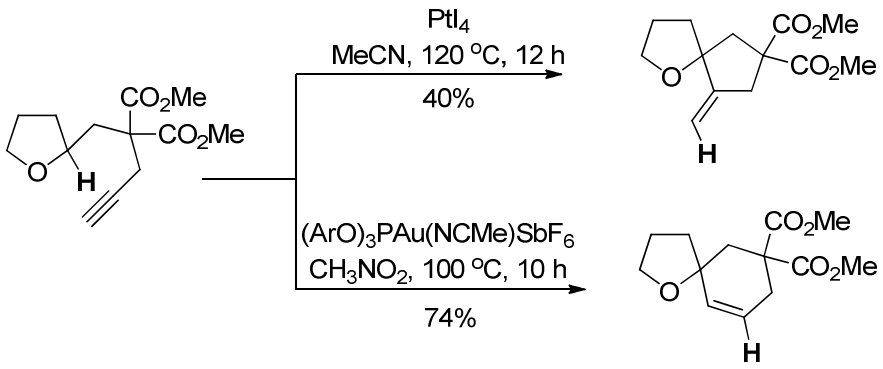


Figure 2.28 – Example of the influence of the catalyst on the reactivity

Although the exact mechanism of this transformation is still unclear, the platinum-catalyzed reaction is likely initiated by the formation of a vinylidene carbene which undergoes a sequence of 1,6-hydride shift, 5-membered ring closure, 1,2-hydride shift and elimination of platinum (Figure 2.29).

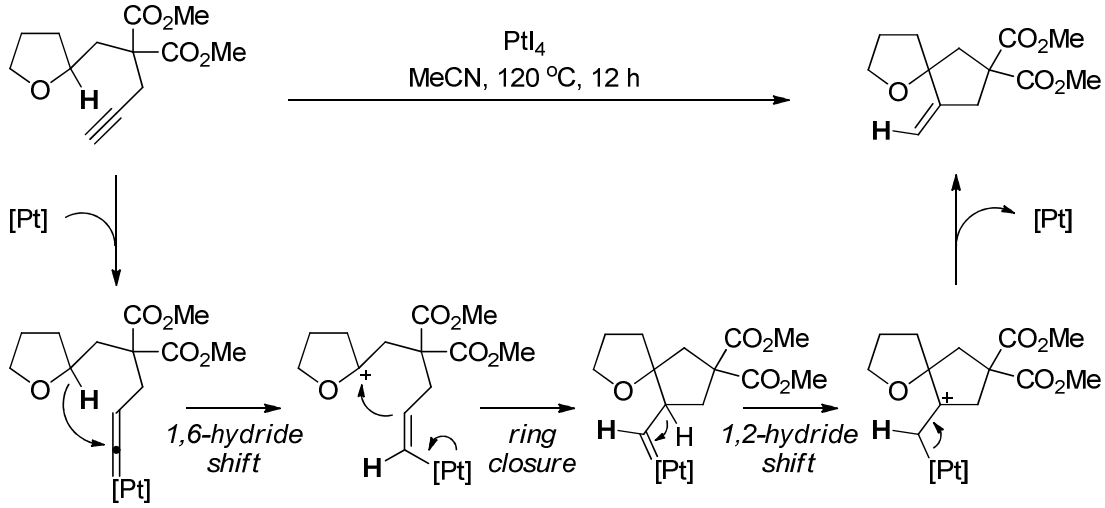


Figure 2.29 – Mechanism for the platinum-catalyzed reaction

As for the gold-catalyzed reaction, the mechanism is initiated by the transfer of a hydride from the tetrahydrofuran moiety to the gold-activated alkyne following a formal 1,5-shift. Back donation of the gold allows the aurate intermediate to form a spiro 5-membered cycle. Then, ring expansion can happen to generate a spiro 6-membered cyclohexene with regeneration of the gold catalyst. (Figure 2.30).

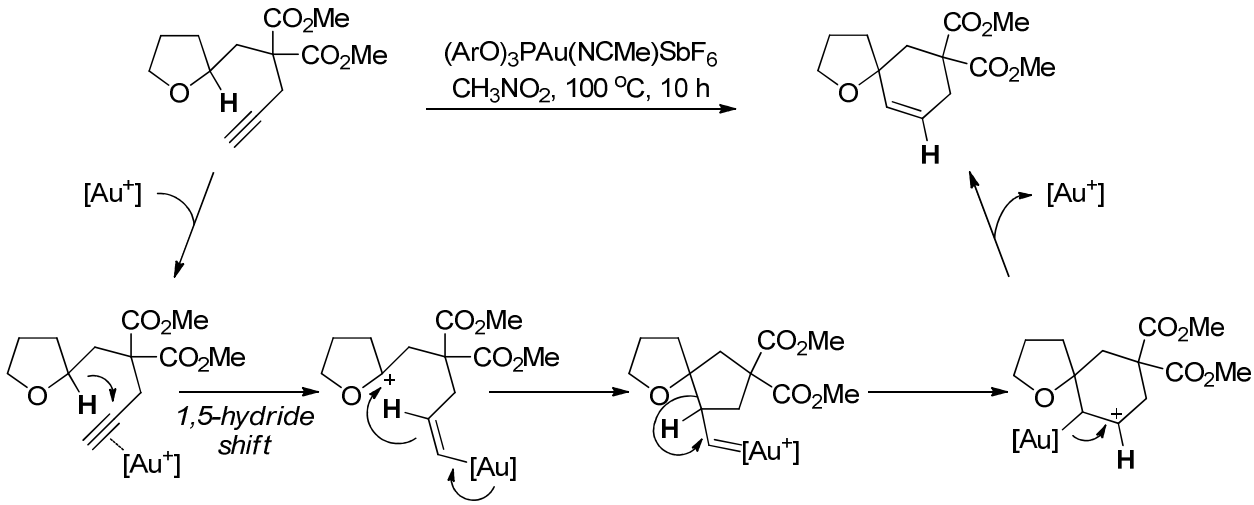


Figure 2.30 – Mechanism for the gold-catalyzed reaction

Internal alkynes can also participate in hydride shift processes. In the following example, the hydride from the benzylic position of the isoindoline can be regioselectively transferred to the alkyne. Subsequent protodeauration leads to the formation of a diene which can react with a dienophile to produce a complex polycyclic compound (Figure 2.31).[143]

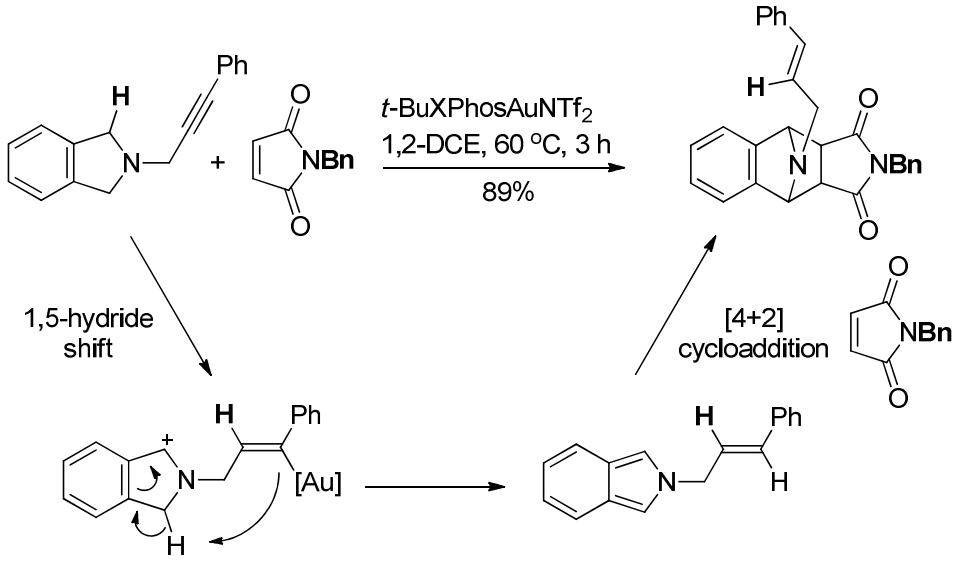


Figure 2.31 – Examples of hydride shift to internal alkynes

[143] Wu, X.; Chen, S.-S.; Hu, Y.; Gong, L.-Z. *Org. Lett.* **2014**, *16*, 3820.

A method for the synthesis of allenes using the hydride shift strategy has been developed by Crabbe *et al.* in the 1979 (Figure 2.32).[144] The reaction starts with the *in-situ* generation a propargyl amine by reaction of a terminal alkyne, an aldehyde and an amine. Then,harsh thermic conditions are required, in addition to a metal-activation of the alkyne, to promote a 1,5-hydride shift. The resulting intermediate can then fragmentate to release an imine and an allene.

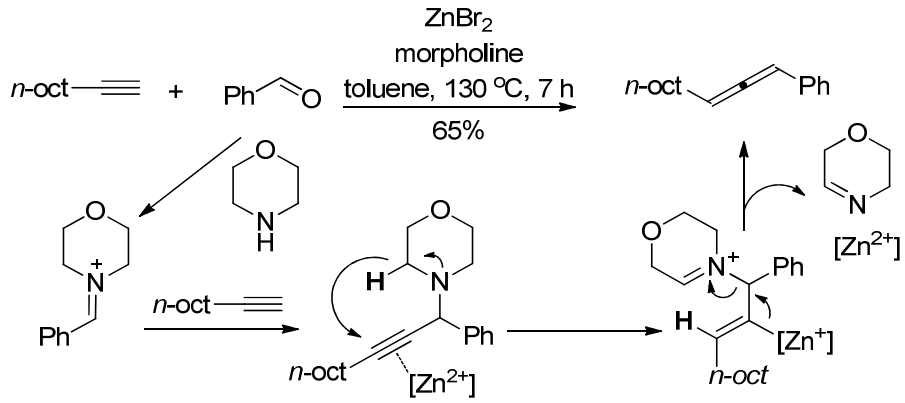


Figure 2.32 – Ma's modification of the Crabbe synthesis of allenes

The following section will present how the later strategy was used for the synthesis of trifluoromethyl allenes and their further applications.

2.3 Gold-catalyzed synthesis of trifluoromethyl allenes from propargyl benzyl ethers

2.3.1 Origin of the project

As discussed in the previous sections, various methods for the synthesis of trifluoromethyl allenes have already been developed (section 2.1.3). However, although being quite complementary, the reported methods suffer from several drawbacks. For instance, intermolecular processes usually present a lack of selectivity leading to the recurrent formation of byproducts which are often hard to separate (trifluoromethyl propargyl alkynes). Besides, the sources of the trifluoromethyl moiety used in these methods are often quite expensive ($TMSCF_3$, Ph_2SCF_3OTf, 2-bromo-3,3,3-trifluoromethylpropene, 1,1-dibromo-3,3,3-trifluoromethylacetone).

[144] Crabbe, P.; Fillion, H.; Andre, D.; Luche, J.L. *Chem. Comm.* **1979**, 859.

Therefore, the development of a selective method for the synthesis of trifluoromethyl allenes involving the use of a cheap source of the trifluoromethyl moiety represents an interesting challenge.

Inspired by the Crabbe homologation of alkynes, our group developed a few years ago a gold-catalyzed synthesis of allenes from propargyl benzyl ethers (Figure 2.33).[145] This method relies on a 1,5-hydride shift, using the benzyloxy moiety as a hydride donor and the gold-activated alkyne as a hydride acceptor.

Upon activation of the alkyne by the gold catalyst, a 1,5-hydride shift can proceed to generate an oxocarbenium intermediate. A fragmentation can then take place to produce an allene with the release of benzaldehyde while the catalyst is regenerated.

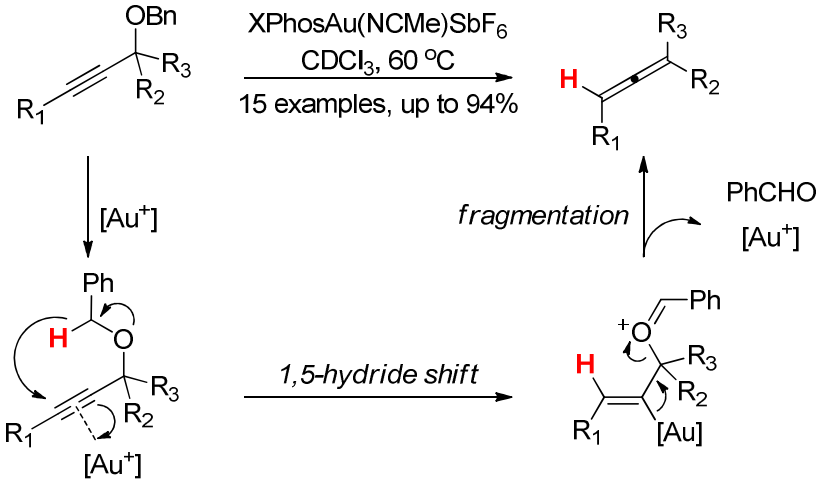


Figure 2.33 – Gold-catalyzed synthesis of allenes from propargyl benzyl ethers

Compared to what has been previously reported in the literature for the synthesis of allenes, this method presents the advantage of proceeding under mild conditions and of being highly selective, with a side-product which is very easy to separate (benzaldehyde).

On the basis of this previous result, we envisaged the possibility to adapt this process to the synthesis of trifluoromethyl allenes from trifluoromethyl propargyl benzyl ethers (Figure 2.34).

[145] Bolte, B.; Odabachian, Y.; Gagosz, F. *J. Am. Chem. Soc.* **2010**, *132*, 7294.

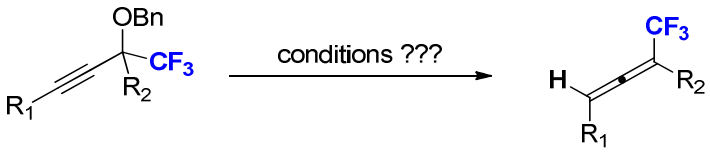


Figure 2.34 - Adaptation to the synthesis of trifluomethyl allenes

However, to make this proposal indisputably advantageous as compared to already reported methods, we needed a cheap source for the trifluoromethyl moiety. For this, we turned our attention to the relatively cheap ethyl trifluoroacetate (Figure 2.35).[146]

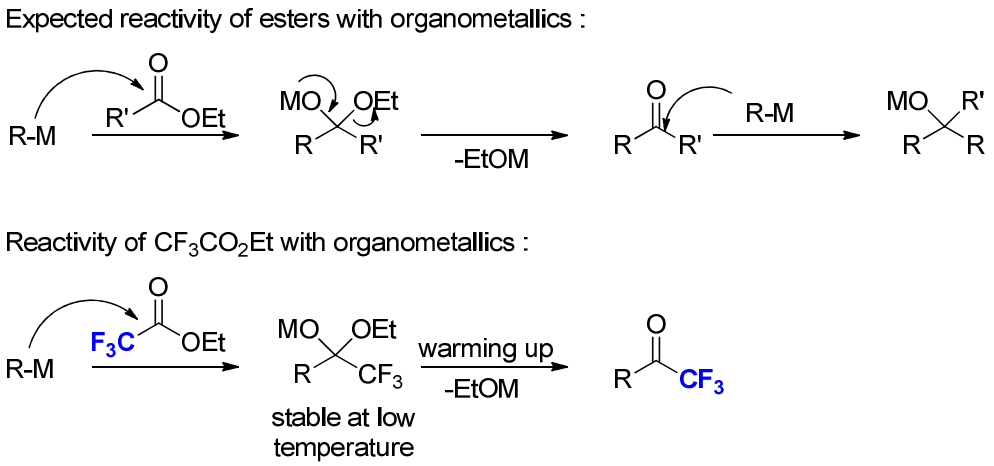


Figure 2.35 - Singular reactivity of ethyl trifluoroacetate with organometallic reagents

While a double addition of nucleophiles is expected to happen with regular esters, to produce tertiary alcohols, the use of ethyl trifluoroacetate may limit the reaction to a single addition. More precisely, after a first nucleophilic addition, the tetrahedral adduct, which normally fragments to give a ketone in the case of regular esters, is actually stable enough at low temperature in the case of ethyl trifluoroacetate and this intermediate can even be trapped (Figure 2.36).[147]

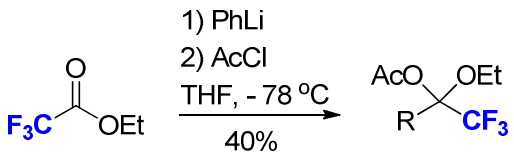


Figure 2.36 – Trapping of the adduct from nucleophilic addition

[146] a) McGrath, T. F.; Levine, R. *J. Am. Chem. Soc.* **1955**, *77*, 3656 ; b) Chen. L. S.; Chen, G. J.; Tamborski, C. *J. Fluorine Chem.* **1981**, *18*,117 ; c) Hanzawa, Y.; Kawagoe, K.; Kobayashi, N.; Oshima, T.; Kobayashi, Y. *Tetetrahedron Lett.* **1985**, *26*, 2877.

[147] Creary, X.; *J. Org. Chem.* **1987**, *52*, 5026.

Based on this reactivity, we designed a straightforward method to prepare trifluoromethyl propargyl benzyl ethers from the cheap ethyl trifluoroacetate as the trifluoromethyl source (Figure 2.37).

The initial step is the addition of one equivalent of an acetylide reagent to ethyl trifluoroacetate at low temperature. Upon warming up, the adduct fragmentates to provide a trifluoromethyl propargyl ketone which can be reduced to provide a secondary alcohol or which can alternatively undergo a nucleophilic addition from another reagent to give a tertiary alcohol. Benzylation of the alcohol precursor then leads to the benzylic propargylic substrate.

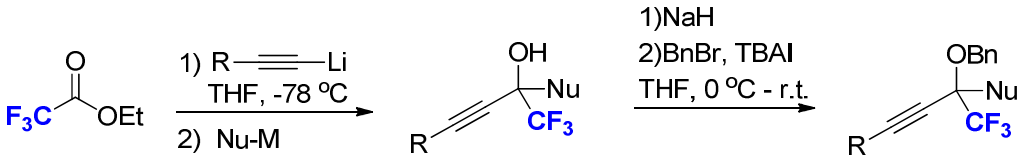


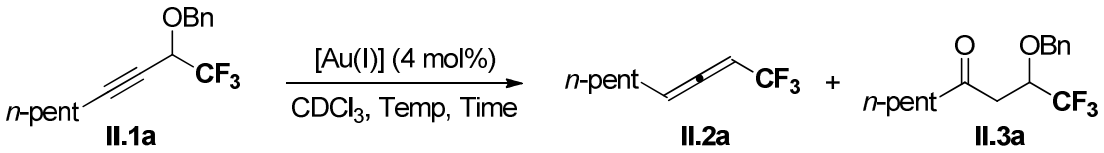
Figure 2.37 –General preparation of the substrates from ethyl trifluoroacetate

2.3.2 Optimization of the reaction

The model substrate **II.1a** was synthesized as described later in 64% yield. We made a first attempt under the experimental conditions previously used by our group with non-fluorinated substrates. Gratifyingly, using 4 mol% of XPhosAu(NCMe)SbF_6 at 60 °C in deuterated chloroform allowed to observe the formation of allene **II.2a**. However, **II.2a** was obtained in very low yield (6% after 24 h) and the formation of a by-product **II.3a**, resulting from gold-catalyzed hydration of the alkyne, was also observed in 4% yield (Table 2.1, entry 1). Satisfyingly, changing the catalyst for the more electrophilic[148] phosphonite-based complex *t*-BuGPhosAu(NCMe)SbF_6 provided the product **II.2a** in much higher yield (77%) after a much shorter reaction time (1 h) (entry 2). However, using these conditions also increased the formation of the by-product **II.3a** which was obtained in 11% yield. With the idea that lower temperature may disfavor the reaction of hydration of the alkyne leading to **II.3a**, we attempted to perform the reaction at room temperature (entry 3). But this led to a slower reaction (7 h to completion) and to a lower yield for **II.2a** while the byproduct **II.3a** was still obtained in an even higher **II.3a** / **II.2a** ratio. So 60 °C was kept as the temperature for this reaction. Changing for the analogous catalyst including the more coordinating counter-anion triflimidate *t*-BuGPhosAu(NCMe)NTf_2 had a dramatically negative effect on the reaction as

[148] See section 1.1.3 for the influence of the ligand on the gold complexes.

almost no product nor by-product was formed (entry 4). Still in an attempt to reduce the hydration side-reaction, we tried to perform the reaction in $CDCl_3$ dried over molecular sieves and we were glad to obtain better result. Indeed, using *t*-BuGPhosAu(NCMe)SbF_6 as the catalyst (4 mol%) at 60 °C in dry deuterated chloroform provided the product **II.2a** was obtained in 85% yield within one hour (entry 5). Thus, we decided to keep later conditions as the optimized conditions for this reaction. It is worth noting that the even more electrophilic phosphite-based catalyst $(ArO)_3PAu(NCMe)SbF_6$ provided comparable results at 60 °C (entry 6). However, phosphite based catalysts are known to lack stability when heated for prolonged reaction time, so we decided to opt for more secure conditions with the more stable ^{t}BuGPhosAu(NCMe)SbF_6 in case the reaction time had to be extended for other substrates.



II.1a **II.2a** **II.3a**

Entry	[Au(I)]	Temp	Time	Yield[a] II.2a	Yield[a] II.3a
1	XPhosAu(NCMe)SbF_6	60 °C	24 h	6%	4%
2	*t*-BuGPhosAu(NCMe)SbF_6	60 °C	1 h	77%	11%
3	*t*-BuGPhosAu(NCMe)SbF_6	r.t.	7 h	70%	13%
4	*t*-BuGPhosAuNTf_2	60 °C	6 h	< 1%	< 1%
5[b]	*t*-BuGPhosAu(NCMe)SbF_6	60 °C	1 h	85%	8%
6	$(ArO)_3PAu(NCMe)SbF_6$	60 °C	0.5 h	77%	11%
7	$(ArO)_3PAu(NCMe)SbF_6$	r.t.	4 h	67%	11%

The reaction were performed on a 0.2 mmol scale in $CDCl_3$ (0.2M) in sealed NMR tubes.
[a] NMR yield using 1,2-DCE as internal standard
[b] $CDCl_3$ dried over MS was used

Table 2.1 – Optimization for gold-catalyzed synthesis of trifluoromethyl allenes

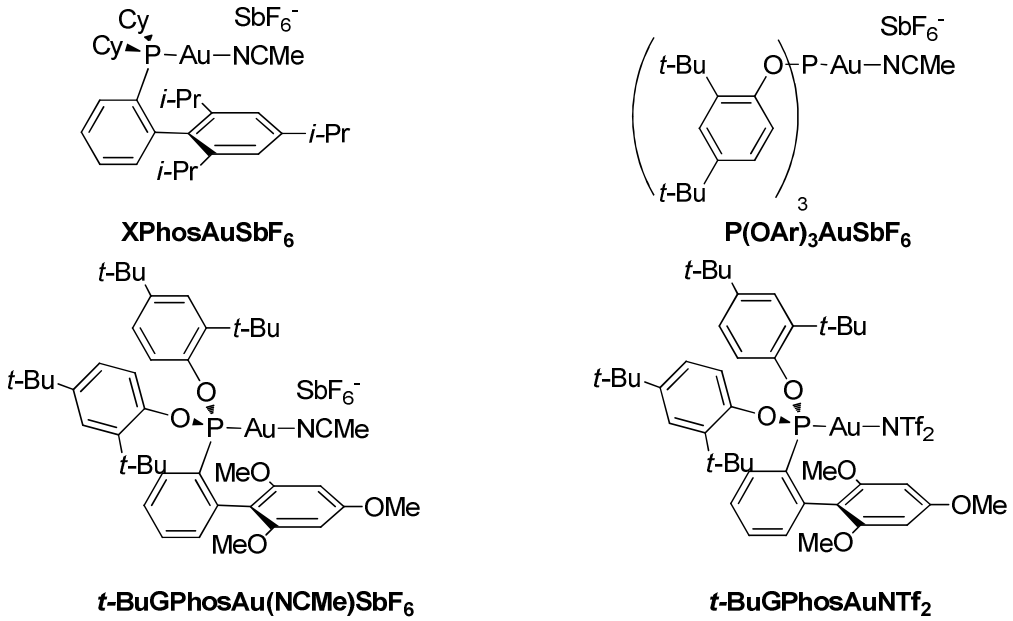


Figure 2.38 – Catalysts used during the optimization process

The difference between the conditions required for this reaction and the conditions which were found to be optimal for substrates which do not possess a trifluoromethyl group can be tentatively explained by having a look into the reaction mechanism in more details.

The 1,5-hydride shift, which relies on two points : the capacity to efficiently activate the C≡C bond and the ability of the hydride donor.

The presence of the trifluoromethyl group at the propargyl position should polarize the C≡C bond in the such a way that the remote alkyne atom would be the more electron deficient. Indeed, because of its high electronegativity, the trifluoromethyl group should pull the electron density of the alkyne toward its own direction. Therefore, the C≡C bond should be polarized in a suitable way for 1,5-hydride shift to occur (Figure 2.39).

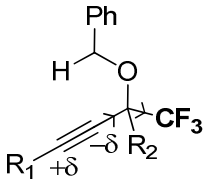


Figure 2.39 – Effect of the trifluoromethyl on the polarization of the triple bond

However, the presence of the trifluoromethyl group also render the alkyne less electron rich and thus less prone to complexation with the catalyst.

Moreover, it is also important to keep in mind that the 1,5-hydride shift is mainly promoted by the assistance of the oxygen atom, which help stabilizing the resulting oxocarbenium intermediate. In our case, the presence of the trifluoromethyl group alters the situation. In the present case, the electron withdrawing character of the trifluoromethyl group decreases the electron density of the oxygen atom and make the substrate less prone to undergo the 1,5-hydride shift (Figure 2.40).

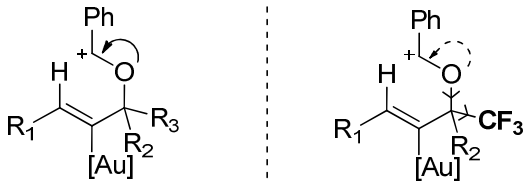


Figure 2.40 – Effect of the trifluoromethyl on the stabilization of the intermediate

In terms of catalytic system, this means that the gold complex must be a stronger Lewis-acid than the one used for substrates which do not possess a trifluoromethyl group, which explains why catalysts including weak σ-donor and strong π-acceptor ligands, such as phosphonites or phosphites, provide better results for this reaction than catalysts including phosphines.

2.3.3 Substrate scope of the reaction

The substrates that we subjected to this reaction were prepared in overall good yields following different procedures according to their substituents. The detailed protocol and experimental data are reported in the experimental part of this manuscript and in the supporting information of the related publication.[149]

[149] Boreux, A.; Lonca, G.H.; Riant, O.; Gagosz, F. *Org. Lett.* **2016**, *18*, 5162

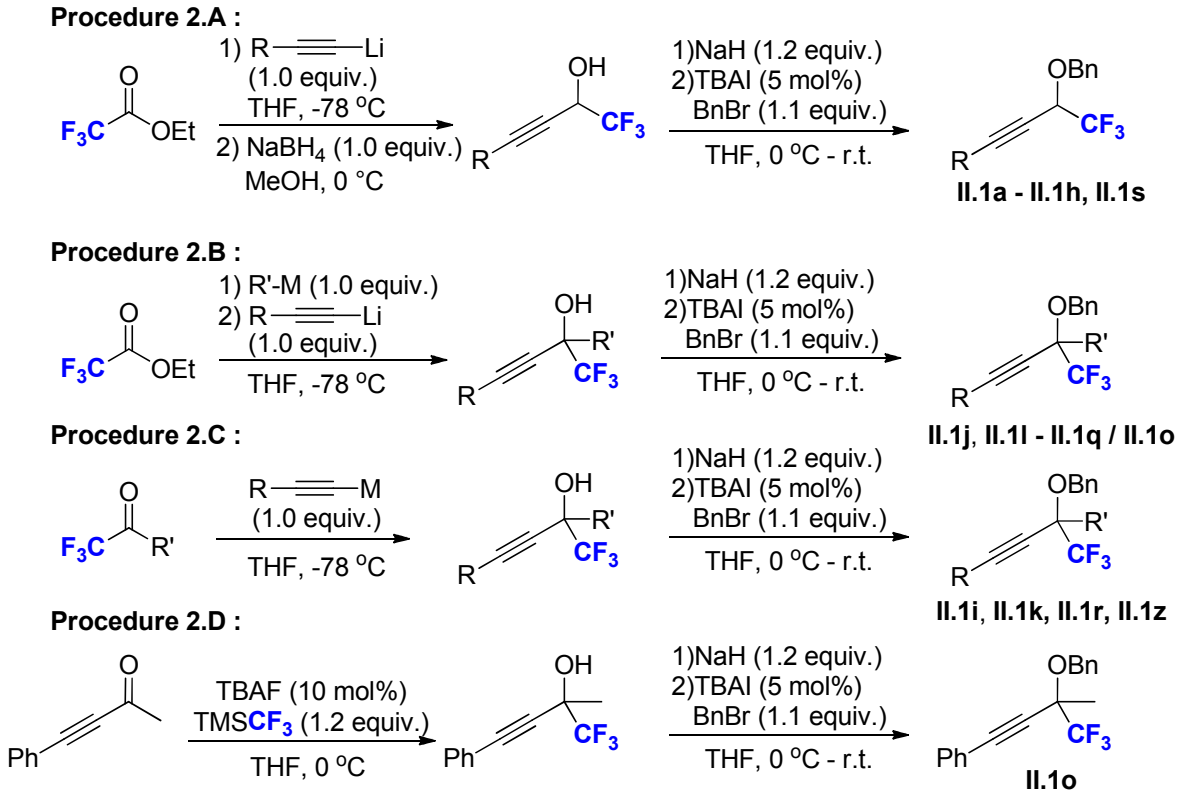
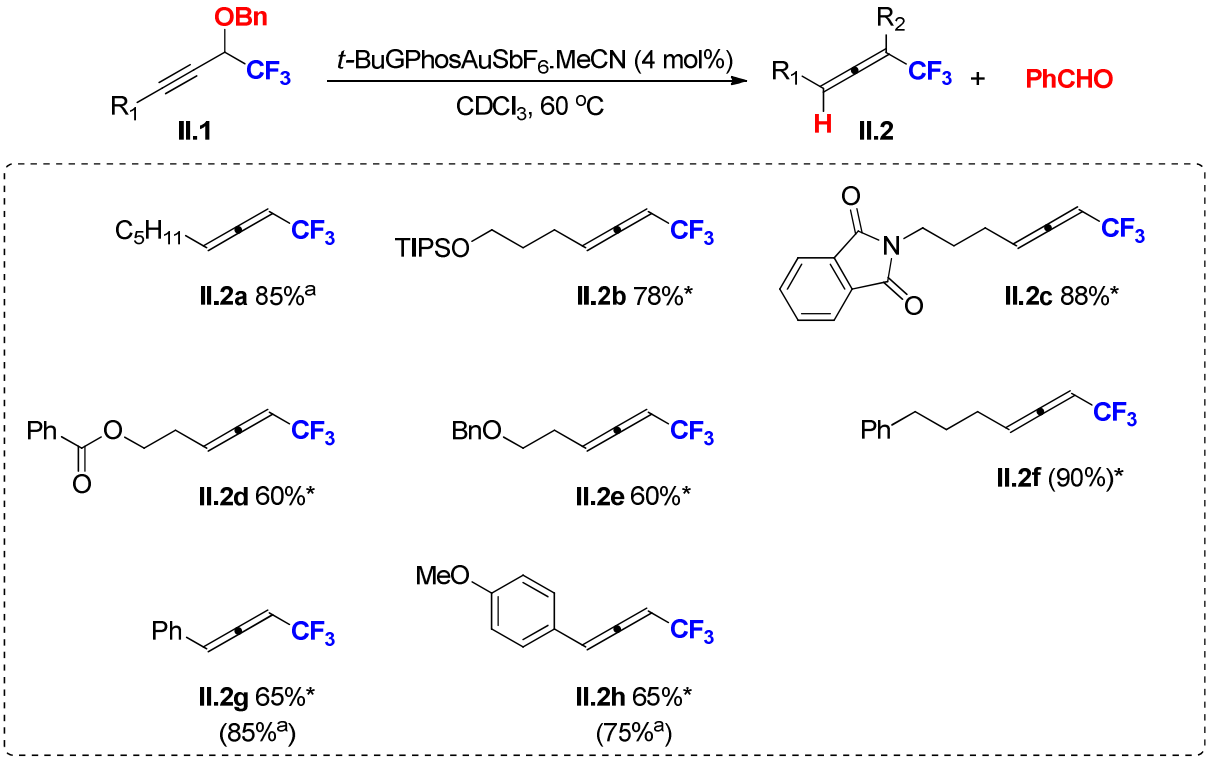


Figure 2.41 – General procedure for the preparation of the substrates

With the optimized conditions in hands (4 mol% of ^{t}BuGPhosAu(NCMe)SbF$_6$ catalyst in deuterated chloroform at a 0.2 M concentration), we started to investigate the substrate scope for the synthesis of di-substituted trifluoromethyl allenes. A series of 1,3-disubstituted trifluoromethyl allenes were firstly targeted (Figure 2.42, **II.2a**-**II.2h**). Gratifyingly, the reaction proceeded in an efficient manner in good to excellent yields. We were pleased to see that phthalimido protected amines (**II.2c**) and esters (**II.2d**) were compatible with our reaction conditions, which would not necessarily be the case for the methods relying on nucleophilic substitutions. The obtention of the trifluoromethyl allene **II.2e** from a substrate bearing two benzyl ether moieties gave us some information about the competition between the different hydride shift which could have happened. For this substrate, the 1,5-hydride shift leading to the formation of the allene was faster than the 1,6-hydride shift which could have involved the other benzyl ether group. When substrates bearing aryl substituent at the acetylenic position were used, no further cyclization happened and the reaction stopped at the formation of the allenes **II.2g** and **II.2h**.



[a] NMR yield with 1,2-DCE as internal standard due to low boiling point of the product

Figure 2.42 – Substrate scope for synthesis of 1,3-di-substituted trifluoromethyl allenes

A special attention was brought to the preparation of 1,1-disubstituted trifluoromethyl allenes as those are known to be difficult to access. A series of them could be prepared in very good yields, including aryl substituted (Figure 2.43, **II.2i**) and alkyl substituted (**II.2j**, **II.2k**) allenes. It must be underlined that this is the first reported method which allows the efficient formation of 1,1-disubstitued trifluoromethyl allenes, especially substituted by an alkyl group, without the formation of trifluoromethyl propargylic byproducts.

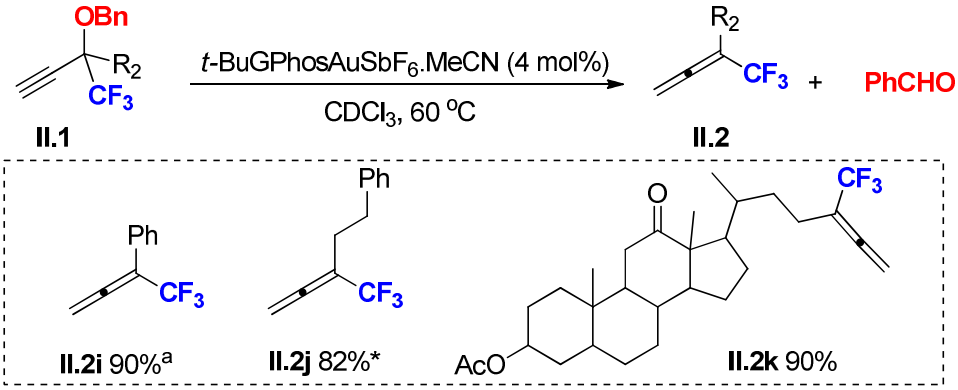
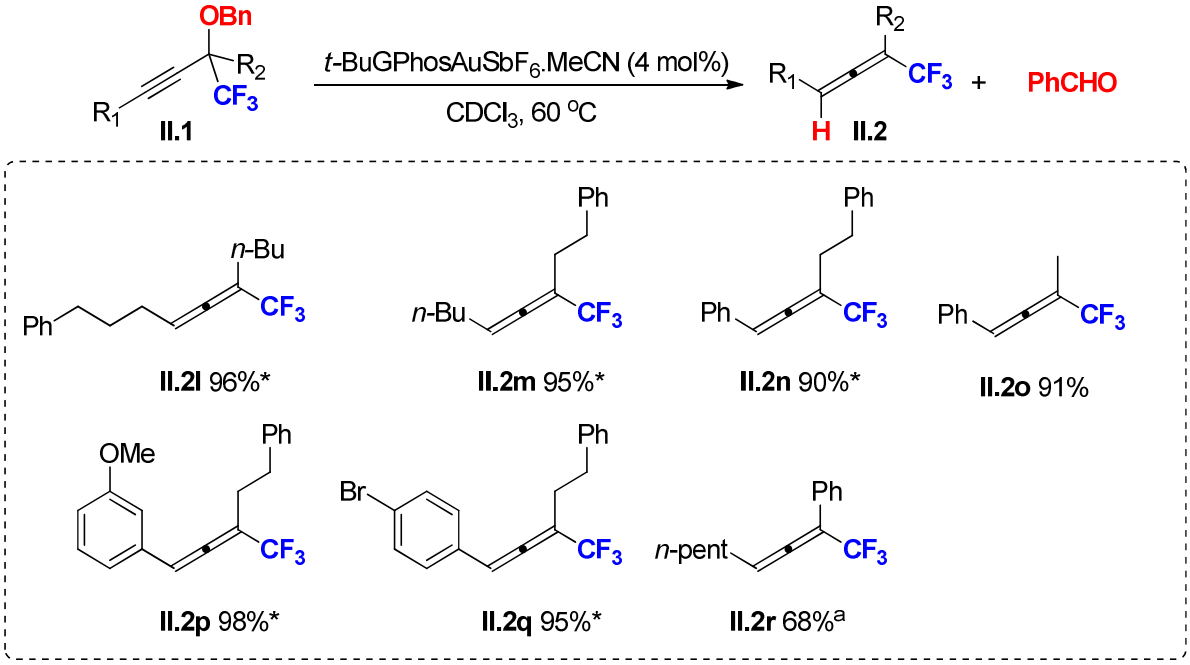


Figure 2.43 – Substrate scope for synthesis of 1,1-di-substituted trifluoromethyl allenes

Encouraged by these results, we then turned our attention to the synthesis of tri-substituted trifluoromethyl allenes. We were happy to see that various tri-substituted allenes could be obtained in excellent yields (Figure 2.44, **II.2l**- **II.2r**) with diverse combinations of alkyl and aryl substituents. It is worth noting that only few methods reported in the literature allow the formation of tri-substituted trifluoromethyl allenes as the presence of one more substituent makes the S_{N2}' nucleophilic substitutions more challenging. Besides, the efficient formation of the brominated allene **II.2q** is appreciable as the presence of this halide atom could have been an issue for the transition metal-mediated reactions reported previously.



[a] obtained using $(ArO)_3PAu(NCMe)SbF_6$ (4 mol%) at r.t.

Figure 2.44 – Substrate scope for synthesis of tri-substituted trifluoromethyl allenes

The present method also allowed the synthesis of the volatile trifluoromethyl propadiene **II.2s**, which is normally obtained by harsh condition and using stoichiometric amounts of expensive trifluoromethyl copper reagents (Figure 2.45). Although it could not be obtained in a pure form because of its low boiling point, this product could easily be prepared *in-situ* and further functionalized.

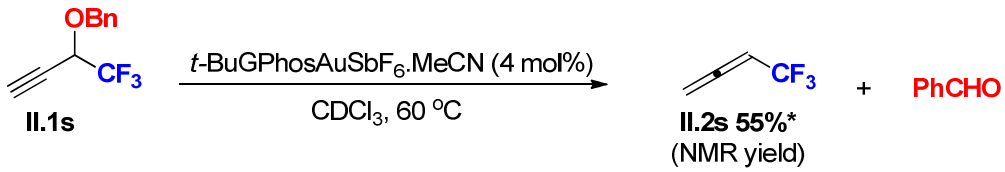


Figure 2.45 – Synthesis of trifluoromethyl propadiene

We were also pleased to see that this method could be adapted to the synthesis of other perfluoroalkylated allenes in good yields, such difluoromethyl (Figure 2.46, **II.2t**) or pentafluoroethyl (**II.2u**, **II.2v** and **II.2m**) allenes.

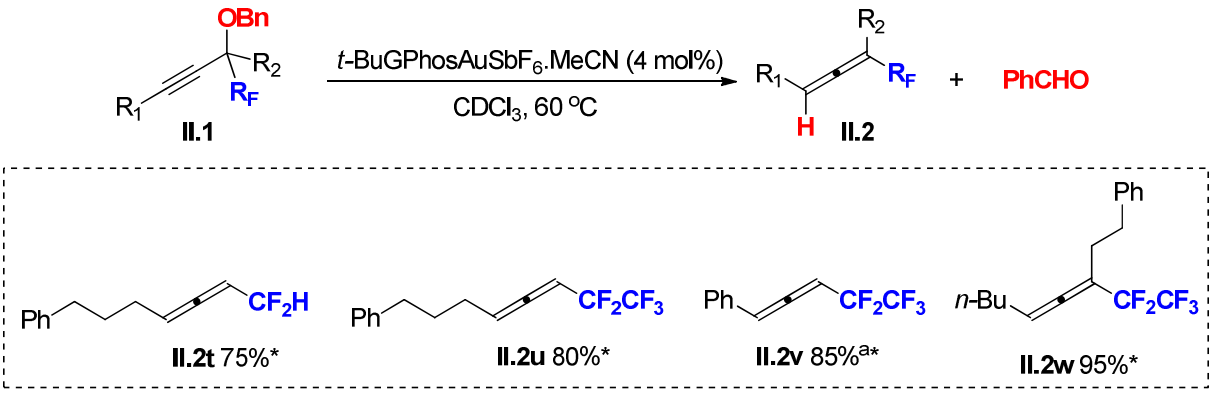


Figure 2.46 – Substrate scope for synthesis of perfluoroalkyl allenes

However, a few substrates were unreactive under these reaction conditions but a lot can be learnt from these negative results.

The unreactivity of substrates **II.4a-II.4c** emphasizes what was discussed in section 2.3.2 concerning the importance of the polarization of the C≡C bond (Figure 2.47). In this case, the presence of a electron withdrawing substituent (4-nitrophenyl, 4-acylphenyl, bromide) at the acetylenic position does not favor the +δ polarization that is required for the 1,5-hydride shift to proceed.

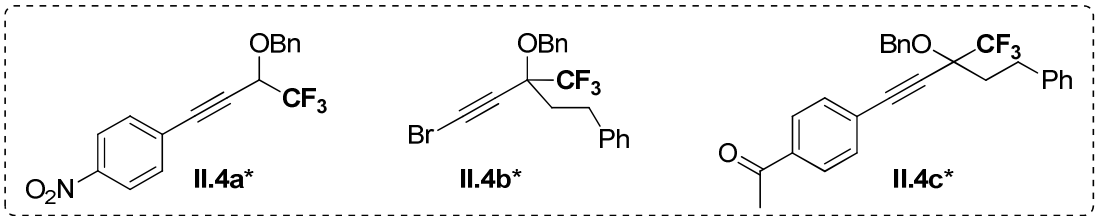


Figure 2.47 – Unreactive substrates showing the importance of the C≡C bond polarization

The unreactivity of substrates **II.4d** and **II.4e** (shown below) demonstrates the detrimental effect of electron withdrawing substituents on the propargyl (Figure 2.48). Here, the presence of the ester or the electron deficient aryl, in addition to the electronegativity of the trifluoromethyl, is apparently pulling too much the electron density of the oxygen atom of the ether, thus diminishing the ability of the benzyl residue to act as a hydride donor.

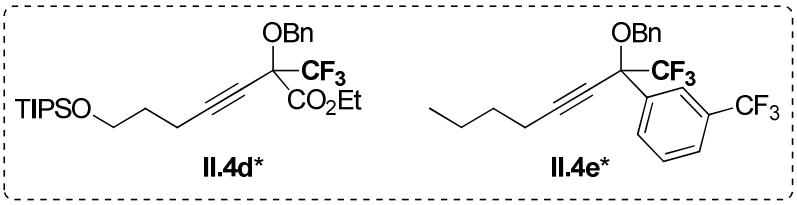


Figure 2.48 – Unreactive substrates showing the detrimental effect of electron withdrawing groups at the propargyl position

Besides, although the negative results obtained in the case of substrates **II.4f** and **II.4m** are difficult to explain, the absence of reaction with substrates **II.4g-II.4l** bring insight of the functional group compatibility issues with the catalyst (Figure 2.49). Indeed, the type of catalyst used for this reaction is one of the most electrophilic gold complexes, after phosphite-based gold complexes. Therefore, it is logical to assume that electron rich functional groups such as azides (**II.4g**), pyridine (**II.4i**), indole (**II.4j**), thiophene (**II.4k**) or furane (**II.4l**) might coordinate the catalyst and make it inactive.

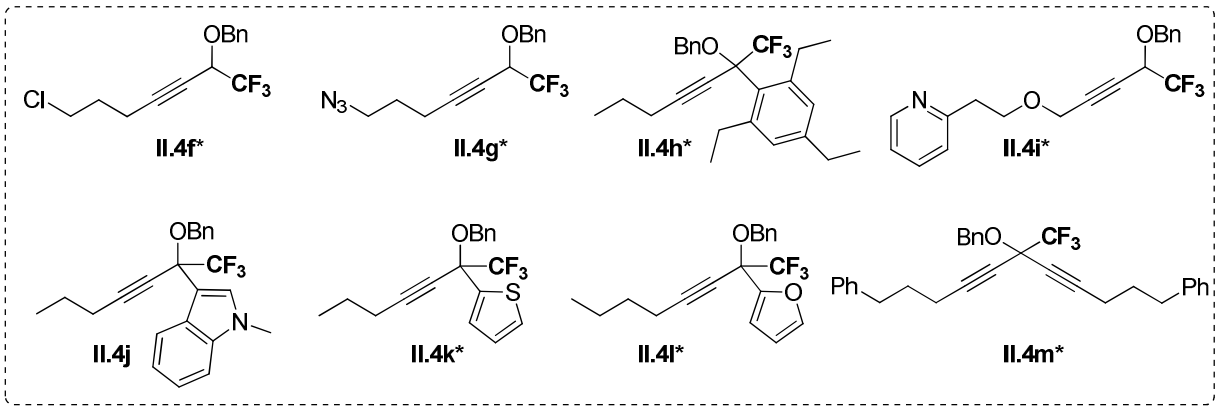


Figure 2.49 – Unreactive substrates showing the incompatibility of the catalyst with electron rich functional groups

Acetal groups were also demonstrated not to be compatible. They could be cleaved under the reaction conditions, as suggested by the following observation (Figure 2.50). Substrate **II.4n** likely undergoes an acetal cleavage to give compound **II.4o** which can then cyclize in a *5-endo-dig* fashion to produce dihydrofuran product **II.5n.**

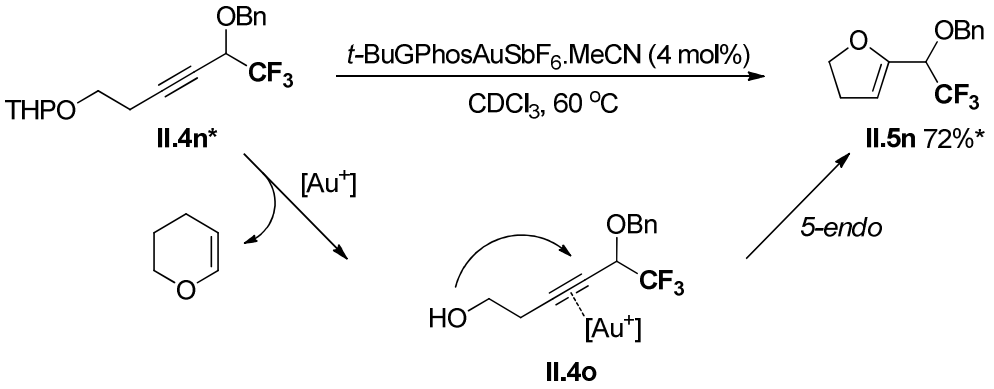


Figure 2.50 – Unreactive substrates showing the incompatibility of the catalyst with electron rich functional groups

2.3.4 Preliminary results for the conversion of chirality

All the results previously described, in the optimization process and in the investigation of the substrate scope, were obtained from racemic substrates. So before closing this project, we were curious to see if our reaction could lead to chiral allenes if chiral substrates were used (Figure 2.51). Mechanistically speaking, the key step in this transfer of chirality should be the fragmentation. Indeed, at this stage, the oxocarbenium intermediate still possesses a central chirality. Therefore, the *anti*-elimination of benzaldehyde should lead to a stereospecific formation of the allene product.

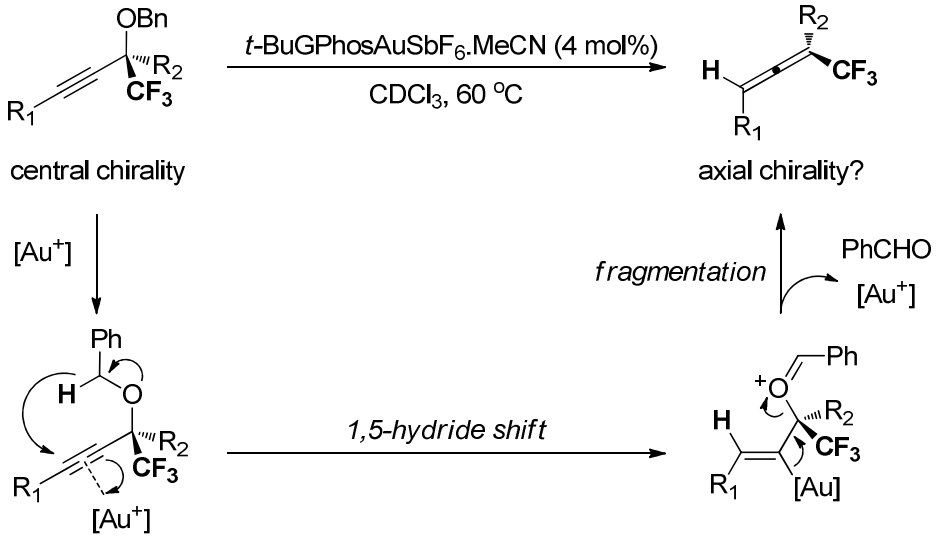
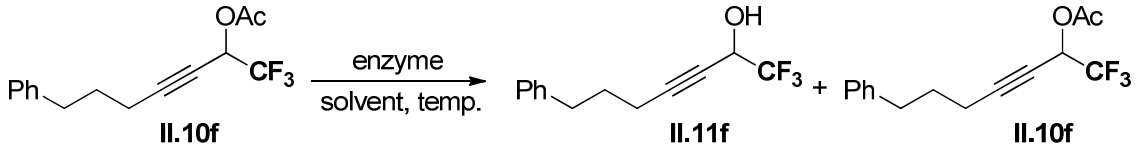


Figure 2.51 – Conversion of central chirality to axial chirality

The chiral substrate **II.1ef** was obtained after a standard benzylation of the chiral propargyl alcohol, which was prepared by kinetic resolution of the racemic acetate **II.10f** via enzymatic hydrolysis.[150] For this purpose, a series of enzymatic reactions conditions were tested. Although no satisfying enantiomeric excess (*ee*) for the alcohol was obtained when the enzymes Candida Rugosa (C. Rugosa) and Amano Lipase PS (Amano PS) were used, the use of the enzyme Candida Antartica Lipase B (CALB) in water at 40 °C provided much better results as one of the enantiomers of the alcohol could be obtained in 98% *ee*.



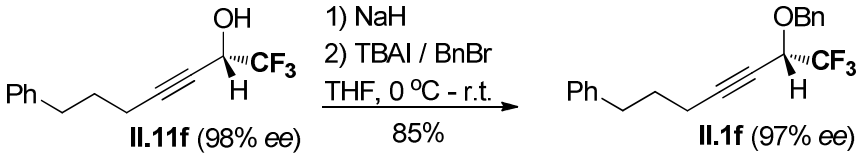
II.10f **II.11f** **II.10f**

Entry	enzyme	solvent	temp.	conversion	*ee*[a] II.11e	*ee*[a] II.310e
1	C. rugosa	water	40 °C	26%	83%	14%
2	C. rugosa	water	50 °C	58%	67%	-8%
3	Amano PS	pH 7 buffer	40 °C	21%	78%	89%
4	Amano PS	pH 7 buffer	50 °C	61%	58%	n.d.
5	Amano PS	water	50 °C	37%	63%	36%
6	CALB	water	40 °C	53%	98%	89%

Table 2.2 – Optimization for synthesis of a chiral trifluoromethyl propargyl alcohol precursor

[150] T. Yamazaki, H. Iwatsubo, T. Kitazume, *Tetrahedron: Asymmetry* **1994**, *5*, 1823-1830.

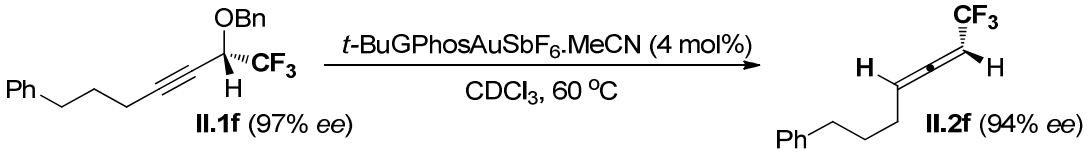
The standard benzylation method was then applied and the enantio-enriched substrate (+)-**II.1f** was obtained with conservation of the chiral information (Figure 2.52).



II.11f (98% *ee*) **II.1f** (97% *ee*)

Figure 2.52 – Benzylation of the enantio-enriched alcohol

Finally the enantio-enriched substrate **II.1f** was subjected to the reaction conditions we used for racemic substrates and we were pleased to see that the central chirality was indeed efficiently converted to an axial chirality as the allene product was obtained in 94% enantiomeric excess.



II.1f (97% *ee*) **II.2f** (94% *ee*)

Figure 2.53 – Gold-catalyzed synthesis of enantio-enriched allene

2.3.5 Derivatization of trifluoromethyl allenes

2.3.5.1 Cascade reactions for the formation of trifluoromethyl cyclic products

As illustrated in Chapter 1, allenes easily undergo (hetero)cyclization reactions under gold catalysis. We took advantage of this reactivity to design cascade reactions leading to trifluoromethyl (hetero)cycles which are very important scaffold in the design of pharmaceuticals and agrochemicals.

First, we studied the reactivity of propargyl alcohol substrates under our reaction conditions, having in mind that the resulting allenic alcohol products might undergo a gold-catalyzed *5-endo-dig* heterocyclization (Figure 2.54).

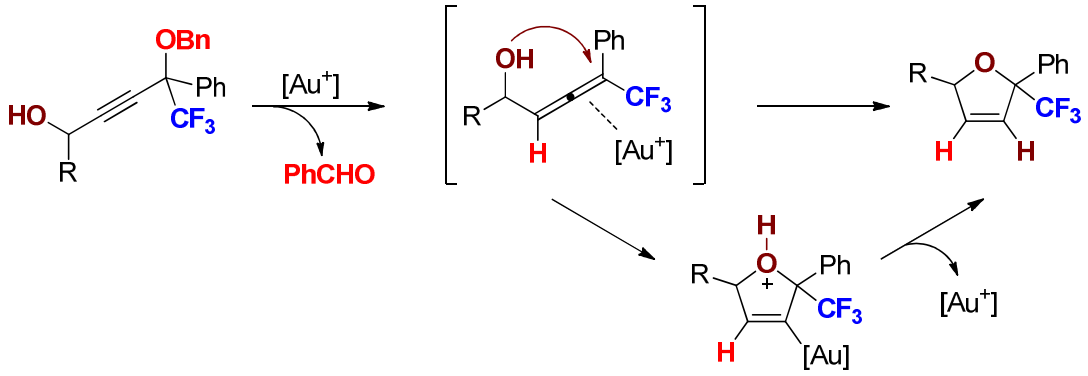


Figure 2.54 – Design of the cascade heterocyclization reaction

Gratifyingly, the expected cascade reaction occurred and trifluoromethyl 2,5-dihydrofuranes **II.6x** and **II.6y** were obtained in very good yields (Figure 2.55). It is worth noting that such kind of heterocycles are valuable synthetic intermediates[151] and that dihydrofurane is a motif present in a number of natural products.[152]

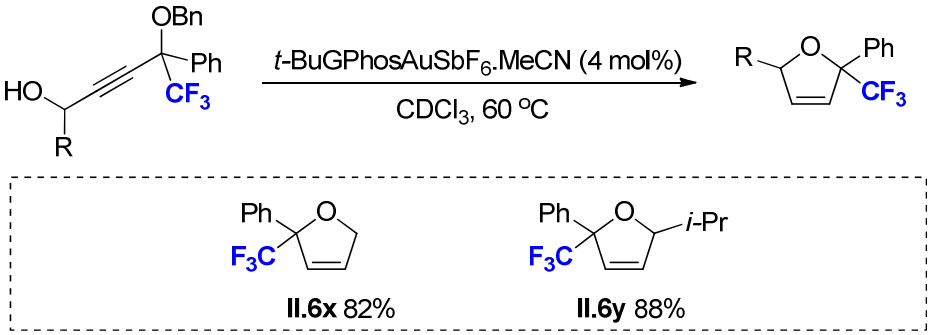


Figure 2.55 – Gold-catalyzed synthesis of trifluoromethyl dihydrofuranes

An attempt to adapt this strategy to the synthesis of trifluoromethyl dihydropyrrols from propargyl tosylamines was made (Figure 2.56). However, no reaction happened and the starting material was recovered. This absence of reaction could be tentatively explained by a coordination of the nitrogen atom to the gold catalyst, leading to an inactivation of the later.

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[151] (a) Doyle, M. P.; Forbes, D. C.; Protopopova, M. N.; Stanley, S. A.; Vasbinder, M. M.; Xavier, K. R. *J. Org. Chem.* **1997**, *62*, 7210. (b) Crotti, P.; Bussolo, V. D.; Favero, L.; Pineschi, M. *Tetrahedron* **1997**, *53*, 1417. (c) Bauer, T. *Tetrahedron* **1997**, *53*, 4763.

[152] (a) Kupchan, S. M.; Davies, V. H.; Fujita, T.; Cox, M. R.; Restivo, R. J.; Bryan, R. F. *J. Org. Chem.* **1973**, *38*, 1853. (b) Semple, J. E.; Wang P. C.; Lysenko, Z.; Joullie, M. M. *J. Am. Chem. Soc.* **1980**, *102*, 7505.

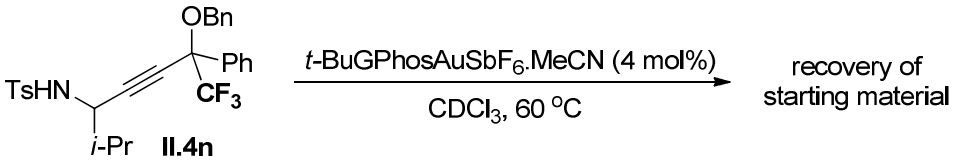


Figure 2.56 – Attempt for a gold-catalyzed synthesis of trifluoromethyl dihydropyrrols

We then turned our attention towards the possibility to perform carbocylization reactions of allenes and envisaged that a phenyl group located at the propargyl position could be a potential carbon nucleophile for such a reaction. In the case of such a substrate, the resulting allene would be perfectly polarized by the trifluoromethyl group and the phenyl group could undergo a *5-endo-trig* cyclization onto the allene (Figure 2.57).

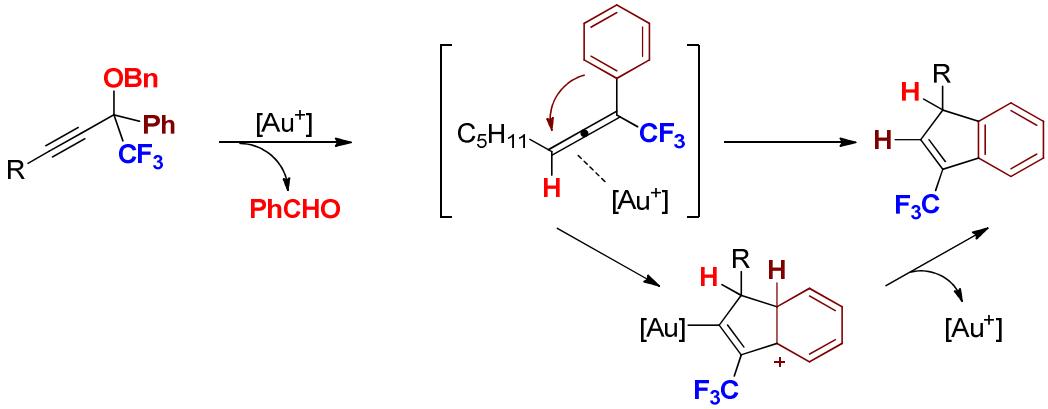


Figure 2.57 – Design of the cascade carbocyclization reaction

The expected cascade was attempted and the desired trifluoromethyl indenes **II.7r** and **II.7z** were obtained in an excellent yield (Figure 2.58).

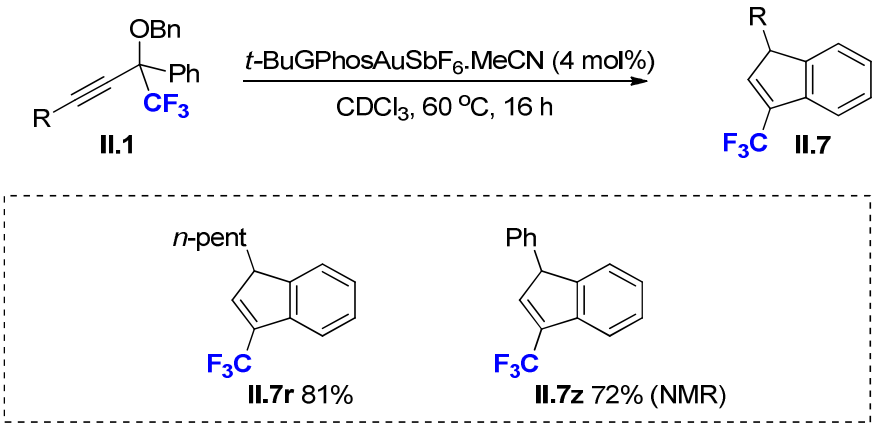


Figure 2.58 – Gold-catalyzed synthesis of trifluoromethyl indene

2.3.5.2 Borylation and silylation of trifluoromethyl allenes

As described succinctly in section 2.1.1, allenes can also be further functionalized and converted, for instance, into vinyl borate derivates. Such a type of transformation has already been demonstrated to be possible with 1,1-disubstituted trifluoromethyl allenes[153] but has never been applied yet to 1,3-disubstituted trifluoromethyl allenes. Thus, we attempted to perform a di-borylation and a mono-borylation of allene **II.2f** following reported procedures.[154]

We were pleased to observe that di-borylation products could be obtained in good yield under palladium-catalyzed conditions, although the E/Z ratio was not really satisfying. We did not try to optimize the reaction conditions any further.

The mono-borylation product could also be produced in comparable yield under copper-catalyzed conditions with, in this case, acceptable E/Z ratio. We did not try to optimize the reaction conditions any further either.

[153] a) Sam, B.; Montgomery, T. P.; Krische, M. *J. Org. Lett.* **2013**, *15*, 3790 ; b) Ambler, B. R.; Peddi, S.; Altman, R. A. *Org. Lett.* **2015**, *17*, 2506.

[154] For a reported procedure for di-borylation of allenes, see : Pelz, N. F.; Woodward, A. R.; Burks, H. E.; Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 16328.

For a reported procedure for mono-borylation of allenes, see : Yuan, W.; Ma, S. *Adv. Synth. Catal.* **2012**, *354*, 1867.

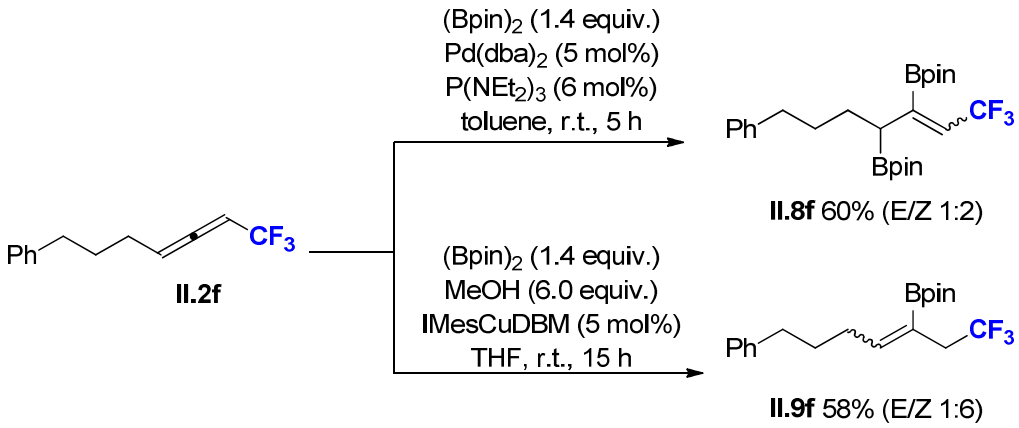


Figure 2.59 – Mono- and di- borylation of allene II.2e

2.4 Conclusion

We have developed a gold-catalyzed method for the synthesis of mono-, di- and tri-trifluoromethyl allenes. This method relies on a 1,5-hydride shift strategy using benzyl ether as a hydride donor leaving group.

Our method presents numerous advantages as compared to previously reported methods. The conditions are mild and the relatively cheap ethyl trifluoroacetate is used as the trifluoromethyl source. The inherent selectivity prevents the formation of recurrent hardly separable by-products such as trifluoromethyl propargyl compounds often obtained in other previously reported methods. Our conditions could even be adapted to the synthesis of other perfluoroalkyl allenes.

Moreover, the present method allows to perform cascade reaction in which the *in-situ* generated allenes can undergo (hetero)cyclization to provide valuable trifluoromethyl 2,5-dihydrofuranes or trifluoromethyl indenes, both being important scaffolds.

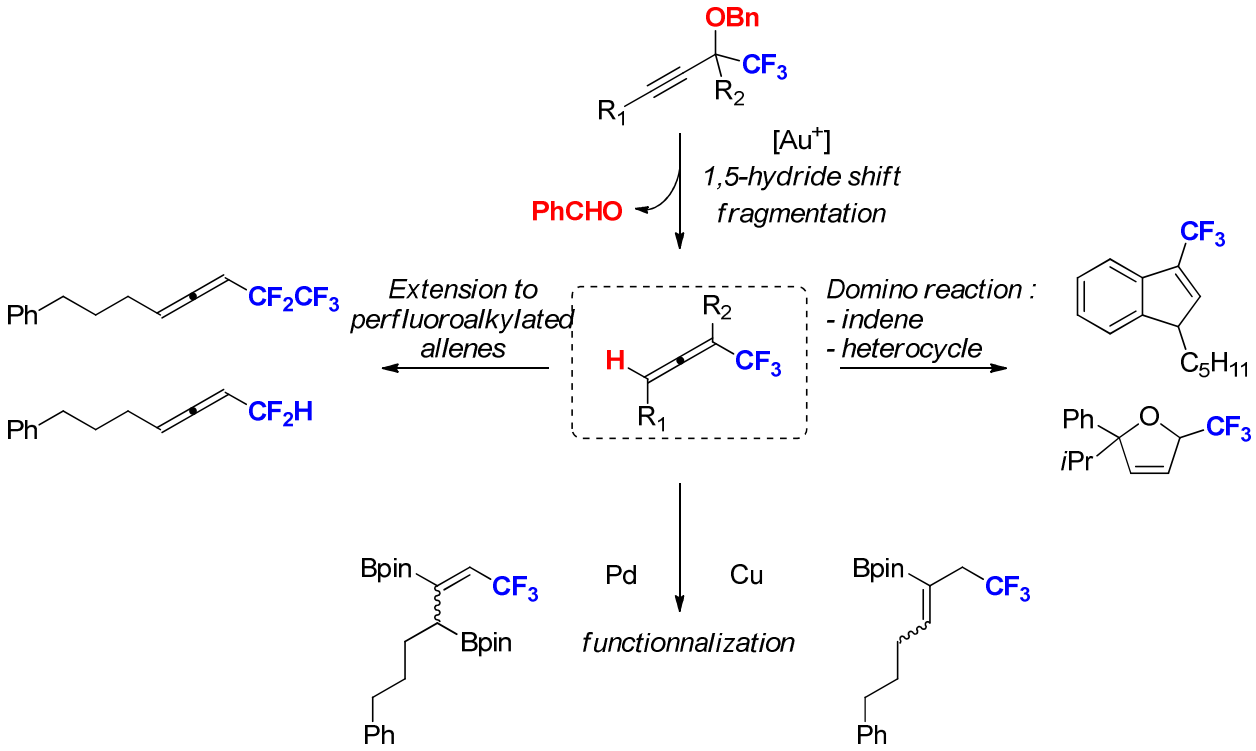


Figure 2.60 – Recapitulative scheme

However, the developed process suffers from some limitations. First of all, tetrasubstituted allenes are intrinsically inaccessible because of the hydride shift implemented in our strategy. The method includes the release of benzaldehyde as a by-product which has to be separated in the end of the process.

We already proved that chiral trifluoromethyl allenes could be obtained from enantio-enriched substrates but an interesting perspective would be to obtain the same result from racemic substrates via a kinetic resolution by a chiral gold catalyst (Figure 2.61). A few chiral ligands could be tried such as the popular BINOL, TADDOL, or BINAP.

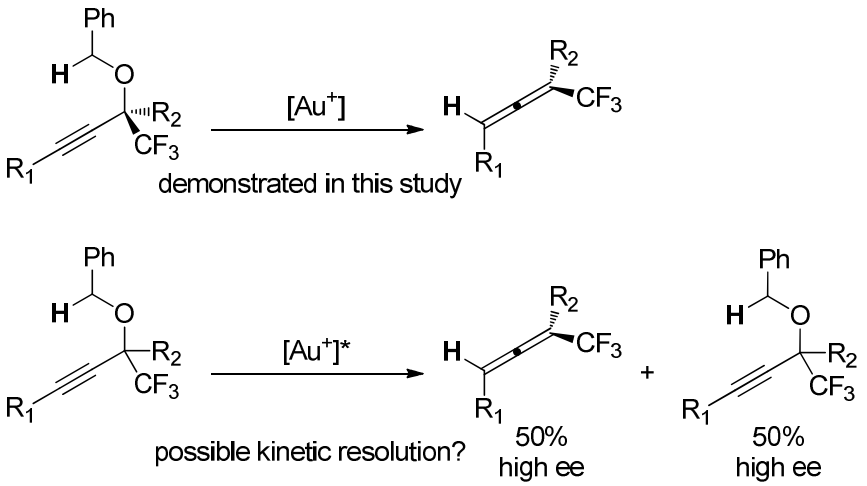


Figure 2.61 – Possible synthesis of chiral trifluoromethyl allenes

Another interesting application would be the use our chemistry in a total synthesis of Celecoxib which is an anti-inflammatory drug.[155] To date, most of the reported methods for the synthesis of Celecoxib and its derivatives rely on the coupling between a hydrazine and a 1,3-diketone derivative under harsh thermic and acidic conditions, leading in many cases to regioselectivity issues.[156] The alternative that we could suggest would consists of forming the pyrrazole moiety via a [3+2] cycloaddition between a 1-trifluoromethyl-3-toluyl allene and a diazene partner which would be perfectly polarized by the sulfonamide substituent. These type of reactions are usually carried out under mild conditions and provides excellent regioselectivity, which represents a significant advantage compared to the previously reported methods.

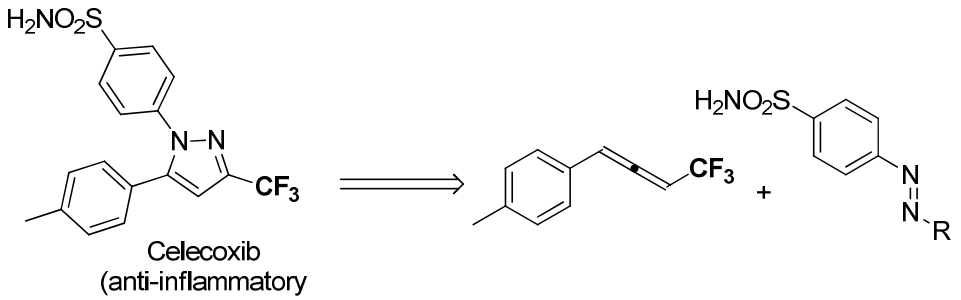


Figure 2.62 – Possible retrosynthesis of Celecoxib from a trifluoromethyl allene

[155] McCormack, P.L. *Drugs* **2011**, *71*, 2457.
[156] Dadiboyena, S.; Hemme II, A.T. *Curr. Org. Chem.* **2012**, *16*, 1390.

Chapter 3 :

Gold-catalyzed synthesis

of *2H*-1,3-oxazines

This project was conducted under the supervision of Dr. Fabien Gagosz and Dr. Shunsuke Chiba in collaboration with Ciputra Tejo who provided part of the results presented hereafter. The results obtained by the author are marked by an asterisk.

The results of this study were published in the following article :

Lonca, G.H; Tejo, C.; Chan, H.L.; Chiba, S.; Gagosz, F. *Chem. Comm.* **2017**, *53*, 736.

3.1 Introduction to *2H*-1,3-oxazines

3.1.1 Structure and properties of *2H*-1,3-oxazines

Oxazines are doubly unsaturated 6-membered ring heterocycles containing one nitrogen atom and one oxygen atom. According to the relative position of these two heteroatoms, oxazines are named 1,2-, 1,3- or 1,4- oxazines (Figure 3.1). Then, the prefix *nH-* is added, with *n* being the position of the atom not engaged in an insaturation.

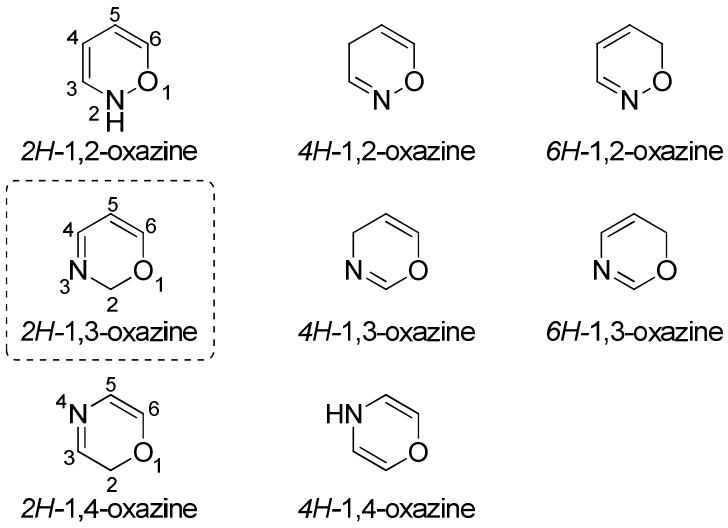


Figure 3.1 – General structure of oxazines

Among this family, 1,3-oxazines are particularly interesting as their derivatives find a plethora of applications, notably thanks to their biological activity.[157] For example, benzo-1,3-oxazines and oxo- or thiono-1,3-oxazines are important scaffolds present in the structure of many

[157] For a report on synthesis and biological activity of 1,3-oxazine derivatives, see : a) Eckstein, Z.; Urbanski, T. *Advances in Heterocyclic Chemistry*, **1963**, *2*, 311 ; b) Zakhs, V.E.; Yakovlev, I.P.; Ivin, B.A. *Chemistry of Heterocyclic Compounds* **1987**, *23*, 1149.

pharmalogically active compounds such as anti-tumoral,[158] anti-bacterial,[159] anti-HIV[160] or anti-malarial[161] drugs (Figure 3.2).

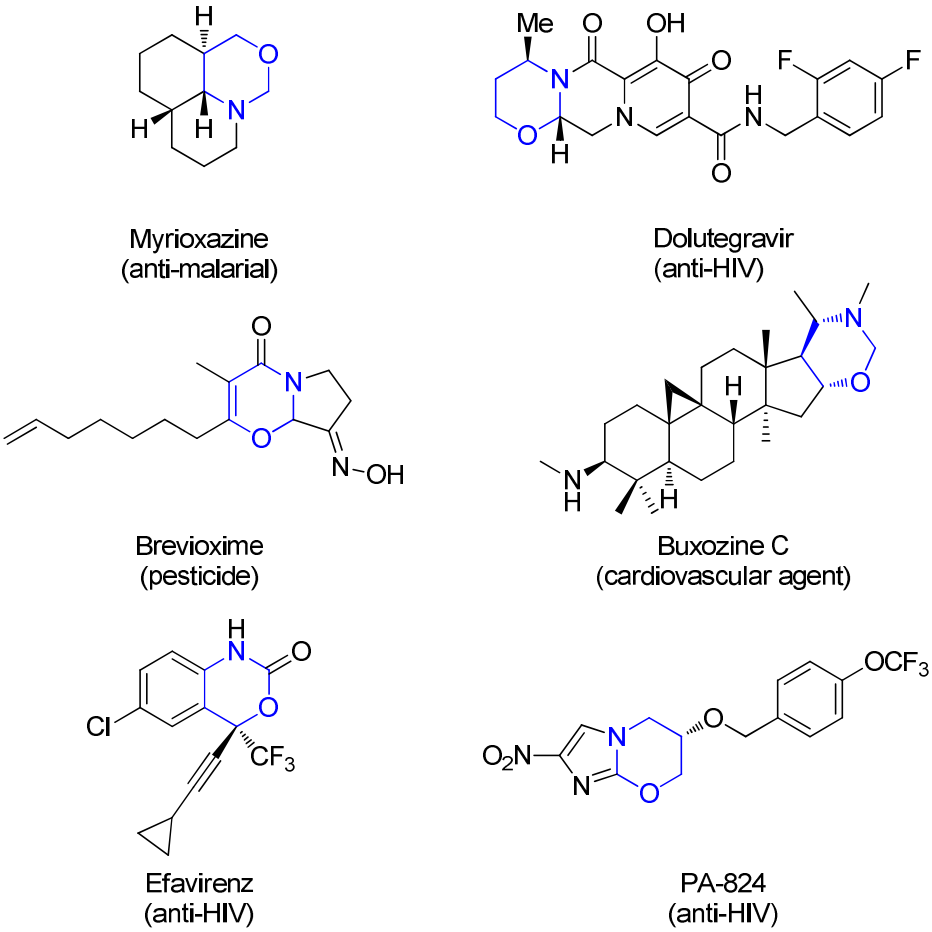


Figure 3.2 – Examples of biologically active compounds Containing a 1,3-oxazine motif

[158] a) Kuehne, M.E.; Konopke, E.A. *J. Med. Chem.* **1962**, *5*, 257 ; b) Chylinska, J.B.; Urbanski, T. *J. Med. Chem.* **1963**, *6*, 484 ; (c) Hsu, L.Y.; Lin, C.H. *Heterocycles* **1996**, *43*, 2687.
[159] a) Chylinska, J.B.; Janowiec, M.; Urbanski, T. *Br. J. Pharmacol.* **1971**, *43*, 649 ; b) Latif, N.; Mishriky, N.; Massad, F. *Aust. J. Chem.* **1982**, *35*, 1037.
[160] a) Pedersen, O.S.; Pedersen, E.B. *Synthesis* **2000**, 479 ; b) Cocuzza, A.J.; Chidester, D.R.; Cordova, B.C.; Jeffrey, S.; Parsons, R.L.; Bacheler, L.T.; Erickson-Viitanen, S.; Trainor, G.L.; Ko, S.S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1177.
[161] Duffin, W.M.; Rollo, I.M.; *Br. J. Pharmacol.* **1957**, *12*, 171.

Moreover, the sensitivity of 1,3-oxazines allowed the development of chromophore detectors for pH change[162] and for the presence of cyanides[163] (Figure 3.3). The idea here is to use an oxazine containing compound which changes color in the presence of hydroxide or cyanide anions. This concept relies on a nucleophilic addition of one of the two latter on the position 2 of the oxazine, followed by a ring opening which leads to a color change.

Following the same strategy, 1,3-oxazine based photoactivable fluorophores were also developed for direct applications in medical imaging.[164]

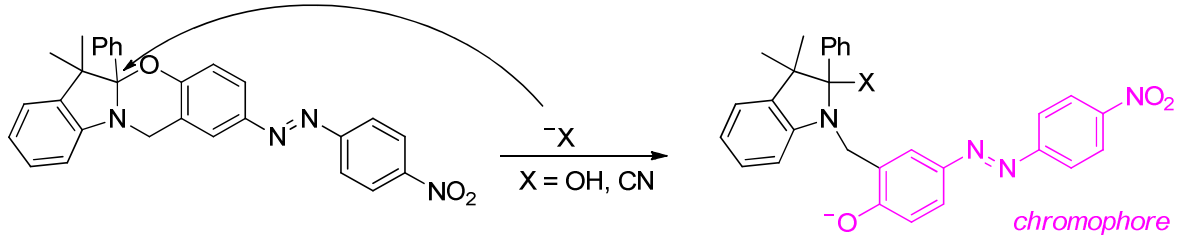


Figure 3.3 – Example of use of oxazines in chromophore cyanide and pH change detectors

1,3-oxazines also find applications in material sciences. Indeed, polymers of 1,3-benzoxazines were proved to possess interesting properties such as good mechanical performance, high thermal stability, low water adsorption and then do not encounter surface cracking issues that normal phenolic resins do.[165]

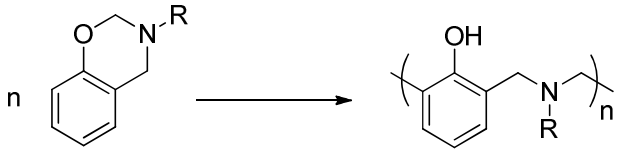


Figure 3.4 – Polymerization of 1,3-benzoxazines

[162] a) Pennakalathil, J.; Kim, T.H.; Kim, K.; Woo, K. Park, J.K.; Hong, J.D. *Langmuir* **2010**, *26*, 11349 ; b) Tomasolu, M.; Yildiz, I.; Raymo, F.M. *J. Phys. Chem. B.* **2006**, *110, 3853.*
[163] Tomasolu, M.; Sortino, S.; White, A.J.P.; Raymo, F.M. *J. Org. Chem.* **2006**, *71*, 744.
[164] Deniz, E.; Tomasulo, M.; Cusido, J.; Yildiz, I.; Petriella, M.; Bossi, M.L.; Sortino, S.; Raymo, F.M. *J. Phys. Chem. C.* **2012**, *116*, 6058.
[165] a) Li, S.; Wang, H.; Tao, M. Designed Monomers and Polymers, **2014**, *17*, 693 ; b) Chernikh, A. "Main chain type benzoxazine polymers for high performance application"

Therefore, *2H*-1,3-oxazines represent a class of interesting intermediates as they can be used as precursors to access a wide range of 1,3-oxazine derivatives. Indeed, their insaturations can be regarded as either an enol ether, an imine, a Michael acceptor or even an aza-diene, which opens the door to a large range of reactivity that can be used for structure diversification (Figure 3.5)

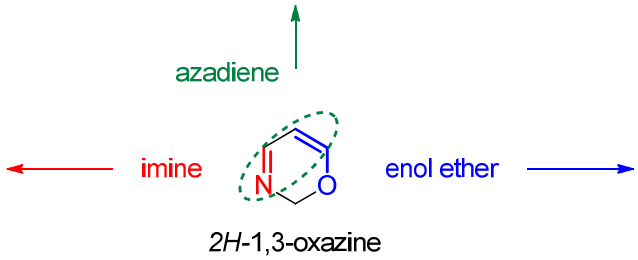


Figure 3.5 – Reactivity of *2H*-1,3-oxazines for derivatization

In summary, the 1,3-oxazine motif is a very important moiety, of which the structure derivatives are present in the structures of a large number of biologically active compounds. Moreover, polymers of 1,3-benzoxazines were proved to represent an interesting alternative to phenolic resins. Among this class of heterocycles, *2H*-1,3-oxazines are excellent precursors to access a large range of other 1,3-oxazines moieties as their structures possess diverse functional groups which can be used for derivatization. As a consequence, notable effort has been devoted to these synthesis.

3.1.2 Background on the synthesis of *2H*-1,3-oxazines

Given the potential of *2H*-1,3-oxazines, many groups have focused their attention on developing methods for their synthesis (Figure 3.6). These strategies include cyclization reactions of azadienes with carbonyl partners, but also cyclizations initiated by a aza-Wittig type reaction. Besides, methods have been developed for the coupling between rhodium carbenes and azirines or isoxazoles.

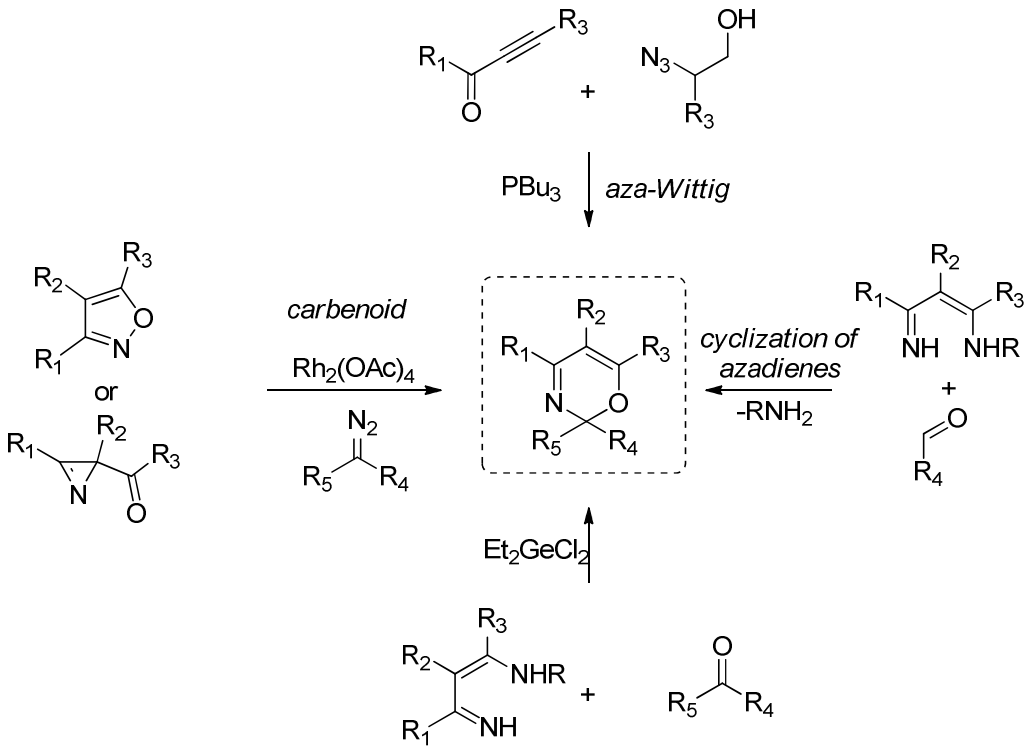


Figure 3.6 – Reported methods for synthesis of *2H*-1,3-oxazines

❖ Germanium-mediated synthesis of *2H*-1,3-oxazines :

The first method for the synthesis of *2H*-1,3-oxazines was developed by Barluenga and coworkers in 1993 and relies on a germanium-mediated formation of a 7-membered ring, followed by a ring contraction (Figure 3.7).[166]

[166] Barluenga, J.; Tomas, M.; Ballesteros, A.; Kong, J.S.; Garcia-Granda, S.; Aguirre, A. *J. Chem. Soc., Chem. Commun*. **1993**, 217.

The mechanism of this reaction starts with the formation of a 6-membered germanium metallocycle from a 4-amino-1-azadiene, followed by a 1,2-insertion on the ketone of a diethyl ketomalonate. Then, the resulting 8-membered metallocycle undergoes a rearrangement to provide, after hydrolysis, a 7-membered heterocycle which also rearranges under thermic conditions to provide a *2H*-1,3-oxazine product.

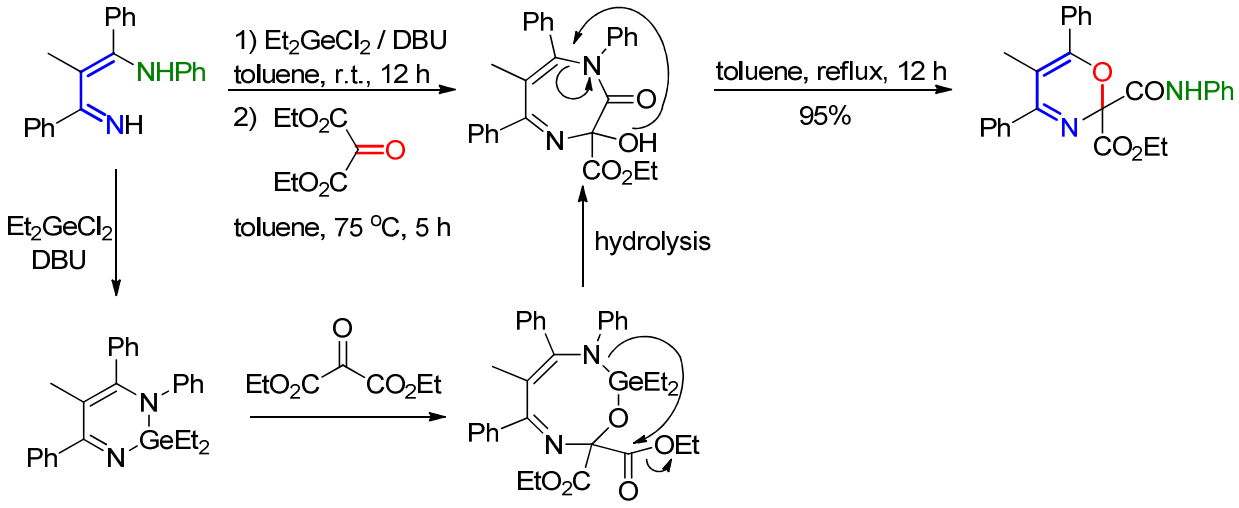


Figure 3.7 – Germanium-mediated synthesis of *2H*-1,3-oxazines

Although this process seems to be efficient, the use of a stoichiometric amount of toxic[167] and relatively expensive diethyl germanium dichloride is obviously a limitation.

❖ Synthesis of *2H*-1,3-oxazines *via* cyclization of 4-amino-1-azadienes :

Later on, the group of Barluenga reported another method, relying on a direct cyclization between the same type of 4-amino-1-azadiene substrates and ethyl glyoxolate with a displacement of the amino part (Figure 3.8).[168] The mechanism is likely to be initiated by a hetero Diels-Alder reaction between the azadiene and the aldehyde partner to give a precursor which, upon elimination of aniline, provides an oxazine product.

[167] For reports on toxicity of germanium, see : a) Arts, J.H.; Til, H.P.; Kuper, C.F.; de Neve, R.; Swennen, B. *Food CHem. Toxicol.* **1994**, *32*, 1037 ; b) Tao, S.H.; Bolger, P.M. *Requl. Toxicol. Pharmacol.* **1997**, *25*, 211.

[168] Barluenga, J.; Tomas, M.; Ballesteros, A.; Kong, J.S. *Tetrahedron* **1996**, *52*, 3095.

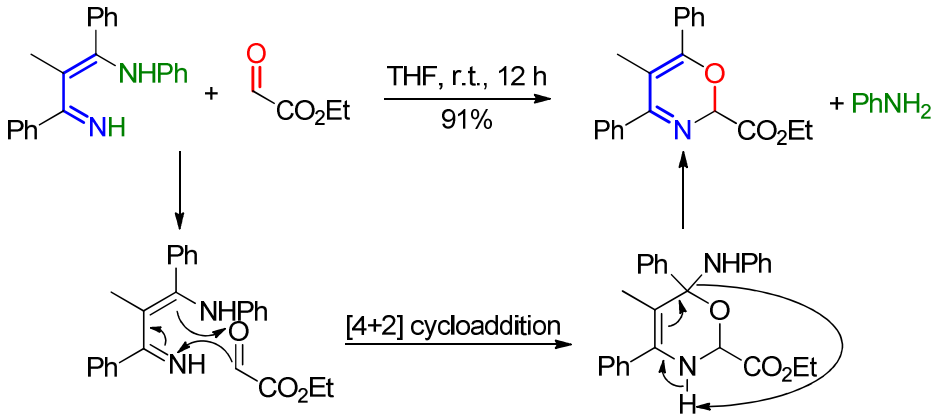


Figure 3.8 – Synthesis of *2H*-1,3-oxazines from cyclization of 4-amino-1-azadienes and ethyl glyoxolate

However, this method presents some drawbacks. For example, the oxazine products are often formed along with some pyrimidine byproducts, resulting from a first condensation of ethyl glyoxolate with the amino group of the substrate, followed by an electro-cyclization.

❖ Synthesis of *2H*-1,3-oxazines *via* aza-Wittig reaction :

Another interesting approach, reported by Taran *et al.*, consists on a phosphine-mediated cyclization between propargyl ketones and β-azido alcohols (Figure 3.9).[169]

The mechanism of this reaction is initiated by the formation of an aza-ylide compound which reacts with the propargyl ketone in an aza-Witting type reaction. The resulting intermediate then evolves *via* a *7-endo-dig* cyclization to provide a 7-membered heterocycle which undergoes a subsequent β-elimination and a *6-exo-trig* cyclization to give an oxazine product.

[169] Francois-Endelmond, C.; Carlin, T.; Thuery, P.; Loreau, O.; Taran, F. *Org. Lett.* **2010**, *12*, 40.

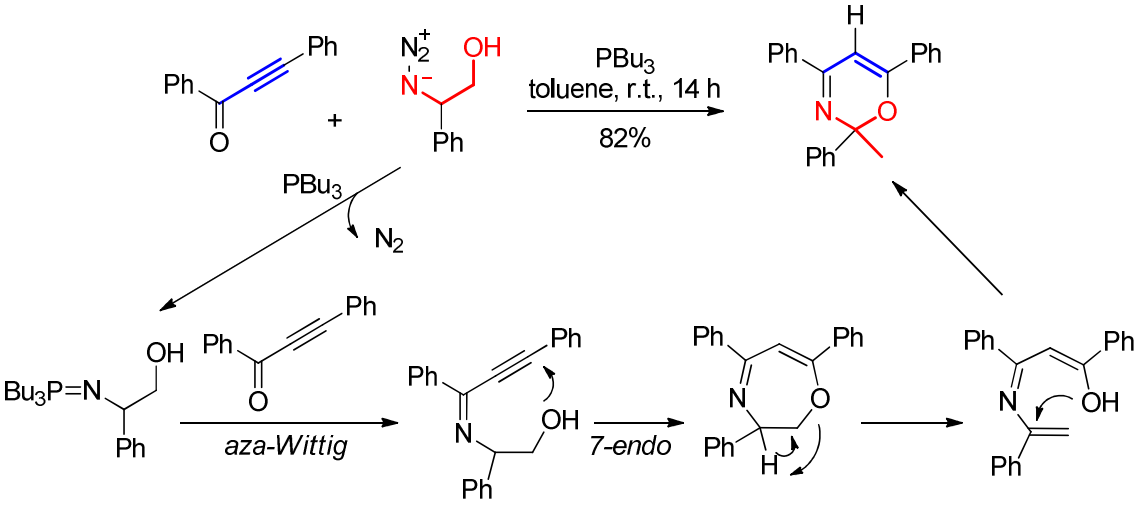


Figure 3.9 – Synthesis of *2H*-1,3-oxazines from cyclization of between propargyl ketones and β-azido alcohols

This method is efficient but presents some issues with regard to the substrate scope. Indeed, an aromatic substituent is necessary on the carbon atom initially bearing the azide moiety, otherwise the β-elimination step does not happen and the reaction stops at the formation of the 7-membered ring intermediate.

❖ Synthesis of *2H*-1,3-oxazines using rhodium carbenoids :

More recently, methods were developed to access *2H*-1,3-oxazines from diazo compounds and azirine-carboxyaldehydes (Figure 3.10, eq. 1)[170] or isoxazoles (eq. 2).[171]

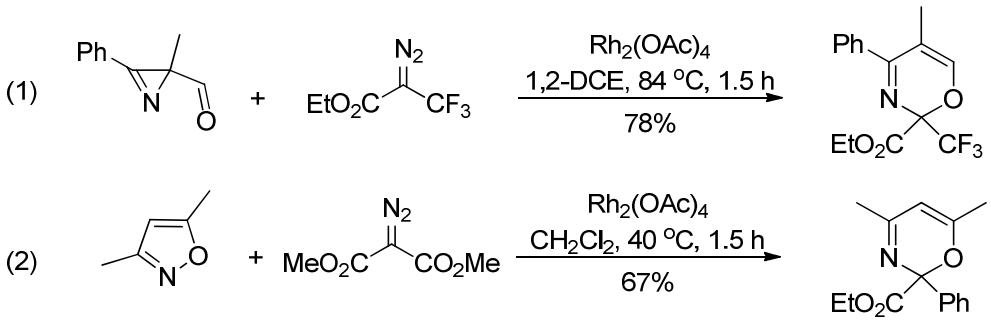


Figure 3.10 - Rhodium-catalyzed synthesis of *2H*-1,3-oxazines

[170] Zavyalov, K.V.; Novikov, M.S.; Khlebnikov, A.F.; Pakalnis, V.V. *Tetrahedron* **2014**, *70*, 3377.
[171] a) Manning, J.R.; Davies, H.M.L. *Tetrahedron* **2008**, *64*, 6901 ; b) Khlebnikov, A.F.; Novikov, M.S.; Gorbunova, Y.G.; Galenko, E.E.; Mikhailov, K.I.; Pakalnis, V.V.; Avdontceva, M.S. *Beilstein J. Org. Chem.* **2014**, *10,* 1896

In both cases, the mechanism is initiated by the generation of a rhodium-carbenoid species. Then, the subsequent addition of the nitrogen atom of the isoxazole / azirine to the carbene, followed by a ring opening provides a common 4-carboxyaldehyde-2-azadiene intermediate which undergoes an electro-cyclization to give an oxazine (Figure 3.11).

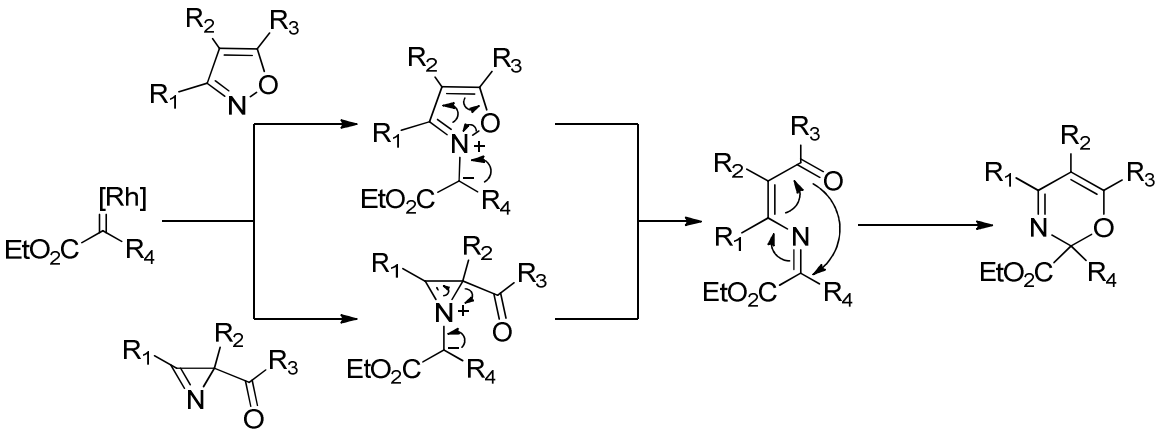


Figure 3.11 – Mechanism of the rhodium-catalyzed synthesis of *2H*-1,3-oxazines

Although, being very elegant, this method allows only a narrow range of modification of the substituents, especially on the 2-position which must bear electron-withdrawing groups to stabilize the diazo group in the precursor.

So far, the methods previously reported in the literature for the synthesis of *2H*-1,3-oxazines suffer from several drawbacks. On one hand, the first methods developed were either relying on the use of stoichiometric amounts of toxic germanium salts or were affected by the systematic formation of pyrimidine byproducts. On the other hand, the methods that were later reported were more efficient but suffered from narrow substrate scopes. Hence our interest to develop an efficient method to access widely substituted *2H*-1,3-oxazines.

To this end, we thought of taking advantage of a powerful tool for the construction of nitrogen containing heterocycles : the azide-yne cyclization. For a better comprehension, the next paragraph will introduce the chemistry of azides under gold catalysis.

3.2 Gold-catalyzed cyclization of azido alkynes

Nitrene are powerful tools for the synthesis of nitrogen containing heterocycles. Under gold catalysis, the addition of nitrenoid groups to gold-activated alkynes leads to the formation of enamine type gold intermediates. The electron delocalization from the gold atom then leads to the generation of α-imino gold carbenes which can evolve following different pathways (Figure 3.12).[172]

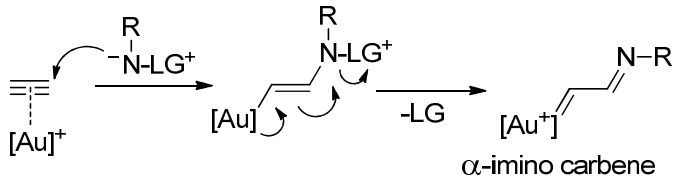


Figure 3.12 – Gold-catalyzed addition of nitrenoids to alkynes

Concretely, nitrene precursors can be azirines[173] or isoxazoles[174] which, after their addition to gold-activated alkynes and back donation from the gold complex, undergo a ring opening. Similarly, azide compounds or *N*-pyridinium aminides[175] can also be used as nitrenoids to be added onto gold-activated alkynes, and respectively undergo extrusion of dinitrogen and pyridine during the formation of the gold carbene (Figure 3.13).

[172] For a review on the use of nitrenoids in heterocycles synthesis, see : Davies, P.W.; Garzon, M. *Asian J. Org. Chem.* **2015**, *4*, 694.
[173] For publications on the use of azirines in gold-catalyzed reactions, see :a) Prechter, A.; Henrion, G.; Faudot dit Bel, P.; Gagosz, F. *Angew. Chem. Int. Ed.* **2014**, *53*, 4959 ; b) Li, T.; Xin, X.; Wang, C.; Wang, D.; Wu, F.; Li, X.; Wan, B. *Org.Lett.* ***2014****, 16*, 4806 ; c) Jin, L.; Wu, Y.; Zhao, X. *J. Org. Chem.* **2015**, *80*, 3547 ; d) Zhu, L.; Lu, Y.; Mao, Z.; Huang, X. *Org. Lett.* **2015**, *17*, 30.
[174] a) Zhou, A.H.; He, Q.; Shu, C.; Yu, Y.F.; Liu, S.; Zhao, T.; Zhang, W.; Lu, X.; Ye, L.W. *Chem. Sci.* **2015**, *6*, 1265 ; b) Jin, H.; Tian, B.; Song, X.; Xie, J.; Rudolph, M.; Rominger, F.; Hashmi, A.S.K. *Angew. Chem. Int. Ed.* **2016**, *55*, 12688.
[175] a) Davies, P.W.; Cremonesi, A.; Dumitrescu, L. *Angew. Chem. Int. Ed.* **2011**, *50*, 8931 ; b) Chatzopoulou, E.; Davies, P.W. *Chem. Commun.* **2013**, *49*, 8617.

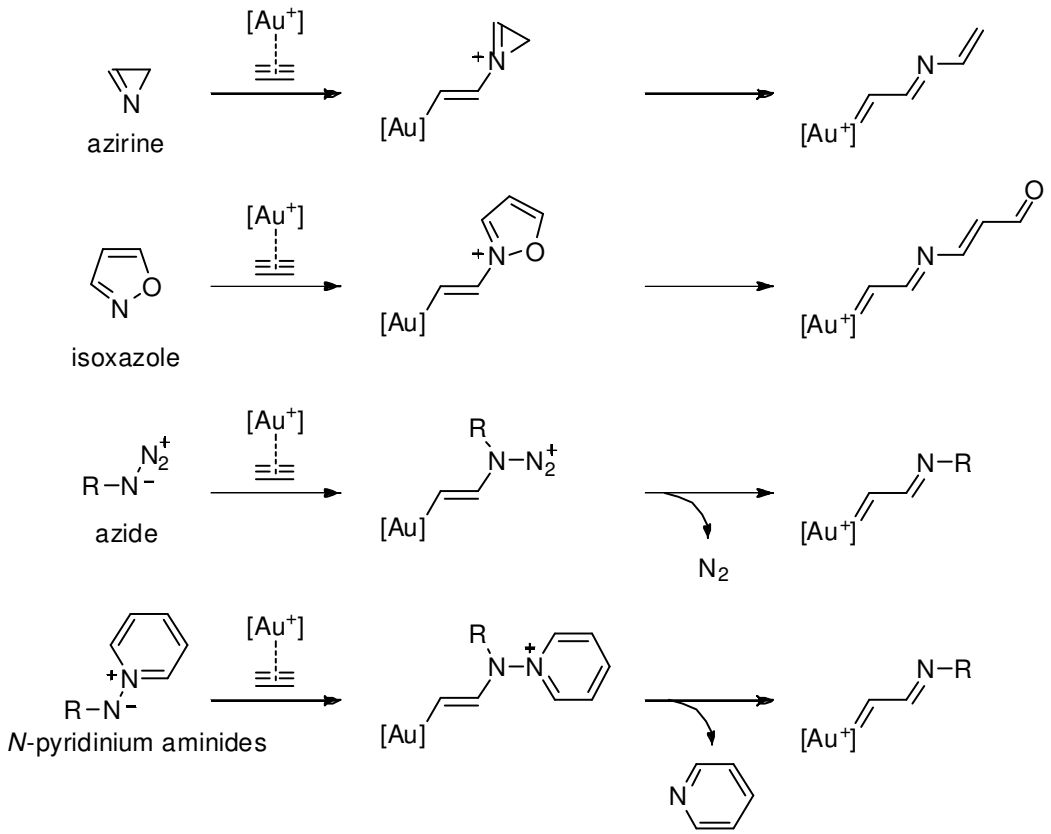


Figure 3.13 – Formation of α-imino gold carbene from different nitrenoids

Among these nitrene, particular attention has been given to azides because of their stability, the easiness of their preparation and their wide range of application. Notably, different types of addition of azides to alkynes have already been explored :

- Intermolecular additions :

External azides can be added to alkynes under gold catalysis conditions. However, because of the low nucleophilicity of azides, activated alkynes such as ynamides are usually required for intermolecular additions (Figure 3.14). Given the strong polarization of the C≡C bond induced by the presence of the nitrogen atom, the azido group adds onto the alkyne to generate a 1,1-diamino vinyl aurate intermediate. Then, the backdonation from the gold complex leads to the formation of an α-amidino gold carbene with the release of dinitrogen. From then, the carbene can be trapped following different pathways. For example, Ye and coworkers developed an efficient method to access 2-aminoindole, relying on a trapping of the carbene by an aryl group connected

to the nitrogen of the ynamide (eq. 1).[176] In another case, the same group used enynamide substrates to synthesize 2-aminopyrrole products. Here, the carbene intermediate undergoes a Nazarov type rearrangement, leading to a pyrrol ring (eq. 2).[177]

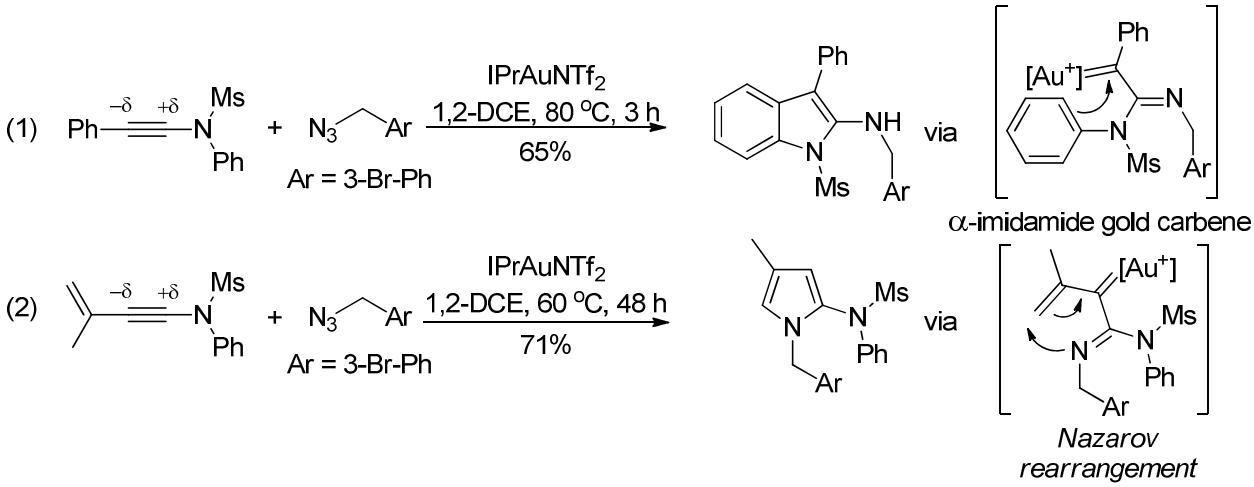


Figure 3.14 – Gold-catalyzed intermolecular addition of azides onto alkynes

In the case of azido alkynes, the intramolecular addition can occur following different modes: a *5-exo*, a *6-exo,* a *5-endo*, or a *6-endo* cyclization.

❖ *5-exo and 6-exo* cyclizations :

In 2012, Zhang and coworkers reported a method to access polycyclic compounds possessing a pyrrol moiety. Their strategy relies on a *5-exo* or *6-exo* cyclization of azido 1,3-enyne. Once the azide-yne cyclization occurred, the pyrrol motif is built by a Nazarov type rearrangement of the resulting carbene intermediate. (eq. 1,2).[178]

[176] Shu, C.; Wang, Y.H.; Zhou, B.; Li, X.L.; Ping, Y.F.; Lu, X.; Ye, L.W. *J. Am. Chem. Soc*. **2015**, *137*, 9567.
[177] Shu, C.; Wang, Y.H.; Shen, C.H.; Ruan, P.P.; Lu, X.; Ye, L.W. *Org. Lett*. **2016**, *18*, 3254.
[178] Yan, Z.Y.; Xiao, J.; Zhang, L. *Angew. Chem. Int. Ed*. **2012**, *51*, 8624.

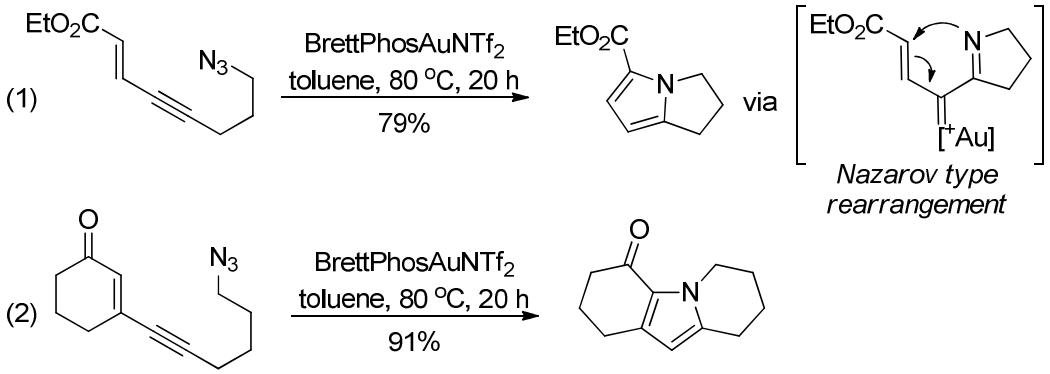


Figure 3.15 – Examples of *exo* cyclization of azide-ynes

❖ *5-endo* cyclizations :

5-endo cyclization of an internal azide to an alkyne is the most common case observed and leads to the formation of a cyclic α-imino gold carbene.

These carbenes can evolve following different pathways, like trapping with external nucleophiles (Figure 3.15). For instance, Zhang and coworkers used anisole as a nucleophile in a synthesis of indoles (eq. 1).[179] In this reaction, the *5-endo* cyclization of a 2-alkynyl aryl azide derivative delivers a carbene which reacts with anisole in a Friedel-Craft type reaction. However, the regioselectivity is not complete and a 1:7 mixture of the ortho and *para* products is obtained.

Similarly, carbenes can be trapped by alcohols. Our group has employed this strategy in a synthesis of 3-oxindoles (eq. 2).[180] Starting with the same type of substrate, the gold carbene can be attacked by a homoallylic alcohol to give a 3-allyloxy indole intermediate. Then, the latter undergoes a Claisen type rearrangement to give a 3-oxindole product.

Similarly, Zhang *et al.* used propargyl alcohols to obtain allenic indolin-3-ones (eq. 3).[181]

Besides, the oxidation of the carbene is also achievable. For instance, in their mechanistic study, Toste *et al.* used diphenyl sulfoxide as an oxene source to trap the carbene thus giving a *2H*-pyrrol-4(*3H*)-one product (eq. 4).[182]

[179] Lu, B.; Luo, Y.; Liu, L.; Ye, L.; Ye, L.; Wang, Y.; Zhang, L. *Angew. Chem. Int. Ed*. **2011**, *50*, 8358.
[180] Wetzel, A.; Gagosz, F. *Angew. Chem. Int. Ed*. **2011**, *50*, 7354.
[181] Li, N.; Wang, T.Y.; Gong, L.Z.; Zhang, L. *Chem. Eur. J*. **2015**, *21*, 3585.
[182] Witham, C.A.; Mauleon, P.; Shapiro, N.D.; Sherry, B.D.; Toste, F.D. *J. Am. Chem. Soc*. **2007**, *129*, 5838.

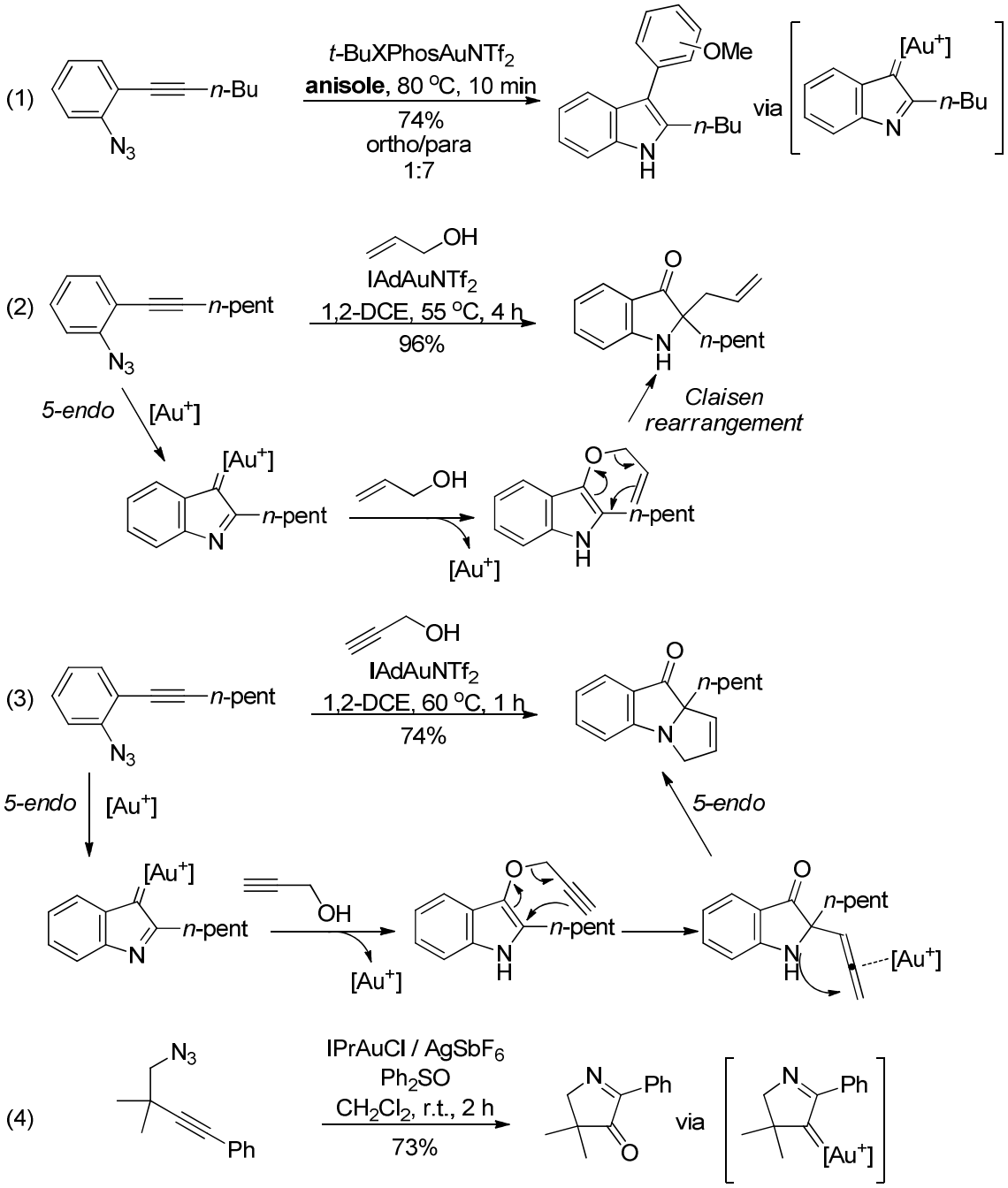


Figure 3.15 – Examples of *5-endo* azide-yne cyclizations followed by intermolecular trapping

In absence of any external nucleophile, the carbene can evolve through different rearrangements. For instance, Toste and his group showed that pyrroles could easily be obtained

by a *5-endo* cyclization of homopropargylic azides (Figure 3.16).[183] In this transformation, the carbene intermediate can undergo a 1,2-hydride shift or a 1,2-alkyl shift to give an intermediate which isomerizes into a pyrrol product. It should be noted that this work by Toste and coworkers is the first one reported in the literature concerning the use of azides as nucleophiles in gold-catalyzed reactions.

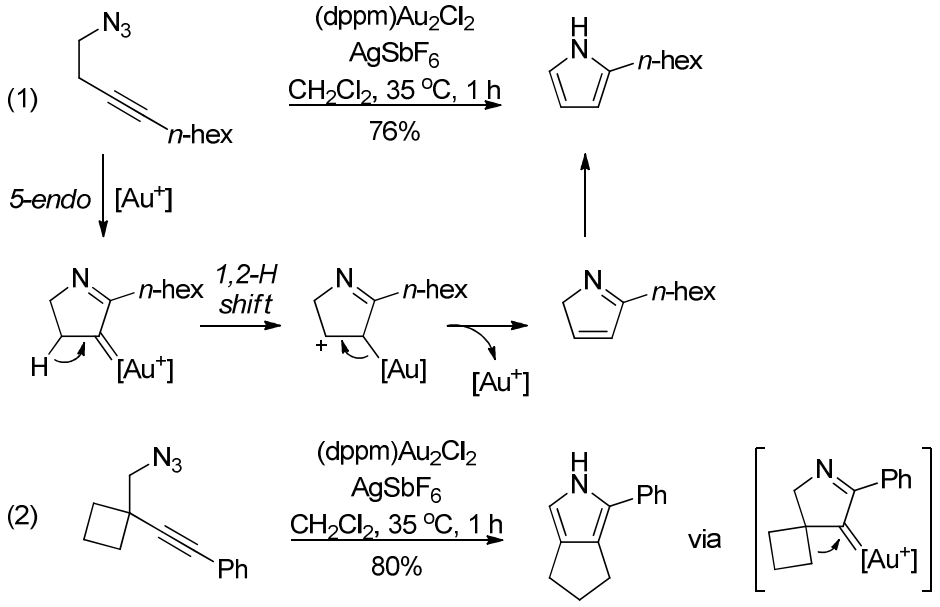


Figure 3.16 – Examples of *5-endo* azide-yne cyclizations followed by rearrangement

❖ *6-endo* cyclizations :

Very few reports can be found about gold-catalyzed *6-endo* cyclization of azides onto alkynes. Yamamoto and coworkers reported the synthesis of isoquinolines *via* a *6-endo* cyclization of 2-alkynyl benzyl azides (Figure 3.17, eq. 2).[184] In this case, after cyclization, a 1,4-hydride shift occurs and the resulting carbocation rearranges to give an isoquinoline product with regeneration of the catalyst. However, these transformations require a high catalyst loading (30 mol%) and are usually carried out at quite high temperature, which unavoidably leads to the formation of triazole byproducts.

[183] Gorin, D.J.; Davis, N.R.; Toste, F.D. *J. Am. Chem. Soc.* **2005**, *127*, 11260.
[184] Huo, Z.; Yamamoto, Y. *Tet. Lett.* **2009**, *50*, 3651.

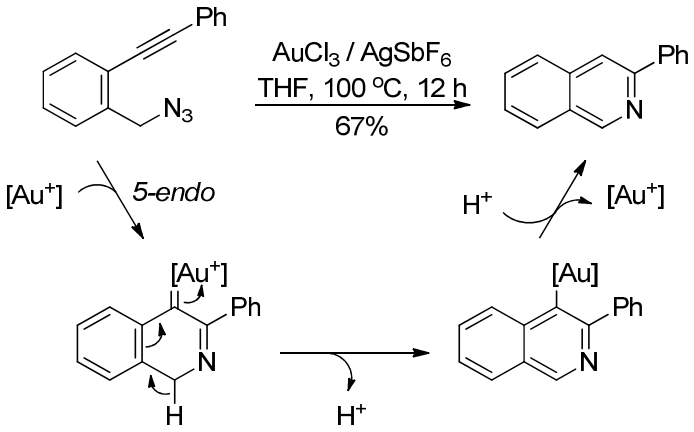


Figure 3.17- Examples of *6-endo* azide-yne cyclizations

In sumary, gold-catalyzed azide-yne cyclization is a useful strategy to access nitrogen containing heterocycles. Indeed, depending on the cyclization mode and the evolution of the resulting gold carbene, this method opens the door to the synthesis of pyrroles, *2H*-pyrrol-4(*3H*)-one, indoles, indolin-3-ones and isoquinolines. More particularly, nitrogen containing 6-membered cycles can be obtained by *6-endo* cyclizations, which could be a springboard for the synthesis of *2H*-1,3-oxazines. The next paragraphs summarize how we exploited this potential pathway.

3.3 Gold–catalyzed synthesis of *2H*-1,3-oxazines

3.3.1 Origin of the project

So far, the reported methods for the synthesis of *2H*-1,3-oxazines all suffer from some drawbacks such as the use of stoichiometric amounts of toxic metal species, restrictions on the substituents or the use of explosive diazo compounds.

Besides, although *5-endo* azide-yne cyclization reactions have been extensively used, *6-endo* azide-yne cyclizations remain anecdotic in the literature.

Thus, we decided to take up a double challenge, which is to develop a method to access *2H*-1,3-oxazines *via* a gold-catalyzed *6-endo* azide-yne cyclization. Indeed, we envisioned that the double insaturation of the heterocycle could be obtained from a gold-catalyzed *6-endo* azide-yne cyclization followed by a 1,2-hydride or group shift (Figure 3.18).

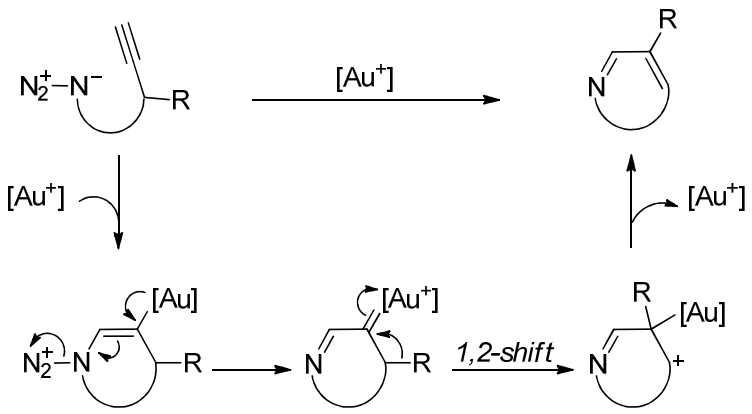


Figure 3.18 – Obtention of the double insaturation of *2H*-1,3-oxazines by gold-catalyzed endo azide-yne cyclization

Based on this hypothesis, we envisioned that using the following substrates under the appropriate gold catalysis conditions could enable the formation of the desired *2H*-1,3-oxazines (Figure 3.19).

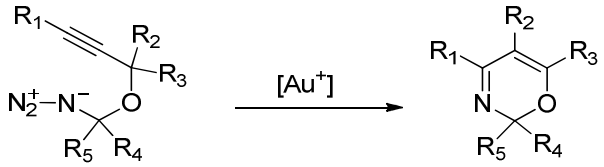


Figure 3.19 – Reaction design

Indeed, in this reaction, we expected the determining step to be the *6-endo* azide-yne cyclization. Therefore, the design of our substrates is optimal for this transformation as two important aspects are satisfied :

First of all, the different groups, R_2, R_3, R_4 and R_5 ensure the contribution of a Thorpe-Ingold effect to make the azido group and the alkyne closer, thus promoting their interaction.[185]

Moreover, the presence of the oxygen atom and an electron donating group R_1 should optimize the polarization of the C≡C bond, by σ-inductive effect and / or mesomeric effect (Figure 3.20).

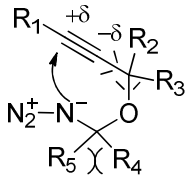
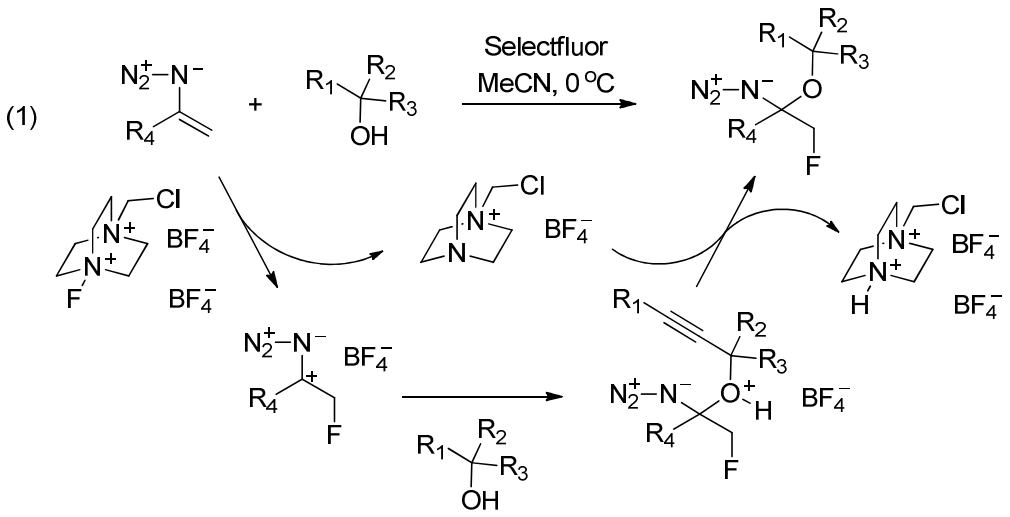


Figure 3.20 – Design of the substrate for Thorpe-Ingold effect and polarization of the C≡C bond

Recently, the group of Chiba developed a method consisting of linking vinyl azides and propargyl alcohols in the presence of Selectfluor® (Figure 3.21).[186] In this reaction, an electrophilic fluorination of a vinyl azide generate an iminium type intermediate. The subsequent trapping of this intermediate by an alcohol partner then leads, after deprotonation, to an azido acetal product. Notably, this coupling can be performed with propargylic alcohols, which represents an efficient way to prepare our substrate. Therefore, both our groups combined our respective knowledge of this linking methodology and of gold chemistry in a collaborative work to prepare these substrates and attempt to convert them into *2H*-1,3-oxazine products.

[185] For a review on the *gem*-disubstituent effect, see : Jung, M.E.; Piizzi, G. Chem. Rev. **2005,** *105*, 1735.
[186] Wang, Y.F.; Hu, M.; Hayashi, H.; Xing, B.; Chiba, S. *Org. Lett.* **2016**, *18*, 992.



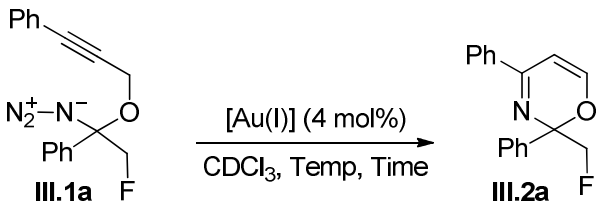
Application to the synthesis of our substrates

Figure 3.21 – Key step in the synthesis of starting material

3.3.2 Optimization and mechanism of the reaction

For the optimization, we used the model substrate **III.1a**, which bears a phenyl on the alkyne terminus to induce a suitable polarization of the C≡C bond, and no substituent at the propargylic position. The phenyl and fluoromethyl substituent on the R_4,R_5 positions were chosen out of convenience for the synthesis of the substrate and to have a significant Thorpe-Ingold effect. The first attempt was performed at a 0.2M concentration in deuterated chloroform, at 60 °C, using 4 mol% of the strongly electrophilic phosphite-based gold complexes[187] (Table 3.1, entry 1) which gratifyingly provided the oxazine product **III.2a** although only in trace amount. Keeping the same reaction conditions but using the less electrophilic phosphonite-based catalyst gave slightly better results as the product **III.2a** could be obtained in 15% yield (entry 2). Satisfyingly, much better results were obtained when the Buchwald biaryl ligand-based catalyst [XPhosAu(NCMe)]SbF_6 was used. This led to full conversion and good yield of the desired product (80%) in 15 mins of reaction (entry 3). Performing the reaction at room temperature did not affect the yield although the reaction time was much longer (entry 4). An enhancement of the yield could be obtained by increasing the σ-donating character of the ligand of the catalysts and the product **III.2a** was obtained in 88% yield using [*t*-BuXPhosAu(NCMe)]SbF_6 (entry 6) [Me_4XPhosAu(NCMe)]SbF_6 (entry 8) and [BrettPhosAu(NCMe)]SbF_6 (entry 11). Replacing the hexafluoroantimonate couter-anion by the bistriflimidate one had different effects, depending on the ligand. While the use of [XPhosAu]NTf_2 (entry 5) led to a drastic drop of the yield, no difference was observed for [*t*-BuXPhosAu]NTf_2 (entry 7) and we were glad to see that using [Me_4XPhosAu]NTf_2 not only did not affect the yield but considerably accelerated the reaction (entry 9), even when the catalyst loading was reduced to 3 mol% (entry 10). Thinking that more electron donating ligand could even more enhance the yield, we tried to use [PPh_3Au(NCMe)]SbF_6 and [IPrAu(NCMe)]SbF_6 catalysts but only low conversions were obtained (entries 12, 13). Therefore, we concluded that performing the reaction at room temperature in chloroform unsing 3 mol% of [Me_4XPhosAu]NTf_2 would be the standard procedure for this reaction.

[187] See section 1.1.3 for the influence of the ligand on gold complexes.



Entry	[Au(I)]	Temp	Time	Yield[a] III.2a
1	$P(OAr)_3Au(NCMe)SbF_6$	60 °C	24 h	< 5%
2	*t*-BuGPhosAu(NCMe)SbF_6	60 °C	24 h	15%
3	XPhosAu(NCMe)SbF_6	60 °C	15 mins	80%
4	XPhosAu(NCMe)SbF_6	r.t.	5 h	80%
5	$XPhosAuNTf_2$	r.t.	24 h	35%
6	*t*-BuXPhosAu(NCMe)SbF_6	r.t.	3 h	88%
7	*t*-BuXPhosAuNTf_2	r.t.	3 h	87 %
8	Me_4XPhosAu(NCMe)SbF_6	r.t.	1.5 h	88%
9	$Me_4XPhosAuNTf_2$	r.t.	10 mins	88%
10[b]	$Me_4XPhosAuNTf_2$	r.t.	20 mins	88%
11	BrettPhosAu(NCMe)SbF_6	r.t.	2 h	87%
12	PPh_3Au(NCMe)SbF_6	r.t.	24 h	10%
13	IPrAu(NCMe)SbF_6	r.t.	24 h	< 5%

The reaction were performed on a 0.2 mmol scale in $CDCl_3$ (0.2M) in sealed NMR tubes.
[a] NMR yield using 1,2-DCE as internal standard
[b] Only 3 mol% of catalyst were used

Table 3.1 – Optimization for the gold-catalyzed synthesis of *2H*-1,3-oxazines*

The structures of the catalysts which were used during the optimization are represented below.

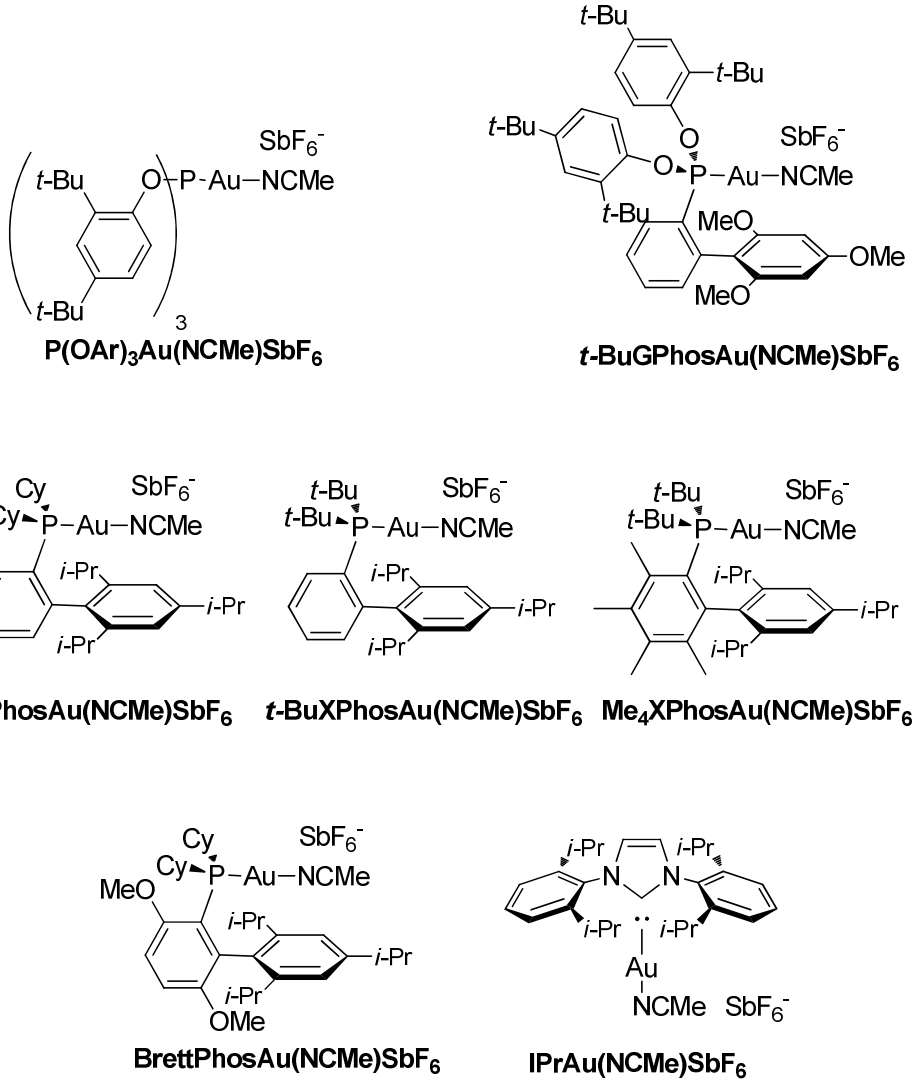


Figure 3.22 – Catalysts used during the optimization

In contradiction with our first idea, the *6-endo* azide-yne cyclization was apparently not the determining step in this reaction. Indeed, it would seem that the design of the substrate was good enough to promote the nucleophilic addition of the azide onto the alkyne without the need of an important activation of the alkyne by a strong Lewis acid such as the phosphite or the phosphonite based gold catalysts.

On the contrary, biaryl phosphine-based catalysts seem to be perfectly suitable for this reaction, which suggests that the determining step might be the extrusion of dinitrogen. Indeed, this step is promoted by the back donation from the gold complexes. It is then normal that π-donor ligands such as Buchwald phosphines provide better result than phosphites or phosphonites. It is

noticeable that the more electron rich the phosphine, the more efficient the reaction (XPhos < ^{t}BuXPhos < Me_4XPhos).

However, it seems that an appropriate balance must be found as the NHC (less π-acidic than the Buchwald phosphines) based catalysts could not perform the reaction efficiently. This ligand being even less π-acceptor than biaryl phosphines, the backdonation from the gold complex cannot be at stake and the reason for the observed low results in this case must be the too low Lewis acidity of this catalyst to promote the nucleophilic addition.

Based on these results, we suggested that this reaction proceeds *via* the following mechanism (Figure 3.23). After activation of the C≡C bond by the gold catalyst, a *6-endo* azide-yne cyclization occurs to give the aurate intermediate **III.A**. Then, back donation from the catalyst happens and extrusion of dinitrogen gives the gold carbene **III.B**. A 1,2-hydride shift then occurs to generate a carbocation intermediate **III.C** which, after regeneration of the catalyst, evolves into the desired *2H*-1,3-oxazine.

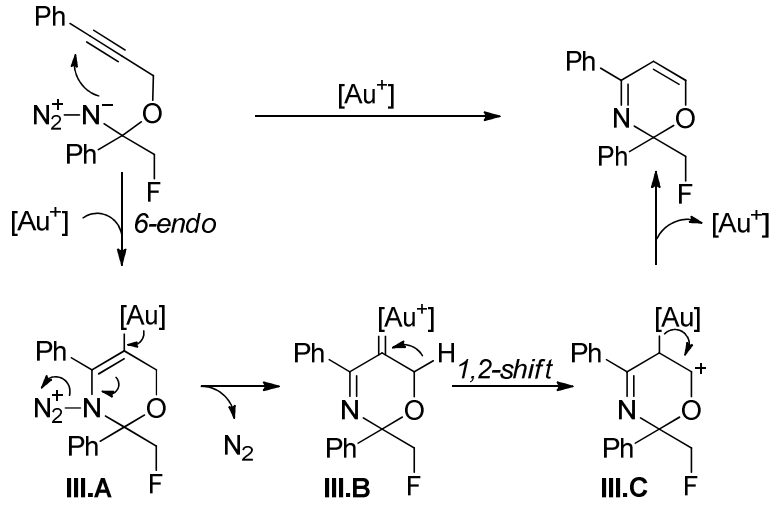


Figure 3.23 – Suggested mechanism

In an attempt to trap one of the intermediates, a reaction in presence of methanol was performed (Figure 3.24, eq. 1). Gratifyingly, trapping of the intermediate **III.C** happened and the compound **III.3a** was obtained in almost quantitative yield. Besides, to make sure that this result indeed resulted from the trapping of **III.C** and not from a subsequent transformation of the product, a control experiment was carried out (eq. 2). When oxazine **III.2a** was treated by the same gold catalyst in the presence of methanol, only an incomplete conversion was obtained after a much

longer reaction time, which tends to prove that the previous result was not arising majorly by a subsequent transformation of the oxazine.

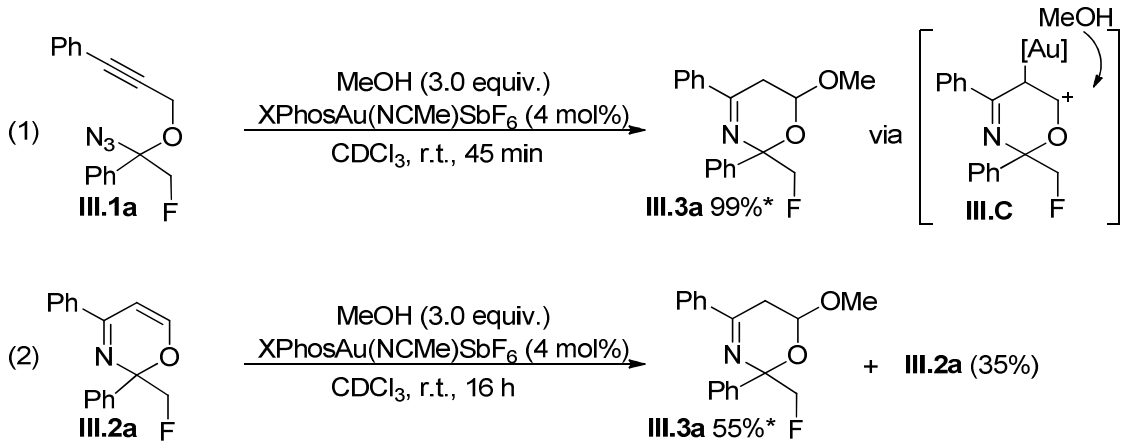


Figure 3.24 – Intermolecular trapping of intermediate III.C

3.3.3 Substrate scope of the reaction

We then focused our attention on the scope and limitations of this new transformation. The substrates that we evaluated in this reaction were prepared in overall good yields following different procedures according to the nature of their substituents. The detailed protocol and experimental data are reported in the experimental part of this manuscript and in the supporting information of the related publication.[188]

[188] Lonca, G.H; Tejo, C.; Chan, H.L.; Chiba, S.; Gagosz, F. *Chem. Comm.* **2017**, *53*, 736.

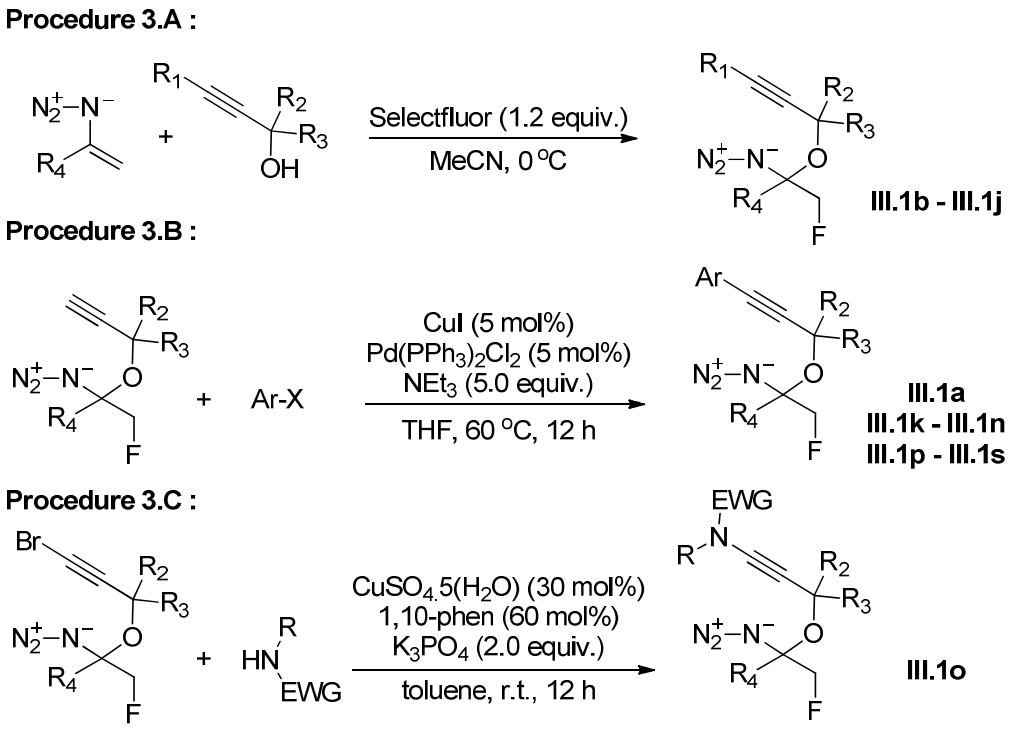
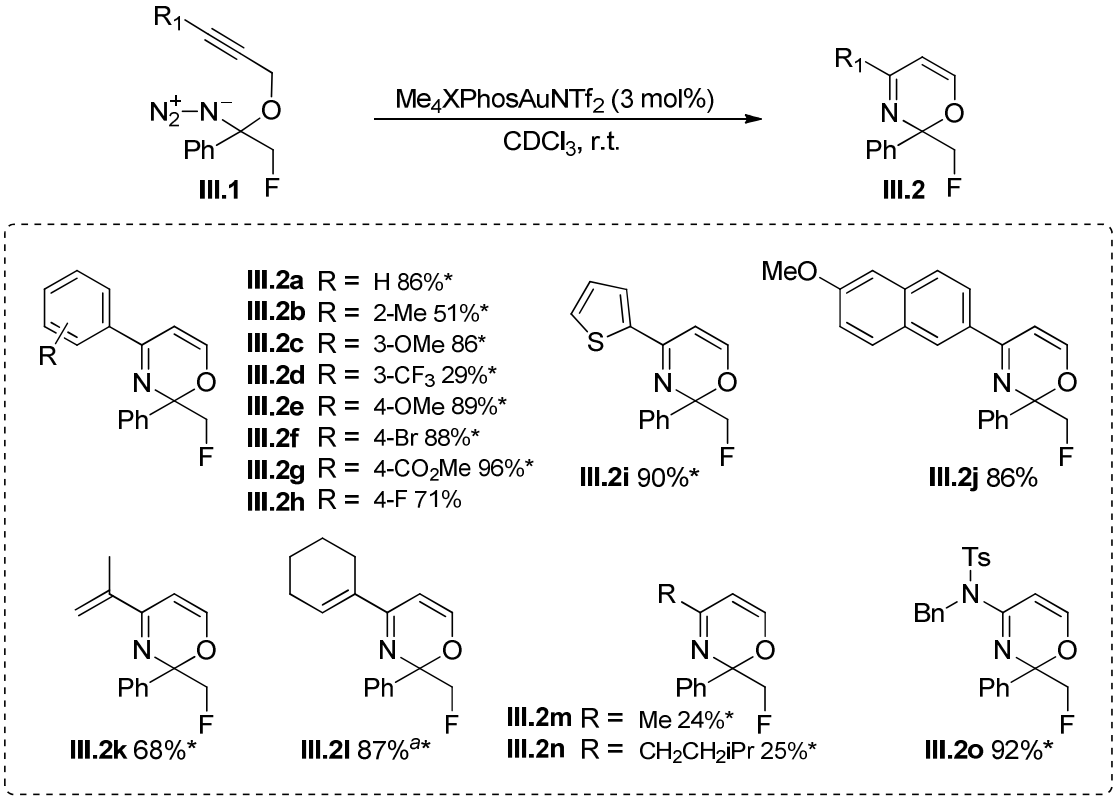


Figure 3.27 – General procedures for the preparation of the substrates

With the optimized conditions in hands ($Me_4XPhosAuNTf_2$ at room temperature, at a 0.2M concentration in chloroform), we started to investigate the substrate scope of the reaction with the variation of the acetylenic substituent in the substrates. Firstly, we tried the reaction with a series of substrates substituted by electron rich (Figure 3.26, **III.2a**, **III.2b**, **III.2c**, **III.2e**) and electron poor (**III.2d**, **III.2f**, **III.2g**, **III.2h**) aryl groups and we were pleased to obtain the corresponding *2H*-1,3-oxazines in good yields. If the good results with electron rich substituents were expected, the success with electron withdrawing substituents was, however, a pleasant surprise as they are supposed to disfavor the good polarization of the C≡C bond. However, this effect can be noticed in the reaction times of the reaction as the reaction proceeds more slowly for substrates bearing electron withdrawing substituents. The slightly lower yield obtained for the substrate **III.1b** can be explained by a steric hindrance generated by the methyl moiety which could hamper the coordination of the catalyst to the alkyne. Heteroaromatic (**III.2i**) and naphthalene type (**III.2j**) substituents were also tolerated and excellent yields were obtained in both cases. Enyne substrates were also tested and nicely were proved to properly react (**III.2k**, **III.2l**). On the contrary, the presence of an alkyl substituent at the acetylenic position led to a dramatic drop of the yield (**III.2m**, **III.2n**), presumably because an alkyl group is not sufficient to induce a good

polarization of the C≡C bond. On the other hand, the tosylynamide substrate provided one of the best result (**III.2o**) as the mesomeric effect favors a proper polarization of the C≡C bond. It is worth noting that none of the previously reported methods for the synthesis of *2H*-1,3-oxazines exhibit such a wide functional group tolerance nor such overall good yields.



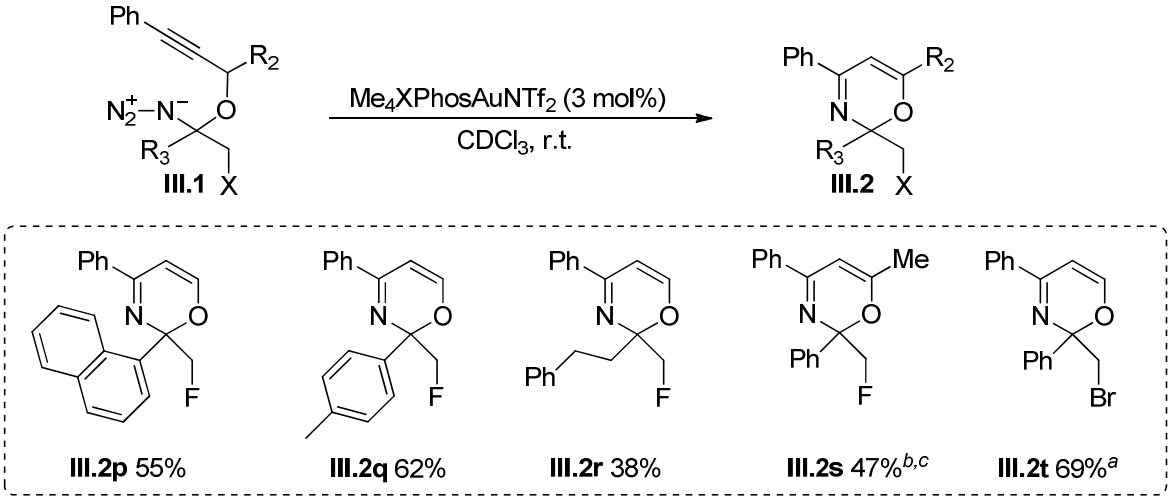
[a] ^{t}BuXPhosAuSbF$_6$.MeCN (3 mol%) was used

Figure 3.26 – Substrate scope of the reaction - Variation of the acetylenic substituent

We then turned our attention to the variation of the substituents of the acetal and at the propargylic positions (Figure 3.27). The phenyl group of the acetal could be replaced by a naphtyl (**III.2p**) or a tolyl (**III.2q**), and more importantly by an alkyl substituent such as a phenethyl (**III.2r**), which was impossible with the methods previously described in the literature. Installation of a methyl group on the propargyl position was not detrimental to the yield[189] although the reaction time was longer (**III.2s**). This might be tentatively explained by assuming that this methyl moiety hampers the activation of the alkyne by the gold catalyst, by creating some steric hindrance during

[189] the substrate being unstable, an overall yield from the propargyl alcohol is given.

the approach of the catalyst to the C≡C bond. Replacement of the fluoromethyl by a bromomethyl substituent (**III.2t**) still delivered the product in good yield although the catalytic loading had to be increased to (10 mol%), which can be tentatively explained by a potential decomposition of the catalyst via oxidative addition of the gold atom into the C-Br bond.[190]



[a] $Me_4XPhosAuNTf_2$ (10 mol%)
[b] $Me_4XPhosAuSbF_6$.MeCN (3 mol%)
[c] Overall yield for the synthesis of the substrate from the propargyl alcohol and key reaction

Figure 3.27 – Substrate scope of the reaction - Variation of the acetal and propargyl substituent

However, the transformation was unsuccessful in the case of a few substrates (Figure 3.28). Not surprisingly, electron withdrawing substituents (**III.1u** and **III.1v**) or the absence of substituent (**III.1x**) at the acetylenic position was detrimental for the reaction as they disfavor the correct polarization of the C≡C bond. The negative result obtained with the boc-ynamide substrate **III.1y** is more difficult to rationalize.

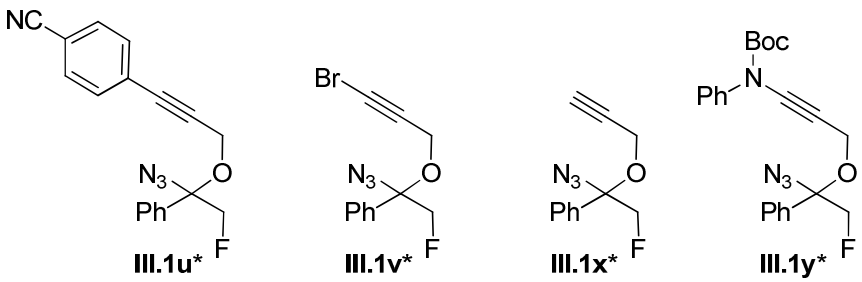


Figure 3.28- Unreactive substrates

[190] Joost, M.; Amgoune, A.; Bourissou, D. *Angew. Chem. Int. Ed.* **2015**, *54*, 15022.

3.3.4 Derivatization of *2H*-1,3-oxazines

3.3.4.1 Electrophilic fluorination of *2H*-1,3-oxazines

To further extol the interest of synthesizing *2H*-1,3-oxazines, we started to investigate their use as cyclic enol ethers and their reactivity toward electrophiles.

As presented in Chapter 2, fluorine is attracting more and more attention because of its properties in medicinal, agrochemical and material chemistry. Thus, we started by investigating the electrophilic fluorination of the product **III.2a** (Figure 3.29). And, after a short optimization, we were successful in performing an efficient fluorination of *2H*-1,3-oxazines by Selectfluor.® and trapping the resulting oxocarbenium intermediate **III.D** by methanol. This led, after deprotonation, to an interesting β-fluoro acetal product **III.4a**, which was obtained as a mixture of unidentified diastereoisomers in a 15:4.6:2:1 ratio.

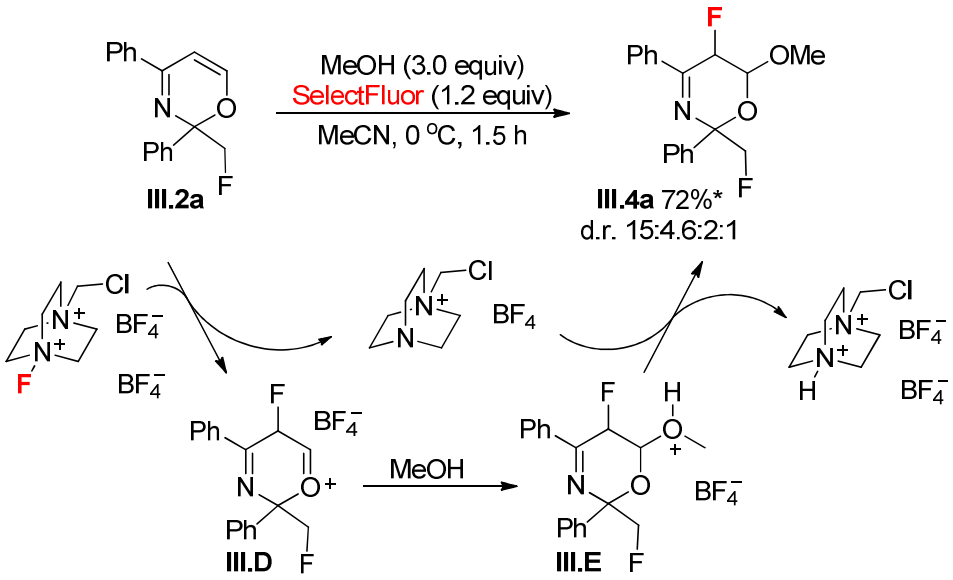


Figure 3.29 – Electrophilic fluorination of oxazines

3.3.4.2 Brominative ring opening of *2H*-1,3-oxazines

Inspired by this derivatization, we attempted an analogous electrophilic bromination of the oxazine products. We were expecting that the treatment of the product **III.2a** with an electrophilic brominating reagent would give the brominated heterocycle **III.F** (Figure 3.30).

However, when **III.2a** was treated with *N*-bromosuccinimide in presence of methanol, the formation of the expected product **III.F** was not observed but another compound was formed, which was determined to be the linear azadiene compound **III.5a**.

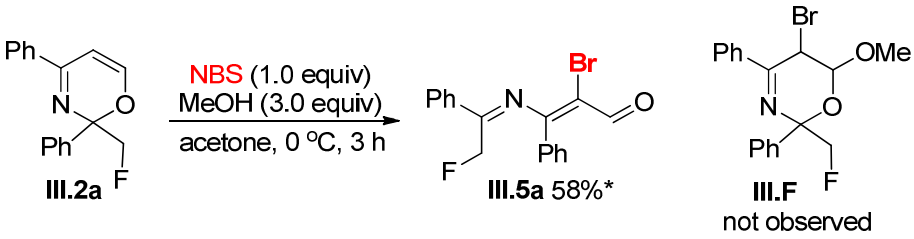


Figure 3.30 – First attempt for bromination of *2H*-1,3-oxazines

The structure of this unexpected product, and more especially the stereochemistry of its insaturations was confirmed by X-ray analysis.

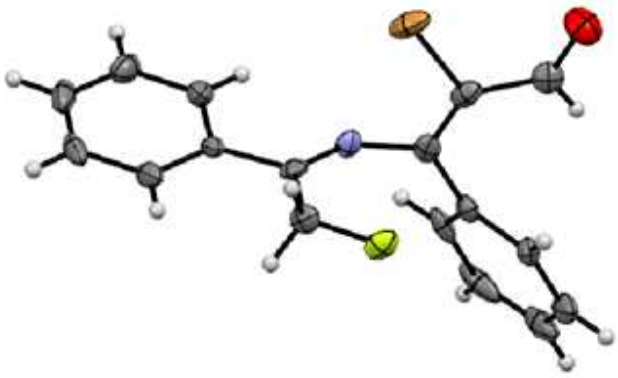


Figure 3.31 – X-ray spectroscopy of compound III.5a

The following mechanism was suggested to explain the formation of **III.5a** (Figure 3.32). The electrophilic bromination of **III.2a** could lead to the formation of an oxocarbenium intermediate **III.G** which could undergo a ring opening to give the cationic intermediate **III.H**. Then, intermediate **III.H** can adopt two conformations, one of which being disfavored by a steric repulsion between the bromide atom and the phenyl substituents. A subsequent deprotonation from the favored conformation leads to the compound **III.5a** with the observed configuration.

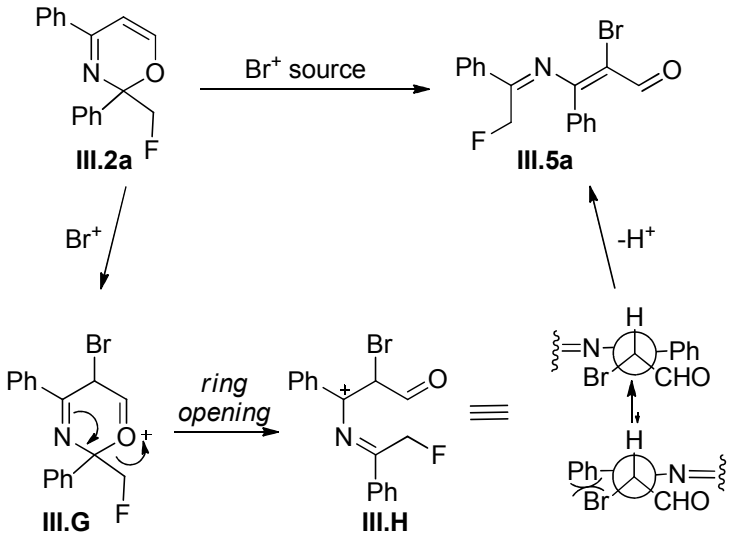
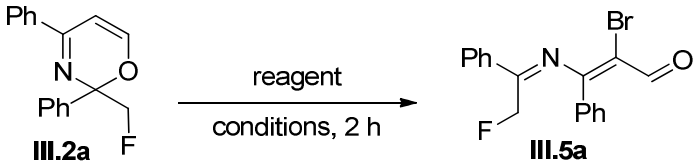
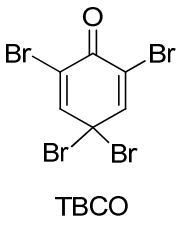


Figure 3.32 – Suggested mechanism for the brominative ring opening

Then, a short optimization revealed that higher yield could be obtained using TBCO as the electrophilic brominating agent and dichloromethane as the solvent at 0 °C.



Entry	Reagent	Solvent	Yield[a] III.5a
1	NBS (1.0 equiv.) / MeOH (3.0 equiv.)	acetone, r.t.	58%
2	TBCO (1.0 equiv.)	CH_2Cl_2, 0 °C	71%



TBCO

The reactions were performed on a 0.3 mmol scale at a 0.1M concentration

[a] NMR yield using 1,2-DCE as internal standard

Table 3.2 Optimization of the brominative ring opening

With the optimized conditions in hand, we performed the brominative ring opening on several oxazine products and we were pleased to see that the transformation could be applied in moderate to good yields with electron rich (Figure 3.33, **III.5e**) or electron deficient (**III.5g**) aryl or even alkenyl (**III.5k**) substituents.

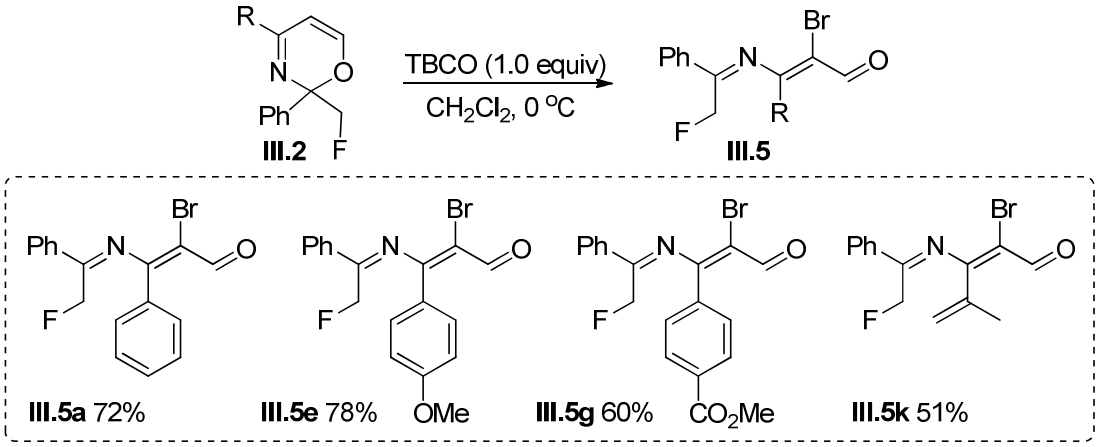
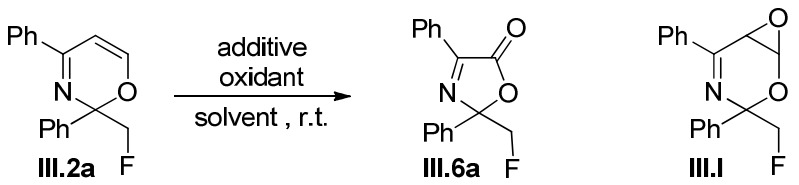


Figure 3.33 – Scope for the bromination / ring opening

3.3.4.3 Oxidative ring contraction of *2H*-1,3-oxazines

After this interesting discovery, we decided to turn our attention to the epoxidation of the C=C bond of the oxazine products. Although the first attempts, using *m*-CPBA, diacetoxyiodobenzene, or iodosobenze as the oxidants, led to complex mixtures or low conversion (Table 3.3, entries 1-6), one reaction led to an intriguing result. Indeed, when treating the product **III.2a** with iodosobenzene and a catalytic amount of *para*-toluenesulfonic acid in a 3:1 mixture of dichloromethane and hexafluoroisopropanol, a main product could be isolated (entry 7). However, this product was not the expected epoxidation product **III.I** but the compound **III.6a**, seemingly resulting from a ring contraction of the oxazine.

During a short optimization, other additives were tested, such as trifluoroacetic acid, triflic acid or copper(II) triflate salt, as well as other solvents, such as acetonitrile and dimethyl formamide. Although for this substrate, the use of copper(II) triflate salt in DMF seems more promising, these reaction conditions gave lower results than the use of *para*-toluenesulfonic acid in acetonitrile for other substrates. We therefore decided to keep the latter conditions for the following work.



Entry	oxidant (equiv)	additive (equiv)	solvent	Yield[a] III.6a
1	m-CPBA (1.5)	-	CH_2Cl_2	complexe mixture
2	m-CPBA (1.5)	Na_2HPO_4 (0.75)	CH_2Cl_2	complexe mixture
3	$PhI(OAc)_2$ (1.5)	-	CH_2Cl_2	complexe mixture
4	$PhI(OAc)_2$ (1.5)	AcOH(1)	CH_2Cl_2	complexe mixture
5	PhIO(1.5)	-	$(CHCl_2)_2$	low conversion
6	PhIO (3)	TsOH(0.1)	CH_2Cl_2	low conversion
7	PhIO (3)	TsOH(0.1)	CH_2Cl_2 / HFIP (3:1)	27%
8	PhIO (4)	TsOH(0.1)	MeCN	36%
9	PhIO (4)	CF_3CO_2H (0.1)	MeCN	low conversion
10	PhIO (4)	CF_3SO_3H (0.1)	MeCN	19%
11	PhIO (4)	$Cu(OTf)_2$ (0.2)	MeCN	32%
12	PhIO (4)	$Cu(OTf)_2$ (0.2)	DMF	40%

The reactions were performed on a 0.20 mmol scale with a 0.1 M concentration.
[a] NMR yield using 1,1,2,2-tetrachloroethane as internal standard

Table 3.3 - First attempts for epoxidation of *2H*-1,3-oxazines

During this process, we also tried to confirm the structure of this unusual product and X-ray spectroscopy gave us the confirmation that the product **III.6a** was indeed an oxazolone product (Figure 3.34).

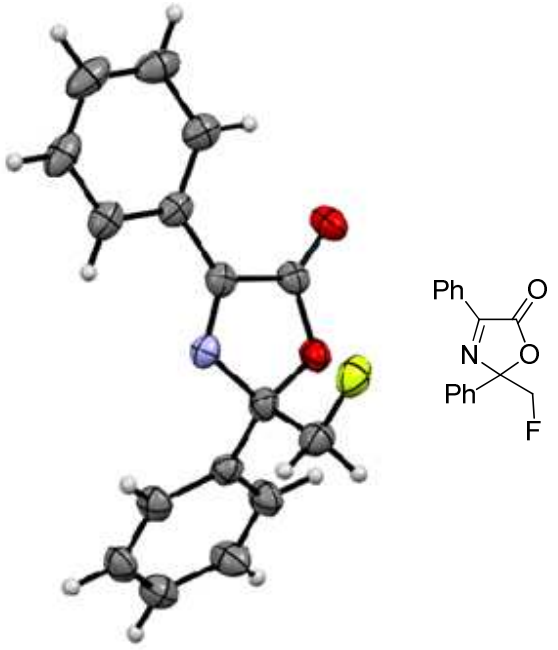


Figure 3.34 - X-ray spectroscopy of compound III.6a

To explain the formation of this oxazolone product, the following mechanism was suggested (Figure 3.35).It is initiated by an epoxidation of **III.2a** that generates the compound **III.I** which can then attack a molecule of iodosobenzene activated by the acid. A subsequent cleavage of the epoxide occurs to give the oxocarbenium intermediate **III.K** which can evolve *via* a ring contraction to give the compound **III.L**. Then, after a 1,2-hydride shift, the oxocarbenium intermediate **III.M** is obtained, which can cyclize to give the compound **III.N**. A final fragmentation eliminates iodobenze and formaldehyde, and delivers the product **III.6a**.

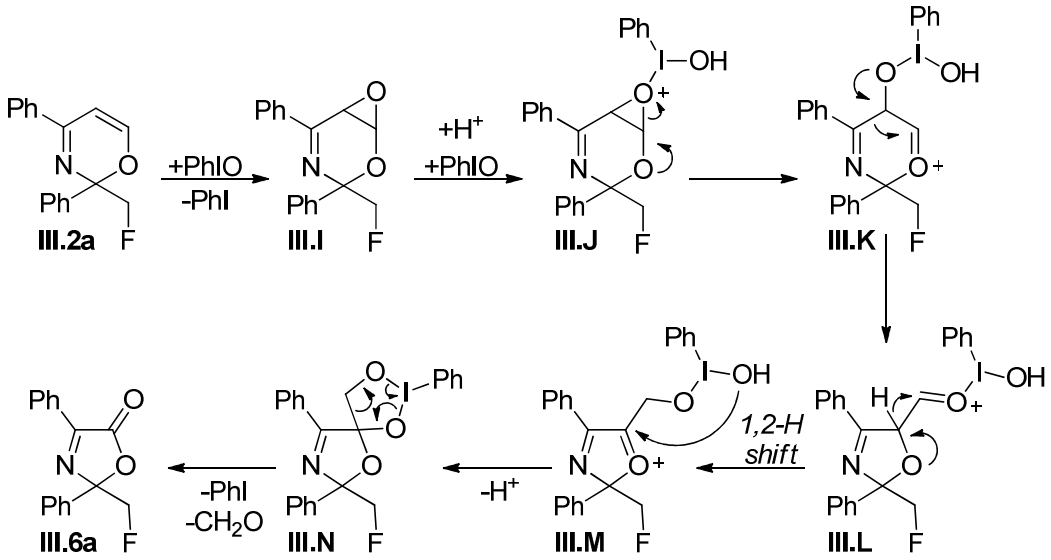


Figure 3.35 – Suggested mechanism for the epoxidation / ring contraction

This transformation was performed on other substrates and we were pleased to obtain in moderate to good yield some ring contraction products bearing electron rich (Figure 3.36, **III.6e**) or electron deficient (**III.6g**) aryl or even heteroaromatic (**III.6i**) substituents.

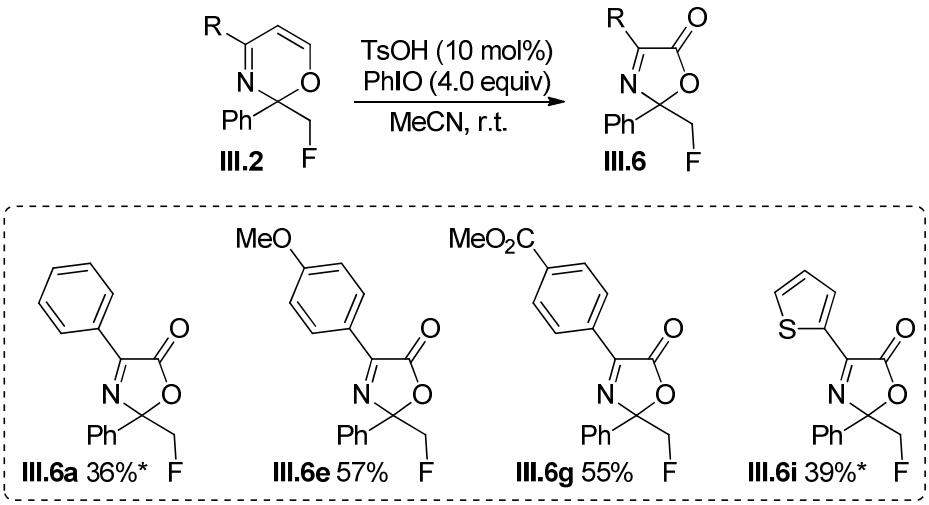


Figure 3.36 – Scope for the epoxidation / ring contraction

4.4 Conclusion

We developed a gold-catalyzed synthesis of *2H*-1,3-oxazines relying on a non-tri*vial* *6-endo* azide-yne cyclization strategy. This method allows the access to an unprecedently large range of polysubstituted *2H*-1,3-oxazines, with good functional group tolerance and in very good yields, and under very mild reaction conditions.

Gratifyingly, these oxazine products could undergo a series of interesting derivatizations. Notably, electrophilic bromination led to the obtention of linear brominated azadienes and attempts of epoxidation ended up in the formation of oxazolone products.

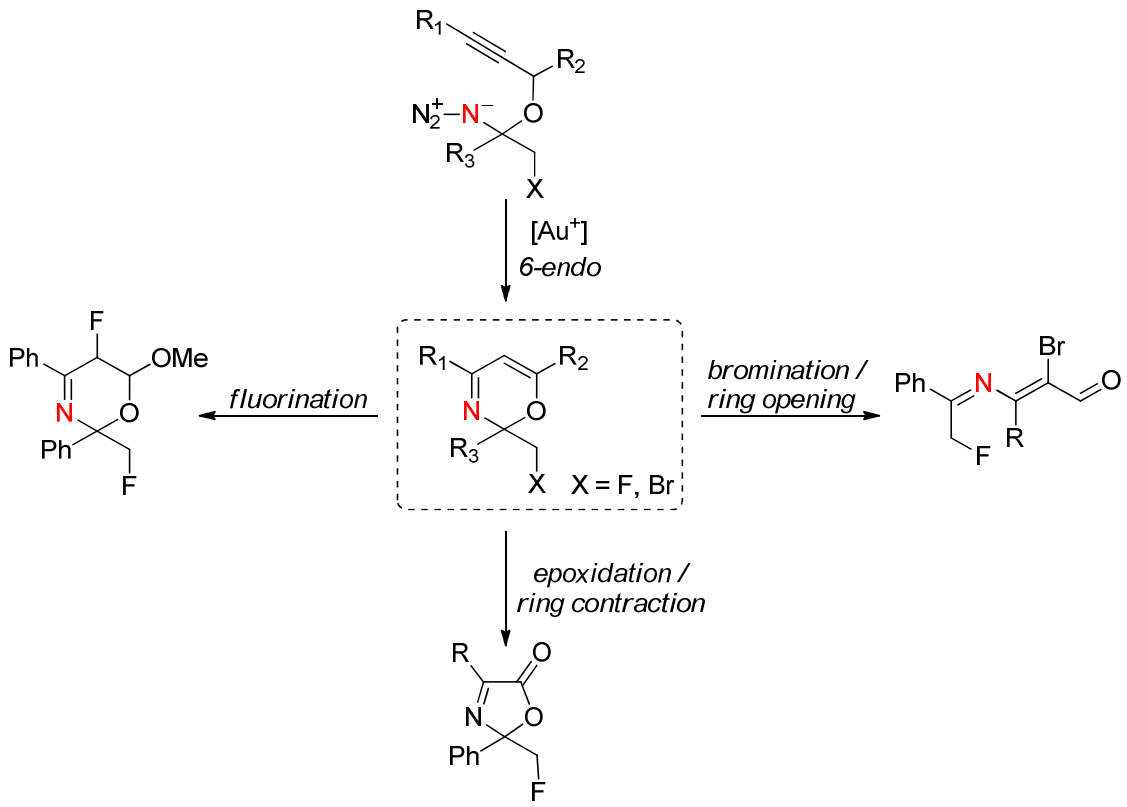


Figure 3.37 – Recapitulative scheme

However, at this stage, our method does not give access to the full range of possible *2H*-1,3-oxazines as one of the substituent is necessarily a hydrogen atom resulting from the 1,2-hydride shift suggested in the mechanism. It would be interesting to design substrates possessing two

substituents on the propargylic position to see if one of these substituents could migrate following a formal 1,2-shift (Figure 3.38).

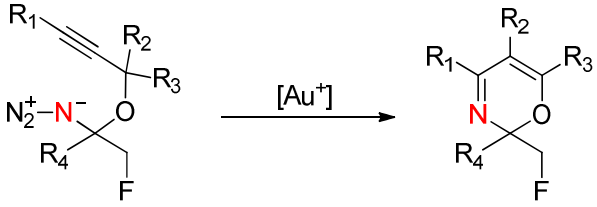


Figure 3.38 – Possible installation of one more substituent

Concerning the derivatization, another possible synthetic application of these oxazine products might be to use them as activated azadiene in [4+2] cycloaddition reactions to access other types of heterocycles. For example, cycloaddition with an alkyne could lead to a bicyclic intermediate which could fragmentate following a retro-[4+2] cycloaddition to give a pyridine product. The oxazines could also react with activated alkenes such as enamides or enol ethers to proceed through a sequence of [4+2] cycloaddition, retro-[4+2] and elimination of respectively an amine or an alcohol to give a pyridine. In the same idea, cycloaddition with imidamides could lead to the formation of pyrimidine products.

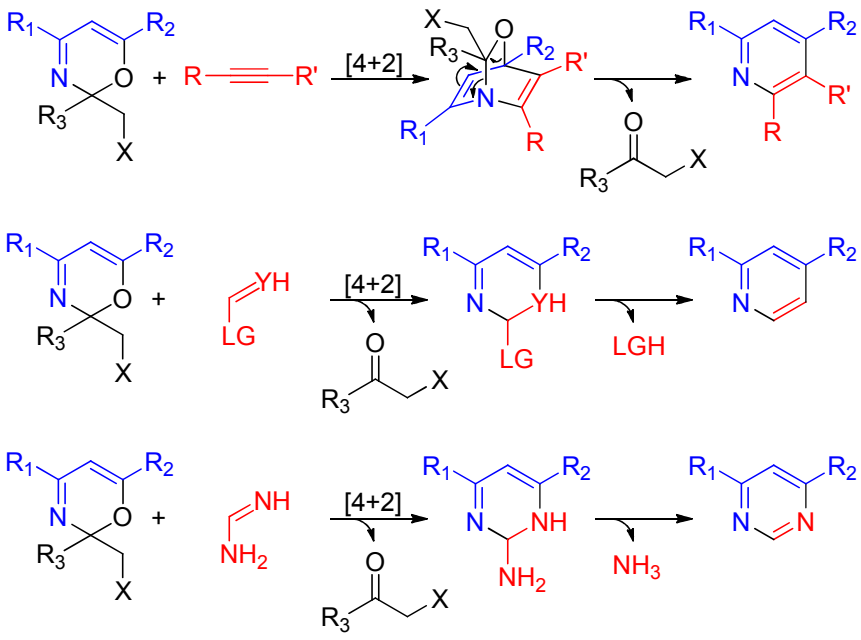


Figure 3.39 – Possible synthetic application of *2H*-1,3-oxazines

It would be interesting as well to see if these oxazine products could be converted to β-amino acids. The reduction of the two insaturations with concomitant cleavage of the acetal leading to 1,3-amino alcohols was already performed in excellent yields by Barluenga.[191] Thus, the determination of appropriate oxidative condition to convert the alcohol moiety to a carboxylic acid would open the door to an efficient synthesis of β-amino acids.

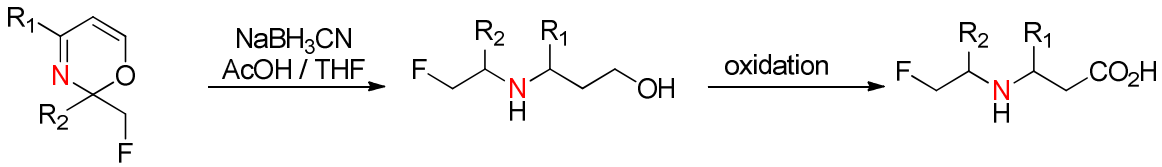


Figure 3.40 – Possible conversion of *2H*-1,3-oxazines to β-amino acids

[191] Barluenga, J.; Tomas, M.; Ballesteros, A.; Kong, J.S. *Tetrahedron* **1996**, *52*, 3095

Chapter 4 :

Copper-catalyzed radical hydrofunctionalization of unactivated alkenes using a benzyloxy moiety as a redox active hydrogen atom donor

This project was conducted under the supervision of Dr. Fabien Gagosz and Dr. Shunsuke Chiba in collaboration with Derek Yiren Ong who provided part of the results presented hereafter. The results obtained by the author are marked by an asterisk.

The results of this study were published in the following article :

Lonca, G.H; Ong D.Y.; Tran, T.M.H.; Tejo, C.; Chiba, S.; Gagosz, F. *Angew. Chem. Int. Ed.* **2017**, *56*, 11440.

4.1 Introduction to radical hydrotrifluoromethylation of alkenes

4.1.1 General introduction to radical trifluoromethylation

As presented in Chapter 2, fluorine chemistry is attracting more and more attention from organic chemists as fluoride or perfluoroalkyl substituents greatly improve the properties of pharmaceuticals, agrochemicals, and materials. More particularly, the trifluoromethyl group (CF_3) has become a very important moiety and can be found in many commercial compounds (Figure 4.1).

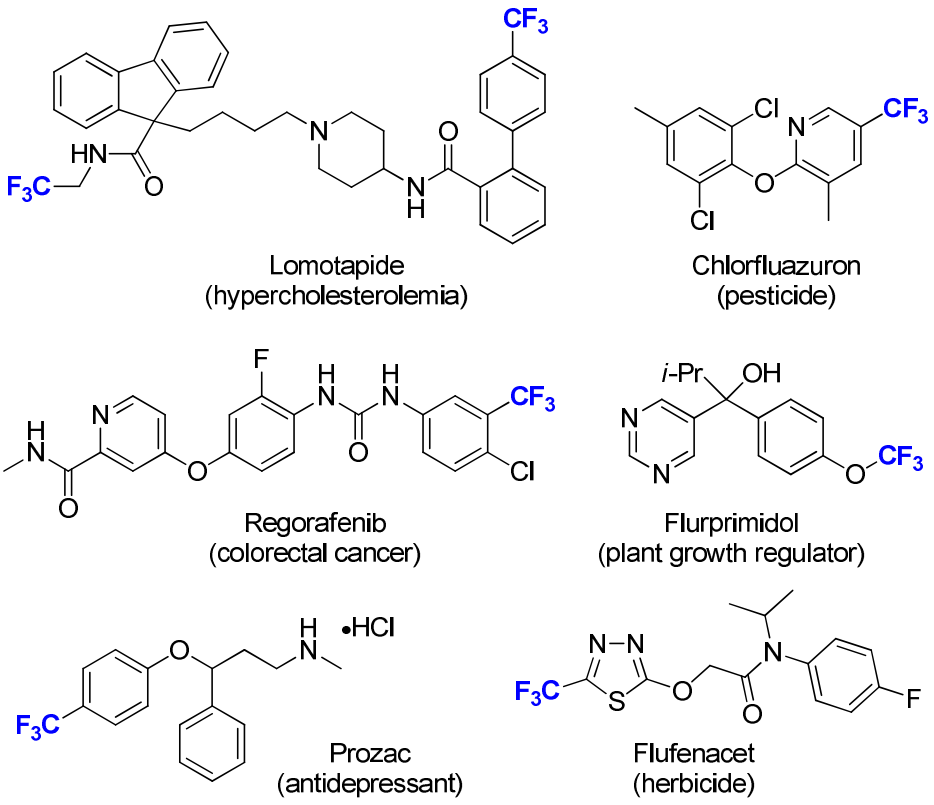


Figure 4.1 – Examples of trifluoromethyl pharmaceuticals and agrochemicals

Therefore, developing methods to introduce the trifluoromethyl moiety to a compound is a very challenging issue. To address it, a large number of reagents have been designed specifically to perform trifluoromethylation reactions. These reagents can be classified in two categories and used in four types of strategies : the nucleophilic trifluoromethylation, the electrophilic trifluoromethylation, the trifluoromethylative cross-coupling reaction and the radical trifluoromethylation.

❖ Nucleophilic trifluoromethylation

One of the first options that one might think about to perform trifluoromethylation is to resort to a classical C-C bond formation by a nucleophilic addition of a trifluoromethyl anion. However, CF_3 anions possess a very singular behavior and can under no circumstances be considered as classical methyl anion analogous, which adds some difficulty to this challenge.

First of all, the trifluoromethyl anion is not thermically stable. Indeed, the important electrostatic repulsion between the anionic charge and the p electron pairs of the fluorine atoms induces a strong destabilization of the CF_3 anion. Studies to generate free CF_3 anions by trapping of the counter cation with crown ethers[192] revealed that CF_3 anions undergo many sorts of decomposition reactions upon warming mostly starting by elimination of fluoride (Figure 4.2).[193]

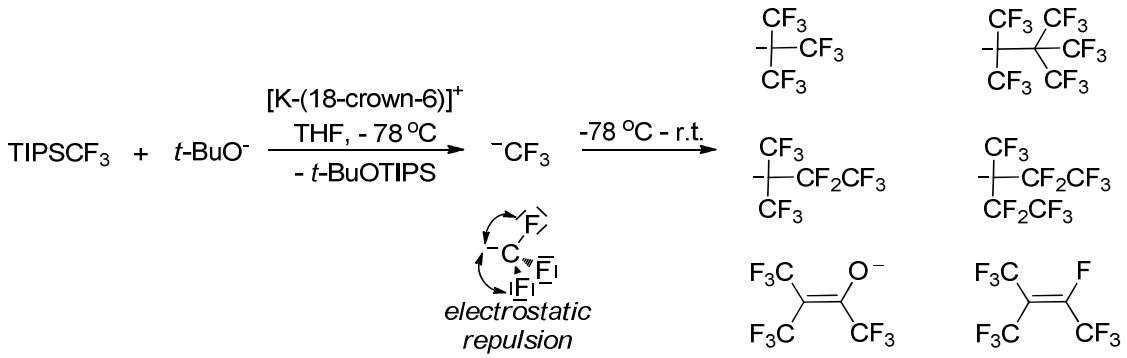


Figure 4.2 – Thermic instability of the trifluoromethyl anion

Therefore, the CF_3 anion must be somehow stabilized. In the case of an alkyl anion, the use of an organometallic specie would be the first idea. Indeed, some stable and well-defined trifluoromethyl organometallic reagent do exist, such as the following copper salts (Figure 4.3) which can be used for nucleophilic reactions (see section 2.1.3).[194]

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[192] Prakash, G.K.S.; Wang, F.; Zhang, Z.; Haiges, R.; Rahm, M.; Christe, K.O.; Mathew, Thomas.; Olah, G.A. *Angew. Chem. Int. Ed.* **2014**, *53*, 1.
[193] Lishchynskyi, A.; Miloserdov, F.M.; Martin, E.; Benet-Buchholz, J.; Escudero-Adan, E.C.; Konovalov, A.I.; Grushin, V.V. *Angew. Chem. Int. Ed.* **2015**, *54*, 15289.
[194] For nucleophilic substitution on benzyl bromide derivatives, see : Kawai, H.; Furukawa, T.; Nomura, Y.; Tokunaga, E.; Shibata, N. *Org. Lett.* **2011**, *13*, 3596.

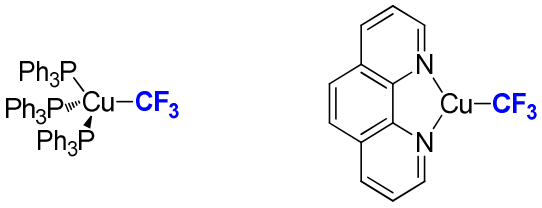

Figure 4.3 – Stable trifluoromethyl organometallic reagent

Yet, in a larger perspective, the use of transition metal is complicated by two factors, the first one being the important strength of the metal-CF_3 bond, originating from a polar contribution and from the back donation of the filled d orbital of the metal to the anti-bonding orbital of the C-F bonds. Moreover, when this backdonation is too important, the decomposition of the metal-CF_3 species can happen to generate the corresponding fluoride salt and a difluoromethyl carbene (Figure 4.4). Therefore, trifluoromethyl organometallic reagents often evolve to undetermined species and their use leads to unpredictable results.

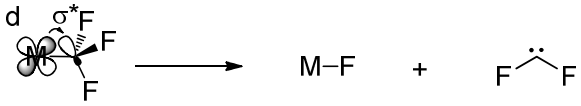

Figure 4.4 – Decomposition of metallated trifluoromethylanion to difluoro carbene

Thus, other alternatives had to be found to get stable surrogates of trifluoromethyl anions and a variety of precursors could be used (Figure 4.5).

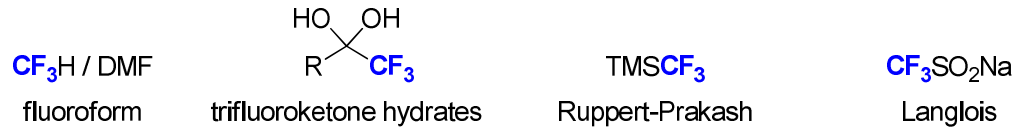

Figure 4.5 Nucleophilic trifluoromethyl reagents

For example, as seen in section 2.3.1, trifluoromethyl tetrahedral adducts are stable at low temperatures. Upon warming up, these adducts undergo fragmentation and a trifluoromethyl moiety can be eliminated (Figure 4.6).

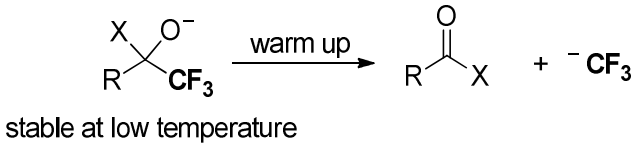

Figure 4.6 – Stability of trifluoromethylated adducts at low temperature

Normant and coworkers took advantage of this property to develop a nucleophilic trifluoromethylation of aldehydes using fluoroform and DMF (Figure 4.7, eq. 1).[195] Indeed, the deprotonation of fluoroform generates a CF_3 anion which is trapped by DMF to form an adduct which is stable at low temperature. In the presence of an aldehyde, this adduct fragmentates and the trifluoromethyl moiety is transferred from the DMF to the more electrophilic aldehyde

In the same way, Colby *et al.* used trifluoromethyl ketone hydrates in an efficient trifluoromethylation of ketones (eq. 2).[196] Indeed, the deprotonation of the hydrate generates a stable salt adduct which can fragmentate to transfer its trifluoromethyl group to the ketone. Here again, the driving force is the better electrophilicity of the ketone compared to that of the trifluoroacetate generated after the transfer.

[195] Folleas, B.; Marek, I.; Normant, J.F.; Saint-Jalmes, L. *Tetrahedron* **2000**, *56*, 275.
[196] Riofski, M. V.; Hart, A. D.; Colby, D. A. *Org. Lett.* **2013**, *15*, 208.

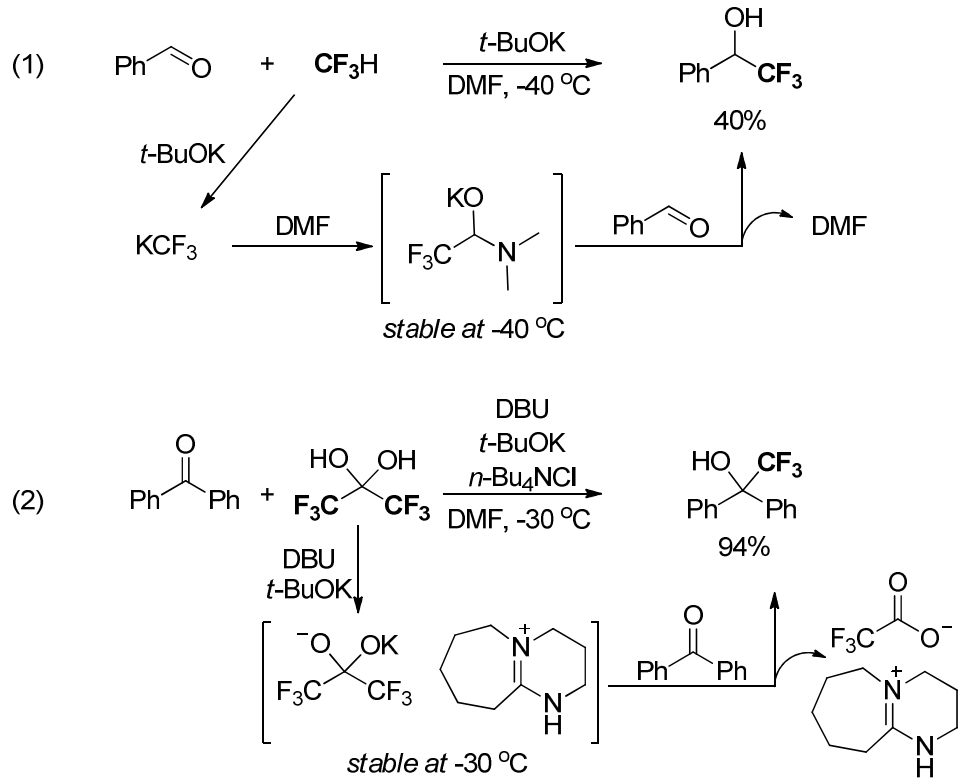

Figure 4.7 – Examples of nucleophilic trifluoromethylation reactions

But the main reagent used for nucleophilic trifluoromethylation is the Ruppert-Prakash reagent $TMSCF_3$. In the presence of an appropriate nucleophilic activator, a pentacoordinated silicium specie is formed and acts as a trifluoromethylating agent toward, for example, carbonyl compounds, imines and azirines to form α-trifluoromethyl alcohols or amines (Figure 4.8).

Interestingly, the nature of the activating agent can modulate the chemioselectivity of the trifluoromethylation. Indeed, the use of tetrabutylammonium fluoride preferentially leads to the trifluoromethylation of carbonyl compounds whereas hydrofluoric acid is an activator of choice for the trifluoromethylation of imines.

In the case of aldehyde and ketones, only a catalytic amount of the fluoride initiator is required. Indeed, because of the oxophilicity of silicium, the alkoxide intermediate resulting from the nucleophilic trifluoromethylation can activate $TMSCF_3$ to start a chain mechanism. The silyl ether product can then be hydrolyzed to give an alcohol.

However, in the case of imine or azirines, such a chain mechanism is not possible and a stoichiometric amount of activating agent is required.

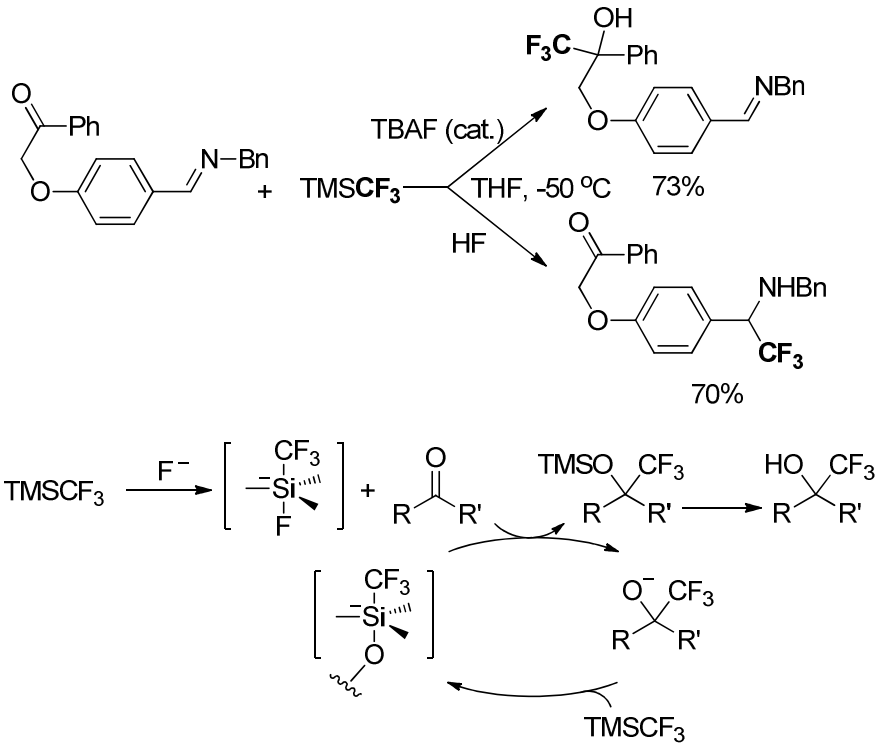

Figure 4.8 - Examples of nucleophilic trifluoromethylation reactions using the Ruppert-Prakash reageant

❖ Electrophilic trifluoromethylation

However, the reagents previously described only allow nucleophilic trifluoromethylations. Therefore, trifluoromethylation of nucleophilic positions remained challenging until new reagents were specifically developed for electrophilic trifluoromethylation. The first reagents of this kind were the trifluoromethyl diaryl sulfonium salts developed by Yagupolskii's[197] and Shreeve's[198] groups. Shortly after, Umemoto developed a series of hypervalent sulfur, selenium and tellurium salts.[199] In this first type of reagents, the umpolung of the trifluoromethyl group is strong enough for the reaction to proceed without additive. Electrophilic reagents based on hypervalent iodine were also developed by Togni's group.[200] But in this case, the reagent needs to be activated by a Lewis acid to promote a sufficient umpolung of the trifluoromethyl group (Figure 4.9).

[197] Kirij, N.V.; Psenok, S.V.; Yagupolskii, Y.L. Tyrra, W.; Naunamm, D. *J. Fluorine Chem.* **2000**, *106*, 217.
[198] Yang, J.J.; Kirchmeier, R.L.; Shreeve, J.M. *J. Org. Chem.* **1998**, *63*, 2656.
[199] a) Umemoto, T.; Ishihara, S. *Tet. Lett.* **1990**, *31*, 3579 ; b) Umemoto, T.; Ishihara, S.; Adashi, K. *J. Fluor. Chem.* **1995**, *74*, 77.
[200] Eisenberger, P.; Gischig, S.; Togni, A. *Chem. Eur. J.* **2006**, *9*, 2579.

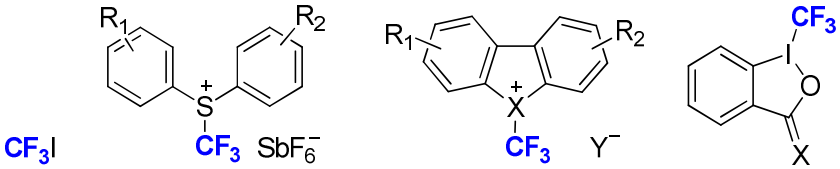

Figure 4.9 - Electrophilic trifluoromethyl reagents

A variety of nucleophilic reagents can be used with the latter surrogates of trifluoromethyl cations. For example, the deprotonation of 1,3-diones compounds in the presence of Umemoto's reagent leads to the trifluoromethylation of the position 2 (Figure 4.10, eq. 1).[201] In the same way, trifluoromethyl alkynes can be easily obtained in good yield by treatment of lithium acetylides with Umemoto's reagent (eq. 2).[202]

Non-ionic nucleophiles such as electron rich aromatic compounds, alcohols or thiols are also eligible to react with electrophilic trifluoromethyl reagents. For instance, aniline can undergo a Friedel-Craft type trifluoromethylation using Shreeve's reagent as the electrophilic specie, leading to a 3.9:1 mixture of *ortho*- and *para*-trifluoromethyl anilines (eq. 3).[203] Here, this good ratio could be explained by a polar interaction between the amino part of the aniline and the sulfonium moiety of the Shreeve reagent, thus placing the trifluoromethyl group closer to the *ortho* position.

In the same way, Togni and coworkers developed an efficient *O*-trifluoromethylation of alcohols using their hypervalent iodine reagent in presence of a zinc(II) triflate salt (eq. 4).[204] Here, the zinc(II) triflate salt acts as a Lewis acid which activated the C=O bond of the Togni reagent, thus polarizing even more the I-CF_3 bond and strengthening the umpolung of the trifluoromethyl which can be attacked by the alcohol.

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[201] a) Umemoto, T.; Ishihara, S. *Tet. Lett.* **1990**, *31*, 3579 ; b) Umemoto, T.; Ishihara, S.; Adashi, K. *J. Fluor. Chem.* **1995**, *74*, 77.
[202] Zhang, C. P.; Cao, H. P.; Wang, Z. L.; Zhang, C. T.; Chen, Q. Y.; Xiao, J. C. *Synlett* **2010**, 1089.
[203] Yang, J.J.; Kirchmeier, R.L.; Shreeve, J. *J. Org. Chem.* **1998**, *63*, 2656.
[204] Koller, R.; Stanek, K.; Stolz, D.; Aardoom, R.; Niedermann, K.; Togni, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 4332.

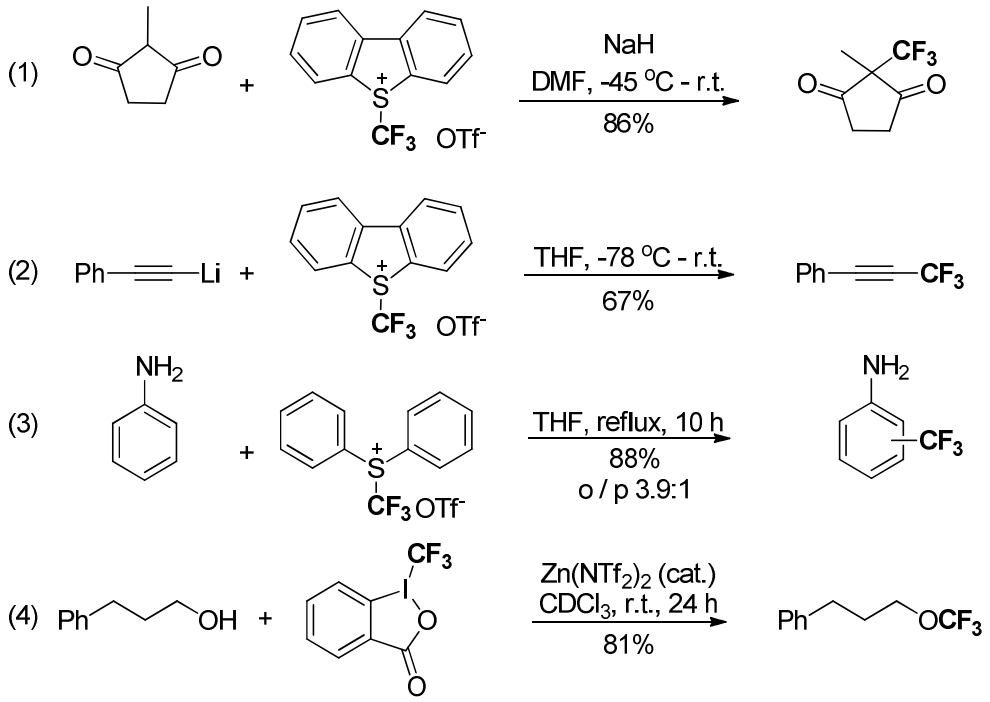

Figure 4.10 - Examples of electrophilic trifluoromethylation reactions

However, these two classes of reagents are not strictly reserved to nucleophilic and electrophilic trifluoromethylation reactions. Indeed, two others categories of transformation are available to incorporate trifluoromethyl groups from these reagents.

❖ Cross-coupling trifluoromethylation

Indeed, both types of reagents can also be used to design trifluoromethylative cross-coupling reactions. For example, Buchwald and coworkers developed an aerobic copper(II) acetate-mediated cross-coupling reaction between boronic acids and the Ruppert-Prakash reagent (Figure 4.11, eq. 1).[205] In this reaction, activation of the $TMSCF_3$ by cesium fluoride provides a CF_3 anion which replaces one of the acetate ligand of the copper(II) salt. Then the activation of the boronic acid by cesium fluoride followed by a transmetallation gives a copper(II) salt with an aromatic and a trifluoromethyl ligand. A reductive elimination then leads to the formation of trifluoromethylated product and of copper which is then oxidized by dioxygen to regenerate the copper(II) salt.

[205] Senecal, T.D.; Parsons, A.T.; Buchwald, S.L. *J. Org. Chem.* **2011**, *76*, 1174.

Electrophilic trifluoromethyl reagents can also be used. Indeed, Liu and coworkers performed a copper(I)-catalyzed cross-coupling reaction between boronic acids and Umemoto's reagent (eq. 2).[206] Here, the process is initiated by the reduction of the Umemoto reagent by copper(I), thus generating a trifluoromethyl copper(III) salt. Then, a transmetallation with the boronic acid specie occurs and the resulting copper(III) salt undergoes a reductive elimination to give the trifluoromethylated product and to regenerate the copper(I) catalyst.

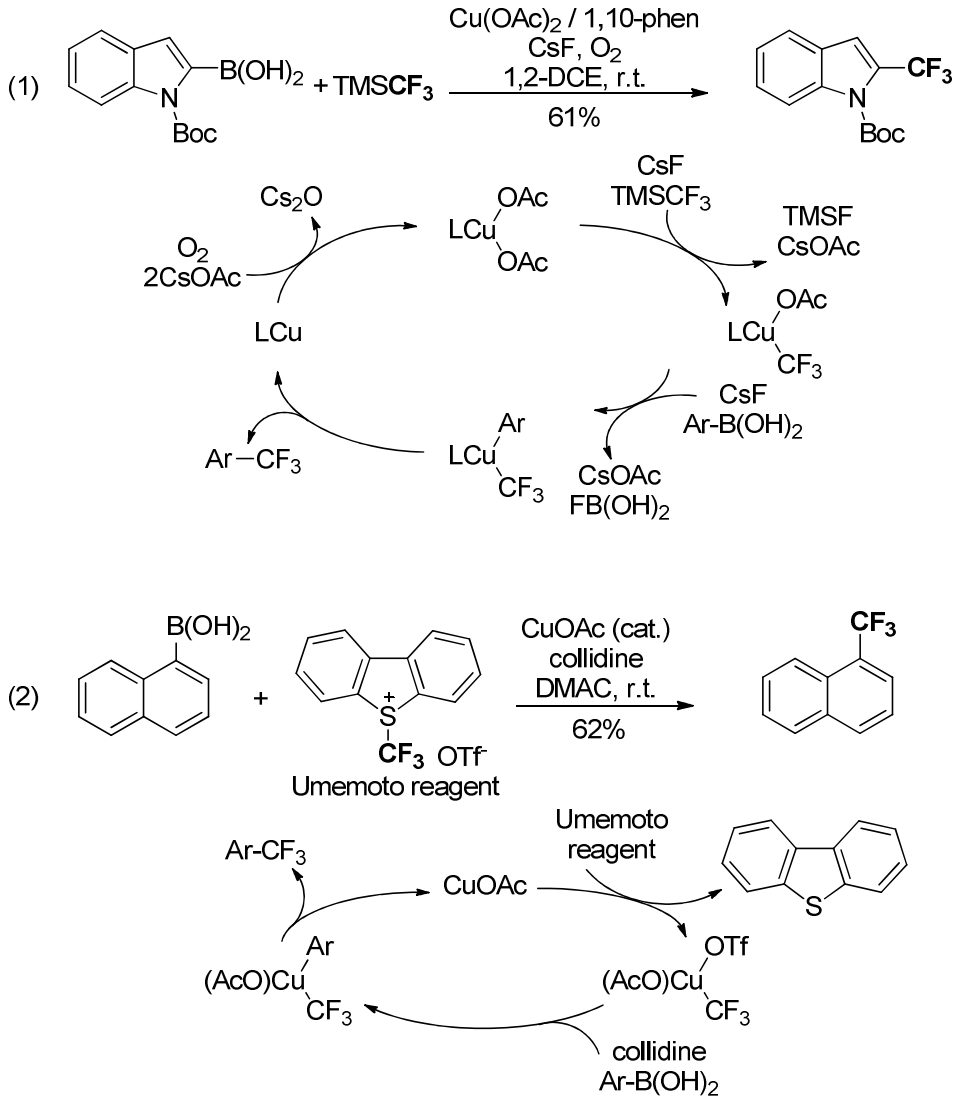

Figure 4.11 - Examples of cross-coupling trifluoromethylation reactions

[206] Xu, J.; Luo, D.F.; Xiao, B.; Liu, Z.J.; Gong, T.J.; Fu, Y.; Liu, L. *Chem. Commun.* **2011**, *47*, 4300.

❖ Radical trifluoromethylation of arenes :

Attention has also been given to generate trifluoromethyl radicals. Two main options are now available for that purpose. (Figure 4.12). On one hand, electrophilic trifluoromethyl reagents can be activated to generate CF_3 cations which can be reduced to CF_3 radicals. This kind of process is called reductive radical trifluoromethylation. On the other hand, oxidative radical trifluoromethylation consists of oxidizing CF_3 anion synthons. The resulting trifluoromethyl radical can then react with a variety of partners such as arenes or alkynes and alkenes.

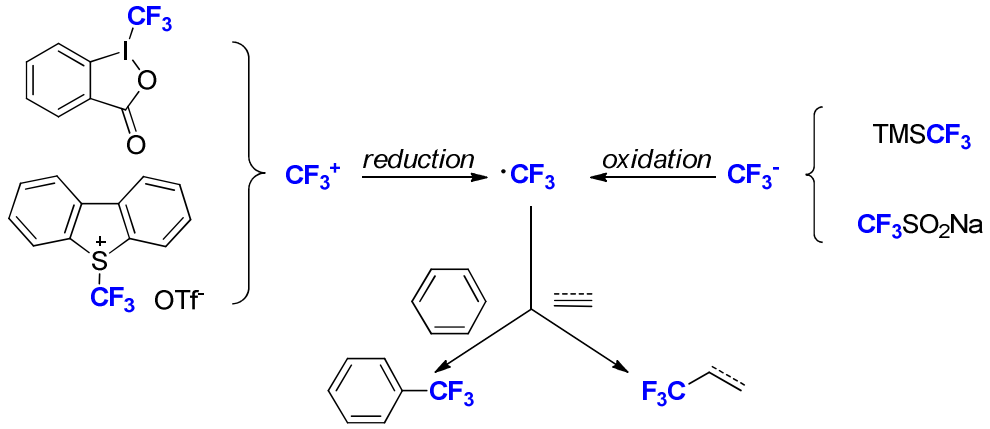

Figure 4.12 – General scheme for generation and use of trifluoromethyl radical

For instance, an efficient oxidative radical trifluoromethylation of heteroaromatic substrates was developed, using the Langlois reagent and *tert*-butylperoxide as the oxidant (Figure 4.13, eq. 1).[207] In this reaction, traces of impurities induce the generation of a *tert*-butyloxy radical from the peroxide. This radical can then oxidize the Langlois reagent, which after extrusion of sulfur dioxide, gives a CF_3 radical which can add to the aromatic ring. Then, the resulting aromatic radical is oxidized by *tert*-butylperoxide, thus regenerating the oxy radical and furnishing an aromatic carbocation which undergoes deprotonation to provide the trifluoromethyl product.

Sanford developed a method for the trifluoromethylation of aromatic rings using the Ruppert-Prakash reagent (eq. 2).[208] Here, a stoichiometric amount of silver (I) salt is used to oxidize both

[207] Ji, Y.; Brueckl, T.; Baxter, R.D.; Fujuwara, Y.; Seiple, I.B.; Su, S.; Blackmond, D.G.; Baran, P.S. *P.N.A.S.* **2011,** *108*, 14411.
[208] Ye, Y.; Lee, S. H.; Sanford, M. S.. *Org. Lett.* **2011**, *13*, 5464.

the CF_3 anion and the intermediate radical. However, it appears that the trifluoromethylation of simple arenes like toluene presents a very poor regioselectivity.

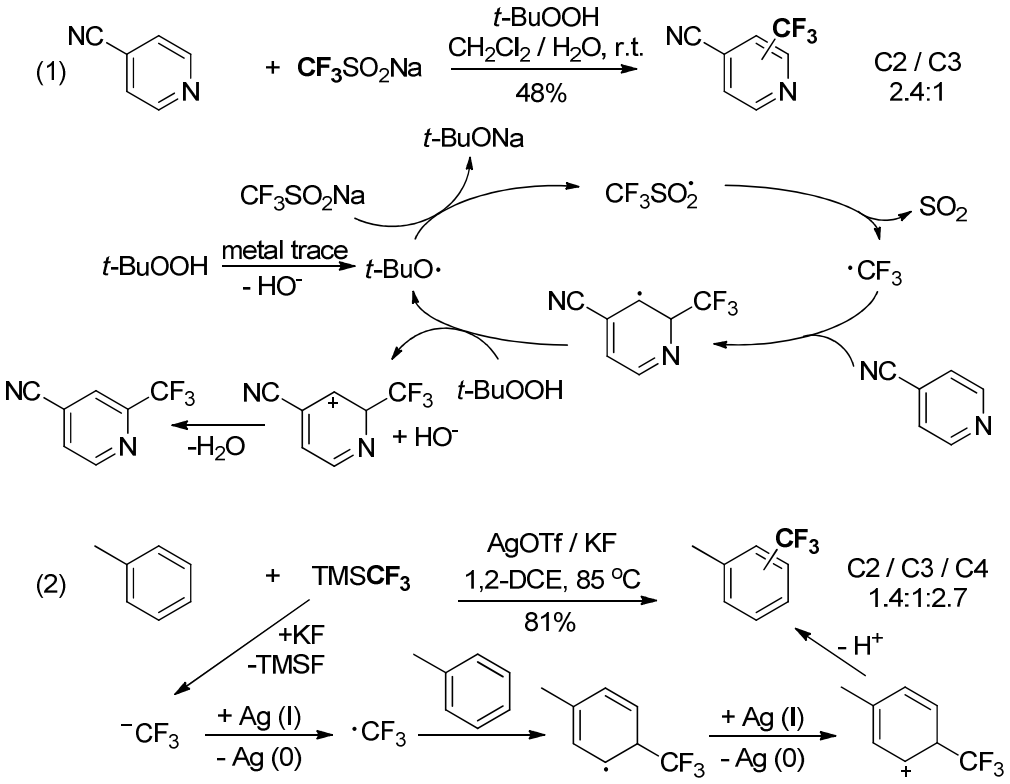

Figure 4.13 – Radical trifluoromethylation of aromatic substrates

So far, we have seen that the development of two classes of trifluoromethylating reagents have enabled synthetic chemists to perform the trifluoromethylation of functional groups. Nucleophilic trifluoromethyl reagents are excellent to convert carbonyl, imine and azirines substrates to α-trifluoromethyl alcohols and amines. Electrophilic trifluoromethyl reagents can be used to introduce a trifluoromethyl moiety at the α position of carbonyl groups, or to obtain *O*-trifluoromethyl ethers. Trifluoromethyl aromatic products can be obtained *via* trifluoromethylating cross-coupling reactions or *via* a direct radical trifluoromethylation of the aromatic moiety, although the radical pathway is less regioselective and often requires strongly oxidative conditions. In the same way, these reagents can be used for the trifluoromethylation of unactivated alkenes, which is presented in the next section.

4.1.2 Radical trifluoromethylation of unactivated alkenes

The functionalization of unactivated alkenes is a difficult task in ionic chemistry. Luckily, radical chemistry represents an advantageous alternative and can be adapted to the trifluoromethylation of unactivated alkenes with various extensions of 1,2-difunctionalization (Figure 4.14).

Indeed, *in-situ* generated CF_3 radicals can add to alkenes, thus generating a carbon centered radical which can evolve following different pathways. The abstraction of a hydrogen atom leads to a hydrotrifluoromethylation. The subsequent addition of this radical onto a carbon-based insaturation leads to a carbotrifluoromethylation reaction. This radical can also be further oxidized to a carbocation. From then, various evolution pathways are conceivable for this carbocation, leading to oxy- or amino-trifluoromethylation, or providing trifluoromethyl allyl products.

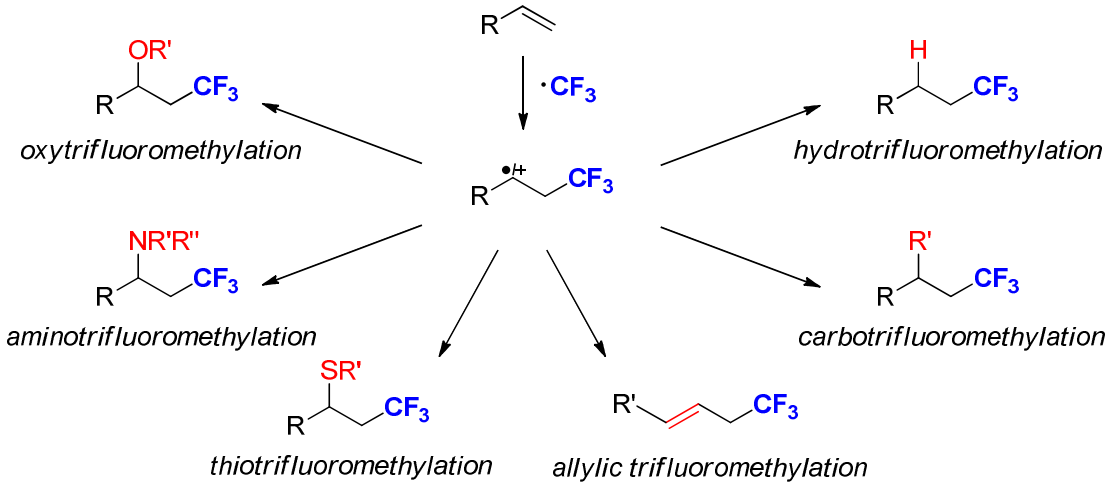

Figure 4.14 – General scheme for radical trifluoromethylation of alkenes

❖ Allylic trifluoromethylation :

As just mentioned, after the addition of a CF_3 radical onto an alkene, the resulting carbon centered radical can be oxidized to a carbocation. If this carbocation is not stabilized by any substituent and if a hydrogen atom is present at its α position, this proton can be eliminated to form a trifluoromethylated allyl product.

In 2011, several groups reported methods for the reductive allylic trifluoromethylation of alkenes, using Togni's reagent (Figure 4.15, eq. 1)[209] or Umemoto's reagent (eq. 2)[210] with copper(I) salts.

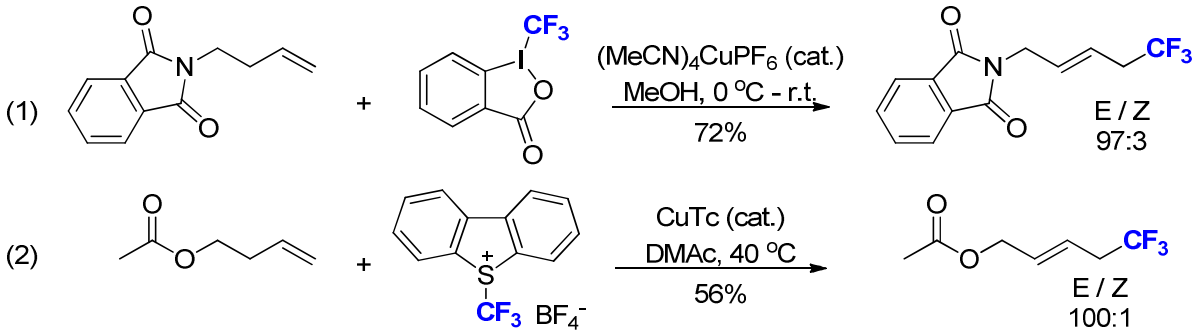

Figure 4.15 – Synthesis of trifluoromethyl allyl compounds

In these reactions, the CF_3 cation precursors are reduced by copper(I), thus generating a copper(II) salt and a CF_3 radical which can add to the alkene (Figure 4.16). The resulting radical can then be oxidized by copper(II) to regenerate the copper(I) catalyst and to give a carbocation which undergoes deprotonation to form a trifluoromethyl allylic product. Concerning the regioselectivity of the deprotonation, Liu and coworkers provided calculation studies which suggest that the formation of trifluoromethylated allyl product prevails over the formation of trifluoromethyl vinyl product because of a lower energy of the transition state.

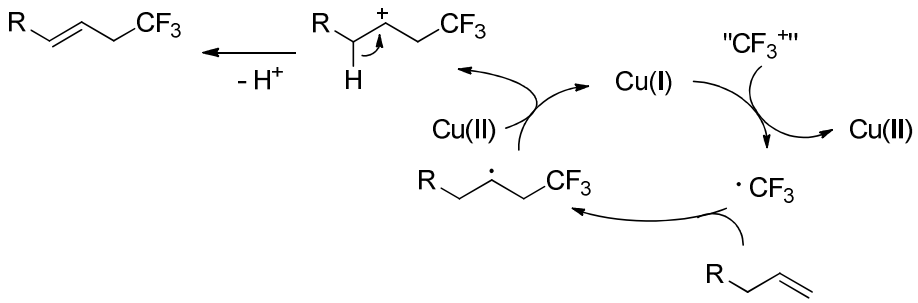

Figure 4.16 - Mechanism for copper catalyzed reductive trifluoromethylation

However, if the resulting carbocation is stabilized, it can live long enough to be trapped by a nucleophile.

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[209] Parsons, A.T.; Buchwald, S.L. *Angew. Chem. Int. Ed.* **2011**, *50*, 9120.
[210] Xu, J.; Fu, Y.; Luo, D.F. ; Jiang, Y.Y.; Xiao, B.; Liu, Z.J.; Gong, T.J. Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 15300.

❖ Oxytrifluoromethylation :

Among the possible trapping agents, oxygen centered nucleophiles have already been extensively used. This strategy opens the door to the straightforward synthesis, in excellent yield, of a variety of trifluoromethylated oxygen containing compounds from simple alkenes (Figure 4.17).

For example, in the case of the trifluoromethylation of styrene type substrates using Togni's reagent and copper, the resulting benzylic carbocation intermediate is stable enough to be trapped directly by the 2-iodobenzoate coming from the reduction of Togni's reagent (eq. 1).[211]

Similarly, styrene substrates can also undergo a reductive oxytrifluoromethylation using Umemoto's reagent and a photoactive catalysts such as iridium or ruthenium complexes. For example, Akita and coworkers developed a photo-catalyzed synthesis of β-trifluoromethyl alcohols using water as the trapping reagent (eq. 2).[212] In the same way, intramolecular trapping is also conceivable. For example, trifluoromethyl lactones can be efficiently obtained by a photo-catalyzed trifluoromethylation of alkene carboxylic acids (eq. 3).[213]

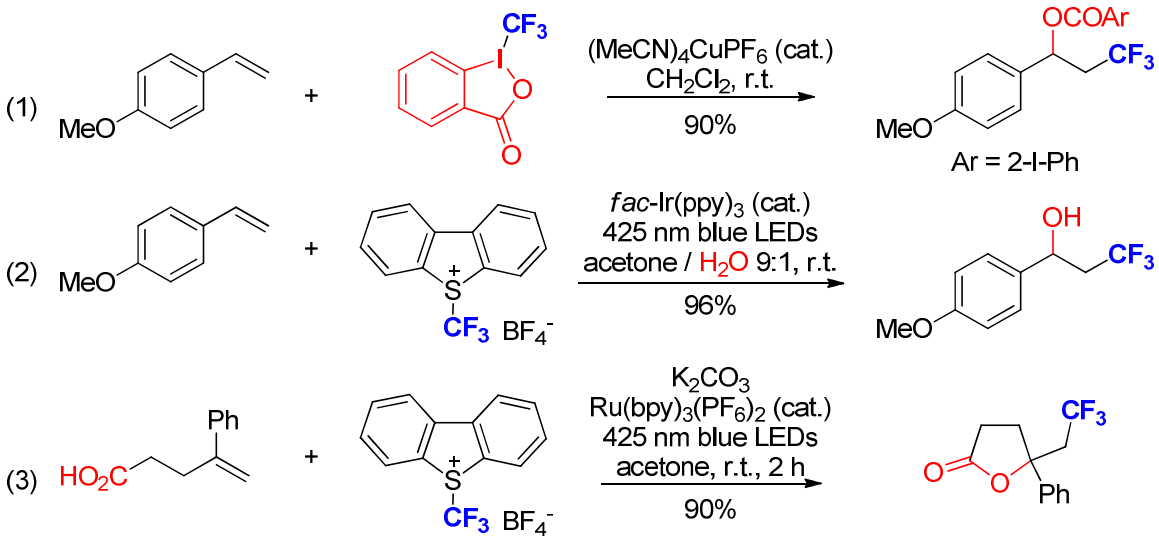

Figure 4.17 – Examples of oxytrifluoromethylation of unactivated alkenes

[211] Egami, H.; Shimizu, R.; Sodeoka, M. *Tetrahedron Lett.* **2012**, *53*, 5503.
[212] Y. Yasu, T. Koike, M. Akita, *Angew. Chem. Int. Ed.* **2012**, *51*, 9567.
[213] Yasu, Y.; Arai, Y.; Tomita, R.; Koike, T.; Akita, M. *Org. Lett.* **2014**, *16*, 780.

In this type of photo-catalyzed reaction, the photo-activation leads to an excited state of the catalyst which then becomes a potential reductant for the CF_3 cation source. Then, the same pathway as described for copper(I) happens and the resulting carbocation intermediate is trapped by a nucleophile.

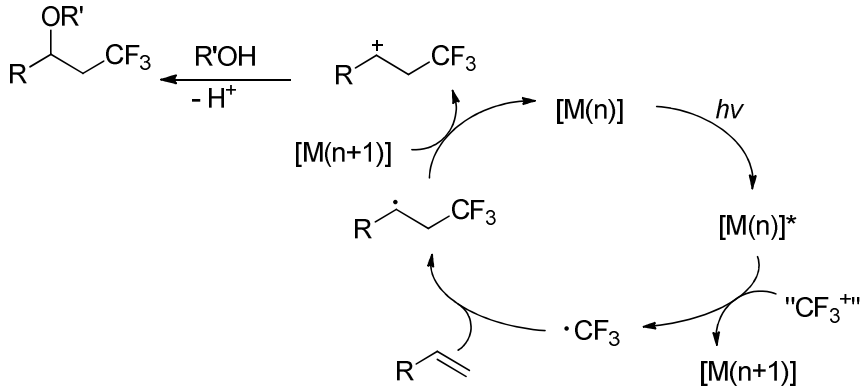

Figure 4.18 - Mechanism for the photocatalyzed reductive trifluoromethylation :

❖ Aminotrifluoromethylation :

Besides, nitrogen partners can also be used to trap the carbocation intermediate, thus allowing the access to a large range of trifluoromethylated nitrogen containing motifs in good yield (Figure 4.19).

For example, Sodeoka and her group developed a method to access β-trifluoromethyl aziridines from allylic amines (eq. 1).[214] Here, the carbocation resulting from the reductive trifluoromethylation of the alkene by the Togni reagent is trapped in an intermolecular fashion by the internal amine.

Similarly, Masson and coworkers reported the formation of β-trifluoromethyl azide compounds which relies on a trapping of the carbocation intermediate by sodium azide (eq. 2).[215]

In the same way, Akita *et al.* focused on the synthesis of trifluoromethyl amides using this aminotrifluoromethylation strategy with nitriles (eq. 3).[216] Indeed, addition of a nitrile to the carbocation intermediate provides a nitrilium intermediate which can be trapped by water to eventually form an amide.

[214] Egami, H.; Kawamura, S.; Miyazaki, A.; Sodeoka, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 7841.
[215] Carboni, A. ; Dagousset, G. ; Magnier, E. ; Masson, G. *Org. Lett.* **2014**, *16*, 1240.
[216] Yasu, Y.; Koike, T.; Akita, M. *Org. Lett.* **2013**, *15*, 2136.

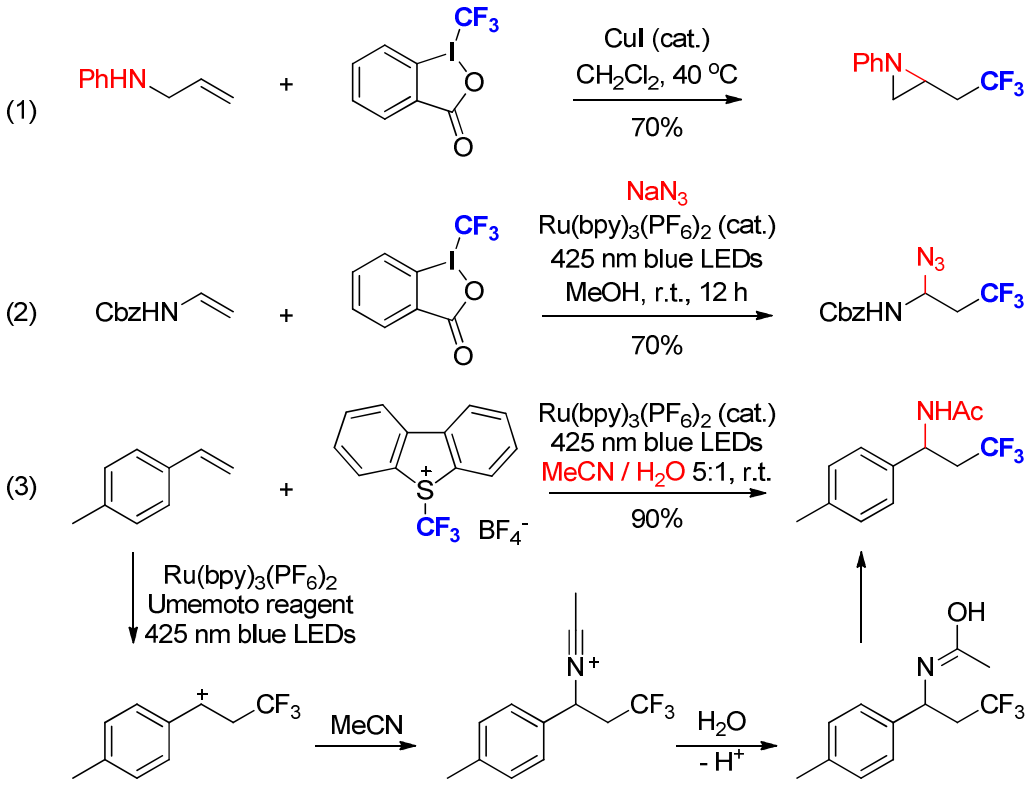

Figure 4.19 – Examples of aminotrifluoromethylation of unactivated alkenes

❖ Thiotrifluoromethylation :

The group of Zard managed to apply the chemistry of xanthates to perform the thiotrifluoromethylation of unactivated alkenes (Figure 4.20).[217] In this reaction, the CF_3 source is a *S*-trifluoromethyl xanthate, which is prepared from the inexpensive trifluoroacetic anhydride and the corresponding xanthate salt. After an initiation step, a CF_3 radical is generated from the xanthate and adds onto the alkene. The resulting secondary radical can then add onto a molecule of *S*-trifluoromethyl xanthate to give an intermediate which fragmentates to provide a CF_3 radical.

[217] Bertrand, F.; Pevere, V.; Quiclet-Sire, B.; Zard, S.Z. *Org. Lett.*, **2001**, *3*, 1069.

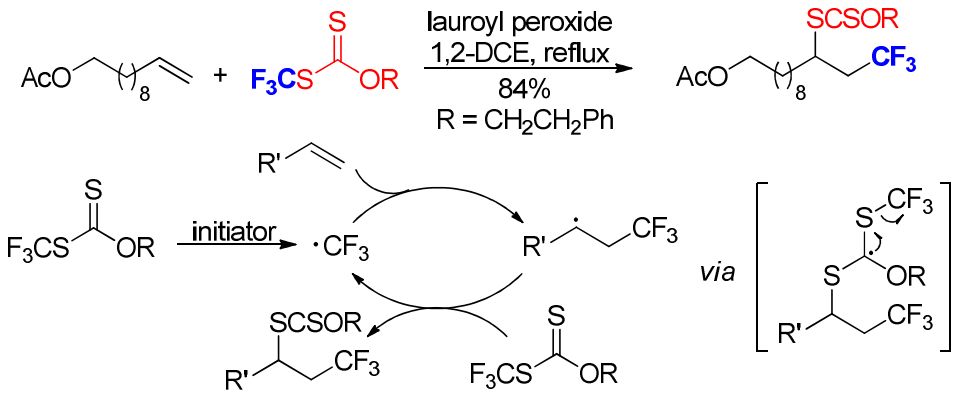

Figure 4.20 – Example of thiotrifluoromethylation of alkenes

❖ Carbotrifluoromethylation :

However, in some cases, the carbon centered radical resulting from the addition of the CF_3 radical to the alkene can be trapped before being oxidized, thus evolving *via* other radical pathways (Figure 4.21). For example, Sodeoka *et al.* reported a carbotrifluoromethylation of alkenes in which the radical intermediate can be trapped by a remote aromatic group. In this case 5- or 6-membered ring products can be formed (Figure 4.21).[218] In the example shown below, a malonate linker is used to increase the Thorpe-Ingold effect and promote the cyclization.

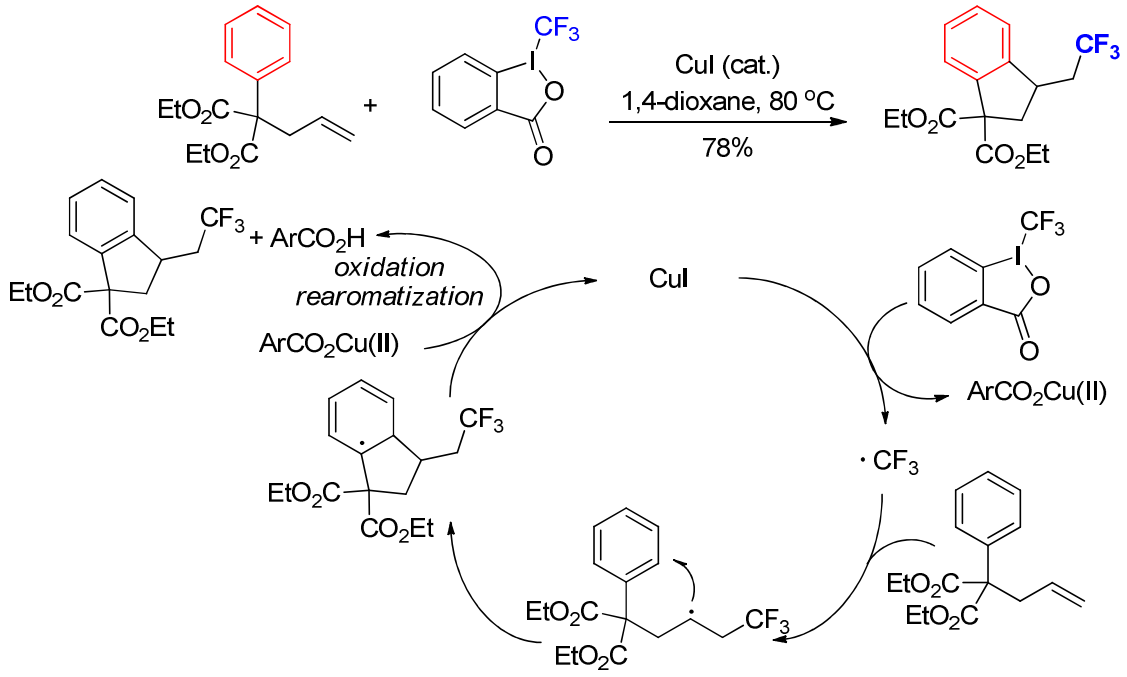

Figure 4.21 – Examples of carbotrifluoromethylation of unactivated alkenes

[218] Sodeoka : Egami, H.; Shimizu, R.; Kawamura, S.; Sodeoka, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 4000.

Similarly, alkenes and alkynes can also be used for the trapping step. For instance, tetrahydropyrrol compounds can be efficiently obtained by a reductive trifluoromethylation of 1,5-enyne substrates. This reaction starts with the addition of the CF_3 radical to the alkene, followed by a *5-exo-dig* addition of the new radical to the alkyne. The resulting vinylic radical intermediate can then be oxidized and trapped, for example by the 2-iodobenzoate formed from the Togni reagent to give a trifluoromethyl tetrahydropyrrol compound (Figure 4.22).[219]

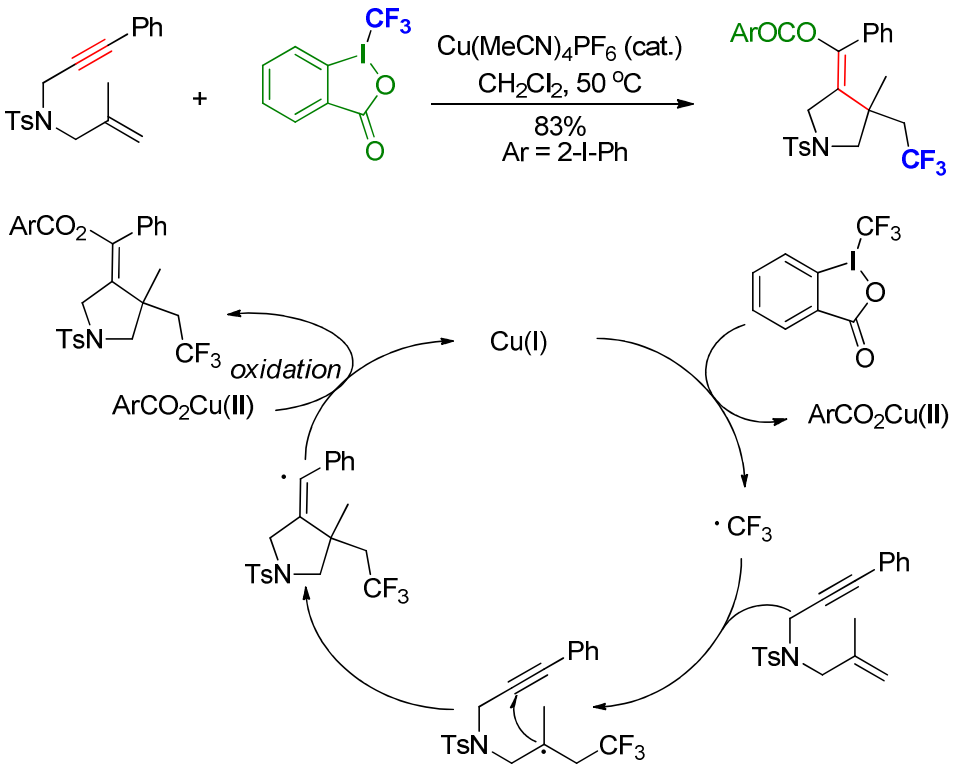

Figure 4.22 – Examples of trifluoromethylation of 1,5-enynes

In summary, the generation of trifluoromethyl radicals and their addition to alkenes is now a very known process, with a variety of possible reductive or oxidative types of initiation (copper-catalysis, photoredox catalysis). The radicals resulting from this addition can then be exploited for the formation of C-O, C-N, C-C, or C=C bonds, giving access, in one step from simple alkenes, to a large range of valuable α- or β-trifluoromethyl functional groups, for which the preparation

[219] Gao, P.; Yan, X.B.; Tao, T.; Yang, F.; He, T.; Song, X.R.; Liu, X.Y.; Liang, Y.M. *Chem. Eur. J.* **2013**, *19*, 14420.

would have been tedious by other manners. Yet, one application hasn't been mentioned so far : the hydrotrifluoromethylation of alkenes, resulting from the formation of a C-H bond.

4.1.3 Radical hydrotrifluoromethylation of unactivated alkenes

Generally speaking, the radical hydrofunctionalization of alkenes is more challenging than the other difunctionalization reactions. The key issue in the radical hydrofunctionalization lies in the formation of the C-H bond. In most cases, this bond is generated *via* a hydrogen abstraction by the newly formed carbon centered radical after the radical addition of the functional group to the alkene. In the case of hydrotrifluoromethylation, the inductive effects of the CF_3 moiety make the new radical intermediate more eager to abstract a hydrogen.

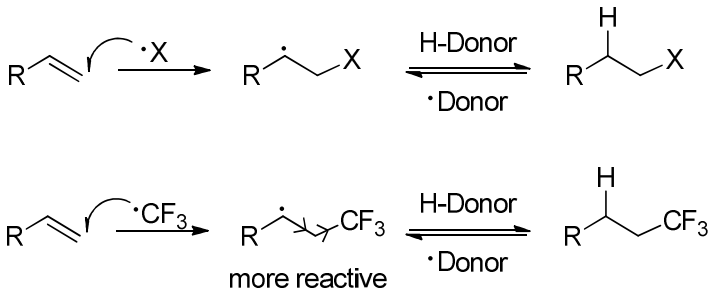

Figure 4.23 – Effect of the trifluoromethyl moiety on the hydrogen abstraction

A number of methods for the hydrotrifluoromethylation of alkenes could be developed, which can be classified according to the strategy used to generate the CF_3 radical : the oxidative and the reductive initiation.

❖ Oxidative radical hydrotrifluoromethylation :

Qing and coworkers were among the first groups to perform a radical hydrotrifluoromethylation of alkenes using the Ruppert Prakash reagent under oxidative conditions (Figure 4.24).[220] In this

[220] Wu, X.; Chu, L.; Qing, F.L. *Angew. Chem. Int. Ed.* **2013**, *52*, 2198.

reaction, the $TMSCF_3$ is activated by sodium acetate and the CF_3 anion is oxidized to the corresponding radical with a combination of silver (I) nitrate and diacetoxyiodobenzene. For the next step, 1,4-cyclohexadiene was used as the hydrogen donor. The driving force of this reaction lies in the fact that the hydrogen abstraction leads to the formation of an allylic radical which is significantly more stable than the secondary radical abstracting the hydrogen. However, this reaction is not very selective as the stoichiometric amounts of oxidants used can promote a further oxidation of the carbon centered radical to the corresponding carbocation which leads to a vinyl and allylic trifluoromethyl byproducts. Moreover, the experimental protocol is not convenient as the reactants have to be added in several portions.

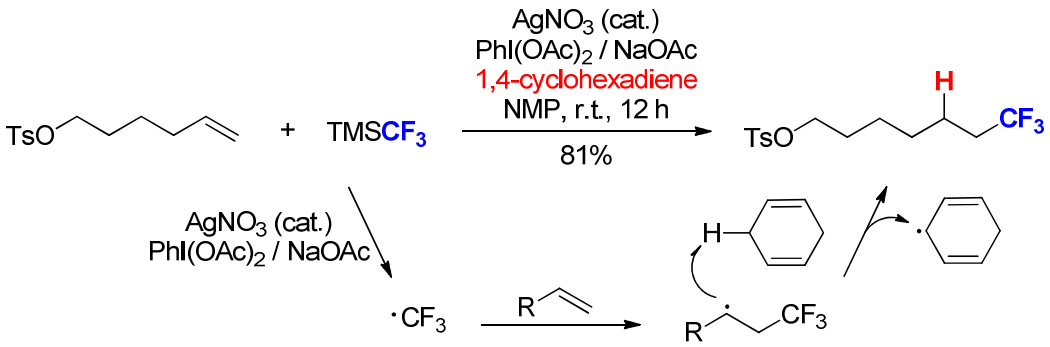

Figure 4.24 – Silver-catalyzed oxidative radical hydrotrifluoromethylation of alkenes

Recently, Zhu *et al.* reported a photo-catalyzed radical hydrotrifluoromethylation of alkenes using the Langlois reagent (Figure 4.25).[221] The relatively high yield obtained with this method can be tentatively explained by the limited number of possible side reactions. Indeed, contrary to the other photo-catalyzed reactions described previously, this process is initiated by an oxidation of the trifluoromethyl source and the regeneration of the catalyst proceeds *via* a reduction of one of the intermediates involved. Therefore, no carbocation intermediate is generated, which reduces the possibilities for side reactions, such as an elimination to give an allylic trifluoromethyl byproduct, or a trapping of the carbocation by nucleophiles. This important aspect of the reaction allowed the use of methanol as both the solvent and the hydrogen source. For the formation of the C-H bond, two mechanisms can be involved. The first one is a hydrogen abstraction from methanol by the carbon centered radical, to generate a methoxy radical which is then reduced to

[221] Zhu, L.; Wang, L.S.; Li, B.; Fu, B.; Zhang, C.P.; Li, W. *Chem. Commun.* **2016**, *52*, 6371.

regenerate the catalyst. The second possible mechanism involves the reduction of the carbon centered radical to the corresponding carbanion which deprotonates methanol.

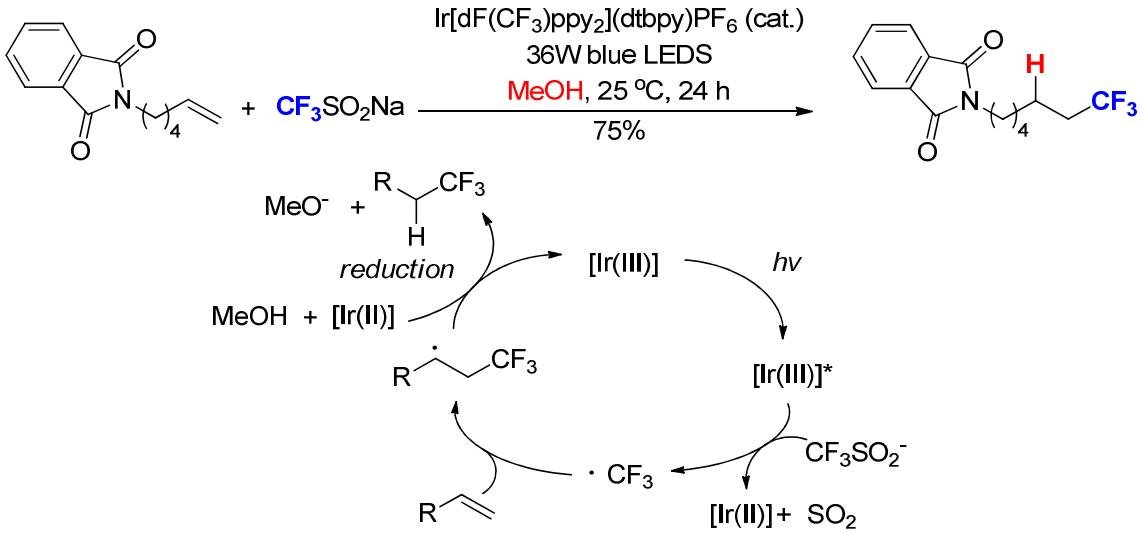

Figure 4.25 – Photo-catalyzed oxidative radical hydrotrifluoromethylation of alkenes

❖ Reductive radical hydrotrifluoromethylation :

The first reductive radical hydrotrifluoromethylation of alkenes was reported by Gouverneur and her group in 2013, using the Umemoto reagent under photo-catalyzed conditions (Figure 4.26).[222] In the same way than the reaction previously described, methanol is used as the hydrogen donor and is eventually converted to formaldehyde upon regeneration of the ruthenium catalyst. However, only moderate yields are obtained. This can be tentatively explained by the possibility for the Ru (III) specie to oxidized the carbon centered radical intermediate, at which time the resulting carbocation can be trapped by methanol or undergo deprotonation.

[222] Mizuta, S.; Verhoog, S.; Engle, K.M.; Khotavivattana, T.; O'Duill, M.; Wheelhouse, K.; Rassias, G.; Medebielle, M.; Gouverneur, V. *J. Am. Chem. Soc.* **2013**, *135*, 2505.

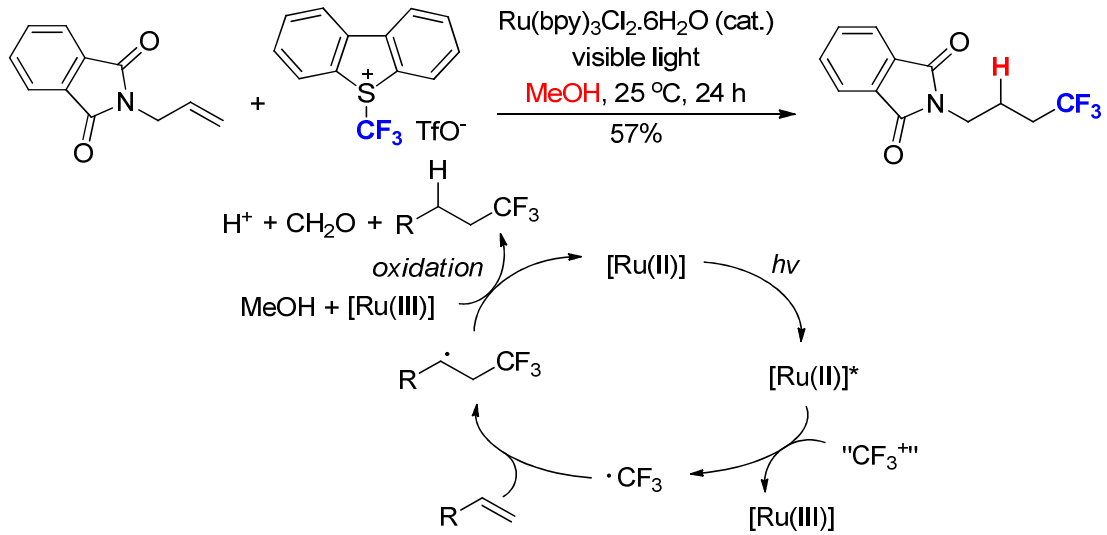

Figure 4.26 – Photo-catalyzed reductive radical hydrotrifluoromethylation of alkenes

One year later, Cho and coworkers developed an interesting hydrotrifluoromethylation of alkenes relying on an electrolysis (Figure 4.27).[223] In this reaction, the electride delivers a first electron which allows to generate a CF_3 radical from trifluoroiodomethane. The radical intermediate is then reduced by the electride to the corresponding carbanion which deprotonates ethanol.

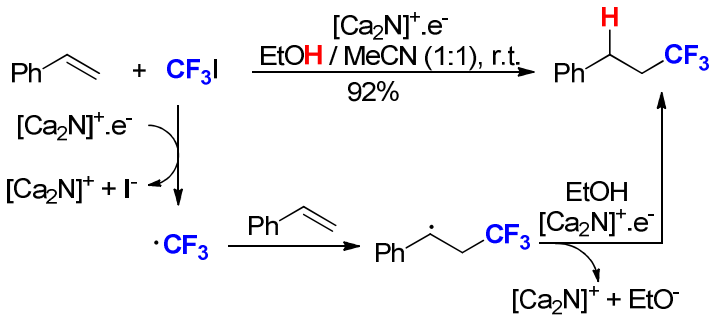

Figure 4.27 – Reductive radical hydrotrifluoromethylation of alkenes *via* electrolysis

[223] Choi, S.; Kim, Y.J.; Kim, S.M.; Yang, J.Y.; Kim, S.W.; Cho, E.J. *Nature Comm.* **2014**, *5*, 4881.

Later on, Sodeoka and Yu reported two methods relying on a simple activation of the Togni reagent by Lewis-bases, respectively potassium carbonate[224] and *N*-methyl morpholine[225] (Figure 4.28). The initiation proceeds presumably by a single electron transfer between the Lewis-base and the Togni reagent which delivers a CF_3 radical which adds to the alkene. The formation of C-H bond is thought to proceed by hydrogen abstraction from the solvent, which both possess activated hydrogen atoms activated by amides. This assumption was confirmed by deuterated label control experiments and by the isolation of a compound resulting from the coupling of 2-iodobenzoate (from the Togni reagent) and a carbocation derived from the solvent DMF. Although these mild and easily set up reaction conditions are a clear advantage, these methods require large excess of Togni reagent and present the downside of being poorly selective and provide only moderate yields.

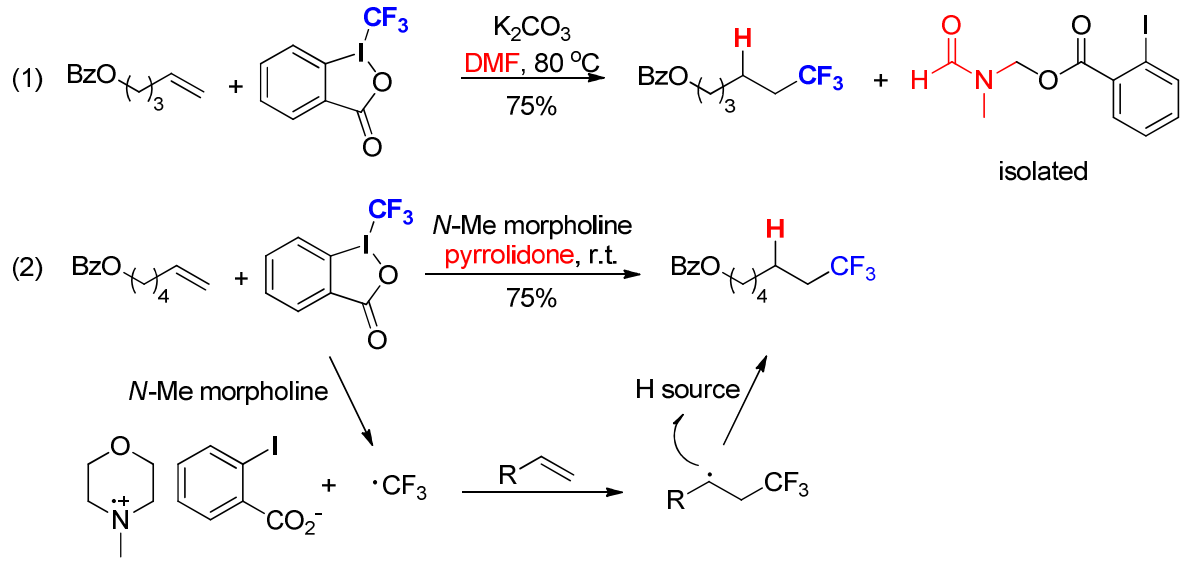

Figure 4.28 – Reductive radical hydrotrifluoromethylation of alkenes *via* activation by Lewis-base

Indirect methods have also been developed. For example, the group of Zard exploited the chemistry of xanthates to perform a 2 steps hydrotrifluoromethylation of alkenes[226] (Figure 4.29). This method relies on a sequence of thiotrifluoromethylation using a *S*-trifluoromethyl xanthate, followed by a reduction by hypophosphorus acid.

[224] Egami, H.; Usui, Y.; Kawamura, S.; Nagashima, S.; Sodeoka, M. *Chem. Asian J.* **2015**, *10*, 2190.
[225] Cheng, Y.; Yu, S. *Org. Lett.* **2016**, *18*, 2962.
[226] Li, S.G.; Zard, S.Z. *Org. Lett.* **2013**, *15*, 5898.

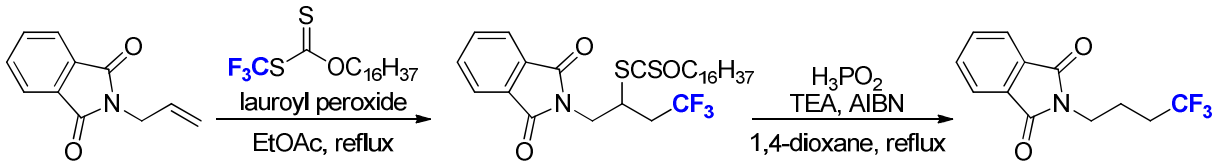

Figure 4.29 – Indirect hydrotrifluoromethylation of alkenes using xanthate's chemistry

In summary, the methods previously reported in the literature for the hydrotrifluoromethylation of unactivated alkenes suffer from various downsides. Most of these methods provideproducts which are often contaminated by allylic or vinylic trifluoromethyl byproducts. The only two methods which provide selective reactions and high yields present some technical drawbacks as they rely on not practical photocatalysis or electrolysis which imply the use of expensive iridium complexes or electrides. Thus, there still is a need for an efficient and easy to set upmethod for hydrotrifluoromethylation of alkenes. While all the previously described methods use an external hydrogen donor, mainly the solvent, we thought of adapting our knowledge on the use of the benzyl ether as hydride donor to develop a method using a benzyloxy moiety as a transient hydrogen donor. The next part will present the work we did around this idea.

4.2 Copper-catalyzed radical hydrotrifluoromethylation of homoallylic benzyl ethers

4.2.1 Origin of the project

This project originated with a serendipitous observation reported by Sodeoka *et al.* during a study of the carbotrifluoromethylation of alkenes (Figure 4.30).[227] While the carbon centered radical intermediate was expected to be trapped by a remote phenyl group to deliver, a 7-membered cycle, the main product observed was the product of a formal 1,6-oxytrifluoromethylation. The mechanism leading to the formation of this product involves a 1,5-hydrogen shift, leading to a more stable benzylic radical which can be oxidized to give a benzylic carbocation that is trapped by the 2-iodobenzoate. In the next years, Liu and coworkers took advantage of this discovery to develop a series of methods for 1,6-bromo-, azido-, cyano- or

[227] Sodeoka : Egami, H.; Shimizu, R.; Kawamura, S.; Sodeoka, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 4000.

alcoxy-trifluoromethylation reactions, thus confirming the reliability of this 1,5-hydrogen transfer.[228]

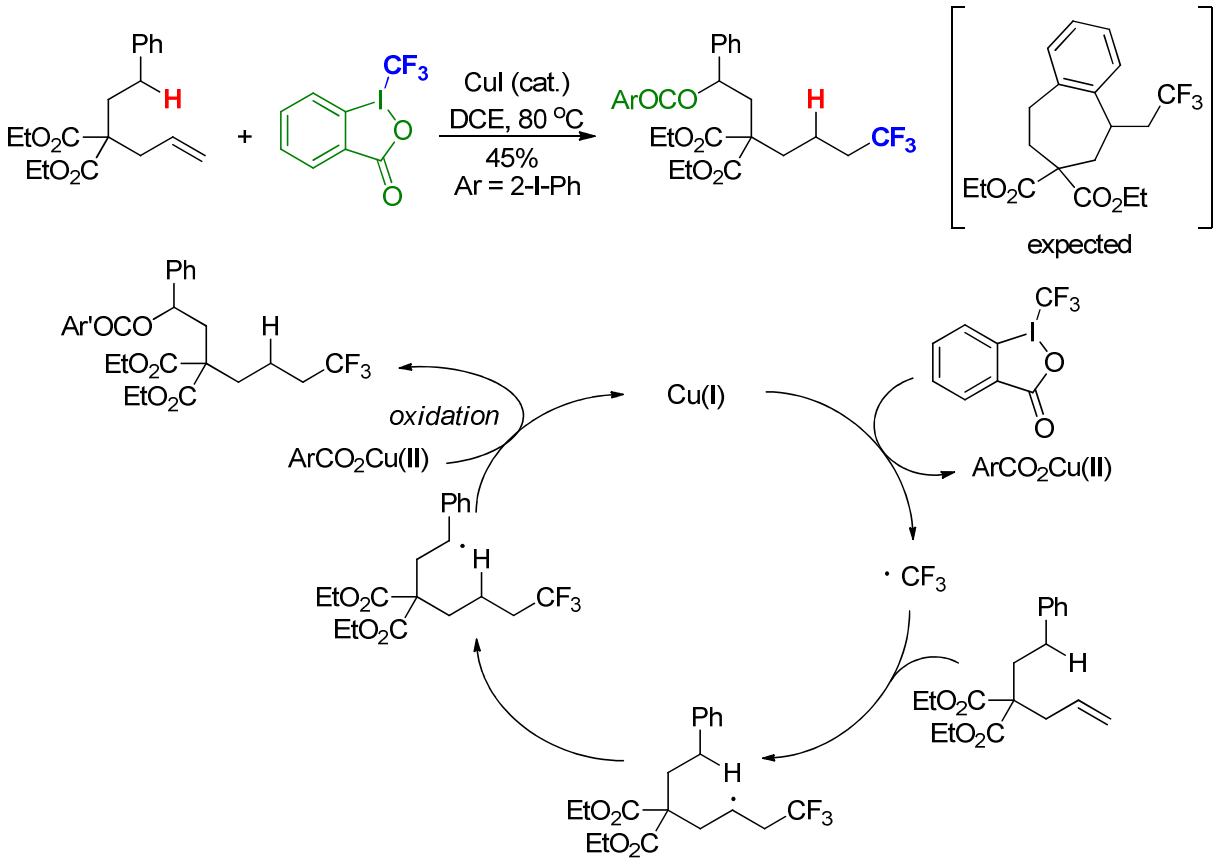

Figure 4.30 – First example of internal delivery of the hydrogen for hydrotrifluoromethylation of alkenes

Based on this observation, we thought of using this 1,5-hydrogen abstraction to design a formal hydrotrifluoromethylation of homoallylic alcohols, using a benzyl ether moiety as a transient hydrogen donor, with a 1,3-asymmetric induction (Figure 4.31). This reaction would proceed *via* the following mechanism, which is described step by step to emphasize on the several advantages of this method.

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[228] a) Yu, P.; Lin, J.S.; Li, L.; Zheng, S.C.; Xiong, Y.P.; Zhao, L.J.; Tan, B.; Liu, X.Y. *Angew. Chem.* **2014**, *126*, 12084 ; b) Yu, P.; Zheng, S.C.; Yang, N.Y.; Tan, B.; Liu, X.Y. *Angew. Chem. Int. Ed.* **2015**, *54*, 1 ; c) Huang, L.; Zheng, S.C.; Tan, B.; Liu, X.Y. *Org. Lett.* **2015**, *17* , 1589 ; d) Huang, L.; Lin, J.S.; Tan, B.; Liu, X.Y. *ACS Catal.*, **2015**, *5* , 2826 ; e) Huang, L.; Zheng, S.C.; Tan, B.; Liu, X.Y. *Chem. Eur. J.* **2015**, *21*, 1 ,5-

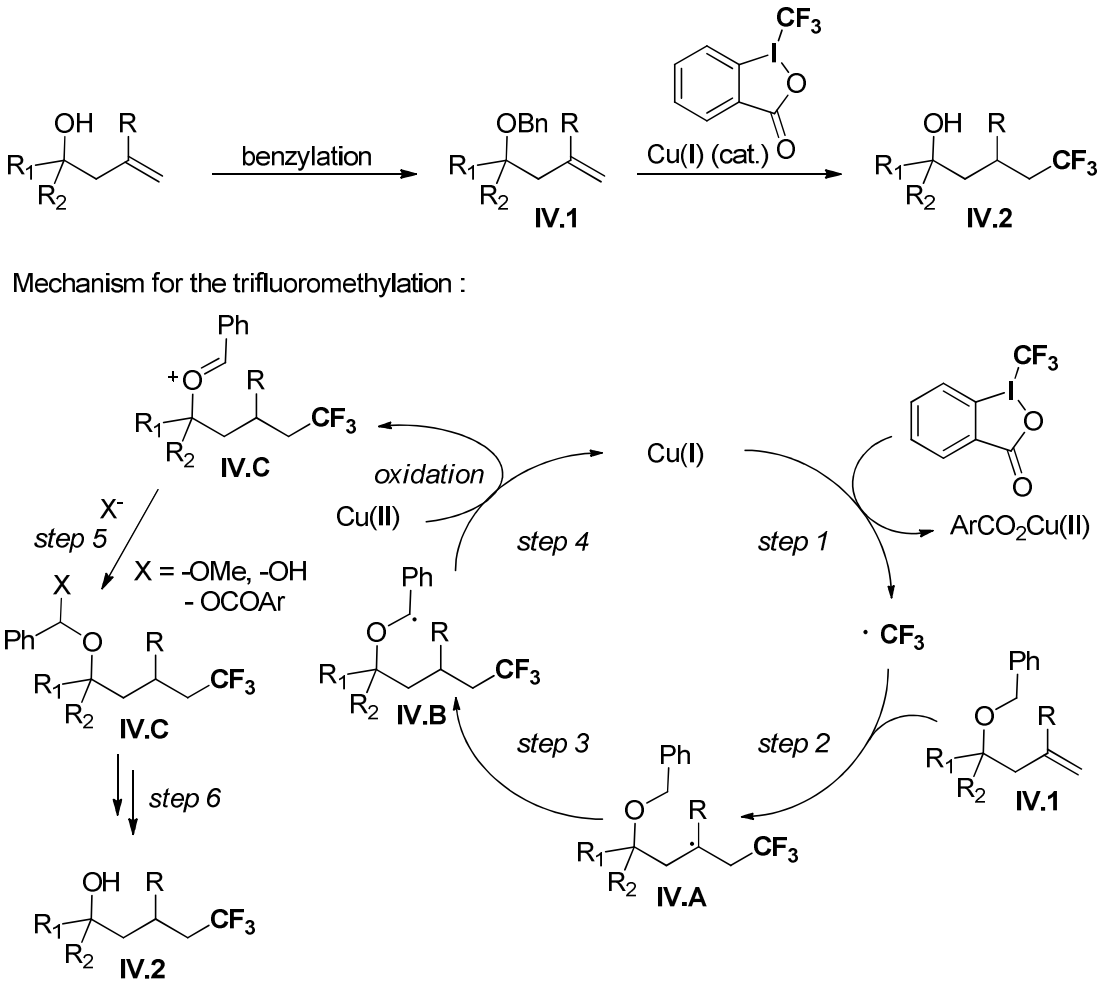


Figure 4.31 – Proposal for a formal hydrotrifluoromethylation of homoallylic alcohols using a benzyl group as a traceless hydrogen donor

❖ Step 1-2 :

The generation of the CF_3 radical, *via* the reduction of the Togni reagent by copper(I), and its addition on the alkene proceeds in the same way than the methods previously described in the literature.

❖ Step 3 :

The first advantage concerns the following step : the 1,5-hydrogen shift. As the driving force of this transfer is the generation of a carbon centered radical **IV.B** which is more stable than the one abstracting the hydrogen (**IV.A**), we assumed that this transfer would be even more facilitated if the hydrogen donor was a benzyl ether. Indeed, the stabilizing effects of both the oxygen and the phenyl could be combined by capto-dative effect.[229]

The efficiency of this hydrogen transfer is primordial as this is the step which would control a very important aspect of our method : the 1,3-asymmetric induction. This idea comes from a work made by our group on the hydrogenation of alkenes *via* 1,5-hydride shift using a benzyl ether as the hydride source (Figure 32). It was observed that, in the case of a substrate possessing an asymmetric center at the carbon bearing the ether moiety and a phenyl substituent at the vinylic position, the chiral information can be transferred to the benzylic carbocation resulting from the protonation of the alkene, at which time the phenyl group is obtained in a *syn* position as compared to the configuration of the first asymmetric center. This 1,3-asymmetric induction is thought to proceed during the hydride shift *via* a pseudo-chair conformation of the transition state, in which the phenyl (more sterically demanding than the methyl) substituent is placed at the pseudo equatorial position. We envisioned that such a transfer of chirality could also be possible on our transformation. In this case, the control of the diastereoselectivity of the process would be dictated by the difference in steric demand between the vinylic substituent of the substrate and the trifluoromethyl group. Theoretically, a smaller substituent would be place in an *anti* position and a bigger substituent in a *syn* position as compared to the configuration of the ether moiety.

[229] Viehe, H.G.; Janousek, Z.; Merenyi, R. *Acc. Chem. Res.* **1985**, *18*, 148.

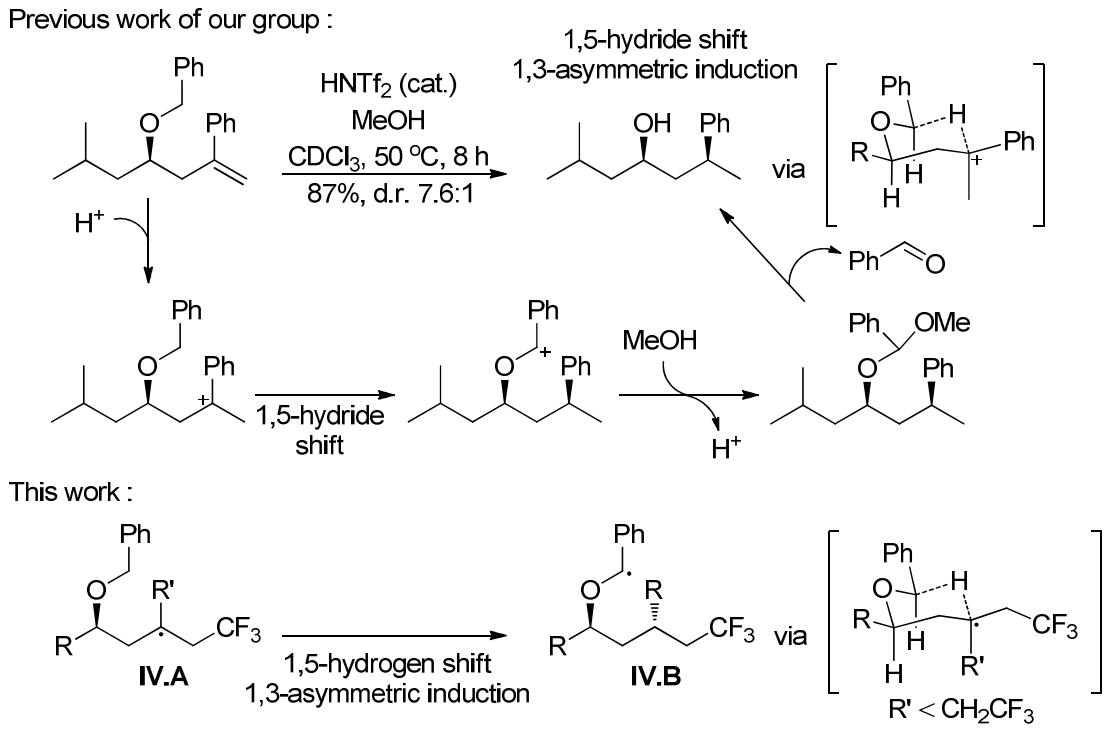


Figure 4.32 – 1,3-asymmetric induction *via* a chaise conformation transition-state

❖ Step 4 :

This 1,5-hydrogen shift generates a new radical intermediate **IV.B** which has to be dealt with. In this strategy, this radical is oxidized by copper(II) to regenerate the copper(I) catalyst and to give a carbocation. We predicted that this oxidation would be facilitated by the presence of the oxygen atom which would make this radical more electron rich and thus, more prompt to undergo oxidation. Moreover, the resulting oxocarbenium intermediate **IV.C** would be more stable than the benzylic carbocation which would be obtained in the absence of the oxygen atom (Figure 4.33).

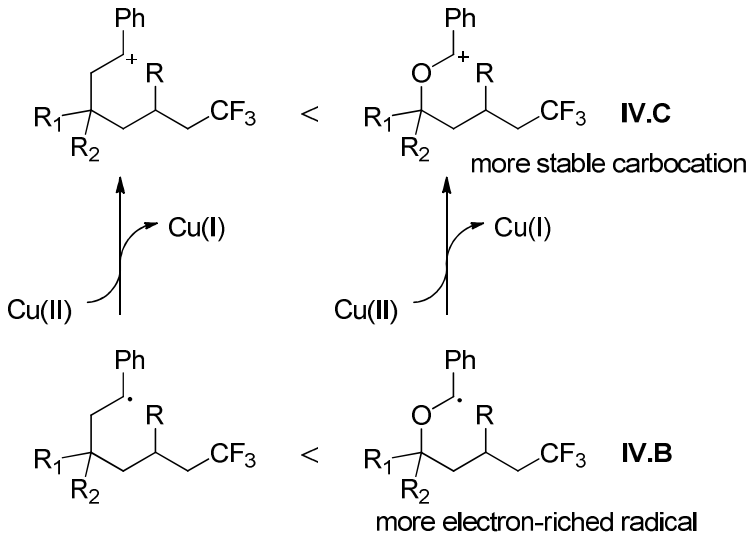


Figure 4.33 – Effect of the oxygen atom on the oxidation of the radical intermediate

❖ Step 5-6 :

After the occurrence of the oxidation, the resulting carbocation can evolve following different pathways. For example, Liu demonstrated that the carbocation intermediate can evolve *via* β-elimination of a proton.[230] In other examples shown by Liu and Sodeoka, the subsequent trapping of this intermediate can lead to a large range of 1,6-trifluoromethylfunctionalization reactions. However, the trapping of this carbocation is not always well-controlled, which unavoidably affects the yield. In our proposal, the same strategy is involved but the advantage is that, once the hydrogen transfer is done, all the possible pathways lead to the formation of the same product. Indeed, in our case, no β-elimination is possible as there is no labile proton, which makes one less possible by-product. Moreover, the trapping of the benzylic carbocation by heteroatom centered nucleophile leads to the formation of acetal type intermediates **IV.D** which should, by an appropriate treatment, be easily cleaved to give the product of the formal one pot / two steps hydrotrifluoromethylation of the homoallylic alcohol (Figure 4.34).

[230] Yu, P.; Zheng, S.C.; Yang, N.Y.; Tan, B.; Liu, X.Y. *Angew. Chem. Int. Ed.* **2015**, *54*, 1.

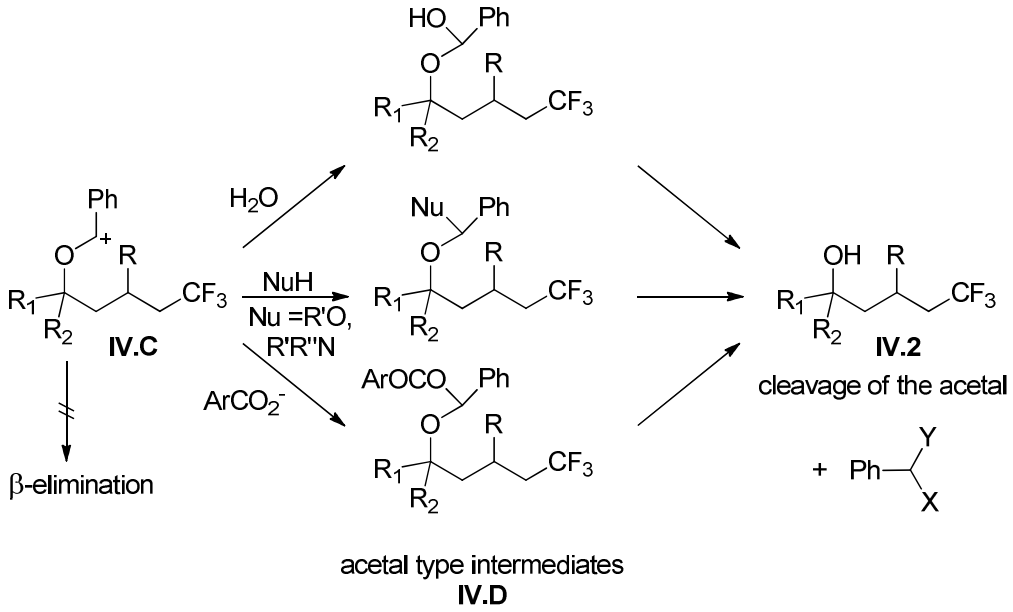


Figure 4.34 – Evolution of the oxocarbenium intermediate to the alcohol product

As the benzylation of alcohols is a well-established and efficient process, we only studied the trifluoromethylation part of this strategy, which is the most challenging aspect of our approach. Thus, all this work was directly performed on benzylic homoallylic ethers.

4.2.2 Optimization of the reaction

To evaluate the feasibility of our proposal, we first decided to study the hydrotrifluoromethylation of monosubstituted alkenes, so that the analysis would not be complicated by the presence of diastereoisomers. For this purpose, we chose the model substrate **IV.1a**, which was prepared in 51% yield.[231] This substrate possesses a heavy phthalimido moiety which will counterbalance the propensity of the trifluoromethyl group to lower the boiling point, and which should not interact with the radical pathways. A first attempt was then realized, using the reactions conditions reported by Sodeoka (20 mol% of copper(I) iodide with 1.2 equivalent of Togni reagent in 1,2-DCE at 60 °C followed by a treatment with an aqueous solution saturated with sodium bicarbonate for 5 mins) and we were glad to see that completion was reached within

[231] The procedures for the preparation of the homoallylic benzylic ether substrates are described in the experimental part.

24 h and that the alcohol hydrotrifluoromethylation product **IV.2a** was obtained (Figure 4.35). However, the main product was the acetal type compound **IV.E**, in a 1:1 diastereoisomeric ratio, resulting from a trapping of the benzylic carbocation by the 2-iodobenzoate (from the Togni reagent). The side product **IV.F** was also obtained in small amount, resulting from an oxidation of the first radical intermediate followed by a subsequent β-elimination of a proton. The obtention of **IV.F** means that, in these conditions, the 1,5-hydrogen shift is not fast enough to completely prevail over the oxidation of the first radical intermediate. However, **IV.F** was only obtained in small amount (less than 5%) and the first priority was to find a suitable treatment to cleave the acetal type intermediate **IV.E** to obtain the alcohol product.

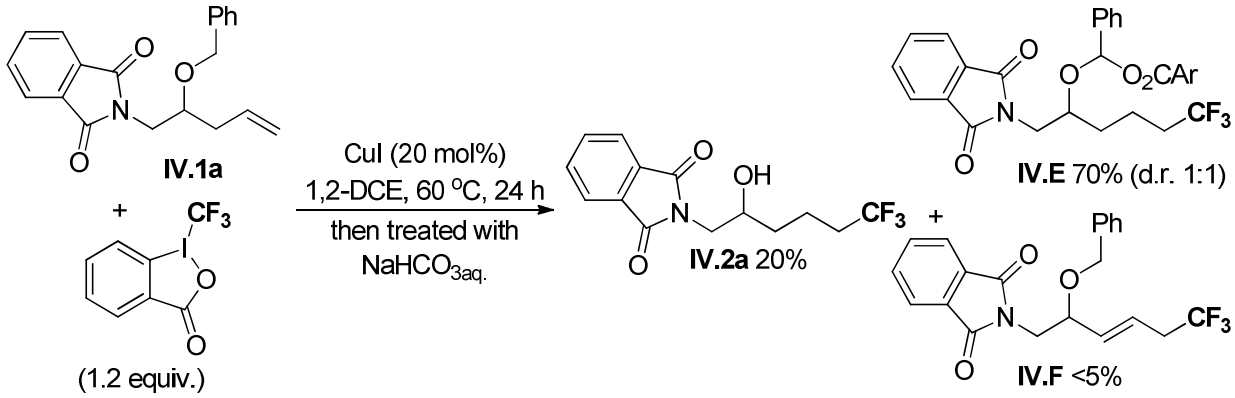
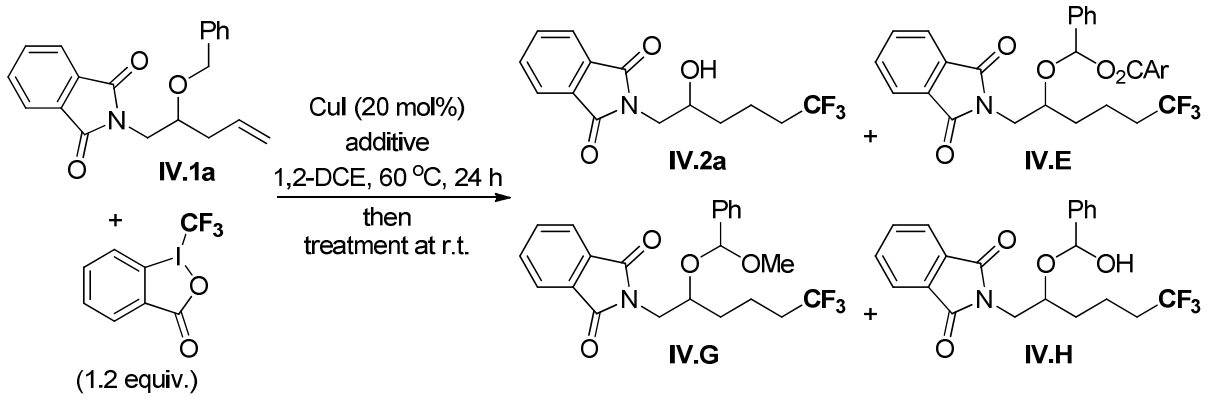


Figure 4.35 – First attempt for the hydrotrifluoromethylation of benzylic homoallylic ethers*

❖ Cleavage of the acetal type intermediates :

One of the first advantages of our proposal is the possibility to cleave the different acetal type intermediates resulting from the trapping of the benzylic carbocation to obtain the alcohol product **IV.2**. For this purpose, we started by treating the reaction mixture with a series of basic or acidic aqueous solutions (Table 4.1, entries 1-4). However, no improvement was obtained and the acetal intermediate was not converted into the alcohol. Another attempt with five equivalents of water as an additive was made with the idea that water could potentially trap the benzylic carbocation to give an unstable hemiacetal intermediate **IV.H** which would give the product **IV.2a** upon hydrolysis (entry 5). No acetal intermediate was then obtained, tending to prove right our assumption. However, for some reason, the yield decreased. We then thought that the acetal moiety of **IV.E** could be cleaved by methanolysis (entry 6). The reaction was quenched with an aqueous solution saturated with sodium bicarbonate and the crude mixture was dissolved in methanol and treated with potassium carbonate at room temperature for one hour. Gratifyingly, with this treatment, the

acetal intermediate was completely cleaved and the alcohol **IV.2a** was obtained as the sole product in 85% yield. We then wondered if this process could be done in a one-pot manner (entry 7). Upon completion of the reaction, potassium carbonate and methanol were added to the reaction mixture which was stirred for an additional one hour at room temperature. However, we were surprised to see that **IV.E** was not converted to the alcohol **IV.2a** but to another acetal intermediate **IV.G**, which results from a copper(I)-mediated transacetalisation between methanol and the 2-iodobenzoate. The subsequent treatment of this mixture with *para*-toluene sulfonic acid (20 mol%) in methanol led to the cleavage of **IV.G** and to the obtention of the alcohol **IV.2a** as the sole product in 90% yield (entry 8). Luckily, this sequence could be shortened and adapted to a one-pot protocole. Upon, completion of the reaction, *para*-toluene sulfonic acid (20 mol%) and methanol were added and the reaction mixture was stirred for one hour at room temperature, after which the mixture was quenched with an aqueous solution saturated with sodium bicarbonate to give the alcohol **IV.2a** in 90% yield (entry 9).



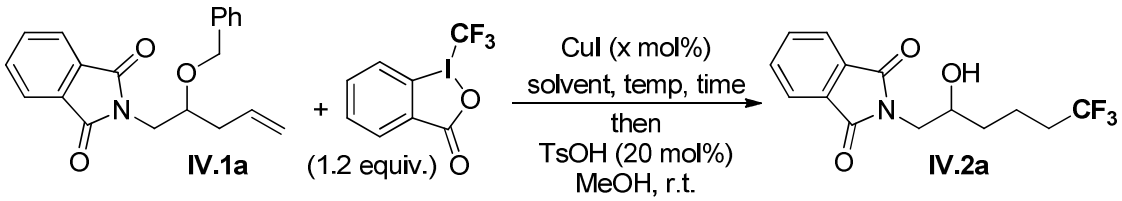
Entry	additive (5.0 equiv.)	treatment	Yield[a] IV.2a	Yield[a] IV.E	Yield[a] IV.G
1	-	$NaHCO_3$ sat.	20%	70%	-
2	-	K_2CO_3 sat.	20%	70%	-
3	-	NaOH (1M)	20%	70%	-
4	-	HCl (1M)	20%	70%	-
5	H_2O	$NaHCO_3$ sat.	57%	-	-
6	-	$NaHCO_3$ sat. then K_2CO_3 / MeOH on crude	85%	-	-
7	-	K_2CO_3 / MeOH then $NaHCO_3$ sat.	20%	-	70%
8	-	entry 7 then TsOH (20 mol%) / MeOH on crude	90%	-	-
9	-	TsOH (20 mol%) / MeOH then $NaHCO_3$ sat.	90%	-	-

The reactions were performed on a 0.2 mmol scale at a 0.3 M concentration in 1,2-DCE under N_2
[a] NMR yield using 1,1,2,2-TCE and α,α,α-trifluorotoluene as internal standards.

Table 4.1 – Optmization of the conditions for the cleavage of the acetal type intermediates*

❖ Optimization of the reaction conditions :

With this established procedure in hand for the cleavage of the acetal intermediates, we then tried to increase further the yield of the alcohol **IV.2a** (Table 4.2). We started with a brief screening of the solvent of the reaction. Changing for acetonitrile or ethyl acetate led to much slower reaction as completion could not be reached within 24 h (entries 2,3). However, the use of 1,4-dioxane as the solvent led to completion and to the obtention of the product **IV.2a** in 95% yield within 24 h (entry 4). Using this solvent, the catalyst loading could even be lowered to 10 mol% (entry 5). Copper(I) iodide being one of the cheapest copper(I) salts, we did not screen the catalyst any further. The last improvement was obtained when methanol was used as a cosolvent of the reaction (entry 6). Indeed, using a 9:1 mixture of 1,4-dioxane and methanol as the solvent accelerated the reaction which completed within 12 h. This improvement can be tentatively explained by the better solubility of the Togni reagent in this solvent system. An attempt was also made to reduce the temperature of the reaction to room temperature but this turned out to be detrimental for the reaction (entry 7).



Entry	CuI (x mol%)	solvent	Temp	Time	Yield[a] IV.2a
1	20 mol%	1,2-DCE	60 °C	20 h	90%
2	20 mol%	MeCN	60 °C	24 h	67%
3	20 mol%	EtOAc	60 °C	24 h	70%
4	20 mol%	1,4-dioxane	60 °C	24 h	95%
5	10 mol%	1,4-dioxane	60 °C	24 h	95%
6	10 mol%	1,4-dioxane / MeOH (9:1)	60 °C	12 h	95%
7	10 mol%	1,4-dioxane / MeOH (9:1)	r.t.	48 h	70 %

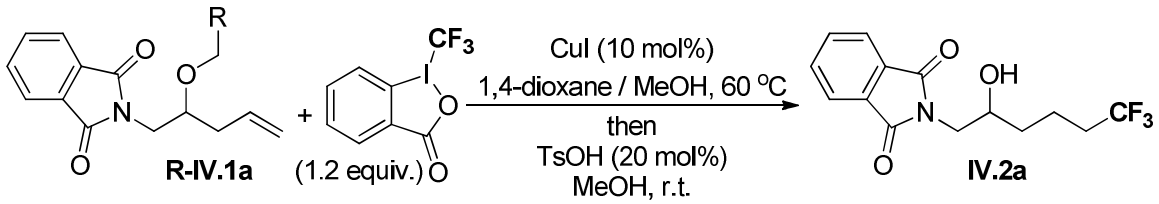
The reactions were performed on a 0.2 mmol scale at a 0.3 M concentration under N_2

[a] NMR yield using 1,1,2,2-TCE and α,α,α-trifluorotoluene as internal standards.

Table 4.2 – Optimization of the reaction conditions for the hydrotrifluoromethylation of alkene*

❖ Optimization of the hydrogen donor :

We then turned our attention to the nature of the hydrogen donor (Table 4.3). With the idea that the oxidation step of the benzylic radical **IV.B** to the oxocarbenium intermediate **IV.C** could be positively affected by an electron-donating substituent on the phenyl moiety, we prepared a *para*-methoxybenzyl ether substrate (entry 1). However, performing the reaction on this substrate invalidated our idea as a longer reaction time was required. This result could be tentatively explained by the fact than this electron-donating substituent on the phenyl moiety reduces the capto-dative effect, and thus, the efficiency of the 1,5-hydrogen shift. Attempts with the more atom economical methoxymethyl (entry 3) and ethyl ether substrates (entry 4) also tended to prove that a phenyl moiety is more suitable for this reaction.



Entry	- R	Yield[a] IV.2a	Recovery of[a] R-IV.1a
1	- C_6H_4-*p*-OMe	79%	16%
2	- Ph	95%	-
3	- OMe	69%	16%
4	- Me	67%	-

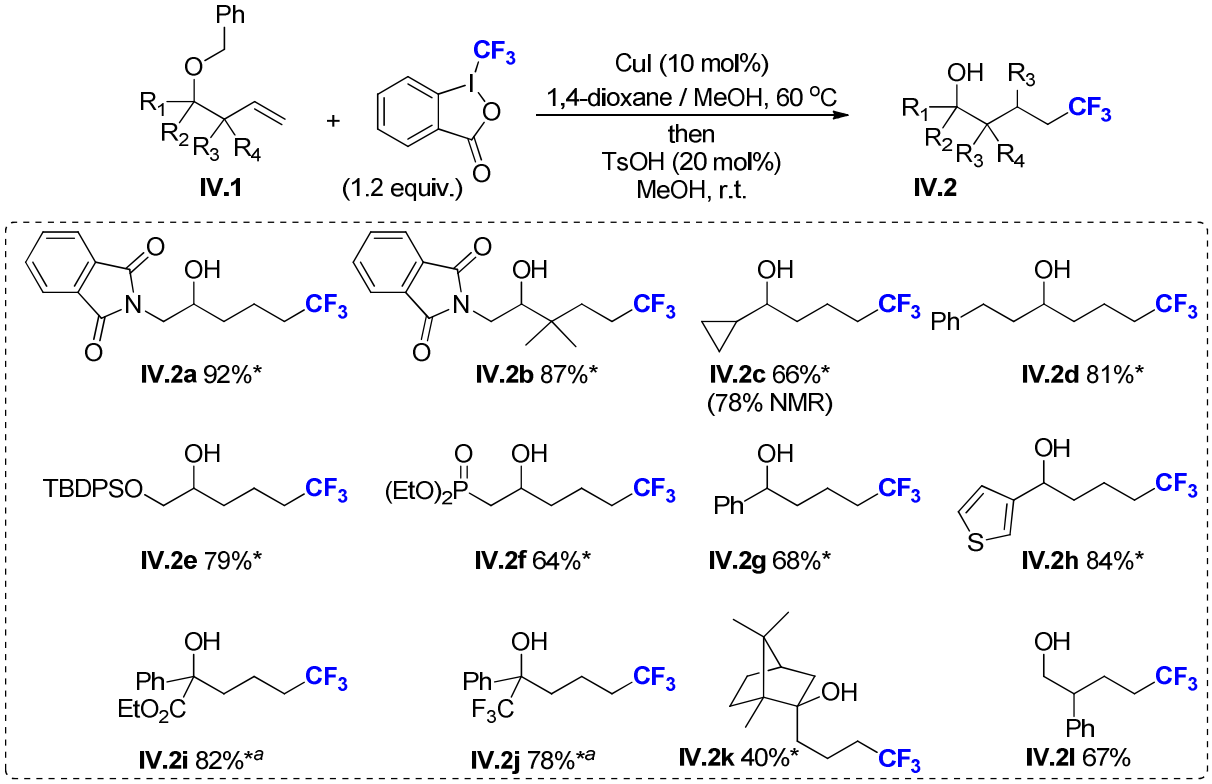
The reactions were performed on a 0.2 mmol scale at a 0.3 M concentration in a 9:1 mixture of 1,4-dioxane / MeOH under a N_2 atmosphere.
[a] NMR yield using 1,1,2,2-TCE and α,α,α-trifluorotoluene as internal standards.

Table 4.3 – Optimization of the hydrogen donor for the hydrotrifluoromethylation of alkene*

4.2.3 Substrate scope of the reaction

With these optimized conditions in hands (10 mol% of copper(I) iodide and 1.2 equivalent of Togni reagent at 60 °C in a 9:1 mixture of 1,4-dioxane and methanol, followed by addition of 20 mol% of *para*-toluenesulfonic acid and methanol) we started to investigate the substrate scope of the reaction on a series of benzylic homoallylic ether substrates with no substituent at the vinylic position (Figure 4.36). A series of secondary alcohol products (**IV.2a**-**IV.2h**) could be obtained in

good to excellent yields, with an excellent functional group tolerance. Notably, protected trifluoromethyl 1,2-aminol (**IV.2a**, **IV.2b**) and 1,2-diol products (**IV.2e**) could be obtained. The obtention in very good yield of the product **IV.2d** gives a good comparison between the speed of the 1,5-hydrogen shift between a standard benzylic position and the benzylic position of the benzyl ether moiety, thus underlining the importance of the oxygen atom. It is also worth noting that the reaction proceeded smoothly with aromatic substituents (**IV.2g** and **IV.2h**), showing that the 1,5-hydrogen transfer is faster than the radical addition to aromatic rings. Tertiary alcohol products could also be obtained (**IV.2i-IV.2k**). However, good yields were only obtained for substrates bearing an electron-withdrawing substituent. This trend can be tentatively explained by the fact that the oxocarbenium intermediate **IV.C** (scheme 4.26) can fragmentate to give a carbocation with the release of benzaldehyde (see substrate **IV.1x** below). These results seem to indicate that the fragmentation of a secondary substrate is not favored. However, the drop of the yield for the product **IV.2k,** as compared to **IV.2i** and **IV.2j,** indicates that a tertiary carbocation is more likely formed, unless a destabilizing electron-withdrawing substituent is present. To finish, we were also pleased to see that a primary alcohol product could also be formed in good yield (**IV.2l**).

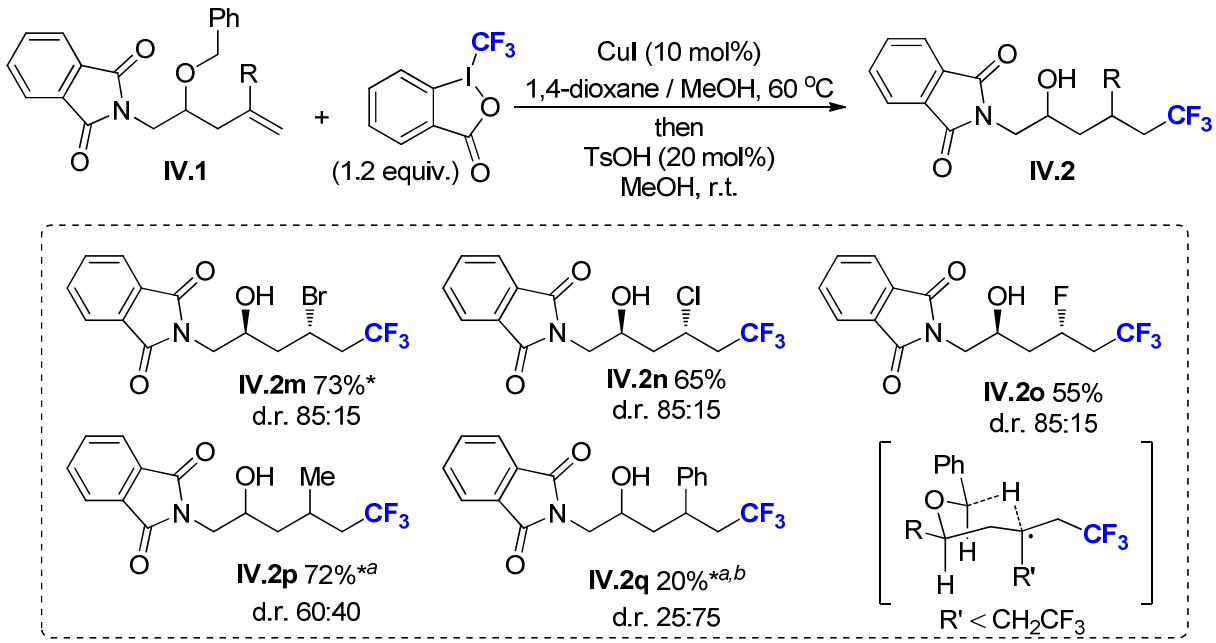


The reactions were performed on a 0.2 mmol scale at a 0.3 M concentration under N_2

Figure 4.36 – Substrates scope of the reaction on monosubstituted alkenes

After confirming the robustness of our method on monosubstituted alkenes, we turned our attention to the most important aspect of our strategy : the 1,3-asymmetric induction. For this purpose, we firstly performed the reaction on the bromide-substituted alkene **IV.1m** and we were pleased to see that the alcohol product **IV.2m** was obtained in good yield and with a very good diastereoisomeric ratio (85:15). Further conversions of this diastereoisomeric mixture (see section 4.2.3) revealed that the major diastereoisomer is the one possessing the *anti* relative configuration. This observation is in accordance with what was discussed in section 4.2.1 about the chair conformation of the transition state during the 1,5-hydrogen abstraction. In this case, the bromide substituent (A value[232] : 0.48) is sterically smaller than the trifluoromethyl moiety (of which the A value should be close to the one of ethyl 1.79) which is placed at the equatorial position. The same reasoning can be applied for products **IV.2n** and **IV.2o** (A value chloride : 0.53; fluoride : 0.25). However, the methyl moiety is, sterically speaking, closer to the trifluoroethyl (A value methyl 1.70) which explains the poor diastereoselectivity obtained for product **IV.2p**. On the contrary, a phenyl moiety is allegedly significantly sterically more demanding than the trifluoroethyl (A value phenyl : 3.0) which explains the better diastereoisomeric ratio obtained for the product **IV.2q**. In this case, it makes sense to assume that the major diastereoisomer is the product possessing the *syn* relative configuration but this could not be confirmed. However, the product **IV.2q** was obtained in very low yield, which can be explained by the too high stability of the first radical intermediate, which can be oxidized before the occurrence of the 1,5-hydrogen abstraction, thus leading to undesired side-reactions.

[232] Eliel, E.L.; Wilen, S.H.; Doyle, M.P. *Basic Organic Stereochemistry*, Wiley, **2001**, 443.



[a] The relative configuration of the two asymmetric centers was not confirmed

[b] This product was not isolated

Figure 4.37 – Substrates scope of the reaction on 1,1-disubstituted alkenes

We then turned our attention to the adaptation of this process to benzylamine substrates and we were pleased to see that a few trifluoromethyl amine products could be obtained in good yields (**IV.2r-IV.2t**).

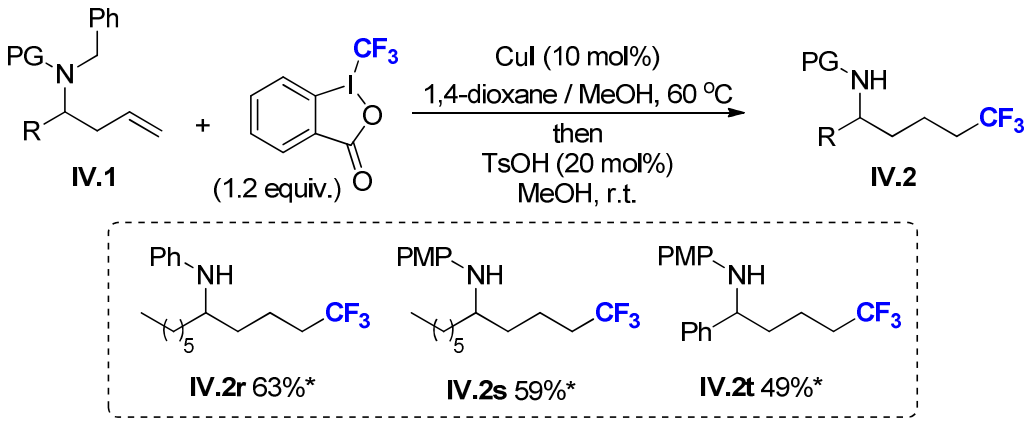


Figure 4.38 – Substrates scope of the reaction on amine substrates

To confirm that the benzyl ether moiety is indeed the hydrogen source of this reaction, we prepared the deuterated substrate **D_2-IV.1a** and we were glad to see that the radical trifluoromethylation of this compound led to the obtention of the deuterated product **D-IV.2a**.

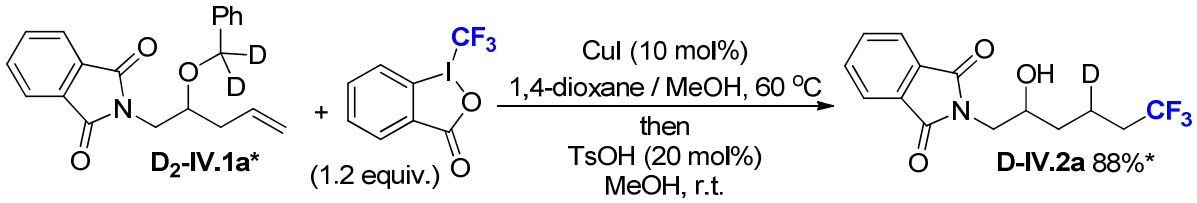


Figure 4.39 – Mechanistic study using a deuterated substrate

However, the desired products could not be obtained when the following substrates were used (Figure 4.40). The reaction on the substrate **IV.1u** mostly led to the formation of the β-elimination product, whereas the substrate **IV.1v** was converted to a complex mixture.

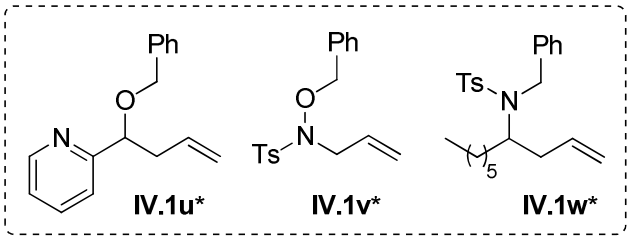


Figure 4.40 – Substrates for which the reaction did not proceed

Moreover, during the preliminary studies for this project, the reaction on the substrate **IV.1x** gave the evidence of a potential fragmentation of the oxocarbenium intermediate. In this case, it seems that the *para*-anisole substituent is enough electron-donating to stabilize the formation of a carbocation upon release of benzaldehyde. This new intermediate can then be trapped by the 2-iodobenzoate or be deprotonated to give respectively the byproducts **IV.I** and **IV.J.**

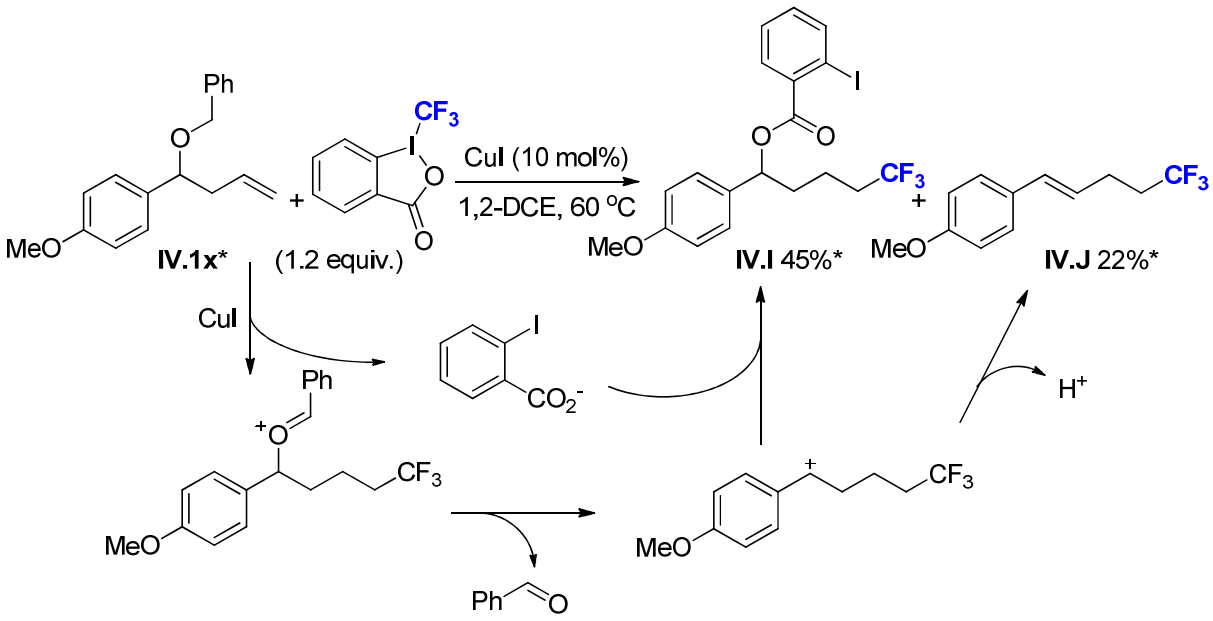
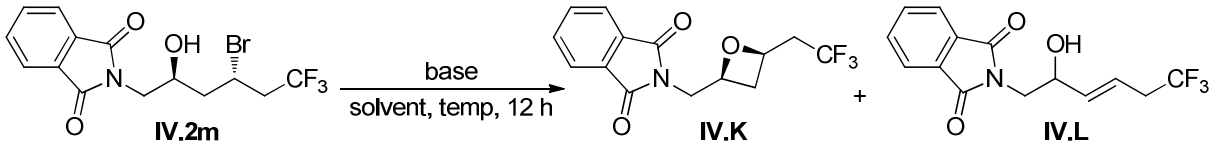


Figure 4.41 – Evidence of the potential fragmentation of the oxocarbenium intermediate

4.2.4 Derivatization

While most of the products are simple trifluoromethyl alcohols difficult to functionalize any further, the product **IV.2m** could be potentially converted into interesting cyclic scaffolds thanks to the presence of the bromide atom and of potentially nucleophilic heteroatoms. Firstly, we attempted to perform a nucleophilic substitution of the alcohol onto the bromide to obtain the oxetane product **IV.K**. The oxetane moiety is a very important scaffold which is present in various natural products and which exhibit many biological activities.[233] Therefore, the development of a method for the synthesis of trifluoromethyl substituted oxetanes would be very valuable. But sadly, none of the methods reported in the literature on the synthesis of oxetanes provided the desired product. In most cases, only recovering of the starting material and the formation of an elimination product was observed.

[233] For a review on oxetanes, see : Bull, J.A.; Croft, R.A.; Davis, O.A.; Doran, R.; Morgan, K.F. *Chem. Rev.* **2016**, *116*, 12150.



Entry	base	solvent	temp	Yield[a] IV.K	Recovery[a] IV.2m	Yield[a] IV.L
1	NaH (1.5 equiv.)	THF	60 °C	-	-	-
2	Na_2CO_3 (2.0 equiv.)	DMF	r.t.	-	90%	10%
3	Ag_2O (3.0 equiv.)	EtOAc	r.t.	-	100%	-
4	DIPEA (15.0 equiv.)	toluene	100 °C	-	30%	70%
5	DMAP (5 mol%) / NEt_3 (5.0 equiv.)	CH_2Cl_2	r.t.	-	15%	85%

Table 4.4 – Attempts for the conversion of bromo-alcohol IV.2m to the oxetane IV.K*

After this failure, we attempted a homologous cyclization with the substitution of the bromide atom by the free amine resulting from the deprotection of the phthalimido moiety. Such a cyclization would lead to a trifluoromethyl pyrrolidine product which would be very valuable as pyrrolidines are very important scaffold present in many biologically active compounds.[234] To avoid any potential complication, the alcohol was protected with a *tert*-butyldimethylsilyl group using *tert*-butyldimethylsilyl triflate and 2,6-lutidine. The classic method for the removal of the phthalimido protection of the amine, using hydrazine, was then performed. We were gladly surprised to see that the free amine intermediate spontaneously underwent cyclization as the pyrrolidine product was directly obtained in 97% under these reaction conditions. A NOESY experiment could also confirmed the configuration of the main diastereoisomer, thus confirming at the same time the configuration of the main diastereoisomer of the alcohol product **IV.2m**.

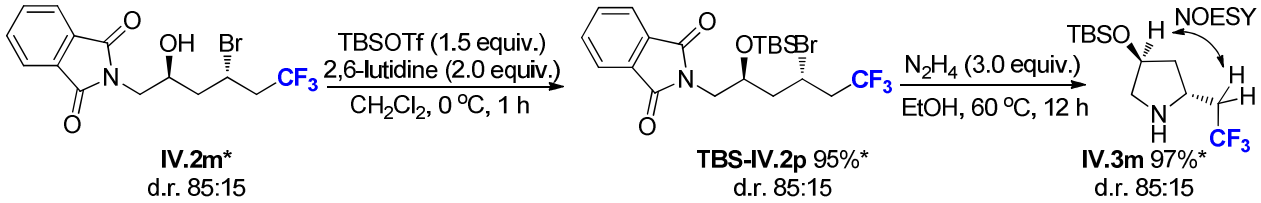


Figure 4.42 – Conversion of the protected amine IV.2m to the oxetane to the pyrrolidine IV.3m

After this success in this hydrotrifluoromethylation of alkenes, presenting a high functional group tolerance and an efficient 1,3-asymmetric induction, we were interested to see if this process could be adapted to other hydrofunctionalization reactions.

[234] Baht, C.; Tilve, S.G. *RSC Adv.* **2014**,*4*, 5405.

4.3 Copper-catalyzed radical hydroazidation of homoallylic benzyl ethers

4.3.1 Introduction to hydroazidation of unactivated alkenes

The incorporation of azido moieties to organic compounds is a very interesting challenge because of the rich chemistry of organic azides.[235]

Nowadays, the radical azidation of unactivated alkenes is a well-established process. In the same way than radical trifluoromethylation, the carbon centered radical resulting from the addition of an azide radical can evolve following different pathways. Using this strategy, a number of methods were developed for fluoroazidation,[236] oxyazidation,[237] cyanoazidation[238] and carboazidation[239] of unactivated alkenes (Figure 4.43).

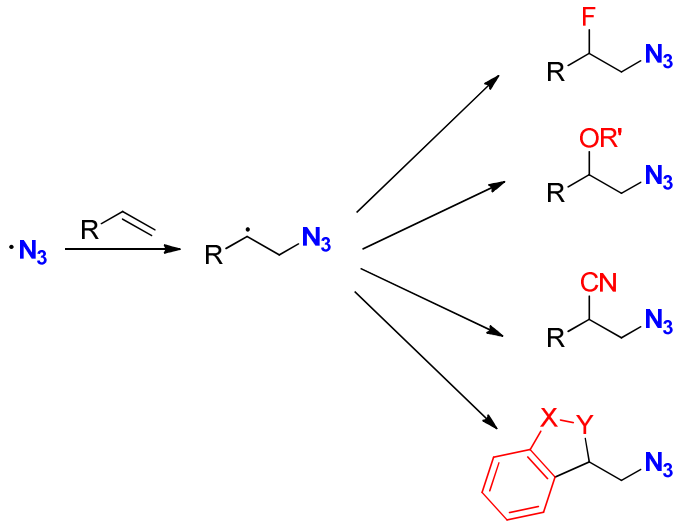


Figure 4.43 – General scheme for the radical azidation of alkenes

[235] a) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem. Int. Ed*. **2005**, *44*, 5188; *Angew. Chem.* **2005**, *117*, 5320; b) Bräse, S.; Banert, K. *Organic Azides: Syntheses and Applications*, Wiley **2010**.
[236] Li, Z.; Zhang, C.; Zhu, L.; Liu, C. ; Li, C. *Org. Chem. Front*. **2014**, *1*, 100.
[237] a) Zhu, L.; Yu, H.; Xu, Z.; Jiang, X.; Lin, L.; Wang, R. *Org. Lett*. **2014**, *16*, 1562 ; b) Zhu, R.; Buchwald, S.L. *J. Am. Chem. Soc*. **2015**, *137*, 8069 ; c) Fumagalli, G.; Rabet, P.T.G.; Boyd, S.; Greaney, M.F. *Angew. Chem. Int. Ed*. **2015**, *54*, 11481 ; d) Lu, M.Z.; Wang, C.Q.; Loh, T.P. *Org. Lett*. **2015**, *17*, 6110 ; e) Yin, H.; Wang, T.; Jiao, N.; *Org. Lett*. **2014**, *16*, 2302 ; f) Li, J.; Liu, M.; Li, Q.; Tian, H.;Shi,Y. *Org. Biomol. Chem.* **2014**, *12*, 9769.
[238] Xu, L.; Mou, X.Q.; Chen, Z.M. ; Wang, S.H. *Chem. Commun.* **2014**, *50*, 10676.
[239] a) Wei, X.H.; Li, Y.M.; Zhou, A.X.; Yang T.T.; Yang, S.D. *Org. Lett.* **2013**, *15*, 4158 ; b) Yuan, Y.; Shen, T.; Wang, K.; Jiao, N. *Chem. Asian J*. **2013**, *8*, 2932.

However, very few examples of *anti*-Markovnikov hydroazidation of unactivated alkenes have been reported so far. Renaud and his group developed a two steps protocol using catecholborane as the hydrogen source and benzylsulfonylazide as the azide source (Figure 4.44).[240] This reaction is initiated by the hydroborylation of the alkene, which determines the *anti*-Markovnikov regioselectivity of the reaction. Then, a radical chain mechanism operates the exchange of the boron substituent by the azide. However, this protocol is tedious, as the excess of catecholborane has to be quenched prior to the second step, and the purification of the product is made difficult by undetermined side-reaction involving the byproduct benzylsulfinyloxycatecholborane.

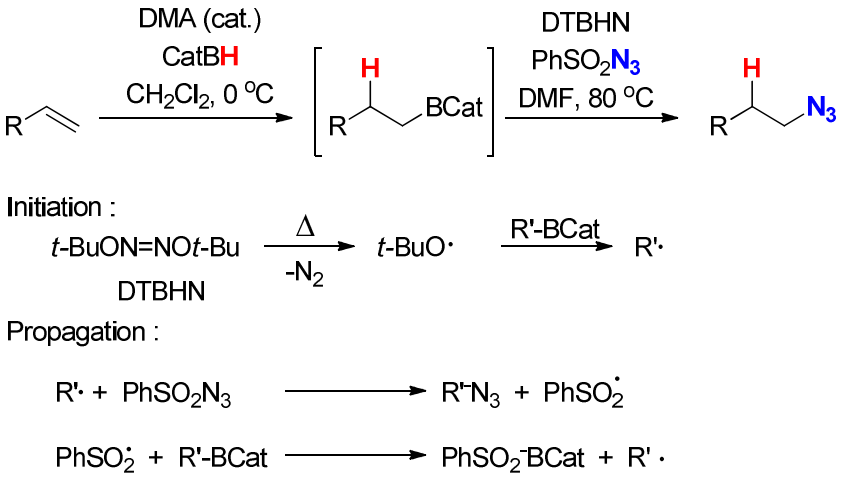


Figure 4.44 – Example of *anti*-Markovnikov hydroazidation of alkenes

Therefore, the development of an easy protocol for a more straightforward *anti*-Markovnikov hydroazidation of unactivated alkenes still represents an interesting challenge. Hence, our attempt to adapt our previous method for this end.

4.3.2 Optimization of the reaction

The same model substrate **IV.1a** was used for a first attempt under the same reaction conditions, except that the 1.2 equivalent of Togni reagent was changed for 1.5 equivalent of the analogous azido hypervalent iodine reagent (Zhdankin reagent). Gratifyingly, the hydroazidation

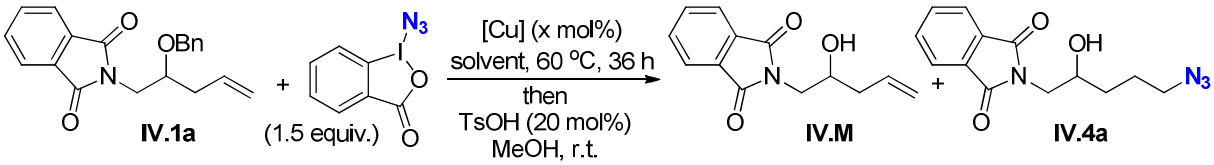
[240] Kapat, A.; Konig, A.; Montermini, F.; Renaud, P. *J. Am. Chem. Soc.* **2011**, *133*, 13890.

product **IV.4a** could be isolated, although in only low yield (Table 4.5, entry 1). Moreover, the product of the removal of the benzyl moiety **IV.M** was also observed. The formation of this byproduct can be tentatively explained by a mechanism involving the abstraction of a benzylic hydrogen by an azide radical.[241] The resulting radical then follows the same pathway than the intermediate **IV.B** (Figure 4.31) and the homoallylic alcohol **IV.M** is obtained.

After a brief research in the literature, it appeared that copper(II) salts were more suitable to promote radical azidation with the Zhdankin reagent. Notably, Loh *et al.* showed that copper(II) triflate promoted efficiently an oxyazidation while copper(I) iodide promoted a diazidation.[242] Based on this observation, we tried to perform the reaction using copper(II) triflate and we were happy to see that the yield of the product **IV.4a** got doubled (entry 2). Keeping this catalyst, we then screened the solvent of the reaction, using acetonitrile, ethyl acetate, methanol and finally 1,2-dichloroethane which turned out to give the best result (entries 3-6). The copper salts were then screened. As expected, the use of copper(I) salts led to a decreasing of the yield (entries 9-11). Other copper(II) salts also gave poorer results, such as copper(II) acetate, copper(II) trifluoroacetylacetonate, except copper(II) bromide which was the first catalyst providing a full conversion after 36 h. Increasing the catalyst loading of copper(II) bromide to 20 mol% gave an even better yield and allowed to shorten the reaction to 20 h (entry 13). Attempts were also made to resort to ligands, such as 1,10-phenantroline or 1,2-bipyridine, but no improvement was obtained in these conditions.

[241] The azide radical was proved to efficiently prone hydrogen abstraction reaction : a) Huang, X.; Groves, J.T .*A. C. S. Catal.* **2016**, *6*, 751 ; b) Sharma, A.; Hartwig, J.F. *Nature* **2015**, *517*, 600 ; c) Wang, Y.; Li, G.X.; Yang, G.; He, G.; Chen, G. *Chem. Sci*. **2016**, *7*, 2679 ; d) Rabet, P.T.G.; Fumagalli, G.; Boyd, S.; Greaney, M.F. *Org. Lett.* **2016**, *18*, 1646.

[242] Lu, M.Z.; Wang, C.Q.; Loh, T.P. *Org. Lett*. **2015**, *17*, 6110.



Entry	[Cu] (x mol%)	solvent	**Yield[a] IV.1a**	**Yield[a] IV.M**	**Yield[a] IV.4a**
1	CuI (10 mol%)	1,4-dioxane/MeOH 9:1	38%	16%	20%
2	$Cu(OTf)_2$ (10 mol%)	1,4-dioxane/MeOH 9:1	33%	10%	38%
3	$Cu(OTf)_2$ (10 mol%)	MeCN	11%	18%	35%
4	$Cu(OTf)_2$ (10 mol%)	EtOAc	16%	11%	44%
5	$Cu(OTf)_2$ (10 mol%)	MeOH	34%	23%	39%
6	$Cu(OTf)_2$ (10 mol%)	1,2-DCE	12%	-	49%
7	$Cu(OAc)_2$ (10 mol%)	1,2-DCE	15%	4%	39%
8	$Cu(CF_3acac)_2$ (10 mol%)	1,2-DCE	8%	6%	34%
9	$Cu(MeCN)_4PF_6$ (10 mol%)	1,2-DCE	38%	11%	22%
10	$Cu(MeCN)_4BF_4$ (10 mol%)	1,2-DCE	29%	10%	25%
11	$Cu(MeCN)_4OTf$ (10 mol%)	1,2-DCE	19%	5%	30%
12	$CuBr_2$ (10 mol%)	1,2-DCE	-	8%	48%
13[b]	$CuBr_2$ (20 mol%)	1,2-DCE	-	13%	59%
14[b]	$CuBr_2$ (30 mol%)	1,2-DCE	-	5%	39%
15[b]	$CuBr_2$ / 1,10-phen (20 mol%)	1,2-DCE	-	3%	36%
16[b]	$CuBr_2$ / 2,2'-bpy (20 mol%)	1,2-DCE	-	-	27%

The reactions were performed on a 0.2 mmol scale at a 0.3 M concentration under N_2

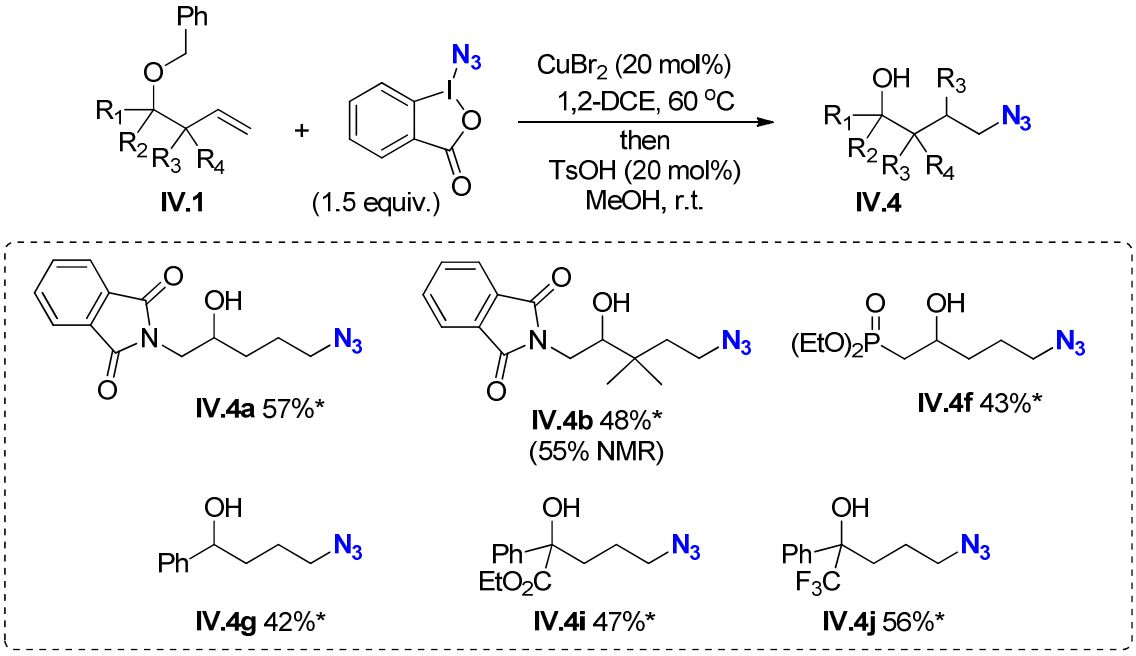
[a] NMR yield using 1,1,2,2-TCE.

[b] the reaction completed within 20 h

Table 4.5 – Optimization of the hydroazidation of unactivated alkenes*

4.3.3 Substrate scope of the reaction

With the optimized conditions in hand (treatment of the benzylic homoallylic ether with 20 mol% of copper(II) bromide and 1.5 equivalent of Zhdankin reagent in 1,2-dichloroethane at 60 °C) we tried to extend the scope of this hydroazidation reaction. We were glad to see that secondary and tertiary 1,4-azidoalcohols could be obtained in moderate to good yield. Among them, the 1,5-diamino-5-alcohol products **IV.4a** and **IV.4b** are of particular interest as they exhibit two amino moieties with orthogonal protected groups.



The reactions were performed on a 0.2 mmol scale at a 0.3 M concentration under N_2

Figure 4.45 – Substrate scope of the *anti*-Markovnikov hydroazidation of alkenes

We then performed the reaction on the 1,1-disubstituted alkene substrate **IV.1m** and were glad to see that the 1,4-azidoalcohol **IV.2m** was obtained with a good diastereoisomeric ratio (80:20). In the same way than for the trifluoromethylation, this ratio can be explained by the fact that the bromide is less sterically demanding than the azidomethyl moiety which is placed at the equatorial position in the transition state of the 1,5-hydrogen shift step.

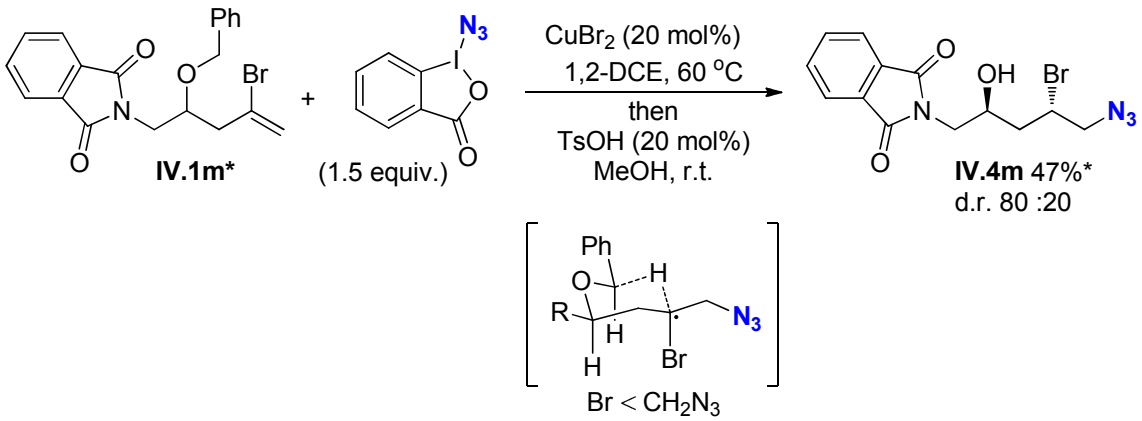


Figure 4.46 - *Anti*-Markovnikov hydroazidation of 1,1-disubstituted alkenes

In the same way than what was done for the trifluoromethyl product, we attempted to convert the azido-alcohol product **IV.4m** to the azido-pyrrolidine product **IV.5m**. Once again, to avoid any complication, we decided to protect the alcohol with a *tert*-butyldimethylsilyl group. Surprisingly, using *tert*-butyldimethylsilyl chloride and imidazole led to a resolution of the diastereoisomeric mixture and only the main product was converted. The silyl ether **TBS-IV.4m** was then converted to pyrrolidine using the same treatment than in the case of the trifluoromethylation (deprotection of the phthalimido moiety by hydrazine followed by spontaneous cyclization). The configuration of this single diastereoisomer was then confirmed by a NOESY experiment.

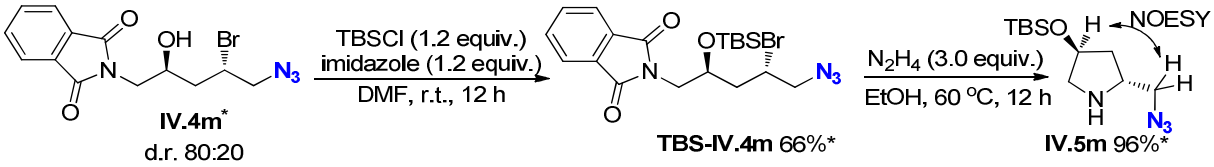


Figure 4.47 – Conversion of the protected amine IV.4p to the azido pyrrolidine IV.5m

In summary, this method constitute an unprecedentedly straightforward and easily set up protocol for the *anti*-Markovnikov hydroazidation of alkenes with a clear advantage brought by the 1,3-asymmetric induction operated on 1,1-disubstituted alkenes. Moreover, these results emphasize the diversity of the potential adaptations of this strategy toward other types of hydrofunctionalization reactions. After this work, we wondered if another type of hydrogen donor could be used and we turned our attention to the hydrotrifluoromethylation of 1-phenylhex-5-en-1-ol substrates.

4.4 Copper-catalyzed radical hydrotrifluoromethylation of 5-alkenols

This section is the continuation of the work which was previously presented but it will be only briefly discussed as most of the results were not provided by the author.

4.4.1 Origin of the project

The last two sections confirmed the strength of the benzyl ether moiety as a hydrogen donor. We then wondered if the same sequence of radical trifluoromethylation of the alkene followed by a 1,5-hydrogen abstraction could be realized using 1-phenylhex-5-en-1-ol type substrates, in which case the benzyl alcohol moiety would play the role of the hydrogen donor (Figure 4.48). In this scenario, a trifluoromethyl radical would add onto the alkene to generate a carbon centered radical intermediate. The occurrence of a 1,5-hydrogen abstraction would then deliver an α-hydroxy radical which can be oxidized to eventually lead to the formation of a ketone product.

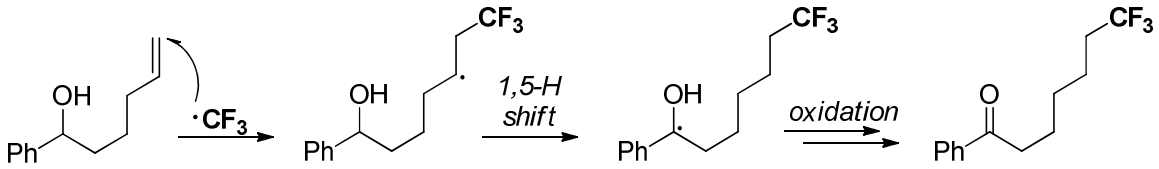
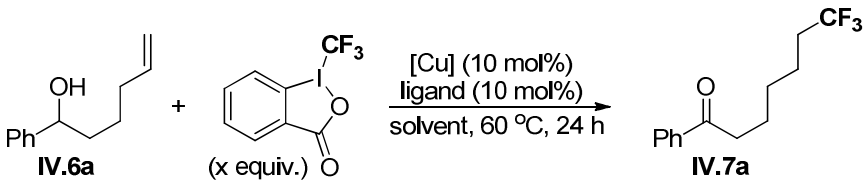


Figure 4.48 – Reaction design for the trifluoromethylation of 1-phenylhex-5-en-1-ol

4.4.2 Optimization of the reaction

The model substrate **IV.6a** was chosen for the optimization of the reaction. For the first attempt, we used the same reactions conditions which were used with the benzyl ether substrates (the substrate was treated with 10 mol% of copper(I) iodide and 1.2 equivalent of Togni reagent at 60 °C in a 9:1 mixture of 1,4-dioxane and methanol). Gratifyingly, the ketone product **IV.7a** was obtained in 71% yield after 24 h (Table 4.6, entry 1) The reaction was then performed using other solvents such as dichloromethane, ethyl acetate and 1,4-dioxane (entries 2-4). Although no completion was obtained after 24 hours with 1,4-dioxane, this result was the more promising. Other copper salts were tried and copper(II) acetate was found to give better results although the reaction still could not reach completion (entries 5,6). Eventually the optimized conditions were obtained by using 10 mol% of copper(II) acetate, 10 mol% of 2,2'-bipyridine as a ligand and 2.0 equivalent of Togni reagent in 1,4-dioxane at 60 °C.



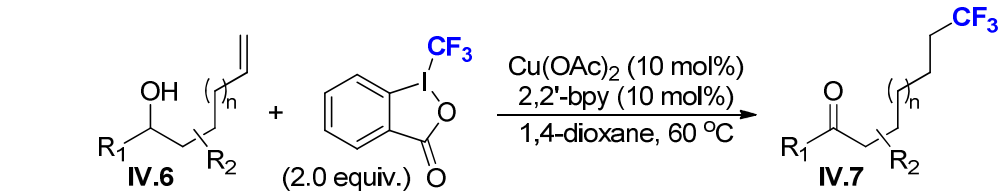
Entry	[Cu]	ligand	Togni reagent x equiv.	solvent	Yield[a] IV.7a	Recovery[a] of IV.6a
1	CuI	-	1.2 equiv.	1,4-dioxane / MeOH 9 :1	71%	0%
2	CuI	-	1.2 equiv.	EtOAc	73%	0%
3	CuI	-	1.2 equiv.	CH_2Cl_2	40%	2%
4	CuI	-	1.2 equiv.	1,4-dioxane	63%	23%
5	$Cu(OTf)_2$	-	1.2 equiv.	1,4-dioxane	57%	28%
6	$Cu(OAc)_2$	-	1.2 equiv.	1,4-dioxane	70%	20%
7	$Cu(OAc)_2$	2,2'-bpy	1.2 equiv.	1,4-dioxane	75%	21%
8	$Cu(OAc)_2$	2,2'-bpy	2.0 equiv.	1,4-dioxane	90%	0%

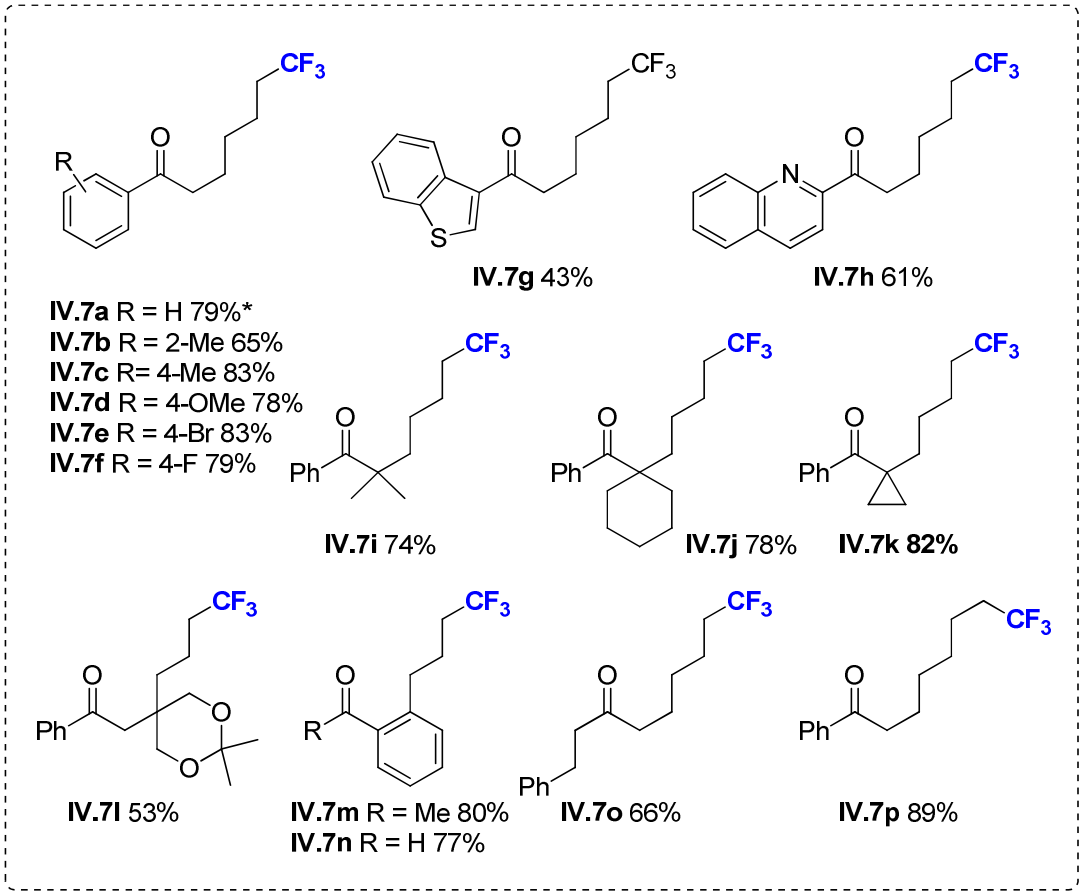
The reactions were performed on a 0.5 mmol scale at a 0.1 M concentration under N_2
[a] NMR yield using 1,1,2,2-TCE and α,α,α-trifluorotoluene as internal standards.

Table 4.6 –Optimization for the trifluoromethylation of 1-phenylhex-5-en-1-ol

4.4.3 Substrate scope of the reaction

With the optimized conditions in hand, the reaction was performed on a series on 5-alkenol type substrates. The reaction proceeded nicely with a variety of substrates possessing electron-rich aryl (**IV.7b-d**), electron-deficient aryl (**IV.7e**, **IV.7f**) or heteroaromatic (**IV.7g, IV.7h**) substituents on the carbon atom bearing the alcohol group. This reactions also tolerates a series of substituents on the aliphatic chain (**IV.7i-l**). Interestingly, the cyclopropyl moiety of the product **IV.7k** was kept intact, while a radical ring opening could have been expected, underlining the high speed of the oxidation step. The necessity of the presence of an aromatic substituent was then questioned and the reaction was performed on normal alkyl substituted alcohol substrates. We were then pleased to see that the reaction still proceeded smoothly and delivered the aldehyde product **IV.7m** and the ketone products **IV.7n** and **IV.7o** in good yields. Lastly, an attempt was made on a homologous substrate and we were delighted to see that our strategy could also be applied for 1,6-hydrogen shift.





The reactions were performed on a 0.5 mmol scale at a 0.1 M concentration under N_2

Figure 4.49 – Substrate scope for the trifluoromethylation of 5-alkenol substrates

4.5 Conclusion

In summary, we developed a novel copper-catalyzed method for the hydrofunctionalization of homoallylic alcohol, which relies on a novel 1,5-hydrogen abstraction. In this strategy, a benzyl group is used as a traceless hydrogen donor which also plays a role in the redox catalytic mechanism of the reaction. This general method can be applied to the hydrotrifluoromethylation of alkenes, using the Togni reagent, or to the hydroazidation of alkenes, using the Zhdankin reagent. Moreover, in the case of 1,1-disubstituted alkenes, a 1,3-asymmetric induction is observed. This diastereoselectivity is controlled by a well-defined transition state of the 1,5-hydrogen shift step.

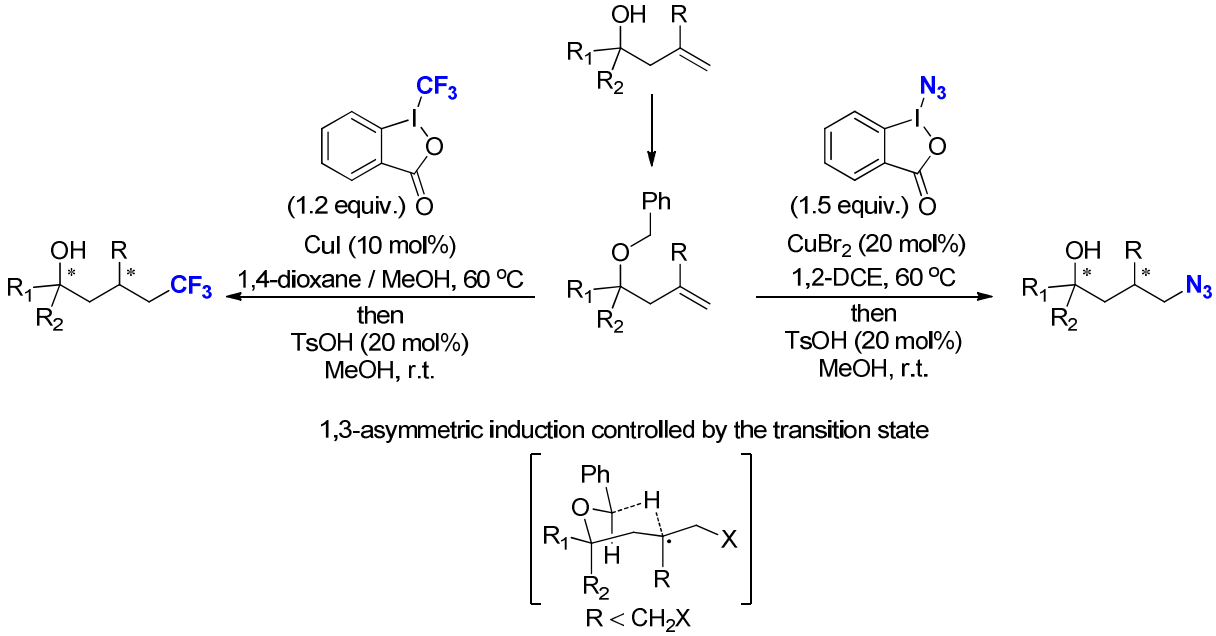


Figure 4.50 – Recapitulative scheme for the hydrotrifluoromethylation and hydroazidation of homoallylic alcohols

This strategy could also be adapted to the hydrotrifluoromethylation of 5-alkenols, which leads to the formation of trifluoromethyl ketones (Figure 4.51).

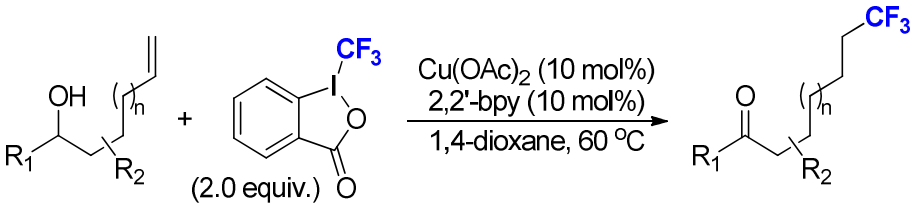


Figure 4.51 – Recapitulative scheme for the hydrotrifluoromethylation of alkenol substrates

In future, an interesting extension would be to convert the diastereoisomerically enriched 1,3-bromoalcohol products into diastereoisomerically enriched heterocycles. For example, the reaction between these compounds and isocyanates could potentially lead to cyclic carbamate products (Figure 4.52).

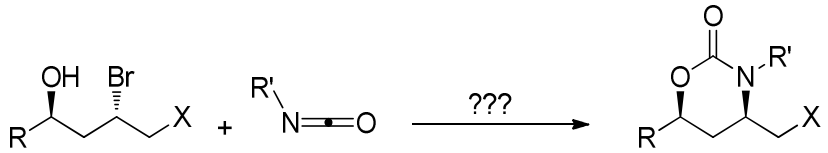


Figure 4.52 – Potential conversion of 1,3-bromoalcohols to cyclic carbamates

It would also be interesting to see if our strategy can be applied to other hydrofunctionalization reaction. For example, the generation of cyanide radicals could be tried starting from the cyano benziodoxole reagent or a combination of trimethylsilylcyanide and diacetoxyiodobenzene. In this case, the reaction would lead to the formation of 1,5-nitrile alcohol products. In the same way, aryl radical could be generated from aryldiazonium salts or diaryliodonium salts to perform a hydroarylation of alkene.

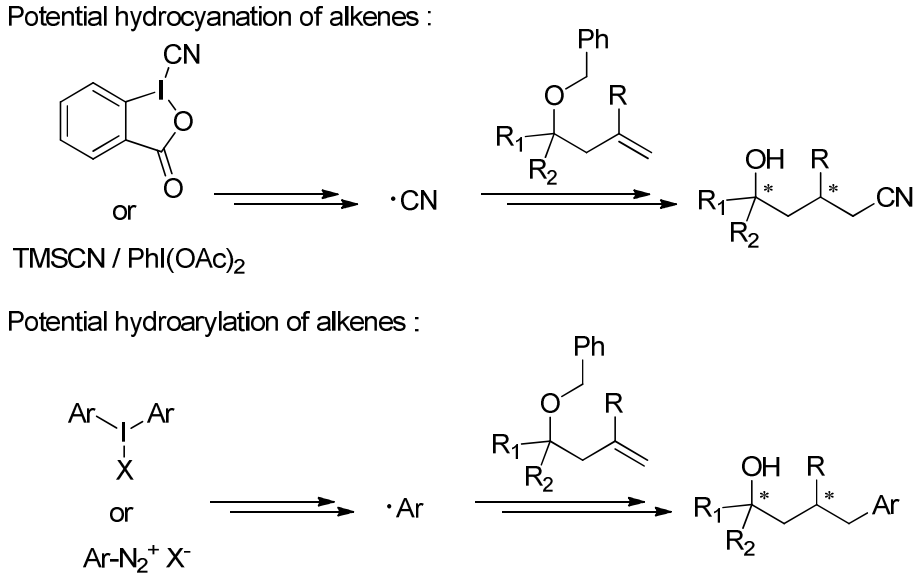
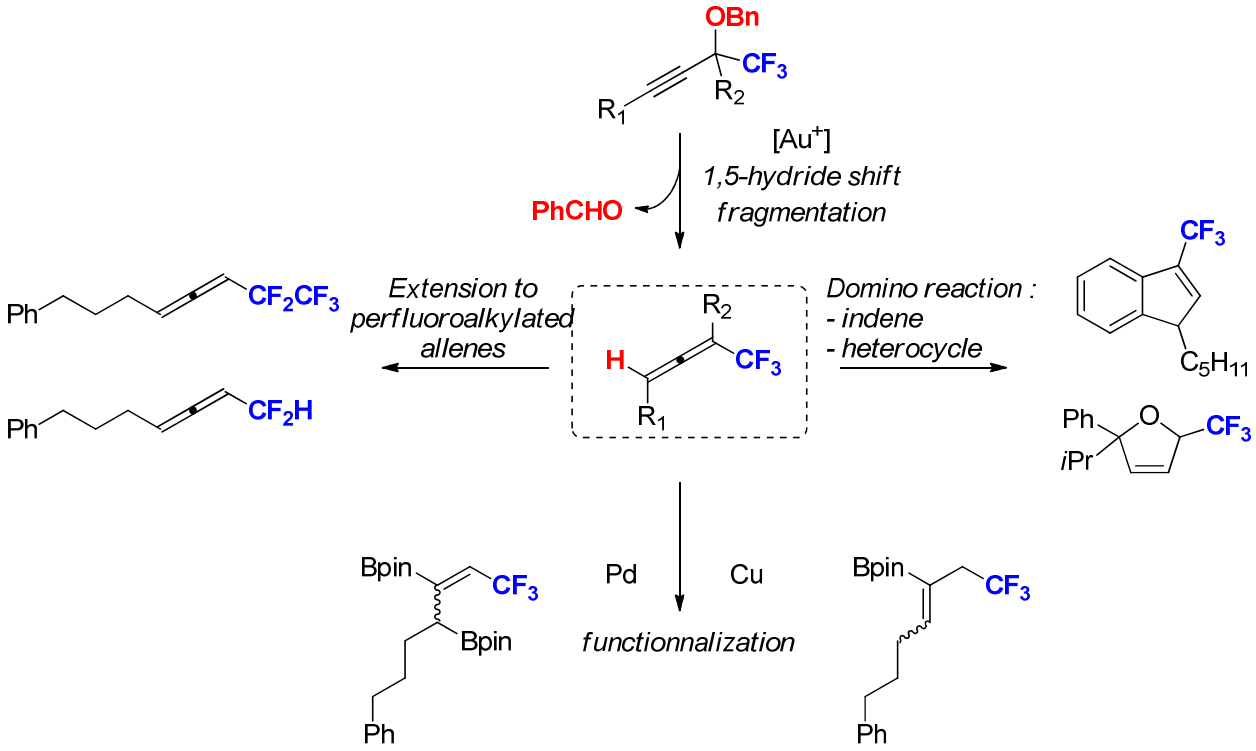


Figure 4.53 – Extension to the hydrocyanation and hydroarylation of alkenes

General conclusion

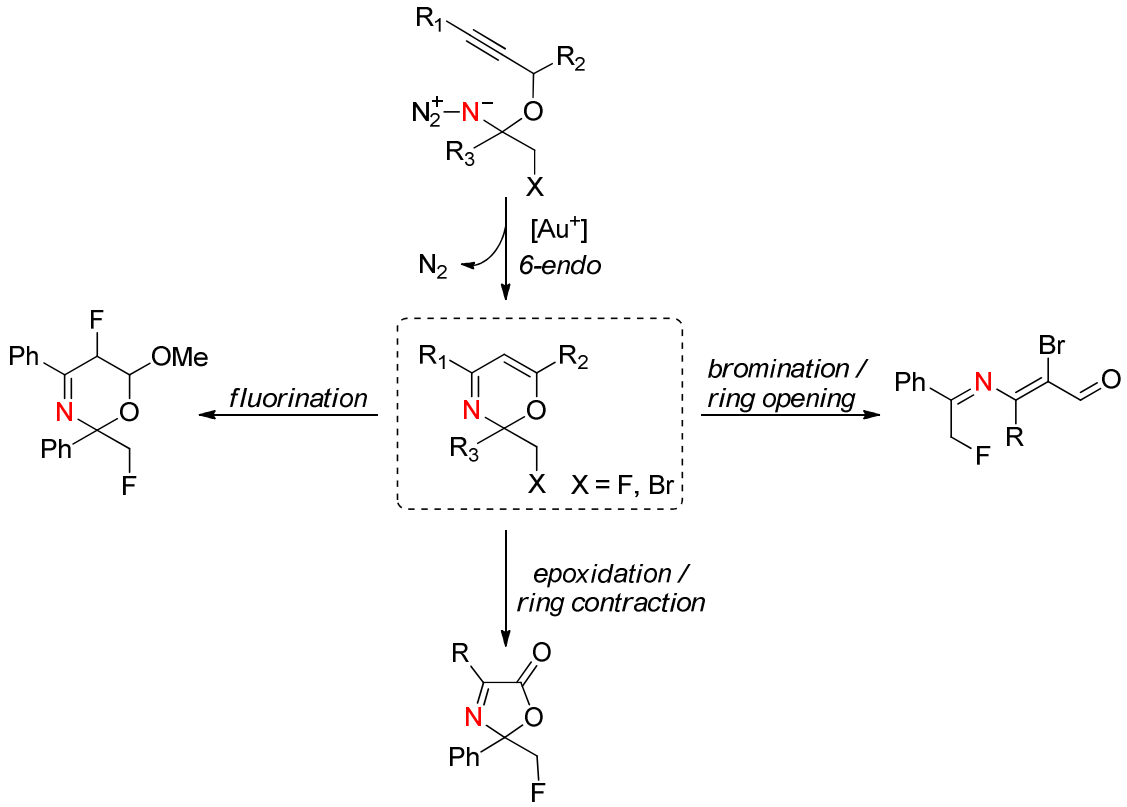
This manuscript has described the results obtained during my PhD work on the development of new gold and copper-catalyzed transformations for organic synthesis. A large part of this work deals with the incorporation of a trifluoromethyl group or with the preparation of trifluoromethyl containing compounds. For this purpose, the Lewis-acidity of gold and the redox potential of copper were exploited.

It was demonstrated that trifluoromethyl allenes can be efficiently prepared from trifluoromethyl propargyl benzyl ethers. This process involves a sequence of gold activation of the alkyne, 1,5-hydride shift from the benzyl ether moiety to the alkyne and fragmentation. This methodology allows the formation of mono-, di- and tri-substituted trifluoromethyl allenes but also perfluoroalkyl allenes in a very selective way as compared to the methods previously reported in the literature. These allenes could also be further functionalized in cascade reactions to provide a series of trifluoromethyl cyclic compounds.



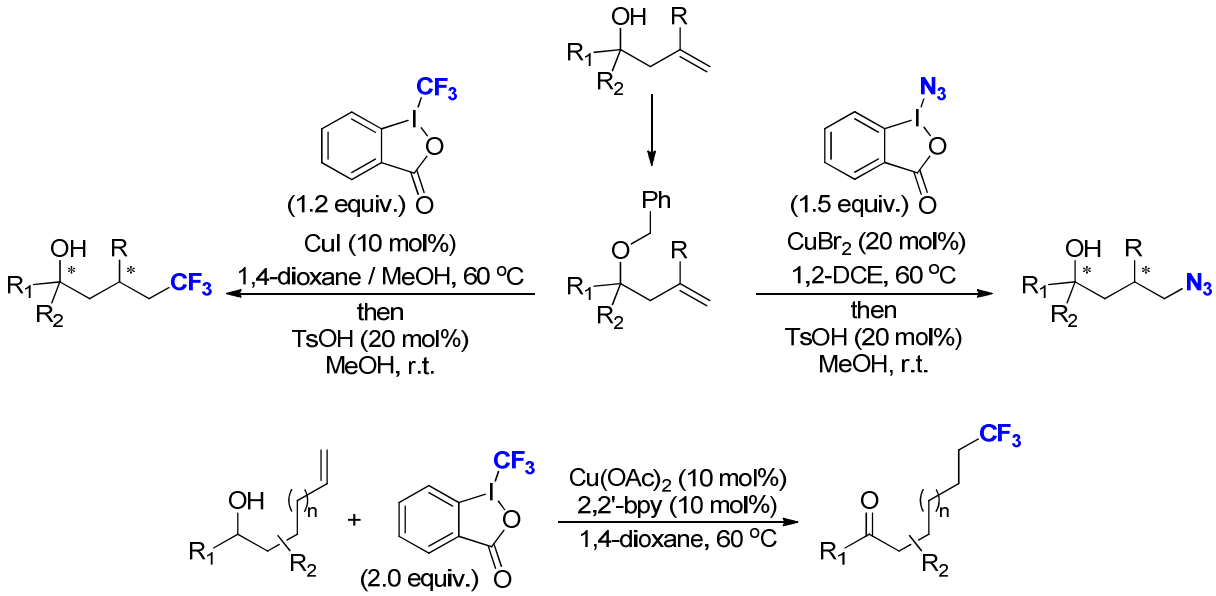
Gold-catalyzed synthesis and derivatization of trifluoromethylated allenes

The ability of gold to promote heterocyclization reactions was then exploited for the synthesis of *2H*-1,3-oxazines from azido alkyne substrates. In this methodology, a gold-catalyzed 6-*endo* azide-yne cyclization is at stake and allows to obtain a large range of polysubstituted *2H*-1,3-oxazines in a very efficient manner. The heterocycles thus obtained could then be derivatized *via* unprecedented brominative ring opening reactions or oxidative ring contractions.



Gold-catalyzed synthesis and derivatization of *2H*-1,3-oxazines

An efficient copper-catalyzed radical hydrofunctionalization of alkenol type substrates was then developed. This process relies on a 1,5-hydrogen shift, using a benzyloxy moiety as a hydrogen donor. The radical hydrotrifluoromethylation and hydroazidation of homoallylic alcohols could thus be efficiently performed using a benzyl moiety as a traceless hydrogen donor group. Moreover, an interesting diastereoselectivity could be obtained when 1,1-disubstituted alkenes were used. The adaptation of this strategy to the hydrotrifluoromethylation of 1,5-alkenol substrates led to the formation of trifluoromethyl ketone products.



Copper-catalyzed hydrofunctionalization of alkenols

Experimental section

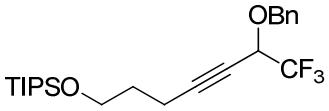
This work was realized in collaboration with Arnaud Boreux (PhD student in Ecole Polytechnique), Dr. Ciputra Tejo (Nanyang Technological University, Singapore) and Derek Yiren Ong (PhD student at Nanyang Technological University, Singapore). Although the overall result was presented in the theoretical part for a better understanding, this part will only describe the experimental data and characterization of the compounds prepared and isolated by the author.

Index of characterized compounds

General informations

Chapter 2 : Gold-catalyzed synthesis of trifluoromethyl allenes

Starting materials



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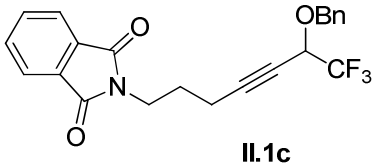

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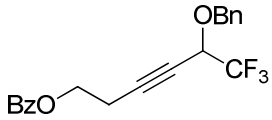

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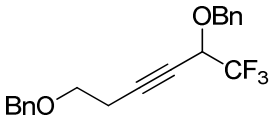

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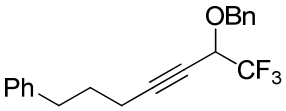

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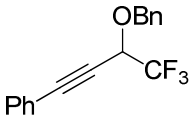

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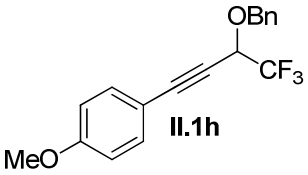

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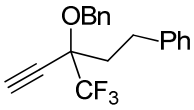

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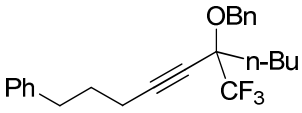
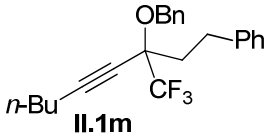
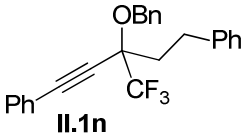


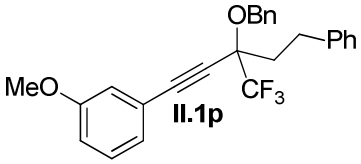
II.1l



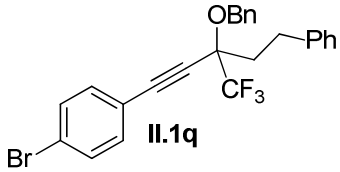
II.1m



II.1n



II.1p



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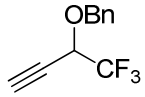

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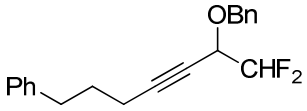

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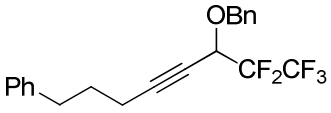
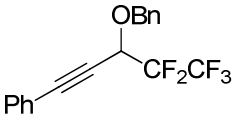
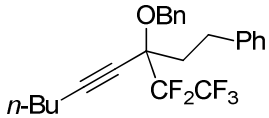


II.1u

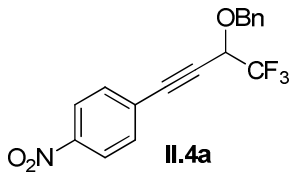


II.1v

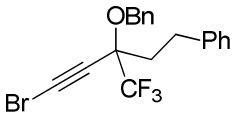


II.1w

Unreactive substrates



II.4a



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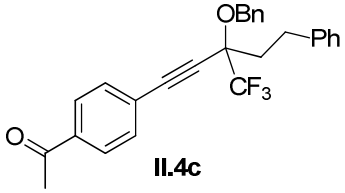
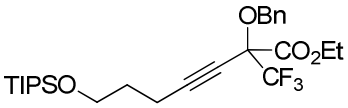


II.4c



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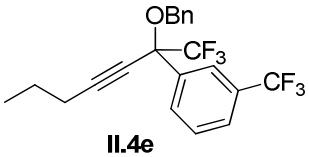

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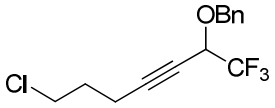

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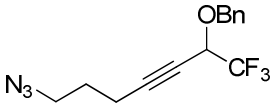
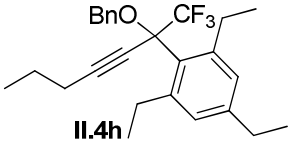


II.4g



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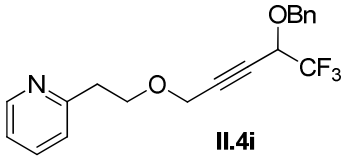

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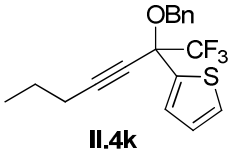

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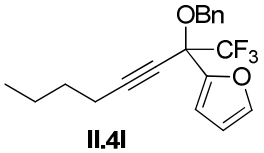
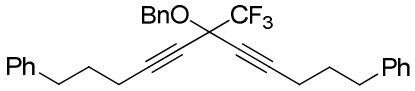


II.4l



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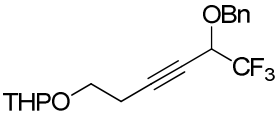
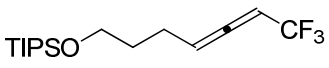
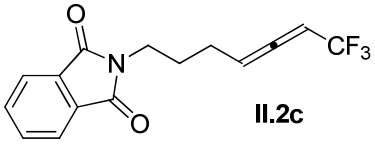


II.4l

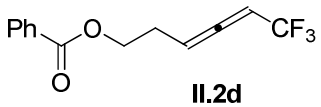
Trifluoromethyl allenes products



II.2b



II.2c



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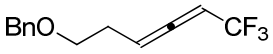

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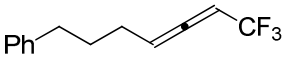
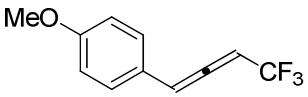


II.2f

II.2g



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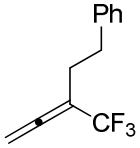

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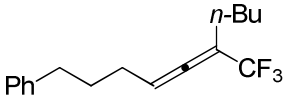

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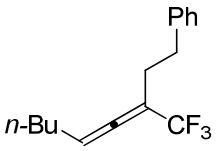

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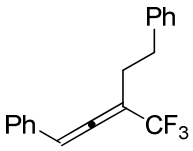

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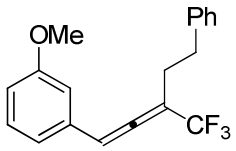
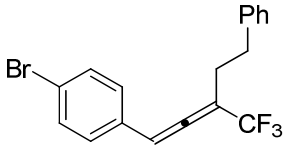


II.2p



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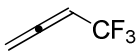
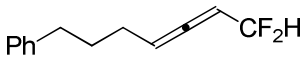


II.2s



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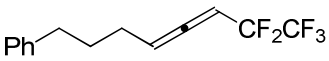

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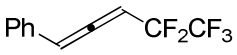

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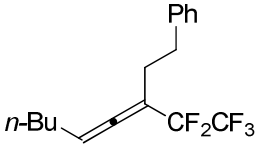
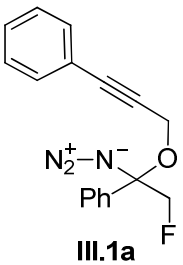
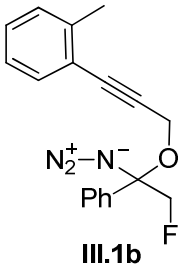


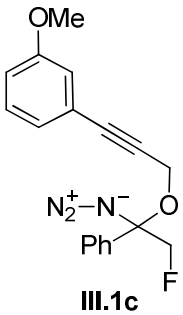
II.2w

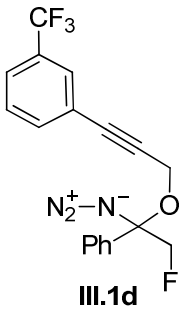
Chapter 3 : Gold-catayzed synthesis of *2H*-1,3-oxazines

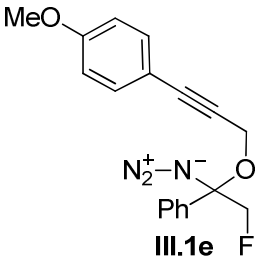
Starting materials

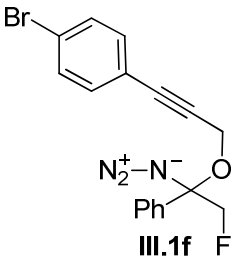

III.1a

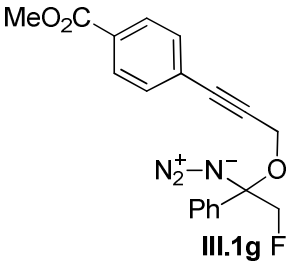

III.1b


III.1c


III.1d


III.1e


III.1f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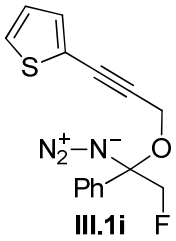
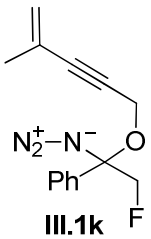
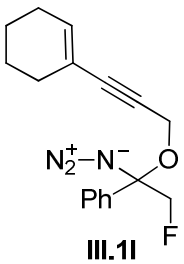
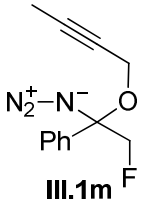

III.1i


III.1k


III.1l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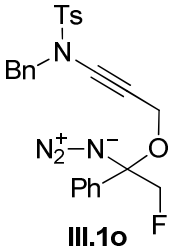
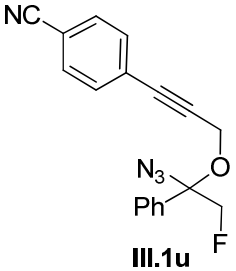
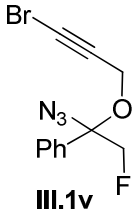

III.1o

Unreactive substrates


III.1u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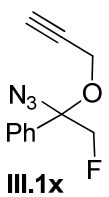
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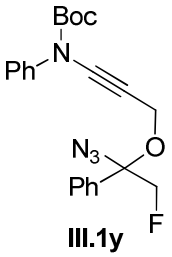
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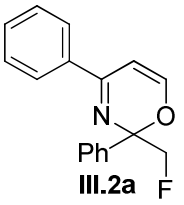
2H-1,3-oxazine products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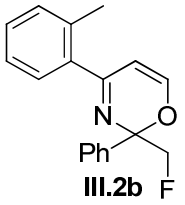
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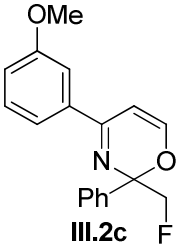
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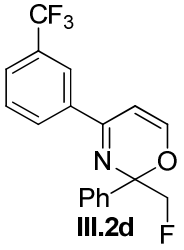
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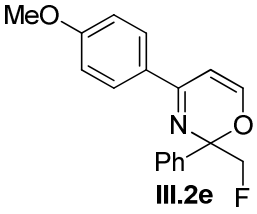
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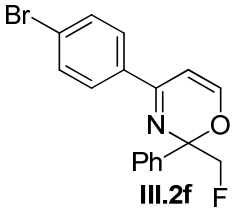
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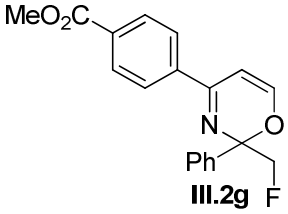
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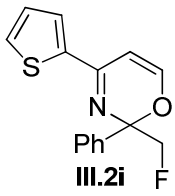
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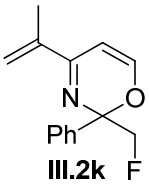
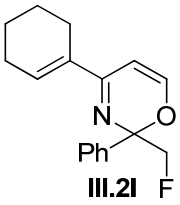

III.2k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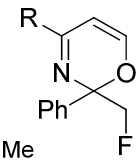
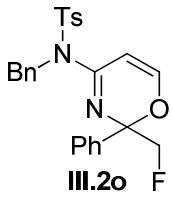
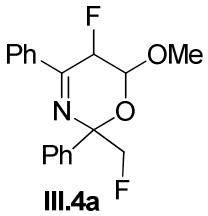
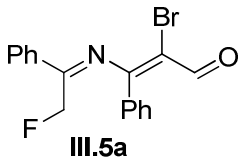

III.2m R = Me
III.2n R = CH_2CH_2iPr


III.2o

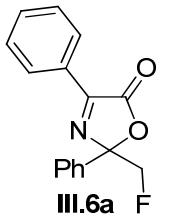
Fluorination of *2H*-1,3-oxazines

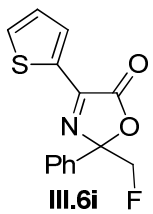

III.4a

Brominative ring opening of *2H*-1,3-oxazines


III.5a

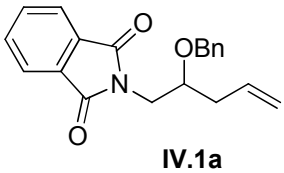
Oxidative ring contraction of *2H*-1,3-oxazines


III.6a


III.6i

Chapter 4 : Copper-catalyzed radical hydrofunctionalization of unactivated alkenes using benzyl oxy moiety as a redox active hydrogen atom donor

Starting materials :



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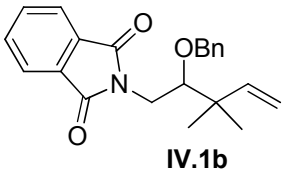

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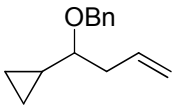

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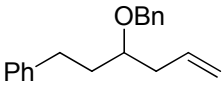

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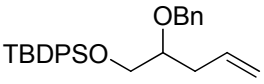

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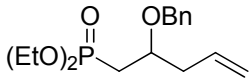

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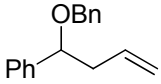

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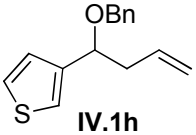

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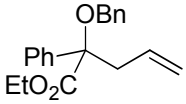

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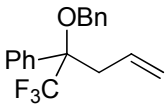

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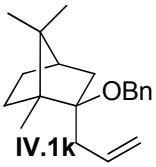

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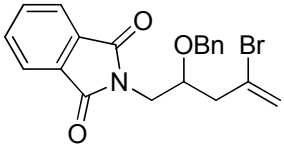

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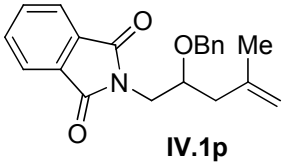

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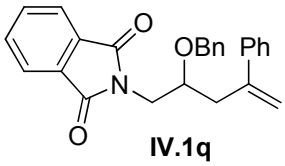
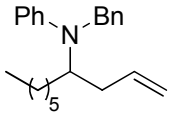


IV.1q



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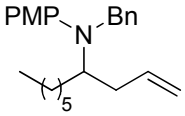

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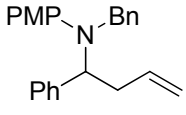

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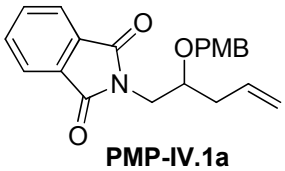
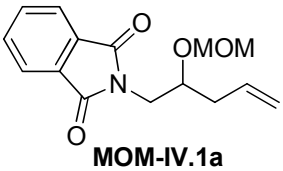
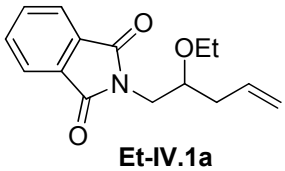


PMP-IV.1a

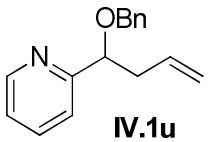


MOM-IV.1a



Et-IV.1a

Substrates for which the reaction failed



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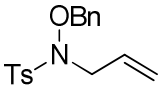
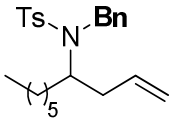
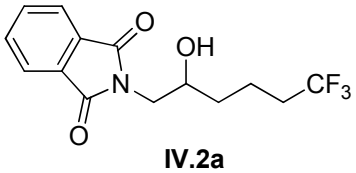


IV.1v



IV.1w

Products of hydrotrifluoromethylation :



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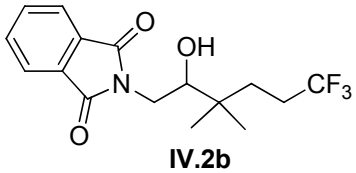
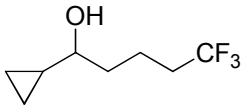
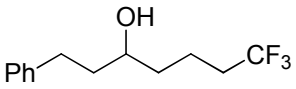


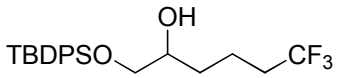
IV.2b



IV.2c



IV.2d



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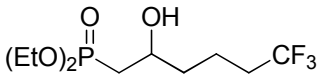
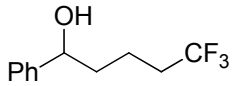


IV.2f



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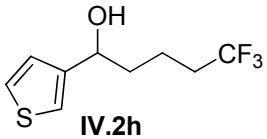

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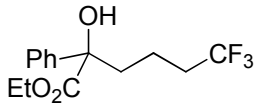
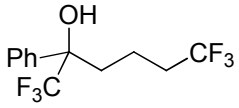
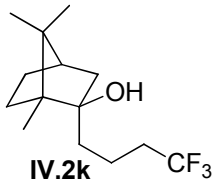


IV.2i



IV.2j



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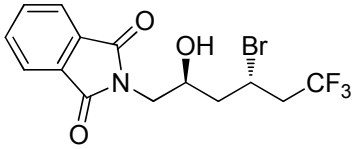
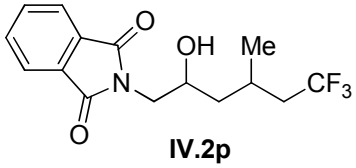
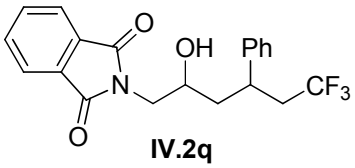


IV.2m
d.r. 85:15



IV.2p
d.r. 60:40



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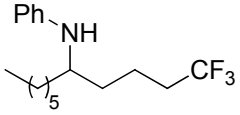
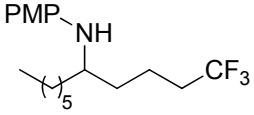
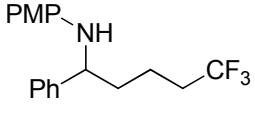


IV.2r

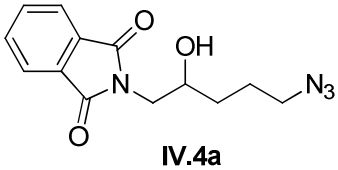


IV.2s

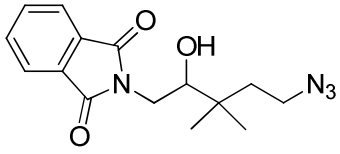


IV.2t

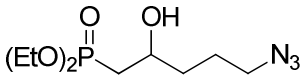
Products of hydroazidation



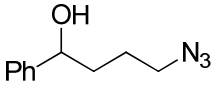
IV.4a



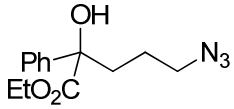
IV.4b



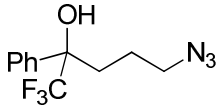
IV.4f



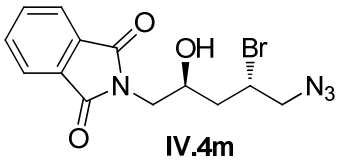
IV.4g



IV.4i

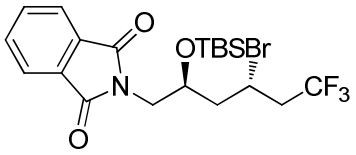


IV.4j

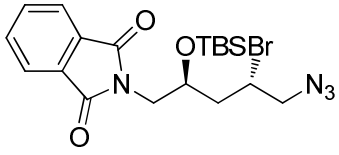


IV.4m
d.r. 80:20

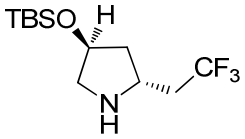
Preparation of the pyrrolidine derivatives



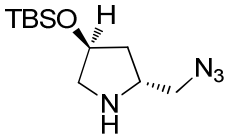
TBS-IV.2m



TBS-IV.4m



IV.3m
d.r. 85:15



IV.5m

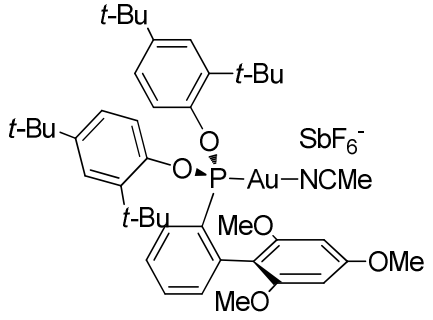
General information

Commercially available reagents were purchased from Sigma-Aldrich, Alfa-Aesar, TCI or Fluorochem. They were used without further purification unless otherwise noted. Dried solvents were obtained from the solvent purification system PS-MD-5. Unless otherwise stated, the reactions were performed under an N_2 atmosphere. The reaction vessels were vacuumed and backfilled with N_2 three times before reagents were added. Thin layer chromatography was performed on TLC Silica Gel 60 F_{254} (from Merck KGaA). Visualization was performed using UV-light (254 nm) and with aqueous $KMnO_4$ solution stain (1.5 g of $KMnO_4$, 10 g of K_2CO_3, 1.25 mL of 10% NaOH, 200 mL of H_2O) or *p*-anisaldehyde stain (3.5 mL of *p*-anisaldehyde, 15 mL of AcOH, 50 mL of conc. H_2SO_4, 350 mL of EtOH). Flash column chromatography was carried out on Merck silica gel 60 with a forced flow of eluent at 1-4 bar pressure and distilled solvents. GPC (gel permeation chloromatography) was performed using LaboACE LC-5060 recycling preparative HPLC.

^1H and ^{13}C NMR spectra were recorded on Bruker Avance AV300, AV400 or BBFO400 spectrometers in $CDCl_3$ using TMS (δ = 0.00) for ^1H and $CDCl_3$ (δ = 77.16) for ^{13}C as internal standard. The following abbreviations were used to explain the multiplicities: s = singlet, brs = broad singlet, d = doublet, dd = doublet of doublet, ddd = doublet of doublet of doublet, t = triplet, q = quartet, sept = septet, m = multiplet. ESI-HRMS spectra were obtained with Q-Tof Premier LC HR mass spectrometer. IR spectra were recorded on a Shimazu IR Prestige-21 FT-IR Spectrometer.

Chapter 2 : Gold-catalyzed synthesis of trifluoromethyl allenes

2.1 Preparation of the catalyst



***t*-BuGPhos(NCMe)Au.SbF$_6$**

Procedure :

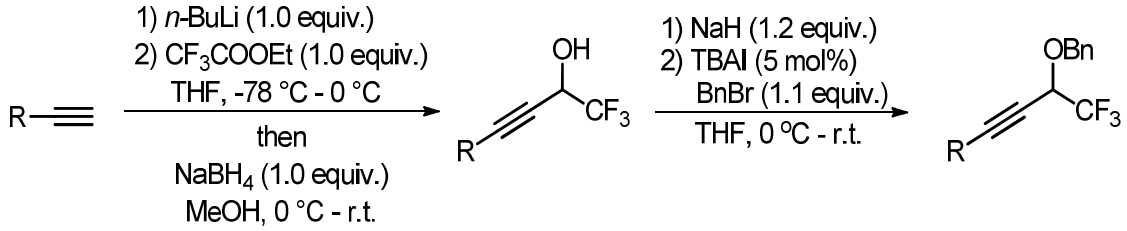
To a solution of $AgSbF_6$ (1 equiv.) dissolved in a mixture of dry DCM and acetonitrile (DCM/MeCN 3:1, 0.1 mol.L^{-1}) was added a solution of [(Phosphonite)AuCl][243] (1 equiv.) in dry DCM (0.1 mol.L^{-1}) under nitrogen. The mixture was stirred 15 minutes at room temperature in the dark, then filtered on a pad of Celite®. The solvents were evaporated and the gold complex was then washed with pentane to be obtained as a white solid.

Overall yield :	53% (1.53 g) of a colorless oil.
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	8.19 – 8.14 (m, 1H, Ar), 7.71 (t, *J* = 7.5 Hz, 1H, Ar), 7.60 (t, *J* = 7.5 Hz, 1H, Ar), 7.38 (s, 2H, Ar), 7.30 (t, *J* = 7.8 Hz, 1H, Ar), 7.20 – 7.18 (m, 4H, Ar), 6.35 (s, 2H, Ar), 3.95 (s, 3H, OMe), 3.63 (s, 6H, OMe), 2.41 (s, 3H, Me of MeCN), 1.30 (s, 2x18H, C($\underline{CH_3}$)$_3$ of *t*-Bu)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	163.4 (C_{Ar}), 159.6 (Ar), 149.5 (d, *J* = 6.2 Hz, Ar), 146.6 (Ar), 139.7 (d, *J* = 6.2 Hz, Ar), 139.4 (d, *J* = 27.3 Hz, Ar), 134.4 (Ar), 134.3 (d, *J* = 11.7 Hz, Ar), 131.1 (d, *J* = 3.7 Hz, Ar), 128.6 (d, *J* = 9.1 Hz, Ar), 125.9 (Ar), 124.7 (Ar), 121.1 (Ar), 118.9 (d, *J* = 12.2 Hz, Ar), 109.1 (d, *J* = 10.7 Hz, Ar), 91.4 (Ar), 56.3 (OMe), 56.2 (OMe), 35.4 ($\underline{C}(CH_3)_3$ of *t*-Bu), 35.1 ($\underline{C}(CH_3)_3$ of *t*-Bu), 31.6 (C($\underline{CH_3}$)$_3$ of *t*-Bu), 30.5 (C($\underline{CH_3}$)$_3$ of *t*-Bu), 2.8 (Me of MeCN)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-79.6
^{31}P NMR (δ, ppm) (121 MHz, $CDCl_3$)	115.8
IR (cm^{-1}, CCl_4)	2966, 2908, 2871, 2333, 2305, 2258, 1606, 1584, 1490, 1463, 1430, 1415, 1398, 1365, 1338, 1274, 1227, 1206, 1183, 1158, 1128, 1079, 1034.

[243] The pre-catalyst was prepared following a protocol described in the literature : G. Henrion, T. E. J. Chavas, X. Le Goff, F. Gagosz, *Angew. Chem. Int. Ed.* **2013**, *52*, 6277.

2.2 Preparation of the **trifluoromethyl propargyl benzyl ether substrates**

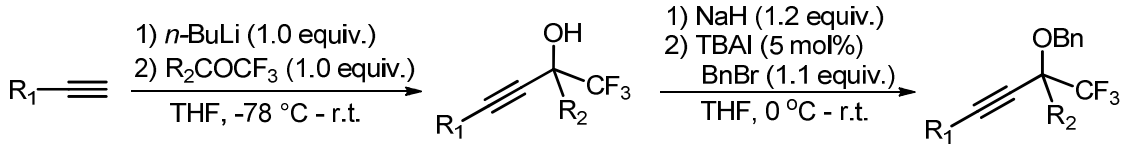
Procedure A :



To a solution of alkyne (1.0 equiv.) in THF (0.5 M) was added dropwise *n*-BuLi (1.1 equiv.) at -78 °C. The mixture was stirred for 1 h at -78 °C and ethyl trifluoroacetate (1.5 equiv.) was added. After the complete consumption of the alkyne (TLC), the mixture was diluted with MeOH (same volume than THF). The mixture was allowed to warm up to 0 °C and $NaBH_4$ (1.0 equiv.) was added. The mixture was stirred overnight while warming up to room temperature. The reaction was then quenched with a saturated solution of NH_4Cl, extracted with Et_2O (x3), washed with water (x3) and brine, dried over $MgSO_4$ and concentrated under reduced pressure to give the α-trifluoromethyl secondary propargylic alcohol. If necessary, the crude alcohol was purified by flash column chromatography.

To a solution of the alcohol dissolved in THF (0.5 M) was added NaH (1.1 equiv.) at 0 °C. Upon the end of the H_2 formation, benzyl bromide (1.2 equiv.) and TBAI (0.05 equiv.) were added. The mixture was stirred overnight while warming up to room temperature. The reaction was quenched with a saturated solution of NH_4Cl, extracted with Et_2O (x3), washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel gave the pure α-trifluoromethyl secondary propargylic benzyl ether.

Procedure B :

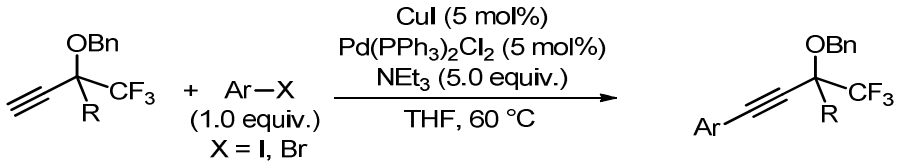


To a solution of alkyne (1.0 equiv.) in THF (0.5 M) was added dropwise *n*-BuLi (1.1 equiv.) at -78 °C. The mixture was stirred for 1 h at -78 °C and the trifluoromethyl ketone (1.0 equiv.) was added. After the complete consumption of the alkyne (TLC), the mixture was quenched with a saturated solution of NH_4Cl, extracted with Et_2O (x3), washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography gave the pure α-trifluoromethyl tertiary propargylic alcohol.

To a solution of the resulting alcohol (1.0 equiv.) in THF (0.5 M) was added NaH (1.1 equiv.) at 0 °C. Upon the end of the H_2 formation, benzyl bromide (1.2 equiv.) and TBAI (0.05 equiv.) were added. The mixture was stirred overnight while warming up to room temperature. The reaction was then quenched with a saturated solution of NH_4Cl, extracted with Et_2O (x3), washed

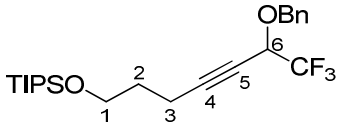
with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography on silica gel gave the pure α-trifluoromethyl tertiary propargylic benzyl ethers.

Procedure C :



To a solution of the aromatic halide (1.0 equiv.) and of the terminal alkyne (1.0 equiv.) in THF (0.5 M) were added copper(I) iodide (0.05 equiv.) and bis(triphenylphosphine)palladium(II) chloride (0.05 equiv.). Then triethylamine (5.0 equiv.) was added and the mixture was heated to 60 °C. Upon reaction completion (TLC), the mixture was quenched with a saturated solution of NH_4Cl, extracted with Et_2O (x3), washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography on silica gel gave the pure product.

(6-(benzyloxy)-7,7,7-trifluorohept-4-ynyloxy)triisopropylsilane (*II.1b*)

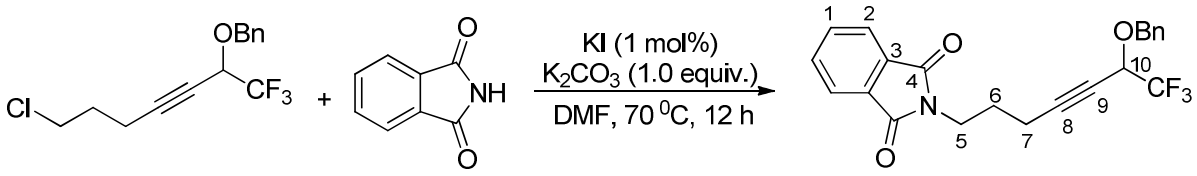


$C_{23}H_{35}F_3O_2Si$
MW = 428.6 g.mol^{-1}

Procedure :	Following procedure A starting with triisopropyl(pent-4-ynyloxy)silane (5.43 mmol).
Purification :	Flash chromatography : PE / Et_2O 50:1
Overall yield :	65% (1.52 g) of a yellow oil.
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.78 – 7.09 (m, 5H, Ar), 4.84 (d, *J* = 11.9 Hz, 1H, H_6), 4.67 (d, *J* = 11.9 Hz, 1H, CH_2 of Bn), 4.48 – 4.44 (qt, *J* = 5.9, 2.1 Hz, 1H, CH_2 of Bn), 3.78 (t, *J* = 6.0 Hz, 2H, H_1), 2.42 (td, *J* = 7.1, 2.0 Hz, 2H, H_3), 1.78 (tt, *J* = 7.1, 6.0 Hz, 2H, H_2), 1.19 – 0.84 (m, 21H, TIPS).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	136.4 (Ar), 128.7 (Ar), 128.4 (Ar), 128.3 (Ar), 122.8 (q, *J* = 280.0 Hz, CF_3), 90.3 (C_4), 71.0 (CH_2 of Bn), 70.5 (q, *J* = 2.4 Hz, C_5), 67.7 (q, *J* = 35.0 Hz, C_6), 61.7 (C_1), 31.6 (C_2), 18.1 (CH_3 of TIPS), 15.3 (C_3), 12.1 (CH of TIPS).
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-78.0
IR (cm^{-1}, CCl_4)	2945, 2893, 2867, 1463, 1245, 1185, 1158, 1140, 1109, 883

MS (HRMS EI) Calcd for $[M–C_3H_7]^+$: $C_{20}H_{28}F_3O_2Si$ 385.1811 Found : 385.1802

2-(6-(benzyloxy)-7,7,7-trifluorohept-4-ynyl)isoindoline-1,3-dione (2e)



$C_{22}H_{18}F_3NO_3$
MW = 401.4 g.mol^{-1}

Procedure : To a solution of ((7-chloro-1,1,1-trifluorohept-3-yn-2-yloxy)methyl)benzene (1.00 mmol) in DMF (1 M) were added phtalimide (1.2 equiv.), potassium carbonate (1.0 equiv.) and potassium iodide (0.01 equiv.). The mixture was heated up to 70 °C and stirred overnight. The reaction was then quenched with a saturated solution of NH_4Cl, extracted with Et_2O (x3), washed water (x3) and brine, dried over $MgSO_4$ and concentrated under reduced pressure.

Purification : Flash chromatography : PE / Et_2O 2:1

Yield : 80% (320 mg) of a white solid.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.83 (dd, *J* = 5.4, 3.1 Hz, 2H, H_1), 7.70 (dd, *J* = 5.4, 3.1 Hz, 2H, H_2), 7.44 – 7.29 (m, 5H, Ar), 4.84 (d, *J* = 11.9 Hz, 1H, CH_2 of Bn), 4.67 (d, *J* = 11.9 Hz, 1H, CH_2 of Bn), 4.40 – 4.37 (m, 1H, H_{10}), 3.80 (t, *J* = 7.0 Hz, 2H, H_5), 2.37 (td, *J* = 7.1, 2.1 Hz, 2H, H_7), 1.97 (p, *J* = 7.1, 7.0 Hz, 2H, H_6).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 168.4 (C_4), 136.3 (Ar), 134.1 (C_1), 132.1 (C_3), 128.7 (Ar), 128.3 (Ar), 128.3 (Ar), 123.4 (C_2), 122.6 (q, *J* = 281.3 Hz, CF_3), 88.8 (C_8), 71.3 (q, *J* = 2.3 Hz, C_9), 71.0 (CH_2 of Bn), 67.5 (q, *J* = 35.1 Hz, C_{10}), 37.1 (C_5), 27.2 (C_6), 16.6 (C_7).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) -77.9

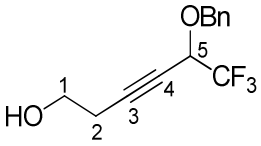
IR (cm^{-1}, CCl_4) 3476, 3067, 3034, 2940, 2875, 1776, 1720, 1395, 1375, 1357, 1275, 1185, 1158, 1141, 1118, 1089, 1028

MS (HRMS EI) Calcd for $C_{22}H_{18}F_3NO_3$: 401.1239 Found : 401.1213

MP 37.2 °C – 38.0 °C

.

5-(benzyloxy)-6,6,6-trifluorohex-3-yn-1-ol (II.4o)



$C_{13}H_{13}F_3O_2$
MW = 258.2 g.mol^{-1}

Procedure : To a solution of 2-(5-(benzyloxy)-6,6,6-trifluorohex-3-ynyloxy)tetrahydro-2H-pyran (3.50 mmol) in methanol (0.3 M) was added TsOH (0.1 equiv.). The reaction was stirred overnight at room temperature and then quenched with water, extracted with Et_2O (x3), washed water (x3) and brine, dried over $MgSO_4$ and concentrated under reduced pressure.

Purification : Flash chromatography PE / Et_2O 5:1

Yield : 85% (770 mg) of a yellow oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.38 – 7.30 (m, 5H, Ar), 4.84 (d, *J* = 11.9 Hz, 1H, CH_2 of Bn), 4.69 (d, *J* = 11.9 Hz, 1H, CH_2 of Bn), 4.52 – 4.44 (m, 1H,H_5), 3.77 (t, *J* = 6.4 Hz, 2H, H_1), 2.81 (br s, 1H, OH), 2.56 (td, *J* = 6.4, 2.0 Hz, 2H, H_2).

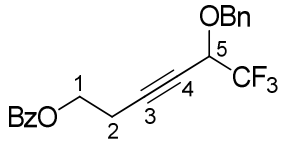
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 136.1 (Ar), 128.6 (Ar), 128.4 (Ar), 128.2 (Ar), 122.6 (q, *J* = 281.3 Hz, CF_3), 87.1 (C_3), 72.1 (q, *J* = 2.4 Hz, C_4), 71.3 (CH_2 of Bn), 67.7 (q, *J* = 35.0 Hz, C_5), 60.5 (C_1), 22.9 (C_2).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) : -77.8

IR (cm^{-1}, CCl_4) : 3620, 3091, 3068, 3034, 2950, 2890, 1732, 1605, 1497, 1456, 1375, 1273, 1167, 1157, 1138, 1077, 1049

MS (HRMS EI) : Calcd for $C_{13}H_{13}F_3O_2$: 258.0868 Found : 258.0871

5-(benzyloxy)-6,6,6-trifluorohex-3-ynyl benzoate (II.1d)



$C_{20}H_{17}F_3O_3$
MW = 362.3 g.mol^{-1}

Procedure : To a solution of 5-(benzyloxy)-6,6,6-trifluorohex-3-yn-1-ol (1.00 mmol) in DCM (1 M) were added DMAP (0.02 equiv.), triethylamine (1.2 equiv.)

and benzoyl chloride (1.1 equiv.). The reaction was stirred for 1 h at room temperature and then quenched with a saturated solution of NH_4Cl, extracted with Et_2O (x3), washed brine, dried over $MgSO_4$ and concentrated under reduced pressure.

Purification : Flash chromatography PE / Et_2O 20:1

Yield : 95% (348 mg) of a colorless oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 8.08 (dd, *J* = 8.3, 1.4 Hz, 2H, Ar), 7.61 – 7.55 (m, 1H, Ar), 7.44 (t, *J* = 7.8 Hz, 2H, Ar), 7.37 – 7.31 (m, 5H, Ar), 4.84 (d, *J* = 11.9 Hz, 1H, CH_2 of Bn), 4.66 (d, *J* = 11.9 Hz, 1H, CH_2 of Bn), 4.52 – 4.46 (m, 1H, H_5), 4.48 (t, *J* = 6.7 Hz, 2H, H_1), 2.79 (td, *J* = 6.6, 2.0 Hz, 2H, H_2).

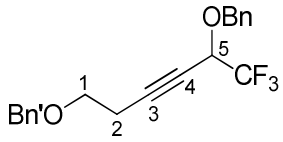
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 166.4, 136.1 (Ar), 133.3 (Ar), 129.9 (Ar), 129.8 (Ar), 128.7 (Ar), 128.6 (Ar), 128.4 (Ar), 128.3 (Ar), 122.6 (q, *J* = 281.2 Hz, CF_3), 86.0 (C_3), 72.3 (q, *J* = 2.3 Hz, C_4), 71.2 (CH_2 of Bn), 67.6 (q, *J* = 35.3 Hz, C_5), 62.2 (C_1), 19.6 (C_2).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) : -77.8

IR (cm^{-1}, CCl_4) : 3091, 3068, 3035, 2985, 1967, 1720, 1603, 1585, 1497, 1454, 1376, 1316, 1275, 1187, 1159, 1139, 1115, 1097, 1072, 1028

MS (HRMS EI) : Calcd for $C_{20}H_{17}F_3O_2$: 362.1130 Found : 362.1121

(((6,6,6-trifluorohex-3-yne-1,5-diyl)bis(oxy))bis(methylene))dibenzene (II.1e)



$C_{20}H_{20}F_3O_2$
MW = 348.4 g.mol^{-1}

Procedure : To a solution of 5-(benzyloxy)-6,6,6-trifluorohex-3-yn-1-ol (1.00 mmol) in THF (0.5 M) was added NaH (1.1 equiv.) at 0 °C. Upon the end of the H_2 formation, benzyl bromide (1.2 equiv.) and TBAI (0.05 equiv.) were added. The mixture was then stirred overnight at room temperature. The reaction was then quenched with a saturated solution of NH_4Cl, extracted with Et_2O (x3), washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure.

Purification : Flash chromatography PE / Et_2O 50:1

Yield : 62% (217 mg) of a colorless oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.36 – 7.26 (m, 10H, Ar), 4.84 (d, *J* = 11.9 Hz, 1H, CH_2 of Bn), 4.67 (d, *J* = 11.9 Hz, 1H, CH_2 of Bn), 4.57 (s, 2H, CH_2 of Bn'), 4.51 – 4.44 (m, *J* = 5.9, 2.1 Hz, 1H, H_5), 3.63 (t, *J* = 6.8 Hz, 2H, H_1), 2.61 (td, *J* = 6.8, 2.0 Hz, 2H, H_2).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 138.0 (Ar), 136.2 (Ar), 128.7 (Ar), 128.6 (Ar), 128.4 (Ar), 128.3 (Ar), 127.9 (Ar), 127.8 (Ar), 122.7 (q, *J* = 281.3 Hz, CF_3), 87.3 (C_3), 73.2 (CH_2

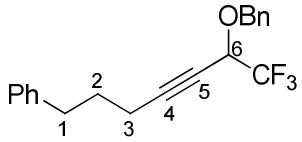
of Bn), 71.5 (q, J = 2.3 Hz, C_4), 71.1 (CH_2 of Bn'), 67.9 (C_1), 67.6 (q, J = 35.0 Hz, C_5), 20.3 (C_2).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$): -77.8

IR (cm^{-1}, CCl_4): 3090, 3068, 3034, 2871, 1497, 1455, 1365, 1273, 1187, 1158, 1139, 1096, 1079, 1029, 1001

MS (HRMS EI): Calcd for $C_{20}H_{19}F_3O_2$: 348.1337 Found : 348.1328

(6-(benzyloxy)-7,7,7-trifluorohept-4-yn-1-yl)benzene (II.1f)



$C_{20}H_{19}F_3O$
MW = 332.4 g.mol^{-1}

Procedure : Following procedure A starting with 5-phenyl-1-pentyne (10.00 mmol)

Purification : Flash chromatography : pure PE to PE/Et_2O 95:5.

Overall yield : 57% (1.90 g) of a colorless oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$): 7.41 – 7.29 (m, 7H, Ar), 7.24 – 7.20 (m, 3H, Ar), 4.88 (d, J = 11.9 Hz, 1H, CH_2 of Bn), 4.71 (d, J = 11.9 Hz, 1H, CH_2 of Bn), 4.51 (qt, J = 5.9, 2.1 Hz, 1H, H_6), 2.78 – 2.74 (m, 2H, H_1), 2.31 (td, J = 7.0, 2.0 Hz, 2H H_3), 1.94 – 1.86 (m, 2H, H_2).

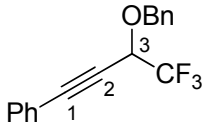
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$): 141.3 (Ar), 136.3 (Ar), 128.7 (Ar), 128.6 (Ar), 128.6 (Ar), 128.4 (Ar), 128.3 (Ar), 126.2 (Ar), 122.8 (q, J = 281.2 Hz, CF_3), 90.0 (C_4), 71.1 (q, J = 2.5 Hz, C_5), 71.1 (CH_2 of Bn), 67.7 (q, J = 35.0 Hz, C_6), 34.8 (C_1), 30.0 (C_2), 18.2 (C_3).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$): -78.0

IR (cm^{-1}, CCl_4): 3067, 3030, 2956, 2865, 2238, 1497, 1455, 1274, 1185, 1157, 1138, 1090

MS (HRMS EI): Calcd for M : $C_{20}H_{19}F_3O$: 332.1388 Found : 332.1390

(3-(benzyloxy)-4,4,4-trifluorobut-1-ynyl)benzene (II.1g)



$C_{17}H_{13}F_3O$
MW = 290.3 g.mol^{-1}

Procedure : Following procedure A starting with phenylacetylene (5.47 mmol)

Purification : Flash chromatography : PE / Et_2O 50:1

Overall yield : 68% (1.08 g) of a yellow oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.54 – 7.48 (m, 2H, Ar), 7.45 – 7.31 (m, 8H, Ar), 4.94 (d, *J* = 11.9 Hz, 1H, CH_2 of Bn), 4.77 (d, *J* = 11.9 Hz, 1H, CH_2 of Bn), 4.71 (q, *J* = 5.8 Hz, 1H, H_3).

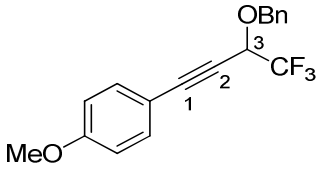
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 136.2 (Ar), 132.2 (Ar), 129.6 (Ar), 128.8 (Ar), 128.5 (Ar), 128.5 (Ar), 128.4 (Ar), 122.7 (q, *J* = 281.4 Hz, CF_3), 121.3 (Ar), 89.0 (C_1), 79.08 (q, *J* = 2.3 Hz, C_2), 71.4 (CH_2 of Bn), 68.1 (q, *J* = 35.2 Hz, C_3).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) : -77.5

IR (cm^{-1}, CCl_4) : 3155, 3088, 3068, 3035, 2930, 2876, 2253, 2232, 1950, 1881, 1805, 1729, 1671, 1600, 1491, 1456, 1445, 1370, 1320, 1276, 1254, 1187, 1150, 1094, 1031, 1015, 997, 909

MS (HRMS EI) : Calcd for $C_{17}H_{13}F_3O$: 290.0918 Found : 290.0912

1-(3-(benzyloxy)-4,4,4-trifluorobut-1-ynyl)-4-methoxybenzene (II.1h)



$C_{18}H_{15}F_3O_2$
MW = 320.3 g.mol^{-1}

Procedure : Following procedure C starting with **III.1s** (0.60 mmol) and 4-iodoanisole (0.60 mmol).

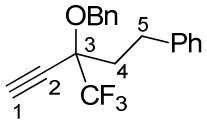
Purification : Flash chromatography : PE / Et_2O 50:1

Yield : 55% (105 mg) of an orange oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.48 – 7.30 (m, 7H, Ar), 6.90 – 6.82 (m, 2H, Ar), 4.92 (d, *J* = 11.9 Hz, 1H, CH_2 of Bn), 4.76 (d, *J* = 11.9 Hz, 1H, CH_2 of Bn), 4.70 (q, *J* = 5.8 Hz, 1H, H_3), 3.83 (s, 3H, OMe)

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	160.6 (Ar), 136.3 (Ar), 133.8 (Ar), 128.7 (Ar), 128.5 (Ar), 128.4 (Ar), 122.8 (q, J = 281.5 Hz, CF_3), 114.2(Ar), 113.3 (Ar), 89.1 (C_1), 77.8 (q, J = 2.2 Hz, C_2), 71.3 (CH_2 of Bn), 68.2 (q, J = 35.2 Hz, C_3), 55.5 (OMe).
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-77.6
IR (cm^{-1}, CCl_4)	2959, 2839, 1608, 1511, 1294, 1277, 1251, 1186, 1150, 1107, 1038, 909
MS (HRMS EI)	Calcd for $C_{18}H_{15}F_3O_2$: 320.1024 Found : 320.1032

***(3-(benzyloxy)-3-(trifluoromethyl)pent-4-yn-1-yl)benzene* (II.1j)**



$C_{19}H_{17}F_3O$
MW = 318.3 g.mol^{-1}

Procedure : Following procedure B starting using a commercial solution of ethynylmagnesium bromide (1.5 eq, 0.5 M in THF) and 1,1,1-trifluoro-4-phenyl-butan-2-one (12.0 mmol in a crude mixture prepared according to a literature procedure[244]).

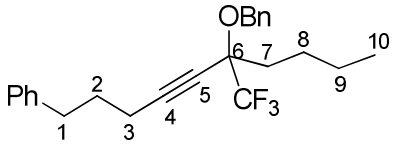
Purification : Flash chromatography: pure PE to PE / EtOAc 98:2.

Overall yield: 61% (2.33 g) of a colorless oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.41 – 7.38 (m, 4H, Ar), 7.38 – 7.27 (m, 3H, Ar), 7.25 – 7.21 (m, 3H, Ar), 4.99 (d, J = 11.1 Hz, 1H, CH_2 of Bn), 4.83 (d, J = 11.1, 1H, CH_2 of Bn), 3.03 – 2.89 (m, 2H, H_5), 2.85 (s, 1H, H_1), 2.34 – 2.10 (m, 2H, H_4).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	141.1 (Ar), 137.8 (Ar), 128.7 (Ar), 128.6 (Ar), 128.6 (Ar), 127.9 (Ar), 128.0 (Ar), 126.3 (Ar), 124.4 (q, J = 288.4 Hz, CF_3), 79.4 (CH_2 of Bn), 76.1 (C_1), 70.0 (q, J = 1.6 Hz, C_2), 37.5 (C_4), 29.9 (C_5).
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-78.4
IR (cm^{-1}, CCl_4)	3304, 3089, 3067, 3032, 2943, 2890, 2252, 2122, 1605, 1498, 1456, 1384, 1299, 1260, 1186, 1129, 1099, 1068, 1052
MS (HRMS EI)	Calcd for $C_{19}H_{17}F_3O$: 318.1231 Found : 318.1229

[244] Fushibe, K.; Jyono, H.; Fujiwara, M.; Kudo, T.; Yokot, M.; Ichikawa, J. *Chem. Eur. J.* **2011**, *17*, 12175.

(6-(benzyloxy)-6-(trifluoromethyl)dec-4-ynyl)benzene (II.1l)[245]



$C_{24}H_{27}F_3O$
MW = 388.5 g.mol^{-1}

Procedure :

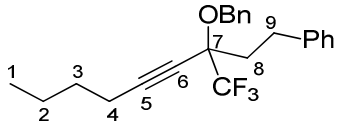
To a solution of 5-phenylpent-1-yne (2.0 equiv.) in THF (0.5 M) was added dropwise *n*-BuLi (2.2 equiv.) at -78 °C. The mixture was stirred for 1 h at -78 °C and ethyl trifluoroacetate (1.0 equiv.) was added. After the complete consumption of the alkyne (TLC), the reaction was quenched with a saturated solution of NH_4Cl, extracted with Et_2O (x3), washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (PE / EtOAc 50:1 to 10:1) gave the alcohol as a yellow oil (33% yield). The product resulting from the double addition of the alkyne on ethyl trifluoroacetate was also isolated as a yellow oil (55% yield).

To a solution of the resulting alcohol in THF (0.5 M) was added NaH (1.1 equiv.) at 0 °C. Upon the end of the H_2 formation, benzyl bromide (1.2 equiv.) and TBAI (0.05 equiv.) were added. The mixture was then stirred overnight at room temperature. The reaction was then quenched with a saturated solution of NH_4Cl, extracted with Et_2O (x3), washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure.

Purification :	Flash chromatography PE / Et_2O 50:1.
Overall yield :	25% of a yellow oil.
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.43 – 7.38 (m, 4H, Ar), 7.37 – 7.30 (m, 3H, Ar), 7.29 – 7.18 (m, 3H, Ar), 4.96 (d, *J* = 11.3 Hz, 1H, CH_2 of Bn), 4.79 (d, *J* = 11.3, 1H, CH_2 of Bn), 2.79 (t, *J* = 8 Hz, 2H, H_1), 2.36 (t, *J* = 6.9 Hz, 2H, H_3), 1.98 – 1.84 (m, 4H, $H_{2,7}$), 1.75 – 1.60 (m, 2H, H_8), 1.50 – 1.35 (m, 2H, H_9), 0.98 (t, *J* = 8 Hz, 3H, H_{10}).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	141.3 (Ar), 138.4 (Ar), 128.6 (Ar), 128.6 (Ar), 128.5 (Ar), 127.8 (x2,Ar), 126.2 (Ar), 124.8 (q, *J* = 288.0 Hz, CF_3), 91.3 (C_4), 77.4 (q, *J* = 29.2 Hz, C_6), 73.3 (C_5), 69.5 (CH_2 of Bn), 35.6 (C_7), 34.8 (C_1), 30.1 (C_2), 25.8 (C_8), 22.8 (C_9), 18.2 (C_3), 14.1 (C_{10}).
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-78.7
IR (cm^{-1}, CCl_4)	3086, 3035, 3029, 2960, 2934, 2868, 1976, 1603, 1496, 1455, 1380, 1292, 1253, 1204, 1156, 1121, 1031
MS (HRMS EI)	Calcd for $C_{24}H_{27}F_3O$: 388.2014 Found : 388.2011

[245] With this procedure, the tertiary alcohol disubstituted by the alkyne was targeted. The described alcohol was obtained as a by-product of the reaction but was found to be interesting for the scope of the reaction.

(3-(benzyloxy)-3-(trifluoromethyl)non-4-ynyl)benzene (II.1m)



$C_{23}H_{25}F_3O$
MW = 374.4 g.mol^{-1}

Procedure : Following procedure B starting with 1-hexyne (2.5 mmol) and 1,1,1-trifluoro-4-phenyl-butan-2-one (crude mixture prepared according to a literature procedure).

Purification : Flash chromatography : PE / Et_2O 100:1

Overall yield : 68% (640 mg) of a yellow oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.31 – 7.24 (m, 4H, Ar), 7.23 – 7.17 (m, 3H, Ar), 7.14 – 7.06 (m, 3H, Ar), 4.86 (d, *J* = 11.3 Hz, 1H, CH_2 of Bn), 4.67 (d, *J* = 11.3 Hz, 1H, CH_2 of Bn), 2.87 – 2.77 (m, 2H, H_9), 2.25 (t, *J* = 7.0 Hz, 2H, H_4), 2.17 – 1.95 (m, 2H, H_8), 1.54 – 1.44 (m, 2H, H_3), 1.43 – 1.32 (m, 2H, H_2), 0.86 (t, *J* = 7.3 Hz, 3H, H_1).

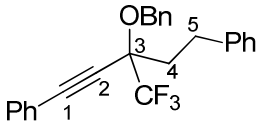
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 141.5 (Ar), 138.4 (Ar), 128.6 (Ar), 128.6 (Ar), 128.5 (Ar), 127.9 (Ar), 127.8 (Ar), 126.1 (Ar), 124.7 (q, *J* = 288.0 Hz, CF_3), 92.4 (C_5), 77.2 (q, *J* = 29.5 Hz, C_7), 72.6 (CH_2 of Bn), 69.6 (C_6), 37.8 (C_8), 30.5 (C_9), 30.1 (C_2), 22.0 (C_3), 18.5 (C_4), 13.6 (C_1).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) : -78.7

IR (cm^{-1}, CCl_4) : 3089, 3067, 3031, 2961, 2937, 2875, 2251, 1604, 1497, 1456, 1381, 1261, 1182, 1148, 1101, 1052

MS (HRMS EI) : Calcd for $C_{23}H_{25}F_3O$: 374.1858 Found : 374.1850

(3-(benzyloxy)-3-(trifluoromethyl)pent-1-yne-1,5-diyl)dibenzene (II.1n)



$C_{25}H_{21}F_3O$
MW = 394.4 g.mol^{-1}

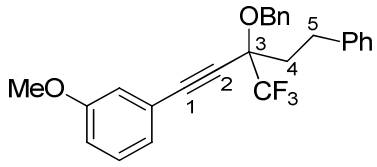
Procedure : Following procedure B starting with phenylacetylene (2.5 mmol) and 1,1,1-trifluoro-4-phenyl-butan-2-one (crude mixture prepared according o a literature procedure).

Purification : Flash chromatography : PE / Et_2O 100:1

Overall yield : 60% (588 mg) of a yellowish oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.65 – 7.58 (m, 2H, Ar), 7.52 – 7.41 (m, 7H, Ar), 7.41 – 7.34 (m, 3H, Ar), 7.34 – 7.24 (m, 3H, Ar), 5.14 (d, *J* = 11.3 Hz, 1H, CH_2 of Bn), 4.96 (d, *J* = 11.3 Hz, 1H, CH_2 of Bn), 3.09 (m, 2H, H_5), 2.37 (m, 2H, H_4).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	141.3 (Ar), 138.1 (Ar), 132.2 (Ar), 129.6 (Ar), 128.7 (Ar), 128.6 (Ar), 128.6 (Ar), 128.6 (Ar), 128.0 (Ar), 127.9 (Ar), 126.3 (Ar), 124.6 (q, *J* = 288.4 Hz, CF_3), 121.3 (Ar), 91.1 (C_1), 81.2 (C_2), 77.6 (q, *J* = 29.7 Hz, C_3), 70.0 (CH_2 of Bn), 37.8 (C_4), 30.2 (C_5).
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-78.1
IR (cm^{-1}, CCl_4)	3088, 3067, 3032, 2974, 2942, 2875, 2255, 2237, 1952, 1883, 1808, 1603, 1492, 1445, 1383, 1320, 1254, 1181
MS (HRMS EI)	Calcd for $C_{25}H_{21}F_3O$: 394.1544 Found : 394.1561

1-(3-(benzyloxy)-5-phenyl-3-(trifluoromethyl)pent-1-yn-1-yl)-3-methoxybenzene (II.1p)

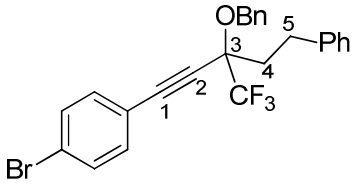


$C_{26}H_{23}F_3O_2$
MW = 424.5 g.mol^{-1}

Procedure :	Following procedure C using **II.1j** (1.50 mmol) and 3-anisole (1.50 mmol).
Purification :	Flash chromatography : PE / Et_2O 50:1
Yied :	85% (540 mg) of a colorless oil.
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.42 – 7.27 (m, 8H, Ar), 7.25 – 7.16 (m, 3H, Ar), 7.12 (dt, *J* = 7.6, 1.2 Hz, 1H, Ar), 7.03 – 7.00 (m, 1H, Ar), 6.96 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H, Ar), 5.03 (d, *J* = 11.2 Hz, 1H, CH_2 of Bn), 4.87 (d, *J* = 11.2 Hz, 1H, CH_2 of Bn), 3.83 (s, 3H, OMe), 3.03 – 2.98 (m, 2H, H_5), 2.35 – 2.20 (m, 2H, H_4)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	159.7 (Ar), 141.3 (Ar), 138.1 (Ar), 129.7 (Ar), 128.7 (Ar), 128.6 (Ar), 128.6 (Ar), 128.0 (Ar), 127.9 (Ar), 126.3 (Ar), 124.8 (Ar), 124.6 (q, *J* = 288.3 Hz, CF_3), 122.3 (Ar), 117.1 (Ar), 116.1 (Ar), 90.9 (C_1), 81.00 (C_2), 77.7 (q, *J* = 29.7 Hz, C_3), 70.0 (CH_2 of Bn), 55.5 (OMe), 37.7 (C_4), 30.2 (C_5).
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-78.2
IR (cm^{-1}, CCl_4)	3067, 3032, 3009, 2964, 2942, 2876, 2838, 2251, 2232, 1711, 1604, 1577, 1482, 1466, 1456, 1322, 1287, 1259, 1225, 1183, 1121, 1095, 1065, 1051

MS (HRMS EI)	Calcd for $C_{26}H_{23}F_3O_2$: 424.1650	Found : 424.1658

***1-(3-(benzyloxy)-5-phenyl-3-(trifluoromethyl)pent-1-yn-1-yl)-4-bromobenzene* (II.1q)**



$C_{25}H_{20}BrF_3O$
MW = 473.3 g.mol^{-1}

Procedure : Following procedure C using **II.1j** (1.50 mmol) and 4-bromoiodobenzene (1.50 mmol).

Purification : Flash chromatography : PE / Et_2O 50:1

Yied : 90% (640 mg) of a colorless oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.53 – 7.49 (m, 2H, Ar), 7.42 – 7.27 (m, 9H, Ar), 7.25 – 7.20 (m, 3H, Ar), 5.03 (d, *J* = 11.2 Hz, 1H, CH_2 of Bn), 4.87 (d, *J* = 11.2 Hz, 1H, CH_2 of Bn), 2.99 (t, *J* = 8.5 Hz, 2H, H_5), 2.40 – 2.19 (m, 2H, H_4).

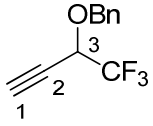
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 141.1 (Ar), 138.0 (Ar), 133.6 (Ar), 131.9 (Ar), 128.7 (Ar), 128.6 (Ar), 128.6 (Ar), 128.0 (Ar), 127.9 (Ar), 126.3 (Ar), 124.5 (q, *J* = 288.4 Hz, CF_3), 124.1 (Ar), 120.2 (Ar), 89.9 (CH_2 of Bn), 82.4 (C_1), 77.6 (q, *J* = 29.9 Hz, C_3), 70.0 (q, *J* = 1.1 Hz, C_2), 37.6 (C_4), 30.1 (C_5).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) : -78.1

IR (cm^{-1}, CCl_4) : 3306, 3089, 3067, 3032, 2942, 2258, 1604, 1587, 1497, 1487, 1456, 1394, 1254, 1184, 1124

MS (HRMS EI)	Calcd for $C_{25}H_{20}BrF_3O$: 472.0650	Found : 472.0653

***((1,1,1-trifluorobut-3-yn-2-yloxy)methyl)benzene* (II.1s)**



$C_{11}H_9F_3O$
MW = 214.2 g.mol^{-1}

Procedure : Following procedure A starting with trimethylsilylacetylene (10.00 mmol). The trimethylsilyl group was removed during the reduction step.

Purification : Flash chromatography : PE / Et_2O 50 : 1

Overall yield : 25% (535 mg) of a yellowish oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.39 – 7.32 (m, 5H, Ar), 4.88 (d, *J* = 11.8 Hz, 1H, CH_2 of Bn), 4.69 (d, *J* = 11.8 Hz, 1H, CH_2 of Bn), 4.47 (qd, *J* = 5.8, 2.3 Hz, 1H, H_3), 2.64 (d, *J* = 2.2 Hz, 1H, H_1).

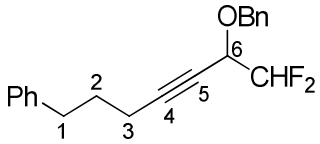
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 135.9 (Ar), 128.8 (Ar), 128.6 (Ar), 128.4 (Ar), 122.5 (q, *J* = 281.4 Hz, CF_3), 77.4 (C_1), 74.2 (q, *J* = 2.2 Hz, C_2), 71.5 (CH_2 of Bn), 67.4 (q, *J* = 35.5 Hz, C_3).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) : -77.7

IR (cm^{-1}, CCl_4) : 3306, 3091, 3069, 3035, 2880, 2258, 1497, 1456, 1370, 1274, 1190

MS (HRMS EI) : Calcd for $C_{11}H_9F_3O$: 214.0605 Found : 214.0599

(6-(benzyloxy)-7,7-difluorohept-4-yn-1-yl)benzene (II.1t)



$C_{20}H_{20}F_2O$
MW = 314.4 g.mol^{-1}

Procedure : Following procedure A starting with 5-phenylpent-1-yne (1.20 mmol) and using ethyl difluoroacetate instead of ethyl trifluoroacetate.

Purification : Flash chromatography : pure PE to PE / EtOAc 95:5.

Overall yield : 66% (251 mg) of a pale yellow oil.

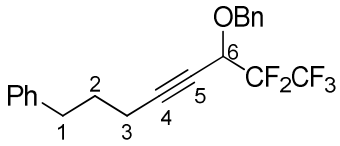
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.38 – 7.29 (m, 7H, Ar), 7.22 – 7.18 (m, 3H, Ar), 5.74 (td, *J* = 55.7, 4.3 Hz, 1H, CHF_2), 4.85 (d, *J* = 11.8 Hz, 1H, CH_2 of Bn), 4.63 (d, *J* = 11.8 Hz, 1H, CH_2 of Bn), 4.34 – 4.27 (m, 1H, H_6), 2.75 (t, *J* = 7.3 Hz, 2H, H_1), 2.30 (td, *J* = 7.2, 2.0 Hz, 2H, H_3), 1.88 (p, *J* = 7.2 Hz, 2H, H_2).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 141.4 (Ar), 136.8 (Ar), 128.7 (Ar), 128.7 (Ar), 128.6 (Ar), 128.3 (Ar), 128.3 (Ar), 126.1 (Ar), 113.8 (t, *J* = 246.2 Hz, CHF_2), 89.8 (C_4), 72.8 (t, *J* = 6.7 Hz, C_5), 71.0 (CH_2 of Bn), 69.0 (t, *J* = 27.5 Hz, C_6), 34.8 (C_1), 30.1 (C_2), 18.3 (C_3).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) : -126.0 (ddd, *J* = 284.2, 55.8, 9.6 Hz), -128.1 (ddd, *J* = 284.2, 55.8, 9.6 Hz)

IR (cm^{-1}, CCl_4)	3088, 3067, 3030, 2928, 2860, 2238, 1604, 1497, 1455, 1382, 1305, 1264, 1100, 1029
MS (HRMS EI)	Calcd for M : $C_{20}H_{20}F_2O$: 314.1482 Found : 314.1490

***(6-(benzyloxy)-7,7,8,8,8-pentafluorooct-4-ynyl)benzene* (II.1u)**



$C_{21}H_{19}F_5O$
MW = 382.4 $g.mol^{-1}$

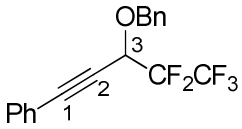
Procedure : Following procedure A starting with 5-phenylpent-1-yne (5.00 mmol) and using ethyl pentafluoropropionate instead of ethyl trifluoroacetate.

Purification : Flash chromatography : PE / Et_2O 50:1

Overall yield : 59% (1.13 g) of a yellowish oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.27 – 7.23 (m, 4H, Ar), 7.23 – 7.16 (m, 3H, Ar), 7.12 – 7.06 (m, 3H, Ar), 4.77 (d, *J* = 11.8 Hz, 1H, CH_2 of Bn), 4.56 (d, *J* = 11.8 Hz, 1H, CH_2 of Bn), 4.54 – 4.47 (m, 1H, H_6), 2.63 (t, *J* = 7.5 Hz, 2H, H_1), 2.19 (td, *J* = 7.2 ,2.0 Hz, 2H, H_3), 1.77 (p, *J* = 7.3 Hz, 2H, H_2).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	141.3 (Ar), 136.2 (Ar), 128.7 (Ar), 128.6 (Ar), 128.6 (Ar), 128.4 (Ar), 128.2 (Ar), 126.2 (Ar), 118.9 (qt, *J* = 285.0, 35.1 Hz, CF_3), 112.0 (ddq, *J* = 261.7, 255.8, 36.2 Hz, CF_2), 91.0 (C_4), 71.0 (CH_2 of Bn), 70.4 (C_5), 67.3 (dd, *J* = 29.8, 24.5 Hz, C_6), 34.7 (C_1), 29.9 (C_2), 18.2 (C_3).
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-82.1, -120.8 (dd, *J* = 273.8, 4.5 Hz), -126.8 (dd, *J* = 274.1, 13.8 Hz)
IR (cm^{-1}, CCl_4)	3088, 3067, 3031, 2947, 2866, 1952, 1876, 1810, 1603, 1497, 1455, 1430, 1368, 1315, 1218, 1203, 1149, 1139, 1078, 1034
MS (HRMS EI)	Calcd for $C_{21}H_{19}F_5O$: 382.1356 Found : 382.1360

***(3-(benzyloxy)-4,4,5,5,5-pentafluoropent-1-ynyl)benzene* (II.1v)**



$C_{18}H_{13}F_5O$
MW = 340.3 $g.mol^{-1}$

Procedure : Following procedure A starting with phenylacetylene (3.00 mmol) and using ethyl pentafluoropropionate instead of ethyl trifluoroacetate.

Purification : Flash chromatography : PE / Et_2O 50 : 1

Overall yield : 35% (360 mg) of a yellow oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.57 – 7.49 (m, 2H, Ar), 7.43 – 7.34 (m, 8H, Ar), 4.96 (d, *J* = 11.9 Hz, 1H, CH_2 of Bn), 4.86 – 4.80 (m, 1H, H_3), 4.76 (d, *J* = 11.9 Hz, 1H, CH_2 of Bn).

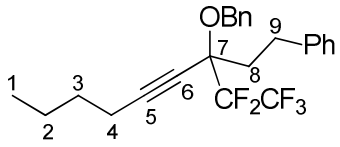
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 136.1 (Ar), 132.3 (Ar), 129.6 (Ar), 128.7 (Ar), 128.6 (Ar), 128.5 (Ar), 128.4 (Ar), 121.4 (Ar), 118.9 (qt, *J* = 287.1, 35.0 Hz, CF_3), 112.0 (ddq, *J* = 262.2, 250.4, 29.7 Hz, CF_2), 90.0 (C_1), 78.5 (t, *J* = 2.9 Hz, C_2), 71.4 (CH_2 of Bn), 67.8 (dd, *J* = 29.9, 24.9 Hz, C_3).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) -82.2 (s), -120.7 (d, *J* = 273.8 Hz), -126.4 (d, *J* = 274.0 Hz)

IR (cm^{-1}, CCl_4) 3088, 3068, 3035, 2930, 2877, 2258, 2238, 1971, 1953, 1885, 1808, 1599, 1491, 1456, 1445, 1368, 1359, 1316, 1260 ,1219, 1199, 1095, 1043

MS (HRMS EI) Calcd for $C_{18}H_{13}F_5O$: 340.0887 Found : 340.0883

(3-(benzyloxy)-3-(perfluoroethyl)non-4-ynyl)benzene (II.1w)



$C_{24}H_{25}F_5O$
MW = 424.5 g.mol^{-1}

Procedure : Following procedure B starting with 1-hexyne (1.3 equiv.), *n*-BuLi (1.2 equiv.) and 1,1,1,2,2-pentafluoro-5-phenylpentan-3-one (1 equiv.) (prepared according to a literature procedure[Erreur ! Signet non défini.] using ethyl pentafluoropropionate instead of ethyl trifluoroacetate) in THF (0.3 M).

Purification : Flash chromatography : PE / Et_2O 100 : 1

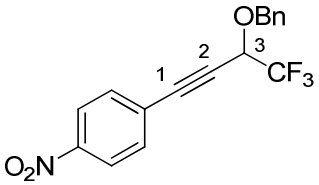
Overall yield : 54% of a colorless oil

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.39 – 7.29 (m, 7H, Ar), 7.24 – 7.20 (m, 3H, Ar), 4.92 (d, *J* = 11.1 Hz, 1H, CH_2 of Bn), 4.78 (d, *J* = 11.1 Hz, CH_2 of Bn), 3.00 – 2.86 (m, 2H, H_9), 2.39 (t, *J* = 6.9 Hz, 2H, H_4), 2.31 – 2.23 (m, 1H, H_8), 2.19 – 2.11 (m, 1H, H_8), 1.64 – 1.57 (m, 2H, H_2), 1.54 – 1.45 (m, 2H, H_3), 0.97 (t, *J* = 7.3 Hz, 3H, H_1).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	141.4 (Ar), 138.1 (Ar), 128.6 (Ar), 128.6 (Ar), 128.5 (Ar), 128.0 (Ar), 127.9 (Ar), 126.2 (Ar), 119.3 (qt, *J* = 288.5, 35.9 Hz, CF_3), 113.9 (tq, *J* = 264.1, 35.1 Hz, CF_2), 93.5 (C_5), 78.1 (t, *J* = 23.3 Hz, C_7), 72.2 (CH_2 of Bn), 69.6 (C_6), 37.9 (C_8), 30.5 (C_9), 30.5 (C_3), 22.0 (C_2), 18.6 (C_4), 13.7 (C_1).
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-79.4 (s), -118.7 (d, *J* = 276.5 Hz), -120.2 (d, *J* = 275.7 Hz)
IR (cm^{-1}, CCl_4)	3089, 3067, 3031, 2961, 2937, 2875, 2259, 1604, 1497, 1455, 1431, 1381, 1342, 1276, 1217, 1183, 1143, 1098, 1074, 1028
MS (HRMS EI)	Calcd for $C_{24}H_{25}F_5O$: 424.1826 Found : 424.1840

Unreactive substrates

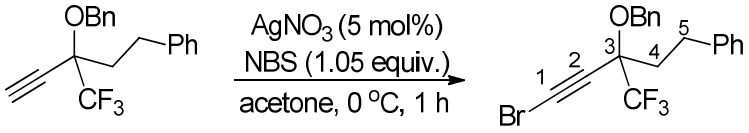
1-(3-(benzyloxy)-4,4,4-trifluorobut-1-yn-1-yl)-4-nitrobenzene (II.4a)



$C_{17}H_{12}F_3NO_3$
MW = 335.3 g.mol^{-1}

Procedure :	Following procedure C using **II.1s** (1.00 mmol) and *p*-iodonitrobenzene (1.00 mmol).
Purification :	Flash chromatography : PE / Et_2O 50:1
Overall yield :	60% (205 mg) of a thick orange oil.
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	8.08 (d, *J* = 8.8 Hz, 2H, Ar), 7.28-7.24 (m, 5H, Ar), 7.20 (d, *J* = 8.8 Hz, 2H, Ar), 7.11-7.08 (m, 1H, H_3), 4.95 (d, *J* = 12.4 Hz, 1H, CH_2 of Bn), 4.71 (d, *J* = 12.4 Hz, 1H, CH_2 of Bn).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	194.2 (q, *J* = 2.1 Hz, C_2), 147.9 (Ar), 138.9 (Ar), 135.5 (Ar), 128.8 (Ar), 128.6 (Ar), 128.4 (Ar), 127.6 (Ar), 127.3 (q, *J* = 40 Hz, C_3), 124.1 (Ar), 120.6 (q, *J* = 272 Hz, CF_3), 112.4 (C_1), 71.7 (CH_2 of Bn).
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-63.8
IR (cm^{-1}, CCl_4)	
MS (HRMS EI)	Calcd for [M] : $C_{17}H_{12}F_3NO_2$ 335.0769 Found : 335.0763

***(3-(benzyloxy)-5-bromo-3-(trifluoromethyl)pent-4-yn-1-yl)benzene* (II.4b)**



$C_{19}H_{16}BrF_3O$
MW = 397.2 g.mol^{-1}

Procedure : To a stirred solution of **II.1j** (0.33 mmol, 105.8 mg) and *N*-bromosuccinimide (0.33 mmol, 58.7 mg) in acetone (1 mL) at 0 °C was added silver nitrate (0.02 mmol, 2.8 mg). The mixture was stirred for one hour and then stirred over celite. The solvents were evaporated and the crude residue was purified by flash chromatography on silica gel.

Purification : Flash chromatography : PE / Et_2O 50:1

Overall yield : 88% (115.0 mg) of a white solid

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.38-7.35 (m, 4H, Ar), 7.35 – 7.27 (m, 3H, Ar), 7.23 – 7.17 (m, 3H, Ar), 4.92 (d, *J* = 11.1 Hz, 1H, CH_2 of Bn), 4.80 (d, *J* = 11.1 Hz, 1H, CH_2 of Bn), 2.96 – 2.83 (m, 2H, H_5), 2.30 – 2.08 (m, 2H, H_4).

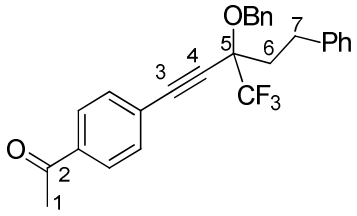
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 140.9 (Ar), 137.7 (Ar), 128.7 (Ar), 128.6 (Ar), 128.6 (Ar), 128.1 (Ar), 127.9 (Ar), 126.3 (Ar), 124.2 (q, *J* = 289 Hz, CF_3), 77.6 (q, *J* = 29.9 Hz, C_3), 73.1 (CH_2 of Bn), 70.1 (q, *J* = 1.5 Hz, C2), 52.0 (C_1), 37.5 (C_4), 29.9 (C_5).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) : -67.9

IR (cm^{-1}, CCl_4) : 3089, 3067, 3031, 2961, 2937, 2875, 2251, 1604, 1497, 1456, 1381, 1261, 1182, 1148, 1101, 1052

MS (HRMS EI) : Calcd for [M] : $C_{19}H_{16}BrF_3O$ 396.0337 Found : 396.0339

***1-(4-(3-(benzyloxy)-5-phenyl-3-(trifluoromethyl)pent-1-yn-1-yl)phenyl)ethanone* (II.4c)**



$C_{27}H_{23}F_3O_2$
MW = 436.5 g.mol^{-1}

Procedure : Following procedure C using **II.1j** (1.27 mmol, 404 mg) and 4'-bromoacetophenone (1.27 mmol, 253 mg).

Purification : Flash chromatography : PE / Et_2O 20:1

Overall yield : 64% (355.1 mg) of a yellow oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.85 (d, *J* = 8.1 Hz, 2H, Ar), 7.49 (d, *J* = 8.0 Hz, 2H, Ar), 7.29 (q, *J* = 8.1 Hz, 4H, Ar), 7.20 (dd, *J* = 13.3, 5.7 Hz, 3H, Ar), 7.16 – 7.07 (m, 3H, Ar), 4.94 (d, *J* = 11.2 Hz, 1H, CH_2 of Bn), 4.79 (d, *J* = 11.2 Hz, 1H, CH_2 of Bn), 2.91 (t, *J* = 8.5 Hz, 2H, H_7), 2.52 (s, 3H, H_1), 2.29 – 2.12 (m, 2H, H_6).

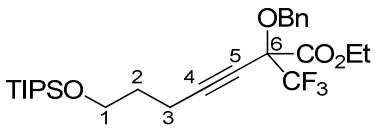
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 197.2 (C_2), 141.0 (Ar), 137.9 (Ar), 137.4 (Ar), 132.4 (Ar), 128.7 (Ar), 128.6 (Ar), 128.6 (Ar), 128.4 (Ar), 128.0 (Ar), 127.9 (Ar), 126.3 (Ar), 125.9 (Ar), 124.5 (q, *J* = 288.4 Hz, CF_3), 90.0 (C_4), 84.3 (C_3), 77.6 (q, *J* = 29.8 Hz, C_5), 69.9 (CH_2 of Bn), 37.5 (C_6), 30.1 (C_7), 26.6 (C_1).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) : -

IR (cm^{-1}, CCl_4) : 3091, 3068, 3034, 2933, 2874, 2240, 1697, 1498, 1455, 1432, 1397, 1366, 1348, 1274, 1186, 1158, 1140, 1091, 1029, 909.

MS (HRMS EI) : Calcd for [M] : $C_{27}H_{23}F_3O_2$ 436.1650 Found : 436.1655

ethyl 2-(benzyloxy)-2-(trifluoromethyl)-7-((triisopropylsilyl)oxy)hept-3-ynoate (II.4d)



$C_{26}H_{39}F_3O_4Si$
MW = 500.7 $g.mol^{-1}$

Procedure : Following procedure B using triisopropyl(pent-4-ynyloxy)silane (4.94 mmo, 1.19 g) and ethyl trifluoropyruvate (7.5 mmol, 0.98 mL).

Purification : Flash chromatography : PE / Et_2O 20:1

Overall yield : 26% (643.4 mg) of a yellow oil.

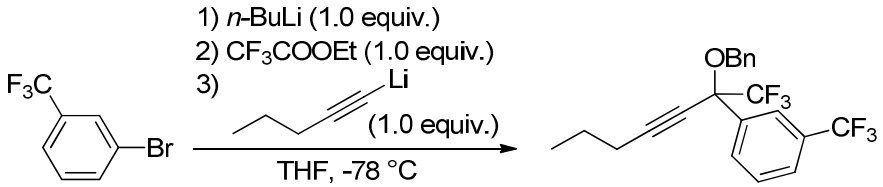
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.38-7.33 (m, 5H, Ar), 4.86 (d, *J* = 11.0 Hz, 1H, CH_2 of Bn), 4.76 (d, *J* = 11.0 Hz, 1H, CH_2 of Bn), 4.21 (q, *J* = 7.12 Hz, 2H, CH_2 of Et), 3.74 (t, *J* = 5.9 Hz, 2H, H_1), 2.45 (t, *J* = 7.0 Hz, 2H, H_3), 1.80 – 1.70 (m, 2H, H_2), 1.32 (t, *J* = 7.12 Hz, CH_3 of Et), 1.09-1.00 (m, 21H, TIPS).

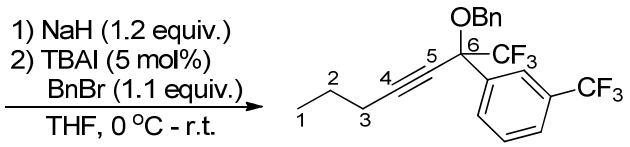
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 164.4, 137.1 (Ar), 134.9 (Ar), 128.8 (Ar), 128.1 (Ar), 121.87 (q, *J* = 286.3 Hz, CF_3), 92.9 (C_4), 78.08 (q, *J* = 32.3 Hz, C_6), 69.7 (CH_2 of Bn), 69.57 (q, *J* = 3.1 Hz), 68.6 (C_5), 63.3 (CH_2 of Et), 61.6 (C_1), 31.4 (C_2), 18.1 (C_3), 15.4 ($C(\underline{C}H_3)_3$ of TIPS), 14.7 (CH_3 of Et), 12 ($\underline{C}(CH_3)_3$ of TIPS).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) : -63.5

IR (cm^{-1}, CCl_4)	3089, 3067, 3031, 2961, 2937, 2875, 2251, 1604, 1497, 1456, 1381, 1261, 1182, 1148, 1101, 1052.
MS (HRMS EI)	Calcd for [M-iPr] : $C_{23}H_{32}F_3O_4Si$ 457.2022 Found : 457.1987

***1-(2-(benzyloxy)-1,1,1-trifluorohept-3-yn-2-yl)-3-(trifluoromethyl)benzene* (II.4e)**





$C_{21}H_{18}F_6O$
MW = 400.3 g.mol^{-1}

Procedure : To a solution of 3-trifluoromethylbromobenzene (3.0 mmol) in THF (10 mL) was added dropwise a solution of *n*-BuLi (3.0 mmol in hexane) at -78 °C. The mixture was stirred for one hour at the same temperature before ethyl trifluoroacetate (3.0 mmol) was added. After one hour, a solution of lithium acetylide (prepared by deprotonation of 1-hexyne by *n*-BuLi) in THF was added dropwise and the reaction mixture was slowly allowed to warm up to r.t. After one hour of stirring at r.t., the reaction mixture was quenched with a saturated solution of NH_4Cl, extracted with Et_2O (x3), washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give the crude α-trifluoromethyl propargylic alcohol.
The standard benzylation condition were then used.

Purification : Flash chromatography : PE

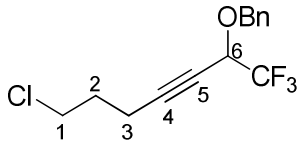
Overall yield : 12% (144.1 mg) of a colorless oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.76 (s, 1H, Ar), 7.67 (d, *J* = 7.9 Hz, 1H, Ar), 7.57 – 7.48 (m, 1H, Ar), 7.41 (t, *J* = 7.9 Hz, 1H, Ar), 7.35 – 7.26 (m, 4H, Ar), 7.23 (ddd, *J* = 8.4, 5.1, 2.4 Hz, 1H, Ar), 4.58 (d, *J* = 11.1 Hz, 1H, CH_2 of Bn), 4.51 (d, *J* = 11.1 Hz, 1H, CH_2 of Bn), 2.29 (ddd, *J* = 15.2, 12.0, 4.1 Hz, 1H, H_3), 2.09 – 1.94 (m, 1H, H_3), 1.35 – 1.20 (m, 1H, H_2), 1.14 – 1.01 (m, 1H, H_2), 0.79 (t, *J* = 7.1 Hz, 3H, H_1).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 138.0 (Ar), 137.7 (Ar), 131.1 (Ar), 130.9 (Ar), 128.9 (Ar), 128.7 (Ar), 128.0 (Ar), 127.4 (Ar), 125.6 (q, *J* = 288 Hz, CF_3), 125.4 (q, *J* = 3.7 Hz, Ar), 124.4 (dd, *J* = 3.8, 1.9 Hz, Ar), 124.2 (q, *J* = 271 Hz, CF_3 of Ar), 81.7 (q, *J* = 26.5 Hz, C_6), 77.2 (C_4), 66.8 (CH_2 of Bn), 66.5 (d, *J* = 1.9 Hz, C_5), 24.7 (C_3), 23.0 (C_2), 13.9 (C_1).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-57.8 (s, CF_3 of Ar), -68.6 (s)
IR (cm^{-1}, CCl_4)	3035, 2962, 2934, 2876, 2257, 1497, 1447, 1332, 1279, 1252, 1169, 1135, 1061, 1029
MS (HRMS EI)	Calcd for [M] : $C_{21}H_{18}F_6O$ 400.1262 Found : 400.1258

((7-chloro-1,1,1-trifluorohept-3-yn-2-yloxy)methyl)benzene (II.4f)



$C_{14}H_{14}ClF_3O$
MW = 290.7 g.mol^{-1}

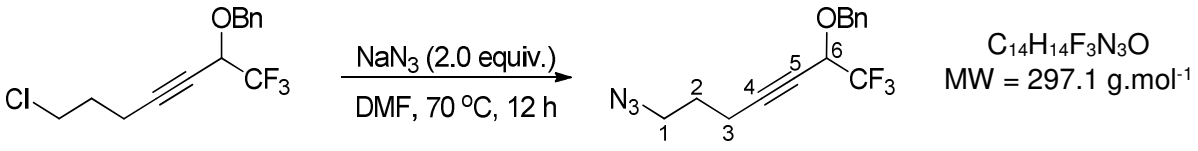
Procedure : Following procedure A starting with 5-chloropent-1-yne (10.00 mmol).

Purification : Flash chromatography : PE / Et_2O 50:1

Overall yield : 53% (1.53 g) of a colorless oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.39 – 7.32 (m, 5H, Ar), 4.84 (d, *J* = 11.9 Hz, 1H, CH_2 of Bn), 4.68 (d, *J* = 11.9 Hz, 1H, CH_2 of Bn), 4.46 (qt, *J* = 5.8, 2.1 Hz, 1H, H_6), 3.65 (t, *J* = 6.3 Hz, 2H, H_1), 2.50 (td, *J* = 6.9, 2.0 Hz, 2H, H_3), 2.04 – 1.98 (m, 2H, H_2).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	136.2 (Ar), 128.7 (Ar), 128.5 (Ar), 128.3 (Ar), 122.7 (q, *J* = 281.3 Hz, CF_3), 88.3 (C_4), 71.7 (d, *J* = 2.3 Hz, C_5), 71.2 (CH_2 of Bn), 67.6 (q, *J* = 35.0 Hz, C_6), 43.6 (C_1), 30.9 (C_2), 16.2 (C_3).
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-78.0
IR (cm^{-1}, CCl_4)	3068, 3034, 2962, 2875, 1497, 1456, 1373, 1354, 1274, 1186, 1162, 1151, 1137, 1091, 909
MS (HRMS EI)	Calcd for $C_{14}H_{14}F_3ClO$: 290.0685 Found : 290.0688

(((7-azido-1,1,1-trifluorohept-3-yn-2-yl)oxy)methyl)benzene (II.4g)



$C_{14}H_{14}F_3N_3O$
MW = 297.1 g.mol^{-1}

Procedure : To a stirred solution of **II.4f** (1.00 mmol, 300 mg) in DMF (3 mL) was added sodium azide (2.00 mmol, 130 mg) and the mixture was heated overnight at 70 °C. The reaction was then quenched with water and the organic materials were extracted with Et_2O. The combined organic layers were washed with water and brine before being dried of $MgSO_4$. The solvents were evaporated *in-vaccuo* and the crude residue was purified y flash chromatography on silica gel.

Purification : Flash chromatography : PE / Et_2O 50:1

Overall yield : 86% (255 mg) of a colorless oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.40-7.38 (m, 5H, Ar), 4.86 (d, *J* = 11.9 Hz, 1H, CH_2 of Bn), 4.69 (d, *J* = 11.9 Hz, 1H, CH_2 of Bn), 4.51-4.48 (m, 1H, H_6), 3.42 (t, *J* = 6.6 Hz, 2H, H_1), 2.42 (td, *J* = 6.9, 2.1 Hz, 2H, H_3), 1.83 (tt, *J* = 6.7 Hz, 2H, H_2).

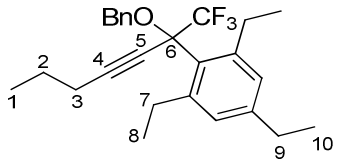
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 136.2 (Ar), 128.7 (Ar), 128.4 (Ar), 128.2 (Ar), 122.7 (q, *J* = 281.2 Hz, CF_3), 88.4 (C_4), 71.7 (d, *J* = 2.3 Hz, C_5), 71.2 (CH_2 of Bn), 67.6 (q, *J* = 35.1 Hz, C_6), 50.1 (C_1), 27.5 (C_3), 16.1 (C_2).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) -72.1

IR (cm^{-1}, CCl_4) 3091, 3068, 3034, 2933, 2874, 2240, 2100, 1498, 1455, 1432, 1397, 1366, 1348, 1274, 1186, 1158, 1140, 1091, 1029, 909

MS (HRMS EI) Calcd for [M-N_2] : $C_{14}H_{14}F_3NO$ 269.1033 Found : 269.1037

2-(2-(benzyloxy)-1,1,1-trifluorohept-3-yn-2-yl)-1,3,5-triethylbenzene (II.4h)



$C_{26}H_{31}F_3O$
MW = 416.2 g.mol^{-1}

Procedure : Following the same procedure than the one used to prepare **II.4e** but using 2,4,6-triethylbromobenzene (5.0 mmol, 1.20 g).

Purification : Flash chromatography : PE

Overall yield : 11% (229.3 mg) of a colorless oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.69 – 7.60 (m, 4H, Ar), 7.56 (t, *J* = 6.9 Hz, 3H, Ar), 5.18 (d, *J* = 11.4 Hz, 1H, CH_2 of Bn), 4.77 (d, *J* = 11.4 Hz, 1H, CH_2 of Bn), 3.61 (dq, *J* = 14.3, 7.1 Hz, 2H, H_7), 3.15 (dq, *J* = 14.7, 7.4 Hz, 2H, H_7), 2.89 (q, *J* = 7.6 Hz, 2H, H_9), 2.62 – 2.50 (m, 2H, H_3), 1.91 – 1.81 (m, 2H, H_2), 1.53

(t, *J* = 7.6 Hz, 3H, H_{10}), 1.45 (t, *J* = 7.3 Hz, 6H, H_8), 1.28 (t, *J* = 7.4 Hz, 3H, H_1).

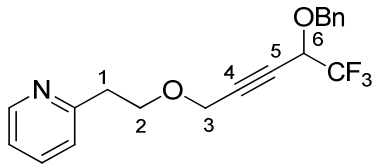
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$): 146.1 (Ar), 144.1 (Ar), 138.2 (Ar), 129.1 (Ar), 128.4 (Ar), 127.7 (Ar), 127.6 (Ar), 127.1 (Ar), 142.4 (q, *J* = 286.7 Hz, CF_3), 91.4 (C_4), 80.2 (q, *J* = 32.2 Hz, C_6), 75.9 (q, *J* = 3.8Hz, C_5), 67.0 (CH_2 of Bn), 28.2 (C_9), 27.6 (C_7), 27.6 (C_7), 21.7 (C_2), 21.2 (C_3), 17.3 (C_8), 15.1 (C_{10}), 13.7 (C_1).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$):

IR (cm^{-1}, CCl_4): 3089, 3067, 3031, 2961, 2937, 2875, 2251, 1604, 1497, 1456, 1381, 1261, 1182, 1148, 1101, 1052.

MS (HRMS EI): Calcd for $C_{26}H_{31}F_3O$ 416.2327 Found : 416.2329

2-(2-((4-(benzyloxy)-5,5,5-trifluoropent-2-yn-1- yl)oxy)ethyl)pyridine (II.4i)



$C_{19}H_{18}F_3NO_2$
MW = 349.3 g.mol^{-1}

Procedure : Following procedure A starting with 2-(2-(prop-2-yn-1-yloxy)ethyl)pyridine (2.00 mmol).

Purification : Flash chromatography : PE / EtOAc 2:1

Overall yield : 20% (139.7 mg) of an orange oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$): δ 8.53 (dd, *J* = 4.8, 0.8 Hz, 1H, Ar), 7.60 (td, *J* = 7.7, 1.8 Hz, 1H, Ar), 7.37 – 7.35 (m, 4H, Ar), 7.35 – 7.33 (m, 1H, Ar), 7.22 (d, *J* = 7.8 Hz, 1H, Ar), 7.13 (ddd, *J* = 7.5, 4.9, 0.9 Hz, 1H, Ar), 4.84 (d, *J* = 11.9 Hz, 1H, CH_2 of Bn), 4.66 (d, *J* = 11.9 Hz, 1H, CH_2 of Bn), 4.51 (qt, *J* = 5.8, 1.6 Hz, 1H, H_6), 4.24 (d, *J* = 1.6 Hz, 2H, H_3), 3.94 (t, *J* = 6.6 Hz, 2H, H_2), 3.10 (t, *J* = 6.6 Hz, 2H, H_1).

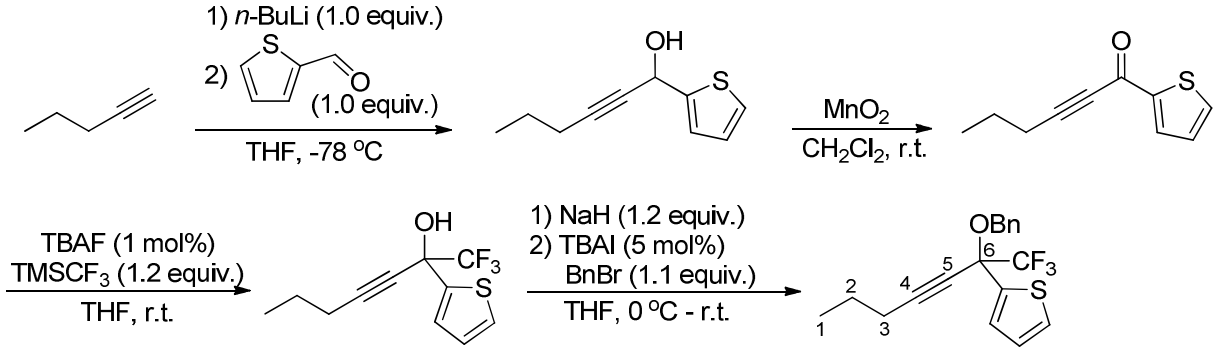
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$): 158.9 (Ar), 149.4 (Ar), 136.6 (Ar), 136.1 (Ar), 128.8 (Ar), 128.5 (Ar), 128.3 (Ar), 123.7 (Ar), 122.6 (d, *J* = 281.5 Hz, CF_3), 121.6 (Ar), 85.6 (C_4), 76.6 (d, *J* = 2.2 Hz, C_5), 71.4 (CH_2 of Bn), 69.6 (C_2), 67.6 (q, *J* = 35.3 Hz, C_6), 58.3 (C_3), 38.5 (C_1).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$):

IR (cm^{-1}, CCl_4): 3091, 3068, 3034, 2933, 2874, 2240, 1498, 1455, 1432, 1397, 1366, 1348, 1274, 1186, 1158, 1140, 1091, 1029, 909

MS (HRMS EI)	Calcd for $C_{19}H_{18}F_3NO_2$ 349.1290	Found : 349.1282

***2-(2-(benzyloxy)-1,1,1-trifluorohept-3-yn-2-yl)thiophene* (II.4k)**



$C_{18}H_{17}F_3OS$
MW = 338.4 g.mol^{-1}

Procedure : To a solution of 1-pentyne (1.2 mmol) in THF (4.5 mL) was added dropwise *n*-BuLi (1.2 mmol) at -78 °C. After one hour of stirring, 2-thiophenecarboxyaldeyde (1.2 mmol) was added and the mixture was allowed to warm-up to r.t.. After one hour of stirring at r.t., the reaction mixture was quenched with a saturated solution of NH_4Cl, extracted with Et_2O (x3), washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give the crude propargylic alcohol.
This crude mixture was then dissolved in CH_2Cl_2 (4.5 mL) and manganese oxide (1.2 mmol) was added. The reaction mixture was stirred at r.t. overnight and then filtrated over Celite to furnish the crude propargyl ketone after removal of the solvent *in-vaccuo*.
This crude mixture was then dissolved in THF (4.5 mmol) and $TMSCF_3$ (1.44 mmol) and TBAF (0.01 mmol) were successively added. After completion of the reaction, a 1M aqueous solution of HCl was added and the reaction was stirred for one hour, extracted with Et_2O (x3), washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give the crude α-trifluoromethyl propargylic alcohol.
The standard benzylation conditions were then used.

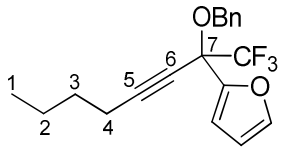
Purification : Flash chromatography : PE / Et_2O 50:1

Overall yield : 53% (215.2 mg) of a yellow oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.42 (d, *J* = 4.7 Hz, 2H, Ar), 7.40 – 7.35 (m, 5H, Ar), 7.06 (dd, *J* = 4.7, 4.0 Hz, 1H, Ar), 4.81 (d, *J* = 11.1 Hz, 1H, CH_2 of Bn), 4.49 (d, *J* = 11.1 Hz, 1H, CH_2 of Bn), 2.38 (t, *J* = 7.0 Hz, 2H, H_3), 1.72 – 1.61 (m, 2H, H_2), 1.08 (t, *J* = 7.4 Hz, 3H, H_1).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	138.5 (Ar), 137.6 (Ar), 129.4 (Ar), 128.3 (Ar), 127.9 (Ar), 127.8 (Ar), 127.8 (Ar), 127.0 (Ar), 122.9 (q, *J* = 284.9 Hz, CF_3), 92.0 (C_4), 73.1 (C_5), 72.3 (C_6), 67.8 (CH_2 of Bn), 21.6 (C_2), 20.9 (C_3), 13.6 (C_1).
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	
IR (cm^{-1}, CCl_4)	3091, 3068, 3034, 2933, 2874, 2240, 2100, 1498, 1455, 1432, 1397, 1366, 1348, 1274, 1186, 1158, 1140, 1091, 1029, 909.
MS (HRMS EI)	Calcd for $C_{18}H_{17}F_3OS$ 338.0952 Found : 338.0959

2-(2-(benzyloxy)-1,1,1-trifluorooct-3-yn-2-yl)furane (II.4l)

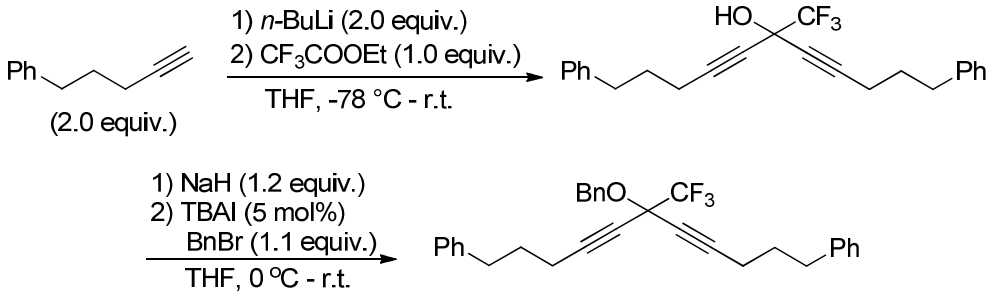


$C_{19}H_{19}F_3O_2$
MW = 336.3 g.mol^{-1}

Procedure :	Following the same procedure than the one used to prepare **II.4j** but using 1-hexyne (3.92 mmol, 0.45 mL) and 2-furanecarboxyaldehyde (3.92 mmol, 0.32 mL).
Purification :	Flash chromatography : PE / Et_2O 50:1
Overall yield :	28% (369.2 mg) of a yellow oil.
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.50 (dd, *J* = 1.7, 0.8 Hz, 1H, Ar), 7.35 – 7.32 (m, 5H, Ar), 6.74 (dd, *J* = 3.3, 0.8 Hz, 1H, Ar), 6.42 (dd, *J* = 3.3, 1.8 Hz, 1H, Ar), 4.75 (d, *J* = 11.2 Hz, 1H, CH_2 of Bn), 4.35 (d, *J* = 11.2 Hz, 1H, CH_2 of Bn), 2.37 (t, *J* = 7.0 Hz, 2H, H_4), 1.59 (ddt, *J* = 14.5, 12.4, 7.1 Hz, 2H, H_3), 1.52 – 1.42 (m, 2H, H_2), 0.95 (t, *J* = 7.3 Hz, 3H, H_1).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	147.4 (Ar), 144.5 (Ar), 137.5 (Ar), 128.4 (Ar), 127.8 (Ar), 127.8 (Ar), 122.6 (q, *J* = 285.3 Hz, CF_3), 113.4 (Ar), 110.6 (Ar), 91.4 (C_5), 73.2 (C_6) 71.5 (CH_2 of Bn), 67.8 (C_7), 30.3 (C_3), 22.0 (C_4), 18.5 (C_2), 13.6 (C_1).
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	
IR (cm^{-1}, CCl_4)	
MS (HRMS EI)	Calcd for $C_{19}H_{19}F_3O_2$ 336.1337 Found : 336.1349

(6-(benzyloxy)-6-(trifluoromethyl)undeca-4,7-diyne-1,11-diyl)dibenzene (II.4m)

$C_{31}H_{29}F_3O$
MW = 474.6
g.mol^{-1}



Procedure : To a solution of 5-phenyl-1-pentyne (5.0 mmol, 0.76 mL) in THF (10 mL) was added a solution of *n*-BuLi (5.0 mmol) in hexane at -78 °C. The reaction mixture was stirred for one hour and ethyl trifluoroacetate (2.5 mmol, 0.30 mL) was added. The reaction mixture was allowed to warm up to r.t. and was then quenched with a saturated solution of NH_4Cl, extracted with Et_2O (x3), washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give a crude residue. Purification by flash chromatography on silica gel gave the alcohol product.
The standard benzylation conditions were then used.

Purification : Flash chromatography : PE / Et_2O 50:1

Overall yield : 32% (759.5 mg) of a colorless oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.48-7.45 (m, 2H, Ar), 7.44 – 7.37 (m, 2H, Ar), 7.36-7.30 (m, 5H, Ar), 7.28 – 7.21 (m, 6H, Ar), 4.94 (s, 2H, CH_2 of Bn), 2.78 (t, *J* = 7.6 Hz, 2H), 2.33 (t, *J* = 7.0 Hz, 2H), 1.92 (p, *J*=7.2 Hz, 2H).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 141.3 (Ar), 137.3 (Ar), 128.6 (Ar), 128.5 (Ar), 128.5 (Ar), 127.9 (Ar), 127.9 (Ar), 126.2 (Ar), 122.1 (q, *J* = 284.1 Hz), 88.5, 73.0, 70.5 (q, *J* = 34.9 Hz), 68.1, 34.7, 29.8, 18.1.

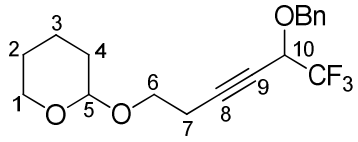
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) -74.8.

IR (cm^{-1}, CCl_4) 3088, 3067, 3032, 2974, 2942, 2875, 2255, 2237, 1952, 1883, 1808, 1603, 1492, 1445, 1383, 1320, 1254, 1181

MS Calcd for $C_{31}H_{29}F_3O$ 474.2171 Found : 474.2171

(HRMS EI)

***2-(5-(benzyloxy)-6,6,6-trifluorohex-3-ynyloxy)tetrahydro-2H-pyran* (II.4n)**



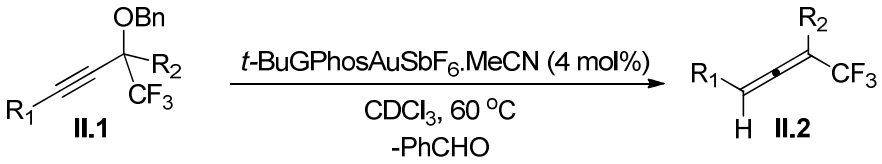
$C_{18}H_{21}F_3O_3$
MW = 342.4 g.mol^{-1}

Procedure :	Following procedure A starting with 2-(but-3-ynyloxy)tetrahydro-2H-pyran (20.00 mmol)
Purification :	Flash chromatography : PE / Et_2O 20:1
Overall yield :	47% (3.24 g) of a yellowish oil obtained as a mixture of diastereomers.
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.38 – 7.31 (m, 5H, Ar), 4.85 (d, *J* = 11.9 Hz, 1H, CH_2 of Bn), 4.67 (d, *J* = 11.9 Hz, 1H, CH_2 of Bn), 4.66 (t, *J* = 3.4 Hz, 1H, H_5), 4.49 – 4.44 (m, 1H, H_{10}), 3.91 – 3.84 (m, 2H, H_6), 3.61 – 3.49 (m, 2H, H_1), 2.59 (td, *J* = 6.9, 2.1 Hz, 2H, H_7), 1.85 – 1.79 (m, 1H, H_4), 1.75 – 1.68 (m, 1H, H_4), 1.63 – 1.49 (m, 4H, $H_{2,3}$)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	136.3 (Ar), 128.7 (Ar), 128.4 (Ar), 128.3 (Ar), 122.7 (q, *J* = 281.1 Hz, CF_3), 99.1 (C_5), 87.6 (C_8), 71.4 (q, *J* = 2.4 Hz, C_9), 71.0 (CH_2 of Bn), 67.6 (q, *J* = 35.1 Hz, C_{10}), 65.2 (C_1), 62.2 (C_6), 30.6 (C_4), 25.5 (C_2), 20.4 (C_3), 19.4 (C_7).
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-77.9
IR (cm^{-1}, CCl_4)	2945, 2875, 1455, 1353, 1274, 1185, 1159, 1139, 1081, 1036, 971, 909, 871
MS (HRMS EI)	Calcd for $C_{18}H_{21}F_3O_3$: 342.1443 Found : 342.1486

* Observed as doublets due to the slight chemical shift difference between the two diastereomers

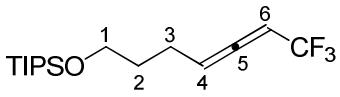
2.3 Preparation of trifluoromethyl allenes

General procedure D :



To a solution of propargylic benzylic ether (1 equiv.) in dry $CDCl_3$ (0.2 mol.L^{-1}) was added PhosphoniteAuSbF_6 (0.04 equiv.) and the reaction was heated up to 60 °C. Upon completion on the reaction (NMR), the solvent was evaporated and purification by flash chromatography gave the pure trifluoromethyl allene.
Crude NMR yield was provided by adding 1,2-dichloroethane as an internal standard.

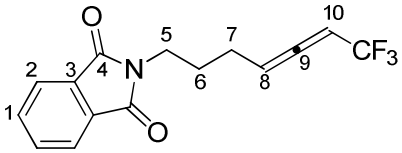
***triisopropyl(7,7,7-trifluorohepta-4,5-dienyloxy)silane* (II.2b)**



$C_{16}H_{29}F_3OSi$
MW = 322.5 g.mol^{-1}

Procedure :	Following procedure D, using **II.1b** (0.10 mmol, 42.9 mg, reaction time : 12 h).
Purification :	Flash chromatography : PE
Yield :	78% (25.1 mg) of a yellow oil (crude NMR yield 89%).
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	5.77 – 5.68 (m, 1H, H_4), 5.45 – 5.37 (m, 1H, H_6), 3.73 (t, *J* = 6.1 Hz, 2H, H_1), 2.23 (dtd, *J* = 8.8, 8.0, 3.2 Hz, 2H, H_3), 1.69 (tt, *J* = 7.3, 6.1 Hz, 2H, H_2), 1.09 – 1.00 (m, 21H, TIPS).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	205.2 (q, *J* = 5.8 Hz, C_5), 123.0 (q, *J* = 270.1 Hz, CF_3), 98.5 (C_4), 86.2 (q, *J* = 39.0 Hz, C_6), 62.3 (C_1), 31.8 (C_2), 24.2 (C_3), 18.1 (CH_3 of TIPS), 12.1 (CH of TIPS).
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-61.6
IR (cm^{-1}, CCl_4)	2959, 2944, 2894, 2867, 1979, 1730, 1464, 1432, 1383, 1261, 1134, 1071, 1013, 996, 965, 909, 883
MS (HRMS EI)	Calcd for $C_{16}H_{29}F_3OSi$: 322.1940 Found : 322.1925

2-(7,7,7-trifluorohepta-4,5-dienyl)isoindoline-1,3-dione (II.2c)



$C_{15}H_{12}F_3NO_2$
MW = 295.3 g.mol^{-1}

Procedure : Following procedure D, using **II.1c** (0.20 mmol, 80.2 mg, reaction time : 12 h).

Purification : Flash chromatography : PE / Et_2O 10:1

Yield : 88% (51.9 mg) of a white solid (crude NMR yield 92 %).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.84 (dd, *J* = 5.5, 3.1 Hz, 2H, H_1), 7.72 (dd, *J* = 5.5, 3.1 Hz, 2H, H_2), 5.77 – 5.68 (m, 1H, H_8), 5.49 – 5.41 (m, 1H, H_{10}), 3.73 (td, *J* = 7.0, 1.2 Hz, 2H, H_5), 2.26 – 2.11 (dtd, *J* = 8.8, 7.2, 3.2 Hz, 2H, H_7), 1.92 – 1.75 (tt, *J* = 8.4, 7.2 Hz, 2H, H_6).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 205.2 (q, *J* = 5.8 Hz, C_9), 168.5 (C_4), 134.1 (C_1), 132.2 (C_3), 123.4 (C_2), 122.9 (q, *J* = 270.3 Hz, CF_3), 97.5 (C_8), 86.7 (q, *J* = 39.0 Hz, C_{10}), 37.3 (C_5), 27.5 (C_6), 25.1 (C_7).

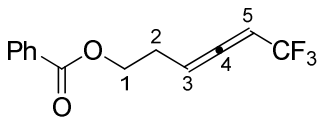
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) : -61.6

IR (cm^{-1}, CCl_4) : 3155, 2984, 2951, 2254, 1981, 1817, 1795, 1774, 1718, 1642, 1469, 1437, 1396, 1297, 1263, 1170, 1133, 1098, 1035, 992, 908

MS (HRMS EI) : Calcd for $C_{15}H_{12}F_3NO_2$: 295.0820 Found : 295.0825

MP : 53.0 – 54.5 °C

6,6,6-trifluorohexa-3,4-dienyl benzoate (II.2d)



$C_{13}H_{11}F_3O_2$
MW = 256.2 g.mol^{-1}

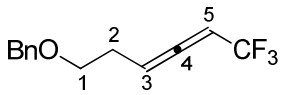
Procedure : Following procedure D, using **II.1d** (0.20 mmol, 72.5 mg, reaction time : 12 h).

Purification : Flash chromatography : PE / Et_2O 50:1

Yield : 60% (30.5 mg) of a colorless oil (crude NMR yield 65 %).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	8.04 (dd, *J* = 8.4, 1.4 Hz, 2H, Ar), 7.64 – 7.53 (m, 1H, Ar), 7.44 (dd, *J* = 8.4, 7.1 Hz, 2H, Ar), 5.84 – 5.71 (m, 1H, H_3), 5.52 – 5.45 (m, 1H, H_5), 4.42 (t, *J* = 6.3 Hz, 2H, H_1), 2.61 (dtd, *J* = 7.2, 6.6, 2.8 Hz, 2H, H_2).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	205.74 (q, *J* = 5.8 Hz, C_4), 166.5 (C=O), 133.2 (Ar), 130.1 (Ar), 129.7 (Ar), 128.5 (Ar), 122.7 (q, *J* = 270.4 Hz, CF_3), 94.8 (C_3), 86.7 (q, *J* = 39.2 Hz, C_5), 63.1 (C_1), 27.5 (C_2).
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-61.5
IR (cm^{-1}, CCl_4)	3066, 3037, 2963, 1983, 1718, 1603, 1585, 1453, 1435, 1429, 1384, 1337, 1316, 1277, 1177, 1138, 1071, 1027
MS (HRMS EI)	Calcd for $C_{13}H_{11}F_3O_2$: 256.0711 Found : 256.0722

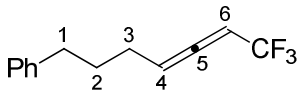
((6,6,6-trifluorohexa-3,4-dienyloxy)methyl)benzene (II.2e)



$C_{13}H_{13}F_3O$
MW = 242.2 g.mol^{-1}

Procedure :	Following procedure D, using **II.1e** (0.20 mmol, 69.6 mg, reaction time : 6 h).
Purification :	Flash chromatography : PE / Et_2O 50:1
Yield :	43% (20.8 mg) of a colorless oil (crude NMR yield 50 %).
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.40 – 7.27 (m, 5H, Ar), 5.81 – 5.72 (m, 1H, H_3), 5.49 – 5.41 (m, 1H, H_5), 4.53 (s, 2H, CH_2 of Bn), 3.59 (t, *J* = 6.4 Hz, 2H, H_1), 2.45 (dtd, *J* = 7.4, 6.4, 3.0 Hz, 2H, H_2).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	205.5 (q, *J* = 5.8 Hz, C_4), 138.2 (Ar), 128.6 (Ar), 127.8 (Ar), 127.8 (Ar), 122.9 (q, *J* = 270.1 Hz, CF_3), 95.6 (C_3), 86.2 (q, *J* = 38.9 Hz, C_5), 73.2 (CH_2 of Bn), 68.8 (C_1), 28.4 (C_2).
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-61.5
IR (cm^{-1}, CCl_4)	3067, 3033, 2958, 2864, 2258, 1981, 1495, 1455, 1429, 1364, 1298, 1261, 1211, 1136
MS (HRMS EI)	Calcd for $C_{13}H_{13}F_3O$: 242.0918 Found : 242.0903

(7,7,7-trifluorohepta-4,5-dien-1-yl)benzene (II.2f)



$C_{13}H_{13}F_3$
MW = 226.2 g.mol^{-1}

Procedure : Following procedure D, using **II.1f** (0.40 mmol, 132.7 mg, reaction time : 1 h 40) and 3 mol% catalyst.

Purification : Flash chromatography : PE/Et_2O 96:4

Yield : 90% (369.3 mg) of a yellow oil (crude NMR yield : 89 %).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.32 – 7.28 (m, 2H, Ar), 7.23 – 7.18 (m, 3H, Ar), 5.74 – 5.66 (m, 1H, H_4), 5.48 – 5.41 (m, 1H, H_6), 2.70 – 2.66 (m, 2H, H_1), 2.19 – 2.13 (m, 2H, H_3), 1.83 – 1.76 (m, 2H, H_2).

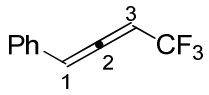
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 205.4 (q, *J* = 5.9 Hz, C_5), 141.8 (Ar), 128.6 (Ar), 128.5 (Ar), 127.0 (Ar), 123.0 (q, *J* = 270.0 Hz, CF_3), 98.3 (C_4), 86.2 (q, *J* = 38.9 Hz, C_6), 30.5 (C_1), 30.2 (C_2), 27.1 (C_3).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) : -61.5

IR (cm^{-1}, CCl_4) : 3029, 2938, 2861, 1979, 1497, 1454, 1297, 1260, 1134, 869

MS (HRMS EI) : Calcd for $C_{13}H_{13}F_3$: 226.0969 Found : 226.0973

(4,4,4-trifluorobuta-1,2-dienyl)benzene (II.2g)



$C_{10}H_7F_3$
MW = 184.2 g.mol^{-1}

Procedure : Following procedure D, using **II.1g** (0.20 mmol, 58.1 mg, reaction time : 6 h).

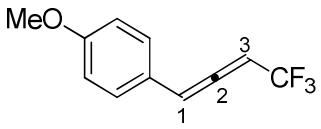
Purification : Flash chromatography : pentane

Yield : colorless oil (crude NMR yield 65 %, the product could not be isolated because of its low boiling point. Some pentane remains present on the spectra).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.42 – 7.28 (m, 5H, Ar), 6.71 – 6.66 (m, 1H, H_1), 5.92 – 5.86 (m, 1H, H_3).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	207.1 (q, *J* = 6.3 Hz, C_2), 130.9 (Ar), 129.1 (Ar), 128.7 (Ar), 127.7 (Ar), 122.5 (q, *J* = 271.0 Hz, CF_3), 101.4 (C_1), 89.8 (q, *J* = 39.3 Hz, C_3).
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-61.2 (d, *J* = 14.3 Hz)
IR (cm^{-1}, CCl_4)	3088, 3069, 3037, 2959, 2928, 2858, 1971, 1497, 1462, 1415, 1301, 1276, 1260, 1135
MS (HRMS EI)	Calcd for $C_{10}H_7F_3$: 184.0500 Found : 184.0493

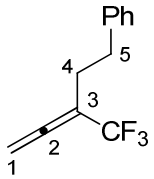
***1-methoxy-4-(4,4,4-trifluorobuta-1,2-dienyl)benzene* (II.2h)**



$C_{11}H_9F_3O$
MW = 214.2 g.mol^{-1}

Procedure :	Following procedure D, using **II.1h** (0.08 mmol, 25.6 mg, reaction time : 7 h).
Purification :	Flash chromatography : pentane
Yield :	65% (11.1 mg) of a yellow oil. (crude NMR yield 75 %).
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.24 (d, *J* = 8.7 Hz, 2H, Ar), 6.89 (d, *J* = 8.7 Hz, 2H, Ar), 6.66 – 6.61 (m, 1H, H_1), 5.88 – 5.82 (m, 1H, H_3), 3.80 (s, 3H, OMe)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	206.8 (q, *J* = 5.8 Hz, C_2), 160.1 (Ar), 128.9 (Ar), 123.0 (q, *J* = 1.5 Hz, Ar), 122.5 (q, *J* = 271.1 Hz, CF_3), 114.6 (Ar), 101.0 (C_1), 89.6 (q, *J* = 39.1 Hz, C_3), 55.5 (OMe).
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-61.3
IR (cm^{-1}, CCl_4)	2959, 2934, 1966, 1607, 1513, 1465, 1441, 1407, 1319, 1302, 1277, 1252, 1174, 1134, 1033
MS (HRMS EI)	Calcd for $C_{11}H_9F_3O$: 214.0605 Found : 214.0610

***(3-(trifluoromethyl)penta-3,4-dienyl)benzene* (II.2j)**



$C_{12}H_{11}F_3$
MW = 212.2 g.mol^{-1}

Procedure : Following procedure D, using **II.1j** (0.20 mmol, 63.7 mg, reaction time : 1 h).

Purification : Flash chromatography : PE

Yield : 87% (36.9 mg) of a yellowish oil (crude NMR yield 91 %).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.33 – 7.28 (m, 2H, Ar), 7.24 – 7.18 (m, 3H, Ar), 5.19 – 5.14 (m, 2H, H_1), 2.80 (t, J = 8 Hz, 2H, H_5), 2.48 – 2.42 (m, 2H, H_4).

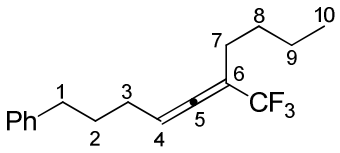
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 206.8 (q, J = 4.1 Hz, C_2), 140.8 (Ar), 128.6 (Ar), 128.6 (Ar), 126.4 (Ar), 124.0 (q, J = 273.2 Hz, CF_3), 98.2 (q, J = 33.1 Hz, C_3), 82.5 (C_1), 33.7 (C_4), 27.8 (C_5).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) : -65.2

IR (cm^{-1}, CCl_4) : 3088, 3066, 3030, 2929, 2862, 1986, 1954, 1730, 1604, 1497, 1455, 1318, 1263, 1056

MS (HRMS EI) : Calcd for $C_{12}H_{11}F_3$: 212.0813 Found : 212.0807

(6-(trifluoromethyl)deca-4,5-dienyl)benzene (II.2l)



$C_{17}H_{21}F_3$
MW = 282.3 g.mol^{-1}

Procedure : Following procedure D, using **II.1l** (0.20 mmol, 77.7 mg, reaction time : 1 h).

Purification : Flash chromatography : PE

Yield : 95% (53.6 mg) of a colorless oil (crude NMR yield 98 %).

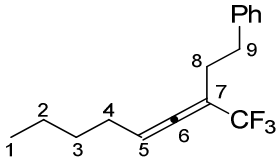
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.34 – 7.28 (m, 2H, Ar), 7.24 – 7.18 (m, 3H, Ar), 5.68 – 5.61 (m, 1H, H_4), 2.69 (t, J = 7.7 Hz, 2H, H_1), 2.18 – 2.11 (m, 4H, $H_{3,7}$), 1.79 (p, J = 7.4 Hz, 2H, H_2), 1.55 – 1.35 (m, 4H, $H_{8,9}$), 0.94 (t, J = 7.2 Hz, 3H, H_{10}).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 202.4 (q, J = 4.3 Hz, C_5), 142.1 (Ar), 128.6 (Ar), 128.5 (Ar), 126.0 (Ar), 124.2 (q, J = 273.3 Hz, CF_3), 99.1 (q, J = 33.4 Hz, C_6), 98.2 (C_4), 35.1 (C_2), 30.3 (C_1), 29.6 (C_8), 27.6 (q, J = 1.4 Hz, C_7), 26.0 (C_3), 22.1 (C_9), 13.8 (C_{10}).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) : -65.2

IR (cm^{-1}, CCl_4)	3086, 3065, 3029, 2960, 2934, 2863, 2252, 1976, 1603, 1496, 1455, 1292, 1253, 1292, 1253, 1156, 1121
MS (HRMS EI)	Calcd for $C_{17}H_{21}F_3$: 282.1595 Found : 282.1584

(3-(trifluoromethyl)nona-3,4-dienyl)benzene (II.2m)



$C_{16}H_{19}F_3$
MW = 268.3 $g.mol^{-1}$

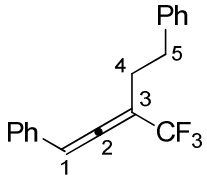
Procedure : Following procedure D, using **II.1m** (0.20 mmol, 74.9 mg, reaction time : 4 h).

Purification : Flash chromatography : PE

Yield : 80% (53.1 mg) of a colorless oil (crude NMR yield 83 %).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.34 – 7.28 (m, 2H, Ar), 7.25 – 7.17 (m, 3H, Ar), 5.62 – 5.54 (m, 1H, H_5), 2.79 (t, *J* = 7.4 Hz, 2H, H_9), 2.53 – 2.39 (m, 2H, H_8), 2.06 – 1.98 (m, 2H, H_4), 1.41 – 1.33 (m, 4H, $H_{2,3}$), 0.91 (t, *J* = 6.9 Hz, 3H, H_1).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	202.6 (q, *J* = 4.2 Hz, C_6), 141.0 (Ar), 128.6 (Ar), 128.5 (Ar), 126.3 (Ar), 124.2 (q, *J* = 273.4 Hz, CF_3), 99.1 (C_5), 98.2 (q, *J* = 33.7 Hz, C_7), 33.8 (C_8), 30.9 (C_9), 28.1 (C_3), 27.9 (C_4), 22.2 (C_2), 13.9 (C_1).
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-65.1
IR (cm^{-1}, CCl_4)	3088, 3030, 2961, 2931, 2862, 2255, 1976, 1604, 1497, 1455, 1305, 1261, 1156, 1119, 1054, 1030
MS (HRMS EI)	Calcd for $C_{16}H_{19}F_3$: 268.1439 Found : 268.1423

(3-(trifluoromethyl)penta-1,2-diene-1,5-diyl)dibenzene (II.2n)



$C_{18}H_{15}F_3$
MW = 288.3 $g.mol^{-1}$

Procedure : Following procedure D, using **II.1n** (0.20 mmol, 78.9 mg, reaction time : 10 h).

Purification : Flash chromatography : PE

Yield : 79% (45.7 mg) of a colorless oil (crude NMR yield 81 %)

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.37 – 7.27 (m, 5H, Ar), 7.25 – 7.19 (m, 5H, Ar), 6.61 – 6.57 (m, 1H, H_1), 2.95 – 2.81 (m, 2H, H_5), 2.73 – 2.58 (m, 2H, H_4).

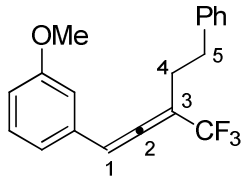
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 204.2 (q, J = 4.1 Hz, C_2), 140.6 (Ar), 132.0 (Ar), 129.0 (Ar), 128.6 (Ar), 128.6 (Ar), 128.3 (Ar), 127.5 (Ar), 126.3 (Ar), 123.7 (q, J = 274.3 Hz, CF_3), 102.4 (q, J = 33.9 Hz, C_3), 102.0 (C_1), 33.6 (C_4), 28.5 (C_5).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) : -64.7

IR (cm^{-1}, CCl_4) : 3088, 3067, 3022, 2958, 2856, 2255, 1964, 1603, 1497, 1462, 1409, 1299, 1282, 1261, 1214, 1152, 1124

MS (HRMS EI) : Calcd for $C_{18}H_{15}F_3$: 288.1126 Found : 288.1123

1-methoxy-3-(5-phenyl-3-(trifluoromethyl)penta-1,2-dienyl)benzene (II.2p)



$C_{19}H_{17}F_3O$
MW = 318.3 g.mol^{-1}

Procedure : Following procedure D, using **II.1p** (0.20 mmol, 84.9 mg, reaction time : 12 h).

Purification : Flash chromatography : PE / Et_2O 50:1

Yield : 91% (57.8 mg) of a colorless oil (crude NMR yield 96 %).

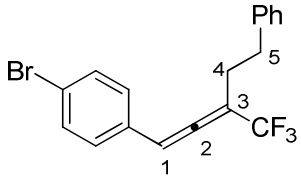
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.27 – 7.21 (m, 3H,Ar), 7.20 – 7.16 (m, 3H, Ar), 6.83 – 6.79 (m, 2H, Ar), 6.76 – 6.75 (m, 1H, Ar), 6.53 (hept, J = 3.3 Hz, 1H, H_1), 3.79 (s, 3H, OMe), 2.90 – 2.77 (m, 2H, H_5), 2.63 – 2.57 (m, 2H, H_4).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 204.2 (q, J = 4.1 Hz, C_2), 160.0 (Ar), 140.6 (Ar), 133.3 (Ar), 130.0 (Ar), 128.6 (Ar), 128.5 (Ar), 126.3 (Ar), 123.6 (q, J = 274.5 Hz, CF_3), 120.1 (Ar), 113.9 (Ar), 112.9 (Ar), 102.5 (q, J = 34.0 Hz, C_3), 101.9 (C_1), 55.4 (OMe), 33.6 (C_4), 28.4 (C_5).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) : -65.0

IR (cm^{-1}, CCl_4)	3066, 3030, 3007, 2940, 2838, 2253, 1965, 1599, 1584, 1493, 1469, 1455, 1440, 1408, 1304, 1288, 1261, 1158, 1125, 1051
MS (HRMS EI)	Calcd for $C_{19}H_{17}F_3O$: 318.1231 Found : 318.1226

1-bromo-4-(5-phenyl-3-(trifluoromethyl)penta-1,2-dienyl)benzene (II.2q)



$C_{18}H_{14}BrF_3$
MW = 367.2 $g.mol^{-1}$

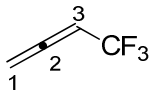
Procedure : Following procedure D, using **II.1q** (0.20 mmol, 94.7 mg, reaction time : 8 h).

Purification : Flash chromatography : PE

Yield : 94% (69.0 mg) of a colorless oil (crude NMR yield 98 %).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.44 – 7.40 (m, 2H, Ar), 7.29 – 7.24 (m, 2H, Ar), 7.23 – 7.17 (m, 3H, Ar), 7.01 – 6.97 (m, 2H, Ar), 6.52 – 6.48 (m, 1H, H_1), 2.93 – 2.79 (m, 2H, H_5), 2.72 – 2.56 (m, 2H, H_4).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	204.3 (q, *J* = 4.1 Hz, C_2), 140.4 (Ar), 132.1 (Ar), 130.9 (q, *J* = 1.4 Hz, Ar), 128.9 (Ar), 128.6 (Ar), 128.6 (Ar), 126.4 (Ar), 123.5 (q, *J* = 274.4 Hz, CF_3), 122.2 (Ar), 102.8 (q, *J* = 34.0 Hz, C_3), 101.0 (C_1), 33.4 (C_4), 28.4 (C_5).
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-64.7
IR (cm^{-1}, CCl_4)	2928, 2856, 1965, 1604, 1589, 1489, 1454, 1387, 1308, 1293, 1261, 1154, 1126
MS (HRMS EI)	Calcd for $C_{18}H_{14}BrF_3$: 366.0231 Found : 366.0227

4,4,4-trifluorobuta-1,2-diene (II.2s)



$C_4H_3F_3$
MW = 108.1 $g.mol^{-1}$

Procedure : Following procedure D, using **II.1s** (0.20 mmol, 42.8 mg, reaction time : 24 h).

Yield : (Crude NMR yield : 55 %, the product could not be isolated because of its low boiling point)

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 5.51 – 5.43 (m, 1H, H_3), 5.29 – 5.24 (m, 2H, H_1).

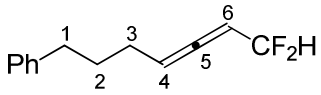
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 209.2 (q, J = 5.8 Hz, C_2), 122.8 (q, J = 269.9 Hz, CF_3), 85.8 (q, J = 39.3 Hz, C_3), 82.0 (C_1).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) : -61.4

IR (cm^{-1}, CCl_4) : 2959, 2934, 1966, 1607, 1513, 1465, 1441, 1407, 1319, 1302, 1277, 1252, 1174, 1134, 1033

MS (HRMS EI) : Calcd for $C_4H_3F_3$: 108.0187 Found : 108.0183

(7,7-difluorohepta-4,5-dien-1-yl)benzene (II.2t)



$C_{13}H_{14}F_2$
MW = 208.3 g.mol^{-1}

Procedure : Following procedure D, using **II.1t** (0.20 mmol, 62.9 mg, reaction time : 1 h).

Purification : Flash chromatography : pentane

Yield : 75% (29.5 mg) of a pale yellow oil (crude NMR yield 79%).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.32 – 7.28 (m, 2H, Ar), 7.23 – 7.17 (m, 3H, Ar), 6.10 (td, J = 56.6, 6.2 Hz, 1H, CF_2H), 5.55 (hex, J = 7.0 Hz, 1H, H_4), 5.40 (m, 1H, H_6), 2.67 (m, 2H,H_1), 2.13 (qd, J = 7.2, 2.0 Hz, 2H, H_3), 1.78 (p, J = 7.5 Hz, 2H, H_2).

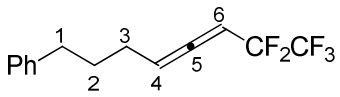
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 206.2 (t, J = 12.2 Hz, C_5), 141.9 (Ar), 128.6 (Ar), 128.5 (Ar), 126.0 (Ar), 114.6 (t, J = 237.1 Hz, CF_2H), 96.0 Hz (t, J = 1.8 Hz, C_4), 88.7 (t, J = 28.8 Hz, C_6), 35.3 (C_2), 30.5 (C_1), 27.4 (t, J = 2.8 Hz, C_3).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) : -108.0 (d, J = 56.6Hz)

IR (cm^{-1}, CCl_4) : 3066, 3029, 2930, 2859, 1973, 1604, 1497, 1439, 1354, 1133, 1102, 1060, 1031, 871

MS (HRMS EI) : Calcd for $C_{13}H_{14}F_2$: 208.1064 Found : 208.1053

(7,7,8,8,8-pentafluoroocta-4,5-dienyl)benzene (II.2u)



$C_{14}H_{13}F_5$
MW = 276.2 g.mol^{-1}

Procedure : Following procedure D, using **II.1u** (0.20 mmol, 76.5 mg, reaction time : 2 h).

Purification : Flash chromatography : PE

Yield : 80% (44.3 mg) of a colorless oil (crude NMR yield 85 %).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.35 – 7.29 (m, 2H, Ar), 7.25 – 7.13 (m, 3H, Ar), 5.78 – 7.70 (m, 1H, H_4), 5.45 – 5.35 (m, 1H, H_6), 2.69 (t, J = 7.7 Hz, 2H, H_1), 2.18 (tdd, J = 6.8, 6.4, 3.2 Hz, 2H, H_3), 1.89 – 1.77 (tt, J = 7.6, 6.4 Hz, 2H, H_2).

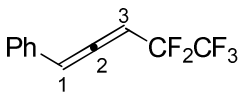
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 206.7 (t, J = 8.0 Hz, C_5), 141.8 (Ar), 128.6 (Ar), 128.6 (Ar), 126.1 (Ar), 119.1 (qt, J = 285.5, 38.3 Hz, CF_3), 111.8 (tq, J = 250.9, 38.1 Hz, CF_2), 98.2 (C_4), 84.2 (t, J = 28.5 Hz, C_6), 35.2 (C_2), 30.2 (C_1), 27.1 (t, J = 2.0 Hz, C_3).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) : -86.2 (d, J = 6.9 Hz), -112.6 (s)

IR (cm^{-1}, CCl_4) : 3087, 3066, 3030, 2940, 2862, 2251, 1976, 1603, 1497, 1454,1422, 1340, 1207, 1174, 1108, 1030

MS (HRMS EI) : Calcd for $C_{14}H_{13}F_5$: 276.0937 Found : 276.0937

(4,4,5,5,5-pentafluoropenta-1,2-dienyl)benzene (II.2v)



$C_{11}H_7F_5$
MW = 234.2 g.mol^{-1}

Procedure : Following procedure D, using **II.1v** (0.18 mmol, 61.2 mg, reaction time : 24 h).

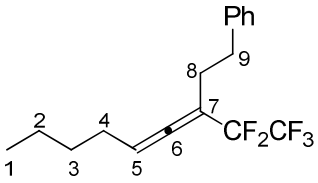
Purification : Flash chromatography : pentane.

Yield : yellow oil (crude NMR yield 85 %, the product could not be isolated because of its low boiling point. Some pentane remains present on the spectra)

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.40 – 7.35 (m, 2H, Ar), 7.34 – 7.29 (m, 3H, Ar), 6.72 – 6.67 (m, 1H, H_1), 6.87 – 6.80 (m, 1 H, H_3).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	208.5 (t, *J* = 8.0 Hz, C_2), 130.7 (t, *J* = 1.9 Hz, Ar), 129.1 (Ar), 128.8 (Ar), 127.7 (Ar), 119.1 (qt, *J* = 284.1, 37.8 Hz, CF_3), 111.4 (tq, *J* = 232.2, 38.6 Hz, CF_2), 101.4 (t, *J* = 1.4 Hz, C_1), 87.9 (t, *J* = 28.8 Hz, C_3).
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-86.1 (s), -112.5 (m)
IR (cm^{-1}, CCl_4)	3068, 3036, 2959, 2928, 2251, 1966, 1497, 1461, 1411, 1340, 1316, 1297, 1265, 1209, 1172, 1116, 1019
MS (HRMS EI)	Calcd for $C_{11}H_7F_5$: 234.0468 Found : 234.0467

(3-(perfluoroethyl)nona-3,4-dienyl)benzene (II.2w)



$C_{17}H_{19}F_5$
MW = 318.3 g.mol^{-1}

Procedure :	Following procedure D, using **II.1w** (0.20 mmol, 84.9 mg, reaction time : 23 h).
Purification :	Flash chromatography : PE
Yield :	80% (51.6 mg) of a colorless oil (crude NMR yield 88 %)
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.33 – 7.28 (m, 2H, Ar), 7.25 – 7.18 (m, 3H, Ar), 5.65 – 5.67 (m, 1H, H_5), 2.85 – 2.72 (m, 2H, H_9), 2.53 – 2.39 (m, 2H, H_8), 2.08 – 1.99 (m, 2H, H_4), 1.39 – 1.32 (m, 4H, $H_{2,3}$), 0.92 (t, *J* = 6.9 Hz, 3H, H_1).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	204.1 (t, *J* = 7.4 Hz, C_6), 141.0 (Ar), 128.5 (Ar), 128.5 (Ar), 126.3 (Ar), 119.4 (qt, *J* = 286.6, 38.9 Hz, CF_3), 113.4 (tq, *J* = 253.2, 37.3 Hz, CF_2), 99.2 (C_5), 96.5 (t, *J* = 26.3 Hz, C_7), 34.0 (C_8), 30.9 (C_9), 27.9 (C_4), 27.9 (C_3), 22.3 (C_2), 13.9 (C_1).
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-84.4 (s), -113.2 (s)
IR (cm^{-1}, CCl_4)	3088, 3066, 3030, 2960, 2930, 2874, 2861, 2252, 1971, 1604, 1497, 1465, 1380, 1364, 1334, 1204, 1129, 1087, 1030
MS (HRMS EI)	Calcd for $C_{17}H_{19}F_5$: 318.1407 Found : 318.1406

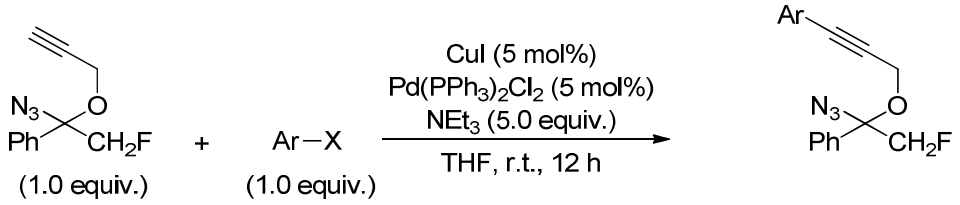
Chapitre 3 : Gold-catalyzed synthesis of *2H*-1,3-oxazines

3.1 Preparation of the azide-yne substrates

Procedure E :

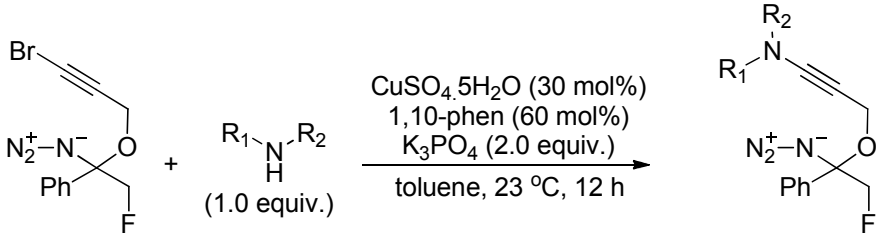
To a suspension of Selectfluor® (1.5 equiv) in MeCN (0.2 M) at 0 °C was added a solution of vinyl azide (1.5 equiv) and propargyl alcohol (1.0 equiv) in MeCN (0.2 M). After the reaction mixture was stirred at 0 °C for 1 h, and then at room temperature for 11 h, the reaction was quenched with H_2O. The organic materials were extracted with EtOAc (x2). The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting crude mixture was then purified by flash column chromatography to give the desired product.

Procedure F :



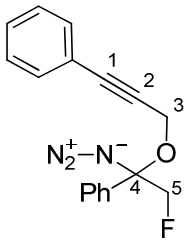
To a solution of the aromatic iodide (1.0 equiv) and (1-azido-2-fluoro-1-(prop-2-yn-1-yloxy)ethyl)benzene[3] in THF (0.5 M) were added copper iodide (5 mol%), bis(triphenylphosphine)palladium(II) chloride (5 mol%), and Et_3N (5.0 equiv). Upon completion of the reaction (monitored by TLC), the reaction was quenched with a saturated solution of NH_4Cl. The organic materials were extracted with Et_2O (x3), and the combined extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude residue was then purified by flash chromatography to give the product.

Procedure G :



To a solution of (1-azido-1-((3-bromoprop-2-yn-1-yl)oxy)-2-fluoroethyl)benzene (1.0 equiv.) and the amine (1.50 equiv.) in toluene (0.3 M) were successively added $CuSO_4 \cdot 5H_2O$ (30 mol%), 1,10-phenanthroline (60 mol%) and K_3PO_4 (2.0 equiv.). The mixture was stirred overnight at room temperature, filtered through celite and concentrated. The resulting crude residue was then purified by flash chromatography to give the product.

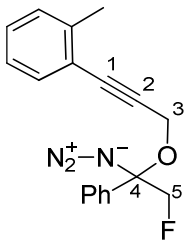
(1-azido-2-fluoro-1-((3-phenylprop-2-yn-1-yl)oxy)ethyl)benzene (III.1a)



$C_{17}H_{14}FN_3O$
MW = 295.1 g.mol^{-1}

Procedure :	Following procedure E using 3-phenylprop-2-yn-1-ol (660.8 mg, 5.00 mmol).
Purification :	Flash chromatography : PE / EtOAc 50:1
Yield :	68% (1.0 g, 3.41 mmol) of a yellow oil including approximately 8% of difluoromethyl derivative based on ^{1}H NMR.
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.56 – 7.53 (m, 2H, Ar), 7.46 – 7.40 (m, 5H, Ar), 7.32 – 7.27 (m, 3H, Ar), 4.70 (dd, *J* = 47.2, 10.0 Hz, 1H, H_5), 4.53 (dd, *J* = 47.2, 10.0 Hz, 1H, H_5), 4.41 (d, *J* = 15.6 Hz, 1H, H_3), 4.34 (d, *J* = 15.6 Hz, 1H, H_3).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	134.6 (d, *J* = 1.1 Hz, Ar), 131.8 (Ar), 129.6 (Ar), 128.8 (Ar), 128.5 (Ar), 128.2 (Ar), 127.0 (Ar), 122.5 (Ar), 94.9 (d, *J* =18.3 Hz, C_4), 86.8 (d, *J* = 185.6 Hz, C_5), 86.3 (C_2), 84.4 (C_1), 53.4 (C_3).
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-217.5 (t, *J* = 47.0 Hz)
IR (cm^{-1}, CCl_4)	3353, 2989, 2120 (N_3), 1898, 1819, 1686, 1612, 1493
MS (HRMS EI)	Calcd for $C_{17}H_{14}FO$ [M–N_3] 253.1029. Found : 253.1026

1-(3-(1-azido-2-fluoro-1-phenylethoxy)prop-1-ynyl)-2-methylbenzene (III.1b)



$C_{18}H_{16}FN_3O$
MW = 309.3 g.mol^{-1}

Procedure : Following procedure E using 3-o-tolylprop-2-yn-1-ol (1.00 mmol, 145 mg).

Purification : Flash chromatography : PE / EtOAc 50:1

Yield : 55% (170.2 mg, 0.55 mmol) of a colorless oil including approximately 3% of difluoromethyl derivative based on ^{1}H NMR.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.59 – 7.54 (m, 2H, Ar), 7.47 – 7.39 (m, 4H, Ar), 7.21 (td, *J* = 6.8, 1.2 Hz, 1H, Ar), 7.20 (m, 1H, Ar), 7.13 (td, *J* = 7.2, 1.8 Hz, 1H, Ar), 4.63 (dd, *J* = 47.2, 9.8 Hz, 1H, H_5), 4.47 (dd, *J* = 46.9, 9.8 Hz, 1H, H_5), 4.40 (d, *J* = 15.6 Hz, 1H, H_3), 4.31 (d, *J* = 15.6 Hz, 1H, H_3), 2.43 (s, 3H, Me).

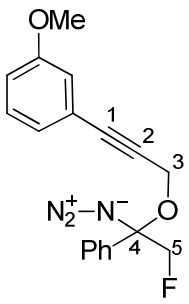
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 140.6 (Ar), 134.8 (d, *J* = 2.1 Hz, Ar), 132.4 (Ar), 129.8 (Ar), 129.5 (Ar), 128.9 (Ar), 128.7 (Ar), 127.2 (Ar), 125.6 (Ar), 122.3 (Ar), 95.1 (d, *J* = 18.4 Hz,C_4), 88.2 (C_2), 87.0 (d, *J* = 186.7 Hz, C_5), 85.4 (C_1), 53.7 (C_3), 20.8 (Me).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) -217.5 (t, *J* = 47.2 Hz)

IR (cm^{-1}, CCl_4) 3031, 2989, 2453, 2226 (C≡C), 2121 (N_3), 1486, 1449, 1371, 1046

MS (HRMS EI) Calcd for $C_{17}H_{14}N_3O$ [M-CH_2F] 276.1137. Found : 276.1138

1-(3-(1-azido-2-fluoro-1-phenylethoxy)prop-1-ynyl)-3-methoxybenzene (III.1c)



$C_{18}H_{16}FN_3O_2$
MW = 325.3 g.mol^{-1}

Procedure : Following B using (1-azido-2-fluoro-1-(prop-2-yn-1-yloxy)ethyl)benzene (110 mg, 0.502 mmol) and 3-iodoanisole (80.0 *µ*L, 0.672 mmol).

Purification : Flash chromatography : PE / EtOAc 50:1

Yield : 55% (89.4 mg, 0.274 mmol) of a colorless oil including approximately 5% of difluoromethyl derivative based on ^{1}H NMR.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.59–7.53 (m, 2H, Ar), 7.47–7.39 (m, 3H, Ar), 7.22 (t, *J* = 7.9 Hz, 1H, Ar), 7.06 (dt, *J* = 7.6, 1.2 Hz, 1H, Ar), 7.00 (dd, *J* = 2.7, 1.4 Hz, 1H, Ar), 6.89 (ddd, *J* = 8.4, 2.6, 1.0 Hz, 1H, Ar), 4.71 (dd, *J* = 47.2, 9.9 Hz, 1H, H_5), 4.54 (dd, *J* = 46.9, 9.9 Hz, 1H, H_5), 4.42 (d, *J* = 15.6 Hz, 1H, H_3), 4.35 (d, *J* = 15.6 Hz, 1H, H_3), 3.80 (s, 3H, OMe).

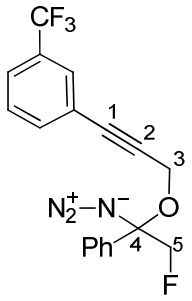
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 159.4 (Ar), 134.7 (d, *J* = 2.0 Hz, Ar), 129.8 (Ar), 129.5 (Ar), 128.9 (Ar), 127.2 (Ar), 124.5 (Ar), 123.6 (Ar), 116.8 (Ar), 115.3 (Ar), 95.1 (d, *J* = 18.6 Hz, C_4), 86.9 (d, *J* = 186.7 Hz, C_5), 86.4 (C_2), 84.4 (C_1), 55.4 (OMe), 53.5 (C_3).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) -217.5 (t, *J* = 47.6 Hz)

IR (cm^{-1}, CCl_4) 2960, 2259 (C≡C), 2123 (N_3), 1711, 1598, 1576, 1490, 1450, 1291, 1210

MS (HRMS EI) Calcd for $C_{18}H_{16}FNO$ [M-N_2] 297.1165. Found : 297.1164

1-(3-(1-azido-2-fluoro-1-phenylethoxy)prop-1-ynyl)-3-(trifluoromethyl)benzene



$C_{18}H_{13}F_4N_3O$
MW = 363.3 g.mol^{-1}

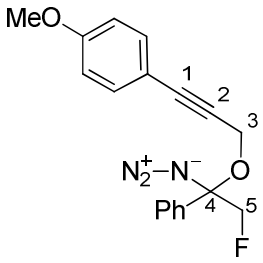
Procedure : Following procedure F , using (1-azido-2-fluoro-1-(prop-2-yn-1-yloxy)ethyl)benzene (0.50 mmol, 110 mg) and 3- bromobenzotrilfuoride (0.50 mmol, 0.07 mL) in NEt_3 at 80 °C.

Purification : Flash chromatography : PE / EtOAc 100:1

Yield : 25% (45.3 mg, 0.12 mmol) of a yellowish oil including approximately 7% of difluoromethyl derivative based on ^{1}H NMR

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.70 (t, *J* = 1.8 Hz, 1H, Ar), 7.62 (d, *J* = 7.9 Hz, 1H, Ar), 7.59 – 7.52 (m, 3H, Ar), 7.47 – 7.40 (m, 4H, Ar), 4.71 (dd, *J* = 47.2, 9.9 Hz, 1H, H_5), 4.55 (dd, *J* = 46.9, 9.9 Hz, 1H, H_5), 4.42 (d, *J* = 15.8 Hz, 1H, H_3), 4.36 (d, *J* = 15.8 Hz, 1H, H_3).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	135.0 (d, *J* = 1.5 Hz, Ar), 134.6 (d, *J* = 2.0 Hz, Ar), 131.1 (q, *J* = 32.7 Hz, Ar), 129.9 (Ar), 129.0 (Ar), 129.0 (Ar), 128.8 (q, *J* = 3.8 Hz, Ar), 127.2 (Ar), 125.3 (q, *J* = 3.7 Hz, Ar), 123.6 (Ar), 122.4 (q, *J* = 272.4 Hz, CF_3), 95.2 (d, *J* = 18.4 Hz, C_4), 87.0 (d, *J* = 187.0 Hz, C_5), 86.3 (C_1), 85.0 (C_2), 53.3 (C_3).
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-58.2 (s), -217.4 (t, *J* = 46.8 Hz)
IR (cm^{-1}, CCl_4)	2232 (C≡C), 2124 (N_3), 1638, 1606, 1235
MS (HRMS EI)	Calcd for $C_{18}H_{13}F_4NO$ [M-N_2] 335.0933. Found : 335.0924

1-(3-(1-azido-2-fluoro-1-phenylethoxy)prop-1-ynyl)-4-methoxybenzene (III.1e)



$C_{18}H_{16}FN_3O$
MW = 325.3 g.mol^{-1}

Procedure : Following procedure F , using (1-azido-2-fluoro-1-(prop-2-yn-1-yloxy)ethyl)benzene (110 mg, 0.502 mmol) and 4-iodoanisole (117 mg, 0.500 mmol).

Purification : Flash chromatography : PE / EtOAc 50:1

Yield : 58% (94.0 mg, 0.289 mmol) of a colorless oil including approximately 7% of difluoromethyl derivative based on ^{1}H NMR

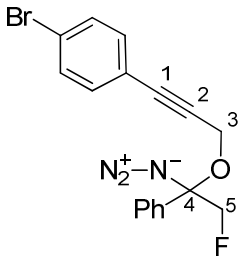
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.59–7.53 (m, 2H, Ar), 7.46–7.41 (m, 3H, Ar), 7.40 (d, *J* = 8.8 Hz, 2H, Ar), 6.84 (d, *J* = 8.8 Hz, 2H, Ar), 4.71 (dd, *J* = 47.3, 9.8 Hz, 1H, H_5), 4.54 (dd, *J* = 46.9, 9.8 Hz, 1H, H_5), 4.41 (d, *J* = 15.5 Hz, 1H, H_3), 4.33 (d, *J* = 15.5 Hz, 1H, H_3), 3.81 (s, 3H, OMe).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	159.9 (Ar), 134.8 (d, *J* = 2.0 Hz, Ar), 133.5 (Ar), 129.7 (Ar), 128.9 (Ar), 127.2 (Ar), 114.7 (Ar), 114.0 (Ar), 95.1 (d, *J* = 18.5 Hz, C_4), 86.9 (d, *J* = 186.5 Hz, C_5), 86.5 (C_2), 83.1 (C_1), 55.4 (OMe), 53.6 (C_3).
^{19}F NMR (δ, ppm)	-217.5 (t, *J* = 46.8 Hz)

(282 MHz, $CDCl_3$)

IR (cm^{-1}, CCl_4) 2958, 2840, 2258 (C≡C), 2123 (N_3), 1607, 1510, 1443, 1366, 1292

MS (HRMS EI) Calcd for $C_{18}H_{16}FNO_2$ [M-N_2] 297.1165. Found : 297.1172

1-(3-(1-azido-2-fluoro-1-phenylethoxy)prop-1-ynyl)-4-bromobenzene (III.1f)



$C_{17}H_{13}BrFN_3O$
MW = 374.2 g.mol^{-1}

Procedure : Following procedure F, using (1-azido-2-fluoro-1-(prop-2-yn-1-yloxy)ethyl)benzene (219 mg, 1.00 mmol) and 1-bromo-4-iodobenzene (283 mg, 1.00 mmol).

Purification : Flash chromatography : PE / EtOAc 50:1

Yield : 49% (182.01 mg, 0.486 mmol) of a colorless oil including approximately 8% of difluoromethyl derivative based on ^{1}H NMR

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.54 (m, 2H, Ar), 7.44 (d, *J* = 8.6 Hz, 2H, Ar), 7.42 (m, 3H, Ar), 7.31 (d, *J* = 8.5 Hz, 2H, Ar), 4.70 (dd, *J* = 47.2, 9.9 Hz, 1H, H_5), 4.53 (dd, *J* = 46.9, 9.9 Hz, 1H, H_5), 4.38 (d, *J* = 15.7 Hz, 1H, H_3), 4.32 (d, *J* = 15.7 Hz, 1H, H_3).

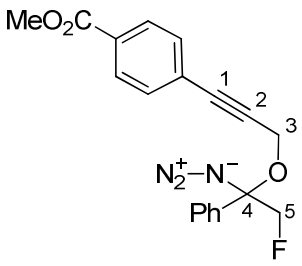
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 134.5 (Ar), 133.4 (Ar), 131.7 (Ar), 129.9 (Ar), 129.0 (Ar), 127.1 (Ar), 123.0 (Ar), 121.5 (Ar), 95.1 (d, *J* = 18.3 Hz, C_4), 87.1 (d, *J* = 187.0 Hz, C_5), 85.7 (C_2), 85.4 (C_1), 53.4 (C_3).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) -217.4 (t, *J* = 47.0 Hz)

IR (cm^{-1}, CCl_4) 2259 (C≡C), 2123 (N_3), 1487, 1247

MS (HRMS ESI) Calcd for $C_{17}H_{14}BrFNO$ [M-N_2+H] 346.0243. Found : 346.0237

methyl 4-(3-(1-azido-2-fluoro-1-phenylethoxy)prop-1-ynyl)benzoate (III.1g)



$C_{19}H_{16}FN_3O_3$
MW = 353.3 g.mol^{-1}

Procedure : Following procedure F, using (1-azido-2-fluoro-1-(prop-2-yn-1-yloxy)ethyl)benzene (219 mg, 1.00 mmol) and methyl 4- iodobenzoate (262 mg, 1.00 mmol).

Purification : Flash chromatography : PE / EtOAc 20:1

Yield : 65% (231.2 mg, 0.654 mmol) of a white solid including approximately 7% of difluoromethyl derivative based on ^{1}H NMR

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.59–7.54 (m, 2H, Ar), 7.47–7.39 (m, 4H, Ar), 7.21 (td, *J* = 6.8, 1.2 Hz, 1H, Ar), 7.20 (m, 1H, Ar), 7.13 (td, *J* = 7.2, 1.8 Hz, 1H, Ar), 4.63 (dd, *J* = 47.2, 9.8 Hz, 1H, H_5), 4.47 (dd, *J* = 46.9, 9.8 Hz, 1H, H_5), 4.40 (d, *J* = 15.6 Hz, 1H, H_3), 4.31 (d, *J* = 15.6 Hz, 1H, H_3), 2.43 (s, 3H, CO_2Me)

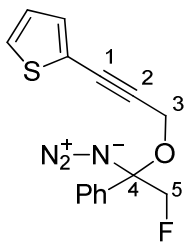
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 166.6 (CO_2Me), 134.5 (Ar), 131.9 (Ar), 129.94 (Ar), 129.89 (Ar), 129.6 (Ar), 129.0 (Ar), 127.2 (Ar), 127.1 (Ar), 95.1 (d, *J* = 18.4 Hz, C_4), 88.0 (C_1), 87.3 (d, *J* = 186.7 Hz, C_5), 85.7 (C_2), 53.4 (C_3), 52.4 (CO_2Me)

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) -217.5 (t, *J* = 47.2 Hz)

IR (cm^{-1}, CCl_4) 3031, 2989, 2453, 2226 (C≡C), 2121 (N_3), 1486, 1449, 1371, 1046

MS (HRMS ESI) Calcd for $C_{19}H_{17}FN_3O_3$ [M+H] 354.1254. Found : 354.1259

2-(3-(1-azido-2-fluoro-1-phenylethoxy)prop-1-ynyl)thiophene (III.1i)



$C_{15}H_{12}FN_3OS$
MW = 301.3 g.mol^{-1}

Procedure : Following procedure F, using (1-azido-2-fluoro-1-(prop-2-yn-1-yloxy)ethyl)benzene (219 mg, 1.00 mmol) and 2-iodothiophene (0.110 mL, 1.00 mmol).

Purification : Flash chromatography : PE / EtOAc 50:1

Yield : 51% (154.3 mg, 0.511 mmol) of a yellow oil including approximately 3% of difluoromethyl derivative based on ^{1}H NMR

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.58–7.53 (m, 2H, Ar), 7.47–7.39 (m, 3H, Ar), 7.26–7.23 (m, 2H, Ar), 6.97 (dd, *J* = 5.1, 3.6 Hz, 1H, Ar), 4.70 (dd, *J* = 47.2, 9.9 Hz, 1H, H_5), 4.53 (dd, *J* = 46.9, 9.9 Hz, 1H, H_5), 4.43 (d, *J* = 15.8 Hz, 1H, H_3), 4.35 (d, *J* = 15.8 Hz, 1H, H_3)

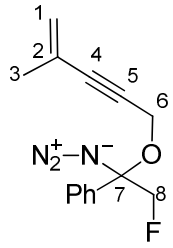
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 134.5 (Ar), 132.8 (Ar), 129.8 (Ar), 128.9 (Ar), 127.6 (Ar), 127.1 (Ar), 127.0 (Ar), 122.4 (Ar), 95.0 (d, *J* = 18.3 Hz, C_4), 88.5 (C_2), 86.9 (d, *J* = 187.3 Hz, C_5), 79.8 (C_1), 53.4 (C_3).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) -217.5 (t, *J* = 46.8 Hz)

IR (cm^{-1}, CCl_4) 2957, 2259 (C≡C), 2122 (N_3), 1450, 1372, 1244

MS (HRMS EI) Calcd for $C_{15}H_{12}FNOS$ [M-N_2] 273.0624. Found : 273.0630

(1-azido-2-fluoro-1-((4-methylpent-4-en-2-yn-1-yl)oxy)ethyl)benzene (III.1k)



$C_{14}H_{14}FN_3O$
MW = 259.3 g.mol^{-1}

Procedure : Following procedure E, using 4-methylpent-4-en-2-yn-1-ol (618 mg, 6.43 mmol)

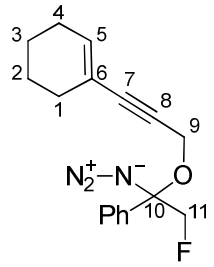
Purification : Flash chromatography : PE / EtOAc 50:1

Yield : 33% (546.2 mg, 2.10 mmol) of a colorless oil including approximately 8% of difluoromethyl derivative based on ^{1}H NMR

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.52 (dd, *J* = 7.8, 2.1 Hz, 2H, Ar), 7.45–7.39 (m, 3H, Ar), 5.33 (d, *J* = 1.9 Hz, 1H, H_1), 5.25 (p, *J* = 1.5 Hz, 1H, H_1), 4.67 (dd, *J* = 47.3, 9.8 Hz, 1H, H_8), 4.51 (dd, *J* = 46.9, 9.8 Hz, 1H, H_8), 4.30 (d, *J* = 15.7 Hz, 1H, H_6), 4.23 (d, *J* = 15.7 Hz, 1H, H_6), 1.89 (t, *J* = 1.3 Hz, 3H, H_3)

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	134.8 (Ar), 129.7 (Ar), 128.9 (Ar), 127.2 (Ar), 126.3 (C_2), 122.8 (C_1), 94.9 (d, J = 18.2 Hz, C_7), 87.7 (C_4), 86.9 (d, J = 186.8 Hz, C_8), 83.5 (C_5), 53.4 (C_6), 23.4 (C_3).
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-217.5 (t, J = 47.0 Hz)
IR (cm^{-1}, CCl_4)	3353, 2989, 2120 (N_3), 1898, 1819, 1686, 1612, 1493
MS (HRMS EI)	Calcd for $C_{14}H_{14}FN_3O$ [M] 259.1121. Found : 259.1115

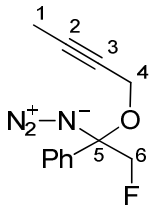
(1-azido-1-(3-cyclohexenylprop-2-ynyloxy)-2-fluoroethyl)benzene (III.1l)



$C_{17}H_{18}FN_3O$
MW = 299.3 g.mol^{-1}

Procedure :	Following procedure E, using 3-cyclohexenylprop-2-yn-1-ol (408 mg, 2.93 mmol)
Purification :	Flash chromatography : PE / EtOAc 50:1
Yield :	60% (540 mg, 1.80 mmol) of a colorless oil including approximately 4% of difluoromethyl derivative based on ^{1}H NMR.
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.52 (m, 2H, Ar), 7.41 (m, 3H, Ar), 6.14 (m, 1H, H_5), 4.67 (dd, J = 47.3, 9.8 Hz, 1H, H_{11}), 4.50 (dd, J = 46.9, 9.8 Hz, 1H, H_{11}), 4.30 (d, J = 15.4 Hz, 1H, H_9), 4.22 (d, J = 15.4 Hz, 1H, H_9), 2.10 (m, 4H, $H_{1,4}$), 1.60 (m, 4H, $H_{2,3}$).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	136.0 (C_5), 134.8 (Ar), 129.7 (Ar), 128.8 (Ar), 127.1 (Ar), 120.1 (C_6), 94.9 (d, J = 18.4 Hz, C_{10}), 88.3 (C_7), 86.9 (d, J = 186.4 Hz, C_{11}), 81.6 (C_8), 53.5 (C_9), 29.1 (C_1), 25.7 (C_4), 22.3 ($C_{2,3}$), 21.5 ($C_{2,3}$).
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-217.6 (t, J = 47.0 Hz)
IR (cm^{-1}, CCl_4)	2935, 2258 (C≡C), 2122 (N_3), 1450, 1280, 1247
MS (HRMS EI)	Calcd for $C_{17}H_{18}FNO$ [M-N_2] 271.1372. Found : 271.1376

(1-azido-1-(but-2-yn-1-yloxy)-2-fluoroethyl)benzene (III.1m)



$C_{12}H_{12}FN_3O$
MW = 223.2 g.mol^{-1}

Procedure : Following procedure E, using but-2-yn-1-ol (3.0 mmol, 408 mg)

Purification : Flash chromatography : PE / EtOAc 100:1

Yield : 51% (119 mg, 1.52 mmol) of a colorless oil including approximately 3% of difluoromethyl derivative based on ^{1}H NMR.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.50 (m, 2H, Ar), 7.40 (m, 3H, Ar), 4.66 (dd, *J* = 47.3, 9.8 Hz, 1H, H_6), 4.49 (dd, *J* = 46.9, 9.8 Hz, 1H, H_6), 4.16 (dq, *J* = 14.9, 2.4 Hz, 1H, H_4), 4.05 (dq, *J* = 14.9, 2.4 Hz, 1H, H_4), 1.87 (t, *J* = 2.4 Hz, 3H, Me).

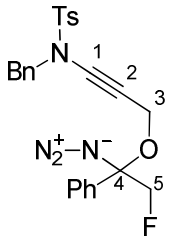
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 134.8 (Ar), 129.7(Ar), 128.9 (Ar), 127.1 (Ar), 94.8 (d, *J* = 18.5 Hz), 87.0 (d, *J* = 186.6 Hz), 83.1 (C_3), 74.5 (C_2), 53.3 (C_4), 3.9 (C_1).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) : -217.6 (t, *J* = 47.2 Hz)

IR (cm^{-1}, CCl_4) : 2259 (C≡C), 2123 (N_3), 1450, 1245

MS (HRMS EI) : Calcd for $C_{12}H_{12}FO$ [M-N_3] 191.0872. Found : 191.0876

N-(3-(1-azido-2-fluoro-1-phenylethoxy)prop-1-yn-1-yl)-N-benzyl-4-methylbenzenesulfonamide (III.1o)



$C_{25}H_{23}FN_4O_3S$
MW = 478.5 g.mol^{-1}

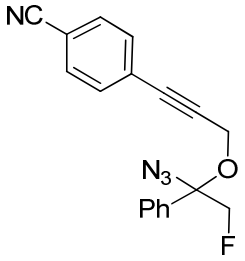
Procedure : Following procedure G, using (1-azido-1-((3-bromoprop-2-yn-1-yl)oxy)-2-fluoroethyl)benzene (447 mg, 1.50 mmol) and *N*-benzyl-4-methylbenzenesulfonamide (392 mg, 1.50 mmol).

Purification : Flash chromatography : PE / EtOAc 20:1

Yield :	42% (300 mg, 0.627 mmol) of a colorless oil including approximately 3% of difluoromethyl derivative based on ^{1}H NMR.
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.77 (d, *J* = 8.2 Hz, 2H, Ar), 7.44 (m, 2H, Ar), 7.40 (m, 3H, Ar), 7.30 (m, 7H, Ar), 4.59 (dd, *J* = 47.3, 9.8 Hz, 1H, H_5), 4.51 (s, 2H, CH_2 of Bn), 4.42 (dd, *J* = 36.1, 11.0 Hz, 1H, H_5), 4.25 (d, *J* = 16.0 Hz, 1H, H_3), 4.18 (d, *J* = 16.1 Hz, 1H, H_3), 2.45 (s, 3H, Me of Ts)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	144.8 (Ar), 134.8 (Ar), 134.6 (Ar), 134.5 (Ar), 129.8 (Ar), 129.7 (Ar), 128.84 (Ar), 128.79 (Ar), 128.6 (Ar), 128.4 (Ar), 127.8 (Ar), 127.0 (Ar), 94.83 (d, *J* = 18.3 Hz, C_4), 86.92 (d, *J* = 186.6 Hz, C_5), 80.1 (C_1), 67.7 (C_2), 55.5 (CH_2 of Bn), 53.2 (C_3), 21.7 (Me of Ts).
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-217.1 (t, *J* = 47.0 Hz)
IR (cm^{-1}, CCl_4)	3068, 3035, 2927, 2264, 2248 (C≡C), 2121 (N_3), 1598, 1496, 1450, 1368
MS (HRMS EI)	Calcd for $C_{25}H_{23}FN_2O_3S$ [M-N_2] 450.1413. Found : 450.1416

Unreactive substrates

4-(3-(1-azido-2-fluoro-1-phenylethoxy)prop-1-yn-1-yl)benzonitrile (III.1u)

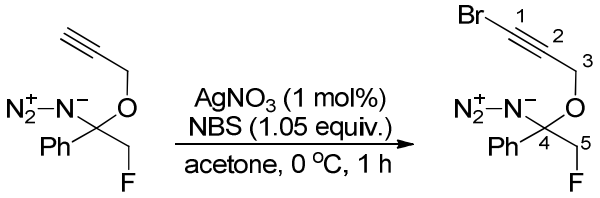


$C_{18}H_{13}FN_4O$
MW = 410.4 g.mol^{-1}

Procedure :	Following B using (1-azido-2-fluoro-1-(prop-2-yn-1-yloxy)ethyl)benzene (110 mg, 0.502 mmol) and 4-cyanobromobenzene (91 mg, 0.502 mmol).
Purification :	Flash chromatography : PE / EtOAc 20:1
Yield :	59% (121.4 mg, 0.30 mmol) of a colorless oil including approximately 5% of difluoromethyl derivative based on ^{1}H NMR.
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.63 – 7.58 (m, 2H), 7.55 – 7.50 (m, 4H), 7.46 – 7.41 (m, 3H), 4.70 (dd, *J* = 47.2, 9.9 Hz, 1H), 4.54 (dd, *J* = 46.9, 9.9 Hz, 1H), 4.91 (d, *J* = 16.0 Hz), 4.36 (d, *J* = 16.0 Hz, 1H)

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	134.5 (d, *J* = 2.2 Hz), 132.4, 132.1, 129.9, 129.0, 127.5, 127.1, 118.5, 112.1, 95.2 (d, *J* = 18.1 Hz), 89.2, 87.0 (d, *J* = 187.3 Hz), 84.8, 53.3.
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-217.3 (t, *J* = 47.2 Hz)
IR (cm^{-1}, CCl_4)	3067, 2959, 2926, 2260 (C≡N), 2232 (C≡C), 2124 (N_3), 1638, 1606, 1501, 1450, 1363, 1235
MS (HRMS EI)	Calcd for $C_{18}H_{13}FN_2O$ [M-N_2] 292.1012. Found : 292.1006

(1-azido-1-((3-bromoprop-2-yn-1-yl)oxy)-2-fluoroethyl)benzene (III.1v)



$C_{11}H_9BrFN_3O$
MW = 298.1 g.mol^{-1}

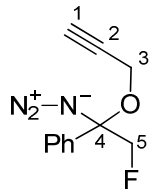
Procedure : To a solution of the (1-azido-2-fluoro-1-(prop-2-yn-1-yloxy)ethyl)benzene (1.10 g, 5.02 mmol) and N-bromosuccinimide (935 mg, 5.25 mmol) in dry acetone (30 mL) was added $AgNO_3$ (8.50 mg, 0.0500 mmol). After completion, the mixture was filtered through celite, concentrated and purified by flash column chromatography.

Purification : Flash chromatography : PE / EtOAc 100:1

Yield : 92% (1.37 g, 4.60 mmol) of a colorless oil including approximately 3% of difluoromethyl derivative based on ^{1}H NMR.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.52–7.47 (m, 2H, Ar), 7.45–7.39 (m, 3H, Ar), 4.67 (dd, *J* = 47.3, 9.9 Hz, 1H, H_5), 4.50 (dd, *J* = 46.9, 9.9 Hz, 1H, H_5), 4.21 (d, *J* = 15.4 Hz, 1H, H_3), 4.13 (d, *J* = 15.4 Hz, 1H, H_3).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	134.5 (d, *J* = 2.1 Hz, Ar), 129.9 (Ar), 129.0 (Ar), 127.1 (Ar), 95.0 (d, *J* = 18.5 Hz, C_4), 86.9 (d, *J* = 187.0 Hz, C_5), 75.6 (C_2), 53.6 (C_3), 46.8 (C_1).
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-217.5 (t, *J* = 46.7 Hz)
IR (cm^{-1}, CCl_4)	2226 (C≡C), 2123 (N_3), 1450, 1247, 1074
MS (HRMS EI)	Calcd for $C_{11}H_{19}BrFO$ [M-N_3] 254.9821. Found : 254.9820

(1-azido-2-fluoro-1-(prop-2-yn-1-yloxy)ethyl)benzene (III.1x)



$C_{11}H_{10}FN_3O$
MW = 219.2 g.mol^{-1}

Procedure : Following procedure E using propargyl alcohol (0.58 mL, 10.0 mmol).

Purification : Flash chromatography : PE / EtOAc 50:1

Yield : 71% (1.56 g, 7.10 mmol) of a yellow oil including approximately 9% of difluoromethyl derivative based on ^{1}H NMR.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.53 – 7.49 (m, 2H, Ar), 7.45 – 7.39 (m, 3H, Ar), 4.67 (dd, *J* = 47.2, 9.9 Hz, 1H, H_5), 4.51 (dd, *J* = 46.9, 9.9 Hz, 1H, H_5), 4.20 (dd, *J* = 15.4, 2.4 Hz, 1H, H_3), 4.11 (dd, *J* = 15.4, 2.5 Hz, 1H, H_3), 2.50 (t, *J* = 2.5 Hz, 1H, H_1).

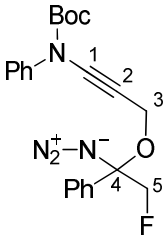
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 134.4, 129.9, 129.3, 127.7, 94.9 (d, *J* = 18.2 Hz, C_4), 87.7 (C_3), 86.9 (d, *J* = 186.8 Hz, C_5), 83.5 (C_1), 53.4 (C_3).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) : -217.5 (t, *J* = 47.0 Hz)

IR (cm^{-1}, CCl_4) : 3353, 2989, 2120 (N_3), 1898, 1819, 1686, 1612, 1493

MS (HRMS EI) : Calcd for $C_{11}H_{10}FO$ [M-N_3] 177.0716. Found : 177.0721

tert-butyl (3-(1-azido-2-fluoro-1-phenylethoxy)prop-1-yn-1-yl)(phenyl)carbamate (III.1y)



$C_{22}H_{23}FN_4O_3$
MW = 410.4 g.mol^{-1}

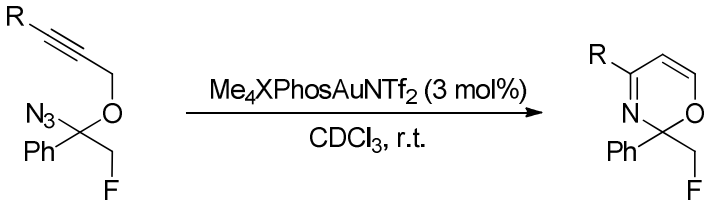
Procedure : Following procedure G, using (1-azido-1-((3-bromoprop-2-yn-1-yl)oxy)-2-fluoroethyl)benzene (298.1 mg, 1.00 mmol) and tert-butyl phenylcarbamate (193.2 mg, 1.00 mmol).

Purification : Flash chromatography : PE / EtOAc 20:1

Overall yield :	35% (141.4 mg, 0.35 mmol) of a colorless oil including approximately 3% of difluoromethyl derivative based on ^{1}H NMR.
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.43 (dd, *J* = 6.5, 3.3 Hz, 2H, Ar), 7.35 (dd, *J* = 10.2, 1.9 Hz, 2H, Ar), 7.30 (dd, *J* = 4.9, 2.6 Hz, 5H, Ar), 7.17 (t, *J* = 7.3 Hz, 1H, Ar), 4.58 (dd, *J* = 47.3, 9.8 Hz, 1H, H_5), 4.41 (dd, *J* = 46.9, 9.8 Hz, 1H, H_5), 4.30 (d, *J* = 15.7 Hz, 1H, H_3), 4.20 (d, *J* = 15.7 Hz, 1H, H_3), 1.46 (s, 9H, Boc).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	153.2, 139.6 (Ar), 134.7 (d, *J* = 1.9 Hz, Ar), 129.7 (Ar), 128.9 (Ar), 128.8 (Ar), 127.1 (Ar), 126.9 (Ar), 125.0 (Ar), 94.9 (d, *J* = 18.4 Hz, C_4), 87.0 (d, *J* = 186.6 Hz, C_5), 83.7 ($\underline{C}(CH_3)$ of Boc), 81.0 (C_1), 65.8 (C_2), 53.4 (C_3), 28.0 ($C(\underline{CH_3})$ of Boc).
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-217.5 (t, *J* = 46.7 Hz)
IR (cm^{-1}, CCl_4)	2231 (C≡C), 2117 (N_3)
MS (HRMS EI)	Calcd for [M-N_2] $C_{22}H_{23}FN_2O_3$ 382.1698 Found : 382.1695

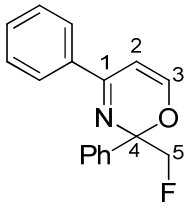
3.2 Preparation of *2H*-1,3-oxazines

Procedure H:



To a solution of substrate 1 in $CHCl_3$ (0.2 M) was added (2-di-*tert*-butylphosphino-3,4,5,6-tetramethyl-2′,4′,6′-triisopropylbiphenyl)gold(I) bis(trifluoromethanesulfonyl)imide (3 mol%). After completion of the reaction, volatile materials were removed in vacuo. The resulting crude product was purified by flash column chromatography to give 2*H*-1,3-oxazine 2.

2-(fluoromethyl)-2,4-diphenyl-2*H*-1,3-oxazine (III.2a)



$C_{17}H_{14}FNO$
MW = 267.3 g.mol^{-1}

Procedure : Following procedure H, using **III.1a** (59.4 mg, 0.201 mmol, reaction time : 20 min).

Purification : Flash chromatography : PE / EtOAc 100:1

Yield : 89% (47.2 mg, 0.179 mmol) of a yellow solid.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.93 (d, *J* = 8.1 Hz, 2H, Ar), 7.71 (d, *J* = 7.6 Hz, 2H, Ar), 7.52–7.45 (m, 3H, Ar), 7.44–7.38 (m, 3H, Ar), 7.11 (s, 1H, H_3), 5.94 (d, *J* = 5.8 Hz, 1H, H_2), 4.78 (d, *J* = 47.4 Hz, 2H).

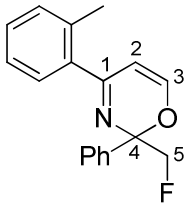
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 160.8 (C_1), 153.1 (C_3), 139.1 (Ar), 136.6 (Ar), 131.0 (Ar), 129.0 (Ar), 128.7 (Ar), 128.2 (Ar), 126.9 (overlapped, 2C, Ar), 99.6 (C_2), 93.0 (C_4), 87.0 (d, *J* = 185.7 Hz, C_5).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) –222.4 (t, *J* = 47.4 Hz)

IR (cm^{-1}, CCl_4) 3067, 1683, 1640 (C=N), 1551, 1449, 1415, 1268, 1231

MS (HRMS EI) Calcd for $C_{17}H_{14}FNO$ [M] 267.1059. Found : 267.1061

2-(fluoromethyl)-2-phenyl-4-o-tolyl-2H-1,3-oxazine (III.2b)



$C_{18}H_{16}FNO$
MW = 281.3 g.mol^{-1}

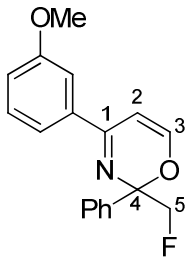
Procedure : Following procedure H, using **III.1b** (32.3 mg, 0.20 mmol, reaction time : 1 h).

Purification : Flash chromatography : PE / EtOAc 100:1

Yield : 51% (28.7 mg, 0.102 mmol) of a colorless oil

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.69 (d, *J* = 2.2 Hz, 1H, Ar), 7.67 (d, *J* = 1.6 Hz, 1H, Ar), 7.44 – 7.38 (m, 3H, Ar), 7.36 (d, *J* = 6.9 Hz, 1H, Ar), 7.29 (d, *J* = 7.4 Hz, 1H, Ar), 7.24 (t, *J* = 7.6 Hz, 2H, Ar), 7.02 (s, 1H, H_3), 5.55 (d, *J* = 5.7 Hz, 1H, H_2), 4.70 (t, *J* = 42.1 Hz, 2H, H_5), 2.42 (s, 3H, Me)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	164.5 (C_1), 152.0 (C_3), 138.9 (Ar), 138.1 (Ar), 135.7 (Ar), 131.1 (Ar), 129.3 (Ar), 129.0 (Ar), 128.2 (Ar), 127.8 (Ar), 126.8 (Ar), 126.1 (Ar), 102.9 (C_2), 92.9 (C_4), 87.1 (d, *J* = 185.5 Hz, C_5), 20.3 (Me).
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-217.5 (t, *J* = 47.4 Hz)
IR (cm^{-1}, CCl_4)	3691, 3405, 3067, 2957, 2260, 2227, 1642 (C=N), 1565, 1492, 1449, 1409, 1300, 1227, 1032
MS (HRMS EI)	Calcd for $C_{18}H_{16}FNO$ [M] 281.1216. Found : 281.1203

2-(fluoromethyl)-4-(3-methoxyphenyl)-2-phenyl-2*H*-1,3-oxazine (III.2c)

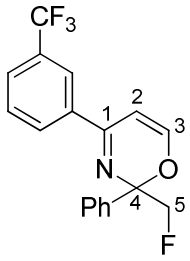


$C_{18}H_{16}FNO_2$
MW = 297.3 g.mol^{-1}

Procedure :	Following procedure H, using **III.1c** (65.2 mg, 0.20 mmol, reaction time : 5 min).
Purification :	Flash chromatography : PE / EtOAc 50:1
Yield :	86% (51.1 mg, 0.172 mmol) of a yellow oil
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.67 (dd, *J* = 7.4, 1.8 Hz, 2H, Ar), 7.49 (t, *J* = 2.2 Hz, 1H, Ar), 7.43 (d, *J* = 8.0 Hz, 1H, Ar), 7.41–7.32 (m, 4H, Ar), 7.08 (s, 1H, Ar), 7.03 (dd, *J* = 8.1, 2.4 Hz, 1H, H_3), 5.90 (d, *J* = 5.9 Hz, 1H, H_2), 4.74 (d, *J* = 46.7 Hz, 2H, H_5), 3.88 (s, 3H, OMe).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	160.6 (C_1), 159.9 (Ar), 153.3 (C_3), 139.2 (Ar), 138.1 (Ar), 129.6 (Ar), 129.0 (Ar), 128.2 (Ar), 126.9 (Ar), 119.4 (Ar), 116.8 (Ar), 112.2 (Ar), 99.9 (C_4), 99.6 (C_2), 86.9 (d, *J* = 185.3 Hz, C_5), 55.5 (OMe).
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-217.6 (t, *J* = 48.6 Hz)
IR (cm^{-1}, CCl_4)	3062, 2991, 2838, 1709, 1599, 1434, 1282

MS (HRMS EI)	Calcd for $C_{18}H_{16}FNO_2$ [M] 297.1165.	Found : 297.1168

2-(fluoromethyl)-2-phenyl-4-(3-(trifluoromethyl)phenyl)-2H-1,3-oxazine (III.2d)



$C_{18}H_{34}F_4NO$
MW = 335.3 g.mol^{-1}

Procedure : Following procedure H, using **III.1c** (36.1 mg, 0.10 mmol, 3 h).

Purification : Flash chromatography : PE / EtOAc 100:1

Yield : 29% (10.2 mg, 0.029 mmol) of a yellow oil

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 8.15 (s, 1H, Ar), 8.07 (d, *J* = 7.9 Hz, 1H, Ar), 7.73 (d, *J* = 7.8 Hz, 1H, Ar), 7.64 (dd, *J* = 7.6, 1.9 Hz, 1H, Ar), 7.57 (t, *J* = 7.8 Hz, 1H, Ar), 7.42 – 7.35 (m, 3H, Ar), 7.12 (d, *J* = 5.9 Hz, 1H, H_3), 5.91 (d, *J* = 5.8 Hz, 1H, H_2), 4.71 (d, *J* = 46.3 Hz, 2H, H_5).

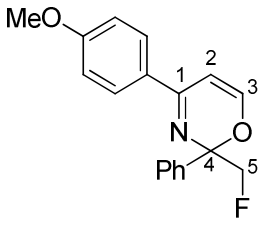
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 159.5 (C_1), 153.9 (C_3), 138.9 (Ar), 137.4 (Ar), 131.2 (q, *J* = 34.3 Hz, Ar), 130.1, 129.2 (Ar), C129.1 (Ar), 128.3 (Ar), 127.5 (q, *J* = 4.3 Hz, Ar), 126.7 (Ar), 124.1 (q, *J* = 270.1Hz, CF_3), 123.8 (q, *J* = 4.2 Hz, Ar), 98.7 (C_2), 95.9 (C_4), 87.1 (d, *J* = 186.2 Hz, C_5).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) : -57.9 (s), -217.4 (t, *J* = 47.3 Hz)

IR (cm^{-1}, CCl_4) : 3066, 2983, 1709, 1639 (C=N), 1437, 1335, 1261, 1170, 1131

MS (HRMS EI)	Calcd for $C_{17}H_{14}F_4NO$ [M] 335.0933.	Found : 335.0942

2-(fluoromethyl)-4-(4-methoxyphenyl)-2-phenyl-2*H*-1,3-oxazine (III.2e)



$C_{18}H_{16}FNO_2$
MW = 297.3 g.mol^{-1}

Procedure : Following procedure H, using **III.1e** (65.2 mg, 0.200 mmol, reaction time : 5 min).

Purification : Flash chromatography : PE / EtOAc 50:1

Yield : 89% (53.1 mg, 0.178 mmol) of a pale yellow oil

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.87 (d, *J* = 8.8 Hz, 2H, Ar), 7.67 (dd, *J* = 7.7, 2.1 Hz, 2H, Ar), 7.42–7.34 (m, 3H, Ar), 7.09 (brs, 1H, H_3), 6.95 (d, *J* = 8.8 Hz, 2H, Ar), 5.90 (d, *J* = 5.9 Hz, 1H, H_2), 4.73 (d, *J* = 46.6 Hz, 2H, H_5), 3.86 (s, 3H, OMe).

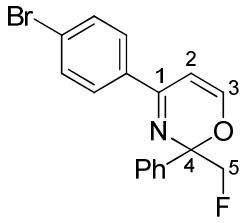
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 162.0 (Ar), 159.9 (C_1), 152.7 (C_3), 139.4 (Ar), 129.2 (Ar), 128.9 (Ar), 128.5 (Ar), 128.1 (Ar), 126.9 (Ar), 114.0 (Ar), 99.7 (C_4), 99.4 (C_2), 86.9 (d, *J* = 184.9 Hz, C_5), 55.5 (OMe).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) : -217.6 (t, *J* = 47.3 Hz)

IR (cm^{-1}, CCl_4) : 3044, 2841, 1710, 1675, 1511, 1283

MS (HRMS EI) : Calcd for $C_{18}H_{16}FNO_2$ [M] 297.1165. Found : 297.1162

4-(4-bromophenyl)-2-(fluoromethyl)-2-phenyl-2*H*-1,3-oxazine (III.2f)



$C_{17}H_{13}BrFNO_2$
MW = 346.2 g.mol^{-1}

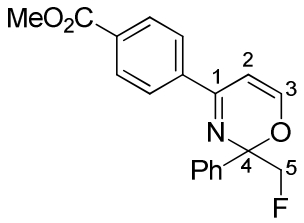
Procedure : Following procedure H, using **III.1f** (75.5 mg, 0.202 mmol, , reaction time : 5 mim).

Purification : Flash chromatography : PE / EtOAc 100:1

Yield : 88% (61.2 mg, 0.177 mmol) of a pale yellow oil

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.77 (d, *J* = 8.6 Hz, 2H, Ar), 7.66–7.62 (m, 2H, Ar), 7.57 (d, *J* = 8.6 Hz, 2H, Ar), 7.42–7.35 (m, 3H, Ar), 7.08 (s, 1H, H_3), 5.86 (d, *J* = 5.9 Hz, 1H, H_2), 4.73 (d, *J* = 46.5 Hz, 2H, H_5).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	159.8 (C_1), 153.3 (C_3), 138.9 (Ar), 135.4 (Ar), 131.8 (Ar) 128.9 (d, *J* = 21.1 Hz, Ar), 128.5 (Ar), 128.2 (Ar), 126.7 (Ar), 125.6 (Ar), 98.9 (C_2), 93.3 (C_4), 87.0 (d, *J* = 185.4 Hz, C_5).
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-217.4 (t, *J* = 47.3 Hz)
IR (cm^{-1}, CCl_4)	1639 (C=N), 1591, 1571, 1418
MS (HRMS EI)	Calcd for $C_{17}H_{13}BrFNO$ [M] 345.0165. Found : 345.0177

methyl 4-(2-(fluoromethyl)-2-phenyl-2*H*-1,3-oxazin-4-yl)benzoate (III.2g)

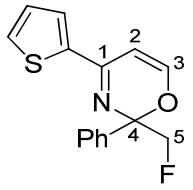


$C_{19}H_{16}FNO_3$
MW = 325.3 g.mol^{-1}

Procedure :	Following procedure H, using **III.1g** (71.2 mg, 0.201 mmol, reaction time : 30 min)
Purification :	Flash chromatography : PE / EtOAc 20:1
Yield :	96% (62.0 mg, 0.191 mmol) of a white solid (mp 110–112 °C)
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	8.11 (d, *J* = 8.5 Hz, 2H, Ar), 7.96 (d, *J* = 8.5 Hz, 2H, Ar), 7.66 (m, 2H, Ar), 7.39 (m, 3H, Ar), 7.10 (brs, 1H, H_3), 5.91 (d, *J* = 5.9 Hz, 1H, H_2), 4.75 (d, *J* = 47.2 Hz, 2H, H_5), 3.94 (s, 3H, $CO_2\underline{Me}$).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	166.6 ($\underline{C}O_2Me$), 160.0 (C_1), 153.4 (C_3), 140.5 (Ar), 138.8 (Ar), 132.1 (Ar), 129.8 (Ar), 129.0 (Ar), 128.2 (Ar), 126.9 (d, *J* = 7.6 Hz, Ar), 126.7 (Ar), 99.2 (C_2), 93.1 (C_4), 87.0 (d, *J* = 185.7 Hz, C_5), 52.4 ($CO_2\underline{Me}$).
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-217.3 (t, *J* = 47.3 Hz)
IR (cm^{-1}, CCl_4)	2955, 2251, 1722 (C=O), 1639 (C=N), 1574, 1438, 1420, 1283
MS	Calcd for $C_{19}H_{16}FNO_3$ [M] 325.1114. Found : 325.1106

(HRMS EI)

2-(fluoromethyl)-2-phenyl-4-(thiophen-2-yl)-2*H*-1,3-oxazine (III.2i)



$C_{15}H_{12}FNOS$
MW = 273.3 g.mol^{-1}

Procedure : Following procedure H, using **III.1i** (60.0 mg, 0.199 mmol, reaction time : 5 min)

Purification : Flash chromatography : PE / EtOAc 50:1

Yield : 90% (49.2 mg, 0.178 mmol) of a yellow oil

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.65 (dd, *J* = 7.6, 2.2 Hz, 2H, Ar), 7.47 (dd, *J* = 5.1, 1.1 Hz, 1H, Ar), 7.43 (dd, *J* = 3.8, 1.1 Hz, 1H, Ar), 7.41–7.33 (m, 3H, Ar), 7.08 (dd, *J* = 5.0, 3.7 Hz, 1H, Ar), 7.05 (s, 1H, H_3) 5.85 (d, *J* = 5.8 Hz, 1H, H_2), 4.68 (t, *J* = 39.3 Hz, 2H, H_5).

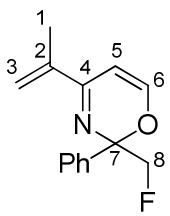
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 155.6 (C_1), 152.9 (C_3), 142.6 (Ar), 139.2 (Ar), 130.1 (Ar), 129.0 (Ar), 128.22 (Ar), 128.17 (Ar), 127.7 (Ar), 126.9 (Ar), 99.4 (C_4), 99.0 (C_2), 86.9 (d, *J* = 185.3 Hz, C_5).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) -217.6 (t, *J* = 47.6 Hz)

IR (cm^{-1}, CCl_4) 3054, 2984, 2957, 1709, 1663, 1552, 1415, 1291, 1230

MS (HRMS EI) Calcd for $C_{15}H_{12}FNOS$ [M] 273.0625. Found : 273.0624

2-(fluoromethyl)-2-phenyl-4-(prop-1-en-2-yl)-2*H*-1,3-oxazine (III.2k)



$C_{14}H_{14}FNO$
MW = 231.3 g.mol^{-1}

Procedure : Following procedure H, using **III.1k** (59.8 mg, 0.200 mmol, , reaction time : 2 h).

Purification : Flash chromatography : PE / EtOAc 100:1

Yield : 68% (32.2 mg, 0.137 mmol) of a colorless oil

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.61 (dd, *J* = 7.3, 1.6 Hz, 2H), 7.42–7.34 (m, 3H), 6.93 (brs, 1H), 5.70 (d, *J* = 6.0 Hz, 1H), 5.55 (s, *J* = 9.0 Hz, 1H), 5.47 (t, *J* = 1.0 Hz, 1H), 4.68 (d, *J* = 42.2 Hz, 2H), 2.08 (t, *J* = 1.0 Hz, 3H)

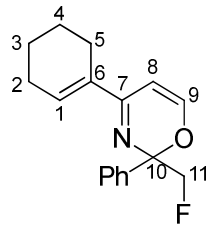
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 161.2, 151.5, 142.5, 139.3, 128.9, 128.1 (overlapped, 2C), 126.9, 119.5, 98.2, 87.0 (d, *J* = 176.7 Hz), 18.88

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) : -217.9 (t, *J* = 44.9 Hz)

IR (cm^{-1}, CCl_4) : 2958, 2259, 1644, 1555, 1423, 1236, 1030

MS (HRMS EI) : Calcd for $C_{14}H_{14}FNO$ [M] 231.1059. Found : 231.1048.

4-cyclohexenyl-2-(fluoromethyl)-2-phenyl-2*H*-1,3-oxazine (III.2l)



$C_{17}H_{18}FNO$
MW = 271.3 $g.mol^{-1}$

Procedure : Following procedure H, using **III.1l** (60.6 mg, 0.202 mmol, reaction time : 1 h) and *t*-BuXPhosAu(NCMe).SbF_6 as the catalyst.

Purification : Flash chromatography : PE / EtOAc 100:1

Yield : 87% (46.9 mg, 0.173 mmol) of a colorless oil

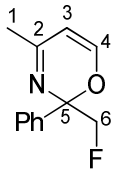
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.62 (d, *J* = 5.9 Hz, 2H, Ar), 7.42–7.32 (m, 3H, Ar), 6.90 (brs, 1H, H_9), 6.41 (t, *J* = 3.9 Hz, 1H, H_1), 5.67 (t, *J* = 10.3 Hz, 1H, H_2), 4.67 (d, *J* = 42.3 Hz, 2H, H_{11}), 2.53–2.37 (m, 2H, H_5), 2.26–2.16 (m, 2H, H_2), 1.77–1.68 (m, 2H, $H_{3,4}$), 1.67–1.60 (m, 2H, $H_{2,4}$).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 161.2 (C_7), 151.3 (C_9), 139.6 (C_6), 136.1 (Ar), 133.3 (Ar), 128.8 (C_1), 128.1 (Ar), 127.0 (Ar), 98.3 (C_8), 92.4 (C_{10}), 87.0 (d, *J* = 185.3 Hz, C_{11}), 26.2 (C_5), 24.5 (C_2), 22.4 ($C_{2,3}$), 22.0 ($C_{2,3}$).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) : -217.1 (t, *J* = 47.1 Hz)

IR (cm^{-1}, CCl_4)	2938, 2862, 1643 (C=N), 1552, 1449, 1425, 1228, 1030
MS (HRMS EI)	Calcd for $C_{17}H_{18}FNO$ [M] 271.1372. Found : 271.1368.

2-(fluoromethyl)-4-methyl-2-phenyl-2H-1,3-oxazine (III.2m)



$C_{12}H_{12}FNO$
MW = 205.2 $g.mol^{-1}$

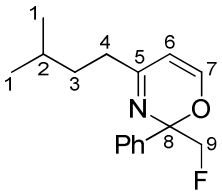
Procedure : Following procedure H, using **III.1m** (47.1 mg, 0.202 mmol, , reaction time : 24 h)

Purification : Flash chromatography : PE / EtOAc 100:1

Yield : 24% (9.9 mg, 0.048 mmol) of a colorless oil

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.62–7.52 (m, 2H, Ar), 7.36 (dd, *J* = 5.0, 2.3 Hz, 3H, Ar), 6.86 (brs, 1H, H_4), 5.31 (d, *J* = 5.6 Hz, 1H, H_3), 4.61 (d, *J* = 49.7 Hz, 2H, H_6), 2.28 (s, 3H, Me).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	166.8 (C_2), 151.8 (C_4), 134.0 (Ar), 128.5 (Ar), 128.1 (Ar), 126.9 (Ar), 102.0 (C_3), 91.2 (C_5), 86.9 (d, *J* = 185.3 Hz, C_6), 35.9 (Me).
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-217.1 (t, *J* = 47.3 Hz)
IR (cm^{-1}, CCl_4)	3064, 2951, 2123, 1710, 1667, 1547, 1092
MS (HRMS EI)	Calcd for $C_{12}H_{12}FNO$ [M] 205.0903. Found : 205.08.97.

2-(fluoromethyl)-4-isopentyl-2-phenyl-2*H*-1,3-oxazine (III.2n)



$C_{16}H_{20}FNO$
MW = 261.3 $g.mol^{-1}$

Procedure : Following procedure H, using **III.1n** (86.5 mg, 0.314 mmol, , reaction time : 3 h).

Purification : Flash chromatography : PE / EtOAc 100:1

Yield : 22% (16.8 mg 0.068 mmol) of a colorless oil

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.60–7.51 (m, 2H, Ar), 7.37 (dd, *J* = 5.0, 2.3 Hz, 3H, Ar), 6.86 (brs, 1H, H_7), 5.30 (d, *J* = 5.6 Hz, 1H, H_6), 4.59 (d, *J* = 49.7 Hz, 2H, H_9), 2.31 (dd, *J* = 9.6, 6.5 Hz, 2H, H_4), 1.59–1.53 (m, 1H, H_2), 1.47 (dt, *J* = 9.7, 6.7 Hz, 2H, H_3), 0.92 (d, *J* = 6.4 Hz, 6H, H_1)

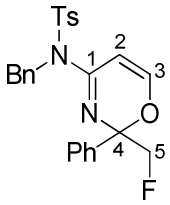
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 166.7 (C_5), 151.8 (C_7), 139.3 (Ar), 128.8 (Ar), 128.1 (Ar), 126.9 (Ar), 101.9 (C_6), 91.2 (C_8), 86.9 (d, *J* = 185.3 Hz, C_9), 36.3 (C_4), 35.6 (C_3), 28.0 (C_2), 22.6 (C_1)

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) : -217.6 (t, *J* = 47.9 Hz)

IR (cm^{-1}, CCl_4) : 3062, 2960, 2119, 1710, 1677, 1547, 1091

MS (HRMS EI) : Calcd for $C_{16}H_{20}FNO$ [M] 261.1529. Found : 261.1529.

N-benzyl-*N*-(2-(fluoromethyl)-2-phenyl-2*H*-1,3-oxazin-4-yl)-4-methylbenzenesulfonamide (III.2o)



$C_{25}H_{23}FN_2O_3S$
MW = 450.5 g.mol^{-1}

Procedure : Following procedure H, using **III.1o** (96.4 mg, 0.201 mmol, , reaction time : 5 min).

Purification : Flash chromatography : PE / EtOAc 100:1

Yield : 92% (83.2 mg, 0.184 mmol) of a colorless oil

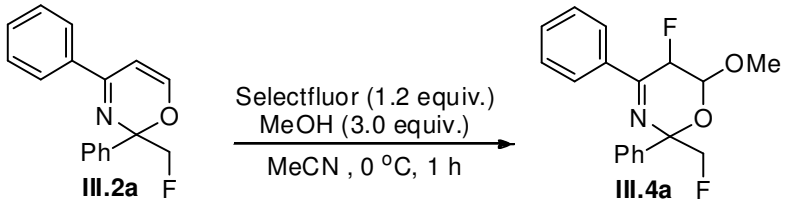
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.68 (d, *J* = 8.4 Hz, 2H, Ar), 7.42 (d, *J* = 6.5 Hz, 2H, Ar), 7.37–7.24 (m, 6H, Ar), 7.18 (t, *J* = 7.6 Hz, 2H, Ar), 7.10 (d, *J* = 7.1 Hz, 2H, Ar), 6.83 (d, *J* = 6.2 Hz, 1H, H_3), 6.11 (d, *J* = 6.2 Hz, 1H, H_2), 5.10 (s, *J* = 15.8 Hz, 2H, CH_2 of Bn), 4.34 (dq, *J* = 22.1, 9.2 Hz, 2H, H_5), 2.45 (s, *J* = 3.2 Hz, 3H, Me of Ts)

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 153.3 (Ar), 152.4 (C_1), 144.4 (C_3), 138.5 (Ar), 137.4 (Ar), 136.4 (Ar), 129.9 (Ar), 128.7 (Ar), 128.5 (Ar), 127.9 (Ar), 127.8 (Ar), 127.4 (Ar),

	127.3 (Ar), 126.6 (Ar), 97.7 (C_2), 93.7 (d, J = 17.9 Hz, C_4), 86.7 (d, J = 186.3 Hz, C_5) 49.9 (CH_2 of Bn), 21.7 (Me of Ts).
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-217.1 (t, J = 47.2 Hz)
IR (cm^{-1}, CCl_4)	3067, 2251, 1641, 1599, 1566, 1410, 1359, 1266, 1227, 1168, 1092, 1027
MS (HRMS EI)	Calcd for $C_{24}H_{21}N_2O_3S$ [M-CH_2F] 417.1273. Found : 417.1280.

3.3 Electrophilic fluorination of *2H*-1,3-oxazines

5-fluoro-2-(fluoromethyl)-6-methoxy-2,4-diphenyl-5,6-dihydro-2*H*-1,3-oxazine (III.4a)



III.2a **III.4a**

d.r. 15:4.6:2:1

$C_{18}H_{17}F_2NO_2$
MW = 317.3 g.mol^{-1}

Procedure : To a solution of oxazine **III.2a** (53.5 mg, 0.200 mmol) and Selectfluor® (70.4 mg, 0.199 mmol) in MeCN at 0 °C was added MeOH (24 µL, 0.59 mmol). The reaction was then stirred at the same temperature for 1.5 h. The reaction was quenched with H_2O, and the organic materials were extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure.

Purification : Flash chromatography : PE / EtOAc 20:1

Yield : 72% (45.7 mg, 0.144 mmol) of a yellow oil as a mixture of four diastereomers A-D (A:B:C:D = 15:4.6:2:1 based on the integration of ^{1}H NMR peaks of the methoxy group protons) with a small amount of unidentified complexes.

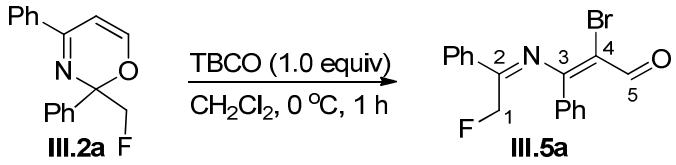
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.02 (d, *J* = 7.2 Hz, 2H for isomer B), 7.93 (d, *J* = 6.8 Hz, 2H, for isomer C), 7.78 (d, *J* = 7.2 Hz, 2H for isomer D), 7.72 (d, *J* = 7.2 Hz, 2H for isomer A), 7.49–7.30 (m, 12H, overlapped), 5.90 (d, *J* = 6.0 Hz, 1H, C*H*OMe for isomer D), 5.50 (dd, *J* = 49.2, 4.0 Hz, 1H, C*H*F for isomer C), 5.38 (d, *J* = 6.0 Hz, 1H, C*H*F for isomer B), 5.30–5.25 (m, 3H, C*H*OMe, overlapped for isomers A, B, and C), 5.01 (d, *J* = 48.4, 2.0 Hz, 1H, C*H*F for isomer A), 4.74–4.53 (m, 9H, CH_2F for all isomers A-D and C*H*F for isomer D), 3.62 (s, 3H for isomer B), 3.59 (s, 3H isomer C), 3.12 (s, 3H for isomer A), 3.09 (s, 3H, for isomer C)

IR (cm^{-1}, CCl_4) 3063, 2994, 2955, 2893, 1651, 1450, 1080

MS (HRMS ESI) Calcd for $C_{18}H_{18}F_2NO_2$ [M+H] 318.1306. Found : 318.1333.

3.4 Bromonative ring opening of *2H*-1,3-oxazines

(*Z*)-2-bromo-3-(((*Z*)-2-fluoro-1-phenylethylidene)amino)-3-phenylacrylaldehyde (III.5a)



$C_{17}H_{13}BrFNO$
MW = 346.2 g.mol^{-1}

Procedure : To a solution of III.2a (581 mg, 2.17 mmol) in CH_2Cl_2 (21.7 mL) at 0 °C was added 2,4,4,6-tetrabromocyclohexa-2,5-dien-1-one (TBCO, 2.17 mmol, 891.1 mg). After the completion of the reaction, the mixture was concentrated and the resulting residue was purified by flash column chromatography.

.

Purification : Flash chromatography : *n*-Hex / EtOAc 1:9

Yield : 71% (536 mg, 1.54 mmol) of a yellow crystal (mp 120–122 °C)

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 9.20 (s, 1H, H_5), 7.83–7.77 (m, 2H, Ar), 7.57–7.52 (m, 3H, Ar), 7.52–7.40 (m, 5H, Ar), 5.48 (d, *J* = 46.6 Hz, 2H, H_1).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 184.0 (C_5), 166.9 (C_3), 159.9 (d, *J* = 15.2 Hz, C_2), 133.9 (Ar), 133.3 (Ar), 132.3 (Ar), 130.8 (Ar), 129.5 (Ar), 128.9 (Ar), 128.7 (Ar), 127.7 (d, *J* = 1.7 Hz, Ar), 106.2 (C_4), 81.6 (d, *J* = 183.4 Hz, C_1).

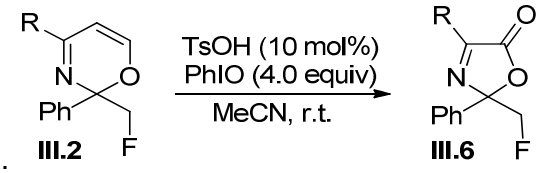
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) : -221.9 (t, *J* = 46.6 Hz)

IR (cm^{-1}, CCl_4) : 3061, 2928, 2857, 1695, 1647, 1578, 1379

MS (HRMS EI) : Calcd for $C_{17}H_{13}BrFNO$ 345.0165. Found : 345.0159.

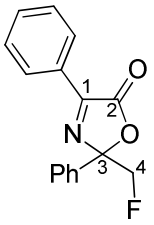
3.5 Oxidative ring contraction of *2H*-1,3-oxazines

Procedure I :



To a suspension of oxazine **III.2** and PhIO (4.0 equiv) in MeCN (0.1 M) was added TsOH•H_2O (10 mol%) and the reaction was stirred at 23 °C. Upon completion, the reaction was quenched with H_2O, extracted with EtOAc, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was then purified by flash column chromatography.

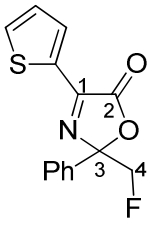
2-(fluoromethyl)-2,4-diphenyloxazol-5(2*H*)-one (III.6a)



$C_{16}H_{12}FNO_2$
MW = 269.3 g.mol^{-1}

Procedure :	Following procedure I, using **III.2a** (53.5 mg, 0.201 mmol, reaction time : 24 h).
Purification :	Flash chromatography : *n*-Hex / EtOAc 50:1
Yield :	36% (19.3 mg, 0.072 mmol) of pale yellow crystals mp 61–63 °C
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	8.46 (d, *J* = 7.2 Hz, 2H, Ar), 7.73–7.71 (m, 2H, Ar), 7.59 (d, *J* = 7.2 Hz, 1H, Ar), 7.53–7.49 (m, 2H, Ar), 7.47–7.44 (m, 3H, Ar), 4.80 (dq, *J* = 46.0, 8.4 Hz, 2H, H_4)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	163.6 (C_2), 158.0 (C_1), 134.0 (d, *J* = 4.0 Hz, Ar), 132.9 (Ar), 129.9 (Ar), 129.0 (Ar), 128.9 (Ar), 128.8 (Ar), 128.3 (Ar), 126.7 (Ar), 104.2 (d, *J* = 18.0 Hz, C_3), 83.3 (d, *J* = 190.0 Hz, C_4)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-223.7 (t, *J* = 46.8 Hz)
IR (cm^{-1}, CCl_4)	3063, 2957, 1782, 1614, 1574, 1493, 1451
MS (HRMS ESI)	Calcd for $C_{16}H_{13}FNO_2$ [M+H] 270.0930. Found : 270.0939.

2-(fluoromethyl)-2-phenyl-4-(thiophen-2-yl)oxazol-5(2*H*)-one (III.6i)



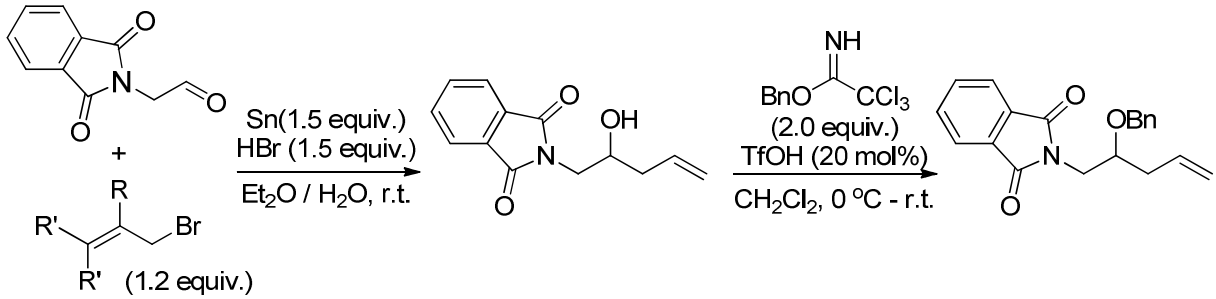
$C_{14}H_{10}FNO_2S$
MW = 275.3 g.mol^{-1}

Procedure :	Following procedure I, using **III.2a** (34.7 mg, 0.127 mmol, reaction time : 24 h)
Purification :	Flash chromatography : *n*-Hex / EtOAc 100:1
Yield :	39% yield (13.7 mg, 0.0498 mmol) of colourless oil
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	8.35 (dd, *J* = 4.0, 1.0 Hz, 1H, Ar), 7.70–7.67 (m, 3H, Ar), 7.46–7.44 (m, 3H, {h), 7.20 (dd, *J* = 4.8, 4.0, Hz, 1H, Ar), 4.77 (d, *J* = 46.8 Hz, 2H, H_4).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	162.9 (C_2), 153.4 (C_1), 134.00 (Ar), 133.96 (Ar), 133.2 (Ar), 131.1 (Ar), 129.9 (Ar), 128.8 (Ar), 128.6 (Ar), 126.7 (Ar), 104.9 (d, *J* = 18.0 Hz, C_3), 83.2 (d, *J* = 190.0 Hz, C_4).
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-223.5 (t, *J* = 46.8 Hz)
IR (cm^{-1}, CCl_4)	2957, 1786, 1616, 1449, 1425
MS (HRMS ESI)	Calcd for $C_{14}H_{11}FNO_2S$ [M+H] 276.0495. Found : 276.0493.

Chapter 4 : Copper-catalyzed radical hydrofunctionalization of unactivated alkenes using benzyl oxy moiety as a redox active hydrogen atom donor

4.1 Preparation of the benzylic homoallylic ether substrates

Procedure J :

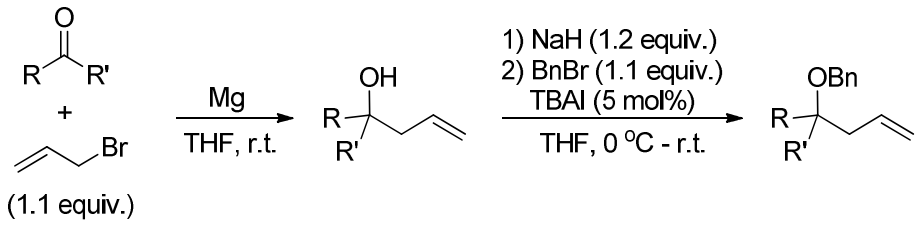


To a solution of allyl bromide (1.2 equiv) in Et_2O / H_2O (1:1, 0.5 M) were successively added tin powder (1.5 equiv), HBr (1.2 equiv, 48% w.w. in water) and 2-(1,3-dioxoisoindolin-2-yl)acetaldehyde[246] at room temperature and the mixture was then stirred at room temperature under an N_2 atmosphere. Upon completion of the reaction, as confirmed by TLC analysis, the mixture was quenched with an aqueous HCl solution (1 M). The organic materials were extracted twice with EtOAc, and the combined extracts were washed with brine and dried over $MgSO_4$. After the removal of the solvents *in vacuo*, the resulting crude product was passed through a pad of silica gel which was washed with EtOAc. EtOAc was removed *under vaccum,* thus furnishing the resulting crude homoallylic alcohol **C** which was used without further purification.

To an ice cold solution of the crude homoallylic alcohol**,** obtained as described above, and benzyl 2,2,2-trichloroacetimidate (2.0 equiv based on 2-(1,3-dioxoisoindolin-2-yl)acetaldehyde) in CH_2Cl_2 (0.2 M) was added TfOH (20 mol%). The reaction was allowed to warm up to room temperature. After completion of the reaction as confirmed by TLC analysis, the reaction was quenched by addition of water. The organic materials were extracted twice with EtOAc, and the combined extracts were washed with brine and dried over $MgSO_4$. After the removal of the volatile materials *in vacuo*, the resulting crude residue was purified by flash column chromatography on silica gel to afford the *O*-benzyl ether product **IV.1**.

[246] J. Russel Falck, Anyu He, Hiroki Fukui, Hideyuki Tsutsui, and Akella Radha, *Angew. Chem. Int. Ed.*, **2007**, *46*, 4527.

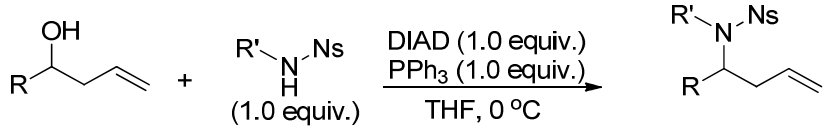
Procedure K :



To a solution of the carbonyl compound (1.0 equiv) and allyl bromide (1.1 equiv) in dry THF (0.3 M) were added magnesium turnings (2.2 equiv). The mixture was stirred at room temperature under a N_2 atmosphere until the carbonyl compound was completely consumed, as confirmed by TLC analysis. The reaction was then quenched with an aquous HCl solution (1 M). The organic materials were extracted twice with Et_2O, and the combined extracts were washed with brine and dried over $MgSO_4$. After the removal of the volatile materials *in vacuo*, the resulting crude product was passed through a pad of silica gel which was washed with EtOAc. The solvent was then removed *in vacuo,* thus furnishing the crude homoallylic alcohol which was used without further purification.

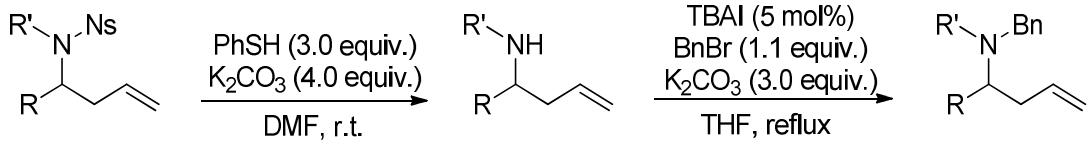
The crude homoallylic alcohol, obtained as described above, was dissolved in dry THF (0.3 M based on the carbonyl compound) before NaH (1.2 equiv) was added at 0 °C under a N_2 atmosphere. After stirring for 30 min, BnBr (1.1 equiv) and TBAI (5 mol%) were successively added to the reaction mixture which was allowed to warm up to room temperature and stirred overnight. The reaction was then quenched by addition of an aqueous HCl solution (1 M), and the organic materials were extracted twice with Et_2O. The combined organic extracts were washed with brine and dried over $MgSO_4$. After the removal of the solvent *in vacuo*, the resulting crude residue was purified by flash column chromatography on silica gel to give the pure *O*-benzyl ether **IV.1**.

Procedure L :



To a 0 °C stirred solution of homoallylic alcohol (1.0 equiv.), 2-nitrobenzenesulfonamide (4.99 mmol, 1.54 g) and PPh_3 (1.0 equiv.) in THF (0.3 M) was added DIAD (1.0 equiv.) under a N_2 atmosphere. The reaction was allowed to warm up to room temperature and stirred until completion, as confirmed by TLC analysis. The reaction was then quenched by addition of water and the organic materials were extracted twice with EtOAc. The combined extracts were washed with brine and dried over $MgSO_4$. After the removal of the volatile materials *in vacuo*, the resulting crude residue was purified by flash column chromatography on silica gel.

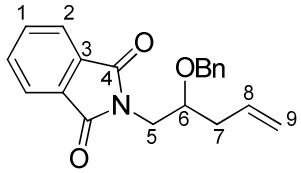
Procedure M :



To a solution of homoallylic 2-nitrobenzenesulfonamide (1.0 equiv.) and K_2CO_3 (4.0 equiv.) in DMF (22 mL) under N_2 was added PhSH (3.0 equiv.) and the reaction was stirred at room temperature. After completion of the reaction, as confirmed by TLC analysis, the reaction was quenched by addition of water. The organic materials were extracted twice with EtOAc, and the combined extracts were washed with brine and dried over $MgSO_4$. The volatile materials were then removed *in vacuo*, thus furnishing the crude amine which was used without further purification.

To a solution of the crude secondary amine, K_2CO_3 (3.0 equiv.) and TBAI (5 mol%) in THF (3 mL) under N_2 was added benzyl bromide (1.1 equiv.). The reaction was then heated to reflux. After completion, as confirmed by TLC analysis, the reaction was quenched by addition of water. The organic materials were extracted twice with EtOAc, and the combined extracts were washed with brine and dried over $MgSO_4$. After the removal of the volatile materials *in vacuo*, the resulting crude residue was purified by flash column chromatography on silica gel.

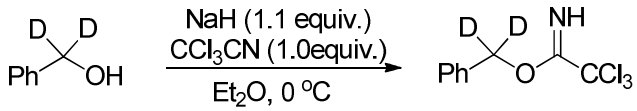
2-(2-(benzyloxy)pent-4-en-1-yl)isoindoline-1,3-dione (IV.1a)



$C_{20}H_{19}NO_3$
MW = 321.4 g.mol^{-1}

Procedure :	Following procedure J, using 2-(1,3-dioxoisoindolin-2-yl)acetaldehyde (10.0 mmol, 1.89 g) and allyl bromide as the substrates.
Purification :	Flash chromatography : Hexane / EtOAc 10:1
Yield :	51% (1.64 g, 5.10 mmol) of a thick colorless oil.
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.80 (dd, *J* = 5.3, 3.1 Hz, 2H, H_1), 7.70 (d, *J* =5.5, 3.0 Hz, 2H, H_2), 7.22 – 7.16 (m, 2H, Ar), 7.14 – 7.07 (m, 3H, Ar), 5.91 (ddt, *J* = 17.2, 10.1, 7.0 Hz, 1H, H_8), 5.14 (dd, *J* = 23.7, 13.7 Hz, 2H, H_9), 4.61 (d, *J* = 11.9 Hz, 1H, CH_2 of Bn), 4.47 (d, *J* = 11.9 Hz, 1H, CH_2 of Bn), 3.88-3.80 (m, 2H, H_5 & H_6), 3.69 (d, *J* = 9.5 Hz, 1H, H_5), 2.45 – 2.36 (m, 2H, H_7).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	168.4 (C_4), 138.3 (C_3), 134.0 (Ar), 133.9 (C_1), 132.2 (Ar), 128.3 (Ar), 128.0 (Ar), 127.6 (C_8), 123.3 (C_2), 117.9 (C_9), 75.8 (C_6), 71.7 (CH_2 of Bn), 41.2 (C_5), 37.3 (C_7).
MS (HRMS ESI)	Calcd for $C_{20}H_{19}NO_3$ [M+H] 322.1443. Found : 322.1447

α,α-D_2 benzyl trichloroacetimidate:



$C_9H_6D_2Cl_3NO$
MW = 254.5 g.mol^{-1}

Procedure :

To a solution of benzyl alcohol α,α-D_2 (5.00 mmol, 550.8 mg)[247] in Et_2O (15 mL) was added NaH (5.50 mmol, 220.1 mg) at 0 °C. After 30 mins, trichloroacetonitrile (5.00 mmol, 0.50 mL) was added. After completion of the reaction, as confirmed by TLC analysis, the reaction was quenched by addition of water. The organic materials were extracted twice with EtOAc, and the combined extracts were washed with brine and dried over $MgSO_4$. After the removal of the volatile materials *in vacuo*, the crude mixture was passed through a pad of silica which was washed with EtOAc. EtOAc was removed *under vaccum,* thus furnishing the resulting crude α,α-D_2 benzyl trichloroacetimidate which was used without further purification.

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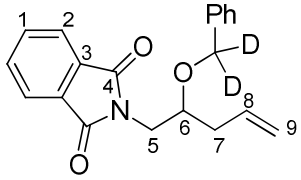
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	8.4 (s, 1H, NH), 7.47 – 7.29 (m, 5H, Ar).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	162.7 (C=N), 135.5 (Ar), 128.6 (Ar), 128.4 (Ar), 127.9 (Ar), 91.5 (CCl_3), 70.2 (p, *J* = 22.9 Hz, CD_2).
MS (HRMS ESI)	Calcd for $C_9H_7D_2Cl_3NO$ [M+H] 253.9721. Found : 253.9711

2-(2-(α,α-D_2 benzyloxy)pent-4-en-1-yl)isoindoline-1,3-dione (D_2-IV.1a)



$C_{20}H_{17}D_2NO_3$
MW = 323.4 g.mol^{-1}

Procedure :	Following procedure J, using the same procedure as for the preparation of **IV.1a** (1.0 mmol, 231.2 mg) and employing α,α-D_2 benzyl trichloroacetimidate (see below for the preparation and characterization of this reagent) as a benzylation reagent.
Purification :	Flash chromatography : Hexane / EtOAc 10:1
Yield :	51% (1.64 g, 5.10 mmol) of a thick colorless oil.
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.80 (dd, *J* = 5.5, 3.0 Hz, 2H, H_1), 7.70 (dd, *J* = 5.4, 3.1 Hz, 2H, H_2), 7.19 (dd, *J* = 7.8, 1.7 Hz, 2H, Ar), 7.13 – 7.08 (m, 3H, Ar), 5.90 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H, H_8), 5.20 – 5.07 (m, 2H, H_9), 3.86 (d, *J* = 7.3

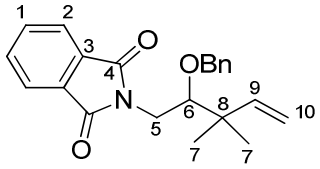
[247] X. Mo, J. Yakiwchuk, J. Dansereau, J. A. McCubbin, D. G. Hall, *J. Am. Chem. Soc.* **2015**, *137*, 9694.

Hz, 1H, H_5), 3.83 (t, *J* = 5.7 Hz, 1H, H_6), 3.69 (d, *J* = 9.4 Hz, 1H, H_5), 2.41 – 2.37 (m, 2H, H_7).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$): 168.4 (C_4), 138.2 (C_3), 134.0 (Ar), 133.9 (C_1), 132.2 (C_8), 128.3 (C_2), 128.1 (Ar), 127.6 (Ar), 123.3 (Ar), 117.9 (C_9), 75.7 (C_6), 71.0 (p, J = 22.2 Hz, CD_2), 41.2 (C_5), 37.3 (C_7).

MS (HRMS ESI): Calcd for $C_{20}H_{17}D_2NO_3$ [M+H] 324.1505. Found : 324.1494

2-(2-(benzyloxy)-3,3-dimethylpent-4-en-1-yl)isoindoline-1,3-dione (IV.1b)



$C_{22}H_{23}NO_3$
MW = 349.4 g.mol^{-1}

Procedure : Following procedure J, using 2-(1,3-dioxoisoindolin-2-yl)acetaldehyde (5.00 mmol, 945.1 mg) and 3,3-dimethylallyl bromide as the substrates.

Purification : Flash chromatography : Hexane / EtOAc 10:1

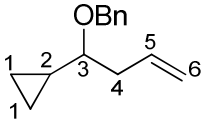
Yield : 42% (738.3 mg, 2.11 mmol) of a thick colorless oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$): 7.71 (dt, *J* = 6.5, 3.5 Hz, 2H, H_1), 7.65 (dt, *J* = 5.1, 3.8 Hz, 2H, H_2), 7.11 (d, *J* = 6.9 Hz, 2H, Ar), 7.06 – 6.98 (m, 2H, Ar), 6.93 (dt, *J* = 4.4, 1.8 Hz, 1H, Ar), 6.01 (dd, *J* = 17.6, 10.8 Hz, 1H, H_9), 5.07 (dd, *J* = 17.0, 14.3 Hz, 2H, H_{10}), 4.60 (d, *J* = 11.8 Hz, 1H, CH_2 of Bn), 4.32 (d, *J* = 11.8 Hz, 1H, CH_2 of Bn), 3.80 (dd, *J* = 13.3, 8.9 Hz, 1H, H_6), 3.61 (dd, *J* = 9.1, 2.9 Hz, 1H, H_5), 3.60 (dd, *J* = 13.6, 2.9 Hz, 1H, H_5), 1.17 (s, 3H, H_7), 1.16 (s, 3H, H_7).

^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$): 168.4 (C_4), 144.7 (Ar), 138.4 (C_3), 133.7 (C_1), 132.2 (C_9), 128.2 (Ar), 128.1 (Ar), 127.3 (Ar), 123.2 (C_2), 112.7 (C_{10}), 83.5 (CH_2 of Bn), 75.5 (C_6), 41.9 (C_5), 39.8 (C_8), 24.5 (C_7), 22.3 (C_7).

MS (HRMS ESI): Calcd for $C_{22}H_{23}NO_3$ [M+H] 350.1756. Found : 350.1760

(((1-cyclopropylbut-3-en-1-yl)oxy)methyl)benzene (IV.1c)



$C_{14}H_{18}O$
MW = 202.3 g.mol^{-1}

Procedure : Following procedure K, using cyclopropanecarboxaldehyde (10.0 mmol, 0.75 mL) as the substrate.

Purification : Flash chromatography : Hexane / EtOAc 200:1

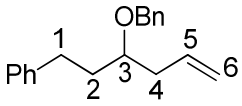
Yield : 41% (830.1 mg, 4.10 mmol) of a colorless oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$) : 7.38 – 7.29 (m, 4H, Ar), 7.29 – 7.22 (m, 1H, Ar), 5.96 (ddt, *J* = 17.2, 10.1, 7.1 Hz, 1H, H_5), 5.08 (dddd, *J* = 12.6, 10.2, 2.1, 1.3 Hz, 2H, H_6), 4.71 (d, *J* = 11.9 Hz, 1H, CH_2 of Bn), 4.56 (d, *J* = 11.9 Hz, 1H, CH_2 of Bn), 2.75 (dt, *J* = 8.5, 5.9 Hz, 1H, H_3), 2.44 (td, *J* = 5.9, 1.1 Hz, 2H, H_4), 0.91 (qt, *J* = 8.4, 5.0 Hz, 1H, H_2), 0.61 (tdd, *J* = 8.0, 5.7, 4.2 Hz, 1H, H_1), 0.53 – 0.42 (m, 1H, H_1), 0.36 (td, *J* = 9.4, 5.2 Hz, 1H, H_1), 0.09 (dt, *J* = 9.3, 5.1 Hz, 1H, H_1).

^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$) : 139.3 (Ar), 135.6 (C_5), 128.4 (Ar), 127.7 (Ar), 127.5 (Ar), 116.5 (C_6), 83.0 (CH_2 of Bn), 70.6 (C_3), 39.9 (C_4), 14.8 (C_2), 4.7 (C_1), 1.4 (C_1).

MS (HRMS ESI) : Calcd for $C_{14}H_{18}O$ [M+H] 203.1436 Found : 203.1440

(3-(benzyloxy)hex-5-en-1-yl)benzene (IV.1d)



$C_{19}H_{22}O$
MW = 266.4 g.mol^{-1}

Procedure : Following procedure K, using hydrocinnamaldehyde (10.0 mmol, 1.32 mL) as the substrate.

Purification : Flash chromatography : Hexane / EtOAc 100:1

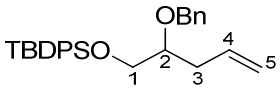
Yield : 39% (1.03 g, 3.87 mmol) of a colorless oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$) : 7.39 – 7.33 (m, 4H, Ar), 7.32 – 7.25 (m, 3H, Ar), 7.20 – 7.12 (m, 3H, Ar), 5.84 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H, H_5), 5.19 – 4.98 (m, 2H, H_6), 4.60 (d, *J* = 11.6 Hz, 1H, CH_2 of benzyl), 4.48 (d, *J* = 11.6 Hz, 1H, CH_2 of benzyl), 3.53 – 3.40 (m, 1H, H_3), 2.84 – 2.72 (m, 1H, H_4), 2.69 – 2.57 (m, 1H, H_4), 2.42 – 2.34 (m, 2H, H_1), 1.91 – 1.77 (m, 2H, H_2).

^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$) : 142.5 (Ar), 138.9 (Ar), 134.9 (C_5), 128.6 (Ar), 128.5 (Ar), 128.5 (Ar), 127.9 (Ar), 127.7 (Ar), 125.9 (Ar), 117.3 (C_6), 77.9 (CH_2 of Bn), 71.1 (C_3), 38.4 (C_4), 35.8 (C_1), 31.8 (C_2).

MS (HRMS ESI) : Calcd for $C_{19}H_{22}O$ [M+H] 267.1749 Found : 267.1743

((2-(benzyloxy)pent-4-en-1-yl)oxy)(tert-butyl)diphenylsilane (IV.1e)



$C_{28}H_{34}O_2Si$
MW = 430.6 g.mol^{-1}

Procedure : Following procedure K, using 2-((tert-butyldiphenylsilyl)oxy)acetaldehyde[248] (4.99 mmol, 1.49 g) as the substrate.

Purification : Flash chromatography : Hexane / EtOAc 100:1

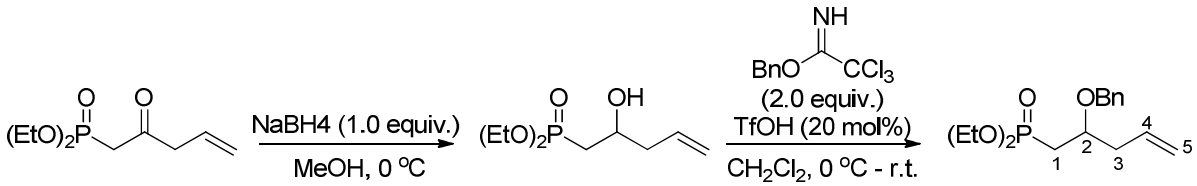
Yield : 36% (775.2 mg, 1.80 mmol) of a colorless oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$) : 7.68 (dd, *J* = 7.7, 1.4 Hz, 4H, Ph of TBDPS), 7.45 – 7.34 (m, 6H, Ph of TBDPS), 7.34 – 7.25 (m, 5H, Ph of Bn), 5.90 – 5.73 (m, 1H, H_4), 5.07 (dd, *J* = 23.4, 6.0 Hz, 2H, H_5), 4.63 (d, *J* = 11.9 Hz, 1H, CH_2 of Bn), 4.54 (d, *J* = 11.9 Hz, 1H, CH_2 of Bn), 3.71 (qd, *J* = 10.6, 5.3 Hz, 2H, H_1 & H_2), 3.56 (dt, *J* = 11.2, 5.6 Hz, 1H, H_1), 2.47 – 2.27 (m, 2H, H_3), 1.06 (s, 9H, *t*-Bu of TBDPS).

^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$) : 139.0 (Ar), 135.8 (Ar), 135.8 (Ar), 135.0 (Ar), 133.7 (C_4), 129.8 (Ar), 128.4 (Ar), 127.8 (Ar), 127.6 (Ar), 117.1 (C_5), 79.6 (CH_2 of Bn), 72.0 (C_2), 65.7 (C_1), 36.2 (C_3), 27.0 (CH_3 of TBDPS), 19.4 ($\underline{C}CH_3$ of TBDPS).

MS (HRMS ESI) : Calcd for $C_{28}H_{34}O_2Si$ [M+H] 431.2406 Found : 431.2409

diethyl (2-(benzyloxy)pent-4-en-1-yl)phosphonate (IV.1f)



$C_{16}H_{25}O_4P$
MW = 313.2 g.mol^{-1}

Procedure :

To a solution of diethyl (2-oxopent-4-en-1-yl)phosphonate[249] (5.00 mmol, 1.10 g) in MeOH (25 mL) was added $NaBH_4$ (5.0 mmol, 189.1 mg) at 0 °C under a N_2 atmosphere. After completion of the reaction, as confirmed by TLC analysis, the reaction was quenched with a saturated aqueous

[248] Gareth P. Howell, Stephen P. Fletcher, Koen Geurts, Bjorn ter Horst, and Ben L. Feringa, *J. Am. Chem. Soc.* **2006**, *128*, 14977.

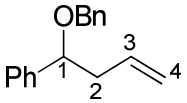
[249] Abdallah Harizi, Béchir Hajjem, Hédi Zantour and Belgacem Baccar *Phosphorus, Sulfur and Silicon and Related Elements*, **2000**, *159*, 37

NH_4Cl solution. The organic materials were extracted with EtOAc and the combined extracts were washed with brine and dried over $MgSO_4$.The solvent were removed *in vacuo*, thus furnishing the crude homoallylic alcohol which was used without further purification.

To a stirred solution of the crude homoallylic alcohol and benzyl 2,2,2-trichloroacetimidate (5.0 mmol, 1.86 mL) in CH_2Cl_2 (25 mL) was added TfOH (88 µL) at 0 °C under a N_2 atmosphere. The reaction was then allowed to warm up to room temperature. After completion of the reaction, as confirmed by TLC analysis (15 h), the reaction was quenched by addition of water (25 mL). The organic materials were extracted with ethyl acetate, and the combined extracts were washed with brine and dried over $MgSO_4$. Removal of the volatile materials *in vacuo* gave a crude residue, which was purified by flash column chromatography.

Purification :	Flash chromatography : hexane / EtOAc / MeOH 3:1:0.1
Yield :	82% (1.28 g, 4.10 mmol) of a yellow oil
^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.40 – 7.27 (m, 5H, Ar), 5.84 (ddt, *J* = 17.4, 10.3, 7.1 Hz, 1H, H_4), 5.14 (ddd, *J* = 10.4, 6.3, 1.5 Hz, 2H, H_5), 4.58 (s, 2H, CH_2 of Bn), 4.16 – 3.98 (m, 4H, CH_2 of Et), 3.99 – 3.86 (m, 1H, H_2), 2.55 – 2.35 (m, 2H, H_3), 2.19 – 1.94 (m, 2H, H_1), 1.30 (t, *J* = 6.0 Hz, 3H, CH_3 of Et), 1.26 (t, *J* = 6.0 Hz, 3H, CH_3 of Et).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	138.3 (Ar), 133.8 (C_4), 128.4 (Ar), 128.0 (Ar), 127.7 (Ar), 118.2 (C_5), 74.0 (d, *J* = 2.2 Hz (C_2), 71.4 (CH_2 of Bn), 61.8 (d, *J* = 6.4 Hz, CH_2 of Et), 61.5 (d, *J* = 6.4 Hz, CH_2 of Et), 39.3 (d, *J* = 10.3 Hz, C_3), 31.1 (d, *J* = 139.4 Hz, C_1), 16.5 (d, *J* = 2.4 Hz, CH_3 of Et), 16.4 (d, *J* = 2.5 Hz, CH_3 of Et).
^{31}P NMR (δ, ppm) (121 MHz, $CDCl_3$)	29.7 (ddt, *J* = 26.3, 17.7, 8.7 Hz).
MS (HRMS ESI)	Calcd for $C_{16}H_{25}O_{4P}$ [M+H] 313.1569 Found : 313.1569

(1-(benzyloxy)but-3-en-1-yl)benzene (IV.1g)

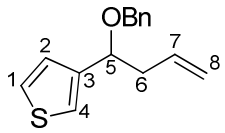


$C_{17}H_{18}O$
MW = 238.3 g.mol^{-1}

Procedure :	Following procedure K, using benzaldehyde (5.00 mmol, 0.51 mL) as the substrate.
Purification :	Flash chromatography : Hexane / EtOAc 100:1
Yield :	33% (398.1 mg, 1.67 mmol) of a colorless oil.
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.39 – 7.25 (m, 10H, Ar), 5.86 – 5.71 (m, 1H, H_3), 5.03 (t, *J* = 12.2 Hz, 2H, H_4), 4.47 (d, *J* = 11.9 Hz, 1H, CH_2 of Bn), 4.36 (t, *J* = 6.8 Hz, 1H,

	H_1), 4.27 (d, J = 11.9 Hz, 1H, CH_2 of Bn), 2.71 – 2.59 (m, 1H, H_2), 2.50 – 2.39 (m, 1H, H_2).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	142.0 (Ar), 138.7 (Ar), 135.0 (C_3), 128.6 (Ar), 128.5 (Ar), 127.8 (Ar), 127.8 (Ar), 127.6 (Ar), 127.0 (Ar), 117.0 (C_4), 81.3 (C_1), 70.5 (CH_2 of Bn), 42.8 (C_2).
MS (HRMS ESI)	Calcd for $C_{17}H_{18}O$ [M+H] 239.1436 Found : 239.1436

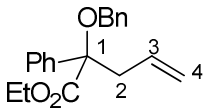
3-(1-(benzyloxy)but-3-en-1-yl)thiophene (IV.1h)



$C_{15}H_{16}OS$
MW = 244.4 g.mol^{-1}

Procedure :	Following procedure K, using 3-thiophenecarboxaldehyde (10.0 mmol, 0.88 mL) as the substrate.
Purification :	Flash chromatography : Hexane / EtOAc 200:1
Yield :	67% (1.64 g, 6.71 mmol) of a yellow oil.
^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.35 – 7.23 (m, 6H, Ar & H_4), 7.15 (dd, J = 2.9, 1.1 Hz, 1H, H_1), 7.09 (dd, J = 5.0, 1.2 Hz, 1H, H_2), 5.78 (ddt, J = 17.2, 10.2, 7.0 Hz, 1H, H_7), 5.12 – 4.95 (m, 2H, H_8), 4.49 (d, J = 11.9 Hz, 1H, CH_2 of Bn), 4.48 (t, J = 6.6 Hz, 1H, H_5), 4.30 (d, J = 11.9 Hz, 1H, CH_2 of Bn), 2.72 – 2.59 (m, 1H, H_6), 2.54 – 2.40 (m, 1H, H_6).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	143.6 (Ar), 138.8 (C_3), 135.0 (C_7), 128.7 (Ar), 128.1 (Ar), 127.8 (Ar), 126.42 (C_1), 126.38 (C_4), 122.4 (C_2), 117.3 (C_8), 77.8 (C_5), 70.6 (CH_2 of Bn), 42.0 (C_6).
MS (HRMS ESI)	Calcd for $C_{15}H_{16}OS$ [M+H] 245.1000 Found : 245.1010

ethyl 2-(benzyloxy)-2-phenylpent-4-enoate (IV.1i)



$C_{20}H_{22}O_3$
MW = 310.4 g.mol^{-1}

Procedure :	Following procedure K, using 3 ethyl benzoylformate (5.00 mmol, 0.79 mL) as the substrate and zinc instead of magnesium as the reagent.
Purification :	Flash chromatography : Hexane / EtOAc 100:1

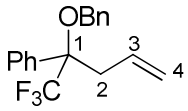
Yield : 49% (758.1 mg, 2.44 mmol) of a yellowish oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.52 (dd, *J* = 10.8, 3.5 Hz, 2H, Ar), 7.41 (d, *J* = 7.2 Hz, 2H, Ar), 7.38 – 7.26 (m, 6H, Ar), 5.72 (ddt, *J* = 24.2, 10.2, 6.9 Hz, 1H, H_3), 5.14 – 5.03 (m, 2H, H_4), 4.58 (d, *J* = 10.9 Hz, 1H, CH_2 of Bn), 4.37 (d, *J* = 10.9 Hz, 1H, CH_2 of Bn), 4.25 – 4.16 (m, 2H, CH_2 of Et), 3.17 – 3.04 (m, 2H, H_2), 1.22 (t, *J* = 7.1 Hz, 3H, CH_3 of Et).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 172.4 (C=O), 139.5 (Ar), 138.5 (Ar), 132.4 (C_3), 128.4 (Ar), 128.4 (Ar), 128.0 (Ar), 127.6 (Ar), 127.5 (Ar), 126.4 (Ar), 118.7 (C_4), 84.1 (C_1), 66.5 (CH_2 of Bn), 61.5 (CH_2 of Et), 40.4 (C_2), 14.3 (CH_3 of Et).

MS (HRMS ESI) : Calcd for $C_{20}H_{22}O_3$ [M+H] 311.1647 Found : 311.1647

(2-(benzyloxy)-1,1,1-trifluoropent-4-en-2-yl)benzene (IV.1j)



$C_{18}H_{17}F_3O$
MW = 306.3 g.mol^{-1}

Procedure : Following procedure K, using 2,2,2-trifluoroacetophenone (3.00 mmol, 0.42 mL) as the substrate.

Purification : Flash chromatography : Hexane

Yield : 52% (478.1 mg, 1.56 mmol) of a colorless oil.

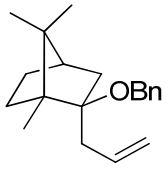
^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$) : 7.56 (d, *J* = 7.0 Hz, 2H, Ar), 7.43 – 7.28 (m, 8H, Ar), 5.80 (td, *J* = 16.9, 7.0 Hz, 1H, H_3), 5.22 – 5.07 (m, 2H, H_4), 4.65 (d, *J* = 11.1 Hz, 1H, CH_2 of Bn), 4.58 (d, *J* = 11.1 Hz, 1H, CH_2 of Bn), 3.16 (dd, *J* = 15.7, 6.9 Hz, 1H, H_2), 2.98 (dd, *J* = 15.7, 6.4 Hz, 1H, H_2).

^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$) : 138.0 (Ar), 135.9 (Ar), 131.5 (C_3), 128.7 (Ar), 128.5 (Ar), 128.4 (Ar), 127.7 (d, *J* = 1.0 Hz, Ar), 127.7 (Ar), 127.3 (Ar), 125.7 (q, *J* = 285.7 Hz, CF_3), 119.1 (C_4), 77.3 (q, *J* =8.3 Hz, C_1), 66.2 (q, *J* = 1.6 Hz, CH_2 of Bn), 37.8 (C_3).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) : -73.4 (s).

MS (HRMS ESI) : Calcd for $C_{18}H_{17}F_3O$ [M+H] 307.1310 Found : 307.1316

(1S,2R,4R)-2-allyl-2-(benzyloxy)-1,7,7-trimethylbicyclo[2.2.1]heptane (IV.1k)



$C_{20}H_{28}O_3$
MW = 284.4 g.mol^{-1}

Procedure : Following procedure K, using the benzylation conditions described in section 2.2 using (1S,2R,4R)-2-allyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol[250] (1.55 mmol, 301.3 mg) as the substrate.

Purification : Flash chromatography : Hexane

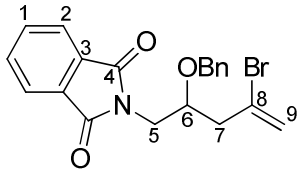
Yield : 37% brsm (76.7 mg, 0.27 mmol) of a colorless oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$) : 7.38 – 7.28 (m, 4H), 7.24 – 7.19 (m, 1H), 5.99 (dddd, *J* = 17.3, 10.2, 9.1, 5.0 Hz, 1H), 5.13 – 4.96 (m, 2H), 4.45 (d, *J* = 12.6 Hz, 1H), 4.41 (d, *J* = 12.6 Hz, 1H), 2.90 – 2.76 (m, 1H), 2.40 – 2.17 (m, 2H), 1.81 – 1.67 (m, 2H), 1.65 – 1.53 (m, 1H), 1.41 (ddd, *J* = 13.5, 11.7, 5.7 Hz, 1H), 1.12 – 1.04 (m, 1H), 1.01 (s, 3H), 0.97 (s, 3H), 0.91 – 0.85 (m, 1H), 0.84 (s, 3H).

^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$) : 140.1, 136.3, 128.2, 127.0, 126.9, 115.8, 85.5, 62.0, 53.5, 50.3, 45.2, 41.6, 40.5, 30.6, 27.3, 21.6, 21.1, 12.2.

MS (HRMS ESI) : Calcd for $C_{20}H_{28}O$ [M+H] 285.2218 Found : 285.2219

2-(2-(benzyloxy)-4-bromopent-4-en-1-yl)isoindoline-1,3-dione (IV.1m)



$C_{20}H_{18}BrNO_3$
MW = 400.3 g.mol^{-1}

Procedure : Following procedure J, using 2-(1,3-dioxoisoindolin-2-yl)acetaldehyde (15.0 mmol, 2.84 g) and 2,3-dibromopropene as the substrates.

Purification : Flash chromatography : Hexane / EtOAc 10:1

Yield : 49% (2.94 g, 7.34 mmol) of a thick colorless oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.80 (dd, *J* = 5.3, 3.2 Hz, 2H, H_1), 7.70 (dd, *J* = 5.4, 3.0 Hz, 2H, H_2), 7.23 (d, *J* = 7.0 Hz, 2H, Ar), 7.14 – 7.08 (m, 3H, Ar), 5.76 (s, 1H, H_9), 5.52 (s, 1H, H_9), 4.63 (d, *J* = 11.7 Hz, 1H, CH_2 of Bn), 4.56 (d, *J* = 11.7

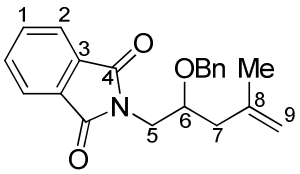
[250] R. S. Vasconcelos, L. F. Silva Jr, A. Giannis, *J. Org. Chem.* **2011**, *76*, 1499.

Hz, 1H, CH_2 of Bn), 4.17 – 4.08 (m, 1H, H_6), 3.84 (dd, *J* = 14.0, 6.6 Hz, 1H, H_5), 3.76 (dd, *J* = 14.0, 4.9 Hz, 1H, H_5), 2.78 (dd, *J* = 14.7, 7.6 Hz, 1H, H_7), 2.65 (dd, *J* = 14.7, 4.7 Hz, 1H, H_7).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$): 168.3 (C_4), 137.9 (C_8), 134.0 (C_1), 132.1 (C_3), 129.8 (Ar), 128.3 (2C, Ar), 127.7 (Ar), 123.4 (C_2), 120.0 (C_9), 74.2 (C_6), 72.5 (CH_2 of Bn), 45.7 (C_5), 40.8 (C_7).

MS (HRMS ESI): Calcd for $C_{20}H_{18}BrNO_3$ [M+H] 400.0548 Found : 400.0554

2-(2-(benzyloxy)-4-methylpent-4-en-1-yl)isoindoline-1,3-dione (IV.1p)



$C_{21}H_{21}NO_3$
MW = 335.4 g.mol^{-1}

Procedure : Following procedure J, using 2-(1,3-dioxoisoindolin-2-yl)acetaldehyde (5.0 mmol, 945.9 mg) and 3-bromo-2-methylpropene as the substrates.

Purification : Flash chromatography : Hexane / EtOAc 10:1

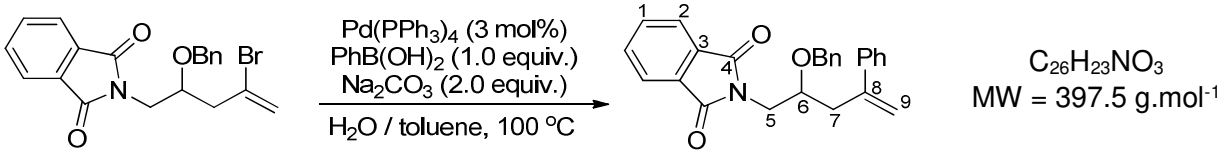
Yield : 45% (754.5 mg, 2.25 mmol) of a thick yellow oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$): 7.82 – 7.76 (m, 2H, H_1), 7.73 – 7.67 (m, 2H, H_2), 7.19 – 7.13 (m, 2H, Ar), 7.11 – 7.04 (m, 3H, Ar), 4.85 (s, 2H, H_9), 4.60 (d, *J* = 11.9 Hz, 1H, CH_2 of Bn), 4.43 (d, *J* = 11.9 Hz, 1H, CH_2 of Bn), 3.94 (qt, *J* = 10.4, 5.2 Hz, 1H, H_6), 3.83 (dd, *J* = 13.9, 7.9 Hz, 1H, H_5), 3.68 (dd, *J* = 13.9, 4.0 Hz, 1H, H_5), 2.43 (dd, *J* = 14.3, 6.6 Hz, 1H, H_7), 2.27 (dd, *J* = 14.3, 6.4 Hz, 1H, H_7), 1.79 (s, *J* = 7.9 Hz, 3H, Me).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$): 168.4 (C_4), 142.0 (C_3), 138.3 (Ar), 133.9 (C_1), 132.3 (C_8), 128.3 (Ar), 128.1 (Ar), 127.6 (Ar), 123.3 (C_2), 113.5 (C_9), 74.5 (C_6), 71.6 (CH_2 of Bn), 41.6 (C_5), 41.5 (C_7), 22.9 (Me).

MS (HRMS ESI): Calcd for $C_{21}H_{21}NO_3$ [M+H] 336.1600 Found : 336.1609

2-(2-(benzyloxy)-4-phenylpent-4-en-1-yl)isoindoline-1,3-dione (IV.1q)



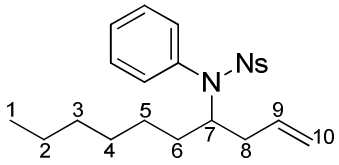
$C_{26}H_{23}NO_3$
MW = 397.5 g.mol^{-1}

Procedure :

To a stirred solution of **IV.1m** (0.50 mmol, 200.3 mg) in a 1:1 mixture of water and toluene (1 mL) were successively added $Pd(PPh_3)_4$ (0.015 mmol, 17.3 mg), sodium carbonate (1.00 mmol, 106.1 mg) and phenyl boronic acid (0.50 mmol, 61.1 mg) under a N_2 atmosphere. The mixture was then heated to 100 °C until completion of the reaction, as confirmed by TLC analysis, the reaction was quenched by addition of water (25 mL). The organic materials were extracted with ethyl acetate, and the combined extracts were washed with brine and dried over $MgSO_4$. Removal of the volatile materials *in vacuo* gave a crude residue, which was purified by flash column chromatography.

Purification :	Flash chromatography : Hexane / EtOAc 20:1
Yield :	52% (103.3 mg, 0.26 mmol) of a thick yellow oil.
^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.76 (dd, *J* = 5.6, 3.0 Hz, 2H, H_1), 7.67 (dd, *J* = 5.6, 3.0 Hz, 2H, H_2), 7.41 – 7.33 (m, 4H, Ar), 7.33 – 7.25 (m, 5H, Ar), 7.21 – 7.13 (m, 1H, Ar), 5.37 (d, *J* = 1.3 Hz, 1H, H_9), 5.24 (d, *J* = 1.1 Hz, 1H, H_9), 4.47 (d, *J* = 11.8 Hz, 1H, CH_2 of Bn), 4.34 (d, *J* = 11.8 Hz, 1H, CH_2 of Bn), 4.12 (q, *J* = 7.1 Hz, 1H, H_6), 3.88 – 3.78 (d, *J* = 9.5 Hz, 1H, H_5), 3.71 (d, *J* = 9.4 Hz, 1H, H_5), 2.88 (dd, *J* = 14.6, 5.8 Hz, 1H, H_7), 2.78 (dd, *J* = 14.6, 4.7 Hz, 1H, H_7).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	168.3 (C_4), 144.8 (C_8), 140.9 (Ar), 138.1 (Ar), 133.8 (Ar), 132.2 (Ar), 128.6 (Ar), 128.2 (Ar), 128.2 (Ar), 127.7 (Ar), 127.5 (Ar), 126.4 (Ar), 123.2 (Ar), 115.6 (C_9), 74.9 (C_6), 72.0 (CH_2 of Bn), 41.6 (C_5), 39.7 (C_7).
MS (HRMS ESI)	Calcd for $C_{26}H_{24}NO_3$ [M+H] 398.1758 Found : 398.1756

_N_-(dec-1-en-4-yl)-2-nitro-_N_-phenylbenzenesulfonamide



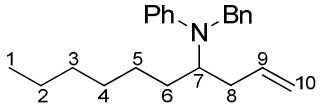
$C_{22}H_{28}N_2O_4S$
MW = 416.5 g.mol^{-1}

Procedure :	Following procedure L, using dec-1-en-4-ol[251] (10.0 mmol, 1.55 g), 2-nitro-*N*-phenylbenzenesulfonamide (10.0 mmol, 2.78 g).
Purification :	Flash chromatography : Hexane / EtOAc 10:1
Yield :	51% (2.12 g, 5.12 mmol) of a colorless oil.

[251] L. Zhang, Z. Zha, Z. Wang, *Synlett.* **2010**, *13*, 1915.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.68 – 7.62 (m, 1H, Ar), 7.59 (dd, *J* = 7.9, 1.3 Hz, 1H, Ar), 7.56 (dd, *J* = 8.0, 1.4 Hz, 1H, Ar), 7.53 – 7.47 (m, 1H, Ar), 7.43 – 7.32 (m, 3H, Ar), 7.11 (dd, *J* = 8.3, 1.3 Hz, 2H, Ar), 5.95 – 5.80 (m, 1H, H_9), 5.10 – 4.98 (m, 2H, H_{10}), 4.41 – 4.28 (m, 1H, H_7), 2.42 – 2.33 (m, 1H, H_8), 2.01 (dt, *J* = 14.1, 7.7 Hz, 1H, H_8), 1.57 – 1.52 (m, 1H, H_6), 1.43 – 1.34 (m, 3H, H_6 & H_5), 1.34 – 1.19 (m, 6H, $H_{2\text{-}4}$), 0.87 (t, *J* = 6.9 Hz, 3H, H_1).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	148.0 (Ar), 135.4 (Ar), 134.3 (Ar), 133.8 (Ar), 133.4 (Ar), 132.9 (Ar), 132.0 (Ar), 131.1 (Ar), 129.3 (C_9), 129.1 (Ar), 123.9 (Ar), 117.7 (C_{10}), 60.6 (C_7), 39.2 (C_8), 33.1 (C_6), 31.8, 29.3, 26.7, 22.7, 14.2 ($C_{1\text{-}5}$).
MS (HRMS ESI)	Calcd for $C_{22}H_{29}N_2O_4S$ [M+H] 417.1848. Found : 417.1857

***N*-benzyl-*N*-(dec-1-en-4-yl)aniline (IV.1r)**



$C_{23}H_{31}N$
MW = 321.5 g.mol^{-1}

Procedure : Following procedure M, using *N*-(dec-1-en-4-yl)-2-nitro-*N*-phenylbenzenesulfonamide (1.72mmol, 715.9 mg)

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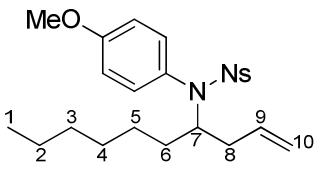
Purification : Flash chromatography : Hexane

Yield : 79% (295.6 mg, 0.92 mmol) of a pale orange oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.30 – 7.21 (m, 4H, Ar), 7.20 – 7.16 (m, 1H, Ar), 7.13 (dd, *J* = 8.9, 7.2 Hz, 2H, Ar), 6.74 (d, *J* = 8.1 Hz, 2H, Ar), 6.65 (t, *J* = 7.2 Hz, 1H, Ar), 5.83 (ddt, *J* = 17.0, 10.1, 7.0 Hz, 1H, C_9), 5.10 – 4.96 (m, 2H, C_{10}), 4.45 (d, *J* = 17.2 Hz, 1H, CH_2 of Bn), 4.39 (d, *J* = 17.2 Hz, 1H, CH_2 of Bn), 4.02 – 3.90 (m, 1H, H_7), 2.46 – 2.36 (m, 1H, H_8), 2.33 – 2.22 (m, 1H, H_8), 1.65 – 1.54 (m, 2H, H_6), 1.44 – 1.31 (m, 2H, H_5), 1.28 – 1.14 (m, 6H, $H_{2\text{-}4}$), 0.84 (t, *J* = 6.9 Hz, 3H, H_1).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	149.9 (Ar), 140.0 (Ar), 136.5 (Ar), 129.0 (Ar), 128.4 (Ar), 126.8 (Ar), 126.5 (C_9), 116.9 (Ar), 116.8 (Ar), 114.5 (C_{10}), 59.5 (C_7), 48.4 (C_8), 37.9 (C_6), 31.9, 29.5, 27.3, 22.7, 14.2 ($C_{1\text{-}5}$).
MS (HRMS ESI)	Calcd for $C_{23}H_{32}NO$ [M+H] 322.2535 Found : 322.2538

_N_-(dec-1-en-4-yl)-_N_-(4-methoxyphenyl)-2-nitrobenzenesulfonamide



$C_{23}H_{30}N_2O_5S$
MW = 446.6 g.mol^{-1}

Procedure : Following procedure L, using dec-1-en-4-ol[252] (5.00 mmol, 781.3 mg), _N_- (4-methoxyphenyl)-2-nitrobenzenesulfonamide[253] (4.99 mmol, 1.54 g)

Purification : Flash chromatography : Hexane / EtOAc 10:1

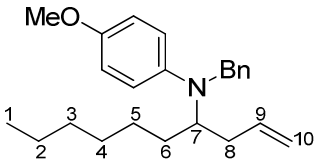
Yield : 47% (1.05 g, 2.35 mmol) of a pale yellow oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.64 (t, *J* = 7.5 Hz, 1H, Ar), 7.61 – 7.55 (m, 2H, Ar), 7.50 (t, *J* = 7.9 Hz, 1H, Ar), 7.02 (d, *J* = 8.8 Hz, 2H, PMP), 6.85 (d, *J* = 8.9 Hz, 2H, PMP), 5.87 (ddt, *J* = 17.0, 10.4, 6.9 Hz, 1H, H_9), 5.09 – 5.00 (m, 2H, H_{10}), 4.41 – 4.28 (m, 1H, H_7), 3.82 (s, 3H, OMe), 2.37 (dd, *J* = 13.8, 6.4 Hz, 1H, H_8), 2.00 (dd, *J* = 14.2, 7.2 Hz, 1H, H_8), 1.51 (d, *J* = 13.7 Hz, 1H, H_6), 1.51 (d, *J* = 13.7 Hz, 1H, H_6), 1.36 (dd, *J* = 17.0, 9.6 Hz, 3H, $H_{2\text{-}5}$), 1.33 – 1.22 (m, 5H, $H_{2\text{-}5}$), 0.87 (t, *J* = 6.7 Hz, 3H, H_1).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 160.1 (Ar), 135.6 (C_9), 133.9 (Ar), 133.8 (Ar), 133.3 (Ar), 132.1 (Ar), 131.2 (Ar), 131.1 (Ar), 126.5 (Ar), 123.9 (Ar), 117.7 (C_{10}), 114.2 (Ar), 60.45 (OMe), 55.6 (C_7), 39.2 (C_8), 33.1, 31.9, 29.3, 26.7, 22.7, 14.2 ($C_{1\text{-}6}$).

MS (HRMS ESI) Calcd for $C_{23}H_{30}N_2O_5S$ [M+H] 447.1954. Found : 447.1962

_N_-benzyl-_N_-(dec-1-en-4-yl)-4-methoxyaniline (IV.1s)



$C_{24}H_{33}NO$
MW = 351.5 g.mol-1

Procedure : Following procedure M, using _N_-(dec-1-en-4-yl)-_N_-(4-methoxyphenyl)-2-nitrobenzenesulfonamide (2.20 mmol, 982.6 mg)

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Purification : Flash chromatography : Hexane / EtOAc 100:1

Yield : 83% (604.7 mg, 1.82 mmol) of a pale orange oil.

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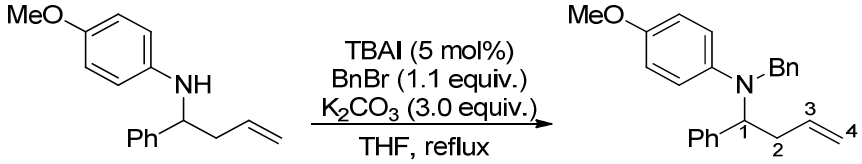
[252] L. Zhang, Z. Zha, Z. Wang, *Synlett.* **2010**, *13*, 1915.
[253] A. Rassadin, A. A. Tomashevskiy, V. V. Sokolov, A. Ringe, J. Magull, A. de Meijere, *J. Org. Chem.*, **2009**, *16*, 2635.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.25 (dt, *J* = 11.3, 7.5 Hz, 4H, Ar), 7.15 (t, *J* = 6.9 Hz, 1H, Ar), 6.71 (s, 4H, PMP), 5.83 (ddt, *J* = 17.1, 10.0, 7.0 Hz, 1H, H_9), 5.02 (dd, *J* = 18.3, 13.7 Hz, 2H, H_{10}), 4.36 (d, *J* = 16.8 Hz, 1H, CH_2 of Bn), 4.30 (d, *J* = 16.8 Hz, 1H, CH_2 of Bn), 3.76 (dt, *J* = 13.8, 7.0 Hz, 1H, H_7), 3.70 (s, 3H, OMe), 2.46 – 2.34 (m, 1H, H_8), 2.22 (dt, *J* = 14.3, 7.2 Hz, 1H, H_8), 1.64 – 1.48 (m, 2H, H_6), 1.41 (ddd, *J* = 14.7, 11.3, 7.2 Hz, 1H, H_5), 1.32 (dd, *J* = 11.7, 6.7 Hz, 1H, H_5), 1.29 – 1.16 (m, 6H, $H_{2\text{-}4}$), 0.85 (t, *J* = 6.7 Hz, 3H, H_1).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	151.9 (Ar), 144.2 (Ar), 140.3 (Ar), 136.9 (C_9), 128.4 (Ar), 127.1 (Ar), 126.5 (Ar), 117.3 (C_{10}), 116.5 (Ar), 114.4 (Ar), 61.4 (OMe), 55.7 (C_7), 37.7 (C_8), 32.8, 31.9, 29.5, 27.3, 22.7, 14.2 ($C_{1\text{-}6}$).
MS (HRMS ESI)	Calcd for $C_{24}H_{34}NO$ [M+H] 352.2640 Found : 352.2645

N-benzyl-4-methoxy-*N*-(1-phenylbut-3-en-1-yl)aniline (IV.1t)



$C_{24}H_{25}NO$
MW = 343.5 g.mol^{-1}

Procedure : Using the same benzylation conditions than procedure M and using 4-methoxy-*N*-(1-phenylbut-3-en-1-yl)aniline[254] (2.00 mmol, 506.6 mg) as the substrate.

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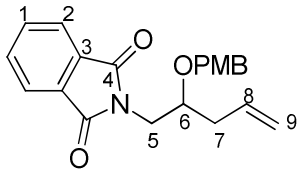
Purification : Flash chromatography : Hexane / EtOAc 100:1

Yield : 88% (604.7 mg, 1.76 mmol) of a white solid.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.38 – 7.24 (m, 5H, Ar), 7.20 (dd, *J* = 11.2, 6.5 Hz, 4H, Ar), 7.18 – 7.11 (m, 1H, Ar), 6.86 – 6.78 (m, 2H, PMP), 6.78 – 6.71 (m, 2H, PMP), 5.87 (ddd, *J* = 23.8, 12.0, 5.7 Hz, 1H, H_3), 5.05 (dd, *J* = 27.6, 17.0 Hz, 2H, H_4), 4.81 (dt, *J* = 14.8, 7.3 Hz, 1H, H_1), 4.27 (t, *J* = 14.9 Hz, 1H, CH_2 of Bn), 4.11 (t, *J* = 14.9 Hz, 1H, CH_2 of Bn), 3.73 (d, *J* = 7.9 Hz, 3H, OMe), 2.80 (dt, *J* = 14.5, 7.4 Hz, 1H, H_2), 2.76 – 2.65 (m, 1H, H_2).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	153.3 (Ar), 143.2 (Ar), 140.7 (Ar), 139.9 (Ar), 136.3 (C_3), 128.3 (Ar), 128.2 (Ar), 128.2 (Ar), 127.6 (Ar), 127.3 (Ar), 126.5 (Ar), 120.1 (Ar), 116.9 (C_4), 114.3 (Ar), 65.4 (OMe), 55.6 (CH_2 of Bn), 51.6 (C_1), 36.7 (C_2).
MS (HRMS ESI)	Calcd for $C_{24}H_{25}NO$ [M+H] 344.2014 Found : 344.2019

[254] F. Hermant, E. Nicolas, Y. Six, *Tetrahedron*, **2014**, *70*, 3924.

2-(2-((4-methoxybenzyl)oxy)pent-4-en-1-yl)isoindoline-1,3-dione (PMB-IV.1a)



$C_{21}H_{21}NO_4$
MW = 351.4 g.mol^{-1}

Procedure :

To a solution of 2-(2-hydroxypent-4-en-1-yl)isoindoline-1,3-dione (1.78 mmol, 412.1 mg) in DMF (4 mL) was added NaH (2.13 mmol, 85.2 mg) at 0 °C under a N2 atmosphere. After 30 mins of stirring, 4-methoxybenzyl chloride (3.54 mmol, 0.48 mL) was added and the reaction was allowed to warm up to room temperature. After stirring overight, the reaction was then quenched with saturated NH4Cl solution at 0 °C. The organic materials were extracted three times with Et2O, and the combined extracts were washed with water and brine and dried over MgSO4. After the removal of the volatile materials *in vacuo*, the resulting crude residue was purified by flash column chromatography.

Purification : Flash chromatography : Hexane / EtOAc 6:1

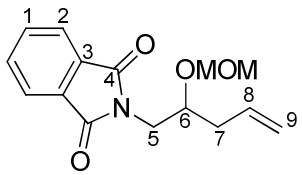
Yield : 30% (186.1 mg, 0.53 mmol) of a thick colorless oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$) : 7.78 (dd, *J* = 5.6, 3.2 Hz, 2H, H_1), 7.69 (dd, *J* = 5.6, 3.2 Hz, 2H, H_2), 7.09 (d, *J* = 8.8 Hz, 2H, PMB), 6.61 (d, *J* = 8.8 Hz, 2H, PMB), 5.90 (ddt, *J* = 17.2, 10.4, 7.2 Hz, 1H, H_8), 5.16 (dd, *J* = 17.2, 1.4 Hz, 1H, H_9), 5.10 (dd, *J* = 10.4, 1.4 Hz, 1H, H_9), 4.54 (d, *J* = 11.6 Hz, 1H, CH_2 of PMB), 4.38 (d, *J* = 11.6 Hz, 1H, CH_2 of PMB), 3.84 – 3.78 (m, 2H, H_5 & H_6), 3.68 – 3.62 (m, 4H, H_5 & OMe), 2.37 (dd, *J* = 7.2, 7.2 Hz, 2H, H_7).

^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$) : 168.2 (C_4), 158.9 (PMB), 133.9 (C_1), 133.7 (C_3), 132.0 (C_8), 130.3 (PMB), 129.5 (PMB), 123.0 (C_2), 117.6 (C_9), 113.4 (PMB), 75.2 (OMe), 71.2 (C_6), 55.0 (CH_2 of PMB), 41.1 (C_5), 37.2 (C_7).

MS (HRMS ESI) : Calcd for $C_{21}H_{21}LiNO_4$ [M+Li] 358.1631. Found : 358.1637

2-(2-(methoxymethoxy)pent-4-en-1-yl)isoindoline-1,3-dione (MOM-IV.1a)



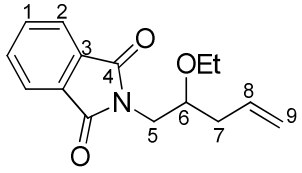
$C_{15}H_{17}NO_4$
MW = 275.3 g.mol^{-1}

Procedure :

To a solution of 2-(2-hydroxypent-4-en-1-yl)isoindoline-1,3-dione[255] (2.00 mmol, 462.4 mg) and *i*-Pr_2NEt (4.00 mmol, 0.70 mL) in CH_2Cl_2 (20 mL) was added MOMCl (3.00 mmol, 0.23 mL) at 0 °C under a N_2 atmosphere. After completion of the reaction, as confirmed by TLC analysis, the reaction was concentrated *in vacuo*. The obtained residue was diluted with EtOAc and water was added. The organic materials were extracted twice with EtOAc, and the combined extracts were washed with brine and dried over $MgSO_4$. After the removal of the volatile materials *in vacuo*, the resulting crude residue was purified by flash column chromatography.

Purification :	Flash chromatography : Hexane / EtOAc 10:1
Yield :	53% (292.0 mg, 1.06 mmol) of a thick colorless oil.
^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.86 (dd, *J* = 5.4, 3.1 Hz, 2H, H_1), 7.72 (dd, *J* = 5.4, 3.0 Hz, 2H, H_2), 5.88 (ddt, *J* = 14.0, 10.0, 7.0 Hz, 1H, H_8), 5.15 (dd, *J* = 23.7, 6.3 Hz, 2H, H_9), 4.64 (d, *J* = 7.0 Hz, 1H, CH_2 of MOM), 4.59 (d, *J* = 7.0 Hz, 1H, CH_2 of MOM), 4.08 – 3.98 (m, 1H, H_6), 3.86 (dd, *J* = 14.0, 7.3 Hz, 1H, H_5), 3.72 (dd, *J* = 14.0, 4.6 Hz, 1H, H_5), 3.18 (s, 3H, CH_3 of MOM), 2.37 (t, *J* = 6.4 Hz, 2H, H_7).
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	168.5 (C_4), 134.1 (C_1), 133.8 (C_3), 132.2 (C_8), 123.4 (C_2), 118.0 (C_9), 96.1 (CH_2 of MOM), 74.8 (C_6), 55.7 (C_5), 41.5 (C_7), 37.9 (CH_3 of MOM).
MS (HRMS ESI)	Calcd for $C_{15}H_{17}NO_4$ [M+H] 276.1236. Found : 276.1248

2-(2-ethoxypent-4-en-1-yl)isoindoline-1,3-dione (Et-IV.1a)



$C_{15}H_{17}NO_3$
MW = 259.3 g.mol^{-1}

Procedure :

To a solution of 2-(2-hydroxypent-4-en-1-yl)isoindoline-1,3-dione (2.00 mmol, 461.7 mg) in THF (6 mL) was added NaH (2.40 mmol, 96.0 mg) at 0 °C under a N_2 atmosphere. After 30 mins of stirring, EtI (3.00 mmol, 0.24 mL) was added and the reaction was allowed to warm up to room temperature. After stirring overight, the reaction was then quenched with a HCl (1M) aqueous solution. The organic materials were extracted twice with EtOAc, and the combined extracts were washed with brine and dried over $MgSO_4$. After the removal of the volatile materials *in vacuo*, the resulting crude residue was purified by flash column chromatography.

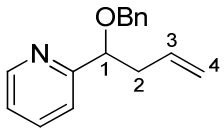
Purification :	Flash chromatography : Hexane / EtOAc 10:1
Yield :	32% (166.2 mg, 0.64 mmol) of a thick colorless oil.

[255] I. S. Kim, M.-Y. Ngai, M. J. Krische, *J. Am. Chem. Soc.* **2008**, *130*, 14891.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.86 (dd, *J* = 5.3, 3.1 Hz, 2H, H_1), 7.72 (dd, *J* = 5.1, 3.2 Hz, 2H, H_2), 5.88 (dq, *J* = 10.2, 7.0 Hz, 1H, H_8), 5.10 (dd, *J* = 24.6, 13.7 Hz, 2H, H_9), 3.84 – 3.76 (m, 1H, CH_2 of Et), 3.75 – 3.67 (m, 2H, H_6 and CH_2 of Et), 3.61 – 3.48 (m, 2H, H_5), 2.31 (t, *J* = 6.2 Hz, 2H, H_7), 1.09 (t, *J* = 7.0 Hz, 3H, CH_3 of Et).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	168.5 (C_4), 134.2 (C_8), 134.1 (C_1), 132.2 (C_3), 123.4 (C_2), 117.6 (C_9), 76.4 (C_6), 65.2 (CH_2 of Et), 41.2 (C_5), 37.4 (C_7), 15.5 (CH_3 of Et).
MS (HRMS ESI)	Calcd for $C_{15}H_{17}NO_3$ [M+H] 260.1287 Found : 260.1289

Substrates for which the reaction failed

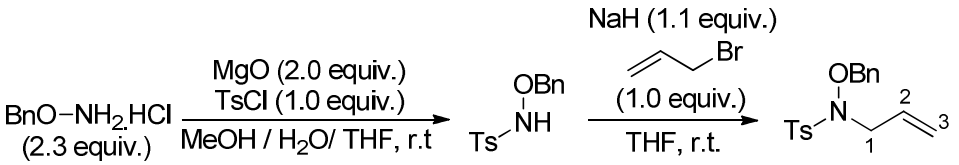
2-(1-(benzyloxy)but-3-en-1-yl)pyridine (IV.1u)



$C_{16}H_{17}NO$
MW = 410.4 g.mol^{-1}

Procedure :	Following procedure K, using pyridine-2-carboxyaldehyde (3.00 mmol, 0.29 mL) as the substrate and zinc instead of magnesium as the reagent.
Purification :	Flash chromatography : Hexane / EtOAc 20:1
Yield :	65% (799.6 mg, 1.95 mmol) of a dark oil.
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	8.58 (ddd, *J* = 4.9, 1.7, 0.9 Hz, 1H, Ar), 7.70 (td, *J* = 7.7, 1.8 Hz, 1H, Ar), 7.47 (d, *J* = 7.9 Hz, 1H, Ar), 7.36 – 7.26 (m, 5H, Ar), 7.19 (ddd, *J* = 7.5, 4.9, 1.2 Hz, 1H, Ar), 5.84 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H, H_3), 5.11 – 4.97 (m, 2H, H_4), 4.58 (t, *J* = 6.4 Hz, 1H, H_1), 4.52 (d, *J* = 11.8 Hz, 1H, CH_2 of Bn), 4.42 (d, *J* = 11.8 Hz, 1H, CH_2 of Bn), 2.64 – 2.58 (tt, *J* = 6.7,1.2 Hz, 2H, H_2).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	161.9 (Ar), 149.2 (Ar), 138.4 (Ar), 136.8 (Ar), 134.5 (C_3), 128.5 (Ar), 127.8 (Ar), 127.7 (Ar), 122.6 (Ar), 120.8 (Ar), 117.3 (C_4), 82.4 (C_1), 71.3 (CH_2 of Bn), 41.2 (C_2).
MS (HRMS ESI)	Calcd for $C_{16}H_{18}NO$ [M+H] 240.1388 Found : 240.1397

N-allyl-N-(benzyloxy)-4-methylbenzenesulfonamide (IV.1v)



$C_{17}H_{19}NO_3S$
MW = 410.4
g.mol^{-1}

Procedure : To a suspension of *O*-benzylhydroxylamine (10.0 mmol, 1.62 g) and magnesium oxide (8.6 mmol, 363 mg) in a 3:2 mixture of methanol and water, was added a solution of tosyl chloride (4.3 mmol, 832.8 mg) in THF (30 mL). The reaction was then stirred overnight at room temperature and then filtrated over celite. Evaporation of the volatile material *under vaccum* gave a crude residue which was purified by flash chromatography on silica gel (hexane / EtOAc 5 :1) to give 1.29 g of *O*-benzyl-*N*-tosylhydroxylamine as a white solid.
This product was then dissolved in THF (15 mL) and sodium hydride (4.80 mmol, 192.2 mg) and allyl bromide (4.10 mmol, 0.41 mL) were successively added and the mixture was stirred overnight at room temperature. The reaction mixture was then quenched with water and the organic materials were extracted with EtOAc. The combined organic layers were then washed with brine and dried over $MgSO_4$. Evaporation of the solvent *in-vaccuo* gave a crude residue which was purified by flash chromatography on silica gel.

Purification : Flash chromatography : Hexane / EtOAc 10:1

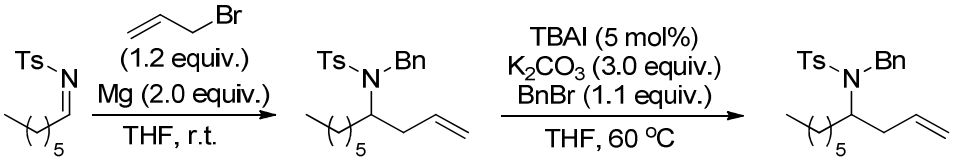
Yield : 61% (832.7 mg, 2.62 mmol) of a white solid.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.76 (d, *J* = 8.3 Hz, 2H, Ar), 7.38 – 7.33 (m, 5H, Ar), 7.31 (d, *J* = 8.2 Hz, 2H, Ar), 5.81 (ddt, *J* = 19.0, 9.7, 6.6 Hz, 1H, H_2), 5.24 – 5.13 (m, 2H, H_3), 5.03 (s, 2H, CH_2 of Bn), 3.52 (s, 2H, H_1), 2.42 (s, 3H Me of Ts)

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 144.9 (Ar), 135.3 (C_2), 131.5 (Ar), 130.4 (Ar), 129.8 (Ar), 129.7 (Ar), 129.7 (Ar), 128.8 (Ar), 128.6 (Ar), 120.4 (C_3), 80.0 (C_1), 56.3 (CH_2 of Bn), 21.8 (Me of Ts).

MS (HRMS ESI) : Calcd for $C_{17}H_{20}NO_3S$ [M+H] 318.1164 Found : 318.1166

N-benzyl-N-(dec-1-en-4-yl)-4-methylbenzenesulfonamide (IV.1w)



$C_{24}H_{33}NO_2S$
MW = 399.6
g.mol^{-1}

Procedure : To a solution of (Z)-N-heptylidene-4-methylbenzenesulfonamide[256] (3.0 mmol, 802.2 mg) in THF (10 mL) were successively added magnesium (6.0 mmol, 145.8 mg) and allyl bromide (3.6 mmol, 0.31 mL) and the reaction mixture was stirred at room temperature. Upon completion, as confirmed by TLC analysis, the reaction was quenched with water and the organic materials were extracted with EtOAc. The combined organic layers were then washed with brine and dried over $MgSO_4$. Evaporation of the solvent *in-vaccuo* gave a crude residue which was used without further purification.
The same benzylation conditions than procedure M were then used.

Purification : Flash chromatography : Hexane / EtOAc 20:1

Yield : 23% (285.4 mg, 0.69 mmol) of a yellow oild.

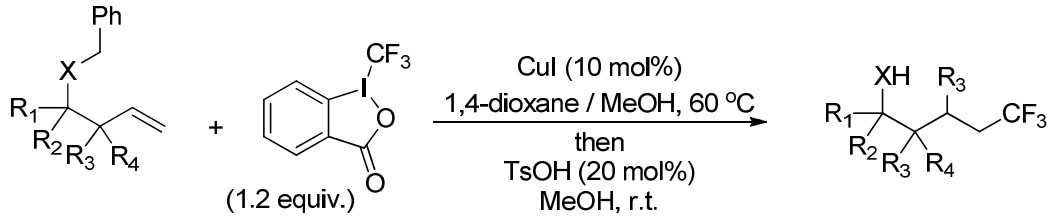
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.69 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 7.0 Hz, 2H), 7.33 – 7.23 (m, 5H), 5.52 (ddt, *J* = 17.1, 10.2, 7.0 Hz, 1H), 4.97 – 4.77 (m, 2H), 4.38 (d, *J* = 15.6 Hz, 1H), 4.28 (d, *J* = 15.7 Hz, 1H), 3.79 – 3.69 (m, 1H), 2.42 (s, 3H), 1.99 (t, *J* = 7.0 Hz, 2H), 1.36 – 1.25 (m, 1H), 1.22 – 1.12 (m, 3H), 1.09 – 0.86 (m, 6H), 0.83 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 143.1, 138.5, 138.3, 135.5, 129.6, 128.7, 128.4, 127.6, 127.3, 117.2, 59.2, 47.7, 38.6, 32.8, 31.7, 29.1, 26.7, 25.4, 22.6, 21.6, 14.2

MS (HRMS ESI) Calcd for $C_{24}H_{34}NO_2S$ [M+H] 400.2310 Found : 400.2323

4.2 Hydrotrifluoromethylation of benzylic homoallylic ethers

Procedure N :

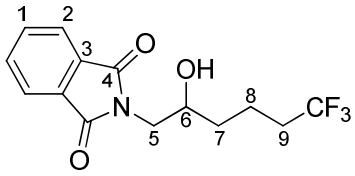


The alkene substrate, CuI (10 mol%) and the Togni reagent (1.2 equiv) were weighted in a Schlenk tube which was subsequently evacuated and backfilled with N_2 (3 times). A mixture of 1,4-dioxane and methanol (9:1, 0.3 M) was then added and the reaction was then stirred at 60 °C. After consumption of substrate 1**,** as confirmed by TLC analysis, TsOH (20 mol%) and MeOH (same volume as the reaction co-solvent system) were added at room temperature and the reaction mixture was stirred for an additional 1 h. The reaction was then quenched with a saturated $NaHCO_3$ aqueous solution, and the organic materials were extracted twice with Et_2O.

[256] Prepared following a protocol reported in *Synlett*, **2014**, *25*, 1709.

The combined extracts were washed with brine and dried over $MgSO_4$. The volatile materials were removed *in vacuo* to give a crude residue which was purified by flash column chromatography on silica gel to afford the hydrotrifluoromethylation product.

2-(6,6,6-trifluoro-2-hydroxyhexyl)isoindoline-1,3-dione (IV.2a)



$C_{14}H_{14}F_3NO_3$
MW = 301.3 g.mol^{-1}

Procedure : Following procedure N, using **IV.1a** (0.20 mmol, 64.2 mg, reaction time 12 h)

Purification : Flash chromatography : Hexane / EtOAc 3:1

Yield : 92% (55.5 g, 0.18 mmol) of a white solid.

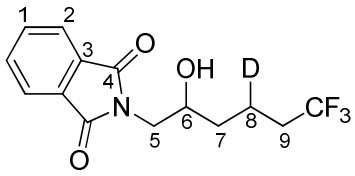
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.87 (dd, *J* = 5.4, 3.1 Hz, 2H, H_1), 7.75 (dd, *J* = 5.5, 3.1 Hz, 2H, H_2), 3.99 – 3.88 (m, 1H, H_6), 3.82 (dd, *J* = 14.3, 3.7 Hz, 1H, H_5), 3.75 (dd, *J* = 14.3, 7.1 Hz, 1H, H_5), 2.62 (s, 1H, OH), 2.25 – 2.04 (m, 2H, H_9), 1.91 – 1.77 (m, 1H, H_8), 1.75 – 1.65 (m, 1H, H_8), 1.64 – 1.47 (m, 2H, H_7)

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 169.1 (C_4), 134.4 (C_1), 132.0 (C_3), 127.2 (q, *J* = 276.1 Hz, CF_3), 123.6 (C_2), 70.3 (C_6), 44.5 (C_5), 34.0 (C_7), 33.7 (q, *J* = 28.6 Hz, C_9), 18.3 (q, *J* = 3.1 Hz, C_8)

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) : -67.4 (t, *J* = 10.9 Hz)

MS (HRMS ESI) : Calcd for $C_{14}H_{14}F_3NO_3$ [M+H] 302.1004. Found : 302.1010

2-(6,6,6-trifluoro-2-hydroxyhexyl)isoindoline-1,3-dione (D-IV.2a)



$C_{14}H_{13}DF_3NO_3$
MW = 302.3 g.mol^{-1}

Procedure : Following procedure N, using **D_2-IV.1a** (0.20 mmol, 64.8 mg, reaction time 24 h)

Purification : Flash chromatography : Hexane / EtOAc 3:1

Yield : 88% (53.3 g, 0.18 mmol) of a white solid.

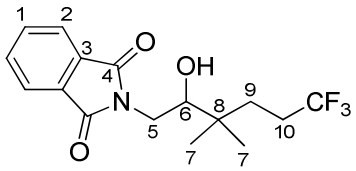
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.86 (dd, *J* = 5.4, 3.1 Hz, 2H, H_1), 7.74 (dd, *J* = 5.5, 3.0 Hz, 2H, H_2), 3.97 – 3.87 (m, 1H, H_6), 3.82 (dd, *J* = 14.3, 3.5 Hz, 1H, H_5), 3.75 (dd, *J* = 14.3, 7.2 Hz, 1H, H_5), 2.58 (d, *J* = 5.6 Hz, 1H, OH), 2.18 – 2.07 (m, 2H, H_9), 1.85 – 1.76 (m, 0.5H, H_8), 1.70 – 1.65 (m, 0.5H, H_8), 1.65 – 1.51 (m, 2H, H_7).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 169.1 (C_4), 134.4 (C_1), 132.0 (C_3), 127.2 (q, *J* = 276.4 Hz, CF_3), 123.7 (C_2), 70.3 (C_6), 44.5 (C_5), 33.9 (C_7), 33.6 (q, *J* = 28.6 Hz, C_9), 18.0 (tq, *J* = 19.0, 2.7 Hz, C_8).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) : -67.4 (t, *J* = 10.9 Hz)

MS (HRMS ESI) : Calcd for $C_{14}H_{13}DF_3NO_3$ [M+H] 303.1037. Found : 303.1034

2-(6,6,6-trifluoro-2-hydroxyhexyl)isoindoline-1,3-dione (IV.2b)



$C_{16}H_{18}F_3NO_3$
MW = 329.3 g.mol^{-1}

Procedure : Following procedure N, using **IV.1b** (0.20 mmol, 69.7 mg, reaction time 20 h)

Purification : Flash chromatography : Hexane / EtOAc 5:1

Yield : 87% (57.2 g, 0.17 mmol) of a white solid.

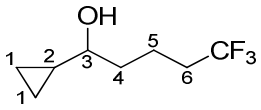
^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$) : 7.85 (dt, *J* = 7.1, 3.5 Hz, 2H, H_1), 7.74 (td, *J* = 5.2, 2.0 Hz, 2H, H_2), 3.96 (dd, *J* = 14.0, 1.7 Hz, 1H, H_5), 3.67 (dd, *J* = 14.0, 9.6 Hz, 1H, H_5), 3.55 (dd, *J* = 9.0, 4.8 Hz, 1H, H_6), 2.58 (d, *J* = 3.9 Hz, 1H, OH), 2.24 – 2.06 (m, 2H, H_{10}), 1.76 (ddd, *J* = 13.6, 9.9, 7.6 Hz, 1H, H_9), 1.54 (ddd, *J* = 13.5, 9.8, 7.5 Hz, 1H, H_9), 1.03 (s, 6H, H_7).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 169.2 (C_4), 134.3 (C_1), 132.1 (C_3), 127.7 (q, *J* = 276.1 Hz, CF_3), 123.6 (C_2), 76.9 (C_6), 41.1 (C_5), 36.5 (C_8), 30.9 (q, *J* = 2.6 Hz, C_9), 29.0 (q, *J* = 28.5 Hz, C_{10}), 23.1 (C_7), 22.4 (C_7).

^{19}F NMR (δ, ppm) (377 MHz, $CDCl_3$) : -67.5 (t, *J* = 10.7 Hz).

MS (HRMS ESI) : Calcd for $C_{16}H_{18}F_3NO_3$ [M+H] 330.1317. Found : 330.1321

1-cyclopropyl-5,5,5-trifluoropentan-1-ol (IV.2c)



$C_8H_{13}F_3O$
MW = 182.2 g.mol^{-1}

Procedure : Following procedure N, using **IV.1c** (0.28 mmol, 56.8 mg, reaction time 15 h)

Purification : Flash chromatography : Hexane / Et_2O 5:1

Yield : 66% (33.7 mg, 0.18 mmol) of a yellow oil

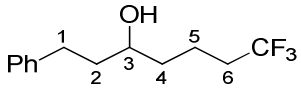
^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$) : 2.90 – 2.77 (m, 1H, H_3), 2.13 (ddd, *J* = 15.6, 8.1, 5.9 Hz, 2H, H_6), 1.83 – 1.63 (m, 4H, H_4 & H_5), 0.99 – 0.84 (m, 1H, H_2), 0.63 – 0.45 (m, 2H, H_1), 0.34 – 0.17 (m, 2H, H_1)

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 127.3 (q, *J* = 276.5 Hz, CF_3), 76.6 (C_3), 36.0 (C_4), 33.9 (q, *J* = 28.4 Hz, C_6), 18.5 (q, *J* = 3.0 Hz, C_5), 18.1 (C_2), 2.9 (C_1), 2.7 (C_1).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) : -67.4 (t, *J* = 10.9 Hz)

MS (HRMS ESI) : Calcd for $C_8H_{13}F_3O$ [M+H] 183.0997. Found : 183.1004

7,7,7-trifluoro-1-phenylheptan-3-ol (IV.2d)



$C_{13}H_{17}F_3O$
MW = 246.3 g.mol^{-1}

Procedure : Following procedure N, using **IV.1d** (0.24 mmol, 63.8 mg, reaction time 17 h)

Purification : Flash chromatography : Hexane / EtOAc 10:1

Yield : 81% (48.0 mg, 0.19 mmol) of a colorless oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.33 – 7.24 (m, 2H, Ar), 7.25 – 7.15 (m, 3H, Ar), 3.61 (ddd, *J* = 11.9, 7.9, 4.4 Hz, 1H, C_3), 2.78 (ddd, *J* = 15.1, 9.1, 6.4 Hz, 1H, H_1), 2.73 – 2.62 (m, 1H, H_1), 2.15 – 1.98 (m, 2H, H_6), 1.85 – 1.68 (m, 3H, $H_{2,4,5}$), 1.67 – 1.45 (m, 3H, $H_{2,4,5}$), 1.43 (s, 1H, OH).

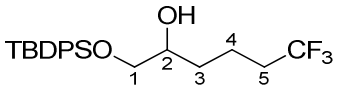
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 141.9 (Ar), 128.6 (Ar), 128.5 (Ar), 127.2 (q, *J* = 276.2 Hz, CF_3), 126.1 (Ar), 70.9 (C_3), 39.2 (C_1), 36.4 (C_4), 33.8 (q, *J* = 28.5 Hz, C_6), 32.1 (C_2), 18.4 (q, *J* = 3.0 Hz, C_5)

^{19}F NMR (δ, ppm) : -67.4 (t, *J* = 10.9 Hz).

(282 MHz, $CDCl_3$)

MS (HRMS ESI) Calcd for $C_{13}H_{17}F_3O$ [M+H] 247.1310 Found : 247.1312

1-((*tert*-butyldiphenylsilyl)oxy)-6,6,6-trifluorohexan-2-ol (IV.2e)



$C_{22}H_{29}F_3O_2Si$
MW = 410.5 g.mol^{-1}

Procedure : Following procedure N, using **IV.1d** (0.11 mmol, 47.3 mg, reaction time 18 h)

Purification : Flash chromatography : Hexane / EtOAc 20:1

Yield : 79% (35.8 mg, 0.09 mmol) of a yellow oil.

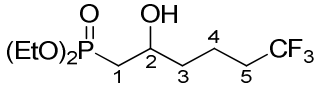
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.65 (d, *J* = 6.5 Hz, 4H, Ph of TBDPS), 7.47 – 7.37 (m, 6H, Ph of TBDPS), 3.74-3.67 (m, 1H, H_2), 3.65 (dd, *J* = 10.1, 3.4 Hz, 1H, H_1), 3.48 (dd, *J* = 10.1, 7.4 Hz, 1H, H_1), 2.49 (s, 1H, OH), 2.14 – 2.01 (m, 2H, H_5), 1.79 – 1.66 (m, 1H, H_4), 1.64 – 1.52 (m, 1H, H_4), 1.45 (dt, *J* = 11.4, 5.2 Hz, 2H, H_3), 1.07 (s, 9H, *t*-Bu of TBDPS)

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 135.68 (Ar), 135.67 (Ar), 133.19 (Ar), 133.16 (Ar), 130.06 (Ar), 130.06 (Ar), 128.7 (q, *J* = 274.5 Hz, CF_3), 128.0 (2C, Ar), 71.6 (C_2), 68.0 (C_1), 33.8 (q, *J* = 28.3 Hz, C_5), 31.8 (C_3), 27.0 (CH_3 of TBDPS), 19.4 ($\underline{C}CH_3$ of TBDPS), 18.4 (q, *J* = 3.0 Hz, C_4)

^{19}F NMR (δ, ppm) (377 MHz, $CDCl_3$) -67.3 (t, *J* = 10.9 Hz).

MS (HRMS ESI) Calcd for $C_{22}H_{29}F_3O_2Si$ [M+H] 411.1967 Found : 411.1973

diethyl (6,6,6-trifluoro-2-hydroxyhexyl)phosphonate (IV.2f)



$C_{10}H_{20}F_3O_4P$
MW = 292.2 g.mol^{-1}

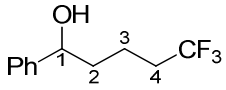
Procedure : Following procedure N, using **IV.1f** (0.20 mmol, 62.7 mg, reaction time 12 h)

Purification : Flash chromatography : EtOAc

Yield : 64% (37.3 mg, 0.13 mmol) of a colorless oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	4.22 – 4.07 (m, 4H, CH_2 of Et), 4.06 – 3.96 (m, 1H, H_2), 3.65 (s, 1H, OH), 2.19 – 2.06 (m, 2H, H_5), 2.01 – 1.86 (m, 2H, H_1), 1.82 – 1.72 (m, 1H, H_4), 1.70 – 1.54 (m, 3H, H_4 & H_3), 1.35 (t, *J* = 7.1 Hz, 3H, CH_3 of Et), 1.34 (t, *J* = 7.1 Hz, 3H, CH_3 of Et).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	127.2 (q, *J* = 276.4 Hz, CF_3), 66.1 (d, *J* = 5.5 Hz, C_2), 62.1 (d, *J* = 6.2 Hz, 2C overlapping, CH_2 of Et), 37.1 (d, *J* = 17.3 Hz, C_3), 33.7 (d, *J* = 138.5 Hz, C_1), 33.6 (q, *J* = 28.5 Hz, C_5), 18.2 (q, *J* = 2.8 Hz, C_4), 16.6 (d, *J* = 3.9 Hz, CH_3 of Et), 16.5 (d, *J* = 3.9 Hz, CH_3 of Et).
^{19}F NMR (δ, ppm) (377 MHz, $CDCl_3$)	-67.3 (t, *J* = 10.9 Hz).
^{31}P NMR (δ, ppm) (162 MHz, $CDCl_3$)	30.30 – 29.76 (m).
MS (HRMS ESI)	Calcd for $C_{10}H_{20}F_3O_4P$ [M+H] 293.1130 Found : 293.1127

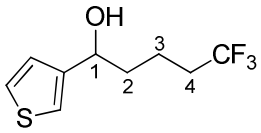
5,5,5-trifluoro-1-phenylpentan-1-ol (IV.2g)



$C_{11}H_{13}F_3O$
MW = 218.2 g.mol^{-1}

Procedure :	Following procedure N, using **IV.1g** (0.20 mmol, 47.7 mg, reaction time 12 h)
Purification :	Flash chromatography : Hexane / EtOAc 10:1
Yield :	68% (29.8 mg, 0.14 mmol) of a colorless oil.
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.39 – 7.25 (m, 5H, Ar), 4.68 (dd, *J* = 7.4, 5.0 Hz, 1H, H_1), 2.17 – 2.02 (m, 2H, H_4), 1.93 (s, 1H, OH), 1.90 – 1.79 (m, 1H, H_3), 1.79 – 1.66 (m, 2H, H_2 & H_3), 1.66 – 1.51 (m, 1H, H_2).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	144.4 (Ar), 128.8 (Ar), 128.0 (Ar), 127.2 (q, *J* = 274.6 Hz, CF_3), 125.9 (Ar), 74.23 (C_1), 37.9 (C_2), 33.7 (q, *J* = 28.5 Hz, C_4), 18.6 (q, *J* = 3.0 Hz, C_3).
^{19}F NMR (δ, ppm) (377 MHz, $CDCl_3$)	-67.3 (t, *J* = 10.9 Hz).
MS (HRMS ESI)	Calcd for $C_{11}H_{13}F_3O$ [M+H] 219.0997 Found : 219.0986

5,5,5-trifluoro-1-(thiophen-3-yl)pentan-1-ol (IV.2h)



$C_9H_{11}F_3OS$
MW = 224.2 g.mol^{-1}

Procedure : Following procedure N, using **IV.1h** (0.30 mmol, 73.4 mg, reaction time 18 h)

Purification : Flash chromatography : Hexane / EtOAc 10:1

Yield : 84% (56.5 mg, 0.25 mmol) of a yellow oil.

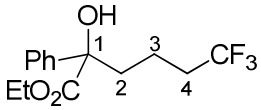
^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$) : 7.32 (dd, *J* = 5.0, 3.0 Hz, 1H, Ar), 7.19 (dd, *J* = 2.3, 0.5 Hz, 1H, Ar), 7.07 (dd, *J* = 5.0, 1.1 Hz, 1H, Ar), 4.79 (t, *J* = 6.7 Hz, 1H, H_1), 2.21 – 2.03 (m, 2H, H_4), 1.91 (s, 1H, OH), 1.94 – 1.80 (m, 2H, H_2), 1.80 – 1.68 (m, 1H, H_3), 1.67 – 1.53 (m, 1H, H_3).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 145.9 (Ar), 127.2 (q, *J* = 276.4 Hz, CF_3), 126.6 (Ar), 125.5 (Ar), 121.1 (Ar), 70.3 (C_1), 37.3 (C_2), 33.7 (q, *J* = 28.5 Hz, C_4), 18.5 (q, *J* = 3.0 Hz, C_3).

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) : -67.3 (t, *J* = 10.9 Hz).

MS (HRMS ESI) : Calcd for $C_9H_{11}F_3OS$ [M+H] 225.0561 Found : 225.0566

ethyl 6,6,6-trifluoro-2-hydroxy-2-phenylhexanoate (IV.2i)



$C_{14}H_{17}F_3O_3$
MW = 290.3 g.mol^{-1}

Procedure : Following procedure N, using **IV.1i** (0.30 mmol, 91.9 mg, reaction time 24 h) and 20 mol% of CuI.

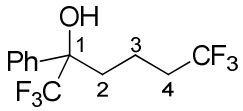
Purification : Flash chromatography : Hexane / EtOAc 200:1

Yield : 78% (67.1 mg, 0.23 mmol) of a colorless oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.60 – 7.56 (m, 2H, Ar), 7.38 – 7.33 (m, 2H, Ar), 7.32 – 7.27 (m, 1H, Ar), 4.34 – 4.17 (m, 2H, CH_2 of Et), 3.78 (s, 1H, OH), 2.28 – 2.18 (m, 1H, H_4), 2.18 – 2.03 (m, 3H, H_2 & H_4), 1.76 – 1.63 (m, 1H, H_3), 1.60 – 1.52 (m, 1H, H_3), 1.29 (t, *J* = 7.1 Hz, 3H, CH_3 of Et).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	175.0 (C=O), 141.5 (Ar), 128.5 (Ar), 128.0 (Ar), 127.2 (q, *J* = 276.4 Hz, CF_3), 125.4 (Ar), 78.2 (C_1), 62.8 (CH_2 of Et), 38.7 (C_2), 33.8 (q, *J* = 28.6 Hz, C_4), 16.8 (q, *J* = 3.1 Hz, C_3), 14.2 (CH_3 of Et).
^{19}F NMR (δ, ppm) (377 MHz, $CDCl_3$)	-67.3 (t, *J* = 10.8 Hz).
MS (HRMS ESI)	Calcd for $C_{14}H_{17}F_3O_3$ [M+H] 291.1208 Found : 291.1210

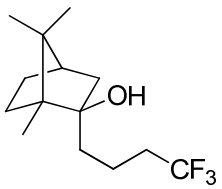
1,1,1,6,6,6-hexafluoro-2-phenylhexan-2-ol (IV.1j)



$C_{12}H_{12}F_6O$
MW = 286.2 g.mol^{-1}

Procedure :	Following procedure N, using **IV.1j** (0.20 mmol, 62.1 mg, reaction time 24 h) and 20 mol% of CuI.
Purification :	Flash chromatography : Hexane / EtOAc 20:1
Yield :	82% (47.6 mg, 0.16 mmol) of a colorless oil.
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.52 (d, *J* = 7.4 Hz, 2H, Ar), 7.47 – 7.34 (m, 3H, Ar), 2.47 (s, 1H, OH), 2.31 – 2.21 (m, 1H, H_4), 2.13 – 1.98 (m, 3H, H_4 & H_2), 1.71 – 1.57 (m, 1H, H_3), 1.38 – 1.23 (m, 1H, H_3).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	135.8 (Ar), 128.9 (Ar), 128.7 (Ar), 127.0 (q, *J* = 276.3 Hz, CF_3), 126.2 (q, *J* = 1.1 Hz, Ar), 125.7 (q, *J* = 285.7 Hz, CF_3), 77.4 (q, *J* = 28.2 Hz, C_1), 34.3 (C_2), 33.6 (q, *J* = 28.7 Hz, C_4), 15.5 (q, *J* = 2.9 Hz, C_3).
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-67.2 (t, *J* = 10.8 Hz), -81.1 (s).
MS (HRMS ESI)	Calcd for $C_{12}H_{12}F_6O$ [M+H] 287.0871 Found : 287.0859

(1S,2R,4R)-1,7,7-trimethyl-2-(4,4,4-trifluorobutyl)bicyclo[2.2.1]heptan-2-ol (IV.2k)



$C_{14}H_{23}F_3O$
MW = 264.2 g.mol^{-1}

Procedure :	Following procedure N, using **IV.1k** (0.21 mmol, 59.8 mg, reaction time 20 h).

Purification : Flash chromatography : Hexane / EtOAc 20:1

Yield : 40% (22.4 mg, 0.08 mmol) of a colorless oil.

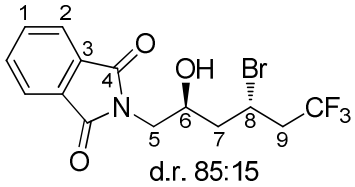
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 2.08 (tdd, *J* = 10.9, 7.7, 3.9 Hz, 2H), 1.96 (dt, *J* = 13.2, 3.7 Hz, 1H), 1.84 – 1.63 (m, 4H), 1.63 – 1.54 (m, 2H), 1.50 – 1.38 (m, 3H), 1.10 (s, 3H), 1.00 (ddd, *J* = 14.7, 7.9, 4.4 Hz, 1H), 0.86 (s, 3H), 0.86 (s, 3H).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 127.4 (q, *J* = 276.5 Hz), 81.1, 52.5, 49.5, 45.8, 45.2, 38.7, 34.5 (q, *J* = 28.2 Hz), 30.6, 27.1, 21.6, 21.2, 17.4 (q, *J* = 2.9 Hz), 10.6.

^{19}F NMR (δ, ppm) (377 MHz, $CDCl_3$) -67.3 (t, *J* = 10.9 Hz).

MS (HRMS ESI) Calcd for $C_{14}H_{23}F_3O$ [M+H] 265.1779 Found : 265.1786

2-(4-bromo-6,6,6-trifluoro-2-hydroxyhexyl)isoindoline-1,3-dione (IV.1m)



d.r. 85:15

$C_{14}H_{13}BrF_3NO_3$
MW = 380.2 g.mol^{-1}

Procedure : Following procedure N, using **IV.1m** (4.62 mmol, 1.85 g, reaction time 20 h).

Purification : Flash chromatography : Hexane / EtOAc 3:1

Yield : 73% (1.28 g, 3.37 mmol) of a white solid (dr = 84:16 as judged by ^{19}F NMR) The relative stereochemistry of the isomers was determined by the NOESY correlation of pyrrolidine derivative **IV.3m**.

Major isomer

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.86 (dd, *J* = 5.4, 3.1 Hz, 2H, H_1), 7.75 (dd, *J* = 5.4, 3.1 Hz, 2H, H_2), 4.51 – 4.41 (m, 1H, H_6), 4.31 – 4.21 (m, 1H, H_8), 3.87 (dd, *J* = 14.4, 3.8 Hz, 1H, H_5), 3.80 (dd, *J* = 14.3, 6.6 Hz, 1H, H_5), 2.91 (d, *J* = 5.1 Hz, 1H, OH), 2.88 – 2.66 (m, 2H, H_9), 1.96 (dd, *J* = 15.2, 7.6 Hz, 2H, H_7).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 169.1 (C_4), 134.47 (C_1), 131.9 (C_3), 125.3 (q, *J* = 278.2 Hz, CF_3), 123.72 (C_2), 68.5 (C_6), 44.3 (C_5), 43.6 (q, *J* = 28.6 Hz, C_9), 43.5 (C_7), 41.6 (q, *J* = 3.1 Hz, C_8).

^{19}F NMR (δ, ppm) (377 MHz, $CDCl_3$) -64.5 (t, *J* = 10.2 Hz).

MS (HRMS ESI) Calcd for $C_{14}H_{13}F_3NO_3Br$ [M+H] 380.0109 Found : 380.0121

Minor isomer

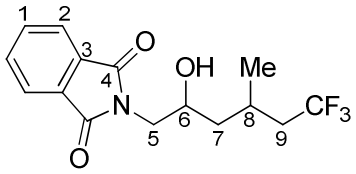
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.86 (dd, *J* = 5.4, 3.1 Hz, 2H, H_1), 7.75 (dd, *J* = 5.4, 3.1 Hz, 2H, H_2), 4.51 – 4.41 (m, 1H, H_6), 4.31 – 4.21 (m, 1H, H_8), 3.87 (dd, *J* = 14.4, 3.8 Hz, 1H, H_5), 3.80 (dd, *J* = 14.3, 6.6 Hz, 1H, H_5), 3.00 (d, *J* = 4.8 Hz, 1H, OH), 2.88 – 2.66 (m, 2H, H_9), 2.13 (dd, *J* = 13.7, 6.7 Hz, 2H, H_7).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 169.2 (C_4), 134.52 (C_1), 131.8 (C_3), 125.5 (q, *J* = 277.9 Hz, CF_3), 123.75 (C_2), 68.8 (C_6), 43.8 (C_5), 42.5 (q, *J* = 28.6 Hz, C_9), 43.0 (C_7), 40.6 (q, *J* = 3.5 Hz, C_8).

^{19}F NMR (δ, ppm) (377 MHz, $CDCl_3$) -64.8 (t, *J* = 10.1 Hz).

MS (HRMS ESI) Calcd for $C_{14}H_{13}F_3NO_3Br$ [M+H] 380.0109 Found : 380.0121

2-(6,6,6-trifluoro-2-hydroxy-4-methylhexyl)isoindoline-1,3-dione (IV.2p)



$C_{15}H_{16}F_3NO_3$
MW = 315.3 g.mol^{-1}

Procedure : Following procedure N, using **IV.1p** (0.62 mmol, 206.8 mg, reaction time 24 h).

Purification : Flash chromatography : Hexane / EtOAc 3:1

Yield : 72% (140.9 mg, 0.45 mmol) of a white solid (dr = 60:40 as judged by ^{1}H NMR) The relative stereochemistry of both isomers was not determined.

Major isomer

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.87 – 7.81 (m, 2H, H_1), 7.73 (dd, *J* = 4.9, 3.2 Hz, 2H, H_2), 4.05-3.97 (m, 1H, H_6), 3.81 – 3.68 (m, 2H, H_5), 2.66 (d, *J* = 0.7 Hz, 1H, OH), 2.28 – 2.10 (m, 2H, H_9), 2.05 – 1.86 (m, 1H, H_8), 1.53 (dd, *J* = 14.2, 7.5 Hz, 1H, H_7), 1.42 – 1.31 (m, 1H, H_7), 1.05 (d, *J* = 6.1 Hz, 3H, Me).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 169.1 (C_4), 134.3 (C_1), 132.0 (C_3), 127.2 (q, *J* = 277.5 Hz, CF_3), 123.6 (C_2), 68.1 (C_6), 45.1 (C_5), 41.8 (C_7), 40.9 (q, *J* = 27.0 Hz, C_9), 24.6 (q, *J* = 2.3 Hz, C_8), 19.2 (Me).

^{19}F NMR (δ, ppm) (377 MHz, $CDCl_3$) -63.06 (t, *J* = 10.6 Hz).

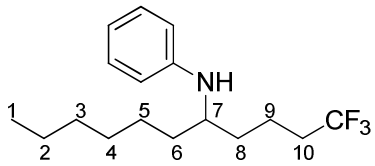
MS (HRMS ESI)	Calcd for $C_{15}H_{16}F_3NO_3$ [M+H] 316.1161	Found : 316.1146

Minor isomer

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.87 – 7.81 (m, 2H, H_1), 7.73 (dd, *J* = 4.9, 3.2 Hz, 2H, H_2), 4.05-3.97 (m, 1H, H_6), 3.81 – 3.68 (m, 2H, H_5), 2.72 (d, *J* = 0.7 Hz, 1H, OH), 2.28 – 2.10 (m, 2H, H_9), 2.05 – 1.86 (m, 1H, H_8), 1.63 – 1.57 (m, 1H, H_7), 1.53 (dd, *J* = 14.2, 7.5 Hz, 1H, H_7), 1.10 (d, *J* = 6.5 Hz, 3H, Me).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	169.1 (C_4), 134.3 (C_1), 132.0 (C_3), 127.2 (q, *J* = 277.5 Hz, CF_3), 123.6 (C_2), 68.2 (C_6), 44.7 (C_5), 41.8 (C_7), 39.6 (q, *J* = 27.0 Hz, C_9), 24.8 (q, *J* = 2.2 Hz, C_8), 20.5 (Me).
^{19}F NMR (δ, ppm) (377 MHz, $CDCl_3$)	-63.09 (t, *J* = 10.7 Hz).

MS (HRMS ESI)	Calcd for $C_{15}H_{16}F_3NO_3$ [M+H] 316.1161	Found : 316.1146

N-(1,1,1-trifluoroundecan-5-yl)aniline (IV.2r)



$C_{17}H_{26}F_3N$
MW = 301.4 g.mol^{-1}

Procedure : Following procedure N, using **IV.1r** (0.20 mmol, 64.3 mg, reaction time 20 h).

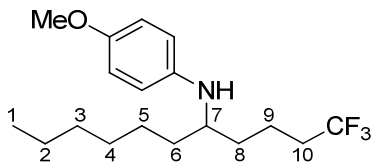
Purification : Flash chromatography : Hexane / EtOAc 50:1

Yield : 63% (37.9 mg, 0.13 mmol) of a yellow oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.51 – 7.44 (m, 2H, Ar), 7.44 – 7.37 (m, 3H, Ar), 3.43 – 3.37 (m, 1H, H_7), 3.19 (bd s, 1H, NH), 2.17 – 2.05 (m, 2H, H_{10}), 1.76 – 1.63 (m, 3H, H_8 & H_9), 1.54 (ddd, *J* = 18.1, 13.3, 7.0 Hz, 4H, $H_{6,8}$), 1.45 – 1.21 (m, 10H, H_{1-5}).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	144.0 (Ar), 129.1 (Ar), 127.4 (q, *J* = 276.5 Hz, CF_3), 124.7 (Ar), 113.5 (Ar), 45.8 (C_7), 38.7 (C_8), 34.4 (q, *J* = 28.2 Hz, C_{10}), 30.8 (C_6), 27.0 (C_5), 21.6, 21.3, 17.7 (q, *J* = 2.9 Hz, C_9), 10.6 (C_{1-4}).
^{19}F NMR (δ, ppm) (377 MHz, $CDCl_3$)	-67.3 (t, *J* = 10.9 Hz).

MS (HRMS ESI)	Calcd for $C_{17}H_{27}F_3N$ [M+H] 302.2091	Found : 302.2096

4-methoxy-N-(1,1,1-trifluoroundecan-5-yl)aniline (IV.2s)



$C_{18}H_{28}F_3NO$
MW = 331.4 g.mol^{-1}

Procedure : Following procedure N, using **IV.1s** (0.20 mmol, 70.2 mg, reaction time 19 h).

Purification : Flash chromatography : Hexane / EtOAc 50:1

Yield : 59% (39.2 mg, 0.12 mmol) of a yellow oil.

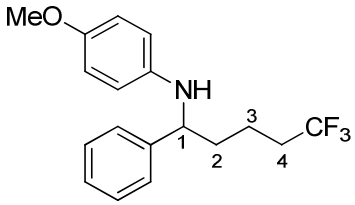
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 6.77 (d, *J* = 8.9 Hz, 2H, PMP), 6.53 (d, *J* = 8.9 Hz, 2H, PMP), 3.74 (s, 3H, OMe), 3.29 – 3.20 (m, 1H, C_7), 3.09 (broad s, 1H, NH), 2.15 – 1.98 (m, 2H, H_{10}), 1.72 – 1.53 (m, 3H, $H_{8,9}$), 1.52 – 1.37 (m, 3H, $H_{6,9}$), 1.36 – 1.19 (m, 8H, $H_{2\text{-}5}$), 0.87 (t, *J* = 4.7 Hz, 3H, H_1).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 152.0 (PMP), 142.2 (PMP), 127.3 (q, *J* = 276.5 Hz, CF_3), 115.2 (PMP), 114.6 (PMP), 56.0 (OMe), 53.8 (C_7) 35.1 (C_8), 34.1 (C_6), 34.0 (q, *J* = 28.4 Hz,C_{10}), 31.9, 29.5, 26.0, 22.7, 18.7 (q, *J* = 3.0 Hz, C_9), 14.2 ($C_{1\text{-}5}$).

^{19}F NMR (δ, ppm) (377 MHz, $CDCl_3$) : -67.3 (t, *J* = 10.9 Hz).

MS (HRMS ESI) : Calcd for $C_{18}H_{28}F_3NO$ [M+H] 332.2201 Found : 332.2202

4-methoxy-N-(5,5,5-trifluoro-1-phenylpentyl)aniline (IV.2t)



$C_{18}H_{20}F_3NO$
MW = 323.4 g.mol^{-1}

Procedure : Following procedure N, using **IV.1t** (0.20 mmol, 68.5 mg, reaction time 16 h).

Purification : Flash chromatography : Hexane / EtOAc 50:1

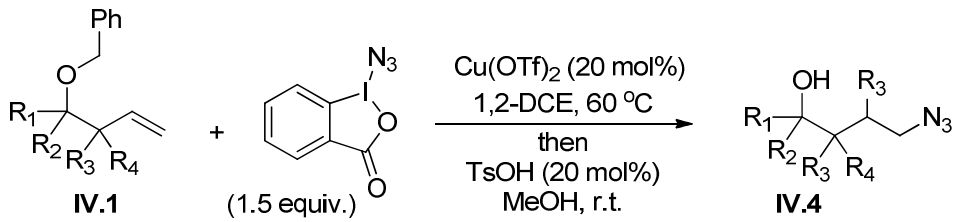
Yield : 49% (31.6 mg, 0.10 mmol) of a yellow oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.33 – 7.29 (m, 4H, Ar), 7.25 – 7.21 (m, 1H, Ar), 6.69 (d, *J* = 8.9 Hz, 2H, PMP), 6.48 (d, *J* = 8.9 Hz, 2H, PMP), 4.25 (t, *J* = 6.7 Hz, 1H, H_1),

	3.75 (bd s, 1H, NH), 3.69 (s, 3H, OMe), 2.14 – 2.00 (m, 2H, H_4), 1.93 – 1.77 (m, 2H, H_3), 1.77 – 1.62 (m, 1H, H_2), 1.62 – 1.51 (m, 1H, H_2).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	152.3 (Ar), 143.6 (Ar), 141.5 (Ar), 128.9 (Ar), 127.4 (Ar), 127.1 (q, *J* = 276.5 Hz, CF_3), 126.5 (Ar), 115.0 (Ar), 114.9 (Ar), 58.9 (C_1), 55.9 (OMe), 37.8 (C_2), 33.7 (q, *J* = 28.6 Hz, C_4), 19.4 (q, *J* = 3.0 Hz C_3).
^{19}F NMR (δ, ppm) (377 MHz, $CDCl_3$)	-67.2 (t, *J* = 10.9 Hz).
MS (HRMS ESI)	Calcd for $C_{18}H_{20}F_3NO$ [M+H] 324.1575 Found : 324.1573

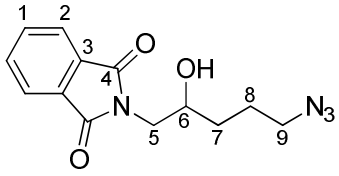
4.3 Hydroazidation of benzylic homoallylic ethers

Procedure O :



The alkene substrate (1.0 equiv), $CuBr_2$ (20 mol%) and the Togni-N_3 reagent were weighted in a Schlenk tube, which was subsequently evacuated and backfilled with N_2 (3 times). To the mixture was then added 1,2-dichloroethane (0.3 M) and the reaction was then stirred at 60 °C. After consumption of the substrate, as confirmed by TLC analysis, TsOH (20 mol%) and MeOH (same volume as 1,2-dichloroethane reaction solvent) were added at room temperature and the reaction mixture was stirred for 1 h. The reaction was then quenched with a saturated $NaHCO_3$ aqueous solution, and the organic materials were extracted with Et_2O. The combined extracts were washed with brine and dried over $MgSO_4$. The volatile materials were removed *in vacuo* to give a crude residue which was purified by flash column chromatography on silica gel to afford the hydroazidation product**.**

2-(5-azido-2-hydroxypentyl)isoindoline-1,3-dione (IV.4a)



$C_{13}H_{14}N_4O_3$
MW = 274.3 g.mol^{-1}

Procedure :	Following procedure O, using **IV.1a** (0.20 mmol, 64.2 mg, reaction time 16 h).
Purification :	Flash chromatography : Hexane / EtOAc 3:1

Yield : 57% (31.2 mg, 0.11 mmol) of a pale yellow oil.

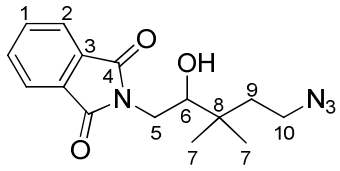
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.87 (dd, *J* = 5.4, 3.1 Hz, 2H, H_1), 7.74 (dd, *J* = 5.4, 3.1 Hz, 2H, H_2), 3.97 – 3.89 (m, 1H, H_6), 3.83 (dd, *J* = 14.3, 3.5 Hz, 1H, H_5), 3.76 (dd, *J* = 14.3, 7.2 Hz, 1H, H_5), 3.34 (t, *J* = 6.3 Hz, 2H, H_9), 2.53 (d, *J* = 3.5 Hz, 1H, OH), 1.90 – 1.81 (m, 1H, H_7), 1.78 – 1.71 (m, 1H, H_7), 1.69 – 1.64 (m, 1H, H_8), 1.59 – 1.50 (m, 1H, H_8).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 169.1 (C_4), 134.4 (C_1), 132.0 (C_3), 123.7 (C_2), 70.3 (C_6), 51.5 (C_9), 44.6 (C_5), 32.2 (C_7), 25.2 (C_8).

IR (cm^{-1}, neat, NaCl) : 2100 (N_3)

MS (HRMS ESI) : Calcd for $C_{13}H_{14}N_4O_3$ [M+H] 275.1144 Found : 275.1140

2-(5-azido-2-hydroxy-3,3-dimethylpentyl)isoindoline-1,3-dione (IV.4b)



$C_{15}H_{18}N_4O_3$
MW = 303.3 $g.mol^{-1}$

Procedure : Following procedure O, using **IV.1b** (0.20 mmol, 69.6 mg, reaction time 12 h).

Purification : Flash chromatography : Hexane / EtOAc 3:1. The pure product was obtained by further purification by GPC

Yield : 48% (26.2 mg, 0.10 mmol) of a colorless oil.

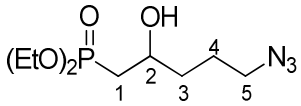
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.87 (dd, *J* = 5.4, 3.1 Hz, 2H, H_1), 7.74 (dd, *J* = 5.4, 3.1 Hz, 2H, H_2), 3.95 (dd, *J* = 14.0, 1.9 Hz, 1H, H_5), 3.68 (dd, *J* = 14.0, 9.6 Hz, 1H, H_5), 3.57 (ddd, *J* = 9.6, 5.5, 1.8 Hz, 1H, H_6), 3.40 (t, *J* = 7.7 Hz, 2H, H_{10}), 2.60 (d, *J* = 5.6 Hz, 1H, OH), 1.83 (dt, *J* = 13.9, 7.8 Hz, 1H, H_9), 1.66 – 1.56 (m, 1H, H_9), 1.06 (s, 3H, H_7), 1.04 (s, 3H, H_7)

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 169.2 (C_4), 134.3 (C_1), 132.1 (C_3), 123.6 (C_2), 77.0 (C_6), 47.7 (C_{10}), 41.0 (C_5), 37.8 (C_9), 36.8 (C_8), 23.6 (C_7), 22.8 (C_7).

IR (cm^{-1}, neat, NaCl) : 2094 (N_3)

MS (HRMS ESI) : Calcd for $C_{15}H_{18}N_4O_3$ [M+H] 303.1457 Found : 303.1461

diethyl (5-azido-2-hydroxypentyl)phosphonate (IV.4f)



$C_9H_{20}N_3O_4P$
MW = 265.2 g.mol^{-1}

Procedure : Following procedure O, using **IV.1f** (0.20 mmol, 62.7 mg, reaction time 10 h).

Purification : Flash chromatography : Hexane / EtOAc 1:5

Yield : 43% (23.1 mg, 0.09 mmol) of an orange oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 4.23 – 4.10 (m, 4H, CH_2 of Et), 4.08-4.00 (m, 1H, H_2), 3.63 (s, 1H, OH), 3.41 – 3.29 (m, 2H, H_5), 2.04 – 1.89 (m, 2H, H_1), 1.89 – 1.77 (m, 1H, H_4), 1.77 – 1.68 (m, 1H, H_4), 1.64 (dd, *J* = 8.5, 4.9 Hz, 2H, H_3), 1.38 (t, *J* = 7.1 Hz, 3H, CH_3 of Et), 1.37 (t, *J* = 7.1 Hz, 3H, CH_3 of Et).

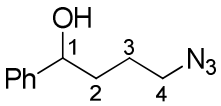
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) : 66.1 (d, *J* = 5.6 Hz, C_2), 62.1 (d, *J* = 6.5 Hz, 2C, CH_2 of Et), 51.5 (C_5), 35.4 (d, *J* = 17.4 Hz, C_3), 33.8 (d, *J* = 138.7 Hz, C_1), 25.1 (C_4), 16.6 (d, *J* = 3.9 Hz, CH_3 of Et), 16.5 (d, *J* = 3.8 Hz, CH_3 of Et).

^{31}P NMR (δ, ppm) (162 MHz, $CDCl_3$) : 30.40 – 29.84 (m).

IR (cm^{-1}, neat, NaCl) : 2098 (N_3)

MS (HRMS ESI) : Calcd for $C_9H_{20}N_3O_4P$ [M+H] 266.1270 Found : 266.1277

4-azido-1-phenylbutan-1-ol (IV.4g)



$C_{10}H_{13}N_3O$
MW = 191.2 g.mol^{-1}

Procedure : Following procedure O, using **IV.1g** (0.20 mmol, 47.8 mg, reaction time 12 h).

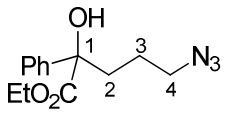
Purification : Flash chromatography : Hexane / EtOAc 10:1.

Yield : 42% (16.2 mg, 0.08 mmol) of a colorless oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) : 7.39 – 7.33 (m, 4H, Ar), 7.32 – 7.27 (m, 1H, Ar), 4.72 (t, *J* = 5.0 Hz, 1H, H_1), 3.30 (ddd, *J* = 12.3, 8.0, 4.6 Hz, 2H, H_4), 1.86 (d, *J* = 2.2 Hz, 1H, H_3), 1.84 – 1.74 (m, 3H, $H_{3,4}$), 1.67 – 1.59 (m, 1H, H_4).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	144.5 (Ar), 128.7 (Ar), 127.9 (Ar), 125.9 (Ar), 74.2 (C_1), 51.5 (C_4), 36.1 (C_2), 25.5 (C_3).
IR (cm^{-1}, neat, NaCl)	2100 (N_3)
MS (HRMS ESI)	Calcd for $C_{10}H_{13}N_3O$ [M+H] 192.1137. Found : 192.1130

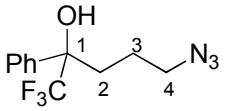
ethyl 5-azido-2-hydroxy-2-phenylpentanoate (IV.4i)



$C_{13}H_{17}N_3O_3$
MW = 263.3 g.mol^{-1}

Procedure :	Following procedure O, using **IV.1i** (0.20 mmol, 62.2 mg, reaction time 14 h).
Purification :	Flash chromatography : Hexane / EtOAc 50:1.
Yield :	47% (24.5 mg, 0.09 mmol) of a colorless oil.
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.61 – 7.57 (m, 2H, Ar), 7.39 – 7.33 (m, 2H, Ar), 7.31 – 7.28 (m, 1H, Ar), 4.34 – 4.20 (m, 2H, CH_2 of Et), 3.79 (s, 1H, OH), 3.37 – 3.23 (m, 2H, C_4), 2.24 (ddd, J = 14.1, 11.0, 5.2 Hz, 1H, H_2), 2.10 (ddd, J = 13.8, 11.1, 4.9 Hz, 1H, H_2), 1.76 – 1.65 (m, 1H, H_2), 1.60 (ddd, J = 11.7, 9.0, 5.5 Hz, 1H, H_2), 1.29 (t, J = 7.1 Hz, 3H, CH_3 of Et).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	175.1 (C=O), 141.5 (Ar), 128.5 (Ar), 128.0 (Ar), 125.5 (Ar), 78.1 (C_1), 62.8 (CH_2 of Et), 51.5 (C_4), 36.9 (C_2), 23.6 (C_3), 14.2 (CH_3 of Et).
IR (cm^{-1}, neat, NaCl)	2094 (N_3)
MS (HRMS ESI)	Calcd for $C_{13}H_{17}N_3O_3$ [M+H] 264.1348. Found : 264.1349

5-azido-1,1,1-trifluoro-2-phenylpentan-2-ol (IV.4j)



$C_{11}H_{12}F_3N_3O$
MW = 259.2 g.mol^{-1}

Procedure :	Following procedure O, using **IV.1j** (0.20 mmol, 61.6 mg, reaction time 20 h).

Purification : Flash chromatography : Hexane / EtOAc 100:1.

Yield : 56% (29.0 mg, 0.11 mmol) of a colorless oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.53 (d, *J* = 7.5 Hz, 2H, Ar), 7.46 – 7.34 (m, 3H, Ar), 3.27 (t, *J* = 6.5 Hz, 2H, H_4), 2.74 (s, 1H, OH), 2.37 – 2.25 (m, 1H, H_2), 2.12 – 2.01 (m, 1H, H_2), 1.64 – 1.56 (m, 1H, H_3), 1.42 – 1.28 (m, 1H, H_3).

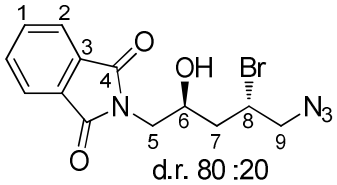
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 136.1 (Ar), 128.7 (Ar), 128.6 (Ar), 126.3 (q, *J* = 1.1 Hz, Ar), 125.7 (q, *J* = 285.7 Hz, CF_3), 77.7 (q, *J* = 35.9 Hz, C_1), 51.4 (C_4), 32.5 (C_2), 22.3 (C_3).

^{19}F NMR (δ, ppm) (377 MHz, $CDCl_3$) -80.2 (s).

IR (cm^{-1}, neat, NaCl) 2094 (N_3)

MS (HRMS ESI) Calcd for $C_{11}H_{12}F_3N_3O$ [M+H] 260.1011. Found : 260.1015

2-(5-azido-4-bromo-2-hydroxypentyl)isoindoline-1,3-dione (IV.4m)



d.r. 80 :20

$C_{13}H_{13}BrN_4O_3$
MW = 353.2 g.mol^{-1}

Procedure : Following procedure O, using **IV.1m** (0.20 mmol, 80.2 mg, reaction time 10 h).

Purification : Flash chromatography : Hexane / EtOAc 3:1.

Yield : 47% (33.0 mg, 0.09 mmol) of a yellow solid (dr = 80:20 as judged by ^{1}H NMR) The relative stereochemistry of the isomers was determined by 2D NOESY experiment performed on pyrrolidine derivative **IV.5m**.

Major isomer

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.87 (dd, *J* = 5.3, 3.1 Hz, 2H, H_1), 7.75 (dd, *J* = 5.2, 3.2 Hz, 2H, H_2), 4.36 (tt, *J* = 12.8, 6.3 Hz, 1H, H_6), 4.24 (m, 1H, H_8), 3.87 (dd, *J* = 14.4, 3.6 Hz, 1H, H_5), 3.80 (dd, *J* = 14.3, 6.5 Hz, 1H, H_5), 3.68 (d, *J* = 5.5 Hz, 2H, H_9), 2.88 (s, 1H, OH), 1.94 (dd, *J* = 8.8, 4.4 Hz, 2H, H_7).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 169.1 (C_4), 134.5 (C_1), 131.9 (C_3), 123.7 (C_2), 68.5 (C_6), 58.0 (C_8), 49.8 (C_9), 44.4 (C_5), 41.0 (C_7).

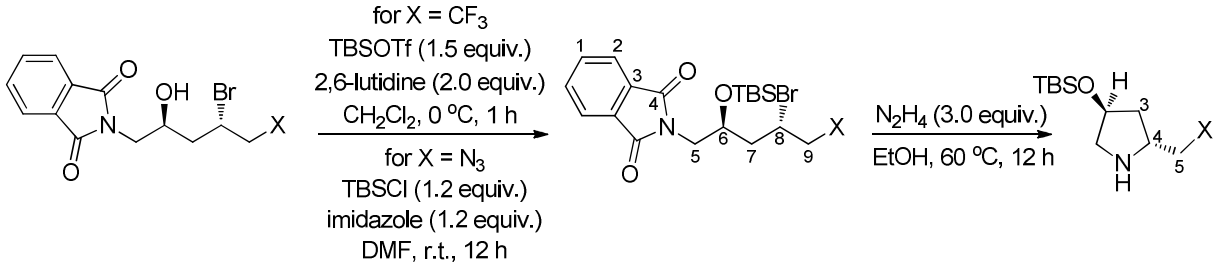
IR (cm^{-1}, neat, NaCl)	2104 (N_3)	
MS (HRMS ESI)	Calcd for $C_{13}H_{13}BrN_4O_3$ [M+H] 353.0249.	Found : 353.0261

Minor isomer

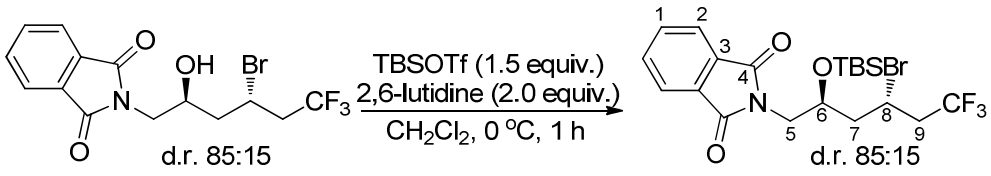
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.87 (dd, *J* = 5.3, 3.1 Hz, 2H, H_1), 7.75 (dd, *J* = 5.2, 3.2 Hz, 2H, H_2), 4.36 (tt, *J* = 12.8, 6.3 Hz, 1H, H_6), 4.18 (m, 1H, H_8), 3.87 (dd, *J* = 14.4, 3.6 Hz, 1H, H_5), 3.80 (dd, *J* = 14.3, 6.5 Hz, 1H, H_5), 3.73 (d, *J* = 5.5 Hz, 2H, H_9), 2.94 (s, 1H, OH), 2.12 (t, *J* = 6.6 Hz, 2H, H_7).	
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	169.2 (C_4), 134.5 (C_1), 131.9 (C_3), 123.8 (C_2), 68.7 (C_6), 56.9 (C_8), 48.8 (C_9), 43.8 (C_5), 40.6 (C_7).	
IR (cm^{-1}, neat, NaCl)	2104 (N_3)	
MS (HRMS ESI)	Calcd for $C_{13}H_{13}BrN_4O_3$ [M+H] 353.0249.	**MS** (HRMS ESI)

4.4 Preparation of the pyrrolidine derivatives :

General strategy :



2-((2S,4S)-4-bromo-2-((tert-butyldimethylsilyl)oxy)-6,6,6-trifluorohexyl)isoindoline-1,3-dione (TBS-IV.2m)



$C_{20}H_{27}BrF_3NO_3Si$
MW = 274.3 $g.mol^{-1}$

Procedure :

To an ice bath cooled solution of **IV.2m** (0.19 mmol, 73.2 mg) and 2,6-lutidine (0.40 mmol, 43.0 mg) in CH_2Cl_2 (0.8 mL) was added TBSOTf (0.30 mmol, 80.5 mg). After completion of the reaction, as confirmed by TLC analysis (1 h), the reaction was quenched with a aqueous HCl (1M) solution. The organic materials were extracted twice with EtOAc, and the combined extracts were washed with brine and dried over $MgSO_4$. The removal of the volatile materials *in vacuo* gave a crude residue which was purified by flash column chromatography on silica gel.

Purification : Flash chromatography : Hexane / EtOAc 20:1.

Yield : 95% (90.0 mg, 0.18 mmol) of a colorless oil and as an inseparable mixture of diastereomers

Major isomer

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.90 (dd, *J* = 5.2, 3.2 Hz, 2H, H_1), 7.78 (dd, *J* = 5.2, 3.3 Hz, 2H, H_2), 4.29 (dd, *J* = 7.5, 4.6 Hz, 2H, $H_{6,8}$), 3.78 – 3.74 (m, 2H, H_5), 2.85 (ddd, *J* = 16.9, 13.6, 8.5 Hz, 1H, H_9), 2.69 (ddd, *J* = 20.2, 13.1, 8.2 Hz, 1H, H_9), 2.04 (dd, *J* = 13.8, 9.8 Hz, 1H, H_7), 1.93 (dd, *J*= 13.8, 11.8 Hz, 1H, H_7), 0.94 (s, 9H, *t*-Bu of TBS), 0.24 (s, 3H, Me of TBS), 0.23 (s, 3H, Me of TBS).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 168.4 (C_4), 134.3 (C_1), 132.1 (C_3), 125.3 (q, *J* = 278.0 Hz, CF_3), 123.6 (C_2), 68.1 (C_6), 45.2 (C_5), 43.8 (q, *J* = 28.7 Hz, C_9), 43.7 (C_7), 41.8 (q, *J* = 3.2 Hz, C_8) ,25.9 (C($\underline{C}H_3)_3$ of TBS), 18.0 ($\underline{C}(CH_3)_3$ of TBS), -4.1 (Me of TBS), -4.6 (Me of TBS).

^{19}F NMR (δ, ppm) (377 MHz, $CDCl_3$) -64.8 (t, *J* = 10.1 Hz).

MS (HRMS ESI) Calcd for $C_{20}H_{27}F_3BrNO_3Si$ [M+H] 494.0974. Found : 494.0976

Minor isomer

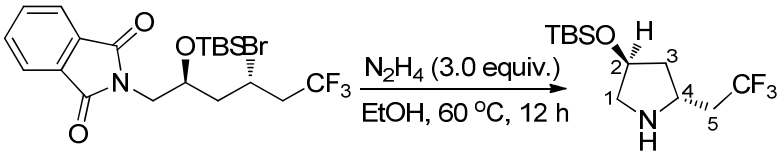
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.90 (dd, *J* = 5.2, 3.2 Hz, 2H, H_1), 7.78 (dd, *J* = 5.2, 3.3 Hz, 2H, H_2), 4.44 – 4.38 (m, 1H, H_6), 4.38 – 4.33 (m, 1H, H_8), 3.81 (d, *J* = 5.5 Hz, 2H, H_5), 2.85 (ddd, *J* = 16.9, 13.6, 8.5 Hz, 1H, H_9), 2.69 (ddd, *J* = 20.2, 13.1, 8.2 Hz, 1H, H_9), 2.17 – 2.12 (m, 2H, H_7), 0.88 (s, 9H, *t*-Bu of TBS), 0.04 (s, 3H, Me of TBS), 0.03 (s, 3H, Me of TBS).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 168.5 (C_4), 134.3 (C_1), 132.1 (C_3), 125.4 (q, *J* = 277.5 Hz, CF_3), 123.5 (C_2), 68.5 (C_6), 44.7 (C_5), 43.4 (q, *J* = 28.2 Hz, C_9), 42.5 (C_7), 40.2 (q, *J* = 3.3 Hz, C_8), 25.8 (C($\underline{C}H_3)_3$ of TBS), 18.0 ($\underline{C}(CH_3)_3$ of TBS), -4.1 (Me of TBS), -4.7 (Me of TBS).

^{19}F NMR (δ, ppm) (377 MHz, $CDCl_3$) -64.5 (t, *J* = 10.1 Hz).

MS (HRMS ESI) Calcd for $C_{20}H_{27}F_3BrNO_3Si$ [M+H] 494.0974. Found : 494.0976

(2R,4S)-4-((tert-butyldimethylsilyl)oxy)-2-(2,2,2-trifluoroethyl)pyrrolidine (IV.3m)



d.r. 85:15 d.r. 85:15

$C_{12}H_{24}F_3NOSi$
MW = 283.4 g.mol^{-1}

Procedure :

To a solution of **TBS-IV.2m** (1.07 mmol, 528.2 mg) in EtOH (10 mL) was added hydrazine (80% in water, 3.20 mmol, 0.20 mL) and the reaction was stirred at 60 °C overnight. The reaction mixture was then cooled down to 0 °C, filtered and washed with cold Et_2O. The filtrate was concentrated, diluted with Et_2O and filtered again. Evaporation of the solvent *under vacuum* gave product **IV.3m**.

Yield : 97% (294.1 mg, 1.04 mmol) of a yellow oil and as an inseparable mixture of diastereoisomers.

Major isomer

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 4.40 (t, *J* = 4.9 Hz, 1H, H_2), 3.70 (dq, *J* = 9.7, 6.5 Hz, 1H, H_4), 3.25 (s broad, 1H, NH), 3.17 (dd, *J* = 11.4, 4.7 Hz, 1H, H_1), 2.91 (dd, *J* = 28.2, 8.0 Hz, 1H, H_1), 2.45 – 2.18 (m, 2H, H_5), 1.97 (dd, *J* = 13.1, 6.4 Hz, 1H, H_3), 1.63 – 1.55 (m, 1H, H_3), 0.90 (s, 9H, *t*-Bu of TBS), 0.08 (s, 3H, Me of TBS), 0.07 (s, 3H, Me of TBS).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 126.5 (q, *J* = 277.1 Hz, CF_3), 72.4 (C_2), 55.6 (C_1), 51.3 (q, *J* = 2.8 Hz, C_4), 42.2 (C_3), 40.0 (q, *J* = 26.9 Hz, C_5), 25.9 ($C(\underline{C}H_3)_3$ of TBS), 18.2 ($\underline{C}(CH_3)_3$ of TBS), - 4.7 (Me of TBS), -4.7 (Me of TBS).

^{19}F NMR (δ, ppm) (377 MHz, $CDCl_3$) -64.2 (t, *J* = 11.1 Hz).

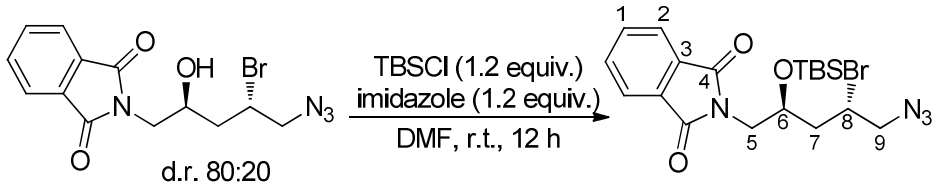
MS (HRMS ESI) Calcd for $C_{12}H_{24}F_3NOSi$ [M+H] 284.1658. Found : 284.1659

Minor isomer

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 4.40 (t, *J* = 4.9 Hz, 1H, H_2), 3.40 (dt, *J* = 13.8, 6.8 Hz, 1H, H_4), 3.25 (s broad, 1H, NH), 3.17 (dd, *J* = 11.4, 4.7 Hz, 1H, H_1), 2.91 (dd, *J* = 28.2, 8.0 Hz, 1H, H_1), 2.45 – 2.18 (m, 2H, H_5), 1.97 (dd, *J* = 13.1, 6.4 Hz, 1H, H_3), 1.63 – 1.55 (m, 1H, H_3), 0.90 (s, 9H, *t*-Bu of TBS), 0.08 (s, 3H, Me of TBS), 0.07 (s, 3H, Me of TBS).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	126.4 (d, *J* = 277.0 Hz, CF_3), 72.9 (C_2), 55.8 (C_1), 52.3 (d, *J* = 2.8 Hz, C_4), 42.1 (C_3), 40.4 (d, *J* = 27.1 Hz, C_5), 25.8 ($C(\underline{C}H_3)_3$ of TBS), 18.1 ($\underline{C}(CH_3)_3$ of TBS), -4.7 (Me of TBS), -4.7 (Me of TBS).
^{19}F NMR (δ, ppm) (377 MHz, $CDCl_3$)	-64.3 (t, *J* = 11.0 Hz).
MS (HRMS ESI)	Calcd for $C_{12}H_{24}F_3NOSi$ [M+H] 284.1658. Found : 284.1659

2-((2S,4S)-5-azido-4-bromo-2-((tert-butyldimethylsilyl)oxy)pentyl)isoindoline-1,3-dione (TBS-IV.4m)



$C_{19}H_{27}BrN_4O_3Si$
MW = 467.4 g.mol^{-1}

Procedure :

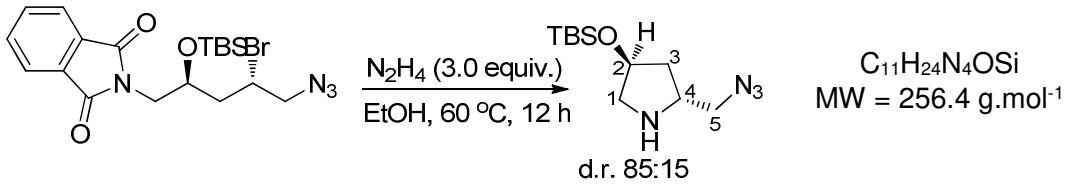
To a solution of **IV.4m** (0.74 mmol, 261.8 mg) and imidazole (1.78 mmol, 123.4 mg) in DMF (2.5 mL) was added TBDMSCl (0.89 mmol, 140.2 mg). The reaction mixture was stirred overnight and then quenched by addition of. The organic materials were extracted twice with EtOAc, and the combined extracts were washed with brine and dried over $MgSO_4$. The removal of the volatile materials *in vacuo* gave a crude residue which was purified by flash column chromatography on silica gel.

Purification :	Flash chromatography : Hexane / EtOAc 20:1.
Yield :	68% (235.2 mg, 0.50 mmol) of a colorless oil. In this case, the major diastereomer of **IV.4m** was preferentially protected as a silyl ether over the minor isomer thus enabling the isolation of **TBS-IV.4m** as a single diastereomer derived from the major isomer of **IV.4m.**
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.86 (dd, *J* = 5.4, 3.1 Hz, 2H, H_1), 7.74 (dd, *J* = 5.4, 3.1 Hz, 2H, H_2), 4.24 (tdd, *J* = 7.7, 5.5, 2.2 Hz, 1H, H_8), 4.16 (dtd, *J* = 8.5, 6.0, 2.5 Hz, 1H, H_6), 3.75 (dd, *J* = 13.7, 5.4 Hz, 1H, H_9), 3.70 (dd, *J* = 11.5, 5.7 Hz, 1H, H_9), 3.65 (dd, *J* = 12.9, 6.1 Hz, 1H, H_5), 3.60 (dd, *J* = 13.0, 5.7 Hz, 1H, H_5), 1.96 (ddd, *J* = 14.6, 9.5, 2.6 Hz, 1H, H_7), 1.85 (ddd, *J* = 14.6, 11.0, 2.3 Hz, 1H, H_7), 0.91 (s, 9H, *t*-Bu of TBS), 0.19 (s, 3H, Me of TBS), 0.18 (s, 3H, Me of TBS).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	168.3 (C_4), 134.3 (C_1), 132.1 (C_3), 123.6 (C_2), 68.0 (C_6), 58.1 (C_8), 49.8 (C_9), 43.8 (C_5), 42.3 (C_7), 25.9 ($C(\underline{C}H_3)_3$ of TBS), 18.1 ($\underline{C}(CH_3)_3$ of TBS), -4.2 (Me of TBS), -4.4 (Me of TBS).

IR (cm^{-1}, neat, NaCl) 2071 (N_3), 1643 (Nphth), 713 (C-Br).

MS (HRMS ESI) Calcd for $C_{16}H_{27}BrN_4O_3Si$ [M+H] 467.1114. Found : 467.1103

(2R,4S)-2-(azidomethyl)-4-((tert-butyldimethylsilyl)oxy)pyrrolidine (IV.5m)



$C_{11}H_{24}N_4OSi$
MW = 256.4 $g.mol^{-1}$

Procedure :

To a solution of **TMS-IV.4m** (0.20 mmol, 96.1 mg) in EtOH (10 mL) was added hydrazine (80% in water, 3.20 mmol, 0.20 mL) and the reaction was stirred at 60 °C overnight. The reaction mixture was then cooled down to 0 °C, filtered and washed with cold Et_2O. The filtrate was concentrated, diluted with Et_2O and filtered again. Evaporation of the solvent *under vacuum* gave product **IV.5m.**

Yield : 96% (50.6 mg, 0.20 mmol) of a colorless oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 4.39-4.35 (m, 1H, H_2), 3.84 (bd s, 1H, NH), 3.67 – 3.57 (m, 1H, H_4), 3.38 (dd, *J* = 12.4, 5.2 Hz, 1H, H_5), 3.33 (dd, *J* = 10.4, 4.7 Hz, 1H, H_5), 3.05 (dd, *J* = 11.7, 4.1 Hz, 1H, H_1), 2.87 (d, *J* = 11.7 Hz, 1H, H_1), 1.85 (dd, *J* = 13.2, 7.0 Hz, 1H, H_3), 1.66 – 1.54 (m, 1H, H_3), 0.86 (s, 9H, *t*-Bu of TBS), 0.04 (s, 3H, Me of TBS), 0.04 (s, 3H, Me of TBS).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 72.9 (C_2), 56.8 (C_5), 55.4 (C_1), 55.3 (C_4), 39.3 (C_3), 25.9 ($C(\underline{C}H_3)_3$ of TBS), 18.1 ($\underline{C}(CH_3)_3$ of TBS), -4.69 (Me of TBS), -4.70 (Me of TBS).

IR (cm^{-1}, neat, NaCl) 3444 (bd, NH), 2100 (N_3).

MS (HRMS ESI) Calcd for $C_{11}H_{25}N_4OSi$ [M+H] 257.1798. Found : 257.1802

université PARIS-SACLAY | ÉCOLE DOCTORALE INTERFACES Approches Interdisciplinaires : Fondements, Applications et Innovation

Title : Development of new reactions of organic synthesis catalyzed by gold and copper.

Key words : gold, copper, catalysis, trifluoromethyl

Summary :

This manuscript presents the development of gold- and copper-catalyzed methods for the synthesis of heterocyclic compounds and trifluoromethylated products.

Firstly, a gold-catalyzed synthesis of trifluoromethyl allenes was developed, relying on a 1,5 hydride shift. This method allows to access, in a very efficient and selective way, a large range of perfluoroalkylated allenes, of which the synthetic potential was also demonstrated.

Afterwards, the catalytic power of gold was then used in a synthesis of *2H*-1,3-oxazines, relying on a *6*-endo type cyclization of azide-yne substrates. This methods allows to access, in very mild condition, an unprecedently large range of polysubstituted oxazines in excellent yields.

Finally, a method for the copper-catalyzed radical hydrofunctionalization of alkenols was developed. The strategy involved relies on a 1,5 hydrogen abstraction, in which a benzyloxy moiety plays the role of the hydrogen donor.

Titre : Développement de nouvelles réactions de synthèse organique catalysées à l'or et au cuivre.

Mots clés : or, cuivre, catalyse, trifluorométhyl

Résumé :

Cette thèse décrit le développement de nouvelles méthodes de catalyse à l'or et au cuivre pour la synthèse de composés hétérocycliques et de produits trifluorométhylés.

Dans un premier temps, une synthèse d'allènes trifluorométhylés par catalyse à l'or a été développée, dont l'étape clé est un transfert d'hydrure 1,5. Cette méthode donne accès de manière efficace et sélective à une large gamme d'allène perfluoroalkylés dont le potentiel synthétique a également été démontré.

Le pouvoir catalytique de l'or a alors été utilisé dans une synthèse de *2H*-1,3-oxazines reposant sur une cyclisation de type *6-endo* d'azido alcynes. Cette méthode donne accès dans des conditions très douces à une gamme sans précédent d'oxazines polysubstituées avec d'excellents rendements.

Dans un dernier temps, une méthode d'hydrofonctionnalisation radicalaire d'alcènols catalysée au cuivre a été développée. La stratégie impliquée repose sur une abstraction d'hydrogène 1,5, dans laquelle un groupement benzyloxy joue le rôle de donneur d'hydrogène.