Multicomponent Reactions toward Heterocycles and Tsuji-Trost Reaction of Allylic Nitro Derivatives

Shuanglong Jia

université PARIS-SACLAY

ENSTA ParisTech université PARIS-SACLAY

NNT : 2018SACLY012

Multicomponent Reactions toward Heterocycles and Tsuji-Trost Reaction of Allylic Nitro Derivatives

Thèse de doctorat de l'Université Paris-Saclay
préparée à École Nationale Supérieure
de Techniques Avancées

École doctorale n°573 : interfaces : approches interdisciplinaires, fondements, applications et innovation (Interfaces)
Spécialité de doctorat: Chimie

Thèse présentée et soutenue à PALAISEAU, le 12 Octobre 2018, par

M. Shuanglong JIA

Composition du Jury :

M. Philippe DAUBAN Directeur de Recherche, ICSN (CESOC)	Président
M. Maxime VITALE Chargé de Recherche (CR1), CNRS (Équipe CSB2D)	Rapporteur
Mme. Laurence GRIMAUD Directrice de Recherche, ENS (Département de chimie)	Rapporteur
M. Laurent ELKAIM Professeur, ENSTA Paris-Saclay (UCP)	Directeur de thèse

Thèse de doctorat

Multicomponent Reactions toward Heterocycles and Tsuji-Trost Reaction of Allylic Nitro Derivatives

Thèse de doctorat de l'Université Paris-Saclay
préparée à École Nationale Supérieure
de Techniques Avancées

École doctorale n°573 : interfaces : approches interdisciplinaires, fondements, applications et innovation (Interfaces)
Spécialité de doctorat: Chimie

Thèse présentée et soutenue à PALAISEAU, le 12 Octobre 2018, par

M. Shuanglong JIA

Composition du Jury :

M. Philippe DAUBAN	
Directeur de Recherche, ICSN (CESOC)	Président
M. Maxime VITALE	
Chargé de Recherche (CR1), CNRS (Équipe CSB2D)	Rapporteur
Mme. Laurence GRIMAUD	
Directrice de Recherche, ENS (Département de chimie)	Rapporteur
M. Laurent ELKAIM	
Professeur, ENSTA Paris-Saclay (UCP)	Directeur de thèse

Table of contents

ACKNOWLEDGEMENTS

First I would like to thank all French people who helped me in their ways during I live in Paris.

The thesis was carried out at **Ecole Nationale Supérieure de Techniques Avancées-ENSTA,** under the direction of **Prof. Dr. Laurent EL Kaïm**.

I do thank my PhD directors **Prof. Dr. Laurent EL Kaïm** for welcoming me to join his group, and giving me an opportunity to work as a member of his research group. He always gives me lots of help whenever I needed him during my doctoral programme. He is very understanding and kind, he takes the time to get to know his students as individuals and for that I am sincerely grateful. I thank him from the bottom of my heart for his keen guidance and efforts he has put into me in the scientific training field.

My sincere thanks to M. Philippe Dauban for agreeing to act as the president of the jury, I also thank to members of the jury and rapporteur of this thesis M. Maxime Vitale and Mme. Laurence Grimaud, I sincerely thank them for reading this thesis and evaluating critically. Their comments have been instrumental in making this thesis more effective and I am grateful for their valuable suggestion and information they have shared with me.

I want to thank Vincent Jactel for helping me analyze the HRMS of all my synthesized compounds.

I also thank Aurélie Dos Santos, researcher Sébastien Prévost, Dr. Noisette Narboni, Mansour Dolè Kerim, Dr. Alaa Zidan and other PhD students, Postdoctors and visiting students. They really gave me a lot of support in the lab.

Finally, I thank the CSC (China Scholarship Council) for founding of my all research in France.

Résumé

Les réactions multicomposants (MCRs) sont des transformations utiles qui permettent à au moins trois composés de réagir en une seule étape pour former un seul produit final, qui comprend la totalité ou la plupart des atomes des produits de départ (figure 1). Elles impliquent généralement une séquence d'étapes élémentaires conduisant à la formation et à la rupture de différentes liaisons, qui se déroulent séquentiellement jusqu'à atteindre une étape irréversible permettant d'obtenir le produit final.

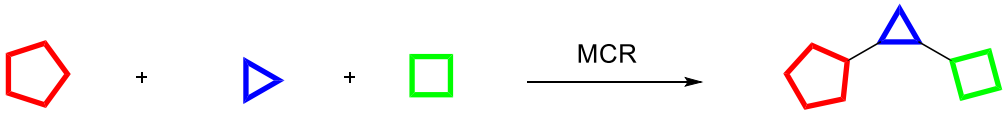


figure 1 une représentation simplifiée de MCRs

Les réactions multicomposants associées à leurs réactions de post-condensation constituent une stratégie de synthèse particulièrement intéressante pour la construction de structures complexes. La grande diversité structurales et la facilité d'accès à des librairies de composés organiques de taille importante associées au développement de nouvelles techniques de « screening haut débit » ont joué un rôle important dans la mise au point de nouveaux médicaments au cours des vingt dernières années.

Un grand nombre de MCRs ont été décrites dans la littérature. Les réactions de Mannich sont probablement les reactions à trois composants les plus importantes, alors que les MCRs à base d'isonitriles sont mieux connues en raison de la grande efficacité des réactions d'Ugi. Dans le cadre de cette thèse, nous nous sommes intéressés à l'utilisation de la réaction de Passerini, un couplage à trois composants à base d'isonitriles. Nous avons ensuite développé une nouvelle réaction de Mannich des hydrazones. La dernière partie de la thèse a été consacrée à une nouvelle réaction de Tsuji-Trost des dérivés nitrés.

La réaction de Passerini fournit un accès rapide aux α-acyloxycarboxamides (schéma 1). La

réaction est très générale, donnant des produits d'addition avec des rendements élevés lorsque les réactions sont effectuées à température ambiante et à forte concentration (molaire ou sans solvant).

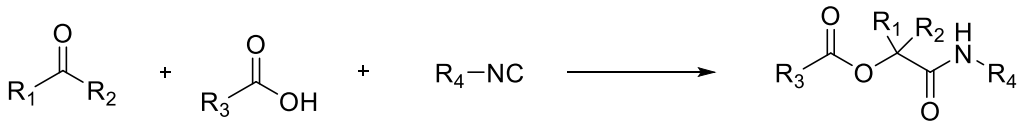
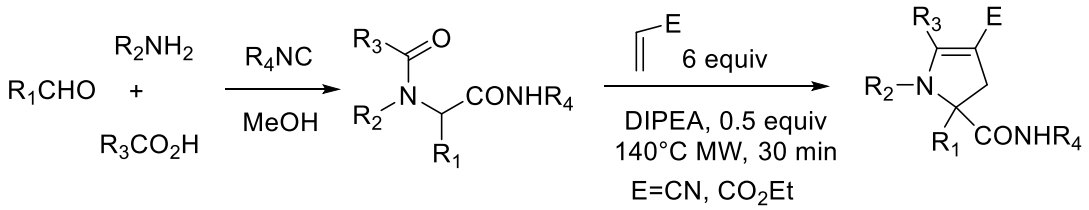


schéma 1 Passerini reaction

L'intérêt synthétique de ces réactions peut encore être augmenté par de simples transformations des adduits de Passerrini (appelées post-condensations) conduisant à des structures plus intéressantes telles que des composés hétérocycliques biologiquement actifs. Le groupe de recherche de l'ENSTA a récemment lancé un programme visant à évaluer le potentiel des adduits d'Ugi dans des réactions intermoléculaires afin d'étendre la diversité structurale accessible par cette réaction. Nous avons été particulièrement intéressés par des additions de Michael sur à la position peptidique des adduits d'Ugi. Malgré la capacité de modifier la nucléophilie du produit d'addition d'Ugi en sélectionnant correctement le partenaire aldéhyde de départ, nous n'avons observé aucun produit addition. Néanmoins, une cycloaddition de type [3 + 2] de ces derniers avec de l'acrylonitrile conduisant à des dérivés du pyrrole a été découverte (schéma 2). Nous avons ensuite décidé d'explorer le comportement des adduits de Passerini dans des réactions similaires. Cette étude a conduit à une nouvelle préparation de γ-butyrolactones, elle fait l'objet de la première partie de la thèse.

Synthèse du pyrrole sur les additifs de Micheal sur les adduits d'Ugi:



Mon travail: les butyrolactones à travers Passerini / Michael tandem

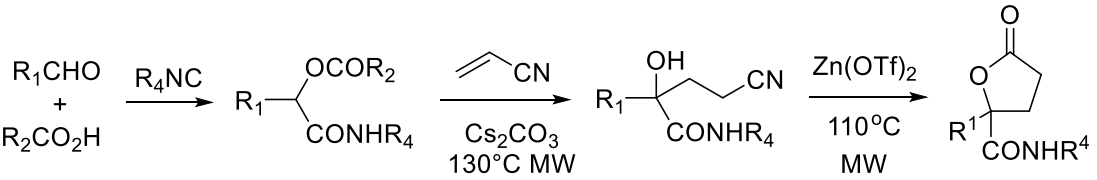


schéma 2

Dans ce contexte, une bibliothèque de produits d'addition de Passerini a été préparée en faisant varier les 3 composants de la réaction. Les α-acyloxycarboxamides ont été obtenus avec des rendements allant de 77 à 99%. Nos essais d'additions de Michael nous ont montré qu'il n'était pas possible de conserver la fonction ester en milieu basique, l'alcool se formant très vite en milieu basique. L'addition d'acrylonitrile sur ce dernier n'a pu être observée dans des conditions douces. Néanmoins, en travaillant avec un large excès d'acrylonitrile (5 équivalents) et au microonde à 130°C, il nous a été possible d'obtenir la formation d'un adduit de Michael en partant directement de l'adduit de Passerini. Dans ce cas, l'utilisation de 2.2 équivalents de Cs_2CO_3 permet de réaliser la saponification et l'addition de Michael dans une même séquence réactionnelle. En exploitant ces conditions, nous avons pu réaliser la synthèse d'une famille d'hydroxynitriles avec des rendements variant de 61 à 95% (schéma 3). Bien que la formation de l'alcool **1** avec perte du fragment acétate ne soit pas bon en termes de diversité, il offre une opportunité intéressante pour la préparation de butyrolactones par cyclisation de l'alcool sur le groupe nitrile.

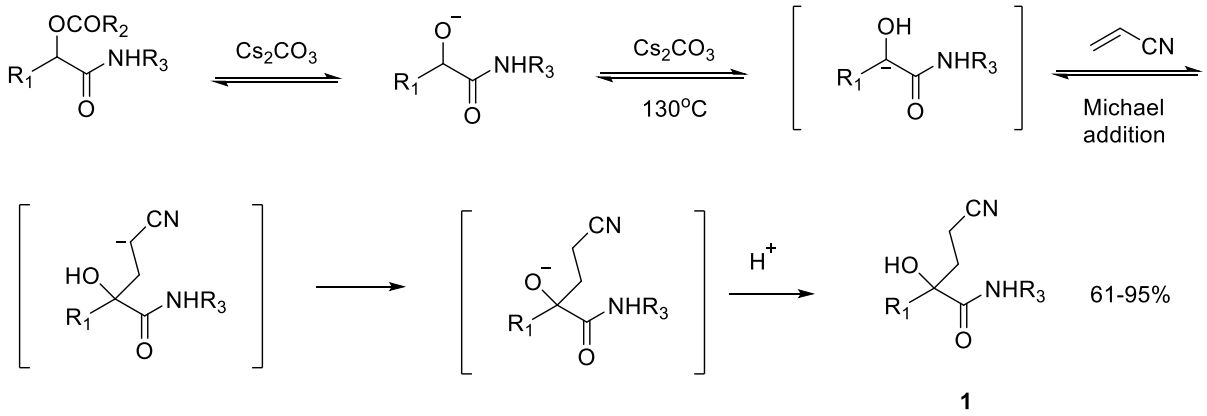


schéma 3 Mécanisme proposé

De manière surprenante la cyclisation des hydroxynitriles s'est révélée difficile à réaliser. Nous avons pu néanmoins observer la formation des γ-butylactones attendues en chauffant les hydroxynitriles à température élevée dans un solvant relativement acide comme le trifluoroéthanol et en présence d'une quantité catalytique de triflate de zinc. Les rendements obtenus sont bons allant de 50 à 92% (schéma 4).

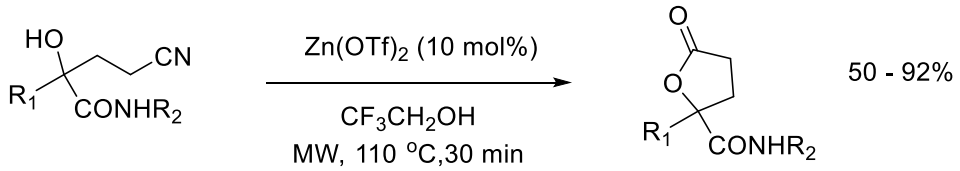


schéma 4

Dans la deuxième partie de la thèse, nous nous sommes intéressés à la réaction de Mannich des hydrazones. La réaction de Mannich est une préparation classique de β-amino-cétones et d'aldéhydes (bases de Mannich) à partir d'aldéhydes ou de cétones enolisables et d'amines. Décrite pour la première fois avec des cétones enolisables, la réaction a été étendue à divers nucléophiles au cours des décennies suivantes.

La réaction de Mannich des hydrazones N-H a été proposée pour la première fois par Keil et

Ried en 1959. La réaction avait été décrite uniquement avec du formaldéhyde et des N-H hydrazones relativement acides susceptibles d'être déprotonées facilement par une amine dans les conditions de la réaction. Contrairement au comportement habituel des anions hydrazonyles dans des alkylations par des halogénures d'alkyles, la réversibilité des attaques sur l'azote de l'hydrazone conduit à une fonctionnalisation au niveau du carbone de l'hydrazone (schéma 5).

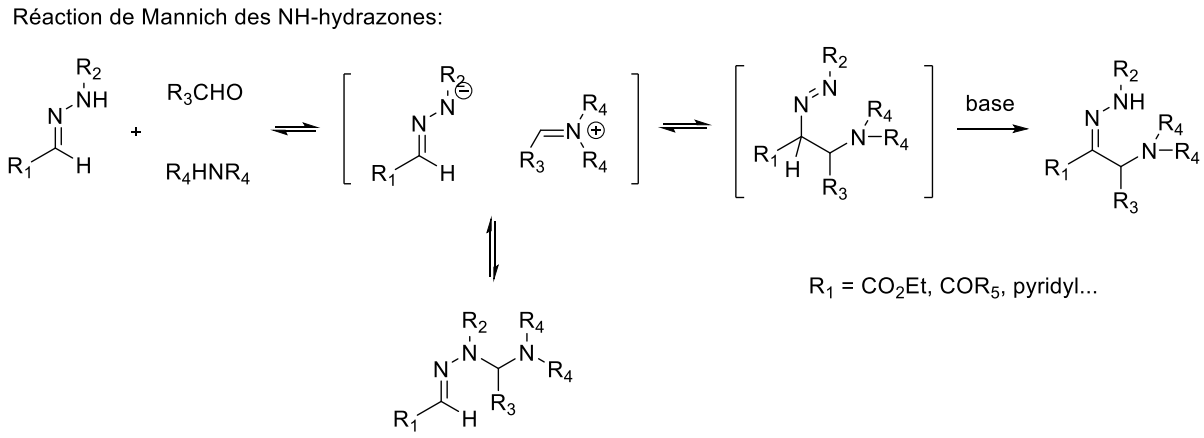


schéma 5

Une tautomérie azo-hydrazone irréversible est indispensable pour l'efficacité du procédé, cette isomérisation n'est observée qu'en milieu basique. Ceci explique la nécessité de substituer l'hydrazone par des groupements attracteurs (cétone, ester ou groupement pyridyle en α de la fonction azo) afin d'augmenter l'acidité de l'intermédiaire azoïque. Compte tenu de ces limitations, nous avons envisagé qu'une NH-hydrazone dérivée du trifluoroacétaldéhyde puisse être suffisamment acide pour être impliquée dans des couplages de type Mannich efficaces. Les adduits de Mannich résultant de cette réaction pourraient par la suite être convertis en différents composés hétérocycliques trifluorométhylés (schéma 6).

Mon travail: Réaction de Mannich des trifluorohydrazones:

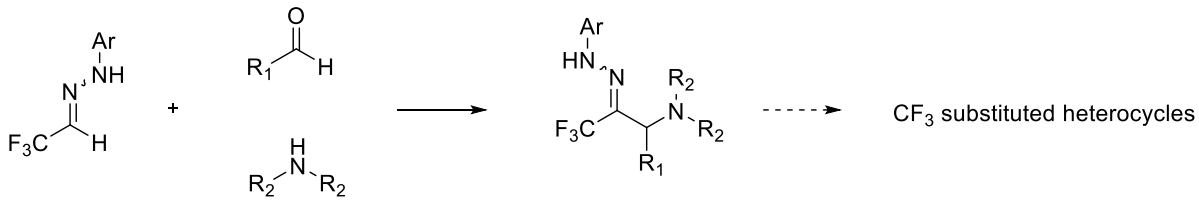


schéma 6

La 4-nitrophényl hydrazone, obtenue avec un rendement de 90% à partir de 4-nitrophényl hydrazine et de trifluoroacétaldéhyde, a été initialement choisie pour maximiser nos chances d'observer un couplage en raison de son acidité plus élevée et de l'effet bénéfique d'un substituant nitro observé dans nos études précédentes sur les couplages de Mannich des hydrazones. Ce choix nous a permis d'obtenir un couplage efficace dans des conditions proches de celles mise au point pour les produits non fluorés. Ensuite, nous avons préparé une bibliothèque de produits d'addition de Mannich en faisant varier les 3 composants de la réaction, et dans le toluène comme solvant. Les nouvelles NH-arylhydrazones C-fonctionnalisées ont été obtenues avec d'excellents rendements dans la plupart des exemples (schéma 7).

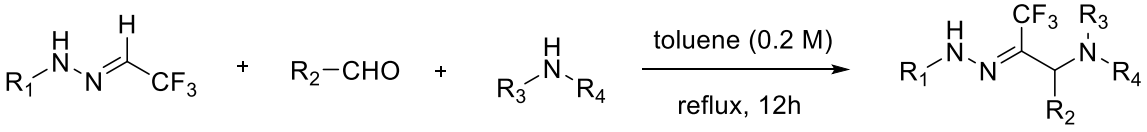


schéma 7

Ces réactions conduisent à de bons rendements principalement avec des amines cycliques secondaires. Dans le cas des amines primaires telles que 1'allylamine ou la 4-méthoxybenzylamine, nous avons pu observer la formation d'une famille de 1,2,4-triazines trifluorées par chauffage de la 4-nitrophénylhydrazone issue du trifluoroacétaldéhyde avec deux équivalents de formaldehyde (schéma 8).

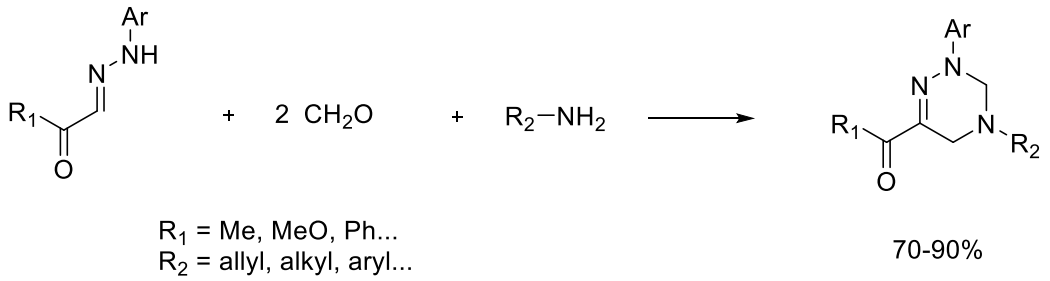


schéma 8

Les applications potentielles des adduits de Mannich obtenus sont principalement associées à la capacité de ces produits de fournir des azoalcènes trifluoromethylés par chauffage à une temperature suffisante pour éliminer l'amine. La formation des azoalcènes à principalement été observées à partir d'hydrazones chlorées ou bromées par réaction d'élimination 1,4 en présence d'une base (schéma 9). La plupart des azoalcènes pauvres en électron sont instables, ils réagissent particulièrement bien dans des réactions de Diels-Alder avec des dienophiles riches en électron.

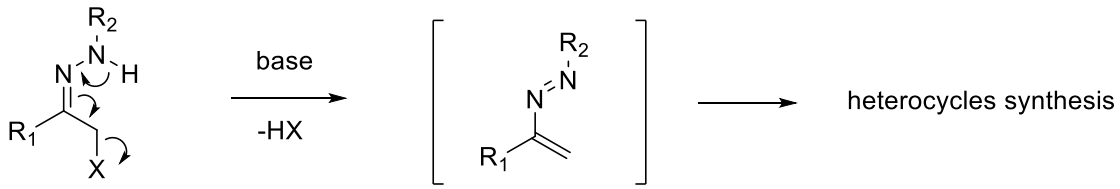


schéma 9

Bien que moins décrite, la préparation des azoalcènes directement à partir d'hydrazonoamines est aussi possible. Elle est en générale observée dans des conditions thermiques (température supérieure à 100°C) et avec des amines volatiles afin d'éviter une réaddition de Michael de l'amine conduisant au produit de départ. Malgré le point d'ébullition relativement élevé de nos amines secondaires, nous avons pu observer la formation d'azoalcènes et leur réaction avec des cétoesters dans des réactions de cycloadditon

de type Diels-Alder conduisant à la formation de 1,2-diazines avec des rendements allant de 58 à 90% (schéma 10). Les cétoesters, ont été utilisés en solvant, ceci permet de pieger l'amine libérer lors de la formation de l'azoalcène tout en formant une enamine plus nucléophile que le cetoester de depart.

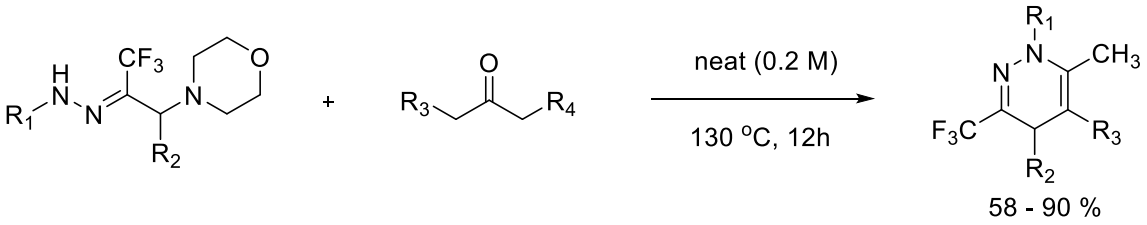


schéma 10

Les résultats expérimentaux ont confirmé nos hypothèses mécanistes initiales: l'élimination thermique de la morpholine permet la formation d'un intermédiaire d'énamine engagé dans une addition de Michael avec l'azoalkène. La cyclisation et l'élimination de la morpholine donnent finalement la 4-hydropyridazine (schéma 11).

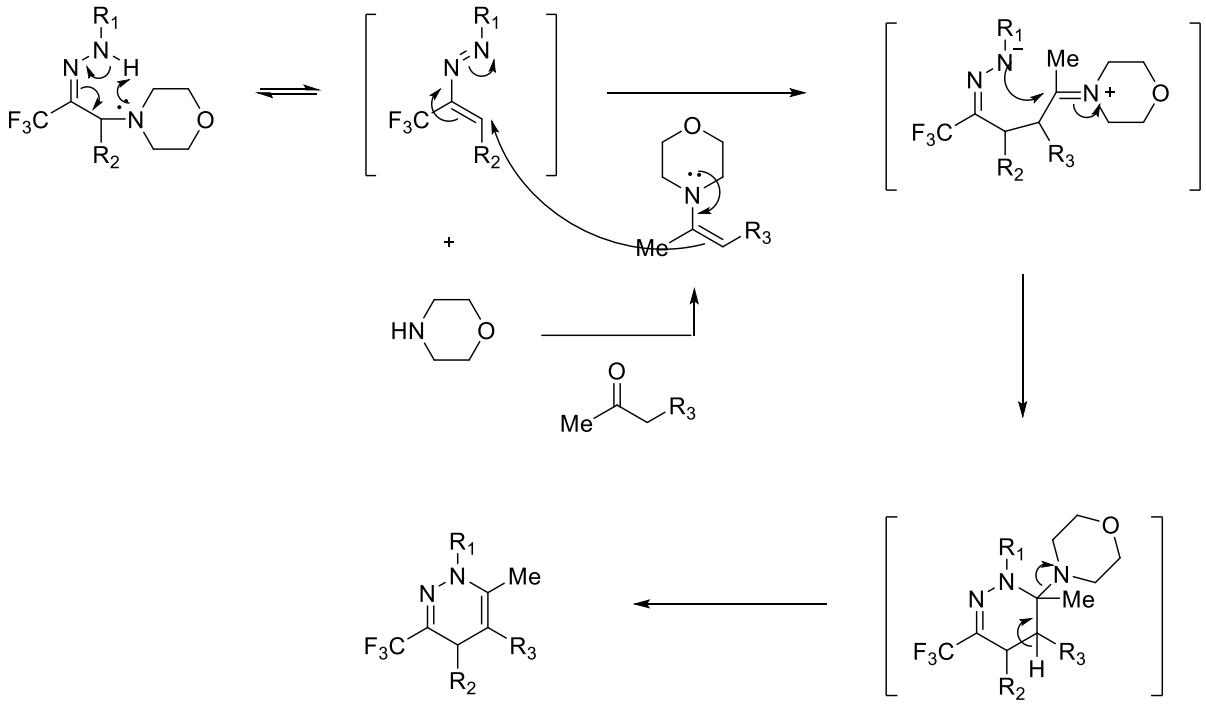


schéma 11 mécanisme proposé

Dans la dernière partie de la thèse, nous avons exploré le potentiel des dérivés nitrés dans les réactions de Tsuji-Trost. L'allylation de nucléophiles carbonés catalysée par le palladium avec des composés allyliques via des complexes π-allylpalladium est appelée réaction de Tsuji-Trost (schéma 12).

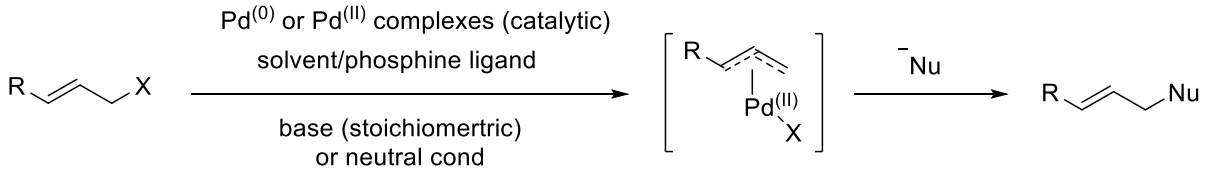


schéma 12

Il est proposé que le palladium coordonne la double liaison du groupe allyle formant un complexe η2 π-allyl-Pd0. Dans l'étape suivante d'addition oxydante, le groupe partant est expulsé avec inversion de configuration et un η3 π-allyl-PdII est créé (étape également

appelée ionisation). Le nucléophile s'additionne ensuite en régénérant le complexe η2 π-allyl-Pd0. Enfin, la dissociation des espèces actives libérent à la fois le produit désiré et le catalyseur au palladium qui intervient à nouveau dans le cycle catalytique (schéma 13).

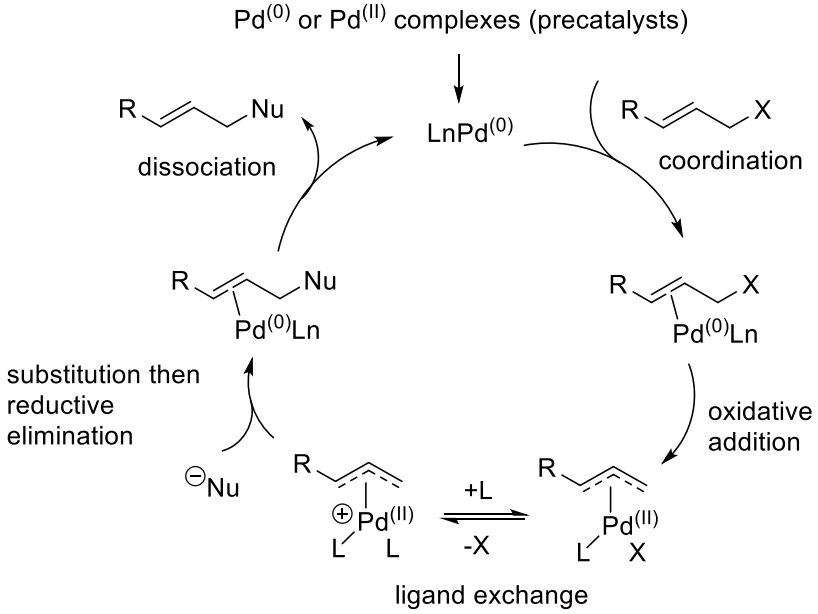


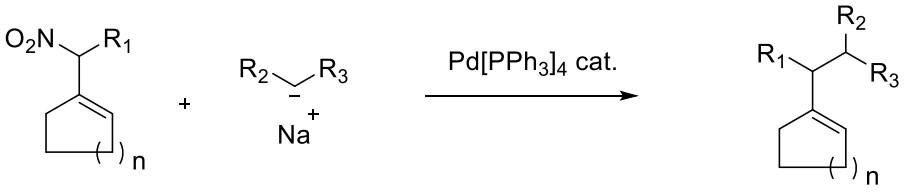
schéma 13

Les nitroalcanes représentent une des familles chimiques les plus polyvalentes et les plus précieuses de la synthèse organique en raison des modifications fonctionnelles très simple du groupe nitro (réduction, oxydation) et du caractère fortement électronégatif de ce dernier. En effet, les nitroalcanes ont tendance à donner, dans des conditions basiques douces, des carbanions stabilisés (anions nitronates) qui sont d'excellents nucléophiles et conduisent à la formation de liaisons carbone-carbone, dans des réactions telle que la réaction de Henry, ou les additions de Michael ou de Mannich.

Contrairement à ces réactions importantes décrites il y a plusieures décennies, la transformation des composés nitro catalysée par des métaux de transition a peu progressé, se limitant principalement à la transformation réductrice du nitro en dérivés d'amines par

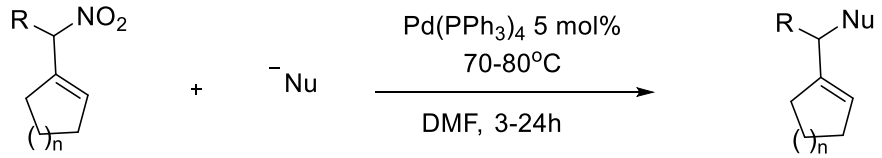
différents donneurs d'hydrogène. Ceci est particulièrement vrai pour les réactions catalysées par le palladium aussi bien sur les composés nitrés aromatiques que les aliphatiques. Il existe cependant quelques rapports dans la littérature où des dérivés nitrés allyliques et benzyliques réagissent avec un catalyseur au palladium (0) pour conduire à l'insertion du métal dans la liaison carbone-NO_2 et au remplacement du nitro par divers dérivés nucléophiles tels que les dérivés malonyles.

Le travail de Hegedus:



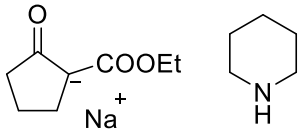
n = 0, 1, 2 R_1 = H, Me R_2, R_3 = COOMe, CN, COOEt

Le travail de Tamura:



R = H, Me n = 1, 2, 3, 4, 8 52-91%

Nu = $NaCH(COOMe)_2$,



n-Pr_2NH

schéma 14

Bien que ces réactions de Tsuji-Trost des produits nitrés permettent d'accéder à des dérivés hautement fonctionnalisés, ces réactions ont été peu exploitées en synthèse. Stimulés par notre intérêt pour les réactions de Tsuji-Trost, nous avons envisagé qu'en l'absence d'un groupe nucléophile potentiel, l'intermédiaire π-allylique dérivé de composés nitro pourrait offrir dans des conditions basiques un accès intéressant à différents composés dièniques (schéma 15). Associé à la formation préalable de composés nitrés, ce processus d'élimination

pourrait fournir une stratégie de synthèse précieuse pour la formation de diènes fortement fonctionnalisés. Le travail de mon collègue Mansour Dolè Kerim a ainsi démontré la pertinence de cette approche sur des dérivés nitrés issus de la cyclohexanone (schéma 15). Il ne nous a malheureusement pas été possible de valoriser les diènes formés dans ce cas dans des réactions ultérieures aboutissant à la formation de produits polycycliques.

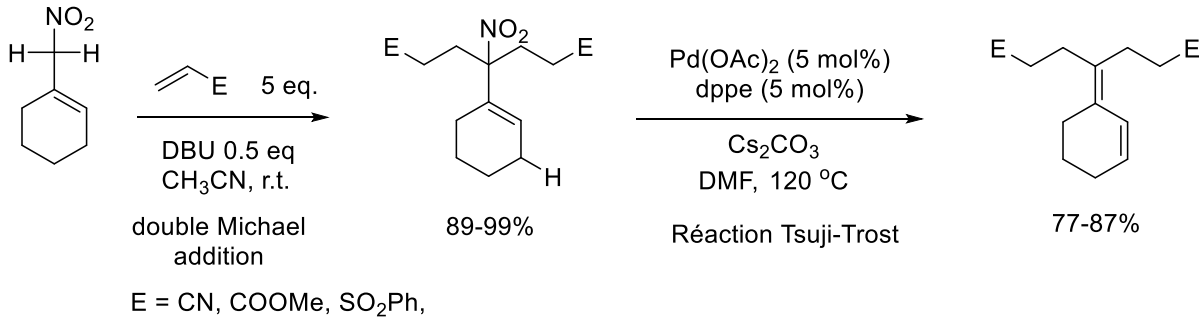


schéma 15

Nous avons envisagé qu'avec un autre noyau benzénique fusionné avec le 1- (nitrométhyl) cyclohex-1-ène, et donc en travaillant avec des dérivés de la tétralone, il nous serait possible d'accéder à des dérivés de naphtalènes plus intéressants sur le plan synthétique (schéma 16).

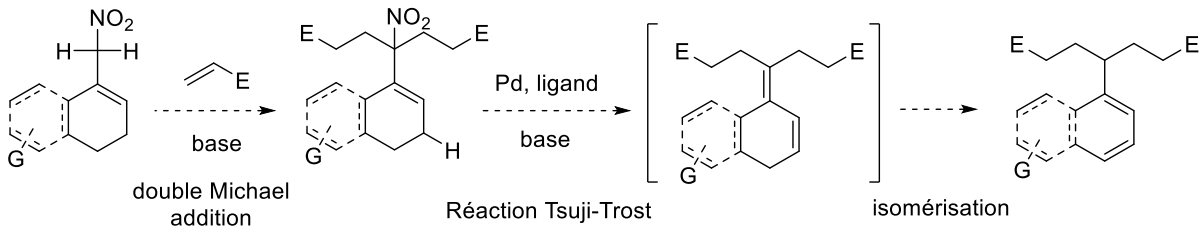
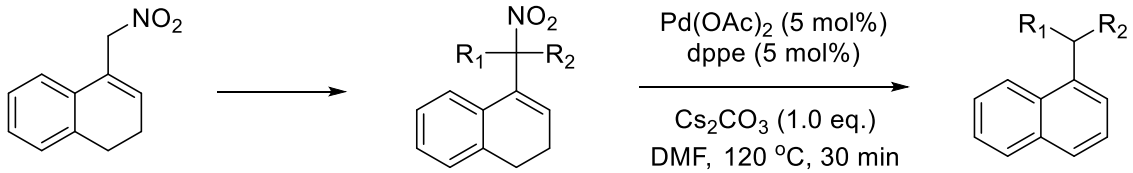


schéma 16

Mon travail sur ce sujet a donc consisté à étendre la formation de diènes mise au point par

Mansour sur des dérivés de tétralone. Si les composes niters de depart se sont révélés plus difficile à former que dans le cas des dérivés de la cyclohexanone, nous avons pu réaliser très facilement l'élimination du groupement nitro dans des conditions proches de celles mises au point par Mansour. Une série de dérives naphthalènique a ainsi pu être préparée avec des rendements allant de 66 à 87% (schèma 17).



R_1= H, CH_2CH_2COOMe, CH_2CH_2CN, CH_2CH_2COMe, CH_2OAC...

R_2= H, CH_2CH_2COOMe, CH_2CH_2CN....

66 - 87 %

schèma 17

Cette approche a principalement été développée sur des dérivés du naphtalène. Nous avons pu cependant démontrer qu'il était possible de modifier le noyau aromatique de ce système pour obtenir des indoles fonctionnalisés par cette méthode. Faute de temps, un seul exemple a été réalisé mais ceci démontre la généralité de l'approche et son potentiel en synthèse hétérocyclique (schéma 18).

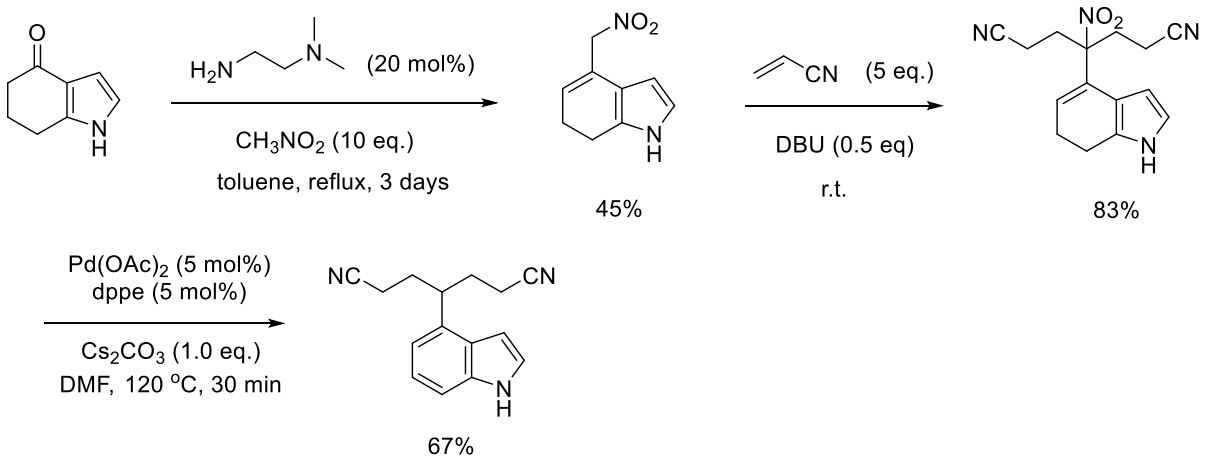

O
N
H
H2N
N
(20 mol%)
CH3NO2 (10 eq.)
toluene, reflux, 3 days
NO2
N
H
45%
CN (5 eq.)
DBU (0.5 eq)
r.t.
NC
NO2
CN
N
H
83%
Pd(OAc)2 (5 mol%)
dppe (5 mol%)
Cs2CO3 (1.0 eq.)
DMF, 120 °C, 30 min
NC
CN
N
H
67%

schéma 18

List of Abbreviations

Functional Groups

Ac	acyl
OAc	acetate
Me	methyl
OMe	methoxy
Et	ethyl
OEt	ethoxy
Bu	butyl
Pr	propyl
cy	cyclohexyl
Ar	aryl
Ph	phenyl
Bn	benzyl
Bz	benzoyl
Boc	tert-butyloxycarbonyl
TMS	trimethylsilyl
OTf	triflate
Ts	tosyl (p-toluenesulfonyl)
CF_3	trifluoromethyl
t-Bu	tert-butyl
i-Pr	isopropyl
NO_2	nitro

Chemical Compounds

MsOH	methanesulfonic acid

HCl	hydrochloric acid
dppe	1,2-bis(diphenylphosphino)ethane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIPEA	diisopropylethylamine
TEBAC	triethylbenzylammonium chloride
DABCO	1,4-diazabicyclo[2.2.2]octane
CH_2N_2	diazomethane
m-CPBA	3-Chloroperbenzoic acid

Solvents

DCM	dichloromethane
DCE	1,2-dichloroethane
THF	tetrahydrofuran
EtOH	ethanol
MeOH	methanol
MeCN	acetonitrile
DMSO	dimethylsulfoxide
DMF	dimethylformamide
DMAP	4-dimethylaminopyridine

Others

aq.	aqueous
r.t.	room temperature
MW	micro-wave
M.S.	molecular Sieve
M.p.	melting point
M.W.	molecular weight
pKa	acidity constant

Nu	nucleophilic
hv	light
E	electrophilic
equiv.	equivalent
cat.	catalytic
t	reaction time
T	temperature
d.r.	diastereomeric ratio
ee	enantiometric excess
EWG	electro-withdrawing group
EDG	electro-donating group
LG	leaving group
L	ligand
C	catalyst

Measuring Units

°C	degree celsius
h	hour
Hz	Hertz
min	minute
g	gram
ppm	particle per million
mol	mole
M	Molar (mol/L)

Chromatography and spectroscopy

TLC	thin-layer chromatography
Rf	retention factor (chromatography)

J	coupling constant
IR	infra-red
HRMS	high resolution mass spectrometry
m	multiplet
s	singlet
d	doublet
t	triplet
NMR	nuclear magnetic resonance
q	quadruplet

General introduction

The past few decades witnessed the development of organic chemistry. A large group of organic molecules exhibited various biological activities which is basis of life and society. However, chemists are still facing a challenge of designing chemical reactions that are highly capable in providing most of the elements of structural complexity and diversity with minimum synthetic steps for the particular molecules with interesting properties. Multicomponent reactions served an access to this “ideal synthesis” with high atoms economy and other advantages.

One major target of this thesis is to discover some new multicomponent reactions and further develop them in heterocyclic synthesis; the other one is to synthesize naphthalene derivatives via palladium catalyzed Tsuji-Trost elimination sequences.

The first chapter will give a brief introduction of isocyanides and multicomponent reactions.

In chapter two, we will illustrate the reactivity of Passerini adducts and their application toward butyrolactones via a Passerini/Michael pathway. The Passerini adducts of aromatic aldehydes act as nucleophiles in Michael additions with acrylonitrile. The reaction proceeds together with hydrolysis of the ester. The resulting γ-hydroxynitrile can be cyclized under acidic conditions to afford γ-butyrolactones.

The third chapter will investigate the Mannich reaction of trifluoromethyl directed hydrazones. The NH-aryl hydrazones derived from trifluoroacetaldehyde hemiacetal can be involved in efficient Mannich type reactions with formaldehydes and aromatic aldehydes. The resulting hydrazones are useful building blocks for the preparation of trifluoromethyl substituted 1,2-diazine derivatives under heating with β-ketoesters.

In chapter four, we will explore the possibility of obtaining naphthalene through Tsuji-Trost

reaction. This reaction may involve the formation of a palladium p-allyl complex followed by a base promoted β-hydride elimination. This reaction combined with the condensation of fused cyclic ketones with nitromethane and the functionalization of the resulting nitrocycloalkenes (Michael, Mannich...) constitute a very powerful synthetic tool for the formation of 1-substituted naphtalenes.

The last part of this context will include the experimental part involving all the procedures employed for the different syntheses, the spectral data and interpretations for all of the organic compounds prepared during the whole study of this thesis.

Chapter I Isocyanides and multicomponent reactions

1. Multicomponent reactions (MCRs)

1.1 Advantages of multicomponent reactions (MCRs)

Over the past decades, organic-chemical syntheses have reached a high degree of skillfulness.[1] It proposed a challenge of obtaining chemical compounds, especially some natural products and drugs, with high efficiency and sustainability. In conventional way, the structural complexity of the molecules often requires multiple synthetic steps, diversified substrates and reagents, harsh reaction conditions and difficulties in the isolation and purification of products, leading to extremely laborious and costly experimental procedures.[2] Hence, the need for an alternative method to conventional multistep synthesis is compulsory.

A number of multicomponent reactions (MCRs) meet the "ideal synthesis" (figure1-1) requirement such as atoms economy, steps with high chemical yields, the use of convergent one-pot reactions, less aggressive reactions conditions to the environment, accessible and cheap substrates, easy operation together with a considerable advantage of this methodology, the ability to quickly build a library of varied and structurally complex compounds.[3]

[1] A.Domling, I. Ugi, *Angew. Chem., Int. Ed.* **2000**, *39*, 3168-3210.
[2] J. Ramon, M. Yus, *Angew Chem Int Ed.* **2005**, *44*, 1602-1634
[3] (a) J. Zhu, Eur. *J. Org. Chem*. **2003**, *2003*, 1133. (b) J. Zhu, H. Bienaymé, Eds. *Multicomponent Reactions; Wiley-VCH: Weinheim, Germany*, **2005**. (c)A. Dömling, *Chem. Rev.* **2006**, *106*, 17.

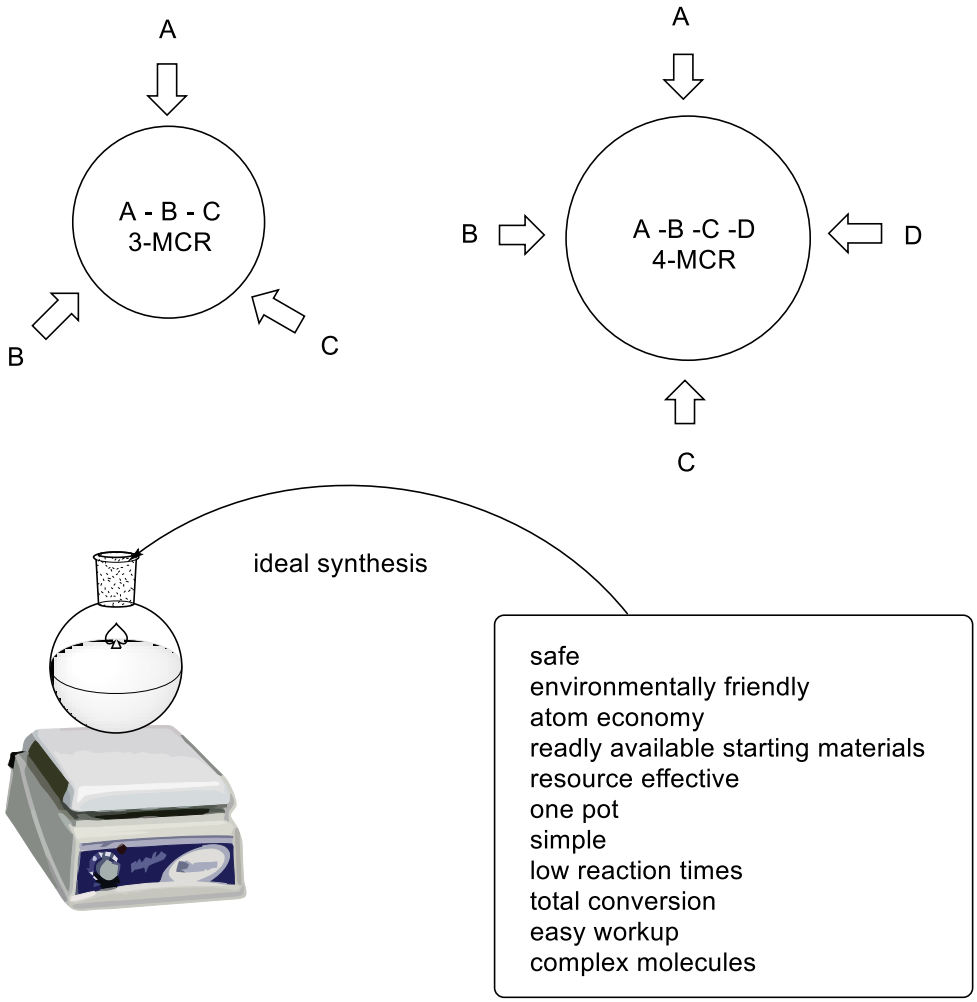


figure 1-1 Schematic representation of multicomponent reactions of three (3-MCR) and four (4-MCR) components.

1.2 Principles of multicomponent reactions

Multicomponent reactions (MCRs) are useful transformations that allow at least three starting materials combined together in only one reaction to form a single final product, which include all or most of the atoms of the starting components (figure 1-2).

They consist of a sequence of elementary stages involving bond breaking and bond formations, which proceed sequentially till reaching an irreversible final step to afford the final product.

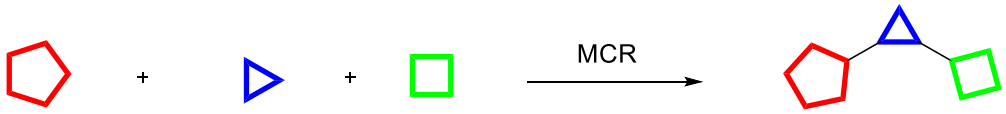


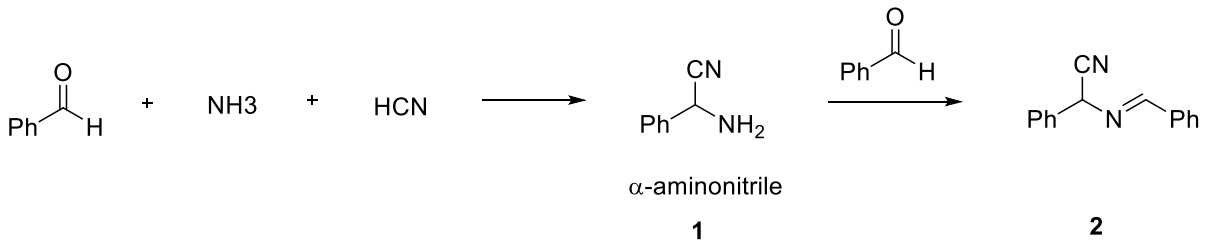
figure 1-2 a simplified representation of MCRs

They can be considered as a special class of tandem reactions as they just allow all starting substrates mixed and react with each other in a single reaction flask without additional modifications of the reaction conditions.

Multicomponent reactions together with their post condensation reactions constitue a particularly attractive synthetic strategy. They provide rapid and efficient accessibility to large libraries of organic compounds with different substituents. Such diversity and easy accessibility to a large number of organic compounds along with the available screening techniques play a significant role in the drug discovery processes.

1.3 History of multicomponent reactions

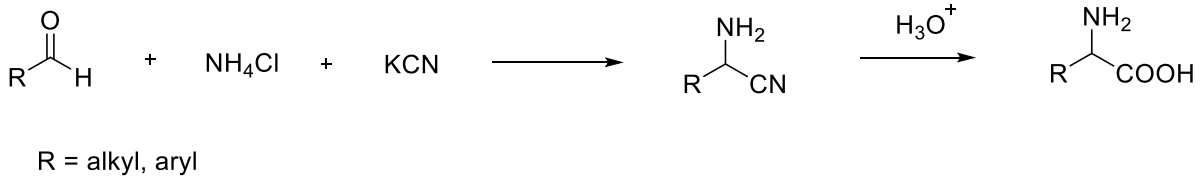
It has been more than 180 years since the first description of a multicomponent reaction was documented by Laurent and Gerhardt, in 1838, who isolated the compound **2** from the intermediate **1** α-aminonitrile which was obtained from reaction between benzaldehyde, hydrocyanic acid and ammonia (scheme 1-1).[4]



scheme 1-1

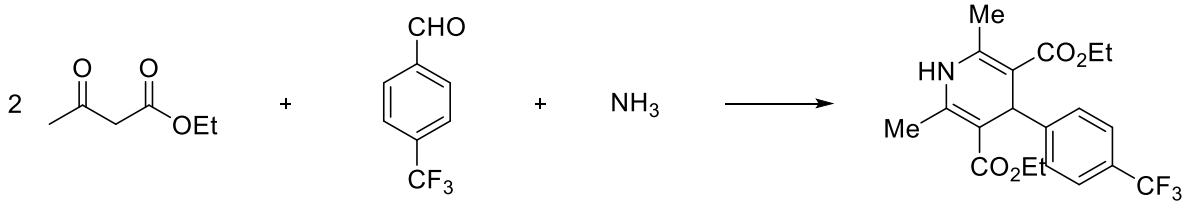
[4] A. Laurent, *Gerhardt CF. Ann Pharm.* **1838**, *28*, 265.

In 1850, Strecker synthesized α-amino acids from α-aminonitriles obtained from condensation of an aldehyde with ammonium chloride in presence of potassium cyanide (scheme 1-2).[5]



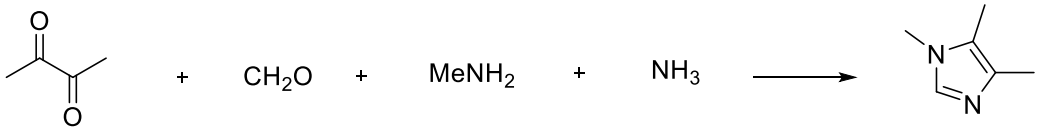
scheme 1-2

After Strecker reaction, lots of different MCRs have been developed over the decades allowing the access to various complex structures. In 1882, Hantzsch synthesized dihydropyridine from an aldehyde, ammonia and twofold of ethyl acetoacetate (scheme 1-3).[6]



scheme 1-3

At the same time, Debus-Radziszewski obtained 1,4,5-trimethyl-1H-imidazole from condensation of biacetyl, formaldehyde, methanamine and ammonia (scheme 1-4).[7]

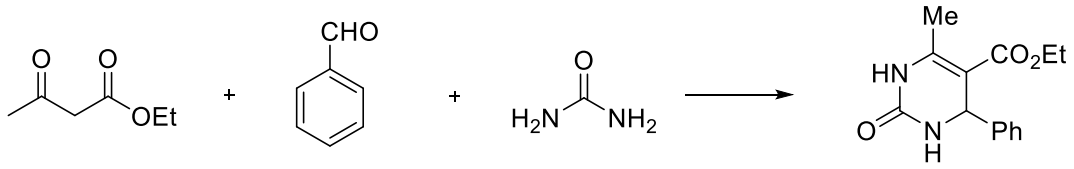


scheme 1-4

In 1891, Biginelli synthesized 3,4-dihydropyrimidin-2(1*H*)-ones from ethyl acetate, an aryl

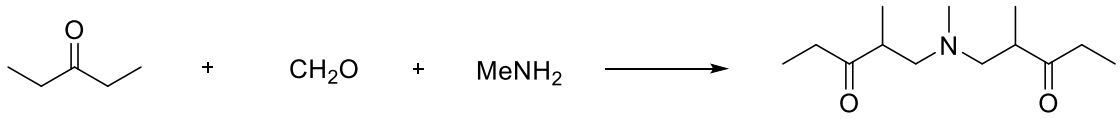
[5] A. Strecker, *Liebigs Ann. Chem.* **1850**, *75*, 27-51
[6] A. Hantzsch, *Justus Liebigs Ann. Chem.* **1882**, *215*, 1.
[7] a) H. Debus, *Justus Liebigs Annalen der Chemie.* **1858**, *107* , 199. b) B. Radzisewski, *Berichte der deutschen chemischen Gesellschaft.*,**1882**, *15* , 2706.

aldehyde(such as benzaldehyde), and urea (scheme 1-5).[8]



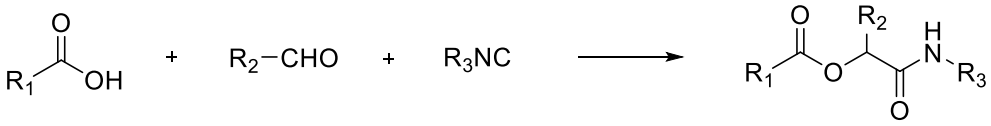
scheme 1-5

The Mannich reaction was discovered in 1912, consists of an amino alkylation of an enol with aldehyde and amine (scheme 1-6).[9]



scheme 1-6

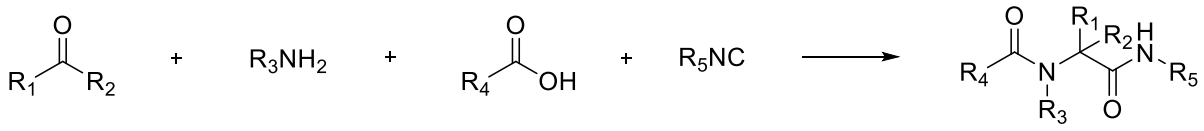
In 1921, Passerini reaction, an efficient access to α-acyloxycarboxamides, was reported (scheme 1-7).[10]



scheme 1-7

The Ugi reaction, disclosed in 1959, involves a ketone or aldehyde, an amine, an isocyanide and a carboxylic acid to give a bis-amide (scheme 1-8).[11]

[8] (a) P. Biginelli, *Ber. Dtsch. Chem. Ges.* **1891**, *24*, 2962. (b) P. Biginelli, *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 447.
[9] C. Mannich, A. Krösche, *Pharm. (Weinheim, Ger.)* **1912**, *250*, 647.
[10] (a) G. Passerini, G.Simone, *Chim. Ital.* **1921**, *51*, 126. (b) G. Passerini, *Chim. Ital*. **1921**, *51*, 181. (c) G. Passerini, *Chim. Ital.* **1922**, *52*, 432. Reviews: (a) L. Banfi, R. Riva, *Org. React.* **2005**, *65*, 1.
[11] (a) I. Ugi, R. Meyr, U. Fetzer, C. Steinbrückner, *Angew. Chem.* **1959**, *71*, 386. (b) I. Ugi, C. Steinbrückner, *Angew. Chem.* **1960**, *72*, 267.



scheme 1-8

A large number of MCRs have been reported in the literature, among which Mannich reactions are very important. IMCRs allow for the synthesis of the largest number of different scaffolds. Before discussing the IMCRs in details, an introduction about isocyanides will be presented.

2 Isocyanides

Isocyanides (also called isonitriles or carbylamines) are organic compound possessing the functional group -N≡C. It is the isomer of the related cyanide (-C≡N), hence the prefix iso. The organic fragment is connected to the isocyanide group via the nitrogen atom, not via the carbon. Usually, they spread strong penetrating, unpleasant odor, thus, isocyanides have been recognized as potential non-lethal weapons.[12]

Isocyanide functional group exists in only few naturally occurring compounds. The first isolated natural product containing isocyanide group, Xantocillin, which was used as an antibiotic, was extracted from the mold Penicillium notatumin in 1950 (figure 1-3).

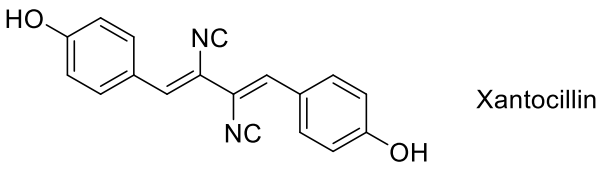
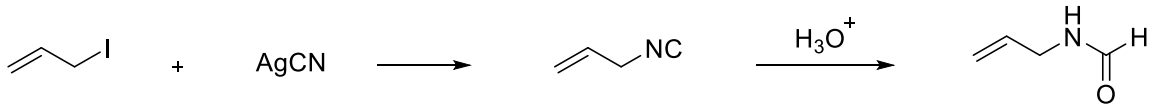


figure 1-3

[12] C. Pirrung, S. Ghorai, R. Ibarra-Rivera, *J. Org. Chem.* **2009**,*74*, 4110.

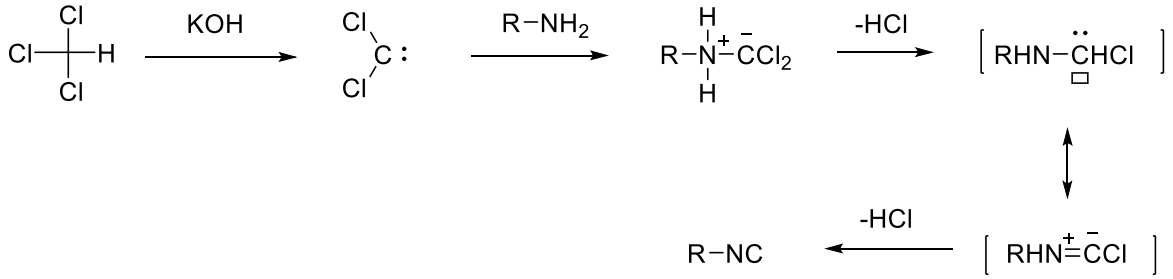
2.1 Synthesis of isocyanides

Isocyanides were first described in the literature by Lieke in 1859,[13] he was surprised to obtain a product with sharp odour which upon hydrolysis gave N-allylformamide instead of the corresponding carboxylic acid. Few years later, in 1869, Gautier proved that this allylation reaction gave allyl isocyanide and demonstrated isomeric relationship between isocyanides and nitriles (scheme 1-9).[14]



scheme 1-9

In 1867, Hofmann developed a new approach to isocyanide through the condensation of a primary amine with dichlorocarbene, which generated in situ by heating chloroform in presence of a base such as potassium hydroxide (scheme 1-10).[15] Despite it looks simple, it is not considered as a general method for the isocyanides synthesis because of the low yields obtained and the difficulties of separating the isocyanides from amines.

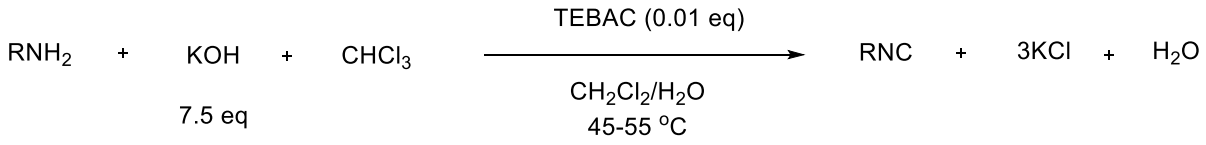


scheme 1-10 Hofmann isocyanides synthesis

In 1972, Weber, Gokel and Ugi modified Hofmann's approach by using a biphasic medium (water/dichloromethane) in the presence of a quaternary ammonium salt as a phase transfer

[13] W. Lieke *Justus Liebigs Ann. Chem.* **1859**, *112*, 316-321
[14] A. Gautier *Justus Liebigs Ann. Chem.* **1869**, *146*, 119-124
[15] (a)W. Hofmann, *Justus Liebigs Ann. Chem.* **1867**, *144*, 114.(b) I. Nef, *Justus U.Liebigs Ann. Chem.* **1897**, *298*, 202.

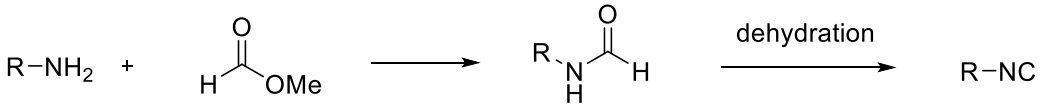
catalyst (PTC). This improved the selectivity of the amine attacking the dichlorocarbene, but it still suffers from the formation of byproducts (scheme 1-11).[16]



scheme 1-11 modified Hofmann isocyanides synthesis

This method could be used to synthesize isocyanides in large-scale even though the yield is moderate, and it is the most frequently applied in our laboratory for preparing the starting isocyanide substrates.

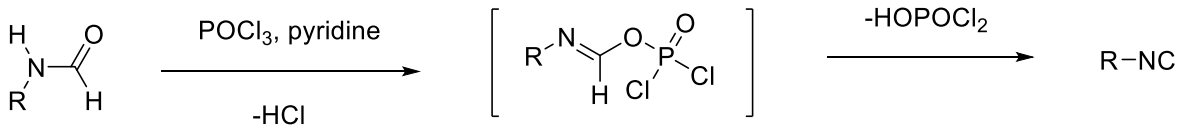
In 1958, Corey and Ugi reported another approach to isocyanides via dehydration of N-monosubstituted formamides, which could be readily prepared by the condensation of a primary amine with methyl formate or formic acid (scheme 1-12).[17]



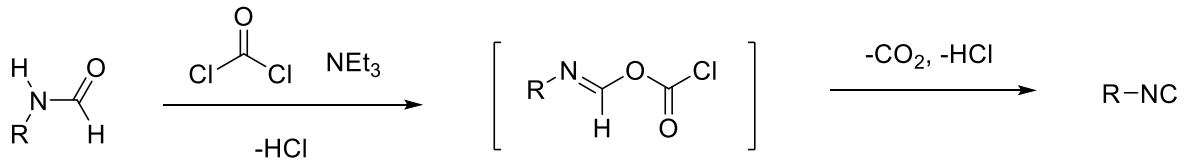
scheme 1-12 isocyanide synthesis by dehydration of formamide

Various dehydrating agent such as diphosgene ($C_2Cl_4O_2$),[18] diphosphorus pentoxide (P_4O_{10}), phosphorus oxychloride ($POCl_3$) or thionyl chloride ($SOCl_2$)[19] in the presence of different bases like pyridine, triethylamine, or DABCO could be used.[20] Few examples are shown in scheme 1-13.

[16] (a) W. Weber, G. Gokel, *Tetrahedron Lett.* **1972**, *11*, 1637. (b) P. Weber, W. Gokel, I. Ugi, *Angew. Chem.* **1972**, *84*, 587.
[17] (a) W. Hertler, J. Corey, *J. Org. Chem.* **1958**, *23*, 1221. (b) I. Ugi, R. Meyr, *Angew. Chem.* **1958**, *70*, 702.
[18] G. Skorna, I. Ugi, *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 259.
[19] I. Ugi, R. Meyr, *Chem. Ber.* **1960**, *93*, 239.
[20] R. Obrecht, R. Hermann, I. Ugi, *Synthesis* **1985**, 400.



using $POCl_3$ as dehydrating agent

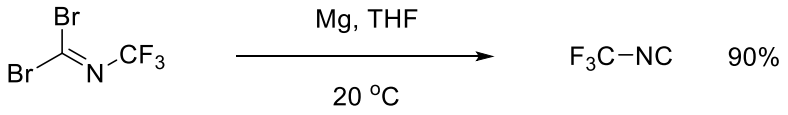


using phosgene as dehydrating agent

scheme 1-13

This method is widely used in the synthesis of isocyanides since it is tolerable with a number of functional groups.

Isocyanides could also be prepared from isocyanide *gem*-dihalides. *Gem*-dihalide of trifluoromethyl isocyanide under the treatment of magnesium could afford trifluoromethyl isocyanide (scheme 1-14).[21]

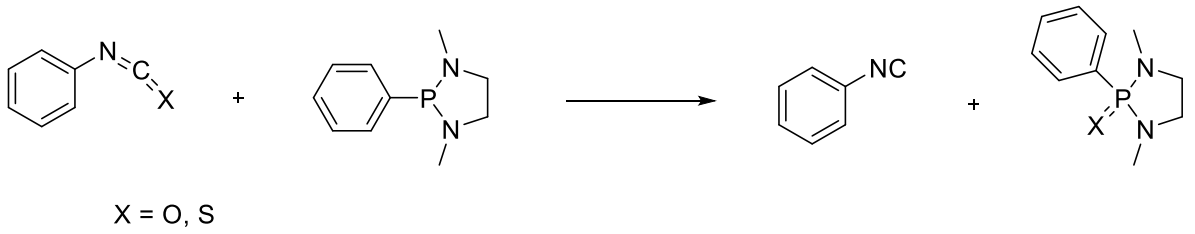


scheme 1-14

Reduction of isocyanates, isothiocyanates or dichloro ketenimine can give corresponding isocyanides. The reduction process could occur at relatively low temperature in presence of 2-phenyl-3-methyl-1,3,2-oxazaphospholidine, (diphenyl-tert-butylsilyl)lithium or a mixture of trichlorosilane-triethylamine (scheme 1-15).[22]

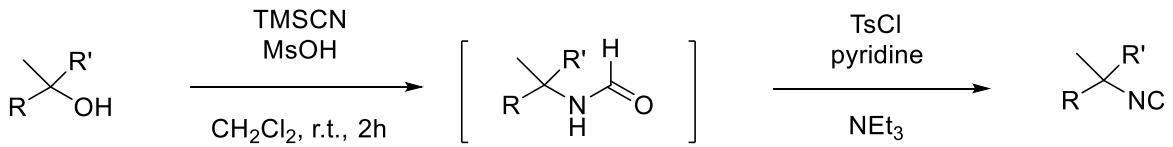
[21] (a) D. Lentz, *J. Fluo. Chem.* **1984**, *24*, 523-530. (b) D. Lentz, *J. Fluo. Chem.* **1985**, *29*, 91. (c) P. Doz, D. Lentz, *Angewandte Chemie*, **1994**, *106*, 1377-1393

[22] (a) T. Mukaiyama, Y. Yokota, Bull. *Chem. Soc. Jpn.* **1965**, *38*, 858. (b) E. Baldwin, C. Bottaro, D. Riordan, E. Derome, *J. Chem. Soc., Chem. Comm.* **1982**, 942. (c) E. Baldwin, E. Derome, D. Riordan, *Tetrahedron* **1983**, *39*, 2989.



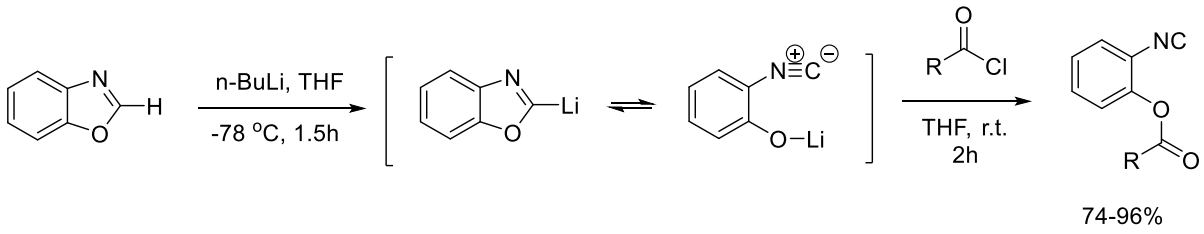
scheme 1-15

In 2011, Kitano *et al.* reported an isocyanide synthesis using corresponding alcohols, trimethylsilyl cyanide and methanesulfonic acid. After dehydration of an intermediate N-formamide and neutralization by triethylamine, the desired isocyanide was obtained (scheme 1-16).[23]



scheme 1-16

In 2006, Pirrung et al. synthesized isocyanides from oxazoles and benzoxazoles. After deprotonation at the 2 position of oxazole, the reaction proceeds via the oxazole ring opening. The formed intermediate is then trapped using various acid chlorides (scheme 1-17).[24]

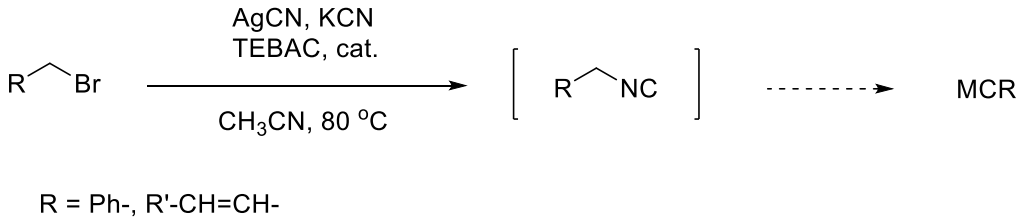


scheme 1-17

Among those various synthetic methods, the purification step is essential, and the horrible smells may be a nightmare for chemists. To avoid this disadvantage, in 2009, our lab

[23] I. Okada, Y. Kitano, *Synthesis* **2011**, 3997.
[24] C. Pirrung, S. Ghorai, *J. Am. Chem. Soc.* **2006**, *128*, 11772.

published an in situ protocol for the synthesis of isocyanides starting from halogenated derivatives with silver and potassium cyanide in the presence of benzyltriethylammonium chloride as a catalyst at 80 ºC (scheme 1-18).[25] The obtained product can be used directly without further purification.

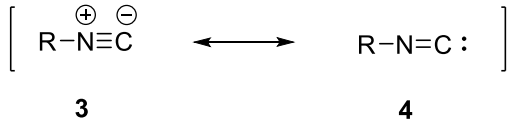


scheme 1-18

2.2 Reactivity of isocyanides

2.2.1 Structure of isocyanide

Isocyanides are described by two resonance structures, one with a triple bond between the nitrogen and the carbon (zwitterions form) and one with a double bond between (divalent carbon form) (scheme 1-19).



3 **4**

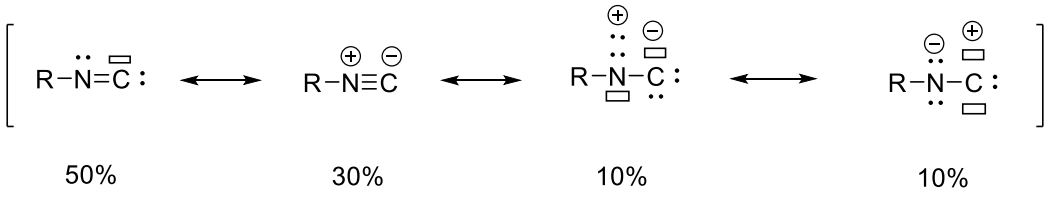
scheme 1-19

In the resonance structure **4**, the carbon possess a carbene-like reactivity while in structure **3**, it involves a dipolar linear resonance

Based on Valence bond calculations for methyl isocyanide, it was found that the carbene-form existed in about 50 %, while the zwitterionic species in about 30 %, the

[25] (a) L. Elkaïm, L. Grimaud, A. Schiltz, *Synlett.* **2009**, 1401. (b) L. Elkaïm, L. Grimaud, A.Schiltz, *Tetrahedron Lett.* **2009**, *50*, 5235. (c) L. Elkaïm, L. Grimaud, A. Schiltz, *Org. Biomol. Chem.*, **2009**, *7*, 3024.

remaining 20 % structures being more complex (scheme 1-20).[26] Thus isocyanides are linear molecules since such geometry allows the resonance between the carbene and the zwitterionic structures.



scheme 1-20 Valence bond calculations for the resonance structures of isocyanides.

Isocyanides are characterized by their high stability in basic mediums, but they are sensitive to acids. In the presence of acidic solutions, they undergo acidic hydrolysis forming formamides. Most isocyanides may polymerize as well in acidic mediums.[27]

2.2.2 Reactivity of the terminal carbon

The terminal carbon reactivity of the isocyanide functional group could be explained on the basis of the Molecular orbital theory. The analysis of the frontier orbitals showed that the largest coefficients in both HOMO (σ) and LUMO (π*) orbitals are situated on the terminal carbon of methylisocyanide (figure1-4)

[26] R. Ramozzi, N. Cheron, B. Braida, P. Hiberty, P. Fleurat-Lessard, *New J. Chem.* **2012**, *36*, 1137.
[27] (a) A. van Beijen, *Macromolecules* **1983**, *16*, 1679. (b) M. Albert, B. van Leusen, E. Hoogenboom, H. Siderius, *Tetrahedron Lett.* **1972**, *13*, 2369.

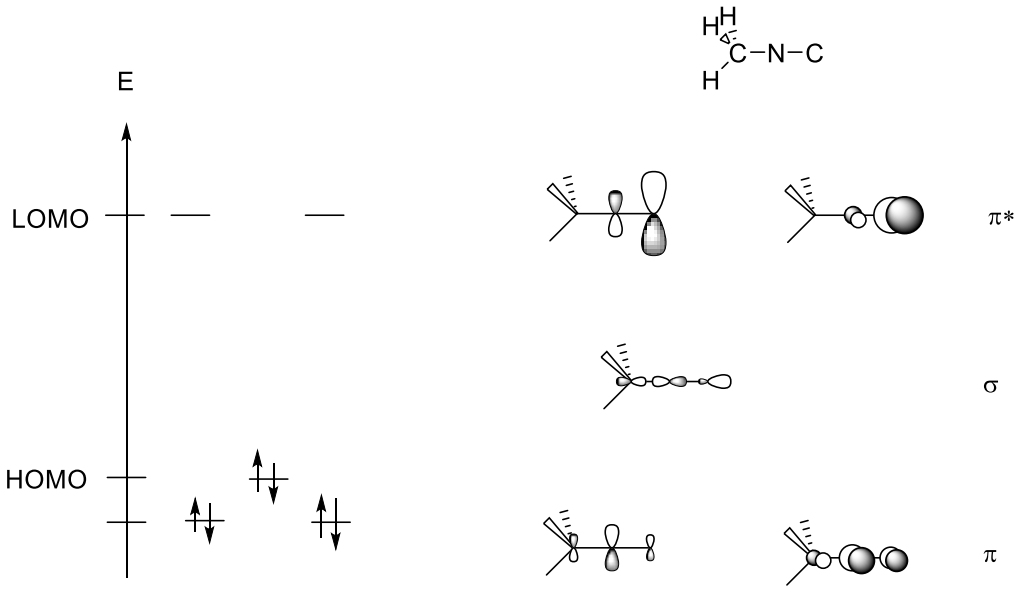


figure 1-4 frontier orbitals of methylisocyanide

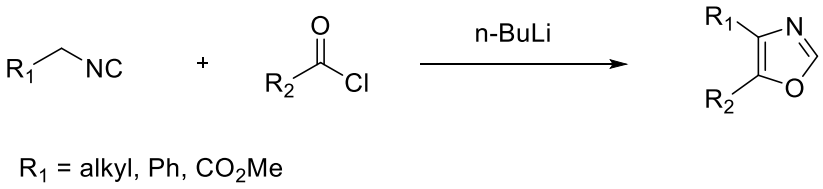
Consequently, both electrophilic and nucleophilic additions occur at the terminal carbon atom of isocyanides

After the attack of a nucleophile on the isocyanide, the divalent carbon becomes nucleophilic and attacks an electrophile and conversely, it can react first with an electrophile and followed by addition of the nucleophile.

2.2.3 α-Acidity of the isocyanide group

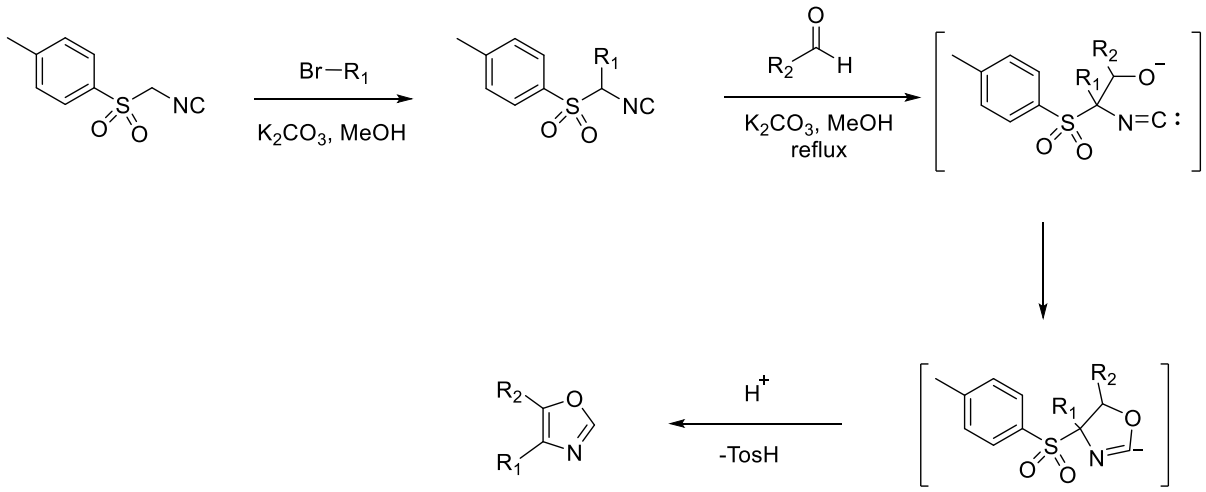
Oxazoles could be synthesized from isocyanides attribute to the acidity of the protons in α-position to the isocyanide functionality, which is enhanced by the electron-withdrawing nature of such group. After α-deprotonation under basic condition, isocyanide react with an acid chloride to afford the target cyclic compound (scheme 1-21).[28]

[28] (a) U. Schöllkopf, R. Schröder, *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 333. (b) D. Hoppe, U. Schöllkopf, *Liebigs Ann. Chem.* **1972**, *763*, 1.



scheme 1-21

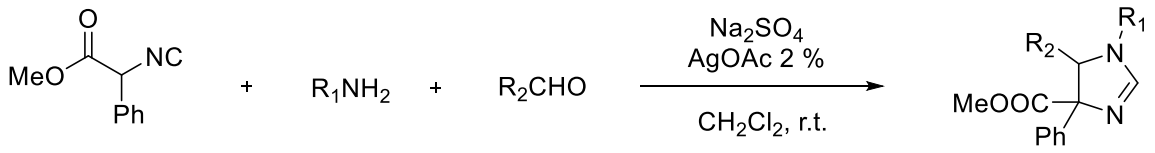
The α-acidity of the isocyanides is further increased by electron-withdrawing substituents like carboxylic ester, amide, nitriles, or sulfonyl group. Based on this property, oxazoles, pyrroles and triazoles can be easily synthesized starting from isocyanides. For instance, 5-functionalized oxazoles were prepared using p-tosylmethylisocyanide with an aldehyde in presence of potassium carbonate (scheme 1-22).[29]



scheme 1-22

α-Isocyanoesters and α-isocyanoamides were widely used in the synthesis of heterocycles. In 2007, Orru et al. synthesized 2-imidazolines using primary amines, aldehydes and α-isocyanoesters in presence of a base and silver acetate as a catalyst (scheme 1-23).[30]

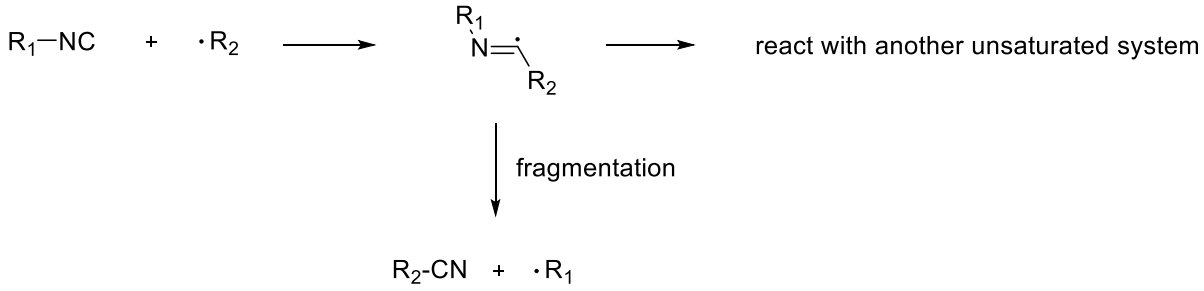
[29] A. Van Leusen, E. Hoogenboom, H. Siderius, *Tetrahedron Lett.* **1972**, *23*, 2369.
[30] N. Elders, F. Schmitz, J. de Kanter, E. Ruitjer, B. Groen, A. Orru, *J. Org. Chem.* **2007**, *72*, 6135.



scheme 1-23

2.2.4 Radical reaction of the isocyanides

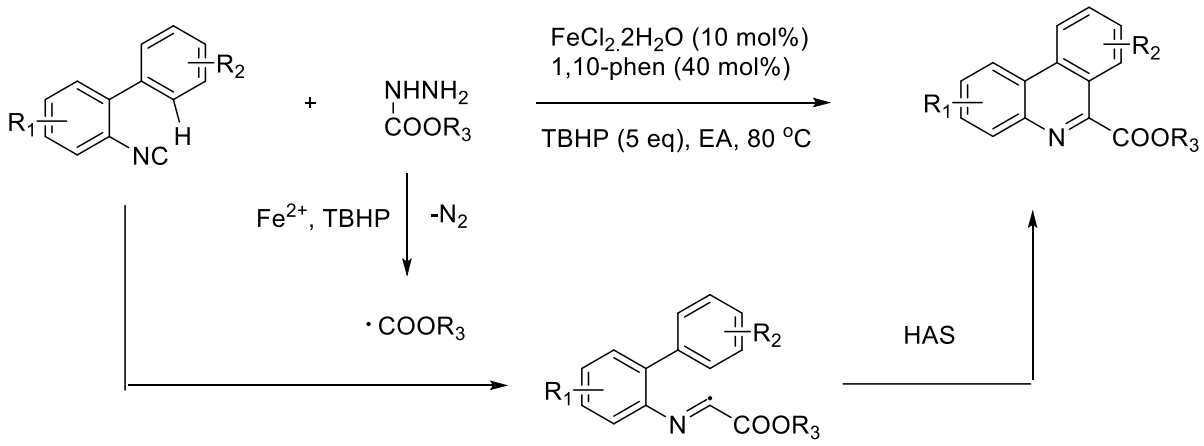
Imidoyl radical was usually formed by the addition of a radical to the terminal carbon of the isocyanide moiety. It can fragment into a cyanide and an alkyl radical or react with an unsaturated system to finally give heterocycles (scheme 1-24).



scheme 1-24

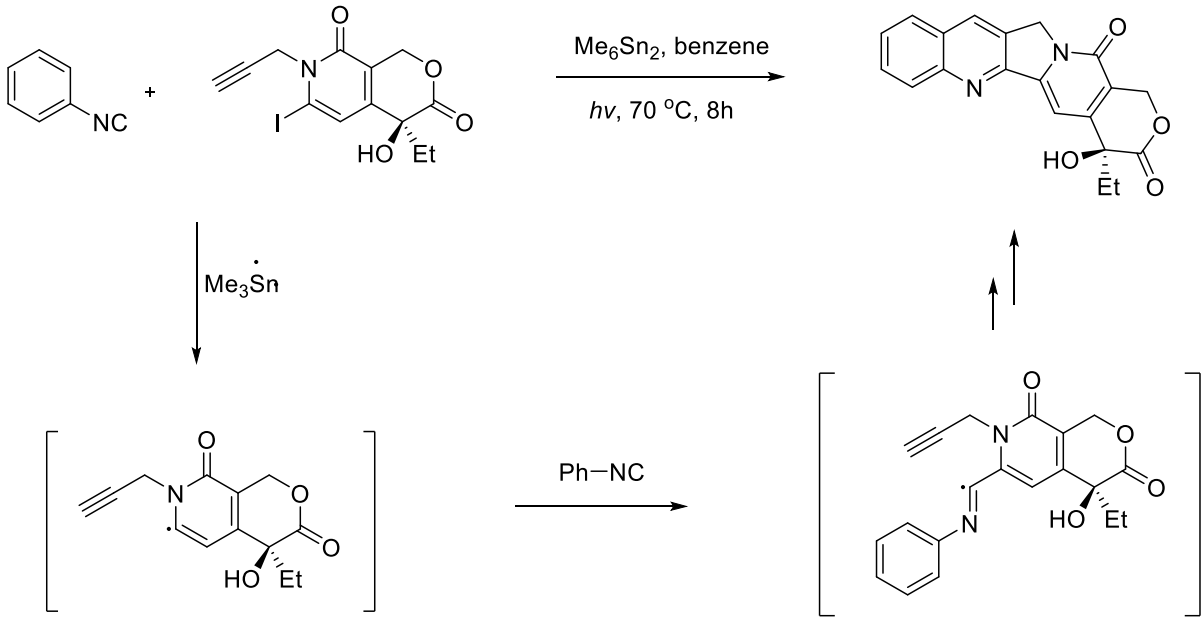
This behavior was first described by Shaw[31] and Saegusa[32], who exploited this reactivity for the formation of various heterocycles. In 2014, Zhu[33] and Yu[34] independently developed a practical route to access phenanthridine-6-carboxylates via a sequential oxidative radical alkoxycarbonylation and aromatization reaction of biaryl isocyanides with carbazates. The C–N bond cleavage of the carbazates with the extrusion of nitrogen gas leads to alkoxycarbonyl radical, the subsequent radical addition to the biaryl isocyanides generated the imidoyl radical intermediate, which underwent intramolecular homolytic aromatic substitution to afford the desired product (scheme 1-25).

[31] H. Shaw, H. Pritchard, *J. Chem.* **1967**, *45*, 2749.
[32] (a) T. Saegusa, S. Kobayashi, Y. Ito, N. Yasuda, *J. Am. Chem. Soc.* **1968**, *90*, 4182. (b) T. Saegusa, Y. Ito, N. Yasuda, T. Hotaka, *J. Org. Chem.* **1970**, *35*, 4238.
[33] C. Pan, J. Han, H. Zhang and C. Zhu, *J. Org. Chem.*, **2014**, *79*, 5374.
[34] G. Wang, S. Chen and X. Yu, *Tetrahedron Lett.*, **2014**, *55*, 5338



scheme 1-25

Radical reactions involving isocyanides were also widely used in the total synthesis of alkaloid like heterocycles or natural products.[35] For instance, this sort of radical reaction plays a key step in the total synthesis of camptothecin, which is a natural product used in cancer chemotherapy (scheme1-26).[36]



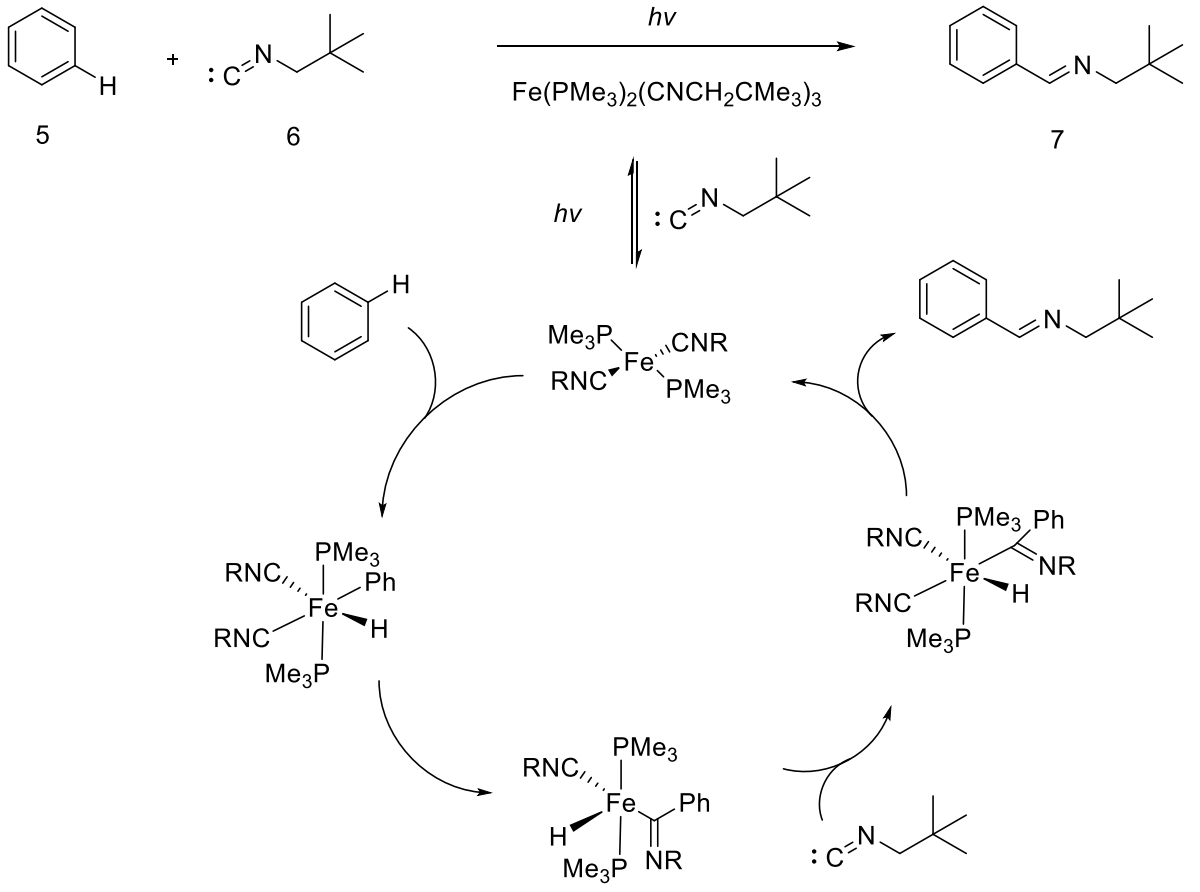
scheme 1-26

[35] (a) D. Bachi, A. Balanov, N. Bar-Ner, *J. Org. Chem.* **1994**, *59*, 7752. (b) B. Bachi, N. Bar-Ner, A. Melman, *J. Org. Chem.* **1996**, *61*, 7116. (c) L. Benati, R. Leardini, M. Minozzi, D. Nanni, R. Scialpi, P. Spagnolo, S. Stazzari, G. Zanardi, *Angew. Chem. Int. Ed.* **2004**, *43*, 3598. (d) P. Curran, H. Liu, *J. Am. Chem. Soc.* **1991**, *113*, 2127.

[36] H. Josien, S. Ko, D. Bom, P. Curran, *Chem. Eur. J.* **1998**, *4*, 67. (b) D. Curran, H. Liu, H. Josien, S. Ko, *Tetrahedron* **1996**, *52*, 11385

2.2.4 Metal-catalyzed C-H insertion reaction

Since the early 1960s, many metal-catalyzed isocyanide insertion reactions have been developed by Saegusa and Ito.[37,38] In 1990, Hessell *et al.* reported an isocyanide insertion which an Iron-Aryl bond generated by a CH activation of benzene (scheme 1-27).[39]



scheme 1-27

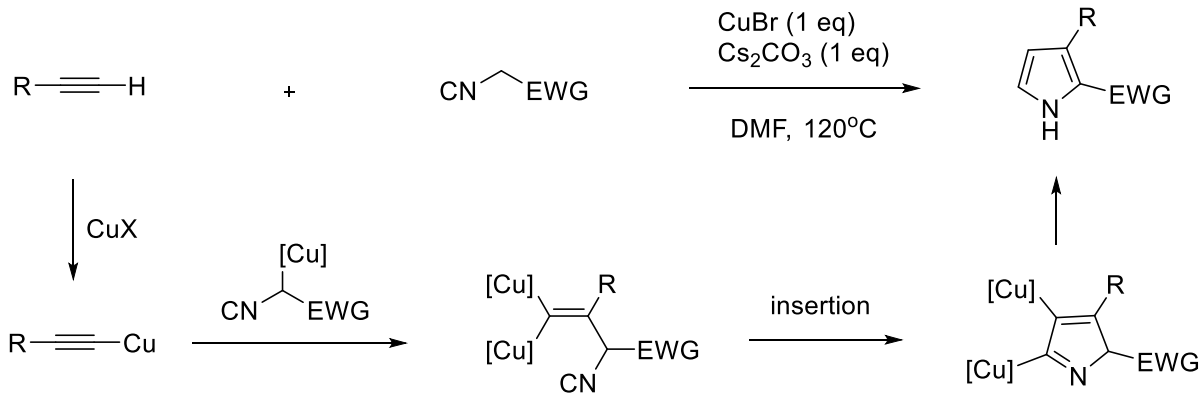
In 2009, Meijere *et al.* synthesized 2,3-disubstituted pyrroles by the reaction of terminal alkynes with substituted methyl isocyanides. An in situ generated copper acetylide interact in this reaction with an isocyanide substituted by an electron withdrawing group.

[37] (a) Y. Ito, I. Ito, T. Hirao and T. Saegusa, *Synth. Commun.*, **1974**, *4*, 97; (b) Y. Ito, T. Hirao and T. Saegusa, *J. Org. Chem.*, **1975**, *40*, 2981; (c) Y. Ito, T. Hirao, N. Ohta and T. Saegusa, *Tetrahedron Lett.*, **1977**, *18*, 1009.

[38] (a) T. Saegusa, Y. Ito, S. Kobayashi and K. Hirota, *Tetrahedron Lett.*, **1967**, *8*, 521; (b) T. Saegusa, S. Kobayashi, Y. Ito, K. Hirota and Y. Okumura, Bull. *Chem. Soc. Jpn.*, **1968**, *41*, 1638; (c) T. Saegusa, Y. Ito, S. Kobayashi, K. Hirota and H. Yoshioka, *Tetrahedron Lett.*, **1966**, *7*, 6121; (d) T. Saegusa, S. Kobayashi, Y. Ito and K. Hirota, *J. Am. Chem. Soc.*, **1967**, *89*, 2240; (e) T. Saegusa, Y. Ito and S. Kobayashi, *Tetrahedron Lett.*, **1968**, *9*, 935.

[39] W. D. Jones and E. T. Hessell, *Organometallics*, **1990**, *9*, 718

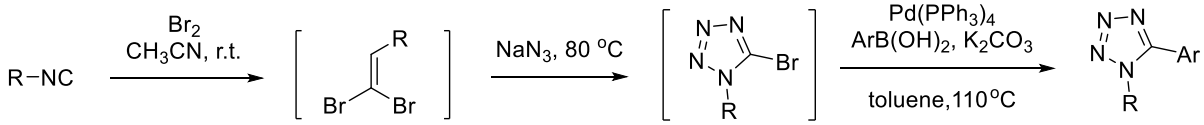
Insertion of isocyanide into the copper–carbon bond gave the 2H-pyrrolenline-4,5-dicopper derivatives. Finally, the following 1,5-H shift and twofold protonation afforded the corresponding pyrroles (scheme 1-28).[40]



scheme 1-28

2.2.5 Oxidation of isocyanides

Isocyanides react with halogens forming gem-dihalogenated isocyanide intermediates[41], which can be used in the synthesis of tetrazoles, upon the reaction with sodium azide followed by a Suzuki-coupling reaction (scheme 1-29).[42]

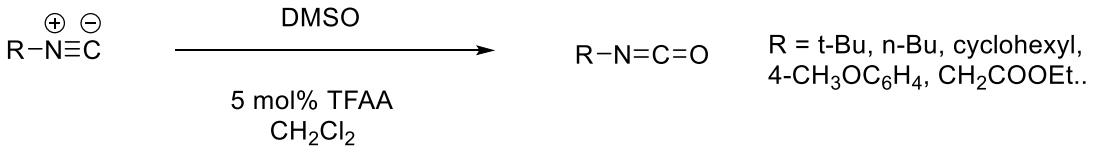


scheme 1-29

In 2011, Bruce and Hoang reported a simple, rapid, and environmentally acceptable procedure for preparing isocyanates from isocyanides. With use of DMSO as the oxidant and 5 mol% TFAA (dichloromethane, -60 to 0 °C), the process was completed in a few minutes,

[40] A. Lygin, O. Larionov, V. Korotkov and A. de Meijere, *Chem. Eur. J.*, **2009**, *15*, 227
[41] (a) E. Kühle, B. Anders, E. Klauke, H. Tarnow, G. Zumach, *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 20. (b) E. Kühle, B. Anders, G. Zumach, *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 649.
[42] L. Elkaïm, L. Grimaud, P. Patil, *Org. Lett.* **2011**, *13*, 1261.

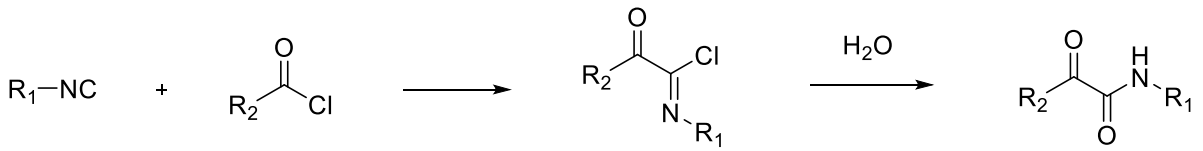
forming dimethyl sulfide as the only byproduct (scheme 1-30).[43]



scheme 1-30

2.2.6 Nef Reaction

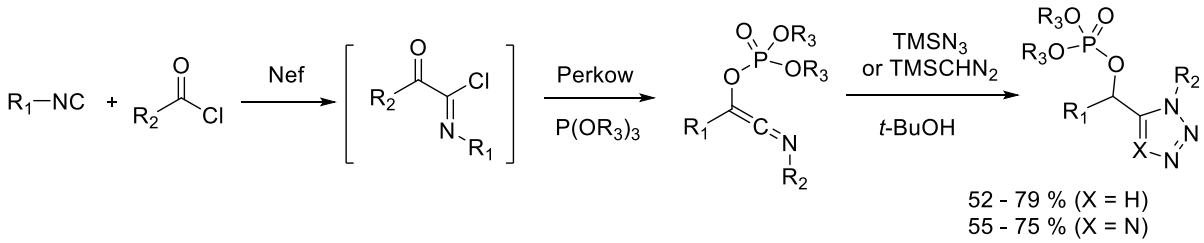
In 1894, the first example about the insertion of an isocyanide into carbon-chlorine bond was described by Nef.[44] The formed intermediate imidoyl chloride after hydrolysis, afforded the corresponding α-ketoamide (scheme 1-31).



scheme 1-31

In 2009, our group reported the synthesis of ketene-imine phosphates using Nef/Perkow sequence. After the addition of trimethylsilylazide or trimethylsilyldiazomethane to the ketene-imine phosphonates, generated in situ, triazole and tetrazole phosphonates was obtained respectively (scheme 1-32).[45]

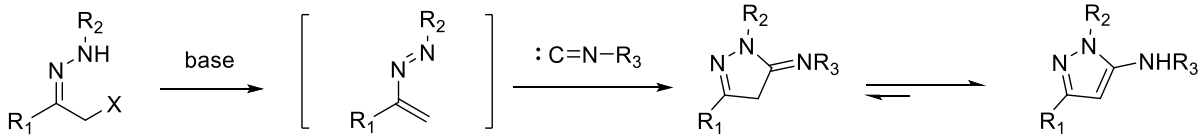
[43] V. Hoang and G. Bruce, *org. lett.* **2011** ,*13*, 2584–2585
[44] U. Nef, *Justus Liebigs Ann. Chem.* **1892**, *210*, 269.
[45] D. Coffinier, L. Elkaïm, L. Grimaud, *Org. Lett.* **2009**, *11*, 1825.



scheme 1-32

2.2.7 Formal cycloaddition reactions

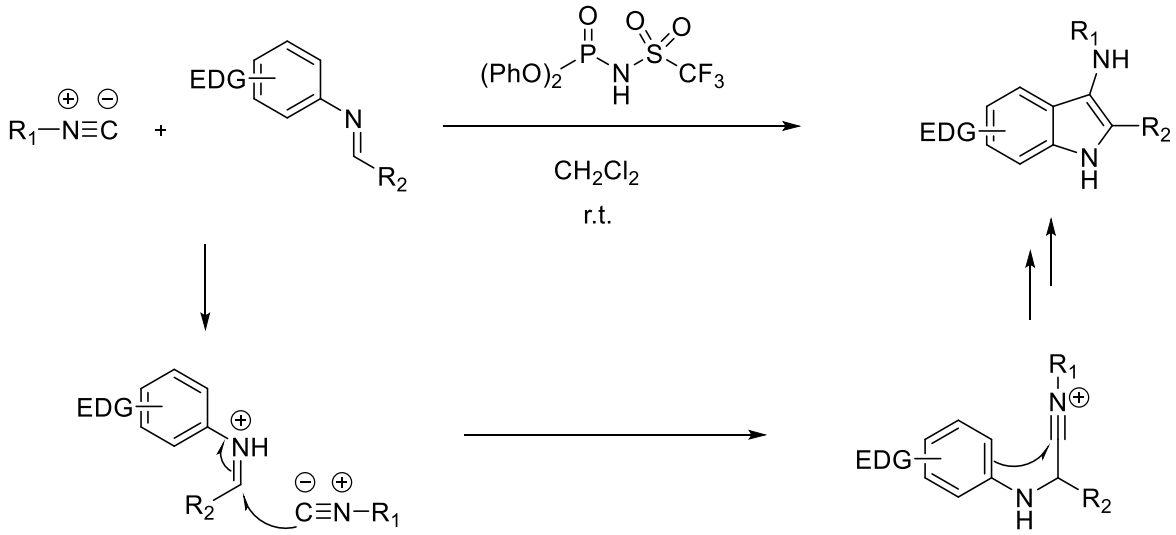
In 2000, our group reported the synthesis of 5-aminopyrrazoles via a [4+1] cycloaddition reaction of isonitriles and azoalkenes, generated in situ from hydrazones (scheme 1-33).[46]



scheme 1-33

In 2009, Sorensen *et al.* synthesized 3-aminoindoles from aldimines, isocyanides in presence of a strong Brønsted acid. A aldimine was traped by an isocyanide to form a α-amino nitrilium ion, after Houben–Hoesch cyclization and tautomerization, desired 3-aminoindole analogue was obtained (scheme 1-34).[47]

[46] V. Atlan, L. Elkaïm, C. Buron, *Synlett* **2000**, 489.
[47] J. Schneekloth, K. Jimin, E. Sorensen, *Tetrahedron* **2009**, *65*, 3096 –3101

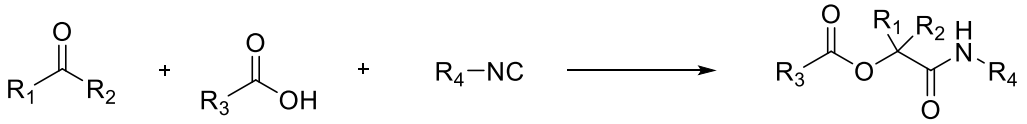


scheme 1-34

3 Isocyanide-based multicomponent reactions (IMCRs)

3.1 Passerini reaction

This reaction was first discovered by Passerini in 1921. It's the first isocyanide based multicomponent reaction. It involves the condensation between a carbonyl substrate (aldehyde or ketone), a carboxylic acid and an isocyanide. And it gives a direct access to α-acyloxycarboxamides in a one-pot reaction (scheme 1-35).[48]

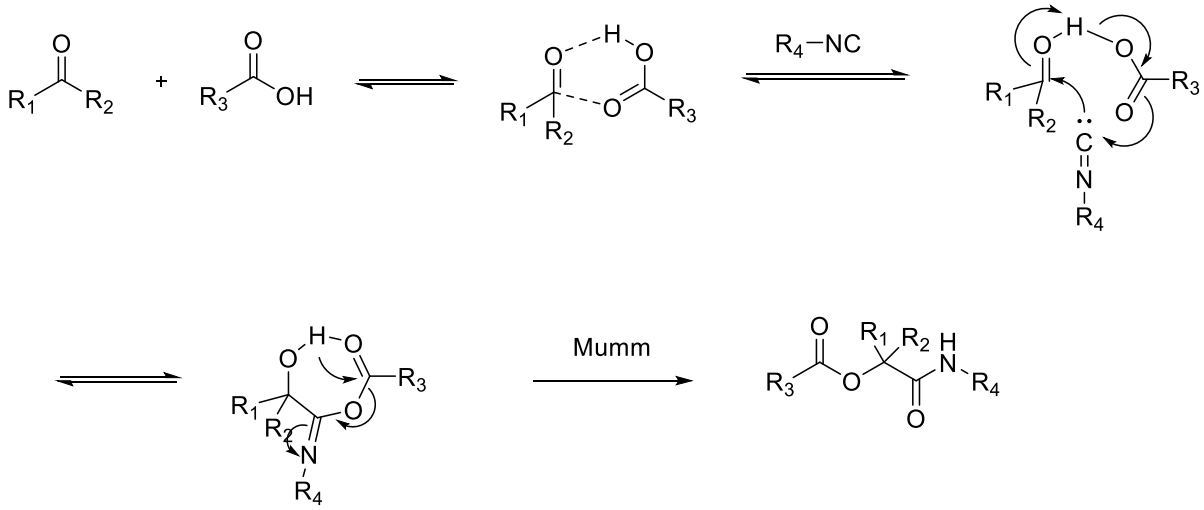


scheme 1-35 Passerini reaction

This reaction is usually carried out in nonpolar aprotic solvents (toluene or dichloromethane) at room temperature in a relatively high concentration. Several examples are conducted as well without solvent. Based on the reactivity differences observed when changing the

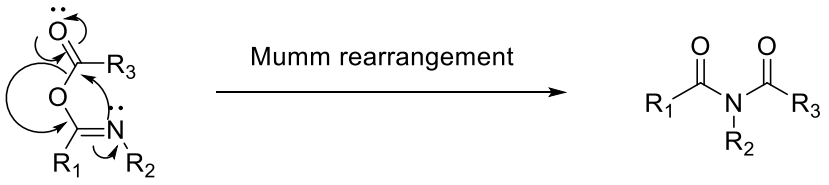
[48] (a) M. Passerini, G. Simone, *Chim. Ital.* **1921**, *51*, 126. (b) M. Passerini, *Chim. Ital.* **1921**, *51*,181. (c) L. Banfi, R. Riva, *Org. React.* **2005**, *65*, 1

reaction solvent, in 1961, Ugi proposed a mechanism for this coupling.[49] It's assumed that the mechanism was non-ionic. Hydrogen bonding plays a crucial role in the formation of the presumed cyclic intermediate in which the isocyanide inserts. A Mumm type rearrangement underwent to give the final adduct (scheme 1-36).



scheme 1-36 mechanism of Passerini reaction

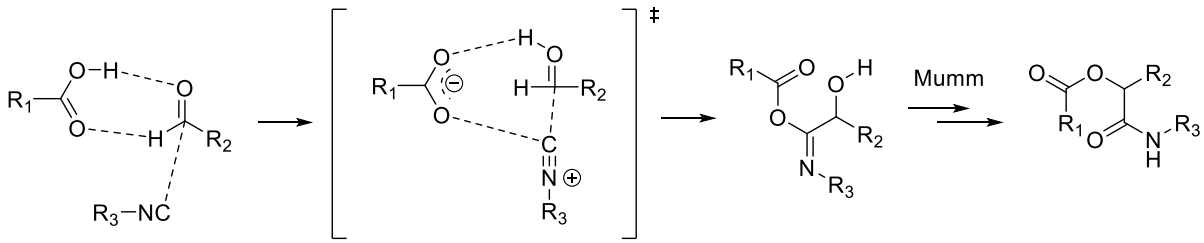
The Mumm rearrangement was first documented in 1910. It is a 1,3 (O,N) acyl transfer of an acyl imidate or isoimide group to an imide (scheme 1-37).



scheme 1-37 Mumm rearrangement

In 2011, Maeda *et al*. proposed a mechanism through a theoretical method, which was close to that suggested by Ugi. It involves the addition of the isocyanide onto the aldehyde, which is activated by the acid. After Mumm rearrangement, the final product was delivered (scheme 1-38).[50]

[49] I. Ugi, R. Meyr, *Chem. Ber.* **1961**, *94*, 2229.
[50] S. Maeda, S. Komagawa, M. Uchiyama, K. Morokuma, *Angew. Chem. Int. Ed.* **2011**, *50*, 644.



scheme 1-38

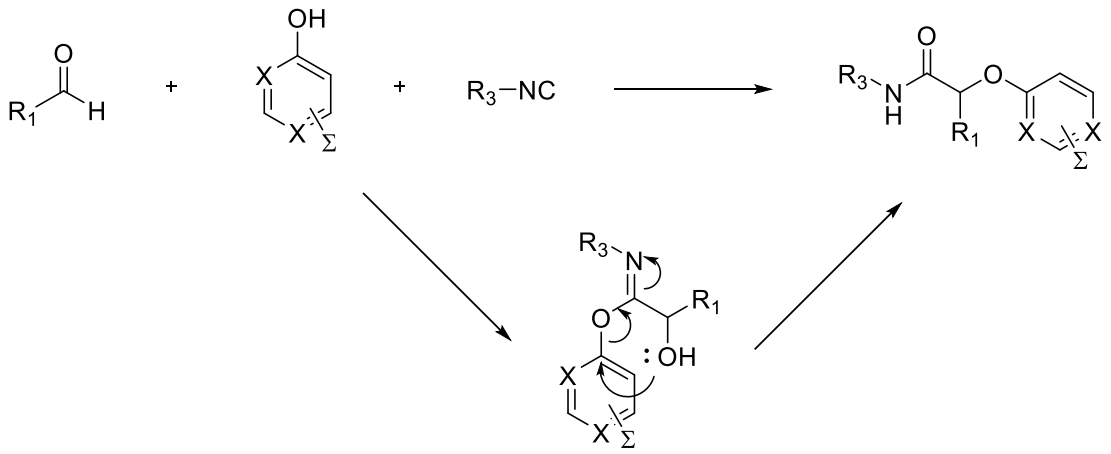
3.2 Scope of Passerini reaction

3.2.1 Scope of acids

Based on the mechanism of the Passerini reaction, it's indicated that the carboxylic acid plays a crucial role in the course of this process, where the activation of aldehyde by the acid compound would start the reaction. Thus a carboxylic acid is normally required and it could be a limitation for the applications of this process to the synthesis of more complex scaffolds.[51]

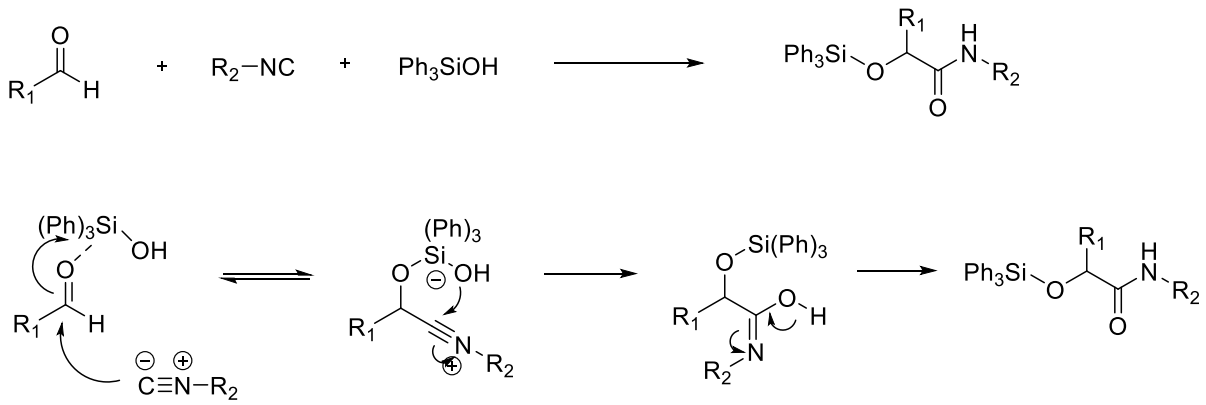
In 2006, our lab reported a three-component addition of isocyanides to phenol derivatives and aldehydes in methanol to form O-arylated compounds. An irreversible smiles rearrangement of intermediate phenoxyimidate adducts is the key step of the conversion. It's the first application of a Smiles rearrangement in a Passerini reaction (scheme 1-39).[52]

[51] E. Marques, P. Herrera, *Multicomponent Reactions* , **2015**, 283-305.
[52] L. Elkaim, M. Gizolme, L. Grimaud, *Org. Lett.* **2006**, *8*, 5021–5023



scheme 1-39 O-arylative Passerini reactions

Recently, Soeta and coworkers successfully introduced silanol derivatives as suitable reagents for giving the corresponding α-siloxyamidederivatives as versatile synthetic intermediates. A wide range of diverse aldehydes and isocyanides are tolerable affording final products in high yields (scheme 1-40).[53]

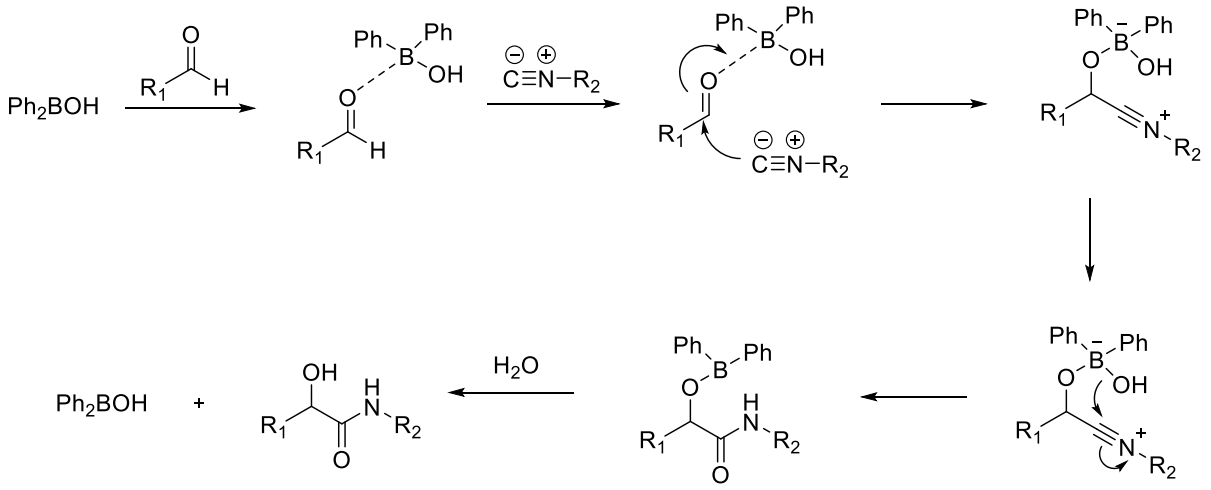


scheme 1-40 O-silylative Passerini reactions

In 2011, Soeta *et al.* synthesized α-hydroxyamides using an aldehyde, an isocyanide and a stoichiometric amount of water in presence of borinic acid.[54] Aldehyde is initially activated by borinic acid through coordination of the carbonyl oxygen to the boron atom. Subsequently, a nitrilium intermediate formed via nucleophilic attack of the isocyanide on the carbonyl

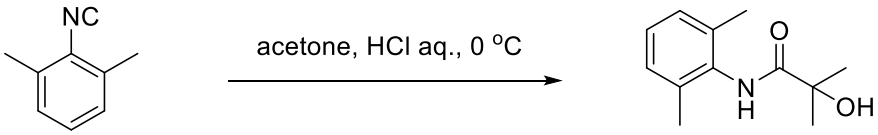
[53] T. Soeta, Y. Kojima, Y. Ukaji, K. Inomata, *Org. Lett.* **2010**, *12*, 4341–4343.
[54] T. Soeta, Y. Kojima, Y. Ukaji, K. Inomata, *Tetrahedron Lett.* **2011**, *52*, 2557–2559.

group. The hydroxy group on the boron atom rearranges to the nitrilium carbon. After tautomerization and hydrolysis, α-hydroxyamide and the borinic acid were regenerated (scheme 1-41).



scheme 1-41 addition of isocyanides catalyzed by borinic acids

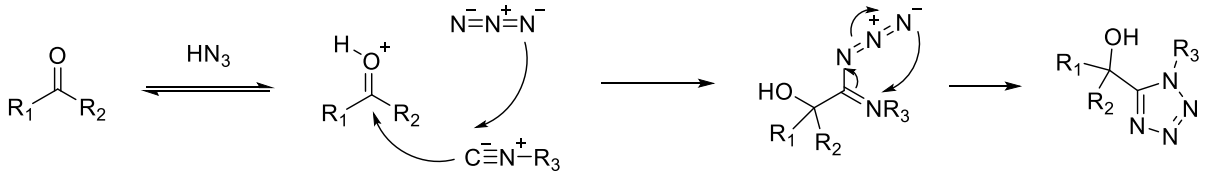
α-hydroxyamides could be also prepared by using various acids[55] such as hydrochloric, hydrobromic, sulfuric, nitric and phosphoric acid in stoichiometric amount and in the presence of water that acts as a nucleophile. The irreversible rearrangement of the imidate to primary amide is the key step of the reaction (scheme 1-42).



scheme 1-42

Hydrazoic acid (HN_3) and azide ions may also be used for the coupling of Passerini forming α-hydroxyterazoles. The equilibriums involved in the reaction are shifted by a final electrocyclization (scheme 1-43).[56]

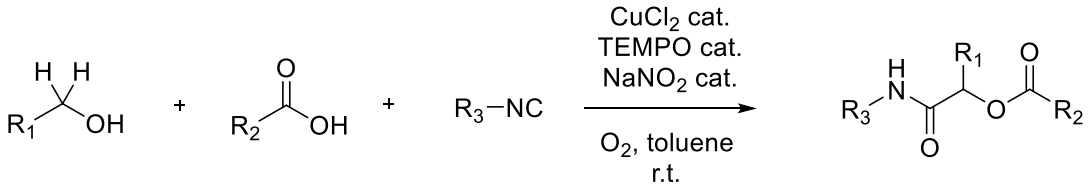
[55] I. Hagedorn, U. Eholzer, *Chem. Ber.* **1965**, *98*, 936.
[56] (a) G. Passerini, *Chim. Ital.* **1924**, *54*, 529. (b) E. Müller, B. Zeeh, *Justus Liebigs Ann. Chem.* **1966**, *696*, 72. (c) E. Müller, B. Zeeh, *Justus Liebigs Ann. Chem* . **1968**, *715*, 47. (d) W. McFarland, *J. Org. Chem.***1963**, *28*, 2179.



scheme 1-43

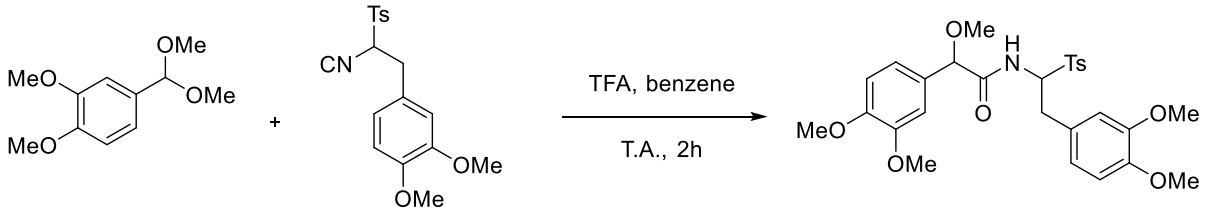
3.2.2 Scope of carbonyl compounds

In 2010, Zhu and his coworkers reported a Passerini reaction starting directly with a primary alcohol. The reaction proceeds via an in situ catalytic oxidation of the alcohol (scheme 1-44).[57]



scheme 1-44 Passerini reaction using primary alcohols.

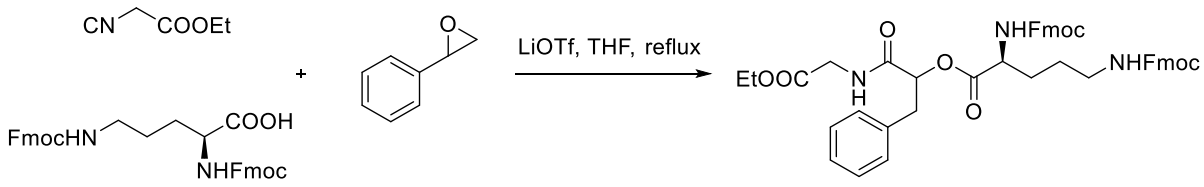
In the presence of Brönsted acids or Lewis acids, the acetals can undergo Passerini coupling to give α – alkoxyamides (scheme 1-45).[58]



scheme 1-45

[57] J. Brioche, G. Masson, Zhu, *J. Org. Lett.* **2010**, *12*, 1432.
[58] M. Barrett, R. Barton, R. Falck, D. Papaioannou, A. Widdowson, *J. Chem. Soc., PerkinTrans. I* **1979**,652.

An epoxide compound could be also introduced in Passerini reaction with an isonitrile and an acid carboxylic acid. A carbonyl derivative was obtained by rearranging the epoxide in the presence of Lewis acid (scheme 1-46).[59]

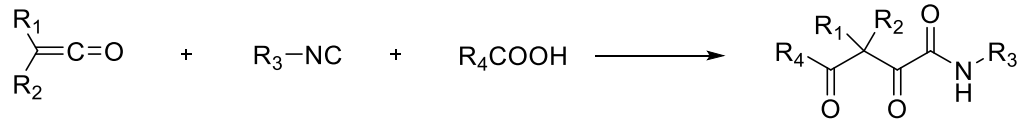


scheme 1-46

In 1964, Neidlein and coworkers reported an addition of an isonitrile on an isocyanate to give N-Alkyl or N-aryl N-N'-diacyloxamides.[60] This was close to the coupling of Nef. (scheme 1-47).

scheme 1-47

Similarly, dioxoamides are obtained by the reaction of ketenes with a carboxylic acid and an isocyanide (scheme 1-48).[61]



scheme 1-48

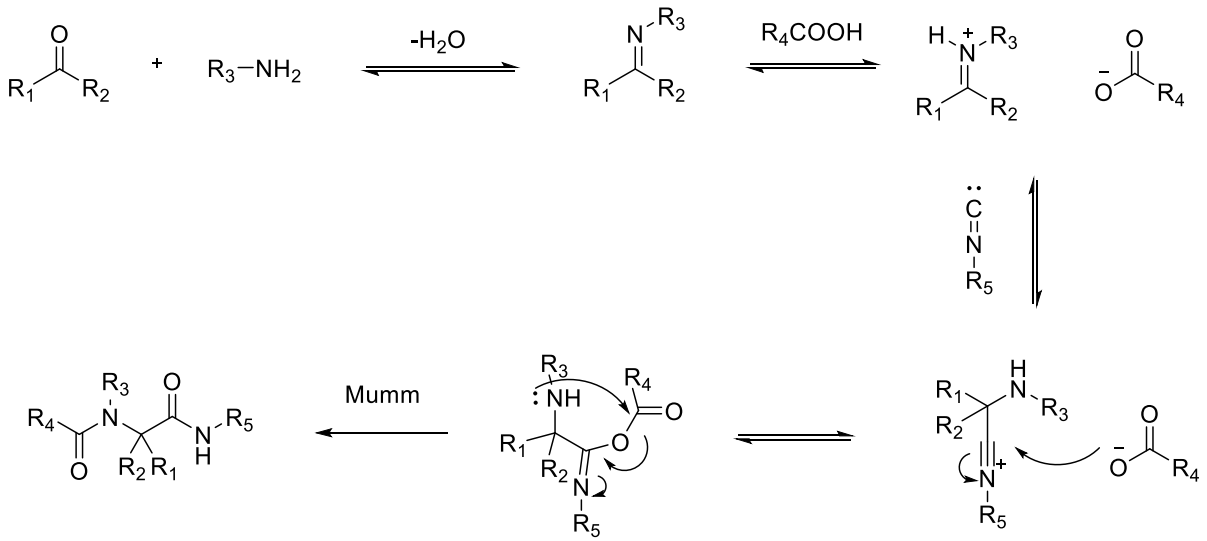
[59] (a) T. Kern,B. Motherwell, *Chem. Comm.* **2003**, 2988. (b) T. Kern, B. Motherwell, *Chem. Comm.* **2005**, 1787.
[60] R. Neidlein, *Naturforsch* **1964**, *19*, 1159.
[61] (a) I. Ugi,K. Rosendahl, *Chem. Ber.* **1961**, *94*, 2233. (b) T. Gomati, J. Firl, I.Ugi, *Chem. Ber.* **1977**, *110*, 1603.

3.3 Ugi reaction

This reaction was discovered by Ugi in 1959.[62] He extended the scope of the Passerini reactions by adding an amine. It can deliver α-amidocarboxamide derivatives via the condensation between a carbonyl group (aldehyde or ketone), an amine, a carboxylic acid and an isocyanide.

This reaction is generally carried out at room temperature and in concentrated polar protic solvents affording very high yields.

Ugi suggested an ionic mechanism involving charged intermediates for this reaction. The mechanism includes a series of reversible equilibrium and begins with formation of an imine. The imine was activated by proton exchange with carboxylic acid, followed by nucleophilic addition of isocyanide yielding nitrilium ion intermediate. Then, the intermediate was trapped by the nucleophilic attack of the carboxylate anion forming acyl imidoyl species. After an irreversible Mumm rearrangement, α-amidocarboxamide was obtained (scheme 1-49).



scheme 1-49

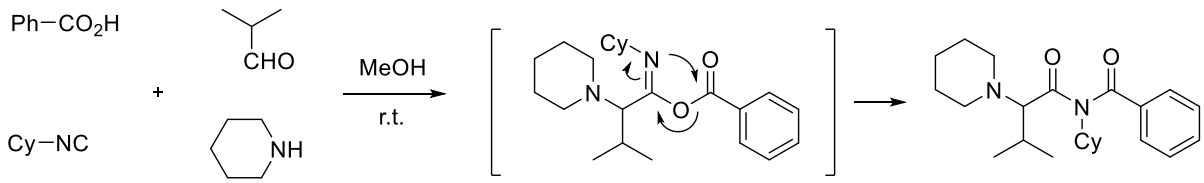
[62] (a) I. Ugi, R. Meyr, U. Fetzer, C. Steinbrückner, *Angew. Chem.* **1959**, *71*, 386. (b) I. Ugi, C. Steinbrückner, *Angew. Chem.* **1960**, *72*, 267.

Lately, many efforts have been conducted towards the development of Ugi reaction to extend its scope of reactivity and the accessibility to diverse libraries of compounds.

3.4 Scope of Ugi reaction

3.4.1 Scope of the amines

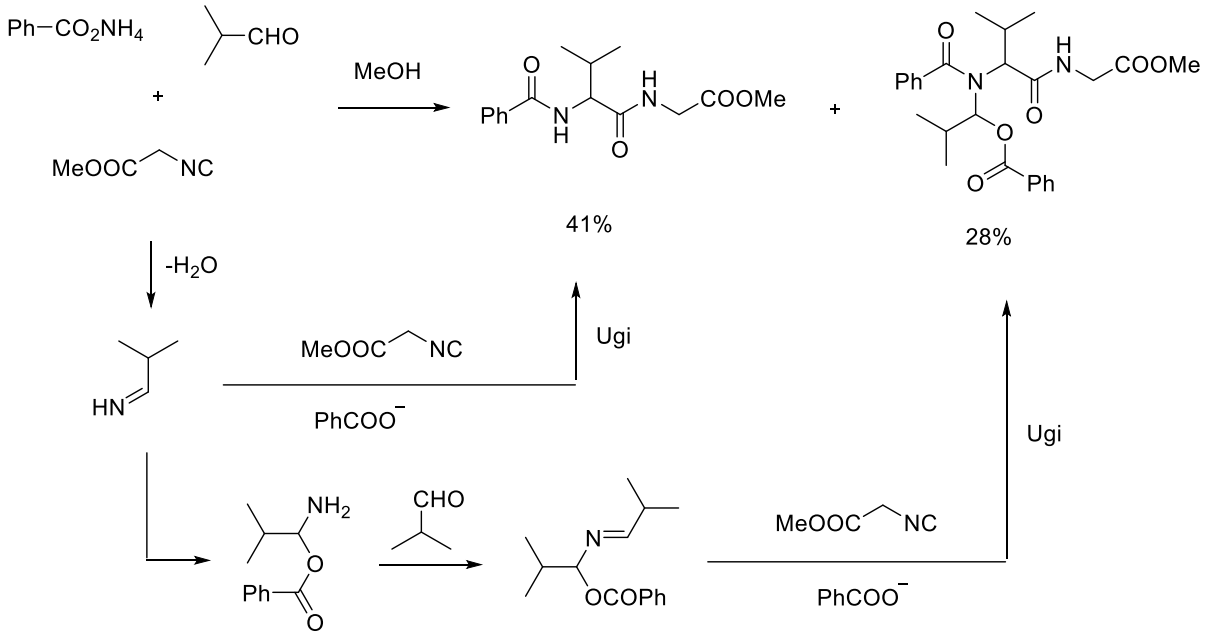
The secondary amines can be used for the Ugi reaction. In this case, the acyl transfer proceeded via [1,3]-shift towards the nitrogen atom of the isocyanide forming α,α'-diacylimide derivatives (scheme 1-50).[63]



scheme 1-50 The employment of secondry amines in Ugi reaction.

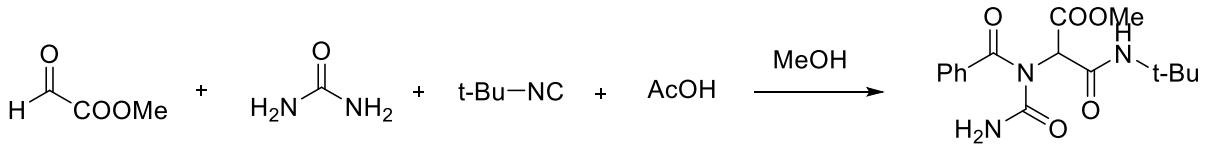
Nonetheless, using ammonia as the amine component in Ugi coupling was widely studied by a number of groups.[64] The desired Ugi adduct is often obtained with moderate yields because of the competition with several byproducts such as: the six-component coupling adduct isolated in this case (scheme 1-51).

[63] I. Ugi, C. Steinbrücker, *Chem. Ber.* **1961**, *94*, 2802.
[64] (a) D. Floyd, A. Harnett, A. Miller, S. Patel, L. Saroglou, M. Whittaker, *Synlett* **1998**, 637. (b) U. Kazmaier, C. Hebach, *Synlett* **2003**, 1591. (c) R. Pick, M. Bauer, U. Kazmaier, C.Hebach, *Synlett* **2005**, 757. (d) J. Thompson, B. Chen, *J. Org. Chem.* **2009**, *74*, 7084.



scheme 1-51 The employment of ammonium benzoate in Ugi reaction.

Other amine derivatives (e.g. hydrazines and hydrazides,[65] hydroxylamines and oximes,[66] as well as hydrazones[67] and ureas[68]) can also be successfully employed as amine partners in the coupling reaction, yielding the corresponding Ugi adduct (scheme 1-52).



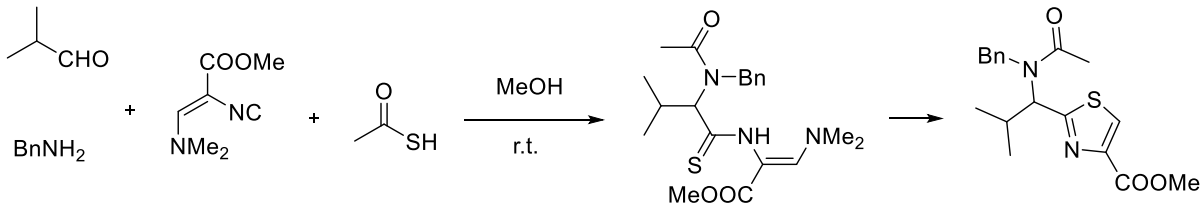
scheme 1-52 Ugi reaction using urea as the amine component

3.4.2 Scope of the acids

Since the discovery of the Ugi reaction, many approaches have been described on the acidic partner variations. In 1962, Ugi proposed the possibility of using thiocarboxylic acid as the acid component. However, it was first reported by Dömling group in synthesis of thiazoles

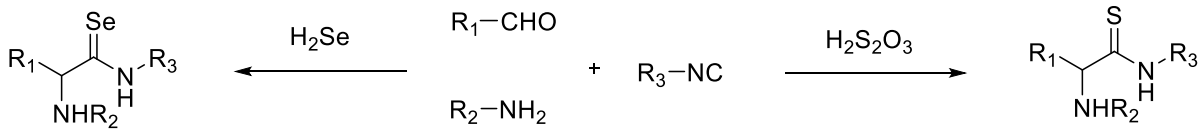
[65] I. Ugi, F. Bodesheim, *Liebigs Ann. Chem.* **1963**, *666*, 61. (b) G. Zinner, Kliegel, W. Arch. *Pharm.* **1966**, *299*, 746. (c) G. Zinner, W. Bock, *Pharm.* **1973**, *306*, 94.
[66] I. Ugi, *Isonitrile Chemistry; Academic Press, New York - London*, **1971**; *Vol. 20.*
[67] A. Santos, L. Kaïm,L. Grimaud, C. Ronsseray, Beilstein *J. Org. Chem.* **2011**, *7*, 1310.
[68] S. Zychlinski, I. Ugi, *Heterocycles* **1998**, *49*, 29.

(scheme 1-53).[69]



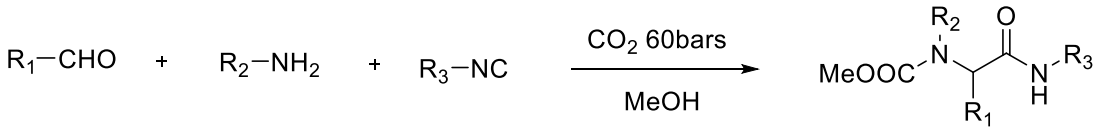
scheme 1-53

The use of hydrogen selenide and thiosulfuric acid as acidic parts in Ugi reaction allowed the synthesis of α-aminoselenocarboxamides and α-aminothiocarboxamides respectively (scheme 1-54).[70]



scheme 1-54

The carbonic acid generated in situ by bubbling carbon dioxide in methanol, can be employed in Ugi reaction to prepare methyl α-carboxamidocarbamates (scheme 1-55).[71]

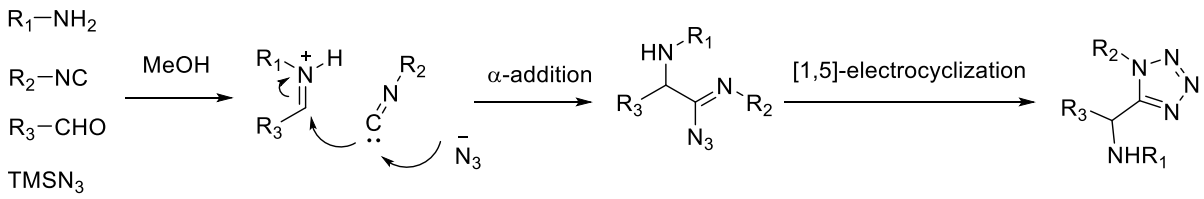


scheme 1-55

The use of hydrazoic acid derivatives represents a particularly important acid variant in Ugi coupling. In this case, an [1,5]-electrocyclization replaced the Mumm rearrangement resulting in the formation of 1,5-disubstituted tetrazoles. Ugi *et al.* described an Ugi/$TMSN_3$

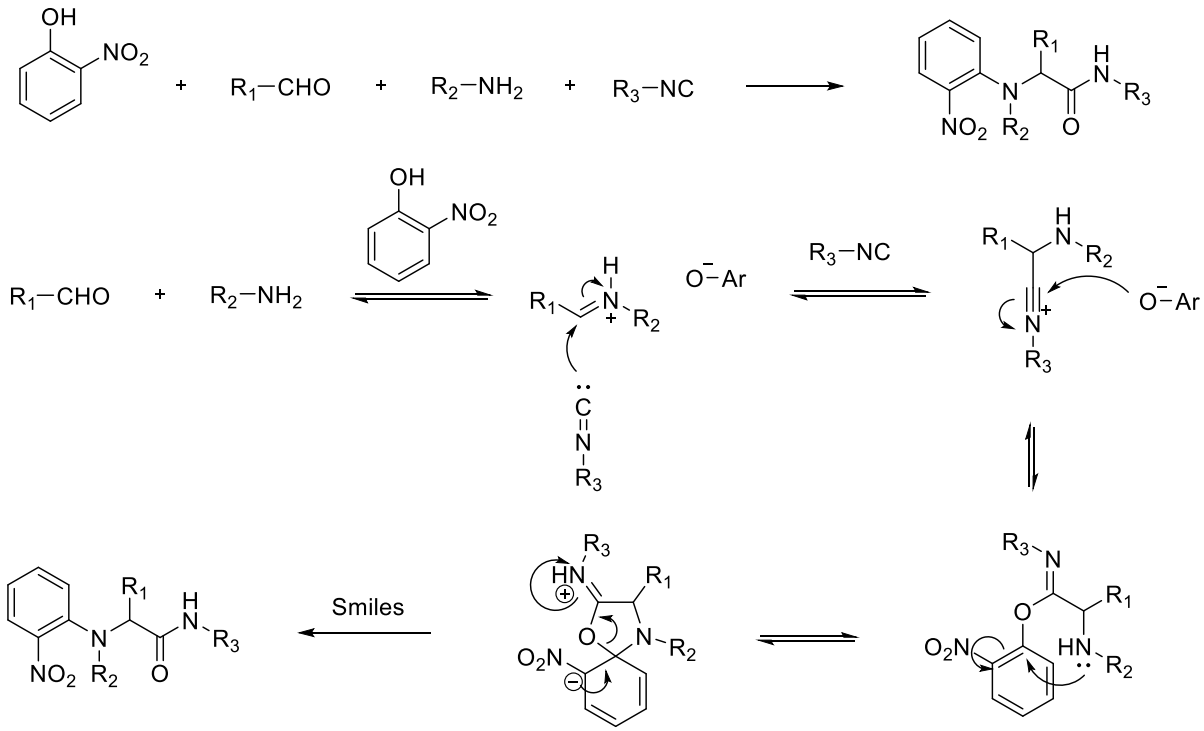
[69] S. Heck, A. Dömling, *Synlett.* **2000**, *3*, 424
[70] I. Ugi, C. Steinbrückner, *Angew. Chem.* **1960**, *72*, 267.
[71] E. Haslinger, *Chem.* **1978**, *109*, 747.

cascade reaction to prepare tetrazoylisoindolinones (Scheme 1-56).[72]



scheme 1-56

In 2005, our lab developed a new Ugi-type coupling. Some electron-deficient phenols could successfully be employed as the acid component. In this case, a final Smiles rearrangement takes place instead of a Mumm acyl transfer (scheme 1-57).[73]



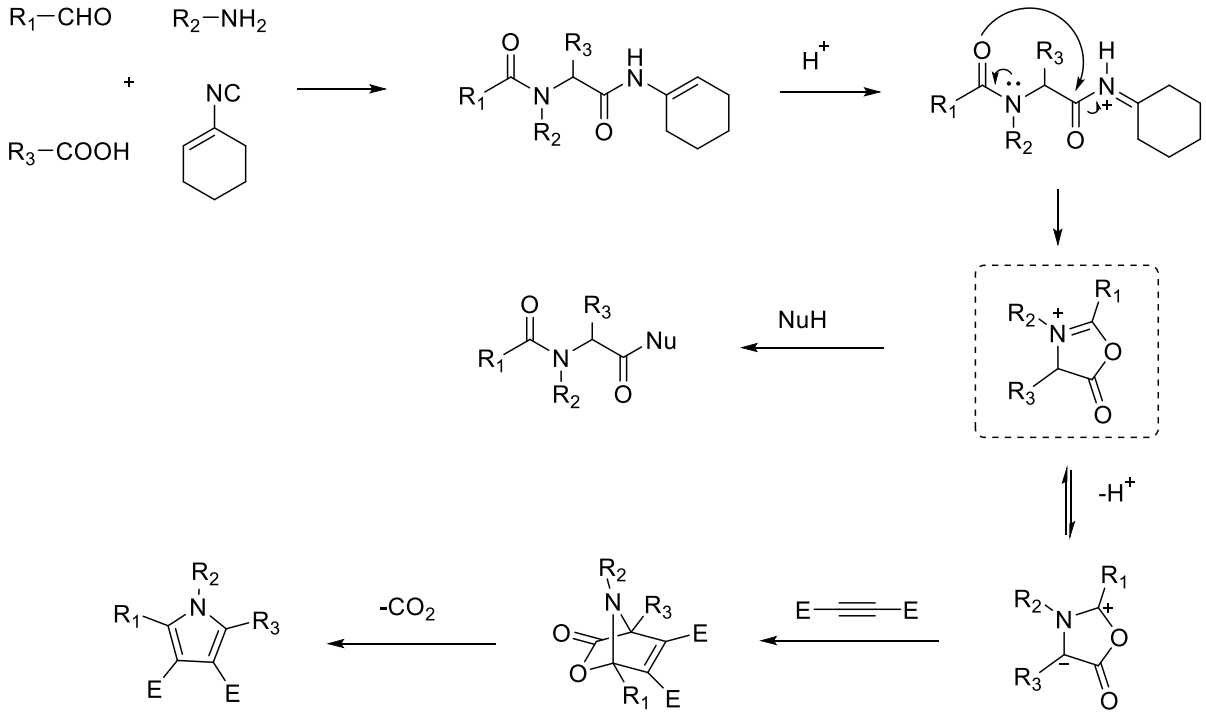
scheme 1-57

3.4.3 Scope of the isocyanides

A facile method for achieving greater functional diversity is the use of convertible

[72] I. Ugi, C. Steinbrückner, *Chem. Ber.* **1961**, *94*, 734.
[73] L. Elkaïm, L. Grimaud, J. Oble, *Angew. Chem. Int. Ed.* **2005**, *44*, 7961.

"universal" isocyanides. Cyclohexenyl isocyanide as a convertible isocyanide in Ugi reaction was introduced by Armstrong. This isocyanide provides an Ugi adduct, which in acidic medium, generates a münchnone in situ. This dipolar species can react with different nucleophiles especially with dienophiles in 1,3-dipolar cycloadditions (scheme 1-58).[74]



scheme 1-58

3.5 Post-condensation reactions

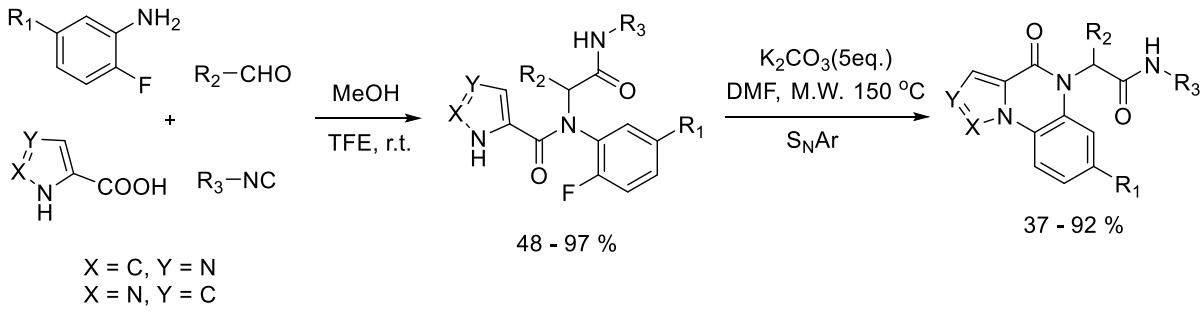
For Passerini post-condensation reactions, I introduced them chapter 2. Here are just some examples performed on Ugi adducts.

3.5.1 Aromatic nucleophilic substitution S_NAr

In 2007, Spatz and co-workers described a synthesis of imidazo- and pyrazolo [1,5-*a*]

[74] a) A. Keating, W. Armstrong, *J. Am. Chem. Soc.* **1996**, *118*, 2574. b) A. Keating, W. Armstrong, *J. Org. Chem.* **1996**, *61*, 8935.

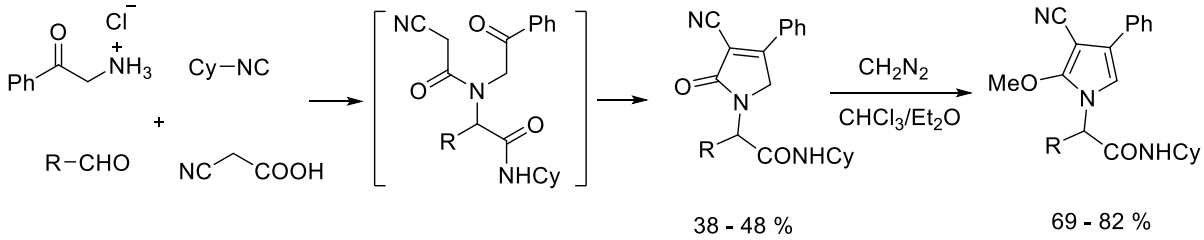
quinoxalines via an Ugi/S_NAr cascade, in which a bifunctional heterocyclic carboxylic acid derivative was used in the Ugi coupling together with an *ortho*-fluoro-substituted aniline derivative (scheme 1-59).[75]



scheme 1-59

3.5.2 Knoevenagel condensation

In 1999, Marcaccini group described a synthesis of variously substituted pyrroles involving an Ugi/Knoevenagel cascade. Starting from cyanoacetic acid and phenacylamine hydrochloride as coupling partners in Ugi reaction, different pyrrolones were obtained. A subsequent methylation of these derivatives afforded the desired pyrroles (scheme 1-60).[76]



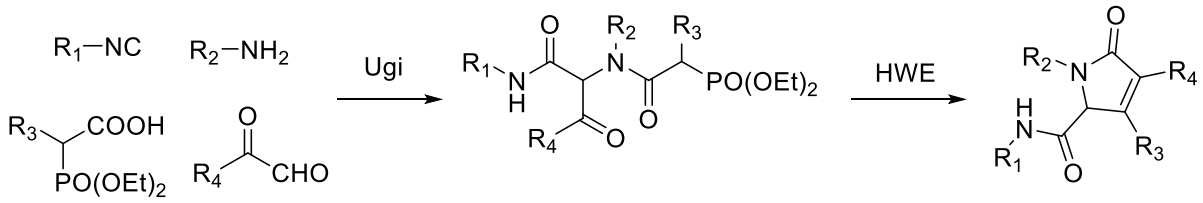
scheme 1-60

3.5.3 Horner-Wadsworth-Emmons condensation

In 2004, the Dömling *et al.* synthesized various substituted pyrrolidinones through an

[75] H. Spatz, M. Umkehrer, C. Kalinski, G. Ross, C. Burdack, J. Kolb, T. Bach, *Tetrahedron Lett.* **2007**, *48*, 8060.
[76] R. Bossio,S. Marcaccini, R. Pepino, T. Torroba, *Heterocycles* **1999**, *50*, 463

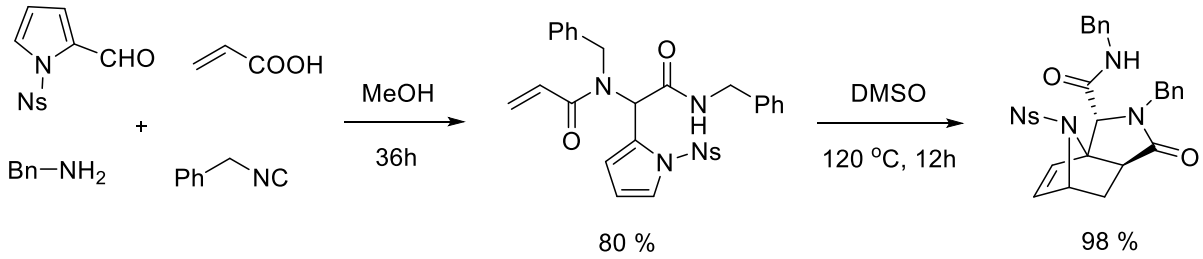
Ugi/Horner-Wadsworth-Emmons tandem (HWE) sequence. Carboxylic acids possessing a phosphonate group and glyoxals were used in the Ugi coupling (scheme 1-61).[77]



scheme 1-61

3.5.4 Diels-Alder reaction

In 2004, Paulvannan synthesized tricyclic nitrogenous heterocycles via an Ugi/Diels-Alder cascade with good yields and high diastereoselectivity. Pyrrole part of Ugi addut was the diene, and acrylic acid part was the dienophile. (Scheme 1-62).[78]



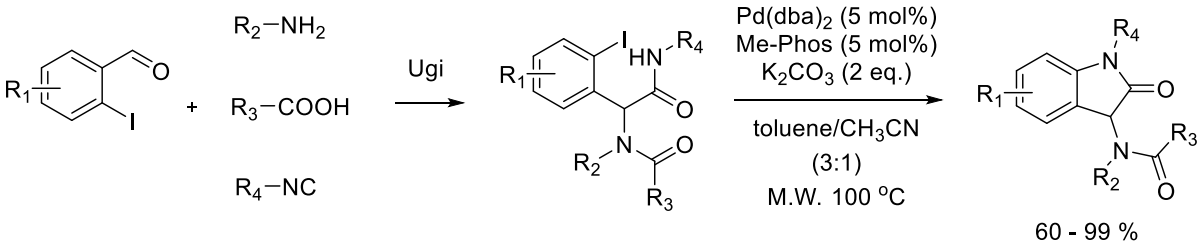
scheme 1-62

3.5.5 Arylation reactions

In 2006, Zhu group propsoed an efficient Ugi/Pd-catalyzed intramolecular N-arylation (intramolecular Buchwald–Hartwig reaction) methodology to access functionalized oxindoles (Scheme 1-63).[79] The reaction was carried out under microwave irradiations, $Pd(dba)_2$ as a catalyst and Me-Phos as a ligand, affording oxindoles in moderate to excellent yields (60–

[77] B. Beck, A. Picard, E. Herdtweck, A. Dömling, *Org. Lett.* **2004**, *6*, 39
[78] K. Paulvannan, *J. Org. Chem.* **2004**, *69*, 1207.
[79] F. Bonnaterre, M. Bois-Choussy, Zhu, *J. Org. Lett.* **2006**, *8*, 4351

99%). No competitive CH activation was observed during their course of study.



scheme 1-63

Chapter II A Passerini/Michael pathway towards butyrolactones

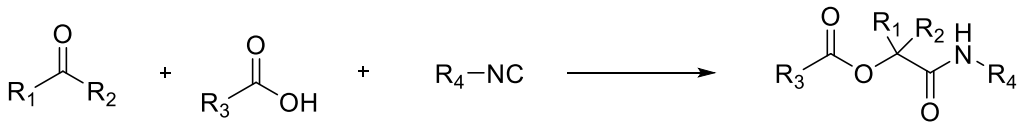
The work described in this chapter has been published on *Eur. J. Org. Chem*:

Shuanglong JIA, Laurent EL Kaïm. *Eur. J. Org. Chem.* 10.1002/ejoc.201800958

1 Introduction

1.1 Passerini post-condensation reactions

In previous chapter, we introduced the Passerini reaction for rapid access to α-acyloxycarboxamides (scheme 2-1), and this reaction could be utilized in the drug discovery process and total syntheses of biologically relevant natural products.[80]



scheme 2-1 Passerini reaction

Passerini reactions are powerful synthetic tools for the synthesis of structurally diverse molecules. The power of these reactions can be further increased by simple transformations of the Passerrini adducts (the so called post-condensations).[81]

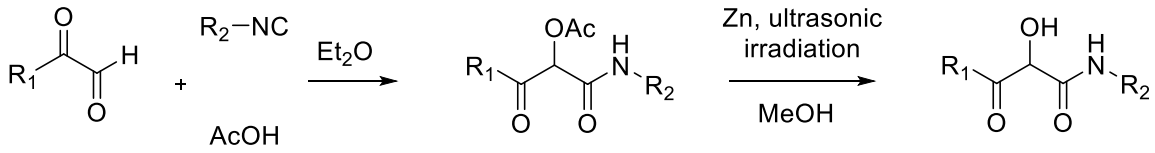
1.1.1 Passerini / O-Deacylation

In 2006, Marcos *et al.* reported a synthesis of acylated tartronamide derivatives from glyoxylamides, isocyanides and acetic acid, after solvolysis catalyzed by zinc under ultrasound irradiation, the tartronamides were obtained. This compound can be used as a retropeptidic surrogate of hydroxyglycine, which may be regarded as a stable transition state analogue for amide bond hydrolysis (scheme 2-2).[82]

[80] a) J. Moran, E. Tellew, Z. Zhao, W. Armstrong, *J. Org. Chem.*, **1993**, *58*, 7848-7859. b) L. Banfi. G. Guanti, R. Riva, *Chem. Commun.*, **2000**, 985-986.c) A. Znabet, M. Polak, E. Janssen, J. de Kanter,J. Turner, A. Orru, E. Ruijter, *Chem. Commun.*, **2010**, *46*,7918-7920. d) W. Armstrong, E. Tellew, J. Moran, *J. Org. Chem.*, **1992**, *57*, 2208-2211. e) H. Otto, T. Schirmeister, *Chem. Rev*., **1997**, *97*, 133-171. f) E. Semple, C. Rowley, K. Brunck, C. Ripka, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 315-320.

[81] A. Kazemizadeh and A. Ramazani, *Current Organic Chemistry*, **2012**, *16*, 418-450

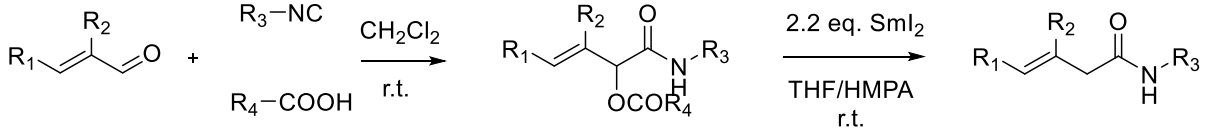
[82] M. Carrillo, G. Neo, L. López-García, S. Marcaccini, F. Marcos, *Green Chem.*, **2006**, *8*, 787-789.



scheme 2-2 O-deacylation

1.1.2 Passerini / Decarboxylation

The Passerini adducts from substituted cinnamaldehydes, isocyanides and carboxylic acids were treated with SmI_2/HMPA in dry tetrahydrofuran (THF) at room temperature, and α,β-unsaturated amides were obtained in moderate yields (scheme 2-3).[83]

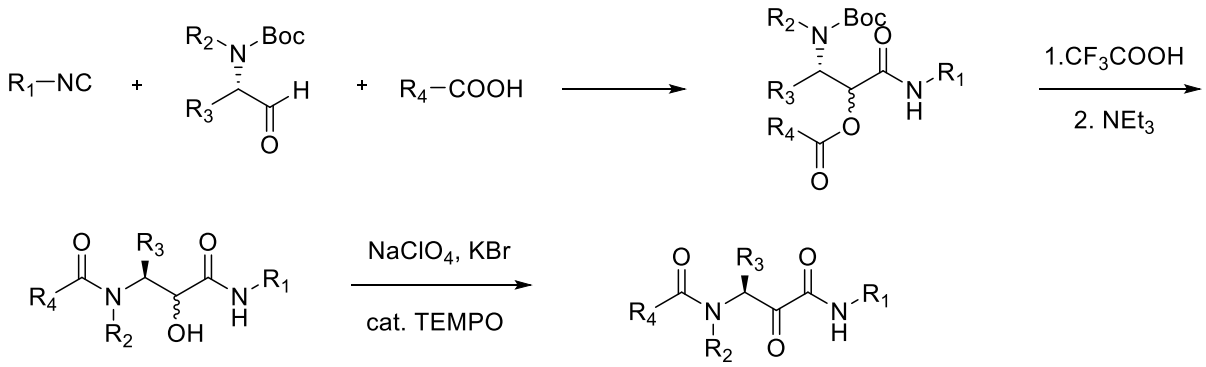


scheme 2-3 Decarboxylation

1.1.3 Passerini / N-Deprotection / Acyl Migration (PADAM)

In 2000, Banfi group reported a three-component Passerini condensation between N-Boc protected α-aminoaldehydes, isocyanides and carboxylic acids to α -acyloxy carboxamides. N-deprotection and acyl migration were then achieved upon treatment with trifluoroacetic acid followed by triethylamine. α-Hydroxy-β-acylamino amides were obtained in good to excellent overall yields. These products can be oxidized to the corresponding α-oxo-β-acylamino amides derivatives (scheme 2-4).[84]

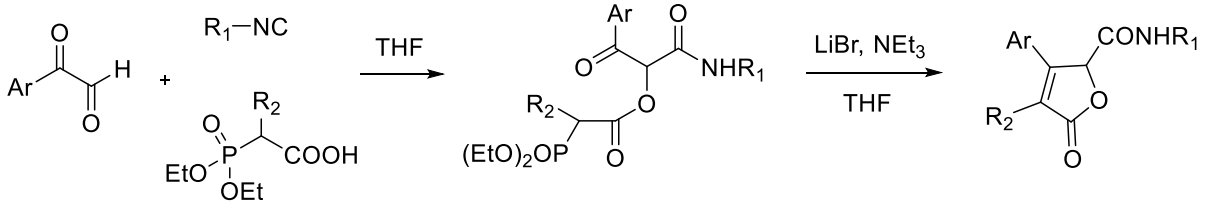
[83] H. Yu, T. Gai, L. Sun, S. Zhang, *Chinese Chem. Lett.*, **2011**, *22*, 379-381.
[84] L. Banfi. G. Guanti, R. Riva, *Chem. Commun.*, **2000**, 985-986.



scheme 2-4 PADAM

1.1.4 Synthesis of heterocycles

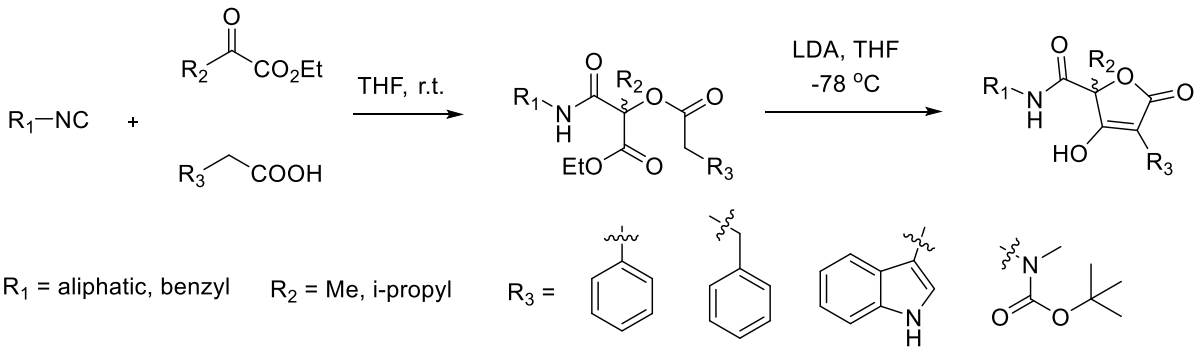
The condensation of isocyanides, glyoxals, and acetophosphonic acid diethylesters led to the Passerini products, which can be cyclized through a Horner-Wadsworth-Emmons reaction with LiBr and Et_3N to afford the 5-acylamino butenolides (scheme 2-5).[85]



scheme 2-5 synthesis of butenolides via Passerini/Horner-Emmons/Wadsworth reactions

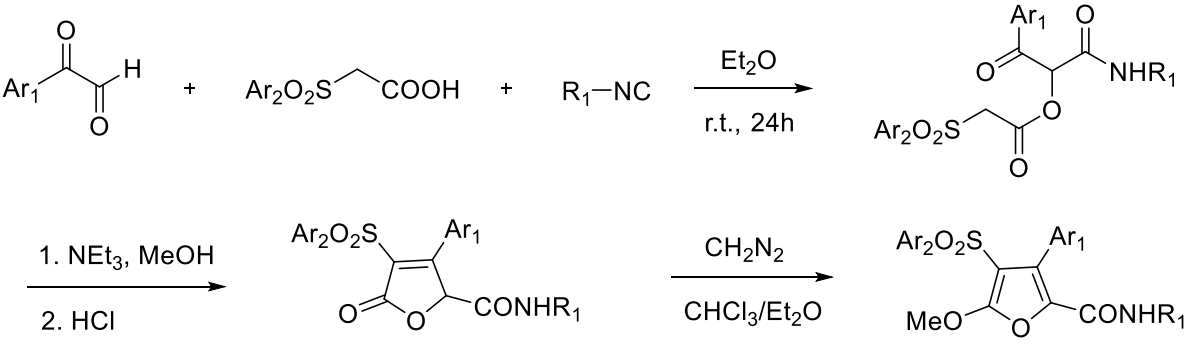
Synthesis of 3-hydroxy-5-oxo-2,5-dihydrofuran-2-carboxamide derivatives as a nonpeptidic inhibitors of HIV-1 protease was reported by a combination of the classical three-component Passerini reaction followed by a strong base triggered Dieckmann condensation to achieve the ring closure (scheme 2-6).[86]

[85] B. Beck, M. Magnin-Lachaux, E. Herdtweck, A. Dömling, *Org. Lett.*, **2001**, *3*, 2875-2878.
[86] M. Yehia, W. Antuch, B. Beck, S. Hess, M. Almstetter, P. Furer, E. Herdtweck, A. Dömling, *Bioorg. Med. Chem. Lett.*, **2004**, *14*, 3121-3125.



scheme 2-6 Passerini/Dieckmann condensation

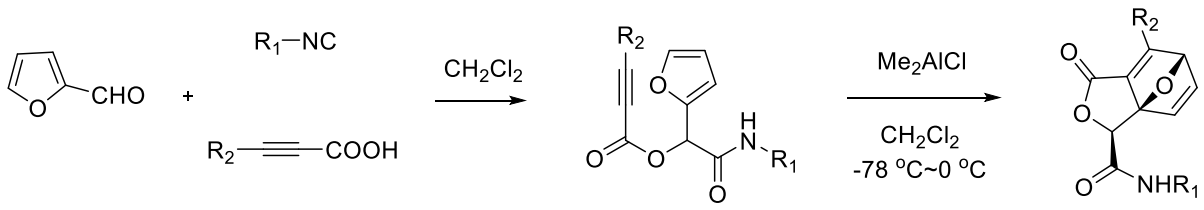
The multicomponent reaction of isocyanides, arylglyoxals, and carboxylic acids led to the Passerini product. The cyclization of the Passerini intermediate, using a Knoevenagel condensation reaction with Et_3N and followed by acidification resulted in the butenolides. A subsequent methylation of these compounds afforded the desired furan derivatives (scheme 2-7).[87]



scheme 2-7 Passerini/ Knoevenagel reactions

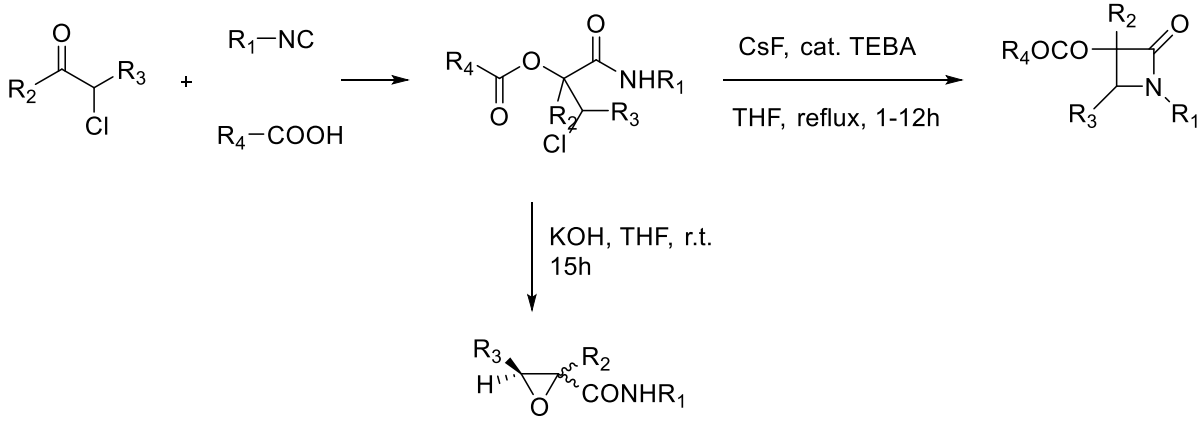
The condensation of 2-furancarboxaldehyde, acetylenic acids and isocyanides gave the Passerini adduct, which underwent Diels-Alder intramolecular cycloaddition upon treatment with Me_2AlCl to give highly functionalized oxabicyclo[2.2.1]heptadiene derivatives (Scheme 2-8).[88]

[87] R. Bossio, S. Marcaccini, R. Pepino, *Liebigs Ann. Chem.*, **1994**, 527-528.
[88] L. Wright, V. Robotham, K. Aboud, *Tetrahedron Lett.*, **2002**, *43*, 943-946.



scheme 2-8 Passerini/intramolecular Diels-Alder cycloaddition reactions

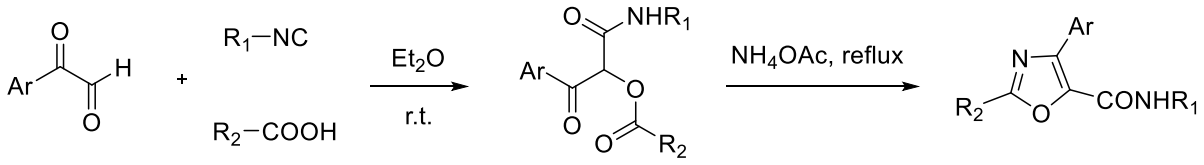
The Passerini reaction of α-chloroketones, isocyanides, and carboxylic acids led to α-acyloxy-β-chlorocarboxamides. The reaction of carboxamides with CsF afforded the 3-acyloxy-2-azetidinones. The treatment of carboxamides with KOH in tetrahydrofuran, led to O-deacylation followed by a Darzens-type O-alkylation to give the functionalized oxiranes (scheme 2-9).[89]



scheme 2-9 β-Lactams and oxiranes from α-acyloxy-β-chlorocarboxamides

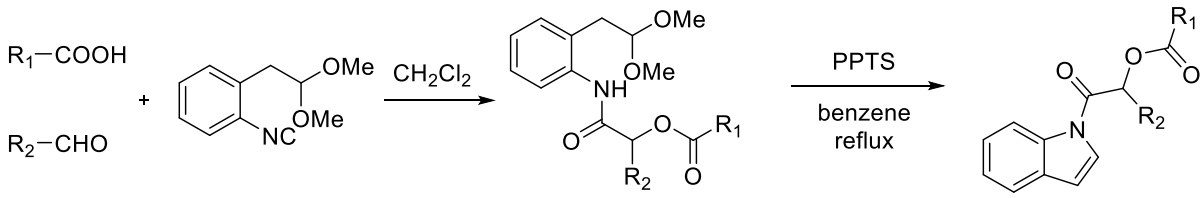
Synthesis N-substituted 2-acyloxy-3-aryl-3-oxopropionamides were reported by the Passerini reaction between arylglyoxals, carboxylic acids and isocyanides, followed by the reaction with ammonium acetate led to trisubstituted oxazole-5-carboxamides via Davidson cyclization (scheme 2-10).[90]

[89] S. Sebti, A. Foucaud, *Synthesis*, **1983**, 546-549.
[90] R. Bossio, S. Marcaccini, R. Pepino, *Liebigs Ann. Chem.*, **1991**, 1107-1108.



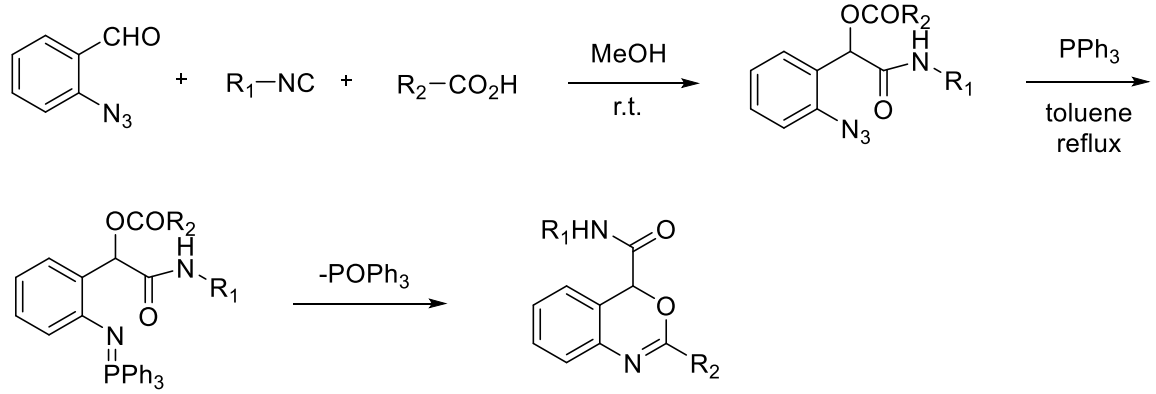
scheme 2-10 Passerini/Davidson cyclization reactions

Refluxing the Passerini products derived from 2-(2,2-dimethoxyethyl) phenyl isocyanide in the presence of pyridinium p-toluenesulfonate (PPTS) as the catalyst in benzene afforded indolyl amides (scheme 2-11).[91]



scheme 2-11 synthesis of indolyl amide derivatives.

The α-acyloxy carboxamide azide derivatives can be obtained from Passerini condensation between *o*-azidobenzaldehyde, isocyanides and carboxylic acids. These α-acyloxy carboxamide azides were reacted with triphenylphosphine to prepare 4-aminocarbonyl substituted 4H-1,3-benzoxazines via sequential Staudinger and intramolecular aza-Wittig reaction (scheme 2-12).[92]

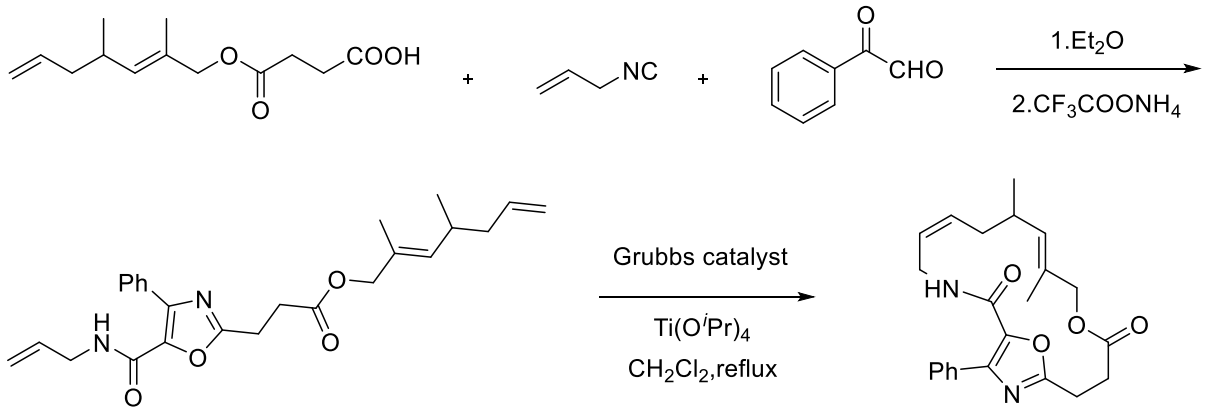


scheme 2-12 Passerini /Staudinger/aza-Wittig sequence.

[91] O. Kreye, B. Westermann, A. Wessjohann, *Synlett*, **2007**, 3188-3192.
[92] P. He, J. Wu, B. Nie, W. Ding, *Tetrahedron Lett.*, **2009**, *65*, 8563-8570.

1.1.5 Synthesis of macrocycles

Passerini reaction of carboxylic acid with allyl isocyanide and glyoxal and the subsequent ring closure to the oxazole led to a long-chain bis allyl compound. RCM of the terminal bisolefin resulted in the formation of a 17-membered oxazole containing macrocycle (scheme 2-13).[93]



scheme 2-13 synthesis of macrocyclic compounds via tandem Passerini/Davidson cyclization/ring closing metathesis reactions.

1.2 γ-Butyrolactones

1.2.1 A brief presentation of γ-butyrolactones

γ-Butyrolactones are a very common structure in organic compounds, present in about 10% of all natural products.[94] A wide variety of mono-, di- and trisubstituted monocyclic γ-butyrolactones are well known, but they are also found as part of more complex frameworks, especially in bicyclic and tricyclic ring systems. γ-Butyrolactones and derivatives, especially in enantiomerically pure form, display an impressive range of biological activities which are important for the development of physiological and therapeutic

[93] B. Beck, G. Larbig, B. Mejat, M. Magnin-Lachaux, A. Picard, E. Herdtweck, A. Dömling, *Org. Lett.*, **2003**, *5*, 1047-1050.
[94] a)Hoffmann HMR, J. Rabe, *Angew Chem Int Ed Engl* **1985**, *24*, 94-110. b) C. Koch, Chamberlin AR., *Studies in Natural Products Chemistry*, Edited by Attaur Rahman. Elsevier Science; **1995**, *Vol. 16*, 687-725.

agents.[95] Some representative members of this family are depicted in Figure 2-1. γ-Butyrolactones serve as an outstanding class of chiral building skeletons for the synthesis of diverse biological active compounds and complex molecules. Various transformations could be performed to access a range of chiral products due to the presence of a highly versatile functional group.

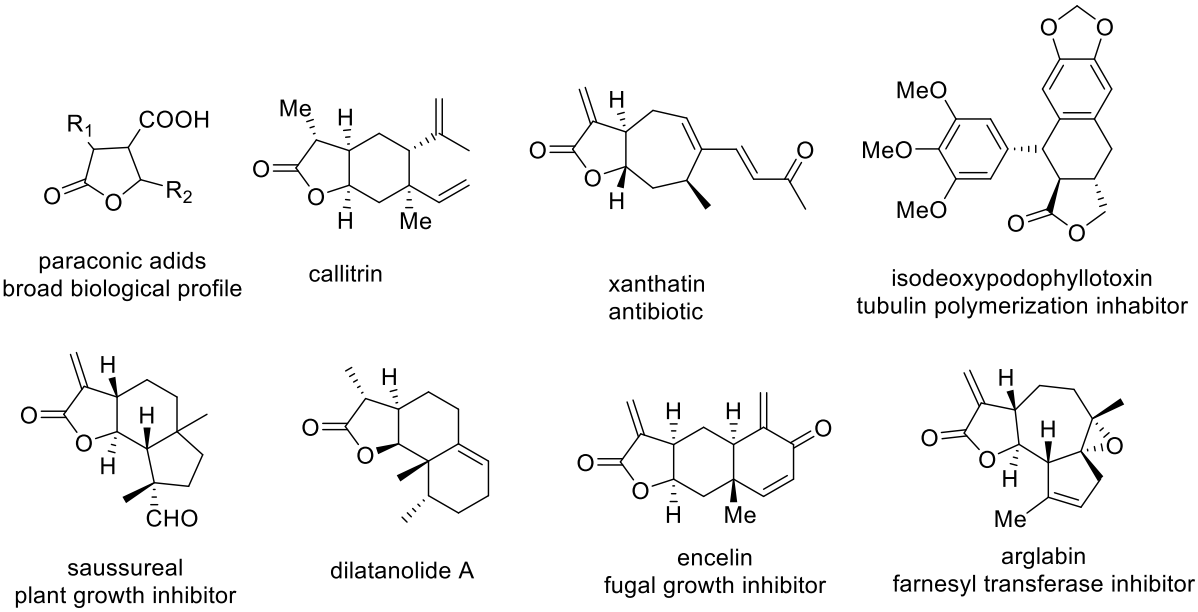


figure 2-1

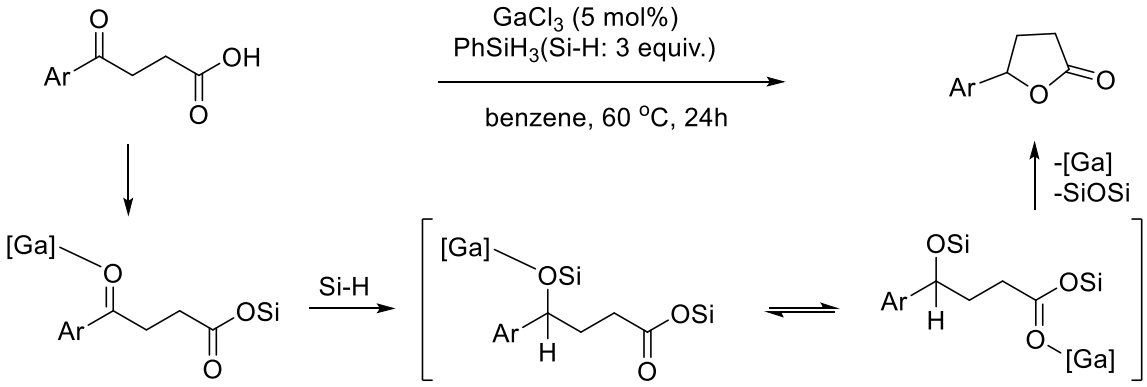
Considering the varying biological activity profiles and wide-ranging structural diversity of the optically active γ-butyrolactone structure, the development of synthetic strategies for assembling such interesting scaffolds has attracted enormous attention from synthetic chemists,[96] and a number of approaches have been well documented.

[95] A. Ottow, M. Brinker, T. Teichmann, E. Fritz, W. Kaiser, M. Brosche, J. Kangasjarvi, X. Jiang, A. Polle, *Plant Physiol.* **2005**, *139*, 1762−1772.
[96] Catalytic Asymmetric Synthesis, 3rded.;I. Ojima, ,Ed.;Wiley-VCH: Hoboken, NJ, 2010.

1.2.2 Synthesis of γ-butyrolactones

1.2.2.1 Reductive lactonization

In 2016, Sakai *et al.* developed a gallium (III)-catalyzed lactonization of γ-keto acids in the presence of $PhSiH_3$, which led to the production of γ-lactone derivatives with a variety of substituents. This reducing system involving $GaCl_3$ and $PhSiH_3$ in benzene retained the formed ester moiety (scheme 2-14).[97]

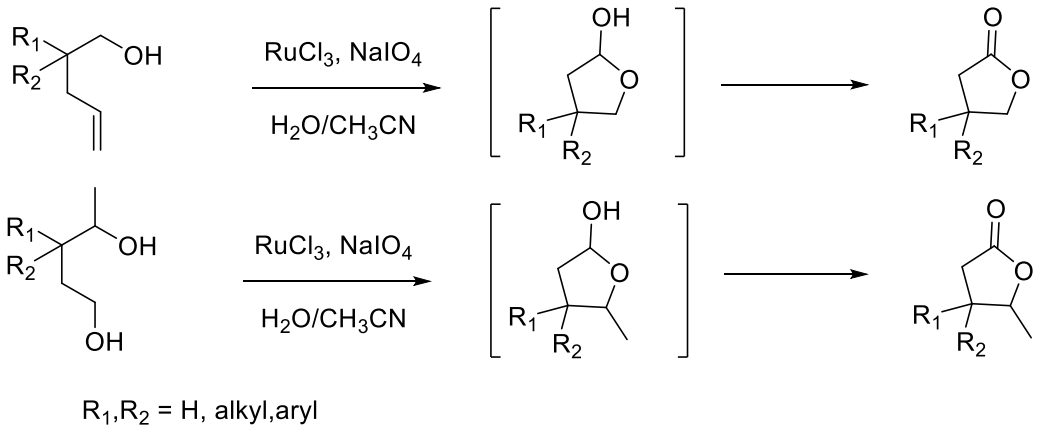


scheme 2-14

1.2.2.2 Oxidative lactonization

In 2015, Canney group described a synthesis of β,β-disubstituted γ-butyrolactones from readily prepared substituted 1,4-diols and γ-hydroxy olefins treated with the $RuCl_3$ /$NaIO_4$ oxidation system in modest to good yields (scheme 2-15).[98]

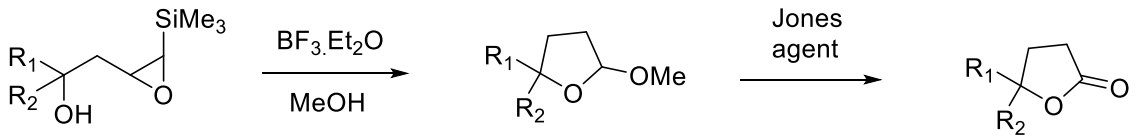
[97] S. Norio, H. Shuhei and O. Yohei, *RSC Adv.*, **2016**, *6*, 81763–81766
[98] G. Rong, F. Rong, C. Daniel, *Synlett.* **2015**, *26*, 661–665



scheme 2-15

1.2.2.3 Oxidation

In 1980, Magnus and co-workers demonstrated that the epoxysilanes treated with methanol in the presence of boron trifluoride etherate could give the lactol methyl ethers. After Jones oxidation, γ-butyrolactones can be obtained (scheme 2-16).[99]

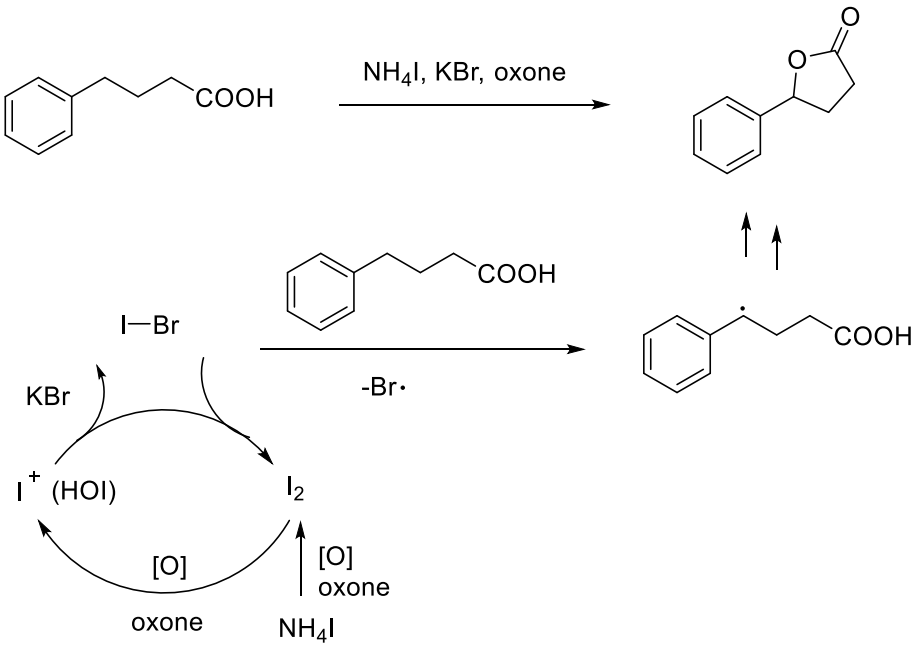


scheme 2-16

1.2.2.4 Radical reaction

In 2013, Yang *et al.* developed an efficient method for direct preparation of aryl-substituted lactones from corresponding aryl carboxylic acids promoted by ammonium iodide, which may involve a radical intramolecular cyclization. It has some advantages such as mild reaction conditions, simple procedure, and moderate to good yields (scheme 2-17).[100]

[99] E. Ehlinger and M. Philip, *J. Am. Chem. SOC.*, **1980**, *102*, 5005
[100] B. Zhang, L. Han, T. Li, J. Yan, and Z.Yang, *Synthetic Communications*, **2014** ,*11*, 1608-1613

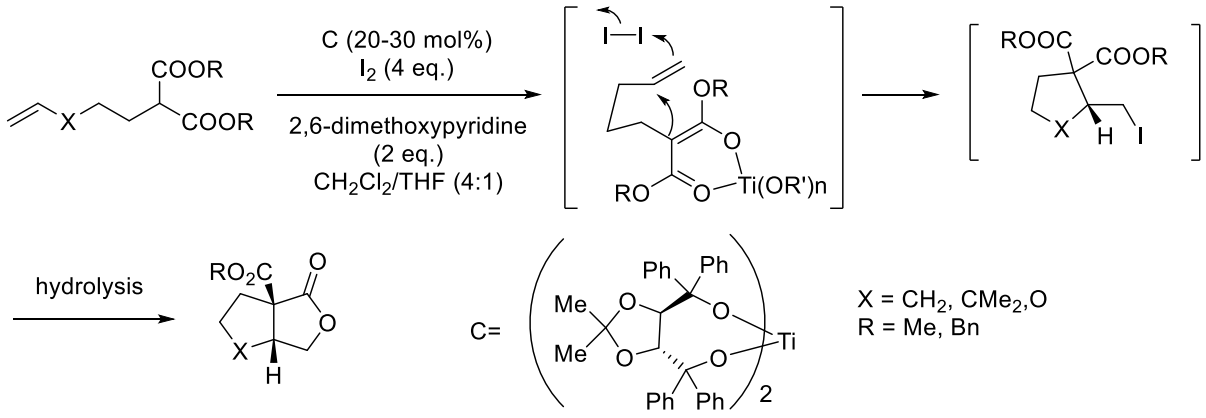


scheme 2-17

1.2.2.5 Enantioselective halolactonization

In 1995, Taguchi *et al.* described the first example of the catalytic desymmetrizing enantioselective iodolactonization of malonate derivatives with iodine in the presence of chiral titanium taddolate to afford the corresponding fused γ-butyrolactone with 96−99% ee (scheme 2-18).[101] The iodocarbocyclization proceeded in a highly enantiofacial selective manner benefited from strong coordination between the chiral titanium taddolate and malonate.

[101] a) T. Inoue, O. Kitagawa, O. Ochiai, M. Shiro, T. Taguchi, *Tetrahedron Lett.* **1995**, *36*, 9333−9336. b) T. Inoue, O. Kitagawa, A. Saito, T. Taguchi, *J. Org. Chem.* **1997**, *62*, 7384−7389.



scheme 2-18

2. Presentation of our strategy

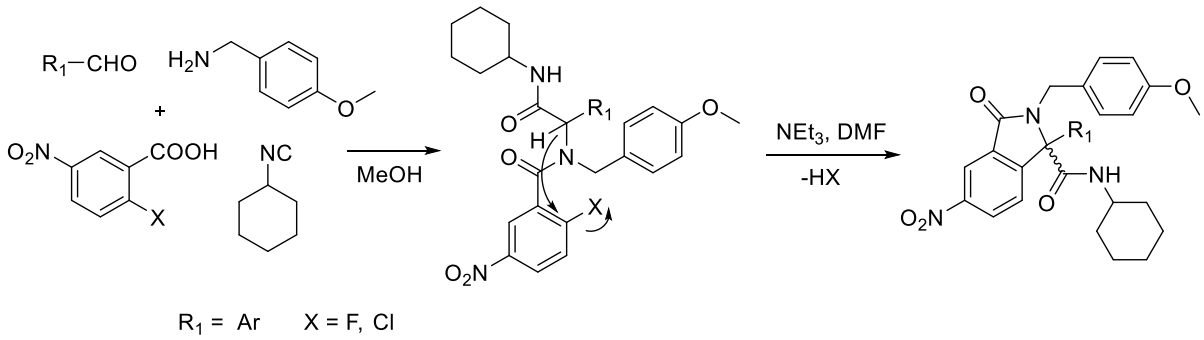
Isocyanide based multicomponent reactions (IMCRs) offer a unique way to generate libraries of heterocycles.[102] These syntheses are usually performed via two-step procedures using first an Ugi reaction as the IMCR affording the highest diversity and functional tolerance. The heterocyclic core is then obtained in a second cyclization step involving additional functionalities proper selected in the starting materials. The peptidyl position of Ugi adducts was often selected as the reactive center due to the ability to tune its acidity by proper selection of the aldehyde partner. After deprotonation which is deeply affected by aldehyde partner, a carbanion is obtained leading to cyclization with properly positioned additional functionality.[103] Most of these reactions have been described with Ugi reaction, we will make a brief summary here.

In 2007, Ivachtchenko *et al.* described a synthesis of 3-oxoiso-indoline-1-carboxamides via

[102] For reviews on IMCRs, see: a) *Multicomponent reactions*; J. Zhu, H. Bienaymé, Eds, Wiley-VCH, Weinheim, **2005**; b) A. Dömling, I. Ugi, *Angew. Chem. Int. Ed*. **2000**, *39*, 3168-3210; c) R. Orru, M. de Greef, *Synthesis* **2003**, 1471-1499; d) C. Hulme, V. Gore, *Curr. Med. Chem*. **2003**, *10*, 51-80; e) A. Dömling, *Chem. Rev*. **2006**, *106*, 17-89; f) A. Dömling, K. Wang, W. Wang, *Chem. Rev.* **2012**, *112*, 3083-3135; g) *Multicomponent Reactions in Organic Synthesis*, J. Zhu, Q. Wang, M. Wang, Eds., Wiley-VCH:Weinheim, Germany, **2014**; h) V. Boyarskiy, N. Bokach, K. Luzyanin, V. Kukushkin, *Chem. Rev*. **2015**, *115*, 2698-2779; i) A. Varadi, T. Palmer, R. Dardashti, S. Majumdar, *Molecules*, **2016**, *21*, 19; (j) J. Lei, J. Meng, D. Tang, B. Frett, Z. Chen, Z. Xu, *Mol. Divers*. 2018, in press, DOI : 10.1007/s11030-017-9811-2

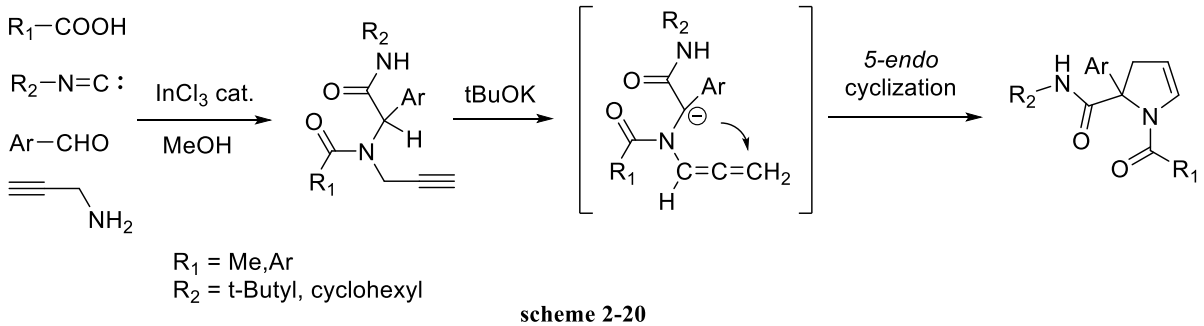
[103] For some intramolecular Ugi post-condensations involving the peptidyl position see: a) R. Bossio, C. Marcos, S. Marcaccini, R. Pepino, *Synthesis* **1997**, 1389-1390; b) A. Salcedo, L. Neuville, J. Zhu, *J. Org. Chem*. **2008**, *73*, 360-3603; c) L. Kaïm, L. Grimaud, X. Goff; M. Menes-Arzate, L. Miranda, *Chem. Commun.* **2011**, *47*, 8145-8147; d) A. Trifilenkov, A. Ilyin, V. Kysil, Y. Sandulenko, A. Ivachtchenko, *Tetrahedron Lett.* **2007**, *48*, 2563-2567; e) L. Polindara-Garcia, L. Miranda, *Org. Lett*. **2012**, *14*, 5408-5411; f) M. Ghandi, N. Zarezadeh, A. Abbasi, *Org. Biomol. Chem*. **2015**, *13*, 8211-8220; g) Z. Li, A. Kumar, A. Peshkov, E. Van der Eycken, *Tetrahedron Lett*. **2016**, *57*, 754–756

an Ugi four component reaction followed by intramolecular cyclization (scheme 2-19).[103d]



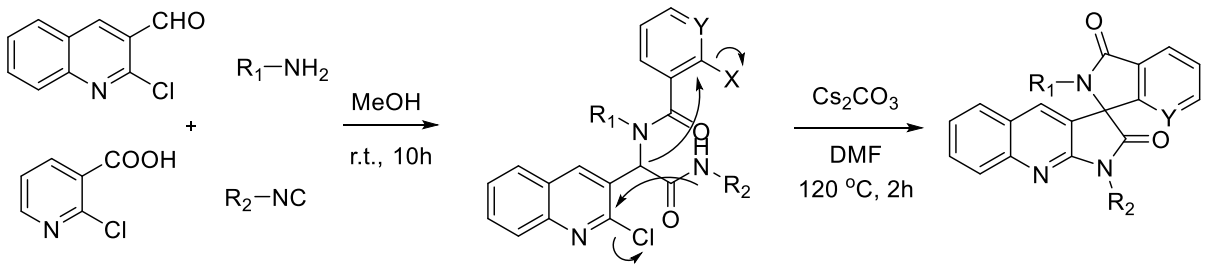
scheme 2-19

In 2012, a two-step synthesis of 2,3-dihydropyrroles via a formal 5-endo cycloisomerization of Ugi 4-CR/propargyl adducts was described by Miranda group (scheme 2-20).[103e]



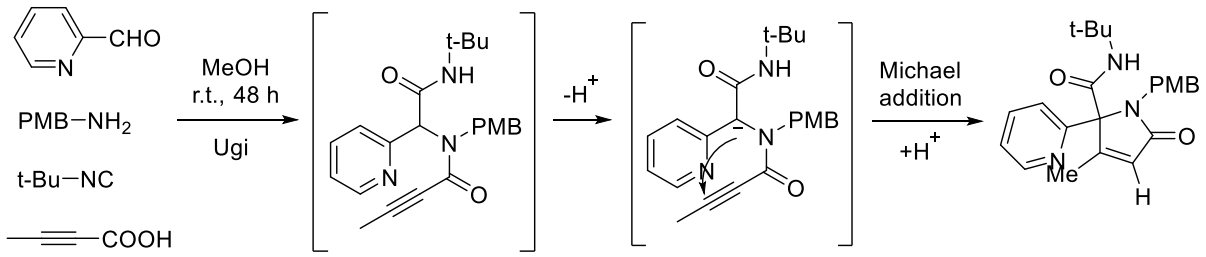
scheme 2-20

In 2015, Ghandi and co-workers reported a one-pot synthesis of a series of spiropyrroloquinoline isoindolinone and spiropyrroloquinoline aza-isoindolinone scaffolds. The reaction proceeds by combination of an Ugi 4CR and two intramolecular cyclizations under metal-free conditions (scheme 2-21).[103f]



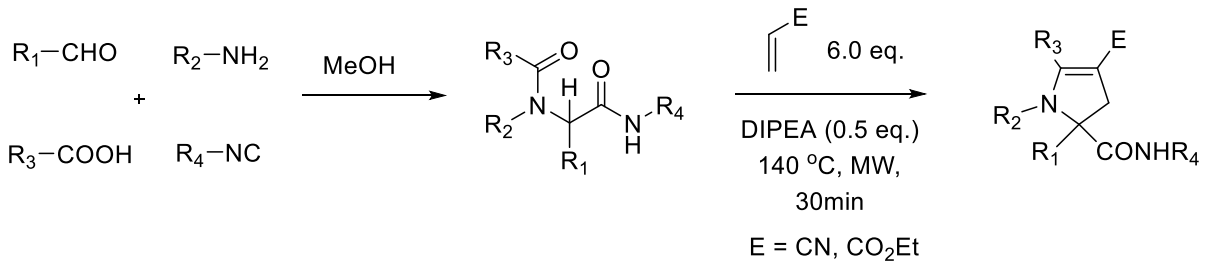
scheme 2-21

In 2016, Eycken group reported a facile domino Ugi/Michael approach for the synthesis of diversely substituted α,β-unsaturated γ–lactams under mild reaction conditions (scheme 2-22).[103g]



scheme 2-22

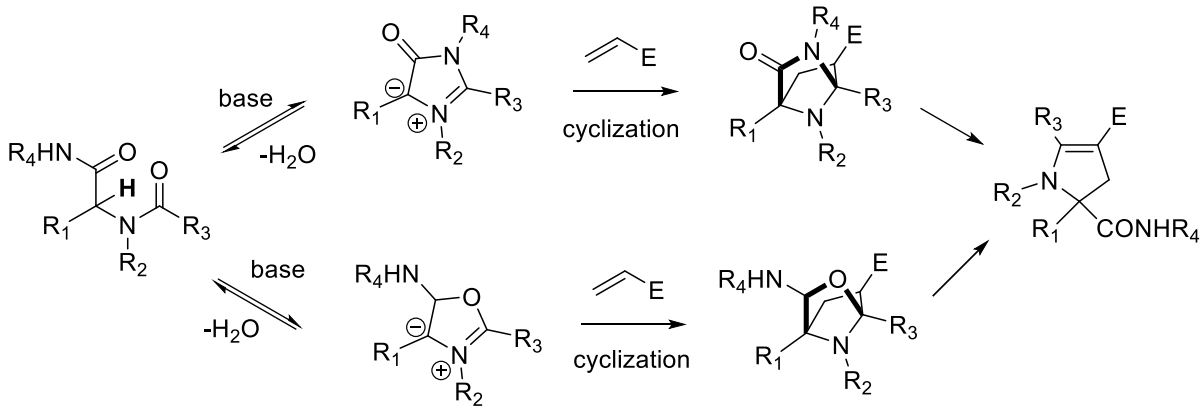
We recently started a program to evaluate the potential of intermolecular reactions of Ugi adducts as a way to expand the diversity and scope of heterocycles accessible by these two-step procedures (scheme 2-23).[104]



scheme 2-23

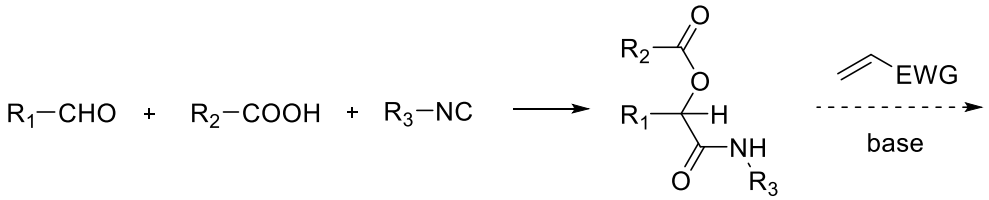
[104] A. Abdessalem, R. Abderrahim, A. Agrebie, A. Santos, L. Elkaïm, A. Komesky, *Chem. Commun*. **2015**, *51*, 1116-1119;

Among the various solutions explored, we discovered a [3+2] type cycloaddition of Ugi adducts with acrylonitrile leading to pyrrole derivatives, no Michael type adducts were obtained. Aware that a Thorpe–Ingold effect could favor the cyclization of our Ugi adducts, we proposed a possible mechanism (scheme 2-24).[105]



scheme 2-24

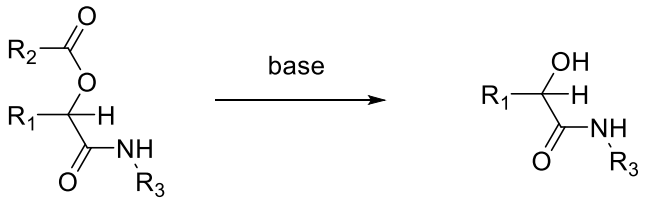
Gratified by this coupling but still failing to observe any Michael addition with Ugi adducts, we decided to explore the behavior of Passerini adducts in similar reactions (scheme 2-25).



scheme 2-25

A number of publications demonstrate that the ester moieties of Passerini adducts are very sensitive under basic conditions with saponification occurring readily (scheme 2-26).[105]

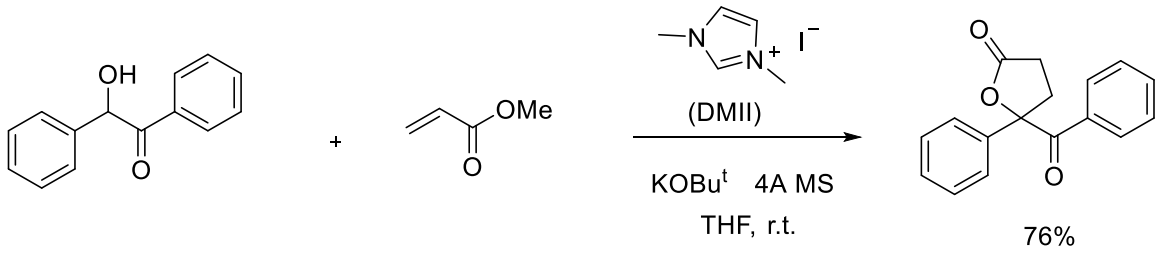
[105] A. Abdessalem, R. Abderrahim, L. Elkaïm, *Synlett* **2015**, *26*, 2537-2540.



scheme 2-26

Looking at the closet analogues of hydroxy Passerini derivatives, we could find various approaches for Michael additions of α-hydroxy keto and ester derivatives. Most examples have been performed with benzoins.

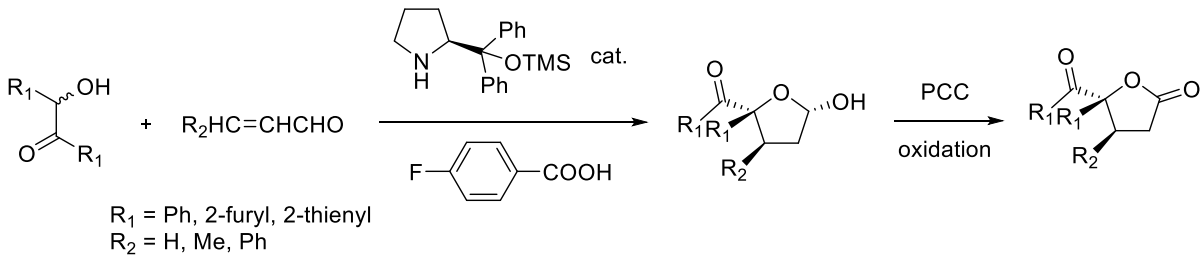
In 2005, Zhai and co-workers described a direct construction of γ,γ-difunctionalized γ-butyrolactones from benzoins promoted by 1,3-dimethyl imidazolin-2-ylidene (scheme 2-27).[106]



scheme 2-27

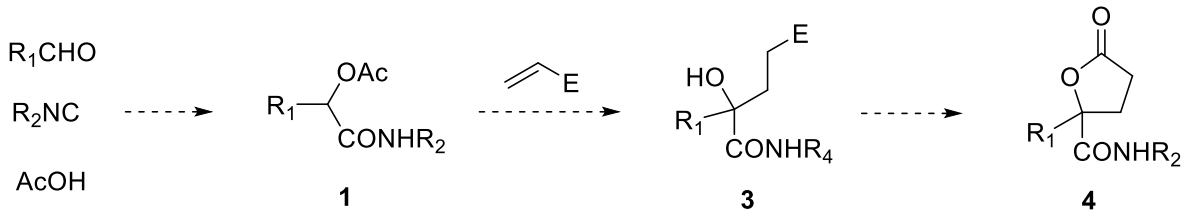
In 2014, Han group reported a synthesis of chiral tetrahydrofuran derivatives bearing multiple functional groups and stereogenic centers. The reaction proceeds with high stereoselectivity of up to 95:5 dr and 96 % ee. The high diastereomeric ratio may be due to the fact that acid promotes not only the iminium ion activation of enals but also the desymmetrization of racemic acyloins (scheme 2-28).[107]

[106] W. Ye, G. Cai, Z. Zhuang, X. Jia and H. Zhai, *Org. Lett.*, **2005**,*7*, 3769–3771.
[107] G. He, a F. Wu, W. Huang, R. Zhou, L. Ouyang, and B. Han, *Adv. Synth. Catal.* **2014**, *356*, 2311–2319



scheme 2-28

Knowing all the above information, we now wish to report a successful Passerini/Michael addition tandem with acrylonitrile and its application to new γ-butyrolactone preparation (scheme 2-29).



scheme 2-29

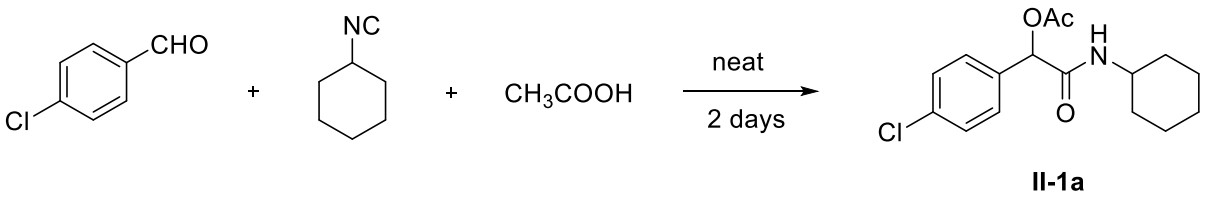
3. Results and discussion

3.1 Towards hydroxy derivatives

3.1.1 Optimization of reaction conditions

Our work as well as reports by others on cyclizations involving the peptidyl position of Ugi adducts showed the importance of selecting aromatic aldehydes for successful selective deprotonation/alkylation strategies. Thus, Passerini adduct **II-1a** was prepared in quantitative yield letting stoichiometric amount of p-chlorobenzaldehyde, cyclohexylisocyanide and acetic acid to react for two days under solvent free conditions (scheme 2-30).[108]

[108] a) D. Koszelewski, W. Szymanski, J. Krysiak, R. Ostaszewski, *Synth. Commun*. **2008**, *38*, 1120-1127; b) T. Bousquet, M.. Jida, M. Soueidan, R. Deprez-Poulain, F. Agbossou-Niedercorn, L. Pelinski, *Tetrahedron Lett.* **2012**, *53*, 306-308.

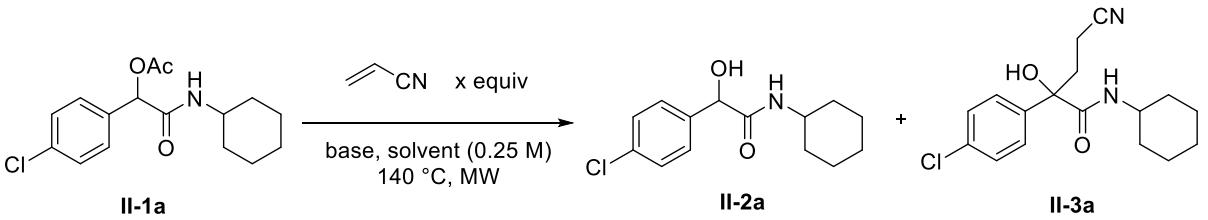


II-1a

scheme 2-30

At the onset of the study, acrylonitrile was chosen as Michael acceptor due to its higher efficiency as electrophile in our previous study on Ugi adducts. In order to get the suitable reaction conditions, the following trials were performed:

Table 2-1 Optimization of reaction conditions



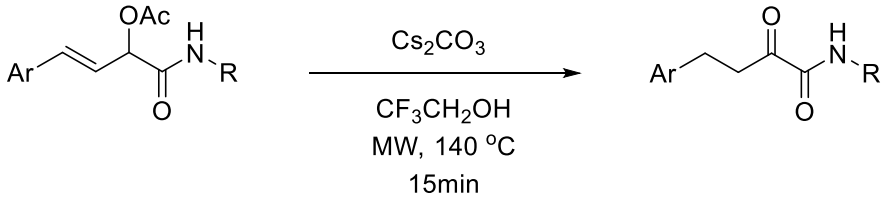
II-1a **II-2a** **II-3a**

entry	x	base	solvent	temperature & time	product
1	6	DIPEA (0.5 equiv.)	MeOH	140 °C, 30 min	**II-2a** 93 %
2	6	DIPEA (0.5 equiv.)	CH_3CN	140 °C, 30 min	**II-2a** 93 %
3	6	t-BuOK (0.5 equiv.)	toluene	140 °C, 30 min	**II-2a** 25 %
4	6	NaH (0.5 equiv.)	CH_3CN	140 °C, 30 min	**II-2a** 80 %
5	6	Cs_2CO_3 (0.5 equiv.)	DMF	140 °C, 30 min	-
6	6	Cs_2CO_3 (0.5 equiv.)	CH_3CN	140 °C, 30 min	**II-3a** 33 %
7	6	Cs_2CO_3 (2.2 equiv.)	CH_3CN	140 °C, 30 min	**II-3a** 81 %
8	3	Cs_2CO_3 (2.2 equiv.)	CH_3CN	130 °C, 45 min	**II-3a** 90 %

When **II-1a** was reacted under standard Michael addition reaction (various amount of DBU, acetonitrile or THF at r.t. or reflux conditions), we could not observe any reaction apart from partial hydrolysis of the acetate.

Microwave conditions were then selected. When **II-1a** was heated in methanol at 140 °C in the presence of diisopropylamine (0.5 equiv) and large excess of acrylonitrile (6 equiv), nearly quantitative yield of alcohol **II-2a** was obtained after 30 min heating (entry 1, table 2-1).

Replacing methanol by acetonitrile (entry 2, table 2-1) didn't change a behavior consistent with the relatively sensitive ester moieties of Passerini adducts as already observed in our recent conversion of Passerini adducts of cinnamaldehyde into α-ketoamides (scheme 2-31).[109]



scheme 2-31

The nature of the base and solvent were then varied working at the same temperature until we luckily observed a modest 33 % isolated yield of expected **II-3a** when cesium carbonate was selected as base in acetonitrile (entry 6, table 2-1). Raising the amount of base to two equivalents led us to a nice 81 % isolated yield (entry 7, table 2-1), whereas lowering the temperature to 130 °C and the excess of acrylonitrile gave us the best yield after 45 min of reaction (entry 8, table 2-1). These conditions were selected for the rest of the study.

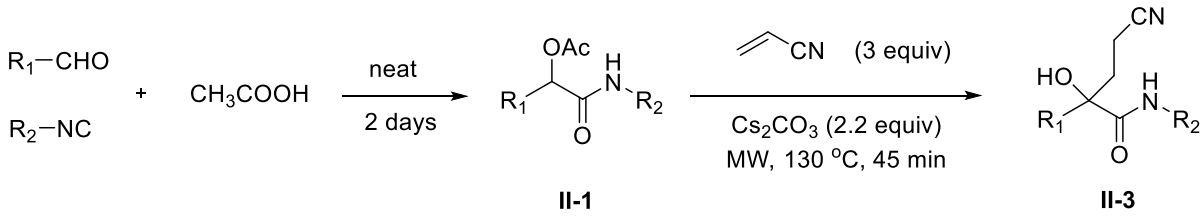
3.1.2 Synthesis of Passerini/Michael adducts

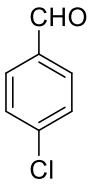
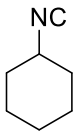
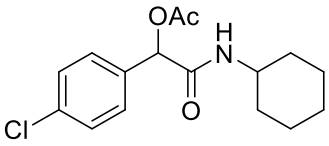
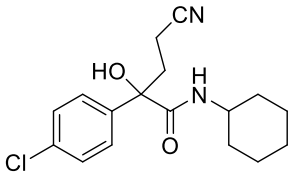
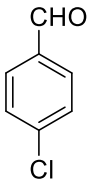
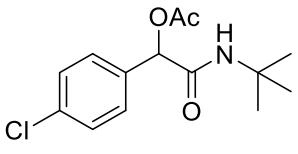
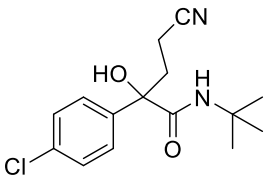
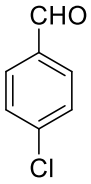
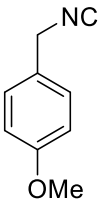
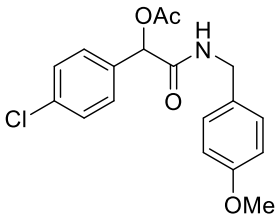
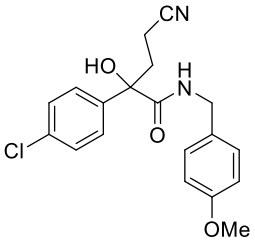
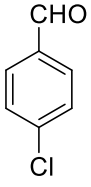
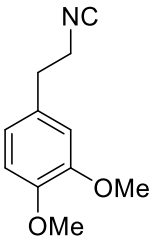
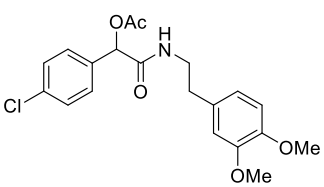
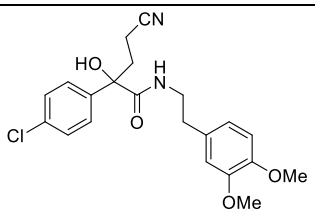
The Passerini reaction has been already highlighted in Chapter 1 involving the condensation of an aldehyde, an acid and an isocyanide at room temperature for 48 hours. Thus we prepared some Passerini adducts varying the 2 components with excellent yields in most

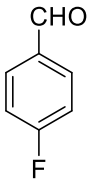
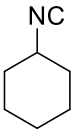
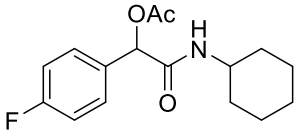
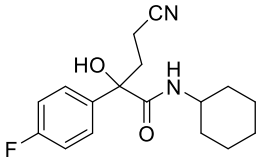
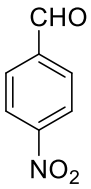
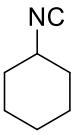
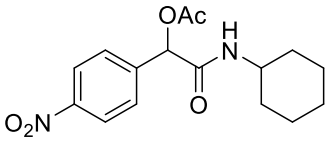
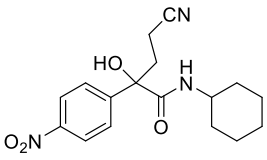
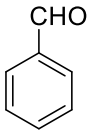
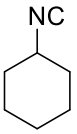
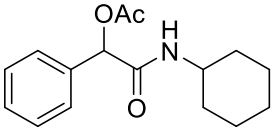
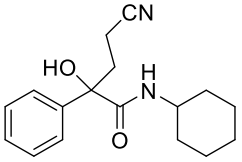
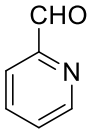
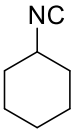
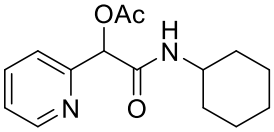
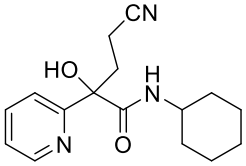
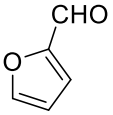
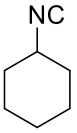
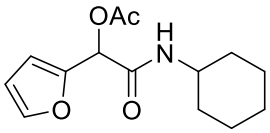
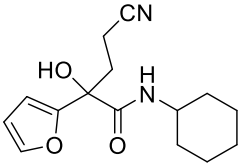
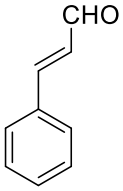
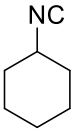
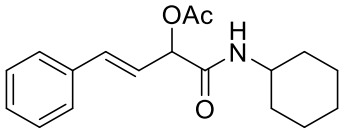
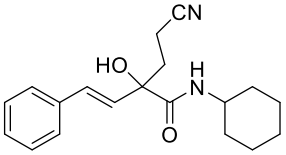
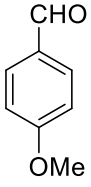
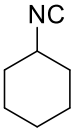
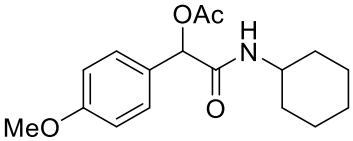
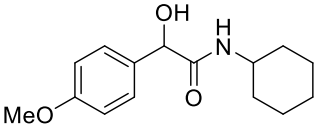
[109] A. Abdessalem, R. Abderrahim, L. Elkaïm, *Synlett* **2015**, *26*, 2537-2540.

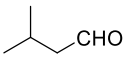
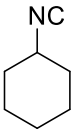
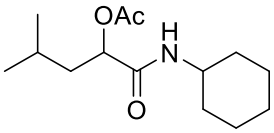
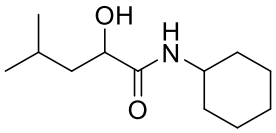
examples. And these products were tested under our selected Michael conditions. The various results are presented thereafter in (see Table 2-2).

Table 2-2 Synthesis of Passerini/Michael adducts



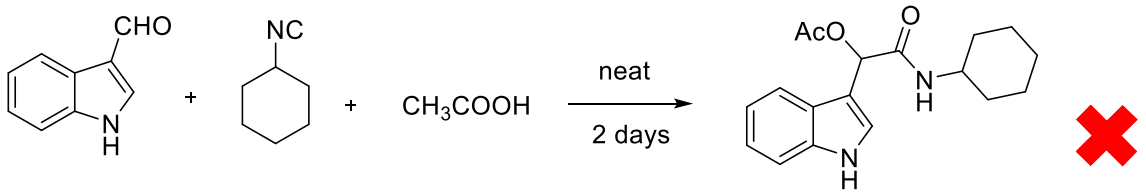
entry	aldehydes	isocyanides	Passerini adducts	Michael adducts
1			 **II-1a** 99 %	 **II-3a** 90 %
2			 **II-1b** 98 %	 **II-3b** 90 %
3			 **II-1c** 80 %	 **II-3c** 95 %
4			 **II-1d** 84 %	 **II-3d** 79 %

5			 **II-1e** 90 %	 **II-3e** 95 %
6			 **II-1f** 99 %	 **II-3f** 39 %
7			 **II-1g** 82 %	 **II-3g** 73 %
8			 **II-1h** 82 %	 **II-3h** 66 %
9			 **II-1i** 78 %	 **II-3i** 99 %
10			 **II-1j** 77 %	 **II-3j** 61 %
11			 **II-1k** 72 %	 **II-2k** 84 %

12			 **II-1l** 88 %	 **II-2l** 96 %

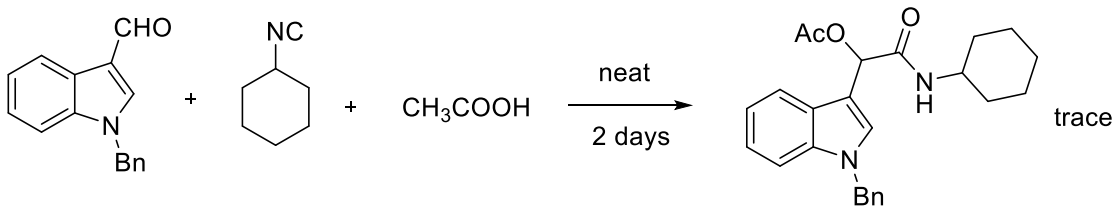
The first Passerini step has the wider scope and gives high yields for most aldedydes and isocyanides tested (table 2-2, entry 1-12). The synthetic sequence is limited to aromatic aldehydes in agreement with the need of a relatively acidic position for the Michael step to proceed (table 2-2, entry 1-10). Indeed, when Passerini adduct **II-1l** (Table 2-2, entry 12) obtained in 88 % isolated yield from isovaleraldehyde was treated with acrylonitrile under our optimized conditions for the Michael addition step, we could not isolated any addition product and only observed a saponification of the ester giving the corresponding hydroxyamide in 96 % isolated yield. Probably due to the OH group is deprotonated faster preventing the required carbanion formation for Michael addition.

When 1H-indole-3-carbaldehyde was used for Passerini reaction, we got nothing except some starting materials (scheme 2-32).



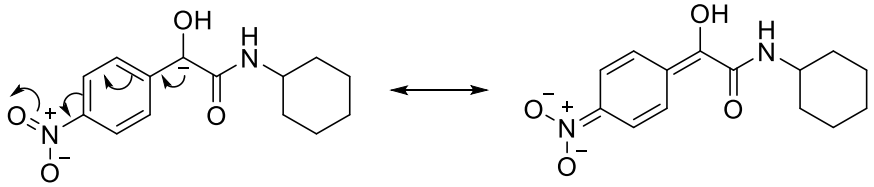
scheme 2-32

When the nitrogen atom was protected by benzyl group, only traces of the corresponding Passerini adduct was obtained. This further proved the low reactivity of indole derivatives in this reaction (scheme 2-33).



scheme 2-33

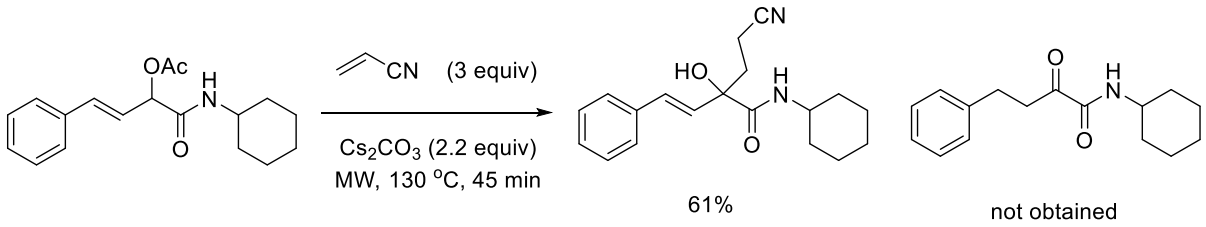
The Passerini adduct of 4-methoxybenzaldehyde behaves similarly probably due to more difficult deprotonation at the α-position. In the opposite direction, the use of 4-nitrobenzaldehyde lead to quantitative formation of Passerini adduct **II-1f** (Table 2-2, entry 6) but the resulting anion is probably too stabilized to give an efficient coupling with acrylonitrile affording **II-3f** only in a moderate 39 % isolated yield (scheme 2-34).



scheme 2-34

The furyl derivative **II-1i** gave us our best yield in the Michael addition step (Table 2-2, entry 9), which was a bit surprising in light of the electronrich nature of the ring and the failure of the 4-methoxyaryl group to participate in the sequence.

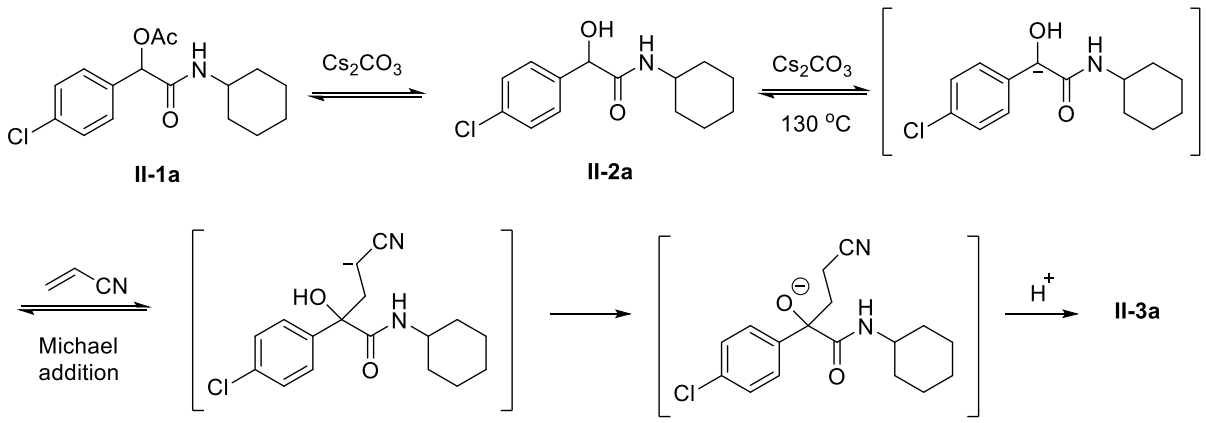
Finally, in the case of cinnamaldehyde derived Passerini adduct **II-1j**, we were delighted to observe the formation of Michael addition product **II-3j** in moderate yield (Table 2-2, entry 10) as such conditions were close to the one we proposed for the conversion of the same Passerini adducts into α-ketoamides (scheme 2-35).



scheme 2-35

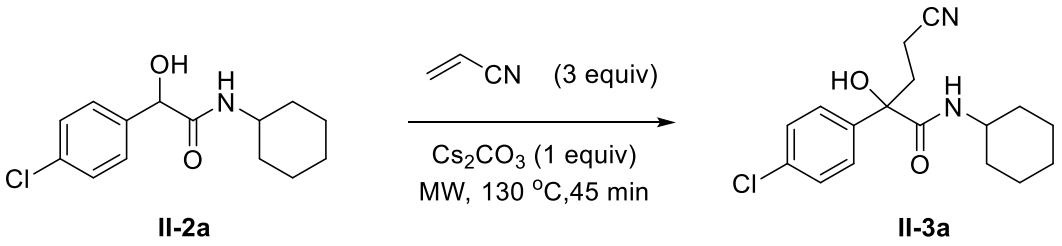
3.1.3 Proposed mechanism

The formation of **II-3a** most probably involves an initial saponification followed by a Michael addition of the resulting hydroxy derivative **II-2a**. The presence of the aryl group in the hydroxyl **II-2a** allows a selective CH deprotonation followed by Michael addition (scheme 2-36).



scheme 2-36 Proposed mechanism

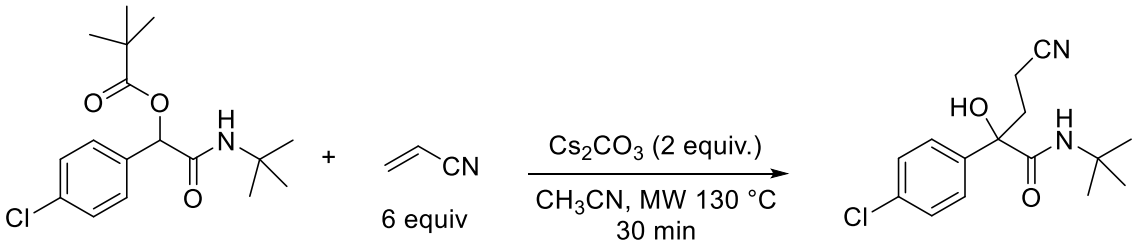
To examine our assumption, **II-2a** was treated under our optimized conditions, **II-3a** was isolated with 89 % yield (scheme 2-37), which bring further elements in support for the proposed timing of the process.



II-2a **II-3a**

scheme 2-37

To progress further on the mechanism of the reaction and determine whether the Michael addition step could be observed before the saponification of the ester, we prepared a Passerini analogue of **II-1b** using pivalic instead of acetic acid. When the pivalate **II-1m** was treated under microwave conditions with 6.0 equiv. of acrylonitrile in acetonitrile, we couldn't indeed isolate any Michael adduct without loss of the pivalate moiety and **II-3b** was again obtained in a low 55 % yield (scheme 2-38). Lowering the amount of base to 1 equiv. afforded **II-3b** in even lower yields supporting further the mechanistic propositions of scheme 2-36.



II-1m **II-3b** 55 %

scheme 2-38

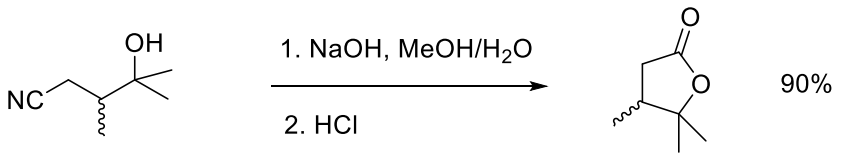
3.2 Towards γ-butyrolactones

Even though the formation of alcohol **II-3a** with loss of the acetate moiety was not a good point in terms of diversity, it offers an interesting opportunity for the preparation of butyrolactones through cyclization of the alcohol onto the nitrile group.

3.2.1 Optimization of cyclization reaction

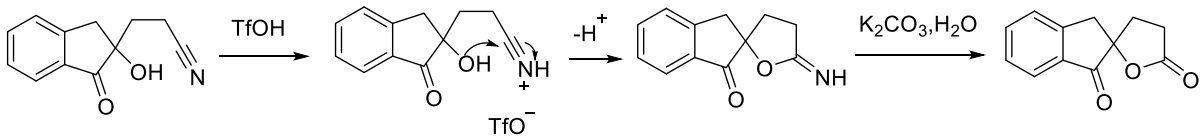
Butyrolactone synthesis from 4-hydroxynitriles is well documented,[110] occurring under both acidic and basic conditions, in most cases the imidate intermediate is not observed leading directly to the butyrolactone.

In 2014, the lactones were synthesized by Citron *et al.* and used in bioassays in which one of the compounds was found to be a strong germination inhibitor for ash seeds, causing necroses in the plant tissue (scheme 2-39).[110b]



scheme 2-39

In 2017, Daïch and co-workers synthesized 2,3-dihydro-1H-inden-1-ones and found that these compounds could be transformed into spiro-lactones (scheme 2-40).[110]

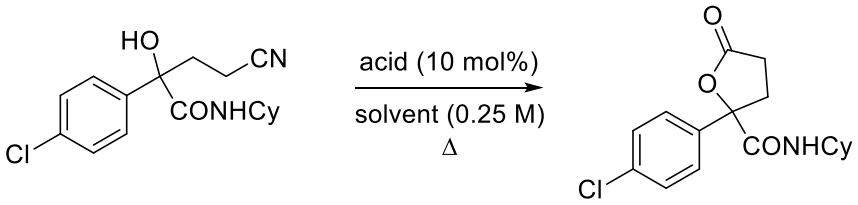


scheme 2-40

Considering the literature on those cyclisations together with the rather harsh basic conditions selected for our Michael addition, the lack of cyclized products was rather a surprise in our case. Thus, the ability of **II-3a** to cyclize was directly tested under acidic conditions (table 2-3).

[110] For some cyclizations to γ-lactones under basic conditions, see: a) K. Sam, S. Auger, V. Luu-The, D. Poirier, *J. Med. Chem*. **1995**, *38*, 4518-4528; b) C. A., C. J. Junker, B. Schulz, J. Dickschat, *Angew. Chem. Int. Ed.* **2014**, *53*, 4346-4349; For a cyclization under acidic conditions: P. Safar, S. Marchalin, M. Soral, J. Moncol, A. Daïch, *Org. Lett.* **2017**, *19*, 4742-4745.

Table 2-3 Optimization of cyclization reaction



II-3a **II-4a**

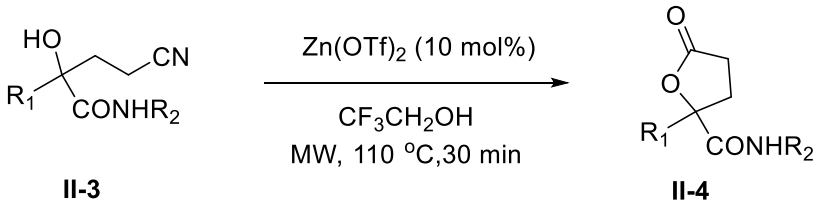
entry	acid	solvent	Temperature & time	yield
1	H_2SO_4	toluene	Reflux, 24 h	30 %
2	TsOH	toluene	MW, 180 °C, 30 min	60 %
3	$BF_3.Et_2O$	toluene	MW, 130 °C, 30 min	26 %
4	$FeCl_3$	toluene	MW, 130 °C, 30 min	50 %
5	$Y(OTf)_3$	toluene	MW, 130 °C, 30 min	46 %
6	$Zn(OTf)_2$	toluene	MW, 110 °C, 30 min	46 %
7	$Zn(OTf)_2$	EtOH	MW, 180 °C, 30 min	-
8	$Zn(OTf)_2$	CH_3CN	MW, 110 °C, 30 min	44 %
9	**$Zn(OTf)_2$**	**CF_3CH_2OH**	**MW, 110 °C, 30 min**	**75 %**

The few trials performed confirmed the relative stability of **II-3a**, nevertheless we could observe the expected butylactone **II-4a** in a good 75 % isolated yield heating the alcohol under microwave conditions in trifluoroethanol as solvent and in the presence of a catalytic amount of zinc triflate (entry 9, table 2-3).

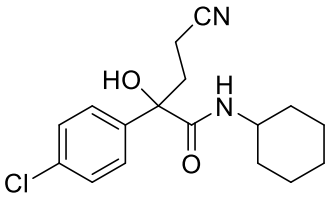
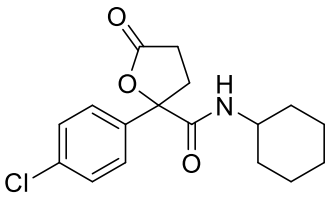
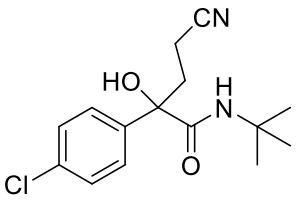
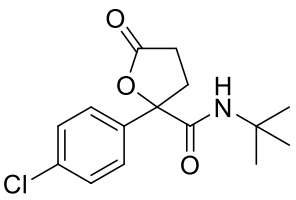
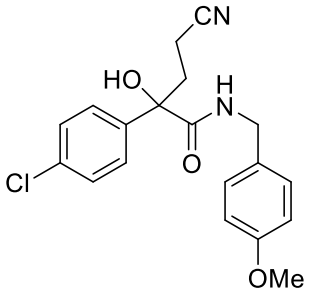
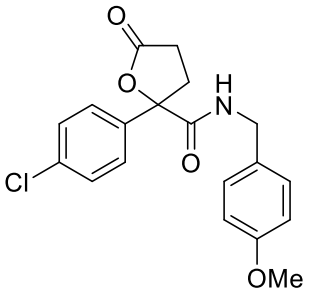
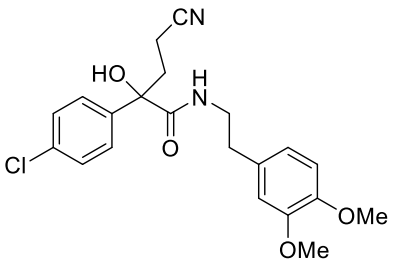
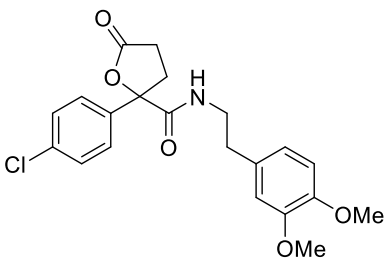
3.2.2 Synthesis of γ-butyrolactones

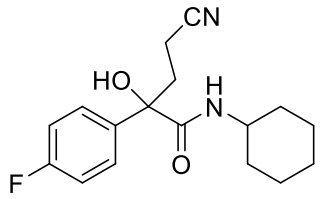
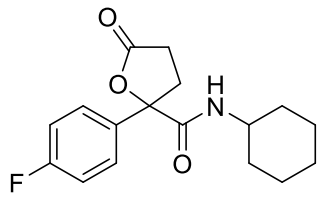
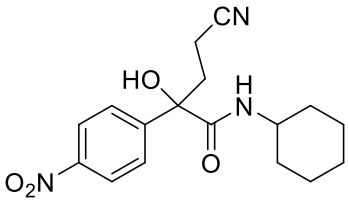
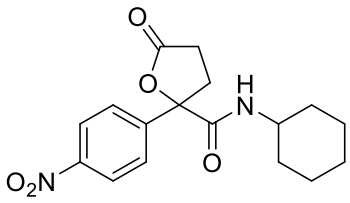
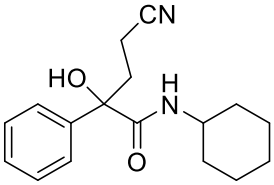
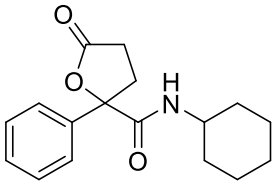
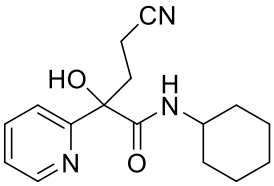
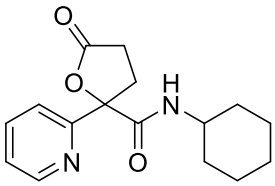
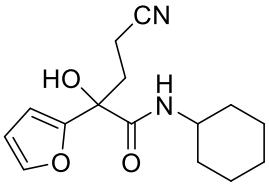
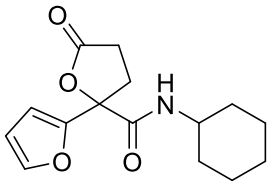
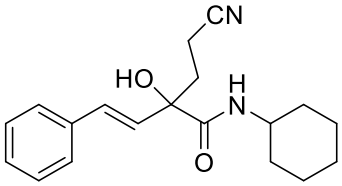
The scope of γ-butyrolactone synthesis was then evaluated on a set of different Michael adducts prepared from Passerini adducts and acrylonitrile under microwave conditions. The results are displayed in Table 2-4.

Table 2-4 scope of γ-butyrolactone synthesis



II-3 **II-4**

entry	4-hydroxynitriles	γ-butyrolactone
1	 **II-3a**	 **II-4a** 75 %
2	 **II-3b**	 **II-4b** 62 %
3	 **II-3c**	 **II-4c** 92 %
4	 **II-3d**	 **II-4d** 86 %

5	 **II-3e**	 **II-4e** 87 %
6	 **II-3f**	 **II-4f** 83 %
7	 **II-3g**	 **II-4g** 72 %
8	 **II-3h**	 **II-4h** 50 %
9	 **II-3i**	 **II-4i** 20 %
10	 **II-3j**	-

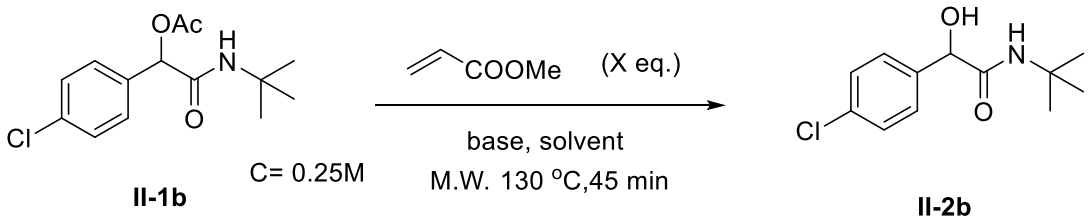
The reaction does not seem to depend much on the nature of the starting aromatic aldehydes as shown by the good yields obtained (Table 2-4, entries 1-7).

The low yield with furan may be just explained by the relative sensibility of the furan ring to Lewis acid triggered ring opening and hydroxyl elimination (Table 2-4, entry 9).

3.3 Other Michael acceptors

Except acrylonitrile, methyl acrylate was also tested for our Passerini/Michael reaction. But no Michael adducts were obtained. We tried various reaction conditions as below (see table 2-5), but the reaction is not clean and we could only recover the product resulting from saponification of **II-1b**.

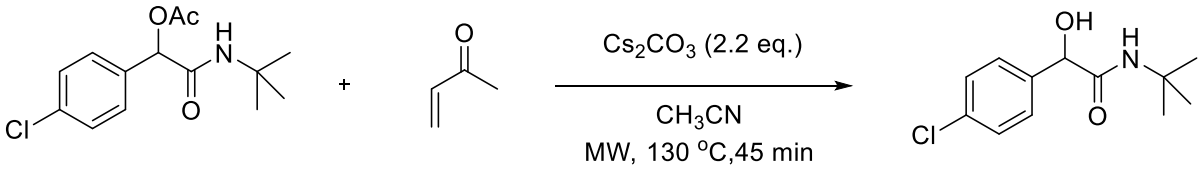
Table 2-5 Reaction conditions of methyl acrylate



entry	base	solvent	Temperature & time	x	product **II-2b**
1	Cs_2CO_3 (2.2 eq.)	DMF	130 °C, 45 min	6	-
2	Cs_2CO_3 (2.2 eq.)	THF	130 °C, 45 min	6	40 %
3	Cs_2CO_3 (2.2 eq.)	toluene	130 °C, 45 min	6	-
4	Cs_2CO_3 (2.2 eq.)	MeOH	130 °C, 45 min	6	92 %
5	Cs_2CO_3 (1.0 eq.)	DMF	110 °C, 30 min	6	47 %
6	*t*-BuOK (10 mol%)	DMF	140 °C, 30 min	3	-
7	Cs_2CO_3 (2.2 eq.)	CH_3CN	Reflux, 10 h	6	67 %
8	DIPEA (0.5 eq.)	MeOH	140 °C, 30 min	6	81 %
9	DBU (2.2 eq.)	CH_3CN	110 °C, 45 min	6	-

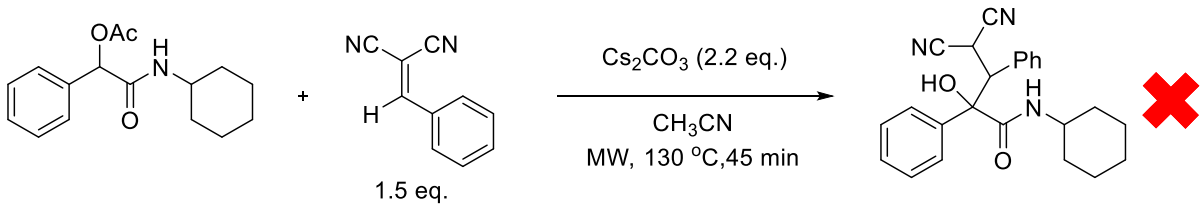
Probably the low reactivity of methyl acrylate, compared to acrylonitrile, prevented the

coupling with the carbanion. The same situation existed in the reaction of but-3-en-2-one and **II-1b** (scheme 2-41).



scheme 2-41

Another Michael acceptor 2-benzylidenemalononitrile was then tested with **II-1g** under our Passerini/Michael reaction condition. Unfortunately, after heating, just some remaining 2-benzylidenemalononitrile could be isolated from the reaction mixture (scheme 2-42).



scheme 2-42

Steric hindrance may prevent the coupling between 2-benzylidenemalononitrile and the carbanion.

4 Conclusion

In this chapter, we have settled a two-step sequence for the preparation of γ-butyrolactones from Passerini adducts of aromatic and heteroaromatic aldehydes. This strategy significantly expanded the scope of the butyrolactones syntheses from benzoin derivatives with microwave conditions allowing to counterbalance the poorer electron-withdrawing group effect of the amide moiety. Further work is under progress to raise the diversity of the synthesis by performing the reaction on a larger array of Michael acceptors.

Chapter III Mannich reaction of trifluoroacetaldehyde hydrazones

The work described in this chapter has been published on *Org. Biomol. Chem.*:

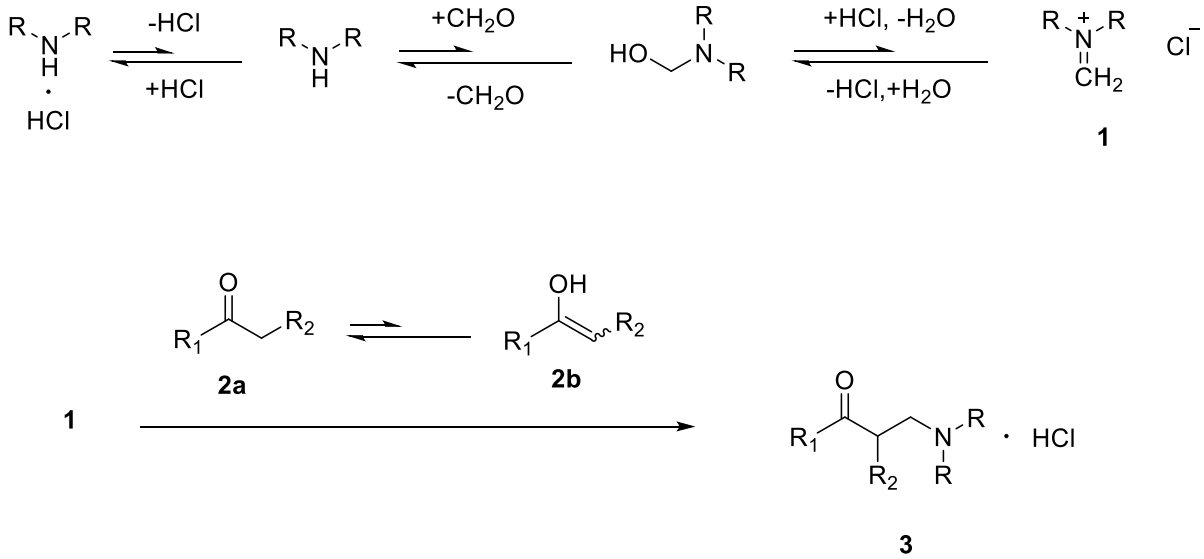
Shuanglong Jia and Laurent El Kaim, *Org. Biomol. Chem.*, **2018**, *16*, 1457-1460

1 Introduction

1.1 A brief overview of Mannich reaction

Carl Mannich, who was the first to describe the aminoalkylation of CH-acidic compounds, recognized the enormous significance of this reaction, and extended this chemistry into a broad based synthetic methodology through systematic research. Thus this reaction carries his name, and has been one of the most important C-C bond-forming reactions in organic synthesis.[111] It's a a typical method for the preparation of β-amino ketones and aldehydes (Mannich bases) and one of most important step in the synthesis of numerous natural products and pharmaceuticals.

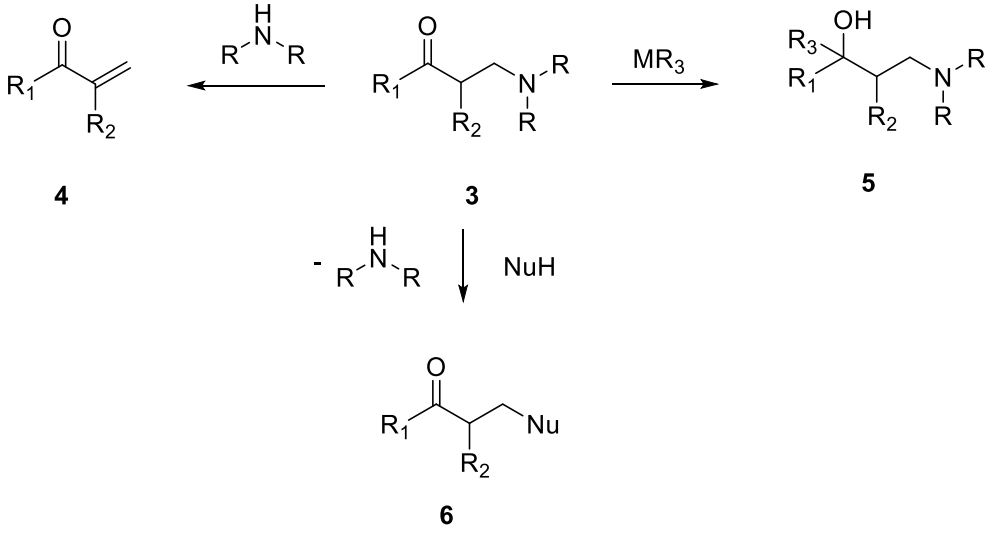
In this reaction, enolizable aldehydes or ketones serve as the CH-acidic scaffolds. In the most important variation, the carbonyl compound react with formaldehyde and an amine hydrochloride in a protic solvent under heating. A simplified mechanism is given in scheme 3-1.



scheme 3-1 Simplified mechanism of the Mannich reaction

[111] Reviews: a) M. Tramontini, L. Angiolini, *Mannich-Bases, Chemistry and Uses*, CRC, Boca Raton, FL, 1994; b) *Tetrahedron* **1990**, *46*, 1791; c) M. Tramontini, L. Angiolini, N. Ghedeni, *Polymer* **1988**, *29*, 771 *46*, 1791; d) M. Tramontini, *Synthesis* **1973**, 703; e) H. Hellmann, G. Opitz, *a-Aminoalkylierung*, Verlag Chemie, Weinheim, 1960; f) B. Reichert, *Die Mannichreaktion*, Springer, Berlin, **1959**; g) F. Blicke, *Org. React.* (*NY*) **1942**,*1*, 303.

It is assumed that only tiny amount of methylene iminium salts **1** are formed by a series of equilibrium reactions. Then, **1** react with the enol tautomer **2b** of the carbonyl compound **2a**, also present in very small amounts, to give the hydrochloride of the β-aminocarbonyl compound **3**, which is called Mannich bases. These kind of compounds are versatile synthetic scaffolds, which can easily be converted into a great quantity of useful and valuable derivatives[112](scheme 3-2).



scheme 3-2 Mannich bases as synthetic building blocks

These derivatives include Michael acceptors **4** (elimination of the amine HNR_2), 1,3-amino alcohols **5** (reduction or addition of organometallic compounds) and functionalized carbonyl compounds **6** (substitution of NR_2 by nucleophiles). [113]

Mannich bases and their derivatives play a significant role in plant protection and in paint and polymer chemistry (hardeners, cross-linkers, and reaction accelerators) and especially pharmaceutical products.[113] Like some examples represented in figure 3-1.

[112] M. Arend, B. Westermann and N. Risch, *Angew. Chem.,Int. Ed.*, **1998**, *37*, 1044–1070

[113] a) A. Kleemann, E. Lindner, J. Engel, *Arzneimittel*, VCH, Weinheim, **1987**; b) S. Ebel, *Synthetische Arzneimittel*, VCH, Weinheim, **1979**; c) P. Traxler, U. Trinks, E. Buchdunger, H. Mett, T. Meyer, M. Muller, U. Regenass, J. Rosel, N. Lydon, *J. Med. Chem.* **1995**, *38*, 2441; d) J. Dimmock, K. Sidhu, M. Chen, R. Reid, T. Allen, G. Kao, G. Truitt, *Eur. J. Med. Chem.* **1993**, *28*, 313.

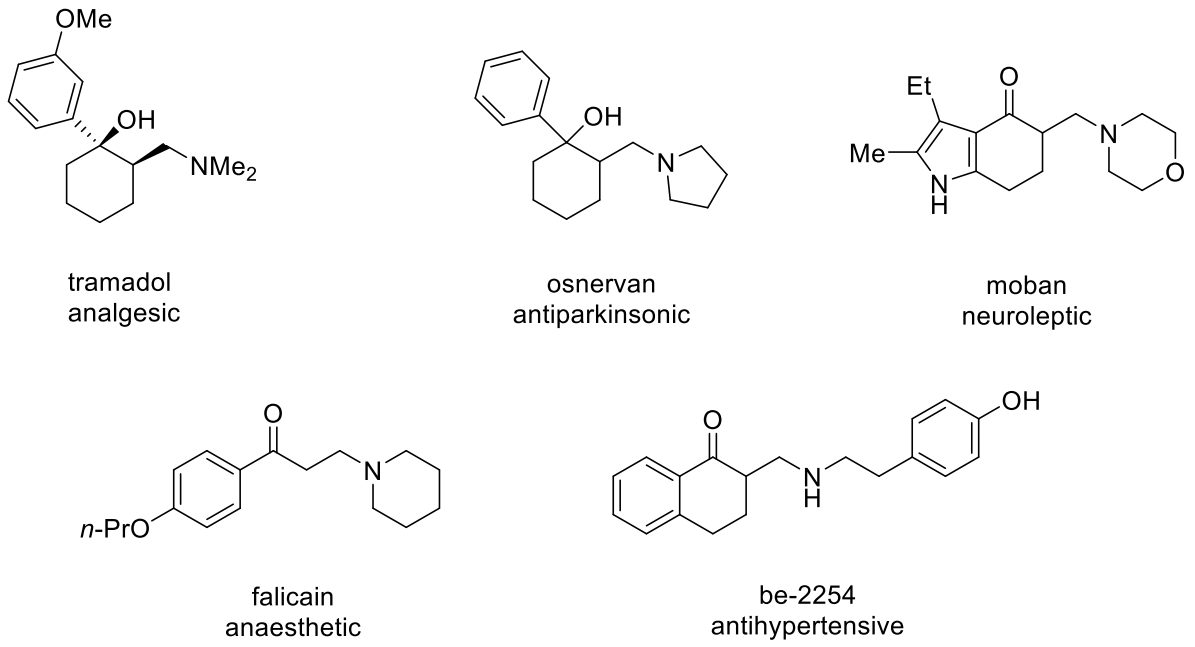


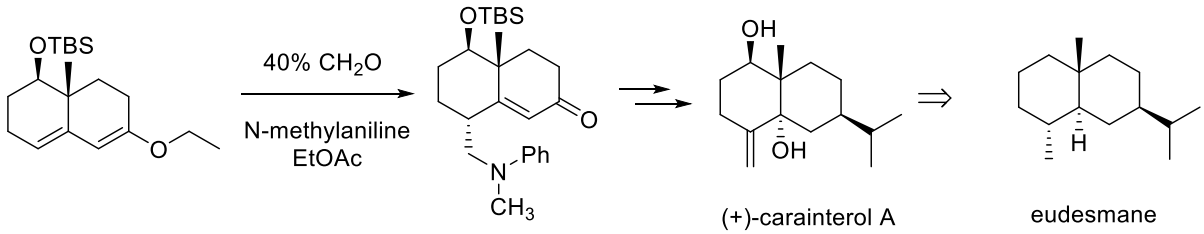
figure 3-1 application of Mannich bases and their derivatives in medicine

As one of the most important 3-component reactions (3-CR), Mannich reaction has all the features, such as atoms economy, accessible and cheap substrates, steps with high chemical yields, environment-friendly, easy operation and, the use of convergent one-pot reactions, the ability to quickly build a library of varied and structurally complex compounds.[114]

Few typical Mannich reactions

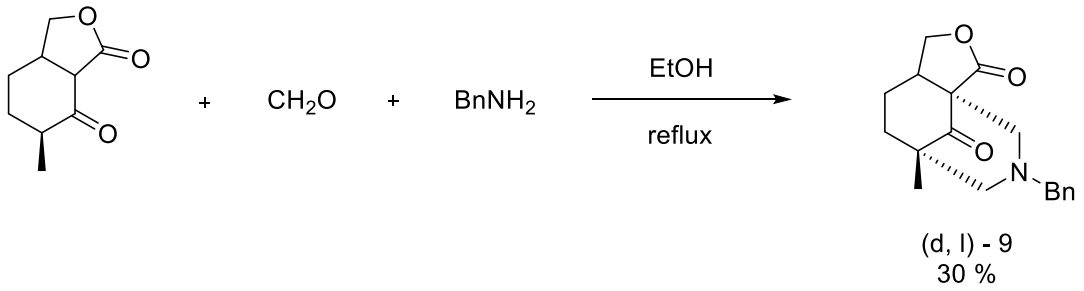
In 2010, Ma and co-workers applied Mannich reaction as the key step to obtain the intermediate into the total synthesis of the sesquiterpene (+)-Carainterol A, that contains a exocyclic double bond in the decalin skeleton.[115] These natural products are drugs with anti-HIV, antifungal, antibacterial and anti-inflammatory activities[116] (scheme 3-3).

[114] A. Domling, *Chem Rev.* **2006**, *106*, 17-89.
[115] a) K. Ma, C. Zhang, M. Liu, *Tetrahedron Lett.* **2010**,*51*,1870-1872. b) M. Heravi, V. Zadsirjan, B. Savadjani, *Curr Org Chem.* **2014**,*18*,2857-2891.
[116] a) Z. Sun, B. Chen, S. Zhang, C. Hu, *J Nat Prod.* **2004**, *67*, 1975-1979. b) M. Fraga, *Nat Prod Rep.* **2007**, *24*, 1350



scheme 3-3 . synthesis of the sesquiterpene (+)-Carainterol A intermediate

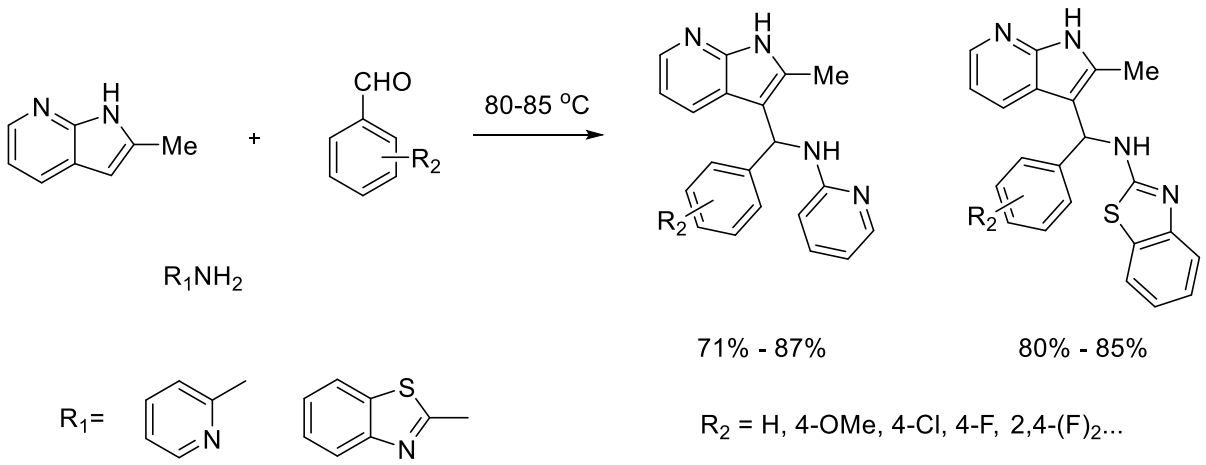
In 2011, Yang and co-workers prepared the C19 - diterpene alkaloids racemic precursor,[117] which has several bioactivities such as analgesic, antiinflammatory, psychotropic, antitumor and anesthetic (scheme 3-4).[118]



scheme 3-4 synthesis of the basic structure of C19-diterpene alkaloids

Environmentally friendly reactions are always welcomed. In 2016, Dongare and co-workers developed a serious of 7-azagramine analogues by reaction of 7-azaindole derivatives, aromatic aldehydes and heterocyclic amines in solvent-free and catalyst-free medium. These azaindole compounds have extensive biological properties, such as inhibitors of kinase and phosphodiesterase enzymes in anticancer therapies (scheme 3-5).[119]

[117] K. Yang, H. Chen, P. Wang, *Tetrahedron*, **2011**, *67*, 4192-4195
[118] F, Chen, L. Chen, H. Chen, P. Wang, *J Nat Prod.* **2009**, *72*, 18-23
[119] B. Dongare, V. Chavan, S. Bhale, B. Mule, S. Kotmale, P. Bandgar. *Chin Chem Lett*. **2016**, *27*, 99-103

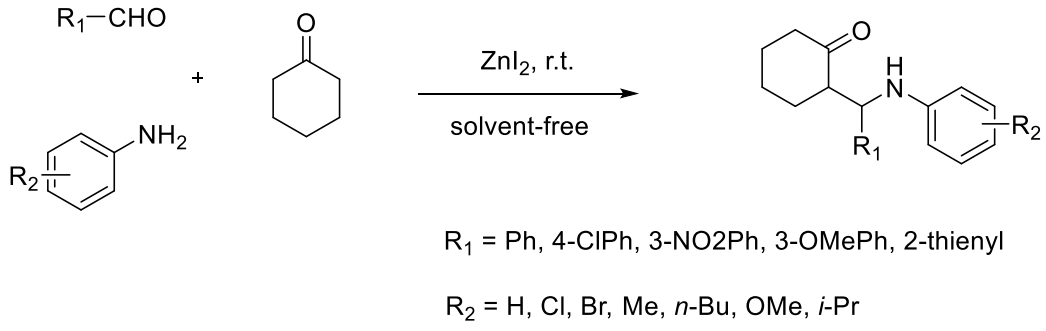


scheme 3-5 Mannich reaction performed in solvent-free and catalyst-free medium

1.2 Catalyst in Mannich reaction

1.2.1 Lewis acids triggered Mannich reaction

Lewis acids, such as Zn^{2+},[120] In^{3+},[121] Fe^{3+}…[122] are widely used in multicomponent Mannich reactions. Azizi and co-workers obtained β-aminocarbonyl cyclohexanones through this method (scheme 3-6).

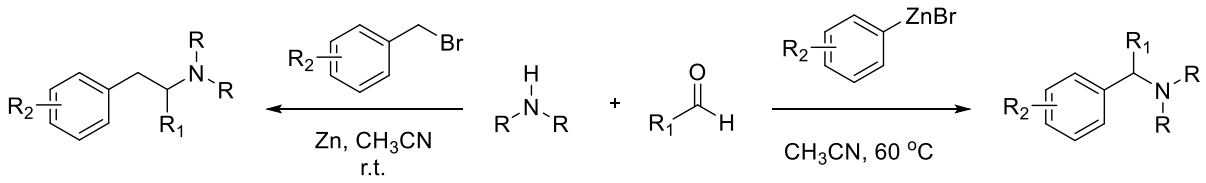


scheme 3-6 Zinc catalysts in multicomponent Mannich reactions

Gall *et al* reported the study of organozinc nucleophiles in the synthesis of α-branched amines

[120] N. Azizi, F. Ebrahimi, R. Saidi, *Trans C: Chem Chem Eng.* **2009**, *16*, 94-98.
[121] P. Loh, L. Chen, *Org Lett.* **2002**, *4*, 3647-3650
[122] J. Halli, G. Manolikakes, *Eur J Org Chem.* **2013**, *33*, 7471-7475.

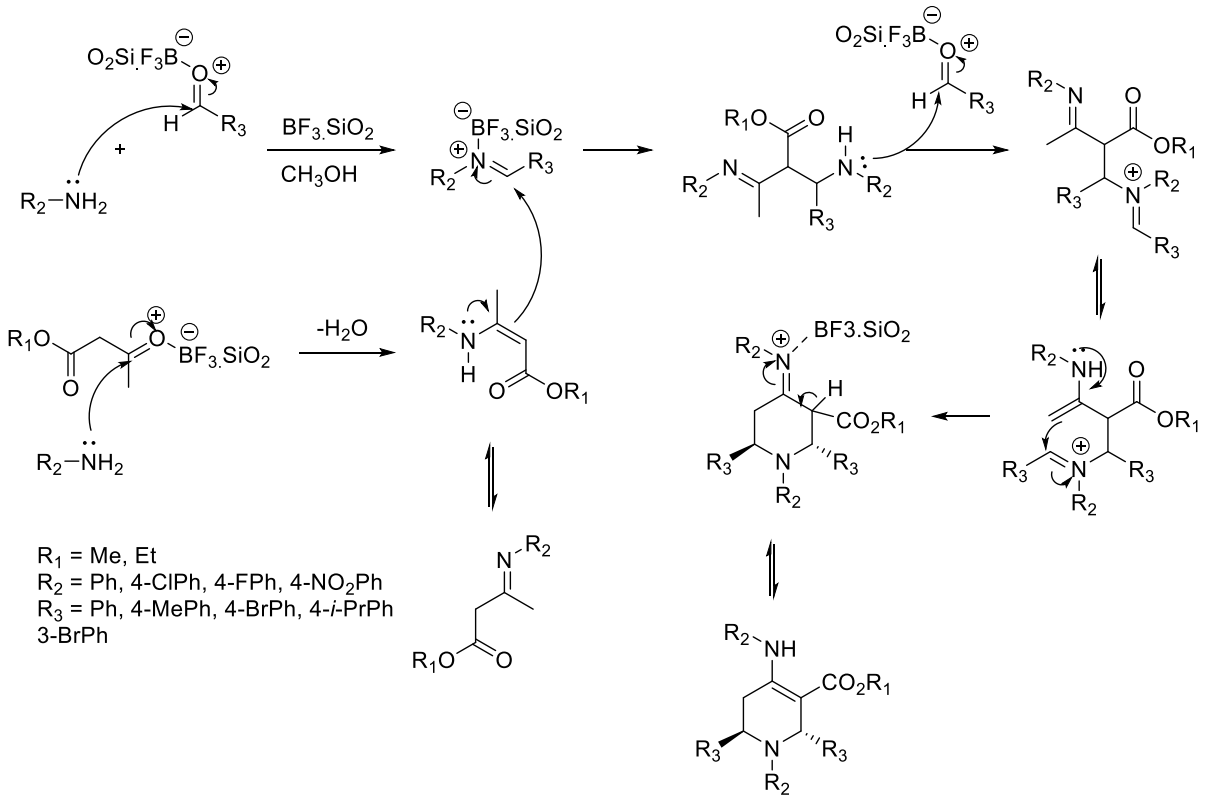
through Barbier-type reaction. In the case of benzyl halide derivatives, the formation of organozinc occurs in situ quantitatively and the reaction proceeds rapidly. For aryl halide, a preformed ArZnBr has been employing due to its comparative low activity (scheme 3-7).[123]



scheme 3-7 synthesis of β -aminocarbonyl compounds using organozinc nucleophiles

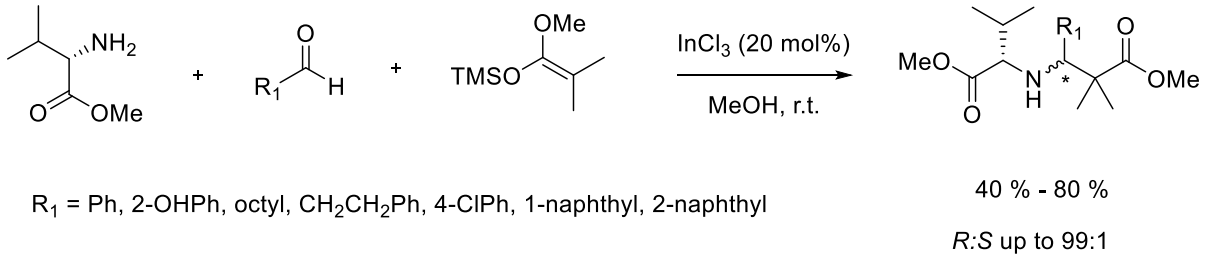
Recently, Ramachandran and co-workers described the synthesis of tetrahydropyridines from a reaction between aldehydes and aromatic amines with β-ketoesters using BF_3 supported on silica ($BF_3.SiO_2$) as catalyst in methanol. The Lewis acid increass the electrophilicity of the aldehyde and favors the attack of amine to obtain the iminium ion. In addition, the $BF_3.SiO_2$ assists enamine generation, which is the nucleophile of Mannich reaction, and contributes to the final formation of the pyridinetetrahydropyridine (scheme 3-8).[124]

[123] a) L. Gall, C. Haurena, S. Sengmany, T. Martens, M. Troupel, *J. Org Chem.* **2010**, *75*, 2645. b) L. Gall, C. Haurena, S. Sengmany, T. Martens, M. Troupel, *J. Org Chem.* **2009**, *74*, 7970.
[124] R. Ramachandran, S. Jayanthi, T. Jeong, *Tetrahedron*. **2012**, *68*, 363.



scheme 3-8 Synthesis of tetrahydropyridines from β-ketoesters catalyzed by BF_3 supported on SiO_2

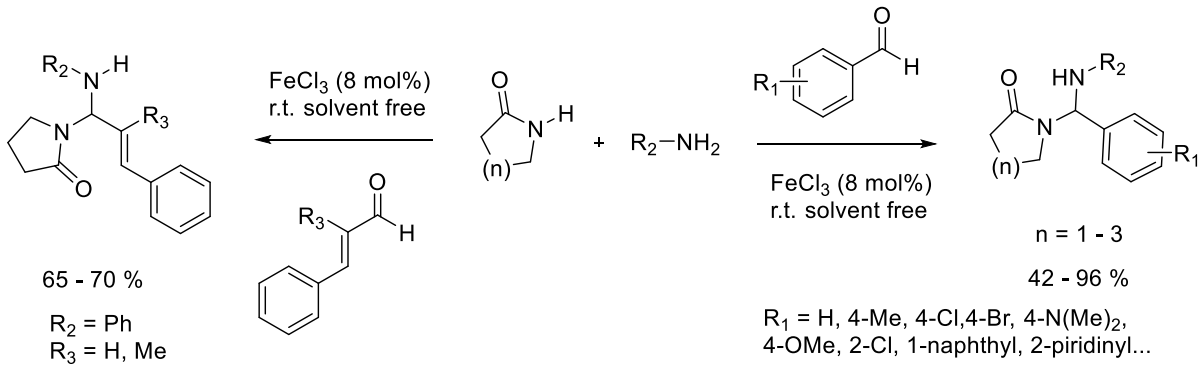
In 2002, Loh and co-workers used $InCl_3$ and methanol medium in synthesis of Mannich bases derived from L-Valine methyl ester (scheme 3-9).[125]



scheme 3-9 multicomponent Mannich reactions catalyzed by $InCl_3$

Sathesh and co-workers used $FeCl_3$ to obtain lactams. The Fe^{3+} promotes imine formation besides increasing its electrophilicity by complexing aldehyde and imine.[126] It has been also believed that the Fe^{3+} ion also catalyzes the ketone enolization step (scheme 3-10).[127]

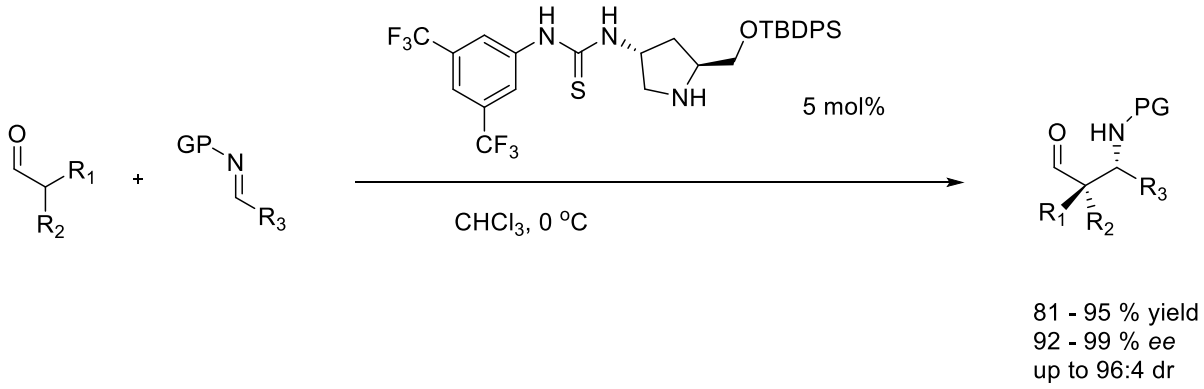
[125] P. Loh, L. Chen, *Org Lett.* **2002**, *4*, 3647.
[126] V. Sathesh, M. Sathishkumar, G. Ramachandran, S. Rathore, I. Sathiyanarayanan, *RSC Adv*. **2013**, *3*, 23035.
[127] K. Behbahani, P. Ziaei, Chin *J Chem.* **2012**, *30*, 65.



scheme 3-10 multicomponent solvent-free Mannich reactions catalyzed by Fe $^{3+}$ ions

1.2.2 Chiral catalyst for enantioselectivity

In 2011, Peng *et al.* described an anti-Mannich reaction where simple aldehydes react with preformed N-Boc and N-Cbz imines in presence of 5 mol% catalyst to give the corresponding products in excellent yields (up to 95 %), diastereoselectivities (up to 96:4 dr) and enantioselectivities (up to >99 % ee)[128](scheme 3-11).

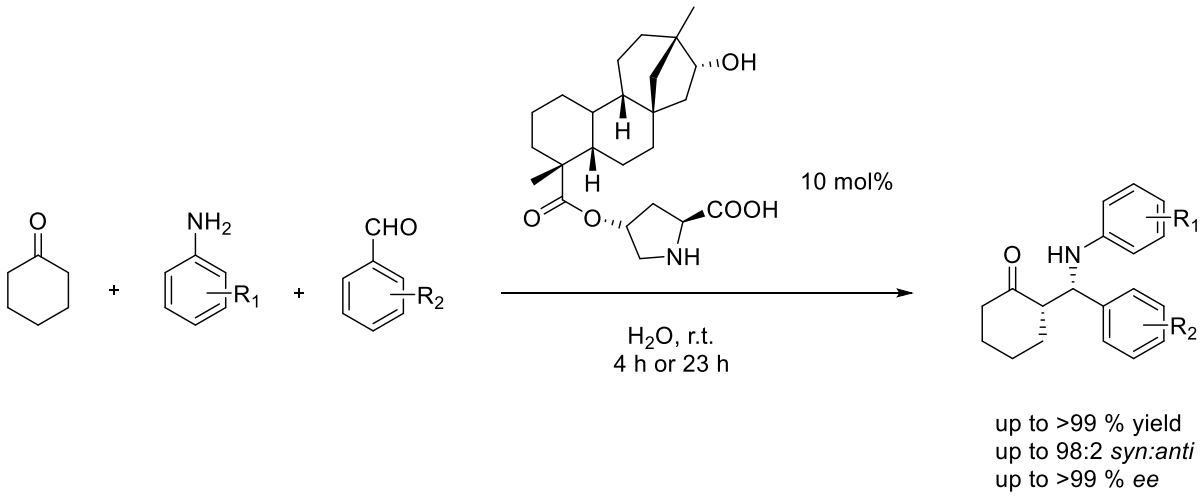


scheme 3-11 chiral bifunctional thioureas catalysed Mannich reaction

Recently, An *et al.* developed the asymmetric three-component Mannich reactions of cyclohexanone, anilines and aromatic aldehydes in the presence of water mediated by Isosteviol–proline as highly efficient amphiphilic organocatalysts, and afforded syn-Mannich products with excellent diastereoselectivities (syn/anti up to 98:2) and enantioselectivities (up

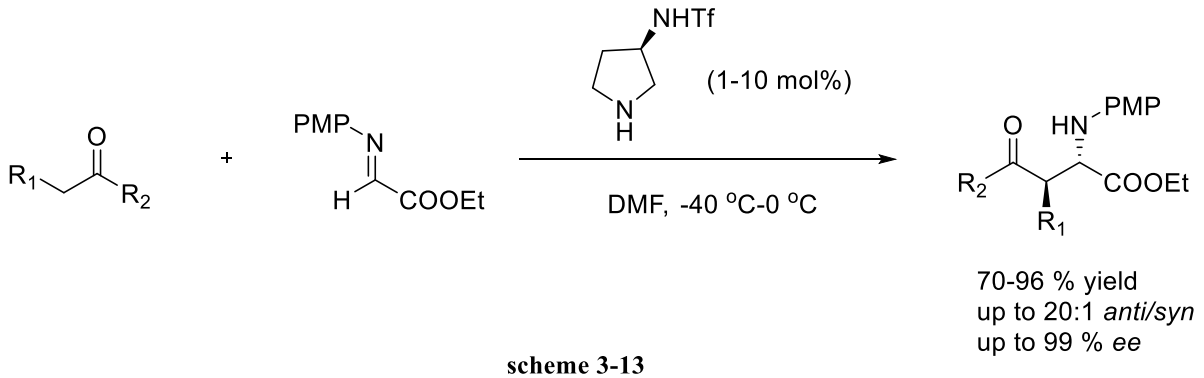
[128] M. Chuan, H. Chen, Z. Gao, H. Zhang, and G. Peng, *Chem. Commun*. **2011**, *47*, 3260-3262

to>99% *ee*) (Scheme 3-12).[129]



scheme 3-12

In 2008, Blanchet and coworkers described an anti-selective direct and three-component Mannich reaction catalysed by 3-trifluoromethanesulfonamido-pyrrolidine. High yields and selectivities for various substrates ranging from linear and branched aldehydes to ketones were obtained. It was indicated that the acidity of the trifluoromethylsulfonamide group was critical to achieve high stereoselectivity, and C-2 symmetry of catalyst was not a key structural feature for a high stereoselectivity(scheme 3-13).[130]



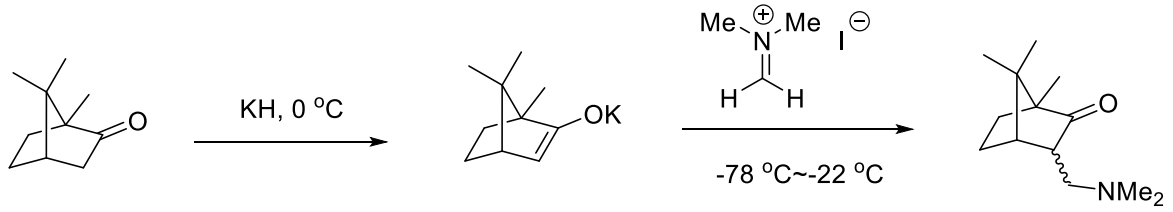
scheme 3-13

[129] J. An, C. Wang, P. Liu, and C. Tao, *Helv. Chim. Acta* **2012**, *95*, 43.
[130] M. Pouliquen, J. Blanchet,C. Lasne, and Rouden, *J. Org. Lett.* **2008**, *10*, 1029

1.3 Extension of the Mannich reaction to other nucleophiles

Due to the very attractive nature of Mannich bases, numerous methods have been developed for the indirect synthesis of β-amino aldehydes and ketones,[131] as well as β-amino carboxylic acid derivatives[132]. Modern versions of the Mannich reaction usually allow a distinctly simpler route into β-aminocarbonyl compounds through the use of preformed nucleophiles (enolates, enol ethers, and enamines). The level of performance and the versatility of these methods have already been powerfully demonstrated in the synthesis of β-amino acid derivatives and β-lactams.[133] Recently, several notable advances have been made in these areas.

In 1979, N. Holy *et al*. reported sterically hindered ketones such as camphor can be aminomethylated via converted into enolates (scheme 3-14).[134]



scheme 3-14

In 1993, Petasis *et al.* demonstrated that boronic acids could act as nucleophiles in the Mannich reaction. Vinyl boronic acids react with adducts of secondary amines and

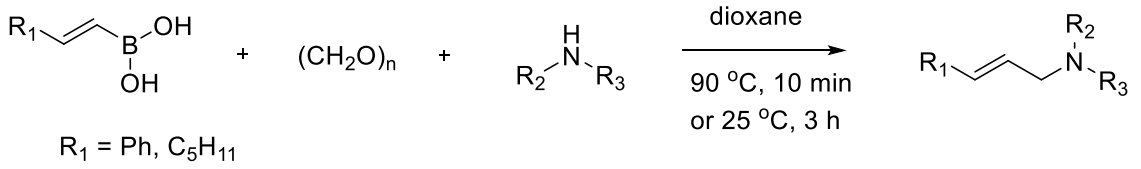
[131] a) J. Barluenga, F. Fernandez-Mari, E. Aguilar, B. Olano, *J. Org. Chem.* **1996**, *61*, 5659, and references therein; b) G. Molander, P. Stengel, *ibid.* **1995**, *60*, 6660; c) S. Davies, T. McCarthy, *Synlett* **1995**, 701; d) C. Louis, S. Mill, V. Mancuso, C. Hootele, Can. *J. Chem.* **1994**, *72*,1347; e) C. Camiletti, D. Dhavale, L. Gentilucci, C. Trombini, *J. Chem. Soc. Perkin Trans.* 1 **1993**, 3157; f) A. Dondoni, D. Perrone, *Synthesis* **1993**, 1162; g) J. Baldwin, R. Adlington, A. Russel, *Synlett* **1993**, 51; h) C. Palomo, J. Aizpurua, J. Odriozola, *J. Org. Chem.* **1994**, *59*, 5184.

[132] a) Enantioselective Synthesis of β-Amino Acids (Ed.: E. Juaristi), *VCH, New York*, **1997**; b) G. Cardillo, C. Tomasini, *Chem. Soc. Rev*. **1996**, *25*, 117; c) Y. Hayashi, J. Rohde, E. Corey, *J. Am. Chem. Soc.* **1996**, *118*, 5502; d) S. Davies, G. Bhalay, *Tetrahedron: Asymmetry* **1996**, *7*, 1595; e) M. Seki, K. Matsumoto, *Tetrahedron Lett.* **1996**, *37*, 3165; f) D. Enders, H. Wahl, W. Bettray, *Angew. Chem.* **1995**, *107*, 527; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 455; g) D. Enders, J. Wiedemann, W. Bettray, *Synlett* **1995**, 369; h) M. Shimano, A. Meyers, *J. Org. Chem.* **1995**, *60*, 7445; i) S. Davies, D. Fenwick, *J. Chem. Soc. Chem. Commun.* **1995**, 1109; j) N. Sewald, K. Hiller, B. Helmreich, *Liebigs Ann.* **1995**, 925.

[133] a) N. Risch, M. Arend, Methoden *Org. Chem*. **1952**,*21*, 1908; b) D. Cole, *Tetrahedron* **1994**, *50*, 9517; c) E. Kleinman in Comprehensive *Organic Synthesis*, **1991**, *2* ,p. 893; d) D. Hart, D. Ha, *Chem. Rev.* **1989**, *89*, 1447; e) M. Brown, *Heterocycles* **1989**, *29*, 2225.

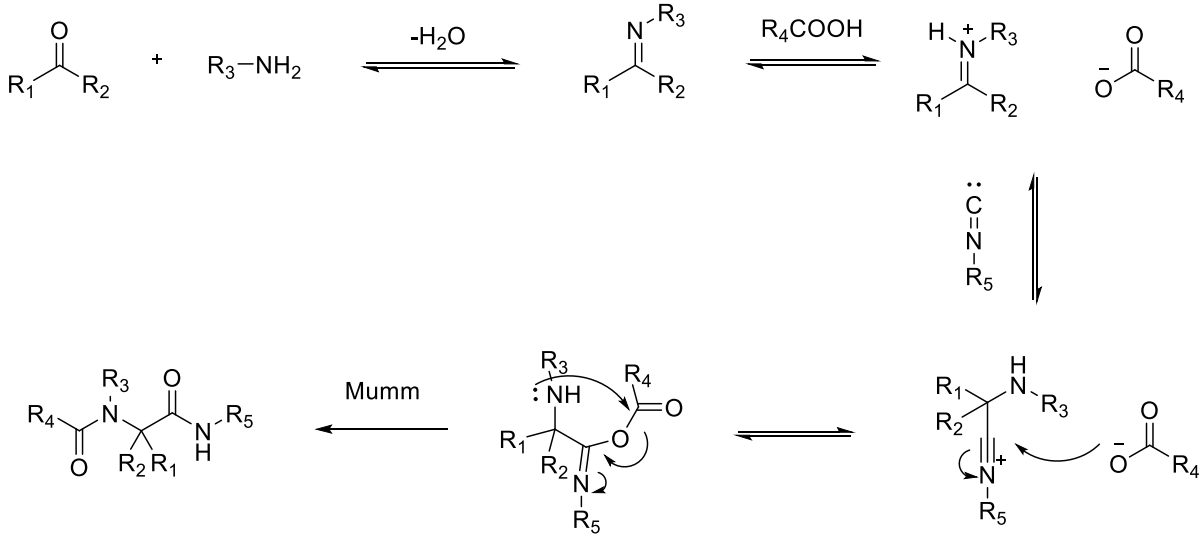
[134] N. Holy, R. Fowler, E. Burnett, R. Lorenz, *Tetrahedron* **1979**, *35*, 613.

paraformaldehyde giving tertiary allylamines with the same geometry. This practical and simple method was used for the synthesis of geometrically pure naftifine, a potent antifungal agent.[135]



scheme 3-15

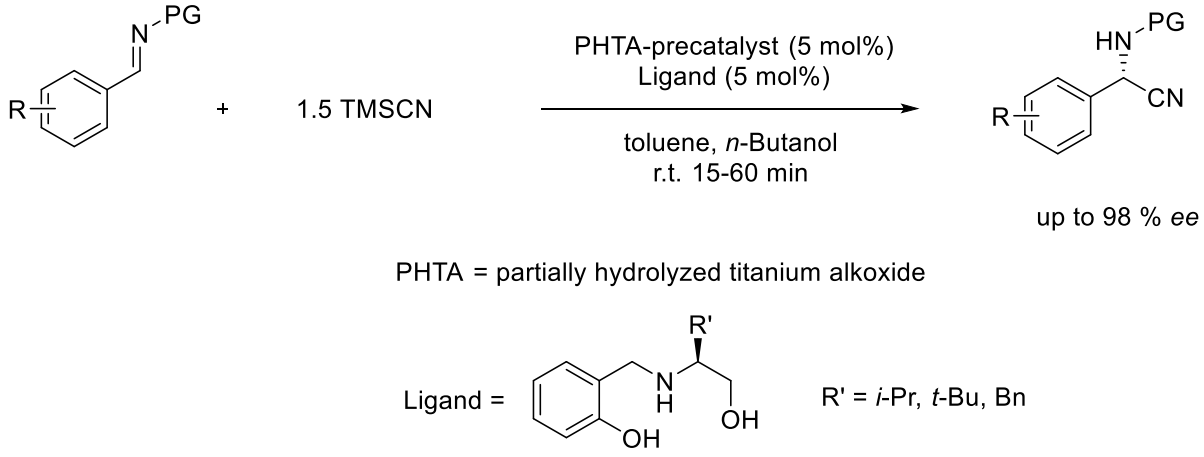
With isocyanide as nucleophile, Ugi reaction could be considered as a sort of Mannich reaction. This reaction was already described in chapter I, we won't discuss here (scheme 3-16).



scheme 3-16 Ugi reaction

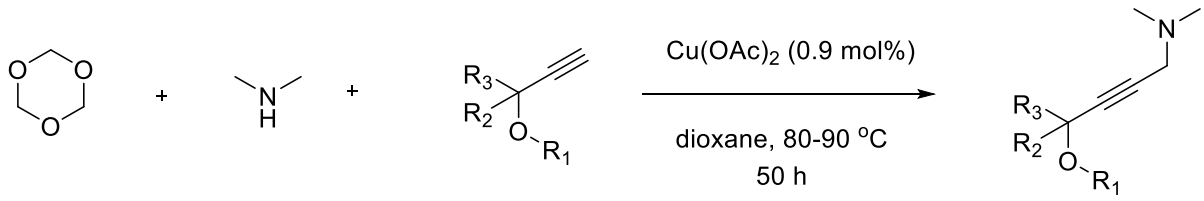
In 2010, Chai and co-workers reported the cyanation of various imines at room temperature at presence of partially hydrolyzed titanium alkoxide (PHTA) catalyst together with salicyl-β-aminoalcohol as the ligand. High enantioselectivities were obtained in the case of various benzhydryl, benzyl, and N-Boc imines (scheme 3-17).[136]

[135] A. Petasis, I. Akritopoulou, *Tetrahedron Lett.***1993**, *34*, 583–586.
[136] A. Seayad, B. Ramalingam, K. Yushinaga, T. Nagata, C. Chai, *Org. Lett.*, **2010**, *12*, 264-267



scheme 3-17 strecker reaction

The A3 coupling (also known as the aldehyde-alkyne-amine reaction) is a Mannich reaction with an alkyne acting as nucleophile. It is a multicomponent reaction involving an aldehyde, an alkyne and an amine which react together to give a propargylamine.[137] The reaction proceeds via direct dehydrative condensation and requires a metal catalyst, typically based on ruthenium, copper, gold or silver.[138] The first example of such a process, the copper catalyzed Mannich reaction of a terminal alkyne, a secondary amine and formaldehyde (trioxane), has been discovered in the middle of the 20th century (scheme 3-18).[139]

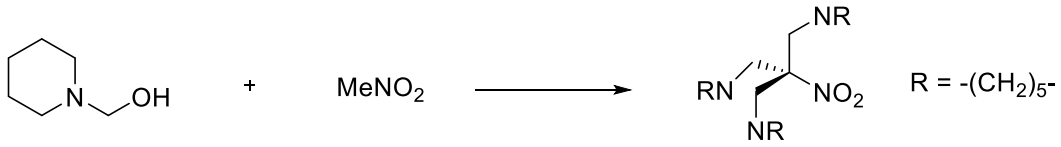


scheme 3-18 A3 coupling reaction

In 1896, Louis Henry reported a nitro-Mannich reaction (aza-Henry reaction) of methanolamine derived from formaldehyde and piperidine, with nitromethane to form the

[137] P. Vsevolod, P. Olga and E. Erik, *Chem. Soc. Rev.*, **2012**, *41*, 3790-3807
[138] Name Reactions A Collection of Detailed Mechanisms and Synthetic Applications **2009** Li, Jie Jack
[139] J. Guermont, *Bull. Soc. Chim. Fr.*, **1953**, 386–390

tripiperidines (scheme 3-19).[140]



scheme 3-19 aza-Henry reaction

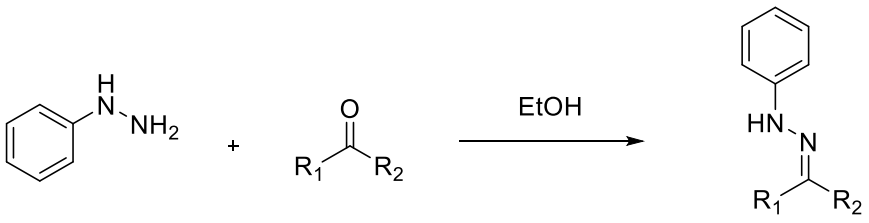
hydrazones may be used as well both as nucleophile or electrophile in Mannich reactions.

1.3 Chemistry of hydrazone

Hydrazones have been utilized in various fields, ranging from medicinal to supramolecular chemistry, due to their modularity, straightforward synthesis, functional diversity, and stability.

1.3.1 Synthesis of hydrazone

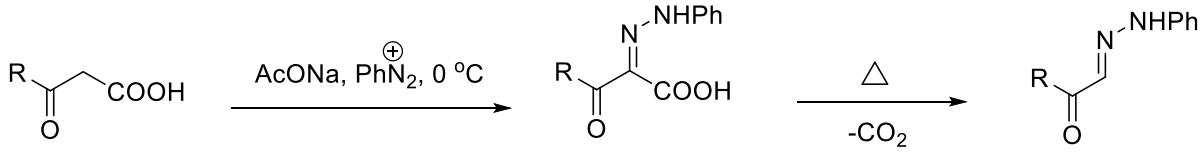
The simplest and most widely used synthetic method to access hydrazones N - mono - or N, N - disubstituted is the condensation of a hydrazine with a carbonyl compound (aldehyde or ketone) in ethanol (scheme 3-20).[141]



scheme 3-20

[140] L. Henry, *Bull. Acad. R. Belg.* **1896**, *32*, 33.
[141] X. Cui, Z. Vlahakis, E. randall, A. Szarek, *Bioorg. Med. Che m.* **2008** , *16* , 1927 - 1947.

The synthesis of α-ketohydrazones by the previous conventional method gives modest yields because of the competition between the two carbonyl groups during condensation. However, the Japp-Klingemann synthesis is specifically useful for preparing these compounds.[142] It is an addition of a diazonium salt on a β-ketoester or β-ketoacid possessing activated methylene, the intermediate azo compound is rearranged to hydrazone. In the case of β-keto acids, these are likely to decarboxylate to give the expected hydrazone (scheme 3-21).



scheme 3-21

1.3.2 Reactivity

The reactivity of hydrazones can be interpreted in two different ways:
These are derivatives of imines which, as such, possess an electrophilic character linked to the polarization of the double bond C=N.

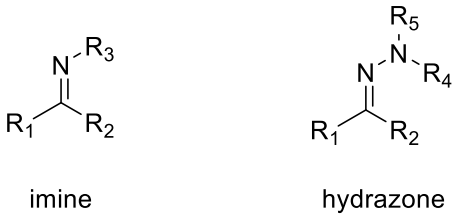


figure 3-2

However, this imine polarization is counterbalanced by the presence of the second nitrogen atom which confers an aza-enamine type behavior due to the π-donor character of the terminal nitrogen (figure 3-3).

[142] R. Phillips, *Organic Reactions* , ed. R. Adams, John Wiley & Sons **1959** , *10* , 144 - 178.

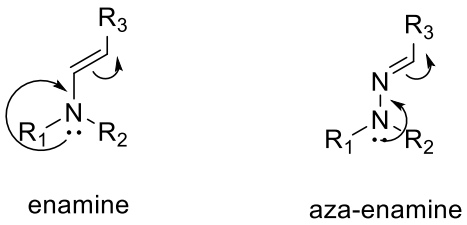


figure 3-3

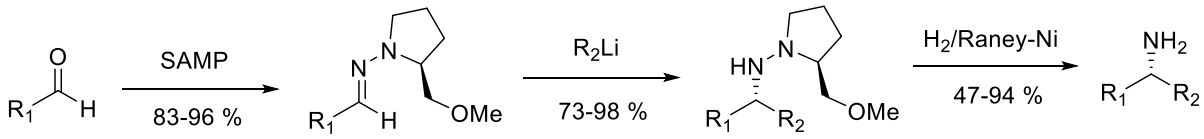
Thus the σ - attractor and π - donor character of the two nitrogen atoms will give on the same terminal carbon both potential nucleophilic and electrophilic reactivity.

1.3.2.1 Electrophilic behavior

The electrophilic reactivity of hydrazones is the best known and the most developed. The use of chiral N, N-dialkylhydrazones has allowed the development of diastereoselective additions.[143]

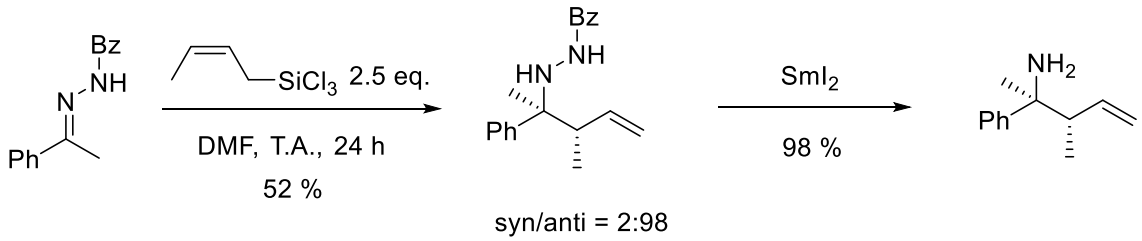
The Enders SAMP/RAMP hydrazone alkylation reaction is an asymmetric carbon-carbon bond formation reaction facilitated by pyrrolidine chiral auxiliaries. It was first discovered by E. J. Corey and D. Enders in 1976[144], and was further developed by D. Enders and his group [145]. The preparation of the hydrazines SAMP ((S) - 1 - amino - 2 - methoxymethylpyrrolidine) and RAMP (the enantiomer (R)) is made in a few steps from (S) - proline and (R) - glutamic acid. The addition of hydrazine to an aldehyde makes it possible to obtain chiral hydrazones, which can react with different organometallic reagents, such as organolithium, organocerium,[146] and Grignard reagents[147] to give N-substituted secondary amine with the simultaneous generation of a new chiral center. A chiral primary amine was obtained after reduction (scheme 3-22).

[143] See the review: The SAMP/RAMP - hydrazone methodology in asymmetric synthesis. A. Job, F. Janeck,W. Bettray, R. Peters, D. Enders, *Tetrahedron* **2002** , *58* , 2253 - 2329.
[144] J. Corey, D. Enders, *Tetrahedron Letters*.**1976**, *17*, 3–6.
[145] L. Kurti, Czako, B. Burlington, MA: *Elsevier Academic Press*.**2005**, 150–151.
[146] E. Denmark, T. Weber, W. Piotrowski, *J. Amer. Chem. Soc.* **1987** , *109* , 2224 - 2225.
[147] D. Enders, E. Chelain, G. Raabe, *Bull. Soc. Chim. Fr.* **1997**, *134* , 299 - 306.



scheme 3-22

In 2002, Kobayashi *et al.* proposed a synthesis of homoallyl α, α - disubstituted amines by a diastereospecific allylation of benzoylhydrazones. The stereoselectivities are always excellent, although yields are sometimes modest. The hydrazine resulting from the addition was then treated with an excess of SmI_2 allowing its conversion to primary amine (scheme 3-23).[148]



scheme 3-23

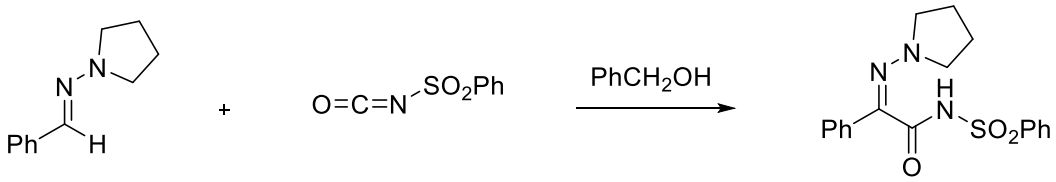
1.3.2.2 Nucleophilic behavior

The reactivity of hydrazones as nucleophiles will strongly depend on their substitution at the terminal nitrogen atom. Thus hydrazone nitrogen atom can be attacked by acylating and alkylating agents, while reactions like Mannich reaction, Michael type addition and halogenation can take place readily at terminal carbon atom.[149]

a. N, N –dialkylhydrazones

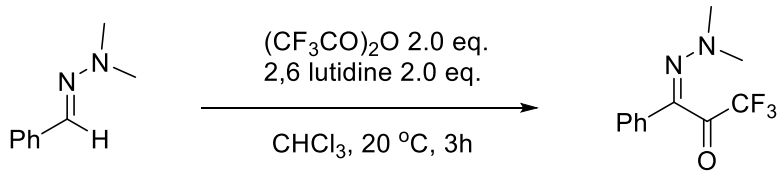
In 1982, Brehme described a reaction of aldehyde-N,N-dimethylhydrazones were substituted on the azomethinecarbon by the electrophilic sulphonylisocyanates (scheme 3-24).[150]

[148] C. Ogawa, M. Sugiura, S. Kobayashi, *J. Org. Chem.* **2002** , *67* , 5359 - 5364.
[149] E. Abdel-Zaher, D. Hicham, A. Nouria and E. Mohammad, *ARKIVOC* **2007**, *2*, 272-315
[150] R. Brehme, *Tetrahedron lett.* **1982**, *23*, 1131 - 1134.



scheme 3-24

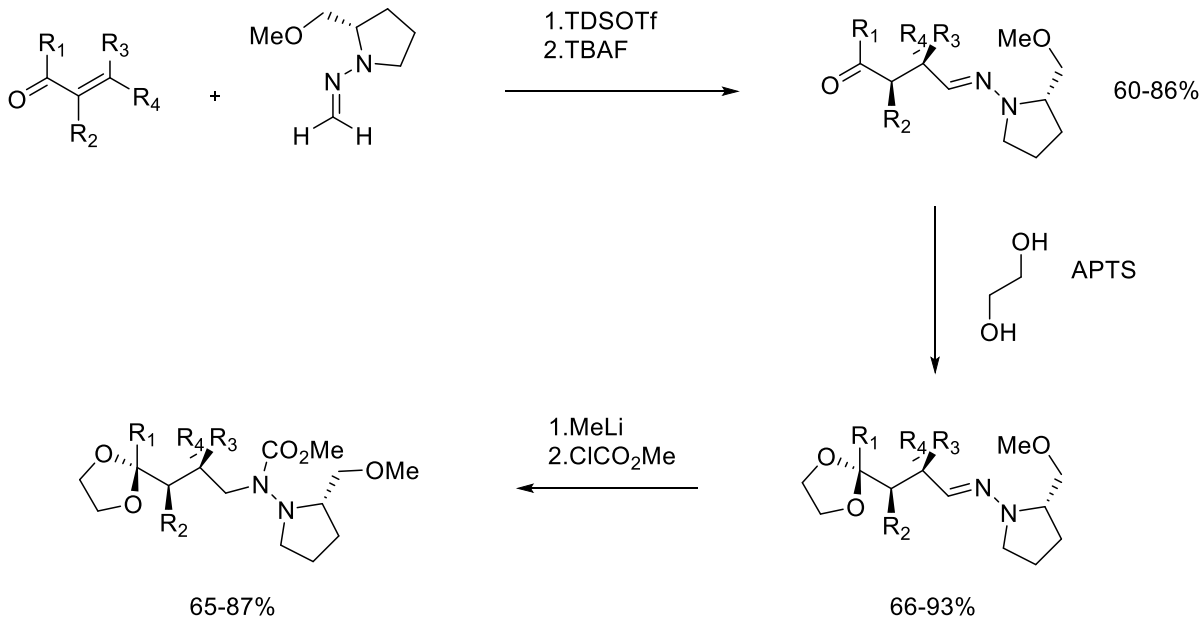
In 1988, Kamitori *et al.* developped trifluoroacetylations of hydrazones using trifluoroacetic anhydride (scheme 3-25).[151]



scheme 3-25

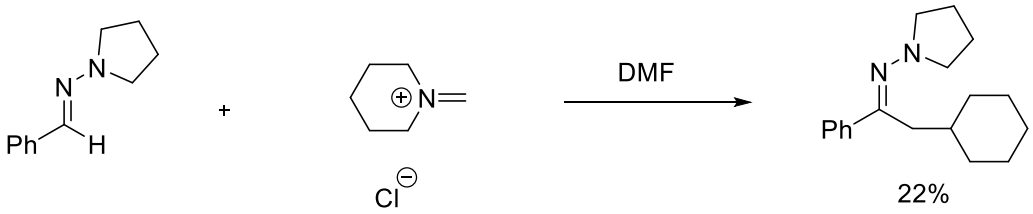
In addition, asymmetric induction was achieved using chiral pyrrolidines. Elegant asymmetric additions to enones,[152] α,β-unsaturated esters,[153] nitroalkenes,[154] α-amino and α- alkoxy-aldehydes[155] were made using Enders SAMP and RAMP hydrazones (scheme 3-26).[156]

[151] Y. Kamitori, M. Hojo, R. Masuda, T. Fujitani, S. Ohara, T. Yokoyama, *J. Org. Chem.* **1988** , *53*,129 - 135
[152] M. Lassaletta, R. Fernandez, E. Martin - Zemora, E. Diez, *J. Am . Chem. Soc.* **1996** , *118*, 7002 - 7003.
[153] D. Enders, M. Lassaletta, R. Fernandez, J. Vazquez, A. Prieto, *Chem. Comm.* **2002**, 498 - 499.
[154] R. Fernandez, C. Gasch, M. Lassaletta, M. Llera, *Tetrahedron Lett.* **1994**, 35, 471.
[155] M. Lassaletta, R. Fernandez, E. Martin - Zemora, C. Pareje, *J. Org. Chem.*, **2001**, *66*, 5201 - 5207.
[156] D. Enders, P. Fey, H. Kipphardt, *Org. Synth.* **1987**, *65*, 173 - 182.



scheme 3-26

Brehme in 1976[157] described a nucleophilic addition of hydrazones with iminiums, but he got low yields (scheme 3-27).



scheme 3-27

The nucleophilic additions of N, N–dialkylhydrazones are often limited in scope giving good yields only for formaldehyde derived hydrazones.

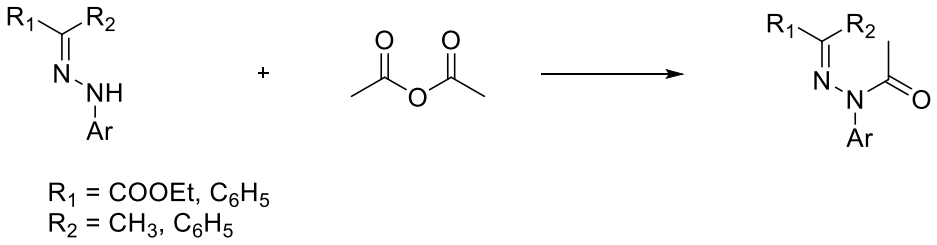
b. N-H hydrazones

For N-H hydrazones, the additions are classically observed at the nitrogen atom which is the more reactive nucleophilic center.

[157] R. Brehme, *Tetrahedron* **1976**, *32*, 731 - 736.

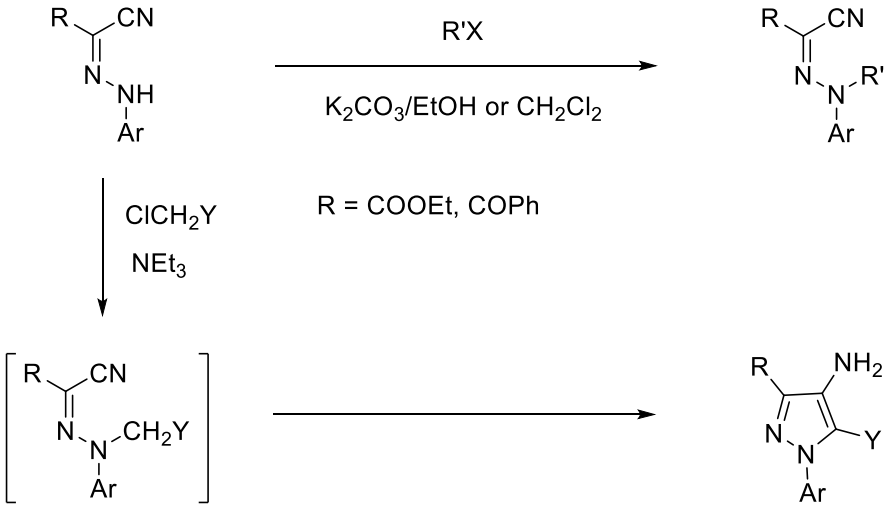
N-acetylation and N-alkylation of N-H hydrazones

In 1949, Sharp reported a N-acetylation of hydrazones with good yields (scheme 3-28).[158] Some electrophiles with sp2 carbon atoms such as carbon disulphide, phenylisothiocyanate, chlorosulfonylisothiocyanate can also be attacked by the hydrazone nitrogen atom.[159]



scheme 3-28 N-acetylation reaction

In 1930, Favrel found that N-H hydrazones can be alkylated under treatment with alkylhalides[160]. In 2006, Salah *et al* got aminopyrazoles through the reaction of hydrazones with chloroacetone, chloroacetonitrile or ethyl chloroacetate.[161] The reaction mechanism may involve a non-isolated acyclic intermediate (scheme 3-29).

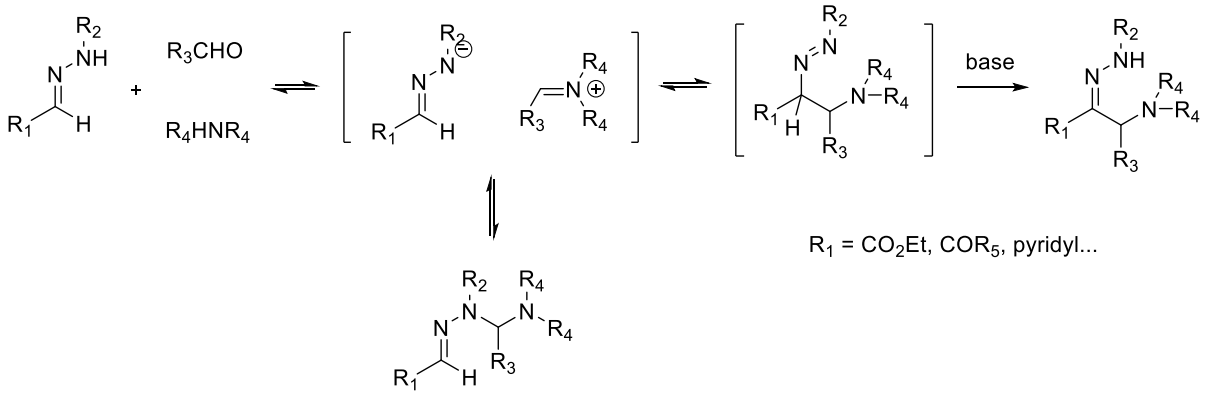


scheme 3-29 N-alkylation reaction

[158] B. Sharp, *J. Am. Chem. Soc.* **1949**, *71*, 1106.
[159] a) V. Patel, S. Fernandes,A. Vyas, *Indian J. Chem. Sect. B.* **1990** , *29*, 1044. b) J. Daniel, N. Dhar, *Heterocycles.* **1991**, *32*, 8
[160] G. Favrel, *Bull. Soc. Chim. Fr.* **1930**, *47*, 1290.
[161] M. Salah, A. Abdallah, F. Radwan, Z. Hassaneen, *Naturforsch*, **2006** , *61b* ,1.

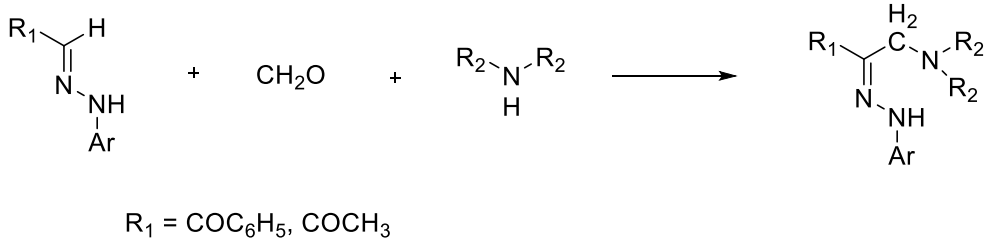
Carbon alkylation of N-H hydrazones

In opposition to the usual behavior of hydrazonyl anions in alkylation, reversible attacks on nitrogen may lead to exclusive functionalisation at the C-position of the hydrazone (scheme 3-30).



Scheme 3-30

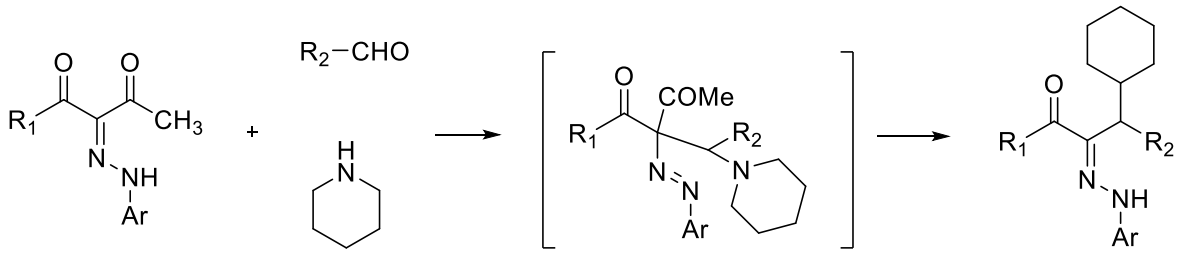
In 1959, Keil and Ried first proposed the Mannich reaction of N–H hydrazones (scheme 3-31). The reaction was described only with formaldehydes and rather acidic hydrazones prone to easy deprotonation under the conditions of the reaction.[162]



scheme 3-31

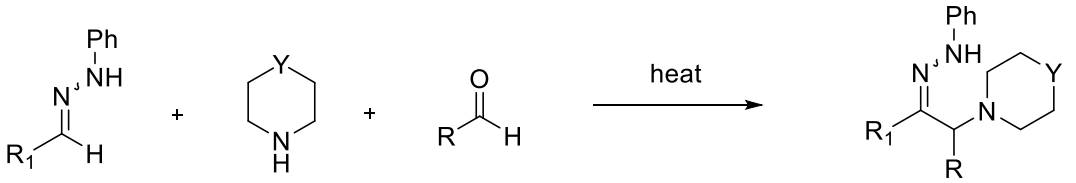
In 1965, Mustafa *et al.* have shown that N-H hydrazones undergo Mannich reaction at hydrazone carbon atom to yield intermediates that readily undergo Japp-Klingemann cleavage yielding corresponding product in good yields (scheme 3-32).[163]

[162] W. Ried and G. Keil, *Liebigs Ann. Chem.*, **1957**, *605*, 167.
[163] A. Mustafa, W. Asker, A. Harhash, N. Nessina, H. Elnagdi, *Tetrahedron* **1965** , *21*, 217.



scheme 3-32

Our lab also made some contribution to N-H hydrazones chemistry. In 2000, we found that aliphatic aldehyde, secondary amines and hydrazones work well to give the new aminohydrazones in good yields. However, in all cases, the reaction remained limited to the coupling of hydrazones possessing electron-withdrawing groups on the hydrazones (R_1 = CO_2Et, COR, CN…), no positive results were observed when simple hydrazones (R_1 = alkyl, aryl) was added in ethanol, toluene or chlorobenzene, even after prolonged heating in the presence of several equivalents of amine and aldehyde (scheme 3-33).[164]



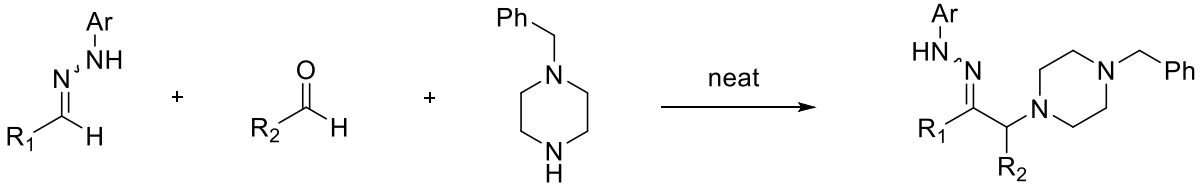
R_1 = COR, COOMe

Scheme 3-33

In 2003, our research group found that when hydrazone with two to three equivalents of a secondary amine and formaldehyde was mixed, the Mannich reaction of hydrazones can be performed smoothly. The new conditions allow the efficient coupling of simple hydrazones derived from aromatic and heteroaromatic aldehydes, and these new conditions widen significantly the scope and interest of the Mannich reaction of hydrazones. However, in Mannich reaction step, only formaldehyde performed well, some aromatic aldehydes only

[164] V. Atlan, H. Bienaymé, L. Kaim and A. Majee, *Chem.Commun.*, **2000**, 1585–1586

react with special starting hydrazones (scheme 3-34).[165]

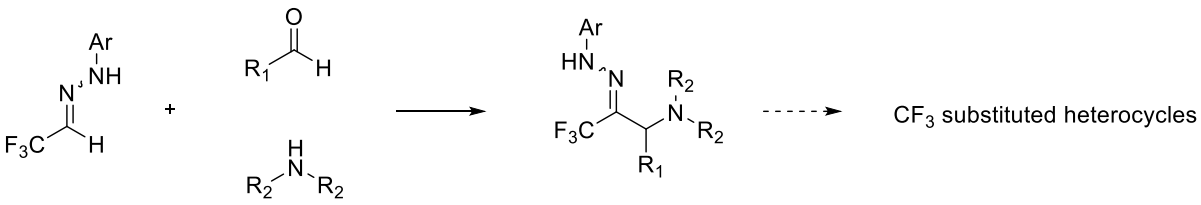


R_1 = COMe, COOMe, aromatic groups

R_2 = H, Ph

Scheme 3-34

In Mannich reaction of hydrazones, a base triggered irreversible azo-hydrazone tautomerism is required for the efficiency of the process. This explains the need for an electron-withdrawing ketone, ester or pyridyl moieties tethered at the α-position of the hydrazone in order to increase the acidity of the azo intermediate.[166] Considering these limitations we envisioned that an NH-hydrazone derived from trifluoroacetaldehyde may be sufficiently acidic to be involved in efficient Mannich type couplings leading in turn to valuable trifluoromethylated heterocycles (Scheme 3-35).



Scheme 3-35

Moreover, trifluoromethyl group can profoundly change the molecular's bioactivity in drug design and agrochemical development.[167] Now it has been estimated that up to 20% of new drugs contain fluorine. Some of the notable examples of fluorinated heterocyclic compounds as commercial drugs and agrochemicals like: the amyotrophic lateral sclerosis drug

[165] L. Elkaïm, L. Gautier, L. Grimaud, L. Harwoodb, V. Michaut, *Green Chemistry*, **2003**, *5*, 477–479
[166] L. Elkaim, L. Gautier, L. Grimaud, V. Michaut, *Synlett*, **2003**, 1844–1846
[167] Y. Zhao, J. Zhu, C. Ni, J. Hu, *Synthesis* **2010**, *11*, 1899–1904

Rilutek-Riluzole; the anti-inflammatory COX-2 inhibitor Celebrex-Celecoxib; fungicides Thifluzamide and insecticides Fipronil (figure 3-4).[168]

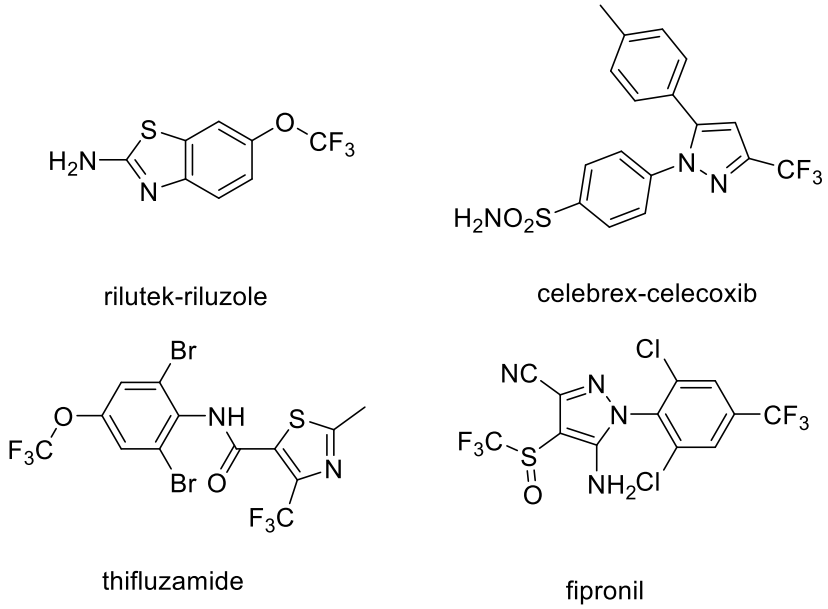


figure 3-4

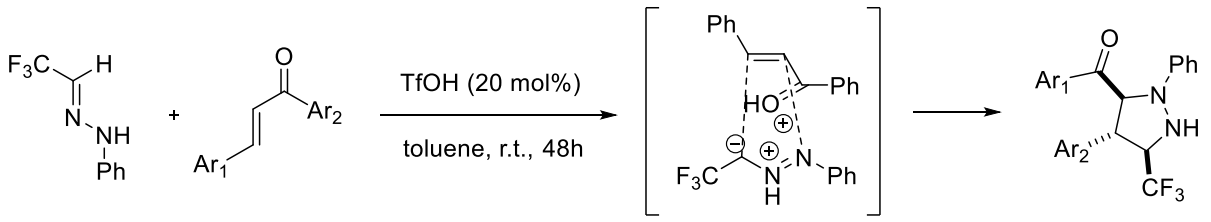
Apart from some oxidative/cycloaddition cascades[169] as well as several Michael additions with α,β-unsaturated aldehydes,[170] the reactivity of NH-trifluoromethyl hydrazones has been poorly studied.

In 2011, Wu *et al.* described an example of diastereoselective 1,3-dipolar cycloaddition of NH-trifluoromethyl hydrazone with α,β-ethenyl ketones. This new method provided synthetically useful, highly substituted pyrazolidine and pyrazoline derivatives with efficiency and high diastereoselectivity (scheme 3-36).[169]

[168] A. Gakh and K. Kirk, *Fluorinated Heterocycles*, **2009**, 1003

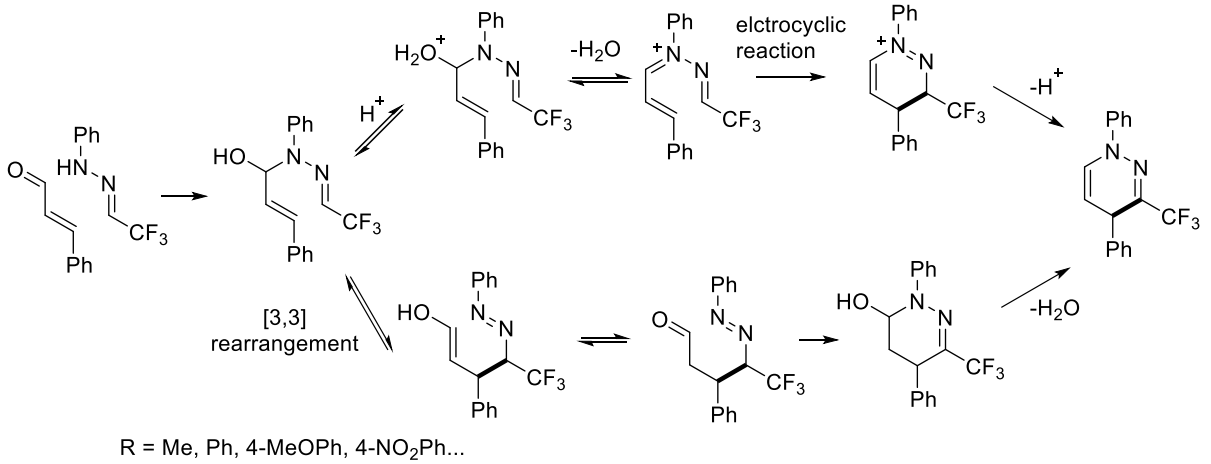
[169] For a selection of [3 + 2] cycloadditions: (a) K. Tanaka, S. Maeno and K. Mitsuhashi, *Chem. Lett.*, **1982**, 543–546; (b) H. Xie, J. Zhu, Z. Chen, S. Li and Y. Wu, *Synthesis*, **2011**, 2767–2774.

[170] (a) H. Xie, J. Zhu, Z. Chen, S. Li and Y. Wu, *Synlett*, **2012**, 935–937; (b) A. Das, C. Volla, I. Atodiresei, W. Bettray and M. Rueping, *Angew. Chem., Int. Ed.*, **2013**, *52*, 8008– 8011; (c) C. Volla, A. Das, L. Atodiresei and M. Rueping, *Chem. Commun.*, **2014**, *50*, 7889–7892.



scheme 3-36

In 2012, Wu and co-workers developed a facile and efficient method for the synthesis of 3-trifluoromethyl-1,4-dihydropyridazine from various readily available α,β-unsaturated aldehyde and (E)-1-phenyl-2-(2,2,2-trifluoroethylidene)hydrazone. The reaction may undergo a Michael addition and followed by cyclization to give the expected 1,4-dihydropyridazine products in good to high yields (scheme 3-37).[171]



scheme 3-37

2 Results and discussion

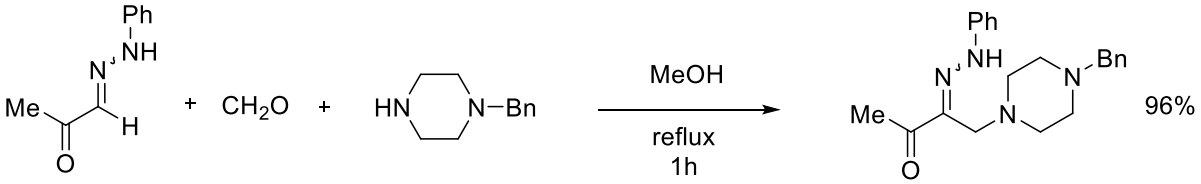
2.1 Preliminary test

These NH-trifluoromethyl hydrazones are easy to obtain under heating trifluoroacetaldehyde hemiacetals and hydrazines in water solution, in the presence of hydrochloric acid.[172] In the

[171] H. Xie, J. Zhu, Z. Chen, S. Li and Y. Wu, *Synlett*, **2012**, 935–937

[172] (a) L. Carrocia, S. Fioravanti, L. Pellacani, P. Tardella, *Synthesis*, **2010**, 4096–4010. See also: (b) K. Tanaka, S. Maeno

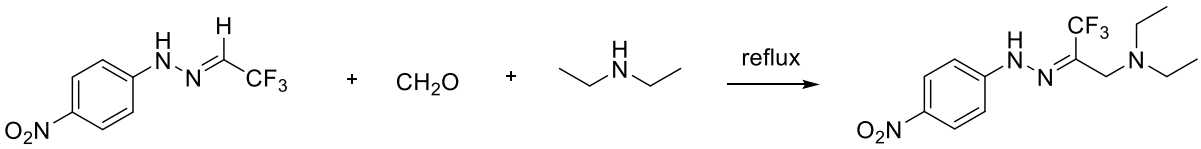
previous work we've done on non-fluorinated NH-hydrazones (scheme 3-38)[165], heating in toluene or alcohol as the solvents was used to conduct the reactions.



scheme 3-38

4-Nitrophenyl hydrazone, obtained in 90 % yield from 4-nitrophenyl hydrazine, was initially selected due to its higher acidity and the reported beneficial effect of a nitro substituent in the Mannich coupling of non-fluorinated NH-arylhydrazones.

For the first trial carried out, we allowed 4-nitrophenyl hydrazine to react with stoichiometric amount of formaldehyde and diethylamine, with methanol and toluene as the solvent respectively. The mixture was refluxed under argon, and the reaction followed by TLC. Fortunately, a good yield was obtained in toluene after 12 h. We were satisfied with this good yield, thus no further optimization was carried out (scheme 3-39).



solvents and reaction time	yield
methanol, 12 h	63%
toluene, 12 h	89%

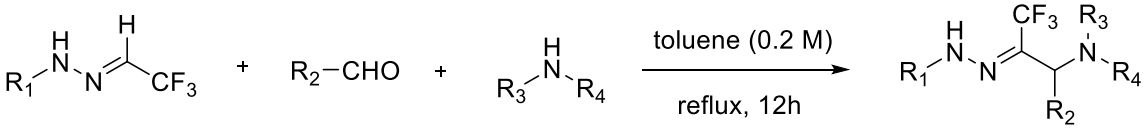
scheme 3-39 preliminary tested reaction conditions

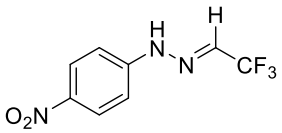
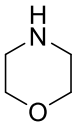
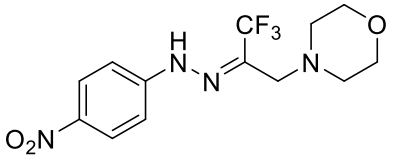
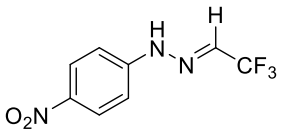
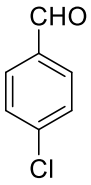
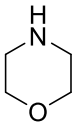
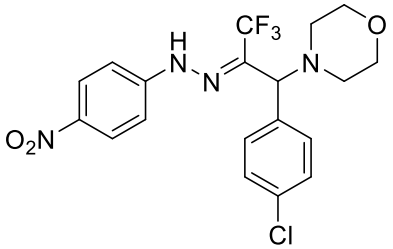
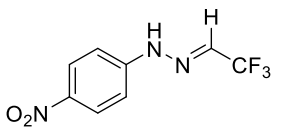
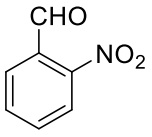
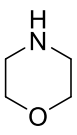
and K. Mitsuhashi, *J. Heterocycl. Chem.*, **1985**, *22*, 565–568; (c) A. Hegarty, M. Cashman and F. Scott, *J. Chem. Soc., Perkin Trans.* **1972**, *2*,1381–1386.

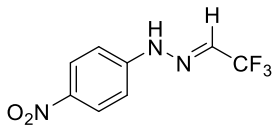
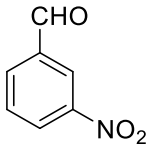
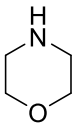
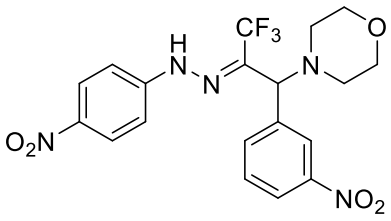
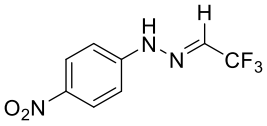
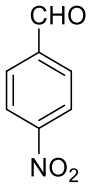
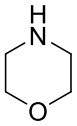
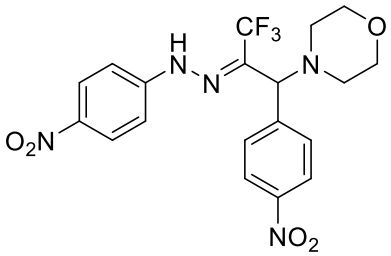
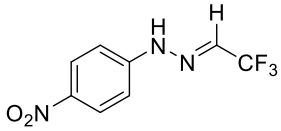
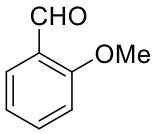
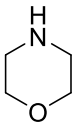
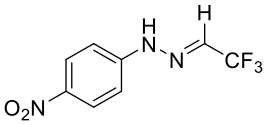
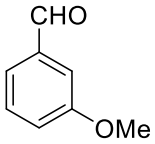
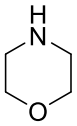
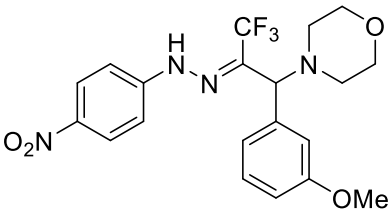
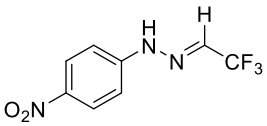
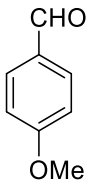
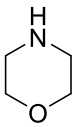
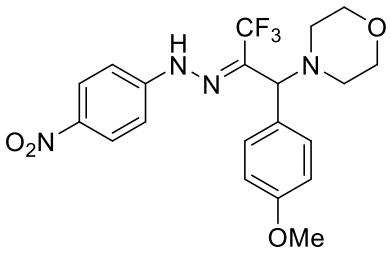
2.2 Mannich reaction of trifluoroacetaldehyde hydrazones

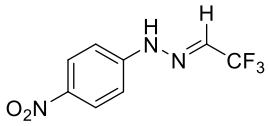
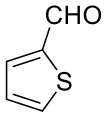
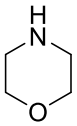
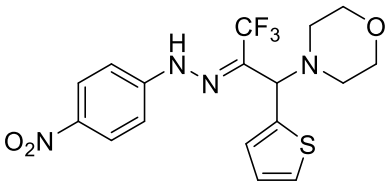
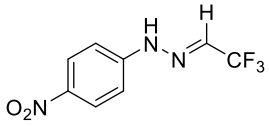
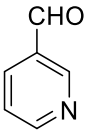
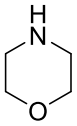
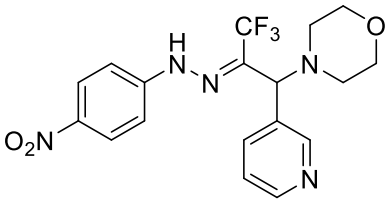
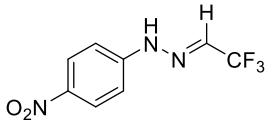
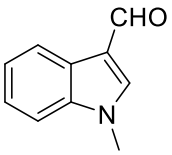
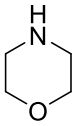
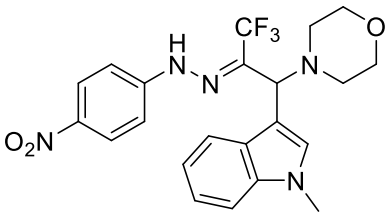
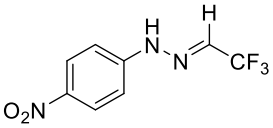
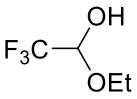
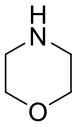
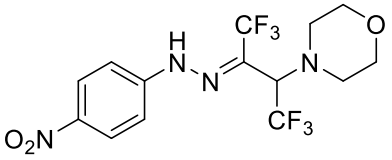
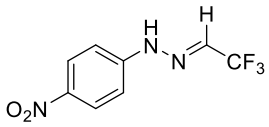
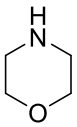
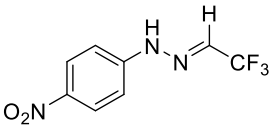
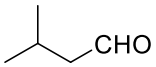
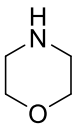
We prepared a library of Mannich adducts varying the 3 components of the reaction, using toluene as the solvent, affording NH-aryl hydrazones with excellent yields in most examples. The various results are presented thereafter in (see Table 3-1).

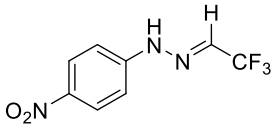
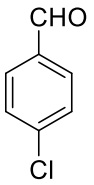
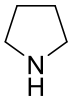
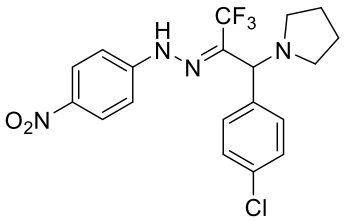
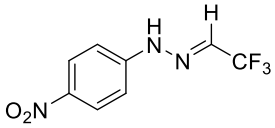
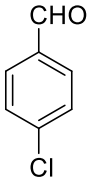
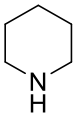
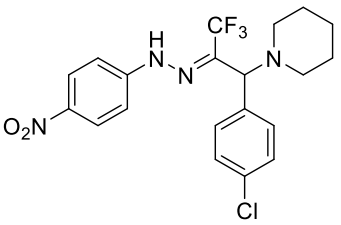
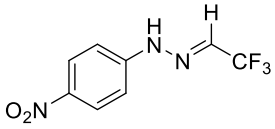
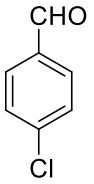
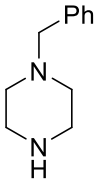
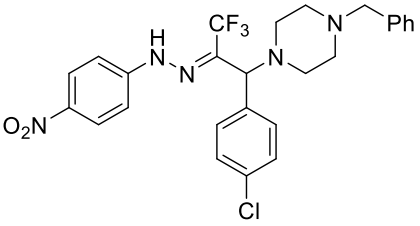
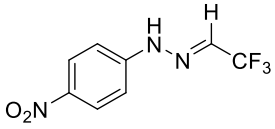
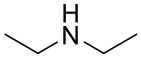
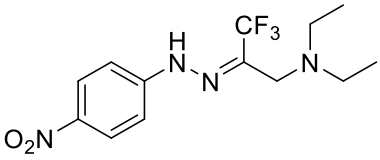
Table 3-1 various of examples of prepared Mannich adducts.



entry	hydrazone	aldehyde	amine	Product & yield[a]
1		CH_2O		 **III-1** 94 %
2				 **III-2** 99 %
3				-

4				 **III-3** 99 %
5				 **III-4** 99 %
6				-
7				 **III-5** 99 %
8				 **III-6** 82 %

9				 **III-7** 48 %
10				 **III-8** 99 %
11				 **III-9** 58 %
12				 **III-10** 79 %
13		CH_3CHO		-
14				-

15				 **III-11** 82 %
16				 **III-12** 87 %
17				 **III-13** 81 %
18		CH_2O		 **III-14** 89 %

a. Isolated yields after column chromatography on silica gel

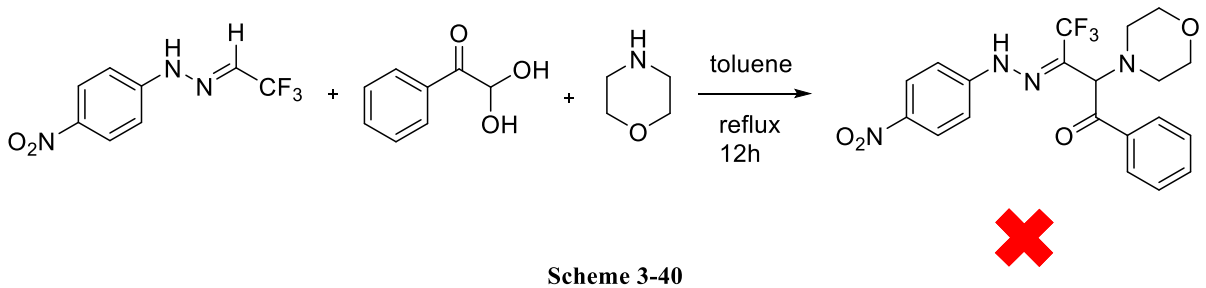
In general, the products of Mannich type reaction were obtained with good to excellent yields from 47 to 99 % (see Table 3-1).

When trifluoromethyl substituted 4-nitrophenylhydrazone was added to morpholine and 4-chlorobenzaldehyde under chosen reaction conditions (equimolar amounts in refluxing

toluene), we were delighted to observe a quantitative formation of a new Mannich fluorinated adduct **III-2** after refluxing the mixture for 12 hours (Table 3-1, entry 2). To evaluate the potential of this coupling, different N-aryl fluorinated hydrazones were prepared and treated together with morpholine and various aldehydes (Table 3-1).

Using nitrosubstituted hydrazone, the reaction does not seem to show a strong dependence on the electronic nature of the aromatic aldehyde, both electron-rich and deficient aromatic aldehydes giving very good yields (Table 3-1, entries 4, 5, 7 and 8).

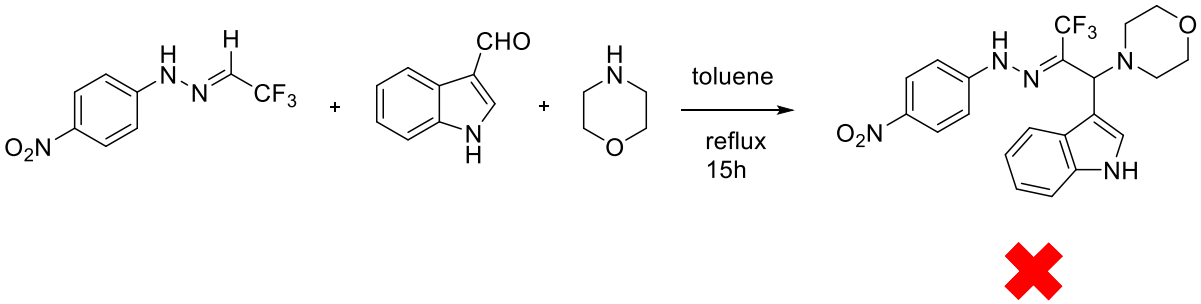
However, when dihydroxyacetophenone was used, the reaction was not clean. This is probably due to both carbonyl groups reacting with morpholine, the competition leads to more by-products generation (scheme 3-40).



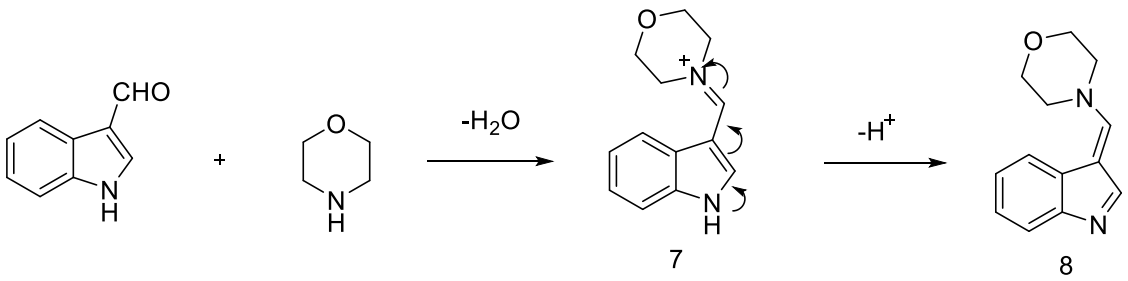
Scheme 3-40

Heteroaromatic aldehydes may be used as well giving lower yields for electron-rich derivatives (indole, thiophene versus pyridine, Table 3-1, entries 9–11).

Indole-3-carbaldehyde failed to couple with 4-nitrophenylhydrazone and morpholine. (scheme 3-41) but N-methyl-indole-3-carbaldehyde works well (Table 3-1,entry 11). A possible reason is that iminium **7** processing an acidic NH can isomerize into **8** which has lower reactivity. This may obstructs the coupling between hydrazone and iminium (scheme 3-42).

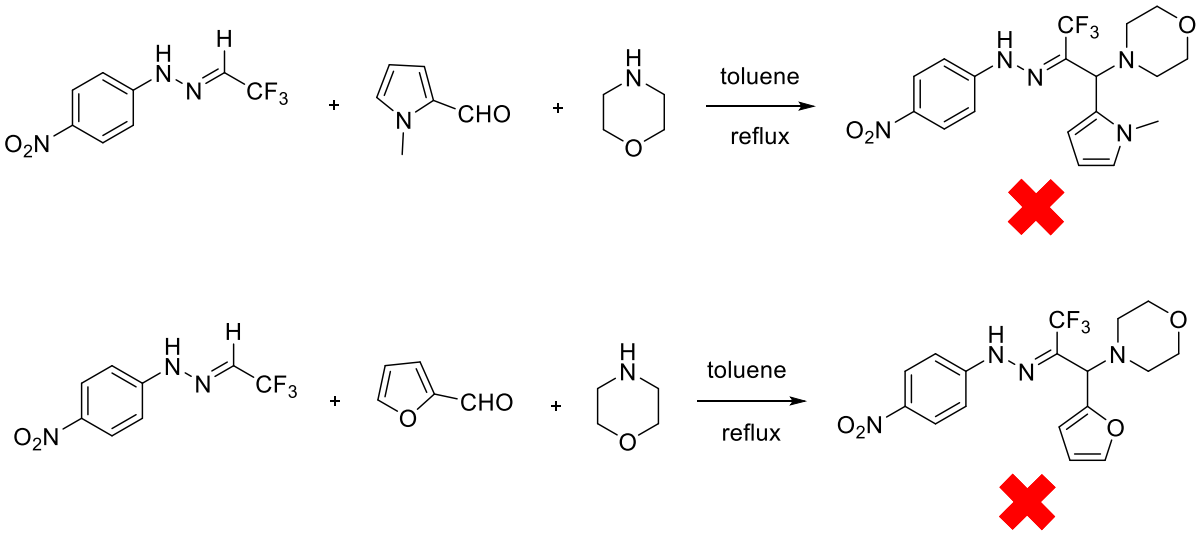


Scheme 3-41



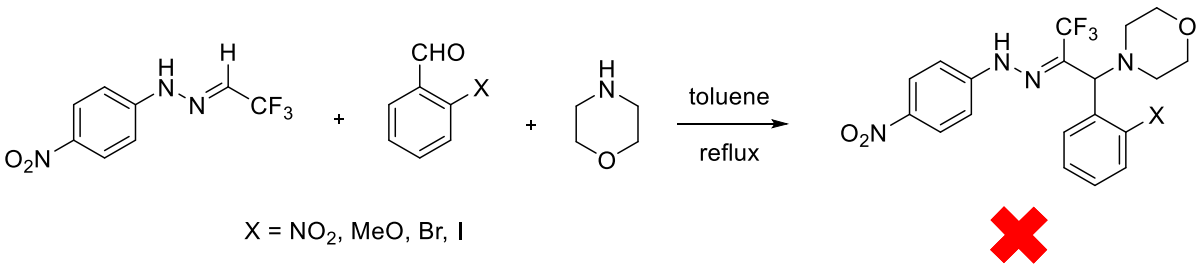
Scheme 3-42

When N-methyl-pyrrole-2-carbaldehyde or furan-2-carbaldehyde was introduced into this Mannich reaction, no corresponding product was observed. For both of them, we just got some starting hydrazones and some color, while thiophene-2-carbaldehyde gave 48% yield (Table 3-1, entry 9). The most probable reason is that pyrrole ring and furan ring are more electron rich than thiophene ring, which decrease the electrophilicity of the carbon of carbonyl group (scheme 3-43).



Scheme 3-43

2-Substituents are not tolerated on the aromatic ring as shown by the lack of any coupling observed with 2-nitro and 2-methoxy benzaldehydes (Table 3-1, entries 3 and 6); the steric hindrance may prevent the iminium formation, which is essential in Mannich reaction. On the other hand, due to the bulkiness of *ortho*-substituent, there is some angle between phenyl plan and iminium plan. This steric hindrance hindered the nuecleophilic attack from top or bottom (figure 3-5). The same situation exists in 2-bromo and 2-iodo benzaldehydes (scheme 3-44).



Scheme 3-44

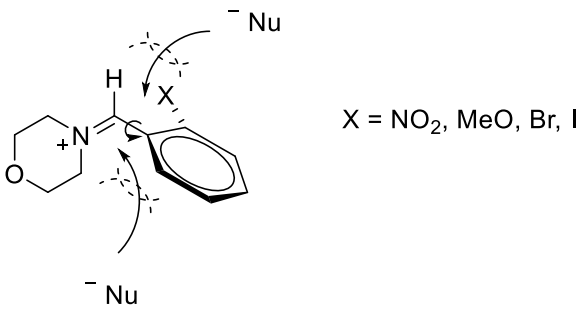
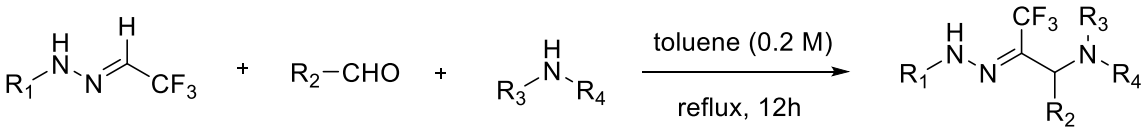
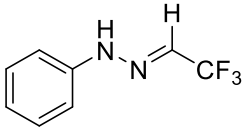
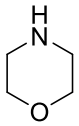
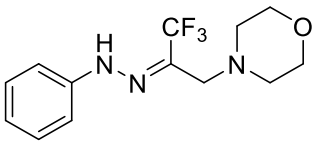
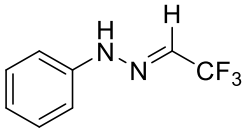
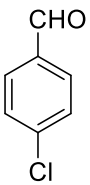
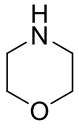
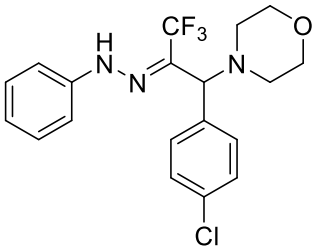


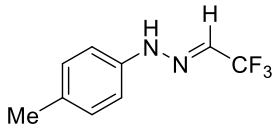
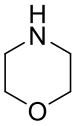
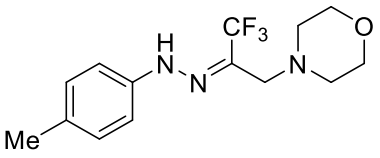
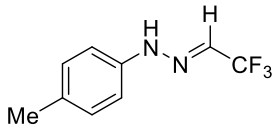
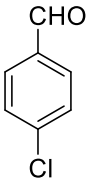
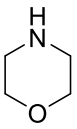
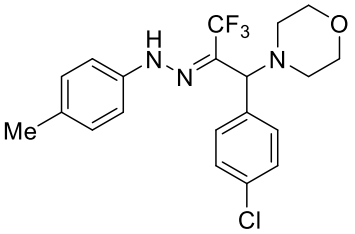
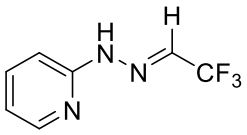
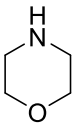
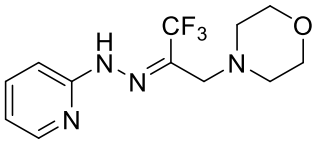
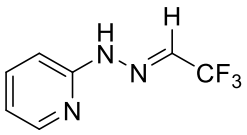
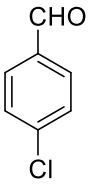
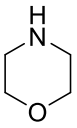
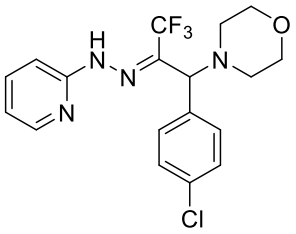
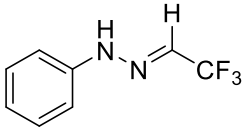
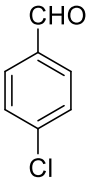
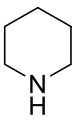
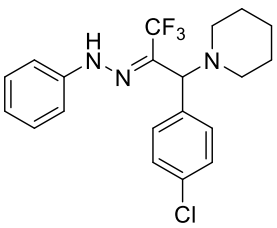
figure 3-5

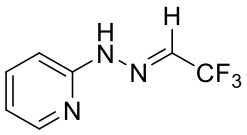
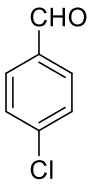
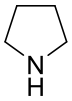
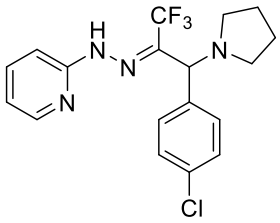
In strong contrast to its non-fluorinated hydrazone analogue, the reaction could not be extended to the coupling of simple aliphatic aldehydes such as acetaldehyde or isovaleraldehyde (Table 3-1, entries 13 and 14). However, more reactive formaldehyde and trifluoroacetaldehyde (used as its hemiacetal) could give some productive couplings (Table 3-1, entries 1, 12, 15, 18 and Table 3-2 entry 3, 5).

Table 3-2 various of examples of prepared Mannich adducts.



1		CH_2O		 **III-15** 95 %
2				 **III-16** 85 %

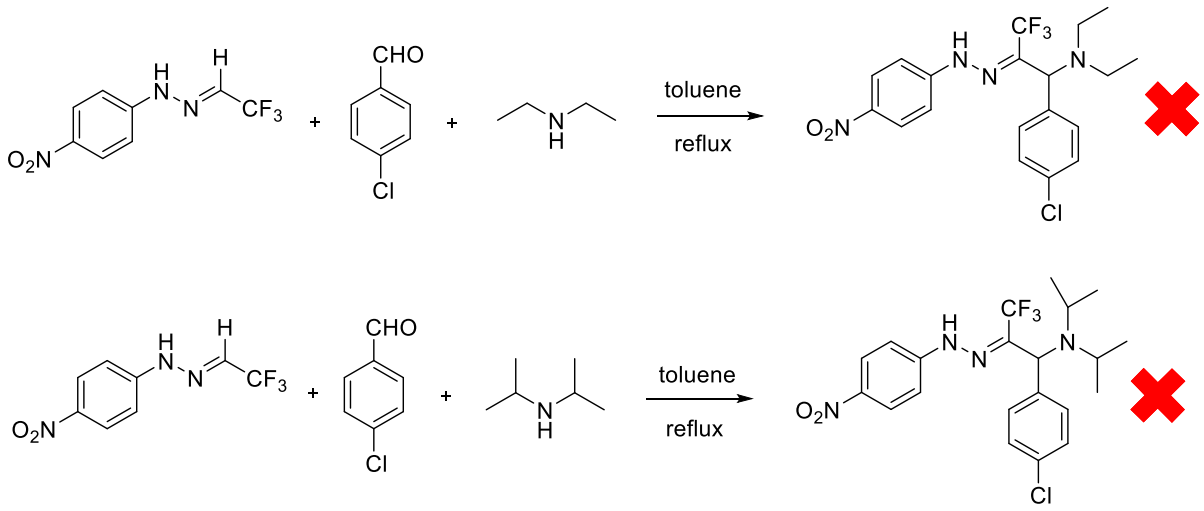
3		CH_2O		 **III-17** 95 %
4				 **III-18** 68 %
5		CH_2O		 **III-19** 81 %
6				 **III-20** 47 %
7				 **III-21** 75 %

8				 **III-22** 58 %

Rewardingly, the reaction was not limited to nitrophenylhydrazone (see Table 3-2). Some simple N-phenyl or N-tolyl trifluoromethylhydrazones afforded Mannich adducts with similar yields compared to their nitro analogues. When comparing the lack of reactivity of the related N-phenyl acetaldehyde hydrazone in Mannich reactions, this behavior clearly demonstrates a strong activating effect of the trifluoromethyl group.

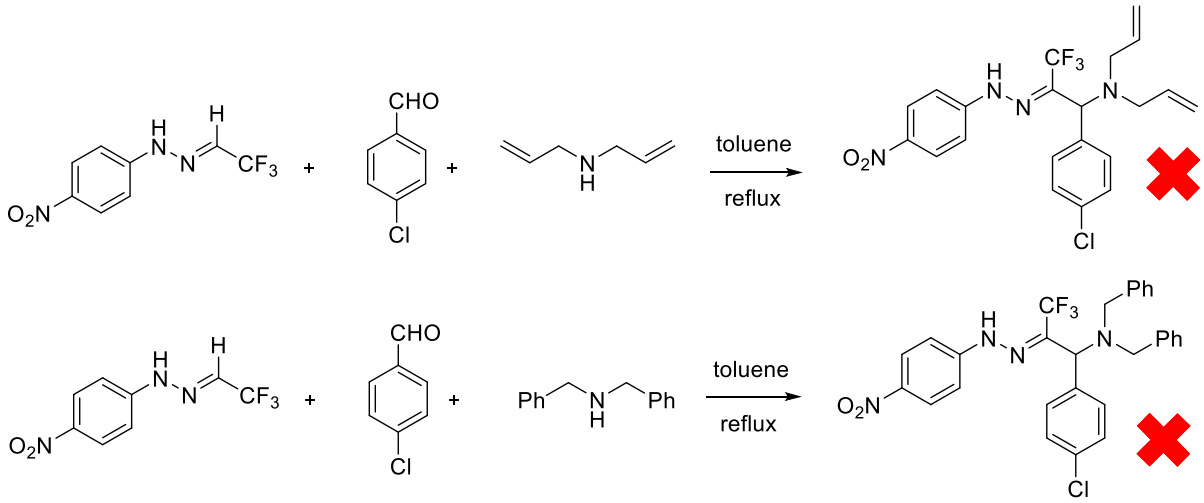
Besides morpholine, the coupling could also be easily extended to other cyclic and non-cyclic secondary amines (Table 3-1, entries 15-18 and Table 3-2, entry 7,8).

However, while diethylamine or diisopropylamine react with 4-nitrophenylhydrazone and 4-chlorobenzaldehyde, no desired results was obtained, just some starting materials remained in the reaction system. This is probably due to the higher nucleophilicity of morpholine compared to both diethylamine and diisopropylamine (scheme 3-45).



Scheme 3-45

Similar situation was observed with diallylamine or dibenzylamine. Because of weaker nucleophilicity and higher steric hindrance, the reaction cannot proceed. We just got some starting materials (scheme 3-46).



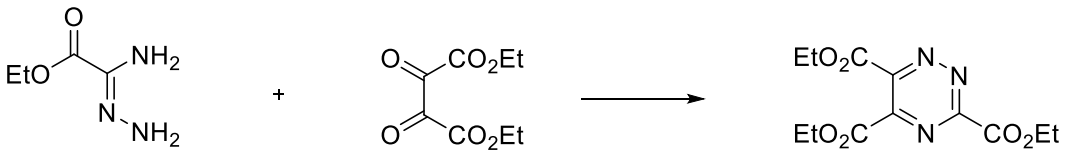
Scheme 3-46

2.3 Towards 1,2,4-Triazine derivatives

1,2,4-Triazine derivatives have been widely reported because of interesting biological

activities such as anti-AIDS,[173] antimicrobial and antiinflammatory[174] and CRF receptor antagonists[175]activities. We developed hence a useful method to afford them.

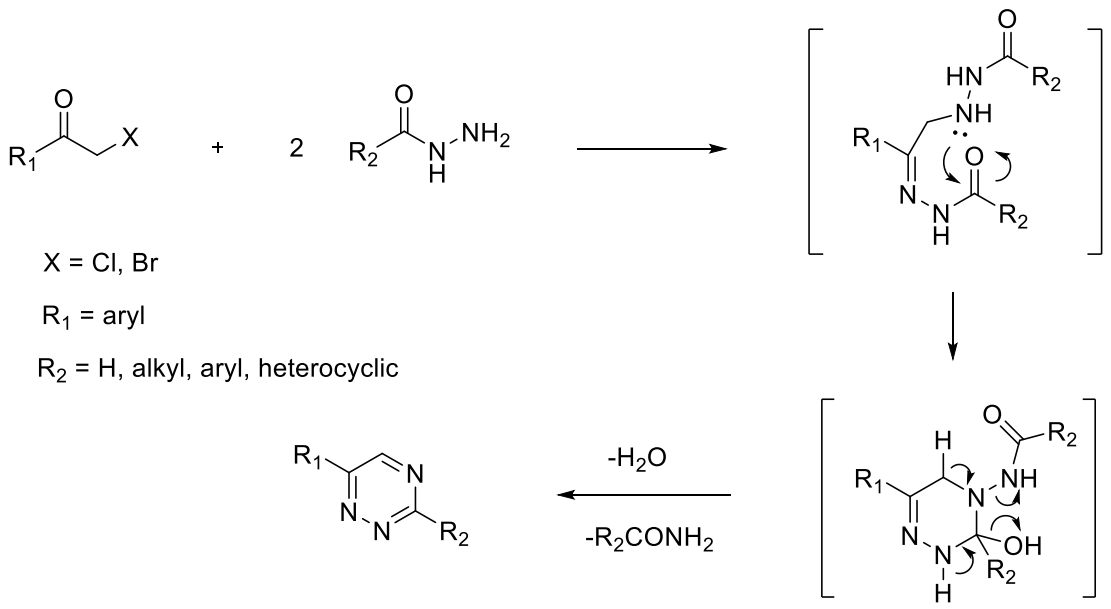
In 1958, 1,2,4-triazine derivatives were first reported by R. Ratz and H. Schroeder. The reaction involved the condensation of ethyl oxalamidrazonate with diethyl diketosuccinate to yield the 1,2,4-triazine-3,5,6-tricarboxylic ethyl ester (scheme 3-47).[176]



scheme 3-47

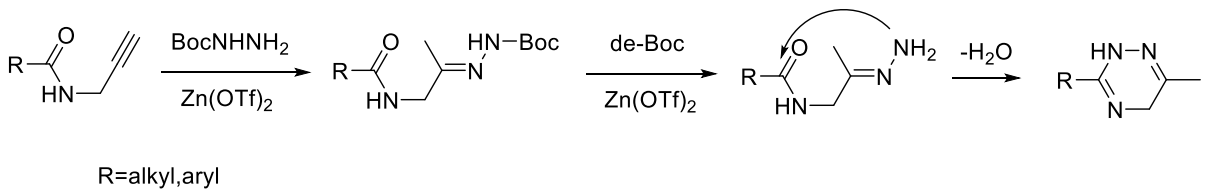
In 1971, Saraswathi and Srinivasan developed a route to 6-aryl- and 3-substituted-6-aryl-1,2,4-triazines by heating a mixture of an acid hydrazine and an ω-haloacetophenone (2:1) in ethanol in presence of stoichiometric amount of sodium acetate for a few minutes (scheme 3-48).[177]

[173] Z. El-Gendy, J. Morsy, H. Allimony, W. Ali, R. Abdel-Rahman, *Pharm*, **2001**, *56*,376-383
[174] J. Hynes, A. Dyckman,K. Leftheris, *J. Med. Chem.* ,**2008**, *51*, 4-16
[175] W. Schmitz, A. Brenner, J. Macor, *Bioorg. Med. Chem. Lett.* , **2010**, *20*, 3579-3583.
[176] R. Ratz and H. Schroeder, *J. Org. Chem.*, **1958**, *23*, 1931.
[177] V. Saraswathi, R. Srinivasan, *Tetrahedron Lett.* **1971**, *12*, 2315−2316.



scheme 3-48

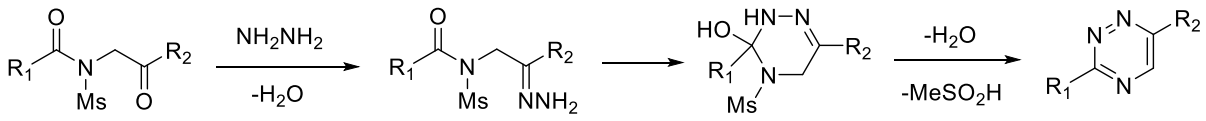
In 2016, Krasavin *et al.* reported a practically simple, one-pot method to prepare 3,6-disubstituted 1,2,4-triazines via a zinc catalyzed hydrohydrazination–cyclodehydration–oxidation sequence involving propargylamides and BocNHNH2, in moderate to good yields (scheme 3-49).[178]



scheme 3-49

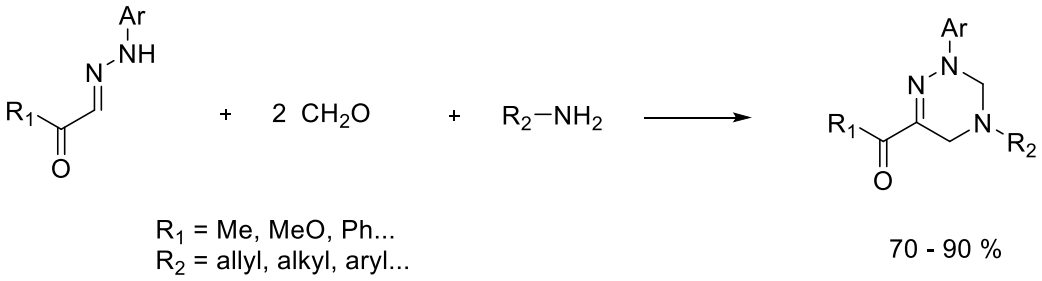
In 2018, Gong *et al.* described a straightforward method for preparing 3,6-disubstituted-1,2,4-triazines through a redox-efficient cyclodehydration of β-keto-N-acylsulfonamides with hydrazine salts (scheme 3-50).[179]

[178] A. Lukin, T. Vedekhina, N. Tovpeko, M. Krasavin, *RSC Advances* ,**2016**, *6(63)*, 57956-57959
[179] D. Matthew, W. Jiao, J. Hou, Y. Jiang, and S. Gong, *J. Org. Chem.* **2018**, *83*, 4229−4238



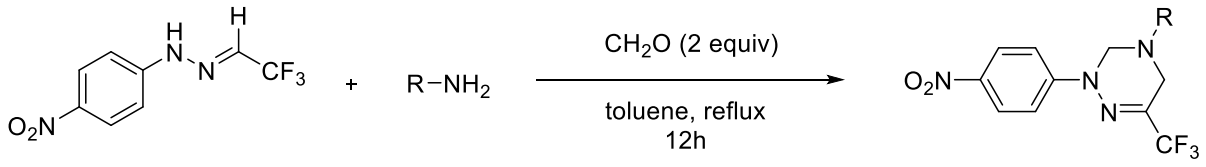
scheme 3-50

In a context of growing medicinal interest for new fluorinated compounds and trifluoromethylated compounds in particular, this reaction offers interesting opportunities for the preparation of new trifluoromethylated heterocycles.[180] A first family of trifluorinated 1,2,4-triazines could be easily obtained when primary amines such as allylamine or 4-methoxybenzylamine were reacted with trifluoroacetaldehyde 4-nitrophenylhydrazone and a twofold excess of formaldehyde (Table 3-2).[181] Before our work, this kind of reaction was already described with formaldehydes and non-fluorinated hydrazones (scheme 3-51).[182]

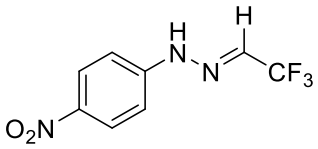
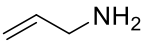
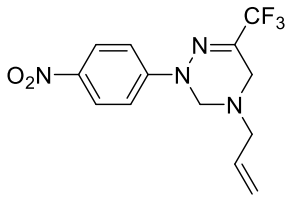
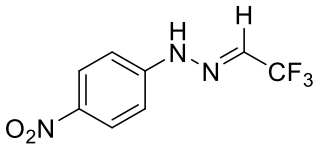
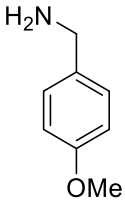
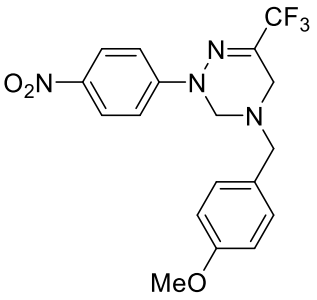
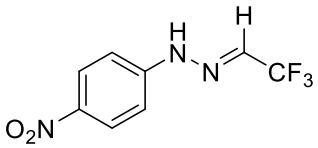
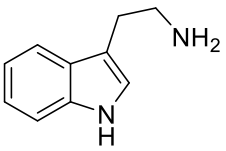
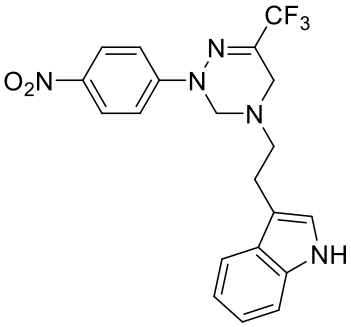


scheme 3-51

Table 3-3 1,2,4-Triazine formation from NH-hydrazones



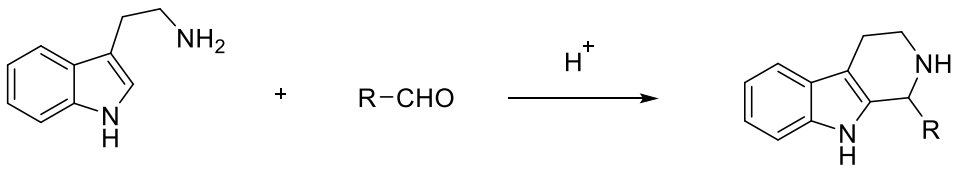
[180] (a) V. Petrov, Fluorinated Heterocyclic Compounds: *Synthesis, Chemistry, and Applications*, Wiley, Hoboken, New Jersey, 2009; (b) *Fluorinated Heterocycles*, ed. A. Gakh and K. Kirk, ACS Symposium Series, 2009, 1003.
[181] (a) N. Saldabol, L. Alekseeva, B. Brizga, L. Kruzmetra, A. Zile, A. Popel, *Pharm. Chem. J*., **1968**, *2*, 626–629; (b) H. Moehrle and G. Keller, Z. Naturforsch., B: *Chem. Sci*., **2003**, *58*, 885–902.
[182] E. Hahn, *Roczniki Chemii*, **1959**, *33*, 1245-7

entry	hydrazone	aldehyde	amine	Product & yield[a]
1		CH_2O		 **III-23** 98 %
2		CH_2O		 **III-24** 99 %
3		CH_2O		 **III-25** 36 %

a. Isolated yields after column chromatography on silica gel

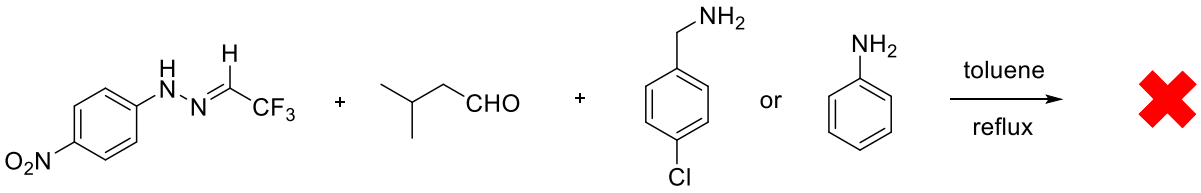
The lowest yield was obtained while using tryptamine. A probable explanation would be a competitive Pictet-Spengler type reaction occurring simultaneously. A tryptamine could undergo ring closure after condensation with an aldehyde while the reaction mixture was heated forming thus a lot of side products (scheme 3-52).[183]

[183] a)A. Pictet, T. Spengler, *Berichte der deutschen chemischen Gesellschaft.* **1911**. *44 (3)* 2030–2036.b) M. Whaley, R. Govindachari, *Org. React.* **1951**, *6*, 74.

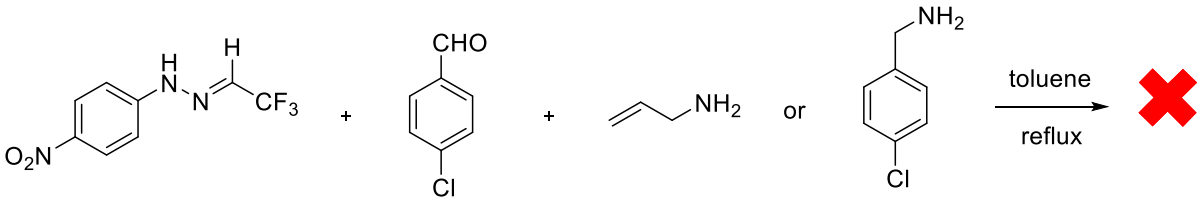


scheme 3-52 Pictet-Spengler type reaction

This reaction was limited to formaldehyde, other aromatic or aliphatic aldehydes such as 4-chlorobenzaldehyde or isovaleraldehyde cannot react (scheme 3-53, 3-54).

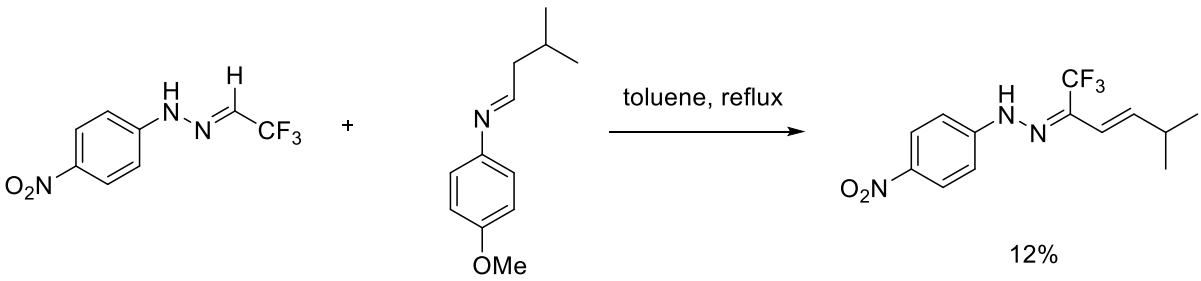


Scheme 3-53



Scheme 3-54

Even when we preformed their iminium and reacted them directly with 4-nitrophenylhydrazone, only traces of elimination product was obtained (scheme 3-55).



Scheme 3-55

2.4 Towards α-(Trifluoromethyl)pyridazine Derivatives

2.4.1 A brief introduction of α-(trifluoromethyl)pyridazine derivatives

The last decades witnessed an increasing interest in α-(trifluoromethyl)pyridazines in medicinal chemistry. The biologically active pyridazines could be a bioisoster of other heterocycles. Due to the influence of trifluoromethyl group on the chemical and physicochemical properties, α-(trifluoromethyl)pyridazines have been an attractive scaffold for medicinal chemists. [184] For example, BMS-911278, possessing a (trifluoromethyl)pyridazine was presented as a potent triple reuptake inhibitor which could possibly be used for the treatment of depression (figure 3-6).[185]

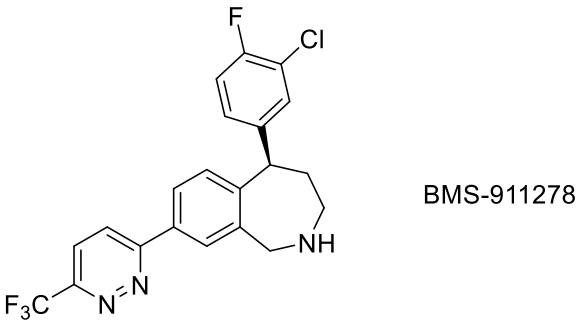
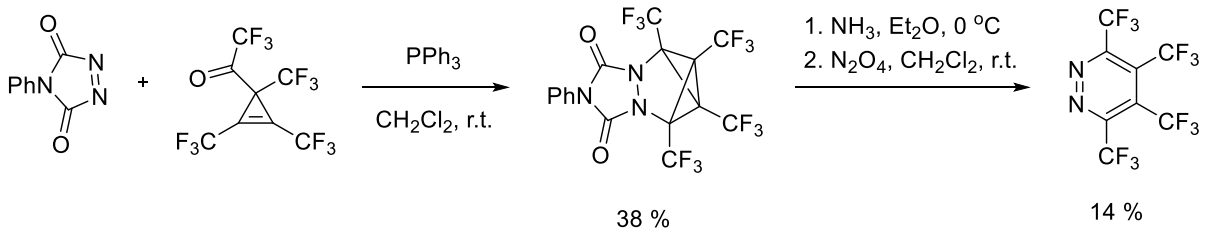


figure 3-6

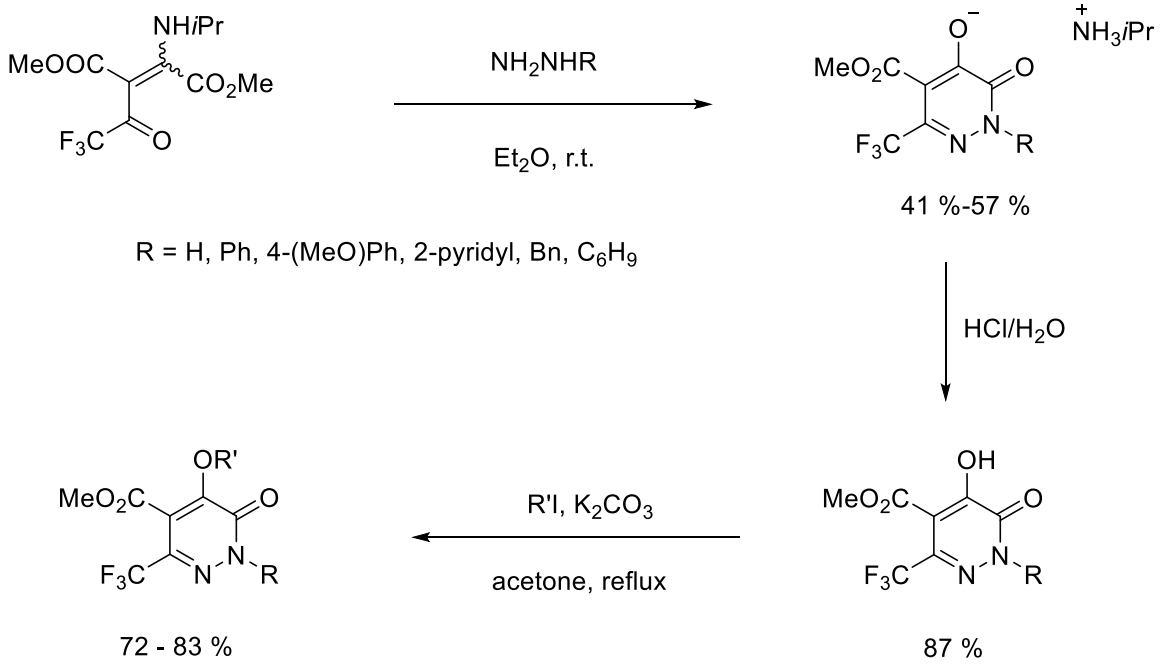
One of the first synthesis of a α-(trifluoromethyl)pyridazine was reported by Kobayashi et al. in 1980. When triazoline was activated by triphenylphosphine, and then react with cyclopropene to afford the polycyclic compound substituted by four CF_3 groups. After treatment with ammonia and dinitrogentetroxide (N_2O_4), the tetrakis-(trifluoromethyl)pyridazine was isolated albeit in a low yield of 14 % (scheme 3-56).[186]

[184] F. Alexandra, G. Domingo, C. Janine, *Eur. J. Org. Chem.* **2018**,0–0
[185] B. Molino,*et al*, R. E.(AMR Technology Inc.) 2007 (US2007/0021408 A1).
[186] Y. Kobayashi, T. Nakano, K. Shirahashi, A. Takeda, I. Kumadaki, *TetrahedronLett.* **1980**, *21*, 4615–4618.



scheme 3-56 synthesis of tetrakis-(trifluoromethyl)pyridazine

In 1993, Hegde *et al.* synthesized pyridazine carboxylate derivatives resulting from the condensation of aryl and alkyl hydrazines with γ-(trifluoromethyl)ketoester, which after treatment with HCl/H_2O, produced hydroxypyridazinone. Hydroxypyridazinone could then be converted to different trifluoromethyl alkoxyderivatives by alkylation of the hydroxy group using alkyliodides in the presence of potassium carbonate (72–83 % yield) (scheme 3-57).[187]

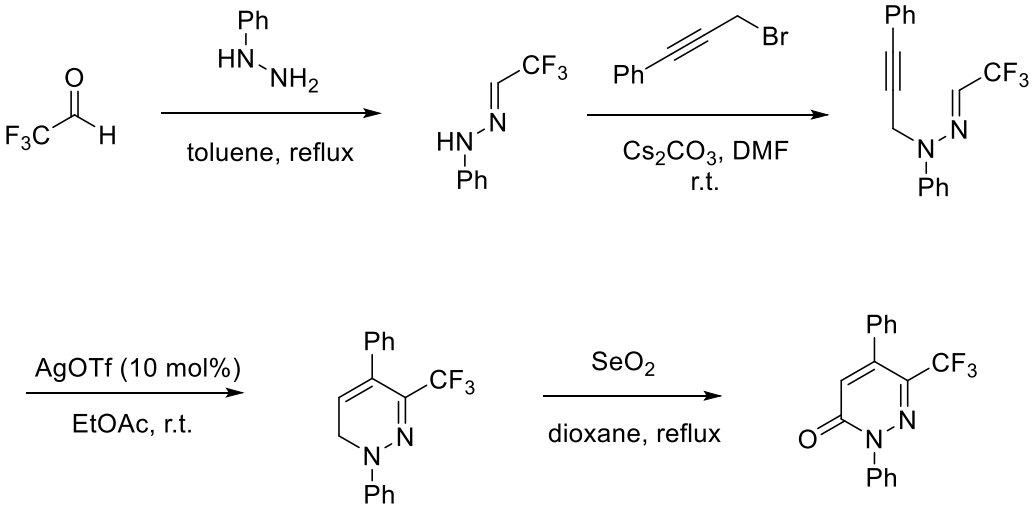


scheme 3-57

In 2016, Zhan et al. reported the synthesis of α-(trifluoro-methyl)dihydropyridazine through a silver-catalyzed sigmatropic rearrangement/[1,3]-hydride shift/6π-aza electrocyclization

[187] S. Hegde, C. Jones, *J. Heterocycl. Chem.* **1993**, *30*, 1501–1508.

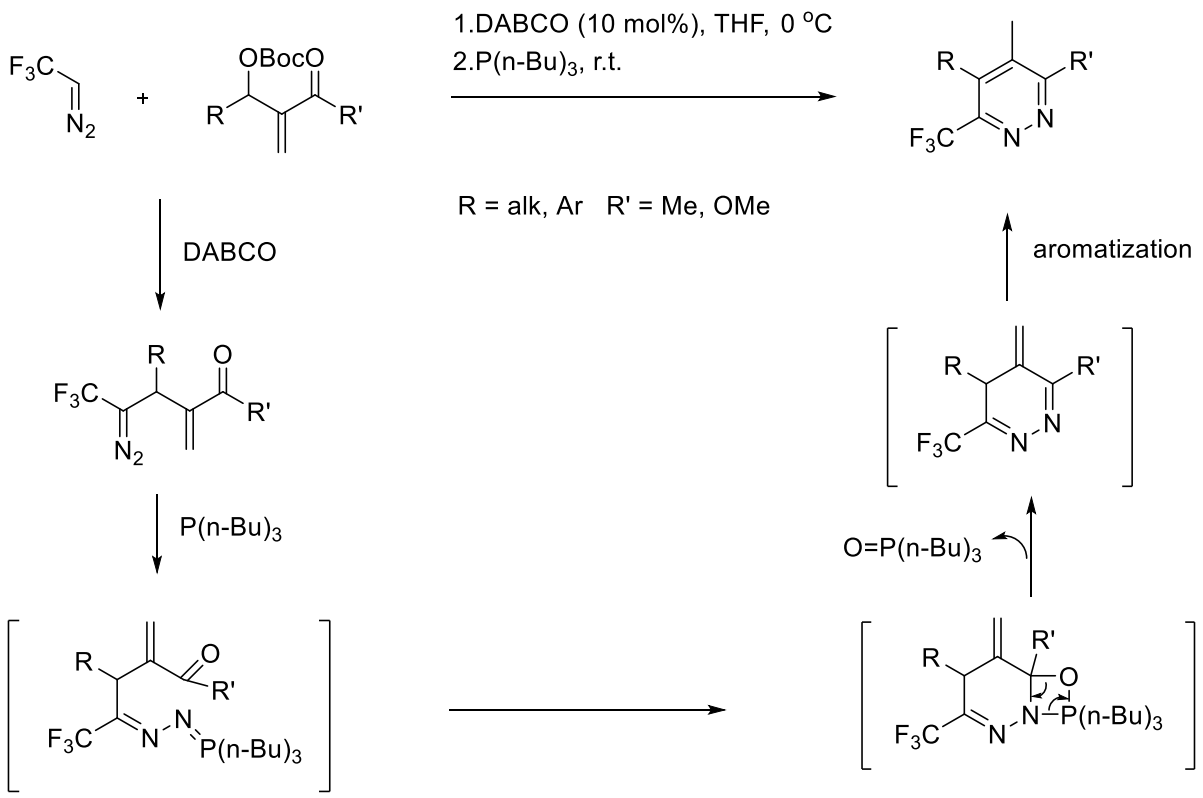
cascade (scheme 3-58).[188]



scheme 3-58

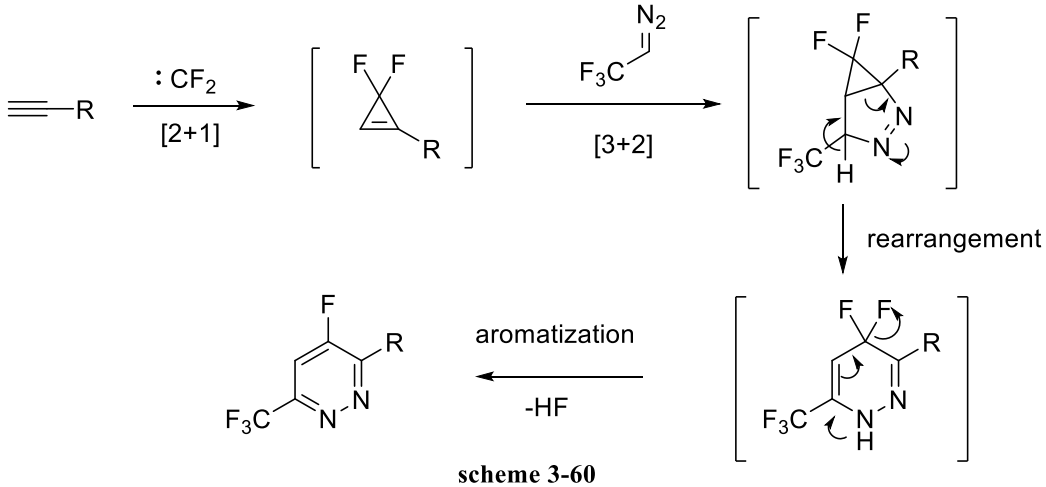
In 2014, Zhu *et al.* reported a one-pot synthesis of (trifluoromethyl)pyridazines from (trifluoromethyl) diazomethane and carbonates (scheme 3-59).[189]

[188] Z. Ding, L. Ju, Y. Yang, X. An, Y. Zhou, R. Li, H. Tang, C. Ding, Z. Zhan, *J. Org. Chem*. **2016**, *81*, 3936–3941
[189] H. Mao, A. Lin, Z. Tang, H. Hu, C. Zhu, Y. Cheng, *Chem. Eur. J.* **2014**, *20*, 2454–2458.



scheme 3-59

In 2017, J. Cossy *et al.* reported the synthesis of α-(trifluoromethyl)pyridazines by using a [2+1]/[3+2]-cycloaddition sequence between a terminal alkyne, a difluorocarbene and (trifluoromethyl)diazomethane (scheme3-60).[190]

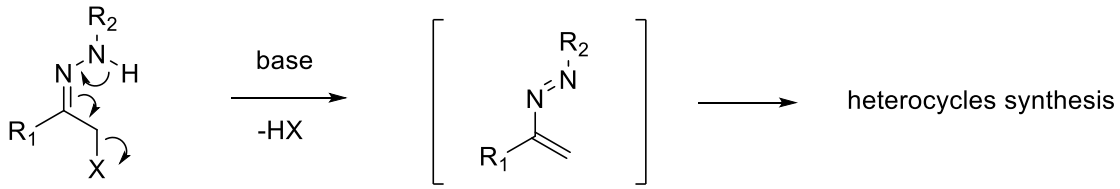


scheme 3-60

[190] A. Feraldi-Xypolia, G. Fredj, G. Tran, T. Tsuchiya, J. Vors, P. Mykhailiuk, D. Pardo, J. Cossy, *Asian J. Org. Chem.* **2017**, *6*, 927–935.

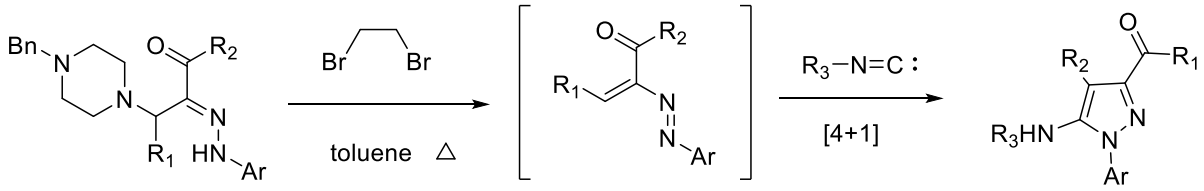
2.4.2 Presentation of our strategy

More interestingly, aminohydrazones such as III-1 represent potential starting materials for the generation of reactive fluorinated azoalkenes. Azoalkenes are usually obtained under basic treatment by means of 1,4-elimination of a good leaving group X (frequently chloride or bromide) in the α-position with respect to a hydrazone function (scheme 3-61).[191]



scheme 3-61

Azoalkenes may also be prepared under simple thermal elimination of amines from hydrazonoamines.[192] Our lab synthesized pyrazoles via a [4+1] cycloaddition of azoalkenes intermediates with isocyanides (scheme 3-62).



scheme 3-62

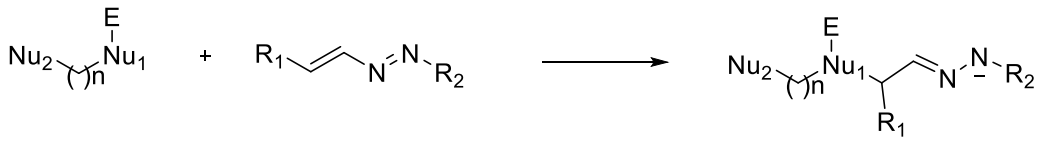
Due to substituted electron-withdrawing groups (esters and ketones tethered on N or carbon atoms) which favour the stability and enhance the electrophilic character of the heterodiene system, azoalkenes have been widely described as efficient Michael acceptors.[193] The typical

[191] For selected recent examples: (a) L. Wei and C. Wang, *Chem. Commun.*, **2015**, *51*, 15374–15377; (b) O. Attanasi, P. Filippone, A. Mei and S. Santeusanio, *Synthesis*, **1984**, 671–672; (c) V. Atlan, C. Buron and L. Kaim, *Synlett*, **2000**, 489–490.

[192] For the generation of azoalkenes from aminohydrazones, see: (a) W. Ried and G. Kiel, *Liebigs Ann. Chem.*, **1958**, *616*, 108–124; (b) V. Atlan, L. Elkaim, L. Grimaud and N. Jana, *Synlett*, **2002**, 352–354; (c) V. Baillez, L. Elkaïm and V. Michaut, *Synth. Commun.*, **2004**, *34*, 109–118

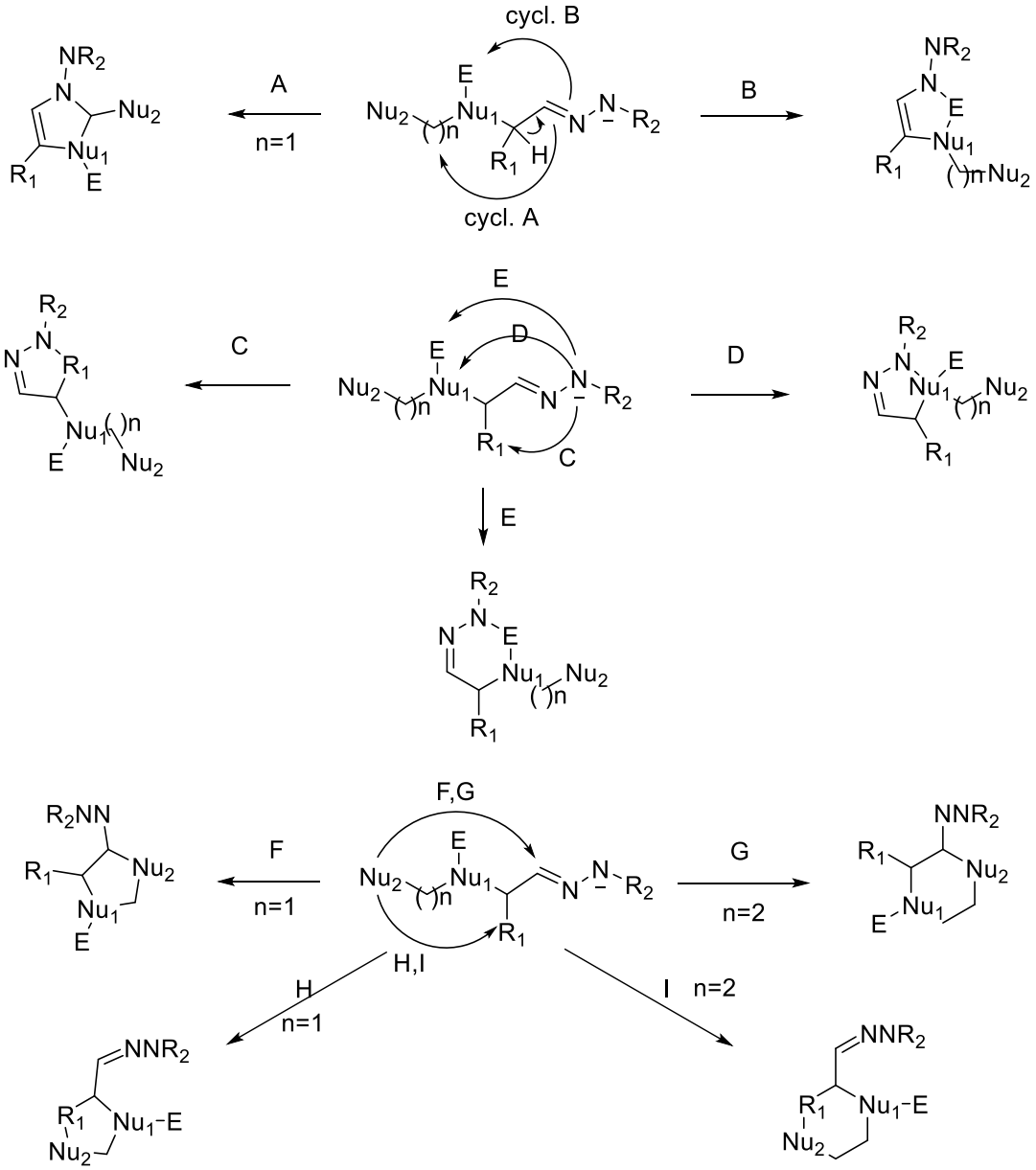
[193] O. Attanasi, L. Crescentini, G. Favi, P. Filippone, F. Mantellini, F. Perrulli and S. Santeusanio, *Eur. J. Org. Chem.*, **2009**, 3109–3127

reaction of azoalkenes is region-selective nucleophilic attack at the terminal carbon atom in the 4-position of the heterodiene system by a variety of carbon and hetero nucleophiles (Nu_1, Scheme 3-63). These Michael-type 1,4-additions produce highly functionalized hydrazones. In this key step, together with the attacking nucleophiles, we can introduce various other nucleophile (Nu_2, scheme 3-63) or electrophile (E, scheme 3-63) functions.



scheme 3-63

These functionalized hydrazones are potential starting materials for further interesting structural modifications through controlled regioselective reactions leading to complex heterocyclic systems. Nucleophilic sites can be either the nitrogen atom from the azo group (A, B, C, D, E), or the new group (Nu_2) inserted in the Michael additions (F, G, H, I). On the other hand, the electrophiles involved can be the hydrazone C=N bond (F, G), the electron-withdrawing group (R_2) in the 4-position of the azo-ene systems (C, H, I) or a new group (E) inserted in the Michael additions (B, E) (scheme 3-64).[193]

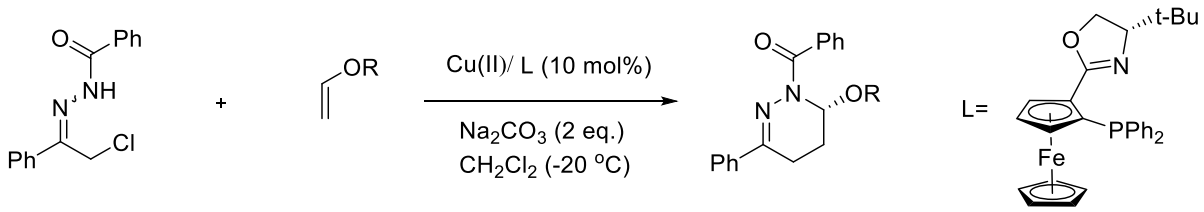


scheme 3-64

The electron-withdrawing groups on the terminal atoms of the azo-ene system also make azoalkenes very good partners in the hetero-Diels–Alder reactions.[194] In 2015, Wang and co-workers described a highly efficient Cu(II)-catalyzed enantioselective inverse-electron-demand aza-Diels-Alder reaction of in situ formed azoalkenes with enol ethers. This methodology provides a facile entry to biologically important and enantioenriched tetrahydropyridazine analogues in good yield (up to 95 % yield) with good to excellent

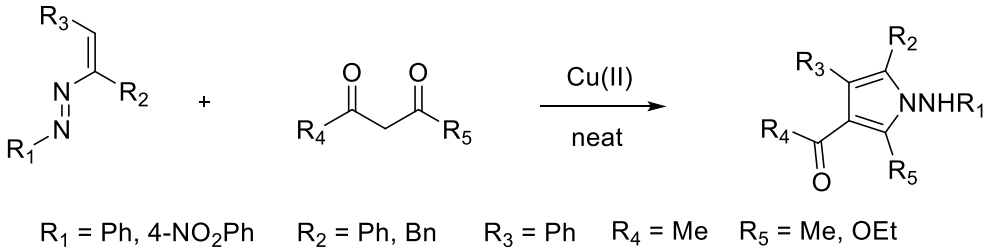
[194] A. Lemos, *Molecules*, **2009**, *14*, 4098–4119.

enantioselectivity (up to 94 % *ee*) (scheme 3-65).[195]



scheme 3-65

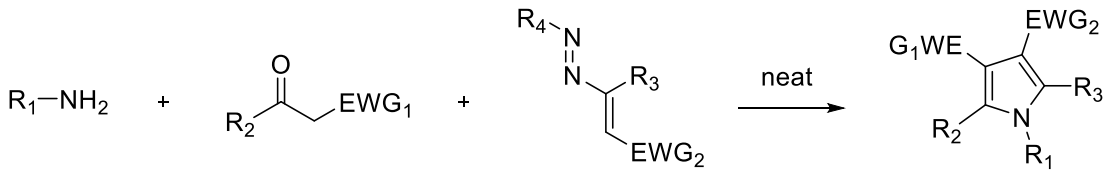
The additions of β-ketoesters to azoalkenes substituted by electron-withdrawing groups are known to afford pyrroles or 1,2-diazines according to the nature and position of the electron-withdrawing groups (scheme 3-66).[196]



scheme 3-66

In 2011, Favi *et al.* reported a synthesis of polysubstituted pyrroles through a sequential three-component reaction of primary aliphatic amines, active methylene compounds, and azoalkenes (scheme 3-67).[197]

[195] L. Wei and C. Wang, *Chem. Commun.*, **2015**, *51*, 15374–15377
[196] O. Attanasi, P. Bonifazi, E. Foresti and G. Pradella, *J. Org. Chem.*, **1982**, *47*, 684–687.
[197] O. Attanasi, G. Favi, F. Mantellini, G. Moscatelli, and S. Santeusanio, *J. Org. Chem.* **2011**, *76*, 2860–2866



R_1 = alkyl, benzyl, allyl R_2 = Me, Et R_3 = Me R_4 = t-buOCO

EWG_1 = COOMe,COOEt, SO_2Ph... EWG_2 = $CONMe_2$

scheme 3-67

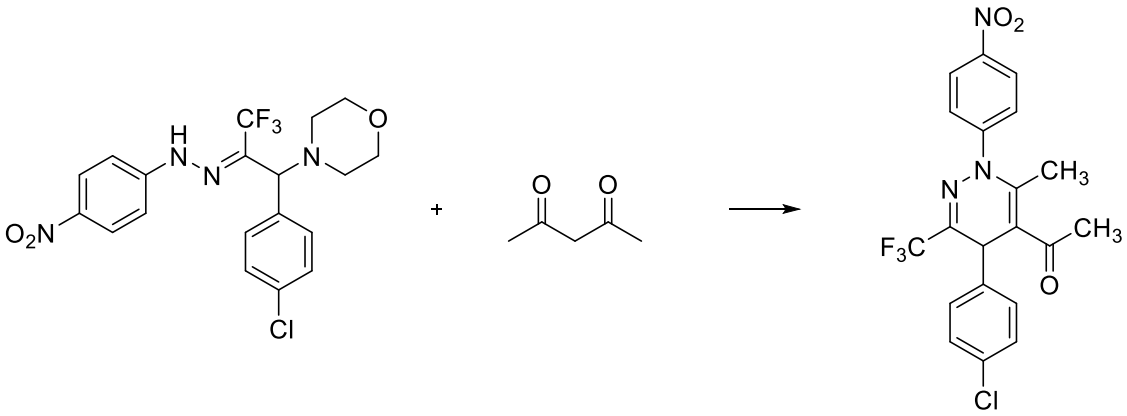
We were interested in examining whether the trifluoromethyl group might be activating enough to allow a Michael cyclization cascade. Thus, we decided to react directly the morpholine Mannich adduct **III-1** using acetylacetone as a solvent. Elimination of amines from the Mannich-type adducts of hydrazones is usually observed for amine partners with a rather low boiling point in order to limit the reverse Michael addition. Thus the temperature was fixed at 130 °C, hoping that the Mannich–azoalkene equilibrium could be shifted by the formation of an enamine intermediate between the morpholine and the diketone.

Rewardingly heating **III-1** in acetylacetone (0.2 M) at 130 °C for 12 hours afforded 4-hydropyridazine in 58% isolated yields (Table 3-4, entry 1).

2.4.3 Optimization of reaction conditions

In order to optimize the conditions, the following trials were performed:

Table 3-4 Optimization of reaction conditions



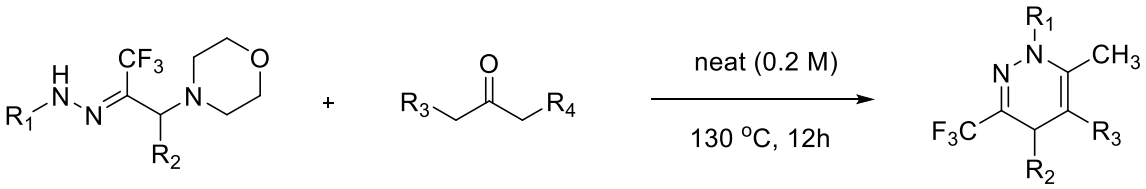
entry	ketone	solvent	Lewis acid	temperature	yield
1	5 equiv.	toluene	$Cu(OAc)_2$ 1.2 equiv	reflux, 24 h	trace
2	as solvent	neat	$Cu(OAc)_2$ 1.2 equiv.	130 ^oC, 12 h	83 %
3	as solvent	neat	$Cu(OAc)_2$ 0.6 equiv.	130 ^oC, 12 h	79 %
4	as solvent	neat	-	130 ^oC, 12 h	80 %

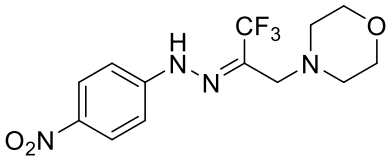
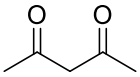
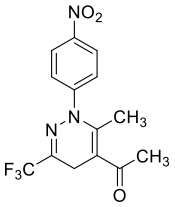
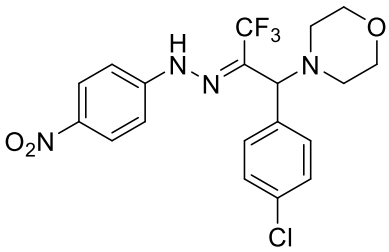
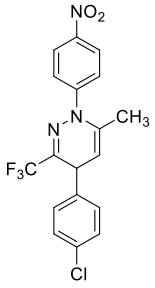
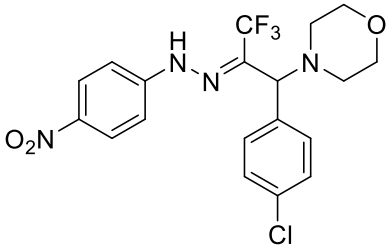
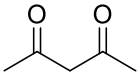
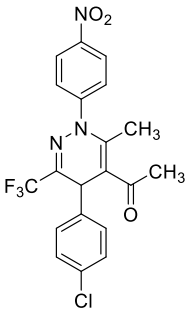
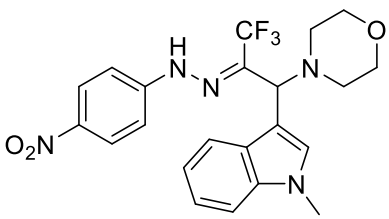
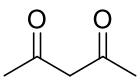
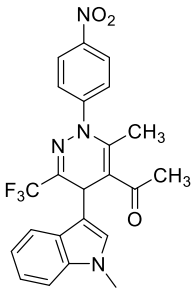
According to the literature, Cu(II) can coordinate with morpholine to accelerate its thermal elimination. However, we found that the reaction could work nicely even without Cu(II). Using ketone as the solvent and heating the mixture to 130 ^oC for 12 h is a suitable reaction condition.

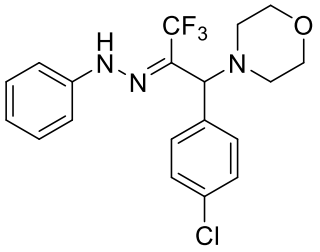
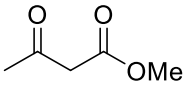
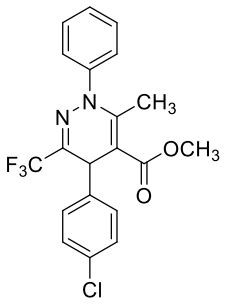
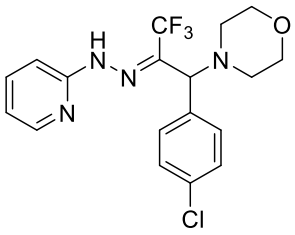
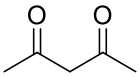
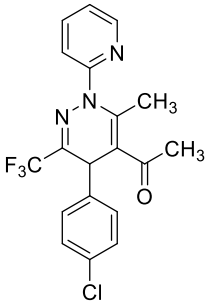
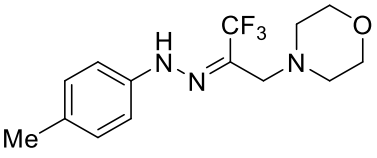
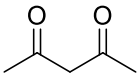
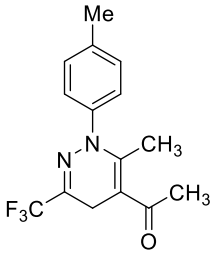
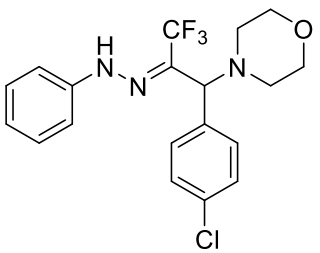
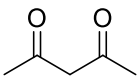
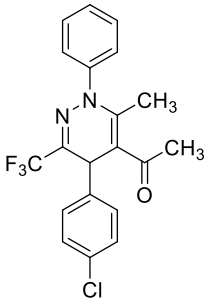
2.4.4 Study of the reaction scope

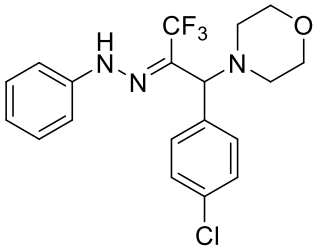
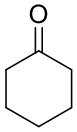
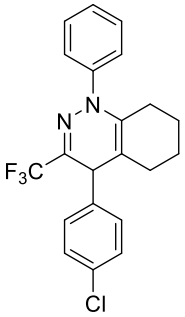
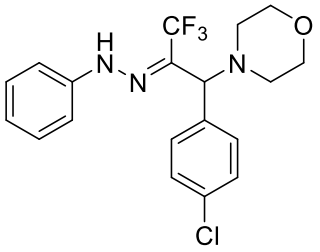
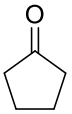
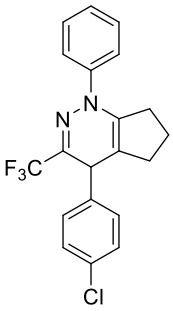
Several Mannich adducts were then treated with ketones under the optimized conditions leading to diazines in moderate to excellent yields (Table 3-5).

Table 3-5 Various 4-Hydropyridazines from Mannich adducts



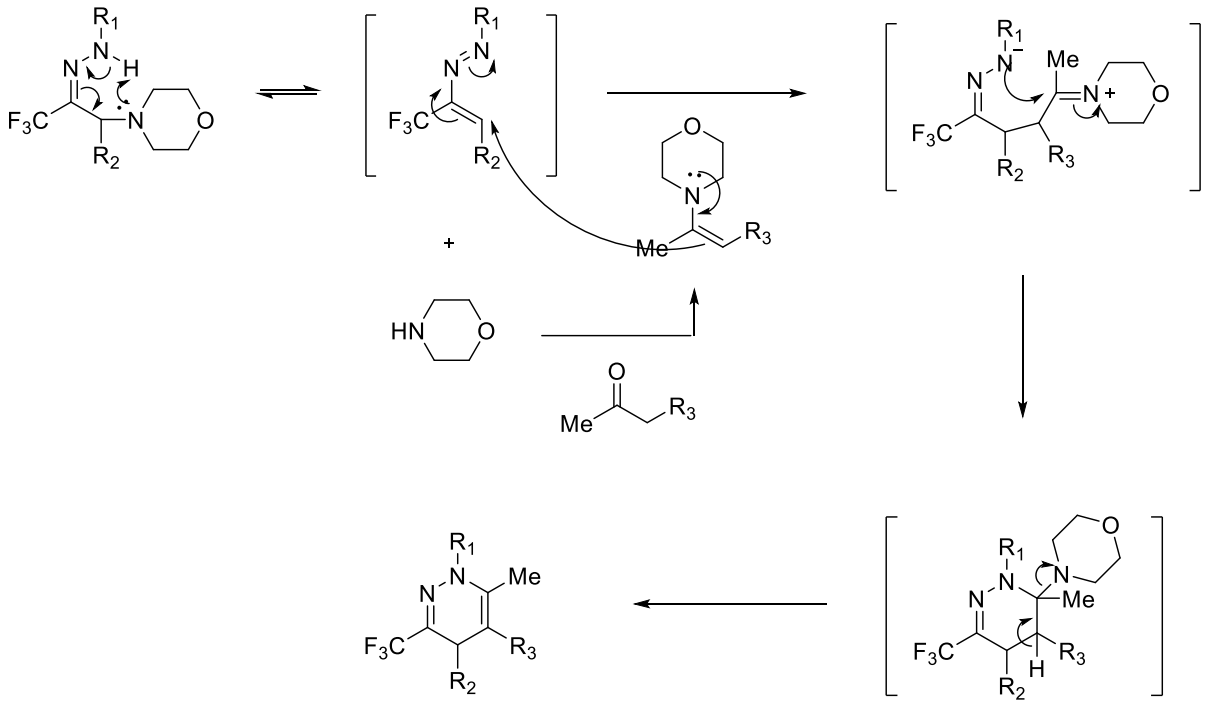
entry	Mannich adduct	ketone	Product & yield[a]
1	 **III-1**		 **III-26** 58 %
2	 **III-2**		 **III-27** 34 %[b]
3	 **III-2**		 **III-28** 80 %
4	 **III-9**		 **III-29** 92 %

5	 **III-12**		 **III-30** 90 %
6	 **III-16**		 **III-31** 56 %
7	 **III-13**		 **III-32** 77 %
8	 **III-12**		 **III-33** 71 %

9	 **III-12**		 **III-34** 68 %
10	 **III-12**		 **III-35** 90 %

a. Isolated yields after column chromatography on silica gel. ***b***. The reaction was performed under microwave conditions at 130 °C for one hour.

The reaction does not seem to depend much on the nature of the starting arylhydrazines as shown by the good yields obtained using nitrophenyl (Table 3-4, entries 1–4), phenyl (Table 3-4, entries 5 and 8–10), methylphenyl(Table 3-4, entry 7) or pyridyl (Table 3-4, entry 6) substituents. The formation of **III-27** in a low 34% yield may be probably explained by the required shorter reaction time associated with the use of microwave conditions. The examples obtained with cyclopentanone and cyclohexanone (Table 3-4, entries 9 and 10) are indicative of the efficiency of the process and further support our initial mechanistic hypotheses: thermal elimination of morpholine allows the formation of an enamine intermediate which is engaged in a Michael addition with the azoalkene. Cyclization and elimination of morpholine finally afford 4-Hydropyridazine. (Scheme 3-68).



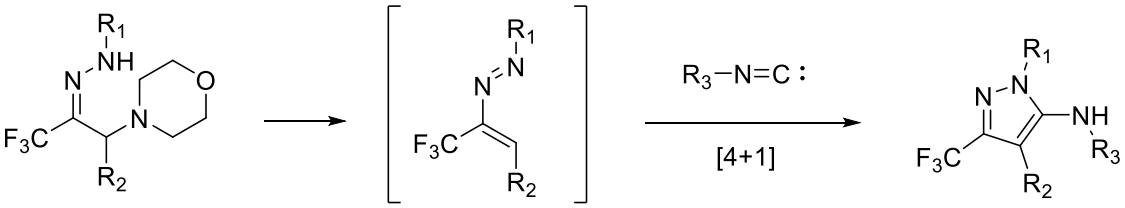
Scheme 3-68 proposed mechanism

3 Conclusions and perspectives

The present study demonstrates the interest in trifluoroacetaldehyde NH-aryl hydrazones as the carbon centered nucleophile in Mannich reactions. The electron-withdrawing properties of the trifluoromethyl group are strongly associated with the success of the couplings allowing various NH-aryl hydrazone derivatives to react with formaldehydes as well as different aromatic aldehydes. The resulting Mannich adducts are valuable starting materials for the generation of azoalkene intermediates and the preparation of trifluoromethyl substituted heterocycles.

Considering the potential of azoalkene intermediates in the construction of five- and six-membered hetero ring systems, we can probably extent this work to [4+1] cycloaddition reaction with isocyanide as we published for non fluorinated system[198] (scheme 3-69).

[198] V. Atlan, L. Elkaïm, C. Buron, *Synlett* **2000**, 489.



scheme 3-69

Chapter IV A novel Tsuji-Trost reaction towards naphthalene

For the work described in this chapter, it's a part of the project; I cooperate with my colleague Mansour Dolè Kerim to finish this project. Some experiment results from him were all clearly declared in the text. This work has been published on *Chem. Commun.*

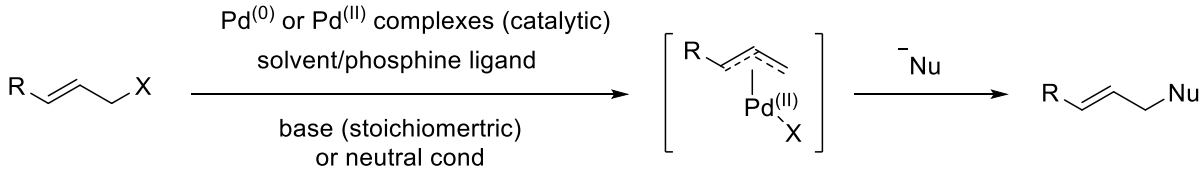
Mansour Dole Kerim[a], **Shuanglong Jia**[a], Chrysoula Theodorakidou[a], Sebastien Prevost* and Laurent El Kaim*, *Chem. Commun.*, **2018**, *54*, 10917 - 10920

1 Introduction

1.1 Tsuji-Trost reaction

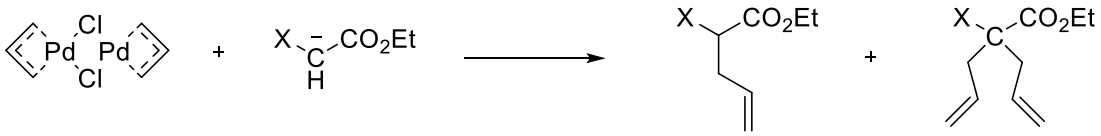
1.1.1 History of Tsuji-Trost reaction

The Pd-catalyzed allylation of carbon nucleophiles with allylic compounds via π-allylpalladium complexes is called the Tsuji-Trost reaction (scheme 4-1).



scheme 4-1

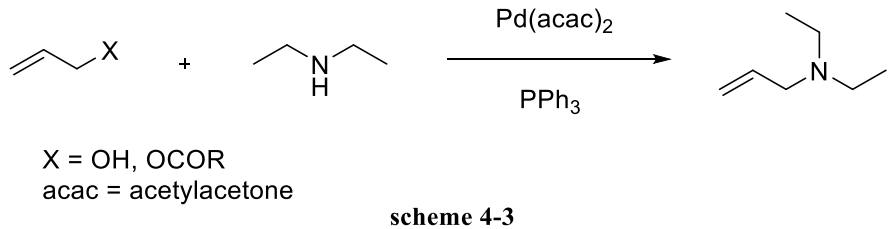
In 1965, Tsuji group first demonstrated that π-allylpalladium chloride could be substituted with certain nucleophiles such as the anions derived from diethyl malonate and ethyl acetoacetate (scheme 4-2).[199]



scheme 4-2

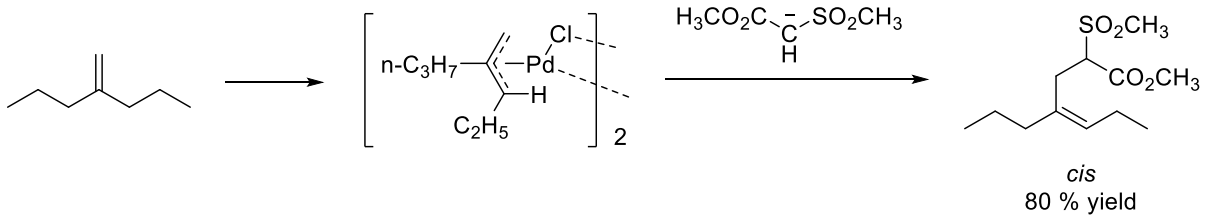
Soon after this initial report, the catalytic version of this transformation was developed by Walker's group. Only a catalytic amount of palladium complex was used in order to trigger the reaction (scheme 4-3).[200]

[199] J. Tsuji, H. Takahashi, M. Morikawa, *Tetrahedron Lett.* **1965**, *49*, 4387.
[200] E. Atkins, E. Walker, M. Manyk, *Tetrahedron Lett*. **1970**, 3821.



scheme 4-3

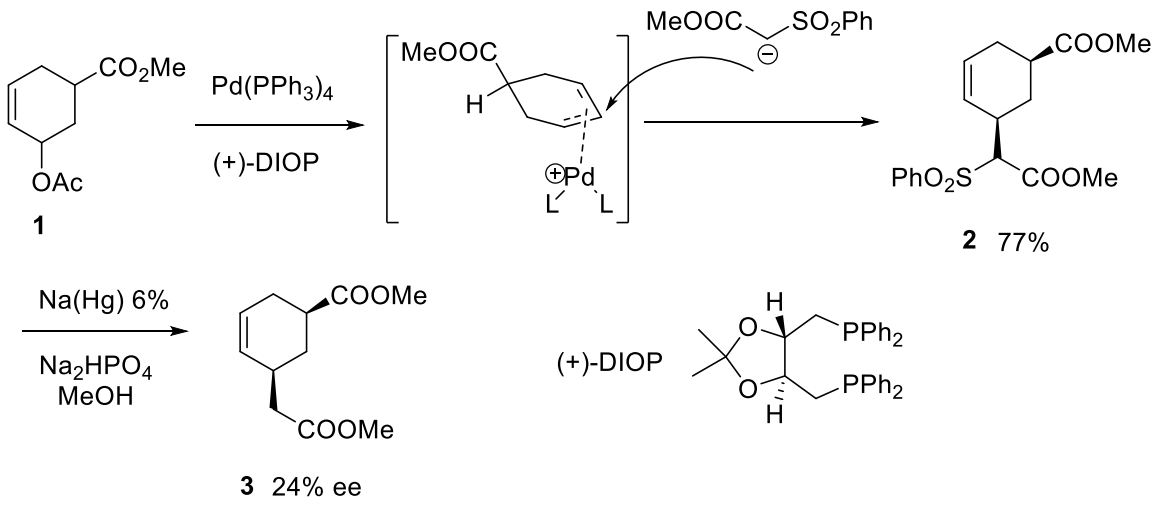
In 1973, Trost group first reported that alkyl-substituted π-allylpalladium complexes could be alkylated with soft carbon nucleophiles with complete regio- and stereoselectivity. However, hard nucleophiles (e.g., alkylithiums, alkylmagnesium halides) failed to react (scheme 4-4).[201]



scheme 4-4

Then, the Trost group developed asymmetric variations of allylic alkylation reaction by selecting proper chiral ligands (scheme 4-5).[202] Chiral ligands are known to enhance both the enantioselectivity and diastereoselectivity under mild conditions, which contributed greatly to expand the application of this reaction.

[201] M. Trost, J. Fullerton, *J. Am. Chem. Soc.* **1973**, *95*, 292-294.
[202] M. Trost, E. Strege, *J. Am. Chem. Soc.* **1977**, 1649.



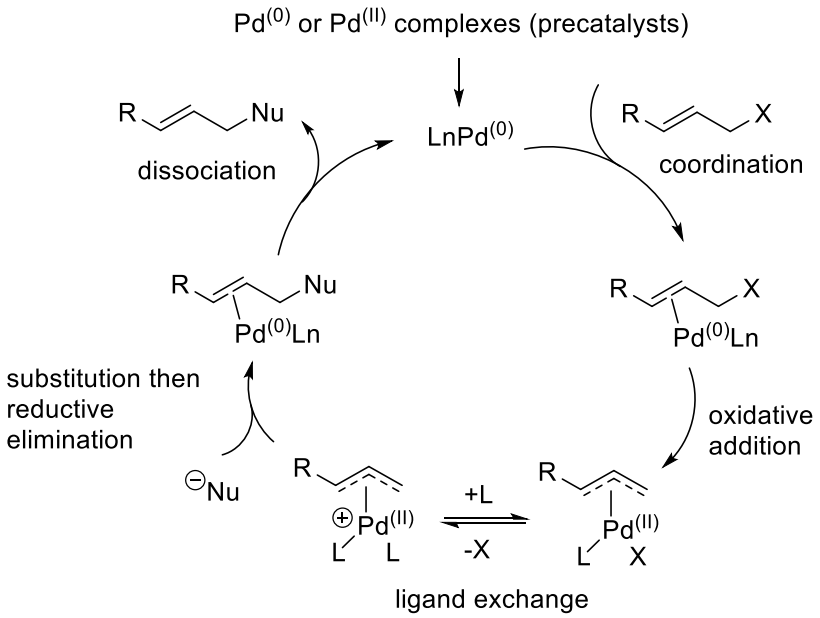
scheme 4-5

After that, this allylation reaction was greatly explored by chemists, because allyl moieties are easily transformed into various versatile functional groups.[203]

1.1.2 Mechanism of Tsuji-Trost reaction

It's proposed that the palladium coordinates the double bond of the allyl group forming a η2 π-allyl-Pd^0 complex. The next step is oxidative addition in which the leaving group is expelled with inversion of configuration and a η3 π-allyl-Pd^{II} is created (also called ionization). The nucleophile then adds to the allyl group regenerating the η2 π-allyl-Pd^0 complex. Finally, dissociation of the active species would occur to release both the desired product and the palladium which gets involved again in the catalytic cycle (scheme 4-6).[204]

[203] N. Mishra, S. Sharma, J. Park, S. Han, and I. Kim, *ACS Catal.*, **2017**, *7* (4), pp 2821–2847
[204] M. Trost, T. Zhang, D. Sieber, *Chem. Sci.* **2010**, *1*, 427–440.



scheme 4-6

1.1.3 Reaction parameters

Many parameters affect the reaction progress, the stereochemistry as well as the regioselectivity.

1.1.3.1 Metal catalyst

A wide variety of metal complexes had been employed in Tsuji-Trost type reaction such as: palladium, [205] nickel, [206] iridium, [207] platinum, [208] rhodium, [209] iron, [210] ruthenium, [211] molybdenum[212] and tungsten[213] complexes.

The choice of the metal complex controls greatly the reaction's regioselectivity. For example,

[205] (a) M. Trost, L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395. (b) M. Trost, R. Machacek, A. Aponick, Acc. *Chem. Res.* **2006**, *39*, 747.
[206] (a) T. Hiyama, N. Wakasa, *Tetrahedron Lett.* **1985**, *26*, 3259. (b) C. Sha, H. Jiang, J. Mao, A. Bellomo, A. Jeong, J. Walsh, *Angew. Chem. Int. Ed.* **2016**, *55*, 1070.
[207] A. Leitner, C. Shu, F. Hartwig, *Org. Lett.* **2005**, *7*, 1093.
[208] M. Trost, K. Chang, *Synthesis* **1993**, *8*, 824.
[209] A. Evans, D. Nelson, *J. Am. Chem. Soc.* **1998**, *120*, 5581.
[210] C. Bolm, J. Legros, L. Paih,L. Zani, *Chem. Rev.* **2004**, *104*, 6217.
[211] W. Zhang, A. Mistsudo, T. Kondo, J. Watanabe, *Organomet. Chem.* **1993**, *450*, 197.
[212] M. Trost, *Org. Process Res. Dev.* **2012**, *16*, 185.
[213] M. Trost, L. Crawley, *Chem. Rev.* **2003**, *103*, 2921.

the reaction of 2-methyl-propenyl acetate with PhMgCl in the presence of $NiCl_2$/dppf allows substitution selectively at the most substituted carbon atom, while using palladium catalyst ($PdCl_2$/dppf) substitution occurrs at the least substituted carbon atom (figure 4-1).

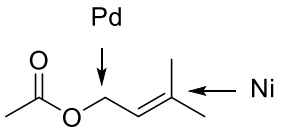


figure 4-1

1.1.3.2 Ligand

The ligands could be monodentate, bidentate or chiral. They might influence the reaction speed, the control of both regioselectivity and enantioselectivity of the reaction.

Usually, π-acceptor ligands such as phosphines enhance the nucleophilic substitution by attracting the electrons of the metal which increases the positive charge on the allylic moiety favoring the substitution.

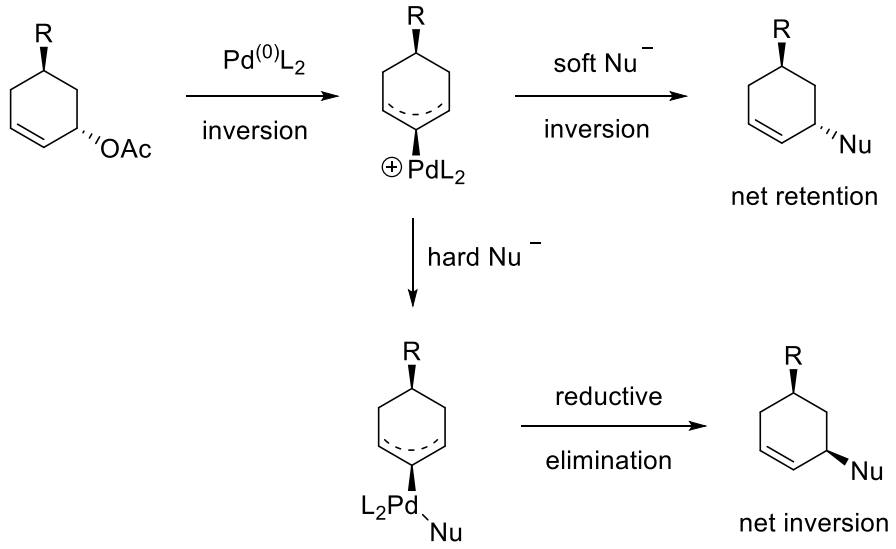
Enantioselective extensions of Tsuji-Trost reaction were successfully achieved by introducing catalytic amounts of chiral ligands. In 1977, the first enantioselective Pd-catalyzed allylation reaction was reported by Trost group.[4] Where the racemic mixture **1** was reacted with the nucleophile, sodium salt of methyl phenylsulfonylacetate, using $Pd(PPh_3)_4$ and the chiral ligand (+)-DIOP as the catalytic system giving **2** in 77% yield. After desulfonylation, the final product **3** was obtained with 24 % ee (scheme 4-5).

Such achievement was the foundation for many asymmetric approaches of Tsuji-Trost reaction. [214] BINAP and Trost ligands are the classically used chiral ligands in palladium-catalyzed asymmetric allylic alkylations.

[214] Y. Hong, M. Stoltz, *Eur. J. Org. Chem.* **2013**, *19*, 2745.

1.1.3.3 Nature of the nucleophile

Nucleophiles, generated in situ as a result of deprotonation using a base, can be divided into two categories: “hard” and “soft” nucleophiles. “Hard” nucleophiles, defined as those derived from conjugate acids whose pKa > 25, attack the metal center via transmetallation followed by reductive elimination lead to retention of configuration of the complex;[215] Whereas for the soft nucleophiles such as: enolates, their conjugate acids whose pKa < 25, they attack the carbon of the allyl group, that may cause inversion of configuration of the π-allyl cationic complex.[216] In both cases, the oxidative addition step of palladium takes place with inversion of configuration (scheme 4-7).



scheme 4-7

1.1.3.4 Allylic reagent

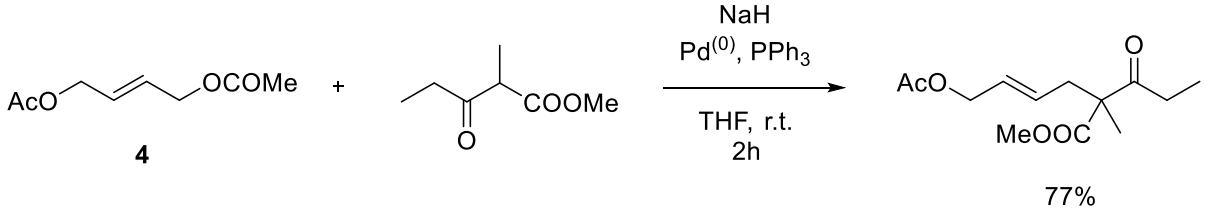
Both cyclic and acyclic substrates are successfully employed in Tsuji-Trost reaction. The most commonly used substrates are the allylic acetates. Moreover, several nucleophiles are also utilized such as: halogens,[217] epoxides,[218] carbonates[219] or alcohols[220]. In case of using

[215] M. Trost, R. Verhoeven, M. Fortunak, *Tetrahedron Lett.***1979**, *20*, 2301.
[216] M. Trost, A. Thaisrivongs, *J. Am. Chem. Soc.* **2008**, *130*, 14092.
[217] K. Sheffy, K. Stille, *J. Am. Chem. Soc.* **1983**, *105*, 7173.
[218] J. Tsuji, *Tetrahedron* **1986**, *42*, 4361.

allyl carbonates, the carbonate group undergoes decarboxylation, in the process a sufficiently basic alkoxide is formed so no extra base is needed (scheme 4-8).

scheme 4-8

When allylic reagent possesses two leaving groups, the substitution would take place selectively at the more reactive site for the reaction. For instance, when using the allyl substrate **4**, nucleophilic substitution occurred at the carbon attached to the more reactive carbonate group affording selectively single product with *E*-configuration (scheme 4-9).



scheme 4-9

1.2 Naphthalene

1.2.1 A brief overview of naphthalene

There are numerous biologically active natural products possessing a naphthalene or naphthoquinone core.[221] For instance, (S)-gossypol (figure 4-2) is known to be an oral antifertility agent in men and male animals. It shows as well potential for the treatment of HIV infections, diabetic complications and cancer.[222]

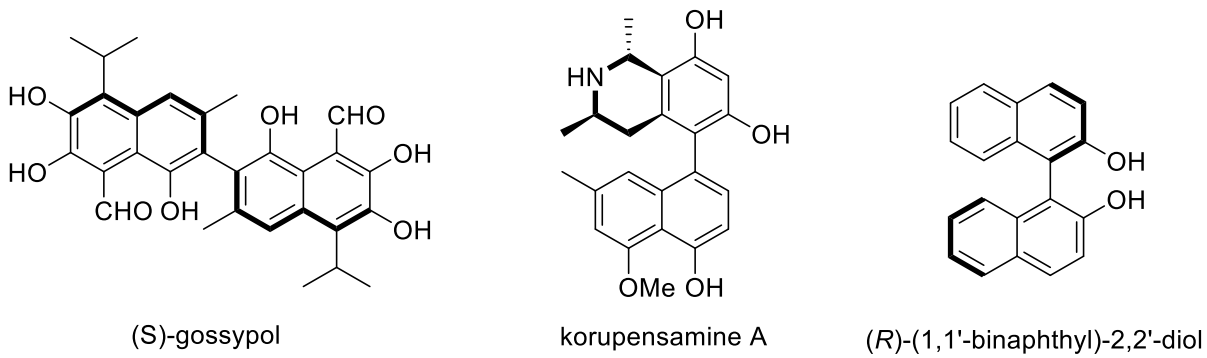
---

[219] (a) J. Tsuji, I. Shimizu, I. Minami, K. Ohashi, T. Sugiura, K. Takahashi, *J. Org. Chem.* **1985**, *50*, 1523. (b) J. Tsuji, I. Shimizu, I. Minami, Y. Ohashi, *Tetrahedron Lett.* **1982**, *23*, 4809.
[220] F. Raffaella, P. Luca, *Current Organic Chemistry*, **2015**, *19*, 106-120
[221] H. Thomson, *Naturally Occurring Quinones IV. Recent Advances,* 4th ed. Chapman & Hall: London, **1997**
[222] I. Meyers, J. Willemsen, *Chem. Commun.* **1997**, 1573–1574.

Other compounds possessing prominent naphthalene motifs are the biaryl naphthylisoquinoline alkaloids such as korupensamine A (figure 4-2), which has anti-malarial properties.[223]

The atropisomers of (1,1'-binaphthyl)-2,2'-diol and its derivatives (figure 4-2) have been widely used in asymmetric synthesis as chiral auxiliaries or ligands. These binaphthols have demonstrated excellent chiral induction in a number of organic transformations ranging from Diels–Alder cycloadditions to polymerisation reactions.[224]

In addition, substituted naphthalene derivatives are frequently employed as starting materials for the preparation of more complex polynuclear aromatic ring systems.[225] Hence, development of new methods for the efficient synthesis of substituted naphthalenes has always been attractive.



(S)-gossypol korupensamine A (*R*)-(1,1'-binaphthyl)-2,2'-diol

figure 4-2

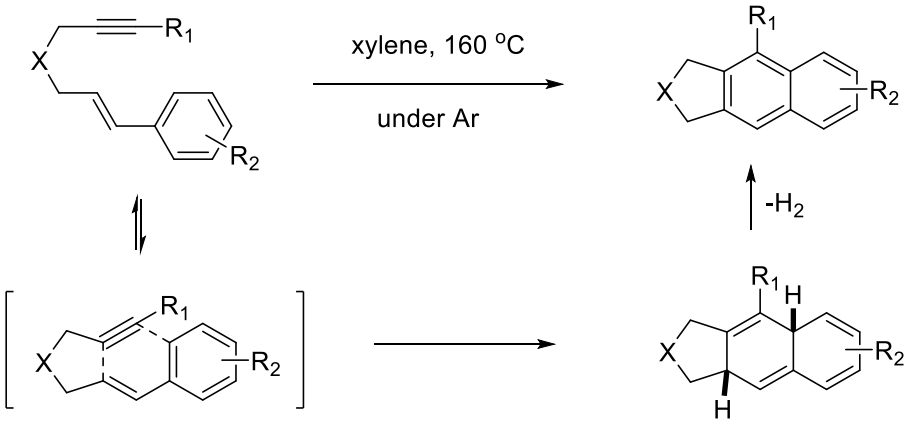
1.2.2 Synthesis of naphthalene

1.2.2.1 Diels-Alder reactions

In 2011, Matsubara and co-workers developed a dehydrogenative Diels-Alder reaction to

[223] F. Hallock, P. Manfredi, W. Blunt,H. Cardellina, M. Schaffer,P. Gulden,G. Bringmann,Y. Lee,J. Clardy,G. Francois, R. Boyd, *J. Org. Chem.* **1994**, *59*, 6349–6355.
[224] a) H. Tye, *J. Chem. Soc., Perkin Trans. 1* **2000**, 275–298. b) L. Pu, *Chem. Rev.* **1998**, *98*, 2405–2494. c) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley: New York, **1994**
[225] B. de Koning, L. Rousseau, L. van Otterlo, *Tetrahedron*, **2002**, *59*, 7-36.

produce polyaromatic cycloadducts from dieneynes (scheme 4-10).[226]



X = NTs, O, CH_2 R_1 = H, Ph, COOEt, $SiMe_3$

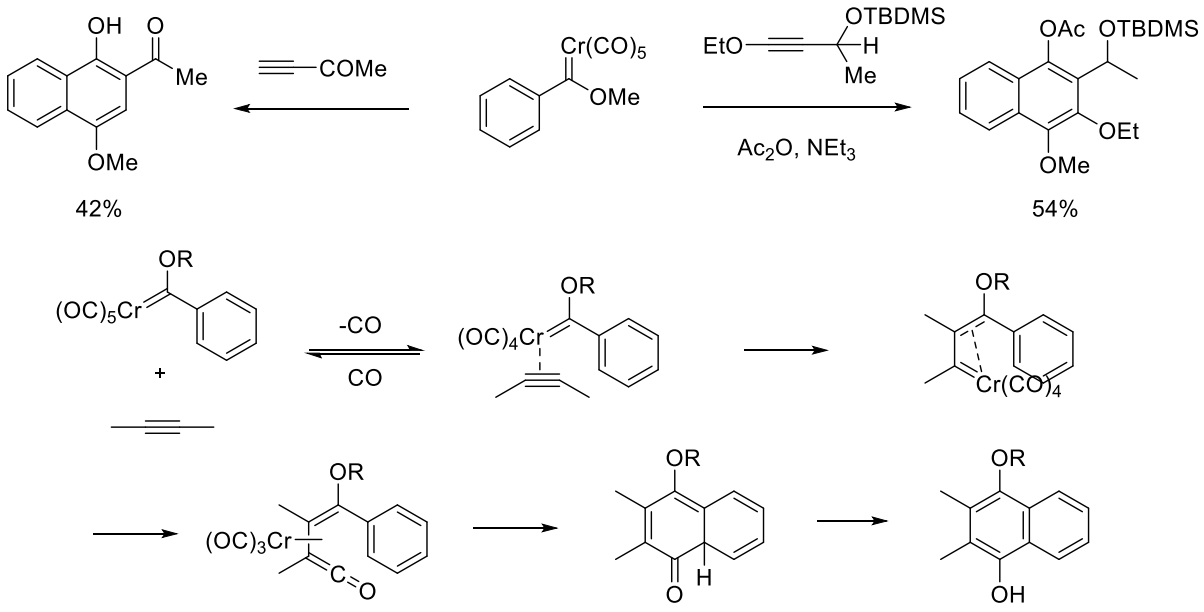
R_2 = H, F , CF_3, OMe, NMe_2....

scheme 4-10

1.2.2.2 Annulation via Fischer carbenes (Dotz reactions)

In 1986, Yamashita and Toy developed a method to synthesis substituted naphthalene from a phenyl chromium carbene complex and alkyne bearing electron withdrawing groups such as conjugated carbonyl groups. However, only moderate yields were observed, a simplified mechanism was shown as scheme 4-11.[227]

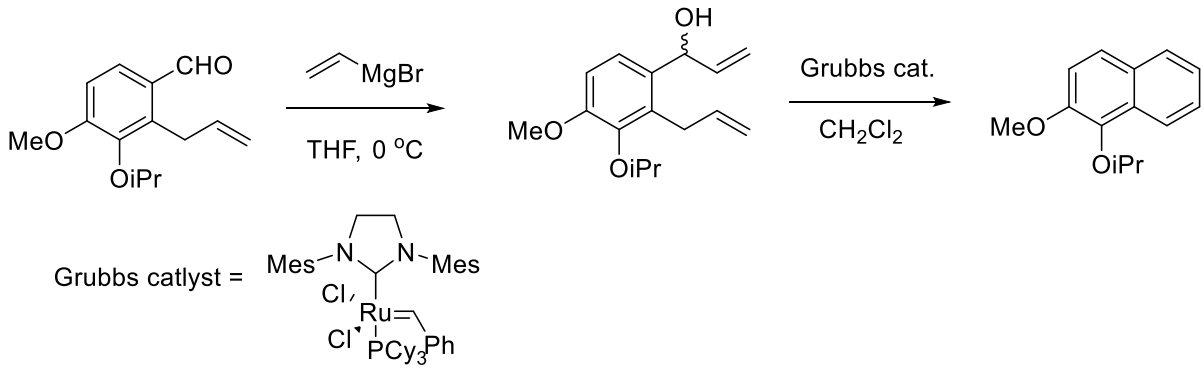
[226] O. Takuya, K. Takuya and M. Seijiro, *Org. lett.*, **2011**, *13*, 5390–5393
[227] A. Yamashita and A. Toy, *Tetrahedron Lett.*, **1986**, *27*, 3471.



scheme 4-11

1.2.2.3 Ring-closing metathesis (RCM)

In 2003, Otterlo *et al.* synthesized a number of naphthols using the Grubbs' second-generation catalyst via RCM reaction (scheme 4-12).[228]

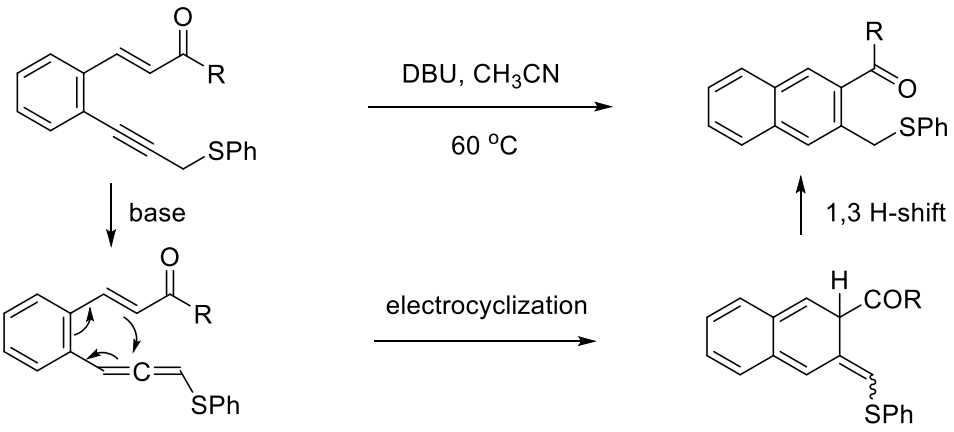


scheme 4-12

[228] W. Otterlo, E. Ngidi, E. Coyanis and C. Koning, *Tetrahedron Letters*, **2003** , *44*, 311–313

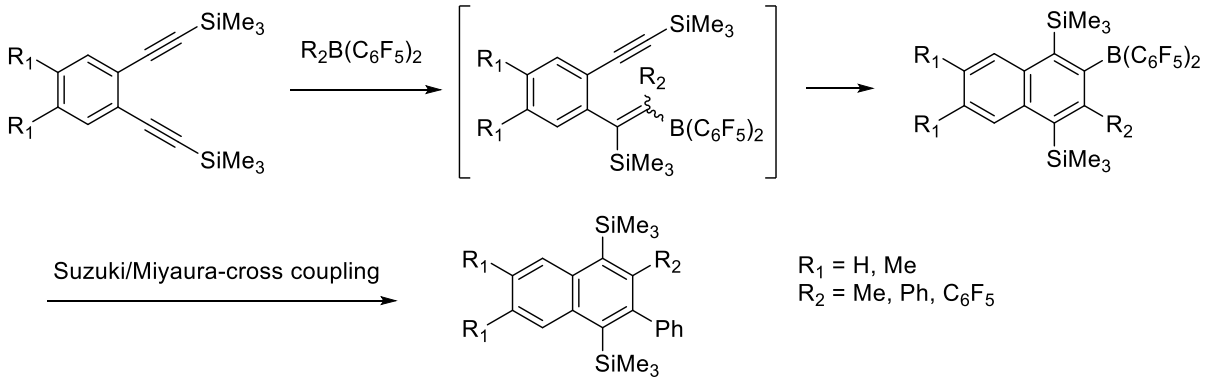
1.2.2.4 Cyclization of aromatic enynes or enediynes

In 2010, Zhou group developed a facile and efficient electrocyclization for the synthesis of naphthalene derivatives via sulfur-assisted propargyl-allenyl isomerization (scheme 4-13).[229]



scheme 4-13

In 2012, Erker *et al.* discovered a modern variant of the 1,1-carboboration reaction to prepare highly substituted, very bulky borylated naphthalene derivatives from readily available bis(alkynyl)arenes. These substrates can be functionalized by transition metal catalyzed cross-coupling reactions (scheme 4-14).[230]

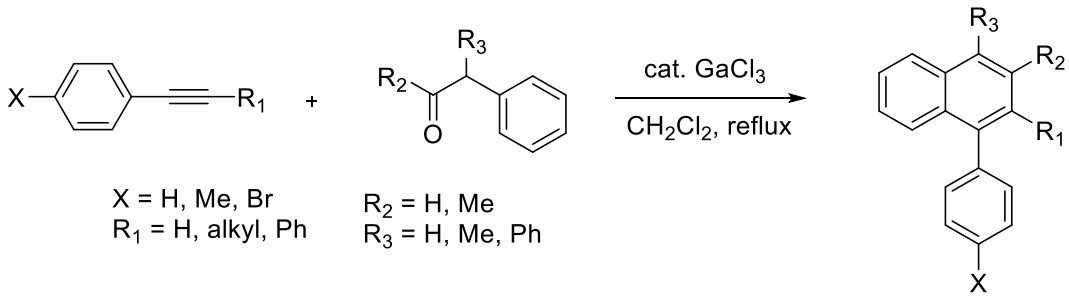


scheme 4-14

[229] H. Zhou, Y. Xing, J. Yao, and J. Chen, *Org. Lett.*, **2010**, *12*, 3674-3677
[230] R. Liedtke, M. Harhausen, R. Frohlich, G. Kehr, G. Erker, *Org. Lett.*, **2012**, *14*, 1448–1451

1.2.2.5 Annulations using alkynes

In 2002, Li group developed a new synthetic strategy to generate polysubstituted naphthalene derivatives with complete regioselectivity through the simple coupling of alkynes and phenyl acetaldehydes (and ketones) catalyzed by gallium trichloride under mild conditions. However, the scope, mechanism, and synthetic applications of this new reaction are still under investigation (scheme 4-15).[231]

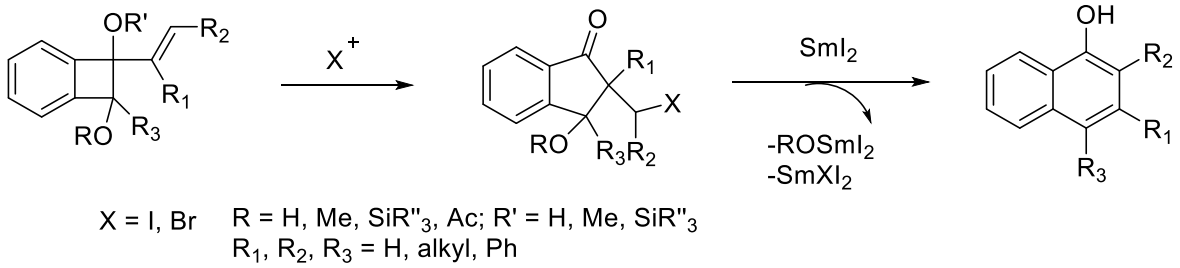


scheme 4-15

1.2.2.6 Rearrangements of strained rings

In 2006, Suzuki group described a facile synthesis of substituted naphthols by successive ring expansion of alkenyl benzocyclobutenol derivatives. The halonium ion (X^+) induces ring expansion of alkenyl benzocyclobutene (four-membered ring) to indanone (five-membered ring), which was promoted by SmI_2 to naphthol (six-membered ring) via intramolecular Barbier-type reaction with concomitant elimination of $ROSmI_2$ (scheme 4-16).[232]

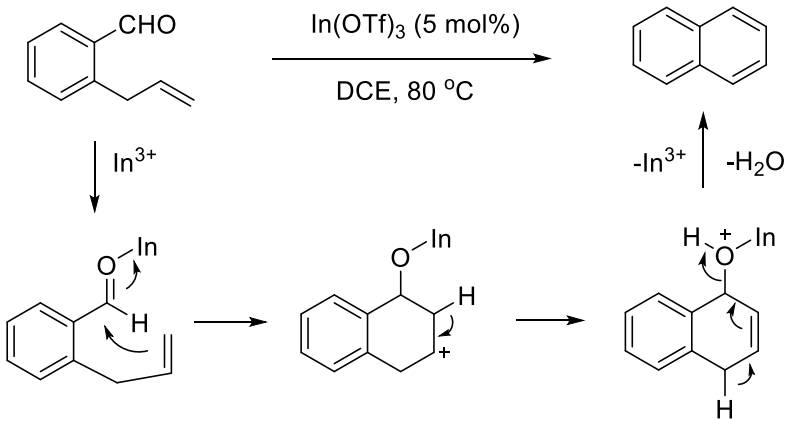
[231] G. Viswanathan, M. Wang, and C. Li, *Angew. Chem. Int. Ed.* **2002**, *41*, 2138-2141
[232] T. Hamura, T. Suzuki, T. Matsumoto, and K. Suzuki, *Angew. Chem. Int. Ed.* **2006**, *45*, 6294–6296



scheme 4-16

1.2.2.7 Lewis acid catalyzed cyclization

In 2011, Kuninobu *et al.* succeeded in synthesizing naphthalene derivatives via dehydrative intramolecular cycloaromatization. In these transformations, generally, $In(OTf)_3$ showed higher catalytic activities (scheme 4-17).[233]

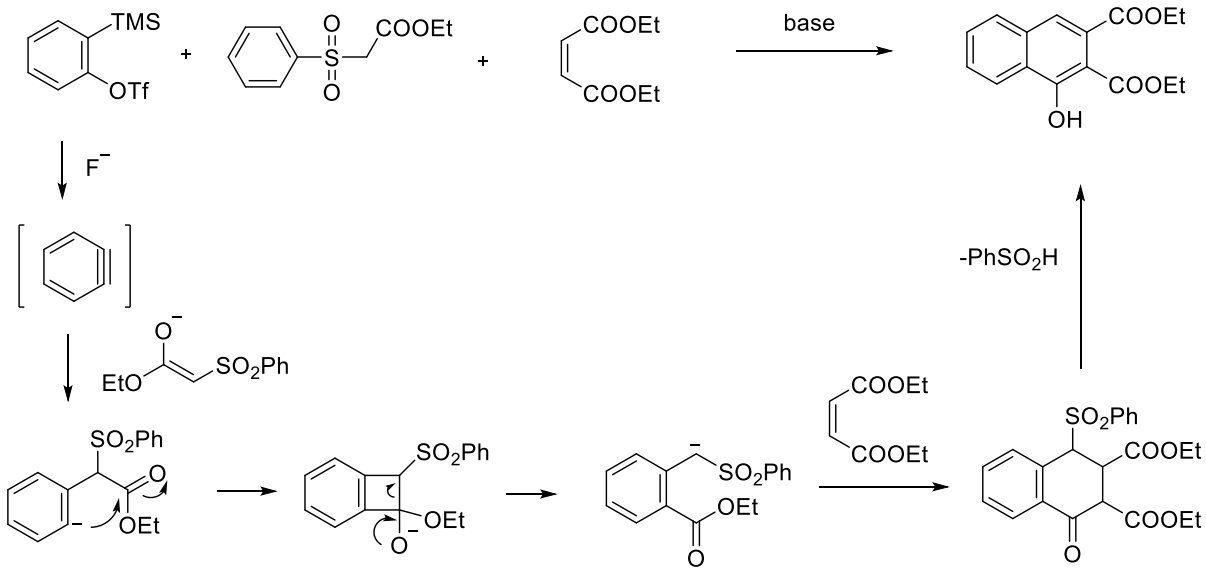


scheme 4-17

1.2.2.8 Multicomponent reaction

In 2007, Huang *et al.* developed a novel three-component reaction of arynes, β-keto sulfones, and Michael-type acceptors for the synthesis of substituted naphthols and naphthalenes. The reaction may proceed via nucleophilic attack on the arynes, intramolecular nucleophilic substitution, Michael addition, ring closure and elimination (scheme 4-18).[234]

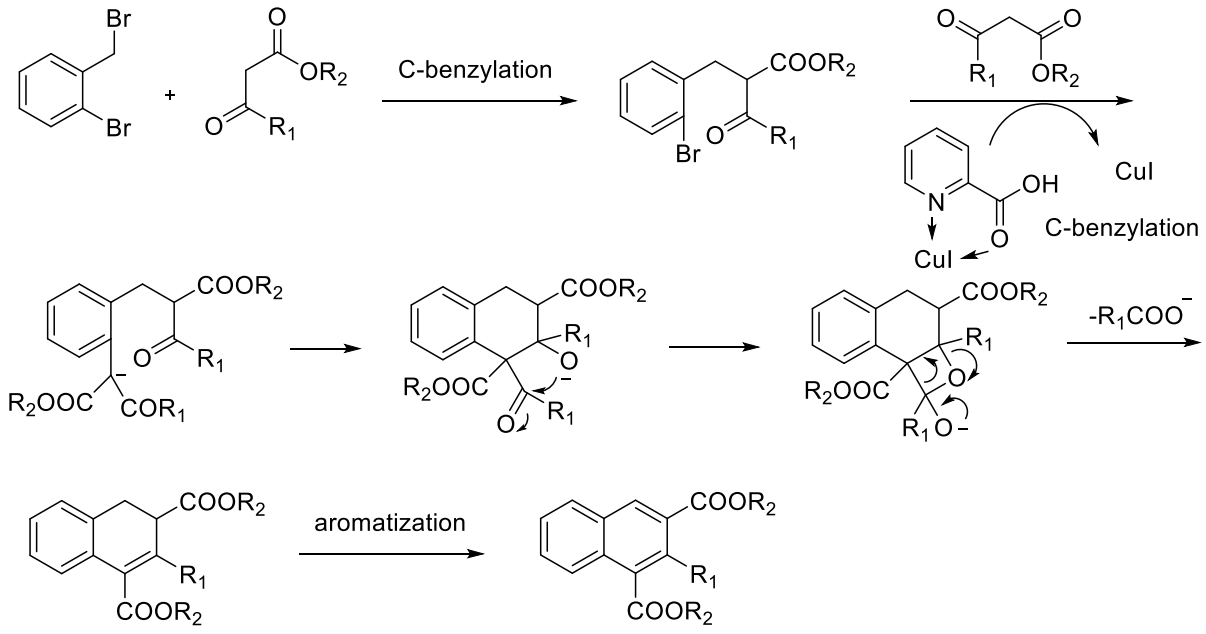
[233] Y. Kuninobu, T. Tatsuzaki, T. Matsuki, and K. Takai, *J. Org. Chem.* **2011**, *76*, 7005–7009
[234] X. Huang, J. Xue, *J. Org. Chem.* **2007**, *72*, 3965-3968



scheme 4-18

1.2.2.9 Cu(I)-Catalyzed domino reactions

In 2011, Beifuss group discovered an easy-to-perform and efficient Cu(I)-catalyzed domino processes using bromobenzyl bromides and twofold excess of β-ketoesters to yield naphthalenes (scheme 4-19).[235]



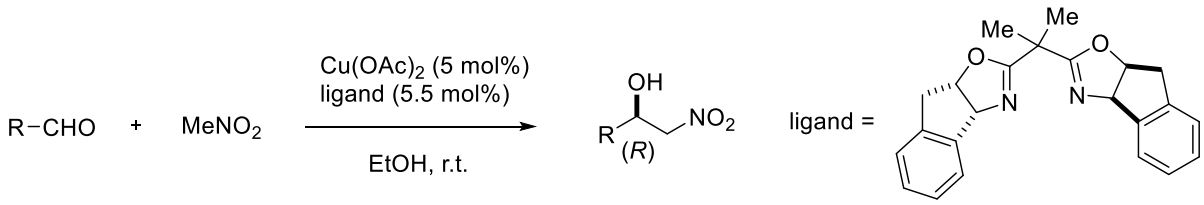
scheme 4-19

[235] C. Malakar, D. Schmidt, J. Conrad, U. Beifuss, *Org. Lett.*, **2011**, *13*, 1972–1975

2 Presentation of our strategy

Nitroalkanes have proven to be one of the most versatile and valuable classes of substances in organic synthesis due to the easy functional modification of the nitro group together with its strong electronwithrawing properties.[236] Indeed, nitroalkanes are prone to afford, under smooth basic conditions, stabilized carbanions (nitronate anions) which are widely used as nucleophiles leading to carbon-carbon single bond formations, such as the Henry, Michael or Mannich reactions.[237]

In 1896, Louis Henry reported the first nitroaldol reaction, later named the Henry reaction.[238] In 2003, Evans *et al.* reported a highly enantioselective, nitroaldol reaction catalyzed by a chiral Cu(II) bis(oxazoline) complex. Both aromatic and aliphatic aldehydes (15 examples) afford corresponding products in good yields and enantioselectivities (87−94% ee) (scheme 4-20).[239]



scheme 4-20

Furthermore, the nitro group can be transformed into other functionalities such as carbonyl,[240] amines,[241] oximes,[242] hydroxylamines[243], nitriles,[244] and isothiocyanates,[245] the obtained

[236] a) H. Feuer, (Ed.) *The Chemistry of the Nitro and Nitrous Groups*, Wiley-Interscience, New York, **1969**, Part. 1; 1970, Part. 2; 1982, Supplement F. b) N. Ono, in: *The Nitro Group in Organic Synthesis*, Wiley-VCH, New York, **2001**. c) R. Ballini, L. Barboni, F. Fringuelli, A. Palmieri, F. Pizzo, L. Vaccaro, *Green Chem.* **2007**, *9*, 823–838. d) R. Ballini, A. Palmieri, L. Barboni, *Chem. Commun.* **2008**, 2975–2985.

[237] a) G. Rosini, The Henry (Nitroaldol) Reaction, in:*Comprehensive Organic Synthesis*, Vol. 2, (Eds. B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp 321–340; b) F. Luzzio, *Tetrahedron* **2001**, *57*, 915–945; c) N. Nishiwaki, *Synthesis of Nitroso, Nitro, and Related Compounds, in: Comprehensive Organic Synthesis*, 2nd edn., *Vol. 6*, (Eds.: P. Knochel, G, A. Molander), Elsevier, Oxford, **2014**, pp 100–130. d) R. Ballini, G. Bosica, D. Fiorini, A. Palmieri, M. Petrini, *Chem. Rev.* **2005**, *105*, 933–971.

[238] L. Henry, *Compt. Rend. Hebd. Seances Acad. Sci.* **1896**, *120*, 1265

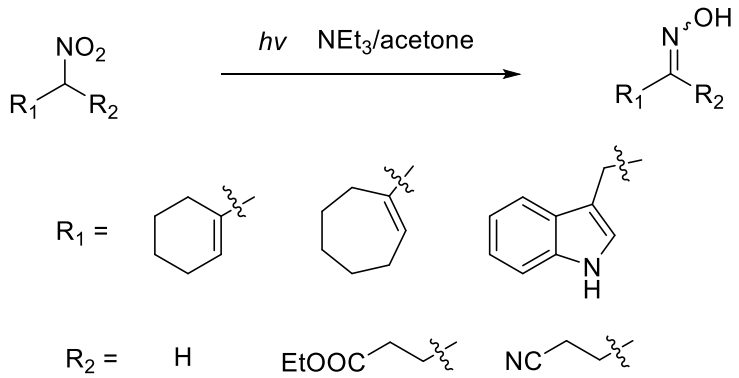
[239] D. Evans, D. Seidel, M. Rueping, H. Lam, J. Shaw, C. Downey, *J. Am. Chem. Soc.*, **2003**, *125*, 12692–12693

[240] a) R. Ballini, M. Petrini, *Tetrahedron* **2004**, *60*, 1017–1047; b) R. Ballini, M. Petrini, *Adv. Synth. Catal.* **2015**, *357*, 2371 2402

[241] a) S. Ram, R. Ehrenkaufer, *Tetrahedron Lett.* **1984**, *25*, 3415–3418; b) N. Yoon, J. Choi, *Synlett* **1993**, 135–136; c) K. Chary, S. Ram, D. Iyengar, *Synlett* **2000**, 683–685; d) R. Ballini, S. Gabrielli, A. Palmieri, M. Petrini, *Curr. Org. Chem.* **2011**,

adducts can be employed as strategic starting materials for the preparation of more substituted nitroalkanes and/or complex structures.

One example of a less familiar conversion may be illustrated by the conversion of aliphatic nitro compounds into oximes by irradiation in acetone in the presence of triethylamine (scheme 4-21).[243]

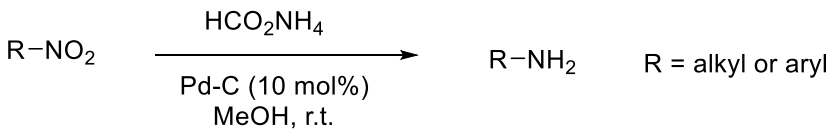


scheme 4-21

Transformation of nitro compounds based on transition metal has made little progress due to the easy reduction of the nitro group into amine and hydroxylamine derivatives by low valent metals. This is particularly true for palladium catalyzed reactions working on both aromatic and aliphatic nitro compounds.

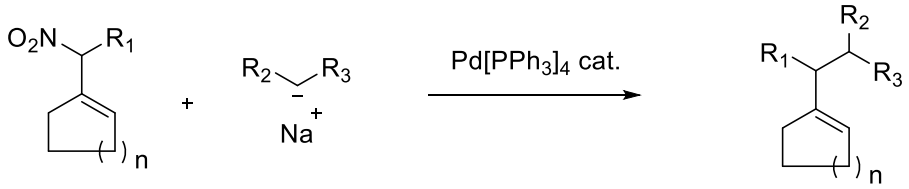
In 1984, Ehrenkaufer *et al.* demonstrated that various aliphatic and aromatic nitro compounds can be selectively and rapidly reduced to their corresponding amino derivatives in good yields using anhydrous ammonium formate and palladium on carbon as catalyst (scheme 4-22).[246]

15, 1482–1506.
[242] a) H. Takechi, M. Machida, *Synthesis* **1989**, 206–207; b) D. Barton, I. Fernandez, C. Richard, S. Zard, *Tetrahedron* **1987**, *43*, 551–558.
[243] A. Kende, J. Mendoza, *Tetrahedron Lett.* **1991**, *32*, 1699–1702.
[244] a) B. Temelli, C. Unaleroglu, *Synlett* **2014**, *46*, 1407–1412; b) S. Tsay, P. Gani, J. Hwu, *J. Chem. Soc. Perkin Trans.* 1 **1991**, 1493–1495; c) R. Chang, K. Kim, *Tetrahedron Lett.* **1996**, *37*, 7791–7794; d) L. Kaim, A. Gacon, *Tetrahedron Lett.* **1997**, *38*, 3391–3394
[245] J. Kim, J. Song, E. Ryu, *Synth. Commun.* **1994**, *24*, 1101–1105
[246] R. Siya, E. Richard, *Tetrahedron Letters*, **1984**,.*25*, 3415-3418



scheme 4-22

There are, however with palladium, a number of interesting reports where the nitro is not reduced. In 1982, Hegedus *et al.* reported a palladium (0) catalyzed allylic alkylation (scheme 4-23).[247]

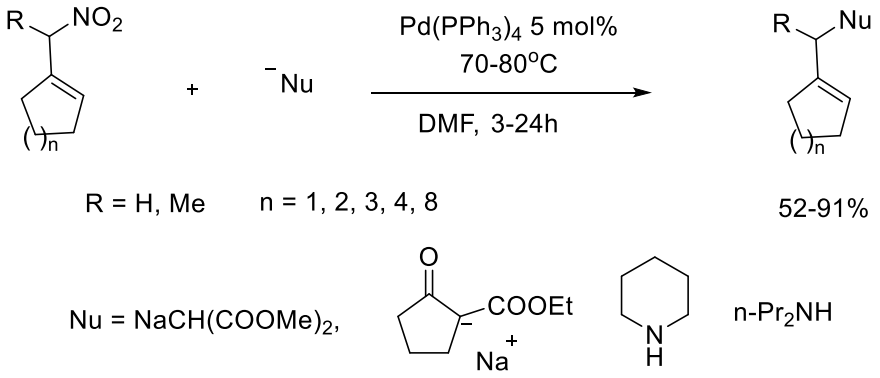


n = 0, 1, 2 R_1 = H, Me R_2, R_3 = COOMe, CN, COOEt

scheme 4-23

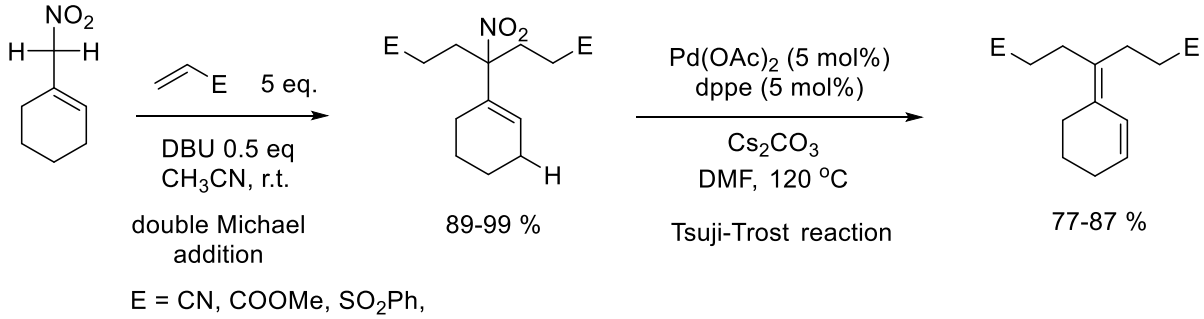
In 1986, Tamura *et al.* demonstrated that primary, secondary, and tertiary allylic nitro compounds could undergo Pd(0)-catalyzed allylic substitution by stabilized carbanions, secondary amines, and benzenesulfinate ion ($PhSO_2^-$). The regiochemistry of these substitutions was related to the structure of the allylic nitro compound and the steric bulk of the nucleophile. Generally, substitution occurred at the less hindered or least substituted site (scheme 4-24).[248]

[247] T. Rui, L. Hegedus, *J. Am. Chem. Soc.*, **1982**, *104*, 3727–3729
[248] R. Tamura, Y. Kai, M. Kakihana, K. Hayashi, M. Tsuji, T. Nakamura, and D. Oda, *J. Org. Chem.* **1986**, *51*, 4375-4385



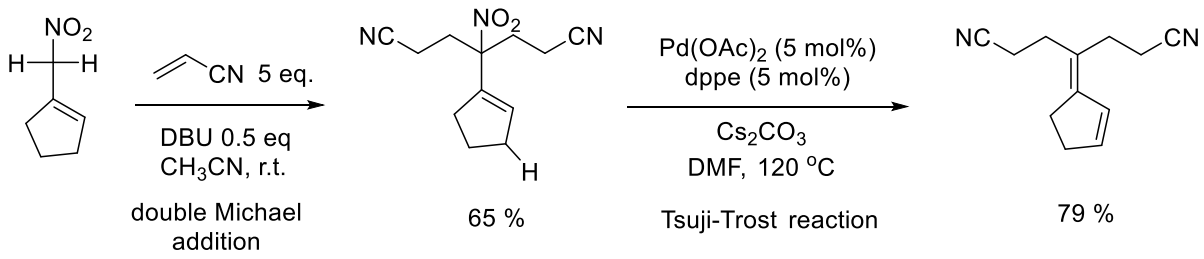
scheme 4-24

Stimulated by our interest in Tsuji-Trost reactions, we envisioned that in the absence of a potential nucleophlic group, the π-allyl intermediate derived from nitro compounds could afford under basic conditions an interesting access to diene, and my colleague Mansour Dolè Kerim discovered a base triggered Tsuji-Trost elimination leading to cyclic diene analogues from nitrocyclohexene derivatives (scheme 4-25).



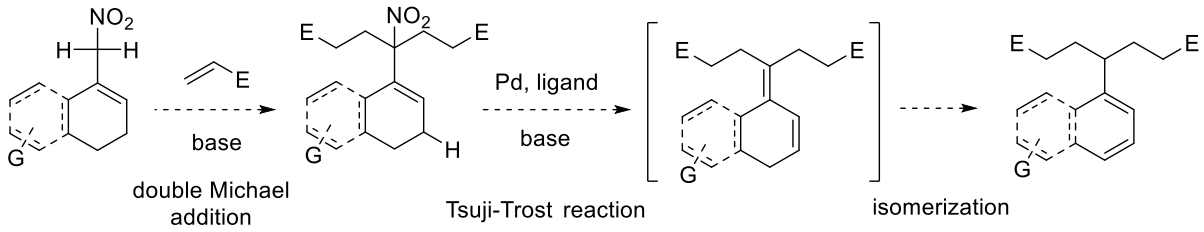
scheme 4-25

Michael additions are known to be easily performed with nitro compounds as nucleophiles. Indeed, many Michael acceptors performed well in this sequence. High yields were obtained in both Michael addition step and Tsuji-Trost step. The reaction could be extended as well to five member ring system (scheme 4-26).



scheme 4-26

Thinking about potential application of this sequence, we envisioned that with another benzene ring fused with 1-(nitromethyl)cyclohex-1-ene, a naphthalene could be formed after isomerization (scheme 4-27).



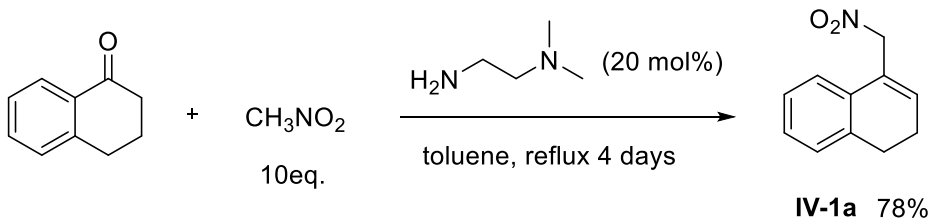
scheme 4-27

3 Results and discussion

3.1 Preliminary test

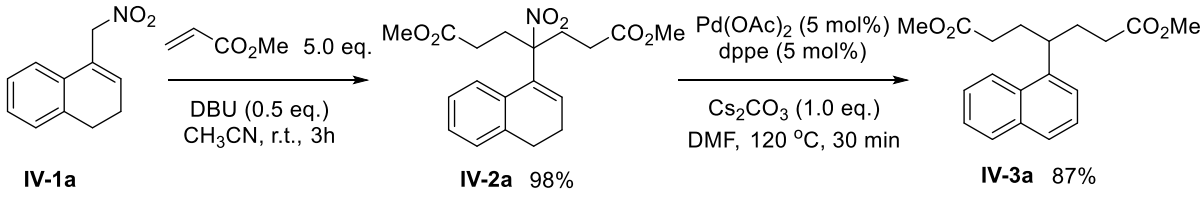
In order to test our hypothesis, 4-(nitromethyl)-1,2-dihydronaphthalene **IV-1a** was prepared through condensation of 3,4-dihydronaphthalen-1(2H)-one and nitromethane in presence of N',N'-dimethylethane-1,2-diamine (20 mol%) (scheme 4-28).[249]

[249] R. Tamura, M. Sato, D. Oda, *J. Org. Chem.* **1986**, *51*, 4368-4375



scheme 4-28

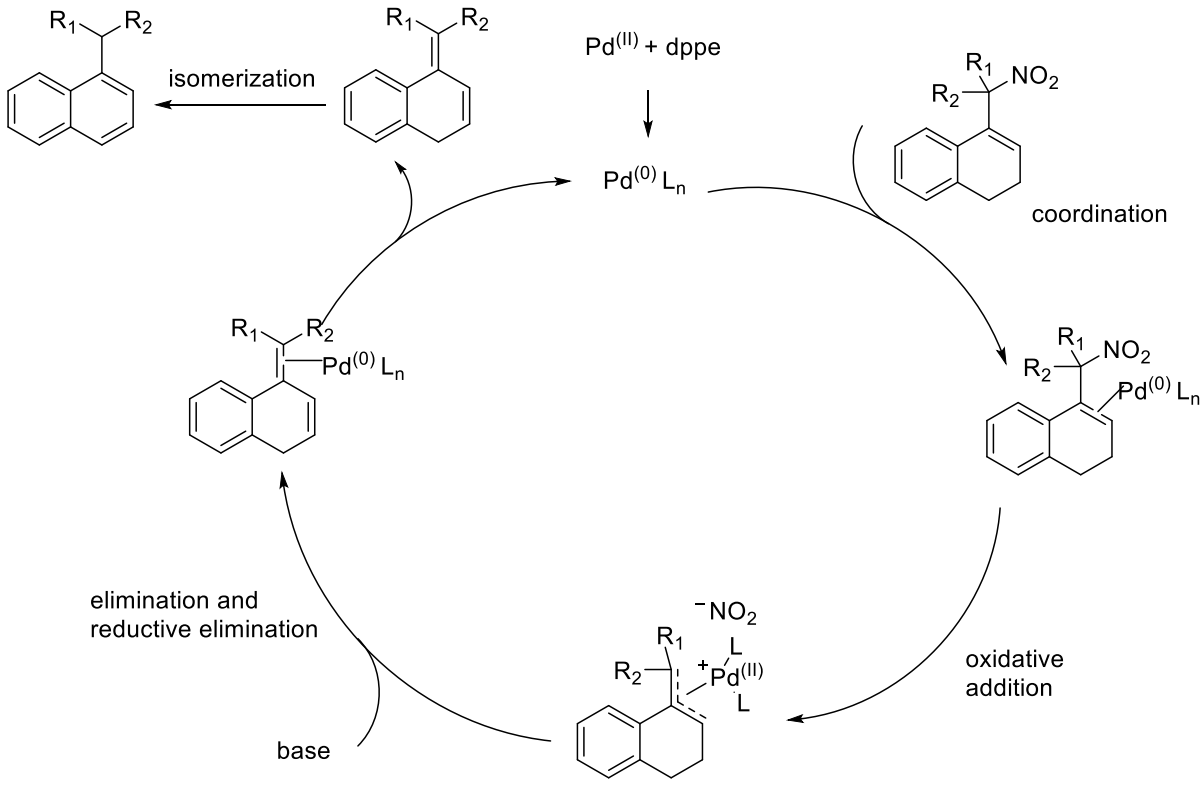
The first trial was carried out under Mansour's diene synthesis reaction conditions: we allowed **IV-1a** to react with 5.0 equiv. of methyl acrylate in presence of 0.5 equiv. of DBU at room temperature for 3 h, the Michael adduct **IV-2a** was obtained in 98 % yield. Then **IV-2a** was dissolved in DMF, followed by addition of 5 mol% $Pd(OAc)_2$, 5 mol% dppe and 1.0 equiv. of Cs_2CO_3, the mixture was heated to 120 ^oC for 30 min, after completion of the reaction, naphthalene derivative **IV-3a** was isolated in 87 % yield. A novel Michael/Tsuji-Trost tandem reaction to synthesize naphthalene derivatives was thus settled (scheme 4-29).



scheme 4-29

3.2 The reaction mechanism

Based on all above information, we proposed a possible mechanism for this Tsuji-Trsot reaction.

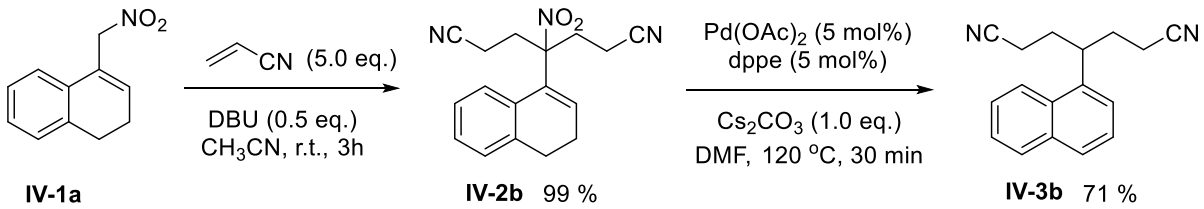


scheme 4-30

3.3 Scope of Michael/Tsuji-Trost reaction

In order to explore the limitations of this reaction, various allylic nitro-compounds were prepared and tested under our selected reaction conditions.

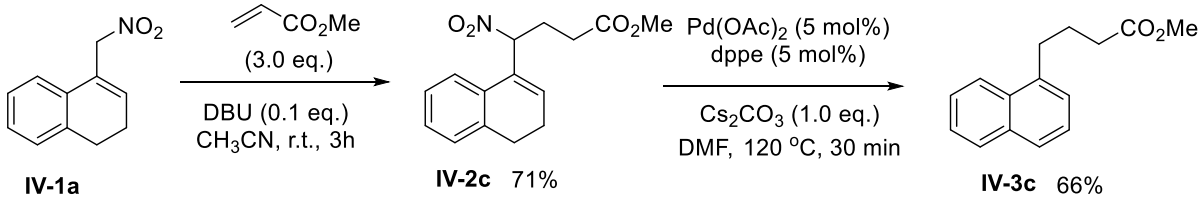
When acrylonitrile was used for double Michael addition, the reaction performed well (scheme 4-31).



IV-1a **IV-2b** 99 % **IV-3b** 71 %

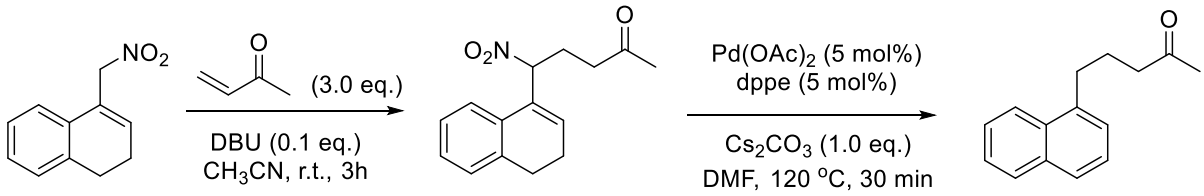
scheme 4-31

When we decreased the amount of Michael acceptors to 3.0 equiv., and using 0.1 equiv. of DBU, a mono Michael addition product was obtained and the following Tsuji-Trost reaction proceeded well (scheme 4-32,4-33).



IV-1a **IV-2c** 71% **IV-3c** 66%

scheme 4-32



IV-1a **IV-2d** 84% **IV-3d** 71%

scheme 4-33

However, some substituted α,β-unsaturated ketones (figure 4-3) failed to couple with **IV-1a** under these conditions probably due to the steric hindrance of the naphthalene moiety.

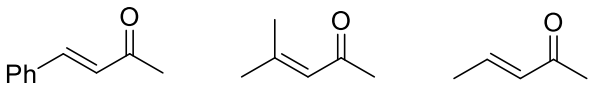
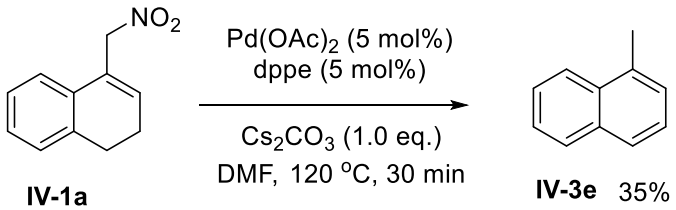


figure 4-3

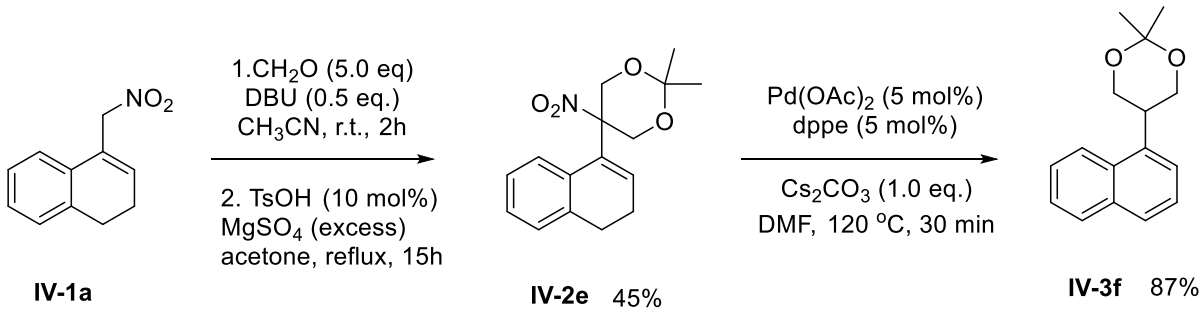
When **IV-1a** was directly treated under Tsuji-Trost reaction conditions, 1-methylnaphthalene was obtained in 35% yield (scheme 4-34). This was rather a surprise for us, as under basic conditions, the nitro group should form a non reactive nitronate with the palladium catalyst.



IV-1a **IV-3e** 35%

scheme 4-34

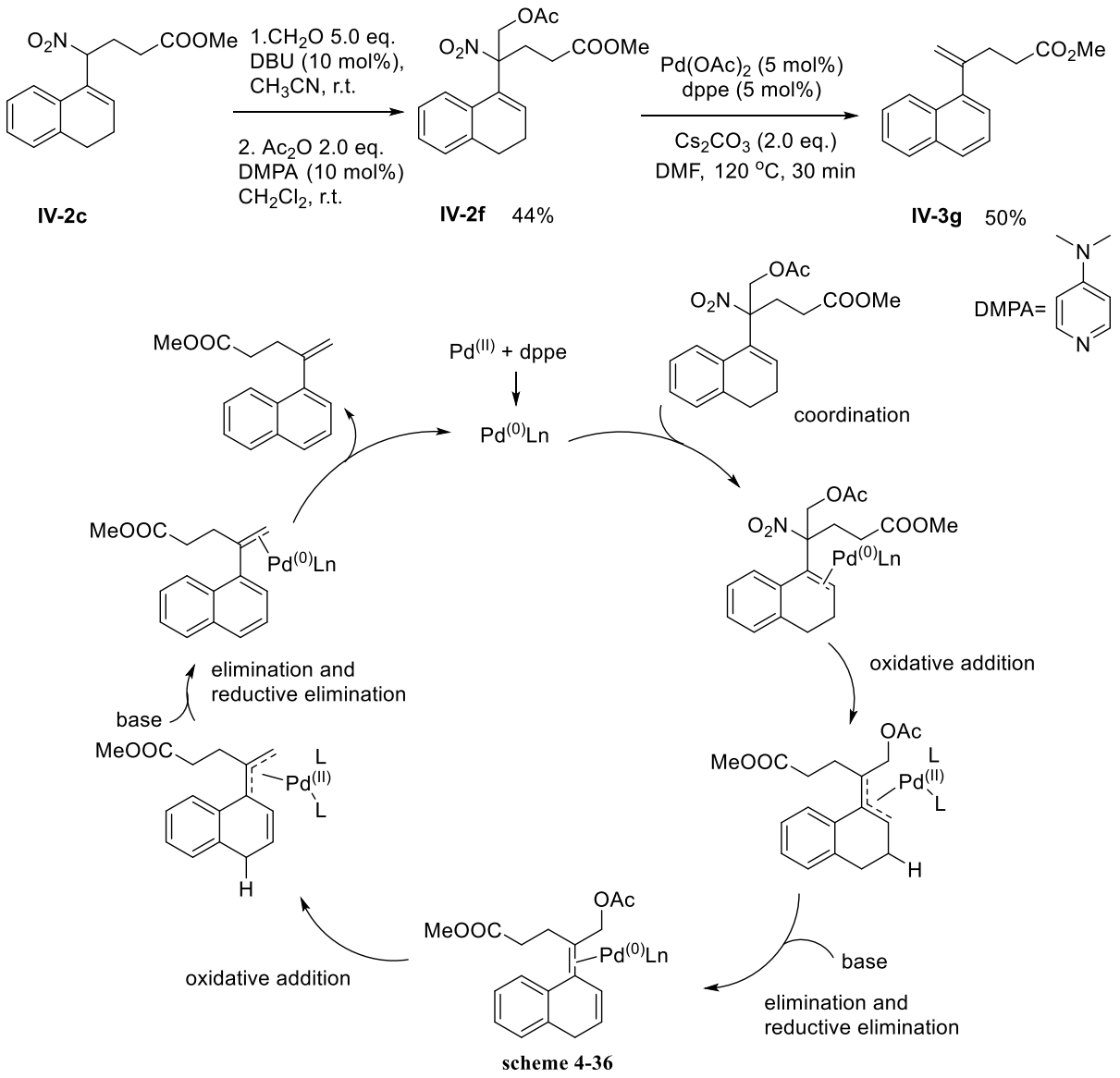
A ketal **IV-2e** was also prepared by 2 steps from **IV-1a**. **IV-3f** was obtained in good yield from **IV-2e** (scheme 4-35).



IV-1a **IV-2e** 45% **IV-3f** 87%

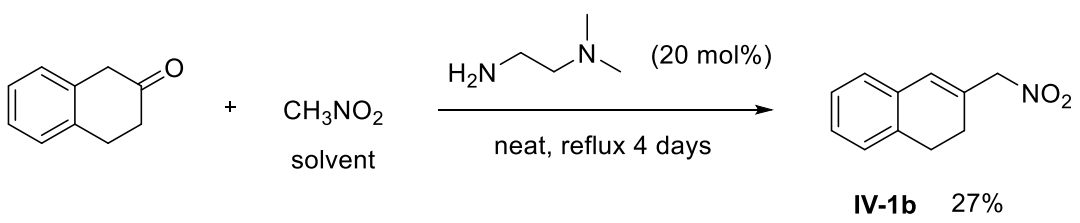
scheme 4-35

To further explore the reaction scope, **IV-2f** was synthesized from **IV-2c**. After Tsuji-Trost reaction, **IV-3g** was obtained in moderate yield. In this case, an interesting cascade involving two Tsuji-Trost eliminations is observed (scheme 4-36).



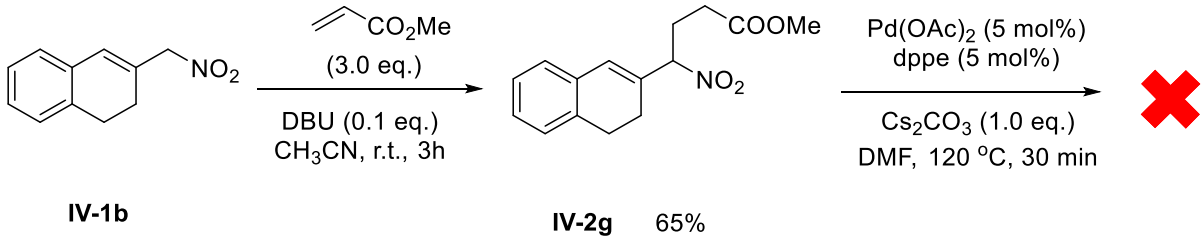
scheme 4-36

To further examine our assumption about the reaction mechanism, **IV-1b** was prepared under similar conditions of preparing **IV-1a** (scheme 4-37).



scheme 4-37

When **IV-1b** was treated under Michael reaction condition, **IV-2g** was obtained in 65% yield. However, for Tsuji-Trost reaction, the reaction is not clean, we could only recover some starting materials **IV-2g** (scheme 4-38).



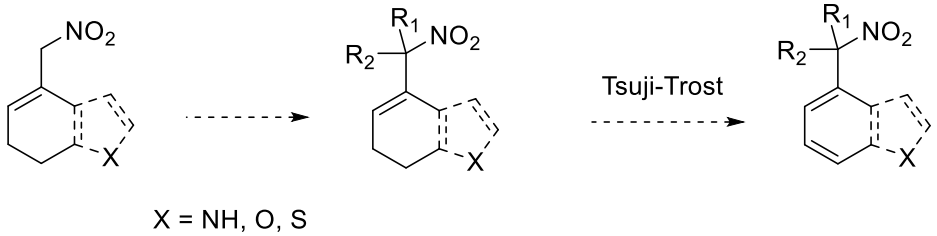
IV-1b **IV-2g** 65%

scheme 4-38

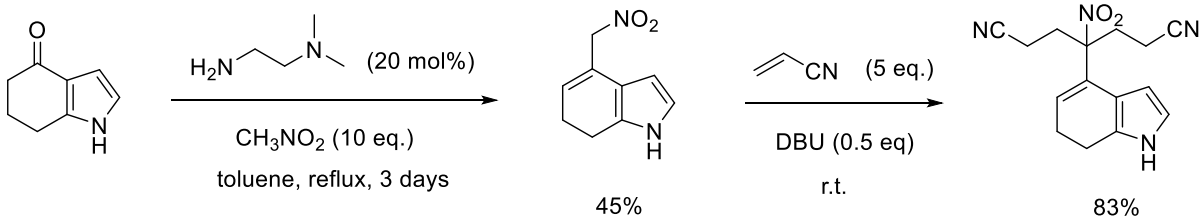
4 Conclusions and perspectives

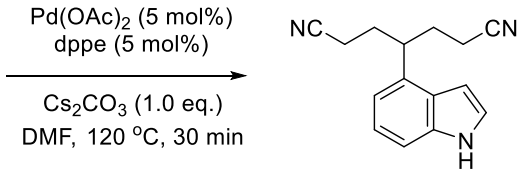
Following my colleague Mansour Dolè Kerim's work on the synthesis of cyclic dienes from nitroallylic derivatives, we have reported an application of this methodology to the formation of 1-substituted naphtalenes from 1-tetralone. This reaction probably involves the formation of a palladium π-allyl complex followed by a base promoted β-hydride elimination. This reaction combined with the condensation of fused cyclic ketones with nitromethane and the functionalization of the resulting nitrocycloalkenes (Michael, Mannich...) constitute a very powerful synthetic tool for the formation of 1-substituted naphtalenes.

If we changed fused benzene ring into another one such as pyrrole, furan, thiophene etc., a series of heteroaromatic compounds would be synthesized (scheme 4-39). In fact, we have just obtained one example of such substituted indole (scheme 4-40).



scheme 4-39



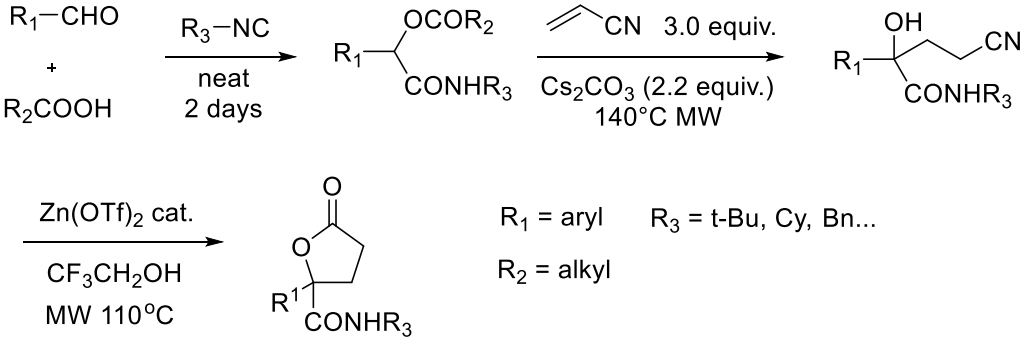


scheme 4-40

General conclusion

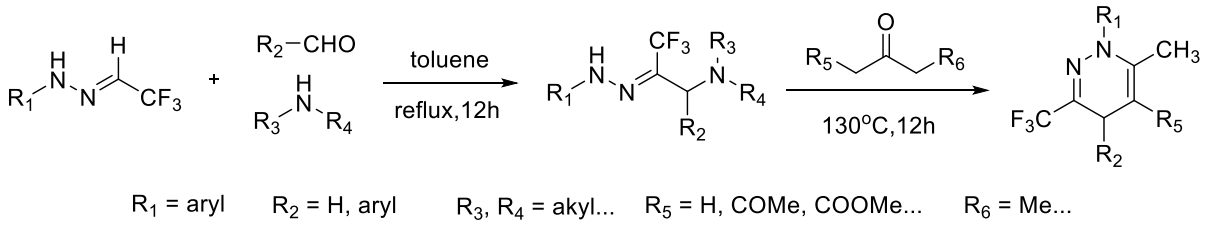
This thesis explores various multicomponent reactions including Passerini reactions and Mannich reactions， and their applications into synthesis of heterocycles such as γ-butyrolactones and 1,2-diazine analogues. It also gives an access to synthesize naphthalene via a palladium catalyzed Tsuji-Trost elimination.

We discovered a two-step sequence for the preparation of γ-butyrolactones from Passerini adducts of aromatic and heteroaromatic aldehydes. This strategy significantly expanded the scope of the butyrolactones syntheses from benzoin derivatives with microwave conditions allowing to counterbalance the poorer electron-withdrawing group effect of the amide moiety (scheme 1).



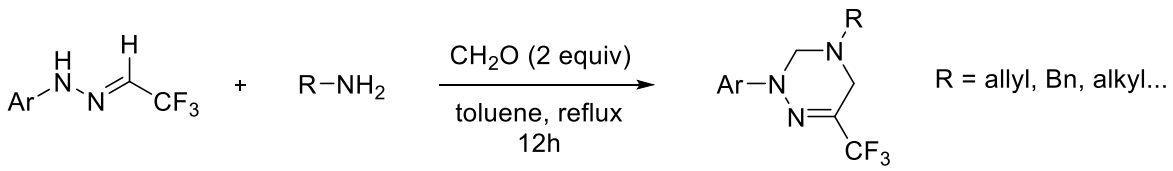
scheme 1

We also explored the reactivity of trifluoroacetaldehyde NH-aryl hydrazones, which can be easily obtained from hydrazine and trifluoroacetaldehyde hemiacetal under acid conditions. As the carbon centered nucleophile in Mannich reactions, the electron-withdrawing properties of the trifluoromethyl group are strongly associated with the success of the couplings allowing various NH-arylhydrazone derivatives to react with formaldehydes as well as different aromatic aldehydes. The resulting Mannich adducts are valuable starting materials for the generation of azoalkene intermediates and the preparation of trifluoromethyl substituted 1,2-diazine derivatives under heating with β-ketoesters (scheme 2)



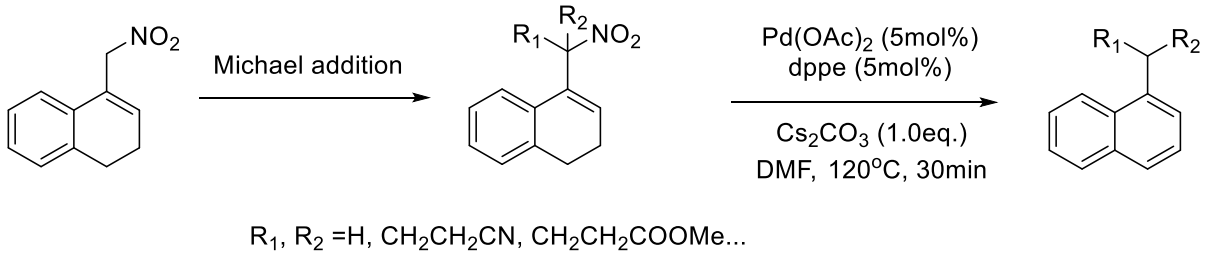
scheme 2

Meanwhile, this reaction offers interesting opportunities for the preparation of trifluoromethylated 1,2,4-triazines (scheme 3).



scheme 3

The final part of the manuscript deals with the application of Tsuji-Trost elimination to the formation of 1-substituted naphtalenes from 1-tetralone. This reaction probably involves the formation of a palladium p-allyl complex followed by a base promoted β-hydride elimination. This reaction combined with the condensation of fused cyclic ketones with nitromethane and the functionalization of the resulting nitrocycloalkenes (Michael, Mannich...) constitute a very powerful synthetic tool for the formation of 1-substituted naphtalenes (scheme 4).



scheme 4

Bibliography

Chapter 1

1 A.Domling; I. Ugi, *Angew. Chem., Int. Ed.* **2000**, *39*, 3168-3210.

2 J. Ramon, M. Yus, *Angew Chem Int Ed.* **2005**, *44*, 1602-1634

3 (a) J. Zhu, Eur. *J. Org. Chem*. **2003**, *2003*, 1133. (b) J. Zhu, H. Bienaymé, Eds. *Multicomponent Reactions; Wiley-VCH: Weinheim, Germany*, **2005**. (c)A. Dömling, *Chem. Rev.* **2006**, *106*, 17.

4 A. Laurent, *Gerhardt CF. Ann Pharm.* **1838**, *28*, 265.

5 A. Strecker, *Liebigs Ann. Chem.* **1850**, *75*, 27-51

6 A. Hantzsch, *Justus Liebigs Ann. Chem.* **1882**, *215*, 1.

7 a) H. Debus, *Justus Liebigs Annalen der Chemie.* **1858**, *107* , 199. b) B. Radzisewski, *Berichte der deutschen chemischen Gesellschaft*.,**1882**, *15* , 2706.

8 (a) P. Biginelli, *Ber. Dtsch. Chem. Ges.* **1891**, *24*, 2962. (b) P. Biginelli, *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 447.

9 C. Mannich, A. Krösche, *Pharm. (Weinheim, Ger.)* **1912**, *250*, 647.

10 (a) G. Passerini, G.Simone, *Chim. Ital.* **1921**, *51*, 126. (b) G. Passerini, *Chim. Ital*. **1921**, *51*, 181. (c) G. Passerini, *Chim. Ital*. **1922**, *52*, 432. Reviews: (a) L. Banfi, R. Riva, *Org. React.* **2005**, *65*, 1.

11 (a) I. Ugi, R. Meyr, U. Fetzer, C. Steinbrückner, *Angew. Chem.* **1959**, *71*, 386. (b) I. Ugi, C. Steinbrückner, *Angew. Chem.* **1960**, *72*, 267.

12 C. Pirrung, S. Ghorai, R. Ibarra-Rivera, *J. Org. Chem.* **2009**,*74*, 4110.

13 W. Lieke *Justus Liebigs Ann. Chem.* **1859**, *112*, 316-321

14 A. Gautier *Justus Liebigs Ann. Chem.* **1869**, *146*, 119-124

15 (a)W. Hofmann, *Justus Liebigs Ann. Chem.* **1867**, *144*, 114.(b) I. Nef, *Justus U.Liebigs Ann. Chem.* **1897**, *298*, 202.

16 (a) W. Weber, G. Gokel, *Tetrahedron Lett.* **1972**, *11*, 1637. (b) P. Weber, W. Gokel, I. Ugi, *Angew. Chem.* **1972**, *84*, 587.

17 (a) W. Hertler, J. Corey, *J. Org. Chem.* **1958**, *23*, 1221. (b) I. Ugi, R. Meyr, *Angew. Chem.* **1958**, *70*, 702.

18 G. Skorna, I. Ugi, *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 259.

19 I. Ugi, R. Meyr, *Chem. Ber.* **1960**, *93*, 239.

20 R. Obrecht, R. Hermann, I. Ugi, *Synthesis* **1985**, 400.

21 (a) D. Lentz, *J. Fluo. Chem.* **1984**, *24*, 523-530. (b) D. Lentz, *J. Fluo. Chem.* **1985**, *29*, 91. (c) P. Doz, D. Lentz, *Angewandte Chemie*, **1994**, *106*, 1377-1393

22 (a) T. Mukaiyama, Y. Yokota, Bull. *Chem. Soc. Jpn.* **1965**, *38*, 858. (b) E. Baldwin, C. Bottaro, D. Riordan, E. Derome, *J. Chem. Soc., Chem. Comm.* **1982**, 942. (c) E. Baldwin, E. Derome, D. Riordan, *Tetrahedron* **1983**, *39*, 2989.

23 I. Okada, Y. Kitano, *Synthesis* **2011**, 3997.

24 C. Pirrung, S. Ghorai, *J. Am. Chem. Soc.* **2006**, *128*, 11772.

25 (a) L. Elkaïm, L. Grimaud, A. Schiltz, *Synlett.* **2009**, 1401. (b) L. Elkaïm, L. Grimaud, A.Schiltz, *Tetrahedron Lett.* **2009**, *50*, 5235. (c) L. Elkaïm, L. Grimaud, A. Schiltz, *Org. Biomol. Chem.*, **2009**, *7*, 3024.

26 R. Ramozzi, N. Cheron, B. Braida, P. Hiberty, P. Fleurat-Lessard, *New J. Chem.* **2012**, *36*, 1137.

27 (a) A. van Beijen, *Macromolecules* **1983**, *16*, 1679. (b) M. Albert, B. van Leusen, E. Hoogenboom, H. Siderius, *Tetrahedron Lett.* **1972**, *13*, 2369.

28 (a) U. Schöllkopf, R. Schröder, *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 333. (b) D. Hoppe, U. Schöllkopf, *Liebigs Ann. Chem.* **1972**, *763*, 1.

29 A. Van Leusen, E. Hoogenboom, H. Siderius, *Tetrahedron Lett.* **1972**, *23*, 2369.

30 N. Elders, F. Schmitz, J. de Kanter, E. Ruitjer, B. Groen, A. Orru, *J. Org. Chem.* **2007**, *72*, 6135.

31 H. Shaw, H. Pritchard, *J. Chem.* **1967**, *45*, 2749.

32 (a) T. Saegusa, S. Kobayashi, Y. Ito, N. Yasuda, *J. Am. Chem. Soc.* **1968**, *90*, 4182. (b) T. Saegusa, Y. Ito, N. Yasuda, T. Hotaka, *J. Org. Chem.* **1970**, *35*, 4238.

33 C. Pan, J. Han, H. Zhang and C. Zhu, *J. Org. Chem.*, **2014**, *79*, 5374.

34 G. Wang, S. Chen and X. Yu, *Tetrahedron Lett.*, **2014**, *55*, 5338

35 (a) D. Bachi, A. Balanov, N. Bar-Ner, *J. Org. Chem.* **1994**, *59*, 7752. (b) B. Bachi, N. Bar-Ner, A. Melman, *J. Org. Chem.* **1996**, *61*, 7116. (c) L. Benati, R. Leardini, M. Minozzi, D. Nanni, R. Scialpi, P. Spagnolo, S. Stazzari, G. Zanardi, *Angew. Chem. Int. Ed.* **2004**, *43*, 3598. (d) P. Curran, H. Liu, *J. Am. Chem. Soc.* **1991**, *113*, 2127.

36 H. Josien, S. Ko, D. Bom, P. Curran, *Chem. Eur. J.* **1998**, *4*, 67. (b) D. Curran, H. Liu, H. Josien, S. Ko, *Tetrahedron* **1996**, *52*, 11385

37 (a) Y. Ito, I. Ito, T. Hirao and T. Saegusa, *Synth. Commun.*, **1974**, *4*, 97; (b) Y. Ito, T. Hirao and T. Saegusa, *J. Org. Chem.*, **1975**, *40*, 2981; (c) Y. Ito, T. Hirao, N. Ohta and T. Saegusa, *Tetrahedron Lett.*, **1977**, *18*, 1009.

38 (a) T. Saegusa, Y. Ito, S. Kobayashi and K. Hirota, *Tetrahedron Lett.*, **1967**, *8*, 521; (b) T. Saegusa, S. Kobayashi, Y. Ito,

K. Hirota and Y. Okumura, Bull. *Chem. Soc. Jpn.*, **1968**, *41*, 1638; (c) T. Saegusa, Y. Ito, S. Kobayashi, K. Hirota and H. Yoshioka, *Tetrahedron Lett.*, **1966**, *7*, 6121; (d) T. Saegusa, S. Kobayashi, Y. Ito and K. Hirota, *J. Am. Chem. Soc.*, **1967**, *89*, 2240; (e) T. Saegusa, Y. Ito and S. Kobayashi, *Tetrahedron Lett.*, **1968**, *9*, 935.

39 W. D. Jones and E. T. Hessell, *Organometallics*, **1990**, *9*, 718

40 A. Lygin, O. Larionov, V. Korotkov and A. de Meijere, *Chem. Eur. J.*, **2009**, *15*, 227

41 (a) E. Kühle, B. Anders, E. Klauke, H. Tarnow, G. Zumach, *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 20. (b) E. Kühle, B. Anders, G. Zumach, *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 649.

42 L. Elkaïm, L. Grimaud, P. Patil, *Org. Lett.* **2011**, *13*, 1261.

43 V. Hoang and G. Bruce, *org. lett.* **2011** ,*13*, 2584–2585

44 U. Nef, *Justus Liebigs Ann. Chem.* **1892**, *210*, 269.

45 D. Coffinier, L. Elkaïm, L. Grimaud, *Org. Lett.* **2009**, *11*, 1825.

46 V. Atlan, L. Elkaïm, C. Buron, *Synlett* **2000**, 489.

47 J. Schneekloth, K. Jimin, E. Sorensen, *Tetrahedron* **2009**, *65*, 3096 –3101

48 (a) M. Passerini, G. Simone, *Chim. Ital.* **1921**, *51*, 126. (b) M. Passerini, *Chim. Ital.* **1921**, *51*,181. (c) L. Banfi, R. Riva, *Org. React.* **2005**, *65*, 1

49 I. Ugi, R. Meyr, *Chem. Ber.* **1961**, *94*, 2229.

50 S. Maeda, S. Komagawa, M. Uchiyama, K. Morokuma, *Angew. Chem. Int. Ed.* **2011**, *50*, 644.

51 E. Marques, P. Herrera, *Multicomponent Reactions* , **2015**, 283-305.

52 L. Elkaim, M. Gizolme, L. Grimaud, *Org. Lett.* **2006**, *8*, 5021–5023

53 T. Soeta, Y. Kojima, Y. Ukaji, K. Inomata, *Org. Lett.* **2010**, *12*, 4341–4343.

54 T. Soeta, Y. Kojima, Y. Ukaji, K. Inomata, *Tetrahedron Lett.* **2011**, *52*, 2557–2559.

55 I. Hagedorn, U. Eholzer, *Chem. Ber.* **1965**, *98*, 936.

56 (a) G. Passerini, *Chim. Ital.* **1924**, *54*, 529. (b) E. Müller, B. Zeeh, *Justus Liebigs Ann. Chem.* **1966**, *696*, 72. (c) E. Müller, B. Zeeh, *Justus Liebigs Ann. Chem* . **1968**, *715*, 47. (d) W. McFarland, *J. Org. Chem.***1963**, *28*, 2179.

57 J. Brioche, G. Masson, Zhu, *J. Org. Lett.* **2010**, *12*, 1432.

58 M. Barrett, R. Barton, R. Falck, D. Papaioannou, A. Widdowson, *J. Chem. Soc., PerkinTrans. I* **1979**,652.

59 (a) T. Kern,B. Motherwell, *Chem. Comm.* **2003**, 2988. (b) T. Kern, B. Motherwell, *Chem. Comm.* **2005**, 1787.

60 R. Neidlein, *Naturforsch* **1964**, *19*, 1159.

61 (a) I. Ugi,K. Rosendahl, *Chem. Ber.* **1961**, *94*, 2233. (b) T. Gomati, J. Firl, I.Ugi, *Chem. Ber.* **1977**, *110*, 1603.

62 (a) I. Ugi, R. Meyr, U. Fetzer, C. Steinbrückner, *Angew. Chem.* **1959**, *71*, 386. (b) I. Ugi, C. Steinbrückner, *Angew. Chem.* **1960**, *72*, 267.

63 I. Ugi, C. Steinbrücker, *Chem. Ber.* **1961**, *94*, 2802.

64 (a) D. Floyd, A. Harnett, A. Miller, S. Patel, L. Saroglou, M. Whittaker, *Synlett* **1998**, 637. (b) U. Kazmaier, C. Hebach, *Synlett* **2003**, 1591. (c) R. Pick, M. Bauer, U. Kazmaier, C.Hebach, *Synlett* **2005**, 757. (d) J. Thompson, B. Chen, *J. Org. Chem.* **2009**, *74*, 7084.

65 I. Ugi, F. Bodesheim, *Liebigs Ann. Chem.* **1963**, *666*, 61. (b) G. Zinner, Kliegel, W. Arch. *Pharm.* **1966**, *299*, 746. (c) G. Zinner, W. Bock, *Pharm.* **1973**, *306*, 94.

66 I. Ugi, *Isonitrile Chemistry; Academic Press, New York - London*, **1971**; *Vol. 20.*

67 A. Santos, L. Elkaïm,L. Grimaud, C. Ronsseray, Beilstein *J. Org. Chem.* **2011**, *7*, 1310.

68 S. Zychlinski, I. Ugi, *Heterocycles* **1998**, *49*, 29.

69 S. Heck, A. Dömling, *Synlett.* **2000**, *3*, 424

70 I. Ugi, C. Steinbrückner, *Angew. Chem.* **1960**, *72*, 267.

71 E. Haslinger, *Chem.* **1978**, *109*, 747.

72 I. Ugi, C. Steinbrückner, *Chem. Ber.* **1961**, *94*, 734.

73 L. Elkaïm,L. Grimaud, J. Oble, *Angew. Chem. Int. Ed.* **2005**, *44*, 7961.

74 a) A. Keating, W. Armstrong, *J. Am. Chem. Soc.* **1996**, *118*, 2574. b) A. Keating, W. Armstrong, *J. Org. Chem.* **1996**, *61*, 8935.

75 H. Spatz, M. Umkehrer, C. Kalinski, G. Ross, C. Burdack, J. Kolb, T. Bach, *Tetrahedron Lett.* **2007**, *48*, 8060.

76 R. Bossio,S. Marcaccini, R. Pepino, T. Torroba, *Heterocycles* **1999**, *50*, 463

77 B. Beck, A. Picard, E. Herdtweck, A. Dömling, *Org. Lett.* **2004**, *6*, 39

78 K. Paulvannan, *J. Org. Chem.* **2004**, *69*, 1207.

79 F. Bonnaterre, M. Bois-Choussy, Zhu, *J. Org. Lett.* **2006**, *8*, 4351

Chapter 2

80 a) J. Moran, E. Tellew, Z. Zhao, W. Armstrong, *J. Org. Chem.*, **1993**, *58*, 7848-7859. b) L. Banfi. G. Guanti, R. Riva, *Chem. Commun.*, **2000**, 985-986.c) A. Znabet, M. Polak, E. Janssen, J. de Kanter,J. Turner, A. Orru, E. Ruijter, *Chem. Commun.*, **2010**, *46*,7918-7920. d) W. Armstrong, E. Tellew, J. Moran, *J. Org. Chem.*, **1992**, *57*, 2208-2211. e) H. Otto, T. Schirmeister, *Chem. Rev.*, **1997**, *97*, 133-171. f) E. Semple, C. Rowley, K. Brunck, C. Ripka, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 315-320.

81 A. Kazemizadeh and A. Ramazani, *Current Organic Chemistry*, **2012**, *16*, 418-450
82 M. Carrillo, G. Neo, L. López-García, S. Marcaccini, F. Marcos, *Green Chem.*, **2006**, *8*, 787-789.
83 H. Yu, T. Gai, L. Sun, S. Zhang, *Chinese Chem. Lett.*, **2011**, *22*, 379-381.
84 L. Banfi. G. Guanti, R. Riva, *Chem. Commun.*, **2000**, 985-986.
85 B. Beck, M. Magnin-Lachaux, E. Herdtweck, A. Dömling, *Org. Lett.*, **2001**, *3*, 2875-2878.
86 M. Yehia, W. Antuch, B. Beck, S. Hess, M. Almstetter, P. Furer, E. Herdtweck, A. Dömling, *Bioorg. Med. Chem. Lett.*, **2004**, *14*, 3121-3125.
87 R. Bossio, S. Marcaccini, R. Pepino, *Liebigs Ann. Chem.*, **1994**, 527-528.
88 L. Wright, V. Robotham, K. Aboud, *Tetrahedron Lett.*, **2002**, *43*, 943-946.
89 S. Sebti, A. Foucaud, *Synthesis*, **1983**, 546-549.
90 R. Bossio, S. Marcaccini, R. Pepino, *Liebigs Ann. Chem.*, **1991**, 1107-1108.
91 O. Kreye, B. Westermann, A. Wessjohann, *Synlett*, **2007**, 3188-3192.
92 P. He, J. Wu, B. Nie, W. Ding, *Tetrahedron Lett.*, **2009**, *65*, 8563-8570.
93 B. Beck, G. Larbig, B. Mejat, M. Magnin-Lachaux, A. Picard, E. Herdtweck, A. Dömling, *Org. Lett.*, **2003**, *5*, 1047-1050.
94 a)Hoffmann HMR, J. Rabe, *Angew Chem Int Ed Engl* **1985**, *24*, 94-110. b) C. Koch, Chamberlin AR., *Studies in Natural Products Chemistry*, Edited by Attaur Rahman. Elsevier Science; **1995**, *Vol. 16*, 687-725.
95 A. Ottow, M. Brinker, T. Teichmann, E. Fritz, W. Kaiser, M. Brosche, J. Kangasjarvi, X. Jiang, A. Polle, *Plant Physiol.* **2005**, *139*, 1762−1772.
96 Catalytic Asymmetric Synthesis, 3rded.;I. Ojima, ,Ed.;Wiley-VCH: Hoboken, NJ, 2010.
97 S. Norio, H. Shuhei and O. Yohei, *RSC Adv.*, **2016**, *6*, 81763–81766
98 G. Rong, F. Rong, C. Daniel, *Synlett.* **2015**, *26*, 661–665
99 E. Ehlinger and M. Philip, *J. Am. Chem. SOC.*, **1980**, *102*, 5005
100 B. Zhang, L. Han, T. Li, J. Yan, and Z.Yang, *Synthetic Communications*, **2014** ,*11*, 1608-1613
101 a) T. Inoue, O. Kitagawa, O. Ochiai, M. Shiro, T. Taguchi, *Tetrahedron Lett.* **1995**, *36*, 9333−9336. b) T. Inoue, O. Kitagawa, A. Saito, T. Taguchi, *J. Org. Chem.* **1997**, *62*, 7384−7389.
102 For reviews on IMCRs, see: a) *Multicomponent reactions*; J. Zhu, H. Bienaymé, Eds, Wiley-VCH, Weinheim, **2005**; b) A. Dömling, I. Ugi, *Angew. Chem. Int. Ed*. **2000**, *39*, 3168-3210; c) R. Orru, M. de Greef, *Synthesis* **2003**, 1471-1499; d) C. Hulme, V. Gore, *Curr. Med. Chem*. **2003**, *10*, 51-80; e) A. Dömling, *Chem. Rev*. **2006**, *106*, 17-89; f) A. Dömling, K. Wang, W. Wang, *Chem. Rev.* **2012**, *112*, 3083-3135; g) *Multicomponent Reactions in Organic Synthesis*, J. Zhu, Q. Wang, M. Wang, Eds., Wiley-VCH:Weinheim, Germany, **2014**; h) V. Boyarskiy, N. Bokach, K. Luzyanin, V. Kukushkin, *Chem. Rev*. **2015**, *115*, 2698-2779; i) A. Varadi, T. Palmer, R. Dardashti, S. Majumdar, *Molecules*, **2016**, *21*, 19; (j) J. Lei, J. Meng, D. Tang, B. Frett, Z. Chen, Z. Xu, *Mol. Divers*. 2018, in press, DOI : 10.1007/s11030-017-9811-2
103 For some intramolecular Ugi post-condensations involving the peptidyl position see: a) R. Bossio, C. Marcos, S. Marcaccini, R. Pepino, *Synthesis* **1997**, 1389-1390; b) A. Salcedo, L. Neuville, J. Zhu, *J. Org. Chem*. **2008**, *73*, 360-3603; c) L. Elkaïm, L. Grimaud, X. Goff; M. Menes-Arzate, L. Miranda, *Chem. Commun.* **2011**, *47*, 8145-8147; d) A. Trifilenkov, A. Ilyin, V. Kysil, Y. Sandulenko, A. Ivachtchenko, *Tetrahedron Lett.* **2007**, *48*, 2563-2567; e) L. Polindara-Garcia, L. Miranda, *Org. Lett.* **2012**, *14*, 5408-5411; f) M. Ghandi, N. Zarezadeh, A. Abbasi, *Org. Biomol. Chem*. **2015**, *13*, 8211-8220; g) Z. Li, A. Kumar, A. Peshkov, E. Van der Eycken, *Tetrahedron Lett*. **2016**, *57*, 754–756
104 A. Abdessalem, R. Abderrahim, A. Agrebie, A. Santos, L. Kaïm, A. Komesky, *Chem. Commun*. **2015**, *51*, 1116-1119;
105 A. Abdessalem, R. Abderrahim, L. Kaïm, *Synlett* **2015**, *26*, 2537-2540.
106 W. Ye, G. Cai, Z. Zhuang, X. Jia and H. Zhai, *Org. Lett.*, **2005**,*7*, 3769–3771.
107 G. He, a F. Wu, W. Huang, R. Zhou, L. Ouyang, and B. Han, *Adv. Synth. Catal.* **2014**, *356*, 2311–2319
108 a) D. Koszelewski, W. Szymanski, J. Krysiak, R. Ostaszewski, *Synth. Commun*. **2008**, *38*, 1120-1127; b) T. Bousquet, M.. Jida, M. Soueidan, R. Deprez-Poulain, F. Agbossou-Niedercorn, L. Pelinski, *Tetrahedron Lett.* **2012**, *53*, 306-308.
109 A. Abdessalem, R. Abderrahim, L. Elkaïm, *Synlett* **2015**, *26*, 2537-2540.
110 For some cyclizations to γ-lactones under basic conditions, see: a) K. Sam, S. Auger, V. Luu-The, D. Poirier, *J. Med. Chem*. **1995**, *38*, 4518-4528; b) C. A., C. J. Junker, B. Schulz, J. Dickschat, *Angew. Chem. Int. Ed.* **2014**, *53*, 4346-4349; For a cyclization under acidic conditions: P. Safar, S. Marchalin, M. Soral, J. Moncol, A. Daïch, *Org. Lett.* **2017**, *19*, 4742-4745.

Chapter 3

111 Reviews: a) M. Tramontini, L. Angiolini, *Mannich-Bases, Chemistry and Uses*, CRC, Boca Raton, FL, 1994; b) *Tetrahedron* **1990**, *46*, 1791; c) M. Tramontini, L. Angiolini, N. Ghedeni, *Polymer* **1988**, *29*, 771 *46*, 1791; d) M. Tramontini, *Synthesis* **1973**, 703; e) H. Hellmann, G. Opitz, *a-Aminoalkylierung*, Verlag Chemie, Weinheim, 1960; f)

B. Reichert, *Die Mannichreaktion*, Springer, Berlin, **1959**; g) F. Blicke, *Org. React.* (*NY*) **1942**,*1*, 303.
112 M. Arend, B. Westermann and N. Risch, *Angew. Chem.,Int. Ed.*, **1998**, *37*, 1044–1070
113 a) A. Kleemann, E. Lindner, J. Engel, *Arzneimittel*, VCH, Weinheim, **1987**; b) S. Ebel, *Synthetische Arzneimittel*, VCH, Weinheim, **1979**; c) P. Traxler, U. Trinks, E. Buchdunger, H. Mett, T. Meyer, M. Muller, U. Regenass, J. Rosel, N. Lydon, *J. Med. Chem.* **1995**, *38*, 2441; d) J. Dimmock, K. Sidhu, M. Chen, R. Reid, T. Allen, G. Kao, G. Truitt, *Eur. J. Med. Chem.* **1993**, *28*, 313.
114 A. Domling, *Chem Rev.* **2006**, *106*, 17-89.
115 a) K. Ma, C. Zhang, M. Liu, *Tetrahedron Lett.* **2010**,*51*,1870-1872. b) M. Heravi, V. Zadsirjan, B. Savadjani, *Curr Org Chem.* **2014**,*18*,2857-2891.
116 a) Z. Sun, B. Chen, S. Zhang, C. Hu, *J Nat Prod.* **2004**, *67*, 1975-1979. b) M. Fraga, *Nat Prod Rep.* **2007**, *24*, 1350
117 K. Yang, H. Chen, P. Wang, *Tetrahedron*, **2011**, *67*, 4192-4195
118 F, Chen, L. Chen, H. Chen, P. Wang, *J Nat Prod.* **2009**, *72*, 18-23
119 B. Dongare, V. Chavan, S. Bhale, B. Mule, S. Kotmale, P. Bandgar. *Chin Chem Lett*. **2016**, *27*, 99-103
120 N. Azizi, F. Ebrahimi, R. Saidi, *Trans C: Chem Chem Eng.* **2009**, *16*, 94-98.
121 P. Loh, L. Chen, *Org Lett.* **2002**, *4*, 3647-3650
122 J. Halli, G. Manolikakes, *Eur J Org Chem.* **2013**, *33*, 7471-7475.
123 a) L. Gall, C. Haurena, S. Sengmany, T. Martens, M. Troupel, *J. Org Chem.* **2010**, *75*, 2645. b) L. Gall, C. Haurena, S. Sengmany, T. Martens, M. Troupel, *J. Org Chem.* **2009**, *74*, 7970.
124 R. Ramachandran, S. Jayanthi, T. Jeong, *Tetrahedron*. **2012**, *68*, 363.
125 P. Loh, L. Chen, *Org Lett.* **2002**, *4*, 3647.
126 V. Sathesh, M. Sathishkumar, G. Ramachandran, S. Rathore, I. Sathiyanarayanan, *RSC Adv*. **2013**, *3*, 23035.
127 K. Behbahani, P. Ziaei, Chin *J Chem.* **2012**, *30*, 65.
128 M. Chuan, H. Chen, Z. Gao, H. Zhang, and G. Peng, *Chem. Commun*. **2011**, *47*, 3260-3262
129 J. An, C. Wang, P. Liu, and C. Tao, *Helv. Chim. Acta* **2012**, *95*, 43.
130 M. Pouliquen, J. Blanchet,C. Lasne, and Rouden, *J. Org. Lett.* **2008**, *10*, 1029
131 a) J. Barluenga, F. Fernandez-Mari, E. Aguilar, B. Olano, *J. Org. Chem.* **1996**, *61*, 5659, and references therein; b) G. Molander, P. Stengel, *ibid.* **1995**, *60*, 6660; c) S. Davies, T. McCarthy, *Synlett* **1995**, 701; d) C. Louis, S. Mill, V. Mancuso, C. Hootele, Can. *J. Chem.* **1994**, *72*,1347; e) C. Camiletti, D. Dhavale, L. Gentilucci, C. Trombini, *J. Chem. Soc. Perkin Trans.* 1 **1993**, 3157; f) A. Dondoni, D. Perrone, *Synthesis* **1993**, 1162; g) J. Baldwin, R. Adlington, A. Russel, *Synlett* **1993**, 51; h) C. Palomo, J. Aizpurua, J. Odriozola, *J. Org. Chem.* **1994**, *59*, 5184.
132 a) Enantioselective Synthesis of β-Amino Acids (Ed.: E. Juaristi), *VCH, New York*, **1997**; b) G. Cardillo, C. Tomasini, *Chem. Soc. Rev*. **1996**, *25*, 117; c) Y. Hayashi, J. Rohde, E. Corey, *J. Am. Chem. Soc.* **1996**, *118*, 5502; d) S. Davies, G. Bhalay, *Tetrahedron: Asymmetry* **1996**, *7*, 1595; e) M. Seki, K. Matsumoto, *Tetrahedron Lett.* **1996**, *37*, 3165; f) D. Enders, H. Wahl, W. Bettray, *Angew. Chem.* **1995**, *107*, 527; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 455; g) D. Enders, J. Wiedemann, W. Bettray, *Synlett* **1995**, 369; h) M. Shimano, A. Meyers, *J. Org. Chem.* **1995**, *60*, 7445; i) S. Davies, D. Fenwick, *J. Chem. Soc. Chem. Commun.* **1995**, 1109; j) N. Sewald, K. Hiller, B. Helmreich, *Liebigs Ann.* **1995**, 925.
133 a) N. Risch, M. Arend, Methoden *Org. Chem*. **1952**,*21*, 1908; b) D. Cole, *Tetrahedron* **1994**, *50*, 9517; c) E. Kleinman in Comprehensive *Organic Synthesis*, **1991**, *2* ,p. 893; d) D. Hart, D. Ha, *Chem. Rev.* **1989**, *89*, 1447; e) M. Brown, *Heterocycles* **1989**, *29*, 2225.
134 N. Holy, R. Fowler, E. Burnett, R. Lorenz, *Tetrahedron* **1979**, *35*, 613.
135 A. Petasis, I. Akritopoulou, *Tetrahedron Lett.***1993**, *34*, 583–586.
136 A. Seayad, B. Ramalingam, K. Yushinaga, T. Nagata, C. Chai, *Org. Lett.*, **2010**, *12*, 264-267
137 P. Vsevolod, P. Olga and E. Erik, *Chem. Soc. Rev.*, **2012**, *41*, 3790-3807
138 Name Reactions A Collection of Detailed Mechanisms and Synthetic Applications **2009** Li, Jie Jack
139 J. Guermont, *Bull. Soc. Chim. Fr.*, **1953**, 386–390
140 L. Henry, *Bull. Acad. R. Belg.* **1896**, *32*, 33.
141 X. Cui, Z. Vlahakis, E. randall, A. Szarek, *Bioorg. Med. Che m.* **2008** , *16* , 1927 - 1947.
142 R. Phillips, *Organic Reactions* , ed. R. Adams, John Wiley & Sons **1959** , *10* , 144 - 178.
143 See the review: The SAMP/RAMP - hydrazone methodology in asymmetric synthesis. A. Job, F. Janeck,W. Bettray, R. Peters, D. Enders, *Tetrahedron* **2002** , *58* , 2253 - 2329.
144 J. Corey, D. Enders, *Tetrahedron Letters*.**1976**, *17*, 3–6.
145 L. Kurti, Czako, B. Burlington, MA: *Elsevier Academic Press*.**2005**, 150–151.
146 E. Denmark, T. Weber, W. Piotrowski, *J. Amer. Chem. Soc.* **1987** , *109* , 2224 - 2225.
147 D. Enders, E. Chelain, G. Raabe, *Bull. Soc. Chim. Fr.* **1997**, *134* , 299 - 306.
148 C. Ogawa, M. Sugiura, S. Kobayashi, *J. Org. Chem.* **2002** , *67* , 5359 - 5364.
149 E. Abdel-Zaher, D. Hicham, A. Nouria and E. Mohammad, *ARKIVOC* **2007**, *2*, 272-315
150 R. Brehme, *Tetrahedron lett*. **1982**, *23*, 1131 - 1134.

151 Y. Kamitori, M. Hojo, R. Masuda, T. Fujitani, S. Ohara, T. Yokoyama, *J. Org. Chem.* **1988** , *53*,129 - 135

152 M. Lassaletta, R. Fernandez, E. Martin - Zemora, E. Diez, *J. Am . Chem. Soc.* **1996** , *118*, 7002 - 7003.

153 D. Enders, M. Lassaletta, R. Fernandez, J. Vazquez, A. Prieto, *Chem. Comm.* **2002**, 498 - 499.

154 R. Fernandez, C. Gasch, M. Lassaletta, M. Llera, *Tetrahedron Lett.* **1994**, 35, 471.

155 M. Lassaletta, R. Fernandez, E. Martin - Zemora, C. Pareje, *J. Org. Chem.*, **2001**, *66*, 5201 - 5207.

156 D. Enders, P. Fey, H. Kipphardt, *Org. Synth.* **1987**, *65*, 173 - 182.

157 R. Brehme, *Tetrahedron* **1976**, *32*, 731 - 736.

158 B. Sharp, *J. Am. Chem. Soc.* **1949**, *71*, 1106.

159 a) V. Patel, S. Fernandes,A. Vyas, *Indian J. Chem. Sect. B.* **1990** , *29*, 1044. b) J. Daniel, N. Dhar, *Heterocycles.* **1991**, *32*, 8

160 G. Favrel, *Bull. Soc. Chim. Fr.* **1930**, *47*, 1290.

161 M. Salah, A. Abdallah, F. Radwan, Z. Hassaneen, *Naturforsch*, **2006** , *61b* ,1.

162 W. Ried and G. Keil, *Liebigs Ann. Chem.*, **1957**, *605*, 167.

163 A. Mustafa, W. Asker, A. Harhash, N. Nessina, H. Elnagdi, *Tetrahedron* **1965** , *21*, 217.

164 V. Atlan, H. Bienaymé, L. Elkaim and A. Majee, *Chem.Commun.*, **2000**, 1585–1586

165 L. Elkaïm, L. Gautier, L. Grimaud, L. Harwoodb, V. Michaut, *Green Chemistry*, **2003**, *5*, 477–479

166 L. Elkaim, L. Gautier, L. Grimaud, V. Michaut, *Synlett*, **2003**, 1844–1846

167 Y. Zhao, J. Zhu, C. Ni, J. Hu, *Synthesis* **2010**, *11*, 1899–1904

168 A. Gakh and K. Kirk, *Fluorinated Heterocycles*, **2009**, 1003

169 For a selection of [3 + 2] cycloadditions: (a) K. Tanaka, S. Maeno and K. Mitsuhashi, *Chem. Lett.*, **1982**, 543–546; (b) H. Xie, J. Zhu, Z. Chen, S. Li and Y. Wu, *Synthesis*, **2011**, 2767–2774.

170 (a) H. Xie, J. Zhu, Z. Chen, S. Li and Y. Wu, *Synlett*, **2012**, 935–937; (b) A. Das, C. Volla, I. Atodiresei, W. Bettray and M. Rueping, *Angew. Chem., Int. Ed.*, **2013**, *52*, 8008– 8011; (c) C. Volla, A. Das, L. Atodiresei and M. Rueping, *Chem. Commun.*, **2014**, *50*, 7889–7892.

171 H. Xie, J. Zhu, Z. Chen, S. Li and Y. Wu, *Synlett*, **2012**, 935–937;

172 (a) L. Carrocia, S. Fioravanti, L. Pellacani, P. Tardella, *Synthesis*, **2010**, 4096–4010. See also: (b) K. Tanaka, S. Maeno and K. Mitsuhashi, *J. Heterocycl. Chem.*, **1985**, *22*, 565–568; (c) A. Hegarty, M. Cashman and F. Scott, *J. Chem. Soc., Perkin Trans.* **1972**, *2*,1381–1386.

173 Z. El-Gendy, J. Morsy, H. Allimony, W. Ali, R. Abdel-Rahman, *Pharm*, **2001**, *56*,376-383

174 J. Hynes, A. Dyckman,K. Leftheris, *J. Med. Chem.* ,**2008**, *51*, 4-16

175 W. Schmitz, A. Brenner, J. Macor, *Bioorg. Med. Chem. Lett.* , **2010**, *20*, 3579-3583.

176 R. Ratz and H. Schroeder, *J. Org. Chem.*, **1958**, *23*, 1931.

177 V. Saraswathi, R. Srinivasan, *Tetrahedron Lett.* **1971**, *12*, 2315−2316.

178 A. Lukin, T. Vedekhina, N. Tovpeko, M. Krasavin, *RSC Advances* ,**2016**, *6(63)*, 57956-57959

179 D. Matthew, W. Jiao, J. Hou, Y. Jiang, and S. Gong, *J. Org. Chem.* **2018**, *83*, 4229−4238

180 (a) V. Petrov, Fluorinated Heterocyclic Compounds: *Synthesis, Chemistry, and Applications*, Wiley, Hoboken, New Jersey, 2009; (b) *Fluorinated Heterocycles*, ed. A. Gakh and K. Kirk, ACS Symposium Series, 2009, 1003.

181 (a) N. Saldabol, L. Alekseeva, B. Brizga, L. Kruzmetra, A. Zile, A. Popel, *Pharm. Chem. J*., **1968**, *2*, 626–629; (b) H. Moehrle and G. Keller, Z. Naturforsch., B: *Chem. Sci*., **2003**, *58*, 885–902.

182 E. Hahn, *Roczniki Chemii*, **1959**, *33*, 1245-7

183 a)A. Pictet, T. Spengler, *Berichte der deutschen chemischen Gesellschaft.* **1911**. *44 (3)* 2030–2036.b) M. Whaley, R. Govindachari, *Org. React.* **1951**, *6*, 74.

184 F. Alexandra, G. Domingo, C. Janine, *Eur. J. Org. Chem.* **2018**,0–0

185 B. Molino,*et al*, R. E.(AMR Technology Inc.) 2007 (US2007/0021408 A1).

186 Y. Kobayashi, T. Nakano, K. Shirahashi, A. Takeda, I. Kumadaki, *TetrahedronLett.* **1980**, *21*, 4615–4618.

187 S. Hegde, C. Jones, *J. Heterocycl. Chem.* **1993**, *30*, 1501–1508.

188 Z. Ding, L. Ju, Y. Yang, X. An, Y. Zhou, R. Li, H. Tang, C. Ding, Z. Zhan, *J. Org. Chem*. **2016**, *81*, 3936–3941

189 H. Mao, A. Lin, Z. Tang, H. Hu, C. Zhu, Y. Cheng, *Chem. Eur. J.* **2014**, *20*, 2454–2458.

190 A. Feraldi-Xypolia, G. Fredj, G. Tran, T. Tsuchiya, J. Vors, P. Mykhailiuk, D. Pardo, J. Cossy, *Asian J. Org. Chem.* **2017**, *6*, 927–935.

191 For selected recent examples: (a) L. Wei and C. Wang, *Chem. Commun.*, **2015**, *51*, 15374–15377; (b) O. Attanasi, P. Filippone, A. Mei and S. Santeusanio, *Synthesis*, **1984**, 671–672; (c) V. Atlan, C. Buron and L. Elkaim, *Synlett*, **2000**, 489–490.

192 For the generation of azoalkenes from aminohydrazones, see: (a) W. Ried and G. Kiel, *Liebigs Ann. Chem.*, **1958**, *616*, 108–124; (b) V. Atlan, L. Elkaim, L. Grimaud and N. Jana, *Synlett*, **2002**, 352–354; (c) V. Baillez, L. Elkaïm and V. Michaut, *Synth. Commun.*, **2004**, *34*, 109–118

193 O. Attanasi, L. Crescentini, G. Favi, P. Filippone, F. Mantellini, F. Perrulli and S. Santeusanio, *Eur. J. Org. Chem.*, **2009**, 3109–3127

194 A. Lemos, *Molecules*, **2009**, *14*, 4098–4119.
195 L. Wei and C. Wang, *Chem. Commun.*, **2015**, *51*, 15374–15377
196 O. Attanasi, P. Bonifazi, E. Foresti and G. Pradella, *J. Org. Chem.*, **1982**, *47*, 684–687.
197 O. Attanasi, G. Favi, F. Mantellini, G. Moscatelli, and S. Santeusanio, *J. Org. Chem.* **2011**, *76*, 2860–2866
198 V. Atlan, L. Elkaïm, C. Buron, *Synlett* **2000**, 489.

Chapter 4

199 J. Tsuji, H. Takahashi, M. Morikawa, *Tetrahedron Lett.* **1965**, *49*, 4387.
200 E. Atkins, E. Walker, M. Manyk, *Tetrahedron Lett*. **1970**, 3821.
201 M. Trost, J. Fullerton, *J. Am. Chem. Soc.* **1973**, *95*, 292-294.
202 M. Trost, E. Strege, *J. Am. Chem. Soc.* **1977**, 1649.
203 N. Mishra, S. Sharma, J. Park, S. Han, and I. Kim, *ACS Catal.*, **2017**, *7* (4), pp 2821–2847
204 M. Trost, T. Zhang, D. Sieber, *Chem. Sci.* **2010**, *1*, 427–440.
205 (a) M. Trost, L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395. (b) M. Trost, R. Machacek, A. Aponick, Acc. *Chem. Res.* **2006**, *39*, 747.
206 (a) T. Hiyama, N. Wakasa, *Tetrahedron Lett.* **1985**, *26*, 3259. (b) C. Sha, H. Jiang, J. Mao, A. Bellomo, A. Jeong, J. Walsh, *Angew. Chem. Int. Ed.* **2016**, *55*, 1070.
207 A. Leitner, C. Shu, F. Hartwig, *Org. Lett.* **2005**, *7*, 1093.
208 M. Trost, K. Chang, *Synthesis* **1993**, *8*, 824.
209 A. Evans, D. Nelson, *J. Am. Chem. Soc.* **1998**, *120*, 5581.
210 C. Bolm, J. Legros, L. Paih,L. Zani, *Chem. Rev.* **2004**, *104*, 6217.
211 W. Zhang, A. Mistsudo, T. Kondo, J. Watanabe, *Organomet. Chem.* **1993**, *450*, 197.
212 M. Trost, *Org. Process Res. Dev.* **2012**, *16*, 185.
213 M. Trost, L. Crawley, *Chem. Rev.* **2003**, *103*, 2921.
214 Y. Hong, M. Stoltz, *Eur. J. Org. Chem.* **2013**, *19*, 2745.
215 M. Trost, R. Verhoeven, M. Fortunak, *Tetrahedron Lett.***1979**, *20*, 2301.
216 M. Trost, A. Thaisrivongs, *J. Am. Chem. Soc.* **2008**, *130*, 14092.
217 K. Sheffy, K. Stille, *J. Am. Chem. Soc.* **1983**, *105*, 7173.
218 J. Tsuji, *Tetrahedron* **1986**, *42*, 4361.
219 (a) J. Tsuji, I. Shimizu, I. Minami, K. Ohashi, T. Sugiura, K. Takahashi, *J. Org. Chem.* **1985**, *50*, 1523. (b) J. Tsuji, I. Shimizu, I. Minami, Y. Ohashi, *Tetrahedron Lett.* **1982**, *23*, 4809.
220 F. Raffaella, P. Luca, *Current Organic Chemistry*, **2015**, *19*, 106-120
221 H. Thomson, *Naturally Occurring Quinones IV. Recent Advances*, 4th ed. Chapman & Hall: London, **1997**
222 I. Meyers, J. Willemsen, *Chem. Commun.* **1997**, 1573–1574.
223 F. Hallock, P. Manfredi, W. Blunt,H. Cardellina, M. Schaffer,P. Gulden,G. Bringmann,Y. Lee,J. Clardy,G. Francois, R. Boyd, *J. Org. Chem.* **1994**, *59*, 6349–6355.
224 a) H. Tye, *J. Chem. Soc., Perkin Trans. 1* **2000**, 275–298. b) L. Pu, *Chem. Rev.* **1998**, *98*, 2405–2494. c) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley: New York, **1994**
225 B. de Koning, L. Rousseau, L. van Otterlo, *Tetrahedron*, **2002**, *59*, 7-36.
226 O. Takuya, K. Takuya and M. Seijiro, *Org. lett.*, **2011**, *13*, 5390–5393
227 A. Yamashita and A. Toy, *Tetrahedron Lett.*, **1986**, *27*, 3471.
228 W. Otterlo, E. Ngidi, E. Coyanis and C. Koning, *Tetrahedron Letters*, **2003** , *44*, 311–313
229 H. Zhou, Y. Xing, J. Yao, and J. Chen, *Org. Lett.*, **2010**, *12*, 3674-3677
230 L. Rene, H. Marcel, F. Roland, K. Gerald and E. Gerhard, *Org. Lett.*, **2012**, *14*, 1448–1451
231 G. Viswanathan, M. Wang, and C. Li, *Angew. Chem. Int. Ed.* **2002**, *41*, 2138-2141
232 T. Hamura, T. Suzuki, T. Matsumoto, and K. Suzuki, *Angew. Chem. Int. Ed.* **2006**, *45*, 6294–6296
233 Y. Kuninobu, T. Tatsuzaki, T. Matsuki, and K. Takai, *J. Org. Chem.* **2011**, *76*, 7005–7009
234 X. Huang, J. Xue, *J. Org. Chem.* **2007**, *72*, 3965-3968
235 C. Malakar, D. Schmidt, J. Conrad, U. Beifuss, *Org. Lett.*, **2011**, *13*, 1972–1975
236 a) H. Feuer, (Ed.) *The Chemistry of the Nitro and Nitrous Groups*, Wiley-Interscience, New York, **1969**, Part. 1; 1970, Part. 2; 1982, Supplement F. b) N. Ono, in: *The Nitro Group in Organic Synthesis*, Wiley-VCH, New York, **2001**. c) R. Ballini, L. Barboni, F. Fringuelli, A. Palmieri, F. Pizzo, L. Vaccaro, *Green Chem.* **2007**, *9*, 823–838. d) R. Ballini, A. Palmieri, L. Barboni, *Chem. Commun.* **2008**, 2975–2985.
237 a) G. Rosini, The Henry (Nitroaldol) Reaction, in:*Comprehensive Organic Synthesis*, Vol. 2, (Eds. B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp 321–340; b) F. Luzzio, *Tetrahedron* **2001**, *57*, 915–945; c) N. Nishiwaki, *Synthesis of Nitroso, Nitro, and Related Compounds, in: Comprehensive Organic Synthesis*, 2nd edn., *Vol. 6*, (Eds.: P. Knochel, G, A. Molander), Elsevier, Oxford, **2014**, pp 100–130. d) R. Ballini, G. Bosica, D. Fiorini, A. Palmieri, M. Petrini, *Chem. Rev.* **2005**, *105*, 933–971.
238 L. Henry, *Compt. Rend. Hebd. Seances Acad. Sci.* **1896**, *120*, 1265

239 D. Evans, D. Seidel, M. Rueping, H. Lam, J. Shaw, C. Downey, *J. Am. Chem. Soc.*, **2003**, *125*, 12692–12693
240 a) R. Ballini, M. Petrini, *Tetrahedron* **2004**, *60*, 1017–1047; b) R. Ballini, M. Petrini, *Adv. Synth. Catal.* **2015**, *357*, 2371 2402
241 a) S. Ram, R. Ehrenkaufer, *Tetrahedron Lett.* **1984**, *25*, 3415–3418; b) N. Yoon, J. Choi, *Synlett* **1993**, 135–136; c) K. Chary, S. Ram, D. Iyengar, *Synlett* **2000**, 683–685; d) R. Ballini, S. Gabrielli, A. Palmieri, M. Petrini, *Curr. Org. Chem.* **2011**, *15*, 1482–1506.
242 a) H. Takechi, M. Machida, *Synthesis* **1989**, 206–207; b) D. Barton, I. Fernandez, C. Richard, S. Zard, *Tetrahedron* **1987**, *43*, 551–558.
243 A. Kende, J. Mendoza, *Tetrahedron Lett.* **1991**, *32*, 1699–1702.
244 a) B. Temelli, C. Unaleroglu, *Synlett* **2014**, *46*, 1407–1412; b) S. Tsay, P. Gani, J. Hwu, *J. Chem. Soc. Perkin Trans.* 1 **1991**, 1493–1495; c) R. Chang, K. Kim, *Tetrahedron Lett.* **1996**, *37*, 7791–7794; d) L. Kaim, A. Gacon, *Tetrahedron Lett.* **1997**, *38*, 3391–3394
245 J. Kim, J. Song, E. Ryu, *Synth. Commun.* **1994**, *24*, 1101–1105
246 R. Siya, E. Richard, *Tetrahedron Letters*, **1984**,.*25*, 3415-3418
247 T. Rui, H. Louis, *J. Am. Chem. Soc.*, **1982**, *104*, 3727–3729
248 R. Tamura, Y. Kai, M. Kakihana, K. Hayashi, M. Tsuji, T. Nakamura, and D. Oda, *J. Org. Chem.* **1986**, *51*, 4375-4385
249 T. Rui, S. Masahiro, O. Daihei, *J. Org. Chem.* **1986**, *51*, 4368-4375

Experimental part

General Considerations

NMR spectra were recorded at 298 K using a Bruker AVANCE 400 spectrometer. ^{1}H NMR spectra were recorded at 400 MHz and residual solvent peaks were used as an internal reference ($CDCl_3$ δ 7.26). Data are reported as follows: chemical shift in ppm, apparent multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet or overlap of nonequivalent resonances), coupling constants, integration. ^{13}C NMR spectra were recorded at 100 MHz and residual solvent peaks were used as an internal reference ($CHCl_3$ δ 77.16). Data are reported as follows: chemical shift in ppm, multiplicity deduced from DEPT experiments (CH_3, CH_2, CH, Cq), apparent multiplicity, coupling constants and integration where relevant. Analytical TLC was performed with Merck silica gel plates, pre-coated with silica gel 60 F254 (0.2 mm). Visualisation was effected by quenching of UV fluorescence (λmax = 254 nm or 360 nm) and by staining with p-anisaldehyde, potassium permanganate or vanillin TLC stain solutions, followed by heating. Flash chromatography employed VWR (230–400 mesh) silica gel. Reactions were conducted under a positive pressure of dry nitrogen or argon in oven-dried or flame dried glassware, and at ambient room temperature, unless specified otherwise. Anhydrous solvents were either obtained from commercial sources or dried with a MBRAUN Solvent Purification System SPS-800. Petroleum ether refers to the 40-60 °C boiling fraction. Commercially available chemicals were used as purchased, or where specified, purified by standard techniques. IR spectra were recorded on a Perkin Elmer Spectrum 65 FT-IR Spectrometer. Melting points were measured on a Stuart SMP3 melting point apparatus and are uncorrected. High resolution mass spectra were recorded on an Agilent 1100 series LC-MS (with a 6310 ion trap) under electrospray ionization (ESI). For compounds containing bromine, the mass of 79Br was used. Monowave 300 produced by Anton Paar was used for the microwave conditions.

Experimental part: chapter II

1 General Procedure

General procedure A: formation of Passerini adducts

In a round bottom flask under Argon was added the aldehyde (10 mmol, 1 equiv.), glacial acetic acid (0.60 g, 0.57 ml, 10 mmol) and the isocyanide (10 mmol, 1 equiv.). The mixture was stirred at room temperature for two days during which times it slowly solidifies. The pure Passerini adducts **II-1a** to **II-1l** were then obtained by column chromatography on silica gel when the crude were not pure enough.

General procedure B: formation of Michael adducts

To a dried microwave tube was charged with **II-1** (0.375 mmol, 100 mol%), acrylonitrile(60 mg, 1.125 mmol, 300 mol%), Cs_2CO_3 (269 mg, 0.825 mmol, 220 mol%) and acetonitrile (1.5 ml). The tube was full of Argon and capped with a silica septum. The mixture was heated to 130 ^oC for 45 min under microwave condition. After completion of present reaction, the solvent was removed under reduced pressure. The residue crude was purified by column chromatography on silica gel to afford desired product **II-3a to II-3j.**

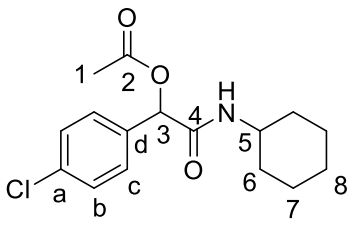
General procedure C: formation of butyrolactones

To a dried microwave tube was charged with **II-3** (0.375 mmol, 100 mol%), $Zn(OTf)_2$ (14 mg, 10 mol%) and 2,2,2-trifluoroethanol (1.5 ml). The tube was full of Argon and capped with a silica septum. The mixture was heated to 110 ^oC for 30 min under microwave condition. After completion of present reaction, the solvent was removed under reduced pressure. The residue crude was purified by column chromatography on silica gel to afford **II-4a** to **II-4i**.

2 Characterization Data

2.1 Synthesis of II-1a to II-1l

1-(4-chlorophenyl)-2-(cyclohexylamino)-2-oxoethyl acetate (**II-1a**)



$C_{16}H_{20}ClNO_3$

309.79 $g.mol^{-1}$

Following general procedure A with para-chlorobenzaldehyde (1.4 g, 10 mmol) and cyclohexyl isocyanide (1.09 g, 1.24 ml; 10 mmol) gave **II-1a** in quantitative yield (3.07 g, 9.9 mmol, 99 %).

Aspect: white solid, m.p. 160.1-161.2 ^oC (after washing with an Et_2O/PE = 5/5 mixture)

Rf: 0.44 (EA:PE = 3:7)

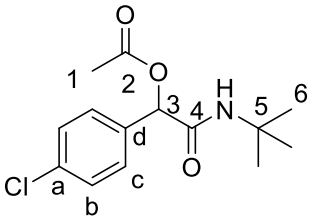
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 4H, H-b,c), 6.04 – 5.99 (m, 2H, H-NH,3), 3.77 (tdt, *J* = 12.2, 8.1, 3.9 Hz, 1H, H-5), 2.18 (s, 3H, H-1), 1.91 – 1.88 (m, 2H, H-cy), 1.71 – 1.59 (m, 3H, H-cy), 1.40 – 1.30 (m, 2H, H-cy), 1.21 – 1.09 (m, 3H, H-cy).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1 (C-2), 166.9 (C-4), 135.0 (C-a), 134.5 (C-d), 129.0 (C-b), 128.9 (C-c), 74.9 (C-3), 48.4 (C-5), 33.1 (C-6), 33.0 (C-6), 25.5 (C-8), 24.9 (C-7), 21.2 (C-1).

HRMS: calculated for $C_{16}H_{20}ClNO_3$:309.1132, found: 309.1133

I.R.(thin film): 3689, 3432, 2937, 2858, 1747, 1681, 1598, 1520, 1492, 1452, 1373, 1222, 1094, 1045, 1016 cm^{-1}

2-(tert-butylamino)-1-(4-chlorophenyl)-2-oxoethyl acetate (**II-1b**)



$C_{14}H_{18}ClNO_3$

283.75 $g.mol^{-1}$

Following general procedure A with *para*-chlorobenzaldehyde (1.4 g, 10 mmol) and *t*-butyl isocyanide (0.83 g, 1.13 ml, 10 mmol), the mixture was purified by column chromatography on silica gel (eluent: PE:Et_2O = 50:50) to afford **II-1b** (2.78 g, 9.8 mmol, 98 %).

Aspect: white solid, m.p. 127.1-127.9 ^oC

Rf: 0.35 (Et_2O:PE = 5:5)

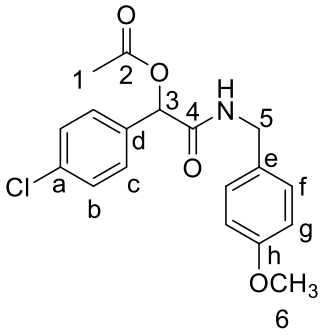
^{1}H NMR (400 MHz, $CDCl_3$) δ7.37 – 7.31 (m, 4H, H-b,c), 5.95 (s, 1H, H-NH), 5.90 (s, 1H, H-3), 2.17 (s, 3H, H-1), 1.35 (s, 9H, H-6).

^{13}C NMR (101 MHz, $CDCl_3$) δ169.1 (C-2), 167.0 (C-4), 134.9 (C-a), 134.6 (C-d), 129.0 (C-b), 128.9 (C-c), 75.0 (C-3), 51.8 (C-5), 28.8 (C-6), 21.2 (C-1).

HRMS: calculated for $C_{14}H_{18}ClNO_3$:283.0975, found: 283.0987

I.R.(thin film): 3433, 2971, 1748, 1685, 1521, 1492, 1456, 1369, 1218, 1093, 1037, 1016cm^{-1}.

1-(4-chlorophenyl)-2-((4-methoxybenzyl)amino)-2-oxoethyl acetate (**II-1c**)



$C_{18}H_{18}ClNO_4$

347.80 $g.mol^{-1}$

Following general procedure A with *para*-chlorobenzaldehyde (1.4 g, 10 mmol) and 1-(isocyanomethyl)-4-methoxybenzene (1.47 g, 10 mmol), the mixture was purified by column chromatography on silica gel (eluent: PE:EA = 70:30) to afford **II-1c** (2.78 g, 8.0 mmol, 80 %).

Aspect: white solid, m.p. 97.1-98.2 ^{o}C

Rf: 0.32 (EA:PE = 3:7)

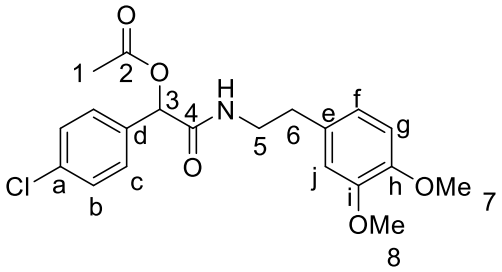
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 4H, H-b,c), 7.11 – 7.08 (m, 2H, H-f), 6.87 – 6.79 (m, 3H, H-g), 6.00 (s, 1H, H-3), 4.31 (qd, *J* = 14.7, 5.8 Hz, 2H, H-5), 3.76 (s, 3H, H-6), 2.11 (s, 3H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3 (C-2), 168.0 (C-4), 159.1 (C-h), 134.9 (C-a), 134.2 (C-d), 129.7 (C-e), 129.0 (C-b), 128.9 (C-c), 128.8 (C-f), 114.1 (C-g), 74.8 (C-3), 55.2 (C-6), 42.8 (C-5), 20.9 (C-1).

HRMS: calculated for $C_{18}H_{18}ClNO_4$: 347.0924, not found, fragment: 287.0708(-HOAc)

I.R.(thin film): 3295, 3072, 2935, 2836, 1742, 1657, 1612, 1512, 1490, 1463, 1438, 1369, 1300, 1222, 1175, 1090, 1033, 1015 cm^{-1}

1-(4-chlorophenyl)-2-((3,4-dimethoxyphenethyl)amino)-2-oxoethyl acetate (**II-1d**)



$C_{20}H_{22}ClNO_5$

391.85 g.mol^{-1}

Following general procedure A with *para*-chlorobenzaldehyde (1.4 g, 10 mmol) and 4-(2-isocyanoethyl)-1,2-dimethoxybenzene (1.91 g, 10 mmol), the mixture was purified by column chromatography on silica gel (eluent: PE:EA = 80:20) to afford **II-1d** (3.29 g, 8.4 mmol, 84 %).

Aspect: white solid, m.p. 104.8-105.7 ^{o}C

Rf: 0.43 (EA:PE = 4:6)

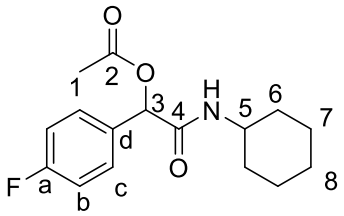
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 4H, H-b,c), 6.77 (d, *J* = 8.1 Hz, 1H, H-f), 6.67 – 6.63 (m, 2H, H-g,j), 6.17 (s, 1H, H-NH), 5.98 (s, 1H, H-3, H-3), 3.86 (s, 3H, H-7),3.84 (s, 3H, H-8), 3.55 - 3.49 (m, 2H, H-5), 2.80 – 2.71 (m, 2H, H-6), 2.10 (s, 3H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1 (C-2), 167.9 (C-4), 149.2 (C-i), 147.9 (C-h), 135.0 (C-d), 134.1 (C-a), 130.9 (C-e), 129.0 (C-c), 128.8 (C-b), 120.8 (C-f), 112.0 (C-j), 111.3 (C-g), 74.8 (C-3), 56.0 (C-7), 56.0 (C-8), 40.6 (C-5), 35.1 (C-6), 21.0 (C-1).

HRMS: calculated for $C_{20}H_{22}ClNO_5$:391.1187, found: 391.1187

I.R.(thin film): 3319, 2936, 2835, 1743, 1661, 1592, 1514, 1491, 1464, 1418, 1370, 1261, 1228, 1156, 1141, 1090, 1027, 1016cm^{-1}

2-(cyclohexylamino)-1-(4-fluorophenyl)-2-oxoethyl acetate (**II-1e**)



$C_{16}H_{20}FNO_3$

293.34 $g.mol^{-1}$

Following general procedure A with *para*-fluorobenzaldehyde (1.24 g, 10 mmol) and cyclohexyl isocyanide (1.09 g, 1.24 ml, 10 mmol), the mixture was purified by column chromatography on silica gel (eluent: PE:Et_2O = 50:50) to afford **II-1e** (2.64 g, 9.0 mmol, 90 %).

Aspect: white solid, m.p. 170.8-171.9 ^oC

Rf: 0.22 (Et_2O:PE = 5:5)

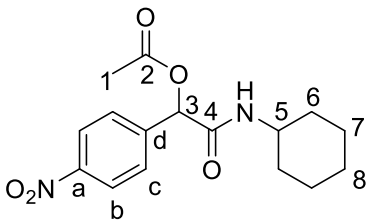
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.38 (m, 2H, H-c), 7.06 – 7.02 (m, 2H, H-b), 6.01 (s, 2H, H-NH,3), 3.83 – 3.75 (m, 1H, H-5), 2.17 (s, 3H, H-1), 1.91 (bs, 2H, H-cy), 1.72 - 1.60 (m, 3H, H-cy), 1.44 – 1.28 (m, 2H, H-cy), 1.25 – 1.07 (m, 3H, H-cy).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2 (C-2), 167.2 (C-4), 163.1(*J* = 246 Hz, C-a), 131.9 (C-d), 129.5 (C-c), 115.9 (C-b), 115.7 (C-b), 74.9 (C-3), 48.4 (C-5), 33.1 (C-6), 25.5 (C-8), 24.9 (C-7), 21.2 (C-1).

HRMS: calculated for $C_{16}H_{20}FNO_3$:293.1427, found: 293.1420

I.R.(thin film): 3296, 2932, 2855, 1747, 1657, 1538, 1510, 1371, 1223, 1159, 1045cm^{-1}

2-(cyclohexylamino)-1-(4-nitrophenyl)-2-oxoethyl acetate (**II-1f**)



$C_{16}H_{20}N_2O_5$

320.35 $g.mol^{-1}$

Following general procedure A with *para*-nitrobenzaldehyde (1.51 g, 10 mmol) and cyclohexyl isocyanide (1.09 g, 1.24 ml, 10 mmol), gave **II-1f** in quantitative yield (3.17 g, 99 %).

Aspect: white solid, m.p. 144.8-145.3 ^{o}C (after washing the solid with an Et_2O:PE = 5/5 mixture)

Rf: 0.31 (EA:PE = 3:7)

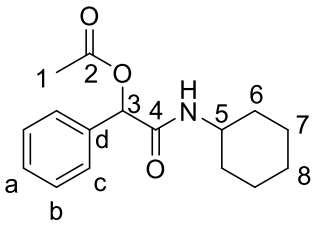
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.7 Hz, 2H, H-b), 7.62 (d, *J* = 8.8 Hz, 2H, H-c), 6.14 – 6.10 (m, 2H, H-NH,3), 3.81 – 3.72 (m, 1H, H-5), 2.23 (s, 3H, H-1), 1.93 – 1.87 (m, 2H, H-cy), 1.73 – 1.61 (m, 3H, H-cy), 1.42 – 1.29 (m, 2H, H-cy), 1.22 – 1.12 (m, 3H, H-cy).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8 (C-2), 166.1 (C-4), 148.2 (C-a), 142.9 (C-d), 128.2 (C-c), 124.0 (C-b), 74.5 (C-3), 48.6 (C-5), 33.1 (C-6), 33.0 (C-6), 25.5 (C-8), 24.9 (C-7), 21.1 (C-1).

HRMS: calculated for $C_{16}H_{20}N_2O_5$: 320.1372, not found, fragment: 195.0534

I.R.(thin film): 3692, 3433, 2938, 2858, 1751, 1682, 1608, 1524, 1452, 1373, 1350, 1217, 1049cm^{-1}

2-(cyclohexylamino)-2-oxo-1-phenylethyl acetate (**II-1g**)



$C_{16}H_{21}NO_3$

275.35 $g.mol^{-1}$

Following general procedure A with benzaldehyde (1.06 g, 10 mmol) and cyclohexyl isocyanide (1.09 g, 1.24 ml, 10 mmol), the mixture was purified by column chromatography on silica gel (eluent: PE:EA = 70:30) to afford **II-1g** (1.65 g, 8.2 mmol, 82 %).

Aspect: white solid m.p. 133.9-140.5 ^{o}C

Rf: 0.46 (EA:PE = 4:6)

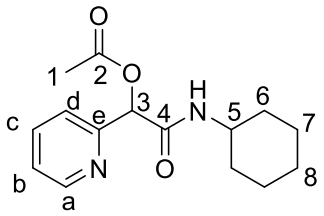
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.40 (m, 2H, H-b), 7.38 – 7.33 (m, 3H, H-a,c), 6.03 – 6.01 (m, 2H, H-NH,3), 3.83 – 3.73 (m, 1H, H-5), 2.17 (s, 3H, H-1), 1.91 – 1.87 (m, 2H, H-cy), 1.71 – 1.58 (m, 3H, H-cy), 1.40 – 1.29 (m, 2H, H-cy), 1.21 – 1.08 (m, 3H, H-cy).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3 (C-2), 167.3 (C-4), 135.9 (C-d), 129.0 (C-a), 128.8 (C-c), 127.5 (C-b), 75.6 (C-3), 48.3 (C-5), 33.0 (C-6), 25.5 (C-8), 24.8 (C-7), 21.2 (C-1).

HRMS: calculated for $C_{16}H_{21}NO_3$: 275.1521, found: 275.1530

I.R.(thin film): 3294, 3066, 2930, 2854, 1739, 1650, 1536, 1495, 1451, 1370, 1223, 1189, 1096, 1042, 1030cm^{-1}

2-(cyclohexylamino)-2-oxo-1-(pyridin-2-yl)ethyl acetate (**II-1h**)



$C_{15}H_{20}N_2O_3$

276.34 $g.mol^{-1}$

Following general procedure A with picolinaldehyde (1.07 g, 10 mmol) and cyclohexyl isocyanide (1.09 g, 1.24 ml, 10 mmol), the mixture was purified by column chromatography on silica gel (eluent: PE:EA = 60:40) to afford **II-1h** (2.27 g, 8.2 mmol, 82 %).

Aspect: white solid, m.p. 95.2-96.3 ^oC

Rf: 0.38 (EA:PE = 4:6)

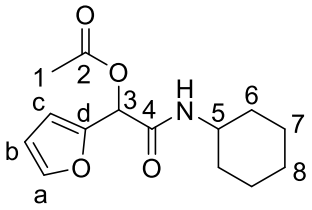
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 – 8.51 (m, 1H, H-a), 7.70 – 7.66 (m, 1H, H-c), 7.52 (d, *J* = 7.8 Hz, 1H, H-d), 7.23 – 7.20 (m, 1H, H-b), 6.72 (d, *J* = 6.4 Hz, 1H, H-NH), 6.05 (s, 1H, H-3), 3.74 – 3.66 (m, 1H, H-5), 2.20 (s, 3H, H-1), 1.87 – 1.52 (m, 5H, H-cy), 1.32 – 1.04 (m, 5H, H-cy).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4 (C-2), 166.0 (C-4), 155.1 (C-e), 149.1 (C-a), 137.2 (C-c), 123.5 (C-b), 122.2 (C-d), 75.7 (C-3), 48.4 (C-5), 32.7 (C-6), 25.5 (C-8), 24.7 (C-7), 21.0 (C-1).

HRMS: calculated for $C_{15}H_{20}N_2O_3$: 276.1474, found: 276.1471

I.R.(thin film): 3690, 3429, 3062, 3019, 2937, 2858, 1746, 1681, 1594, 1575, 1525, 1473, 1452, 1438, 1373, 1256, 1228, 1152, 1112, 1047cm^{-1}

2-(cyclohexylamino)-1-(furan-2-yl)-2-oxoethyl acetate (**II-1i**)



$C_{14}H_{19}NO_4$

265.31 $g.mol^{-1}$

Following general procedure A with furan-2-carbaldehyde (0.96 g, 10 mmol) and cyclohexyl isocyanide (1.09 g, 1.24 ml, 10 mmol), the mixture was purified by column chromatography on silica gel (eluent: PE:EA = 70:30) to afford **II-1i** (2.07 g, 7.8 mmol, 78 %).

Aspect: white solid m.p. 131.8-132.6 ^oC

Rf: 0.44 (EA:PE = 4:6)

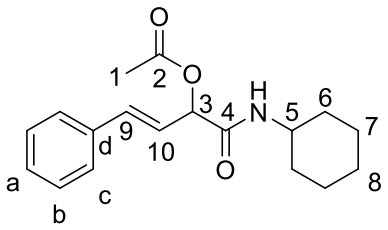
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 1.8, 0.8 Hz, 1H, H-a), 6.45 (d, *J* = 3.2 Hz, 1H, H-b), 6.33 (dd, *J* = 3.3, 1.9 Hz, 1H, H-c), 6.14 – 6.11 (m, 2H, H-NH,3), 3.84 – 3.75 (m, 1H, H-5), 2.13 (s, 3H, H-1), 1.94 – 1.86 (m, 2H, H-cy), 1.71 – 1.56 (m, 3H, H-cy), 1.39 – 1.28 (m, 2H, H-cy), 1.23 – 1.09 (m, 3H, H-cy).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1 (C-2), 165.0 (C-4), 148.3 (C-d), 143.5 (C-a), 111.2 (C-b), 110.7 (C-c), 68.8 (C-3), 48.4 (C-5), 32.9 (C-6), 32.8 (C-6), 25.5 (C-8), 24.8 (C-7), 20.9 (C-1).

HRMS: calculated for $C_{14}H_{19}NO_4$:265.1314, found: 265.1312

I.R.(thin film): 3296, 2932, 2855, 1749, 1659, 1536, 1451, 1370, 1222, 1151, 1097, 1032, 1014cm^{-1}

(E)-1-(cyclohexylamino)-1-oxo-4-phenylbut-3-en-2-yl acetate (**II-1j**)



$C_{18}H_{23}NO_3$

301.39 $g.mol^{-1}$

Following general procedure A with cinnamaldehyde (1.32 g, 10 mmol) and cyclohexyl isocyanide (1.09 g, 1.24 ml, 10 mmol), the mixture was purified by column chromatography on silica gel (eluent: PE:EA = 70:30) to afford **II-1j** (2.71 g, 9.0 mmol, 90 %). The spectra data are in agreement with the literature report.[1]

Aspect: white solid m.p. 141.8-142.6 °C

Rf: 0.49 (EA:PE = 4:6)

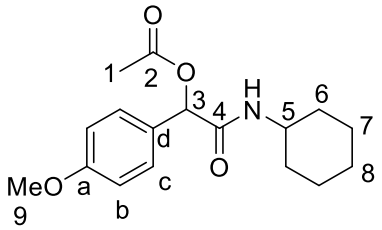
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.4 Hz, 2H), 7.35 – 7.27 (m, 3H), 6.74 (d, *J* = 16.0 Hz, 1H), 6.28 (dd, *J* = 16.0, 6.9 Hz, 1H), 5.91 (d, *J* = 7.6 Hz, 1H), 5.72 (d, *J* = 6.9 Hz, 1H), 3.86 – 3.77 (m, 1H), 2.22 (s, 3H), 1.96 – 1.93 (m, 2H), 1.74 – 1.62 (m, 3H), 1.43 – 1.33 (m, 2H), 1.23 – 1.16 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4 (C-2), 167.2 (C-4), 135.8 (C-9), 134.9 (C-d), 128.8 (C-b), 128.5 (C-a), 127.0 (C-c), 122.8 (C-10), 74.6 (C-3), 48.4 (C-5), 33.1 (C-6), 25.6 (C-8), 24.9 (C-7), 21.3 (C-1).

HRMS: calculated for $C_{18}H_{23}NO_3$: 301.1678, found: 301.1678

I.R.(thin film): 3288, 2931, 2854, 1743, 1659, 1546, 1449, 1371, 1230, 1031cm^{-1}

2-(cyclohexylamino)-1-(4-methoxyphenyl)-2-oxoethyl acetate (**II-1k**)



$C_{17}H_{23}NO_4$

305.37 $g.mol^{-1}$

Following general procedure A with *para*-methoxybenzaldehyde (1.36 g, 10 mmol) and cyclohexyl isocyanide (1.09 g, 1.24 ml, 10 mmol), the mixture was purified by column chromatography on silica gel (eluent: PE:EA = 70:30) to **II-1k** (2.20 g, 7.2 mmol, 72 %). The spectra data are in agreement with the literature report.[1]

Aspect: white solid m.p.162.5-163.4 ^{o}C

Rf: 0.33 (EA:PE = 4:6)

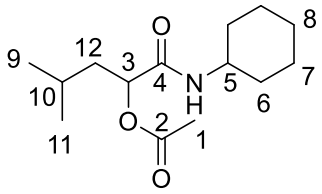
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.32 (m, 2H, H-c), 6.88 – 6.86 (m, 2H, H-b), 6.03 – 5.98 (m, 2H, H-NH,3), 3.85 – 3.78 (m, 4H, H-5,9), 2.14 (s, 3H, H-1), 1.89 – 1.86 (m, 2H, H-cy), 1.70 – 1.59 (m, 3H, H-cy), 1.38 – 1.29 (m, 2H, H-cy), 1.19 – 1.11 (m, 3H, H-cy).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4 (C-2), 167.6 (C-4), 160.1 (C-a), 129.1 (C-c), 128.0 (C-d), 114.2 (C-b), 75.2 (C-3), 55.4 (C-9), 48.3 (C-5), 33.0 (C-6), 33.0 (C-6), 25.5 (C-8), 24.8 (C-7), 21.2 (C-1).

HRMS: calculated for $C_{17}H_{23}NO_4$: 305.1627, found: 305.1623

I.R.(thin film): 3299, 2931, 2854, 1742, 1650, 1611, 1535, 1512, 1450, 1370, 1227, 1176, 1031cm^{-1}

1-(cyclohexylamino)-4-methyl-1-oxopentan-2-yl acetate (**II-1l**)



$C_{14}H_{25}NO_3$

255.36 $g.mol^{-1}$

Following general procedure A with isovaleraldehyde (0.86 g, 10 mmol) and cyclohexyl isocyanide (1.09 g, 1.24 ml, 10 mmol), the mixture was purified by column chromatography on silica gel (eluent: PE:Et_2O = 50:50) to afford **II-1l** (2.25 g, 8.8 mmol, 88 %). The spectra data are in agreement with the literature report.[250]

Aspect: white solid m.p.87.2-88.6 ^oC

Rf: 0.32 (Et_2O:PE = 5:5)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (s, 1H, H-NH), 5.12 – 5.09 (m, 1H, H-3), 3.77 – 3.69 (m, 1H, H-5), 2.11 (s, 3H, H-1), 1.92-1.86 (m, 2H, H-cy), 1.71 – 1.56 (m, 6H, H-10,12,cy), 1.37 – 1.28 (m, 2H, H-cy), 1.15 – 1.11 (m, 3H, H-cy), 0.98 – 0.88 (m, 6H, H-9,11).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9 (C-2), 169.3 (C-4), 73.0 (C-3), 47.9 (C-5), 40.8 (C-12), 33.0 (C-6), 25.5 (C-8), 24.8 (C-7), 24.6 (C-10), 23.2 (C-9), 21.9 (C-11), 21.1 (C-1).

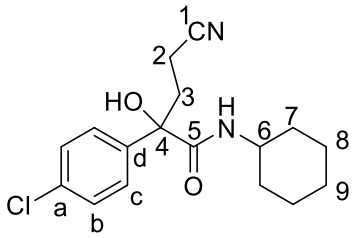
HRMS: calculated for $C_{14}H_{25}NO_3$: 255.1834, found: 255.1837

I.R.(thin film): 3288, 2930, 2855, 1744, 1648, 1536, 1450, 1370, 1224, 1063, 1028cm^{-1}

[250] Marie Cordier, Aurelie Dos Santos, Laurent El Kaim and Noisette Narboni, *Chem. Commun.*, **2015**, *51(29)*, 6411-6415

2.2 Synthesis of II-3a to II-3j

2-(4-chlorophenyl)-4-cyano-N-cyclohexyl-2-hydroxybutanamide (**II-3a**)



$C_{17}H_{21}ClN_2O_2$

320.82 $g.mol^{-1}$

Following general procedure B with 1-(4-chlorophenyl)-2-(cyclohexylamino)-2-oxoethyl acetate **II-1a** (116 mg, 0.375 mmol, 100 mol%), the mixture was purified by column chromatography on silica gel (eluent: PE:EA = 70:30) to afford **II-3a** (108 mg, 0.338 mmol, 90 %).

Aspect: colourless oil

Rf: 0.31(EA:PE = 3:7)

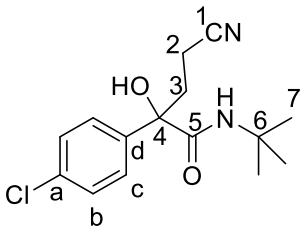
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.43 (m, 2H, H-c), 7.35 – 7.32 (m, 2H, H-b), 6.51 (d, *J* = 8.2 Hz, 1H, H-NH), 3.88 (s, 1H, H-OH), 3.68 – 3.59 (m, 1H, H-6), 2.66 – 2.59 (m, 1H, H-2), 2.45 – 2.27 (m, 3H, H-2,3), 1.85 – 1.58 (m, 5H, H-cy), 1.37 – 1.25 (m, 2H, H-cy), 1.18 – 1.02 (m, 3H, H-cy).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2 (C-5), 139.7 (C-d), 134.5 (C-a), 129.0 (C-c), 126.7 (C-b), 119.8 (C-1), 77.5 (C-4), 48.8 (C-6), 35.1 (C-3), 33.0 (C-7), 32.8 (C-7), 25.5 (C-9), 24.8 (C-8), 24.8 (C-8), 12.3 (C-2).

HRMS: calculated for $C_{17}H_{21}ClN_2O_2$: 320.1292, found: 320.1284

I.R.(thin film): 3591, 3417, 2937, 2858, 1671, 1598, 1519, 1491, 1452, 1401, 1350, 1253, 1206, 1096, 1014cm^{-1}.

N-(tert-butyl)-2-(4-chlorophenyl)-4-cyano-2-hydroxybutanamide (**II-3b**)



$C_{15}H_{19}ClN_2O_2$

294.78 $g.mol^{-1}$

Following general procedure B with 2-(tert-butylamino)-1-(4-chlorophenyl)-2-oxoethyl acetate **II-1b** (111 mg, 0.375 mmol, 100 mol%), the mixture was purified by column chromatography on silica gel (eluent:PE:Et_2O = 50:50) to afford **II-3b** (99 mg, 0.338 mmol, 90 %).

Aspect: colourless oil

Rf: 0.44 (Et_2O:PE = 6:4)

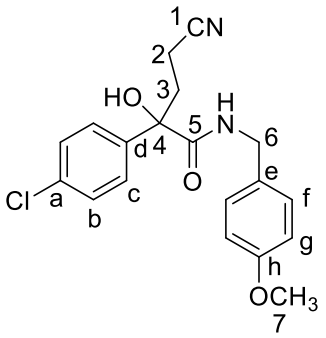
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.41 (m, 2H, H-c), 7.37 – 7.33 (m, 2H, H-b), 6.34 (s, 1H, H-NH), 3.56 (s, 1H, H-OH), 2.67 – 2.53 (m, 1H, H-2), 2.49 – 2.23 (m, 3H, H-2,3), 1.29 (s, 9H, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2 (C-5), 139.8 (C-d), 134.6 (C-a), 129.1 (C-c), 126.7 (C-b), 119.8 (C-1), 77.6 (C-4), 51.8 (C-6), 35.1 (C-3), 28.6 (C-7), 12.3 (C-2).

HRMS: calculated for $C_{15}H_{19}ClN_2O_2$:294.1135, found: 294.1139

I.R.(thin film): 3691, 3590, 2971, 2935, 2260, 1678, 1598, 1519, 1491, 1457, 1394, 1368, 1268, 1223, 1096, 1014cm^{-1}.

2-(4-chlorophenyl)-4-cyano-2-hydroxy-N-(4-methoxybenzyl)butanamide (**II-3c**)



$C_{19}H_{19}ClN_2O_3$

358.82 $g.mol^{-1}$

Following general procedure B with 1-(4-chlorophenyl)-2-((4-methoxybenzyl)amino)-2-oxoethyl acetate **II-1c** (130 mg, 0.375 mmol, 100 mol%) the mixture was purified by column chromatography on silica gel (eluent:PE:EA = 70:30) to afford **II-3c** (128 mg, 0.356 mmol, 95 %).

Aspect: yellow oil

Rf: 0.49 (EA:PE = 5:5)

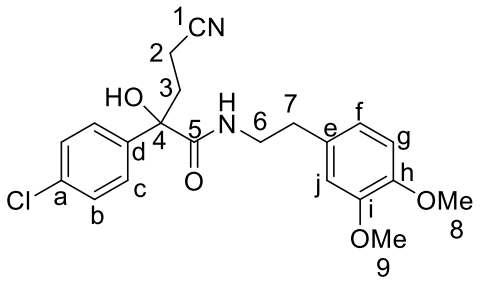
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.7 Hz, 2H, H-b), 7.30 (d, *J* = 8.7 Hz, 2H, H-c), 7.07-7.02 (m, 2H, H-f), 6.81 - 6.79 (m, 3H, H-g,NH), 4.24 (qd, *J* = 14.6, 5.8 Hz, 2H, H-6), 4.16 (s, 1H, H-OH), 3.77 (s, 3H, H-7), 2.64 – 2.54 (m, 1H, H-2), 2.35 – 2.23 (m, 3H, H-2,3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5 (C-5), 159.1 (C-h), 139.6 (C-d), 134.3 (C-a), 129.4 (C-e), 128.8 (C-f), 128.7 (C-c), 126.7 (C-b), 119.7 (C-1), 114.2 (C-g), 77.5 (C-4), 55.3 (C-6), 43.0 (C-5), 34.7 (C-3), 12.0 (C-2).

HRMS: calculated for $C_{19}H_{19}ClN_2O_3$: 358.1084, found: 358.1093

I.R.(thin film): 3690, 3590, 3426, 3007, 2937, 2839, 1676, 1613, 1514, 1491, 1465, 1303, 1251, 1176, 1096, 1035, 1014cm^{-1}.

2-(4-chlorophenyl)-4-cyano-N-(3,4-dimethoxyphenethyl)-2-hydroxybutanamide (**II-3d**)



$C_{21}H_{23}ClN_2O_4$

402.88 $g.mol^{-1}$

Following general procedure B with 1-(4-chlorophenyl)-2-((3,4-dimethoxyphenethyl)amino)-2-oxoethyl acetate **II-1d** (147 mg, 0.375 mmol, 100 mol%), the mixture was purified by column chromatography on silica gel (eluent: PE:EA = 80:20) to afford **II-3d** (119 mg, 0.296 mmol, 79 %).

Aspect: colourless oil

Rf: 0.48 (EA:PE = 4:6)

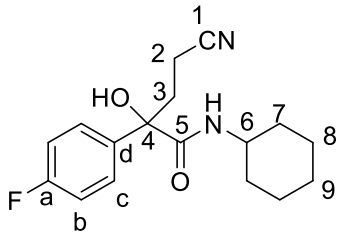
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.35 (m, 2H, H-b), 7.33 – 7.29 (m, 2H, H-c), 6.73 – 6.70 (m, 1H, H-g), 6.61 (d, *J* = 1.9 Hz, 1H, H-j), 6.58 – 6.48 (m, 2H, H-f,NH), 3.85 (s, 3H, H-8), 3.81 (s, 3H, H-9), 3.75 (s, 1H, H-OH), 3.51 – 3.41 (m, 2H, H-6), 2.70 – 2.64 (m, 2H, H-7), 2.59 – 2.47 (m, 1H, H-2), 2.32 – 2.22 (m, 3H, H-2,3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1 (C-5), 149.1 (C-i), 147.9 (C-h), 139.4 (C-d), 134.5 (C-a), 130.7 (C-e), 129.0 (C-c), 126.7 (C-b), 120.8 (C-f), 119.7 (C-1), 111.8 (C-j), 111.4 (C-g), 77.6 (C-4), 56.0 (C-6), 56.0 (C-6), 40.8 (C-7), 35.1 (C-3), 35.0 (C-3), 12.1 (C-2).

HRMS: calculated for $C_{21}H_{23}ClN_2O_4$: 402.1346, found: 402.1348

I.R.(thin film): 3691, 3593, 3427, 2938, 1676, 1594, 1516, 1491, 1262, 1238, 1158, 1142, 1028, 1014cm^{-1}.

4-cyano-N-cyclohexyl-2-(4-fluorophenyl)-2-hydroxybutanamide (**II-3e**)



$C_{17}H_{21}FN_2O_2$

304.37 $g.mol^{-1}$

Following general procedure B with 2-(cyclohexylamino)-1-(4-fluorophenyl)-2-oxoethyl acetate **II-1e** (110 mg, 0.375 mmol, 100 mol%), the mixture was purified by column chromatography on silica gel (eluent:PE:Et_2O = 30:70) to afford **II-3e** (108 mg, 0.356 mmol, 95 %).

Aspect: yellow oil

Rf: 0.44 (Et_2O:PE = 7:3)

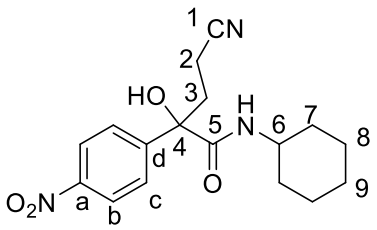
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.47 (m, , 2H, H-c), 7.06 – 7.02 (m, 2H, H-b), 6.57 (d, *J* = 7.5 Hz, 1H, H-NH), 3.89 (s, 1H, H-OH), 3.64 (bs, 1H, H-6), 2.63 – 2.60 (m, 1H, H-2), 2.43 – 2.30 (m, 3H, H-2,3), 1.85 – 1.66 (m, 5H, H-cy), 1.334 - 1.06 (m, 5H, H-cy).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4 (C-5), 162.7(*J* = 246 Hz, C-a), 137.0 (C-d), 127.1 (C-c), 119.9 (C-1), 115.8 (C-b), 77.5 (C-4), 48.7 (C-6), 35.1 (C-3), 33.0 (C-7), 32.8 (C-7), 25.5 (C-9), 24.8 (C-8), 12.3 (C-2).

HRMS: calculated for $C_{17}H_{21}FN_2O_2$: 304.1587, found: 304.1583

I.R.(thin film): 3345, 2932, 2855, 1646, 1602, 1525, 1506, 1451, 1225, 1161, 1092cm^{-1}.

4-cyano-N-cyclohexyl-2-hydroxy-2-(4-nitrophenyl)butanamide (**II-3f**)



$C_{17}H_{21}N_3O_4$

331.37 $g.mol^{-1}$

Following general procedure B with 2-(cyclohexylamino)-1-(4-nitrophenyl)-2-oxoethyl acetate **II-1f** (120 mg, 0.375 mmol, 100 mol%), the mixture was purified by column chromatography on silica gel (eluent: PE:EA = 70:30) to afford **II-3f** (48 mg, 0.146 mmol, 39 %).

Aspect: yellow oil

Rf: 0.53 (EA:PE = 4:6)

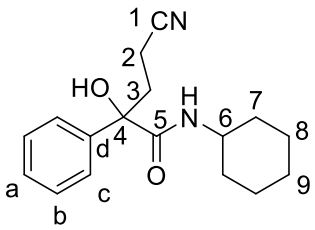
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 9.0 Hz, 2H, H-b), 7.76 (d, *J* = 9.0 Hz, 2H, H-c), 6.71 (d, *J* = 8.3 Hz, 1H, H-NH), 4.38 (s, 1H, H-OH), 3.67 – 3.58 (m, 1H, H-6), 2.77 – 2.68 (m, 1H, H-2), 2.42 – 2.31 (m, 3H, H-2,3), 1.87 – 1.82 (m, 2H, H-cy), 1.73 – 1.57 (m, 3H, H-cy), 1.37 – 1.01 (m, 5H, H-cy).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4 (C-5), 148.4 (C-a), 147.8 (C-d), 126.4 (C-c), 123.8 (C-b), 119.6 (C-1), 77.9 (C-4), 48.9 (C-6), 35.2 (C-3), 33.0 (C-7), 32.7 (C-7), 25.4 (C-9), 24.8 (C-8), 24.7 (C-8), 12.3 (C-2).

HRMS: calculated for $C_{17}H_{21}N_3O_4$:331.1532,not found, fragment: 248.0671

I.R.(thin film): 3691, 3589, 3417, 2937, 2858, 1674, 1606, 1524, 1452, 1350cm^{-1}.

4-cyano-N-cyclohexyl-2-hydroxy-2-phenylbutanamide (**II-3g**)



$C_{17}H_{22}N_2O_2$

286.38 $g.mol^{-1}$

Following general procedure B with 2-(cyclohexylamino)-2-oxo-1-phenylethyl acetate **II-1g** (103 mg, 0.375 mmol, 100 mol%), the mixture was purified by column chromatography on silica gel (eluent: PE:EA = 70:30) to afford **II-3g** (78 mg, 0.274 mmol, 73 %).

Aspect: white solid, m.p. 107.3 - 108.6 °C

Rf: 0.50 (EA:PE = 4:6)

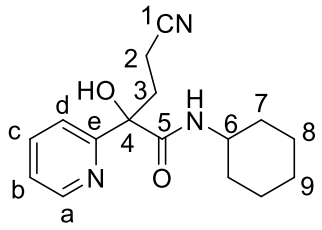
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.46 (m, 2H, H-b), 7.39 – 7.32 (m, 3H, H-c,a), 6.48 (d, *J* = 8.2 Hz, 1H, H-NH), 3.77 (s, 1H, H-OH), 3.68 – 3.61 (m, 1H, H-6), 2.64 – 2.59 (m, 1H, H-2), 2.44 – 2.28 (m, 3H, H-2,3), 1.84 – 1.75 (m, 2H, H-cy), 1.67 – 1.56 (m, 3H, H-cy), 1.35 – 1.25 (m, 2H, H-cy), 1.18 – 1.06 (m, 3H, H-cy).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6 (C-5), 141.1 (C-d), 129.0 (C-c), 128.5 (C-a), 125.2 (C-b), 119.9 (C-1), 77.8 (C-4), 48.7 (C-6), 35.1 (C-3), 33.0 (C-7), 32.8 (C-7), 25.5 (C-9), 24.8 (C-8), 12.3 (C-2).

HRMS: calculated for $C_{17}H_{22}N_2O_2$: 286.1681, found: 286.1681

I.R.(thin film): 3349, 2932, 2855, 1646, 1524, 1448, 1350, 1316, 1253, 1207, 1152, 1076cm^{-1}.

4-cyano-N-cyclohexyl-2-hydroxy-2-(pyridin-2-yl)butanamide (**II-3h**)



$C_{16}H_{21}N_3O_2$

287.36 $g.mol^{-1}$

Following general procedure B with 2-(cyclohexylamino)-2-oxo-1-(pyridin-2-yl)ethyl acetate **II-1h** (104 mg, 0.375 mmol, 100 mol%), the mixture was purified by column chromatography on silica gel (eluent: PE:EA = 70:30) to afford **II-3h** (71 mg, 0.248 mmol, 66 %).

Aspect: cream-coloured oil

Rf: 0.51 (EA:PE = 4:6)

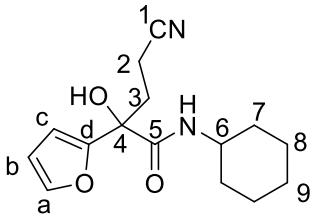
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 – 8.48 (m, 1H, H-a), 7.91 – 7.88 (m, 1H, H-d), 7.79 – 7.75 (m, 1H, H-c), 7.32 – 7.29 (m, 2H, H-b), 6.33 (s, 1H, H-NH), 3.71 – 3.61 (m, 1H, H-6), 2.58 – 2.51 (m, 1H, H-2), 2.38 – 2.23 (m, 3H, H-2,3), 1.88 – 1.85 (m, 1H, H-cy), 1.76 – 1.55 (m, 5H, H-cy), 1.40 – 1.25 (m, 2H, H-cy), 1.22 – 1.06 (m, 3H, H-cy).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1 (C-5), 157.4 (C-e), 147.2 (C-a), 138.0 (C-c), 123.7 (C-b), 121.4 (C-d), 119.5 (C-1), 76.6 (C-4), 48.6 (C-6), 36.7 (C-3), 33.0 (C-7), 32.8 (C-7), 25.5 (C-9), 24.8 (C-8), 12.2 (C-2).

HRMS: calculated for $C_{16}H_{21}N_3O_2$:287.1634,not found, fragment: 161.0707

I.R.(thin film): 3405, 3287, 2937, 2858, 1670, 1593, 1573, 1517, 1468, 1452, 1437, 1395, 1350, 1253, 1214, 1154, 1137, 1094, 1052cm^{-1}.

4-cyano-N-cyclohexyl-2-(furan-2-yl)-2-hydroxybutanamide (**II-3i**)



$C_{15}H_{20}N_2O_3$

276.34 $g.mol^{-1}$

Following general procedure B with 2-(cyclohexylamino)-1-(furan-2-yl)-2-oxoethyl acetate **II-1i** (99 mg, 0.375 mmol, 100 mol%), the mixture was purified by column chromatography on silica gel (eluent: PE:EA = 70:30) to afford **II-3i** (102 mg, 0.371 mmol, 99 %).

Aspect: white solid, m.p. 104.8-105.8 ^oC

Rf: 0.38 (EA:PE = 4:6)

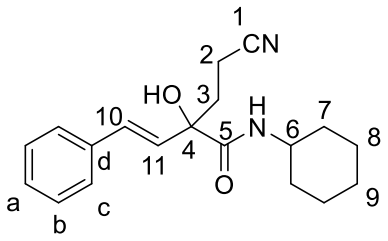
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 1.8, 0.8 Hz, 1H, H-d), 6.41 – 6.32 (m, 3H, H-c,b,NH), 4.16 (s, 1H, H-OH), 3.77 – 3.69 (m, 1H, H-6), 2.39 – 2.37 (m, 4H, H-2,3), 1.92 – 1.81 (m, 2H, H-cy), 1.72 – 1.59 (m, 3H, H-cy), 1.38 – 1.30 (m, 2H, H-cy), 1.24 – 1.08 (m, 3H, H-cy).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8 (C-5), 152.8 (C-5), 142.9 (C-d), 119.4 (C-a), 111.2 (C-1), 108.1 (C-b), 74.0 (C-c), 49.2 (C-4), 34.7 (C-6), 32.9 (C-3), 32.8 (C-7), 25.5 (C-9), 24.7 (C-8), 12.0 (C-2).

HRMS: calculated for $C_{15}H_{20}N_2O_3$: 276.1474, found: 276.1473

I.R.(thin film): 3691, 3594, 3418, 2937, 2858, 1675, 1602, 1525, 1452, 1375, 1350, 1317, 1253, 1221, 1150, 1128, 1066, 1006cm^{-1}.

(E)-2-(2-cyanoethyl)-N-cyclohexyl-2-hydroxy-4-phenylbut-3-enamide (**II-3j**)



$C_{19}H_{24}N_2O_2$

312.41 $g.mol^{-1}$

Following general procedure B with (E)-1-(cyclohexylamino)-1-oxo-4-phenylbut-3-en-2-yl acetate **II-1j** (113 mg, 0.375 mmol, 100 mol%), the mixture was purified by column chromatography on silica gel (eluent: PE:EA = 70:30) to afford **II-3j** (78 mg, 0.251 mmol, 67 %).

Aspect: yellow oil

Rf: 0.33 (EA:PE = 3:7)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.31 (m, 5H, H-a,b,c), 6.77 (d, *J* = 16.2 Hz, 1H, H-10), 6.55 (d, *J* = 8.1 Hz, 1H, H-NH), 6.44 (d, *J* = 16.2 Hz, 1H, H-11), 3.82 – 3.75 (m, 1H, H-6), 3.27 (s, 1H, H-OH), 2.57 – 2.38 (m, 3H, H-2,3), 2.22 – 2.14 (m, 1H, H-2), 1.97 – 1.87 (m, 2H, H-cy), 1.81 – 1.65 (m, 3H, H-cy), 1.45 – 1.36 (m, 2H, H-cy), 1.28 – 1.16 (m, 3H, H-cy).

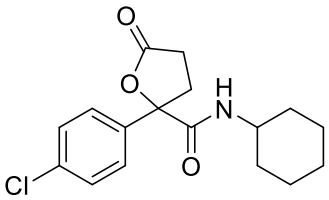
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2 (C-5), 135.7 (C-d), 130.8 (C-10), 129.7 (C-11), 128.9 (C-b), 128.5 (C-a), 126.9 (C-c), 119.9 (C-1), 48.8 (C-6), 35.2 (C-3), 33.2 (C-7), 33.0 (C-7), 25.5 (C-9), 24.9 (C-8), 12.1 (C-2).

HRMS: calculated for $C_{19}H_{24}N_2O_2$: 312.1838, not found, fragment (-C_6H_{11}CONH): 186.0914

I.R.(thin film): 3387, 2932, 2855, 1642, 1525, 1449cm^{-1}.

2.3 Synthesis of II-4a to II-4i

2-(4-chlorophenyl)-N-cyclohexyl-5-oxotetrahydrofuran-2-carboxamide (**II-4a**)



$C_{17}H_{20}ClNO_3$

321.80 $g.mol^{-1}$

Following general procedure C with 2-(4-chlorophenyl)-4-cyano-N-cyclohexyl-2-hydroxybutanamide **II-3a** (120 mg, 0.375 mmol, 100 mol%), the mixture was purified by column chromatography on silica gel (eluent: PE:EA = 90:10) to afford **II-4a** (90 mg, 0.281 mmol, 75 %).

Aspect: white solid, m.p. 113.2-113.7 ^oC

Rf: 0.47 (EA:PE = 3:7)

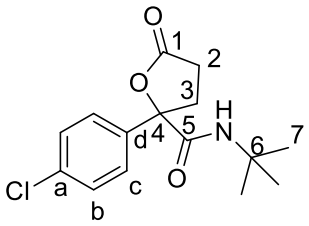
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.3 Hz, 2H, H-c), 7.34 (d, *J* = 8.4 Hz, 2H, H-b), 6.29 (d, *J* = 7.4 Hz, 1H, H-NH), 3.70 – 3.63 (m, 1H, H-6), 3.11 – 3.04 (m, 1H, H-3), 2.65 – 2.43 (m, 3H, H-2,3), 1.90-1.88 (m, 1H, H-cy), 1.71 – 1.57 (m, 4H, H-cy), 1.37 – 1.00 (m, 5H, H-cy).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0 (C-1), 169.1 (C-5), 137.5 (C-d), 134.8 (C-a), 128.9 (C-c), 126.2 (C-b), 87.5 (C-4), 48.9 (C-6), 33.6 (C-2), 33.0 (C-7), 32.7 (C-7), 28.3 (C-3), 25.4 (C-9), 24.9 (C-8), 24.8 (C-8).

HRMS: calculated for $C_{17}H_{20}ClNO_3$: 321.1132, not found, fragment: 295.0970

I.R.(thin film): 3422, 2937, 2858, 1788, 1677, 1598, 1521, 1490, 1452, 1403, 1351, 1286, 1255, 1222, 1186, 1173, 1156, 1095, 1061, 1015cm^{-1}.

N-(tert-butyl)-2-(4-chlorophenyl)-5-oxotetrahydrofuran-2-carboxamide (**II-4b**)



$C_{15}H_{18}ClNO_3$

295.76 $g.mol^{-1}$

Following general procedure C with N-(tert-butyl)-2-(4-chlorophenyl)-4-cyano-2-hydroxybutanamede **II-3b** (111 mg, 0.375 mmol, 100 mol%), the mixture was purified by column chromatography on silica gel (eluent: PE:Et_2O = 80:20) to afford **II-4b** (69 mg, 0.233 mmol, 62 %).

Aspect: white solid, m.p. 94.2-95.7 ^oC

Rf: 0.48 (Et_2O:PE = 5:5)

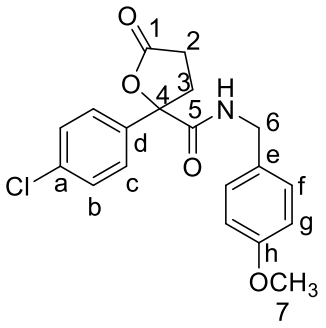
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.46 (m, 2H, H-b), 7.35 - 7.33 (m, 2H, H-c), 6.19 (s, 1H, H-NH), 3.09-3.02 (m, 1H, H-2), 2.65 – 2.39 (m, 3H, H-2,3), 1.29 (s, 9H, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ175.0 (C-1), 169.1 (C-5), 137.6 (C-d), 134.7 (C-a), 128.9 (C-c), 126.1 (C-b), 87.7 (C-4), 51.9 (C-6), 33.6 (C-2), 28.6 (C-7), 28.3 (C-3).

HRMS: calculated for $C_{15}H_{18}ClNO_3$: 295.0975, found: 295.0980

I.R.(thin film): 3691, 3423, 2972, 2260, 1787, 1683, 1599, 1520, 1491, 1458, 1395, 1368, 1279, 1219, 1187, 1173, 1095, 1065, 1040cm^{-1}.

2-(4-chlorophenyl)-N-(4-methoxybenzyl)-5-oxotetrahydrofuran-2-carboxamide (**II-4c**)



$C_{19}H_{18}ClNO_4$

359.81 $g.mol^{-1}$

Following general procedure C with 2-(4-chlorophenyl)-4-cyano-2-hydroxy-N-(4-methoxybenzyl) butanamide **II-3c** (135 mg, 0.375 mmol, 100 mol%), the mixture was purified by column chromatography on silica gel (eluent: PE:EA = 80:20) to afford **II-4c** (124 mg, 0.345 mmol, 92 %).

Aspect: white solid, m.p. 162.5-163.1 ^{o}C

Rf: 0.42 (EA:PE = 4:6)

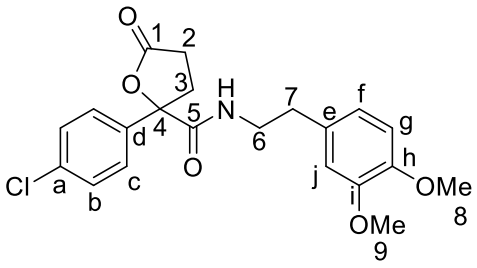
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.48 (m, 2H, H-b), 7.37 – 7.33 (m, 2H, H-c), 7.08 – 7.05 (m, 2H, H-f), 6.83 – 6.79 (m, 2H, H-g), 6.74 (s, 1H, H-NH), 4.37 - 4.27 (m, 2H, H-6), 3.77 (s, 3H, H-7), 3.15 – 3.08 (m, 1H, H-2), 2.65 – 2.45 (m, 3H, H-3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8 (C-1), 169.9 (C-5), 159.3 (C-h), 137.3 (C-d), 134.9 (C-a), 129.2 (C-e), 129.1 (C-f), 129.0 (C-c), 126.2 (C-b), 114.3 (C-g), 87.5 (C-4), 55.4 (C-7), 43.3 (C-6), 33.7 (C-2), 28.2 (C-3).

HRMS: calculated for $C_{19}H_{18}ClNO_4$: 359.0924, found: 359.0913

I.R.(thin film): 3691, 3431, 2958, 2937, 2839, 1789, 1682, 1613, 1514, 1491, 1442, 1303, 1250, 1224, 1176, 1113, 1094, 1065, 1036cm^{-1}.

2-(4-chlorophenyl)-N-(3,4-dimethoxyphenethyl)-5-oxotetrahydrofuran-2-carboxamide (**II-4d**)



$C_{21}H_{22}ClNO_5$

403.86 $g.mol^{-1}$

Following general procedure C with 2-(4-chlorophenyl)-4-cyano-N-(3,4-dimethoxyphenethyl)-2-hydroxybutanamide **II-3d** (151 mg, 0.375 mmol, 100 mol%), the mixture was purified by column chromatography on silica gel (eluent: PE:EA = 70:30) to afford **II-4d** (130 mg, 0.323 mmol, 86 %).

Aspect: white solid, m.p. 101.1-102.4 ^{o}C

Rf: 0.50 (EA:PE = 4:6)

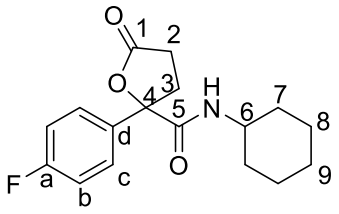
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.7 Hz, 2H, H-b), 7.32 (d, *J* = 8.7 Hz, 2H, H-c), 6.71 (d, *J* = 8.1 Hz, 1H, H-g), 6.59 (d, *J* = 1.8 Hz, 1H, H-j), 6.54 (dd, *J* = 8.1, 1.8 Hz, 1H, H-f), 6.44 (s, 1H, H-NH), 3.84 (s, 3H, H-8), 3.80 (s, 3H, H-9), 3.52 – 3.42 (m, 2H, H-6), 3.09 – 3.02 (m, 1H, H-2), 2.69 (t, *J* = 6.9 Hz, 2H, H-7), 2.49 (t, *J* = 7.9 Hz, 2H, H-3), 2.43 – 2.36 (m, 1H, H-2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8 (C-1), 167.0 (C-5), 149.1 (C-i), 147.8 (C-h), 137.4 (C-d), 134.8 (C-a), 130.6 (C-e), 128.9 (C-c), 126.1 (C-b), 120.8 (C-f), 111.8 (C-j), 111.3 (C-g), 87.6 (C-4), 56.0 (C-8), 55.9 (C-9), 40.8 (C-6), 35.1 (C-7), 33.5 (C-2), 28.1 (C-3).

HRMS: calculated for $C_{21}H_{22}ClNO_5$: 403.1187, found: 403.1190

I.R.(thin film): 3691, 3606, 3432, 3009, 2938, 2839, 1788, 1683, 1599, 1516, 1491, 1466, 1263, 1237, 1158, 1142, 1095, 1028cm^{-1}.

N-cyclohexyl-2-(4-fluorophenyl)-5-oxotetrahydrofuran-2-carboxamide (**II-4e**)



$C_{17}H_{20}FNO_3$

305.35g.mol^{-1}

Following general procedure C with 4-cyano-N-cyclohexyl-2-(4-fluorophenyl)-2-hydroxybutanemide **II-3e** (114 mg, 0.375 mmol, 100 mol%), the mixture was purified by column chromatography on silica gel (eluent: PE:Et_2O = 50:50) to afford **II-4e** (99 mg, 0.326 mmol, 87 %).

Aspect: colourless oil

Rf: 0.58 (Et_2O:PE = 7:3)

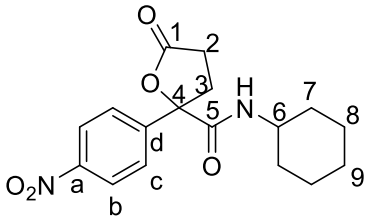
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.51 (m, 2H, H-c), 7.08 – 7.03 (m, 2H, H-b), 6.29 (d, *J* = 7.8 Hz, 1H, H-NH), 3.67 (tdt, *J* = 12.1, 8.1, 3.9 Hz, 1H, H-6), 3.10 -3.03 (m, 1H, H-2), 2.65 – 2.45 (m, 3H, H-2,3), 1.91 – 1.88 (m, 1H, H-cy), 1.74 – 1.56 (m, 4H, H-cy), 1.38 – 0.99 (m, 5H, H-cy).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.1 (C-1), 169.3 (C-5), 162.9(d, *J* = 246 Hz, C-a), 134.8 (C-d), 126.7 (C-c), 115.8 (C-b), 115.6 (C-b), 87.6 (C-4), 48.8 (C-6), 33.7 (C-2), 33.1 (C-7), 32.7 (C-7), 28.3 (C-3), 25.4 (C-9), 24.9 (C-8), 24.8 (C-8).

HRMS: calculated for $C_{17}H_{20}FNO_3$:305.1427, found: 305.1426

I.R.(thin film): 3348, 2931, 2855, 1784, 1666, 1603, 1506, 1451, 1225, 1182, 1152, 1106, 1060cm^{-1}.

N-cyclohexyl-2-(4-nitrophenyl)-5-oxotetrahydrofuran-2-carboxamide (**II-4f**)



$C_{17}H_{20}N_2O_5$

332.36 $g.mol^{-1}$

Following general procedure C with 4-cyano-N-cyclohexyl-2-hydroxy-2-(4-nitrophenyl) butanamide **II-3f** (124 mg, 0.375 mmol, 100 mol%), the mixture was purified by column chromatography on silica gel (eluent: PE:EA = 90:10) to afford **II-4f** (103 mg, 0.311 mmol, 83 %).

Aspect: white solid, m.p. 151.2-152.1 ^{o}C

Rf: 0.56 (EA:PE = 4:6)

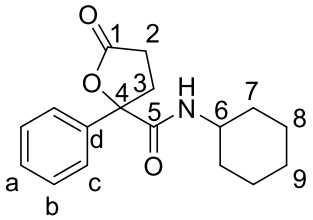
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 – 8.21 (m, 2H, H-b), 7.79 – 7.75 (m, 2H, H-c), 6.36 (d, *J* = 8.1 Hz, 1H, H-NH), 3.71 – 3.62 (m, 1H, H-6), 3.21 – 3.14(m, 1H, H-2), 2.69 – 2.44 (m, 3H, H-2,3), 1.92 – 1.88 (m, 1H, H-cy), 1.72 – 1.56 (m, 4H, H-cy), 1.35 – 1.02 (m, 5H, H-cy).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4 (C-1), 168.3 (C-5), 148.1 (C-d), 145.8 (C-a), 125.9 (C-c), 123.9 (C-b), 87.2 (C-4), 49.1 (C-6), 33.8 (C-2), 33.0 (C-7), 32.6 (C-7), 28.1 (C-3), 25.4 (C-9), 24.9 (C-8), 24.8 (C-8).

HRMS: calculated for $C_{17}H_{20}N_2O_5$: 332.1372, not found, fragment: 206.0449

I.R.(thin film): 3691, 3421, 2938, 2858, 1803, 1680, 1606, 1525, 1494, 1453, 1352, 1184, 1170, 1155, 1062cm^{-1}.

N-cyclohexyl-5-oxo-2-phenyltetrahydrofuran-2-carboxamide (**II-4g**)



$C_{17}H_{21}NO_3$

287.36 $g.mol^{-1}$

Following general procedure C with 4-cyano-N-cyclohexyl-2-hydroxy-2-phenylbutanamide **II-3g** (107 mg, 0.375 mmol, 100 mol%), the mixture was purified by column chromatography on silica gel (eluent: PE:EA = 80:20) to afford **II-4g** (78 mg, 0.27 mmol, 72 %).

Aspect: cream-coloured solid

Rf: 0.46 (EA:PE = 3:7)

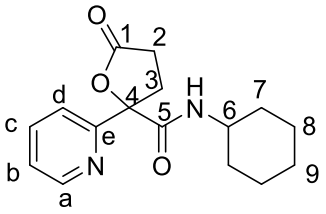
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.52 (m, 2H, H-b), 7.39 – 7.33 (m, 3H, H-c,a), 6.28 (d, *J* = 7.8 Hz, 1H, H-NH), 3.71 – 3.64 (m, 1H, H-6), 3.11 – 3.06 (m, 1H, H-2), 2.63 – 2.50 (m, 3H, H-2,3), 1.92 – 1.88 (m, 1H, H-cy), 1.74 – 1.56 (m, 4H, H-cy), 1.35 – 1.02 (m, 5H, H-cy).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3 (C-1), 169.4 (C-5), 139.0 (C-d), 128.8 (C-c), 128.7 (C-a), 124.7 (C-b), 88.1 (C-4), 48.8 (C-6), 33.5 (C-2), 33.1 (C-7), 32.7 (C-7), 28.4 (C-3), 25.5 (C-9), 24.9 (C-8), 24.8 (C-8).

HRMS: calculated for $C_{17}H_{21}NO_3$:287.1521, found: 287.1522

I.R.(thin film): 3349, 2931, 2854, 1783, 1666, 1518, 1449, 1224, 1183, 1153, 1109, 1085, 1054cm^{-1}

N-cyclohexyl-5-oxo-2-(pyridin-2-yl)tetrahydrofuran-2-carboxamide (**II-4h**)



$C_{16}H_{20}N_2O_3$

288.35 $g.mol^{-1}$

Following general procedure C with 4-cyano-N-cyclohexyl-2-hydroxy-2-(pyridin-2-yl) butanamide **II-3h** (108 mg, 0.375 mmol, 100 mol%), the mixture was purified by column chromatography on silica gel (eluent: PE:EA = 50:50) to afford **II-4h** (54 mg, 0.188 mmol, 50 %).

Aspect: white solid, m.p. 109.9-110.5 ^{o}C

Rf: 0.34 (EA:PE = 5:5)

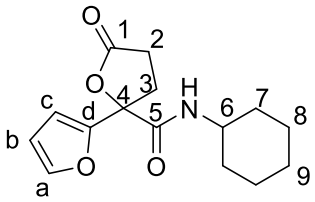
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 – 8.60 (m, 1H, H-a), 7.74 – 7.69 (m, 1H, H-d), 7.52 – 7.50 (m, 1H, H-c), 7.29 – 7.26 (m, 1H, H-b), 6.72 (d, *J* = 7.7 Hz, 1H, H-NH), 3.82 – 3.73 (m, 1H, H-6), 3.01 – 2.94 (m, 1H, H-2), 2.85 – 2.63 (m, 3H, H-3,2), 1.89 – 1.85 (m, 2H, H-cy), 1.71 – 1.57 (m, 3H, H-cy), 1.39 – 1.28 (m, 2H, H-cy), 1.20 – 1.11 (m, 3H, H-cy).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.9 (C-1), 168.6 (C-5), 157.3 (C-e), 149.5 (C-a), 137.3 (C-c), 123.8 (C-b), 120.6 (C-d), 88.0 (C-4), 48.6 (C-6), 32.9 (C-2), 31.9 (C-7), 28.7 (C-3), 25.5 (C-9), 24.8 (C-8).

HRMS: calculated for $C_{16}H_{20}N_2O_3$: 288.1474, not found, fragment: 288.1476

I.R.(thin film): 3691, 3606, 3421, 2937, 2858, 1786, 1677, 1589, 1524, 1470, 1452, 1435, 1226, 1181, 1157, 1109, 1066cm^{-1}.

N-cyclohexyl-2-(furan-2-yl)-5-oxotetrahydrofuran-2-carboxamide (**II-4i**)



$C_{15}H_{19}NO_4$

277.32 g.mol^{-1}

Following general procedure C with 4-cyano-N-cyclohexyl-2-(furan-2-yl)-2-hydroxybutanamide **II-3i** (104 mg, 0.375 mmol, 100 mol%), the mixture was purified by column chromatography on silica gel (eluent: PE:Et_2O = 80:20) to afford **II-4i** (21 mg, 0.075 mmol, 20 %).

Aspect: yellow oil

Rf: 0.42 (EA:PE = 4:6)

^{1}H NMR (400 MHz, $CDCl_3$) δδ 7.42-7.39 (m, 1H, H-d), 6.47-6.35 (m, 3H, H-c,b,NH), 3.81 (tdd, *J* = 12.1, 8.2, 4.0 Hz, 1H, H-6), 2.87 – 2.74 (m, 3H, H-2,3), 2.68 – 2.55 (m, 1H, H-2), 1.97 – 1.89 (m, 2H, H-cy), 1.76 – 1.61 (m, 3H, H-cy), 1.42 – 1.32 (m, 2H, H-cy), 1.24- 1.16 (m, 3H, H-cy).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.2 (C-1), 167.4 (C-5), 150.5 (C-d), 143.8 (C-a), 110.8 (C-b), 109.5 (C-c), 83.7 (C-4), 48.9 (C-6), 33.0 (C-7), 32.9 (C-7), 30.2 (C-2), 28.6 (C-3), 25.5 (C-9), 24.9 (C-8), 24.9 (C-8).

HRMS: calculated for $C_{15}H_{19}NO_4$: 277.1314, found: 277.1310

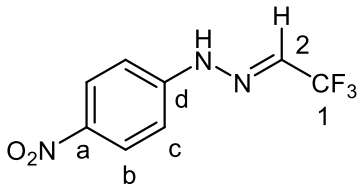
I.R.(thin film): 3361, 2931, 2855, 1757, 1710, 1663, 1529, 1451, 1347, 1259, 1185, 1154, 1098, 1067, 1009cm^{-1}.

Experimental part: chapter III

1 General Procedure

1.1 Synthesis of hydrazones

Trifluoroacetaldehyde 4-nitrophenylhydrazone



$C_8H_6F_3N_3O_2$

233.15g.mol^{-1}

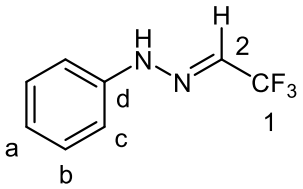
Trifluoroacetaldehyde 4-nitrophenylhydrazone was prepared by dissolving 4-nitrophenylhydrazine (380 mg, 2.5 mmol) in water (10 ml) containing concentrated hydrochloric acid (d = 1.18, 0.2 ml); Trifluoroacetaldehyde (0.4 ml, 5 mmol) was added and the solution was heated at 45 ^{o}C for 10 min, it was then kept at room temperature for 1.5 h during which time trifluoroacetaldehyde 4-nitrophenylhydrazone separated as fine yellow solid (525 mg, 90 %, 210.1^{o}C-212.5 ^{o}C). The spectra data are in agreement with the literature report.[251]

^{1}H NMR (400 MHz,DMSO) δ 11.80(s, 1H, H-NH), 8.19 (d, *J* = 9.2 Hz, 2H, H-b),7.54 (q, *J* =4.3Hz, 1H, H-2), 7.19 (d, *J* = 9.2 Hz, 2H, H-c)

^{13}C NMR (101 MHz, DMSO) δ 149.2 (C-d), 140.5 (C-a), 126.8(q, *J* = 37 Hz, C-2), 126.1 (C-b), 121.2(q, *J* = 267 Hz, C-1), 112.5 (C-c).

[251] Wojciechowska, Agata; Jasiński, Marcin; Kaszyński, Piotr ,*Tetrahedron*, **2015** , *71*, ,2349 – 2356.

Trifluoroacetaldehyde phenylhydrazone



$C_8H_7F_3N_2$

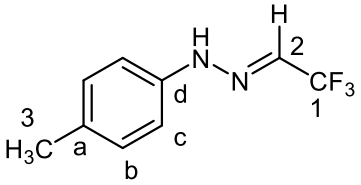
188.15 g.mol^{-1}

Trifluoroacetaldehyde phenylhydrazone was prepared by dissolving phenylhydrazine (271 mg, 2.5 mmol) in water (10 ml) containing concentrated hydrochloric acid (d = 1.18, 0.2 ml); Trifluoroacetaldehyde (0.4 ml, 5 mmol) was added and the solution was heated at 45 ^{o}C for 10 min, it was then kept at room temperature for 1.5 h during which time trifluoroacetaldehyde phenylhydrazone separated as fine yellow solid (385 mg, 82 %, 68.2 ^{o}C-69.8 ^{o}C). The spectra data are in agreement with the literature report.[1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H, H-NH), 7.24-7.20 (m, 2H, H-b), 7.01-6.98 (m, 2H, H-c), 6.94 – 6.87 (m, 1H, H-a), 6.87 – 6.79 (m, 1H, H-2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.7(C-d), 129.6(C-b), 122.4(q, *J* = 39 Hz, C-2), 122.3(C-c), 121.2(q, *J* = 268 Hz, C-1), 113.6 (C-c)

Trifluoroacetaldehyde 4-methylphenylhydrazone



$C_9H_9F_3N_2$

202.18 g.mol^{-1}

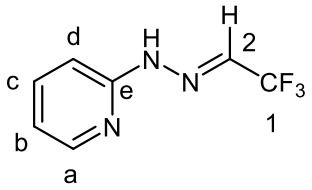
Trifluoroacetaldehyde 4-methylphenylhydrazone was prepared by dissolving 4-methylphenylhydrazine (306 mg, 2.5 mmol) in water (10 ml) containing concentrated hydrochloric acid (d = 1.18, 0.2 ml); Trifluoroacetaldehyde (0.4 ml, 5 mmol) was added and the solution was heated at 45 ^{o}C for 10 min, it was then kept at room temperature for 1.5 h during which time trifluoroacetaldehyde 4-methylphenylhydrazone separated as fine yellow solid (355 mg, 70 %, 89.7 ^{o}C-90.6 ^{o}C). The spectra data are in agreement with the literature

report.[1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H, H-NH), 7.15-7.13 (m, 2H, H-b), 7.04-6.98 (m, 2H, H-c), 6.90 (q, *J* =4.1Hz, 1H, H-2), 2.34(s, 3H, H-3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.3 (C-d), 131.7 (C-a), 129.9 (C-b), 121.7(q, *J* = 39 Hz, C-2), 121.2(q, *J* = 268 Hz, C-1), 113.6 (C-c), 20.6 (C-3).

(E)-2-(2-(2,2,2-trifluoroethylidene)hydrazinyl)pyridine



$C_7H_6F_3N_3$

189.14 g.mol^{-1}

A solution of 2-bromopyridine (1.42 g, 9 mmol) and hydrazine hydrate (20 mmol) was placed in a three-necked flask fitted with mechanical stir, a dropping funnel and thermometer. The reaction mixture was stirred at reflux for 4h under an inert atmosphere of N_2. The reaction mixture was next extracted at room temperature with Et_2O (3×50 ml). The organic layer was evaporated under reduced pressure to provide, in 50% yield, the 2-hydrazinepyridye as a white oil (850 mg, 50 %).[252]

2-hydrazinepyridye (1 mmol) was added to a solution of Trifluoroacetaldehyde (1.25 mmol) in EtOH (2 ml) .The stirred mixture was heated to reflux for 10 h under Ar. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was washed by n-hexane (3×5 ml) to afford a white solid (170 mg, 90 %,159.6 ^{o}C-161.9 ^{o}C).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99 (s, 1H, H-NH), 8.16 (d, *J* = 4.9 Hz, 1H, H-a), 7.79 – 7.67 (m, 1H, H-c), 7.42 (d, *J* = 8.4 Hz, 1H, H-d), 7.13 (q, *J* = 3.9 Hz, 1H, H-2), 7.02 – 6.92 (m, 1H, H-b).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1 (C-e), 146.4 (C-a), 139.2 (C-c), 124.9(q, *J* = 39 Hz, C-2), 120.9(q, *J* = 268 Hz, C-1), 117.7 (C-b), 108.7 (C-d).

HRMS: calculated for $C_{13}H_{15}F_3N_4O_3$: 189.0514, found: 189.0510

[252] Todeschini, Adriane R.; Barreiro, Eliezer J. *European Journal of Medicinal Chemistry,* **1998** , *33*, 189 - 199

I.R.(thin film): 3334,1626,1599, 1580, 1519, 1446, 1354, 1301, 1290, 1266, 1136, 1092cm^{-1}.

1.2 General procedure for the formation of Mannich adducts

Hydrazone (0.5 mmol) was added to a solution of secondary amine (0.5 mmol) and aldehyde (0.5 mmol) in 3ml toluene. The stirred mixture was heated to reflux under Ar for 12 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel to afford the desired product.

1.3 General procedure for the formation of 1,2,4-Triazine derivatives

Hydrazone (0.5 mmol) was added to a solution of primary amine (0.5 mmol) and aldehyde (1 mmol) in 3ml toluene. The stirred mixture was heated to reflux under Ar for 12 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel to afford the desired product.

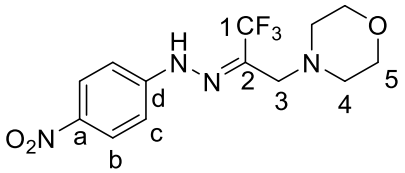
1.4 General procedure for the formation of dihydropyridazine derivatives.

Mannich adduct (0.5 mmol) was dissolved in 3 mL diketone, and the stirred mixture was heated to 130 ^{o}C under Ar for 12 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel to afford the desired product.

III-2 was dissolved in 3 ml acetone and the mixture was heated to 130 ^{o}C under microwave condition for 1 h.

2 Characterization Data

(Z)-4-(3,3,3-trifluoro-2-(2-(4-nitrophenyl)hydrazono)propyl)morpholine **III-1**



$C_{13}H_{15}F_3N_4O_3$

332.28 $g.mol^{-1}$

Trifluoroacetaldehyde 4-nitrophenylhydrazone (0.5 mmol, 117 mg, 1.0 eq) was added to a solution of morpholine (0.5 mmol, 44 mg, 1.0 eq) and formaldehyde (0.5 mmol, 41 mg, 37 %, 1.0 eq) in 3 ml toluene. The stirred mixture was heated to reflux under Ar for 12 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE = 50:50) to afford the desired product **III-1** (94 %, 156 mg).

Aspect: light yellow solid, m. p. 118.5-119.7 ^oC.

Rf: 0.43 (Et_2O:PE = 50:50)

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.72 (s, 1H, H-NH), 8.18 (d, *J* = 9.2 Hz, 2H, H-b), 7.12 (d, *J* = 9.2 Hz, 2H, H-c), 3.76 (bs, 4H, H-5), 3.52 (s, 2H, H-3), 2.55 (bs, 4H, H-4).

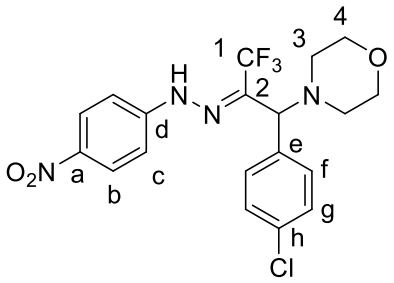
^{13}C NMR (101 MHz, $CDCl_3$) δ 148.7 (C-d), 141.9 (C-a), 130.8(q, *J* = 34 Hz, C-2), 126.1(C-b), 121.2(q, *J* = 271 Hz, C-1), 112.8(C-c), 67.0(C-5), 54.8(C-3), 52.8(C-4).

HRMS: calculated for $C_{13}H_{15}F_3N_4O_3$: 332.1096, found: 332.1081

I.R.(thin film): 3689, 2838, 1595, 1511, 1377, 1338, 1325, 1258, 1207, 1124, 1111, 1052, 1005cm^{-1}.

(Z)-4-(1-(4-chlorophenyl)-3,3,3-trifluoro-2-(2-(4-nitrophenyl)hydrazono)propyl)morpholine

III-2



$C_{19}H_{18}ClF_3N_4O_3$

442.82 $g.mol^{-1}$

Trifluoroacetaldehyde 4-nitrophenylhydrazone (0.5 mmol, 117 mg, 1.0 eq) was added to a solution of morpholine (0.5 mmol, 44 mg, 1.0 eq) and p-chlorobenzaldehyde (0.5 mmol, 70 mg, 1.0 eq) in 3 ml toluene. The stirred mixture was heated to reflux under Ar for 12 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE = 60:40) to afford the desired product **III-2** (99 %, 220 mg).

Aspect: light yellow solid, m. p. 88.2-90.1 ^oC.

Rf: 0.50 (Et_2O:PE = 60:40)

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.61 (s, 1H, H-NH), 8.22 (d, *J* = 9.2 Hz, 2H, H-b), 7.36-7.31 (m, 4H, H-f,g), 7.20 (d, *J* = 9.1 Hz, 2H, H-c), 4.22 (s, 1H, H-3), 3.74 (bs, 4H, H-5), 2.47 (bs, 4H, H-4).

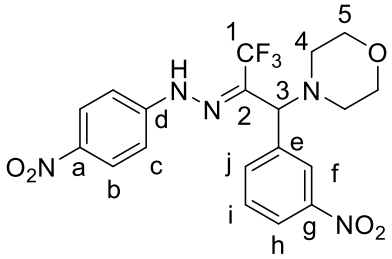
^{13}C NMR (101 MHz, $CDCl_3$) δ 148.4 (C-d), 142.0 (C-a), 135.4 (C-h), 133.4 (C-e), 132.6(q, *J* = 33 Hz, C-2), 130.2 (C-f), 129.8 (C-g), 126.2 (C-b), 121.3(q, *J* = 272 Hz, C-1), 112.8 (C-c), 71.1 (C-3), 67.1 (C-5), 52.2 (C-4).

HRMS: calculated for $C_{19}H_{18}ClF_3N_4O_3$: 442.1020, found: 442.1016

I.R.(thin film): 3691, 2973, 2853, 1595, 1511, 1494, 1337, 1256, 1209, 1159, 1122, 1112, 1016cm^{-1}

(Z)-4-(3,3,3-trifluoro-1-(3-nitrophenyl)-2-(2-(4-nitrophenyl)hydrazono)propyl)morpholine

III-3



$C_{19}H_{18}F_3N_5O_5$

453.38 $g.mol^{-1}$

Trifluoroacetaldehyde 4-nitrophenylhydrazone (0.5 mmol, 117 mg, 1.0 eq) was added to a solution of morpholine (0.5 mmol, 44 mg, 1.0 eq) and 3-nitrobenzaldehyde (0.5 mmol, 76 mg, 1.0 eq) in 3 ml toluene. The stirred mixture was heated to reflux under Ar for 12 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: EA:PE = 40:60) to afford the desired product **III-3** (99 %, 225 mg).

Aspect: yellow solid, m. p. 155.1-156.6 ^{o}C.

Rf: 0.47 (EA:PE = 40:60)

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.46 (s, 1H, H-NH), 8.30 – 8.20 (m, 4H, H-b,h,i), 7.76 (d, *J* = 7.8 Hz, 1H, H-j), 7.61 (t, *J* = 8.0 Hz, 1H, H-f), 7.27 – 7.20 (m, 2H, H-c), 4.39 (s, 1H, H-3), 3.91 – 3.64 (m, 4H, H-5), 2.65 – 2.41 (m, 4H, H-4).

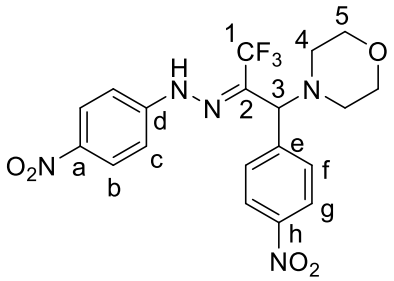
^{13}C NMR (101 MHz, $CDCl_3$) δ 148.8 (C-g), 148.1 (C-d), 142.4 (C-a), 137.0 (C-e), 134.6 (C-j), 131.2(q, *J* = 33 Hz, C-2), 130.8 (C-f), 126.2 (C-b), 124.4 (C-h), 123.9 (C-i), 123.7(q, *J* = 272 Hz, C-1), 113.1 (C-c), 70.8 (C-3), 67.0 (C-5), 52.3 (C-4).

HRMS: calculated for $C_{19}H_{18}F_3N_5O_5$: 453.1260, found: 453.1252.

I.R.(thin film): 3692, 3094, 2973, 2854, 2258, 1595, 1536, 1513, 1351, 1338, 1257, 1249, 1210, 1160, 1123, 1123, 1112, 1035cm^{-1}

(Z)-4-(3,3,3-trifluoro-1-(4-nitrophenyl)-2-(2-(4-nitrophenyl)hydrazono)propyl)morpholine

III-4



$C_{19}H_{18}F_3N_5O_5$

453.38 g.mol^{-1}

Trifluoroacetaldehyde 4-nitrophenylhydrazone (0.5 mmol, 117 mg, 1.0 eq) was added to a solution of morpholine (0.5 mmol, 44 mg, 1.0 eq) and 3-nitrobenzaldehyde (0.5 mmol, 76 mg, 1.0 eq) in 3 ml toluene. The stirred mixture was heated to reflux under Ar for 12 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: EA:PE = 20:80) to afford the desired product **III-4** (99 %, 224 mg).

Aspect: yellow solid m.p. 123.5-124.6 ^{o}C

Rf: 0.20 (EA:PE = 20:80)

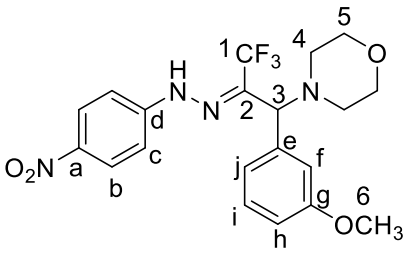
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.51 (s, 1H, H-NH), 8.25-8.21 (m, 4H, H-b,g), 7.61 (d, *J* = 8.7 Hz, 2H, H-f), 7.22 (d, *J* = 9.1 Hz, 2H, H-c), 4.38 (s, 1H, H-3), 3.90 – 3.67 (m, 4H, H-5), 2.63 – 2.41 (m, 4H, H-4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.4 (C-h), 148.1 (C-d), 142.3 (C-a), 142.0 (C-e), 131.2(q, *J* = 33 Hz, C-2), 129.9 (C-f), 126.2 (C-b), 124.7 (C-g), 121.2(q, *J* = 270 Hz, C-1), 113.0 (C-c), 70.9 (C-3), 67.0 (C-5), 52.3 (C-4).

HRMS: calculated for $C_{19}H_{18}F_3N_5O_5$:453.1260, found: 453.1269

I.R.(thin film): 2972, 2854, 1594, 1529, 1338, 1245, 1151, 1123, 1112, 1034cm^{-1}

(Z)-4-(3,3,3-trifluoro-1-(3-methoxyphenyl)-2-(2-(4-nitrophenyl)hydrazono)propyl)morpholine **III-5**



$C_{20}H_{21}F_3N_4O_4$

438.41 $g.mol^{-1}$

Trifluoroacetaldehyde 4-nitrophenylhydrazone (0.5 mmol, 117 mg, 1.0 eq) was added to a solution of morpholine (0.5 mmol, 44 mg, 1.0 eq) and 3-methoxybenzaldehyde (0.5 mmol, 68 mg, 1.0 eq) in 3 ml toluene. The stirred mixture was heated to reflux under Ar for 12 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE = 50:50) to afford the desired product **III-5** (99 %, 216 mg).

Aspect: yellow oil

Rf: 0.38 (Et_2O:PE = 50:50)

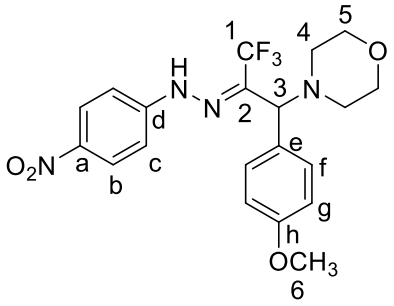
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.67 (s, 1H, H-NH), 8.22 (d, *J* = 9.2 Hz, 2H, H-b), 7.29 (t, *J* = 8.0 Hz, 1H, H-h), 7.22 – 7.15 (m, 2H, H-c), 7.00 – 6.86 (m, 3H, H-f,i,j), 4.20 (s, 1H, H-3), 3.77(s,3H, H-6), 3.75 (bs ,4H, H-5), 2.49 (bs, 4H, H-4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.2 (C-g), 148.5 (C-d), 141.9 (C-a), 136.4 (C-e), 133.0(q, *J* = 32 Hz, C-2), 130.6 (C-h), 126.2 (C-b), 121.3(q, *J* = 273 Hz, C-1) 121.0 (C-f), 115.3 (C-j), 113.9 (C-i), 112.7 (C-c), 71.7 (C-3), 67.2 (C-5), 55.4 (C-6), 52.2 (C-4).

HRMS: calculated for $C_{20}H_{21}F_3N_4O_4$: 438.1515, found: 438.1499.

I.R.(thin film): 3692, 3109, 2971, 2853, 2838, 1596, 1511, 1455, 1336, 1255, 1209, 1159, 1122, 1034cm^{-1}

(Z)-4-(3,3,3-trifluoro-1-(4-methoxyphenyl)-2-(2-(4-nitrophenyl)hydrazono)propyl)morpholine **III-6**



$C_{20}H_{21}F_3N_4O_4$

438.41 g.mol^{-1}

Trifluoroacetaldehyde 4-nitrophenylhydrazone (0.5 mmol, 117 mg, 1.0 eq) was added to a solution of morpholine (0.5 mmol, 44 mg, 1.0 eq) and 3-methoxybenzaldehyde (0.5 mmol, 68 mg, 1.0 eq) in 3ml toluene. The stirred mixture was heated to reflux under Ar for 12 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE = 50:50) to afford the desired product **III-6** (82 %, 179 mg).

Aspect: light yellow solid, m. p. 189.9-192.1 ^oC.

Rf: 0.35 (Et_2O:PE = 50:50)

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.75 (s, 1H, H-NH), 8.22 (d, *J* = 9.2 Hz, 2H, H-b), 7.29-7.18 (m, 4H, H-f,c), 6.88 (d, *J* = 8.8 Hz, 2H, H-g), 4.19 (s, 1H, H-3), 3.79 (s, 3H, H-6), 3.75(bs, 4H, H-5), 2.47 (bs, 4H, H-4).

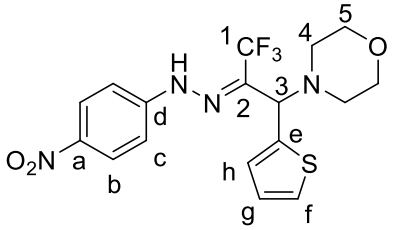
^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3 (C-h), 148.6 (C-d), 141.7 (C-a), 133.7(q, *J* = 32 Hz, C-2), 130.2 (C-f), 126.8 (C-e), 126.2 (C-b), 121.3(q, *J* = 273 Hz, C-1), 114.8 (C-g), 112.7 (C-c), 71.2 (C-3), 67.2 (C-5), 55.4 (C-6), 52.1 (C-4).

HRMS: calculated for $C_{20}H_{21}F_3N_4O_4$: 438.1515, found: 438.1520.

I.R.(thin film): 3689, 2971, 2853, 2839, 1596, 1513, 1457, 1336, 1255, 1207, 1157, 1112, 1034cm^{-1}

(Z)-4-(3,3,3-trifluoro-2-(2-(4-nitrophenyl)hydrazono)-1-(thiophen-2-yl)propyl)morpholine

III-7



$C_{17}H_{17}F_3N_4O_3S$

414.40 g.mol^{-1}

Trifluoroacetaldehyde 4-nitrophenylhydrazone (0.5 mmol, 117 mg, 1.0 eq) was added to a solution of morpholine (0.5 mmol, 44 mg, 1.0 eq) and thiophene-2-carbaldehyde (0.5 mmol, 57 mg, 1.0 eq) in 3 ml toluene. The stirred mixture was heated to reflux under Ar for 15 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE = 50:50) to afford the desired product **III-7** (48 %, 100 mg).

Aspect: black solid, m. p. 135.1-137.2 ^{o}C.

Rf: 0.5 (Et_2O:PE = 50:50)

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.14 (s, 1H, H-NH), 8.26 – 8.19 (m, 2H, H-b), 7.30 (dd, *J* = 4.2, 0.7 Hz, 1H, H-g), 7.22 – 7.16 (m, 2H, H-c), 7.12 (dd, *J* = 3.5, 1.0 Hz, 1H, H-h), 6.99 (dd, *J* = 5.1, 3.6 Hz, 1H, H-f), 4.59 (s, 1H, H-3), 3.75 (bs, 4H, H-5), 2.65 – 2.36 (m, 4H, H-4).

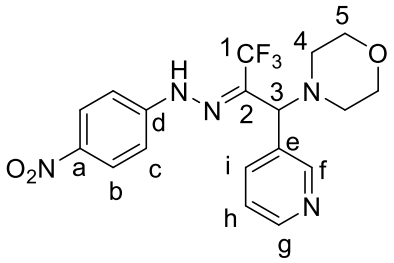
^{13}C NMR (101 MHz, $CDCl_3$) δ 148.2 (C-d), 142.1 (C-a), 136.2 (C-e), 131.8(q, *J* = 33 Hz, C-2), 129.6 (C-h), 127.2 (C-g), 127.0 (C-f), 126.2 (C-b), 121.3(q, *J* = 272 Hz, C-1), 112.9 (C-c), 67.2 (C-5), 65.5 (C-3), 51.9 (C-4).

HRMS: calculated for $C_{17}H_{17}F_3N_4O_3S$: 414.0973, found: 414.0974.

I.R.(thin film): 3689, 1596, 1511, 1337, 1254, 1210, 1160, 1112, 1032cm^{-1}

(Z)-4-(3,3,3-trifluoro-2-(2-(4-nitrophenyl)hydrazono)-1-(pyridin-3-yl)propyl)morpholine

III-8



$C_{18}H_{18}F_3N_5O_3$

409.37 $g.mol^{-1}$

Trifluoroacetaldehyde 4-nitrophenylhydrazone (0.5 mmol, 117 mg, 1.0 eq) was added to a solution of morpholine (0.5 mmol, 44 mg, 1.0 eq) and nicotinaldehyde (0.5 mmol, 54 mg, 1.0 eq) in 3 ml toluene. The stirred mixture was heated to reflux under Ar for 15 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE = 50:50) to afford the desired product **III-8** (99 %, 201 mg).

Aspect: white solid, m. p. 182.6-183.4 ^oC.

Rf: 0.45 (Et_2O:PE = 50:50)

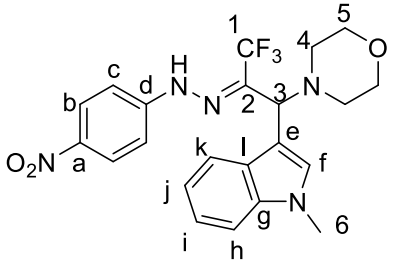
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.52 (s, 1H, H-NH), 8.71 – 8.58 (m, 2H, H-f,g), 8.20 (d, *J* = 9.1 Hz, 2H, H-b), 7.73 (dd, *J* = 7.9, 1.6 Hz, 1H, H-i), 7.33 (dd, *J* = 7.9, 4.8 Hz, 1H, H-h), 7.25 – 7.15 (m, 2H, H-c), 4.28 (s, 1H, H-3), 3.76 (bs, 4H, H-5), 2.49 (bs, 4H, H-4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.7 (C-g), 150.1 (C-f), 148.2 (C-d), 142.1 (C-a), 136.1 (C-i), 131.8(q, *J* = 33 Hz, C-2), 131.0 (C-e), 126.1 (C-b), 124.3 (C-h), 121.1(q, *J* = 272 Hz, C-1), 112.9 (C-c), 69.1 (C-3), 66.9 (C-5), 52.2 (C-4).

HRMS: calculated for $C_{18}H_{18}F_3N_5O_3$: 409.1362, found: 409.1373.

I.R.(thin film): 3689, 3039, 2973, 2916, 2895, 2854, 2836, 2768, 2446, 2233, 1595, 1513, 1456, 1337, 1264, 1209, 1159, 1123, 1112, 1035cm^{-1}

(Z)-4-(3,3,3-trifluoro-1-(1-methyl-1H-indol-3-yl)-2-(2-(4-nitrophenyl)hydrazono)propyl)morpholine **III-9**



$C_{22}H_{22}F_3N_5O_3$

461.45 g.mol^{-1}

Trifluoroacetaldehyde 4-nitrophenylhydrazone (0.5 mmol, 117 mg, 1.0 eq) was added to a solution of morpholine (0.5 mmol, 44 mg, 1.0 eq) and 1-methyl-1*H*-indole-3-carbaldehyde (0.5 mmol, 80 mg, 1.0 eq) in 3ml toluene. The stirred mixture was heated to reflux under Ar for 15 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE = 50:50) to afford the desired product **III-9** (58 %, 133 mg).

Aspect: gray solid, m. p. 178.1-180.0 ^{o}C.

Rf: 0.42 (Et_2O:PE = 50:50)

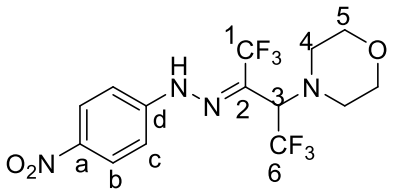
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.75 (s, 1H, H-NH), 8.24 (d, *J* = 9.0 Hz, 2H, H-b), 7.63 (d, *J* = 7.9 Hz, 1H, H-k), 7.39 – 7.10 (m, 6H, H-c,f,h,i,j), 4.64 (s, 1H, H-3), 3.77 (s, 3H, H-6), 3.72(bs, 4H, H-5), 2.60 (bs, 4H, H-4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.8 (C-d), 141.6 (C-a), 136.6 (C-g), 135.2(q, *J* = 31 Hz, C-2), 128.1 (C-f),127.2 (C-l), 126.2 (C-b), 122.5 (C-i), 121.2(q, *J* = 273 Hz, C-1), 120.4 (C-j), 118.5 (C-k), 112.5 (C-c), 109.9 (C-h), 107.3 (C-e), 67.3 (C-5), 61.6 (C-3), 51.9 (C-4), 33.2 (C-6).

HRMS: calculated for $C_{22}H_{22}F_3N_5O_3$: 461.1675, not found, fragment 373.0319

I.R.(thin film): 3689, 2971, 2853, 1596, 1509, 1425, 1334, 1297, 1256, 1207, 1154, 1113, 1071, 1034, 1005cm^{-1}

(Z)-4-(1,1,1,4,4,4-hexafluoro-3-(2-(4-nitrophenyl)hydrazono)butan-2-yl)morpholine **III-10**



$C_{14}H_{14}F_6N_4O_3$

400.28 g.mol^{-1}

Trifluoroacetaldehyde 4-nitrophenylhydrazone (0.5 mmol, 117 mg, 1.0 eq) was added to a solution of morpholine (0.5 mmol, 44 mg, 1.0 eq) and trifluoroacetaldehyde (0.5 mmol, 65 mg, 1.0 eq) in 3 ml toluene. The stirred mixture was heated to reflux under Ar for 12 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE = 50:50) to afford the desired product **III-10** (79 %, 158 mg).

Aspect: brown solid, m. p. 198.6-199.5 ^{o}C.

Rf: 0.44 (Et_2O:PE = 50:50)

^{1}H NMR (400 MHz, MeOD) δ 8.15 (d, *J* = 9.1 Hz, 2H, H-b), 7.28 (d, *J* = 4.2 Hz, 1H, H-3), 7.15 (d, *J* = 9.1 Hz, 2H, H-c), 3.68 – 3.59 (m, 4H, H-5), 2.78 (2.82-2.73, m, 4H, H-4).

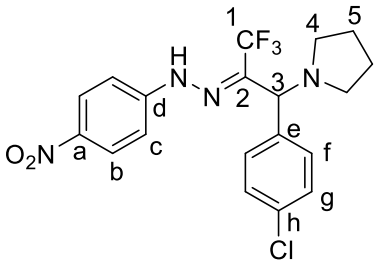
^{13}C NMR (101 MHz, MeOD) δ 150.7 (C-d), 142.6 (C-a), 127.4(q, *J* = 39 Hz, C-2), 126.9 (q, *J* = 291 Hz, C-6), 126.8 (C-b), 122.5(q, *J* = 267 Hz, C-1), 113.4 (C-c), 84.2(q, *J* = 27 Hz, C-3), 68.3 (C-5), 51.0 (C-4).

HRMS: calculated for $C_{14}H_{14}F_6N_4O_3$: 400.0970, not found, fragment 234.0365

I.R.(thin film): 3691, 2968, 2860, 1596, 1454, 1339, 1273, 1251, 1161, 1117, 1021cm^{-1}

(Z)-1-(1-(4-chlorophenyl)-3,3,3-trifluoro-2-(2-(4-nitrophenyl)hydrazono)propyl)pyrrolidine

III-11



$C_{19}H_{18}ClF_3N_4O_2$

426.82 $g.mol^{-1}$

Trifluoroacetaldehyde 4-nitrophenylhydrazone (0.5 mmol, 117 mg, 1.0 eq) was added to a solution of pyrrolidine (0.5 mmol, 36 mg, 1.0 eq) and p-chlorobenzaldehyde (0.5 mmol, 70 mg, 1.0 eq) in 3 ml toluene. The stirred mixture was heated to reflux under Ar for 12 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2:PE = 50:50) to afford the desired product **III-11** (82 %, 175 mg).

Aspect: yellow oil

Rf: 0.47 (CH_2Cl_2:PE = 50:50)

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.63 (s, 1H, H-NH), 8.08 (d, *J* = 9.2 Hz, 2H, H-b), 7.25 – 7.17 (m, 4H, H-g,h), 7.03 (d, *J* = 9.2 Hz, 2H, H-c), 4.09 (s, 1H, H-3), 2.39 (bs, 4H, H-4), 1.91-1.84 (m, 4H, H-5).

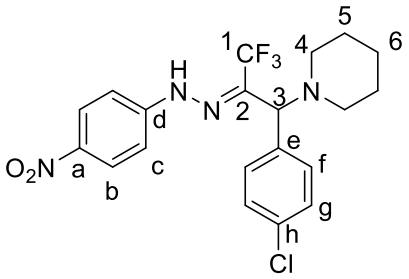
^{13}C NMR (101 MHz, $CDCl_3$) δ 148.9 (C-d), 141.7 (C-a), 135.8 (C-e), 134.9 (C-f), 133.8(q, *J* = 32 Hz, C-2), 129.7 (C-g), 129.5 (C-f), 126.1 (C-b), 121.3(q, *J* = 272 Hz, C-1), 112.8 (C-c), 69.6 (C-3), 53.1 (C-4), 23.6 (C-5).

HRMS: calculated for $C_{19}H_{18}ClF_3N_4O_2$:426.1070, found:426.1076.

I.R.(thin film): 3691, 2976, 2824, 1594, 1509, 1493, 1336, 1254, 1208, 1161, 1127, 1111, 1015cm^{-1}

(Z)-1-(1-(4-chlorophenyl)-3,3,3-trifluoro-2-(2-(4-nitrophenyl)hydrazono)propyl)piperidine

III-12



$C_{20}H_{20}ClF_3N_4O_2$

440.85 $g.mol^{-1}$

Trifluoroacetaldehyde 4-nitrophenylhydrazone (0.5 mmol, 117 mg, 1.0 eq) was added to a solution of piperidine (0.5 mmol, 43 mg, 1.0 eq) and p-chlorobenzaldehyde (0.5 mmol, 70 mg, 1.0 eq) in 3 ml toluene. The stirred mixture was heated to reflux under Ar for 12 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2:PE = 40:60)to afford the desired product **III-12** (87 %, 191 mg).

Aspect: light yellow solid, m.p. 192.9-194.4 ^oC

Rf: 0.50 (DCM:PE = 40:60)

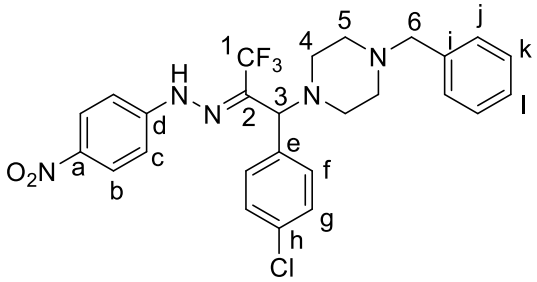
^{1}H NMR (400 MHz, $CDCl_3$) δ 13.03 (s, 1H, H-NH), 8.21 (d, *J* = 9.2 Hz, 2H, H-b), 7.32 (s, 4H, H-f,g), 7.23 – 7.14 (m, 2H, H-c), 4.17 (s, 1H, H-3), 2.40 (bs, 4H, H-4), 1.70 – 1.50 (m, 6H, H-5,6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.8 (C-d), 141.7 (C-a), 135.0 (C-h), 134.7 (C-e), 133.7(q, *J* = 32 Hz, C-2), 130.2 (C-f), 129.6 (C-g), 126.2 (C-b), 121.3(q, *J* = 273 Hz, C-1), 112.6 (C-c), 71.3 (C-3), 52.8 (C-4), 26.5 (C-5), 24.0 (C-6).

HRMS: calculated for $C_{20}H_{20}ClF_3N_4O_2$:440.1227, found: 440.1218.

I.R.(thin film): 3692, 2943, 2817, 1594, 1510, 1492, 1386, 1254, 1214, 1161, 1111, 1025, 1016cm^{-1}

(Z)-1-benzyl-4-(1-(4-chlorophenyl)-3,3,3-trifluoro-2-(2-(4-nitrophenyl)hydrazono)propyl)piperazine **III-13**



$C_{26}H_{25}ClF_3N_5O_2$

531.96 g.mol^{-1}

Trifluoroacetaldehyde 4-nitrophenylhydrazone (0.5 mmol, 117 mg, 1.0 eq) was added to a solution of 1-benzylpiperazine (0.5 mmol, 88 mg, 1.0 eq) and p-chlorobenzaldehyde (0.5 mmol, 70 mg, 1.0 eq) in 3 ml toluene. The stirred mixture was heated to reflux under Ar for 12 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE = 70:30) to afford the desired product **III-13** (81 %, 215 mg).

Aspect: white solid, m. p. 84.1-85.9 ^{o}C.

Rf: 0.40 (Et_2O:PE = 70:30)

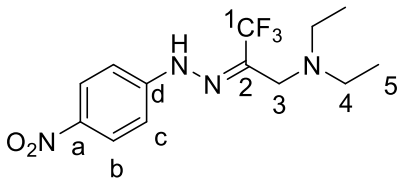
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.81 (s, 1H, H-NH), 8.23 (d, *J* = 9.1 Hz, 2H, H-b), 7.39 – 7.24 (m, 9H, H-f,g,j,k,l), 7.16 (d, *J* = 8.8 Hz, 2H, H-c), 4.22 (s, 1H, H-3), 3.56 (s, 2H, H-6), 2.50 (bs, 8H, H-4,5).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.6 (C-d), 141.8 (C-a), 137.2 (C-i), 135.2 (C-h), 134.2 (C-e), 133.2(q, *J* = 33 Hz, C-2), 130.2 (C-f), 129.7 (C-g), 129.2 (C-j), 128.4 (C-k), 127.4 (C-l), 126.2 (C-b), 121.2(q, *J* = 272 Hz, C-1) ,112.7 (C-c), 70.8 (C-3), 62.7 (C-5), 53.2 (C-6), 51.7 (C-4).

HRMS: calculated for $C_{26}H_{25}ClF_3N_5O_2$: 531.1649, found: 531.1628

I.R.(thin film): 3691, 3088, 3031, 2973, 2833, 2770, 2444, 1902, 1595, 1510, 1494, 1458, 1373, 1336, 1297, 1254, 1208, 1159, 1127, 1111, 1095, 1037cm^{-1}

(Z)-N,N-diethyl-3,3,3-trifluoro-2-(2-(4-nitrophenyl)hydrazono)propan-1-amine **III-14**



$C_{13}H_{17}F_3N_4O_2$

318.30 $g.mol^{-1}$

Trifluoroacetaldehyde 4-nitrophenylhydrazone (0.5 mmol, 117 mg, 1.0 eq) was added to a solution of diethylamine (0.5 mmol, 37 mg, 1.0 eq) and formaldehyde (0.5 mmol, 41 mg, 37 %, 1.0 eq) in 3 ml toluene. The stirred mixture was heated to reflux under Ar for 12 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2:PE = 50:50) to afford the desired product **III-14** (89 %, 141 mg).

Aspect: yellow solid, m. p. 78.2-79.6 ^oC.

Rf: 0.43 (CH_2Cl_2:PE = 50:50)

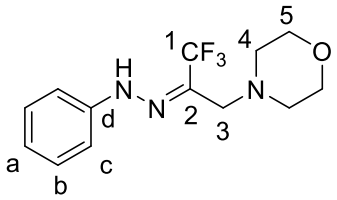
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 12.32 (s, 1H, H-NH), 8.16 (d, *J* = 9.0 Hz, 2H, H-b), 7.07 (d, *J* = 9.0 Hz, 2H, H-c), 3.56 (s, 2H, H-3), 2.60 (q, *J* = 7.1 Hz, 4H, H-4), 1.12 (t, *J* = 7.1 Hz, 6H, H-5).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 149.0 (C-d), 141.5 (C-a), 132.4(q, *J* = 33 Hz, C-2), 126.1 (C-b), 121.3(q, *J* = 271 Hz, C-1), 112.5 (C-c), 50.6 (C-3), 46.7 (C-4), 11.5 (C-5).

HRMS: calculated for $C_{13}H_{17}F_3N_4O_2$: 318.1304, found: 318.1305

I.R.(thin film): 3691, 3105, 2976, 2938, 2878, 2843, 2444, 1918, 1596, 1528, 1509, 1458, 1438, 1427, 1383, 1335, 1298, 1258, 1206, 1158, 1111, 1065, 1041cm^{-1}

(Z)-4-(3,3,3-trifluoro-2-(2-phenylhydrazono)propyl)morpholine **III-15**



$C_{13}H_{16}F_3N_3O$

287.29 $g.mol^{-1}$

Trifluoroacetaldehyde phenylhydrazone (0.5 mmol, 94 mg, 1.0 eq) was added to a solution of morpholine (0.5 mmol, 44 mg, 1.0 eq) and formaldehyde (0.5 mmol, 41 mg, 37 %, 1.0 eq) in 3 ml toluene. The stirred mixture was heated to reflux under Ar for 12 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2:PE = 50:50) to afford the desired product **III-15** (95 %, 136 mg).

Aspect: colourless solid, m. p. 127.9-128.9 ^oC.

Rf: 0.41 (CH_2Cl_2:PE = 50:50)

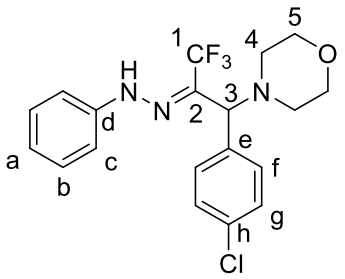
^{1}H NMR (400 MHz, $CDCl_3$) δ 11.02 (s, 1H, H-NH), 7.36 – 6.84 (m, 5H, H-a,b,c), 3.75 (bs, 4H, H-5), 3.45 (s, 2H, H-3), 2.51 (bs, 4H, H-4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.7 (C-d), 129.5 (C-b), 126.3(q, *J* = 34 Hz, C-2), 121.9(q, *J* = 270 Hz, C-1), 121.8 (C-a), 113.4 (C-c), 67.1 (C-5), 54.4 (C-3), 52.7 (C-4).

HRMS: calculated for $C_{13}H_{16}F_3N_3O$: 287.1245, found: 287.1247.

I.R.(thin film): 3172, 3107, 3030, 2973, 2858, 2833, 1601, 1523, 1496, 1456, 1376, 1346, 1296, 1251, 1155, 1119, 1053, 1005cm^{-1}

(Z)-4-(1-(4-chlorophenyl)-3,3,3-trifluoro-2-(2-phenylhydrazono)propyl)morpholine **III-16**



$C_{19}H_{19}ClF_3N_3O$

397.83 g.mol^{-1}

Trifluoroacetaldehyde phenylhydrazone (0.5 mmol, 94 mg, 1.0 eq) was added to a solution of morpholine (0.5 mmol, 44 mg, 1.0 eq) and p-chlorobenzaldehyde (0.5 mmol, 70 mg, 1.0 eq) in 3 ml toluene. The stirred mixture was heated to reflux under Ar for 12 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE = 40:60) to afford the desired product **III-16** (85 %, 169 mg).

Aspect: white solid, m. p. 135.8-136.7 ^oC.

Rf: 0.51 (Et_2O:PE = 40:60)

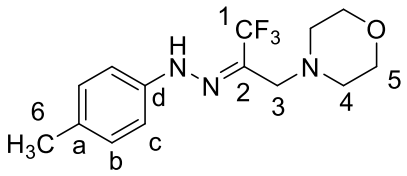
^{1}H NMR (400 MHz, $CDCl_3$) δ 11.94 (s, 1H, H-NH), 7.39-7.32(m, 6H, H-b,f,g), 7.19-7.16 (m, 2H, H-c), 7.02-6.98 (m, 1H, H-a), 4.16 (s, 1H, H-3), 3.76 (bs, 4H, H-5), 2.47 (bs, 4H, H-4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.4 (C-d), 134.9 (C-h), 134.6 (C-e), 130.3 (C-f), 129.6 (C-b), 129.5 (C-h), 127.7(q, *J* = 32 Hz, C-2), 121.9 (C-a), 121.9(q, *J* = 272 Hz, C-1), 113.3 (C-c), 70.7 (C-3), 67.2 (C-5), 52.2 (C-4).

HRMS: calculated for $C_{19}H_{19}ClF_3N_3O$: 397.1169, found: 397.1172.

I.R.(thin film): 3691, 3169, 3031, 2971, 2916, 2883, 2855, 1599, 1514, 1493, 1456, 1364, 1245, 1210, 1164, 1119, 1096, 1035cm^{-1}

(Z)-4-(3,3,3-trifluoro-2-(2-(p-tolyl)hydrazono)propyl)morpholine **III-17**



$C_{14}H_{18}F_3N_3O$

301.31 g.mol^{-1}

Trifluoroacetaldehyde 4-methylphenylhydrazone (0.5 mmol, 101 mg, 1.0 eq) was added to a solution of morpholine (0.5 mmol, 44 mg, 1.0 eq) and formaldehyde (0.5 mmol, 41 mg, 37 %, 1.0 eq) in 3 ml toluene. The stirred mixture was heated to reflux under Ar for 12 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE = 40:60) to afford the desired product **III-17** (95 %, 143 mg).

Aspect: yellow oil

Rf: 0.34 (Et_2O:PE = 40:60)

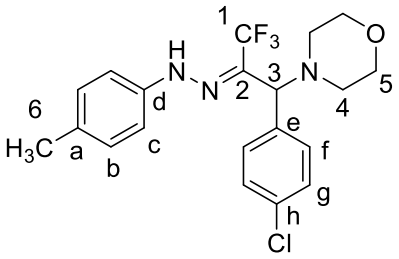
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.91 (s, 1H, H-NH), 7.12 (d, *J* = 8.4 Hz, 2H, H-b), 7.06 – 6.98 (m, 2H, H-c), 3.74 (bs, 4H, H-5), 3.44 (s, 2H, H-3), 2.51 (bs, 4H, H-4), 2.32 (s, 3H, H-6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.5 (C-d), 131.2 (C-a), 129.9 (C-b), 125.5(q, *J* = 34 Hz, C-2), 121.9(q, *J* = 270 Hz, C-1), 113.4 (C-c), 67.1 (C-5), 54.3 (C-3), 52.7 (C-4), 20.8 (C-6).

HRMS: calculated for $C_{14}H_{18}F_3N_3O$:301.1402, found: 301.1404

I.R.(thin film): 3691, 3171, 3026, 2973, 2859, 2834, 1606, 1525, 1456, 1376, 1346, 1273, 1251, 1174, 1118,1053, 1005cm^{-1}

(Z)-4-(1-(4-chlorophenyl)-3,3,3-trifluoro-2-(2-(p-tolyl)hydrazono)propyl)morpholine **III-18**



$C_{20}H_{21}ClF_3N_3O$

411.85 g.mol^{-1}

Trifluoroacetaldehyde 4-methylphenylhydrazone (0.5 mmol, 101 mg, 1.0 eq) was added to a solution of morpholine (0.5 mmol, 44 mg, 1.0 eq) and p-chlorobenzaldehyde (0.5 mmol, 70 mg, 1.0 eq) in 3 ml toluene. The stirred mixture was heated to reflux under Ar for 12 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2:PE = 50:50) to afford the desired product **III-18** (68 %, 140 mg).

Aspect: yellow oil

Rf: 0.34 (DCM:PE = 50:50)

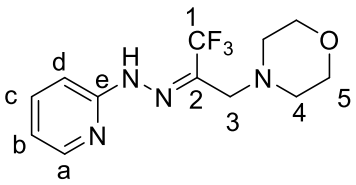
^{1}H NMR (400 MHz, $CDCl_3$) δ 11.85 (s, 1H, H-NH), 7.40-7.32 (m, 4H, H-f,g), 7.20 – 7.05 (m, 4H, H-b,c), 4.16 (s, 1H, H-3), 3.76 (bs, 4H, H-5), 2.47 (bs, 4H, H-4), 2.34 (s, 3H, H-6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.2 (C-d), 134.9 (C-h), 134.7 (C-e), 131.4 (C-a), 130.3 (C-b), 130.1 (C-f), 129.5 (C-g), 127.0(q, *J* = 32 Hz, C-2), 122.0(q, *J* = 272 Hz, C-1), 113.3 (C-c), 70.6 (C-3), 67.2 (C-5), 52.2 (C-4), 20.8 (C-6).

HRMS: calculated for $C_{20}H_{21}ClF_3N_3O$:411.1325, found: 411.1306

I.R.(thin film): 3691, 3170, 2971, 2856, 1604, 1524, 1493, 1455, 1364, 1287, 1244, 1205, 1164, 1096, 1035cm^{-1}

(Z)-4-(3,3,3-trifluoro-2-(2-(pyridin-2-yl)hydrazono)propyl)morpholine **III-19**



$C_{12}H_{15}F_3N_4O$

288.27 $g.mol^{-1}$

(E)-2-(2-(2,2,2-trifluoroethylidene)hydrazinyl)pyridine (0.5 mmol, 90 mg, 1.0 eq) was added to a solution of morpholine (0.5 mmol, 44 mg, 1.0 eq) and formaldehyde (0.5 mmol, 41 mg, 37 %, 1.0 eq) in 3 ml toluene. The stirred mixture was heated to reflux under Ar for 12 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: EA:PE = 50:50) to afford the desired product **III-19** (81 %, 116 mg).

Aspect: yellow oil

Rf: 0.54 (EA:PE = 50:50)

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.24 (s, 1H, H-NH), 8.24 (d, *J* = 4.7 Hz, 1H, H-a), 7.66 (dd, *J* = 10.8, 4.8 Hz, 1H, H-c), 7.38 – 7.21 (m, 1H, H-d), 6.94 – 6.79 (m, 1H, H-b), 3.89 – 3.69 (m, 4H, H-5), 3.49 (s, 2H, H-3), 2.54 (bs, 4H, H-4).

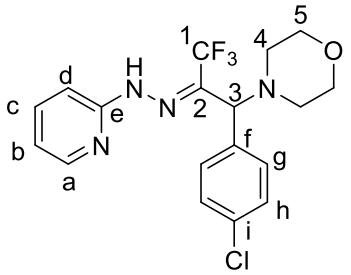
^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1(C-e), 147.9 (C-a), 138.2 (C-c), 128.4(q, *J* = 34 Hz, C-2), 121.4(q, *J* = 271 Hz, C-1), 117.4 (C-b), 107.6 (C-d), 66.8 (C-5), 54.3 (C-3), 52.8 (C-4).

HRMS: calculated for $C_{12}H_{15}F_3N_4O$:288.1198, found: 288.1200.

I.R.(thin film): 3172, 2972, 2899, 2863, 2830, 1597, 1577, 1515, 1444, 1375, 1345, 1296, 1268, 1178, 1146, 1058cm^{-1}

(Z)-4-(1-(4-chlorophenyl)-3,3,3-trifluoro-2-(2-(pyridin-2-yl)hydrazono)propyl)morpholine

III-20



$C_{18}H_{18}ClF_3N_4O$

398.81 $g.mol^{-1}$

(E)-2-(2-(2,2,2-trifluoroethylidene)hydrazinyl)pyridine (0.5 mmol, 90 mg, 1.0 eq) was added to a solution of morpholine (0.5 mmol, 44 mg, 1.0 eq) and p-chlorobenzaldehyde (0.5 mmol, 70 mg, 1.0 eq) in 3 ml toluene. The stirred mixture was heated to reflux under Ar for 15 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: EA:PE = 40:60) to afford the desired product **III-20** (47 %, 93 mg).

Aspect: yellow oil

Rf: 0.63(EA:PE = 40:60)

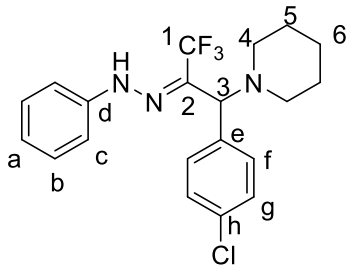
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.11 (s, 1H, H-NH), 8.27 – 8.19 (m, 1H, H-a), 7.63 (t, *J* = 7.8 Hz, 1H, H-c), 7.41 (d, *J* = 8.2 Hz, 2H, H-g), 7.35 – 7.26 (m, 3H, H-h,d), 6.89 (dd, *J* = 8.1, 4.0 Hz, 1H, H-b), 4.16 (s, 1H, H-3), 3.87 – 3.73 (m, 4H, H-5), 2.45 (bs, 4H, H-4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9 (C-e), 148.1 (C-a), 138.4 (C-c), 135.0 (C-i), 134.3 (C-f), 130.3 (C-g), 129.6(q, *J* = 32 Hz, C-2), 129.4 (C-h), 121.5(q, *J* = 272 Hz, C-1), 117.6 (C-b), 107.6 (C-d), 70.7 (C-3), 66.8 (C-5), 52.3 (C-4).

HRMS: calculated for $C_{18}H_{18}ClF_3N_4O$:398.1121, found: 398.1131.

I.R.(thin film): 3173, 2970, 2860, 2828, 1596, 1575, 1510, 1493, 1443, 1362, 1297, 1269, 1169, 1146, 1120, 1094, 1036cm^{-1}

(Z)-1-(1-(4-chlorophenyl)-3,3,3-trifluoro-2-(2-phenylhydrazono)propyl)piperidine **III-21**



$C_{20}H_{21}ClF_3N_3$

395.85 $g.mol^{-1}$

Trifluoroacetaldehyde phenylhydrazone (0.5 mmol, 94 mg, 1.0 eq) was added to a solution of piperidine (0.5 mmol, 43 mg, 1.0 eq) and p-chlorobenzaldehyde (0.5 mmol, 70 mg, 1.0 eq) in 3 ml toluene. The stirred mixture was heated to reflux under Ar for 12 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2:PE = 10:90) to afford the desired product **III-21** (75 %, 148 mg).

Aspect: yellow oil

Rf: 0.78 (DCM:PE = 10:90)

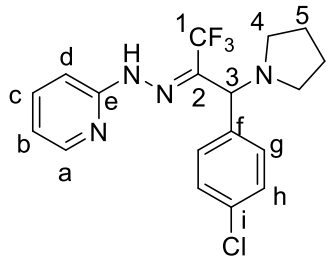
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.29 (s, 1H, H-NH), 7.39-7.33 (m, 6H, H-b,f,g), 7.21 (d, *J* = 7.3 Hz, 2H, H-c), 7.03-7.00 (m, 1H, H-a), 4.14 (d, *J* = 4.4 Hz, 1H, H-3), 2.42 (bs, 4H, H-4), 1.78 – 1.42 (m, 6H, H-5,6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.8 (C-d), 135.9 (C-e), 134.5 (C-h), 130.2 (C-f), 129.5 (C-b), 129.3 (C-g), 128.8(q, *J* = 32 Hz, C-2), 122.0(q, *J* = 271 Hz, C-1),121.5 (C-a),113.2 (C-c), 71.0 (C-3), 52.8 (C-4), 26.5 (C-5), 24.2 (C-6).

.**HRMS:** calculated for $C_{20}H_{21}ClF_3N_3$:395.1376, found: 395.1363.

I.R.(thin film): 3692, 2942, 1600, 1492, 1247, 1164, 1114, 1095, 1016cm^{-1}

(Z)-2-(2-(3-(4-chlorophenyl)-1,1,1-trifluoro-3-(pyrrolidin-1-yl)propan-2-ylidene)hydrazinyl) pyridine **III-22**



$C_{18}H_{18}ClF_3N_4$

382.82 $g.mol^{-1}$

(E)-2-(2-(2,2,2-trifluoroethylidene)hydrazinyl)pyridine (0.5 mmol, 90 mg, 1.0 eq) was added to a solution of pyrrolidine (0.5 mmol, 36 mg, 1.0 eq) and p-chlorobenzaldehyde (0.5 mmol, 70 mg, 1.0 eq) in 3 ml toluene. The stirred mixture was heated to reflux under Ar for 15 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE = 30:70) to afford the desired product **III-22** (58 %, 111 mg).

Aspect: yellow oil

Rf: 0.56 (Et_2O:PE = 30:70)

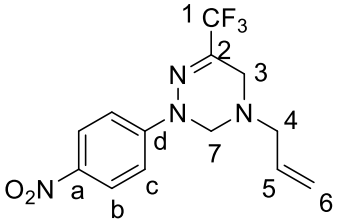
^{1}H NMR (400 MHz, $CDCl_3$)δ 12.24 (s, 1H, H-NH), 8.30 – 8.23 (m, 1H, H-a), 7.67 (td, *J* = 8.2, 1.8 Hz, 1H, H-c), 7.52 – 7.44 (m, 2H, H-g), 7.31-7.28(m, 3H, H-h,d), 6.92 (ddd, *J* = 7.2, 5.0, 0.9 Hz, 1H, H-b), 4.21 (s, 1H, H-3), 2.55 (bs, 4H, H-4), 2.01 – 1.88 (m, 4H, H-5).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.3 (C-e), 148.0 (C-a), 138.3 (C-c), 136.5 (C-i), 134.4 (C-f), 131.1(q, *J* = 32 Hz, C-2), 129.8 (C-g), 129.2 (C-h), 121.6(q, *J* = 273 Hz, C-1), 117.3 (C-b), 107.7 (C-d), 69.4 (C-3), 53.2 (C-5), 23.6 (C-4).

HRMS: calculated for $C_{18}H_{18}ClF_3N_4$:382.1172, found: 382.1172.

I.R.(thin film): 3691, 2976, 2817, 1597, 1575, 1511, 1492, 1442, 1359, 1295, 1268, 1169, 1124, 1093, 1016cm^{-1}

4-allyl-2-(4-nitrophenyl)-6-(trifluoromethyl)-2,3,4,5-tetrahydro-1,2,4-triazine **III-23**



$C_{13}H_{13}F_3N_4O_2$

314.27 $g.mol^{-1}$

Trifluoroacetaldehyde 4-nitrophenylhydrazone (0.5 mmol, 117 mg, 1.0 eq) was added to a solution of aqueous formaldehyde (1 mmol, 82 mg, 37 %, 2.0 eq) and allylamine (0.5 mmol, 57 mg, 1.0 eq) in 3 ml toluene. The stirred mixture was heated to reflux under Ar for 12 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: PE:Et_2O = 60:40)to afford the desired product **III-23** (98 %, 154 mg).

Aspect: white solid m.p. 86.3°C-87.5 °C

Rf: 0.39 (PE:Et_2O = 60:40)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 9.4 Hz, 2H, H-b), 7.23 (d, *J* = 9.4 Hz, 2H, H-c), 5.86 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H, H-5), 5.29 – 5.09 (m, 2H, H-6), 4.62 (s, 2H, H-7), 3.57 (s, 2H, H-3), 3.17 (d, *J* = 6.6 Hz, 2H, H-4).

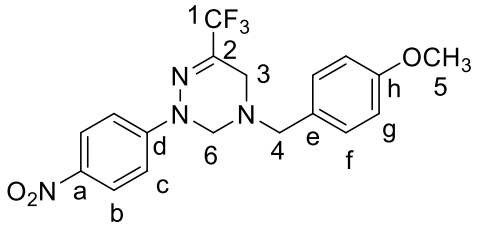
^{13}C NMR (101 MHz, $CDCl_3$) δ 149.7 (C-d), 141.8 (C-a), 133.4 (C-5), 133.0(q, *J* = 35 Hz, C-2), 125.6 (C-b), 120.6(q, *J* = 271 Hz, C-1), 120.3 (C-6), 113.1 (C-c), 63.0 (C-7), 56.7 (C-4), 45.4 (C-3).

HRMS: calculated for $C_{13}H_{13}F_3N_4O_2$:314.0991, found: 314.0987

I.R.(thin film): 3086, 2928, 2846, 1593, 1506, 1422, 1405, 1337, 1281, 1222, 1205, 1179, 1132, 1132, 1068, 1022cm^{-1}

4-(4-methoxybenzyl)-2-(4-nitrophenyl)-6-(trifluoromethyl)-2,3,4,5-tetrahydro-1,2,4-triazine

III-24



$C_{18}H_{17}F_3N_4O_3$

394.35 $g.mol^{-1}$

Trifluoroacetaldehyde 4-nitrophenylhydrazone (0.5 mmol, 117 mg, 1.0 eq) was added to a solution of aqueous formaldehyde (1 mmol, 82 mg, 37 %, 2.0 eq) and para-methoxybenzyl-amine (0.5 mmol, 69 mg, 1.0 eq) in 3 ml toluene. The stirred mixture was heated to reflux under Ar for 12 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: PE:Et_2O = 50:50)to afford the desired product **III-24** (98 %, 193 mg).

Aspect: yellow oil

Rf: 0.38 (PE:Et_2O = 50:50)

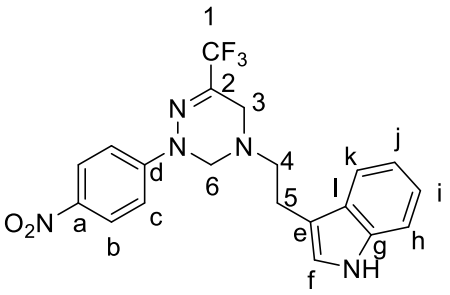
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 9.2 Hz, 2H, H-b), 7.23 – 7.12 (m, 4H, H-f,g), 6.86 (d, *J* = 8.3 Hz, 2H, H-c), 4.55 (s, 2H, H-6), 3.80 (s, 3H, H-5), 3.68-3.65 (m, 4H, H-4,3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6 (C-h), 149.7 (C-d), 141.8 (C-a), 132.9(q, *J* = 35 Hz, C-2), 130.5 (C-f), 128.1 (C-e), 125.6 (C-b), 120.6(q, *J* = 272 Hz, C-1), 114.2 (C-c), 113.1 (C-g), 62.5 (C-6), 57.1 (C-4), 55.4 (C-5), 45.6 (C-3).

HRMS: calculated for $C_{18}H_{17}F_3N_4O_3$:394.1253, found: 394.1265

I.R.(thin film): 3470, 1595, 1529, 1509, 1386, 1337, 1326, 1258, 1168, 1158, 1130, 1112, 1068cm^{-1}

3-(2-(2-(4-nitrophenyl)-6-(trifluoromethyl)-2,5-dihydro-1,2,4-triazin-4(3H)-yl)ethyl)-1H-indole **III-25**



$C_{20}H_{18}F_3N_5O_2$

417.39 g.mol^{-1}

Trifluoroacetaldehyde 4-nitrophenylhydrazone (0.5 mmol, 117 mg, 1.0 eq) was added to a solution of aqueous formaldehyde (1 mmol, 82 mg, 37 %, 2.0 eq) and tryptamine (0.5 mmol, 80 mg, 1.0 eq) in 3 ml toluene. The stirred mixture was heated to reflux under Ar for 12 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: PE:Et_2O = 50:50)to afford the desired product **III-25** (36 %, 75 mg).

Aspect: yellow solid m.p. 198.6^{o}C-199.5 ^{o}C

Rf: 0.47 (PE:CH_2Cl_2 = 50:50)

^{1}H NMR (400 MHz, $CDCl_3$) δ11.96 (s, 1H, H-NH), 8.10 (dd, *J* = 8.0, 2.9 Hz, 2H, H-b), 7.85 (s, 1H, H-k), 7.53 (s, 1H, H-f), 7.41 – 7.30 (m, 1H, H-h), 7.29 – 7.10 (m, 2H, H-i,j), 7.09 – 6.94 (m, 2H,H-c), 3.80 (bs, 4H, H-4,6), 3.03-2.97 (m, 4H, H-3,5).

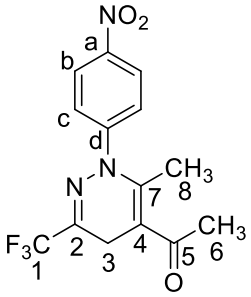
^{13}C NMR (101 MHz, $CDCl_3$) δ148.7 (C-d), 141.7 (C-a), 136.2 (C-g), 131.0(q, *J* = 34 Hz, C-2), 129.9 (C-l), 126.8 (C-f), 126.0 (C-b), 122.2 (C-i), 121.3(q, *J* = 273 Hz, C-1), 119.9 (C-j), 118.2 (C-k), 112.9 (C-c), 111.1 (C-h), 107.9 (C-e), 54.0 (C-6), 50.5 (C-4), 50.0 (C-3), 21.3 (C-5).

HRMS: calculated for $C_{20}H_{18}F_3N_5O_2$:417.1413, found: 417.1428

I.R.(thin film): 2840, 1592, 1513, 1336, 1284, 1259, 1205, 1175, 11131, 1111, 1067, 1021cm^{-1}

1-(3-methyl-2-(4-nitrophenyl)-6-(trifluoromethyl)-2,5-dihydropyridazin-4-yl)ethan-1-one

III-26



$C_{14}H_{12}F_3N_3O_3$

327.26 g.mol^{-1}

Mannich adduct **III-1** (0.5 mmol, 166 mg) was dissolved in 2.5 mL pentane-2,4-dione, and the stirred mixture was heated to 130 ^{o}C under Ar for 12 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE = 50:50) to afford the desired product **III-26** (58 %, 95 mg).

Aspect: yellow solid, m.p. 159.6-161.2 ^{o}C

Rf: 0.29 (Et_2O:PE=50:50)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 9.2 Hz, 2H, H-b), 7.49 (d, *J* = 9.2 Hz, 2H, H-c), 3.29 (s, 2H, H-3), 2.36 (s, 3H, H-6), 2.22 (s, 3H, H-8).

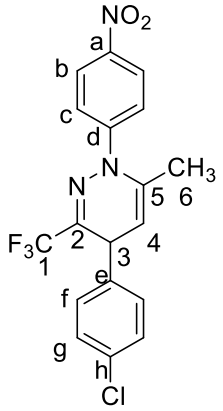
^{13}C NMR (101 MHz, $CDCl_3$) δ 197.0 (C-5), 147.3 (C-d), 145.7 (C-a), 144.8 (C-7), 137.7(q, *J* = 36 Hz, C-2), 124.9 (C-b), 124.7 (C-c), 120.5(q, *J* = 272 Hz, C-1), 106.9 (C-4), 30.2 (C-6), 23.0 (C-3), 18.3 (C-8).

HRMS: calculated for $C_{14}H_{12}F_3N_3O_3$:327.0831, found: 327.0821.

I.R.(thin film): 1675, 1595, 1572, 1524, 1349, 1310, 1251, 1221, 1201, 1137, 1040cm^{-1}

4-(4-chlorophenyl)-6-methyl-1-(4-nitrophenyl)-3-(trifluoromethyl)-1,4-dihydropyridazine

III-27



$C_{18}H_{13}ClF_3N_3O_2$

395.77 g.mol^{-1}

Mannich adduct **III-2** (0.5 mmol, 221 mg) was dissolved in 2.5 mL acetone, and the stirred mixture was heated to 130 ^{o}C under microwave for 1 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE = 50:50) to afford the desired product **III-27** (34 %, 67 mg).

Aspect: yellow oil

Rf: 0.7(Et_2O:PE = 50:50)

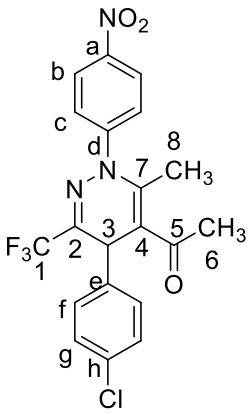
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 9.2 Hz, 2H, H-c), 7.47 (d, *J* = 9.1 Hz, 2H, H-g), 7.30 (d, *J* = 8.5 Hz, 2H, H-b), 7.12 (d, *J* = 8.4 Hz, 2H, H-f), 5.11 (dd, *J* = 6.3, 1.1 Hz, 1H, H-4), 4.41 (d, *J* = 6.2 Hz, 1H, H-3), 1.93 (s, 3H, H-6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.8 (C-d), 145.1 (C-a), 140.2 (C-e), 134.7(q, *J* = 34 Hz, C-2), 134.4 (C-5), 133.7 (C-h), 129.4 (C-b), 128.6 (C-f), 124.7 (C-c), 123.7 (C-g), 121.2(q, *J* = 273 Hz, C-1), 104.5 (C-4), 37.4 (C-3), 19.5 (C-6).

HRMS: calculated for $C_{18}H_{13}ClF_3N_3O_2$:395.0648, found: 395.0652.

I.R.(thin film): 2932, 1668, 1595, 1522, 1491, 1387, 1346, 1257, 1214, 1189, 1113, 1095, 1016cm^{-1}

1-(5-(4-chlorophenyl)-3-methyl-2-(4-nitrophenyl)-6-(trifluoromethyl)-2,5-dihydropyridazin-4-yl)ethan-1-one **III-28**



$C_{20}H_{15}ClF_3N_3O_3$

437.80 g.mol^{-1}

Mannich adduct **III-2** (0.5 mmol, 221 mg) was dissolved in 2.5 mL pentane-2,4-dione, and the stirred mixture was heated to 130 ^{o}C under Ar for 12 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE = 50:50) to afford the desired product 7c (80 %, 175 mg).

Aspect: yellow oil

Rf: 0.37 (Et_2O:PE = 50:50)

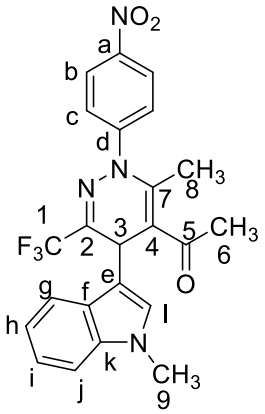
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 7.9 Hz, 2H, H-c), 7.55 (d, *J* = 8.0 Hz, 2H, H-b), 7.31 (d, *J* = 7.2 Hz, 2H, H-g), 7.14 (d, *J* = 7.6 Hz, 2H, H-f), 5.14 (s, 1H, H-3), 2.42 (s, 3H, H-6), 2.35 (s, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.8 (C-5), 146.9 (C-d), 146.1 (C-a), 143.2 (C-e), 139.0(q, *J* = 35 Hz, C-2), 137.7 (C-7), 134.2 (C-h), 129.5 (C-g), 128.4 (C-f), 125.1 (C-b), 125.0 (C-c), 120.7(q, *J* = 273 Hz, C-1), 113.4 (C-4), 37.3 (C-3), 30.4 (C-6), 18.8 (C-8).

HRMS: calculated for $C_{20}H_{15}ClF_3N_3O_3$:437.0754, found: 437.0734.

I.R.(thin film): 1674, 1595, 1526, 1492, 1349, 1310, 1292, 1221, 1198, 1142, 1039, 1015cm^{-1}

1-(3-methyl-5-(1-methyl-1H-indol-3-yl)-2-(4-nitrophenyl)-6-(trifluoromethyl)-2,5-dihydrop-yridazin-4-yl)ethan-1-one **III-29**



$C_{23}H_{19}F_3N_4O_3$

456.43 g.mol^{-1}

Mannich adduct **III-9** (0.5 mmol, 231 mg) was dissolved in 2.5 mL pentane-2,4-dione, and the stirred mixture was heated to 130 ^{o}C under Ar for 12 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE = 50:50) to afford the desired product **III-29** (92 %, 210 mg).

Aspect: yellow oil

Rf: 0.29 (Et_2O:PE = 50:50)

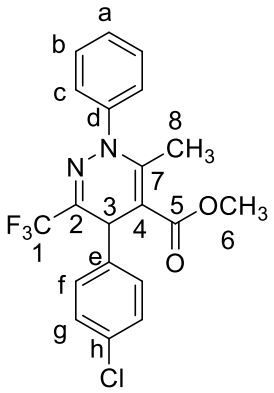
^{1}H NMR (400 MHz, $CDCl_3$) δ8.38 – 8.29 (m, 2H, H-b), 7.62 (d, *J* = 8.0 Hz, 1H, H-ar), 7.59 – 7.52 (m, 2H, H-c), 7.32 – 7.20 (m, 2H, H-ar), 7.17-7.13 (m, 1H, H-ar), 6.78 (s, 1H, H-ar), 5.33 (s, 1H, H-3), 3.71 (s, 3H, H-9), 2.37 (s, 3H, H-6), 2.30 (s, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.9 (C-5), 147.4 (C-d), 145.8, 142.2, 140.1(q, *J* = 34 Hz, C-2), 137.1, 127.6, 126.0, 125.9, 125.0, 124.8, 122.3, 120.9(q, *J* = 273 Hz, C-1), 120.0, 118.9, 114.2, 113.3, 112.9, 109.8, 33.0 (C-9), 30.1 (C-6), 29.6 (C-3), 18.9 (C-8).

HRMS: calculated for $C_{23}H_{19}F_3N_4O_3$:456.1409, found: 456.1409.

I.R.(thin film): 2939, 1672, 1595, 1524, 1495, 1348, 1310, 1293, 1221, 1197, 1139, 1111, 1040cm^{-1}

Methyl-5-(4-chlorophenyl)-3-methyl-2-phenyl-6-(trifluoromethyl)-2,5-dihydropyridazine-4-carboxylate **III-30**



$C_{20}H_{16}ClF_3N_2O_2$

408.80 g.mol^{-1}

Mannich adduct **III-16** (0.5 mmol, 199 mg) was dissolved in 2.5 mL methyl 3-oxobutanoate, and the stirred mixture was heated to 130 ^{o}C under Ar for 12 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE = 40:60) to afford the desired product **III-30** (90 %, 184 mg).

Aspect: yellow oil

Rf: 0.52 (Et_2O:PE = 40:60)

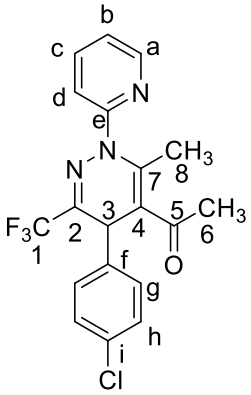
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.42 (m, 2H, H-b), 7.40 – 7.34 (m, 1H, H-a), 7.33 – 7.26 (m, 4H, H-c,g), 7.21 – 7.15 (m, 2H, H-f), 5.04 (s, 1H, H-3), 3.76 (s, 3H, H-6), 2.26 (s, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9 (C-5), 146.8 (C-e), 142.3 (C-d), 139.7 (C-7), 136.9(q, *J* = 35 Hz, C-2), 133.6 (C-h), 129.5 (C-b), 129.2 (C-g), 128.6 (C-f), 128.0 (C-a), 126.1 (C-c), 121.0(q, *J* = 273 Hz, C-1), 100.9 (C-4), 51.8 (C-6), 36.5 (C-3), 17.8 (C-8).

HRMS: calculated for $C_{20}H_{16}ClF_3N_2O_2$:408.0852, found: 408.0838.

I.R.(thin film): 2953, 1701, 1595, 1491, 1436, 1384, 1221, 1199, 1138, 1093, 1035, 1016cm^{-1}

1-(5-(4-chlorophenyl)-3-methyl-2-(pyridin-2-yl)-6-(trifluoromethyl)-2,5-dihydropyridazin-4-yl)ethan-1-one **III-31**



$C_{19}H_{15}ClF_3N_3O$

393.79 g.mol^{-1}

Mannich adduct **III-20** (0.5 mmol, 199 mg) was dissolved in 2.5mL pentane-2,4-dione, and the stirred mixture was heated to 130 ^{o}C under Ar for 12 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE = 50:50) to afford the desired product **III-31** (56 %, 110 mg).

Aspect: yellow oil

Rf: 0.41 (Et_2O:PE = 50:50)

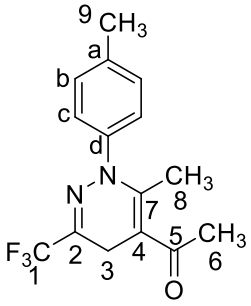
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (ddd, *J* = 4.9, 1.9, 0.7 Hz, 1H, H-a), 7.87 (ddd, *J* = 8.2, 7.4, 1.9 Hz, 1H, H-c), 7.66 (dd, *J* = 7.4, 0.8 Hz, 1H, H-d), 7.32 – 7.22 (m, 5H, H-b,g,h), 5.09 (s, 1H, H-3), 2.43 (s, 3H, H-8), 2.38 (s, 3H, H-6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.0 (C-5), 154.6 (C-e), 148.0 (C-a), 144.5 (C-7), 138.8 (C-c), 138.6 (C-f), 138.0(q, *J* = 34 Hz, C-2), 133.9 (C-i), 129.3 (C-g), 129.0 (C-h), 122.0 (C-b), 120.9(q, *J* = 273 Hz, C-1), 118.5 (C-d), 113.1 (C-4), 37.4 (C-3), 30.9 (C-6), 18.7 (C-8).

HRMS: calculated for $C_{19}H_{15}ClF_3N_3O$:393.0856, found: 393.0847.

I.R.(thin film): 3063, 3014, 1671, 1581, 1490, 1470, 1439, 1381, 1360, 1317, 1292, 1222, 1199, 1140, 1093, 1041cm^{-1}

1-(3-methyl-2-(p-tolyl)-6-(trifluoromethyl)-2,5-dihydropyridazin-4-yl)ethan-1-one **III-32**



$C_{15}H_{15}F_3N_2O$

296.29 $g.mol^{-1}$

Mannich adduct **III-17** (0.5 mmol, 151 mg) was dissolved in 2.5mL pentane-2,4-dione, and the stirred mixture was heated to 130 ^oC under Ar for 12 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE = 10:90) to afford the desired product **III-32** (77 %, 114 mg).

Aspect: yellow oil

Rf: 0.33 (Et_2O:PE = 20:80)

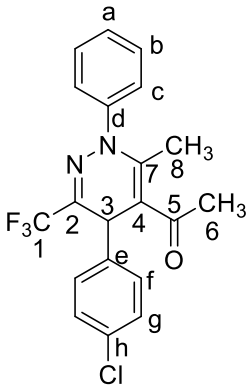
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.21 (m, 2H, H-b), 7.19 – 7.14 (m, 2H, H-c), 3.27 (s, 2H, H-3), 2.38 (s, 3H, H-9), 2.31 (s, 3H, H-6), 2.12 (s, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.0 (C-5), 147.1 (C-7), 140.1 (C-d), 137.8 (C-a), 135.0(q, *J* = 35 Hz, C-2), 130.0 (C-b), 126.1 (C-c), 120.9(q, *J* = 271 Hz, C-1), 102.8 (C-4), 30.3 (C-6), 22.4 (C-3), 21.2 (C-9), 18.0 (C-8).

HRMS: calculated for $C_{15}H_{15}F_3N_2O$: 296.1136, found:296.1122.

I.R.(thin film): 3039, 2924, 1664, 1562, 1512, 1420, 1393, 1381, 1360, 1319, 1243, 1219, 1190, 1111, 1039, 1018cm^{-1}

1-(5-(4-chlorophenyl)-3-methyl-2-phenyl-6-(trifluoromethyl)-2,5-dihydropyridazin-4-yl)ethan-1-one **III-33**



$C_{20}H_{16}ClF_3N_2O$

392.81 g.mol^{-1}

Mannich adduct **III-16** (0.5 mmol, 199 mg) was dissolved in 2.5 mL pentane-2,4-dione, and the stirred mixture was heated to 130 ^{o}C under Ar for 12 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE = 20:80) to afford the desired product **III-33** (71 %, 140 mg).

Aspect: yellow oil

Rf: 0.36 (Et_2O:PE = 30:70)

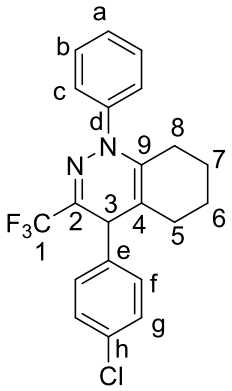
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.44 (m, 2H, H-b), 7.40 – 7.34 (m, 1H, H-a), 7.32 – 7.25 (m, 4H, H-g,c), 7.17-7.15 (m, 2H, H-f), 5.05 (s, 1H, H-3), 2.34 (s, 3H, H-6), 2.23 (s, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.7 (C-5), 145.3 (C-7), 142.1 (C-d), 138.9 (C-e), 137.1(q, *J* = 35 Hz, C-2), 133.8 (C-h), 129.6 (C-b), 129.3 (C-c), 128.6 (C-f), 128.2 (C-a), 126.1 (C-g), 121.0(q, *J* = 273 Hz, C-1),110.0 (C-4), 36.7 (C-3), 30.6 (C-6), 18.7 (C-8).

HRMS: calculated for $C_{20}H_{16}ClF_3N_2O$: 392.0903, found:392.0901.

I.R.(thin film): 2969, 1667, 1637, 1592, 1557, 1489, 1382, 1350, 1243, 1214, 1189, 1122, 1091, 1037, 1024, 1013cm^{-1}

4-(4-chlorophenyl)-1-phenyl-3-(trifluoromethyl)-1,4,5,6,7,8-hexahydrocinnoline **III-34**



$C_{21}H_{18}ClF_3N_2$

390.83 $g.mol^{-1}$

Mannich adduct **III-16** (0.5 mmol, 199 mg) was dissolved in 2.5mL cyclohexanone and the stirred mixture was heated to 130 ^oC under Ar for 12 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE = 20:80) to afford the desired product **III-34** (68 %, 132 mg).

Aspect: gray oil

Rf: 0.80 (Et_2O:PE=40:60)

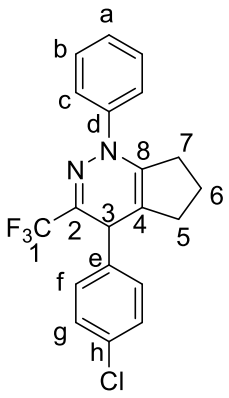
^{1}H NMR (400 MHz, $CDCl_3$)δ 7.40-7.36 (m, 2H, H-b), 7.32 – 7.22 (m, 5H, H-a,c,g), 7.19 – 7.12 (m, 2H, H-f), 4.11 (s, 1H, H-3), 2.27 – 2.05 (m, 2H, H-5,8), 2.00 – 1.87 (m, 1H, H-5), 1.80 – 1.46 (m, 5H, H-8,6,7).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.0 (C-d), 140.8 (C-e), 133.3 (C-h), 131.6 (C-9), 129.9(q, *J* = 34 Hz, C-2), 129.1 (C-b), 129.0 (C-g), 128.9 (C-f), 126.6 (C-a), 125.5 (C-c), 121.9(q, *J* = 273 Hz, C-1),109.9 (C-4), 41.7 (C-3), 27.1 (C-5), 26.7 (C-8), 22.9 (C-6), 22.3 (C-7).

HRMS: calculated for $C_{21}H_{18}ClF_3N_2$: 390.1111, found:390.1120.

I.R.(thin film): 3043, 2933, 2904, 2887, 2834, 1674, 1607, 1593, 1490, 1386, 1315, 1265, 1216, 1179, 1149, 1115, 1105, 1074, 1032, 1015, 1002cm^{-1}

4-(4-chlorophenyl)-1-phenyl-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-cyclopenta[c]pyridaz-ine **III-35**



$C_{20}H_{16}ClF_3N_2$

376.81 g.mol^{-1}

Mannich adduct **III-16** (0.5 mmol, 199 mg) was dissolved in 2.5 mL cyclopentanone and the stirred mixture was heated to 130 ^{o}C under Ar for 12 h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE = 20:80) to afford the desired product **III-35** (90 %, 169 mg).

Aspect: brown oil

Rf: 0.80 (Et_2O:PE=40:60)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.35 (m, 2H, H-b), 7.33 – 7.25 (m, 4H, H-g,c), 7.24-7.18 (m, 1H, H-a), 7.15 – 7.13 (m, 2H, H-f), 4.48 (s, 1H, H-3), 2.79-2.72 (m, 1H, H-7), 2.38 – 2.14 (m, 3H, H-5,7), 1.98 – 1.80 (m, 2H, H-6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5 (C-d), 140.5 (C-e), 135.1 (C-8), 133.3 (C-h), 130.7(q, *J* = 33 Hz, C-2), 129.1 (C-b), 129.0 (C-f), 129.0 (C-g), 125.8 (C-a), 122.6 (C-c), 120.1(q, *J* = 273 Hz, C-1),115.0 (C-4), 40.6 (C-3), 32.1 (C-7), 31.5 (C-5), 21.2 (C-6).

HRMS: calculated for $C_{20}H_{16}ClF_3N_2$: 376.0954, found:376.0941.

I.R.(thin film): 3042, 2956, 2850, 1679, 1594, 1584, 1496, 1489, 1379, 1329, 1294, 1225, 1186, 1160, 1117, 1090, 1077, 1014cm^{-1}

Experimental part: chapter IV

1 General procedure

1.1 Synthesis of nitroalkanes

In a round-bottomed flask fitted with a Dean and Stark trap was added ketone (100 mmol, 14.6 g, 100 mol%), nitromethane (1 mol, 61 g, 10 eq), N,N-dimethylethane-1,2-diamine (30 mmol, 2.6 g, 30 mol%), and toluene (50 ml), the mixture was refluxed for 96 h. After evaporation of solvent under reduced pressure, the residue crude was purified by column chromatography on silica gel to afford the desired product.

1.2 Synthesis of double Michael addition adducts

To a solution of nitroalkanes (0.5 mmol, 100 mol%) in acetonitrile (1.5 ml) was added Michael acceptors (2.5 mmol, 5 eq) and DBU (38 mg, 50 mol%), the mixture was stirred for 3 h at r.t. under Ar. After evaporation of solvent under reduced pressure, the residue crude was purified by column chromatography on silica gel to afford the desired product.

1.3 Synthesis of mono Michael addition adducts

To a solution of nitroalkanes (0.5 mmol, 100 mol%) in acetonitrile (1.5 ml) was added Michael acceptors (1.5 mmol, 3 eq) and DBU(15 mg, 10 mol%), the mixture was stirred for 2 h at r.t. under Ar. After evaporation of solvent under reduced pressure, the residue crude was purified by column chromatography on silica gel to afford the desired product.

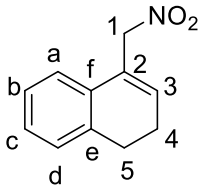
1.4 Synthesis of naphthalene

To a solution of mono or double Michael addition adducts (0.5 mmol, 100 mol%) in DMF (1.5 ml) was added Cs_2CO_3 (0.5 mmol, 163 mg, 100 mol%), $Pd(OAc)_2$ (5 mol%), and dppe (5 mol%), the mixture was stirred for 30 min at 120 ^oC under Ar. After evaporation of solvent

under reduced pressure (*vacuum*, 80 ^{o}C), the residue crude was purified by column chromatography on silica gel to afford the desired product.

2 Characterization Data

4-(nitromethyl)-1,2-dihydronaphthalene (**IV-1a**)



$C_{11}H_{11}NO_2$

189.21 $g.mol^{-1}$

In a round-bottomed flask fitted with a Dean and Stark trap was added α-tetralone (100 mmol, 14.6 g, 100 mol%), nitromethane (1 mol, 61 g, 10 eq), N,N-dimethylethane-1,2-diamine (30 mmol, 2.6 g, 30 mol%), and toluene (50 ml), the mixture was refluxed for 96 h. After evaporation of solvent under reduced pressure, the residue crude was purified by column chromatography on silica gel (eluent: DCM:PE = 30:70) to afford the desired product 4-(nitromethyl)-1,2-dihydronaphthalene (78 %, 14.8 g), The spectra data are in agreement with the literature report.[253]

Aspect: brown oil

Rf: 0.56 (DCM:PE = 5:5)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.15 (m, 4H, H-a,b,c,d), 6.33 (t, *J* = 4.6 Hz, 1H, H-3), 5.29 (s, 2H, H-1), 2.84 (t, *J* = 8.1 Hz, 2H, H-5), 2.43 (td, *J* = 8.1, 4.7 Hz, 2H, H-4).

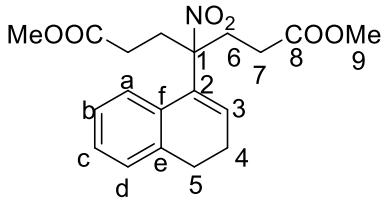
^{13}C NMR (101 MHz, $CDCl_3$) δ 136.1 (C-e), 136.0 (C-c), 132.0 (C-f), 128.2 (C-d), 128.1 (C-b), 127.9 (C-2), 126.9 (C-a), 122.3 (C-3), 78.2 (C-1), 27.4 (C-5), 23.4 (C-4).

HRMS: calculated for $C_{11}H_{11}NO_2$: 189.0790, found: 189.0789

I.R.(thin film): 2944, 2836, 1557, 1491, 1431, 1369, 1308, 1239, 1022cm^{-1}.

[253] Rui Tamura, Masahiro Sato, and Daihei Oda. *J. Org. Chem.* **1986**, *51*, 4368-4375

dimethyl 4-(3,4-dihydronaphthalen-1-yl)-4-nitroheptanedioate (**IV-2a**)



$C_{19}H_{23}NO_6$

361.39 $g.mol^{-1}$

To a solution of 4-(nitromethyl)-1,2-dihydronaphthalene (0.5 mmol, 90 mg, 100 mol%) in acetonitrile (1.5 ml) was added methyl acrylate (2.5 mmol, 215 mg, 5 eq) and DBU(38 mg, 50 mol%), the mixture was stirred for 3 h at r.t. under Ar. After evaporation of solvent under reduced pressure, the residue crude (412 mg) was purified by column chromatography on silica gel (eluent: Et_2O:PE = 40:60) to afford the desired product (98 %, 177 mg),

Aspect: colourless oil

Rf: 0.25 (Et_2O:PE = 4:6)

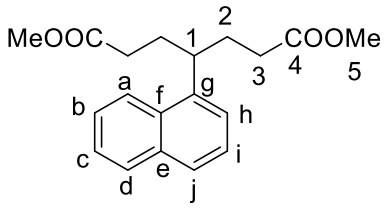
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 – 7.05 (m, 3H, H-a,c,d), 6.88 (d, *J* = 7.5 Hz, 1H, H-b), 6.38 (t, *J* = 4.8 Hz, 1H, H-3), 3.61 (s, 6H, H-9), 2.70 (t, *J* = 7.8 Hz, 2H, H-5), 2.62-2.58 (m, 4H, H-7), 2.39 – 2.30 (m, 2H, H-4), 2.27 – 2.16 (m, 4H, H-6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4 (C-8), 137.3 (C-e), 133.4 (C-f), 131.8 (C-c), 131.3 (C-2), 128.4 (C-d), 127.6 (C-b), 126.7 (C-a), 122.5 (C-3), 94.1 (C-1), 52.0 (C-9), 51.9 (C-9), 29.8 (C-6), 29.1 (C-7), 28.1 (C-5), 23.3 (C-4).

HRMS: calculated for $C_{19}H_{23}NO_6$: 361.1525, not found, fragment (-HNO_2): 314.1518

I.R.(thin film): 3066, 3001, 2954, 2893, 2837, 1737, 1542, 1487, 1452, 1439, 1379, 1348, 1293, 1202, 1179cm^{-1}.

dimethyl 4-(naphthalen-1-yl)heptanedioate (**IV-3a**)



$C_{19}H_{22}O_4$

314.38 g.mol^{-1}

To a solution of dimethyl 4-(3,4-dihydronaphthalen-1-yl)-4-nitroheptanedioate (0.5 mmol, 181 mg, 100 mol%) in DMF (1.5 ml) was added Cs_2CO_3 (0.5 mmol, 163 mg, 100 mol%), $Pd(OAc)_2$ (5 mol%), and dppe (5 mol%), the mixture was stirred for 30 min at 120 ^oC under Ar. After evaporation of solvent under reduced pressure (*vacuum*, 80 ^oC), the residue crude (384 mg) was purified by column chromatography on silica gel (eluent: Et_2O:PE = 20:80) to afford the desired product (87 %, 137 mg),

Aspect: colourless oil

Rf: 0.67 (Et_2O:PE = 4:6)

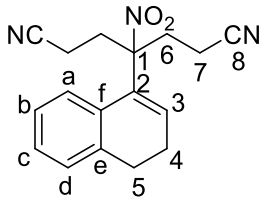
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.2 Hz, 1H, H-h), 7.89 – 7.82 (m, 1H, H-d), 7.73 (d, *J* = 8.1 Hz, 1H, H-i), 7.54 – 7.42 (m, 3H, H-b,c,j), 7.38 (d, *J* = 6.6 Hz, 1H, H-a), 3.56 (s, 6H, H-1,5), 2.26 – 1.96 (m, 8H, H-3,2).

^{13}C NMR (101 MHz, $CDCl_3$) δ173.8 (C-4), 139.6 (C-g), 133.9 (C-e), 132.6 (C-f), 129.0 (C-d), 126.9 (C-i), 125.9 (C-j), 125.6 (C-b), 125.5 (C-c), 122.8 (C-a), 51.4 (C-5), 36.7 (C-1), 31.7 (C-3), 31.5 (C-2).

HRMS: calculated for $C_{19}H_{22}O_4$: 314.1518, found: 314.1528

I.R.(thin film): 3047, 3001, 2953, 2848, 1731, 1597, 1511, 1457, 1438, 1419, 1396, 1368, 1326, 1259, 1202, 1174, 1014 cm^{-1}.

4-(3,4-dihydronaphthalen-1-yl)-4-nitroheptanedinitrile (**IV-2b**)



$C_{17}H_{17}N_3O_2$

295.34 $g.mol^{-1}$

To a solution of 4-(nitromethyl)-1,2-dihydronaphthalene (0.5 mmol, 90 mg, 100 mol%) in acetonitrile (1.5 ml) was added acrylonitrile (2.5 mmol, 265 mg, 5 eq) and DBU (38 mg, 50 mol%), the mixture was stirred for 3 h at r.t. under Ar. After evaporation of solvent under reduced pressure, the residue crude (316 mg) was purified by column chromatography on silica gel (eluent: PE 100 % - Et_2O 100 %) to afford the desired product (99 %, 292 mg).

Aspect: colourless oil

Rf: 0.22 (Et_2O:PE = 7:3)

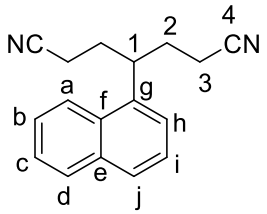
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.19 (m, 2H, H-c,d), 7.18 – 7.13 (m, 1H,H-a), 6.80 (d, *J* = 7.7 Hz, 1H, H-b), 6.36 (t, *J* = 4.9 Hz, 1H, H-3), 2.80 – 2.66 (m, 6H, H-5,6), 2.45 – 2.34 (m, 4H, H-7), 2.32-2.24 (m, 2H, H-4).

^{13}C NMR (101 MHz, $CDCl_3$) δ137.5 (C-2), 133.2 (C-e), 131.8 (C-f), 130.4 (C-c), 129.0 (C-d), 128.5 (C-b), 127.1 (C-a), 122.1 (C-3), 118.0 (C-8), 93.5 (C-1), 30.9 (C-5), 27.9 (C-6), 23.4 (C-4), 13.2 (C-7).

HRMS: calculated for $C_{17}H_{17}N_3O_2$: 295.1321, not found, fragment: 249.1386

I.R.(thin film): 2944, 2889, 2835, 1542, 1487, 1452, 1426, 1344, 1275, 1026cm^{-1}.

4-(naphthalen-1-yl)heptanedinitrile (**IV-3b**)



$C_{17}H_{16}N_2$

248.33 g.mol^{-1}

To a solution of 4-(3,4-dihydronaphthalen-1-yl)-4-nitroheptanedinitrile (0.5 mmol, 148 mg, 100 mol%) in DMF (1.5 ml) was added Cs_2CO_3 (0.5 mmol, 163 mg, 100 mol%), $Pd(OAc)_2$ (5 mol%), and dppe (5 mol%), the mixture was stirred for 30 min at 120 ^{o}C under Ar. After evaporation of solvent under reduced pressure (*vacuum*, 80 ^{o}C), the residue crude (357 mg) was purified by column chromatography on silica gel (eluent: Et_2O:PE = 70:30) to afford the desired product (71 %, 88 mg).

Aspect: colourless oil

Rf: 0.32 (Et_2O:PE = 7:3)

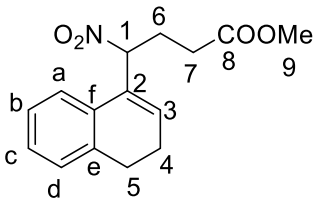
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 7.8 Hz, 1H, H-a), 7.94 – 7.87 (m, 1H, H-d), 7.82 (d, *J* = 8.2 Hz, 1H, H-j), 7.61-7.49 (m, 3H, H-c,i,b), 7.36 (d, *J* = 7.1 Hz, 1H, H-h), 3.87 (s, 1H, H-1), 2.27 – 2.08 (m, 8H, H-2,3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.7 (C-g), 134.1 (C-e), 132.6 (C-f), 129.3 (C-d), 128.1 (C-i), 126.9 (C-j), 126.2 (C-b), 125.7 (C-c), 122.7 (C-a), 122.3 (C-h), 119.4 (C-4), 36.4 (C-1), 32.4 (C-2), 15.2 (C-3).

HRMS: calculated for $C_{17}H_{16}N_2$:248.1313, found 248.1313

I.R.(thin film):3047, 2934, 2871, 1596, 1511, 1454, 1422, 1397, 1362, 1257, 1168, 1028 cm^{-1}

Methyl 4-(3,4-dihydronaphthalen-1-yl)-4-nitrobutanoate (**IV-2c**)



$C_{15}H_{17}NO_4$

275.30 $g.mol^{-1}$

To a solution of 4-(nitromethyl)-1,2-dihydronaphthalene (0.5 mmol, 90 mg, 100 mol%) in acetonitrile (1.5 ml) was added methyl acrylate (1.5 mmol, 129 mg, 3 eq) and DBU (15 mg, 10 mol%), the mixture was stirred for 2 h at r.t. under Ar. After evaporation of solvent under reduced pressure, the residue crude (267 mg) was purified by column chromatography on silica gel (eluent: DCM:PE = 40:60) to afford the desired product (71 %, 98 mg).

Aspect: colourless oil

Rf: 0.49 (DCM:PE = 5:5)

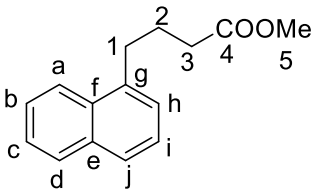
^{1}H NMR (400 MHz, $CDCl_3$) δ7.25 (d, *J* = 7.6 Hz, 1H, H-c), 7.20 – 7.04 (m, 3H, H-a,b,d), 6.30 (t, *J* = 4.5 Hz, 1H, H-3), 5.63-5.59 (m, 1H, H-1), 3.61 (s, 3H, H-9), 2.69-2.65 (m, 2H, H-5), 2.60 – 2.51(m, 1H, H-7), 2.38 – 2.25 (m, 5H, H-7,6,4).

^{13}C NMR (101 MHz, $CDCl_3$) δ172.5 (C-8), 136.4 (C-2), 132.2 (C-e), 131.8 (C-f), 130.6 (C-c), 128.2 (C-d), 127.9 (C-b), 126.9 (C-a), 122.2 (C-3), 86.2 (C-1), 52.0 (C-9), 30.3 (C-7), 27.8 (C-5), 27.6 (C-6), 23.1 (C-4).

HRMS: calculated for $C_{15}H_{17}NO_4$: 275.1158, found: 275.1161

I.R.(thin film): 2953, 2892, 2836, 1736, 1553, 1489, 1439, 1371, 1258, 1230, 1204, 1176,1023cm^{-1}.

Methyl 4-(naphthalen-1-yl)butanoate (**IV-3c**)



$C_{15}H_{16}O_2$

228.29 g.mol^{-1}

To a solution of methyl 4-(3,4-dihydronaphthalen-1-yl)-4-nitrobutanoate (0.5 mmol, 138 mg, 100 mol%) in DMF (1.5 ml) was added Cs_2CO_3 (0.5 mmol, 163 mg, 100 mol%), $Pd(OAc)_2$ (5 mol%), and dppe (5 mol%), the mixture was stirred for 30 min at 120 ^{o}C under Ar. After evaporation of solvent under reduced pressure (*vacuum*, 80 ^{o}C), the residue crude (361 mg) was purified by column chromatography on silica gel (eluent: Et_2O:PE = 10:90) to afford the desired product (66 %, 75 mg),

Aspect: colourless oil

Rf: 0.46 (Et_2O:PE = 1:9)

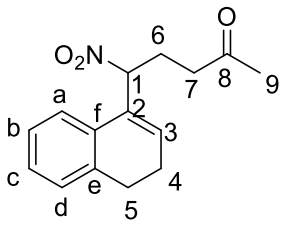
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.3 Hz, 1H, H-a), 7.87 (d, *J* = 7.9 Hz, 1H, H-d), 7.74 (d, *J* = 8.1 Hz, 1H, H-j), 7.56-7.47 (m, 2H, H-c,i), 7.41 (t, *J* = 7.6 Hz, 1H, H-b), 7.33 (d, *J* = 6.9 Hz, 1H, H-h), 3.70 (s, 3H, H-5), 3.13 (t, *J* = 7.7 Hz, 2H, H-1), 2.44 (t, *J* = 7.3 Hz, 2H, H-3), 2.11 (p, *J* = 7.4 Hz, 2H, H-2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1 (C-4), 137.6 (C-g), 134.0 (C-f), 131.9 (C-a), 128.9 (C-d), 127.0 (C-i), 126.3 (C-j), 126.0 (C-e), 125.6 (C-b), 125.6 (C-c), 123.9 (C-h), 51.7 (C-5), 33.8 (C-1), 32.4 (C-3), 25.9 (C-2).

HRMS: calculated for $C_{15}H_{16}O_2$: 228.1150, found: 228.1144

I.R.(thin film): 3065, 2953, 1731, 1597, 1511, 1438, 1395, 1367, 1251, 1220, 1168, 1147, 1011cm^{-1}.

5-(3,4-dihydronaphthalen-1-yl)-5-nitropentan-2-one (**IV-2d**)



$C_{15}H_{17}NO_3$

259.31g.mol^{-1}

To a solution of 4-(nitromethyl)-1,2-dihydronaphthalene (0.5 mmol, 90 mg, 100 mol%) in acetonitrile (1.5 ml) was added but-3-en-2-one (1.5 mmol, 105 mg, 3 eq) and DBU(15 mg, 10 mol%), the mixture was stirred for 3 h at r.t. under Ar. After evaporation of solvent under reduced pressure, the residue crude (229 mg) was purified by column chromatography on silica gel (eluent: Et_2O:PE = 30:70) to afford the desired product (84 %, 109 mg).

Aspect: colourless oil

Rf: 0.26 (Et_2O:PE = 3:7)

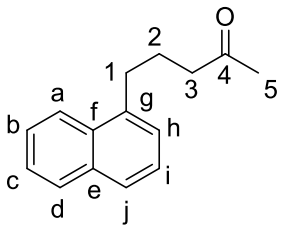
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 7.3 Hz, 1H, H-c), 7.25 – 7.13 (m, 3H, H-a,b,d), 6.37 (t, *J* = 4.7 Hz, 1H, H-3), 5.66-5.62 (m, 1H, H-1), 2.76-2.72 (m, 2H, H-5), 2.62 – 2.45 (m, 3H, H-4,7), 2.40 – 2.29 (m, 3H, H-6,7), 2.14 (s, 3H, H-9).

^{13}C NMR (101 MHz, $CDCl_3$) δ 206.7 (C-8), 136.2 (C-2), 132.2 (C-e), 131.8 (C-f), 130.4 (C-c), 128.1 (C-d), 127.8 (C-b), 126.8 (C-a), 122.1 (C-3), 86.2 (C-1), 39.3 (C-7), 30.0 (C-9), 27.5 (C-5), 26.4 (C-6), 23.0 (C-4).

HRMS: calculated for $C_{15}H_{17}NO_3$:259.1208, found 259.1201

I.R.(thin film): 3064, 3024, 2944, 2893, 2836, 1717, 1551, 1489, 1451, 1437, 1428, 1366, 1167, 1023cm^{-1}.

5-(naphthalen-1-yl)pentan-2-one (**IV-3d**)



$C_{15}H_{16}O$

212.29 $g.mol^{-1}$

To a solution of 5-(3,4-dihydronaphthalen-1-yl)-5-nitropentan-2-one (0.5 mmol, 130 mg, 100 mol%) in DMF (1.5 ml) was added Cs_2CO_3 (0.5 mmol, 163 mg, 100 mol%), $Pd(OAc)_2$ (5 mol%), and dppe (5 mol%), the mixture was stirred for 30 min at 120 ^oC under Ar. After evaporation of solvent under reduced pressure (*vacuum*, 80 ^oC), the residue crude (300 mg) was purified by column chromatography on silica gel (eluent: Et_2O:PE = 20:80) to afford the desired product (71 %, 75 mg),

Aspect: colourless oil

Rf: 0.51 (Et_2O:PE = 3:7)

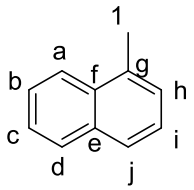
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.4 Hz, 1H, H-a), 7.91 – 7.84 (m, 1H, H-d), 7.74 (d, *J* = 8.2 Hz, 1H, H-j), 7.59 – 7.46 (m, 2H, H-c,i), 7.45 – 7.37 (m, 1H, H-b), 7.32 (d, *J* = 6.8 Hz, 1H, H-h), 3.10(t, *J* = 8.0 Hz, 2H, H-1), 2.52 (t, *J* = 7.2 Hz, 2H, H-3), 2.14 (s, 3H, H-5), 2.06 (p, *J* = 8.0 Hz, 2H, H-2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.9 (C-4), 137.8 (C-g), 133.9 (C-e), 131.9 (C-f), 128.8 (C-d), 126.9 (C-i), 126.2 (C-j), 125.9 (C-b), 125.6 (C-c), 125.5 (C-a), 123.9 (C-h), 43.1 (C-1), 32.3 (C-3), 30.1 (C-5), 24.6 (C-2).

HRMS: calculated for $C_{15}H_{16}O$: 212.1201, found: 212.1205

I.R.(thin film): 3044, 2941, 1710, 1595, 1509, 1396, 1354, 1262, 1218, 1180, 1162, 1080, 1027cm^{-1}.

1-methylnaphthalene (**IV-3e**)



$C_{11}H_{10}$

142.20 $g.mol^{-1}$

To a solution of 4-(nitromethyl)-1,2-dihydronaphthalene (0.5 mmol, 90 mg, 100 mol%) in DMF (1.5 ml) was added Cs_2CO_3 (0.5 mmol, 163 mg, 100 mol%), $Pd(OAc)_2$ (5 mol%), and dppe (5 mol%), the mixture was stirred for 30 min at 120 ^oC under Ar. After evaporation of solvent under reduced pressure (*vacuum*, 80 ^oC), the residue crude (297 mg) was purified by column chromatography on silica gel (eluent: PE) to afford the desired product (35 %, 25 mg).

Aspect: colourless oil

Rf: 0.75 (Et_2O:PE = 0.5:9.5)

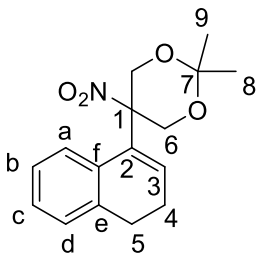
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.1 Hz, 1H, H-d), 7.89 (d, *J* = 7.4 Hz, 1H, H-a), 7.75 (d, *J* = 8.1 Hz, 1H, H-j), 7.59 – 7.48 (m, 2H, H-c,i), 7.41 (t, *J* = 7.5 Hz, 1H, H-b), 7.36 (d, *J* = 6.9 Hz, 1H, H-h), 2.74 (s, 3H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 134.4 (C-g), 133.7 (C-e), 132.7 (C-f), 128.7 (C-d), 126.7 (C-i), 126.5 (C-h), 125.8 (C-j), 125.7 (C-b), 125.7 (C-c), 124.2 (C-a), 19.5 (C-1).

HRMS: calculated for $C_{11}H_{10}$:142.0783, found 142.0784

I.R.(thin film): 3071, 2949, 2865, 1598, 1509, 1465, 1441, 1398, 1382, 1264, 1215, 1167, 1077, 1020cm^{-1}.

5-(3,4-dihydronaphthalen-1-yl)-2,2-dimethyl-5-nitro-1,3-dioxane (**IV-2e**)



$C_{16}H_{19}NO_4$

289.33 $g.mol^{-1}$

To a solution of 4-(nitromethyl)-1,2-dihydronaphthalene (0.5 mmol, 90 mg, 100 mol%) in 1.5 ml CH_3CN was added formaldehyde solution (2.5 mmol, 5 eq) and DBU (50 mol%), the mixture was stirred at r.t. for 2 h under Ar. After evaporation of solvent under reduced pressure, the residue crude was purified by column chromatography on silica gel (EA:PE = 4:6) to afford the 2-(3,4-dihydronaphthalen-1-yl)-2-nitropropane-1,3-diol (66 %, 82 mg, colourless oil).

In a round-bottomed flask was added 2-(3,4-dihydronaphthalen-1-yl)-2-nitropropane-1,3-diol (0.5 mmol, 125 mg, 100 mol%), p-toluenesulfonic acid (8 mg, 10 mol%),excess MgSO4(1 g) and 1.5 ml acetone. The mixture was heated to reflux for 15 h, after evaporation of solvent under reduced pressure, the residue crude was purified by column chromatography on silica gel(Et_2O:PE = 30:70) to afford the desired product(45 %,65 mg)

Aspect: colourless oil

Rf: 0.67 (EA:PE = 4:6)

^{1}H NMR (400 MHz, $CDCl_3$)δ 7.17-7.12 (m, 3H, H-a,c,d), 7.07 – 7.05 (m, 1H, H-b), 6.47-6.45 (m, 1H, H-3), 4.84 (d, *J* = 12.8 Hz, 2H, H-6), 4.25 (d, *J* = 12.8 Hz, 2H, H-6), 2.71 (t, *J* = 7.8 Hz, 2H, H-5), 2.35 (dt, *J* = 12.7, 6.5 Hz, 2H, H-4), 1.46 (s, 3H, H-8), 1.43 (s, 3H, H-9).

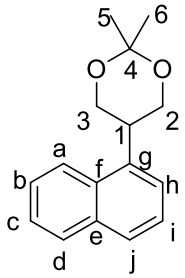
^{13}C NMR (101 MHz, $CDCl_3$) δ137.4 (C-2), 132.4 (C-e), 132.3 (C-f), 131.0 (C-c), 128.5 (C-d), 127.8 (C-b), 126.8 (C-a), 123.1 (C-3), 100.0 (C-7), 89.2 (C-1), 65.0 (C-6), 27.9 (C-5), 25.7 (C-8), 23.4 (C-9), 21.6 (C-4).

HRMS: calculated for $C_{16}H_{19}NO_4$: 289.1314, not found, fragment: 246.1380.

I.R.(thin film):3413, 2986, 2938, 2852, 1542, 1485, 1445, 1370, 1223, 1200, 1155, 1080,

1015 cm^{-1}

2,2-dimethyl-5-(naphthalen-1-yl)-1,3-dioxane (**IV-3f**)



$C_{16}H_{18}O_2$

242.32g.mol^{-1}

To a solution of 5-(3,4-dihydronaphthalen-1-yl)-2,2-dimethyl-5-nitro-1,3-dioxane (0.5 mmol, 145 mg, 100 mol%) in DMF (1.5 ml) was added Cs_2CO_3 (0.5 mmol, 163 mg, 100 mol%), $Pd(OAc)_2$ (5 mol%), and dppe (5 mol%), the mixture was stirred for 30 min at 120 ^oC under Ar. After evaporation of solvent under reduced pressure (*vacuum*, 80 ^oC), the residue crude (346 mg) was purified by column chromatography on silica gel (eluent: Et_2O:PE = 10:90) to afford the desired product (87 %, 105 mg),

Aspect: white solid m.p. 107.9-108.6 ^oC

Rf: 0.61 (Et_2O:PE = 3:7)

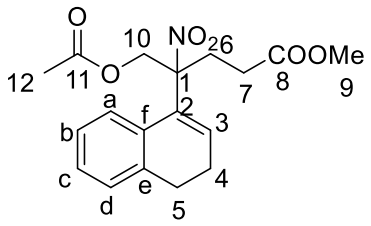
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.4 Hz, 1H, H-a), 7.88 (d, *J* = 7.5 Hz, 1H, H-d), 7.78 (d, *J* = 7.7 Hz, 1H, H-j), 7.59 – 7.42 (m, 4H, H-c,i,b,h), 4.24 – 4.13 (m, 4H, H-2,3), 4.04-3.98 (m, 1H, H-1), 1.63 (s, 3H, H-5), 1.57 (s, 3H, H-6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.1 (C-g), 134.1 (C-e), 131.9 (C-f), 129.2 (C-d), 127.7 (C-i), 126.5 (C-j), 125.9 (C-b), 125.5 (C-c), 123.7 (C-a), 122.9 (C-h), 98.3 (C-4), 65.2 (C-2,3), 36.2 (C-1), 28.5 (C-5), 20.1 (C-6).

HRMS: calculated for $C_{16}H_{18}O_2$: 242.1307, found: 242.1300

I.R.(thin film):3396, 3047, 2991, 2941, 2876, 1597, 1511, 1398, 1371, 1259, 1196, 1151, 1132, 1071, 1029 cm^{-1}

Methyl 5-acetoxy-4-(3,4-dihydronaphthalen-1-yl)-4-nitropentanoate (**IV-2f**)



$C_{18}H_{21}NO_6$

347.37g.mol^{-1}

To a solution of methyl 4-(3,4-dihydronaphthalen-1-yl)-4-nitrobutanoate (0.5 mmol, 138 mg, 100 mol%) in 1.5 ml CH_3CN was added formaldehyde solution (2.5 mmol, 5 eq) and DBU (10 mol%), the mixture was stirred at r.t. for 3 h under Ar. After evaporation of solvent under reduced pressure, the residue crude was dissolved in 1.5 ml dichloromethane, and then acetic anhydride (1 mmol) and DMAP (10 mol%) was added, the mixture was stirred at r.t. for 2 h under Ar. After evaporation of solvent under reduced pressure, the final crude was purified by column chromatography on silica gel (eluent: EA:PE = 30:70) to afford the desired product (44 %, 77 mg).[254]

Aspect: colourless oil

Rf: 0.54 (EA:PE = 4:6)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 – 7.06 (m, 3H, H-c,d,a), 6.96 (d, *J* = 7.0 Hz, 1H, H-b), 6.26 (t, *J* = 4.9 Hz, 1H, H-3), 4.76 (d, *J* = 11.6 Hz, 1H, H-10), 4.69 (d, *J* = 11.6 Hz, 1H, H-10), 3.56 (s, 3H, H-9), 2.87 – 2.61 (m, 4H, H-5,7), 2.36 – 2.12 (m, 4H, H-4,6), 2.06 (s, 3H, H-12).

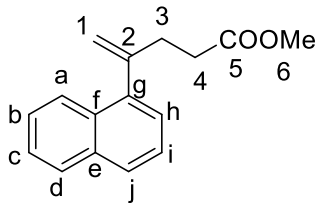
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2 (C-8), 170.0 (C-11), 137.2 (C-2), 131.8 (C-e), 131.8 (C-f), 130.9 (C-c), 128.4 (C-d), 127.8 (C-b), 126.8 (C-a), 122.4 (C-3), 92.8 (C-1), 65.2 (C-10), 51.9 (C-9), 29.2 (C-6), 27.8 (C-5), 27.0 (C-7), 23.2 (C-4), 20.6 (C-12).

HRMS: calculated for $C_{18}H_{21}NO_6$: 347.1369, not found

I.R.(thin film): 2949, 2906, 1738, 1544, 1487, 1439, 1367, 1339, 1226, 1160, 1104, 1065cm^{-1}.

[254] Bernard Barlaam, Jean Boivin, Laurent Elkaim,sarah Elton-Farr,and Samir Z.Zard. *Tetrahedron,* **1995**,*Vol 51*, No.6, 1675-1684

methyl 4-(naphthalen-1-yl)pent-4-enoate (**IV-3g**)



$C_{16}H_{16}O_2$

240.30 g.mol^{-1}

To a solution of methyl 5-acetoxy-4-(3,4-dihydronaphthalen-1-yl)-4-nitropentanoate (0.5 mmol, 174 mg, 100 mol%) in DMF (1.5 ml) was added Cs_2CO_3 (0.5 mmol, 163 mg, 100 mol%), $Pd(OAc)_2$ (5 mol%), and dppe (5 mol%), the mixture was stirred for 30 min at 120 ^oC under Ar. After evaporation of solvent under reduced pressure (*vacuum*, 80 ^oC), the residue crude (400 mg) was purified by column chromatography on silica gel (eluent: DCM:PE = 30:70) to afford the desired product (50 %, 120 mg),

Aspect: colourless oil

Rf: 0.60 (DCM:PE = 5:5)

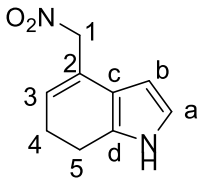
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.86 (m, 2H, H-j,d), 7.76 – 7.74 (m, 1H, H-a), 7.67 (d, *J* = 8.2 Hz, 2H, H-h,b), 7.39 – 7.31 (m, 1H, H-i), 7.18 (d, *J* = 7.0 Hz, 1H, H-c), 5.34 (s, 1H, H-1), 5.03 (s, 1H, H-1), 3.53 (s, 3H, H-6), 2.76 (t, *J* = 7.6 Hz, 2H, H-4), 2.36 (t, *J* = 7.7 Hz, 2H, H-3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5 (C-5), 147.1 (C-2), 140.4 (C-g), 133.8 (C-e), 131.3 (C-f), 128.4 (C-d), 127.6 (C-j), 126.0 (C-h), 125.8 (C-b), 125.7 (C-c), 125.3 (C-i), 116.1 (C-1), 51.7 (C-6), 33.6 (C-3), 32.8 (C-4).

HRMS: calculated for $C_{16}H_{16}O_2$:240.1150, found: 240.1147

I.R.(thin film):3043 ,2989, 2949, 1734, 1638, 1590, 1506, 1435, 1361, 1252, 1194, 1156, 1062, 1024 cm^{-1}.

4-(nitromethyl)-6,7-dihydro-1H-indole



$C_9H_{10}N_2O_2$

178.19 $g.mol^{-1}$

In a round-bottomed flask fitted with a Dean and Stark trap was added 1,5,6,7-tetrahydro-4H-indol-4-one (5 mmol, 676 mg, 100 mol%), nitromethane (50 mmol, 1.53 g, 10 eq), N,N-dimethylethane-1,2-diamine (1.5 mmol, 132 mg, 30 mol%), and toluene (25 ml), the mixture was refluxed for 72 h. After evaporation of solvent under reduced pressure, the residue crude was purified by column chromatography on silica gel (eluent: EA:PE = 30:70) to afford the desired product 4-(nitromethyl)-6,7-dihydro-1H-indole (45 %, 401 mg).

Aspect: yellow solid, m.p. 145.8-146.5 ^{o}C

Rf: 0.57 (EA:PE = 5:5)

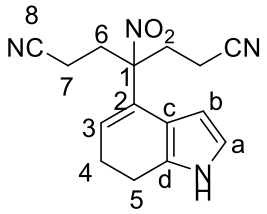
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H, H-NH), 7.41 (t, *J* = 1.6 Hz, 1H, H-a), 6.76 – 6.68 (m, 1H, H-b), 6.31 (dd, *J* = 3.2, 2.4 Hz, 1H, H-3), 3.26 – 3.23 (m, 2H, H-1), 2.74 (t, *J* = 6.3 Hz, 2H, H-5), 2.02 – 1.96 (m, 2H, H-4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.3 (C-d), 139.0 (C-2), 127.7 (C-3), 119.4 (C-a), 115.2 (C-c), 104.3 (C-b), 26.5 (C-1), 23.1 (C-5), 22.7 (C-4).

HRMS: calculated for $C_9H_{10}N_2O_2$:178.0742, found: 178.0740

I.R.(thin film): 3270, 2941, 1572, 1546, 1503, 1459, 1413, 1329, 1301, 1240, 1182, 1139, 1100,1018cm^{-1}.

4-(6,7-dihydro-1H-indol-4-yl)-4-nitroheptanedinitrile



$C_{15}H_{16}N_4O_2$

284.32g.mol^{-1}

To a solution of 4-(nitromethyl)-6,7-dihydro-1H-indole (0.5 mmol, 89 mg, 100 mol%) in acetonitrile (1.5 ml) was added acetonitrile (2.5 mmol, 265 mg, 5 eq) and DBU(38 mg, 50 mol%), the mixture was stirred for 3 h at r.t. under Ar. After evaporation of solvent under reduced pressure, the residue crude (410 mg) was purified by column chromatography on silica gel (eluent: EA:PE = 30:70) to afford the desired product (83 %, 118 mg),

Aspect: yellow oil

Rf: 0.56 (EA:PE = 5:5)

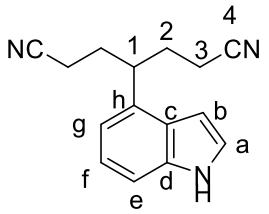
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H, H-NH), 6.58 (t, *J* = 2.5 Hz, 1H, H-a), 5.80 (d, *J* = 2.2 Hz, 1H, H-b), 5.53 (t, *J* = 4.5 Hz, 1H, H-3), 2.74 – 2.57 (m, 6H, H-5,4,6), 2.53 – 2.42 (m, 4H, H-6,7), 2.38 6– 2.28 (m, 2H, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ 130.4 (C-2), 129.5 (C-d), 119.7 (C-a), 118.4 (C-8), 116.8 (C-3), 112.9 (C-c), 103.4 (C-b), 94.1 (C-1), 30.8 (C-5), 24.2 (C-6), 20.6 (C-4), 13.1 (C-7).

HRMS: calculated for $C_{15}H_{16}N_4O_2$: 284.1273, found: 284.1267

I.R.(thin film): 3401, 2942, 1542, 1450, 1422, 1348, 1086cm^{-1}.

4-(1H-indol-4-yl)heptanedinitrile



$C_{15}H_{15}N_3$

237.31 g.mol^{-1}

To a solution of methyl 4-(6,7-dihydro-1H-indol-4-yl)-4-nitroheptanedinitrile (0.5 mmol, 142 mg, 100 mol%) in DMF (1.5 ml) was added Cs_2CO_3 (0.5 mmol, 163 mg, 100 mol%), $Pd(OAc)_2$ (5 mol%), and dppe (5 mol%), the mixture was stirred for 30 min at 120 ^oC under Ar. After evaporation of solvent under reduced pressure (*vacuum*, 80 ^oC), the residue crude (410 mg) was purified by column chromatography on silica gel (eluent: EA:PE = 30:70) to afford the desired product (67 %, 80 mg).

Aspect: light yellow oil

Rf: 0.51 (EA:PE = 4:6)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H, H-NH), 7.34 (d, *J* = 8.2 Hz, 1H, H-e), 7.24 – 7.23 (m, 1H, H-g), 7.17 (t, *J* = 7.7 Hz, 1H, H-f), 6.91 (d, *J* = 7.2 Hz, 1H, H-a), 6.61 – 6.60 (m, 1H, H-b), 3.26 – 3.20 (m, 1H,H-1), 2.22 – 2.05 (m, 8H, H-2,3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.2 (C-d), 131.6 (C-h), 127.1 (C-a), 124.7 (C-c), 122.5 (C-f), 119.7 (C-4), 117.9 (C-g), 110.6 (C-e), 100.5 (C-b), 42.0 (C-1), 31.6 (C-2), 15.6 (C-3).

HRMS: calculated for $C_{15}H_{15}N_3$:237.1266, found: 237.1269

I.R.(thin film):3396, 2930, 1612, 1550, 1503, 1417, 1338, 1200, 1157, 1119, 1090 cm^{-1}.

***

université PARIS-SACLAY
ÉCOLE DOCTORALE
INTERFACES
Approches Interdisciplinaires : Fondements, Applications et Innovation

Titre : Hétérocycles par Réactions multicomposants et réaction de Tsuji-Trost des dérivés nitrés allyliques.

Mots clés : réactions multicomposants, hétérocycles, hydrazones, réactions de Tsuji-Trost, naphtalène

Résumé : Les réactions multicomposants jouent un rôle important en chimie organique. Elles permettent de coupler au moins trois produits de départ ensemble fournissant des adduits qui ont été largement utilisés pour la synthèse de molécules complexes et de composés bioactifs. Les réactions multicomposants à base d'isonitriles ont été plus particulièrement développées pour la préparation de bibliothèques de structures organiques exploitées dans la recherche pharmaceutique.
La réaction de Passerini, combinée à des additions de Michael suivies de cyclisation, a permis un accès rapide aux γ-butyrolactones avec de bons rendements. Les adduits de Passerini des aldéhydes aromatiques agissent comme des nucléophiles dans les additions de Michael avec l'acrylonitrile. La réaction se déroule conjointement avec l'hydrolyse de l'ester. Le γ-hydroxynitrile résultant peut être cyclisé dans des conditions acides pour donner des γ-butyrolactones.
Les NH-aryl hydrazones dérivées du trifluoroacétaldéhyde hémiacétal peuvent être impliquées dans des réactions de type Mannich avec le formaldéhyde ou des aldéhydes aromatiques. Nous avons démontrés que cette réaction à trois composants peut être utilisée pour la formation d'hétérocycles substitutés par des groupes CF3. Ainsi le chauffage des hydrazones adduits de Mannich avec des β-cetoesters conduit à l'élimination de l'amine avce formation de 1,2-diazine. La réaction fait probablement intervenir des azoalcènes intermédiaires.
Nous avons dans une troisième partie préparé de nouveaux dérivés du naphtalène en travaillant sur des élimination de type Tsuji-Trost de composés nitrés allyliques. Couplée à la chimie des dérivés nitrés, cette synthèse de diène fournit un outil synthétique puissant pour la formation de naphtalènes 1-substitués.

Title : Multicomponent Reactions toward Heterocycles and Tsuji-Trost Reaction of Allylic Nitro Derivatives

Keywords : multicomponent reactions, heterocycles, hydrazones, Tsuji-Trost reactions, naphthalene

Multicomponent reactions play an important role in organic chemistry. They make it possible to couple at least three starting materials together providing adducts that have been widely used for the synthesis of complex molecules and bioactive compounds. The multicomponent reactions based on isonitriles have been developed more particularly for the preparation of libraries of organic structures used in pharmaceutical research.
The Passerini reaction, combined with Michael additions followed by cyclization, allowed rapid access to γ-butyrolactones in good yields. Passerini adducts of aromatic aldehydes act as nucleophiles in Michael additions with acrylonitrile. The reaction proceeds in conjunction with the hydrolysis of the ester. The resulting γ-hydroxynitrile can be cyclized under acidic conditions to give γ-butyrolactones.
NH-aryl hydrazones derived from trifluoroacetaldehyde hemiacetal can be involved in Mannich reactions with formaldehyde or aromatic aldehydes. We have demonstrated that this three-component reaction can be used for the formation of CF3-substituted heterocycles. Thus, heating hydrazone Mannich adducts with β-ketoesters leads to the elimination of the amine with the formation of 1,2-diazines. The reaction probably involves intermediate azoalkenes.
In a third part, we have prepared new naphthalene derivatives by working on Tsuji-Trost elimination of allylic nitro compounds. Coupled with the chemistry of nitro compounds, this diene synthesis provides a powerful synthetic tool for the formation of 1-substituted naphthalenes.

Université Paris-Saclay
Espace Technologique / Immeuble Discovery
Route de l'Orme aux Merisiers RD 128 / 91190 Saint-Aubin, France