



# Multicomponent reactions for the synthesis of some nitrogenous heterocyclic compounds and studies of their biological activities

Alaa Zidan

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# Réactions multicomposants pour la préparation de composés hétérocycliques azotés à haut potentiel biologique

Thèse de doctorat de l'Université Paris-Saclay  
préparée à l'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 26 Juin 2018, par

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***"One sometimes finds what one is not looking for!"***

**Sir Alexander Fleming ...**



**In the memory of my Grandmother**

**Dedicated to**

**My lovely parents,**

**Adorable brothers,**

**Supportive family**

**And wonderful friends all over the world ..**

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## Résumé





## Résumé

Les réactions multicomposantes (RMC) sont des transformations dans lesquelles au moins trois produits de départ sont combinées ensemble en une seule réaction pour former un produit final qui incorpore la totalité ou la plupart des atomes des composants de départ (Figure 1). Les réactions multicomposantes à base d'isonitrile (IMCR) ont été à la base du développement de ce domaine, la réaction la plus étudiée étant le couplage de Ugi. L'intégration d'une IMCR dans une cascade réactionnelle de deux à trois étapes (réactions de post-condensation) permet de fournir une diversité structurale plus complexe, propriété particulièrement mise en valeur pour la recherche de nouveaux médicaments.

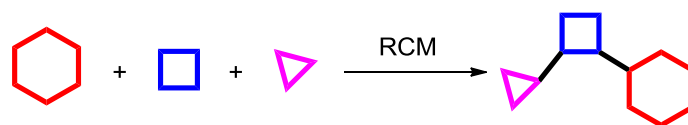


Figure 1

Dans le cadre de cette thèse, nous nous sommes intéressés plus particulièrement à la réaction d'Ugi qui implique un aldéhyde ou une cétone, une amine, un isonitrile et un acide carboxylique (Schéma 1). La réaction Ugi a démontré son intérêt pour la synthèse de nombreux échafaudages hétérocycliques grâce à sa grande tolérance fonctionnelle.

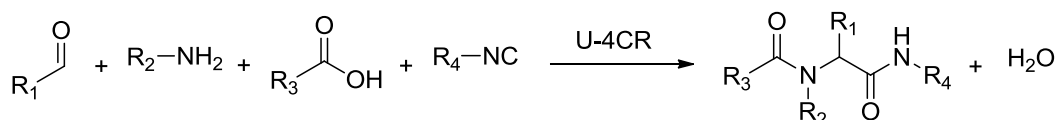


Schéma 1

Malgré les nombreuses applications de la réaction Ugi, cette réaction possède toujours un certain nombre de limitations et l'ensemble des post-condensations qui ont été décrites sur les adduits de Ugi concerne principalement des réactions de cyclisation qui n'étendent pas la diversité de ce premier couplage.

En examinant la littérature, nous pouvons clairement trouver de nombreux exemples de produits Ugi exploitant des aldéhydes comme composant carbonyle, mais en ce qui concerne les cétones et les cétones aromatiques plus particulièrement, seuls quelques exemples sont décrits. Dans le cadre de cette thèse, nous nous sommes intéressés aux fonctionnalisations de produits de Ugi exploitant des réactions d'addition intermoléculaires

sur le site peptidique issu des réactions de Ugi d'aldéhydes aromatiques. Ce site est relativement acide et de nombreuses études proposant des cyclisations en milieu basique ont déjà été publiées. Les réactions intermoléculaires sont beaucoup plus difficiles de part le fort encombrement stérique autour de cette position. Notre travail s'est donc concentré sur la mise au point de conditions permettant d'augmenter la nucléophilie de cette position et de réaliser des réactions d'alkylation dans des conditions relativement douces. Cette approche nous a permis par ailleurs d'apporter une solution à la faible réactivité des cétones aromatiques dans la réaction de Ugi. En effet, après alkylation de la position peptidique, le produit formé est un adduit de Ugi formel impliquant une cétone aromatique (Schéma 2).

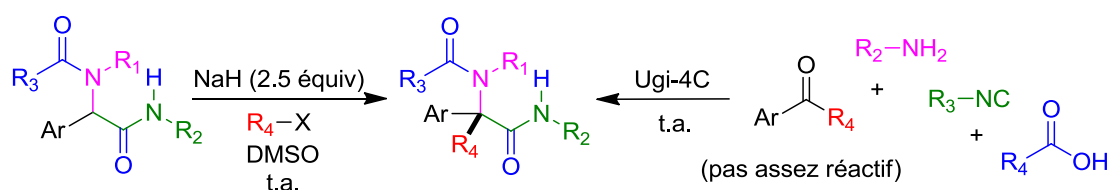


Schéma 2

Afin de rendre les réactions post-condensation intermoléculaires d'Ugi plus aisées, nous avons introduit un nouveau protocole impliquant l'utilisation de dianions 1,3-amide issus des adduits Ugi pour améliorer la nucléophilie de la position du peptidyl C-H vis-à-vis des réactions intramoléculaires.

Dans ce contexte, une bibliothèque d'adduits Ugi a été préparée en faisant varier les 4 composants de la réaction. Les  $\alpha$ -amidocarboxamides préparés ont été obtenus avec des rendements de 67 à 97% avec une grande diversité structurale notamment quant à la structure des aldéhydes de départ. La réaction de Tsuji-Trost a été choisie comme premier exemple de réaction de post-condensation. Plusieurs conditions ont été testées, le couple NaH dans le DMSO a été choisie comme la combinaison optimale base / solvant pour cette réaction. L'emploi de 2,5 équivalents de NaH dans le DMSO a permis la formation d'amidures dianioniques issus des adduits de Ugi à température ambiante, ces derniers ont été allylés avec de bons rendements en une heure à température ambiante. Un couple  $\text{Pd}(\text{dba})_2/\text{PPh}_3$  a été utilisés comme système catalytique dans la réaction. Une C-alkylation sélective a été observée, donnant un ensemble de dérivés de pent-4-énamide avec des rendements bons à excellents allant de 49 à 96 % (Schéma 3).

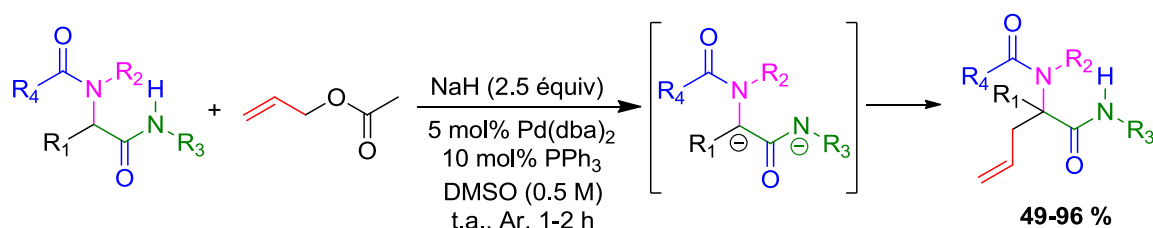


Schéma 3

Nous avons proposé que le mécanisme réactionnel passe par une première déprotonation de la position du peptidyl C-H formant un monoanion qui n'est pas suffisamment nucléophile pour attaquer le complexe  $\pi$ -allyl palladium (pas de réaction dans les mêmes conditions avec un équivalent de base). Une deuxième déprotonation fournit un intermédiaire de dianion beaucoup plus nucléophile qui attaque sélectivement le complexe  $\pi$ -allyle sur la position peptidique. Le produit final est obtenu après hydrolyse acide du milieu réactionnel (Schéma 4).

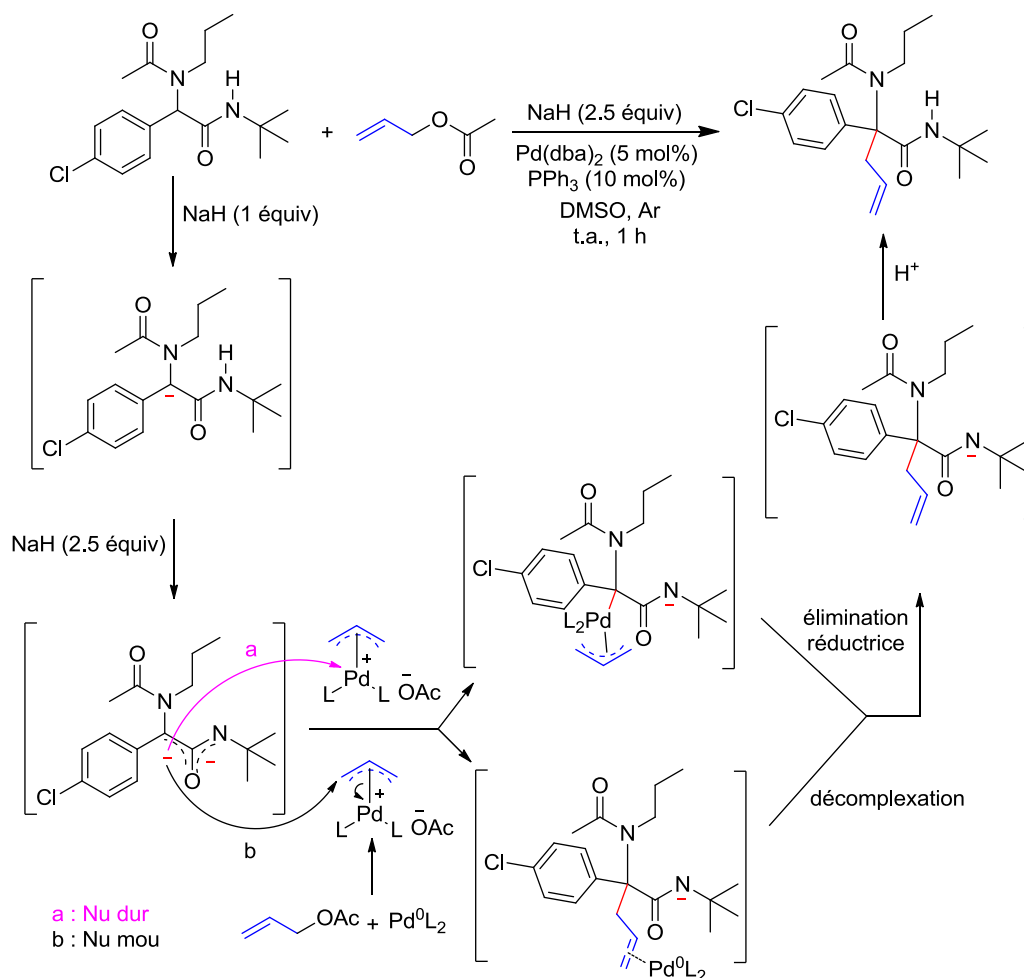


Schéma 4

Dans le cas des produits de Ugi dérivés de la propargylamine, la réaction de Tsuji-Trost n'a pas donné le produit attendu, mais une cycloisomérisation vers un 2,3-dihydropyrrole a été observée. Une telle réactivité a déjà été rapportée en 2012 par Miranda *et al.*, par traitement des adduits de Ugi propargyliques par du *t*-BuOK (2,5 équiv.) dans le THF. Cette réaction implique une isomérisation probable en allénamide suivie de la cyclisation en dihydropyrrole. Il convient de mentionner qu'en utilisant notre protocole, une forte amélioration de la réaction a été observée, les produits cycliques étant obtenus avec de meilleurs rendements (Schéma 5).

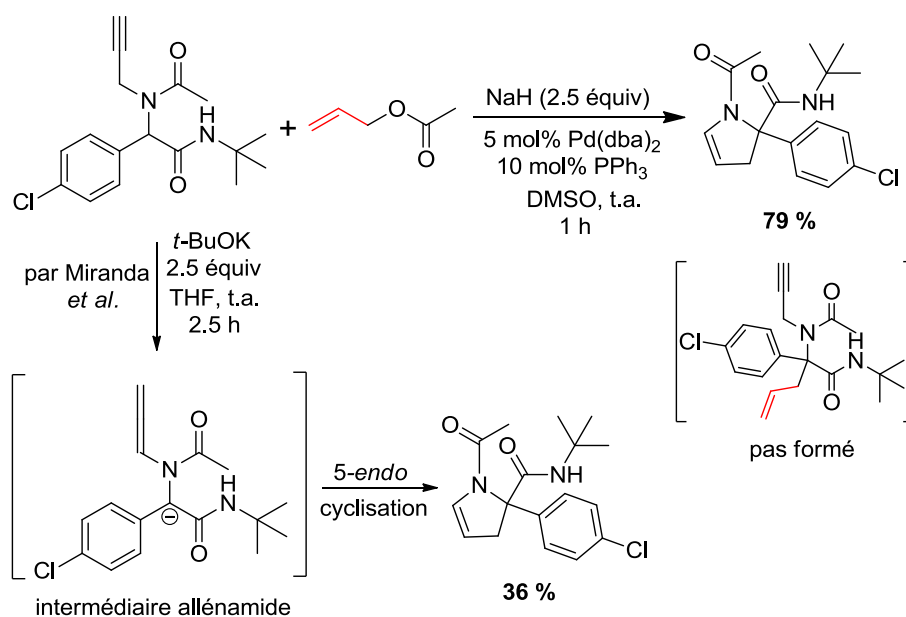


Schéma 5

Dans l'objectif de limiter cette réaction de cyclisation, nous avons voulu tester des conditions susceptibles de fournir des produits alkylés avec des cinétiques plus rapides. Par conséquent, nous avons examiné l'utilisation d'halogénure d'allyle comme agent alkylant. En travaillant sur un adduit de Ugi non propargylique, le composé cible a été obtenu avec succès en utilisant du bromure d'allyle à température ambiante pendant 1 heure. Aucune source de palladium n'était nécessaire dans ce cas. Bien que le rendement ait légèrement diminué (96% dans le cas de l'utilisation de l'acétate d'allyle contre 83% avec le bromure d'allyle), cela peut aussi être considéré comme une bonne méthode pour obtenir le produit cible (Schéma 6).

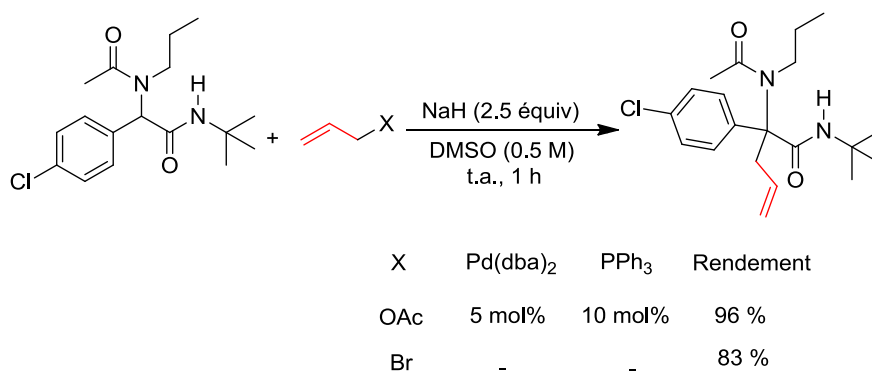


Schéma 6

En utilisant un produit d'addition Ugi dérivé de propargylamine, on ajoute d'abord le bromure d'allyle à l'adduit d'Ugi dans du DMSO suivi de la base. Après une heure, le produit de départ a été complètement converti en un produit allylé qui a été isolé avec un rendement de 58 % (Schéma 7). Ces résultats indiquent que le taux d'allylation est beaucoup plus rapide que celui de l'isomérisation-cyclisation. Ainsi, ayant l'électrophile déjà présent dans le milieu réactionnel, dès que l'espèce 1,3-dianionique est générée, il pourrait attaquer instantanément le bromure d'allyle formant le produit allylé cible.

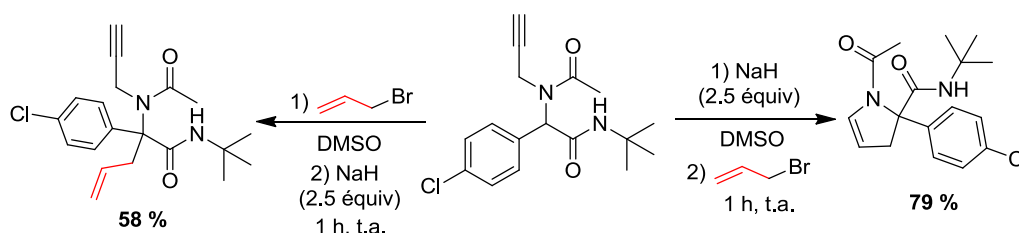


Schéma 7

Cette réaction n'est pas limitée à l'exploitation du bromure d'allyle d'halogénures d'alkylation a été examinée dans la réaction donnant le produit souhaité dans des rendements modérés à excellents (Schéma 8). Ainsi, à la fois les bromures de cinnamyle et de prényle ont donné les produits correspondants avec de bons rendements de 88 % et 74 % respectivement. Alors que le 3-bromocyclohex-1-ène donnait le produit cible avec un rendement de 30 %, ce qui est dû à l'encombrement stérique des halogénures d'alkyle secondaires. Les dérivés alkyls simples ont également montré une réactivité remarquable, où l'iodure d'éthyle a donné le produit cible avec un rendement de 94 %, tandis que le bromure de *p*-méthylbenzyle a donné le produit correspondant avec un rendement de 79 %.

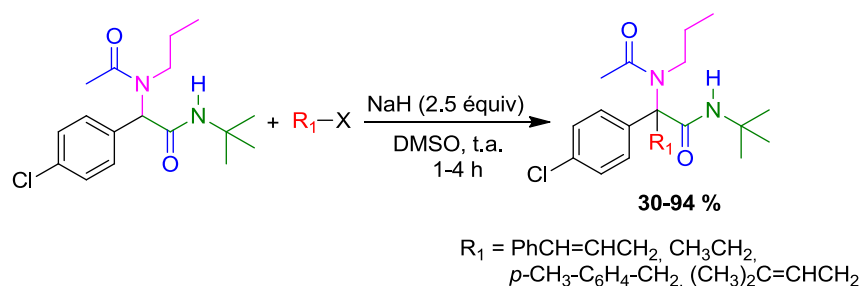


Schéma 8

L'efficacité de ces alkylations et la possibilité de les réaliser en l'absence d'une catalyse au palladium nous ont poussé à mettre au point des conditions expérimentales ne nécessitant pas de purification intermédiaire. En effet les éventuels trace d'isonitrile n'ayant pas réagi ne sont pas susceptible d'inhiber dans ce cas la réaction. La réaction de Ugi a donc été réalisée dans du méthanol à température ambiante pendant 24 heures. Après évaporation du solvant, l'étape suivante est réalisée sur le mélange brut comme auparavant (Schéma 9). Ce changement de solvants est nécessaire car le DMSO n'est pas un solvant adapté pour la réaction d'Ugi.

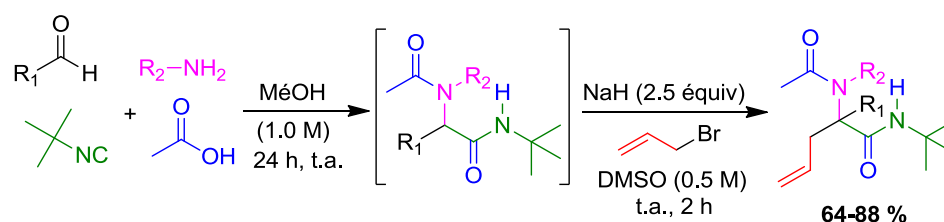


Schéma 9

Dans la plupart des cas, les rendements de la réaction effectuée sans purification du produit de Ugi étaient comparables à ceux obtenus à partir d'une séquence en deux étapes en utilisant un complexe de  $\pi$ -allyle palladium comme réactif d'allylation et avec une purification intermédiaire.

La simplicité de la procédure et les rendements élevés observés nous ont poussé à mettre en valeur cette approche dans différentes synthèses d'hétérocycles. S'agissant des réactions d'allylation, nous nous sommes évidemment tournés rapidement vers des réactions de métathèse cyclisante (RCM) du fait des nombreuses possibilités offerte par la réaction de Ugi pour l'introduction de groupements alcényles complémentaires.

Nous avons ainsi réalisé différentes réactions de Ugi à partir de l'allylamine. Après allylation de ces derniers, les métathèses ont été réalisées très facilement pour donner les composés cibles. La deuxième génération de catalyseur de Hoveyda-Grubbs a été choisie comme catalyseur en utilisant le toluène comme solvant de réaction. La réaction a été réalisée à 60 °C pendant 4 heures. En appliquant cette méthodologie, une série de 3,4-déhydropipéridines a été synthétisée avec des rendements bons à excellents allant de 64 à 89 % (Schéma 10).

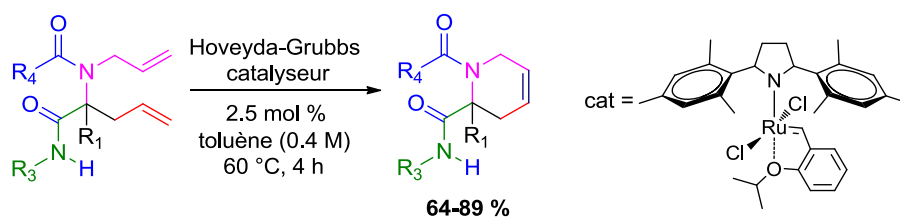


Schéma 10

Un protocole similaire, mais exploitant cette fois l'acide cinnamique à la place de l'allylamine comme source de fonction éthylénique nous a permis d'obtenir une famille hétérocyclique proche. Dans ce cas, des dérivés de 3,4-déhydropipéridine-2-one ont été obtenus avec succès avec des rendements de 72 et 82 % (Schéma 11).

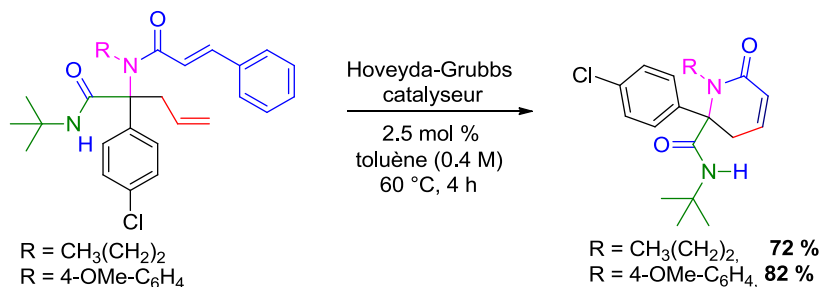


Schéma 11

Dans le cas des produits de métathèse issus de l'allylamine, les 2,3-déhydropipéridine sont facilement accessibles par migration de la double liaison finale catalysée par un complexe  $\text{RuClH}(\text{CO})(\text{PPh}_3)_3$  (réaction effectuée au reflux du toluène pendant 1,5 heure). Le composé cible a été obtenu sélectivement avec un rendement de 81% (Schéma 12).



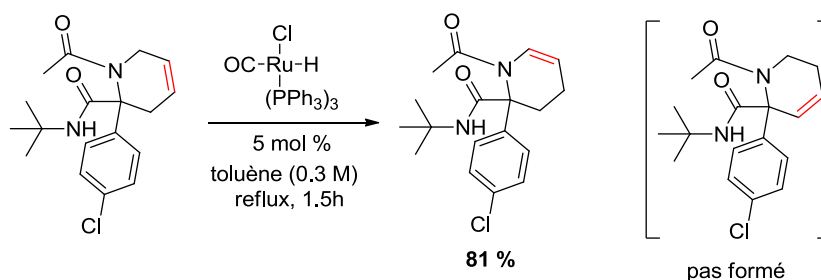


Schéma 12

Après avoir exploré des réactions d'alkylation relativement simples, nous avons voulu exploité pleinement la formation du dianion dans des séquences impliquant une double alkylation de la position peptidique et de l'azote de l'amidure. Pour ce faire nous avons envisagé l'utilisation de différents bis-électrophiles pour donner des échafaudages cycliques finaux. Le diiodométhane a été choisi comme bis-électrophile relativement peu exploré en espérant observer la formation de  $\beta$ -lactames. L'intérêt biologique de ces derniers apporte en effet une motivation complémentaire à cette étude. En étudiant la littérature, nous avons trouvé une approche intéressante proposée par Hirari *et al.* en 1979. En travaillant sur des 1,3-dianions d'un dérivé d' $\alpha$ -thio-amide, ils observent avec des rendements faibles la formation de  $\beta$ -lactames par traitement par du diiodométhane. Malgré un protocole simple, cette méthodologie n'a été l'objet d'aucune étude complémentaire. En effet, le mécanisme proposé implique un intermédiaire episulfonium qui suggère un champ synthétique relativement limité (Schéma 13). Seulement 4 exemples sont décrits avec de faibles rendements allant de 26,8 à 53,5%.

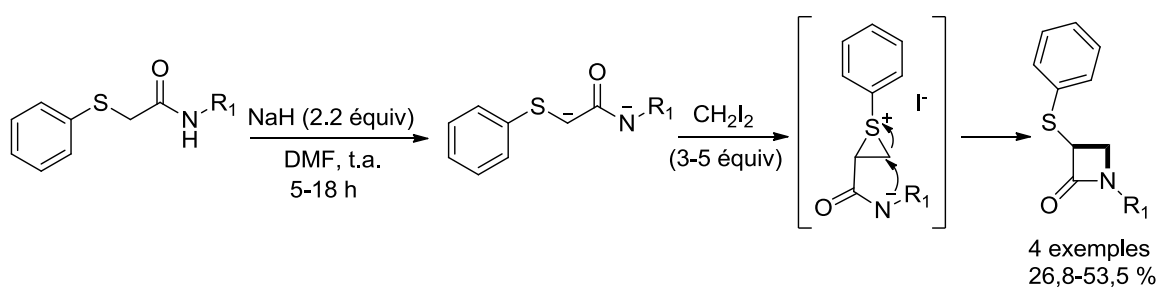


Schéma 13

Ils observent par ailleurs la formation de dimères dès la concentration augmente sensiblement (Schéma 14).

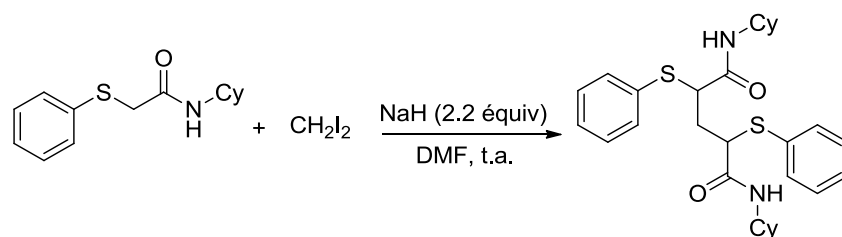


Schéma 14

Contrairement à ce que suggère l'étude de Hirari et al, nous avons montré que l'addition de diiodométhane sur des amidures dianioniques est une approche très efficace et large pour la synthèse de  $\beta$ -lactames. Dans le cas des adduits de Ugi, l'utilisation de NaH dans le DMSO s'est de nouveau avéré être la combinaison base/solvant optimale pour la réaction. Nous avons pu ainsi accéder à une banque de  $\beta$ -lactames à 4 composants par une cycloaddition formelle [3+1] avec de bons rendements. Les lactames sont obtenus très facilement à température ambiante au bout d'une heure (Schéma 15).

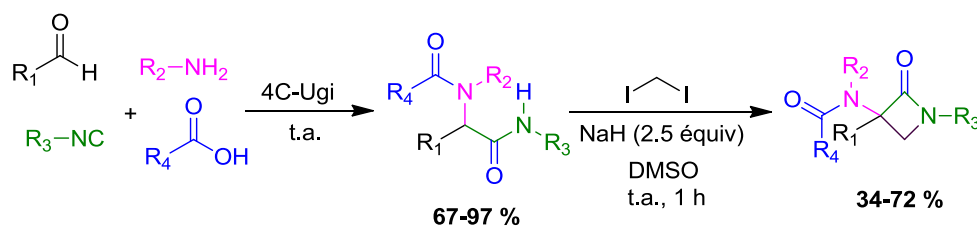


Schéma 15

Afin de rationaliser le mécanisme de réaction, une étude DFT a été réalisée par notre confrère "Julian Garrec" (professeur assistant à l'Unité Chimie et Procédés de l'ENSTA-ParisTech). Les résultats obtenus sont résumés ci-dessous à la Figure 2.

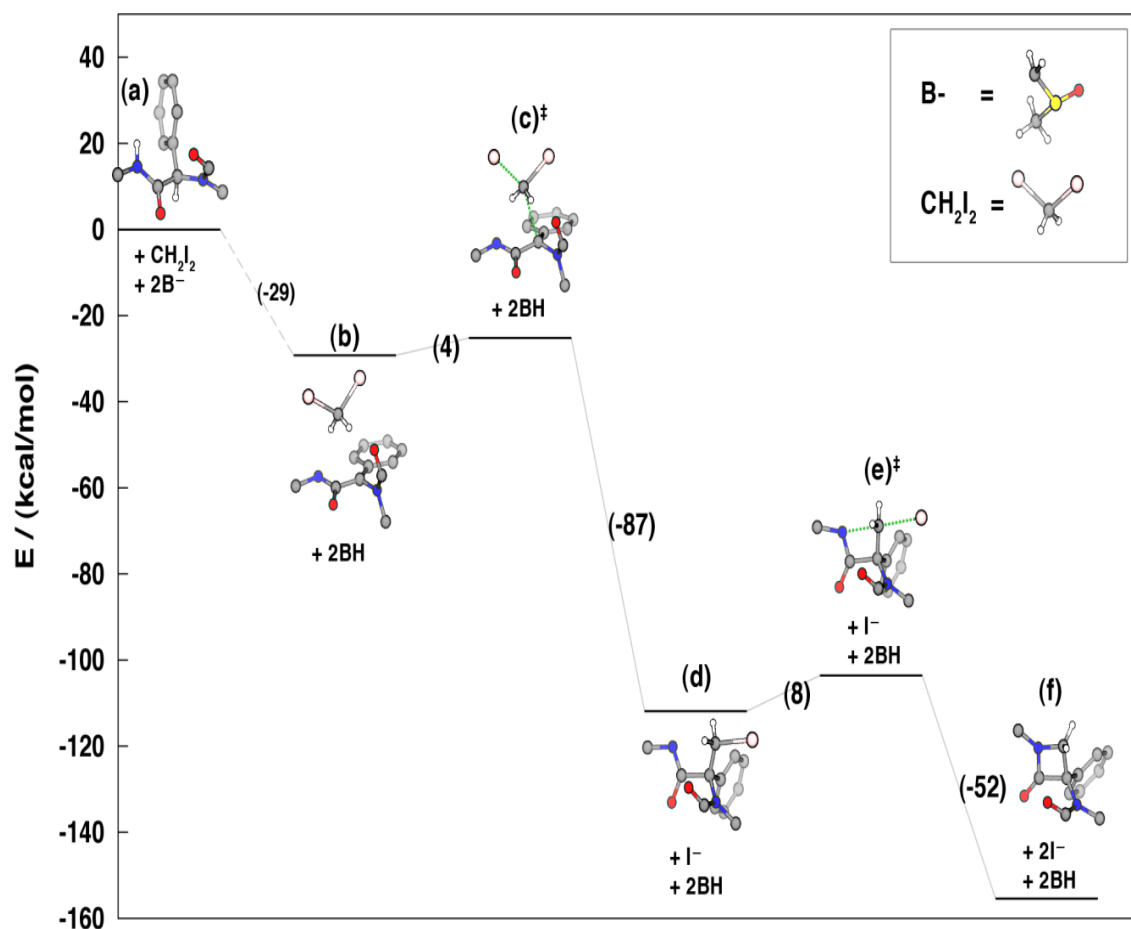


Figure 2

Les calculs ont montré une légère différence d'énergie entre la *C*-alkylation initiale et la *N*-alkylation; par conséquent, la *C*-alkylation initiale est légèrement favorisée. Ceci est en accord avec la formation de l'intermédiaire *C*-méthylé observée au cours de l'étude (Schéma 16).

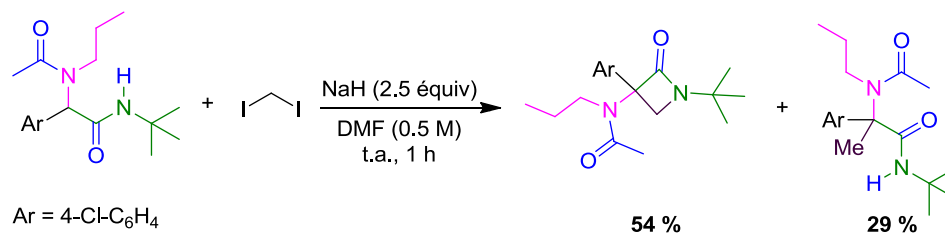
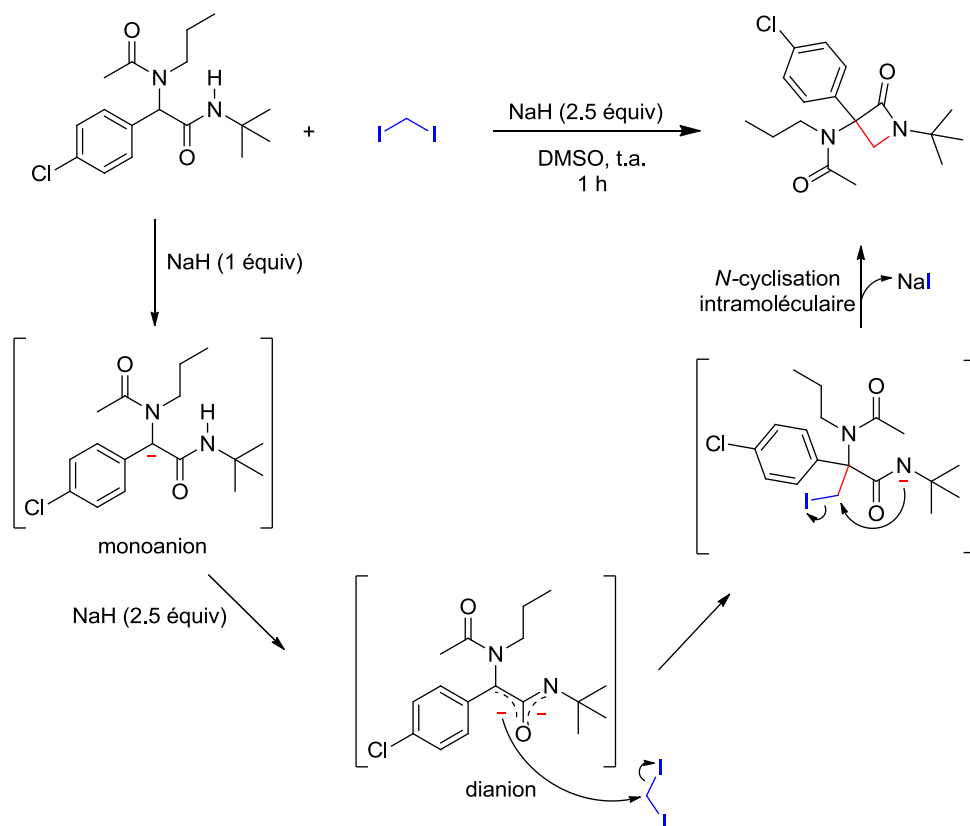


Schéma 16

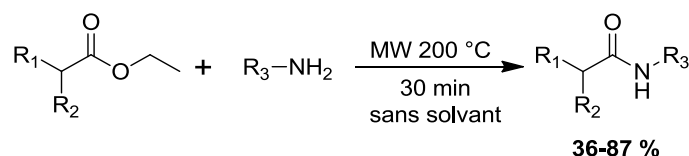
En conséquence, le mécanisme le plus probable pour cette réaction est présenté dans le schéma 17. La déprotonation commence à la position peptidyle formant le monoanion qui n'est pas suffisamment nucléophile pour attaquer le diiodométhane. Comme précédemment

une deuxième déprotonation fournit un dianion beaucoup plus réactif vis-à-vis du diiodométhane. Enfin, une *N*-alkylation intramoléculaire a lieu pour donner le  $\beta$ -lactame final.



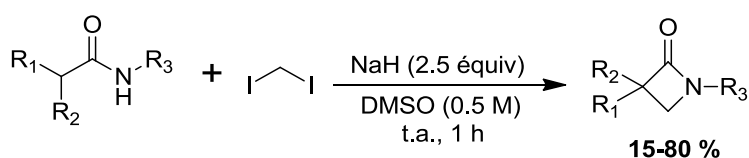
**Schéma 17**

Le succès de cette approche sur les adduits de Ugi nous a encouragé à étendre cette cycloaddition formelle  $[3 + 1]$  à d'autres amides plus simples. Dans ce but, différents amides ont été préparés à partir d'esters maloniques. En complément de l'étude d'Hirari, l'importance d'avoir des substituants  $\text{R}_1$  et  $\text{R}_2$  différents de l'hydrogène a été mise en évidence. Cela permet notamment de supprimer la formation de produits secondaires issus de l'élimination intermédiaire de  $\text{HI}$ , pour former des  $\beta$ -lactames sélectivement et avec des rendements élevés. La synthèse d'amide d'ester malonique implique la condensation d'un malonate avec diverses amines à  $200\text{ }^\circ\text{C}$  pendant 30 minutes sous irradiation micro-ondes (Schéma 18). Ainsi, un ensemble d'esters amides maloniques et de dérivés apparentés a été synthétisé avec des rendements modérés à excellents (36 à 87 %).



**Schéma 18**

Les amides formés ont été traités dans les conditions mises au point pour les produits de Ugi NaH (2,5 équiv.), diiodométhane (1,5 équiv.) dans le DMSO (0,5 M) à température ambiante pendant une heure) pour donner de nouveaux  $\beta$ -lactames avec des rendements modérés à bons (15 à 80 %) (Schéma 19).

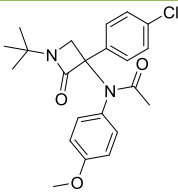
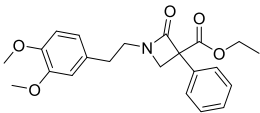
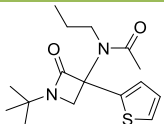
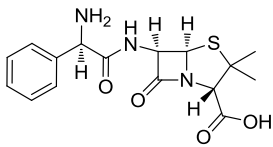


**Schéma 19**

Ensuite, les  $\beta$ -lactames nouvellement synthétisés ont été testés *in vitro* pour leur activité antimicrobienne dans le "centre de biologie" de la Faculté de Pharmacie (Université Mansoura, Egypte). L'activité a été déterminée contre une bactérie à gram négatif (*Escherichia coli*), une bactérie à gram positif (*Staphylococcus aureus*) en plus des espèces fongiques (*Candida albicans*). L'Ampicilline et le fongicide Colitrimazole ont été choisis comme références pour évaluer les propriétés biologiques de produits formés en utilisant une solution de 1 mg/ml dans du DMSO pour chaque échantillon. L'effet antimicrobien a été déterminé par deux paramètres principaux, les valeurs du diamètre de la zone d'inhibition en mm et le pourcentage d'indice d'activité.

Nous avons trouvé que parmi les séries de  $\beta$ -lactames synthétisés, trois présentaient une réactivité proche de celle de l'Ampicilline (Tableau 1). Ces résultats sont d'autant plus intéressants que nos produits sont préparés en seulement deux étapes à partir de produit simples et commerciaux.

Tableau 1

Composé	Diamètre de la zone d'inhibition en mm [% Indice d'activité]		
	<i>Escherichia coli</i>	<i>Staphylococcus aureus</i>	<i>Candida albicans</i>
	25 [96.1]	24 [100.0]	26 [96.3]
	23 [88.5]	23 [95.8]	24 [88.9]
	21 [80.8]	23 [95.8]	19 [70.4]
<b>Ampicillin</b> 	26 [100.0]	24 [100.0]	-

Enfin, nous avons décrit la construction du squelette tricyclique des alcaloïdes dérivés de la Crispine à partir des adduits acycliques Ugi par une cascade propargylation / cyclisation 5-exo-dig / Pictet-Spengler en une seule étape. Malgré le fait que les réactions de Pictet-Spengler aient été largement exploitées pour la construction du squelette benzoindolizinone, nous avons décrit une approche particulièrement rapide à partir d'adduits d'Ugi dans une suite réactionnelle monotope. L'intérêt d'utiliser des adduits de Ugi dans cette cascade est clairement démontré en augmentant la diversité des alcaloïde synthétisés.

La première étape d'une telle cascade implique la réaction du dianion d'amide d'Ugi avec le bromure de propargyle en tant que bis-électrophile pour fournir les dérivés de pyrrolidin-2-one. Il existe plusieurs voies réactionnelles possibles pour une telle réaction, certaines d'entre elles sont présentées dans le Schéma 20. La première implique l'attaque nucléophile (mécanisme  $S_N^1$ ) du carbanion peptidyle sur le bromure de propargyle donnant le dérivé de  $\beta$ -alkynylamide de forme ouverte. La seconde provient de l'attaque nucléophile du carbanion peptidyle sur le bromure de propargyle, suivie d'une *N*-cyclisation subséquente 5-

*exo-dig* donnant des 5-*exo*-méthylène-pyrrolidin-2-ones. Néanmoins, l'attaque nucléophile pourrait être suivie d'une *N*-cyclisation 6-*endo-dig*, donnant des 3,4-dihydropyridin-2-ones.

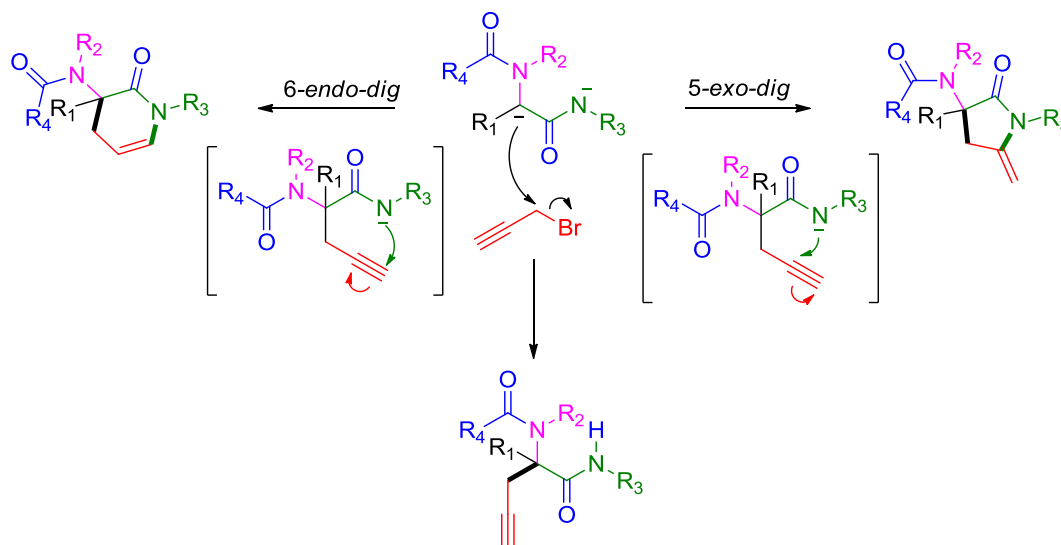


Schéma 20

L'hydroamidation d'alcynes est une réaction bien connue particulièrement décrite dans ses versions intramoléculaires. Habituellement, l'attaque nucléophile d'amides sur une triple liaison est légèrement exothermique ou thermo-neutre, mais elle est moins favorisée cinétiquement en raison de la répulsion entre le nucléophile et les électrons  $\pi$  de la triple liaison de l'alcyne. En conséquence, les hydroamidations non catalytiques doivent impliquer soit des acides forts pour protoner le triple liaison, facilitant ainsi l'attaque nucléophile, soit des bases fortes pour générer des amides métalliques nucléophiles améliorant ainsi leur addition sur l'alcyne. Alors que dans le cas des hydroamidations catalytiques, le métal se coordonne habituellement à la triple liaison, réduisant sa densité électronique, permettant ainsi l'addition nucléophile. Les catalyseurs de transfert de phase sont également souvent utilisés pour améliorer la nucléophilie des amides.

En conséquence, l'effet de plusieurs bases, acides de Lewis et catalyseurs de transfert de phase a été examiné sur la propargylation des adduits de Ugi. L'optimisation des conditions expérimentales nous a conduit à sélectionner l'utilisation de NaH (2,5 équiv.) et de bromure de propargyle (1,5 équiv.) en présence de TBAF (1,0 équiv.) dans du DMSO (0,4 M) à 50 °C. La réaction est terminée en une heure (Schéma 21). La séquence de propargylation / cyclisation 5-*exo-dig* a donné une série de 5-*exo*-méthylène-pyrrolidin-2-ones avec des rendements bons à élevés (55-83 %).

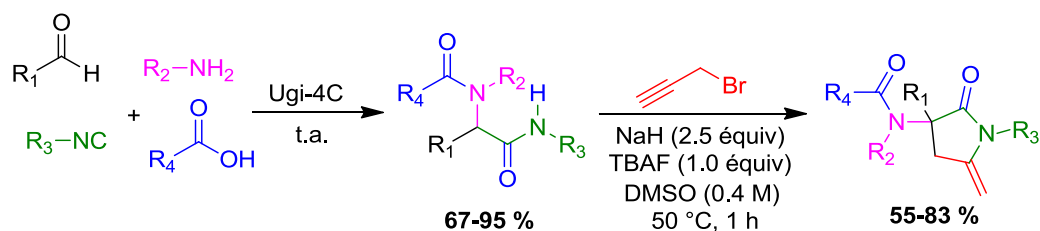


Schéma 21

Contrairement aux études précédemment réalisées pendant cette thèse, il n'a pas été facile de déterminer si la propargylation de l'adduit de Ugi implique un monanion ou un dianion. Les deux équivalents de base ne sont dans ce cas probablement pas indispensables car la cyclisation finale conduit à un anion vinylique susceptible de déprotoner les produits de départ (Schéma 22).

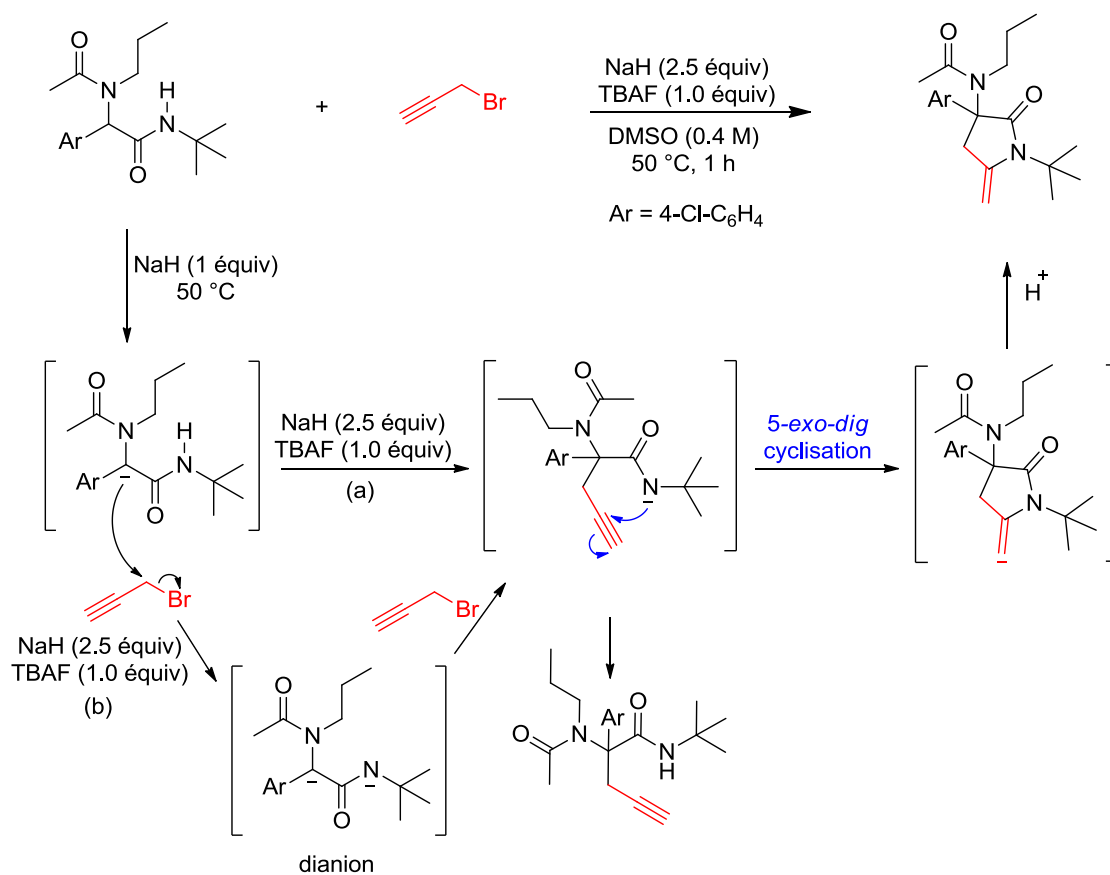


Schéma 22

Nous avons ensuite évalué l'utilité synthétique de la fonctionnalité enamide cyclique. Sachant que l'énamide existe en équilibre avec son ion *N*-acyliminium dans des conditions acides, il serait possible de piéger ce dernier avec différents nucléophiles. Dans ce contexte, la pyrrolidin-2-one a été traitée avec 1,0 équiv. d'indole en présence de TsOH.H<sub>2</sub>O (10 mol%)



dans du toluène à 60 °C pendant 2 heures (Schéma 23). Le produit d'addition a été obtenu avec un rendement de 71%. Dans ce cas, l'addition nucléophile de l'indole s'est accompagnée d'une élimination du groupe *N*-propylacétamide. Le potentiel de cette réaction et plus particulièrement la présence d'un nouveau groupe carbonyle  $\alpha,\beta$ -insaturé cyclique, pourrait être exploité dans différentes additions de Michael.

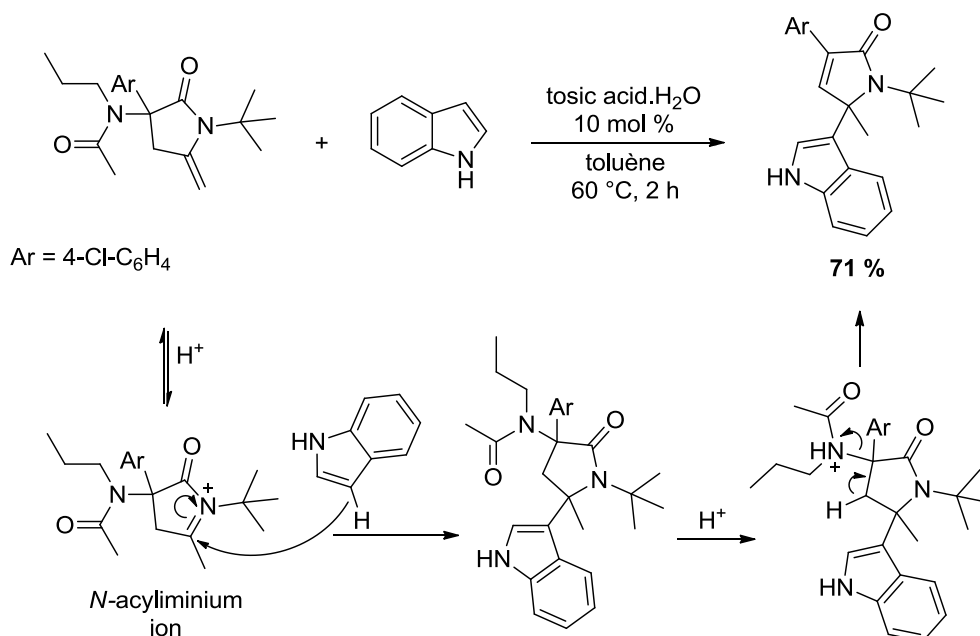


Schéma 23

Enfin, nous avons exploité cette stratégie dans différents piégeages intramoléculaires de type Pictet-Spengler pour former des structures de type benzoindolizidinone. Dans ce but, des adduits Ugi ont été préparés en utilisant un isonitrile de  $\beta$ -aryléthyle riche en électrons. Selon l'observation précédente, il est possible que la cyclisation de Pictet-Spengler soit suivie d'une réaction d'élimination (Schéma 24).

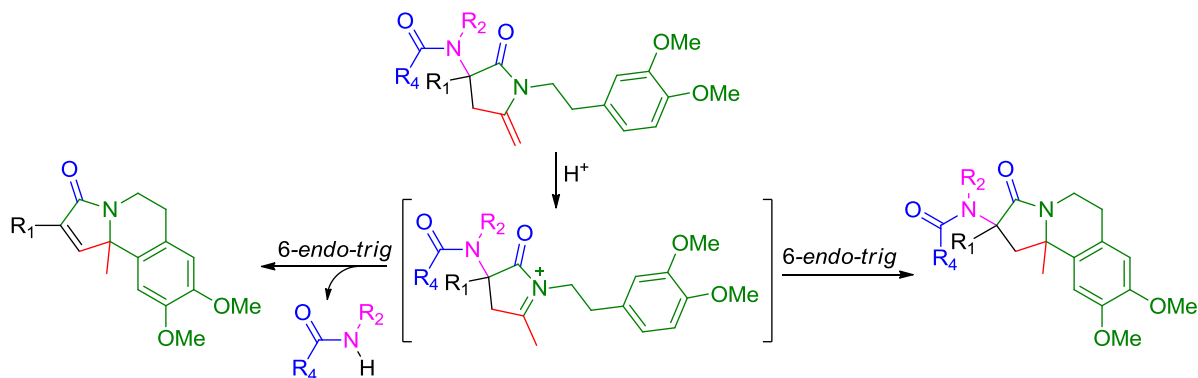


Schéma 24

La réaction de Pictet-Spengler a été réalisée en utilisant de l'acide trifluoroacétique dans de le dichlorométhane à température ambiante. Par la suite, nous avons examiné la possibilité d'effectuer la propargylation et la réaction de Pictet-Spengler en une seule étape. Il n'a pas été possible de réaliser la cascade entière dans le DMSO qui s'est révélé incompatible avec les conditions de la cyclisation de Pictet-Spengler. Nous avons pu néanmoins réaliser la séquence sans purification intermédiaire en effectuant une extraction et un changement de solvant. Avec ce protocole modifié, une série d'analogues d'alcaloïdes de la famille des benzoindolizidinone a été préparé avec des rendements modérés à bons (35 à 68 %).

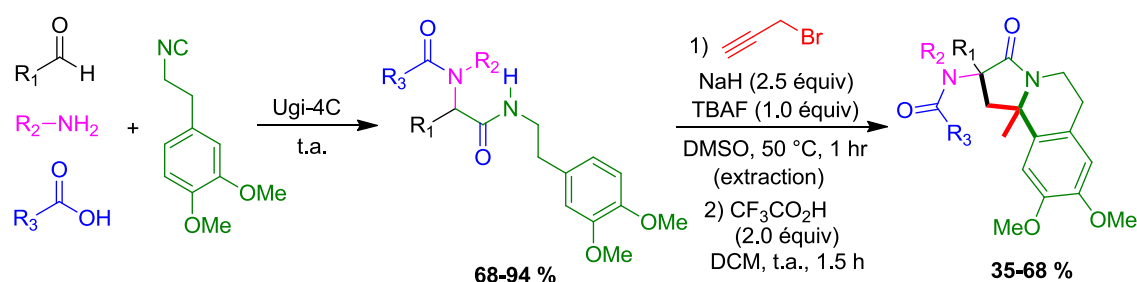


Schéma 25

La formation d'un seul diastéréoisomère a été observée dans ces cyclisations. La stéréochimie a pu être confirmée grâce à des analyses RX.

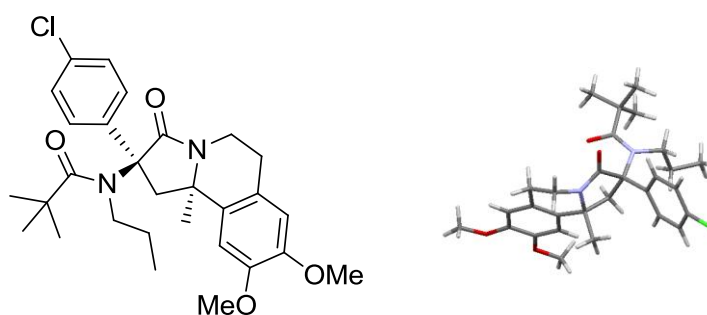


Figure 3



## List of Abbreviations

### Functional Groups

Ac	Acyl
Acac	Acetylacetone
OAc	Acetate
Me	Methyl
Et	Ethyl
Bu	Butyl
Pr	Propyl
Cy	Cyclohexyl
dba	Dibenzylideneacetone
Ar	Aryl
Ph	Phenyl
Bn	Benzyl
Bz	Benzoyl
Boc	<i>Tert</i> -butoxycarbonyl
TMS	Trimethylsilyl
OTf	Triflate
Fmoc	Fluorenylmethoxycarbonyl
Ts	Tosyl ( <i>p</i> -toluenesulfonyl)
<i>p</i> -tol	<i>Para</i> -tolyl
<i>i</i> -Bu	Isobutyl
<i>t</i> -Bu	<i>Tert</i> -butyl
<i>i</i> -Pr	Isopropyl

### Chemical Compounds

NaHMDS	sodium bis(trimethylsilyl)amide
XPhos	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
XantPhos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
Johnphos	2-(di- <i>tert</i> -butylphosphino)biphenyl
Py	pyridine
Dppf	bis(diphenylphosphino)ferrocene
DIOP	2,3-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
Dppe	1,2-bis(diphenylphosphino)ethane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIPEA	diisopropylethylamine
DIPA	diisopropylamine
LDA	lithium diisopropylamide
TFA	trifluoroacetic acid
TEBAC	triethylbenzylammonium chloride
TEA	triethylamine

## **Solvents**

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

## **Others**

aq.	aqueous
NS	nucleophilic substitution
r.t.	Room Temperature
MW	Micro-wave
M.S.	Molecular Sieve
M.p.	Melting Point
MCRs	MultiComponent Reactions
M.W.	Molecular Weight
p <sub>ka</sub>	acidity constant
Nu	nucleophilic
h $\nu$	light
E	electrophilic
equiv.	Equivalent
Cat.	Catalyst
t	Reaction time
T	temperature
d.r.	diastereomeric ratio
ee	enantiometric excess
EWG	electron-withdrawing group
LG	leaving group
L	ligand
HOMO	highest occupied molecular orbital
LUMO	lowest unoccupied molecular orbital

## **Measuring Units**

°C	Degree Celsius
h	hour
d	day
Hz	Hertz
min	minute
g	gram
W	Watt
ppm	Particle per million
mol	mole
M	Molar (mol/L)

**Chromatography and spectroscopy**

TLC	thin-layer chromatography
J	coupling constant
IR	Infra-Red
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
m	multiplet
s	singlet
d	doublet
t	triplet
NMR	nuclear magnetic resonance
q	quadruplet



## General Introduction

Pharmacological/biological activities play a pivotal role among the various properties of organic compounds. The capability to vary the structure of organic compounds and evaluate the biological effects based on these structural changes, helps in the development of drugs for treating different infectious diseases. Multicomponent reactions serve very well in this field, since they not only allow the synthesis of diversity oriented libraries of organic structures, but also lead to the formation of multiple bonds in one single step with high atom efficiency. It is an environmentally friendly reaction which saves time, effort and chemical products.

Thus, multicomponent reactions field is becoming an attracting domain for research to both academic and industrial organic chemists. Nevertheless, the combination of established multicomponent reactions with suitable post-condensation transformations opens a large access to heterocycles. The heterocyclic moieties are found in numerous natural products as well as the skeleton of molecules possessing biological activities.

The major target of this thesis is to discover new post-condensations for Ugi adducts that will provide a gateway to biologically important heterocycles.

The first chapter will cover a brief introduction on isocyanides and multicomponent reactions, especially Ugi reaction and its previous post-condensations, described in the literature.

In Chapter two, we will illustrate the underestimated 1,3-amide dianionic reactivity of Ugi adducts and its reaction with mono-electrophiles via a tandem Ugi/alkylation reaction. This strategy opened an access to Ugi 5-CR and allowed a formal synthesis of Ugi adducts derived from aromatic ketones. The resulting Ugi adducts were then employed in a ring-closure metathesis reaction affording a group of 3,4-dehydropiperidine derivatives, which are present in the main core of various alkaloids.

The third chapter will involve the investigation of the dianionic reactivity of Ugi products towards biselectrophiles. For such purpose, diiodomethane was employed as a



biselectrophile thus allowing a formal [3+1] cycloaddition reaction to synthesize a four-component library of  $\beta$ -lactams. This methodology was extended to include several malonate ester amides and their derivatives, thus transforming the protocol into a general efficient procedure for the synthesis of  $\beta$ -lactams. Additionally, the antibacterial effects of all the newly prepared  $\beta$ -lactams were examined.

The fourth chapter will illustrate the possibility of obtaining 5-*exo*-methylene- $\gamma$ -lactams through an Ugi/propargylation cascade involving a metal-free hydroamidation cyclization mechanism. More interestingly, the benzoindolizidine alkaloids analogues could be obtained via an Ugi/propargylation/Pictet-Spengler sequence in a two-step protocol.

The last part of this manuscript will include the experimental part addressing 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**



## I.1 Multicomponent reactions (MCRs)

The classical multistep syntheses suffer from several drawbacks. The treatment and purification of each step, the isolation and analysis of every intermediates, wasting both solvent and time and finally the high costs with overall low yields are the major stumbling blocks that render such way of synthesis less convenient.

The ideal synthesis for every organic chemist requires the formation of the target compound within the minimum number of steps in overall good yield and using environmentally friendly reagents (Figure I.1).<sup>1</sup> Hence, the need for an alternative method to conventional multistep synthesis is compulsory. Multicomponent reactions<sup>2</sup> meet the criteria of such ideal synthesis. They are sequential reactions with a simple procedure starting from readily available starting materials, affording complex structures with high atomic efficiency in one or two steps.

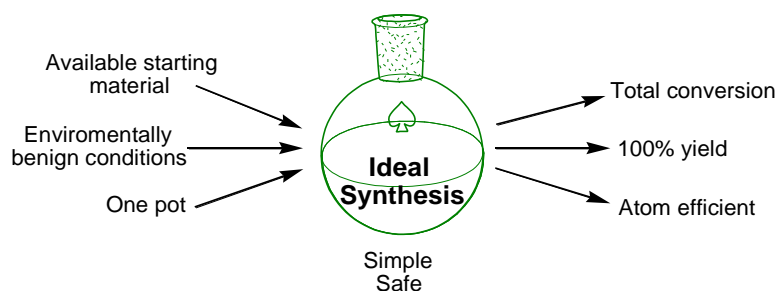


Figure I.1. General considerations for ideal synthesis.

## I.2 The principles of multicomponent reactions

Multicomponent reactions (MCRs) are powerful transformations in which at least three starting materials are combined together in a single reaction to form a final sole product that basically incorporates all or most of the atoms of the starting components (Figure I.2). They often involve a sequence of consecutive steps including bond breaking and bond formations, which proceed sequentially till reaching an irreversible final step that traps the final product.

<sup>1</sup> (a) Wender, P. A. *Chem. Rev.* **1996**, 96, 1. (b) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, 39, 3168.

<sup>2</sup> (a) Zhu, J. *Eur. J. Org. Chem.* **2003**, 2003, 1133. (b) Zhu, J.; Bienaymé, H., Eds. *Multicomponent Reactions*; Wiley-VCH: Weinheim, Germany, **2005**. (c) Dömling, A. *Chem. Rev.* **2006**, 106, 17.

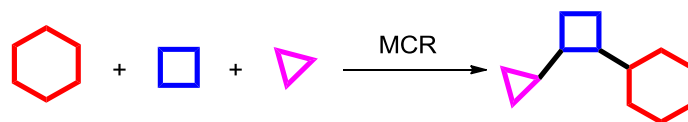


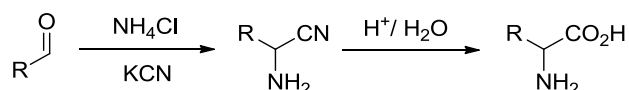
Figure I.2. A representation for a multicomponent reaction.

They can be considered as a special class of tandem reactions as they are usually performed by mixing all substrates in a single reaction flask without additional modifications of the reaction conditions.

Multicomponent reactions together with their post condensation reactions comprise a particularly attractive synthetic strategy. They provide easy and rapid accessibility to large libraries of organic compounds with different substitution patterns. Such diversity and easy accessibility to a large number of organic compounds along with the available screening techniques renders MCRs a leader in the drug discovery processes.

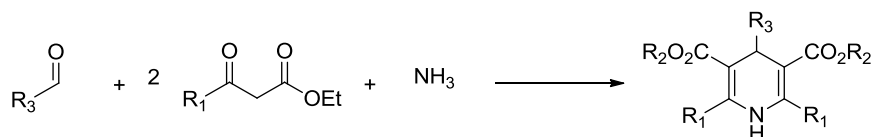
### I.3 Historical background of MCRs

The terminology MCRs dates back to the 60's. The first multicomponent reaction was reported by Strecker in 1850.<sup>3</sup> He described the condensation of an aldehyde with ammonium chloride in presence of potassium cyanide affording  $\alpha$ -aminonitrile, which upon hydrolysis gave the corresponding  $\alpha$ -amino acid (Scheme I.1).



Scheme I.1. Strecker amino acid synthesis.

In 1882, Hantzsch documented the first multicomponent synthesis of heterocycles.<sup>4</sup> It involved the reaction of an aldehyde with 2.0 equiv. of a  $\beta$ -ketoester and a nitrogen source such as: ammonia to form 1,4-dihydropyridines (Scheme I.2).

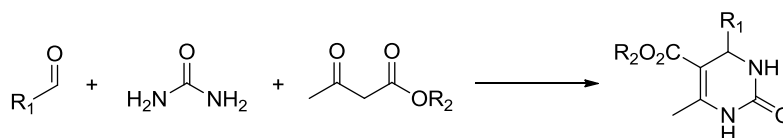


Scheme I.2. Hantzsch dihydropyridine synthesis.

<sup>3</sup> Strecker, A. *Liebigs Ann. Chem.* **1850**, 75, 27.

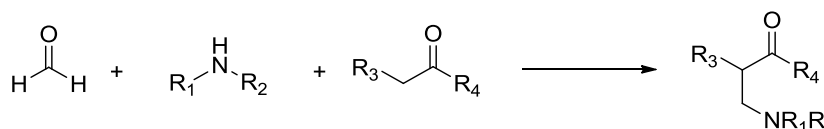
<sup>4</sup> Hantzsch, A. *Justus Liebigs Ann. Chem.* **1882**, 215, 1.

This reaction was modified afterwards by Biginelli in 1891,<sup>5</sup> by switching the nitrogen source to urea instead of ammonia. This allowed him to prepare 3,4-dihydropyrimidin-2(1H)-ones (Scheme I.3).



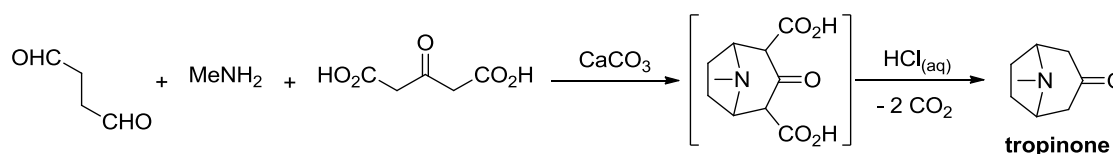
**Scheme I.3. The synthesis of 3,4-dihydropyrimidin-2(1H)-ones by Biginelli.**

Few years later, one of the most important MCRs was discovered. Mannich reaction<sup>6</sup> that involves an amino alkylation of an enol using an aldehyde together with an amine was published in 1912 (Scheme I.4).



**Scheme I.4. Mannich reaction.**

Mannich reactions are widely employed in organic synthesis. One of the earliest applications of MCRs in natural product synthesis is the total synthesis of the alkaloid “tropinone” in 1917 by Robinson<sup>7</sup> as a precursor to atropine. He performed a double-Mannich reaction using succinaldehyde, methylamine and acetonedicarboxylic acid followed by decarboxylation to prepare the bridged bicyclic “tropinone” (Scheme I.5).



**Scheme I.5. Robinson's double-Mannich reaction.**

An enormous number of MCRs is reported in the literature, among which IMCRs (isocyanide based multicomponent reactions) are the most documented. Before discussing the IMCRs in details, an introduction about isocyanides will be presented.

<sup>5</sup> (a) Biginelli, P. *Ber. Dtsch. Chem. Ges.* **1891**, 24, 2962. (b) Biginelli, P. *Ber. Dtsch. Chem. Ges.* **1893**, 26, 447.

<sup>6</sup> Mannich, C.; Krösche, W. *Arch. Pharm. (Weinheim, Ger.)* **1912**, 250, 647.

<sup>7</sup> Robinson, R. *J. Chem. Soc.* **1917**, 111, 762.

## I.4 Isocyanides

Isocyanides (also called isonitriles or carbylamines) represent a class of organic compounds carrying the functional group  $\text{-N}\equiv\text{C}$ . They are the isomers of their corresponding cyanides ( $\text{-C}\equiv\text{N}$ ), thus given the prefix 'iso'. They are well known for their strong penetrating, unpleasant odor. As a result of such sharp odor, isocyanides have been recognized as potential non-lethal weapons.<sup>8</sup>

Isocyanide functional group is present in only few naturally occurring compounds. The first isolated natural product containing isocyanide group, Xantocillin, was extracted from the mold *Penicillium notatum* in 1950 (Figure I.3).<sup>9</sup> Later on, xantocillin was used as an antibiotic.

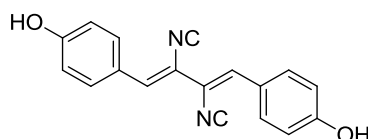
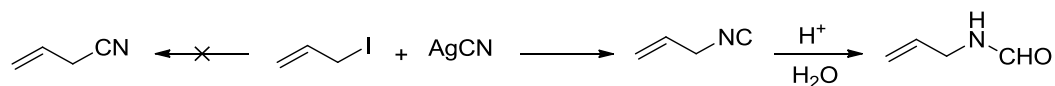


Figure I.3. The structure of xantocillin.

### 1) Synthesis of isocyanides

The first described synthesis of isocyanides in literature was in 1859 by Lieke.<sup>10</sup> While preparing allyl nitrile from allyl iodide and silver cyanide, he was surprised to obtain a product with sharp odour which upon hydrolysis gave *N*-allylformamide instead of the corresponding carboxylic acid. At this stage, he could not determine the structure of the formed product. Few years later, in 1869, Gautier<sup>11</sup> demonstrated that this allylation reaction resulted in the formation of allyl isocyanide and could successfully characterize it (Scheme I.6).



Scheme I.6. Lieke isocyanide synthesis.

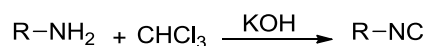
<sup>8</sup> Pirrung, M. C.; Ghorai, S.; Ibarra-Rivera, T. R. *J. Org. Chem.* **2009**, 74, 4110.

<sup>9</sup> (a) Rothe, W. *Pharmazie* **1950**, 5, 190. (b) Chang, W. J.; Scheuer, P. J. *Topics in Current Chemistry*; Springer-Verlag-Berlin, **1993**. For reviews, see: (a) Garson, M. J.; Simpson, J. S. *Nat. Prod. Rep.* **2004**, 21, 164. (b) Edenborough, M. S.; Herbert, R. B. *Nat. Prod. Rep.*, **1988**, 5, 229.

<sup>10</sup> Lieke, W. *Justus Liebigs Ann. Chem.* **1859**, 112, 316.

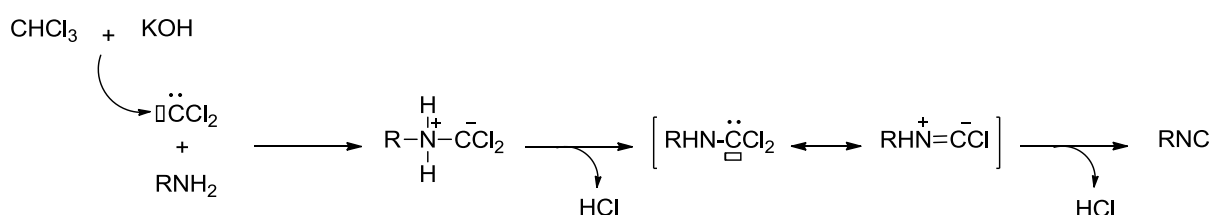
<sup>11</sup> (a) Gautier, A. *Justus Liebigs Ann. Chem.* **1867**, 142, 289. (b) Gautier, A. *Justus Liebigs Ann. Chem.* **1869**, 146, 119.

In 1867, Hofmann released the “carbylamine method” for the synthesis of isocyanides.<sup>12</sup> A primary amine was condensed with chloroform in presence of a base such as: potassium hydroxide in ethanol converting the primary amine into isocyanides (Scheme I.7). Despite being a simple approach, it is not considered as a general method for the isocyanides synthesis due to the low yields obtained in addition to the difficulties of separating the isocyanides from amines.



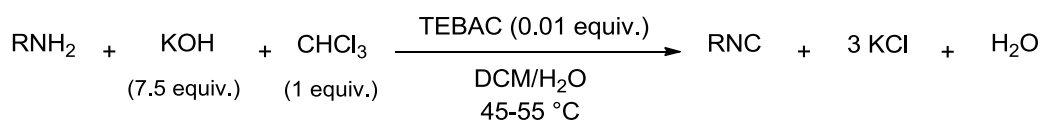
**Scheme I.7. Hofmann isocyanides synthesis.**

The mechanism of this approach was explained by Nef in 1897.<sup>13</sup> He reported the generation of the dichlorocarbene in situ from the reaction of the chloroform with the base. Then, the nucleophilic attack of the amine onto the carbene produces an intermediate, which upon two successive  $\beta$ -eliminations of two hydrogen chloride molecules, leads to the desired isocyanide (Scheme I.8).



**Scheme I.8. Mechanism of carbylamine method by Nef.**

Hofmann’s approach was amended by Weber, Gokel and Ugi in 1972.<sup>14</sup> They carried out the reaction in a biphasic medium (water/dichloromethane) in the presence of a quaternary ammonium salt as a phase transfer catalyst (PTC) (Scheme I.9). This improved the selectivity of the amine attacking the dichlorocarbene and limited as well the formation of byproducts.



**Scheme I.9. Modified Hofmann isocyanide synthesis.**

<sup>12</sup> Hofmann, A. W. *Justus Liebigs Ann. Chem.* **1867**, 144, 114.

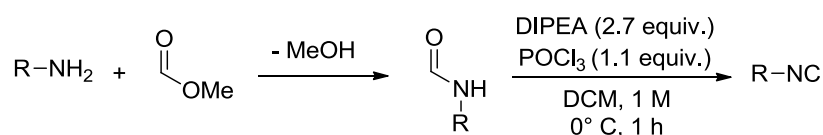
<sup>13</sup> Nef, I.; *Justus U. Liebigs Ann. Chem.* **1897**, 298, 202.

<sup>14</sup> (a) Weber, W.; Gokel, G. *Tetrahedron Lett.* **1972**, 11, 1637. (b) Weber, W. P.; Gokel, G. W.; Ugi, I. *Angew. Chem.* **1972**, 84, 587.



Such modification furnished a more reproducible reaction; though, the yields remain moderate. A purification of the isocyanide either by distillation or by column chromatography is essential to eliminate the solvent and unreacted amine. However, this method could be used to synthesize large-scale isocyanides and it is the most frequently applied in our laboratory for preparing the starting isocyanide substrates.

The second well known method for isocyanide synthesis was presented by Corey and Ugi in 1958.<sup>15</sup> It involved the dehydration of *N*-formamides using a dehydrating agent and a base, affording isocyanides. *N*-monosubstituted formamides are readily prepared by the condensation of a primary amine with methyl formate or formic acid (Scheme I.10).



**Scheme I.10. Isocyanide synthesis by dehydration of formamide.**

Initially, phosgene ( $\text{COCl}_2$ ) was used as a dehydrating agent,<sup>16</sup> but this didn't last long due to its high toxicity. Then, several dehydrating agents were examined such as: diphosgene ( $\text{C}_2\text{Cl}_4\text{O}_2$ )<sup>17</sup>, diphosphorus pentoxide ( $\text{P}_4\text{O}_{10}$ ), phosphorus oxychloride ( $\text{POCl}_3$ ) or thionyl chloride ( $\text{SOCl}_2$ )<sup>18</sup> in the presence of various bases such as: pyridine, triethylamine, or DABCO.<sup>19</sup> This method is widely used in the synthesis of isocyanides since it is compatible with a number of functional groups.

There are other pathways for isocyanide synthesis, but they are limited by the nature of the substrates or the required experimental conditions. Among these is the reduction of isocyanates, isothiocyanates or dichloro ketenimine. Isocyanates can be reduced in the presence of triethylphosphite  $\text{P}(\text{OEt})_3$ , while triethylphosphine  $\text{PEt}_3$ , triphenyltin hydride  $(\text{C}_6\text{H}_5)_3\text{SnH}$  or triphenylphosphine-copper (I) hydride  $[(\text{C}_6\text{H}_5)_3\text{PCuH}]_6$  were used to reduce isothiocyanates. The application of this method is limited since it requires heating at quite high temperature leading to possible polymerization of the isocyanides. Such limitation could be overcome by using more complex reducing agents like: 2-phenyl-3-methyl-1,3,2-

<sup>15</sup> (a) Hertler, W.; Corey, E. J. *J. Org. Chem.* **1958**, 23, 1221. (b) Ugi, I.; Meyr, R. *Angew. Chem.* **1958**, 70, 702.

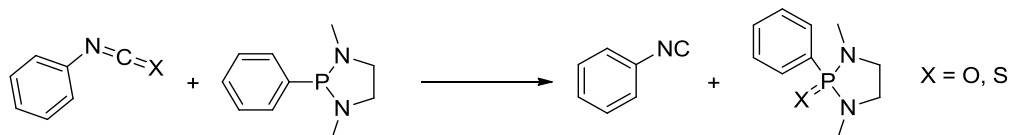
<sup>16</sup> Ugi, I.; Fetzner, U.; Eholzer, U.; Knupfer, H.; Offermann, K. *Angew. Chem., Int. Ed. Engl.* **1965**, 4, 472.

<sup>17</sup> Skorna, G.; Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1977**, 16, 259.

<sup>18</sup> Ugi, I.; Meyr, R. *Chem. Ber.* **1960**, 93, 239.

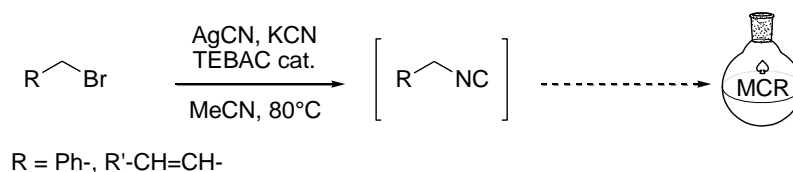
<sup>19</sup> Obrecht, R.; Hermann, R.; Ugi, I. *Synthesis* **1985**, 400.

oxazaphospholidine, (diphenyl-*tert*-butylsilyl)lithium or a mixture of trichlorosilane - triethylamine that allowed the reduction process to occur at relatively low temperature (5-36 °C) (Scheme I.11).<sup>20</sup>



Scheme I.11. Isocyanide synthesis by reduction process.

The synthesis of Leike was the starting point for several isocyanide preparations.<sup>21</sup> In 2009, our laboratory 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 °C (Scheme I.12).<sup>22</sup> The significant advantage of this method is the ability to use the synthesized isocyanide directly without further purification, thus avoiding the spreading of the isocyanide horrible smell during the purification step.



Scheme I.12. Isocyanide in situ synthesis from halide derivatives.

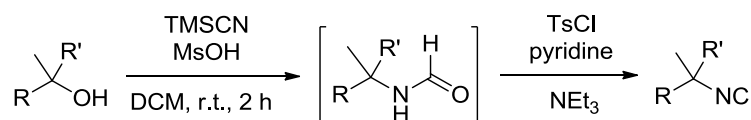
Kitano *et al.*<sup>23</sup> proposed an isocyanide synthesis starting from the corresponding alcohols, trimethylsilyl cyanide and methanesulfonic acid. An intermediate *N*-formamide was formed which undergo dehydration using *p*-toluenesulfonyl chloride and pyridine affording the desired isocyanide after the neutralization of the reaction mixture by triethylamine (Scheme I.13).

<sup>20</sup> (a) Mukaiyama, T.; Yokota, Y. *Bull. Chem. Soc. Jpn.* **1965**, 38, 858. (b) Baldwin, J. E.; Bottaro, J. C.; Riordan, P. D.; Derome, A. E. *J. Chem. Soc., Chem. Comm.* **1982**, 942. (c) Baldwin, J. E.; Derome, A. E.; Riordan, P. D. *Tetrahedron* **1983**, 39, 2989.

<sup>21</sup> Kitano, Y.; Manoda, T.; Miura, T.; Chiba, K.; Tada, M. *Synthesis* **2006**, 405.

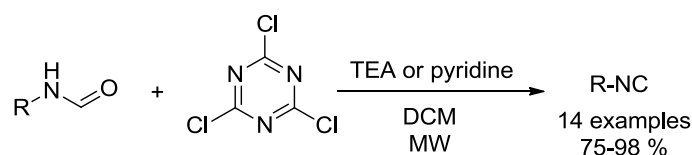
<sup>22</sup> (a) El Kaïm, L.; Grimaud, L.; Schiltz, A. *Synlett.* **2009**, 1401. (b) El Kaïm, L.; Grimaud, L.; Schiltz, A. *Tetrahedron Lett.* **2009**, 50, 5235. (c) El Kaïm, L.; Grimaud, L.; Schiltz, A. *Org. Biomol. Chem.* **2009**, 7, 3024.

<sup>23</sup> Okada, I.; Kitano, Y. *Synthesis* **2011**, 3997.



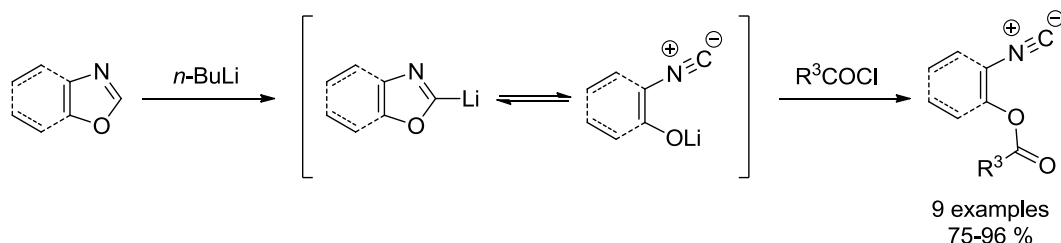
Scheme I.13. Isocyanide synthesis from the corresponding alcohol.

Porcheddu and his co-workers<sup>24</sup> proposed a different pathway for the *N*-formamide dehydration using trichlorotriazine under microwave irradiation. This method proved to be effective for both aliphatic and aromatic isocyanides (Scheme I.14).



Scheme I.14. New isocyanide synthesis under microwave irradiation.

In 2006, the group of Pirrung<sup>25</sup> used oxazoles and benzoxazoles as starting materials to deliver isocyanides. The reaction proceeds via the oxazole ring opening at position 2 followed by trapping the formed intermediate using various acid chlorides (Scheme I.15). They observed that such strategy of synthesis afforded odorless isocyanides.



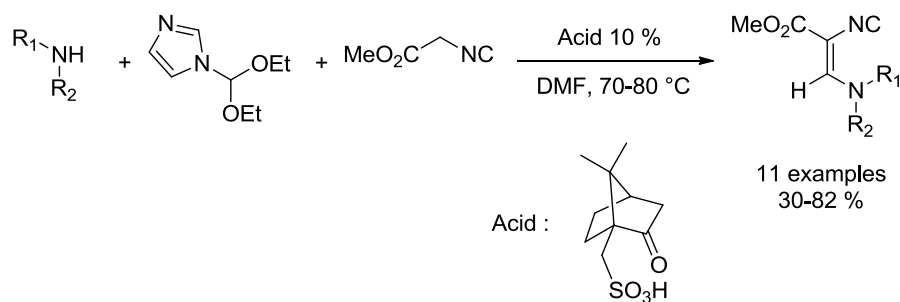
Scheme I.15. Ring opening of oxazoles towards isocyanides.

It is possible as well to prepare functionalized isocyanides from commercially available simple ones. Thereby, Bienaymé<sup>26</sup> described a synthesis for complex isocyanides using the Bredereck reaction (Scheme I.16).

<sup>24</sup> Porcheddu, A.; Giacomelli, G.; Salaris, M. *J. Org. Chem.* **2005**, 70, 2361.

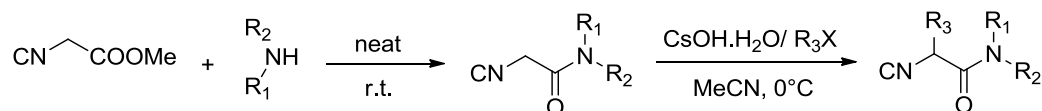
<sup>25</sup> Pirrung, M. C.; Ghorai, S. *J. Am. Chem. Soc.* **2006**, 128, 11772.

<sup>26</sup> Bienaymé, H. *Tetrahedron Lett.* **1998**, 39, 4255.



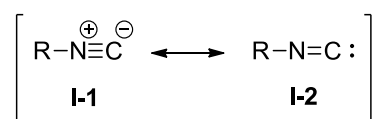
Scheme I.16. Isocyanide synthesis using Bredereck reaction.

Another example involved the reaction of primary or secondary amines with methyl  $\alpha$ -isocyanoacetate to synthesize  $\alpha$ -isocyanoamides in a rapid and efficient way.<sup>27</sup> The latter can undergo monoalkylation reaction under basic conditions yielding a wide range of  $\alpha$ -substituted- $\alpha$ -isocyanoamides (Scheme I.17).<sup>28</sup>

Scheme I.17. The synthesis of  $\alpha$ -substituted- $\alpha$ -isocyanoamides.

## 2) Reactivity of isocyanides

Isocyanides alike carbon monoxide, exhibits two resonance structures between the divalent carbon **I-1** and the zwitterionic **I-2** species. In the resonance structure **I-1**, the carbon possess a carbene-like reactivity while in structure **I-2**, it involves a dipolar linear resonance (Scheme I.18).



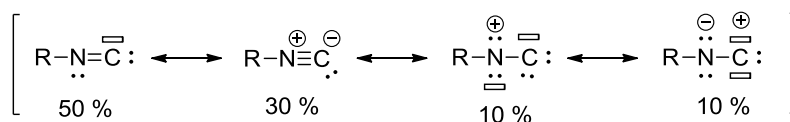
Scheme I.18. Resonance structures of isocyanides.

The ratio between the various resonance structures of isocyanides was obtained from the valence bond calculations for methyl isocyanide.<sup>29</sup> It indicated that the carbene-form existed in about 50 %, while the zwitterionic species in about 30 %. The remaining 20 % are more complex structures (Scheme I.19). Therefore, isocyanides are linear molecules since such geometry allows the resonance between the carbene and the zwitterionic structures.

<sup>27</sup> Dömling, A.; Beck, B.; Fuchs, T.; Yazback, A. *J. Comb. Chem.* **2006**, 8, 872.

<sup>28</sup> Housseman, C.; Zhu, J. *Synlett* **2006**, 11, 1777.

<sup>29</sup> Ramozzi, R.; Cheron, N.; Braidia, B.; Hiberty, P.; Fleurat-Lessard, P. *New J. Chem.* **2012**, 36, 1137.



Scheme I.19. Valence bond calculations for the resonance structures of isocyanides.

Isocyanides are characterized by their high stability in basic mediums and their sensitivity towards acids. In the presence of acids, they undergo acidic hydrolysis forming formamides. Most isocyanides may polymerize as well in acidic mediums.<sup>30</sup>

## 2. a) 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 ( $\sigma$ ) and LUMO ( $\pi^*$ ) orbitals are situated on the terminal carbon of methylisocyanide (Figure I.4).

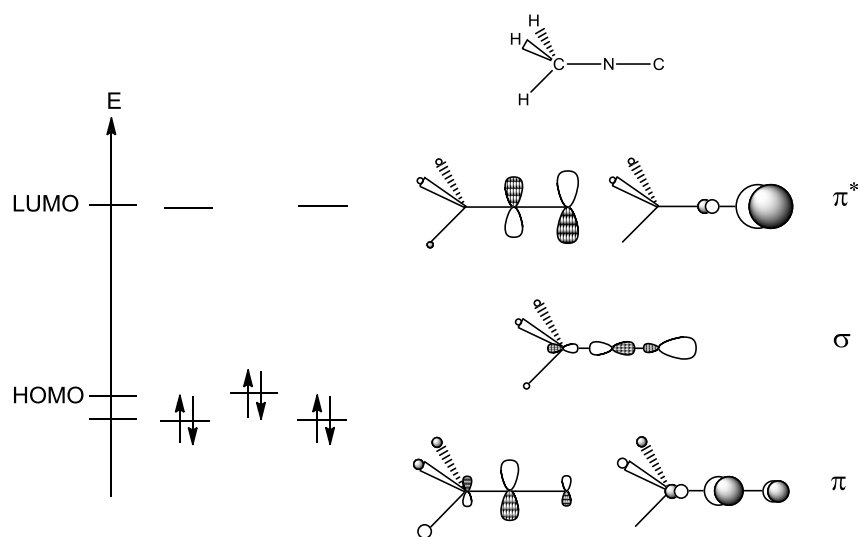
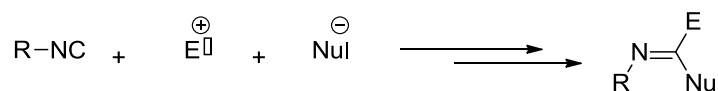


Figure I.4. Frontier orbitals of methylisocyanide.

Consequently, both the electrophilic and nucleophilic additions occur at the terminal carbon atom of isocyanides (Scheme I.20).

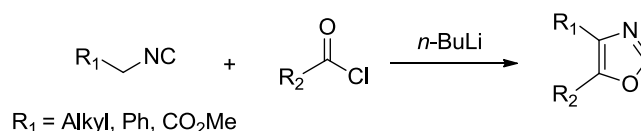


Scheme I.20. Double isocyanide reactivity.

<sup>30</sup> (a) van Beijen, A. *Macromolecules* **1983**, *16*, 1679. (b) Albert, M.; van Leusen, B.; Hoogenboom, E.; Siderius, H. *Tetrahedron Lett.* **1972**, *13*, 2369.

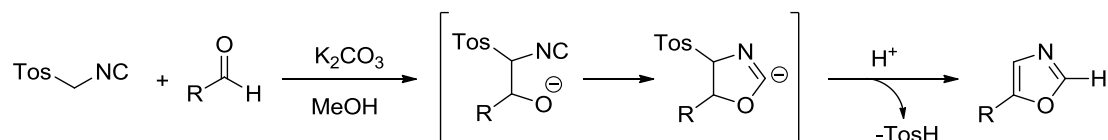
## 2. b) $\alpha$ -Acidity of the isocyanide group

The acidity of the protons in  $\alpha$ -position to the isocyanide functionality is enhanced by the electron-withdrawing nature of such group. This feature was used to develop a new pathway for the synthesis of oxazoles from isocyanides.<sup>31</sup> Using a strong base, the isocyanide undergoes  $\alpha$ -deprotonation in presence of an acid chloride affording the target cyclic compound (Scheme I.21).



**Scheme I.21. Isocyanide synthesis of oxazoles.**

The presence of a second electron-withdrawing group such as: ester, amide or sulfonyl group further increases the  $\alpha$ -acidity of isocyanides. Hence, 5-functionalized oxazoles were prepared using *p*-tosylmethylisocyanide with an aldehyde in presence of potassium carbonate. It represented one of the early examples of exploring such reactivity in heterocyclic synthesis (Scheme I.22).<sup>32</sup>



**Scheme I.22. Isocyanide synthesis of 5-substituted oxazoles.**

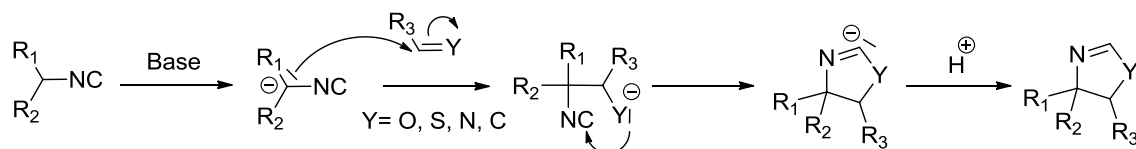
This property had been intensely studied by Schöllkopf<sup>33</sup> and Van Leusen<sup>34</sup> varying the employed electrophile in the reaction. This variation enabled the synthesis of diverse heterocycles (Scheme I.23).

<sup>31</sup> (a) Schöllkopf, U.; Schröder, R. *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 333. (b) Hoppe, D.; Schöllkopf, U. *Liebigs Ann. Chem.* **1972**, 763, 1.

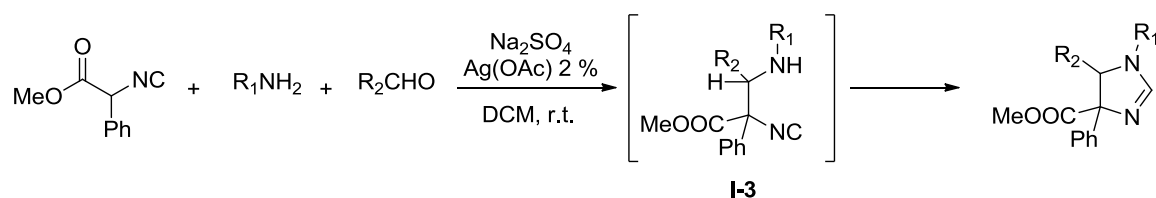
<sup>32</sup> Van Leusen, A. M.; Hoogenboom, B. E.; Siderius, H. *Tetrahedron Lett.* **1972**, *23*, 2369.

<sup>33</sup> (a) Hoppe, D. *Angew. Chem. Int. Ed.* **1974**, *13*, 789. (b) Schöllkopf, U. *Angew. Chem. Int. Ed.* **1977**, *16*, 339. (c) Schröder, R.; Schöllkopf, U.; Blume, E.; Hoppe, I. *Liebigs Ann. Chem.* **1975**, 533. (d) Schöllkopf, U.; Porsch, P.; Blume, E. *Liebigs Ann. Chem.* **1976**, 7122. (e) Meyer, R.; Schöllkopf, U.; Böhme, P. *Liebigs Ann. Chem.* **1977**, 1183.

<sup>34</sup> (a) Leusen, A. M. V.; Siderius, H.; Hoogenboom, B. E.; Leusen, D. V. *Tetrahedron Lett.* **1972**, *13*, 5337. (b) Leusen, A. M. V.; Hoogenboom, B. E.; Houwing, H. A. *J. Org. Chem.* **1976**, *41*, 711. (c) Leusen, A. M. V.; Weildeman, J.; Oldenziel, O. *J. Org. Chem.* **1977**, *42*, 1153. (d) Leusen, A. M. V. *Synthesis* **1991**, 531.

Scheme I.23. Applying the  $\alpha$ -acidity of isocyanides in the synthesis of heterocycles.

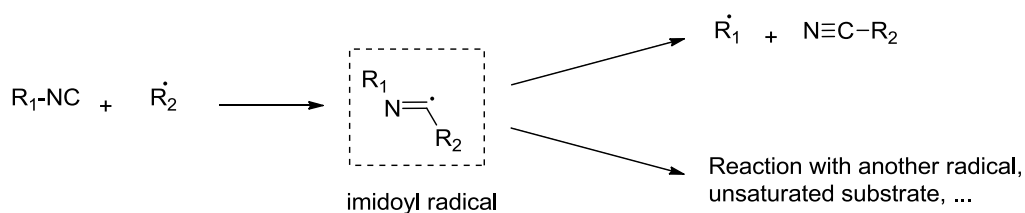
$\alpha$ -Isocynoesters and  $\alpha$ -isocynoamides were widely used in the synthesis of heterocycles.<sup>35</sup> In 2007, Orru *et al.*<sup>36</sup> introduced a new multicomponent synthesis of 2-imidazolines using primary amines, aldehydes and  $\alpha$ -isocynoesters. In presence of a base and silver acetate as a catalyst, the condensation of the deprotonated isocyanide and the imine generated *in situ* from the amine and aldehyde results in the Mannich intermediate **I-3** (Scheme I.24).



Scheme I.24. Multicomponent synthesis of 2-imidazolines.

## 2. c) Radical reaction

Radicals usually add on the terminal carbon of the isocyanide moiety forming imidoyl radical. The latter can either undergo fragmentation forming a cyanide and an alkyl radical or be trapped by another radical or unsaturation in another reactant (Scheme I.25).

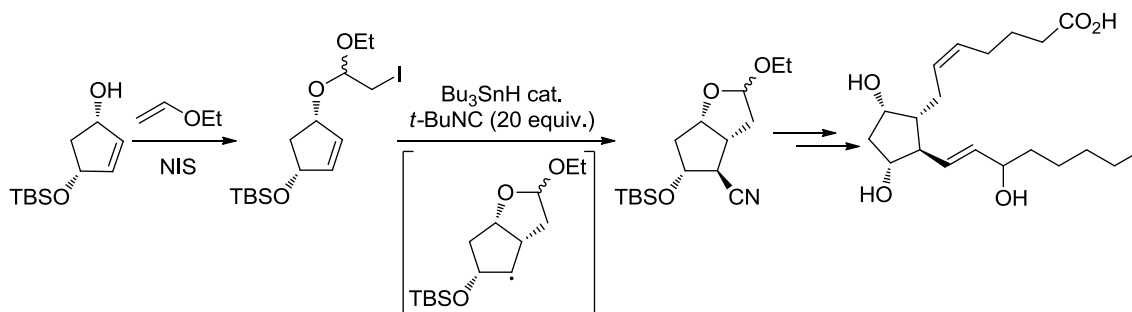


Scheme I.25. Radical addition on isocyanides.

<sup>35</sup> For a recent review, see: Gulevich, A. V.; Zhdanko, A. G.; Orru, R. V. A.; Nenajdenko, V. G. *Chem. Rev.* **2010**, *110*, 5235.

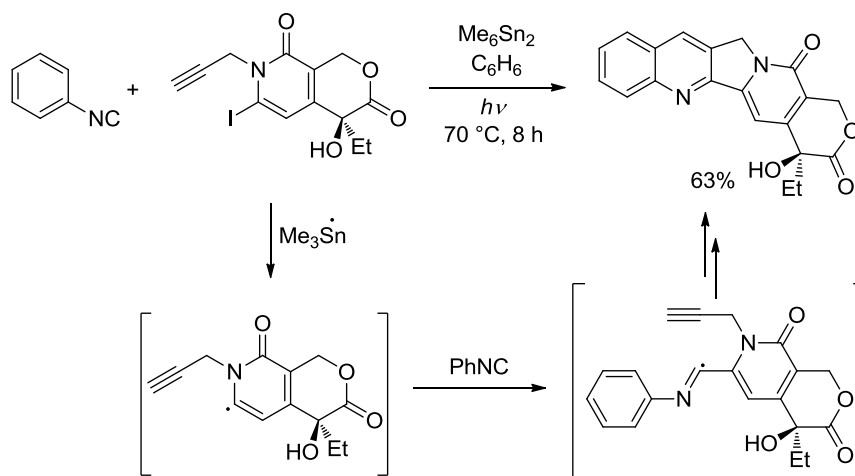
<sup>36</sup> Elders, N.; Schmitz, R. F.; de Kanter, F. J. J.; Ruitjer, E.; Groen, M. B.; Orru, R. V. A. *J. Org. Chem.* **2007**, *72*, 6135.

This sort of reactivity was first approached by Shaw<sup>37</sup> and Saegusa<sup>38</sup>. Based on their study, Stork and Sher<sup>39</sup> developed a new stereo and regio-selective synthesis of functionalized nitriles. This methodology was successfully applied for the introduction of a cyanide group during the synthesis of (+) prostaglandine F2 $\alpha$  (Scheme I.26).<sup>40</sup> The latter is medically used to induce labor.



Scheme I.26. Stork and Sher's synthesis of (+) prostaglandine F2 $\alpha$ .

Thereafter, isocyanide radical reactions were widely used in the total synthesis of various heterocyclic compounds.<sup>41</sup> For instance, the total synthesis of Camptothecin reported by the group of Curran (Scheme I.27).<sup>42</sup> It is a natural product used in cancer chemotherapy.



Scheme I.27. Curran's synthesis of Camptothecin.

<sup>37</sup> Shaw, D. H.; Pritchard, H. *Can. J. Chem.* **1967**, *45*, 2749.

<sup>38</sup> (a) Saegusa, T.; Kobayashi, S.; Ito, Y.; Yasuda, N. *J. Am. Chem. Soc.* **1968**, *90*, 4182. (b) Saegusa, T.; Ito, Y.; Yasuda, N.; Hotaka, T. *J. Org. Chem.* **1970**, *35*, 4238.

<sup>39</sup> (a) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1983**, *105*, 6765. (b) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303.

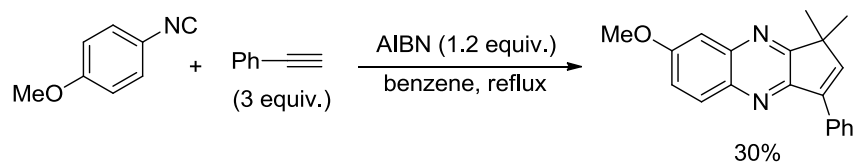
<sup>40</sup> Stork, G.; Sher, P. M.; Chen, H.-L. *J. Am. Chem. Soc.* **1986**, *108*, 6384.

<sup>41</sup> (a) Bachi, M. D.; Balanov, A.; Bar-Ner, N. *J. Org. Chem.* **1994**, *59*, 7752. (b) Bachi, M. B.; Bar-Ner, N.; Melman, A. *J. Org. Chem.* **1996**, *61*, 7116. (c) Benati, L.; Leardini, R.; Minozzi, M.; Nanni, D.; Scialpi, R.; Spagnolo, P.; Stazzari, S.; Zanardi, G. *Angew. Chem. Int. Ed.* **2004**, *43*, 3598. (d) Curran, D. P.; Liu, H. *J. Am. Chem. Soc.* **1991**, *113*, 2127.

<sup>42</sup> Josien, H.; Ko, S.-B.; Bom, D.; Curran, D. P. *Chem. Eur. J.* **1998**, *4*, 67. (b) Curran, D.; Liu, H.; Josien, H.; Ko, S.-B. *Tetrahedron* **1996**, *52*, 11385.



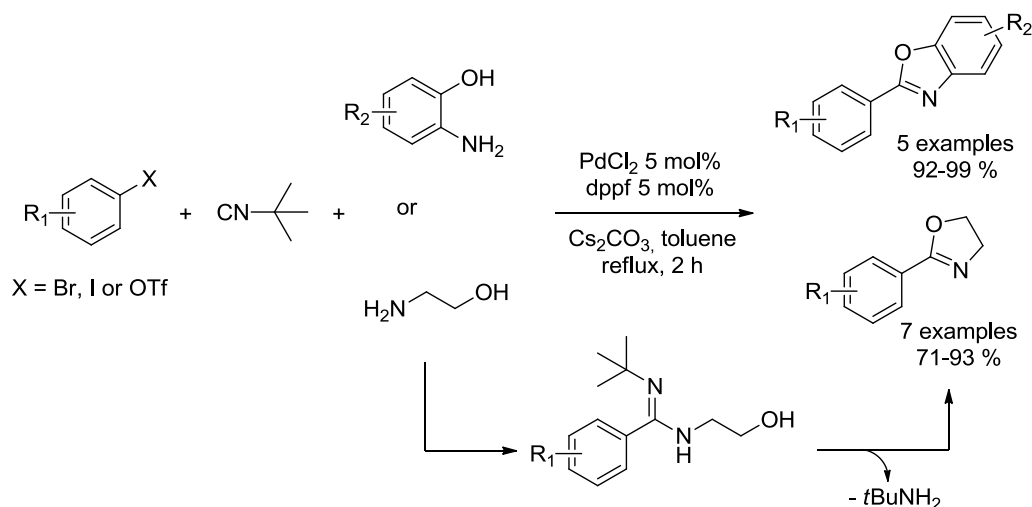
These radical reactions are applied as well in multicomponent syntheses. Nanni *et al.*<sup>43</sup> described an isocyanide three-component radical reaction towards quinoxaline (Scheme I.28). It involves a vinyl radical addition onto the isocyanide substrate. This radical is generated from the addition of  $\alpha$ -cyano radical obtained from the AIBN, onto the phenylacetylene.



Scheme I.28. Isocyanide three-component radical synthesis of quinoxaline.

## 2. d) Metal-catalyzed insertion reaction

Isocyanides react with transition metals through their divalent carbene nature. There are several reported examples in the literature describing the reaction of isocyanides with aryl halides using palladium catalysts.<sup>44</sup> This reactivity was developed in three-component couplings for the synthesis of aminoquinazolines,<sup>45</sup> isoquinolinones<sup>46</sup> and oxazolines (Scheme I.29).<sup>47</sup>



Scheme I.29. Synthesis of oxazolines and benzoxazoles.

<sup>43</sup> (a) Nanni, D.; Pareschi, P.; Rizzoli, C.; Sgarabotto, P.; Tundo, A. *Tetrahedron* **1995**, *51*, 9045. (b) Leardini, R.; Nanni, D.; Zanardi, G. *J. Org. Chem.* **2000**, *65*, 2763.

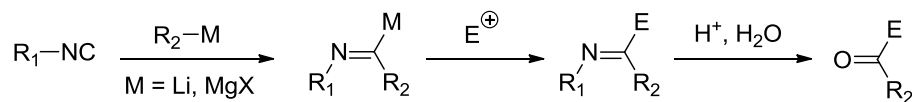
<sup>44</sup> For recent review, see: Vlaar, T.; Ruijter, E.; Maes, B. U.; Orru, R. V. *Angew. Chem., Int. Ed.* **2013**, *52*, 7084.

<sup>45</sup> Baelen, G. V.; Kuijter, S.; Ryek, L.; Sergeyev, S.; Janssen, E.; de Kanter, F. J. J.; Maes, B. U. W.; Ruijter, E.; Orru, R. V. A. *Chem. Eur. J.* **2011**, *17*, 15039.

<sup>46</sup> Tyagi, V.; Khan, S.; Giri, A.; Gauniyal, H. M.; Sridhar, B.; Chauhan, P. M. S. *Org. Lett.* **2012**, *14*, 3126.

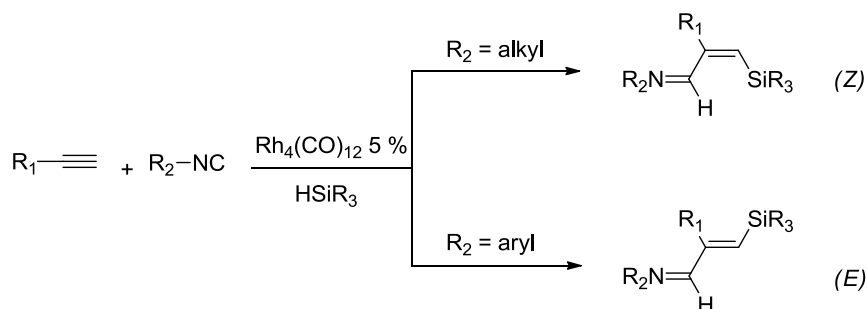
<sup>47</sup> Boissarie, P. J.; Hamilton, Z. E.; Lan, S.; Murphy, J. A.; Suckling, C. J. *Org. Lett.* **2011**, *13*, 6256.

They are considered as excellent ligands for transition metals.<sup>48</sup> Additionally, the organometallic reagents such as: organolithium and organomagnesium can attack the terminal carbene of the isocyanide forming imido intermediate.<sup>49</sup> The latter upon coupling with electrophiles and acid hydrolysis deliver the corresponding carbonyl derivatives (Scheme I.30).



**Scheme I.30. Reaction of isocyanides with organometallic compounds.**

Recently, an intramolecular palladium-catalyzed C(sp<sup>2</sup>)-H and C(sp<sup>3</sup>)-H activations were reported by Zhu<sup>50</sup> and Takemoto<sup>51</sup> groups, respectively. Chatani *et al.*<sup>52</sup> described a rhodium-catalyzed stereoselective silylation of alkynes in presence of isocyanides. The reaction's regioselectivity was determined by the nature of the employed isocyanide in the reaction (Scheme I.31).



**Scheme I.31. Rh-catalyzed stereoselective silylation of alkynes in presence of isocyanides.**

## 2. e) Insertion reactions

The carbene-like nature of isocyanides enables their engagement in insertion reactions either in presence or in absence of transition metals.

<sup>48</sup> For recent review, see: Boyarskiy, V. P.; Bokach, N. A.; Luzyanin, K. V.; Kukushkin, V. Y. *Chem. Rev.* **2015**, *115*, 2698.

<sup>49</sup> Periasamy, M. P.; Walborsky, H. M. *J. Org. Chem.* **1974**, *39*, 611.

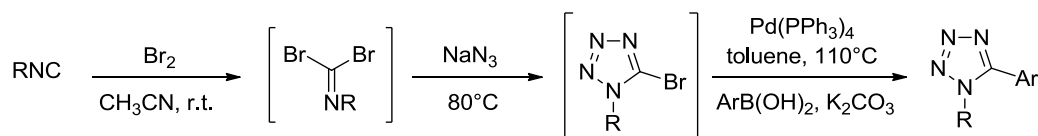
<sup>50</sup> (a) Wang, Y.; Wang, H.; Peng, J.; Zhu, Q. *Org. Lett.* **2011**, *13*, 4604. (b) Peng, J.; Liu, L.; Hu, Z.; Huang, J. Zhu, Q. *Chem. Commun.* **2012**, *48*, 3772.

<sup>51</sup> Nanjo, T.; Tsukano, C.; Takemoto, Y. *Org. Lett.* **2012**, *14*, 4270.

<sup>52</sup> Fukumoto, Y.; Hagihara, M.; Kinashi, F.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 10014.

➤ Insertion in a non-polarized bond (Halogens)

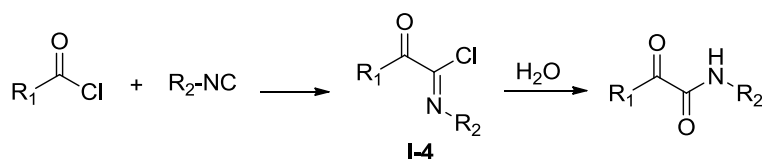
Isocyanides react with halogens forming *gem*-dihalogenated isocyanide intermediates.<sup>53</sup> This particular reactivity was exploited in the synthesis of tetrazoles, upon the reaction with sodium azide followed by a Suzuki-coupling reaction (Scheme I.32).<sup>54</sup>



Scheme I.32. Isocyanide synthesis of tetrazoles.

➤ Insertion in a polarized bond (Nef reaction)

The first example of the insertion of an isocyanide into a polarized bond was described by Nef.<sup>55</sup> He published the insertion of isocyanides into the carbon-chlorine bond of an acyl chloride. The formed intermediate **I-4** after hydrolysis, afforded the corresponding  $\alpha$ -ketoamide (Scheme I.33).

Scheme I.33. Nef reaction of isocyanides and acyl chlorides towards  $\alpha$ -ketoamides.

Several studies had been elaborated to study the mechanism of this reaction. In 1961, Ugi proposed a one-step mechanism based on kinetic studies.<sup>56</sup> In 2011, Fleurat-Lessard *et al.*<sup>57</sup> presented theoretical calculations that suggested a concerted mechanism for the Nef reaction including a single transition state and not an addition elimination mechanism (Scheme I.34).

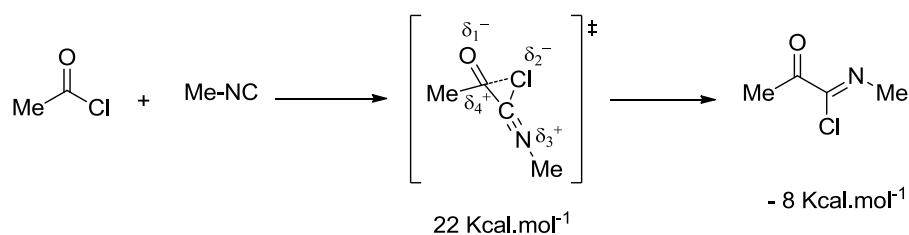
<sup>53</sup> (a) Kühle, E.; Anders, B.; Klauke, E.; Tarnow, H.; Zumach, G. *Angew. Chem. Int. Ed. Engl.* **1969**, 8, 20. (b) Kühle, E.; Anders, B.; Zumach, G. *Angew. Chem. Int. Ed. Engl.* **1967**, 6, 649.

<sup>54</sup> El Kaïm, L.; Grimaud, L.; Patil, P. *Org. Lett.* **2011**, 13, 1261.

<sup>55</sup> Nef, J. U. *Justus Liebigs Ann. Chem.* **1892**, 210, 269.

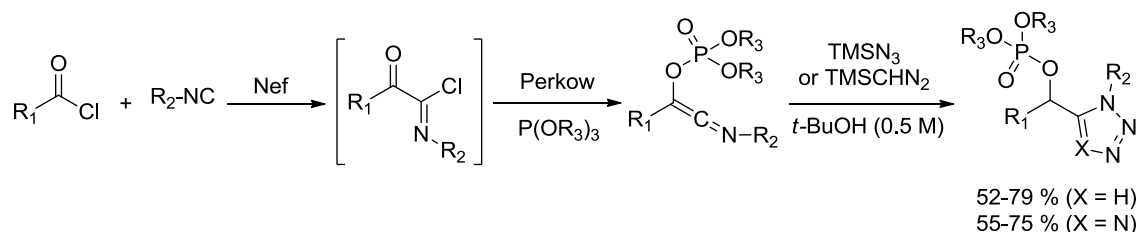
<sup>56</sup> Ugi, I.; Fetzer, U. *Chem. Ber.* **1961**, 94, 1116.

<sup>57</sup> Chéron, N.; El Kaïm, L.; Grimaud, L.; Fleurat-Lessard, P. *J. Phys. Chem. A* **2011**, 115, 10106.



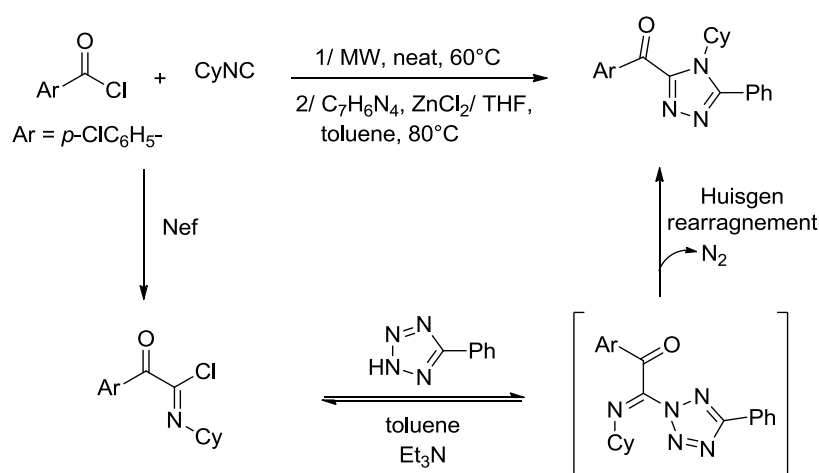
Scheme I.34. Transition state of Nef reaction.

Lately, the interest of using Nef reaction has increased. An application towards the synthesis of ketene-imine phosphates using Nef/Perkow sequence has been reported by El Kaïm and his coworkers.<sup>58</sup> The strategy involves the addition of trimethylsilylazide or trimethylsilyldiazomethane to the ketene-imine phosphonates, generated *in situ*, affording triazole and tetrazole phosphonates respectively (Scheme I.35).



Scheme I.35. Nef/Perkow sequence towards the synthesis of triazole and tetrazole phosphates.

Meanwhile, another triazole synthetic pathway was presented.<sup>59</sup> It involves the addition of a tetrazole to the Nef adduct, in presence of Lewis acid, leading to a Huisgen rearrangement and final triazoles (Scheme I.36).

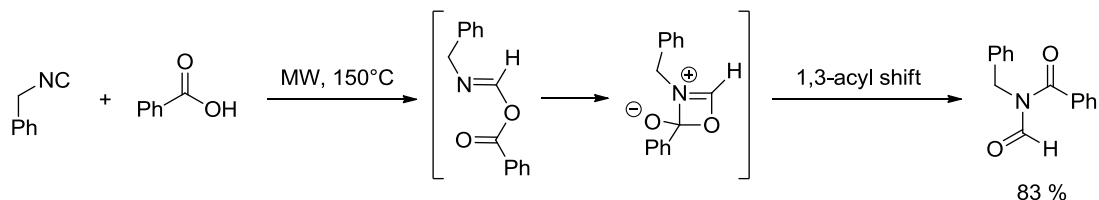


Scheme I.36. Triazole synthesis using Nef reaction.

<sup>58</sup> Coffinier, D.; El Kaïm, L.; Grimaud, L. *Org. Lett.* **2009**, *11*, 1825.

<sup>59</sup> El Kaïm, L.; Grimaud, L.; Wagschal, S. *Synlett* **2009**, *8*, 1315.

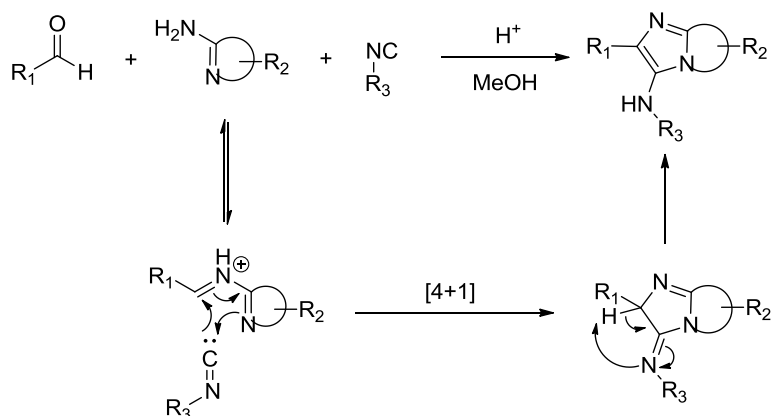
Similarly, the carboxylic acids can add onto the isocyanides.<sup>60</sup> This type of reaction usually requires activation either by heating or microwave irradiations. It proceeds via 1,3-acyl transfer forming *N*-formylamide (Scheme I.37).



Scheme I.37. Addition of carboxylic acids onto isocyanides.

## 2. f) Formal cycloaddition reactions

Isocyanides could undergo formal cycloaddition reactions as a result of possessing a divalent carbon. In 1998, Groebke,<sup>61</sup> Blackburn<sup>62</sup> and Bienaymé<sup>63</sup> introduced a new three-component synthesis involving an aldehyde, aromatic amine and isocyanide in presence of Lewis or Brønsted acids. The suggested mechanism proceeds via a non-concerted [4+1] annulation between the iminium ion and the isocyanide (Scheme I.38). Bienaymé *et al.* succeeded in employing a wide range of heterocyclic amines in this reaction proving its efficiency and generality.



Scheme I.38. Groebke-Blackburn-Bienaymé reaction mechanism.

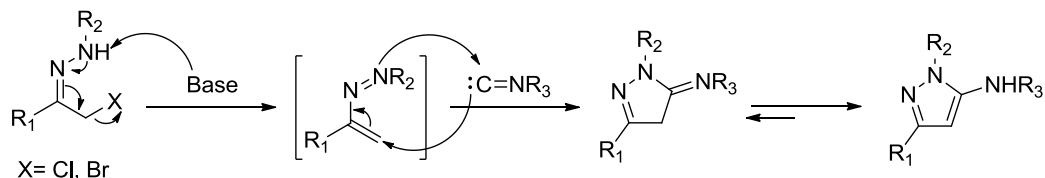
<sup>60</sup> (a) Li, X. C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 5446. (b) Jones, G. O.; Li, X. C.; Hayden, A. E.; Houk, K. N.; Danishefsky, S. J. *Org. Lett.* **2008**, *10*, 4093. (c) Li, X. C.; Yuan, Y.; Berkowitz, W. F.; Todaro, L. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 13222. (d) Basso, A.; Banfi, L.; Galatini, A.; Guanti, G.; Rastrelli, F.; Riva, R. *Org. Lett.* **2009**, *11*, 4068.

<sup>61</sup> Groebke, K.; Weber, L.; Mehlin, F. *Synlett* **1998**, 661.

<sup>62</sup> Blackburn, C.; Guan, B.; Fleming, P.; Shiosaki, K.; Tsai, S. *Tetrahedron Lett.* **1998**, *39*, 3635.

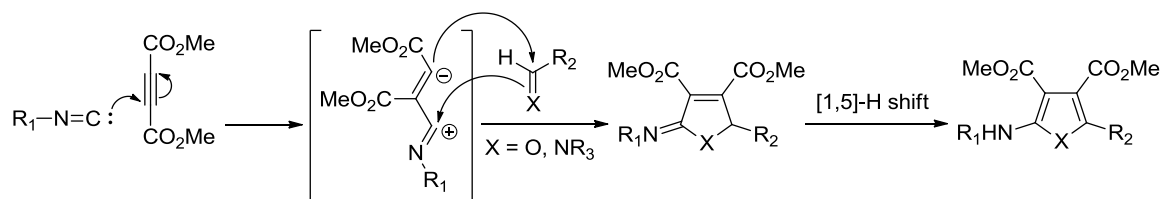
<sup>63</sup> Bienaymé, H.; Bouzid, K. *Angew. Chem. Int. Ed.* **1998**, *37*, 2234.

In 2000, El Kaïm *et al.*<sup>64</sup> reported the synthesis of 5-aminopyrrazoles via a [4+1] cycloaddition reaction of isonitriles and azoalkenes, generated *in situ* from hydrazones (Scheme I.39).



**Scheme I.39. [4+1] Cycloaddition of isonitriles to prepare 5-aminopyrrazoles.**

Nair and his coworkers<sup>65</sup> reported an isocyanide cycloaddition reaction to synthesize pyrroles and furans. The reaction commences with the addition of isonitriles onto activated alkynes leading to the formation of a zwitterionic intermediate, which then undergoes a cycloaddition reaction with an electrophile (aldehyde or imine). A [1,5]-hydrogen shift then delivers the corresponding heterocyclic product (Scheme I.40).



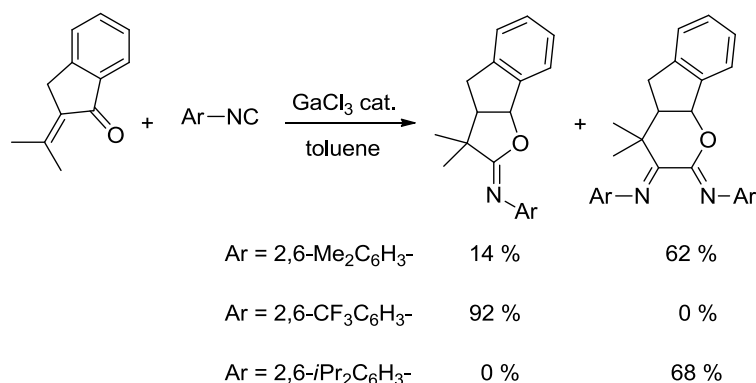
**Scheme I.40. Nair's synthesis of pyrroles and furans.**

Chatani *et al.*<sup>66</sup> reported a [4+1] cycloaddition reaction of isocyanides and  $\alpha,\beta$ -unsaturated ketones in presence of gallium (III) chloride as a catalyst. This reaction proceeds through a non-concerted mechanism. A double insertion of isocyanides was observed depending on the nature of the employed isocyanide (Scheme I.41).

<sup>64</sup> Atlan, V.; El Kaïm, L.; Buron, C. *Synlett* **2000**, 489.

<sup>65</sup> Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. *Acc. Chem. Res.* **2003**, 36, 899.

<sup>66</sup> (a) Oshita, M.; Yamashita, K.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2005**, 127, 761. (b) Chatani, N.; Oshita, M.; Tibisu, M.; Ishii, Y.; Murai, S. *J. Am. Chem. Soc.* **2003**, 125, 7812.



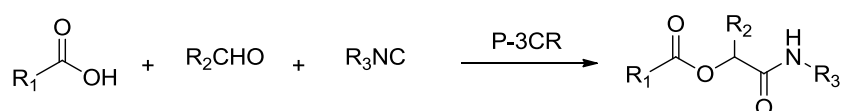
Scheme I.41. Ga(III)-catalyzed cycloaddition reaction of isocyanides.

## I.5 Isocyanide-based multicomponent reactions (IMCRs)

The dual electrophilic and nucleophilic reactivity of isocyanides was particularly exploited in MCRs. Isocyanide-based multicomponent reactions are of special interest in organic synthesis. Their most common examples are: the Passerini and the Ugi reactions.

### I.5.1 Passerini reaction (P-3CR)

This reaction was first documented by Passerini in 1921.<sup>67</sup> It involves the condensation between a carbonyl substrate (aldehyde or ketone), an acid and an isonitrile. It is a three-component reaction that allows the synthesis of  $\alpha$ -acyloxycarboxamides in a one-pot reaction (Scheme I.42).

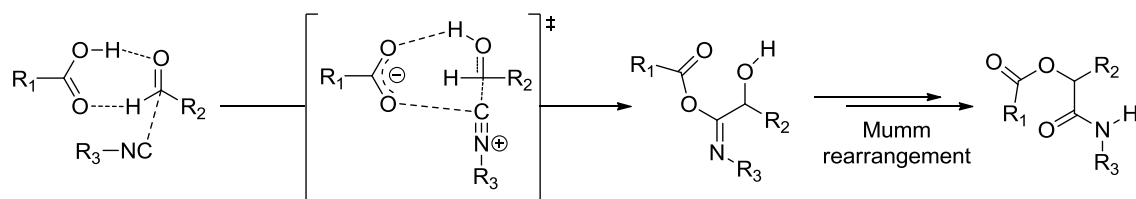


Scheme I.42. Passerini reaction.

This reaction usually takes place at room temperature, in nonpolar aprotic solvents (toluene or dichloromethane) in a relatively high concentration. Several examples are conducted as well without solvent.

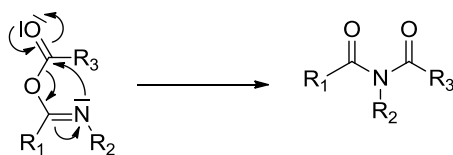
<sup>67</sup> (a) Passerini, M.; Simone, L. *Gazz. Chim. Ital.* **1921**, 51, 126. (b) Passerini, M. *Gazz. Chim. Ital.* **1921**, 51, 181. (c) Passerini, M. *Gazz. Chim. Ital.* **1922**, 52, 432. Reviews: (a) Banfi, L.; Riva, R. *Org. React.* **2005**, 65, 1. (b) Kazemizadeh, A. R.; Ramazani, A. *Curr. Org. Chem.* **2012**, 16, 418.

The mechanism for the Passerini reaction was proposed by Ugi in 1961.<sup>68</sup> On the basis of the reactivity differences observed when changing the reaction solvent, he suggested that the mechanism was non-ionic. In 2011, a theoretical approach presented by Maeda *et al.*,<sup>69</sup> proposed a mechanism which was close to that suggested by Ugi. It involves the addition of the isocyanide onto the aldehyde, which is activated by the acid. Then, a Mumm rearrangement step, which includes an intramolecular acyl transfer, would deliver the final adduct (Scheme I.43).



**Scheme I.43. The mechanism of Passerini reaction.**

Mumm rearrangement was first documented in 1910.<sup>70</sup> It involves a 1,3-(O,N) shift of an acyl group (Scheme I.44).



**Scheme I.44. Mumm rearrangement.**

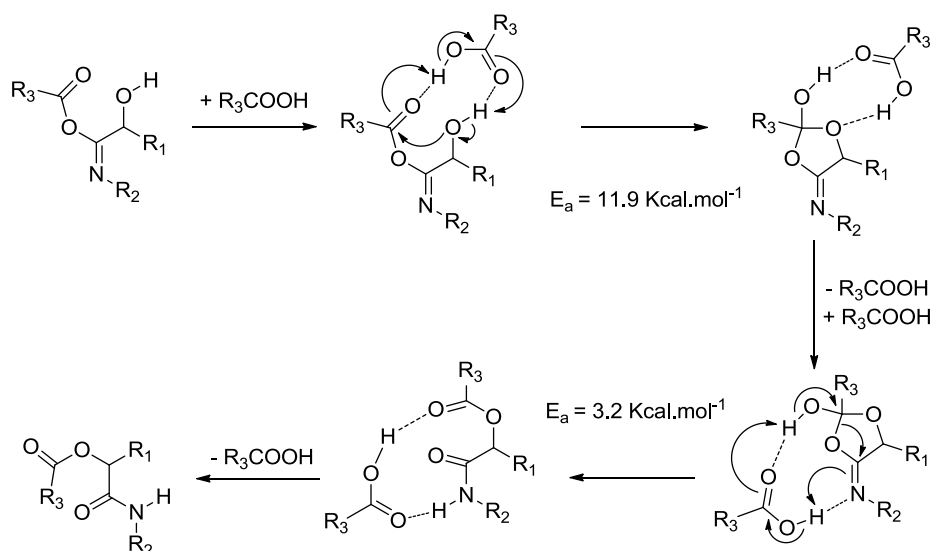
Maeda *et al.* hypothesized that the mechanism involved two molecules of the carboxylic acid. Where, the second one assists in the proton transfer during the Mumm rearrangement (Scheme I.45).

<sup>68</sup> Ugi, I.; Meyr, R. *Chem. Ber.* **1961**, 94, 2229.

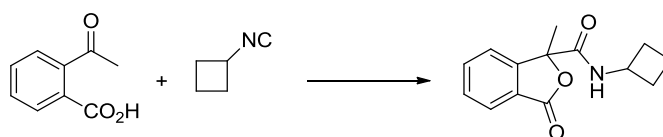
<sup>69</sup> Maeda, S.; Komagawa, S.; Uchiyama, M.; Morokuma, K. *Angew. Chem. Int. Ed.* **2011**, 50, 644.

<sup>70</sup> (a) Mumm, O. *Ber. Dtsch. Chem. Ges.* **1910**, 43, 886. (b) Mumm, O.; Hesse, H.; Volquartz, H. *Ber. Dtsch. Chem. Ges.* **1915**, 48, 379.

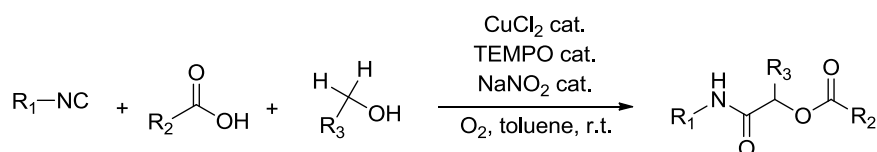




Passerini<sup>71</sup> proposed the employment of bifunctional substrates in the Passerini reaction to deliver cyclic adducts. He used 2-acetylbenzoic acid as a bifunctional component together with isocyanide forming  $\gamma$ -lactones (Scheme I.46).



In 2010, Zhu and his coworkers<sup>72</sup> reported the possibility of replacing the aldehyde in the Passerini reaction by a primary alcohol. The reaction proceeds via an in situ catalytic oxidation of the alcohol (Scheme I.47).

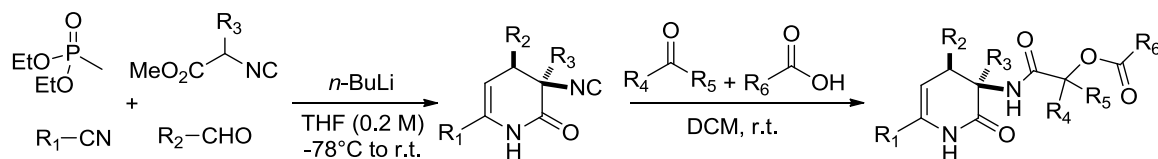


Passerini reaction is considered as an efficient and rapid process for the synthesis of  $\alpha$ -acyloxycarboxamides from simple precursors in one step with high atom economy. Based on

<sup>71</sup> Passerini, M. *Gazz. Chim. Ital.* **1923**, 53, 331.

<sup>72</sup> Brioché, J.; Masson, G.; Zhu, J. *Org. Lett.* **2010**, 12, 1432.

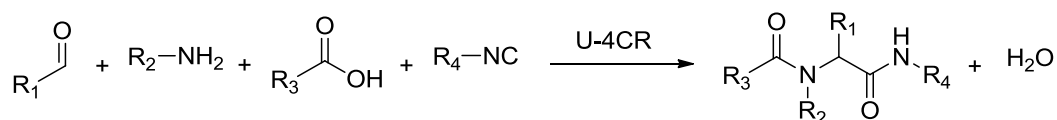
the fact that it allows the construction of a peptide bond, it has been applied for the asymmetric synthesis of dipeptides (Scheme I.48).<sup>73</sup>



Scheme I.48. Passerini reaction for the synthesis of dipeptides.

### I.5.2 Ugi reaction (U-4CR)

This reaction was discovered by Ugi in 1959.<sup>74</sup> It is a four-component reaction that involves a condensation between a carbonyl group (aldehyde or ketone), an amine, a carboxylic acid and an isocyanide. It delivers  $\alpha$ -amidocarboxamide derivatives in a one step reaction (Scheme I.49).



Scheme I.49. Ugi reaction.

This reaction is generally carried out at room temperature and in concentrated medium affording very high yields. Unlike Passerini reaction, it is usually carried out in polar protic solvents such as: methanol, ethanol and trifluoroethanol. Some examples in the literature demonstrated that it can be performed as well in polar aprotic solvents like: MeCN and DMF. While, the non-polar aprotic solvents such as: toluene and benzene are rarely utilized in this reaction.

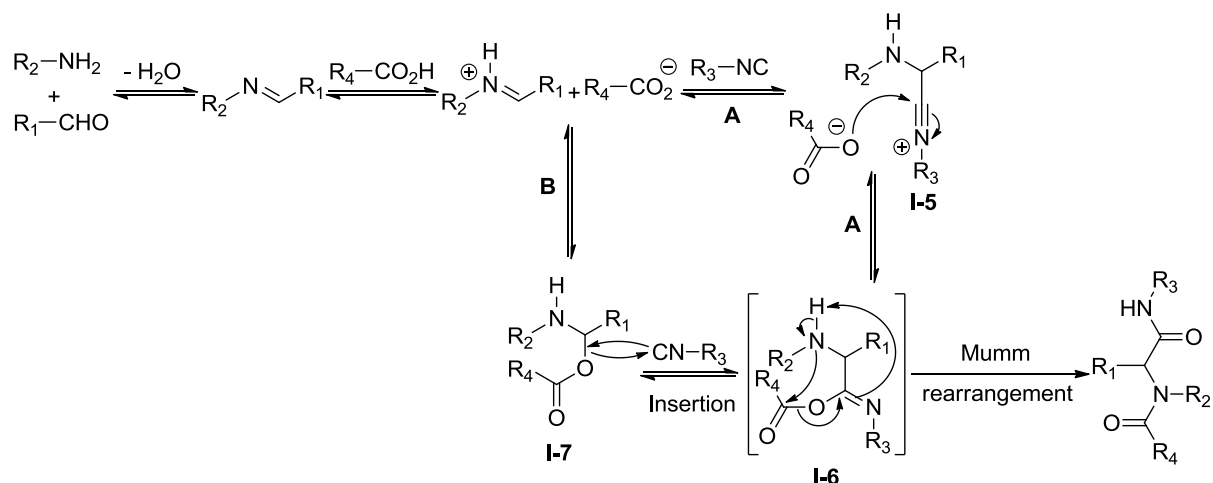
Such experimental observations concerning the solvent choice, led Ugi to suggest an ionic mechanism involving charged intermediates for his reaction (Scheme I.50, **A**). The mechanism includes a series of reversible reactions that begins with an imine formation, which upon protonation by the carboxylic acid affords the iminium ion. The latter is highly reactive towards the nucleophilic addition of the isocyanide yielding nitrilium intermediate **I-5**. Then, the intermediate **I-5** is trapped by the nucleophilic attack of the carboxylate anion

<sup>73</sup> Paravidino, M.; Scheffelaar, R.; Schmitz, R. F.; de Kanter, F. J. J.; Groen, M. B.; Ruijter, E.; Orru, R. V. A. *J. Org. Chem.* **2007**, 72, 10239.

<sup>74</sup> (a) Ugi, I.; Meyr, R.; Fetzer, U.; Steinbrückner, C. *Angew. Chem.* **1959**, 71, 386. (b) Ugi, I.; Steinbrückner, C. *Angew. Chem.* **1960**, 72, 267.

forming the imidate intermediate **I-6**. The final step, like Passerini reaction, involves an irreversible Mumm rearrangement. Such step delivers the final  $\alpha$ -amidocarboxamide adduct in excellent yields.

Another mechanistic pathway has been proposed (Scheme I.50, **B**). It was based on considering the competition between the two nucleophiles, the carboxylate and the isocyanide species. Thus, it imposes the reaction between the iminium and the carboxylate ions to form a hemiaminal **I-7**. In this case, the imidate **I-6** is obtained via the insertion of the isocyanide which then undergoes Mumm rearrangement. Therefore according to both suggested mechanisms, the key step of the reaction is the Mumm rearrangement of the imidate **I-6** forming the final adducts.



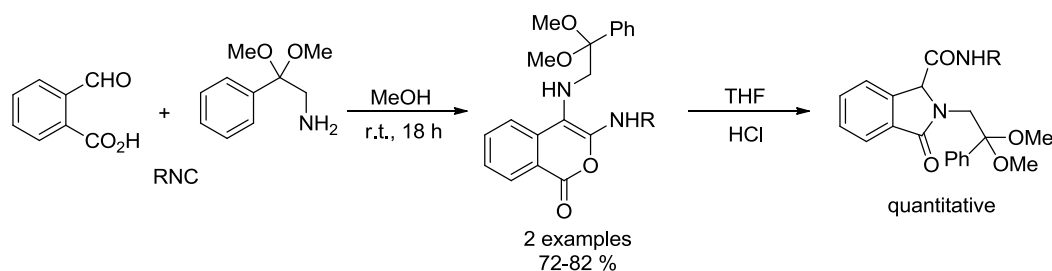
Scheme I.50. Suggested mechanism for Ugi reaction.

Due to the importance of this reaction, a number of studies had been conducted in order to rationalize its mechanism. In 2012, a theoretical study for Ugi reaction mechanism was published by Fleurat-Lessard *et al.*<sup>75</sup>. The DFT calculations demonstrated that only the pathway A (Scheme I.50) was observed.

Consequently, the mechanism definitely includes the acyl imidate intermediate. The latter, was successfully isolated by Marcaccini group<sup>76</sup> while using *o*-formylbenzoic acid as a bifunctional substrate in Ugi reaction. In this case, Ugi adduct was obtained upon treating the reaction medium with traces of HCl (Scheme I.51).

<sup>75</sup> Chéron, N.; Ramozzi, R.; El Kaïm, L.; Grimaud, L.; Fleurat-Lessard, P. *J. Org. Chem.* **2012**, 77, 1361.

<sup>76</sup> Faggi, C.; Garca-Valverde, M.; Marcaccini, S.; Menchi, G. *Org. Lett.* **2010**, 12, 788.

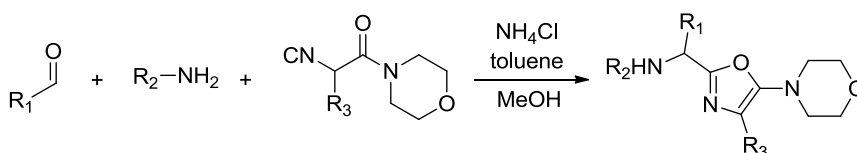
Scheme I.51. Ugi reaction using *ortho*-formylbenzoic acid.

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

### ✚ Scope of Ugi reaction

#### 1. Scope of the isocyanides

Zhu *et al.*<sup>77</sup> used isocyanoacetamides to synthesize poly-functionalized oxazoles with high yields (65 to 92 %). Where, the attack of the  $\alpha$ -amidoisonitrile on the formed imine affords  $\alpha$ -amidoisonitrilium, which undergoes an intramolecular cyclization after the enolization of the amide (Scheme I.52).<sup>78</sup>



Scheme I.52. Synthesis of poly-functionalized oxazoles using Ugi reaction.

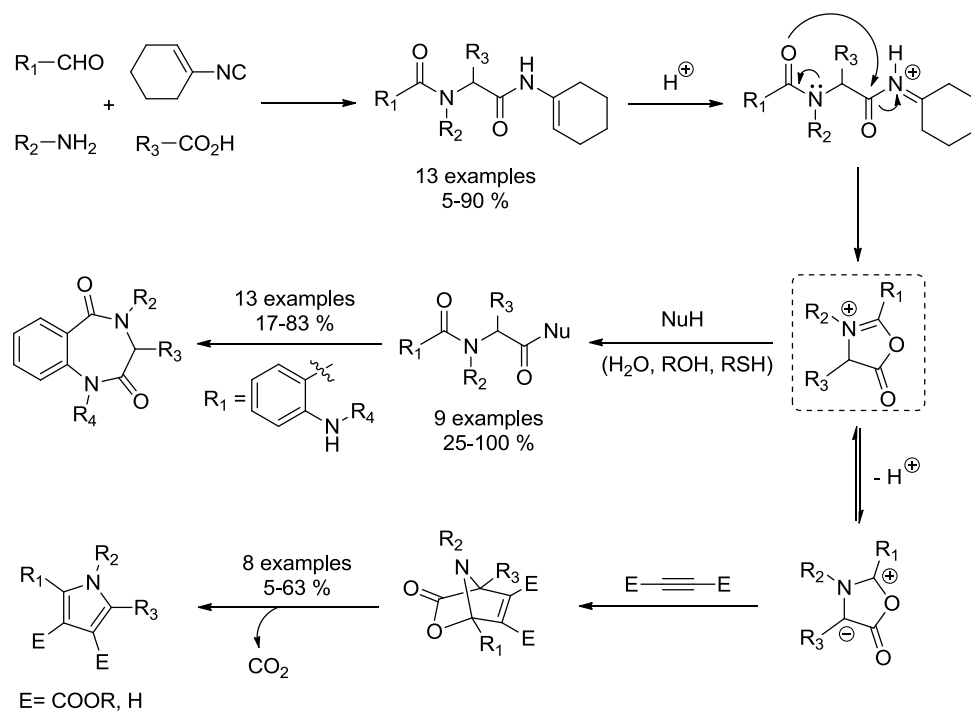
A promising method for achieving greater functional diversity is the use of convertible “universal” isocyanides. Armstrong<sup>79,80</sup> proposed the use of cyclohexenyl isocyanide as a convertible isocyanide in Ugi reaction. Such isocyanide provides an Ugi adduct, which in acidic medium, generates a münchnone *in situ*. This dipolar species is likely to react with different nucleophiles especially with dienophiles in 1,3-dipolar cycloadditions. Using *ortho*-aminobenzoic acid, a series of benzodiazepines could be prepared (Scheme I.53).

<sup>77</sup> (a) Janvier, P.; Sun, X.; Bienaymé, H.; Zhu, J. *J. Am. Chem. Soc.* **2002**, *124*, 2560. (b) Bonne, D.; Dekhane, M.; Zhu, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 2485.

<sup>78</sup> Sun, X.; Janvier, P.; Zhao, G.; Bienaymé, H.; Zhu, J. *J. Org. Lett.* **2001**, *3*, 877.

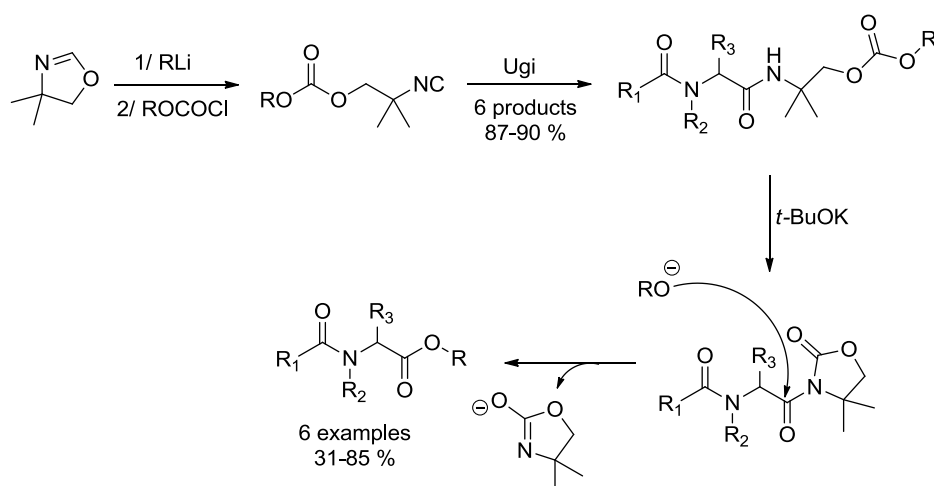
<sup>79</sup> Keating, T. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 2574.

<sup>80</sup> Keating, T. A.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 8935.



Scheme I.53. Ugi 4-CR using a convertible isocyanide.

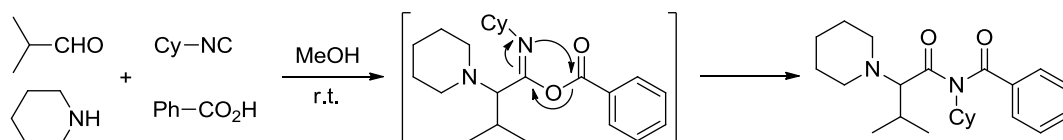
However, this isonitrile is unstable and difficult to synthesize. Therefore, an alternative method was proposed by Ugi employing ( $\beta$ -isocyanoethyl) alkylcarbonates.<sup>81</sup> In basic medium, the amide of Ugi adducts attacks the carbonate moiety forming a cyclic intermediate. The latter, upon nucleophilic attack and elimination of 4,4-dimethyl-2-oxazoline-2-one anion, results in the desired *N*-acylated- $\alpha$ -aminoacid derivatives (Scheme I.54).

Scheme I.54. Ugi reaction towards *N*-acylated- $\alpha$ -aminoacid derivatives.

<sup>81</sup> Lindhorst, T.; Bock, H.; Ugi, I. *Tetrahedron* **1999**, 55, 7411.

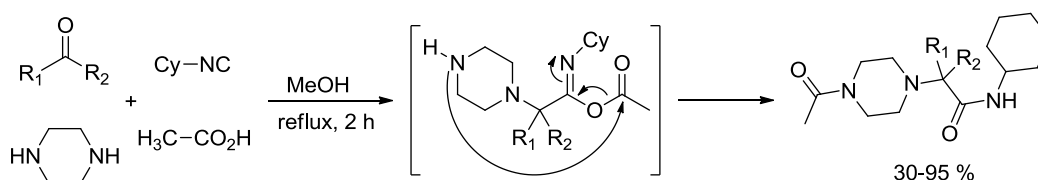
## 2. Scope of the amines

The use of secondary amines in Ugi reaction demonstrated a 1,3-(*O,N*) Mumm rearrangement.<sup>82</sup> In this case, the acyl transfer proceeded via [1,3]-shift towards the nitrogen atom of the isocyanide forming  $\alpha,\alpha'$ -diacylimide derivatives (Scheme I.55).



**Scheme I.55.** The employment of secondary amines in Ugi reaction.

Tron and his coworkers<sup>83</sup> studied the use of piperazine as a secondary amine in Ugi coupling. In this particular case, the acyl transfer is observed at the distal nitrogen of the diamine (Scheme I.56).



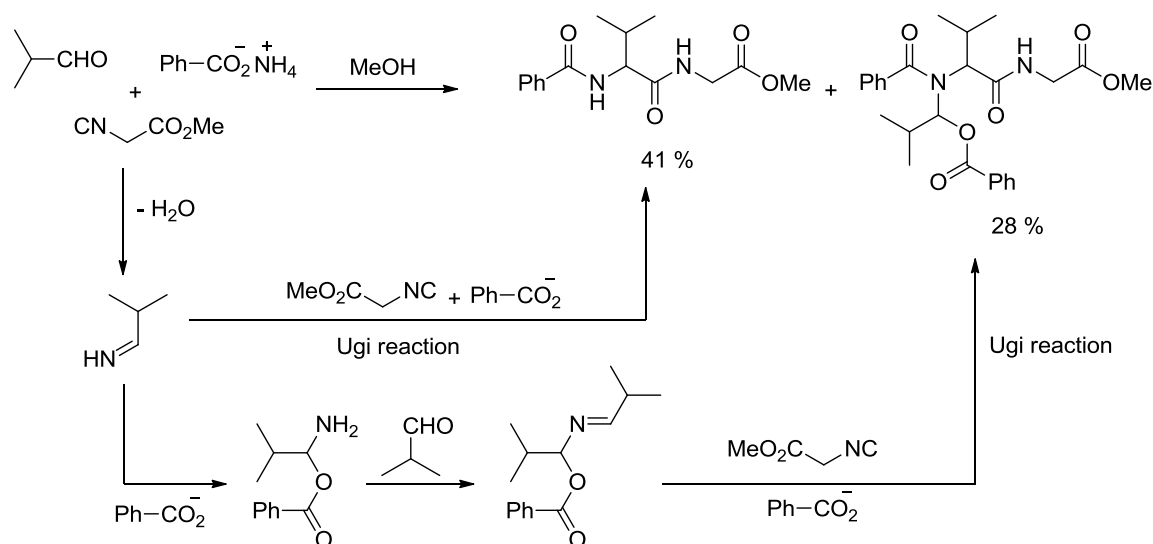
**Scheme I.56.** Ugi coupling using piperazine as a secondary amine partner.

Nonetheless, using ammonia as the amine component in Ugi coupling was widely studied by a number of groups.<sup>84</sup> The desired Ugi adduct is often obtained with moderate yields, due to the competition with several byproducts such as: the six-component coupling adduct isolated in this study (Scheme I.57).

<sup>82</sup> Ugi, I.; Steinbrücker, C. *Chem. Ber.* **1961**, *94*, 2802.

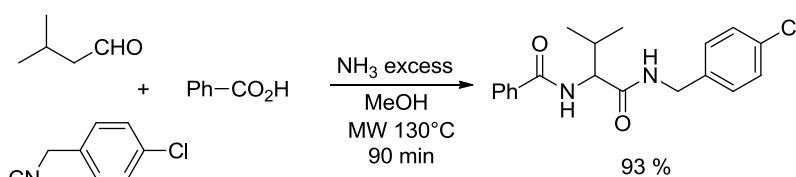
<sup>83</sup> Giovenzana, G.; Tron, G.; Paola, D. D.; Menegotto, I.; Pirali, T. *Angew. Chem. Int. Ed.* **2006**, *118*, 1099.

<sup>84</sup> (a) Floyd, C. D.; Harnett, L. A.; Miller, A.; Patel, S.; Saroglou, L.; Whittaker, M. *Synlett* **1998**, 637. (b) Kazmaier, U.; Hebach, C. *Synlett* **2003**, 1591. (c) Pick, R.; Bauer, M.; Kazmaier, U.; Hebach, C. *Synlett* **2005**, 757. (d) Thompson, M. J.; Chen, B. *J. Org. Chem.* **2009**, *74*, 7084.



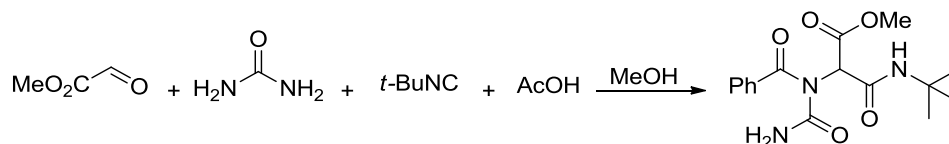
Scheme I.57. Ugi coupling using ammonium acetate as the amine partner.

In 2010, our group developed a new protocol that allowed the formation of Ugi-derived ammonia adducts in excellent yields.<sup>85</sup> Hence, using excess of ammonia under microwave irradiations prevents the degassing of ammonia and delivers selectively the desired product (Scheme I.58).



Scheme I.58. Ugi-derived ammonia under microwave irradiations.

Other amine derivatives such as: hydrazines and hydrazides,<sup>86</sup> or hydroxylamines and oximes<sup>87</sup> as well as hydrazones<sup>88</sup> and ureas,<sup>89</sup> can be successfully employed as amine partners in the coupling reaction, yielding the corresponding Ugi adduct (Scheme I.59).



Scheme I.59. Ugi reaction using urea as the amine component.

<sup>85</sup> El Kaïm, L.; Gizzi, M.; Grimaud, L. *Synlett* **2010**, 1771.

<sup>86</sup> (a) Ugi, I.; Bodesheim, F. *Liebigs Ann. Chem.* **1963**, 666, 61. (b) Zinner, G.; Kliegel, W. *Arch. Pharm.* **1966**, 299, 746. (c) Zinner, G.; Bock, W. *Arch. Pharm.* **1973**, 306, 94. (d) Krasavin, M.; Bushkova, E.; Parchinsky, V.; Shumsky, A. *Synthesis* **2010**, 933.

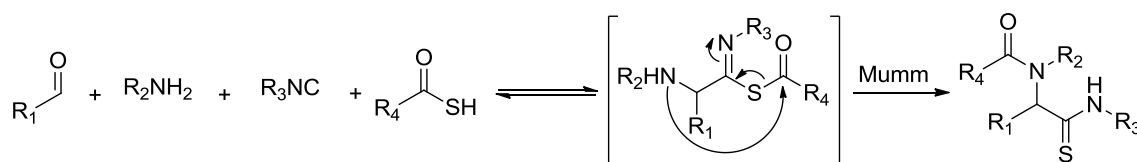
<sup>87</sup> Ugi, I. *Isonitrile Chemistry*; Academic Press, New York - London, **1971**; Vol. 20.

<sup>88</sup> Dos Santos, A.; El Kaïm, L.; Grimaud, L.; Ronsseray, C. *Beilstein J. Org. Chem.* **2011**, 7, 1310.

<sup>89</sup> Zychlinski, S.; Ugi, I. *Heterocycles* **1998**, 49, 29.

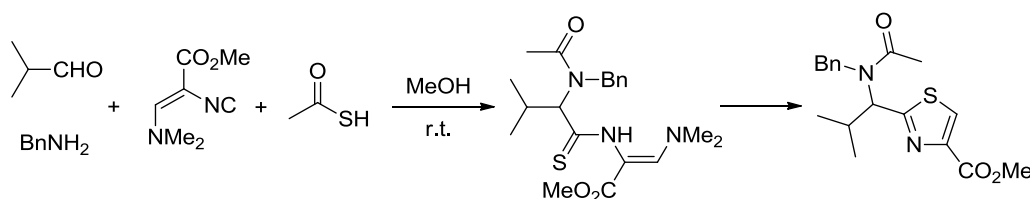
### 3. Scope of the acids

Since the discovery of the Ugi reaction, many approaches have been described on the acidic partner variations. In 1962, Ugi<sup>90</sup> suggested the possibility of using thiocarboxylic acid as the acid component in his reaction. However it was reported for the first time by Dömling group, forty years later. Herein, the final Mumm rearrangement step, in a similar pattern, involved the migration of the acyl group from the sulfur atom to the nitrogen of the amine moiety (Scheme I.60).



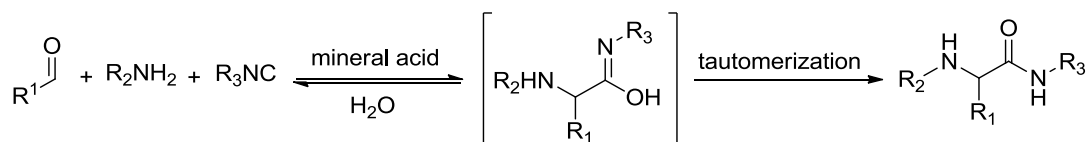
Scheme I.60. Ugi coupling using thiocarboxylic acids.

Thereby, Dömling<sup>91</sup> described the synthesis of thiazoles using methyl  $\beta$ -(*N,N*-dimethylamino)- $\alpha$ -isocyanoacrylate and thioacetic acid (Scheme I.61).



Scheme I.61. Synthesis of thiazoles using thioacetic acid.

Ugi coupling could be catalyzed using mineral acids in aqueous solutions leading to the formation of  $\alpha$ -aminocarboxamides (Scheme I.62).<sup>92</sup>



Scheme I.62. Ugi reaction catalyzed by mineral acids.

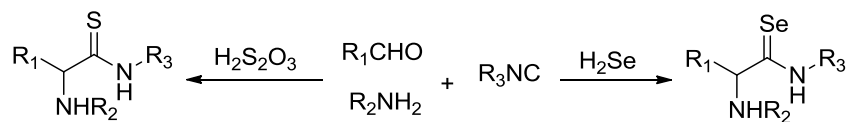
<sup>90</sup> Ugi, I. *Angew. Chem. Int. Ed.* **1962**, 1, 8.

<sup>91</sup> Heck, S.; Dömling, A. *Synlett.* **2000**, 3, 424.

<sup>92</sup> (a) Opitz, G.; Mer, W. *Justus Liebigs Ann. Chem.* **1962**, 652, 163. (b) Mcfarland, J. J. *J. Org. Chem.* **1963**, 28, 2179. (c) Kreutzkamp, N.; Lämmerhirt, K. *Angew. Chem. Int. Ed. Engl.* **1968**, 7, 372. (d) Weber, L. *Drug Disc. Today* **1998**, 3, 379.

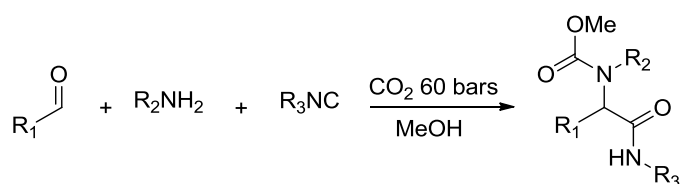


The use of hydrogen selenide and thiosulfuric acid as acidic components in Ugi reaction allowed the synthesis of  $\alpha$ -aminoselenocarboxamides and  $\alpha$ -aminothiocarboxamides respectively (Scheme I.63).<sup>93</sup>



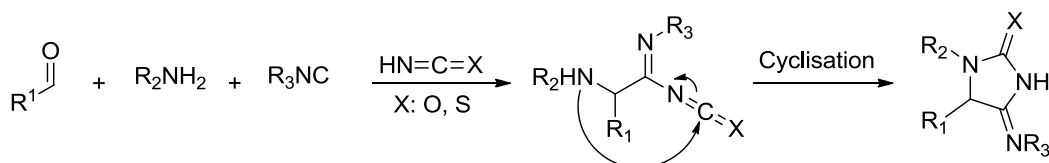
Scheme I.63. Ugi coupling using hydrogen selenide and thiosulfuric acid.

The carbonic acid generated *in situ* by bubbling carbon dioxide in methanol, was employed in Ugi coupling to prepare methyl  $\alpha$ -carboxamidocarbamates (Scheme I.64).<sup>94</sup>



Scheme I.64. Ugi reaction under CO<sub>2</sub> atmosphere.

Other acidic partners such as: cyanic and thiocyanic acids have been introduced into the Ugi reaction to synthesize aminohydantoins or thiohydantoins.<sup>95</sup> The reaction mechanism is significantly different from that described in case of using carboxylic acids (Scheme I.65).



Scheme I.65. Ugi reaction towards aminohydantoins and thiohydantoins.

The use of hydrazoic acid derivatives represents a particularly important acid variant in Ugi coupling. In this case, the Mumm rearrangement step is replaced by an [1,5]-electrocyclization resulting in the formation of 1,5-disubstituted tetrazoles. In 2008, Marcaccini *et al.*<sup>96</sup> described an Ugi/TMSN<sub>3</sub> cascade reaction to prepare

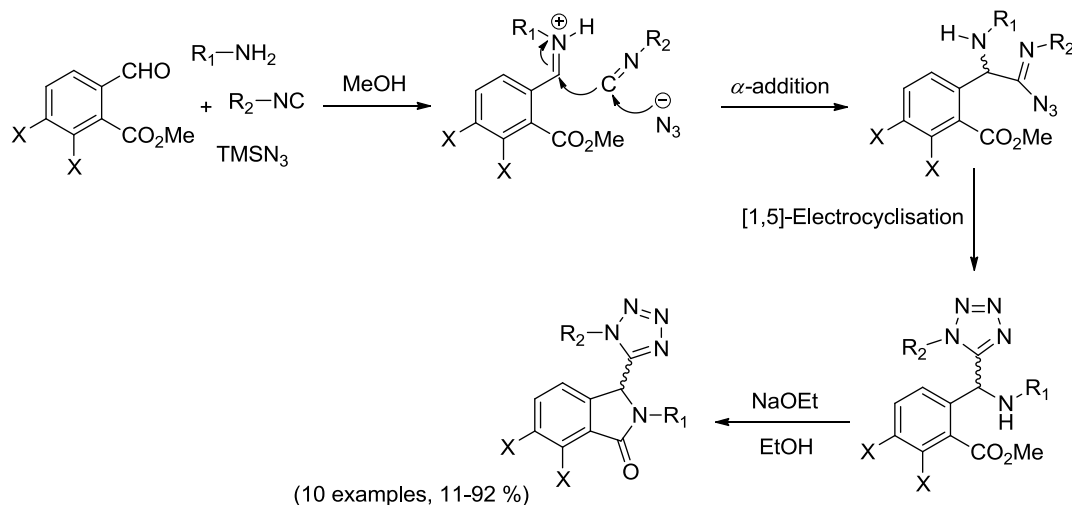
<sup>93</sup> Ugi, I.; Steinbrückner, C. *Angew. Chem.* **1960**, 72, 267.

<sup>94</sup> (a) Haslinger, E. *Monatsh. Chem.* **1978**, 109, 747. (b) Grob, H.; Gloede, J.; Keitel, I.; Kunath, D. *J. Prakt. Chem.* **1968**, 37, 192. (c) Keating, T.; Armstrong, R. *J. Org. Chem.* **1998**, 63, 867.

<sup>95</sup> Ugi, I.; Rosendahl, F.; Bodesheim, F. *Liebigs Ann. Chem.* **1963**, 666, 54.

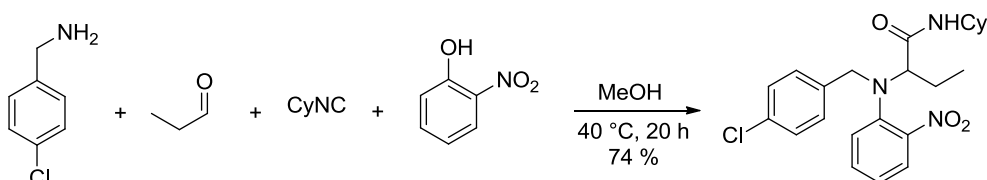
<sup>96</sup> (a) Ugi, I. *Angew. Chem.* **1960**, 72, 639. (b) Ugi, I.; Steinbrückner, C. *Chem. Ber.* **1961**, 94, 734. (c) Opitz, G.; Griesinger, A.; Schubert, H. *Justus Liebigs Ann. Chem.* **1963**, 665, 91. (d) Neidlein, R. *Arch. Pharm.* **1965**, 298, 491. (e) Bienaymé, H.; Bouzid, K. *Tetrahedron Lett.* **1998**, 39, 2735. (f) Nixey, T.; Kelly, M.; Semin, D.; Hulme, C. *Tetrahedron Lett.* **2002**, 43, 3681. (g) Achatz, S.; Dömling, A. *Bioorg. Med. Chem. Lett.* **2006**, 16, 6360.

tetrazoylisoindolinones (Scheme I.66). Hydrazoic acid is usually generated *in situ* in methanol using trimethylsilyl azide TMSN<sub>3</sub> for security reasons.



**Scheme I.66. Intramolecular Ugi-azide condensation sequence.**

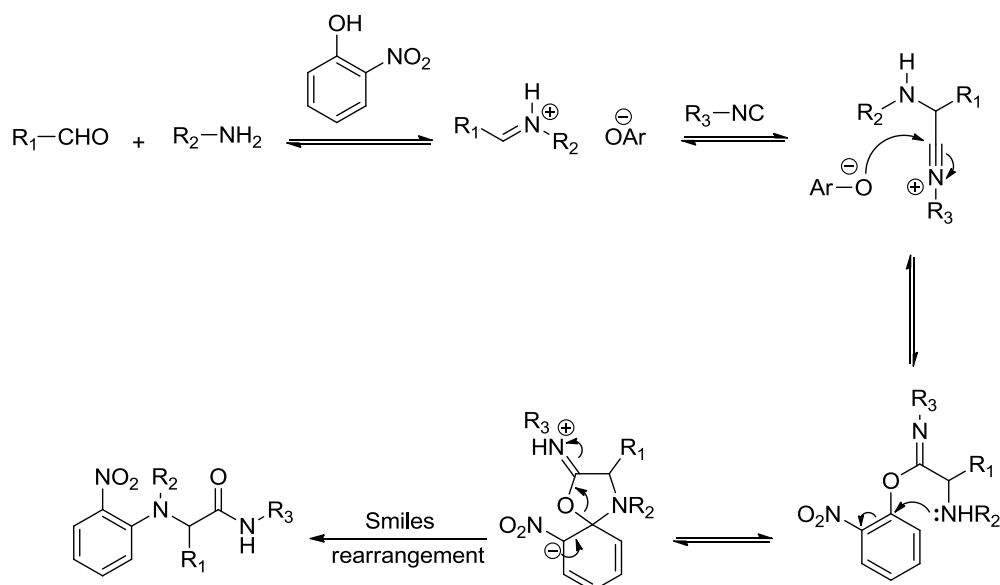
In 2005, another acid variant was introduced by El Kaïm and Grimaud.<sup>97</sup> They demonstrated that an electron deficient phenol such as: *o*-nitrophenol could successfully be employed as the acid component in Ugi reaction. In this case, a Smiles rearrangement takes place rather than a Mumm one (Scheme I.67).



**Scheme I.67. Ugi-Smiles coupling reaction.**

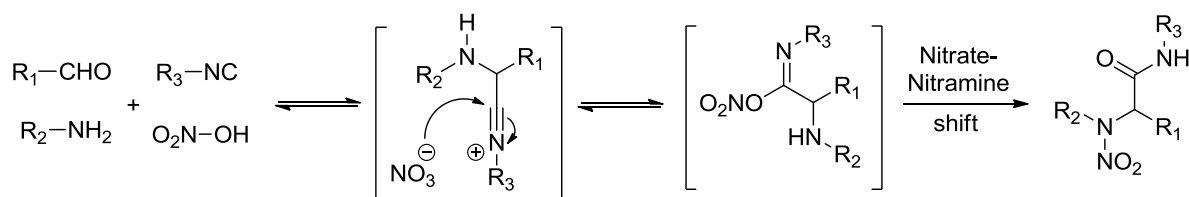
The mechanism begins with the usual imine formation step. The protonation of the imine by the phenolic proton activates it towards the nucleophilic attack of the isocyanide. Then, the formed intermediate is trapped by the phenolate anion. A final Smiles rearrangement takes place as a result of the presence of electron-withdrawing group in the phenolic ring affording *N*-arylcarboxamide (Scheme I.68).

<sup>97</sup> (a) El Kaïm, L.; Grimaud, L.; Oble, J. *Angew. Chem. Int. Ed.* **2005**, *44*, 7961. (b) El Kaïm, L.; Grimaud, L.; Gizolme, M.; Oble, J. *Org. Lett.* **2006**, *8*, 4019. (c) El Kaïm, L.; Grimaud, L.; Gizolme, M.; Oble, J. *J. Org. Chem.* **2007**, *72*, 4169. Recent review: El Kaïm, L.; Grimaud, L. *Eur. J. Org. Chem.* **2014**, *35*, 7749.



Scheme I.68. Suggested mechanism for Ugi-Smiles reaction.

In 2017, our group<sup>98</sup> displayed the use of the inorganic nitric acid as the acid component in the first aminative Ugi-type coupling. The mechanism involves trapping of the nitrilium intermediate by the nucleophilic nitrate anion. A final intramolecular nitration step results in the nitramine adducts (Scheme I.69).



Scheme I.69. Nitric acid as the acidic partner in Ugi couplings.

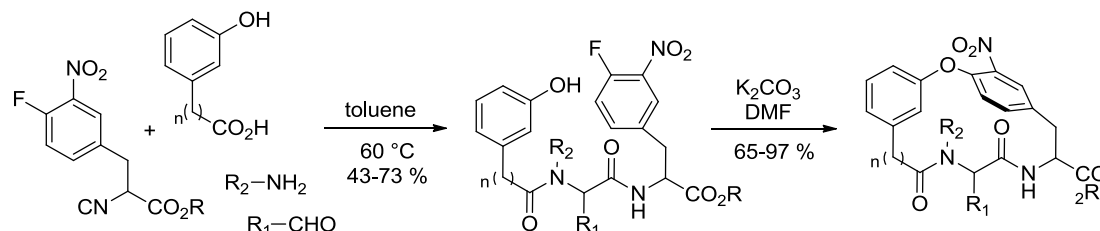
### Ugi post-condensation reactions

Ugi reaction provides important scaffolds that can be further transformed through post-modifications, depending on the functional groups integrated in the different partners, into valuable heterocycles. These two-step strategies (Ugi/post-condensation reaction) represent a viable synthetic tool for medicinal chemistry as well as pharmaceutical industry. Hereinafter, we discuss selected examples for such reactions from the literature.

<sup>98</sup> Mercalli, V.; Nyadanu, A.; Cordier, M.; Tron, G. C.; Grimaud, L.; Kaïm, L. *Chem. Commun.* **2017**, 53, 2118.

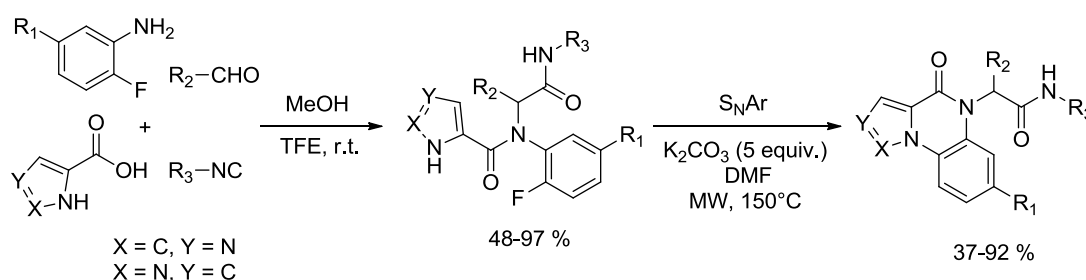
## 1. Aromatic nucleophilic substitution S<sub>N</sub>Ar

This type of post-condensation reactions was widely explored in the literature. In 2001, Zhu *et al.*<sup>99</sup> proposed a rapid approach towards the biaryl ether macrocycles via an Ugi/intramolecular S<sub>N</sub>Ar-based cycloetherification cascade (Scheme I.70).



Scheme I.70. Macrocyclization synthesis via Ugi/S<sub>N</sub>Ar cascade.

In 2007, Spatz and his coworkers<sup>100</sup> described a new synthesis of imidazo- and pyrazolo [1,5-*a*] quinoxalines via an Ugi/S<sub>N</sub>Ar cascade. Where, a bifunctional heterocyclic carboxylic acid derivative was employed in the Ugi coupling together with an *ortho*-fluoro-substituted aniline derivative (Scheme I.71).



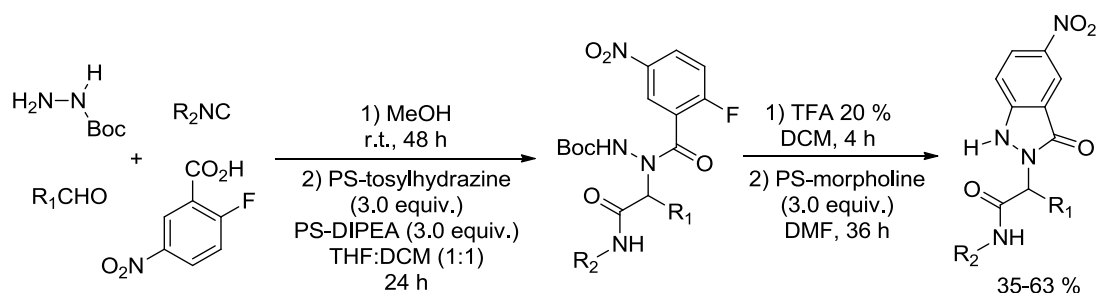
Scheme I.71. Synthesis of imidazo- and pyrazolo[1,5-*a*]quinoxalines via Ugi/S<sub>N</sub>Ar tandem.

The Hulme group<sup>101</sup> is among the pioneers who developed these post-condensations by using the “UDC” (Ugi/deprotection/cyclisation) strategy. They used 2-fluoro-5-nitro-benzoic acid and *t*-butyl carbazate to design their Ugi products. The subsequent deprotection of the latter followed by an intramolecular S<sub>N</sub>Ar-type cyclization, allowed the synthesis of indazolinone derivatives (Scheme I.72).

<sup>99</sup> (a) Cristau, P.; Vors, J.-P.; Zhu, J. *Org. Lett.* **2001**, 3, 4079. (b) Cristau, P.; Vois, J.-P.; Zhu, J. *Tetrahedron* **2003**, 59, 7859.

<sup>100</sup> Spatz, J. H.; Umkehrer, M.; Kalinski, C.; Ross, G.; Burdack, C.; Kolb, J.; Bach, T. *Tetrahedron Lett.* **2007**, 48, 8060.

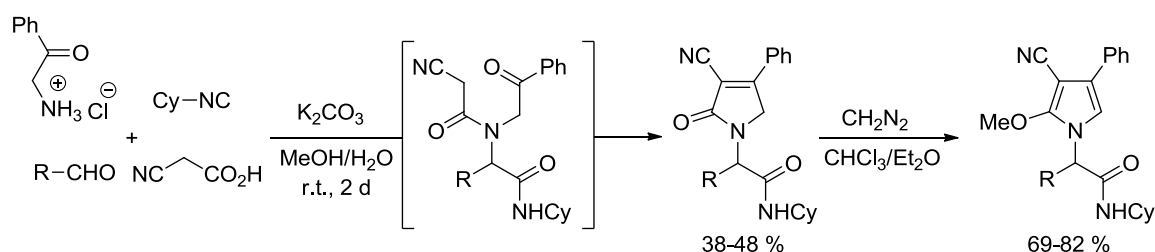
<sup>101</sup> (a) Tempest, P.; Ma, V.; Kelly, M. G.; Jones, W.; Hulme, C. *Tetrahedron Lett.* **2001**, 42, 4963. (b) Tempest, P.; Pettus, L.; Gore, V.; Hulme, C. *Tetrahedron Lett.* **2003**, 44, 1947.

Scheme I.72. Synthesis of indazolinones via Ugi/deprotection/S<sub>N</sub>Ar sequence.

## 2. Condensations

### ➤ Knoevenagel condensation

A new synthesis of variously substituted pyrroles, involving an Ugi/Knoevenagel cascade, was described by the Marcaccini group in 1999.<sup>102</sup> Starting from cyanoacetic acid and phenacylamine hydrochloride as coupling partners in Ugi reaction, different pyrrolones were obtained. A subsequent methylation of these derivatives using diazomethane, resulted in the desired pyrroles (Scheme I.73).

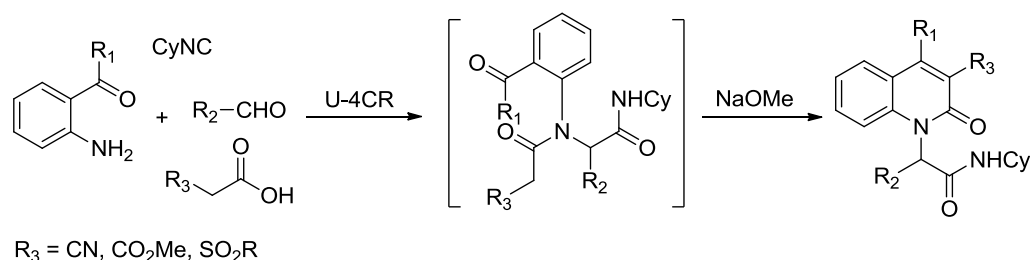


Scheme I.73. Ugi/Knoevenagel cascade towards pyrrole derivatives.

Following the same reaction principle, the same group examined the synthesis of quinolin-2-(1H)-ones.<sup>103</sup> The employment of malonic or tosylacetic acids and *ortho*-acylanilines in the Ugi four-component coupling, allowed successfully the subsequent Knoevenagel condensation upon basic treatment (Scheme I.74).

<sup>102</sup> Bossio, R.; Marcaccini, S.; Pepino, R.; Torroba, T. *Heterocycles* **1999**, *50*, 463.

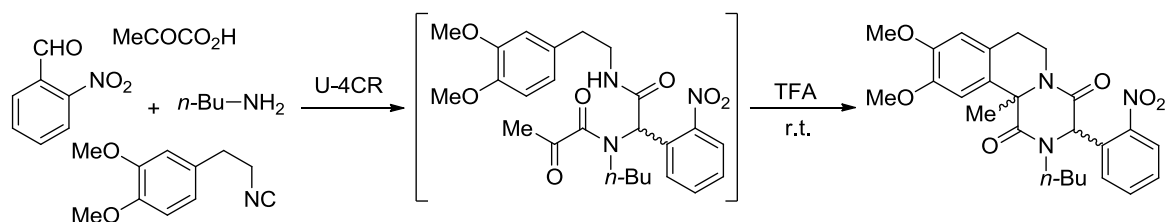
<sup>103</sup> Marcaccini, S.; Pepino, R.; Pozo, M. C.; Basurto, S.; García-Valverde, M.; Torroba, T. *Tetrahedron Lett.* **2004**, *45*, 3999.



Scheme I.74. Ugi/Knoevenagel cascade to synthesize quinolin-2-(1H)-ones.

## ➤ Pictet-Spengler condensation

The Ugi/Pictet-Spengler tandem reaction was first described by El Kaïm *et al.* in 2007.<sup>104</sup> This reaction sequence delivered tricyclic 2,5-diketopiperazine derivatives (Scheme I.75). Similar approaches were reported, in particular, by Dömling and his coworkers.<sup>105</sup> Orru *et al.*<sup>106</sup> have also investigated the possibility of the asymmetric synthesis of new polycyclic alkaloids via an Ugi-4CR/Pictet-Spengler cascade.

Scheme I.75. Ugi/Pictet-Spengler cascade by El Kaïm *et al.*.

## ➤ Horner-Wadsworth-Emmons condensation

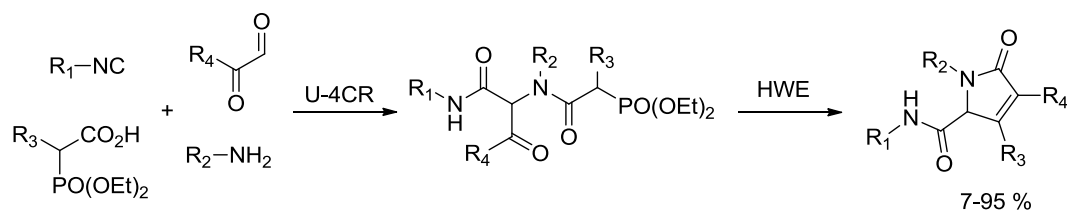
In 2004, the Dömling *et al.*<sup>107</sup> proposed the synthesis of variously substituted pyrrolidinones through an Ugi/Horner-Wadsworth-Emmons tandem (HWE) sequence. They used carboxylic acids possessing a phosphonate group and glyoxals in the Ugi coupling (Scheme I.76).

<sup>104</sup> El Kaïm, L.; Gageat, M.; Gaultier, L.; Grimaud, L. *Synlett* **2007**, 3, 500.

<sup>105</sup> (a) Liu, H.; Dömling, A. *J. Org. Chem.* **2009**, 74, 6895. (b) Wang, W.; Herdtweck, E.; Dömling, A. *Chem. Commun.*, **2010**, 46, 770. (c) Sinha, M. K.; Khoury, K.; Herdtweck, E.; Dömling, A. *Chem. Eur. J.* **2013**, 19, 8048.

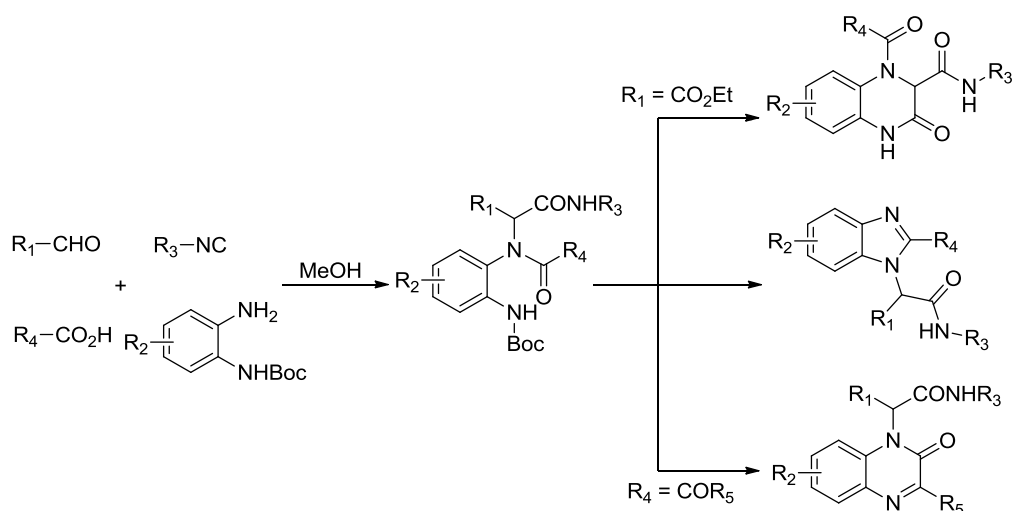
<sup>106</sup> Znabet, A.; Zonneveld, J.; Janssen, E.; de Kanter, F. J. J.; Helliwell, M.; Turner, N. J.; Ruijter, E.; Orru, R. V. A. *Chem. Commun.* **2010**, 46, 7706.

<sup>107</sup> Beck, B.; Picard, A.; Herdtweck, E.; Dömling, A. *Org. Lett.* **2004**, 6, 39.



Scheme I.76. Ugi/(HWE) cascade.

The UDC (Ugi/deprotection/cyclization) strategy, aforementioned, is widely employed in the synthesis of nitrogenous heterocyclic compounds. Hulme and his coworkers described the preparation of dihydroquinoxalinones,<sup>108</sup> benzimidazoles,<sup>109</sup> and quinoxalinones<sup>110</sup> using the UDC cascade, starting from a protected *ortho*-aminoaniline (Scheme I.77). They exploited this sequence in the synthesis of imidazolines<sup>111</sup> and ketopiperazines<sup>112</sup> on a solid support, so as to simplify the purification process afterwards.



Scheme I.77. Application of the UDC cascade in the heterocyclic synthesis.

### 3. Cycloadditions

Akritopoulou-Zanze group<sup>113</sup> documented two types of post-cycloadditions, [2+2] and [3+2], on Ugi adducts. The use of propargylamine together with  $\alpha$ -azido carboxylic acid enabled the post-intramolecular cycloaddition of Ugi adducts, yielding a bicyclic triazole derivatives (Scheme I.78).

<sup>108</sup> Hulme, C.; Cherrier, M.-P. *Tetrahedron Lett.* **1999**, 40, 5295.

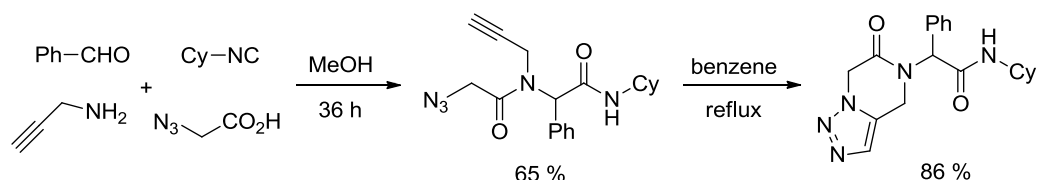
<sup>109</sup> Tempest, P.; Ma, V.; Thomas, S.; Hua, Z.; Kelly, M. G.; Hulme, C. *Tetrahedron Lett.* **2001**, 42, 4959.

<sup>110</sup> Nixey, T.; Tempest, P.; Hulme, C. *Tetrahedron Lett.* **2002**, 43, 1637.

<sup>111</sup> Hulme, C.; Ma, L.; Romano, J.; Morrisette, M. *Tetrahedron Lett.* **1999**, 40, 7925.

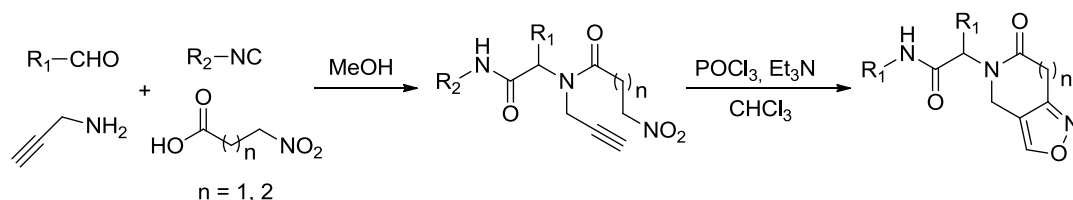
<sup>112</sup> Hulme, C.; Peng, J.; Louridas, B.; Menard, P.; Krolkowski, P.; Kumar, N. V. *Tetrahedron Lett.* **1998**, 39, 8047.

<sup>113</sup> Akritopoulou-Zanze, I.; Gracias, V.; Djuric, S. *Tetrahedron Lett.* **2004**, 45, 8439.



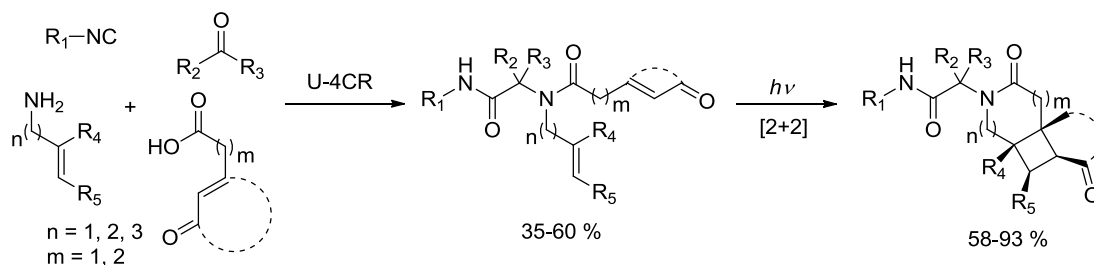
Scheme I.78. Ugi/[3+2] cycloaddition sequence.

The Ugi/intramolecular nitrile oxide cycloaddition (INOC) tandem led to the preparation of isoxazoles and isoxazolines in two steps.<sup>114</sup> The Ugi reaction should involve an allyl or propargylamine and a carboxylic acid having a nitro group, which is then converted to nitrile oxide. Thereafter, the formed adduct undergoes an intramolecular cycloaddition to give the desired bicyclic derivative (Scheme I.79).



Scheme I.79. Synthesis of isoxazoles via an Ugi/INOC sequence.

In a similar manner, an Ugi/photocycloaddition sequence involving an alkene and an enone, affords variously functionalized bi- and tricyclic compounds (Scheme I.80).<sup>115</sup>



Scheme I.80. Ugi/photocycloaddition cascade.

### ➤ Diels-Alder reaction

Wright<sup>116</sup> and Paulvannan<sup>117</sup> introduced furan derivatives as dienes in the Ugi/Diels-Alder tandems. The employment of pyrrole derivatives, as diene, and acrylic acid, as

<sup>114</sup> Akritopoulou-Zanze, I.; Gracias, V.; Moore, J.; Djuric, S. *Tetrahedron Lett.* **2004**, 45, 3421.

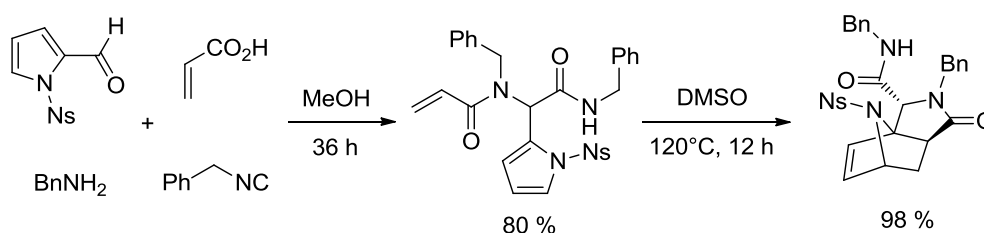
<sup>115</sup> Akritopoulou-Zanze, I.; Whitehead, A.; Waters, J.; Henry, R.; Djuric, S. *Org. Lett.* **2007**, 9, 1299.

<sup>116</sup> Wright, D. L.; Robotham, C. V.; Aboud, K. *Tetrahedron Lett.* **2002**, 43, 943.

<sup>117</sup> (a) Paulvannan, K.; Jacobs, J.W. *Tetrahedron* **1999**, 55, 7433. (b) Paulvannan, K. *Tetrahedron Lett.* **1999**, 40, 1851.



dienophile, in Ugi/Diels-Alder cascade was proposed as well by Paulvannan.<sup>118</sup> This allowed him to synthesize tricyclic nitrogenous heterocycles, with good yields and high diastereoselectivity (Scheme I.81).



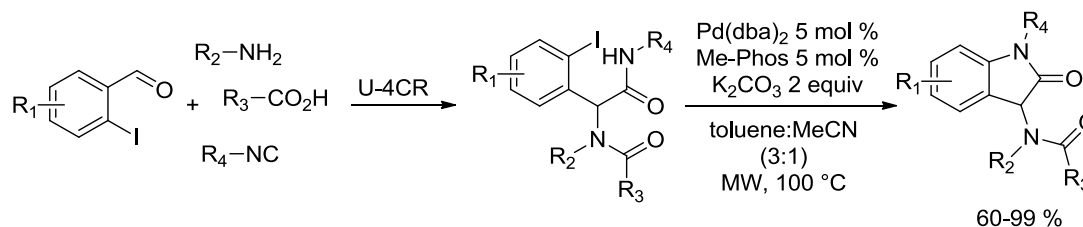
Scheme I.81. Ugi/Diels-Alder cascade.

#### 4. Organometallic couplings

The development of organometallic reaction cascades using Ugi adducts forming stereoselectively carbon-carbon or carbon-heteroatom bonds, has been widely described over the last decade. Several approaches either sequential "One-pot" or multi-steps, have been developed starting from Ugi adducts and leading to highly functionalized products.

##### ➤ Arylation reactions

Zhu *et al.*<sup>119</sup> reported an efficient Ugi/Pd-catalyzed intramolecular *N*-arylation (intramolecular Buchwald–Hartwig reaction) methodology to access functionalized oxindoles (Scheme I.82). They used Pd(dba)<sub>2</sub> as a catalyst and Me-Phos as a ligand under microwave irradiations, affording oxindoles in moderate to excellent yields (60–99%). No competitive C-H activation was observed during their course of study.



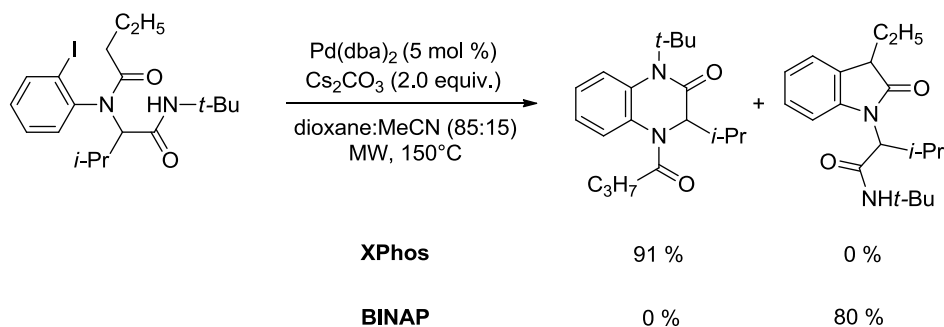
Scheme I.82. Ugi/*N*-arylation cascade towards oxindoles.

Palladium has been extensively used as a catalyst for carbon-carbon and carbon-heteroatom single bond formation in a selective and efficient manner. The choice of the ligand

<sup>118</sup> Paulvannan, K. *J. Org. Chem.* **2004**, 69, 1207.

<sup>119</sup> Bonnaterre, F.; Bois-Choussy, M.; Zhu, J. *Org. Lett.* **2006**, 8, 4351.

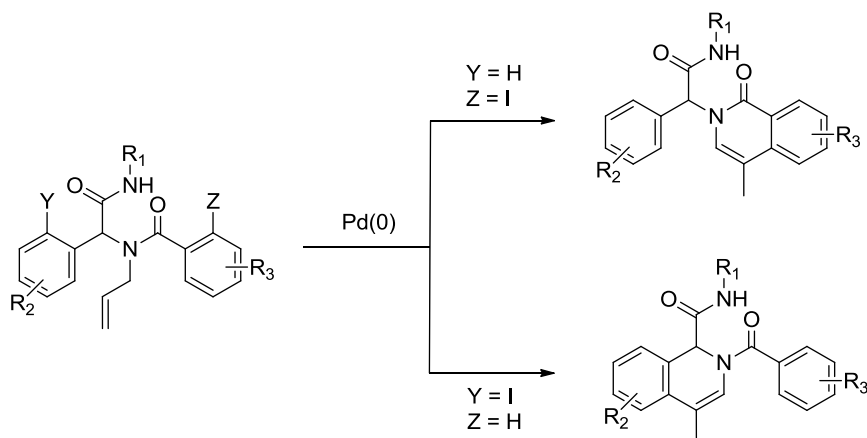
that coordinates to the palladium during the catalytic cycle is one of the main parameters influencing both the stereo- and regioselectivity of the reaction. This is well demonstrated in the following study concerning the influence of the ligand on the palladium-catalyzed post-condensations.<sup>120</sup> It was observed that the use of XPhos led to the selective synthesis of the quinoxalinones, while using BINAP resulted in oxindoles (Scheme I.83).



**Scheme I.83.** Influence of the ligand on the Pd-catalyzed arylation of Ugi products.

#### ➤ Heck coupling

Several isoquinolines were synthesized via an Ugi/Heck couplings tandem. The Ugi coupling should comprise an *ortho*-iodinated benzene ring in either the aldehyde or the acid partners. In any case, isomerization of the double bond is usually observed and moderate yields, ranging from 50 to 60 %, for these two-steps are obtained (Scheme I.84).<sup>121</sup>



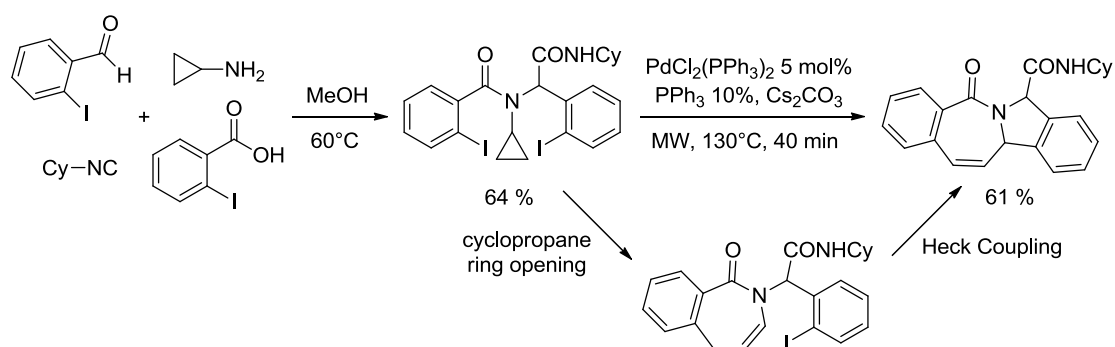
**Scheme I.84.** Ugi/Heck tandem for the synthesis of isoquinolines.

<sup>120</sup> (a) Erb, W.; Neuville, L.; Zhu, J. *J. Org. Chem.* **2009**, 74, 3109.

<sup>121</sup> Xiang, Z.; Luo, T.; Lu, K.; Cui, J.; Shi, X.; Fathi, R.; Chen, J.; Yang, Z. *Org. Lett.* **2004**, 6, 3155.

Meanwhile, Gracias and his colleagues<sup>122</sup> presented the possibility of preventing the isomerization of the exocyclic double bond by carrying out the Heck reaction under microwave irradiations. Ugi/Heck tandem proved to be a powerful tool for total synthesis. Fukuyama *et al.*<sup>123</sup> team proposed the employment of the Ugi/Heck cascade for the construction of the tetracyclic structural unit of (+)-Naphthyridinomycin. It is also considered as a key step in the total synthesis of Ecteinasidin 743.<sup>124</sup>

The combination of the palladium-catalyzed aminocyclopropane ring opening with a second post-condensation (Heck coupling in this case) proved to be effective for obtaining a complex heterocyclic structure. For such cascade, *ortho*-iodobenzaldehyde, cyclopropylamine and *ortho*-iodobenzoic acid are used as coupling partners in the Ugi reaction (Scheme I.85).<sup>125</sup>



Scheme I.85. Ugi/cyclopropane ring opening/Heck coupling cascade.

## 5. Radical reactions

Our group has demonstrated thorough studies for using radical reactions as Ugi-post modifications. Xanthate precursors were successfully involved in the carbon-carbon bond formation using alkenes<sup>126</sup> and alkynes.<sup>127</sup> Usually either magnesium (III) acetate<sup>128</sup> or copper acetate<sup>129</sup> catalyzes such type of radical post-transformations. Hereinafter, we present one of these studies involving Ugi/copper-catalyzed radical oxidative cascade to synthesize spiroindolines (Scheme I.86).

<sup>122</sup> Gracias, V.; Moore, J. D.; Djuric, S. W. *Tetrahedron Lett.* **2004**, 45, 417.

<sup>123</sup> Mori, K.; Rikimaru, K.; Kan, T.; Fukuyama, T. *Org. Lett.* **2004**, 6, 3095.

<sup>124</sup> Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, 124, 6552.

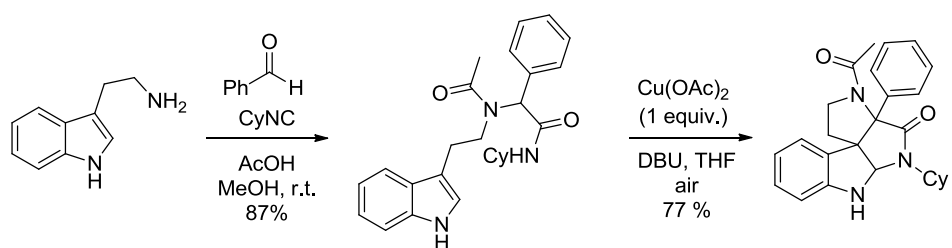
<sup>125</sup> Dos Santos, A.; El Kaïm, L.; Grimaud, L.; Ramozzi, R. *Synlett*, **2012**, 438.

<sup>126</sup> El Kaïm, L.; Grimaud, L.; Miranda, L. D.; Vieu, E. *Tetrahedron Lett.* **2006**, 47, 8259.

<sup>127</sup> El Kaïm, L.; Grimaud, L.; Miranda, L. D.; Vieu, E.; Cano-Herrera, M. A.; Perez-Labrada, K. *Chem. Commun.* **2010**, 46, 2489.

<sup>128</sup> El Kaïm, L.; Grimaud, L.; Vieu, E. *Org. Lett.* **2007**, 9, 4171.

<sup>129</sup> El Kaïm, L.; Grimaud, L.; Le Goff, X.F.; Menes-Arzate, M.; Miranda, L. D. *Chem. Commun.* **2011**, 47, 8145.



**Scheme I.86. Ugi/Cu-catalyzed radical oxidative cascade.**



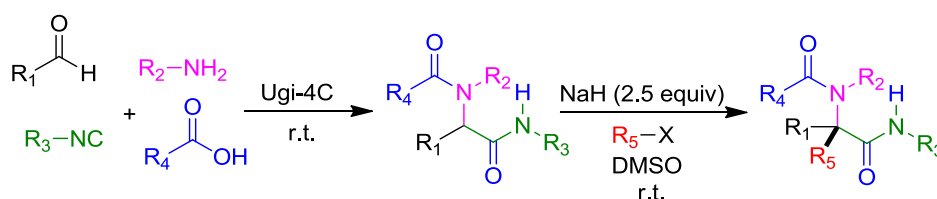
## **Chapter II : Alkylation of Ugi adduct through dianionic intermediates**



## II.1 Overview

In the frame of this thesis, we are particularly interested in Ugi reaction<sup>130</sup> which involves an aldehyde or ketone, an amine, an isocyanide and a carboxylic acid. Ugi reaction not only serves as a tool for providing a diversity of structures as a four component reaction, but also helps in synthesizing an array of various heterocyclic scaffolds thanks to the different functional groups that could be introduced in the Ugi adduct.<sup>131</sup> Hence, Ugi reaction has a wide range of applications compared to the 3-component Passerini reaction.

The most common application of Ugi couplings is their post-condensation reactions that usually involve two or more functional groups already present in the different components constituting the Ugi product. Thinking out of the box, we recently described a method to introduce an additional functionality to the already existing 4-components raising the capacity of Ugi adduct in terms of synthetic potential. We here demonstrate Ugi/Intermolecular Alkylation cascades which lead to the substitution of the peptidyl C-H position in Ugi product by several electrophiles. Such sequence was successfully achieved by means of 1,3-C,N-amide dianion intermediates (Scheme II.1).



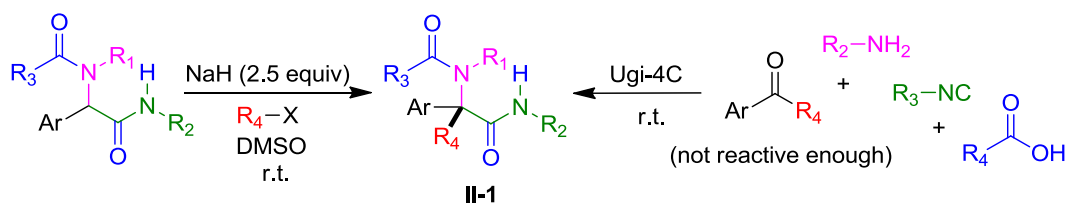
**Scheme II.1. Ugi/Intermolecular alkylation cascade.**

From another point of view, it is familiar that aromatic ketones are the least reactive carbonyl partners in Ugi reaction. Thus employing our strategy could be considered as an alternative approach to access formally ketone-derived Ugi product **II-1**, which could be typically obtained using aromatic ketones as carbonyl component in Ugi reaction (Scheme II.2).

<sup>130</sup> (a) El Kaïm, L.; Grimaud, L. *Tetrahedron* **2009**, 65, 2153. (b) Hulme, C.; Dietrich, J.; *Mol. Divers.* **2009**, 13, 195.

<sup>131</sup> For review, see: (a) Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, 39, 3168. (b) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, 6, 3321. (c) Dömling, A. *Curr. Opin. Chem. Biol.* **2002**, 6, 306. (d) Ugi, I.; Werner, B.; Dömling, A. *Molecules* **2003**, 8, 53. (e) *Multicomponent Reactions*; Zhu, J.; Bienaymé, H., Eds.; Wiley-VCH: Weinheim, **2005**. (f) Dömling, A. *Chem. Rev.* **2006**, 106, 17. (g) Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. *Angew. Chem. Int. Ed.* **2011**, 50, 6234. (h) *Isocyanide Chemistry: Applications in Synthesis and Material Science*; Nenajdenko, V. G., Ed.; Wiley-VCH: Weinheim, **2012**. (i) *Multicomponent Reactions in Organic Synthesis*; Zhu, J.; Wang, Q.; Wang, M.-X., Eds.; Wiley-VCH: Weinheim, **2014**.



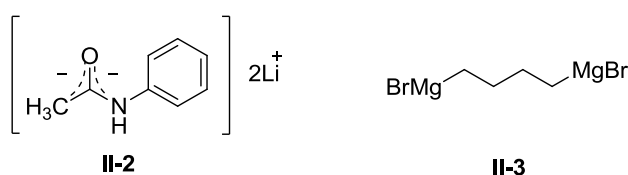


Scheme II.2. A new access to ketone-derived Ugi adducts.

Before presenting the results obtained, a brief literature survey about the chemistry of dianions, ketones in Ugi reaction and reactions involving the peptidyl C-H position in Ugi products is displayed.

## II.2 Chemistry of dianions

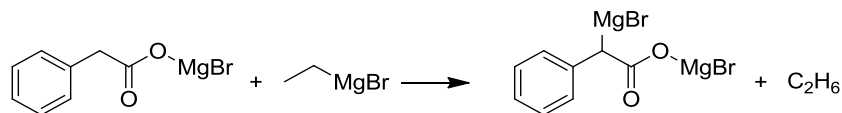
Dianions are reactive organic species possessing two negative charges at carbon, oxygen, nitrogen or sulfur centers. They are usually generated by treatment with two or more molar equiv. of powerful bases such as: lithium diisopropylamide (LDA) or *n*-butyllithium (*n*-BuLi) through deprotonation since the second deprotonation usually have high range of acidity from 20-35 pka units. There are several classifications of the dianions. They are classified according to the distance between the negative charges on the two anions into 1,*n*-dianions (where *n* = 1, 2, 3, ...). They are also classified as: ambident dianions (where one or two negative charges are delocalized) and nonambident dianions (where the negative charges are localized), for instance the 1,3-dianion of acetic anilide **II-2** and 1,4-di(bromomagnesio)butane **II-3** (Scheme II.3). The ambident dianions attract greater interest as a result of the usual high regioselectivity accompanying their reaction with electrophiles.<sup>132</sup>



Scheme II.3. Localized and non-localized dianions.

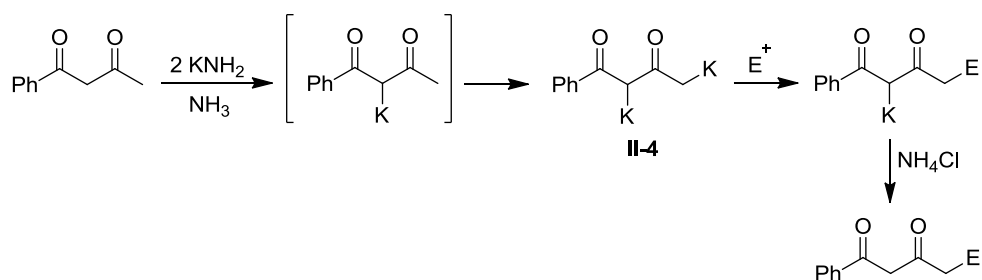
<sup>132</sup> Reviews of dianions: (a) Maercker, A. *Methoden Org. Chem.* (Houben-Weyl) 4. Aufl., Bd. E19d, **1993**, 448. (b) Saalfrank, R. W. *Methoden Org. Chem.* (Houben-Weyl) 4. Aufl., Bd. E19d, **1993**, 567. (c) Thompson, C. M.; Green, D. *Tetrahedron* **1991**, 47, 4223. (d) Kaiser, E. M.; Petty, J. D.; Knutson, P. L. A. *Synthesis* **1977**, 509. (e) Bates, R. B. in Buncel, E., Durst, T. *Dianions and Polyanions, Comprehensive Carbanion Chemistry*; Elsevier: Amsterdam, **1980**; Part A, pp 1-53. (f) Petragnani, N.; Yonashiro, M. *Synthesis* **1982**, 521. (g) von Schleyer, P. R. *Pure Appl. Chem.* **1983**, 55, 355. (h) Thompson, C. M. *Dianion Chemistry in Organic Synthesis*; CRC Press: Boca Raton, **1994**. (e) Langer, P.; Freiberg, W. *Chem. Rev.* **2004**, 104, 4125.

Dianion intermediates have been known since Grignard prepared the first dianion of phenylacetic acid from bromomagnesium phenylacetate and ethylmagnesium bromide in 1904 (Scheme II.4).<sup>133</sup>



Scheme II.4. α,O-dimagnesium dibromide phenylacetate.

The earliest broadly studied dianions were those of β-diketones and β-ketoaldehydes<sup>134</sup>, since Morgan and Harris highlighted the regioselective carbon-carbon bond formation of benzoylacetone via dianions.<sup>135</sup> The dialkali derivatives of either β-diketones or β-ketoaldehydes were obtained instantly upon their treatment with 2 mol equiv. of alkali metal amides in liquid ammonia. The latter base was afterwards replaced by lithium diisopropylamide in ethereal solvents. In order to illustrate the early basic concepts of dianion chemistry, Kaiser and his coworkers selected the dipotassiobenzoylacetone **II-4** as a model to discuss its synthesis and reactivity (Scheme II.5).<sup>136</sup>



Scheme II.5. Regioselective alkylation of benzoylacetone.

They considered the most acidic site to be deprotonated first is that either on a carbon atom in α-position to two electron-withdrawing groups or on a heteroatom (nitrogen, oxygen or sulfur) leading to a relatively non-nucleophilic intermediate. The second deprotonation afforded a strongly nucleophilic intermediate compared to the initial non-nucleophilic one. The condensation between the resulting dialkali intermediate with electrophiles usually results in a regiospecific reaction at the latter anionic position regardless the amount of electrophile used.

<sup>133</sup> Grignard, V. *Bull. Soc. Chim. Fr.* **1904**, 31, 751.

<sup>134</sup> Harris, T. M.; Harris, C. M. *Org. React.* **1969**, 17, 155.

<sup>135</sup> Morgan, G. T.; Harris, T. M. *J. Am. Chem. Soc.* **1958**, 80, 6360.

<sup>136</sup> Kaiser, E. M.; Petty, J. D.; Knutson, P. L. A. *Synthesis* **1977**, 8, 509.

Among all the various types of 1,*n*-dianions, we are particularly interested in the reactivity of the 1,3-dianions.

### **1,3-Dianion synthons**

Dianions could be further organized according to their primary site of deprotonation whether being a carbon or heteroatom depending on the substrate nature. Thus, 1,3-dianions might be classified into 1,3-(C,C)-, 1,3-(N,C)-, 1,3-(O,C)- and 1,3-(S,C)-dianions.

We will focus on the literature concerning 1,3-(N,C)-dianions that is in direct relation with our project.

### **1,3-(N,C)-Dianion intermediates**

Such dianions are accessed by deprotonation at the nitrogen atom first followed by a carbanion formation. The reactivity of 1,3-carboxamides towards deprotonation is greatly affected by the nature of substituents on both nitrogen and carbon atoms. They are usually activated by being bonded to strong electron withdrawing groups, for example: carbonyl or aryl substituents.<sup>132d</sup>

N,C-Dianions could be sub-classified into amide dianions, amine dianions (including indole and pyrrole), amidine dianions, thioamide and sulfonamide dianions.<sup>132c</sup> Among all, we will only discuss the amide dianions that is directly involved in the Ugi bis-deprotonation.

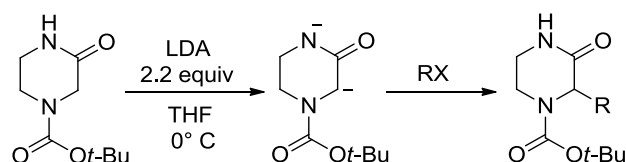
The synthetic use of these dianions has been the subject of many investigations. They are generally involved in two main types of reactions; the alkylation and the cycloaddition reactions.

### **1,3-Amide dianion alkylation reaction**

Regioselective C-3 alkylation of protected piperazinones using different electrophiles had been described by Kane.<sup>137</sup> This reaction confirmed the selectivity of dianions as no *N*- or *O*-alkylations were observed (Scheme II.6).

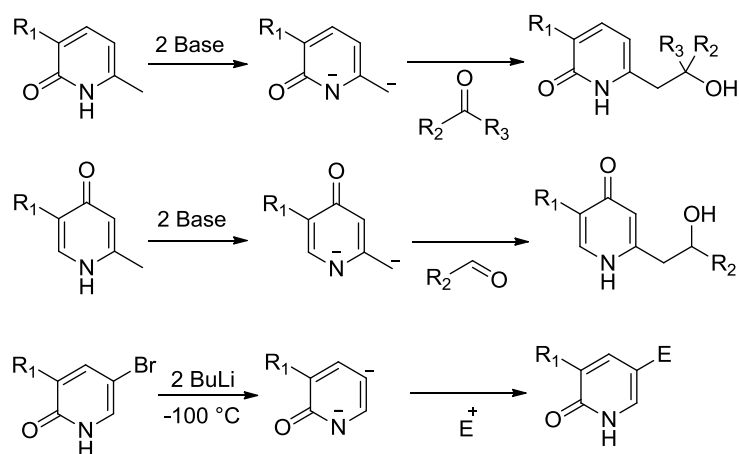
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<sup>137</sup> Kane, J. M.; Carr, A. A. *Tetrahedron Lett.* **1980**, 21, 3019.



**Scheme II.6. Regioselective C-3 alkylation of piperazinones.**

The group of Domagala<sup>138</sup> had published the acylation of cyclic amides as a way to access pyridones having various functional groups in the side chain. Pyridone dianions were also used to introduce substituents at position (5) in the ring, through a halogen lithium exchange at -100 °C leading to regioselective substitution upon reaction with electrophiles (Scheme II.7).<sup>139</sup>



**Scheme II.7. Amide dianions towards pyridone derivatives.**

Various electrophiles were examined against amide dianions. For example, reaction with nitroolefins gave nitroamides,<sup>140</sup> with nitriles afforded iminoamides<sup>141</sup> and with diazo compounds produced amidohydrazones<sup>142</sup> (Scheme II.8).

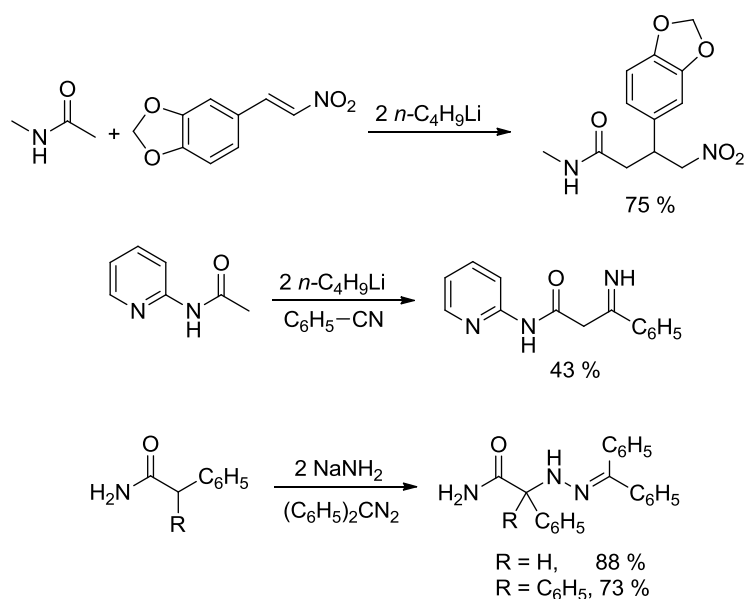
<sup>138</sup> DeJohn, D.; Domagala, J. M.; Kaltenbronn, J. S.; Krolls, U. *J. Heterocycl. Chem.* **1983**, 20, 1295.

<sup>139</sup> Domagala, J. M. *J. Heterocycl. Chem.* **1984**, 21, 1705.

<sup>140</sup> Ehrig, V.; Seebach, D. *Chem. Ber.* **1975**, 108, 1961.

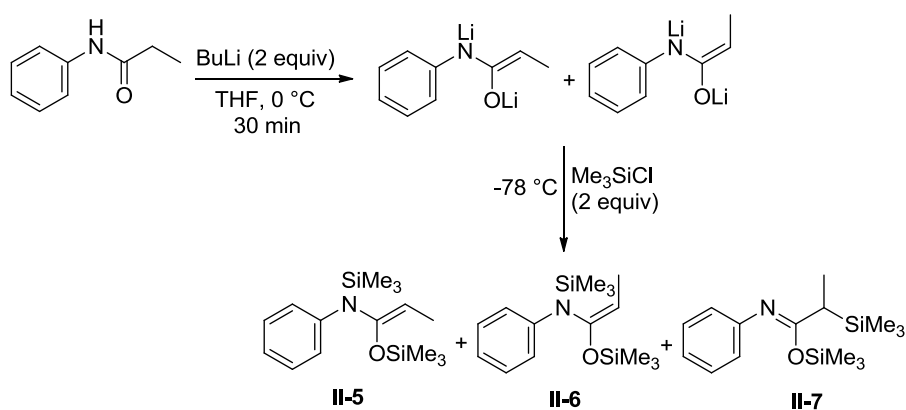
<sup>141</sup> Barnish, I. T.; Hauser, C. R.; Wolfe, J. F. *J. Org. Chem.* **1968**, 33, 2116.

<sup>142</sup> Kaiser, E. M.; Warner, C. D. *J. Organomet. Chem.* **1971**, 31, C17.



Scheme II.8. Amide dianion reaction with various electrophiles.

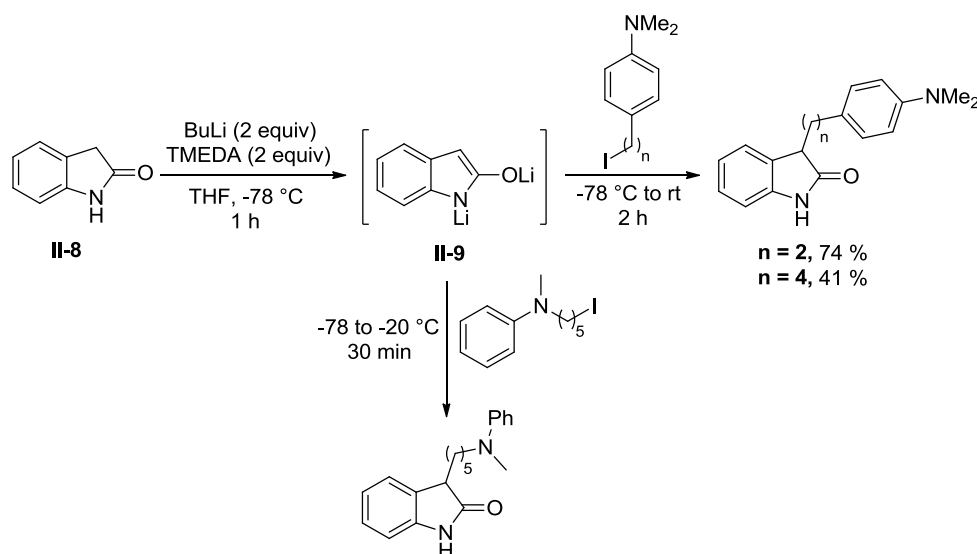
In 2005, Gullickson *et al.*<sup>143</sup> published a study to determine the predominant stereoisomer of dilithio derivative of propionanilide. They prepared the dianionic species upon treatment of propionanilide with 2.0 equiv. of BuLi in THF. The latter was trapped using 2.0 equiv. of trimethylsilyl chloride at -78 °C. Based on the <sup>1</sup>H-NMR spectrum, they obtained the *Z*-isomer **II-5**, *E*-isomer **II-6** and  $\alpha$ -silylated silyliminoester **II-7** in the ratio 19.5:1:1.7. Accordingly, they proved that the *Z*-isomer predominates as the only stereoisomer for the dilithiated propionanilide (Scheme II.9).



Scheme II.9. Trapping of propionanilide dianions.

<sup>143</sup> Gullickson, G. C.; Khan, M. A.; Walters, J. A.; Baughman, R. G.; Lewis, D. E. *Synthesis* **2005**, 17, 2906.

Recently, the alkylation of oxindole dianionic species to produce new oxindoles which suppress the oxidative stress-induced neuronal cell death, was reported by Furuta *et al.*<sup>144</sup> Where, the addition of 2.0 equiv. of BuLi to oxindole **II-8** afforded the dianion **II-9** which regioselectively reacts at C-3 position with alkyl halide (Scheme II.10).



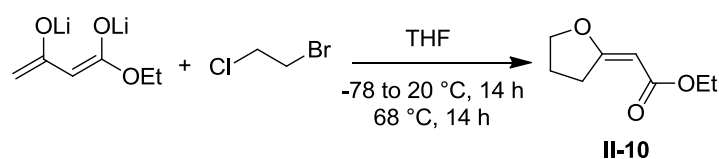
Scheme II.10. C-3 Alkylation of oxindole dianions.

### 1,3-Amide dianion cyclization reaction

There are two general mechanistic pathways for the cyclization reactions of 1,3-dianions.<sup>132e</sup>

#### Mechanism “A”

The dianion reacts as a bisnucleophile with two electrophilic positions of a biselectrophile, where the cyclic product is obtained in one step without the isolation of an intermediate. For example, the cyclization of ethyl acetoacetate with 1-bromo-2-chloroethane affording 2-alkylidenetetrahydrofuran **II-10** (Scheme II.11).

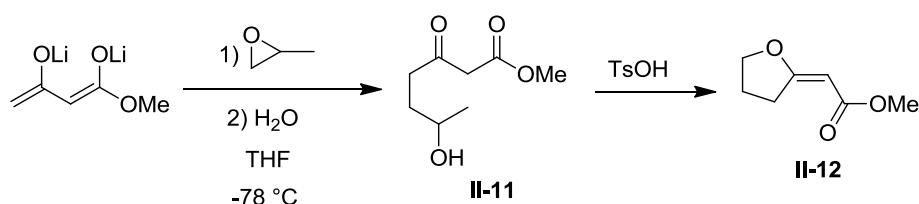


Scheme II.11. Cyclization following Mechanism A.

<sup>144</sup> Furuta, K.; Kawai, Y.; Mizuno, Y.; Hattori, Y.; Koyama, H.; Hirata, Y. *Bioorg. Med. Chem. Lett.* **2017**, 27, 4457.

### Mechanism “B”

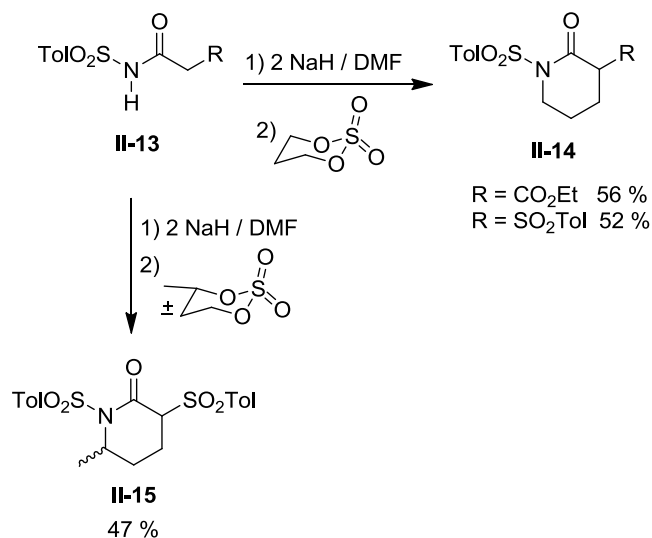
The dianion is reacting as a mono nucleophile with a mono electrophile, leading to a monoanion that subsequently attacks a functional group in the former dianion moiety. In this case, the intermediate should be isolated and the cyclization reaction is performed as a single step. For example, the cyclization of methyl acetoacetate with propenoxide resulting in the formation of the open chain product **II-11**. The product **II-11**, upon the addition of acid, was cyclized into 2-alkyldienetetrahydrofuran **II-12** (Scheme II.12).



Scheme II.12. Cyclization following Mechanism B.

### Amide Dianion Cyclization

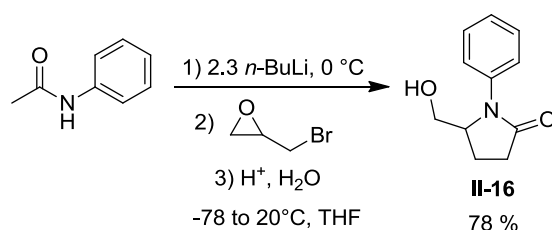
Gallagher<sup>145</sup> reported the reaction of the amide **II-13** with 1,3-cyclic sulfates as a biselectrophile in presence of sodium hydride as a base in DMF affording the  $\delta$ -lactams **II-14** and **II-15** (Scheme II.13). The mechanism involves regioselectively C- then N-alkylation, where the C-alkylation proceeds smoothly at room temperature, while the intramolecular N-alkylation requires refluxing for one day.



Scheme II.13. Cyclization of amide dianion with cyclic sulfates.

<sup>145</sup> Eskici, M.; Gallagher, T. *Synlett* **2000**, 9, 1360.

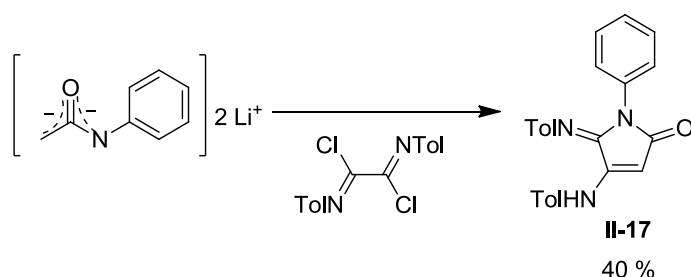
The reaction of acetanilide with epibromohydrin in presence of *n*-butyllithium as a base in THF afforded 5-hydroxymethylpyrrolidin-4-one **II-16** (Scheme II.14).<sup>146</sup> The cyclization proceeds via the regioselective attack of the carbon atom of the dianionic species onto the bromide group, followed by the attack of the nitrogen atom on the epoxide. It could also be considered as an attack of the dianion on the epoxide, followed by “Payne rearrangement”.



**Scheme II.14.** Cyclization of *N*-phenylacetamide dianion with epibromohydrin.

The regioselectivity of the cyclization results from the higher nucleophilicity of the nitrogen atom with respect to the oxygen atom. The application of this reaction was extended to other 1,3-amide dianions such as: *N*-trimethylsilylacetic amide, propionic anilide and thioacetic anilide. It was used as well to prepare axially chiral  $\gamma$ -butyrolactams in racemic form.<sup>136</sup>

Langer described the cyclization of amide dianions with oxalic acid-bis(imidoyl)dichlorides affording  $\gamma$ -iminotetramic acid amides **II-17** again by regioselective *C,N*-cyclization (Scheme II.15).<sup>147</sup>



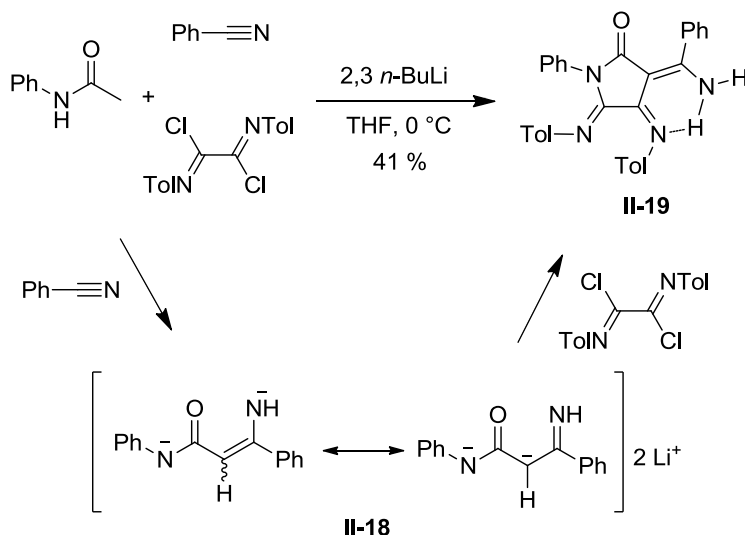
**Scheme II.15.** Cyclization of acetanilide diamide with bis(imidoyl)dichlorides.

<sup>146</sup> (a) Curran, D. P.; Qi, H.; Geib, S. J.; DeMello, N. C. *J. Am. Chem. Soc.* **1994**, *116*, 3131. (b) Fujita, M.; Kitagawa, O.; Izawa, H.; Dobashi, A.; Fukaya, H.; Taguchi, T. *Tetrahedron Lett.* **1999**, *41*, 1941, and references therein. (c) Kitagawa, O.; Fujita, M.; Kohriyama, M.; Hasegawa, H.; Taguchi, T. *Tetrahedron Lett.* **2000**, *41*, 8539. (d) Godfrey, C. R. A.; Simpkins, N. S.; Walker, M. D. *Synlett* **2000**, *3*, 388. (e) Freifeld, I.; Armbrudt, H.; Langer, P. *Synthesis* **2006**, *11*, 1807.

<sup>147</sup> Langer, P.; Döring, M.; Görls, H.; Beckert, R. *Liebigs Ann./Receuil* **1997**, 2553.



Based on the previous results, one-pot reaction of amide dianions with nitriles and oxalic acid-bis(imido)l)dichlorides was developed. The reaction starts with the attack of the dianion onto the nitrile forming the intermediate **II-18**. A subsequent regioselective C,N-cyclization takes place giving the final product **II-19** (Scheme II.16).<sup>148</sup>



Scheme II.16. One-pot reaction of acetanilide dianion, nitriles and oxalic acid-bis(imido)l)dichlorides.

### II.3 Ketones in Ugi reaction

Despite the fact that Ugi reaction is widely applicable among various known MCRs, it still has some limitations. Upon screening the literature, we can clearly find many examples of Ugi product using aldehyde as the carbonyl component, but when it comes to ketones, only few examples are described.

Ugi reactions involving simple aliphatic ketones as the carbonyl moiety are known to proceed smoothly with high yields for example using: acetone, cyclopentanone and cyclohexanone.<sup>149</sup> *N*-alkyl and *N*-aryl piperidones as well are considered as good carbonyl partners affording Ugi adducts in good yields.<sup>150</sup>

<sup>148</sup> (a) Langer, P.; Döring, M. *Synlett* **1998**, 4, 399. (b) Langer, P.; Döring, M.; Schreiner, P. R.; Görls, H. *Chem. Eur. J.* **2001**, 7, 2617.

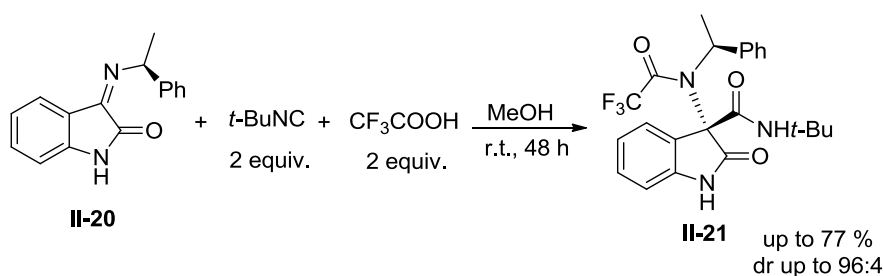
<sup>149</sup> See for example: (a) Mironov, M. A.; Tokareva, M. I.; Ivantsova, M. N.; Mokrushin, V. S. *Russ. J. Org. Chem.* **2004**, 40, 847. (b) Kalinski, C.; Umkehrer, M.; Gonnard, S.; Jager, N.; Ross, G.; Hiller, W. *Tetrahedron Lett.* **2006**, 47, 2041.

<sup>150</sup> (a) Beck, B.; Hess, S.; Dömling, A. *Bioorg. Med. Chem. Lett.* **2000**, 10, 1701. (b) Dömling, A.; Achatz, S.; Beck, B. *Bioorg. Med. Chem. Lett.* **2007**, 17, 5483. (c) Habashita, H.; Kokubo, M.; Hamano, S.; Hamanaka, N.; Toda, M.; Shibayama, S.; Tada, H.; Sagawa, K.; Fukushima, D.; Maeda, K.; Mitsuya, H. *J. Med. Chem.* **2006**, 49, 4140.

However in order to introduce aromatic ketones as the carbonyl partner in Ugi reaction, one of the following strategies is followed:

- a) Using previously prepared imine.

Ugi 3-component reaction is performed involving ketimine, acid and isocyanide. For instance, using isatin-derived ketimine **II-20** in the synthesis of chiral 3,3-disubstituted 3-aminoxindoles **II-21** (Scheme II.17).<sup>151</sup> Where, the former was prepared separately by reacting isatin with (S)-phenyl ethylamine in the presence of  $\text{MgSO}_4$ .<sup>152</sup> Their trials to achieve a 4-component Ugi reaction using isatin failed to give the Ugi adduct, despite adding  $\text{MgSO}_4$  to enhance the ketimine formation. In this case, the presence of a further electron withdrawing group (amide group) conjugated to the imine, enhances its electrophilicity towards the nucleophilic addition of isocyanides.



Scheme II.17. Isatin derived Ketimine in Ugi 3CR.

- b) Using  $\gamma$ -ketoacids as a bifunctional precursor.

Intramolecular Ugi 3-component reaction is carried out involving  $\gamma$ -ketoacid, isocyanide and amine. For example, using 3-benzoylpropionic acid in the synthesis of five-membered lactam ring under microwave conditions (Scheme II.18).<sup>153</sup> Early trials using classical Ugi conditions afforded from 20 to 75 % of target compound after 48 hours of stirring. Heating was required sometimes to raise the reaction yield.<sup>154,155</sup> In this case, the reaction proceeds due to the intramolecular activation by the carboxylic acid group.

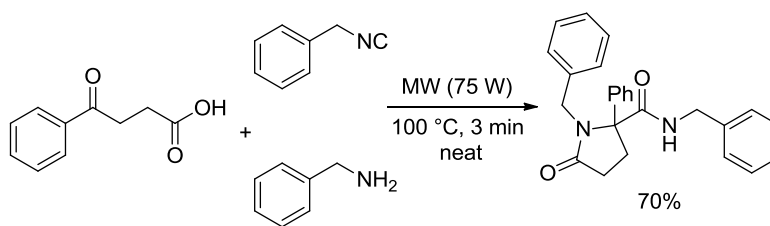
<sup>151</sup> Lesma, G.; Meneghetti, F.; Sacchetti, A.; Stucchi, M.; Silvani, A. *Beilstein J. Org. Chem.* **2014**, *10*, 1383.

<sup>152</sup> Sacchetti, A.; Silvani A. Gatti, F. G.; Lesma, G.; Pilati, T.; Trucchi, B. *Org. Biomol. Chem.* **2011**, *9*, 5515.

<sup>153</sup> Jida, M.; Malaquin, S.; Deprez-Poulain, R.; Laconde, G.; Deprez, B. *Tetrahedron Lett.* **2010**, *51*, 5109.

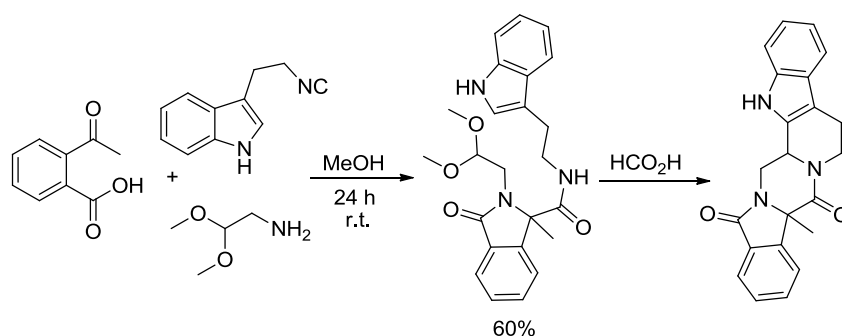
<sup>154</sup> Harriman, G. C. B. *Tetrahedron Lett.* **1997**, *38*, 5591.

<sup>155</sup> (a) Short, K. M.; Mjalli, A. M. M. *Tetrahedron Lett.* **1997**, *38*, 359. (b) Short, K. M.; Ching, B. W.; Mjalli, A. M. M. *Tetrahedron* **1997**, *19*, 6653.



**Scheme II.18. Intramolecular Ugi 3-CR involving  $\gamma$ -ketoacid.**

Another widely studied example, is utilizing 2-acetylbenzoic acid as  $\gamma$ -ketoacid to synthesize the bicyclic isoindolin-1-one derivatives.<sup>156</sup> We selected the one reported by Dömling *et al.* in 2010.<sup>157</sup> He published an intramolecular Ugi 3-CR/Pictet Spengler cascade towards highly complex polycyclic indole derivatives (Scheme II.19). Previously, Ivar Ugi mentioned that the reaction requires reflux for 48 hours in order to get the Ugi adduct, otherwise the reaction will stop at the imine formation step.<sup>158</sup>



**Scheme II.19. Polycyclic indole alkaloid-type through Ugi 3CR.**

The above described methods have a general drawback of losing the diversity of Ugi reaction by shifting from 4-component to 3-component Ugi type, in addition to the commercial limited availability of the starting materials.

An alternative approach to ketone-derived Ugi adducts using different set of components was reported by Simoneau *et al.*<sup>159</sup> They suggested a four component reaction between nitriles, organometallic reagents (organolithium or Grignard reagents), carboxylic

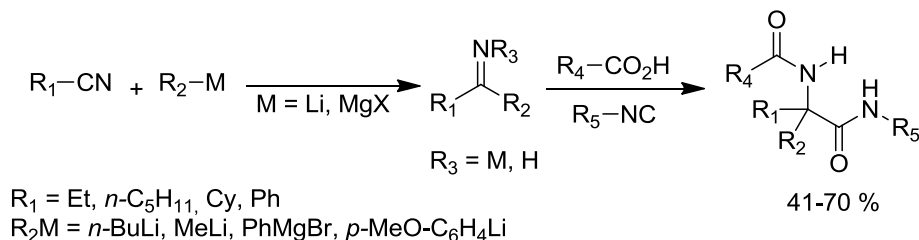
<sup>156</sup> See for example: (a) Xu, Z.; Ayaz, M.; Cappelli, A. A.; Hulme, C. *ACS Comb. Sci.* **2012**, *14*, 460. (b) Chen, Z.-Z.; Zhang, J.; Tang, D.-Y.; Xu, Z.-G. *Tetrahedron Lett.* **2014**, *55*, 2742. (c) Macsari, I.; Besidski, Y.; Csajenyik, G.; Nilsson, L. I.; Sandberg, L.; Yngve, U.; Ahlin, K.; Bueters, T.; Eriksson, A. B.; Lund, P.-E.; Venyike, E.; Oerther, S.; Blakeman, K. H.; Luo, L. Arvidsson, P. I. *J. Med. Chem.* **2012**, *55*, 6866.

<sup>157</sup> Wang, W.; Herdtweck, E.; Dömling, A. *Chem. Commun.* **2010**, *46*, 770.

<sup>158</sup> Hanusch-Kompa, C.; Ugi, I. *Tetrahedron Lett.* **1998**, *39*, 2725.

<sup>159</sup> Simoneau, C. A.; George, E. A.; Ganem, B. *Tetrahedron Lett.* **2006**, *47*, 1205.

acids and isocyanides affording Ugi products in moderate yields (Scheme II.20). In this case, the yields obtained when either  $R_1$  or  $R_2$  = aryl groups were low, ranging from 41 to 45 %.



Scheme II.20. Ugi reaction based on the reaction of organometallic reagents with nitriles.

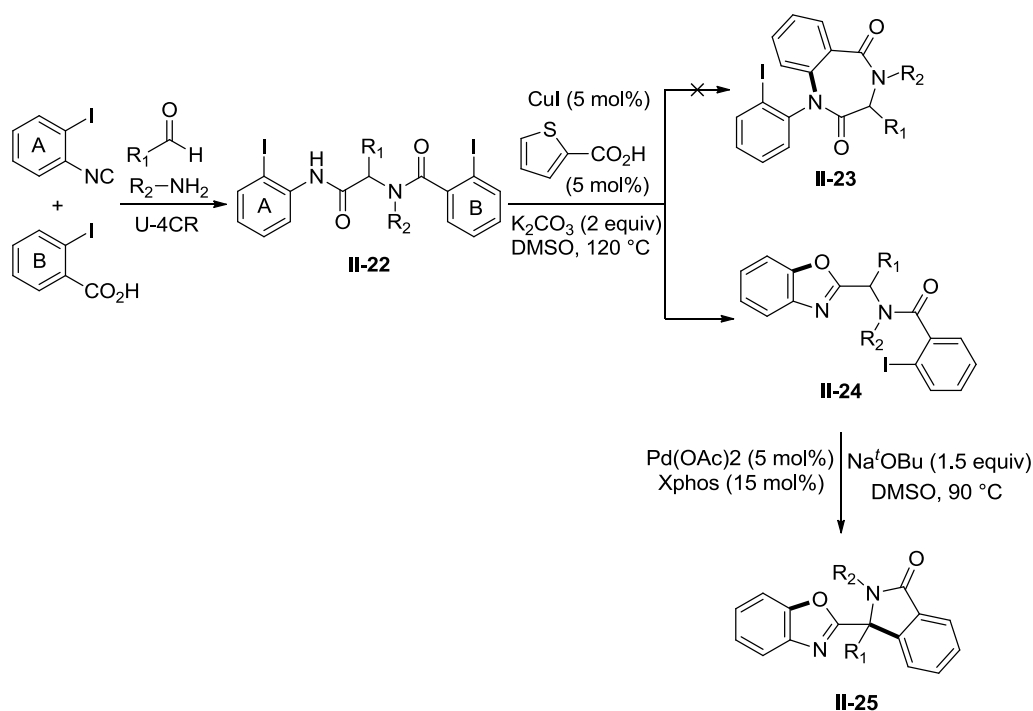
## II.4 Intramolecular/Intermolecular Ugi post-condensation

Intramolecular post-condensation reactions at the peptidyl C-H position of aldehyde-derived Ugi adducts proceed more readily than the intermolecular ones. The latter is known to be difficult due to the steric bulkiness around such position. There are many examples in the literature dealing with such intramolecular reactions. In contrast, the intermolecular ones are rarely described. Hereinafter, we are discussing some of them.<sup>160</sup>

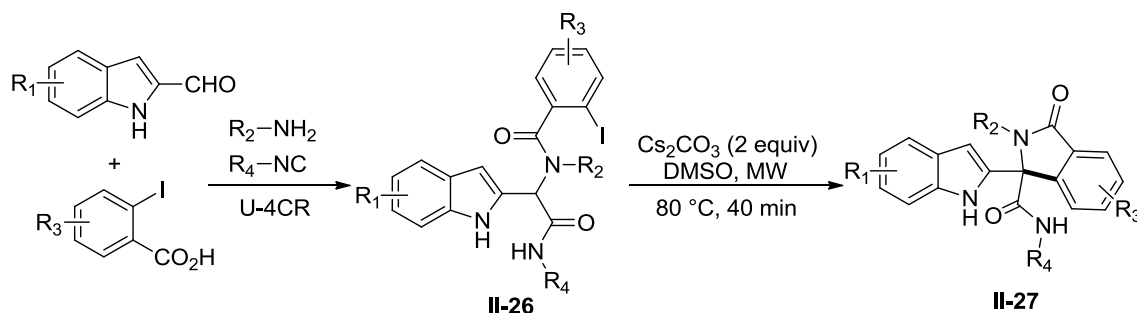
A sequential intramolecular *O*- and *C*-arylation via two consecutive metal-catalyzed reactions was documented by Zhu and his co-workers.<sup>161</sup> Using Ugi adduct **II-22** possessing two aryl iodide moieties, a Cu-catalyzed reaction was carried out resulting in a regioselective *O*-arylation affording benzoxazole **II-24** followed by a Pd-catalyzed intramolecular process leading to a *C*-arylation of peptidyl C-H position yielding benzoxazolyloisoindolinone **II-25**. The benzodiazepinedione **II-23** accessed through intramolecular *N*-arylation was not observed (Scheme II.21). They concluded that the oxidative addition of aryl iodide (ring A) to Cu(I) occurred preferentially over ring B despite being electronically poorer than ring A.

<sup>160</sup> For more examples on Ugi-Intramolecular arylations, see review: Sharma, U. K.; Sharma, N.; Vachhani, D. D.; Van der Eycken, E. V. *Chem. Soc. Rev.* **2015**, *44*, 1836.

<sup>161</sup> Salcedo, A.; Neuville, L.; Zhu, J. *J. Org. Chem.* **2008**, *73*, 3600.

Scheme II.21. A sequential Cu/Pd-catalyzed intramolecular *O*- and *C*-arylation of Ugi product.

Moreover, the isoindolinone ring was established afterwards through a metal-free approach to activate the  $sp^3$ -hybridized C-H bond. The group of Liu<sup>162</sup> described an intramolecular *C*-arylation of indole-aldehyde derived Ugi **II-26** using 2.0 equiv. of  $Cs_2CO_3$  in DMSO under microwave irradiation affording **II-27** in 79 to 94 % yield (Scheme II.22).

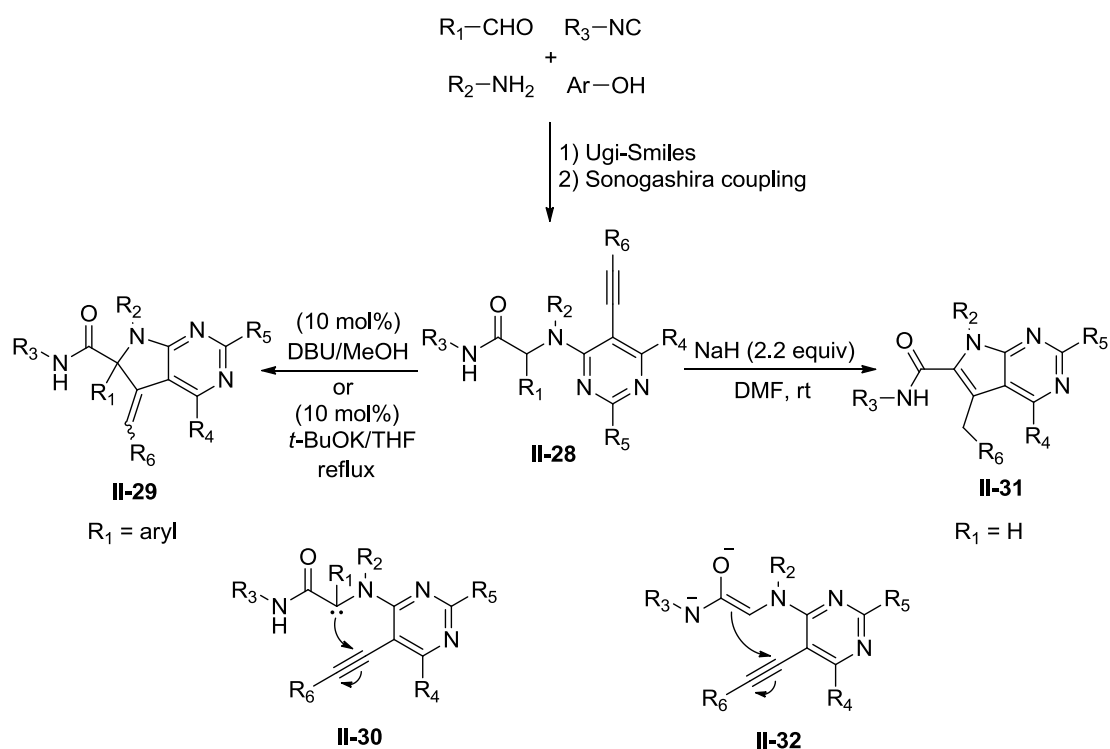
Scheme II.22. Metal free intramolecular *C*-arylation of  $sp^3$ -hybridized C-H bond in Ugi adduct.

One of the remarkable examples applying the chemistry of dianions to enhance the intramolecular post-condensations of Ugi Smiles adducts was performed by Simon Wagschal during his PhD work.<sup>163</sup> He described an Ugi Smiles/Sonogashira/Cyclization strategy affording pyrrolo[2,3-*d*]pyrimidines derivatives. He prepared the adduct **II-28** by Ugi-Smiles

<sup>162</sup> Zhang, L.; Zhao, F.; Zheng, M.; Zhai, Y.; Liu, H. *Chem. Commun.* **2013**, 49, 2894.

<sup>163</sup> (a) El Kaïm, L.; Grimaud, L.; Wagschal, S. *J. Org. Chem.* **2010**, 75, 5343. (b) Thesis of Simon Wagschal, “Synthèse d'hétérocycles et réactions pallado-catalysées”, Ecole polytechnique, **2010**.

coupling followed by a Sonogashira reaction, which then undergoes intramolecular cyclization under basic conditions. Using  $R_1$  = aryl group, only catalytic amounts of either DBU or *t*-BuOK were sufficient for the intramolecular cyclization leading to pyrrolidinopyrimidines **II-29** through the stabilized intermediate **II-30**. While using Ugi-Smiles product prepared from formaldehyde, which obviously results in less acidic adduct, 2.0 equiv. of NaH were needed for the cyclization to occur forming pyrrolo [2,3-*d*] pyrimidines **II-31**. A suggested plausible pathway starts with the deprotonation of amide forming a poorly nucleophilic anion that upon further deprotonation at the peptidyl C-H position results in a strongly nucleophilic dianion intermediate **II-32** which could undergo 5-*exo-dig* cyclization at room temperature (Scheme II.23).

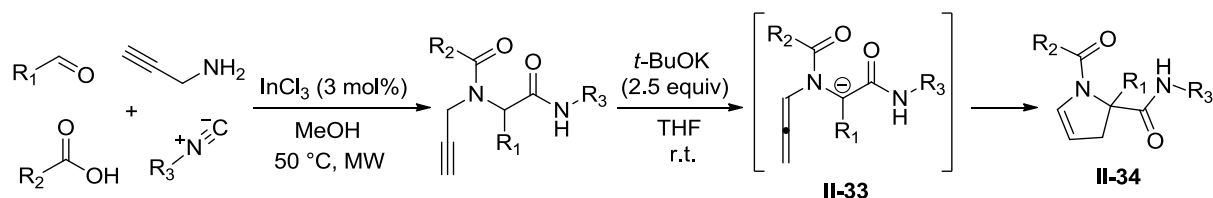


Scheme II.23. Ugi smiles/Sonogashira/Intramolecular cyclization cascade.

Another interesting example was reported by Miranda *et al.* in 2012.<sup>164</sup> They displayed a two-step synthesis protocol for 2,3-dihydropyrroles via 5-*endo* cycloisomerization of Ugi propargyl products. When the latter were treated with 2.5 equiv. of *t*-BuOK, a base-induced isomerization took place affording allenamide intermediates **II-33** which then underwent cyclization affording 2,3-dihydropyrrole derivatives (Scheme II.24). The use of 1.0 equiv of *t*-

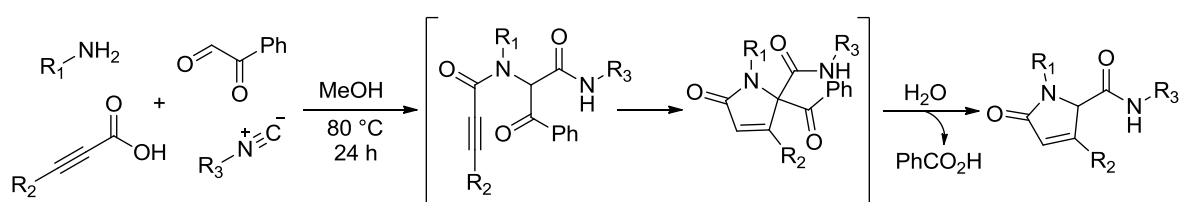
<sup>164</sup> Polindara-García, L. A.; Miranda, L. D. *Org. Lett.* **2012**, *14*, 5408.

BuOK resulted only in traces of the desired product **II-34**. Having *o*-bromo substituent in the aldehyde moiety hindered the cyclization and the reaction stopped at the isomerization level giving the corresponding allenamide. Although they did not mention that the mechanism includes an amide dianion intermediate, it appears to be the most logical explanation for the need of 2.5 equiv. of base according to our study.



**Scheme II.24.** Ugi propargyl 5-*endo* cycloisomerization.

In 2014, Van der Eycken *et al.*<sup>165</sup> reported a cascade transformation involving Ugi reaction/5-*endo-dig* carbocyclization/retro-Claisen fragmentation. Such transformation was based on the use of phenyl glyoxal as the carbonyl source in Ugi reaction that could readily undergo enol-isomerization leading to cyclization. This cyclization was enhanced by the Michael acceptor nature of a triple bond conjugated with an amide group as well as the presence of an electron-withdrawing group at the enolizable position. This is followed by retro-Claisen fragmentation involving the loss of benzoyl group (Scheme II.25). When the reaction was carried out using paraformaldehyde, only the acyclic Ugi adduct was recovered. This observation proved the limitation of such transformation to glyoxal derivatives.



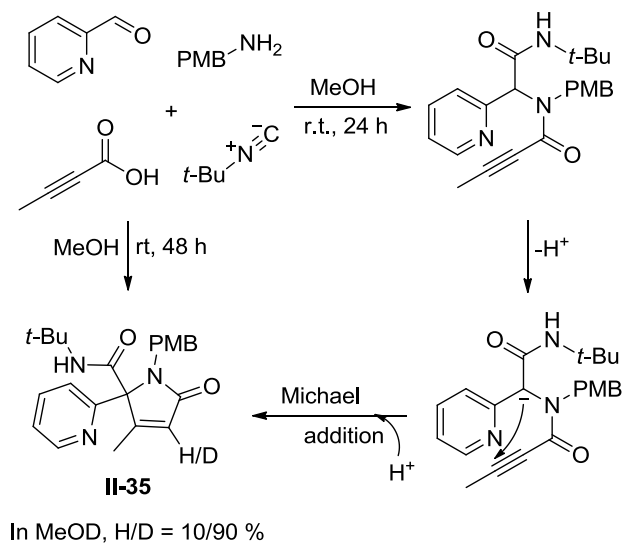
**Scheme II.25.** Ugi cascade intramolecular 5-*endo-dig* cyclization.

Later on, they published another Ugi/Michael addition cascade that provided  $\alpha,\beta$ -unsaturated  $\gamma$ -lactams based on heterocyclic aldehydes as the carbonyl moiety.<sup>166</sup> In order to rationalize the reaction mechanism, they carried out the Ugi reaction in methanol- $d_4$ . They

<sup>165</sup> Peshkov, A. A.; Peshkov, V. A.; Li, Z.; Pereshivko, O. P.; Van der Eycken, E. V. *Eur. J. Org. Chem.* **2014**, 29, 6390.

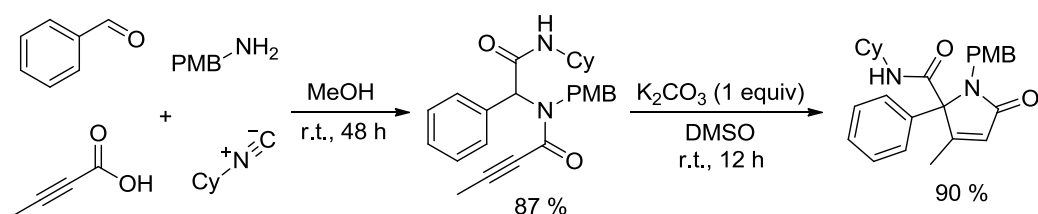
<sup>166</sup> Li, Z.; Kumar, A.; Peshkov, A.; Van der Eycken, E. V. *Tetrahedron Lett.* **2016**, 57, 754.

observed the incorporation of deuterium in the endocyclic double bond of  $\gamma$ -lactam **II-35**, thus they supposed that the pyridine acts as the base for the Michael addition step (Scheme II.26).



**Scheme II.26.** Suggested reaction mechanism for Ugi/Michael addition cascade.

Nonetheless, the reaction scope was successfully extended to include aromatic aldehydes by treating the Ugi adduct with 1.0 equiv. of  $K_2CO_3$  in DMSO (Scheme II.27).

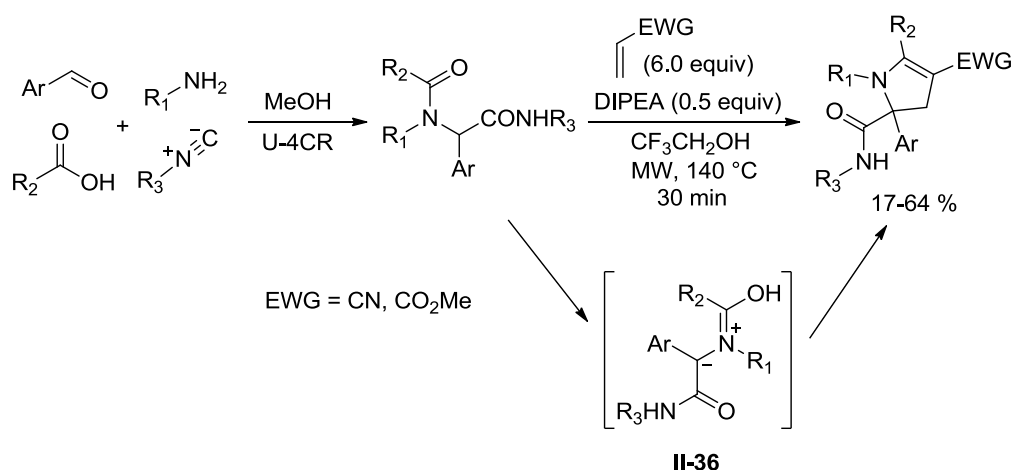


**Scheme II.27.** Extended Ugi/Michael addition cascade to aromatic aldehydes.

Switching to the relatively difficult intermolecular reactions at the peptidyl C-H position in aldehyde-based Ugi adducts, more drastic conditions are required for such reactions to proceed. For example, the [3+2] cycloaddition of Ugi adducts derived from aromatic aldehydes and Michael acceptors reported by Ben Abdessalam *et al.* in 2014.<sup>167</sup> The reaction was performed in presence of 0.5 equiv of DIPEA and excess amount of Michael acceptor in trifluoroethanol under microwave irradiations. They proposed a mechanism that involved an azomethine ylide intermediate **II-36** (Scheme II.28).

<sup>167</sup> Ben Abdessalam, A.; Abderrahim, R.; Agrebi, A.; Dos Santos, A.; El Kaïm, L.; Komesky, A. *Chem. Commun.* **2015**, 51, 1116.





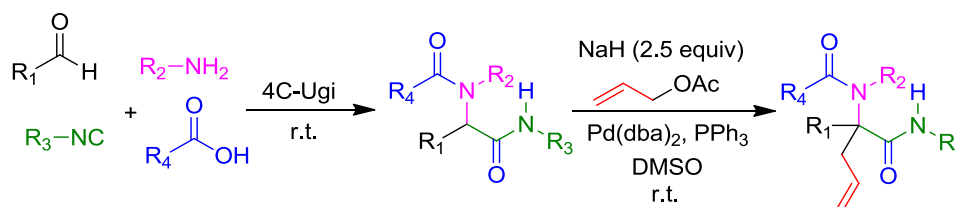
Scheme II.28. Intermolecular [3+2] cycloaddition of Ugi product with Michael acceptor.

Consequently, our target was to develop a simple protocol allowing the intermolecular reaction at the peptidyl C-H position in Ugi adducts to proceed smoothly without the need of such high temperature and large excess of reagents.

## II.5 Ugi/Intermolecular Alkylation cascade

### Presentation of our strategy

We present a new protocol for the intermolecular alkylation of peptidyl C-H position in aldehyde-derived Ugi adducts by means of 1,3-amide dianion intermediates. Tsuji-Trost reaction was chosen as an example for the alkylation reaction. The allylation reaction was carried out using 2.5 equiv. of NaH as a base, allyl acetate and palladium source in DMSO (Scheme II.29). Such strategy allowed us to prepare C-allylated Ugi products in moderate to excellent yields (40-96 %).

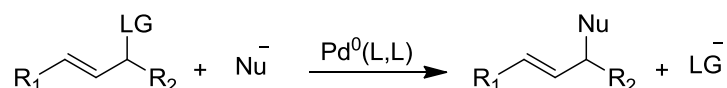


Scheme II.29. Intermolecular C-allylation of Ugi adducts.

Before presenting the results obtained, a brief bibliography concerning Tsuji-Trost reaction is presented.

## II.6 Tsuji-Trost reaction

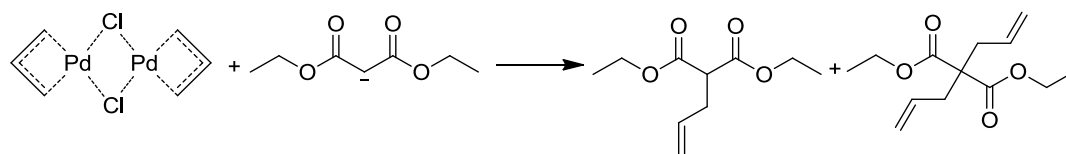
It is a palladium-catalyzed nucleophilic substitution reaction involving an allylic substrate that possesses a leaving group (Scheme II.30).<sup>168</sup> It is widely applied in medicinal chemistry and natural product synthesis due to its employment in constructing carbon-carbon, carbon-oxygen and carbon-nitrogen bonds.



Scheme II.30. Representation of Tsuji-Trost reaction.

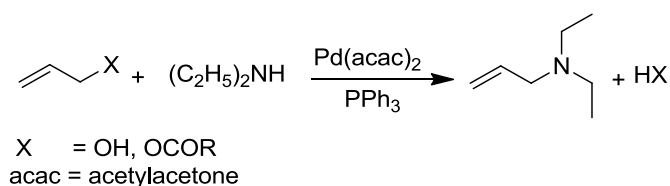
### Background

Tsuji *et al.* highlighted the first allylic alkylation reaction in 1965.<sup>169</sup> They obtained a mixture of ethyl allylmalonate and ethyl diallylmalonate as a result of the allylation of sodium salt of diethyl malonate using  $\pi$ -allylpalladium chloride dimer (Scheme II.31).



Scheme II.31. Mono and diallylation of ethyl malonate.

In 1970, the reaction was modified by Walker's group to use only a catalytic amount of palladium complex in order to trigger the reaction (Scheme II.32).<sup>170</sup>



Scheme II.32. Catalytic allylation of amines.

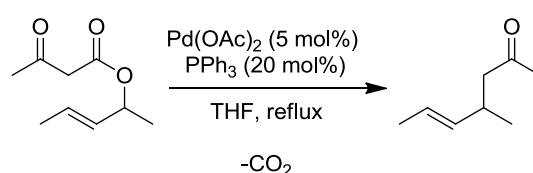
<sup>168</sup> For some early reviews see: (a) Consiglio, G.; Robert, M.; Waymouth, M. *Chem. Rev.* **1989**, 89, 257. (b) Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, 3, 1089. (c) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, 96, 395.

<sup>169</sup> Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett.* **1965**, 49, 4387.

<sup>170</sup> Atkins, K. E.; Walker, W. E.; Manyk, R. M. *Tetrahedron Lett.* **1970**, 3821.

The Trost group<sup>171</sup> then developed asymmetric variations of this reaction thanks to the application of chiral ligands. Chiral ligands are known to enhance both the enantioselectivity and diastereoselectivity under mild conditions, which contributed greatly to expand the application of this reaction.

By 1980, Tsuji *et al.*<sup>172</sup> applied the palladium catalyzed allylation reaction to various allylic esters of acetoacetic acid. The latter undergoes a rearrangement reaction accompanied by the elimination of carbon dioxide to provide  $\gamma,\delta$ -unsaturated methyl ketones in almost quantitative yields using catalytic amount of palladium complex (Scheme II.33).



**Scheme II.33. Palladium catalyzed rearrangement of allylic esters.**

### Reaction mechanism

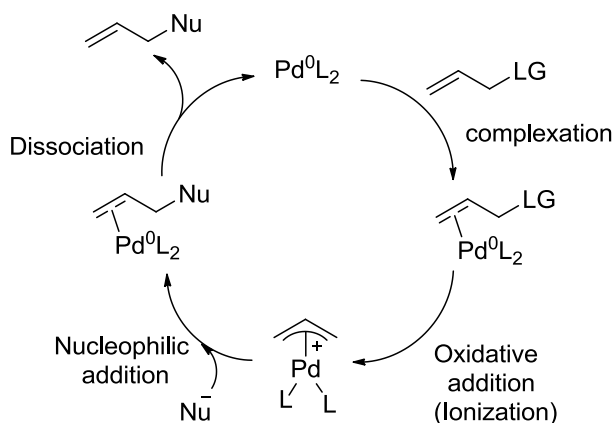
It was initially proposed that the palladium complexes the double bond of the allyl group. Then an oxidative addition step would take place forming a  $\eta^3$ -allyl cationic intermediate. This is followed by a nucleophilic addition on the latter intermediate resulting in a  $\eta^2$ -allylic complex in which the palladium (0) is coordinated to the double bond. Finally, dissociation of the active species would occur to release both the substitution product and the palladium which gets involved again in the catalytic cycle (Scheme II.34).<sup>173,174</sup>

<sup>171</sup> Trost, B. M.; Strege, P. E. *J. Am. Chem. Soc.* **1977**, 1649.

<sup>172</sup> Shimizu, I.; Yamada, T.; Tsuji, J. *Tetrahedron Lett.* **1980**, 21, 3199.

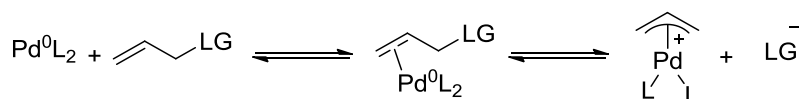
<sup>173</sup> Yamamoto, Y.; Akimoto, M.; Saito, O.; Yamamoto A. *Organometallics* **1986**, 5, 1559.

<sup>174</sup> Kurosawa, H. *J. Organomet. Chem.* **1987**, 334, 243.



**Scheme II.34.** Early proposed mechanism for palladium catalyzed allylation reaction.

A mechanistic study, proposed afterwards by Jutand *et al.*, demonstrated that the reaction of allylic carboxylates<sup>175</sup> and carbonates<sup>176</sup> with palladium (0) complexes was reversible and took place in 2 steps. This occurs regardless the nature of ligands, whether monodentate or bidentate phosphines are employed (Scheme II.35).



**Scheme II.35.** Palladium-catalyzed allylation mechanism proposed by Jutand.

However, only the kinetic studies were able to prove the existence of the  $\eta^2$ -allylic complex.<sup>177</sup>

## Reaction parameters

There are various parameters controlling the reaction progress and stereochemistry as well as the regioselectivity.

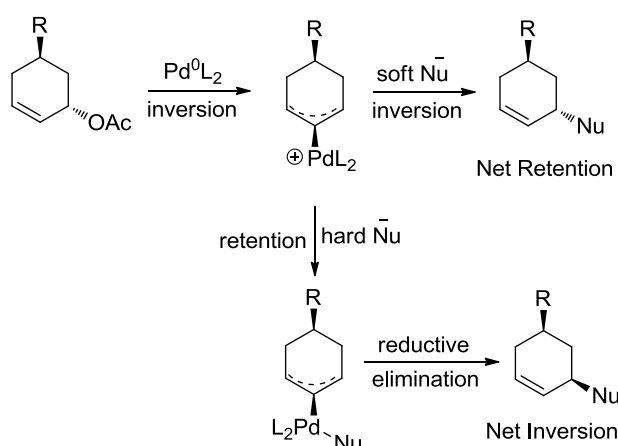
<sup>175</sup> (a) Amatore, C.; Jutand, A.; Meyer, G.; Mottier, L. *Chem. Eur. J.* **1999**, 5, 466. (b) Amatore, C.; Gamez, S.; Jutand, A.; *Chem. Eur. J.* **2001**, 7, 1273. (c) Amatore, C.; Gamez, S.; Jutand, A.; Meyer, G.; Mottier, L. *Electrochimica Acta* **2001**, 46, 3237. (d) Agenet, N.; Amatore, C.; Gamez, S.; Gérardin, H.; Jutand, A.; Meyer, G.; Orthwein, C. *ARKIVOC* **2002**, 92.

<sup>176</sup> Amatore, C.; Gamez, S.; Jutand, A.; Meyer, G.; Moreno-Mañas, M.; Morral, L.; Pleixats, R. *Chem. Eur. J.* **2000**, 6, 3372.

<sup>177</sup> Amatore, C.; Gamez, S.; Jutand, A. *Chem. Eur. J.* **2001**, 7, 1273.

### (1) Nature of the nucleophile

They are generated in situ as a result of deprotonation using a base. Nucleophiles, used in Tsuji-Trost reaction, are divided into two categories; “hard” and “soft” nucleophiles depending on the pKa of their conjugate acids. Hard nucleophiles are accompanied by conjugate acids of pKa higher than 25, whereas for the soft nucleophiles such as: malonates, their conjugate acids have pKa lower than 25.<sup>178</sup> This criterion affects the stereoselectivity of the product, whereas soft or stabilized nucleophiles cause inversion of configuration of the  $\pi$ -allyl cationic complex since they attack the carbon of the allyl group. While hard or unstabilized nucleophiles, lead to retention of configuration of the complex as they attack the metal center via transmetalation followed by reductive elimination.<sup>179</sup> In both cases, the oxidative addition step of palladium takes place with inversion of configuration (Scheme II.36).



Scheme II.36. Stereochemistry of Tsuji-Trost product using hard and soft nucleophiles.

### (2) Allylic reagent

Both cyclic and acyclic substrates are successfully employed in the reaction. The most commonly used substrates are the allylic acetates. Moreover, several nucleophiles are also utilized such as: halogens,<sup>180</sup> epoxides<sup>181</sup> or carbonates<sup>182</sup>. In case of using allyl carbonates,

<sup>178</sup> Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc.* **2008**, *130*, 14092.

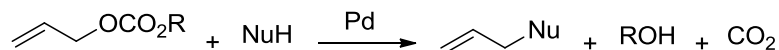
<sup>179</sup> Trost, B. M.; Verhoeven, T. R.; Fortunak, J. M. *Tetrahedron Lett.* **1979**, *20*, 2301.

<sup>180</sup> Sheffy, F. K.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 7173.

<sup>181</sup> Tsuji, J. *Tetrahedron* **1986**, *42*, 4361.

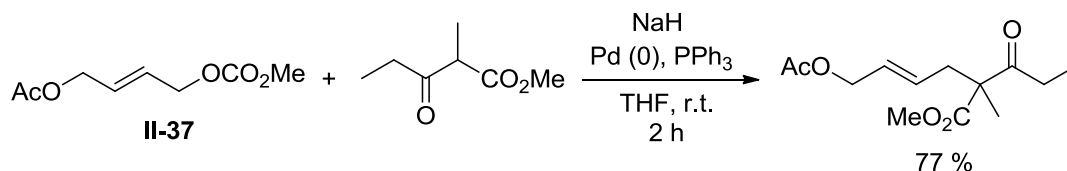
<sup>182</sup> (a) Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, K.; Sugiura, T.; Takahashi, K. *J. Org. Chem.* **1985**, *50*, 1523. (b) Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y. *Tetrahedron Lett.* **1982**, *23*, 4809.

the carbonate group undergoes decarboxylation providing alkoxy anion which will play the role of the base to deprotonate the nucleophile (Scheme II.37).



**Scheme II.37. General representation for allyl carbonate reaction.**

In case of using allylic reagent that possess two leaving groups, the substitution would take place selectively at the more reactive site for the reaction. For instance, when using the allyl substrate **II-37**, nucleophilic substitution took place at the carbon attached to the more reactive carbonate group affording selectively single product with *E*-configuration (Scheme II.38).



**Scheme II.38. Regioselective nucleophilic substitution of bifunctional allyl substrate.**

### (3) Metal catalyst

A wide variety of metal complexes had been employed in such type of reaction such as: nickel,<sup>183</sup> palladium,<sup>184</sup> iridium,<sup>185</sup> platinum,<sup>186</sup> rhodium,<sup>187</sup> iron,<sup>188</sup> ruthenium,<sup>189</sup> molybdenum<sup>190</sup> and tungsten complexes.<sup>191</sup>

The choice of the metal complex affects greatly the reaction's regioselectivity. For instance, the reaction of 2-methyl-propenyl acetate with PhMgCl in the presence of NiCl<sub>2</sub>/dppf allows substitution selectively at the most substituted carbon atom, while using palladium catalyst (PdCl<sub>2</sub>/dppf) substitution is observed at the least substituted carbon atom.

<sup>183</sup> (a) Hiyama, T.; Wakasa, N. *Tetrahedron Lett.* **1985**, 26, 3259. (b) Sha, S.-C.; Jiang, H.; Mao, J.; Bellomo, A.; Jeong, S. A.; Walsh, P. J. *Angew. Chem. Int. Ed.* **2016**, 55, 1070.

<sup>184</sup> (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, 96, 395. (b) Trost, B. M.; Machacek, M. R.; Aponick, A. *Acc. Chem. Res.* **2006**, 39, 747.

<sup>185</sup> Leitner, A.; Shu, C.; Hartwig, J. F. *Org. Lett.* **2005**, 7, 1093.

<sup>186</sup> Trost, B. M.; Chang, V. K. *Synthesis* **1993**, 8, 824.

<sup>187</sup> Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, 120, 5581.

<sup>188</sup> Bolm, C.; Legros, J.; Paih, J. L.; Zani, L. *Chem. Rev.* **2004**, 104, 6217.

<sup>189</sup> Zhang, S. W.; Mistsudo, T. A.; Kondo, T.; Watanabe, Y. *J. Organomet. Chem.* **1993**, 450, 197.

<sup>190</sup> Trost, B. M. *Org. Process Res. Dev.* **2012**, 16, 185.

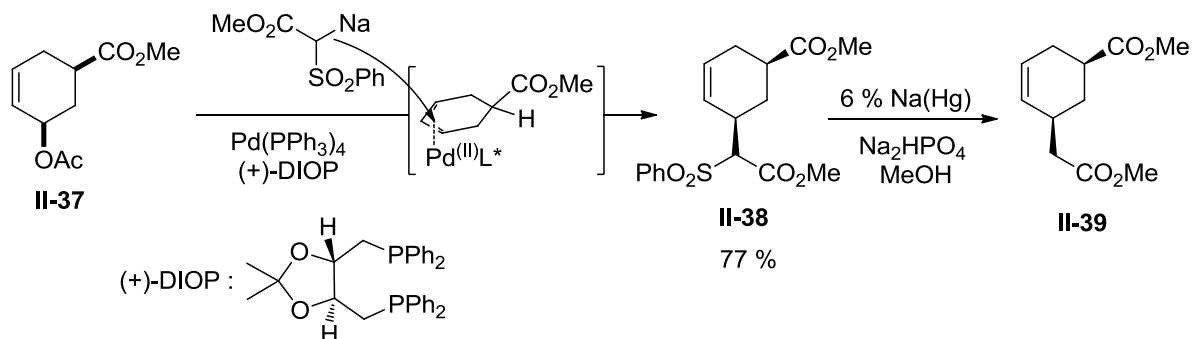
<sup>191</sup> Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, 103, 2921.

#### (4) Ligand

The ligands could be monodentate, bidentate and/or chiral. They might influence the reaction speed, the control of both regioselectivity and enantioselectivity of the reaction. Such ligands can adjust the properties of metal catalyst such as the steric bulkiness and electronic properties.

Usually,  $\pi$ -acceptor ligands like 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 the Tsuji-Trost reaction were successfully achieved employing catalytic amounts of chiral ligands. The first enantioselective Pd-catalyzed allylation reaction was reported in 1977.<sup>192</sup> Where the racemic mixture **II-37** was treated with the nucleophile, sodium salt of methyl phenylsulfonylacetate, using Pd(PPh<sub>3</sub>)<sub>4</sub> and the chiral ligand (+)-DIOP as the catalytic system giving **II-38** in 77 % yield. The latter upon desulfonylation produced the final product **II-39** with 24 % ee (Scheme II.39).



**Scheme II.39. Enantioselective Pd-catalyzed Tsuji-Trost reaction.**

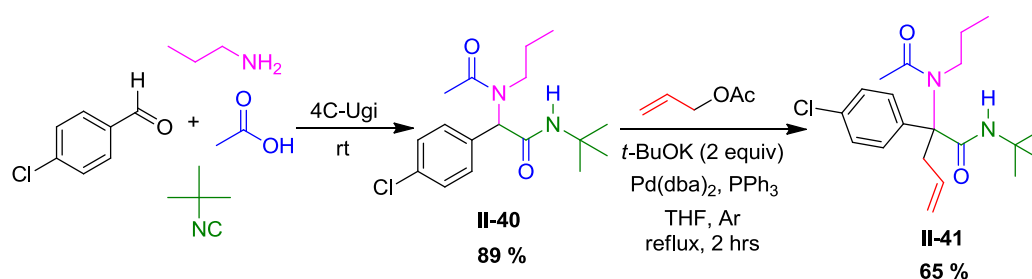
Such achievement was the base for many asymmetric approaches of Tsuji-Trost reaction.<sup>193</sup> Trost, PHOX and BINAP are the classically used chiral ligands in palladium-catalyzed asymmetric allylic alkylations.

<sup>192</sup> Trost, B. M.; Strege, P. E. *J. Am. Chem. Soc.* **1977**, 99, 1649.

<sup>193</sup> Hong, A. Y.; Stoltz, B. M. *Eur. J. Org. Chem.* **2013**, 19, 2745.

## II.7 Preliminary test

The first trial was carried out using the Ugi product **II-40** which was obtained in 89 % yield upon the condensation of 4-chlorobenzaldehyde, propylamine, acetic acid and *tert*-butyl isocyanide. We allowed this Ugi **II-40** to react with 2.5 equiv. of *t*-BuOK in THF at room temperature for 10 minutes till a homogenous solution was obtained. Then, 5 mol % of bis(dibenzylideneacetone)palladium(0) [Pd(dba)<sub>2</sub>], 10 mol % of triphenylphosphine and 1.5 equiv. of allyl acetate were added respectively. The resulting mixture was refluxed for two hours under argon, where a new product was detected by TLC, which upon purification and identification proved to be the target product **II-41** (Scheme II.40). The latter was obtained in 65 % yield.



Scheme II.40. First Intermolecular allylation trial of Ugi adduct.

### Optimization of the reaction conditions

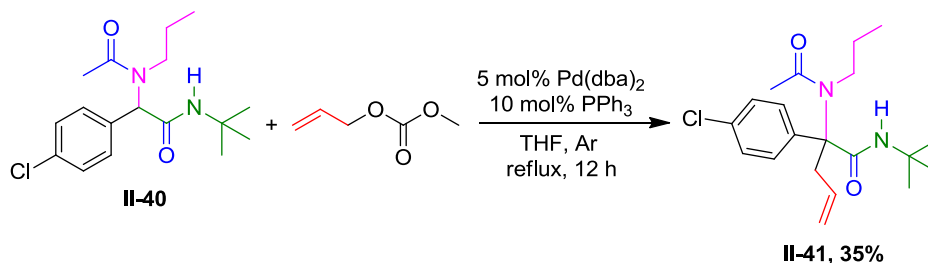
Such promising result encouraged us to study the various reaction parameters in order to reach the optimum condition. Thus the type of allylating reagent, effect of base together with its number of equivalents, palladium source, solvent and temperature of the reaction were investigated.

#### (1) The choice of allylating reagent

Allyl methyl carbonate was chosen as a second allylating reagent along with allyl acetate. In this case, the leaving group is methyl carbonate that usually undergoes decarboxylation affording methoxy anion.<sup>43</sup> The latter generally acts as a base in the reaction, thus, no additional base is required. Therefore, the product **II-40** was treated with 2.0 equiv. of allyl methyl carbonate in THF, followed by the addition of 5 mol % of Pd(dba)<sub>2</sub> and 10 mol % of PPh<sub>3</sub>. After refluxing the reaction for 12 hours under argon atmosphere, only 35 % of **II-**



**41** was obtained (Scheme II.41). This is probably due to the incapability of the methoxy anion to generate the 1,3-amide dianion intermediate compared to the *t*-BuOK used with allyl acetate. Accordingly, allyl methyl carbonate was excluded from the study.

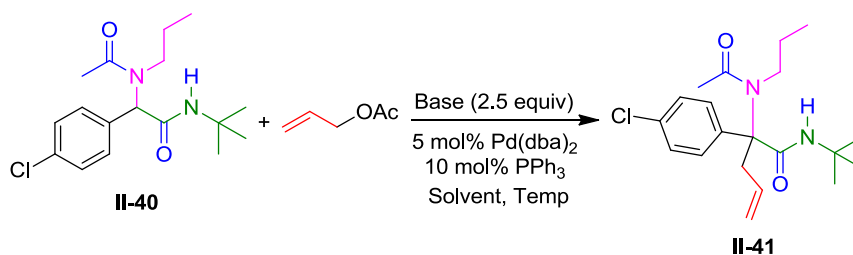


**Scheme II.41.** Intermolecular allylation of Ugi adduct using allyl methyl carbonate.

## (2) Base-Solvent combination

After the procurement of **II-41** in moderate yield (65 %) using *t*-BuOK in THF, the effect of using strong bases in various solvents on the generation of 1,3-amide dianion intermediate was studied. Thus, NaH and KHMDS were selected as powerful bases in addition to *t*-BuOK to be tested in a group of polar solvents such as: DMF, DMSO together with THF. A number of trials were performed using the same starting material **II-40**, 2.5 equiv. of base, allyl acetate as allylating reagent and [Pd(dba)<sub>2</sub>PPh<sub>3</sub>] as palladium source at varying temperature under argon (see Table II-1). The reaction time was determined according to the reaction progress checked by TLC.

**Table II-1. Optimization of Base/Solvent combination.**



Entry	Base	Solvent	Temp	Time	Yield
1	NaH	THF	reflux	12 h	45 %
2	NaH	DMF	70 °C	12 h	50 %
3	<i>t</i> -BuOK	DMF	70 °C	12 h	70 %
4	KHMDS	THF	reflux	1 h	95 %
5	KHMDS	THF	50 °C	1 h	93 %
6	KHMDS	THF	r.t.	1 h	88 %
7	NaH	DMSO	r.t.	1 h	96 %

The use of NaH in both THF and DMF at relatively elevated temperature did not improve the reaction yield (affording 45 % and 50 % respectively). Trying *t*-BuOK in DMF instead of THF resulted in a slight increase in the reaction yield (70 % instead of 65 %). Whereas, using KHMDS in THF at refluxing temperature for only 1 hour resulted in an excellent 95 % yield. Thus KHMDS afforded higher yield in shorter reaction time, however, when carrying out the reaction at lower temperatures, the yield slightly dropped (entries 5,6). The use of a combination of NaH in DMSO allowed us to get the highest yield (96 %) working at room temperature for 1 hour. This is attributed to the fact that NaH in DMSO is known to generate the powerful Brønsted base dimethyl sodium “NaDMSO”. The pKa of DMSO is around 35 which is comparable to that of KHMDS and considered as well in the range required to generate the 1,3-amide dianion intermediates.

Thus, NaH in DMSO was chosen as the optimal base/solvent combination for the reaction. The later allowed the generation of Ugi amide dianion at room temperature which in return afforded the product **II-41** with excellent yield in one hour.

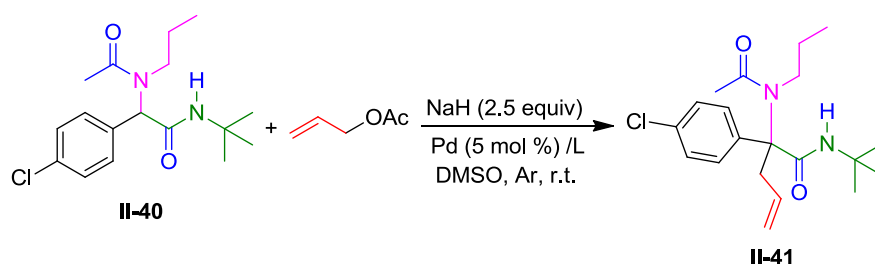
### **(3) The choice of palladium catalytic system**

Using the previously optimized conditions (2.5 equiv. of NaH in DMSO and 1.5 equiv. of allyl acetate at room temperature for 1 hour); the effect of palladium/ligand catalyst was examined. The reactivity of various monodentate and bidentate ligands in this reaction was investigated. We used 5 mol % of Pd catalyst and variable amount of ligand depending on its nature whether being monodentate (10 mol %) or bidentate (5 mol %) during the course of study. Pd(dba)<sub>2</sub>, Pd(PPh<sub>3</sub>)<sub>4</sub> and Pd(OAc)<sub>2</sub> were chosen as palladium catalysts, Cy<sub>3</sub>P.HBF<sub>4</sub>

and Johnphos were chosen as the examples for monodentate ligands and Xantphos and Dppe were chosen as bidentate ligands.

In case of using Johnphos, lower yield (80 %) was obtained compared to that obtained using  $\text{PPh}_3$  (96 %), whereas using  $\text{Cy}_3\text{P.HBF}_4$  resulted in the lowest yield (45 %) (see Table II-2). This might be owing to the lower  $\pi$ -acid character of Johnphos and  $\text{Cy}_3\text{P.HBF}_4$  compared to  $\text{PPh}_3$ . While using bidentate ligands afforded only traces of **II-41** probably due to the steric bulkiness of such ligands that would hinder the approach of the *tert*-carbanion of **II-40** from the  $\pi$ -allyl palladium complex. Whereas using  $\text{Pd}(\text{PPh}_3)_4$  afforded 94 % yield which is comparable with that obtained using  $\text{Pd}(\text{dba})_2$  and  $\text{PPh}_3$  (96 %). The use of  $\text{Pd}(\text{OAc})_2/\text{PPh}_3$  afforded the product **II-41** with 60 % yield. It is known that  $\text{Pd}(\text{OAc})_2$  can be reduced to Pd (0) at room temperature to participate in the catalytic cycle.<sup>194</sup> No reaction was reported in absence of palladium source.

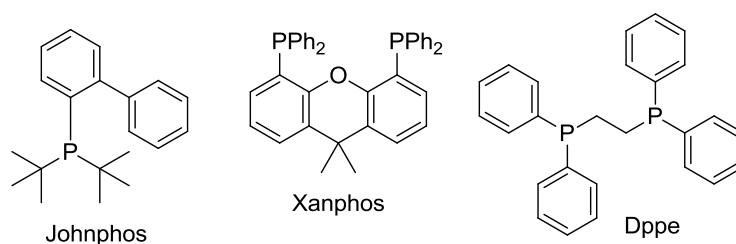
Table II-2. Optimization of palladium catalytic system.



Entry	Palladium catalyst	Ligand	Time	Yield
1	$\text{Pd}(\text{dba})_2$	$\text{PPh}_3$ (10 mol %)	1 h	96 %
2	$\text{Pd}(\text{dba})_2$	Xantphos (5 mol %)	12 h	traces
3	$\text{Pd}(\text{dba})_2$	Dppe (5 mol %)	12 h	traces
4	$\text{Pd}(\text{dba})_2$	$\text{Cy}_3\text{P.HBF}_4$ (10 mol %)	12 h	45 %
5	$\text{Pd}(\text{dba})_2$	Johnphos (10 mol %)	12 h	80 %
6	$\text{Pd}(\text{PPh}_3)_4$	-	1 h	94 %
7	$\text{Pd}(\text{OAc})_2$	$\text{PPh}_3$ (10 mol %)	1 h	60 %
8	-	-	12 h	-

The structures of the employed ligands are presented in Scheme II.42.

<sup>194</sup> Amatore, C.; Jutand, A.; Thuilliez, A. *Organometallics* **2001**, 20, 3241.



Scheme II.42. Structures of ligands used in Tsuji-Trost reaction.

The previous results confirmed the prior choice of  $\text{Pd}(\text{dba})_2$  and  $\text{PPh}_3$  as the palladium source in the reaction.

#### (4) Number of equivalents of base

Finally, the exact number of base equiv. required for the reaction had to be adjusted. Two trials were carried out using 0.9 and 1.3 equiv. of NaH adopting the aforementioned optimum conditions. In case of using 0.9 equiv. of NaH, the product **II-41** was not detected and only starting Ugi **II-40** was recovered. While using 1.3 equiv. of NaH gave the product **II-41** with 37 % yield. Such results indicates the need for excess amount of base in order to generate the more reactive dianionic species, for the reaction to proceed smoothly at room temperature (see Table II-3).

Table II-3. Optimizing the number of base equivalents.

Entry	No of Base equivalents	Yield
<b>1</b>	<b>2.5</b>	<b>96 %</b>
<b>2</b>	1.3	37 %
<b>3</b>	0.9	-

## II.8 Reaction mechanism

In order to rationalize more the reaction mechanism, two control experiments were performed. They were carried out by employing 0.9 and 2.5 equiv. of NaH to Ugi **II-40** in  $\text{DMSO-d}_6$  for 5 min followed by a  $^1\text{H-NMR}$  analysis. In case of using 0.9 equiv. of NaH, a complex spectrum was obtained that showed a lowered integration peak for the C atom at the peptidyl position, whereas for the amidic NH, an interfering number of peaks appeared in the

aromatic region that could not be distinguished. The complex spectrum resulted from the fact that when the  $^1\text{H}$ -NMR spectrum of Ugi adduct **II-40** is carried out in  $\text{DMSO-d}_6$ , the Ugi adduct exists as a mixture of rotamers. In case of using 2.5 equiv. of NaH, the spectrum becomes clearer revealing that both the peptidyl C-H and the amidic N-H were completely deprotonated (Figure II.1).

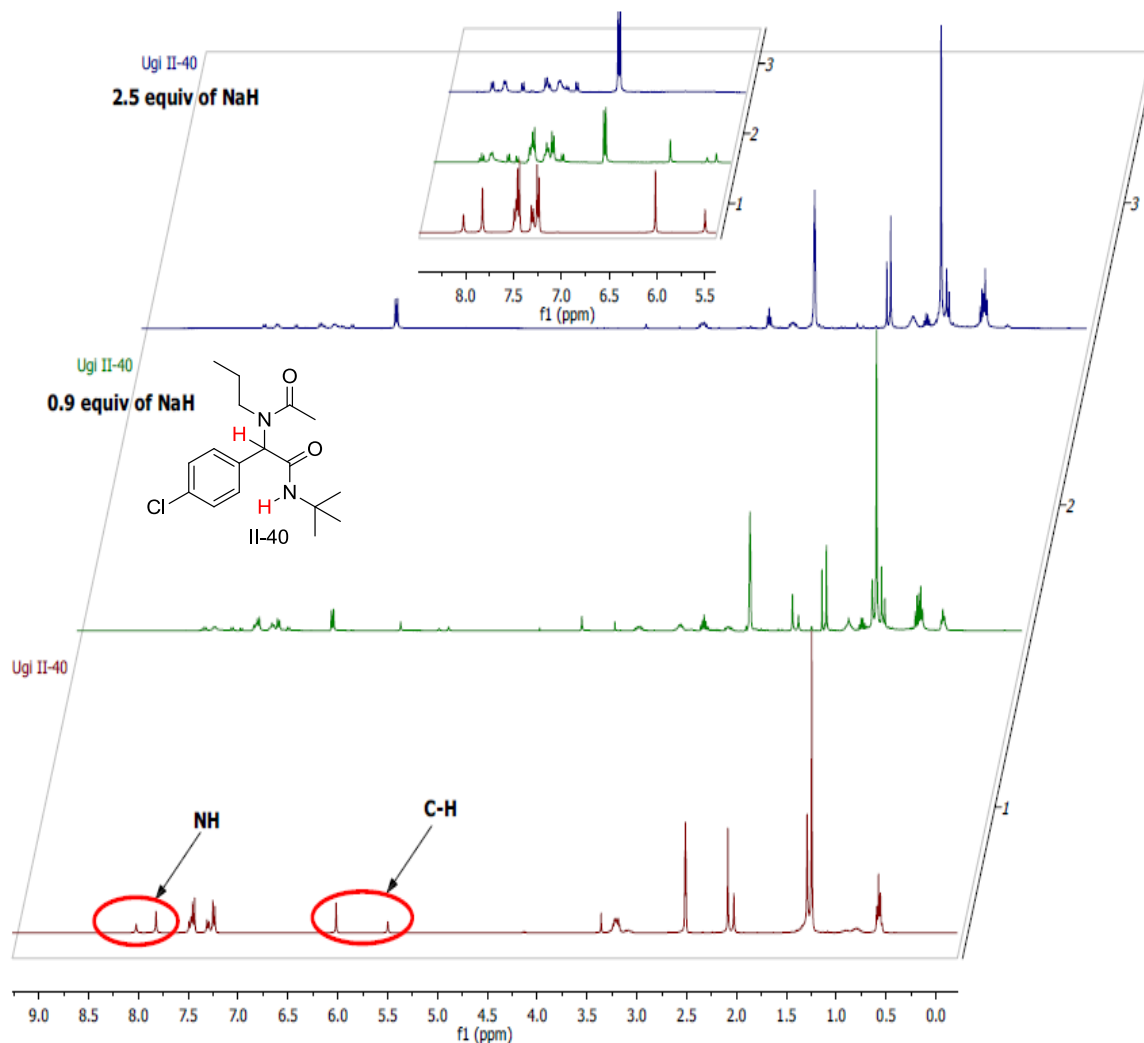


Figure II.1.  $^1\text{H}$ -NMR spectra for Ugi **II-40** and its reaction with 0.9 and 2.5 equiv of base in  $\text{DMSO-d}_6$ .

Trying to understand more the effect of 0.9 equiv. of base, the experiment was repeated, but this time we quenched the reaction with  $\text{CD}_3\text{OD}$ . After purification of the Ugi adduct,  $^1\text{H}$ -NMR using  $\text{CDCl}_3$  as solvent disclosed that 91% of deuterium was incorporated in the peptidyl C-H position (Figure II.2). Moreover, when carrying out the Tsuji-Trost allylation reaction using 0.9 equiv. of NaH, only traces of the allylated product **II-41** was obtained. This indicates that using 0.9 equiv. of NaH leads to the formation of the mono

carbanion, which is not nucleophilic enough to undergo the allylic alkylation reaction at room temperature. Whereas using 1.3 equiv. of NaH, 37 % of the product **II-41** was isolated. This shows that as soon as you start to deprotonate the NH, a powerful dianionic nucleophile is produced. The latter together with some reactivity of the monoanion afforded the desired product **II-41** in 37 % yield.

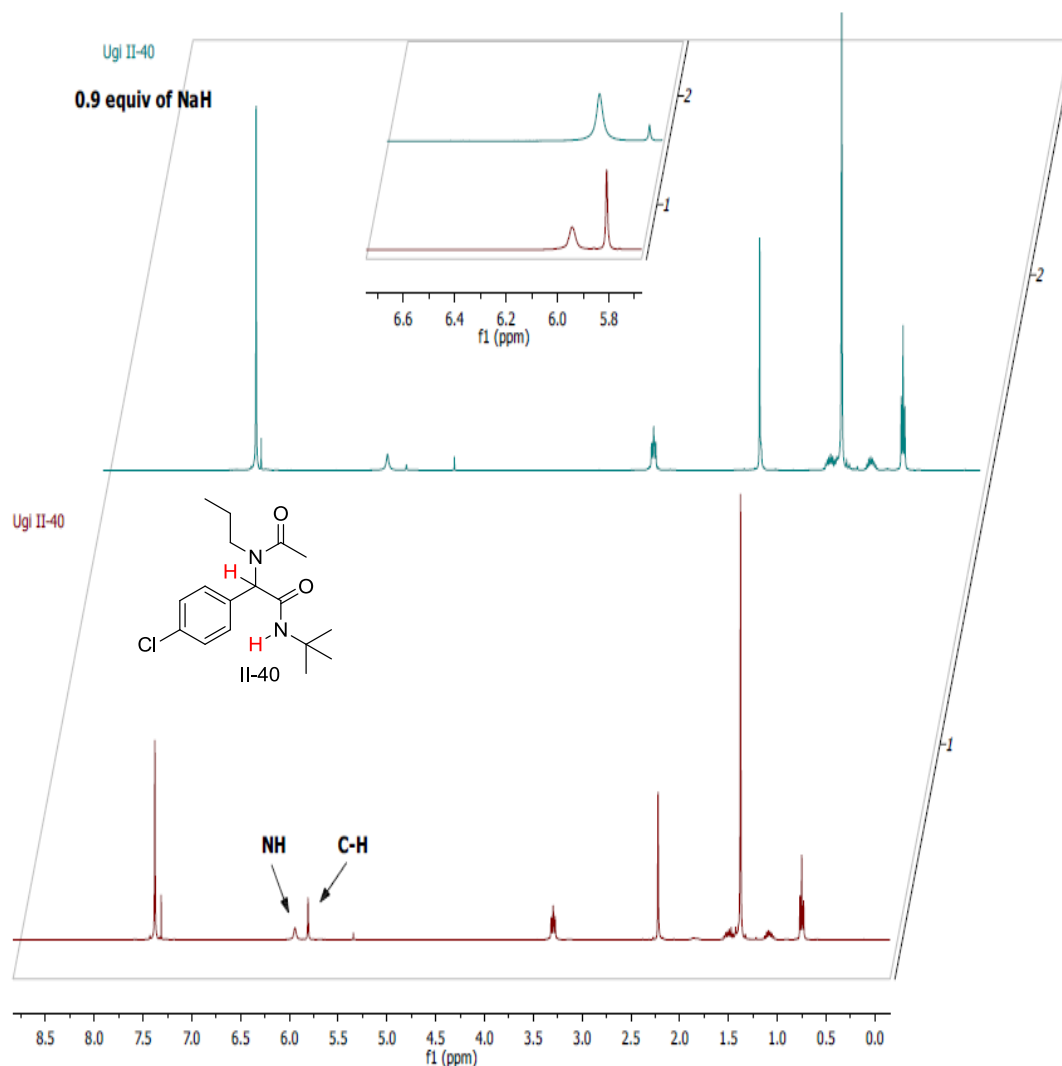
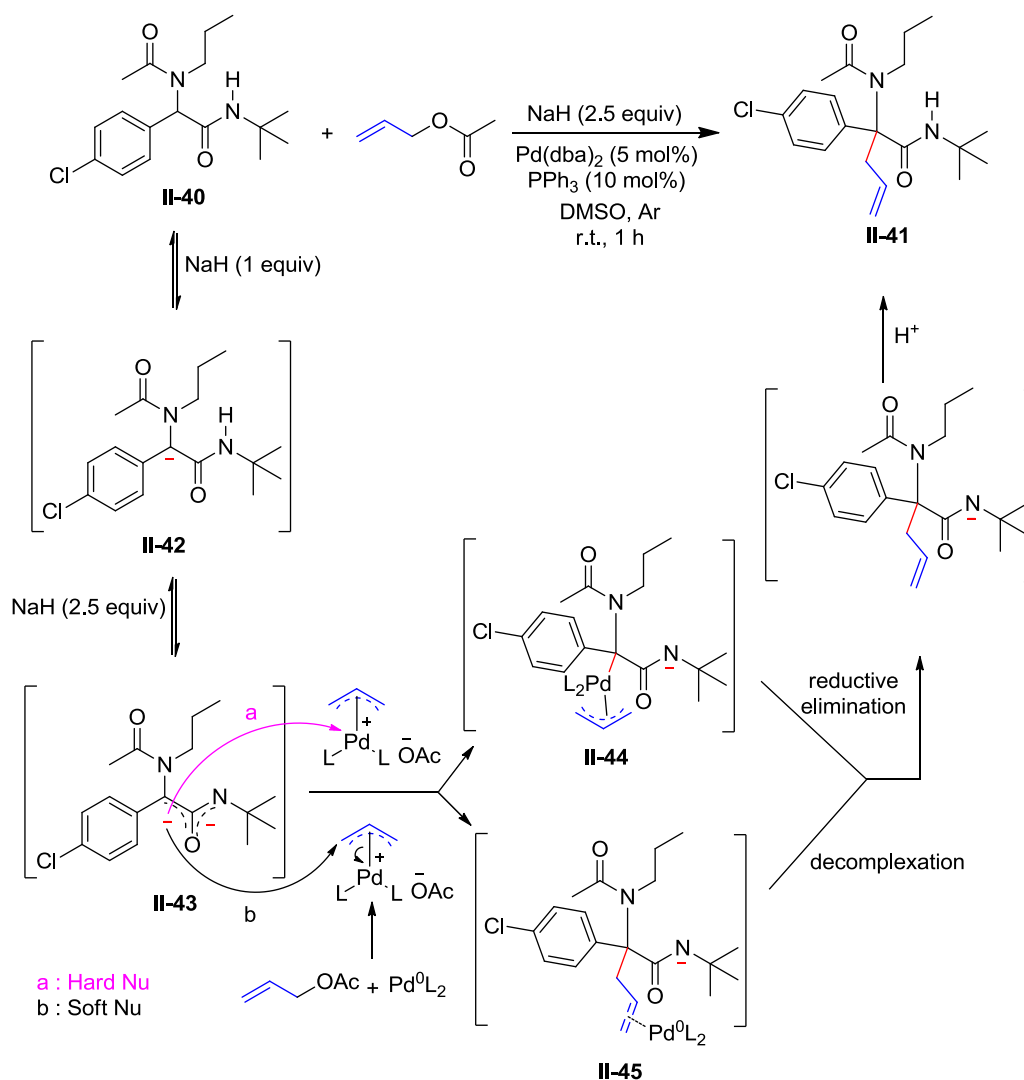


Figure II.2.  $^1\text{H}$ -NMR spectrums for Ugi **II-40** and its reaction with 0.9 equiv. of base in  $\text{CDCl}_3$ .

Consequently, we suggested that the deprotonation started at the peptidyl C-H position forming the intermediate **II-42** which is not nucleophilic enough to attack the  $\pi$ -allyl palladium complex. While the bisdeprotonation resulted in a powerful nucleophilic stabilized dianion intermediate **II-43**, its peptidyl carbanion selectively attacks the  $\pi$ -allyl complex. Depending on whether the nucleophile **II-43** is considered among the hard or soft nucleophile categories, the peptidyl carbanion of the intermediate **II-43** attacks either the metallic center

(pathway a) affording the intermediate **II-44** or the carbon of the allyl group (pathway b) of the  $\pi$ -allyl complex affording the intermediate **II-45**. A final protonation step will deliver the target product **II-41** (Scheme II.43).

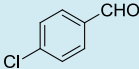
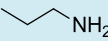

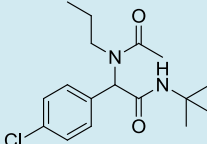
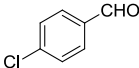
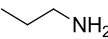


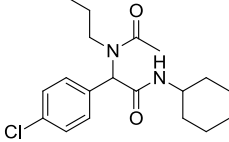
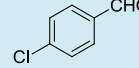
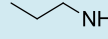

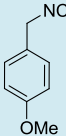
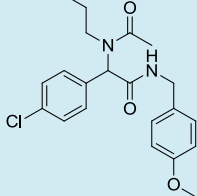
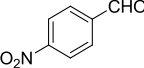
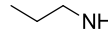

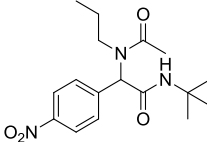
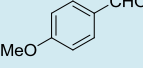
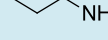

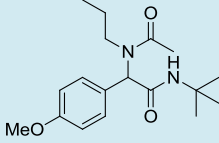


Scheme II.43. Proposed mechanism for Ugi/intermolecular Tsuji-trost reaction.

## II.9 Synthesis of Ugi adducts

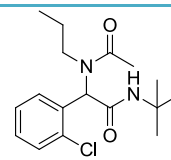
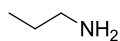
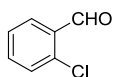
The Ugi reaction as already highlighted in chapter I involves the condensation of an aldehyde, an amine, an acid and an isocyanide in the proper solvent at room temperature for 24 hours. Thus we prepared a library of Ugi adducts varying the 4 components of the reaction, using methanol as the solvent, affording diversity oriented  $\alpha$ -amidocarboxamides with excellent yields in most examples. The various results are presented thereafter in Table II-4.

Table II-4. Various examples of prepared Ugi adducts.

$R_1-\text{CHO} + R_2-\text{NH}_2 + R_3-\text{NC} + R_4-\text{COOH} \xrightarrow[1 \text{ day, r.t.}]{\text{MeOH (1 M)}} R_1-\text{CH}(\text{N}(\text{R}_2)\text{C}(=\text{O})\text{N}(\text{R}_3)\text{C}(=\text{O})\text{R}_4)$					
Entry	Aldehyde	Amine	Acid	Isocyanide	Ugi adduct Yield
1				<i>t</i> -Bu-NC	 <b>II-40</b> 89%
2					 <b>II-46</b> 85%
3					 <b>II-47</b> 90%
4				<i>t</i> -Bu-NC	 <b>II-48</b> 89 %
5				<i>t</i> -Bu-NC	 <b>II-49</b> 93 %



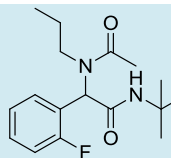
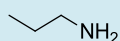
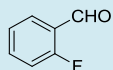
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**II-50**

80%

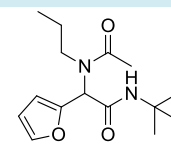
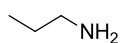
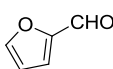
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**II-51**

95 %

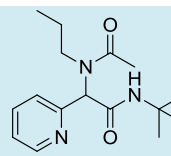
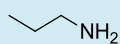
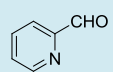
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**II-52**

88 %

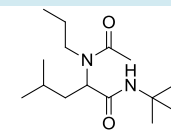
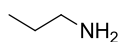
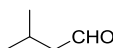
9



**II-53**

84%

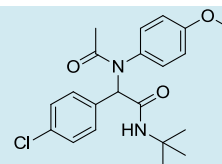
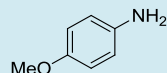
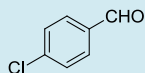
10



**II-54**

73 %

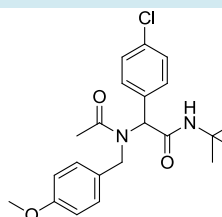
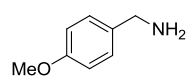
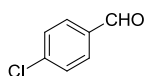
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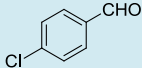
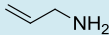

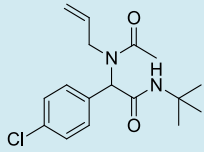
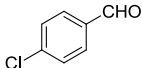
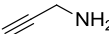

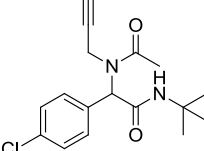
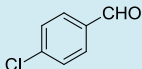
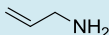


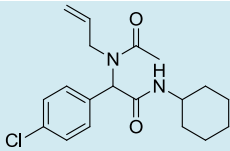
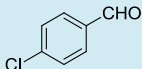
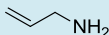


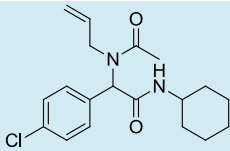
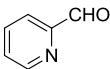
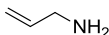

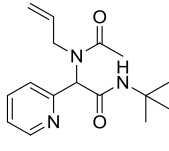
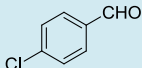
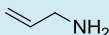
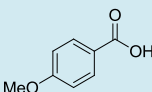
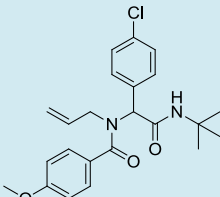
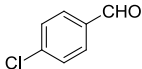
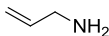
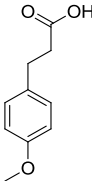
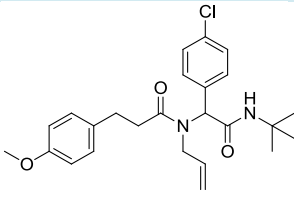


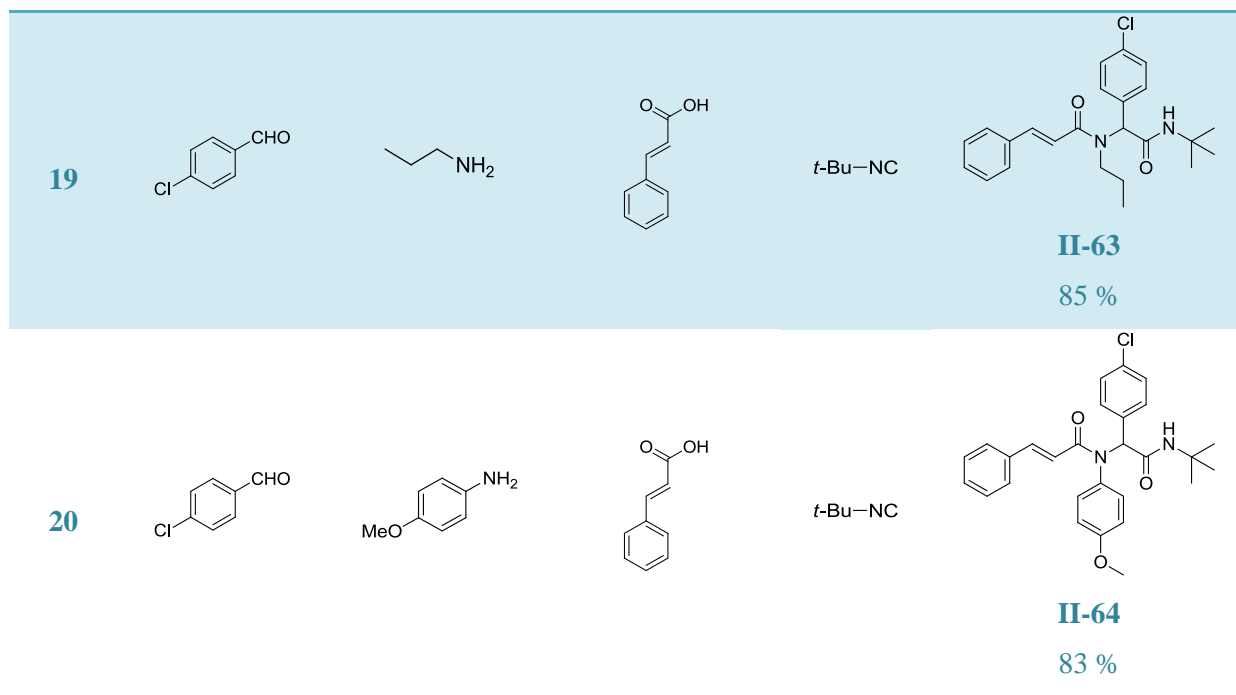
**II-55**

95%

12



13				$t\text{-Bu-NC}$		II-56 95%
14				$t\text{-Bu-NC}$		II-57 70 %
15						II-58 90 %
15						II-59 97%
16				$t\text{-Bu-NC}$		II-60 97 %
17				$t\text{-Bu-NC}$		II-61 70 %
18				$t\text{-Bu-NC}$		II-62 68 %

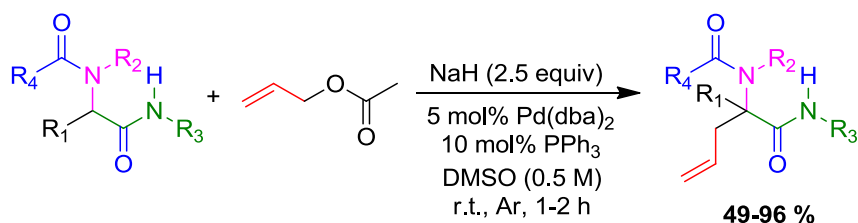


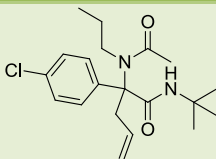
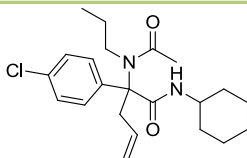
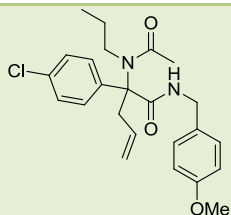
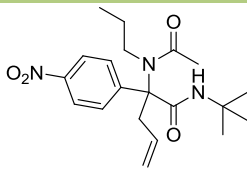
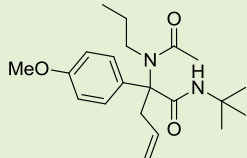
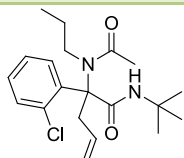
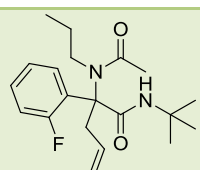
In general, this reaction allowed us to prepare a library of  $\alpha$ -amidocarboxamides with good to excellent yields from 67 to 97 %.

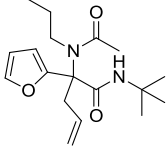
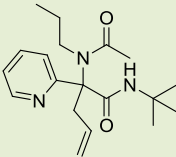
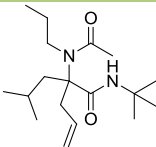
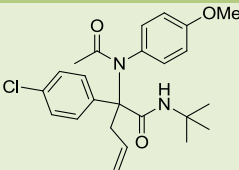
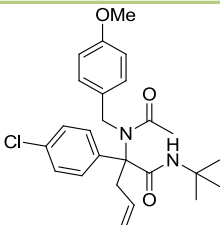
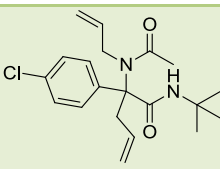
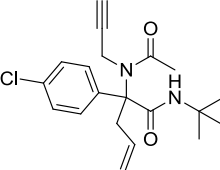
## II.10 Study of the reaction scope

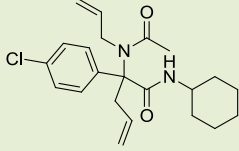
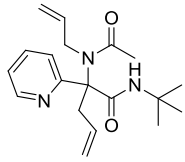
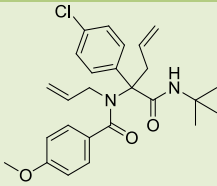
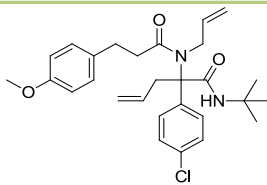
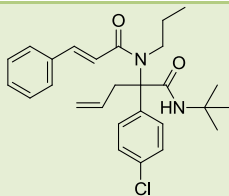
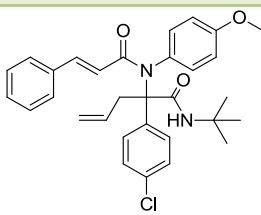
The latter prepared series of Ugi adducts was then subjected to the reaction with NaH (2.5 equiv.) and allyl acetate (1.5 equiv.) in presence of catalytic amounts of  $\text{Pd}(\text{dba})_2$  (5 mol %) and  $\text{PPh}_3$  (10 mol %) in DMSO (0.5 M) at room temperature under argon atmosphere. This reaction afforded an array of pent-4-enamide derivatives. The different results are displayed in Table II-5 below.

**Table II-5. Scope of intermolecular Ugi Tsuji-Trost reaction.**



Entry	Ugi adduct	Isolated product	Yield
1	II-40	 <b>II-61</b>	96 %
2	II-46	 <b>II-65</b>	81 %
3	II-47	 <b>II-66</b>	55 %
4	II-48	 <b>II-67</b>	75 %
5	II-49	 <b>II-68</b>	70 %
6	II-50	 <b>II-69</b>	- (SM)
7	II-51	 <b>II-70</b>	- (SM)

8	II-52	 <b>II-71</b>	77 %
9	II-53	 <b>II-72</b>	92 %
10	II-54	 <b>II-73</b>	- (SM)
11	II-55	 <b>II-74</b>	60 %
12	II-56	 <b>II-75</b>	56 %
13	II-57	 <b>II-76</b>	95 %
14	II-58	 <b>II-77</b>	-*

15	II-59	 II-78	82 %
16	II-60	 II-79	83 %
17	II-61	 II-80	64 %
18	II-62	 II-81	66 %
19	II-63	 II-82	49 %
20	II-64	 II-83	63 %

\*Another product was isolated.

In general, the products of Tsuji-Trost reaction were obtained with good to excellent yields from 49 to 96 % (see Table II-5).

The reaction proceeded well with Ugi adducts derived from several isocyanides, where the highest yield is obtained using *tert*-butyl isocyanide **II-41** (96 %), probably due to its bulkiness, it enhances the selectivity of the reaction towards *C*-allylic alkylation. While the lowest yield was obtained using *p*-methoxybenzyl isocyanide **II-66** (55 %), whereas using cyclohexyl isocyanide afforded **II-65** in 81 % yield. This is in agreement with the potential *N*-allyl product formation using the less bulky *p*-methoxybenzyl isocyanide.

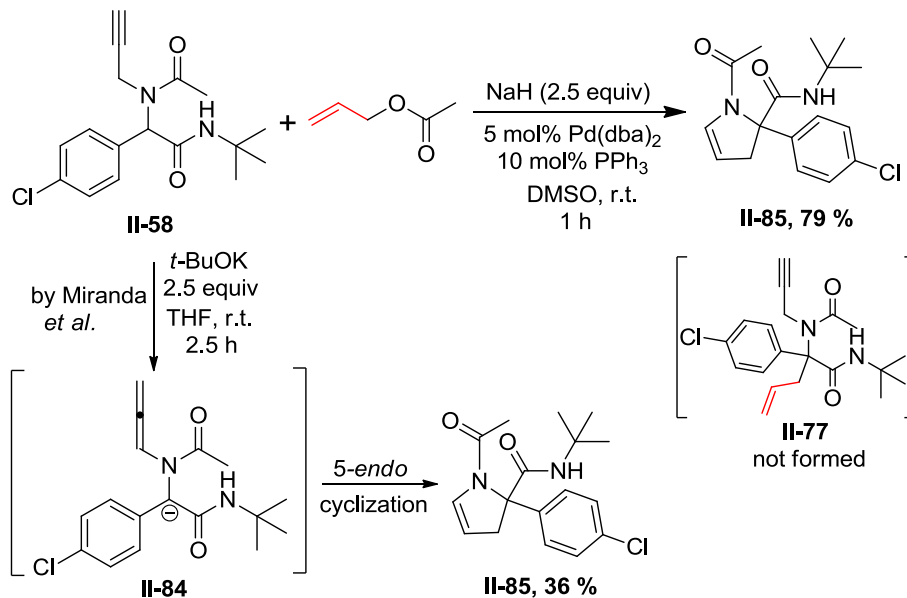
Varying the aldehyde group in Ugi adducts between electron deficient and electron rich benzene rings slightly lowered the reaction yield 75 % and 70 % respectively (Table II-5, entries 4,5). The use of Ugi adducts derived heterocyclic aldehydes as, furan-2-carboxaldehyde afforded **II-71** in 77 % and pyridine-2-carboxaldehyde produced **II-72** in 92 % yield. This is due to the effect of electron-deficient aldehydes in enhancing the acidity of C-H peptidyl position to be deprotonated.

Ugi adducts derived from *o*-substitued aldehydes were poorly efficient in this reaction. When Ugi **II-50** derived from *o*-chlorobenzaldehyde and that derived from *o*-fluorobenzaldehyde **II-51** were subjected to the reaction, no product was formed, only starting materials were recovered. This is probably due to the bulkiness of the substituents in *ortho*-position which might result in twisting of the aromatic group, thus suppressing the deprotonation of the peptidyl C-H.

Ugi products derived from aliphatic aldehydes for example: isovaleraldehyde **II-54** failed to give any allylated product under our reaction conditions, where the reaction mixture just included starting material. This could be due to the inability of the basic system to generate the 1,3-dianionic species in this particular case as a result of the low activation due to the absence of aromatic substituent.

Ugi precursors derived from both aliphatic and aromatic amines were submitted successfully to the reaction giving the desired products in moderate to good yields. However, applying the Ugi derived from propargylamine **II-58** did not result in the expected product **II-77**, instead a cycloisomerization occur affording the 2,3-dihydropyrrole derivative **II-85**. Such reactivity was previously reported in 2012 by Miranda *et al.*,<sup>164</sup> where they stated that Ugi propargyl adducts when subjected to *t*-BuOK (2.5 equiv) in THF (0.1 M) at room temperature, a base-induced isomerization occurs affording allenamide intermediate **II-84**

which then undergoes cyclization affording 2,3-dihydropyrrole derivative. It is worth mentioning that they isolated the product **II-85** in 36 % yield, while using our protocol, a major improvement in the reaction was observed affording the product with 79 % yield (Scheme II.44).



Inversing the order of reagents, adding allyl acetate and  $\text{Pd}(\text{dba})_2/\text{PPh}_3$  to Ugi adduct **II-58** in DMSO followed by 2.5 equiv of NaH afforded a number of products. Herein, the product **II-85** was obtained in 54 % yield together with a complex mixture of allylated products due to the isomerization of the triple bond.

Both aliphatic and aromatic acids derived Ugi adducts afforded the allylated products in good yields. The simple acetic acid afforded the highest yields as in case of **II-41** and **II-76** (96 % and 95 % yields respectively) compared to the more complex cinnamic acid that afforded **II-82** in 49 % yield and **II-83** in 63 % yield, or the 3-(4-methoxyphenyl)propanoic acid which gave **II-81** in 66 % yield. While using *p*-methoxybenzoic acid afforded **II-80** in 64 % yield.

Next, the ability to perform the Tsuji-Trost reaction in an enantioselective fashion was examined.



## II.11 Towards enantioselective version of allylation

After presenting a novel efficient method for the intermolecular allylation of the peptidyl C-H position in Ugi adducts, we were interested in the asymmetric version of this reaction using chiral ligands to afford enantiomerically rich allylated Ugi products. However, we were very limited in the choice of the ligands since not all of them could afford the desired product as previously mentioned during the course of study for choosing the catalytic system.

First, we evaluated the use of 5 mol % of the bidentate (R)-BINAP ligand **II-86** under the optimal reaction conditions using Ugi adduct **II-40**. A slight improvement in the reaction enantioselectivity was achieved using BINAP ligand (Figure II.3). Then, we decided to lower the temperature to 0 °C by working in a mixture of solvents THF:DMSO = 1:1. The idea was to extend the reaction time in order to get better selectivity, however this trial did not improve the enantioselectivity.

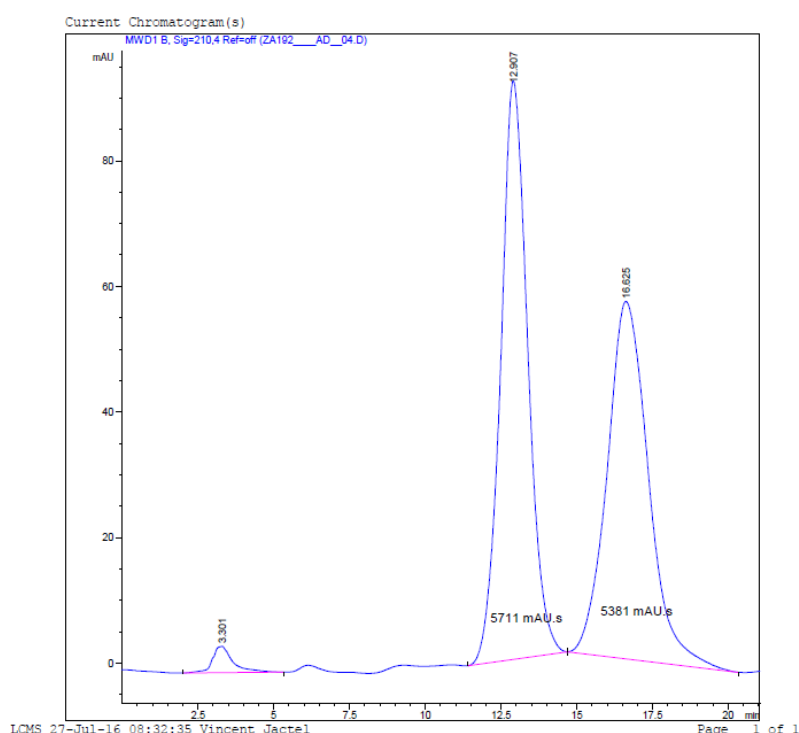
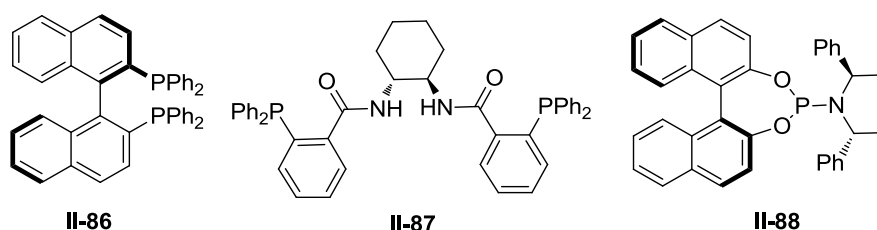


Figure II.3. Chromatogram for enantiomeric ratio of Ugi allylated product **II-41**.

Afterwards, we tried 5 mol % of the bidentate trost ligand **II-87**, which is known to be an efficient ligand that affords the highest enantioselectivity with respect to Tsuji-Trost reaction. Surprisingly, the reaction did not progress at all. In this case, only the starting

material was recovered, probably due to the bulkiness of such ligand. Hence, we decided to change the catalytic system to iridium instead of palladium catalyst where 2 mol % of Ir[(1,5-cod)Cl]<sub>2</sub> / 4 mol % of monodentate ligand **II-88** were used. Unfortunately, such catalytic system failed as well to deliver the target product and the starting material remained unreacted (see the structures of ligands in Scheme II.45).

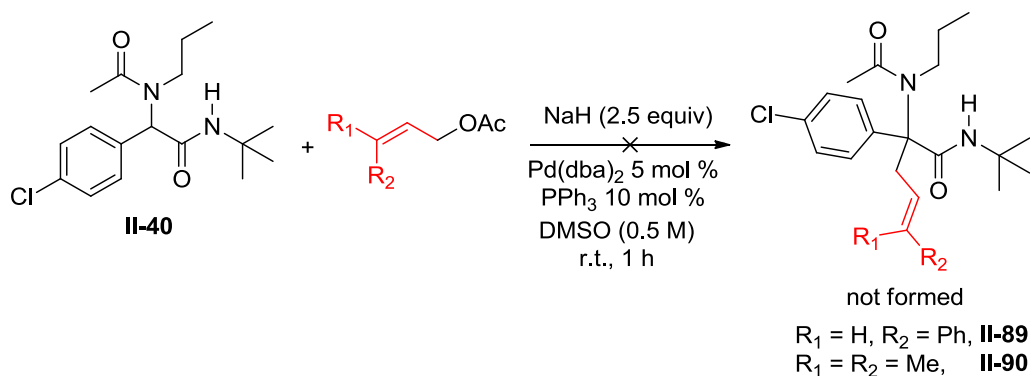


Scheme II.45. Structures of chiral ligands used in enantioselective allylation of Ugi adducts.

These results directed our thoughts towards extending the value of our study in a different way to include various electrophiles so as to convert the protocol into a general methodology for the alkylation of Ugi adducts.

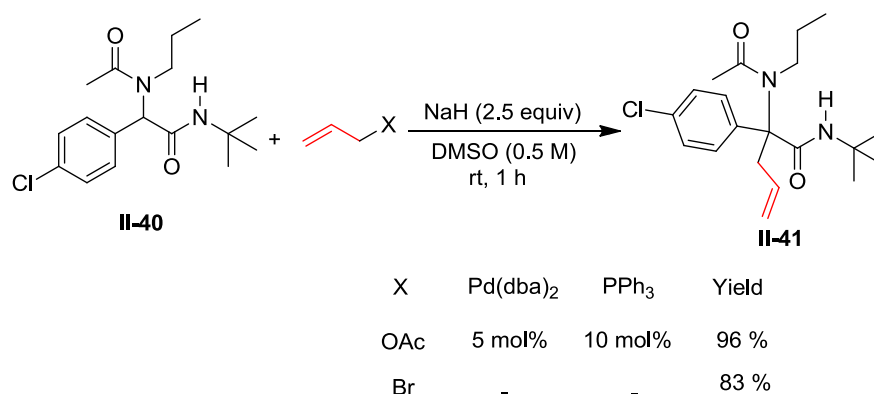
## II.12 Scope of electrophiles

We started our course of study with allyl acetate derivatives. Using cinnamyl acetate, the target product **II-89** was not formed, only cinnamyl alcohol was isolated that results from a saponification reaction. This could be due to the steric bulkiness of such electrophile which might hinder the reaction. The use of prenyl acetate did not deliver the expected product **II-90** as well, probably for similar steric reasons (Scheme II.46).



Scheme II.46. Allyl acetate derivatives in Ugi Intermolecular Tsuji-Trost reaction.

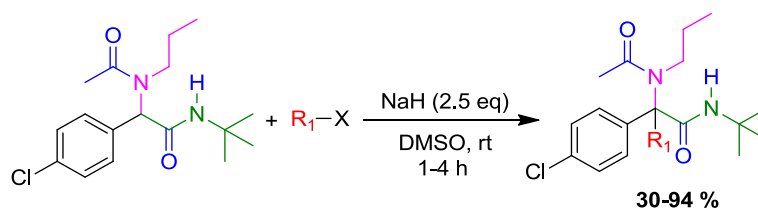
Consequently, we shifted to halide derivatives. First, we employed allyl bromide, to afford the same product **II-41** obtained using allyl acetate. The target compound was successfully obtained using Ugi **II-40**, NaH (2.5 equiv.) in DMSO (0.5 M) followed by adding allyl bromide (1.5 equiv.) and leaving the reaction at room temperature for 1 hour. No palladium source was required in this case. Although, the yield slightly dropped (96 % in case of using allyl acetate compared to 83 % using allyl bromide), this could still be considered as a good method for obtaining the target product (Scheme II.47).



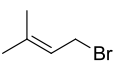
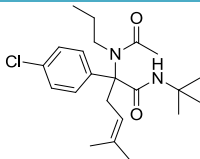

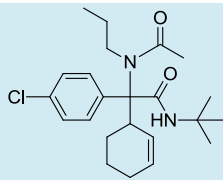

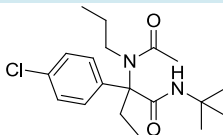
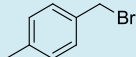
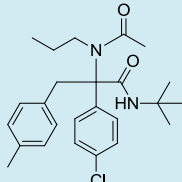
Scheme II.47. Comparing allyl acetate and allyl bromide in Ugi Intermolecular allylation reaction.

Hence, due to the high yields obtained, a range of alkylating halides was examined in the reaction. The obtained results are summarized in Table II-6.

Table II-6. Scope of alkylation of Ugi adduct.



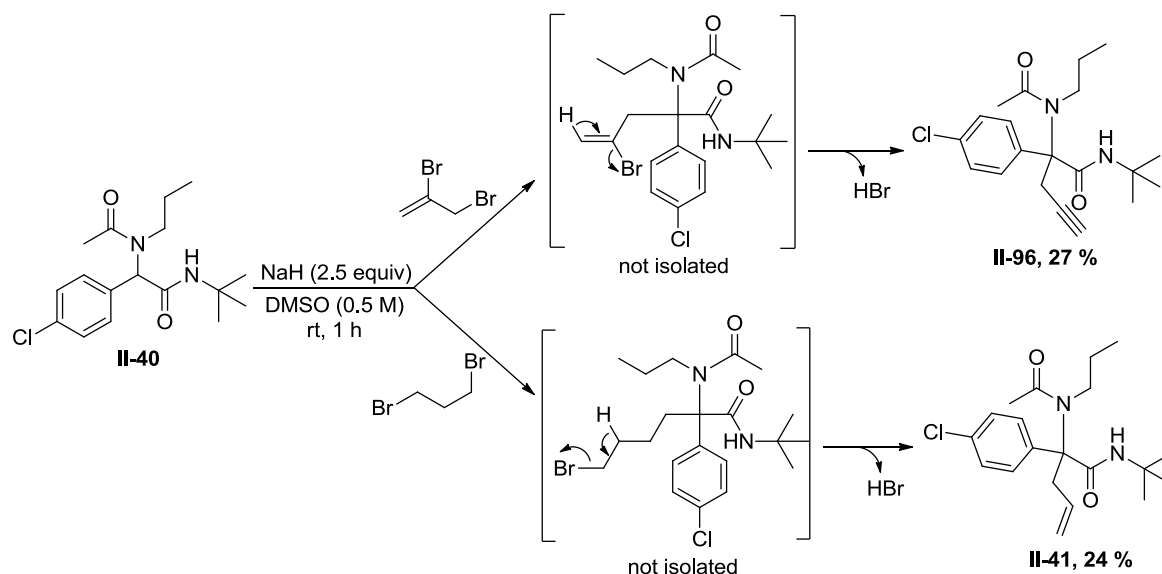
Entry	Alkylating agent	Product	Yield
1		 <b>II-91</b>	88 %

2			74 %
3			30 %
4			94 %
5			79 %

A series of allyl bromide derivatives were subjected to the same reaction conditions. In contrast with allyl acetate derivatives, both cinnamyl and prenyl bromides afforded the products **II-91** and **II-92** in good yields of 88 % and 74 % respectively. While 3-bromocyclohex-1-ene gave the product **II-93** in 30 % yield, which is due to the lower reactivity of the secondary alkyl halides with respect to the primary ones in the nucleophilic substitution reactions.

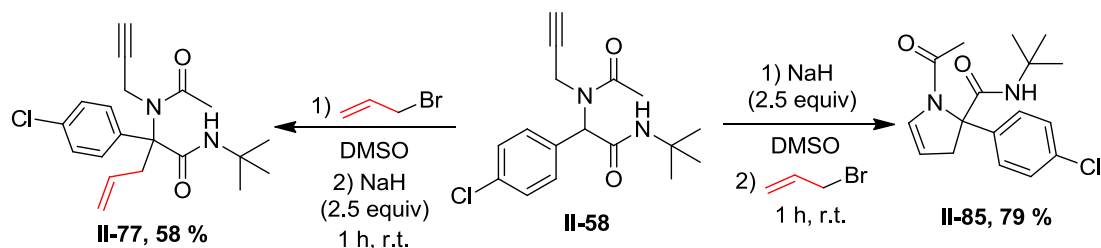
The use of ethyl iodide in the reaction gave the product **II-94** in 94 % yield. Where the iodide derivatives provide better yield in comparison with the bromide due to the weakness of C-I bond compared to C-Br bond. Nevertheless, *p*-methylbenzyl bromide was congruent as well in the reaction producing **II-95** with 79 % yield. This ensures that our protocol could be considered as a general method for the intermolecular alkylation of peptidyl C-H position in Ugi product providing Ugi five-component adducts.

However, the reaction with dibromo alkyl derivatives did not afford the target products but instead, they underwent hydrogen bromide elimination together with the nucleophilic substitution reaction. This led to decreasing the overall reaction yield. Thus, using 1,3-dibromopropane afforded the allylated product **II-96** in 27 % yield, while the reaction with 2,3-dibromoprop-1-ene gave the propargylated product **II-41** with 24 % yield (Scheme II.48). An alternative way to overcome such problem would be using for example:  $\alpha,\alpha'$ -dibromo-*o*-xylene to avoid the hydrogen bromide elimination.



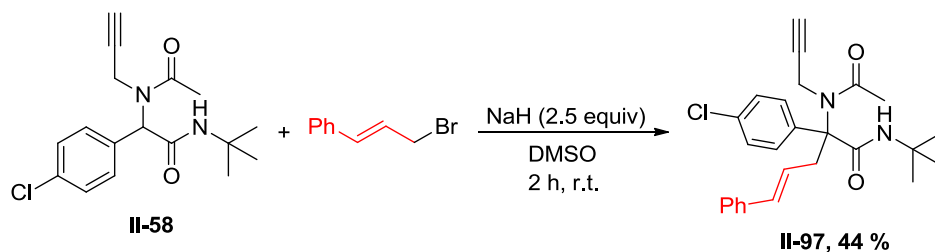
Scheme II.48. Intermolecular alkylation using dibromo derivatives.

Regarding the efficiency of allyl bromide in the alkylation of Ugi adducts, we decided to examine its reactivity towards the allylation of propargyl amine derived Ugi adduct **II-58**. When allyl acetate and palladium catalyst were added to the Ugi **II-58** in DMSO followed by the addition of 2.5 equiv of NaH, the allylated adduct could be detected in the complex NMR spectrum of the crude. Consequently, we decided to add first the allyl bromide to the Ugi **II-58** in DMSO followed by the base. After one hour, a complete conversion of the starting material to one single product was detected by TLC. Interestingly, this product was found to be the allylated adduct **II-77** obtained in 58 % yield. Inversing the protocol by stirring first the base and the Ugi **II-58** in DMSO followed by adding the allyl bromide resulted selectively in the cyclic product **II-85** (Scheme II.49). These results indicated that the rate of allylation is much faster than the isomerization-cyclization. Thus, having the electrophile already present in the reaction medium, as soon as the 1,3-dianionic species is generated, it could attack instantly the allyl bromide forming the allylated product **II-77**.



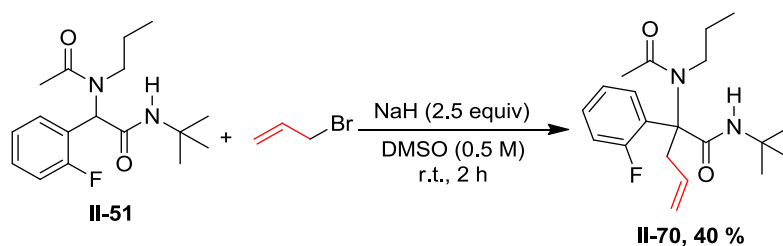
Scheme II.49. Inter- and intramolecular reactions of Ugi propargyl adducts.

Following the same protocol, cinnamyl bromide was added to the Ugi adduct **II-58** in DMSO, followed by the addition of 2.5 equiv. of NaH. After stirring the reaction at room temperature for 2 hours, the desired product **II-97** was obtained selectively in 44 % yield (Scheme II.50). The lower yield in this case is due to the decreased reactivity of cinnamyl bromide with respect to the allyl bromide.

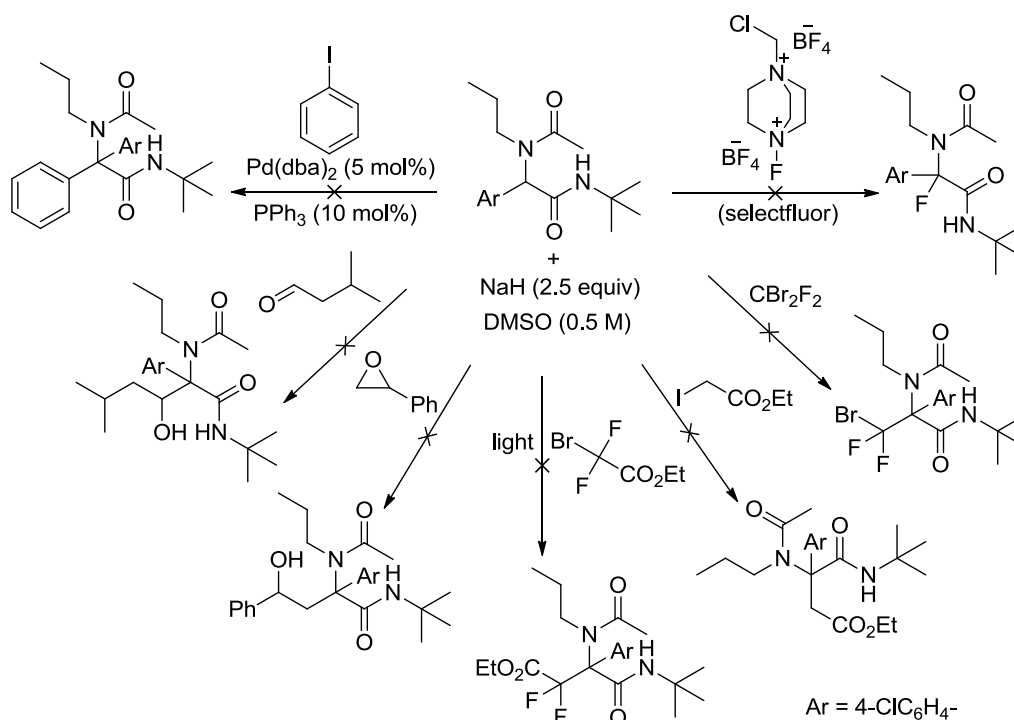


Scheme II.50. Inter- and intramolecular alkylation of Ugi propargyl adducts using cinnamyl bromide.

In a similar manner, we explored the efficiency of allyl bromide towards Ugi adducts that failed to give the corresponding allylated Ugi products using allyl acetate (i.e Ugi **II-50**, **II-51** and **II-54**). The addition of 2.5 equiv. of NaH to the Ugi **II-51**, which was derived from *o*-fluorobenzaldehyde in DMSO followed by adding allyl bromide, resulted in 40 % yield of the product **II-70** along with 45 % yield of the starting Ugi **II-51** after two hours (Scheme II.51). Extending the reaction time to 24 hours did not improve the reaction yield. Whereas, Ugi **II-50** and **II-54** derived from *o*-chlorobenzaldehyde and isovaleraldehyde respectively could not afford their desired allylated products under these conditions. This could be rationalized by the bulkiness of the chloro group in the *ortho*-position resulting in twisting of the aryl group, thus preventing the deprotonation of the peptidyl C-H. While, using the less bulky fluoro group, the reaction could progress but still could not be derived to completion. Whereas in case of the Ugi adduct **II-54**, the dianion could not be generated as well due to the absence of the aromatic substituent.

Scheme II.51. Alkylation of Ugi derived *o*-fluorobenzaldehyde.

Several other types of electrophiles were tested including isovaleraldehyde, styrene oxide, ethyl iodoacetate, selectfluor, phenyl iodide, dibromodifluoromethane (by an expected SRN1 type reaction) and ethyl bromodifluoroacetate under the same reaction conditions. Yet the reaction did not work in these cases even after prolonged reaction time to 24 hours (Scheme II.52), only starting Ugi compound was recovered. In most cases, it is probably due to the incompatibility of such electrophiles with the strong basic conditions employed in the reaction.



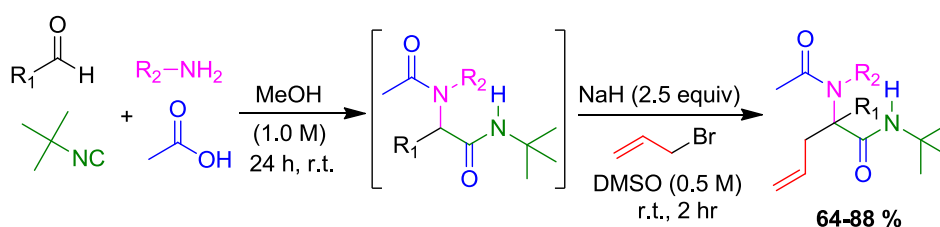
Scheme II.52. Failed trials with various electrophiles.

## II.13 Cascade one-pot Ugi/intermolecular allylation reaction

The success of application of allyl bromide in allylation of Ugi adducts with good yield (83 % for **II-41**) inspired us to carry out the two steps in a one-pot cascade reaction.

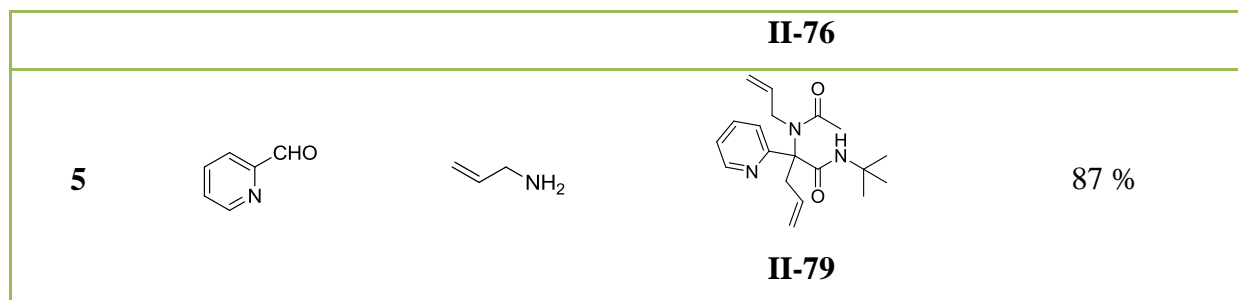
This cascade is composed of Ugi coupling followed by intermolecular allylation using allyl bromide. In this case, Ugi reaction is carried out in methanol (1.0 M) at room temperature for 24 hours, followed by evaporation of solvent under reduced pressure and its replacement with DMSO (0.5 M), to which NaH (2.5 equiv.) and allyl bromide (1.5 equiv.) were added respectively. The intermediate change of solvents is necessary as DMSO is not a usual solvent for Ugi reaction; generally it is carried out in methanol. While carrying the allylation step in methanol is not possible as DMSO plays an important role in the formation of the 1,3-dianion intermediate which is the key step for the reaction to take place. The various results obtained are displayed in Table II-7.

Table II-7. Cascade one-pot Ugi/Intermolecular allylation reaction.



Entry	aldehyde	amine	Isolated product	Yield (one pot)
1				81 %*
2				78 %
3				64 %
4				88 %





\*The yield obtained from the two step reaction was 83 %

In most cases, the yields of the cascade one pot reaction were comparable with that obtained from two step reaction using  $\pi$ -allyl palladium complex as allylating reagent with intermediate purification. Consequently it could be widely applied in the synthesis of alkylated Ugi adducts instead of the two step procedure. The development of such Ugi/intermolecular alkylation cascade renders the approach of synthesis much more important, as it paves the way for an environmentally friendly type of reactions where the isolation of intermediates is not necessary.

Furthermore, the alkylated Ugi type products obtained using the aforementioned strategy could be useful as building blocks for the synthesis of heterocycles. This could be achieved if the starting Ugi adducts were suitably functionalized for further transformations prior to submitting into the Ugi reaction. For instance, as an application of allylated Ugi adducts previously functionalized with double bond in one of its components, a Ring Closure Metathesis could be executed affording various heterocycles.

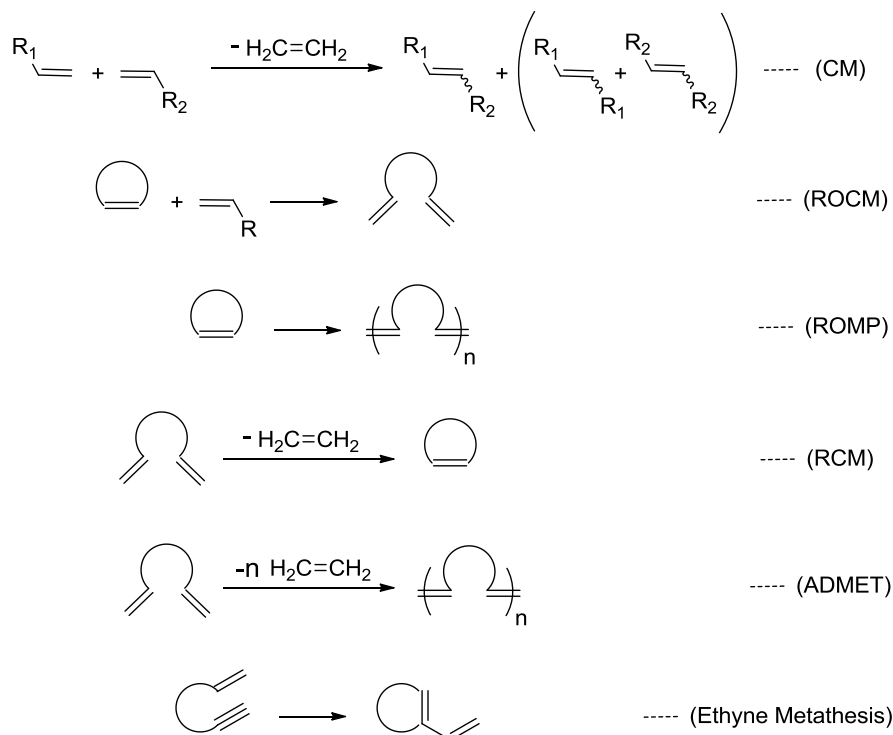
Before presenting the results obtained, a brief introduction on Metathesis reaction is illustrated.

## II.14 Olefin Metathesis

It is a transition metal catalyzed organic reaction that involves breaking and formation of carbon-carbon double bonds between olefins.<sup>195</sup>

<sup>195</sup> (a) Grubbs, R. H.; Pine, S. H. in *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I.; Paquette, L. A. Eds.; Pergamon: New York, **1991**, Vol. 5, Chapter 9.3. (b) Schrock, R. R. in *TheStrem Chemiker*, Vol. XIV, Strem Chemicals, Newburgport, **1992**, No. 1, p. 1-6. (c) Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Metathesis Polymerization*, Academic Press, San Diego, **1997**.

There are various types of olefin metathesis depending on the type of starting material involved and the product obtained: Cross Metathesis (CM), Ring-Opening Cross Metathesis (ROCM), Ring-Opening Metathesis polymerization (ROMP), Ring-Closure Metathesis (RCM), Acyclic Diene Metathesis (ADMET) and Ethyne Metathesis (Scheme II.53),<sup>196</sup> among which we are concerned in particular with ring-closure metathesis.



**Scheme II.53. Various kinds of Olefin Metathesis reactions.**

### Ring Closure Metathesis (RCM)

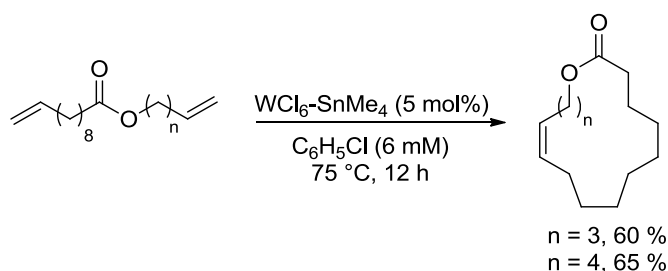
It is a powerful class of olefin metathesis, widely applied for the construction of cyclic compounds (cycloalkenes) via intramolecular carbon-carbon double bond formation between two terminal alkenes.<sup>197</sup>

<sup>196</sup> For selected reviews on olefin metathesis, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Kenneth, J. I. *J. Mol. Catal. A: Chem.* **1998**, *133*, 1. (c) Schuster, M.; Blechert, S. *Angew. Chem. Int. Ed.* **1997**, *36*, 2036. (d) Furstner, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3012. (e) Grubbs, R. H. *Angew. Chem. Int. Ed.* **2006**, *45*, 3760. (f) Samojłowicz, C.; Bieniek, M.; Grela, K. *Chem. Rev.* **2009**, *109*, 3708. (g) Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Rev.* **2010**, *110*, 1746.

<sup>197</sup> For some selected reviews see: (a) Furstner, A. *Top. Catal.* **1997**, *4*, 285. (b) Armstrong, S. K. *J. Chem. Soc., Perkin Trans.* **1998**, *1*, 371. (c) Monfette, S.; Fogg, D. E. *Chem. Rev.* **2009**, *109*, 3783.

RCM is vastly employed as a key step in the synthesis of natural products<sup>198</sup>, and heterocycles<sup>199</sup> of different ring sizes, as well as in polymer chemistry through either pre-functionalization of peptides or post-polymerization functionalization of polymers.<sup>200</sup>

Villemin in 1980 reported the first example of ring-closure metathesis.<sup>201</sup> He used  $WCl_6$ -SnMe<sub>4</sub> catalyst in the ring closure of terminal dienes to afford 15- and 16-membered macrocyclic lactones (macrolides) in 60 % and 65 % yield respectively (Scheme II.54).



Scheme II.54. First report of RCM by Villemin.

### General Mechanism

In 1970s, Chauvin proposed that the active catalyst in the general olefin metathesis reactions was a metal-carbene complex and that the formation of the product proceeded by means of a four-membered metallacycle derivatives.<sup>202</sup> Concerning the ring closing metathesis in particular, Piers *et al.* characterized the key steps for the whole process.<sup>203</sup> Afterwards a detailed DFT based computational protocol reported in 2014 supported the suggested mechanism, displaying a full comprehension of the RCM reaction profile.<sup>204</sup>

<sup>198</sup> For example: (a) Furstner, A.; Radkowski, K.; Grabowski, J.; Wirtz, C.; Mynott, R. *J. Org. Chem.* **2000**, *65*, 8758. (b) Gradillas, A.; Perez-Castells, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6086. (c) Dhara, K.; Mandal, T.; Das, J.; Dash, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 15831. (d) Jacques, R.; Pal, R.; A. Parker, N. A.; Sear, C. E.; Smith, P. W.; Ribaucourt, A.; Hodgson, D. M. *Org. Biomol. Chem.* **2016**, *14*, 5875. (e) Lecourt, C.; Dhambri, S.; Allievi, L.; Sanogo, Y.; Zeghib, N.; Othman, R. B.; Lannou, M.-I.; Sorin, G.; Ardisson, J. *Nat. Prod. Rep.* **2018**, in press, DOI: 10.1039/c7np00048k.

<sup>199</sup> For instance, see review: Villar, H.; Frings, M.; Bolm, C. *Chem. Soc. Rev.* **2007**, *36*, 55.

<sup>200</sup> For recent articles and reviews, see: (a) Gleeson, E. C.; Jackson, W. R.; Robinson, A. J. *Tetrahedron Lett.* **2016**, *57*, 4325. (b) Buchmeiser, M. R. *Polym. Rev.* **2016**, DOI: 10.1080/15583724.2015.1136643. (c) Cromm, P. M.; Schaubach, S.; Spiegel, J.; Furstner, A.; Grossmann, T. N.; Waldmann, H. *Nat. Commun.* **2016**, DOI: 10.1038/ncomms11300. (d) Sinclair, F.; Alkattan, M.; Prunet, J.; Shaver, M. P. *Polym. Chem.* **2017**, *8*, 3385.

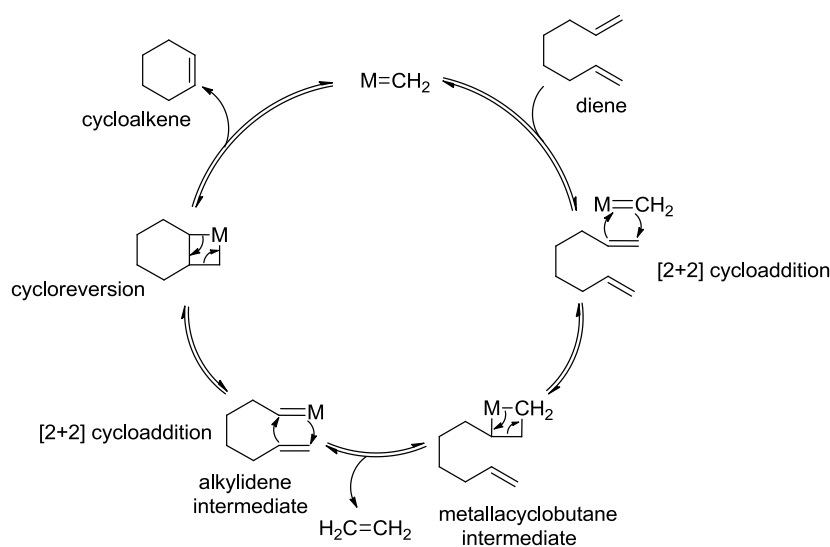
<sup>201</sup> Villemin, D. *Tetrahedron Lett.* **1980**, *21*, 1715.

<sup>202</sup> (a) Herisson, J. L.; Chauvin, Y. *Makromol. Chem.* **1971**, *141*, 161. (b) Schrock, R. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 3748.

<sup>203</sup> (a) Romero, P. E.; Piers, W. E. *J. Am. Chem. Soc.* **2007**, *129*, 1698. (b) van der Eide, E. F.; Piers, W. E. *Nat. Chem.* **2010**, *2*, 571.

<sup>204</sup> Poater, A.; Pump, E.; Vummaleti, S. V. C.; Cavallo, L. *J. Chem. Theory Comput.* **2014**, *10*, 4442.

The mechanism begins with a [2+2] cycloaddition reaction of the active metal carbene catalyst with one of the diene double bonds forming a metallacyclobutane intermediate, which then cycloreverts either to give the same starting materials (destructive route) or to form a new catalytic species with the loss of ethylene (constructive route). The new formed metal alkylidene species then undergoes an intramolecular [2+2] cycloaddition with the second terminal alkene followed by cycloreversion producing the desired product together with a metal carbene complex that reinitiates the catalytic cycle (Scheme II.55). All the catalytic cycle steps are reversible, thus increasing the possibility of other metathesis processes to intersect with RCM depending on the conditions and starting substances.



**Scheme II.55. Transition metal catalyzed RCM cycle.**

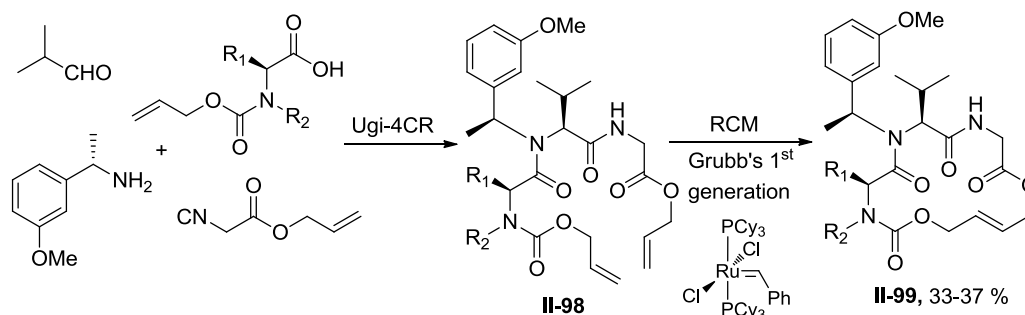
Based on the proposed mechanism, the design of metal-carbene catalysts had been modified.

RCM is widely used as an Ugi post-condensation reaction to provide medium to macro cyclic rings.<sup>205</sup> Where, the pre-functionalization of Ugi adduct with two terminal olefinic bonds is recommended for a subsequent RCM. For example the stereoselective Ugi-RCM strategy, described by Kazmaier and his co-workers in 2005.<sup>206</sup> They used allyl

<sup>205</sup> For some examples on RCM as an Ugi post-condensation reaction, see: (a) Hebach, C.; Kazmaier, U. *Chem. Commun.* **2003**, 596. (b) Krelaus, R.; Westermann, B. *Tetrahedron Lett.* **2004**, 45, 5987. (c) Banfi, L.; Basso, A.; Guanti, G.; Riva, R. *Tetrahedron Lett.* **2003**, 44, 7655. (d) Ribelin, T. P.; Judd, A. S.; Akritopoulou-Zanze, I.; Henry, R. F.; Cross, J. L.; Whittern D. N.; Djuric, S. W. *Org. Lett.* **2007**, 9, 5119. (e) L. Banfi, A. Basso, G. Damonte, F. De Pellegrini, J. L.; Galatini, A.; Guanti, G.; Monfardini, I.; Riva, R.; Scapolla, C. *Bioorg. Med. Chem. Lett.* **2007**, 17, 1341. (f) Oikawa, M.; Naito, S.; Sasaki, M. *Heterocycles* **2007**, 73, 377.

<sup>206</sup> Kazmaier, U.; Hebach, C.; Watzke, A.; Maier, S.; Mues H.; Huch, V. *Org. Biomol. Chem.* **2005**, 3, 136.

isocyanoacetate and various alloc-protected amino acids for preparing 16-membered macrocycles **II-99**. Starting from enantiomerically pure amines and amino acids, they could obtain the Ugi adduct **II-98** with moderate to high diastereoselectivity. Then, RCM using Grubb's first generation catalyst was carried out resulting in the desired product with > 95 % trans-selectivity (Scheme II.56).



Scheme II.56. Stereoselective Ugi-RCM to synthesize 16-membered rings.

In our case, RCM was employed as a post-Ugi condensation reaction for the allylated Ugi adducts “Ugi 5-C” to synthesize various dehydropiperidine derivatives. Before displaying the results obtained, a brief introduction concerning the biological activity and previous synthesis of such heterocycles is outlined.

## II.15 Dehydropiperidine ring

The dehydropiperidine nucleus is found in the core of the anticholinergic alkaloids which blocks the neurotransmitter acetylcholine in the central and peripheral nervous system. They inhibit the parasympathetic nerve impulses that are responsible for the involuntary movement of smooth muscles found in the gastrointestinal tract, urinary tract, lungs and various body parts. For example: Eburnamenine, Noroliveroline and Pleiocarpamine.<sup>207</sup> It is found as well in Anatabine,<sup>208</sup> which is one of the minor alkaloids found in plants like tomato and tobacco (see Figure II.4).

<sup>207</sup> Naaz, H.; Singh, S.; Pandey, V. P.; Singh, P.; Dwivedi, U. N. *Indian J. Biochem. Biophys.* **2013**, 50, 120.

<sup>208</sup> Dewey, R. E.; Xie, J. *Phytochemistry* **2013**, 94, 10.

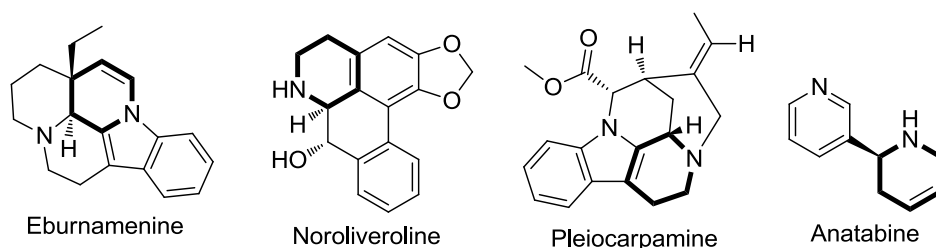


Figure II.4. The structures of alkaloids containing dehydropiperidine nucleus.

It is also a motif present in a wide number of drugs as: Droperidol (an antidopaminergic drug used as an antiemetic (i.e. to treat nausea) and as an antipsychotic, that is often used as a sedative in intensive-care treatment)<sup>209</sup>, Brexpiprazole (which is an antipsychotic used to treat schizophrenia, and as an adjunctive treatment for depression)<sup>210</sup>, Phenindamine (an antihistamine and anticholinergic closely related to cyproheptadine that is used to treat symptoms of the common cold and allergies, such as sneezing, itching, rashes, and hives)<sup>211</sup> and Xaliproden (it acts as a 5HT<sub>1A</sub> agonist.<sup>212</sup> It has neurotrophic and neuroprotective effects *in vitro*,<sup>213</sup> and has been used in the treatment of several neurodegenerative conditions including amyotrophic lateral sclerosis (ALS)<sup>214</sup> and Alzheimer's disease<sup>215</sup>). It is also the main structure of the MPTP, which is a prodrug to the neurotoxin MPP<sup>+</sup> that causes permanent symptoms of Parkinson's disease by destroying dopaminergic neurons in the substantia nigra of the brain.<sup>216</sup> Structures are drawn in Figure II.5.

<sup>209</sup> Scuderi, P. E. *Anesthesiology* **2003**, 98, 289.

<sup>210</sup> "FDA approves new drug to treat schizophrenia and as an add on to an antidepressant to treat major depressive disorder". *FDA Newsroom*. FDA. Retrieved 14 July **2015**.

<sup>211</sup> (a) US Patent 2546652 - Pyridindenes and process for their manufacture. (b) *J. Pharm. Sci.* **1980**, 69, 342.

<sup>212</sup> Appert-Collin, A.; Duong, F. H.; Degrace, P.; Warter, J. M.; Poindron, P.; Gies, J. P. *Int. J. Immunopathol. Pharmacol.* **2005**, 18, 21.

<sup>213</sup> (a) Labie, C.; Lafon, C.; Marmouget, C.; Saubusse, P.; Fournier, J.; Keane, P. E.; Le Fur, G.; Soubrié, P. *Br. J. Pharmacol.* **1999**, 127, 139. (b) Duong, F. H.; Warter, J. M.; Poindron, P.; Passilly, P. *Br. J. Pharmacol.* **1999**, 128, 1385.

<sup>214</sup> Meininger, V.; Bensimon, G.; Bradley, W. R.; Brooks, B.; Douillet, P.; Eisen, A. A.; Lacomblez, L.; Leigh, P. N.; Robberecht, W. *Amyotroph. Lateral Scler. Other Motor Neuron Disord.* **2004**, 5, 107.

<sup>215</sup> Lemaire, L.; Fournier, J.; Ponthus, C.; Le Fur, Y.; Confort-Gouny, S.; Vion-Dury, J.; Keane, P.; Cozzone, P. *Invest. Radiol.* **2002**, 37, 321.

<sup>216</sup> Vinken, P. J.; Bruyn, G. W. (1994). *Intoxications of the Nervous System*. Elsevier Health Sciences. p. 369.

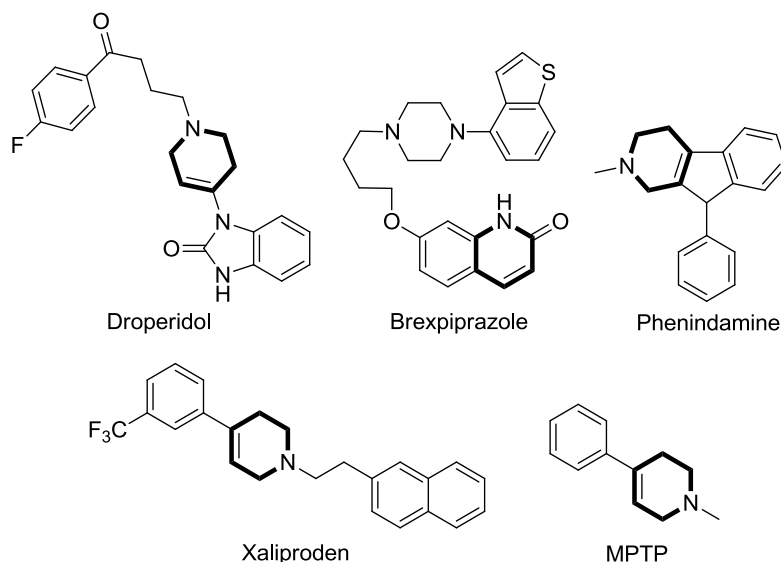
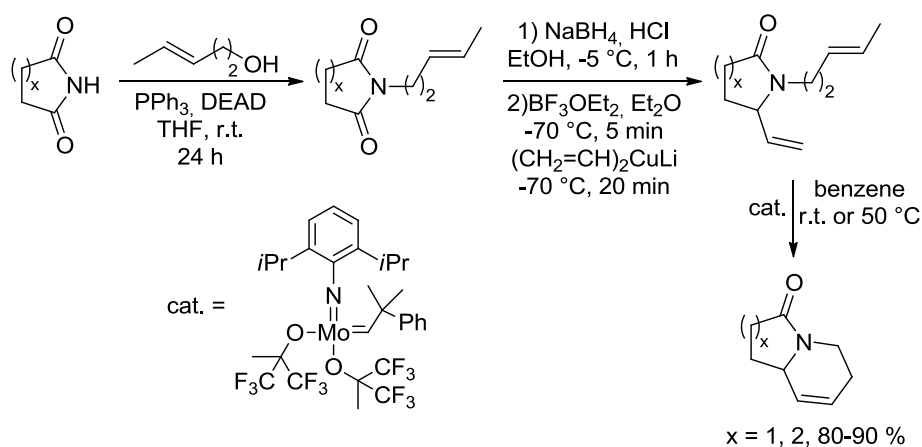


Figure II.5. Dehydropiperidine derivatives as drugs.

## Synthesis

RCM is considered a powerful tool for the construction of the dehydropiperidine moiety. The reaction usually involves a ring closure metathesis of diallylated scaffolds using one of the Grubb's catalysts. Herein, we present some of the examples from the literature.

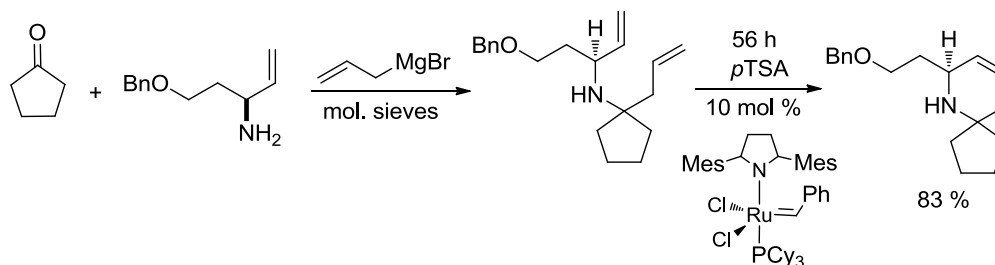
In 1994, Martin and his coworkers<sup>217</sup> were the first to illustrate that RCM could be applied to synthesize bicyclic dehydropiperidines. They used Shrock's catalyst in the metathesis of  $\alpha,\omega$ -dienes obtained from succinimide and glutarimide (Scheme II.57).



Scheme II.57. Employing RCM to synthesize bicyclic dehydropiperidines.

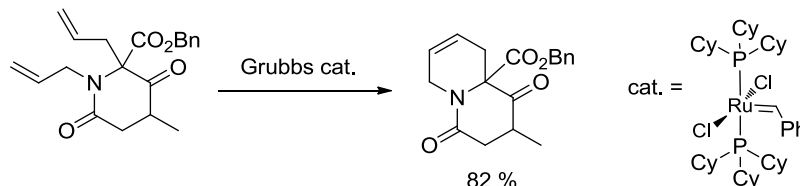
<sup>217</sup> Martin, S. F.; Liao, Y.; Chen, H.-J.; Pätzelt, M.; Ramser, M. N. *Tetrahedron Lett.* **1994**, 35, 6005.

In 2000, an approach towards the spirocyclic core of halichlorine and pinnanic acid was presented.<sup>218</sup> The authors described an imine allylation/RCM sequence to prepare spiro dehydropiperdines (Scheme II.58). They succeeded in performing the RCM using free amines, which are known to be incompatible with metathesis due to catalyst inhibition by the basic amine. They used 1.1 equiv of *p*TSA, in order to generate the corresponding ammonium salts *in situ*, together with Grubbs catalyst second generation to afford the spirobicyclic product.



**Scheme II.58. Imine allylation/RCM sequence to prepare spiro dehydropiperdines.**

In 2003, Chai *et al.*<sup>219</sup> reported the ring closure metathesis of diallylated piperazinedione using first generation Grubb's catalyst. The reaction allowed the synthesis of bicyclic dehydropiperidine in 82 % yield (Scheme II.59).



**Scheme II.59. Ring Closure Metathesis of diallylated piperazinedione.**

## II.16 Towards dehydropiperidine derivatives

Allylated Ugi adducts derived from allyl amines underwent RCM smoothly to afford the target compounds. Hoveyda-Grubbs catalyst second generation was chosen as the catalyst for RCM since according to the literature, it showed better catalytic activity compared to other different Grubbs catalysts. In addition to, its ease of handling and air stability.<sup>196f</sup> Among the classical solvents reported for the metathesis,<sup>196f</sup> toluene was chosen as the reaction solvent. The reaction temperature and time were adjusted according to the reaction progress by TLC

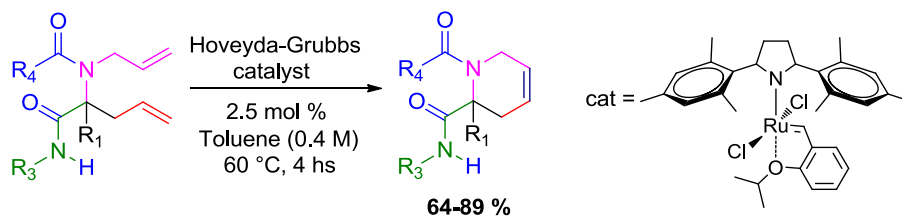
<sup>218</sup> Wright, D. L.; Schulte II, J. P.; Page, M. A. *Org. Lett.* **2000**, 2, 1847.

<sup>219</sup> Chai, C. L. L.; Elix, J. A.; Huleatt, P. B. *Tetrahedron Lett.* **2003**, 44, 263.

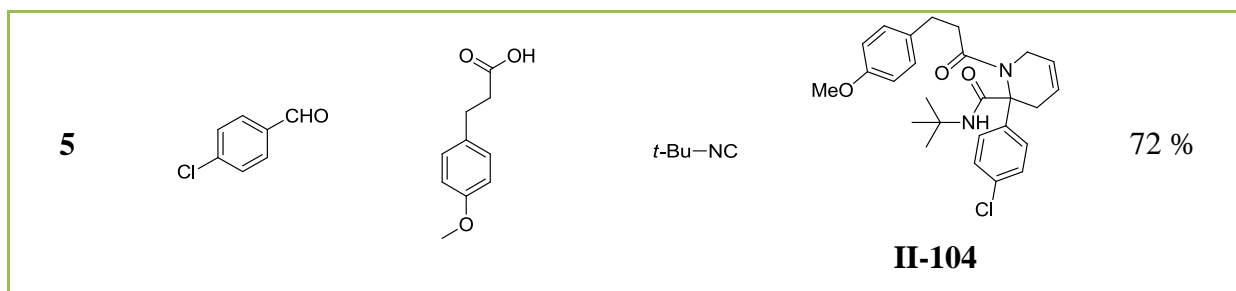


into 60 °C for 4 hours. Applying this methodology, a group of 3,4-dehydropiperidine derivatives has been synthesized. The results are reported in Table II-8.

Table II-8. From Ugi-5C towards 3,4-dehydropiperidine derivatives.

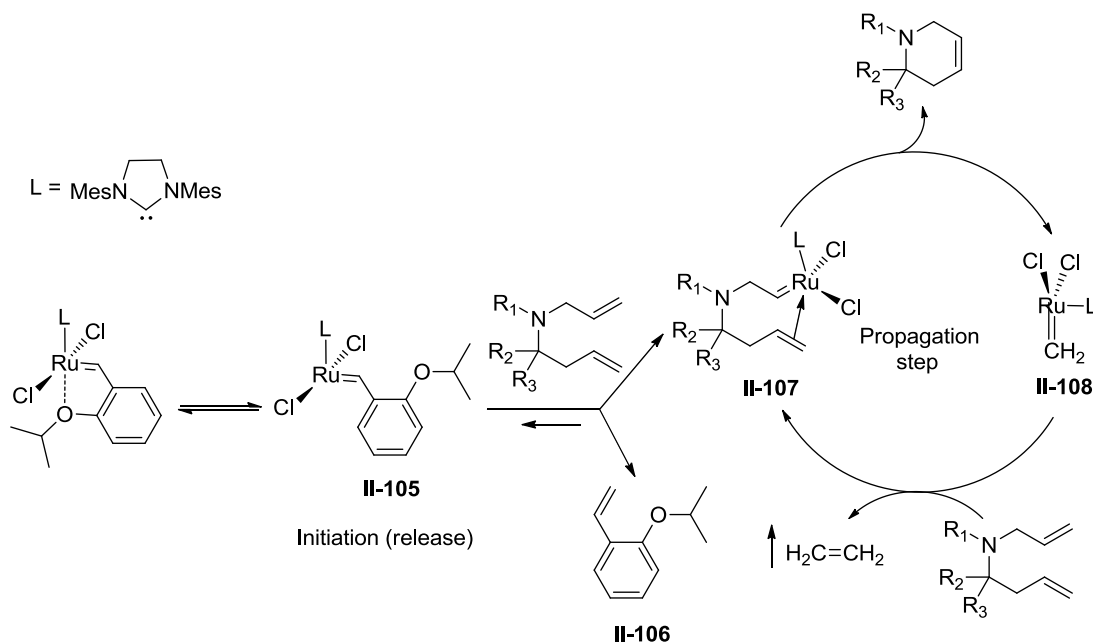


Entry	Aldehyde	Acid	Isocyanide	Isolated product	Yield
1			<i>t</i> -Bu-NC	 <b>II-100</b>	89 %
2				 <b>II-101</b>	64 %
3			<i>t</i> -Bu-NC	 <b>II-102</b>	72 %
4			<i>t</i> -Bu-NC	 <b>II-103</b>	68 %



Thus, as shown above various examples of 3,4-dehydropiperidine were obtained in good to excellent yields from 64 to 89 %. The described method was efficient for different Ugi adducts varying either the acid, aldehyde or isocyanide moieties. All the obtained yields were comparable favoring the cyclization.

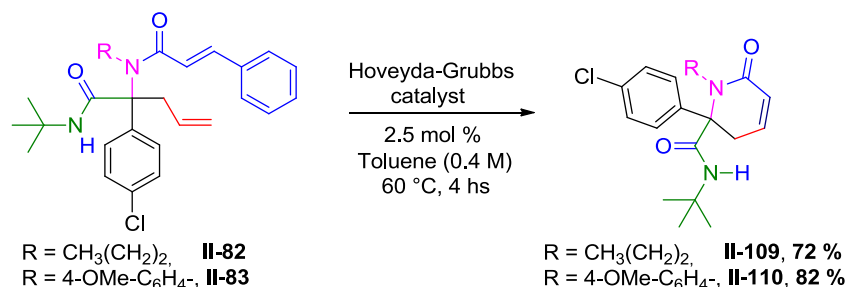
The proposed reaction mechanism, as previously reported,<sup>196f</sup> initiates with the dissociation of the Ru-O coordination bond to form the 14-electron complex **II-105**.<sup>220</sup> The latter undergo several [2+2] metallocycloaddition with the release of **II-106** leading to the two propagating species **II-107** and **II-108** which afford the desired product via a catalytic cycle (Scheme II.60). The catalyst could be regenerated through the reaction of **II-108** and **II-106** as a termination step.



**Scheme II.60.** Proposed reaction mechanism for RCM using Hoveyda-Grubbs 2<sup>nd</sup> generation catalyst.

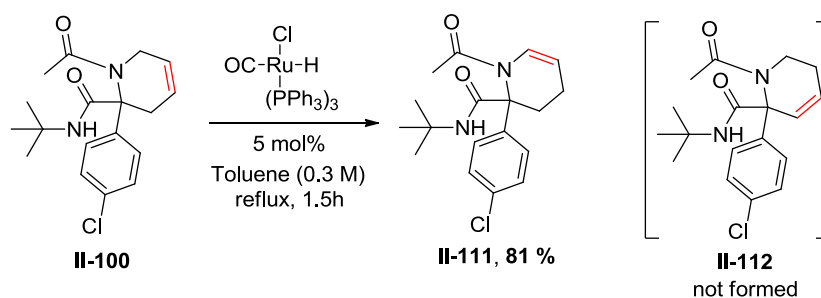
<sup>220</sup> (a) Love, J. A.; Morgan, J. P.; Trnka, T. M.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, 41, 4035. (b) Kingsburg, J. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, 127, 4510.

Following the same protocol, using Ugi adduct derived from cinnamic acid instead of allyl amine another heterocyclic scaffold could be easily accessed. Thus, using Ugi adducts **II-82** and **II-83** under the same previously mentioned reaction conditions, 3,4-dehydropiperidin-2-one derivatives **II-109** and **II-110** were obtained with 72 and 82 % yields respectively (Scheme II.61).



Scheme II.61. From Ugi-5C towards 3,4-dehydropiperidin-2-one derivatives.

Furthermore, following a simple isomerization reaction, 2,3-dehydropiperidine derivative could be delivered. Such isomerization reactions are known to progress using acid, base or organometallic catalysts. RuClH(CO)(PPh<sub>3</sub>)<sub>3</sub> is one of the common catalysts used for this reaction.<sup>221</sup> Using the classical conditions in literature,<sup>222</sup> the reaction was performed with 5 mol % of the RuClH(CO)(PPh<sub>3</sub>)<sub>3</sub> complex in toluene under reflux. After 1.5 hours, the target compound **II-111** was obtained as a single product in 81 % yield. The other possible isomer **II-112** was not observed (Scheme II.62).

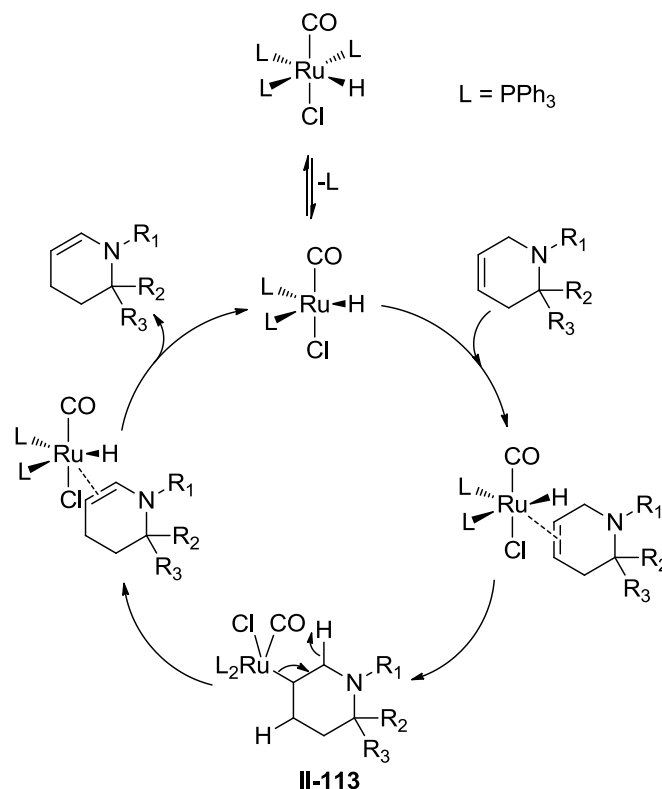


Scheme II.62. Isomerization of 3,4-dehydropiperidine into 2,3-dehydropiperidine derivatives.

<sup>221</sup> Among the interesting examples in the literature, see: (a) Bingham, D.; Webster, D. E.; Wells, P. B. *J. Chem. Soc., Dalton Trans.* **1974**, 1519. (b) Matsuda, I.; Kato, T.; Sato, S.; Izumi, Y. *Tetrahedron Lett.* **1986**, 27, 5747. (c) Suzuki, H.; Yashima, H.; Hirose, T.; Takahashi, M.; Moro-oka, Y.; Ikawa, T. *Tetrahedron Lett.* **1980** 21, 4927. (d) Hirai, K.; Suzuki, H.; Moro-oka, Y.; Ikawa, T. *Tetrahedron Lett.* **1980**, 21, 3413. (e) Hirai, K.; Suzuki, H.; Kashiwagi, H.; Morooka, Y.; Ikawa, T. *Chem. Lett.* **1982**, 23. (f) Hiraki, K.; Matsunaga, T. *Organometallics* **1994**, 13, 1878.

<sup>222</sup> Wakamatsu, H.; Nishida, M.; Adachi, N.; Mori, M. *J. Org. Chem.* **2000**, 65, 3966.

The mechanism proceeds through a metal hydride addition-elimination sequence.<sup>223</sup> Where, the olefin coordinates to the metal hydride complex. Then, the olefin double bond is inserted into the Ru-H bond of the ruthenium (II) hydride complex yielding a ruthenium alkyl intermediate **II-113**. This is followed by a  $\beta$ -hydride elimination giving isomerized product and regenerates the catalytic species (Scheme II.63).



**Scheme II.63. Plausible mechanism for Ru-hydride catalyzed isomerization of double bond.**

## II.17 Conclusion

In this chapter, we reported a novel methodology for the intermolecular alkylation of Ugi adducts paving the way to Ugi 5-CR. We presented two general protocols; Ugi/Intermolecular Tsuji-Trost reaction and Ugi/Intermolecular alkylation reaction. Both protocols proceeded at room temperature using 2.5 equiv. of NaH in DMSO by means of 1,3-dianion intermediates. Such dianionic species proved to be the key step for enhancing the nucleophilicity of the peptidyl carbanion allowing the reaction to progress smoothly at room temperature to completion in almost 1 hour for most of the examples. A selectively C-alkylation was attained. The scope of this reaction was explored with various Ugi substrates. It was limited to Ugi adducts derived from aromatic aldehydes.

<sup>223</sup> McGrath, D. V.; Grubbs, R. H. *Organometallics* **1994**, 13, 224.

From another point of view, it could be considered as an alternative approach to access diverse aromatic ketone derived-Ugi products via a two-step procedure.

More interestingly, the reaction could be carried out under one-pot condition reducing both the time consumed and chemicals used for the purification of intermediates. Such cascade proved to be efficient affording the desired alkylated Ugi products in high yields.

As an additional value to the study, we tested the synthetic utility of such allylated Ugi 5-C applying Ugi-post condensation reaction like: RCM. This latter allowed preparing various biologically important dehydropiperidine derivatives using different ruthenium complexes. Hence, both 3,4-dehydropiperidine and 3,4-dehydropiperidin-2-one derivatives could be easily prepared in two steps (cascade Ugi/intermolecular allylation then RCM) employing our strategy.

## Chapter III : General methodology for $\beta$ -lactam synthesis

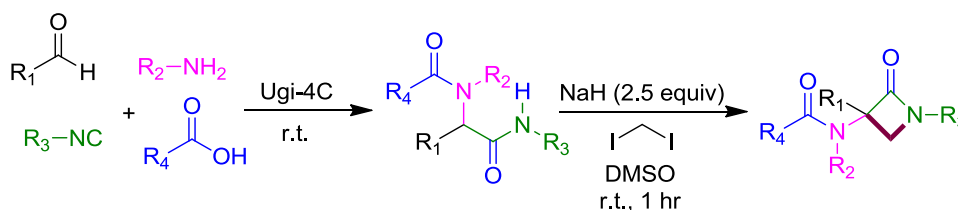
The chemistry described in this chapter has been published in:

Zidan, A.; Garrec, J.; Cordier, M.; El-Naggar, A. M.; Abd El-Sattar, N. E. A.; Ali, A. K.; Hassan, M. A.; El Kaïm, L. *Angew. Chem. Int. Ed.* **2017**, 56, 12179.



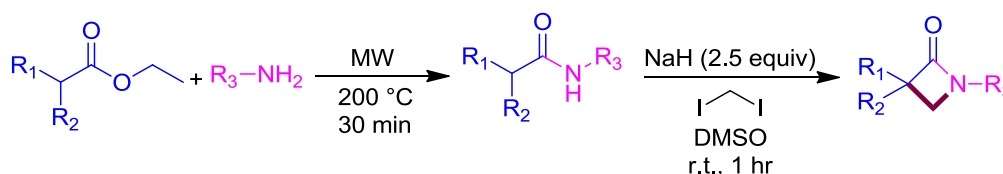
### III.1 Presentation of the Project

In this project, we explored the nucleophilic character of the Ugi amide dianion intermediates towards biselectrophiles yielding cyclic scaffolds. Diiodomethane was chosen as an example for the biselectrophiles. Thus, Ugi adducts were allowed to react with diiodomethane in presence of 2.5 equiv. of NaH for 1 hour in DMSO at room temperature (Scheme III.1). This reaction opened an access to 4-component libraries of  $\beta$ -lactams through a formal [3+1] cycloaddition.



**Scheme III.1. Ugi/Intermolecular [3+1] cycloaddition.**

This procedure could be successfully extended to various malonic ester amides and other related derivatives affording diverse  $\beta$ -lactams (Scheme III.2). Hence, this turns the proposed strategy into a general efficient protocol for the synthesis of antibacterial  $\beta$ -lactams.



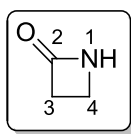
**Scheme III.2. General  $\beta$ -Lactam synthesis through [3+1] cycloaddition.**

Before discussing the results obtained, a brief literature survey about  $\beta$ -lactams, their antibacterial effects, synthesis and reactivity is displayed.

### III.2 $\beta$ -Lactam ring

It is a four-membered cyclic amide (lactam) ring, where the nitrogen atom is attached to the  $\beta$ -carbon atom relative to the carbonyl group (i.e  $\beta$ -lactam) (Figure III.1).



Figure III.1. The simplest  $\beta$ -Lactam “2-Azetidinone”.

$\beta$ -Lactams attracted the attention of many chemists due to their well-known antibacterial activities,<sup>224</sup> as well as their utility as a synthetic building block (synthon) in organic synthesis.<sup>225</sup> It is a highly strained and reactive cyclic amide. The numbering of the  $\beta$ -lactam ring begins at the nitrogen atom and continues towards the carbonyl carbon following the IUPAC rules.

### A brief History: Antibiotic discovery

The world's first antibiotic discovery dates back to 1928, when Alexander Fleming, a Scottish bacteriologist, discovered benzylpenicillin (Penicillin G) from the mould *Penicillium notatum*.<sup>226</sup> While working on another bacteriological problem, he observed that one of his petri dishes containing *Staphylococcus aureus* bacteria was contaminated with a fungus which affected the growth of the neighboring bacteria. This fungus was *Penicillium notatum*, he was able to describe and isolate the compound around this fungus that inhibited the bacterial growth *in vitro* (Figure III.2) and termed it as "Penicillin".

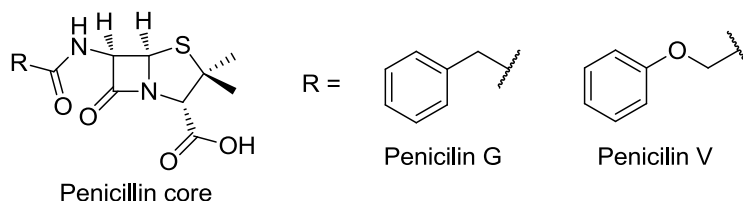


Figure III.2. Chemical structure of Penicillin.

<sup>224</sup> See for example: (a) von Nussbaum, F.; Brands, M.; Hinzen, B.; Weigand, S.; Habich, D. *Angew. Chem., Int. Ed.* **2006**, 45, 5072. (b) Singh, G. S. *Mini-Rev. Med. Chem.* **2004**, 4, 69. (c) Singh, G. S. *Mini-Rev. Med. Chem.* **2004**, 4, 93. (d) Buynak, J. D. *Curr. Med. Chem.* **2004**, 11, 1951. (e) Veinberg, G.; Vorona, M.; Shestakova, I.; Kanepe, I.; Lukevics, E. *Curr. Med. Chem.* **2003**, 10, 1741. (f) Kidwai, M.; Sapra, P.; Bhushan, K. R. *Curr. Med. Chem.* **1999**, 6, 195.

<sup>225</sup> Some selected reviews: (a) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Rev.* **2007**, 107, 4437. (b) Deshmukh, A. R. A. S.; Bhawal, B. M.; Krishnaswamy, D.; Govande, V. V.; Shinkre, B. A.; Jayanthi, A. *Curr. Med. Chem.* **2004**, 11, 1889. (c) Alcaide, B.; Almendros, P. *Curr. Med. Chem.* **2004**, 11, 1921. (d) Ojima, I. F.; Delaloge, F. *Chem. Soc. Rev.* **1997**, 26, 377. (e) Manhas, M. S.; Wagle, D. R.; Chiang, J.; Bose, A. K. *Heterocycles* **1988**, 27, 1755.

<sup>226</sup> Fleming, A. *Br. J. Exp. Pathol.* **1929**, 10, 226.

A second revolution in the history of antibiotics began in 1938, when Howard Florey together with Chain and Heatley decided to culture the *Penicillium notatum* fungus to provide them with sufficient amount of penicillin required to test it for the first time as a drug.<sup>227</sup> By 1940, the first penicillin trial experiment involving mice was carried out. The mice were injected with a severe dosage of group A streptococcus bacteria, where some of them were given afterwards a dose of penicillin, while another group served as a control. They found that only the ones which had received the penicillin cure survived. This experiment demonstrated the potential of penicillin as a life-saving drug.

The major challenge that brightened up thereafter was the production of pure penicillin in large quantities to start the human trials. The first patient who received penicillin as a drug was a woman suffering from terminal cancer. Soon she got fever and rigor that were caused by impurities accompanying penicillin. As a result, Florey *et al.* pointed out the necessity of additional purification of penicillin before serving it to other patients. The second patient was a policeman suffering from staphylococcal and streptococcal infection. After receiving several doses of purified penicillin, he seemed responding to the treatment and his health was improved. But unfortunately due to the shortage of penicillin, his case deteriorated and he died in a short time.

Thereafter, penicillin proved a prominent effect in the therapy of bacterial infections without any side effects. And by 1946, it was widely described as medicine.<sup>228</sup> In 1945, a Noble prize in medicine was awarded to Fleming, Florey and Chain thanks to their discovery of penicillin and its therapeutic effect in several infectious diseases.<sup>229</sup> The chemical structure of penicillin was confirmed by Hodgkin *et al.* by means of X-ray crystallography in 1945 (Figure III.3).<sup>230</sup>

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<sup>227</sup> (a) Heatley, N. *Penicillin and Luck: Good Fortune in the Development of the miracle Drug*: RCJT Books; **2004**. (b) Cranston, D. Sidebottom E. *Penicillin and the legacy of Norman Heatley*: Wordsbydesign; **2016**.

<sup>228</sup> Fraser, I. *Br. Med. J. (Clin. Res. Ed.)*. **1984**, 289 (6460), 1723.

<sup>229</sup> The Nobel Prize in Physiology or Medicine **1945**. Available from: [http://www.nobelprize.org/nobel\\_prizes/medicine/laureates/1945/](http://www.nobelprize.org/nobel_prizes/medicine/laureates/1945/).

<sup>230</sup> Crowfoot, D.; Bunn, C. W.; Rogers-Low, B. W.; Turner-Jones, A. *In Chemistry of Penicillin*; Clarke, H. T., Johnson, J. R., Robinson, R., Eds.; Princeton University Press: Princeton, NJ, **1949**, 310-367.

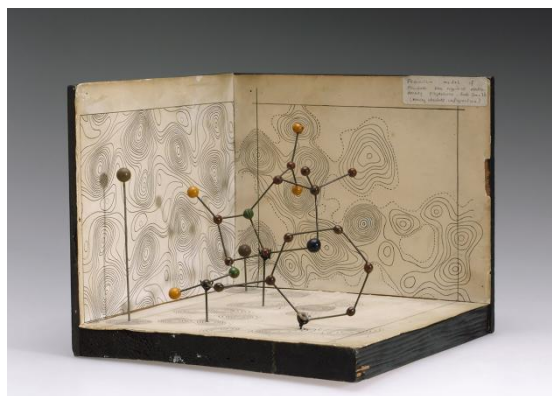


Figure III.3. Molecular model of penicillin by Hodgkin, 1945.

The discovery of penicillin was a key step in the history of medicine and since then a greater attention has been paid to discover and develop more powerful antibiotics.<sup>231</sup>

### $\beta$ -Lactam as antibiotics

$\beta$ -Lactam ring is the main core structure of various families of antibiotics, therefore they are named  $\beta$ -lactam antibiotics. Among these different classes are: penams (penicillin derivatives), penems, carbapenams, carbapenems, oxapenams, cepheems, carbacepheems and oxacepheems (see general structures in Figure III.4). They differ mainly in the structure of the fused ring to the  $\beta$ -lactam, whether being saturated or unsaturated 5-membered or 6-membered ring.<sup>232</sup>

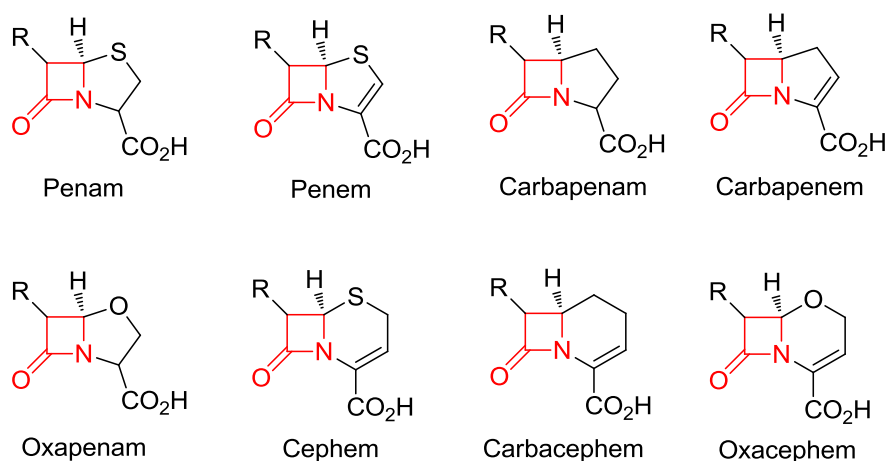


Figure III.4. Fused  $\beta$ -lactam core structure of diverse  $\beta$ -lactam antibiotics.

<sup>231</sup> Lobanovska, M.; Pilla, G. *Yale J. Biol. Med.* **2017**, 90, 135.

<sup>232</sup> Dalhoff, A.; Janjic, N.; Echols, R. *Biochem. Pharmacol.* **2006**, 71 (7), 1085.

Penams contain a  $\beta$ -lactam ring fused to a thiazolidine one.<sup>232</sup> Penicillin derivative as Penicillin G and V, are the main elements of such  $\beta$ -lactam antibiotics category. Penicillin antibiotics were among the first effective treatments against many bacterial infections caused by staphylococci and streptococci. They are still widely used nowadays.

$\beta$ -Lactam antibiotics are usually prescribed for the treatment of infectious bacterial diseases caused by susceptible organisms. At the beginning, they were mainly active only against Gram-positive bacteria, but recently a broad array of  $\beta$ -lactam antibiotics active against different Gram-negative organisms has been developed.

Another family of  $\beta$ -lactam antibiotics is monobactam antibiotics in which the  $\beta$ -lactam ring is not fused to any other ring. Those monobactams unlike other  $\beta$ -lactam antibiotics are effective only towards Gram-negative bacteria. The common examples for the monobactams are: aztreonam,<sup>233</sup> tigemonam,<sup>234</sup> carumonam,<sup>235</sup> nocardicin A, and tabtoxinine,<sup>236</sup> among which aztreonam is the only commercially available monobactam antibiotic used for the treatment of bone and joint infections (structures are presented in Figure III.5). Nocardicin A was the first isolated monobactam having biological properties.<sup>237</sup> The antibacterial effect associated with the monobactam antibiotics suggested that the biological activity is correlated to the presence of a suitably functionalized  $\beta$ -lactam and does not necessarily require a conformational constrained bicyclic structure.<sup>238</sup>

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<sup>233</sup> (a) *British national formulary: BNF 69* (69 ed.). British Medical Association. **2015**, p. 381. (b) *"WHO Model List of Essential Medicines (20th List)"* World Health Organization. March **2017**.

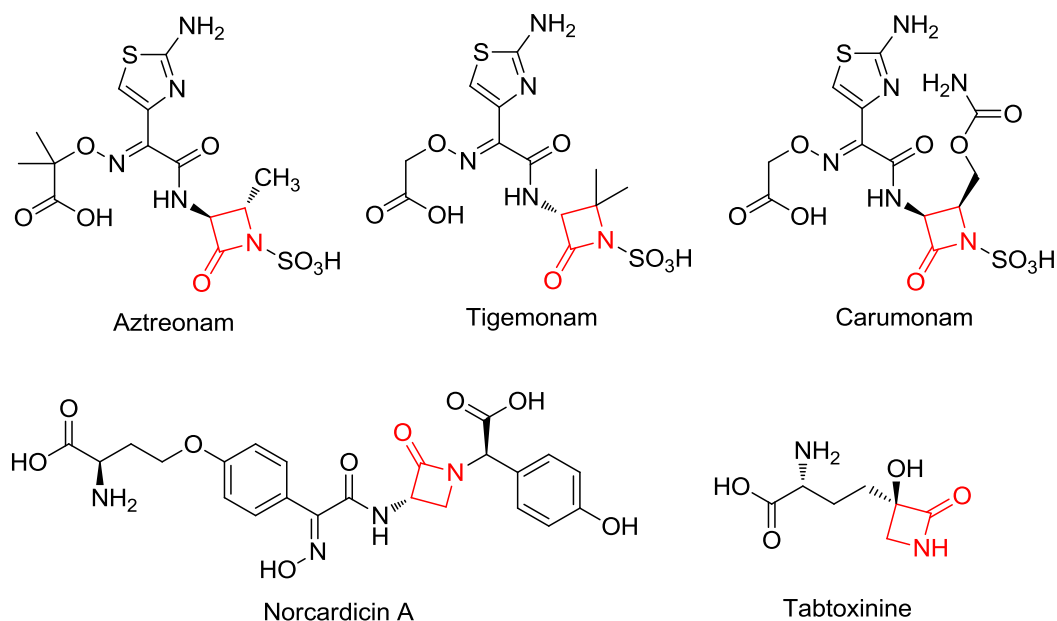
<sup>234</sup> Fuchs, P. C.; Jones, R. N.; Barry, A. L. *Antimicrob. Agents Chemother.* **1988**, 32 (3), 346.

<sup>235</sup> McNulty, C. A.; Garden, G. M.; Ashby, J.; Wise, R. *Antimicrob. Agents Chemother.* **1985**, 28 (3), 425.

<sup>236</sup> Thomas, M. D.; Langston-Unkefer, P. J.; Uchytel, T. F.; Durbin, R. D. *Plant Physiol.* **1983**, 71 (4), 912.

<sup>237</sup> (a) Aoki, H. *J. Antibiof.* **1976**, 29, 492. (b) Hashimoto, H.; Komori, T. Kamiya, T. *J. Am. Chem. Soc.* **1976**, 98, 3023.

<sup>238</sup> (a) Koster, W. H.; Cimarusti, Ch. M. In *Chemistry and Biology of  $\beta$ -Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, **1982**. (b) Imada, A.; Kitano, K.; Kintaka, K.; Murio, M.; Asai, M. *Nature* **1981**, 289, 590.



**Figure III.5. Structures of monobactam antibiotics.**

Usually such antibiotics block the ability of the bacteria to biosynthesize their cell wall. This inhibition leads to a bacterial death. Bacteria, in return, produce  $\beta$ -lactamases which is a type of enzymes that breaks the  $\beta$ -lactam ring; hence it resists the  $\beta$ -lactam antibiotics using such enzyme. More than 1,800 different  $\beta$ -lactamase enzymes have been reported in different kinds of bacteria.<sup>239</sup> Consequently, the production of new  $\beta$ -lactam antibiotics and searching for innovative efficient methodologies for their synthesis is an utmost necessity.

Nevertheless, an alternative approach to overcome this sort of bacterial resistance has been adopted. It includes the development of inhibitors for the bacterial  $\beta$ -lactamase enzymatic cleavages. This class of enzyme inhibitors is called  $\beta$ -lactamase inhibitors.<sup>240</sup>  $\beta$ -Lactamase inhibitors themselves have low antibiotic activity,<sup>241</sup> that's why they should be combined with a  $\beta$ -lactam antibiotic. Those inhibitors prevent the bacterial degradation of the antibiotics and therefore enhance their antibacterial effect.<sup>242</sup> Many  $\beta$ -lactamase inhibitors are known, for example: clavulanic acid, sulbactam and tazobactam (see structures in Figure III.6).

<sup>239</sup> Brandt, C. ; Braun, S. D.; Stein, C.; Slickers, P.; Ehrlich, R.; Pletz, M. W.; Makarewicz, O. *Scientific Reports* **2017**, 7, 43232.

<sup>240</sup> (a) Essack, S. Y. *Pharm. Res.* **2001**, 18 (10), 1391. (b) Drawz, S. M.; Bonomo, R. A. *Clin. Microbiol. Rev.* **2010**, 23, 160.

<sup>241</sup> Lee, N. L. S.; Yuen, K. Y.; Kumana, C. R. *JAMA* **2001**, 285, 386.

<sup>242</sup> Watson, I. D.; Stewart, M. J.; Platt, D. J. *Clin. Pharmacokinet.* **1988**, 15 (3), 133.

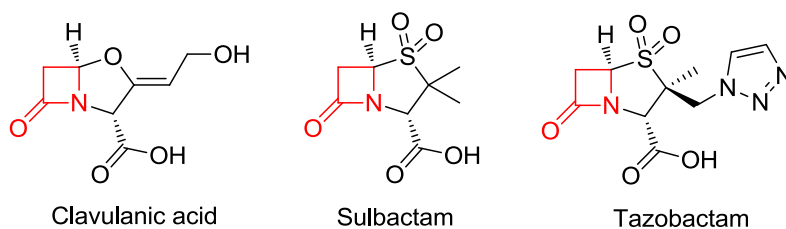


Figure III.6. Structures of the  $\beta$ -lactamase inhibitors.

In medicine,  $\beta$ -lactamase inhibitors are not sold individually as drugs. Instead, they exist as a combination of  $\beta$ -lactam antibiotic/ $\beta$ -lactamase inhibitors with comparable half-life. A number of antibiotics are available in market nowadays for example: Augmentin (a combination of amoxicillin, a  $\beta$ -lactam antibiotic, and potassium clavulanate, a  $\beta$ -lactamase inhibitor),<sup>243</sup> Unasyn (a combination of ampicillin, a  $\beta$ -lactam antibiotic, and sulbactam, a  $\beta$ -lactamase inhibitor),<sup>244</sup> Zosyn (a combination of piperacillin, a  $\beta$ -lactam antibiotic, and tazobactam, a  $\beta$ -lactamase inhibitor).<sup>245</sup> Full structures are displayed below in Figure III.7.

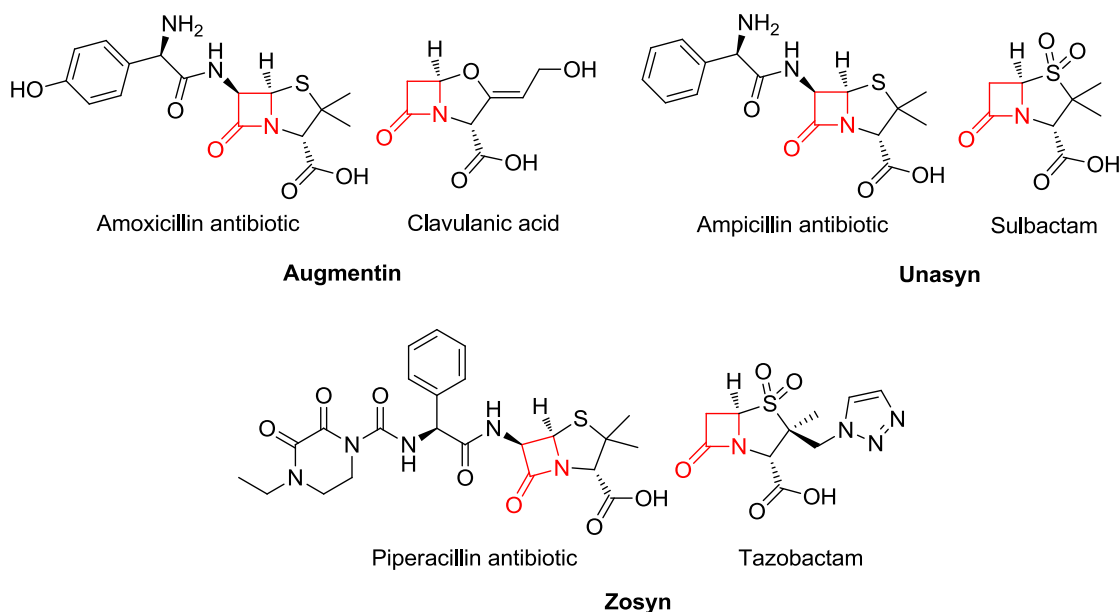


Figure III.7. Structures of some commercial antibiotics.

We are particularly interested in expanding the scope of the monobactam rings syntheses and evaluating their antibacterial activity.

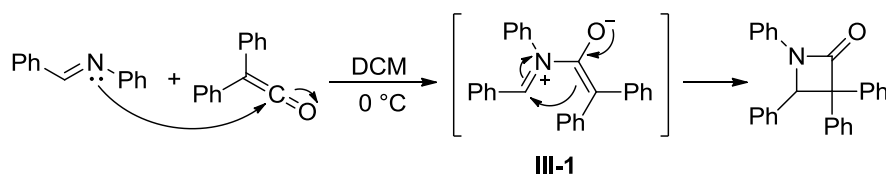
<sup>243</sup> It was approved for medical use in the United States in 1984, and is among the WHO list (19<sup>th</sup> list) of essential medicines, April 2015.

<sup>244</sup> It was used in the United States since 1987.

<sup>245</sup> It was approved for medical use in the United States in 1993.

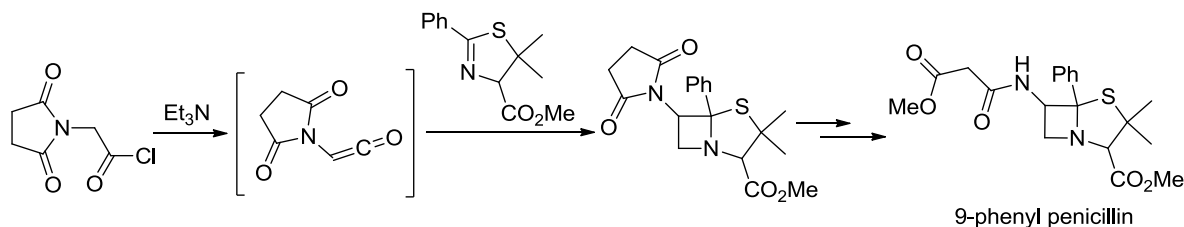
### III.3 $\beta$ -Lactam synthesis survey

The first synthesis of  $\beta$ -lactam was carried out by Hermann Staudinger in 1907.<sup>246</sup> It was named after him as Staudinger synthesis. It involved a [2+2] cycloaddition of an imine to a diphenylketene yielding  $\beta$ -lactam (Scheme III.3). It proceeds via a stepwise ketene imine cycloaddition, which begins with a nucleophilic attack of the imine onto the ketene forming a zwitterionic intermediate **III-1**. The  $\beta$ -lactam is then obtained via a conrotatory electrocyclic ring closure.<sup>247</sup>



**Scheme III.3. Staudinger synthesis of  $\beta$ -lactam.**

The first synthetic penicillin was prepared using the [2+2] cycloaddition approach in 1950 (see Scheme III.4).<sup>248</sup>



**Scheme III.4. First synthesis of 9-phenyl penicillin.**

Since then, several modifications and approaches have been described towards the synthesis of the biologically valuable  $\beta$ -lactams.<sup>249</sup> We will focus on the ones with the highest impact on the general synthesis of  $\beta$ -lactams and those relevant to our project.

<sup>246</sup> (a) Staudinger, H. *Justus Liebigs Ann. Chem.* **1907**, 356, 51. (b) Tidwell, T. T. *Angew. Chem. Int. Ed.* **2008**, 47, 1016.

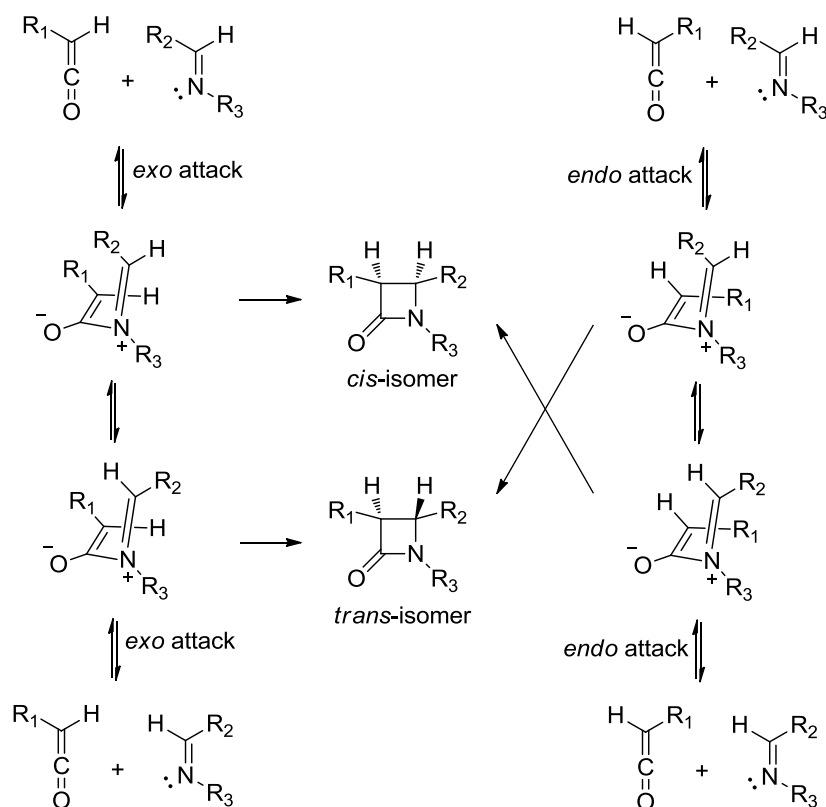
<sup>247</sup> Georg, G. I.; Ravikumar, V. T. *The Organic Chemistry of  $\beta$ -Lactams*; Georg, G. I., Ed.; Verlag Chemie: New York, **1993**; pp 295-368 and references therein.

<sup>248</sup> Sheehan, J. C.; Buhle, E. L.; Corey, E. J.; Laubach, G. D.; Ryan, J. J. *J. Am. Chem. Soc.* **1950**, 72, 3828.

<sup>249</sup> See reviews for example: (a) Ratcliffe, R. W.; Albers-Schonberg, G. In *Chemistry and Biology of  $\beta$ -Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, **1982**, Vol. 2. (b) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, **1990**. (c) Southgate, R.; Branch, C.; Coulton, S.; Hunt, E. In *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products*; Lukacs, G., Ed.; Springer-Verlag: Berlin, **1993**, Vol. 2. (d) Isaacs, N. S. *Chem. Soc. Rev.* **1976**, 5, 181.

## (1) [2+2] ketene-imine cycloaddition

A general explanation for the stereoselectivity of this reaction was provided by Xu and his co-workers in 2006.<sup>250</sup> Based on Hammett analyses, they outlined the origin of the *cis/trans*-ratio of the  $\beta$ -lactam product as follows: (1) the *cis/trans*-ratio originates from the competition between the direct ring closure and the isomerization of the imine part in the zwitterionic intermediate; (2) the intramolecular ring closure results from the nucleophilic addition of the enolate to the imine moiety, which is affected by the electronic effect of the substituents of both ketene and imine; (3) electron-donating ketene substituents and electron-withdrawing imine ones enhance the ring closure, increasing the ratio of the *cis*- $\beta$ -lactam formation, while electron-withdrawing ketene substituents and electron-donating imine ones decelerate the ring closure, increasing the ratio of the *trans*- $\beta$ -lactam formation; and (4) the electronic effect of the substituents on the isomerization does not influence greatly the *cis/trans*-ratio.

Scheme III.5. General mechanism for the formation of *cis*- and *trans*- $\beta$ -lactams.

(e) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, 3223. (f) Singh, G. S. *Tetrahedron* **2003**, 59, 7631. (g) Brandi, A.; Cicchi, S.; Cordero, F. M. *Chem. Rev.* **2008**, 108, 3988. (h) Pitts, C. R.; Lectka, T. *Chem. Rev.* **2014**, 114, 7930. (i) Singh, G. S.; Sudheesh, S. *ARKIVOC* **2014**, (i), 337.

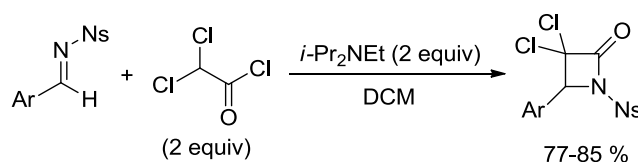
<sup>250</sup> Jiao, L.; Liang, Y.; Xu, J. *J. Am. Chem. Soc.* **2006**, 128, 6060.



They proved as well that the reaction selectivity depends on the solvent polarity. Where, non-polar solvents favour the *cis*- $\beta$ -lactam formation, while polar solvents favour the *trans*- $\beta$ -lactam formation. This is due to the stabilization of the zwitterionic intermediate in the polar solvent allowing the isomerization to the more stable isomer having (Z)-imine configuration prior to the ring closure.<sup>251</sup>

The Staudinger synthesis is considered as one of the efficient methods for the synthesis of  $\beta$ -lactams due to its broad scope and handling simplicity.<sup>249f</sup> Several new ketene precursors have been developed from which the ketenes are generated in situ.<sup>252</sup> This is due to the fact that many ketenes are unstable and readily undergo oligomerization except for the stable ones like: diphenyl ketene<sup>253</sup> and (trimethylsilyl)ketene.<sup>254</sup>

The most common in situ generation of ketenes is performed using an acyl chloride with a base, usually a tertiary amine due to the accessibility of its precursors.<sup>255</sup> For example, the synthesis of 3,3-dichloro- $\beta$ -lactams using dichloroacetyl chloride and *N*-nosyl imines.<sup>256</sup> In this case, DIPEA is used as a Lewis acid to generate the dichloroketene through the dehydrohalogenation of dichloroacetyl chloride (Scheme III.6). The reaction temperature and time vary with changing the substrates. Another protocol for the reaction of acetyl chloride with imines was reported using Yb(OTf)<sub>3</sub> in ionic liquid.<sup>257</sup> Where, catalytic amount of the latter was employed as a Lewis acid instead of adding base, affording selectively *trans*- $\beta$ -lactams. Moreover, a microwave free-solvent method was described for such cycloaddition reaction using K<sub>2</sub>CO<sub>3</sub> on alumina support.<sup>258</sup>



**Scheme III.6.** [2+2] cycloaddition of dichloroacetyl chloride and imines towards dichloro- $\beta$ -lactams.

<sup>251</sup> Wang, Y.; Liang, Y.; Jiao, L.; Du, D.-M.; Xu, J. *J. Org. Chem.* **2006**, 71, 6983.

<sup>252</sup> Tidwell, T. T. *Eur. J. Org. Chem.* **2006**, 563.

<sup>253</sup> Staudinger, H. *Ber. Dtsch. Chem. Ges.* **1905**, 38, 1735.

<sup>254</sup> Pelotier, B.; Rajzmann, M.; Pons, J.-M.; Campomanes, P.; Lopez, R.; Sordo, T. L. *Eur. J. Org. Chem.* **2005**, 2599.

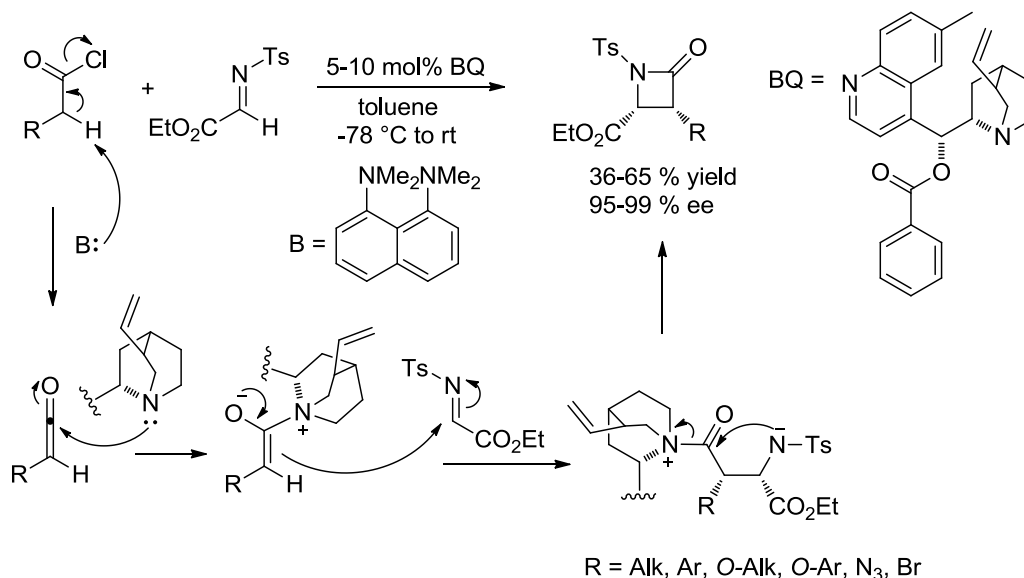
<sup>255</sup> (a) Arumugam, N.; Raghunathan, R. *Tetrahedron Lett.* **2006**, 47, 8855. (b) Jarrahpour, A.; Khalili, D. *Tetrahedron Lett.* **2007**, 48, 7140.

<sup>256</sup> Tato, F.; Reboul, V.; Metzner, P. *J. Org. Chem.* **2008**, 73, 7837.

<sup>257</sup> Chen, R.; Yang, B.; Su, W. *Synth. Commun.* **2006**, 36, 3167.

<sup>258</sup> Dandia, A.; Singh, R.; Sharma, P. *Heteroatom Chem.* **2003**, 14, 468.

In 2000, Lectka *et al.*<sup>259</sup> developed a catalytic asymmetric reaction of ketenes and poorly nucleophilic imines using a chiral nucleophilic amine as catalyst to afford  $\beta$ -lactams with high diastereoselectivity and enantioselectivity. They used the proton sponge as a base to generate the ketene from the acyl chloride. Cinchona alkaloid BQ was employed as a chiral organocatalyst for the asymmetric synthesis of  $\beta$ -lactams. In this case, the tertiary nitrogen in the quinuclidine ring attacks the electrophilic carbon in the ketene forming a chiral ketene enolate. Thereafter, this latter attacks the electrophilic carbon of the imine followed by a subsequent ring closure towards the target  $\beta$ -lactam with the regeneration of the chiral organocatalyst (Scheme III.7). Thus, in this case the imine acts as an electrophile opposite to its role in Staudinger synthesis. This method is widely applied for the enantioselective synthesis of  $\beta$ -lactams.



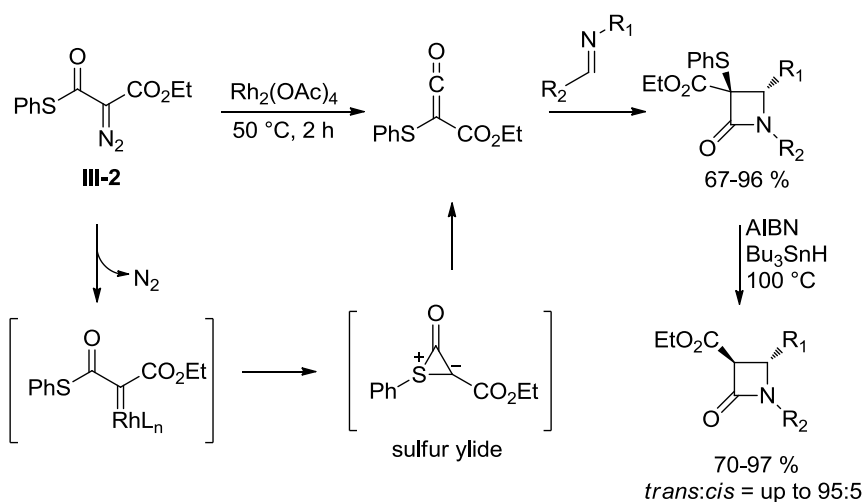
**Scheme III.7. Lectka catalytic asymmetric synthesis of  $\beta$ -lactams.**

Despite the usefulness of the cycloaddition of acyl halides to imines in  $\beta$ -lactam synthesis, low yields of the corresponding  $\beta$ -lactams are obtained when using electron poor acyl halides conjugated to carbonyl or sulfonyl groups. Alternatively, acids<sup>260</sup> and  $\alpha$ -diazocarbonyl compounds were used for the generation of ketenes, for instance the reported

<sup>259</sup> (a) Taggi, A.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J.; Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831. (b) Taggi, A.; Hafez, A. M.; Wack, H.; Young, B.; Ferrarais, D.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 6626. (c) France, S.; Shah, M.; Weatherwax, A.; Wack, H.; Roth, J.; Lectka, T. *J. Am. Chem. Soc.* **2005**, *127*, 1206.

For recent approaches see : (a) Smith, S. R.; Douglas, J.; Prevet, H.; Shapland, P.; Slawin, A. M. Z.; Smith, A. D. *J. Org. Chem.* **2014**, 79, 1626. (b) Rai, A.; K. Singh, P. K.; Shukla, P.; Rai, V. K. *Tetrahedron Lett.* **2016**, 57, 5084. (c) Zarei, M.; Jarrahpour, A. *Synlett.* **2011**, 2572 (d) Zavar, S.; Zarei, M.; Saraei, M. *Synth. Commun.* **2016**, 46, 2031. (e) Zarei, M.; Karimi-Jaberi, Z.; Movahedi, A. *Synth. Commun.* **2013**, 43, 728.

synthesis of 3-alkoxycarbonyl  $\beta$ -lactams using  $\alpha$ -diazocarbonyl derivative **III-2** and imines.<sup>261</sup> Usually the  $\alpha$ -diazocarbonyl compounds undergo Wolff rearrangement either thermally or photo-chemically to generate ketenes which then react with imines to form the desired  $\beta$ -lactam. In this case, the ketenes were formed through a rhodium-catalyzed thia-Wolff rearrangement of compound **III-2**.<sup>262</sup> Then, a desulfurization step delivered the final  $\beta$ -lactams in good yields with high diastereoselectivity (Scheme III.8).



Scheme III.8. A rhodium-catalyzed [2+2] cycloaddition of diazothioether and imines towards  $\beta$ -lactams.

## (2) [2+2] Cycloaddition reaction

The [2+2] cycloaddition methodology was extended to several precursors other than ketenes and imines. A set of [2+2] ester enolates-imines,<sup>263</sup> alkynes-nitrone<sup>264</sup> and isocyanates-alkenes<sup>265</sup> cycloadditions has been introduced. Herein, we present briefly the alkyne-nitrone cycloaddition only as an example.

One of the earliest approaches for the synthesis of  $\beta$ -lactams was Kinugasa reaction.<sup>264,266</sup> It described the reaction between Cu (I) acetylide and nitrones under nitrogen

<sup>261</sup> Jiao, L.; Zhang, Q.; Liang, Y.; Zhang, S.; Xu, J. *J. Org. Chem.* **2006**, 71, 815.

<sup>262</sup> Lawlor, M. D.; Lee, T. W.; Danheiser, R. L. *J. Org. Chem.* **2000**, 65, 4375.

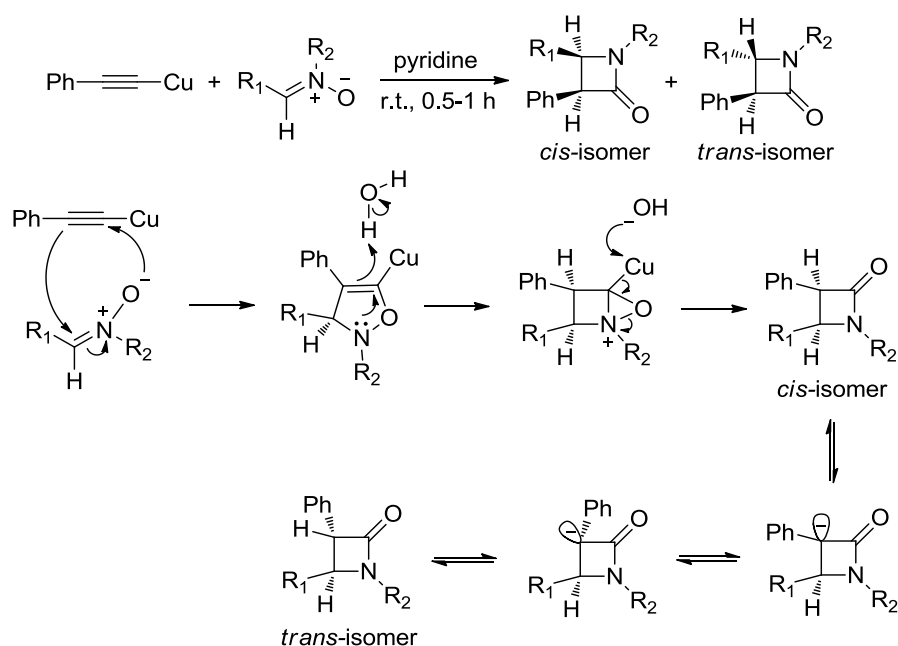
<sup>263</sup> See for example: (a) Hart, D. J.; Ha, D.-C. *Chem. Rev.* **1989**, 89, 1447. (b) Gilman, H.; Speeter, H. *J. Am. Chem. Soc.* **1943**, 65, 2250. (c) Schunk, S.; Enders, D. *Org. Lett.* **2000**, 2, 907. (d) Kanai, K.; Wakabayashi, H.; Honda, T. *Heterocycles* **2002**, 58, 47. (e) Chen, L.; Zhao, G.; Ding, Y. *Tetrahedron Lett.* **2003**, 44, 2611. (f) Ghatak, A.; Becker, F. F.; Banik, B. K. *Heterocycles* **2000**, 53, 2769. (g) Jan, S.-Z.; Ma, C.; Wang, Y.-G. *Synthesis* **2005**, 725. (h) Yuan, Q.; Jian, S.-Z.; Wang, Y.-G. *Synlett* **2006**, 1113.

<sup>264</sup> Marco-Contelles, J. *Angew. Chem., Int. Ed.* **2004**, 43, 2198.

<sup>265</sup> See for example: (a) Gyarmaty, Z. C.; Liljeblad, A.; Argay, G.; Kalman, A.; Bernath, G.; Kanerva, L. T. *Adv. Synth. Catal.* **2004**, 346, 566. (b) Tanaka, M.; Oba, M.; Ichiki, T.; Suemune, H. *Chem. Pharm. Bull.* **2001**, 49, 1178. (c) Lee, S. H. *Bull. Korean Chem. Soc.* **2013**, 34, 121.

<sup>266</sup> (a) Kinugasa, M.; Hashimoto, S. *J. Chem. Soc., Chem. Commun.* **1972**, 466.

atmosphere (to prevent the oxidative coupling of the acetylide)<sup>267</sup> at room temperature producing selectively *cis*- $\beta$ -lactams. Generally, the kinetically stable *cis*- $\beta$ -lactam is obtained. However, depending on the substituents and reaction conditions, epimerization results in the predominance of the thermodynamically favoured *trans*-isomer.<sup>263b</sup> In 1976, Ding and Irwin<sup>268</sup> suggested a mechanism for this reaction which is still acceptable nowadays (Scheme III.9). In 1990's, Miura and his group<sup>269</sup> introduced an efficient modification to the main Kinugasa reaction. They used phenyl acetylene,  $K_2CO_3$  and catalytic amount of CuI instead of Cu (I) acetylide, as well as introducing the use of chiral ligands.<sup>270</sup>



**Scheme III.9.** Kinugasa reaction together with the proposed mechanism by Ding and Irwin.

In 2014, Lee *et al.*<sup>271</sup> reported a rhodium-catalyzed oxygenative [2+2] cycloaddition of terminal alkynes and imines. They used a Rh(I) catalyst to form a rhodium vinylidene complex from the alkyne. Then, in presence of catalytic amount of 4-picoline *N*-oxide as an oxidant, an Rh-ketene intermediate is generated. Thereafter, a nucleophilic attack of imine onto the Rh-Ketene complex afforded selectively the *trans*-isomer (Scheme III.10).

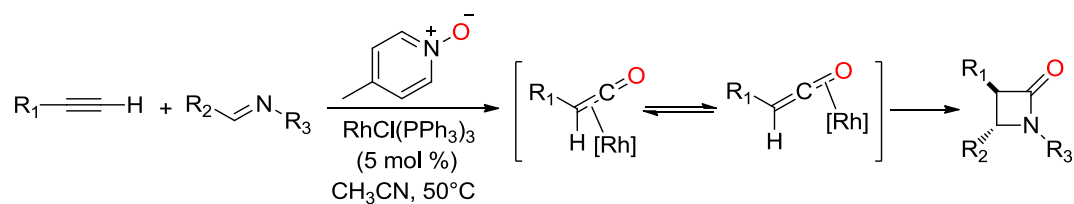
<sup>267</sup> (a) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Sarjant, K. H. *J. Chem. Soc.* **1947**, 1679. (b) Armitage, J. B.; Cook, C. L.; Entwistle, N.; Jones, E. R. H.; Whiting, M. C. *ibid* **1962**, 1998.

<sup>268</sup> Ding, L. K.; Irwin, W. J. *J. Chem. Soc., Perkin Trans.1* **1976**, 2382.

<sup>269</sup> Okuro, K.; Enna, M.; Miura, M.; Nomura, M. *J. Chem. Soc., Chem. Commun.* **1993**, 1107.

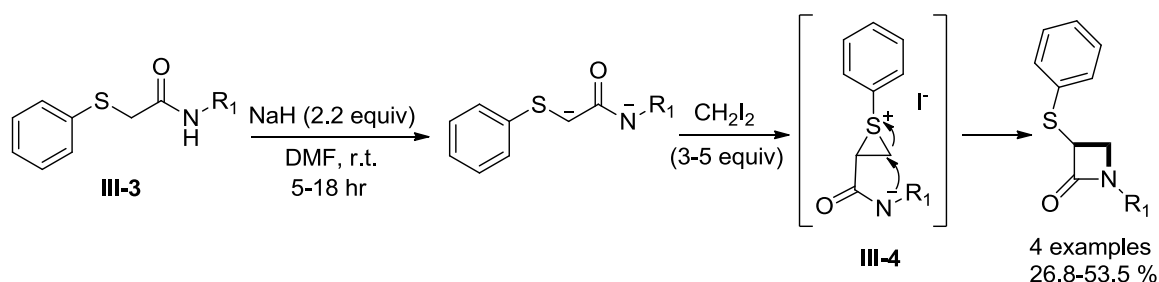
<sup>270</sup> Miura, M.; Enna, M.; Okuro, K.; Nomura, M. *J. Org. Chem.* **1995**, 60, 4999.

<sup>271</sup> Kim, I.; Roh, S. W.; Lee, D. G.; Lee, C. *Org. Lett.* **2014**, 16, 2482.

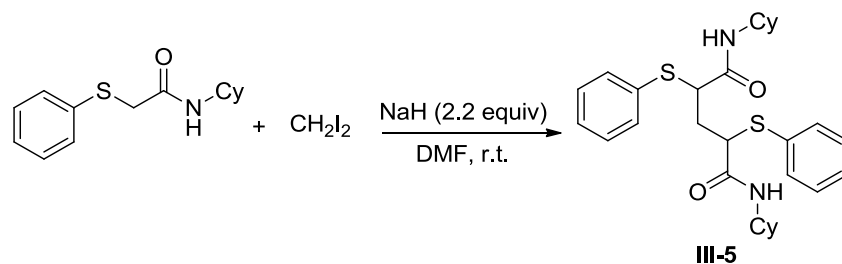
Scheme III.10. A rhodium-catalyzed oxidativecycloaddition of alkynes and imines towards  $\beta$ -lactams.

### (3) [3+1] Formal cycloaddition

In 1979, Hirari *et al.*<sup>272</sup> reported a synthetic method for  $\beta$ -lactams using 1,3-dianions of compound **III-3** and diiodomethane. They used 2.0 equiv of NaH in DMF to generate the dianion followed by a subsequent addition to  $\text{CH}_2\text{I}_2$ . They proposed a reaction mechanism that involved an episulfonium intermediate **III-4**, therefore their approach was only limited to thio derivatives (Scheme III.11). They described only 4 examples with low yields from 26.8 to 53.5 %. Despite the simplicity of the protocol, it was not further investigated by other chemists.

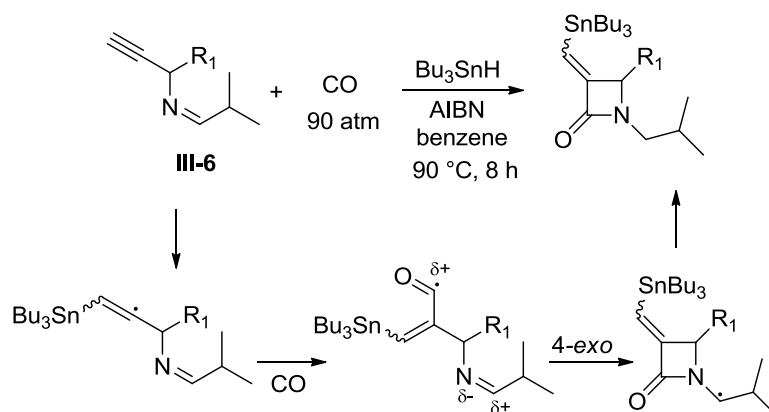
Scheme III.11. [3+1] Cycloaddition involving diiodomethane towards  $\beta$ -lactams.

Nevertheless, they clarified that it is important to carry out the reaction in less than 3 % W/V, since increasing the concentration lead to the formation of the dimeric product **III-5** (Scheme III.12).

Scheme III.12. Dimeric product resulting from addition of  $\text{CH}_2\text{I}_2$  to amides.

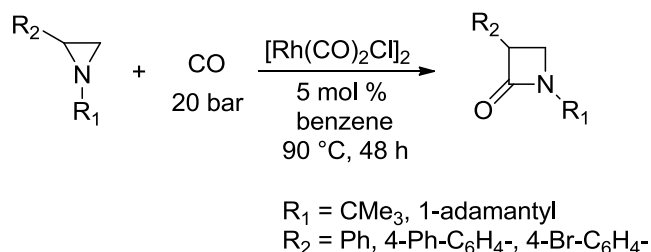
<sup>272</sup> Hirari, K.; Iwano, Y. *Tetrahedron Lett.* **1979**, 22, 2031.

In 2003, a free-radical mediated stannylcarbonylation of  $\alpha$ -azaynyenes **III-6** affording  $\alpha$ -stannylmethylene-2-azetidinones was presented.<sup>273</sup> The carbonylative cyclization proceeds via a radical mechanism that involves a carbonyl insertion onto the alkyne from an  $\alpha,\beta$ -unsaturated acyl radical. This latter undergoes 4-*exo* “polarity-matched” *N*-philic cyclization onto the imine (Scheme III.13). When  $R_1 = H$ , 32/68 (E/Z ratio) was obtained, while if it is any group other than hydrogen, the tributyltin group tends to attain a syn-configuration with respect to the carbonyl group to avoid the steric strain.



**Scheme III.13.** Radical carbonylative cyclization affording  $\alpha$ -stannylmethylene  $\beta$ -lactams.

Another powerful example of the [3+1] cyclization synthesizing functionalized  $\beta$ -lactams is the carbonylation of aziridines.<sup>274</sup> The first example of this approach was presented by Alper and his coworkers in 1983.<sup>275</sup> They reported a regiospecific synthesis of 3-arylazetidin-2-ones with 97 to 100 % yield by treatment of 2-arylaziridines with 20 bar of carbon monoxide using catalytic amount of rhodium(I) catalyst  $[\text{Rh}(\text{CO})_2\text{Cl}]_2$  in benzene for 48 hours at 90 °C. The reaction involves a regioselective insertion of the carbon monoxide into the aziridine carbon–nitrogen bond bearing the aryl substituent (Scheme III.14).



**Scheme III.14.** Rhodium-catalyzed regiospecific carbonylation of 2-arylaziridines.

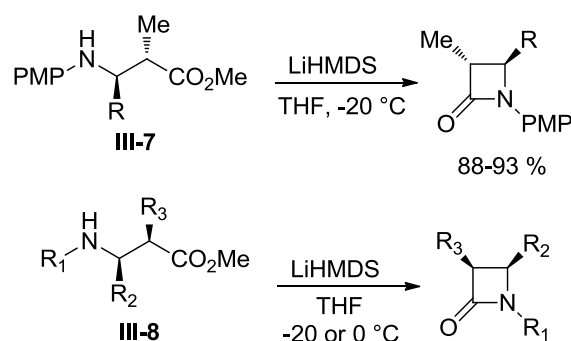
<sup>273</sup> Ryu, I.; Miyazato, H.; Kuriyama, H.; Matsu, K.; Tojino, M.; Fukuyama, T.; Minakata, S.; Komatsu, M. *J. Am. Chem. Soc.* **2003**, *125*, 5632.

<sup>274</sup> See recent microreview: Piens, N.; D'hooghe, M. *Eur. J. Org. Chem.* **2017**, 5943. DOI: 10.1002/ejoc.201700698.

<sup>275</sup> Alper, H.; Urso, F.; Smith, D. J. H. *J. Am. Chem. Soc.* **1983**, *105*, 6737.

**(4) Intramolecular cyclization**

The most common intramolecular cyclization reaction described for the synthesis of  $\beta$ -lactams is that of  $\beta$ -amino acids and esters. Where the activation of the carboxylic acid can be achieved using carbodiimides, 2-chloro-1-methylpyridinium iodide (Mukaiyama's reagent) or the redox pair di(2-pyridinyl) disulfide/triphenylphosphine.<sup>276</sup> For the cyclization of  $\beta$ -amino esters, a base is usually employed such as: EtMgBr, MeMgI, *n*-BuLi, *t*-BuOK, LiHMDS, LiOH and KOH. For example, the cyclization of chiral amino esters **III-7** and **III-8** using LiHMDS, afforded the corresponding  $\beta$ -lactams in high yield with retention of their relative configurations (Scheme III.15).<sup>277</sup>



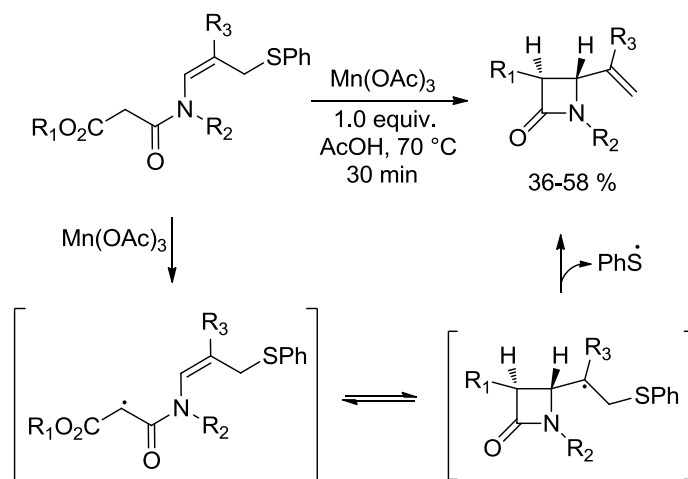
**Scheme III.15.** Base-catalyzed cyclization of chiral  $\beta$ -amino esters towards enantioselective  $\beta$ -Lactams.

A radical cyclization of enamides derived from malonate ester amides to prepare  $\beta$ -lactams was described by Attenni *et al.* in 1998.<sup>278</sup> They used 1.0 equiv. of  $\text{Mn}(\text{OAc})_3$  in acetic acid at 70  $^\circ\text{C}$  for 30 min. to generate the radicals which then achieved the 4-*exo-trig* cyclization (Scheme III.16).

<sup>276</sup> For some examples of the use of such reagents, see: (a) Turner, J. J.; Sikkema, F. D.; Filippov, D. V.; van der Marel, G. A.; van Boom, J. H. *Synlett* **2001**, 1727. (b) Lee, J. C.; Kim, G. T.; Shim, Y. K.; Kang, S. H. *Tetrahedron Lett.* **2001**, 42, 4519. (c) Bull, S. D.; Davies, S. G.; Kelly, P. M.; Gianotti, M.; Smith, A. D. *J. Chem. Soc., Perkin Trans.* **2001**, 1, 3106. (d) Vassiliou, S.; Dimitropoulos, C.; Magriotis, P. A. *Synlett* **2003**, 2398. (e) Whisler, M. C.; Beak, P. J. *Org. Chem.* **2003**, 68, 1207. (f) Chippindale, A. M.; Davies, S. G.; Iwamoto, K.; Parkin, R. M.; Smethurst, C. A. P.; Smith, A. D.; Rodriguez-Solla, H. *Tetrahedron* **2003**, 59, 3253. (g) Pandey, G.; Dumbre, S. G.; Khan, M. I.; Shabab, M.; Puranik, V. G. *Tetrahedron Lett.* **2006**, 47, 7923.

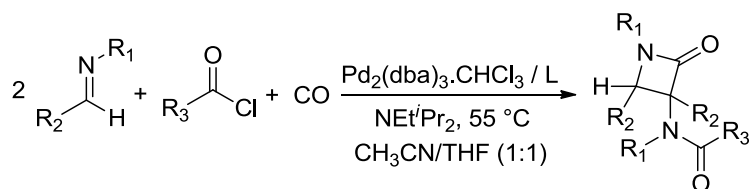
<sup>277</sup> (a) Kim, S.-C.; Kim, H.-K. *Bull. Korean Chem. Soc.* **2000**, 21, 1047. (b) Notz, W.; Tanaka, F.; Watanabe, S.-I.; Chowdari, N. S.; Turner, J. M.; Thayumanavan, R.; Barbas, C. F., III *J. Org. Chem.* **2003**, 68, 9624. (c) Iza, A.; Vicario, J. L.; Carrillo, L.; Badía, D. *Synthesis* **2006**, 4065.

<sup>278</sup> Attenni, B.; Cerreti, A.; D'Annibale, A.; Resta, S.; Trogolo, C. *Tetrahedron* **1998**, 54, 12029.

Scheme III.16. Mn(III)-catalyzed 4-*exo* radical cyclization to give  $\beta$ -lactams.

### (5) One-pot Multicomponent synthesis

In 2006, a palladium-catalyzed multicomponent coupling towards 3-amido- $\beta$ -lactams was described by Arndtsen and his group.<sup>279</sup> The reaction involves the coupling between two imines (either similar or different), acid chloride and carbon monoxide in presence of 1.0 equiv. of a sterically hindered amine base (Scheme III.17).

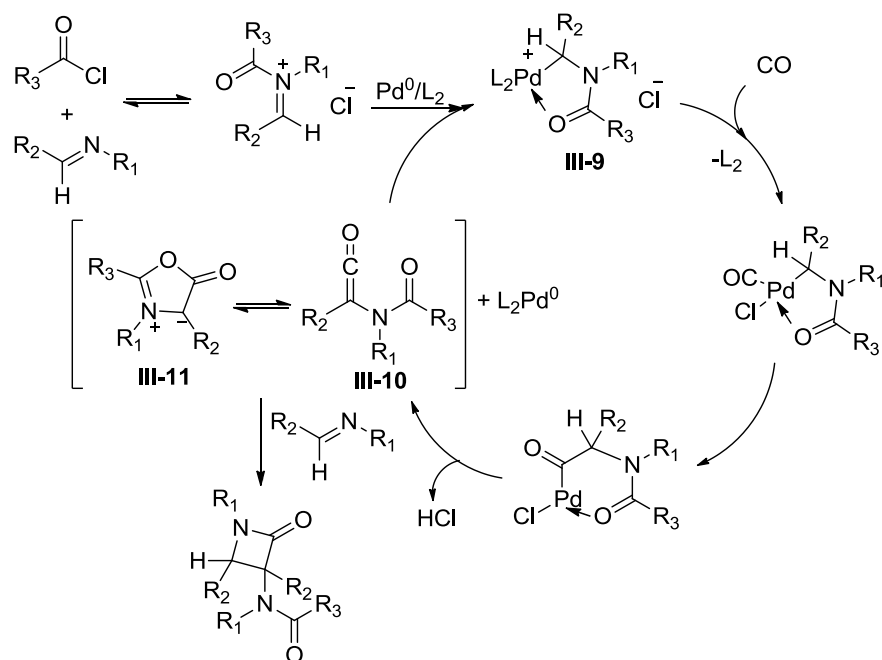
Scheme III.17. Pd-catalyzed synthesis of 3-amido- $\beta$ -lactams from imine, acid chloride and CO.

The postulated mechanism for this reaction involves the CO insertion into the Pd-C bond of the intermediate **III-9**, followed by the elimination of HCl which yielded the ketene species **III-10**. The ketene intermediate is known to be in dynamic equilibrium with the mesoionic Münchnone structure **III-11**.<sup>280</sup> Having the second equiv. of imine in the reaction medium, the ketene intermediate **III-10** undergoes [2+2] cycloaddition affording the corresponding  $\beta$ -lactam (Scheme III.18).

<sup>279</sup> Dhawan, R.; Dghaym, R. D.; St. Cyr, D. J.; Arndtsen, B. A. *Org. Lett.* **2006**, 8, 3927.

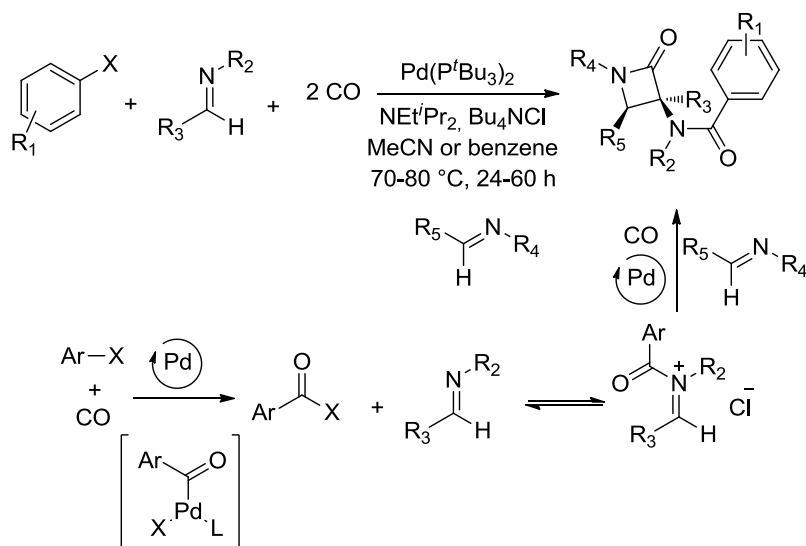
<sup>280</sup> (a) Croce, P. D.; Ferraccioli, R.; La Rosa, C. *Tetrahedron* **1995**, 51, 9385. (b) Huisgen, R.; Funke, E.; Schaefer, F. C.; Knorr, R. *Angew. Chem., Int. Ed.* **1967**, 6, 367.





**Scheme III.18.** Mechanism for the Pd-catalyzed synthesis of  $\beta$ -lactams from imine, acid chloride and CO.

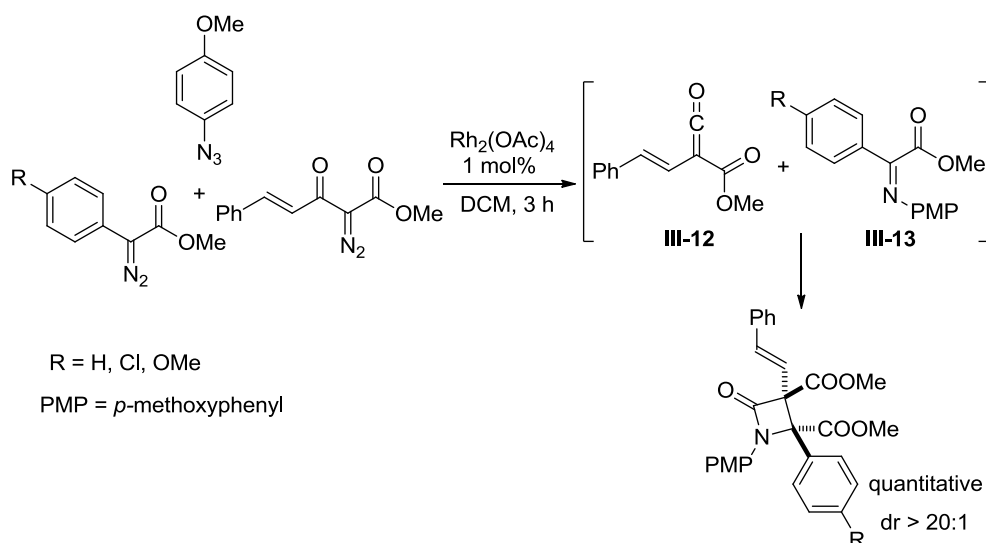
In 2016, they reported a new five-component approach towards  $\beta$ -lactams from imines, aryl halides and CO.<sup>281</sup> In this study, two palladium carbonylation catalytic cycles are described. The first one affords the acid halide, while the second one leads to the formation of the Münchnone that is in equilibrium with the ketene species (as previously described in Scheme III.18). Then, the ketene intermediate is trapped by the second imine producing the target  $\beta$ -lactam as a single isomer (Scheme III.19).



**Scheme III.19.** Mechanism for the Pd-catalyzed synthesis of  $\beta$ -lactams from aryl halide, imine and CO.

<sup>281</sup> Torres, G. M.; De la Higuera, M.; Quesnel, J. S.; Williams, O. P.; Yempally, V.; Bengali, A.; Arndtsen, B. A. *J. Org. Chem.* **2016**, 81 (24), 12106.

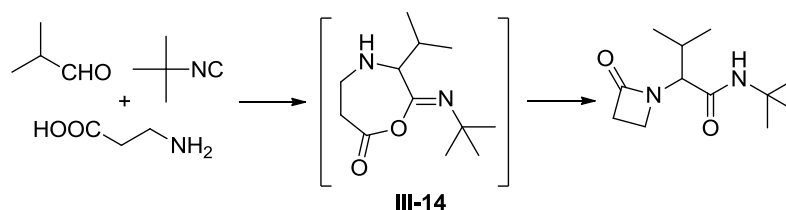
Doyle and his coworkers<sup>282</sup> presented a one-pot, multicomponent Staudinger synthesis of  $\beta$ -lactams using aryl diazoacetates, *p*-anisylazide and enonediazoacetates. It starts with a rhodium-catalyzed reaction between the aryl diazoacetate and the azide, to yield the imine intermediate **III-13**. Meanwhile, the diazoacetoacetate enone undergoes a Wolff rearrangement catalyzed by dirhodium(II) acetate forming a stable ketene **III-12**. The latter reacts with the imine to produce the  $\beta$ -lactam ring with high diastereoselectivity in quantitative yield (Scheme III.20).



Scheme III.20. One pot Multicomponent synthesis of  $\beta$ -lactams from azides and two diazo compounds.

### (6) Ugi-based $\beta$ -lactam synthesis

In 1982, Ugi reported an Ugi-3CR of isopropyl aldehyde, *tert*-butyl isocyanide and  $\beta$ -alanine to synthesize  $\beta$ -lactams.<sup>283</sup> He suggested that the reaction proceeds via a seven-membered ring **III-14**, which upon *O,N*-acyl transfer delivers the  $\beta$ -lactam ring (Scheme III.21).

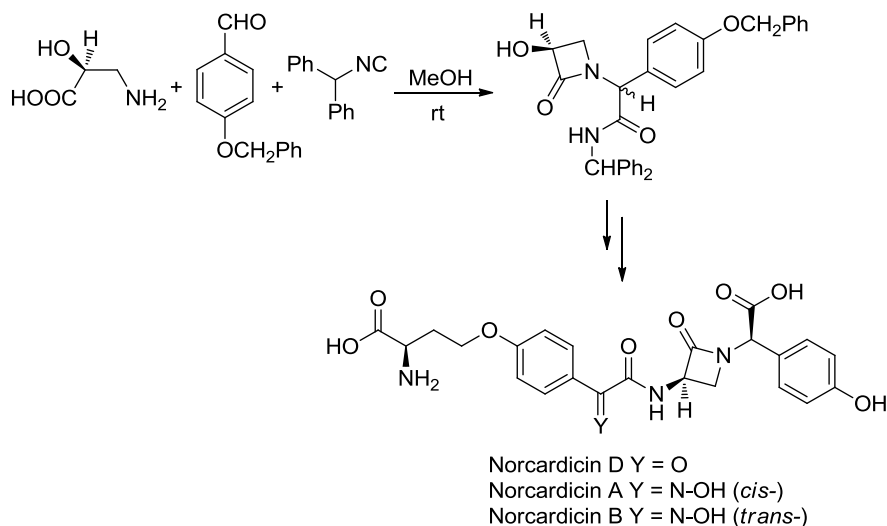


Scheme III.21. First Ugi-based  $\beta$ -lactam synthesis.

<sup>282</sup> Mandler, M. D.; Truong, P. M.; Zavaliy, P. Y.; Doyle, M. P. *Org. Lett.* **2014**, *16*, 740.

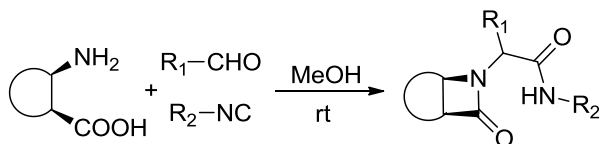
<sup>283</sup> Ugi, I. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 810.

This method was applied for the early total synthesis of various monobactams. For example the total synthesis of Norcardicins, that was carried out by Hofheinz *et al.* in 1983.<sup>284</sup> The first step of this synthesis was an Ugi-3CR between L-isoserine, *p*-(benzyloxy)benzaldehyde and diphenylmethyl isocyanide (Scheme III.22).



**Scheme III.22.** Ugi-3C based  $\beta$ -lactam towards the total synthesis of Norcardicins.

In 2002, several examples were reported employing alicyclic *cis*- $\beta$ -amino acids instead of the acyclic one, to prepare alicyclic *cis*- $\beta$ -lactams (Scheme III.23).<sup>285</sup>



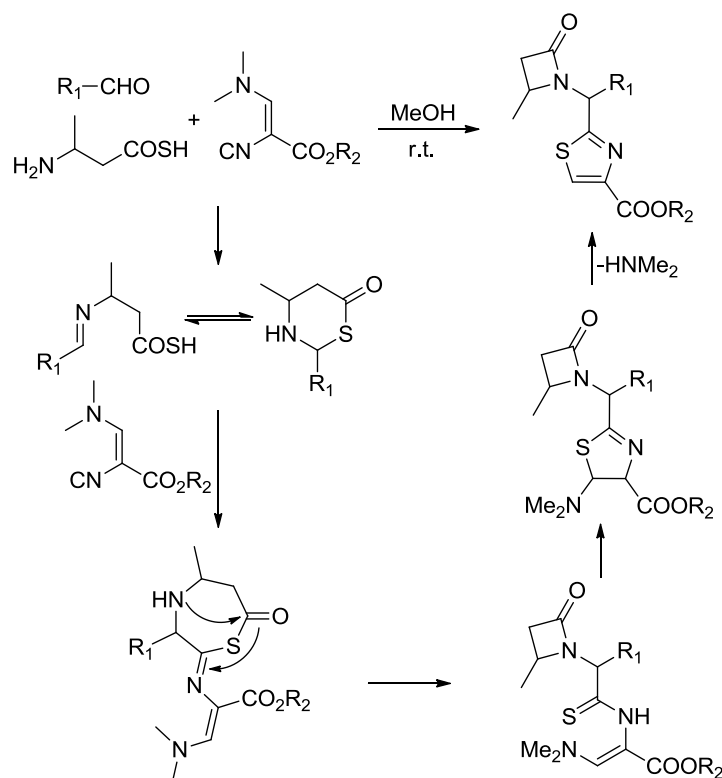
**Scheme III.23.** Alicyclic  $\beta$ -lactams via Ugi 3CR.

Meanwhile, Dömling *et al.*<sup>286</sup> described a new multicomponent reaction between  $\beta$ -aminothiocarboxylic acids, aliphatic aldehydes, and 3-dimethylamino-2-isocyanoacrylate. Where two heterocyclic rings, a  $\beta$ -lactam and a thiazole rings, are constructed simultaneously (Scheme III.24).

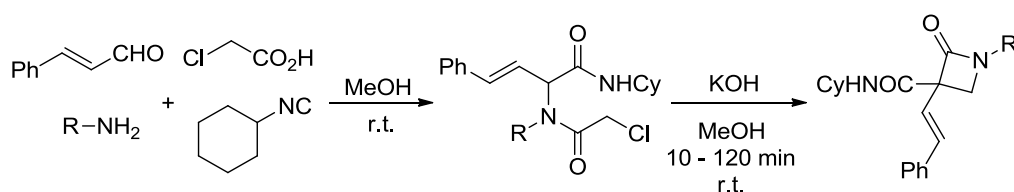
<sup>284</sup> Isenring, U. P.; Hofheinz, W. *Tetrahedron* **1983**, 39, 2591.

<sup>285</sup> Gedey, S.; Van der Eycken, J.; Fulop, F. *Org. Lett.* **2002**, 4, 1967.

<sup>286</sup> Kolb, J.; Beck, B.; Dömling, A. *Tetrahedron Lett.* **2002**, 43, 6897.

Scheme III.24. One pot Ugi-3C synthesis of thiazole- $\beta$ -lactams.

To the best of our knowledge, the first Ugi post-condensation reaction affording  $\beta$ -lactams was reported by Marcaccini and his coworkers in 1997.<sup>287</sup> They presented an Ugi condensation between cinnamaldehyde, chloroacetic acid, cyclohexyl isocyanide and various amines. Then, the formed adducts underwent an intramolecular ring-closure reaction giving  $\beta$ -lactams upon treatment with KOH in MeOH (Scheme III.25).

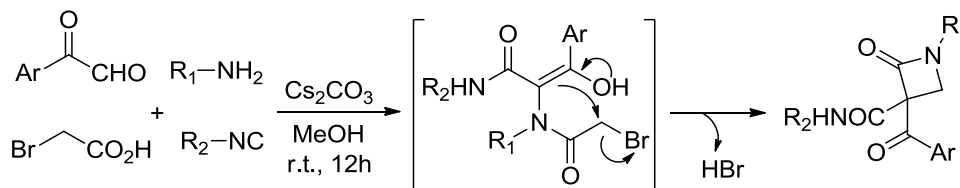
Scheme III.25. Ugi post-condensation intramolecular ring-closure for  $\beta$ -lactam synthesis.

In 2014, Ding *et al.*<sup>288</sup> modified the previous protocol (Scheme III.25) to be a one-pot cascade Ugi reaction/intramolecular peptidyl *C*-alkylation affording regioselectively  $\beta$ -lactams. In their course of study, they used arylglyoxals, primary amines, bromoacetic acid

<sup>287</sup> Bossio, R.; Marcos, C. F.; Marcaccini, S.; Pepino, R. *Tetrahedron Lett.* **1997**, 38, 2519.

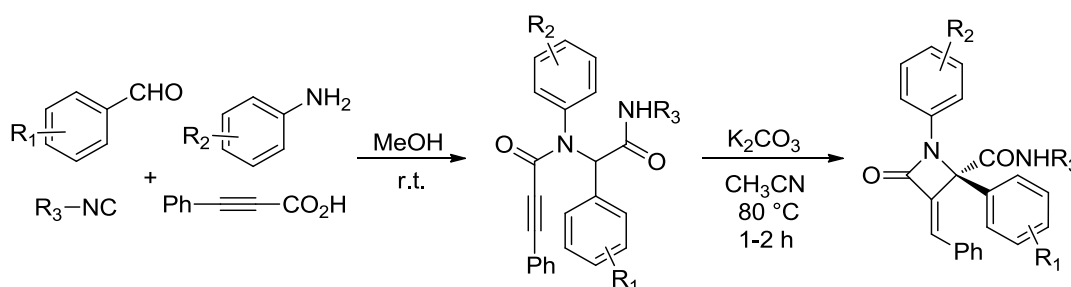
<sup>288</sup> Zeng, X.-H.; Wang, H.-M.; Yan, Y.-M.; Wu, L.; Ding, M.-W. *Tetrahedron* **2014**, 70, 3647.

and isocyanides in presence of  $\text{Cs}_2\text{CO}_3$  as a base. The reaction is presented in details in Scheme III.26.



**Scheme III.26.** One-pot cascade Ugi/intramolecular C-alkylation for  $\beta$ -lactam synthesis.

Meanwhile, another approach was outlined describing a successive Ugi/metal-free intramolecular cyclization to synthesize  $\beta$ -lactams.<sup>289</sup> Where a condensation between aromatic aldehydes, aromatic amines, isocyanides and phenyl propionic acid delivered the Ugi adduct. The latter in presence of 1.0 equiv. of  $\text{K}_2\text{CO}_3$  at 80 °C underwent a metal free intramolecular nucleophilic cycloaddition to the alkyne forming stereoselectively one  $\beta$ -lactam isomer (Scheme III.27).

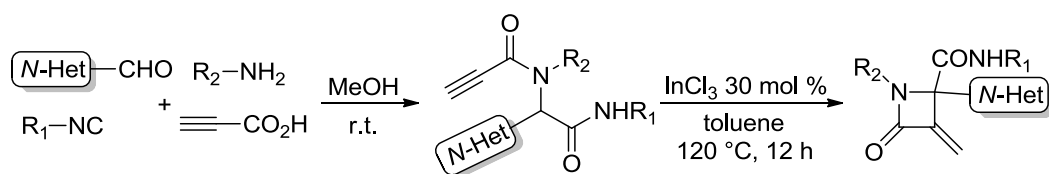


**Scheme III.27.** Synthesis of  $\beta$ -lactams through metal-free sequential Ugi-4CR/ cyclization.

In 2015, Van der Erycken and his coworkers<sup>290</sup> developed an Ugi/ $\text{In(III)}$ -catalyzed intramolecular nucleophilic cyclization for  $\beta$ -lactam synthesis. They generated the Ugi adduct with terminal alkynes using heterocyclic aldehydes, amines, isocyanides and propionic acid. The application of 30 mol % of  $\text{InCl}_3$  at 120 °C in toluene, afforded the *exo*-cyclized  $\alpha$ -methylene- $\beta$ -lactams in good yields (Scheme III.28). Interestingly, they demonstrated that switching the catalyst to  $\text{AlCl}_3$  (10 mol %) using DCE resulted in the synthesis of the unsaturated  $\gamma$ -lactam selectively through a 5-*endo-dig* ring closure.

<sup>289</sup> Ghabraie, E.; Balalaie, S.; Mehrparvar, S.; Rominger, F. J. *Org. Chem.* **2014**, 79 (17), 7926.

<sup>290</sup> Li, Z.; Sharma, U. K.; Liu, Z.; Sharma, N.; Harvey, J. N.; Van der Eycken, E. V. *Eur. J. Org. Chem.* **2015**, 3957.



**Scheme III.28.**  $\text{InCl}_3$ -catalyzed cyclization for the synthesis of  $\alpha$ -methylene- $\beta$ -lactams.

Thus, we can conclude that both the Ugi and post-Ugi condensation reactions are considered as a powerful tool for the synthesis of  $\beta$ -lactams. This is demonstrated by the simple procedures employed and wide variety previously mentioned. The fact that using different combinations of precursors towards various libraries of Ugi adducts can result in broad scope of diverse substituted  $\beta$ -lactams, raises the value of such pathway of synthesis.

### III.4 Reactivity of $\beta$ -lactams

Beside the well known biological activity of  $\beta$ -lactams, they are employed as valuable intermediates in organic synthesis. This dates back to the introduction of the term “ $\beta$ -lactam synthon method” by Ojima around 20 years ago.<sup>291</sup>

The  $\beta$ -lactam ring opening is enhanced by the ring strain and can occur through any of the four single bonds. Among those four possible cleavages, the amide bond breaking is the most versatile. It usually takes place with nucleophiles. In another words, the resistance of the bacteria towards  $\beta$ -lactam antibiotics originates from the hydrolytic amide bond breaking which is catalyzed by the  $\beta$ -lactamase enzyme.<sup>225a</sup>

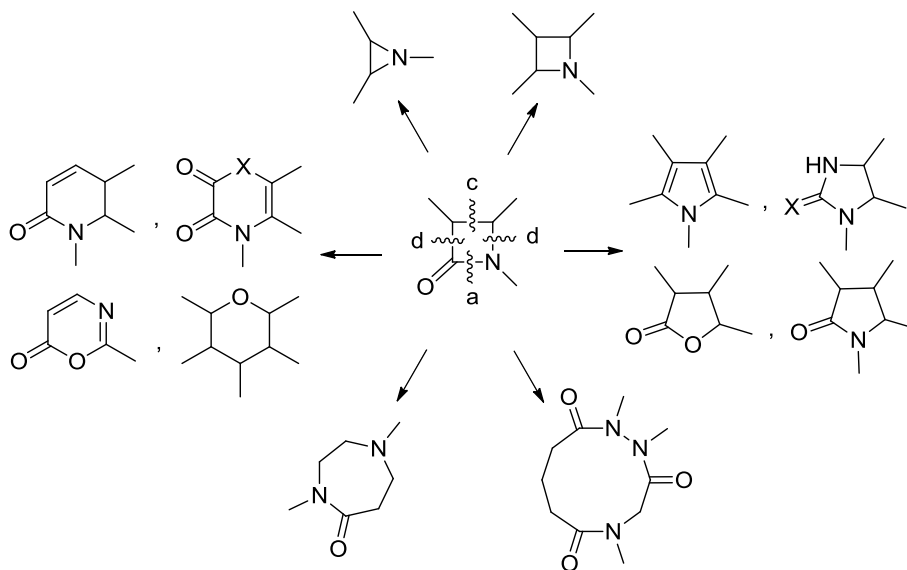
There are a large number of articles describing the reactivity of  $\beta$ -lactams as a synthetic tool for various compounds. Hereinafter, we will discuss briefly the most significant among them.

#### (1) Synthesis of Diverse-Sized Heterocycles

$\beta$ -lactams have been used as precursors for the synthesis of different-sized valuable heterocycles. The synthesis ranges between contraction to three-membered rings, rearrangements to different four-membered heterocycles or expansion to five-membered, six-

<sup>291</sup> Ojima, I. *Adv. Asym. Synth.* **1995**, *1*, 95.

membered rings and macrocycles as well as bicycles (Scheme III.29).<sup>225</sup> Recently, the transformation of  $\beta$ -lactams to five-membered heterocyclic has been widely investigated.<sup>292</sup>



**Scheme III.29. Schematic representation of  $\beta$ -lactam as synthon for various heterocycles.**

## (2) Synthesis of $\beta$ -amino acids

Several methodologies were described in the literature for the synthesis of  $\beta$ -amino acids and esters from  $\beta$ -lactams.<sup>293</sup> They involved the amide bond cleavage using *N*- or *O*-nucleophiles. The rigidity of the four-membered  $\beta$ -lactam ring rendered the ring cleavage highly stereoselective.<sup>294</sup> When the nucleophile used is an amino acid,  $\beta$ -peptides are obtained. The presence of electron-withdrawing groups attached to the nitrogen atom of the  $\beta$ -lactam ring is necessary to activate the carbonyl group towards the nucleophilic attack. Herein, the synthesis of the chiral  $\beta$ -amino acid pharmacophore **III-16** from the azetidinone **III-15** is presented as an example for such transformation.<sup>295</sup> Sodium methoxide in methanol was used as an *O*-nucleophile to bring about the ring cleavage followed by catalytic

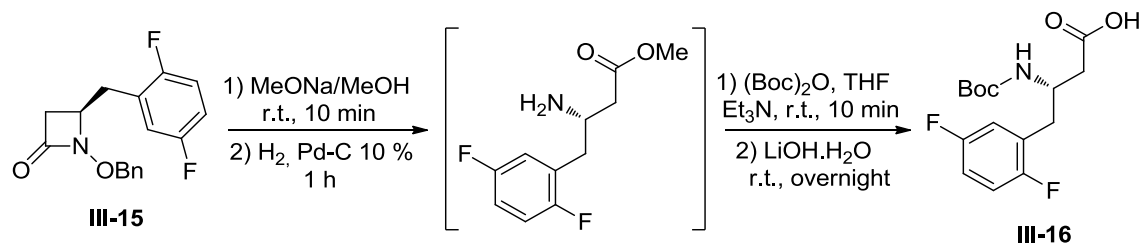
<sup>292</sup> Drazic, T.; Roje, M. *Chem. Heterocycl. Compd.* **2017**, *53*, 953.

<sup>293</sup> For selected reviews, see: (a) Boge, T. C.; Georg, G. I. In *Enantioselective Synthesis of  $\beta$ -Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, **1997**, Chapter 1, pp 1-43. (b) Palomo, C.; Aizpurua, J. M.; Ganboa, I. In *Enantioselective Synthesis of  $\beta$ -Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, **1997**, Chapter 14, pp 279-357. (c) Ojima, I. In *The Organic Chemistry of  $\beta$ -Lactams*; Georg, G. I., Ed.; VCH: New York, **1993**, Chapter 4, pp 197-255. (d) Palomo, C.; Aizpurua, J. M.; Ganboa, I., Oiarbide, M. In *Enantioselective Synthesis of  $\beta$ -Amino Acids*, 2nd ed.; Juaristi, E., Soloshonok, V., Ed.; Wiley-Interscience: New Jersey, **2005**, Chapter 20, pp 477-495. (e) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Curr. Med. Chem.* **2004**, *11*, 1837. (f) Palomo, C.; Aizpurua, J. M.; Ganboa, I., Oiarbide, M. *Synlett* **2001**, 1813. (g) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Amino Acids*, **1999**, *16*, 321.

<sup>294</sup> Duhamel, P.; Goument, B.; Plaquevent, J. C. *Tetrahedron Lett.* **1987**, 28, 2595.

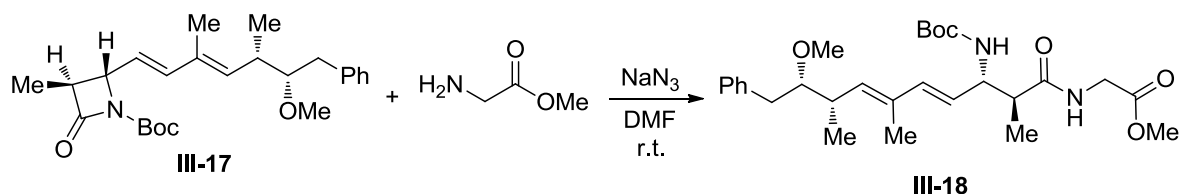
<sup>295</sup> Angelaud, R.; Zhong, Y.-L.; Maligres, P.; Lee, J.; Askin, D. *J. Org. Chem.* **2005**, 70, 1949.

hydrogenation to deliver the corresponding  $\beta$ -amino ester which underwent saponification instantly towards the  $\beta$ -amino acid. Trapping with the Boc-protecting group, afforded the desired  $\beta$ -amino acid **III-16** in overall 85 % yield (Scheme III.30). This method was applied for a kilogram scale synthesis of  $\beta$ -amino acids.



Scheme III.30. Enantioselective *O*-nucleophilic ring opening of  $\beta$ -lactams to synthesize  $\beta$ -amino acids.

As an example for the amide bond cleavage using *N*-nucleophiles, is the ring opening of the azetidinone **III-17** using glycine methyl ester and sodium azide at room temperature (Scheme III.31).<sup>296</sup> This reaction allowed the synthesis of the dipeptide **III-18**.



Scheme III.31. *N*-Nucleophilic ring opening of  $\beta$ -lactams to prepare dipeptides.

### (3) Synthesis of medically active compounds

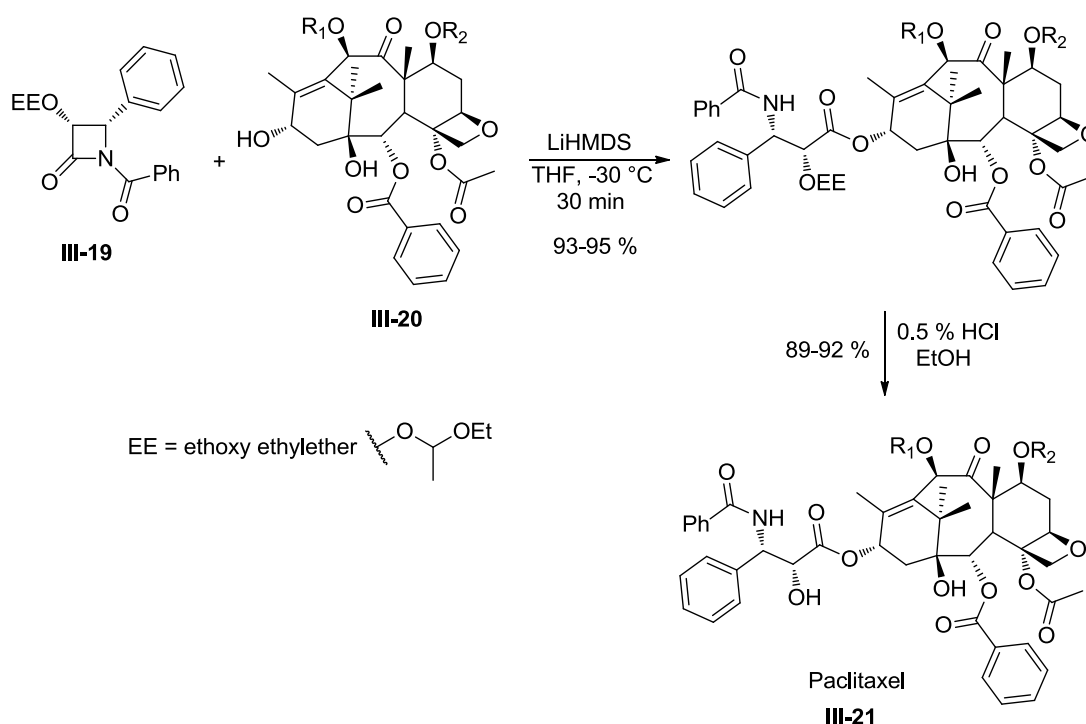
The  $\beta$ -lactam synthon method plays a vital role in the total synthesis of many biologically outstanding structures. The synthesis of paclitaxel is displayed as an example.<sup>297</sup> It was prepared through the ring opening of the  $\beta$ -lactam **III-19**, followed by coupling with TES-baccatin **III-20** at the C13 position (Scheme III.32). A final deprotection step with 0.5 % HCl in ethanol delivered the target medicine **III-21** in overall high yield. Paclitaxel is a complex diterpene approved by FDA for the treatment of different kinds of cancer.<sup>298</sup>

<sup>296</sup> Cundy, D. J.; C. Donohue, A. C.; McCarthy, T. D. *J. Chem. Soc., Perkin Trans. 1* **1999**, 559.

<sup>297</sup> (a) Ojima, I. *Acc. Chem. Res.* **1995**, 28, 383. (b) Kamath, A.; Ojima, I. *Tetrahedron* **2012**, 68, 10640.

<sup>298</sup> (a) Rowinsky, E. K.; Onetto, N.; Canetta, R. M.; Arbuck, S. G. *Semin. Oncol.* **1992**, 19, 646. (b) Rowinsky, E. K. *Annu. Rev. Med.* **1997**, 48, 353. (c) Kingston, D. G. I. *J. Nat. Prod.* **2009**, 72, 507.



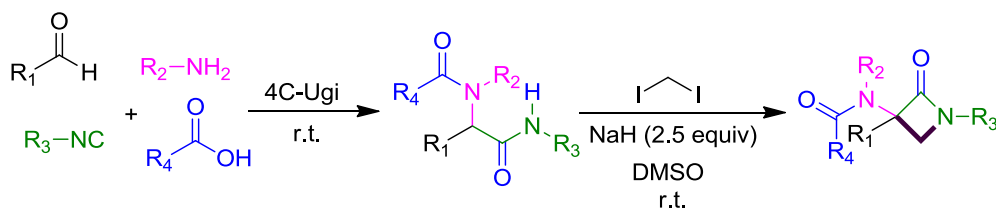


Scheme III.32.  $\beta$ -lactam synthesis of paclitaxel.

### III.5 New Methodology for synthesis of 4-component $\beta$ -lactams

#### Presentation of the protocol

Our goal was to trap the 1,3-amide dianions using biselectrophiles. Among the interesting electrophiles is diiodomethane leading to 4-component libraries of  $\beta$ -lactams. Thus in contrast to Hirari's approach,<sup>272</sup> we present a thio-free efficient methodology for the synthesis of  $\beta$ -lactams using Ugi adducts (Scheme III.33).

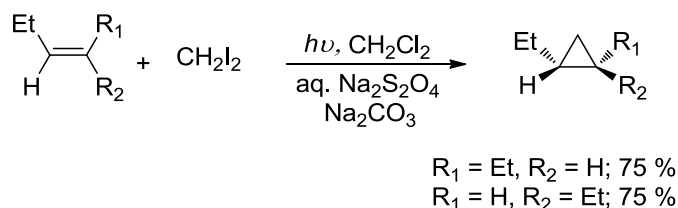


Scheme III.33. An Ugi/intermolecular formal [3+1] cycloaddition sequence towards  $\beta$ -lactams.

Before discussing the results obtained, a brief summary on utilizing diiodomethane in organic synthesis is presented.

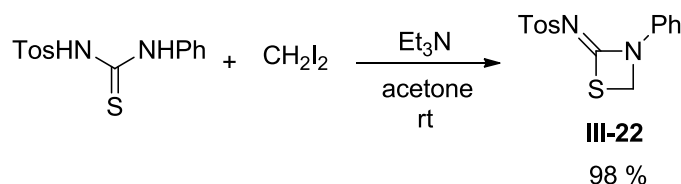
### III.6 Reactivity of diiodomethane

Diiodomethane is a widely used alkene-cyclopropanation reagent. The simplest procedure for such reaction is the photolysis of  $\text{CH}_2\text{I}_2$ .<sup>299</sup> Usually this reaction results in a mixture of products with low yields, however the addition of iodine and acid scavengers improves the reaction selectivity. In general, the geometry of the alkene is retained in the cyclic product (Scheme III.34).



**Scheme III.34.** Cyclopropanation of alkenes using diiodomethane.

Diiodomethane is used as well in the alkylative cyclizations. For example, the [3+1] cycloaddition of thioureas and diiodomethane to prepare 2-imino-1,3-thiazetidines **III-22** (Scheme III.35). Where one of the thiourea nitrogen atoms, should be deactivated as sulfonamide or amide in order to obtain only one isomer.<sup>300</sup>



**Scheme III.35.** The [3+1] cycloaddition of thioureas and diiodomethane towards 1,3-thiazetidines.

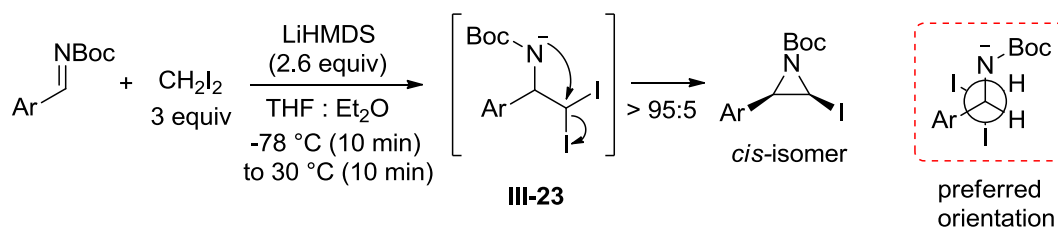
Besides, it is used as a precursor for  $\text{MCH}_2\text{I}$  and  $\text{MCHI}_2$  nucleophiles.<sup>301</sup> Recently, such reactivity was employed in the first synthesis of iodo-aziridines.<sup>302</sup> Whereas, the authors described the addition of diiodomethyl lithium  $\text{LiCHI}_2$  to *N*-Boc-imines yielding iodo-aziridines with high yields and diastereoselectivity through the cyclization of an amino gem-diiodide intermediate **III-23** (Scheme III.36).

<sup>299</sup> (a) Blomstrom, D. C.; Herbig, K.; Simmons, H. E. *J. Org. Chem.* **1965**, 30, 959. (b) Pienta, N. J.; Kropp, P. J. *J. Am. Chem. Soc.* **1978**, 100, 655. (c) Kropp, P. J.; Pienta, N. J.; Sawyer, J. A.; Polniaszek, R. P. *Tetrahedron* **1981**, 37, 3229. (d) Kropp, P. J. *Acc. Chem. Res.* **1984**, 17, 131.

<sup>300</sup> Ried, W.; Möisinger, O. *Chem. Ber.* **1978**, 111, 143.

<sup>301</sup> (a) Imamoto, T.; Hatajima, T.; Takiyama, N.; Takeyama, T.; Kamiya, Y.; Yoshizawa, T. *J. Chem. Soc., Perkin Trans. I* **1991**, 3127. (b) Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, 27, 3891.

<sup>302</sup> Bull, J. A.; Boulwood, T.; Taylor, T. A. *Chem. Commun.* **2012**, 48, 12246.

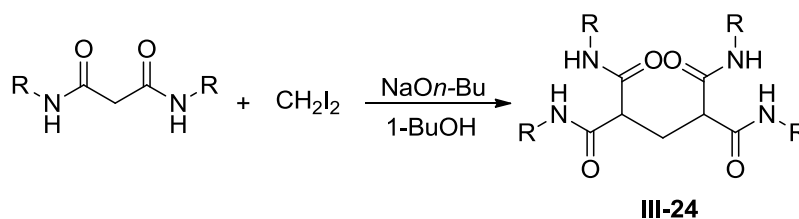


Scheme III.36. One-pot synthesis of iodoaziridines using diiodomethyl lithium.

### III.7 Reaction conditions

#### Early trial

According to Hirari *et al.* approach,<sup>272</sup> the presence of the thioether group is a prerequisite since they proposed, as aforementioned, that the reaction proceeds via an episulfonium ion intermediate. Thus, based on this assumption our Ugi adducts are considered incompatible with such methodology. Additionally their low reported yields are probably attributed to the use of secondary carbanions that would lead to byproducts such as: the dimeric adduct **III-24** obtained in case of using sodium *n*-butylate in butanol (Scheme III.37).<sup>303</sup>

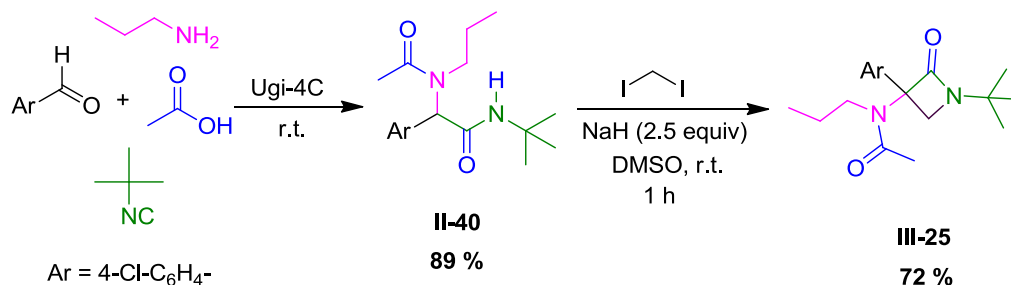


Scheme III.37. Dimerization of malonate amide using diiodomethane.

In order to verify the validity of this assumption, we carried out the first trial using our optimal conditions discussed in chapter II. Thus, we used the Ugi product **II-40** which was obtained in 89 % yield upon the condensation of 4-chlorobenzaldehyde, propylamine, acetic acid and *tert*-butyl isocyanide as previously mentioned in chapter II. We allowed this Ugi **II-40** to react with 2.5 equiv. of NaH in DMSO at room temperature for 10 minutes till a homogenous solution was obtained. Thereafter, 1.5 equiv. of diiodomethane was added. The resulting mixture was stirred at room temperature for one hour, where a new product was

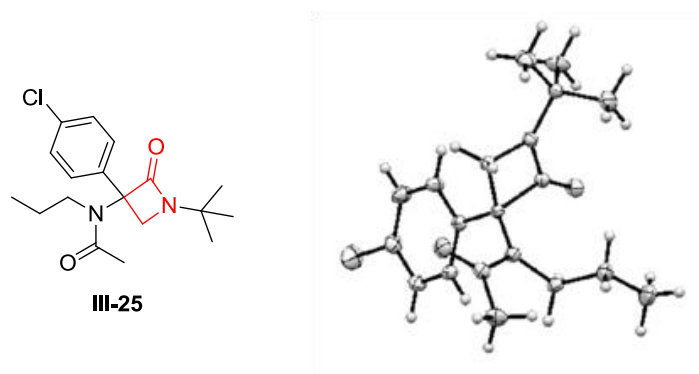
<sup>303</sup> Braeuniger, H.; Stens, B. *Pharmazie* **1963**, 18, 585.

detected by TLC. Which then upon purification and identification, proved to be the desired  $\beta$ -lactam **III-25** isolated with 72 % yield (Scheme III.38). This proved that the presence of thioether group is not mandatory for the reaction to occur.



**Scheme III.38.** First Ugi/Intermolecular [3+1] cycloaddition towards  $\beta$ -lactam.

The isolated  $\beta$ -lactam **III-25** was crystallized from a mixture of toluene and dichloromethane by slow evaporation at room temperature affording single-crystals. The analysis of the crystals obtained using X-ray confirmed the cyclic structure (Figure III.8).



**Figure III.8.** X-ray structure of  $\beta$ -lactam **III-25**.

### Optimization of the reaction conditions

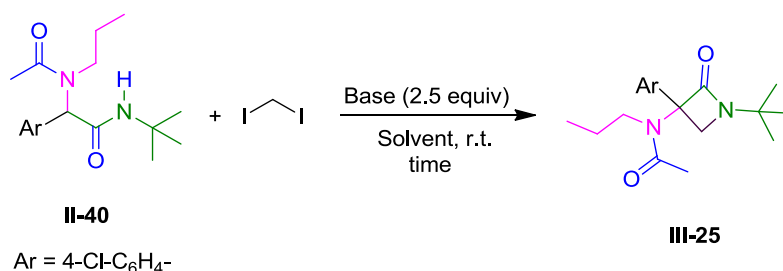
This promising result motivated us to study the effect of various base-solvent combinations on the reaction. Nonetheless, the effects of the number of base equivalents and different dihalomethanes on the reaction progress were also investigated.

#### (1) Base-Solvent combination

After the procurement of **III-25** in good yield (72 %) using NaH in DMSO, the effect of using strong bases in various solvents on the reaction progression was studied. Thus,

KHMDS and LiHMDS were selected as powerful bases in addition to NaH to be tested in a group of polar solvents as: DMF, DMSO together with THF. A number of trials were performed using the same starting material **II-40**, 2.5 equiv. of base, 1.5 equiv. of diiodomethane at room temperature (see Table III-1). The reaction time was determined according to the reaction progress checked by TLC.

Table III-1. Optimization of Base/Solvent combination.



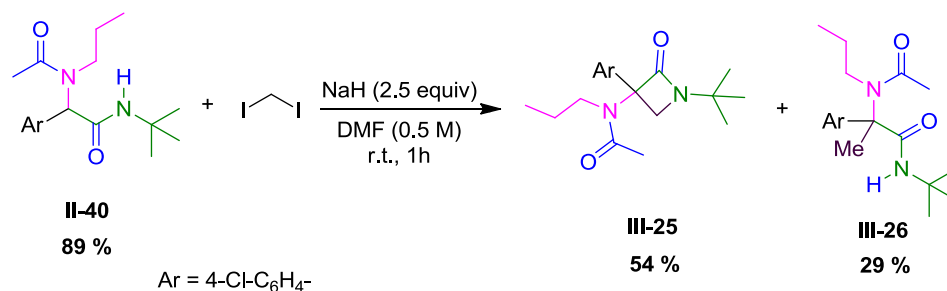
Entry	Base	Solvent	Time	Yield (III-25)
<b>1</b>	NaH	DMSO	1 h	72 %
<b>2</b>	KHMDS	THF	1 h	18 %
<b>3</b>	KHMDS	DMF	1 h	32 %
<b>4</b>	LiHMDS	THF	1 h	- <sup>1</sup>
<b>5</b>	NaH	DMF	1 h	54 % <sup>2</sup>
<b>6</b>	NaH	DMSO	12 h	71 %

<sup>1</sup>Decomposition of starting material.

<sup>2</sup>Another product was obtained in addition to  $\beta$ -lactam in 29 % yield.

The use of KHMDS in THF gave the corresponding  $\beta$ -lactam **III-25** with only 18 % yield. Trying KHMDS in DMF instead of THF resulted in a slight increase in the reaction yield (32 % instead of 18 % yield). Whereas, using LiHMDS in THF resulted in a complete decomposition of the starting material. All the results are displayed above in Table III-1.

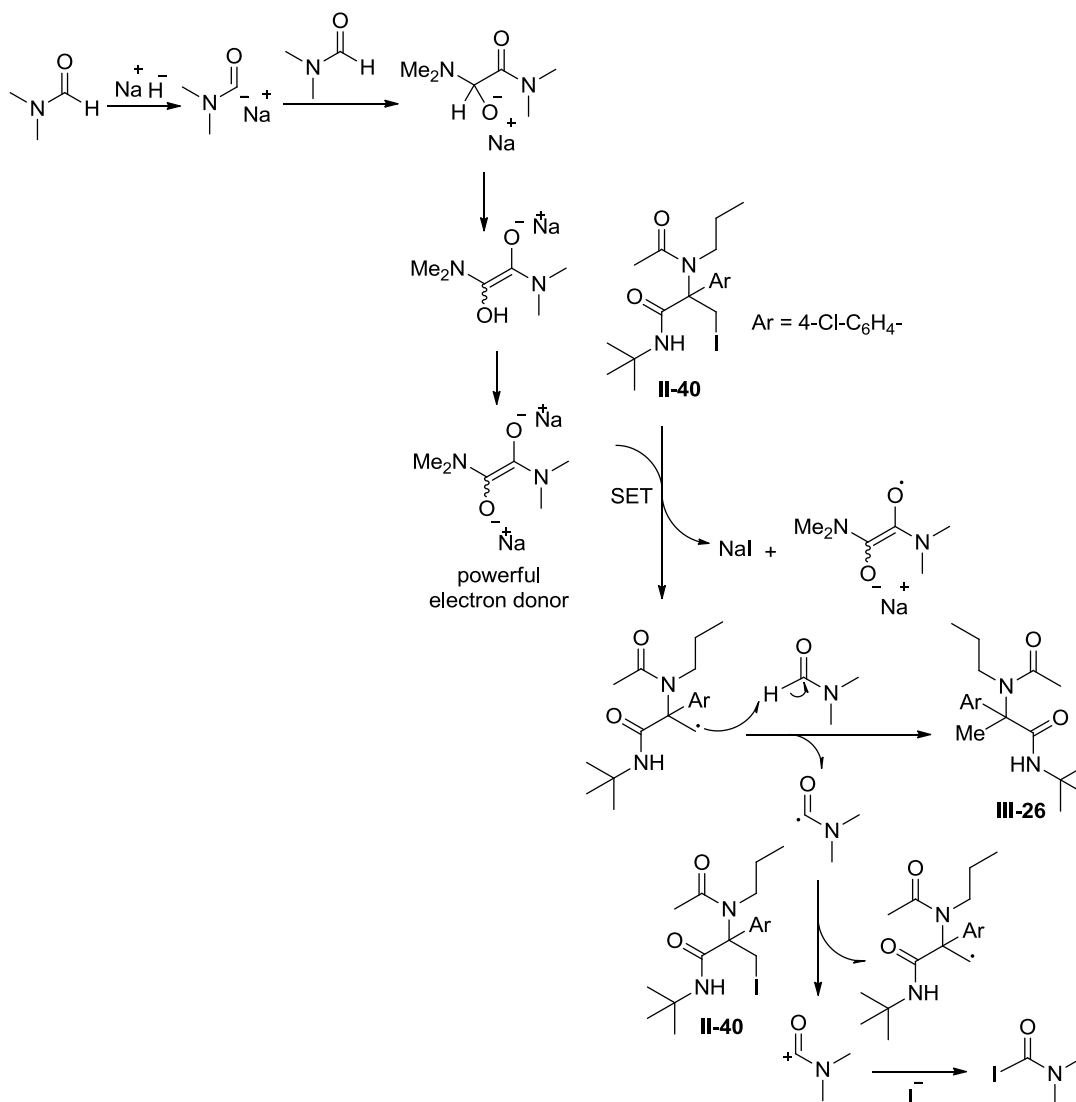
The use of NaH in DMF (the conditions adopted by Hirari during his study), afforded 54 % of  $\beta$ -lactam **III-25** together with 29 % yield of the intermediate **III-26** (Scheme III.39). This indicates that such condition is not the appropriate one for this reaction since it often results in side products.

Scheme III.39. The use of Hirari conditions for the  $\beta$ -lactam synthesis.

This intermediate **III-26** results from a reduction reaction, which could be explained by a single-electron transfer process that is sometimes observed using strong bases in DMF.<sup>304</sup> A suggested mechanism for this reduction reaction is presented in Scheme III.40. Murphy *et al.* proposed that the presence of strong bases in DMF leads to the deprotonation of DMF. The resulting anion can then add onto another DMF molecule forming a powerful electron donor dianion that engages in a single-electron transfer process.

In our case, the Ugi dianion species as well could be considered as a powerful electron donor to initiate the radical reaction. The produced radical then abstracts hydrogen radical from DMF molecule forming the product **III-26** together with a formamide radical which is then involved in the propagation step. A termination step could be possible by the loss of electron from the formamide radical producing formamide cation, which then can form carbamic iodide derivative that can undergo further hydrolysis in basic medium.

<sup>304</sup> a) Pichette Drapeau, M.; Fabre, I.; Grimaud, L.; Ciofini, I.; Ollevier, T.; Taillefer, M. *Angew. Chem. Int. Ed. Engl.* **2015**, *36*, 10587; *Angew. Chem.* **2015**, *127*, 10733. b) Barham, J. P.; Coulthard, G.; Emery, K. J.; Doni, E.; Cumine, F.; Nocera, G.; John, M. P.; Berlouis, L. E. A.; McGuire, T.; Tuttle, T.; Murphy, J. A. *J. Am. Chem. Soc.* **2016**, *138*, 7402.

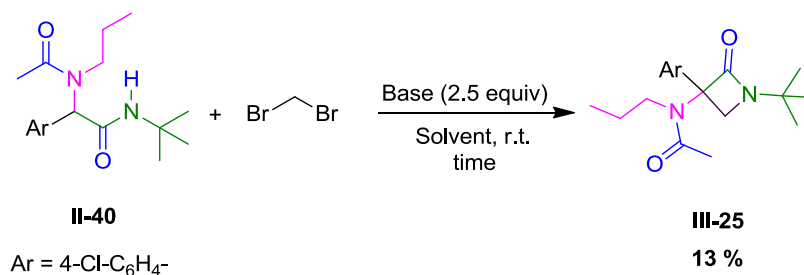


Scheme III.40. Suggested mechanism for the single-electron transfer reduction process.

Consequently, NaH in DMSO again was chosen as the optimal base/solvent combination for the reaction. Such basic system allowed us to get selectively the  $\beta$ -lactam **III-25** with the highest yield (72 %) working at room temperature for 1 hour. The further increase in the reaction time did not improve the reaction yield (71 %).

## (2) The dihalomethane reagent

Using the previously optimized conditions (2.5 equiv. of NaH in DMSO and 1.5 equiv. of biselectrophile at room temperature for 1 hour), the effect of using different halide reagent was examined. The trial using dibromomethane instead of diiodomethane provided a sluggish reaction with only 13 % yield of the corresponding  $\beta$ -lactam **III-25** (Scheme III.41).



Scheme III.41. Structures of ligands used in Tsuji-Trost reaction.

Accordingly, the prior choice of diiodomethane as the biselectrophile to afford  $\beta$ -lactams was confirmed.

### (3) Number of equivalents of base

Finally, the exact number of base equiv. required for the reaction had to be adjusted. Thus, 1.2 equiv. of NaH were added to Ugi adduct **II-40** in DMSO at room temperature followed by 1.5 equiv. of diiodomethane. In this case, the  $\beta$ -lactam **III-25** was obtained in only 17 % yield after one hour. This indicates that the use of stoichiometric amount of base is insufficient and an excess amount of base is required to generate the 1,3-dianion intermediate in order for the reaction to progress (see Table III-2). Additionally, using 1.2 equiv. of NaH, the expected moniodo derivative was not observed.

Table III-2. Optimizing the number of base equivalents.

Entry	No of Base equivalents	Yield
<b>1</b>	<b>2.5</b>	<b>72 %</b>
<b>2</b>	1.2	17 %

Having the optimized conditions in hand, a library of Ugi starting adducts has been prepared to study the scope of the intermolecular formal [3+1] cycloaddition.

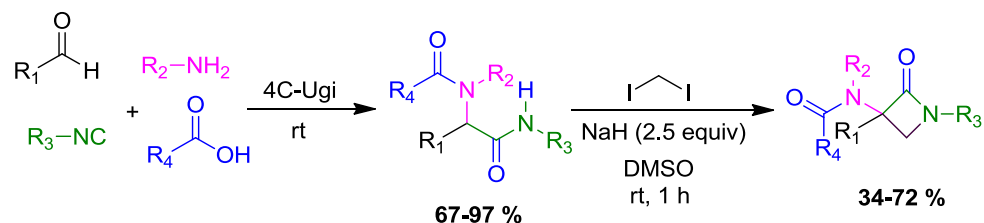
## III.8 Results & Discussion

### (a) Results

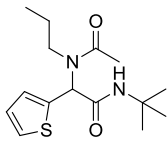
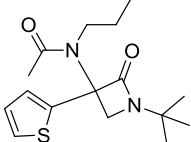
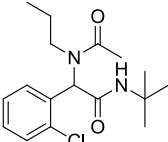
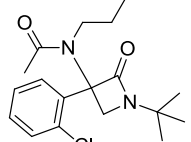
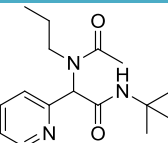
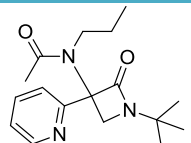
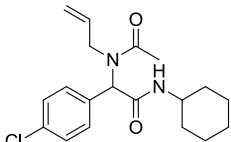
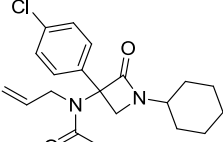
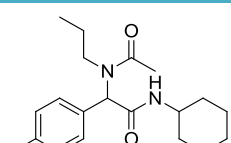
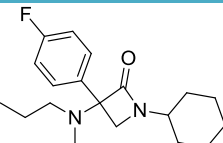
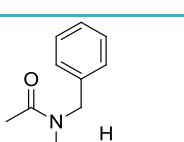
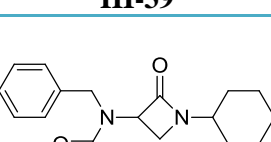
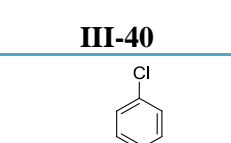
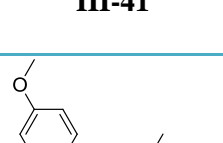
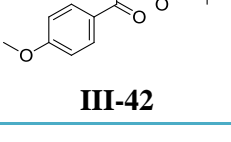
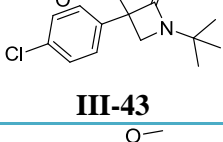
A series of Ugi adducts was prepared varying the four reaction components with good to excellent yields from 67 to 97 % (the Ugi reaction has been already described in chapter II,

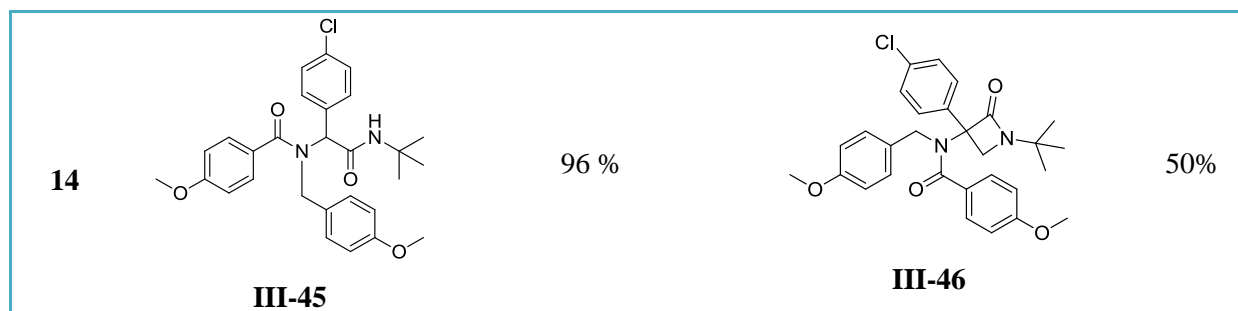


section II.9). This series was subjected to the reaction with NaH (2.5 equiv) and diiodomethane (1.5 equiv) in DMSO (0.5 M) at room temperature for one hour. The [3+1] cycloaddition reaction afforded an array of 4-component  $\beta$ -lactams with moderate to good yields. The various results are presented thereafter in Table III-3.

Table III-3. The scope of  $\beta$ -lactam synthesis from Ugi products.

Entry	Ugi adduct	Yield	$\beta$ -lactam	Yield
1	 <b>II-40</b>	89 %	 <b>III-25</b>	72%
2	 <b>II-46</b>	85 %	 <b>III-27</b>	71%
3	 <b>II-47</b>	90 %	 <b>III-28</b>	51%
4	 <b>III-29</b>	92 %	 <b>III-30</b>	61%
5	 <b>III-31</b>	83 %	 <b>III-32</b>	65%

6	 <p><b>II-33</b></p>	67 %	 <p><b>III-34</b></p>	44%
7	 <p><b>II-50</b></p>	80 %	 <p><b>III-35</b></p>	0% (SM)
8	 <p><b>II-53</b></p>	84 %	 <p><b>III-36</b></p>	44%
9	 <p><b>II-59</b></p>	97 %	 <p><b>III-37</b></p>	71%
10	 <p><b>III-38</b></p>	81 %	 <p><b>III-39</b></p>	65%
11	 <p><b>III-40</b></p>	81 %	 <p><b>III-41</b></p>	0% (SM)
12	 <p><b>III-42</b></p>	77 %	 <p><b>III-43</b></p>	47%
13	 <p><b>II-55</b></p>	95 %	 <p><b>III-44</b></p>	34%



### (b) Discussion

In general, the 4-component  $\beta$ -lactams were obtained with moderate to good yields from 34 to 72 % (see Table III-3).

The reaction proceeded well with Ugi adducts derived from several isocyanides, where the highest yield was obtained using *tert*-butyl isocyanide **III-25** (72 %) and a comparable yield was obtained using cyclohexyl isocyanide **III-27** (71 %). While, using 4-(2-isocyanoethyl)-1,2-dimethoxybenzene afforded **III-30** in 61 % yield and the lowest one was obtained using *p*-methoxybenzyl isocyanide **III-28** (51 %). This goes along with the results obtained in case of Tsuji-Trost allylation, where the bulky *tert*-butyl groups afforded the highest yields.

Using aldehyde group with electron deficient substituent in *m*-position did not alter the reaction yield (**III-32** was isolated with 65 % yield). The use of Ugi adducts derived heterocyclic aldehydes resulted in lowering the reaction yield. This is demonstrated in the use of thiophene-2-carboxaldehyde and pyridine-2-carboxaldehyde which afforded respectively **III-34** and **III-36** in 44 % yields each.

Both Ugi adducts **II-50** and **III-40** derived from *o*-chlorobenzaldehyde and aliphatic formaldehyde respectively, failed to undergo any reaction with diiodomethane. In these cases, the reaction mixture just included starting materials. This could be due to the inability of the basic medium to generate the 1,3-dianionic species in these two particular cases as a result of the non-planarity of the molecule (using **II-50**) and the lack of activation due to the absence of aromatic substituent (using **III-40**) respectively.

Ugi precursors derived from both aliphatic and aromatic amines were submitted successfully to the reaction giving the desired products in moderate to good yields. The lowest reported yield was obtained using aromatic amines (*p*-anisidine) which afforded **III-44** with 34 % yield. This is due to the enhanced electron-donating effect which decreases the acidity at the peptidyl C-H position.

Both aliphatic and aromatic acids derived Ugi adducts afforded the corresponding  $\beta$ -lactams in good yields. In general, the simple acetic acid resulted in better yields compared to *p*-methoxybenzoic acid. The latter provided **III-43** and **III-46** with 47 % and 50 % yields respectively.

### **III.9      Reaction mechanism**

In order to rationalize more the reaction mechanism, a DFT study has been performed by our colleague “Julian Garrec” (an Assistant Professor working at Unité Chimie et Procédés at ENSTA-ParisTech). The results obtained are summarized below in Figure III.9.

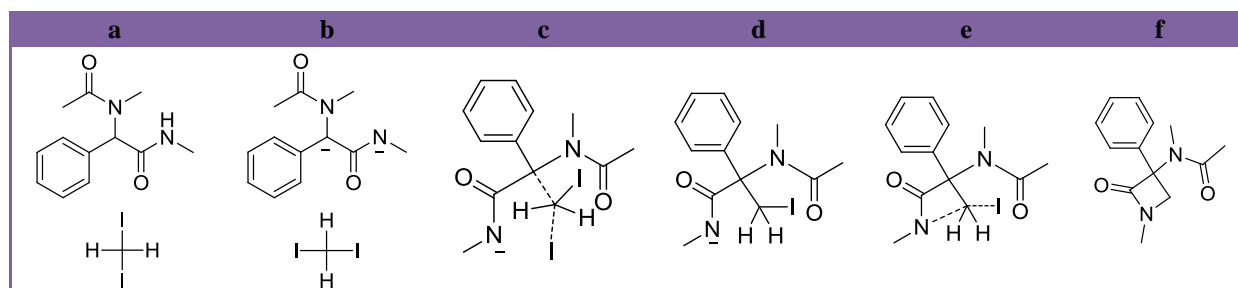
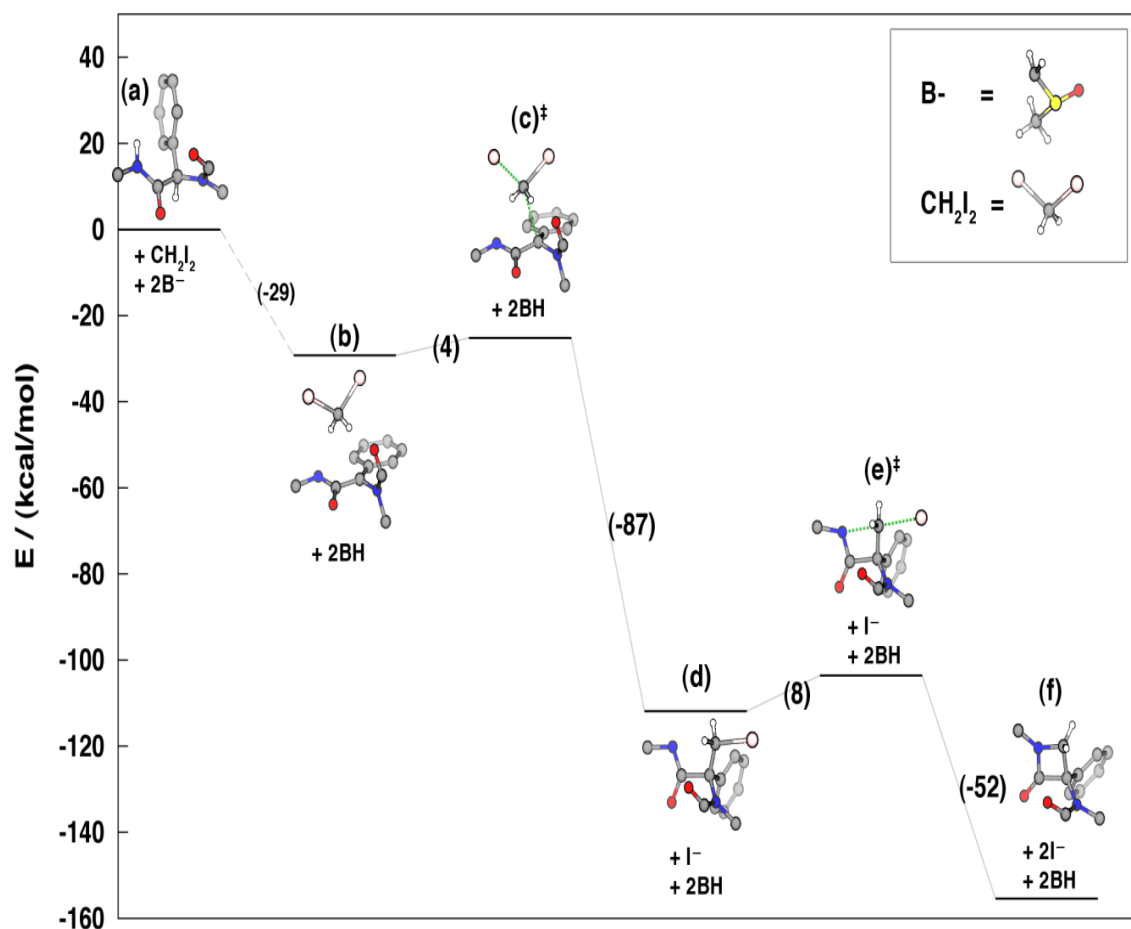


Figure III.9. Simplified potential energy diagram for  $\beta$ -lactam synthesis using Ugi **III-47**.

The calculations were based on using a simple theoretical Ugi adduct **III-47** derived from benzaldehyde, methylamine, acetic acid and methylisocyanide (Figure III.10) together with diiodomethane and the dimethyl anion in DMSO. A relation between the energy in kcal/mol and molecular reorganization in space was plotted.

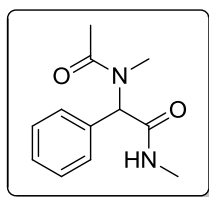
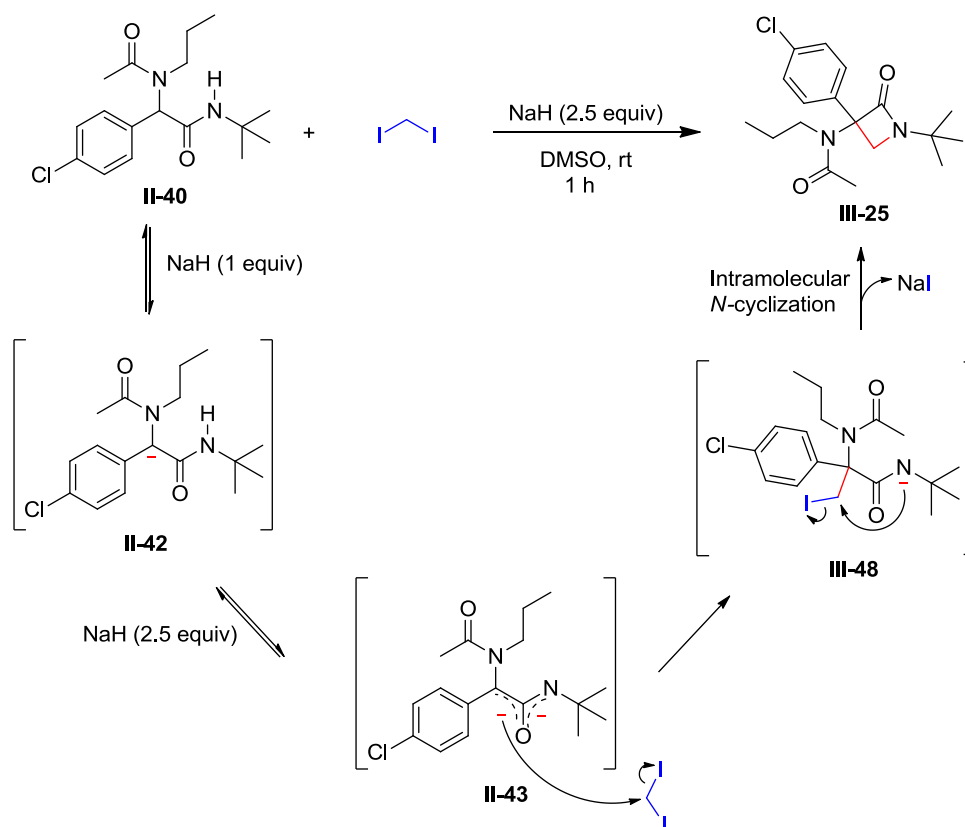


Figure III.10. The structure of Ugi III-47.

The study begins with the formation of the dianion intermediate (step b, Figure III.9). Then, the *C*-alkylation reaction in step c had a very low energy barrier, thus favoring the nucleophilic addition. The calculations showed a slight energy difference between the initial *C*-alkylation and *N*-alkylation; consequently, the initial *C*-alkylation is slightly favored. This is in agreement experimentally with the separation of the *C*-methylated intermediate during the course of study. The formation of the monoalkylated intermediate in step d was accompanied by a high energy release. Thereafter, the cyclization in step e possessed again a very low energy barrier; releasing energy towards the final cyclic  $\beta$ -lactam in step f. Hence, the overall process is smooth and facilitated by the very low energy barriers and high exothermicity.

Accordingly, the most probable reaction mechanism is presented in Scheme III.42. The deprotonation started at the peptidyl C-H position forming the intermediate **II-42** that is not nucleophilic enough to attack the diiodomethane. The further deprotonation resulted in a powerful nucleophilic delocalized dianion intermediate **II-43** that attacked the diiodomethane through the peptidyl carbanion forming the intermediate **III-48**. The initial attack by the peptidyl carbanion is supported by the isolation of the *C*-methylated intermediate **III-26** together with the Tsuji-Trost allylation products presented in chapter II. Finally, an intramolecular *N*-alkylation took place towards the final  $\beta$ -lactam **III-25**.

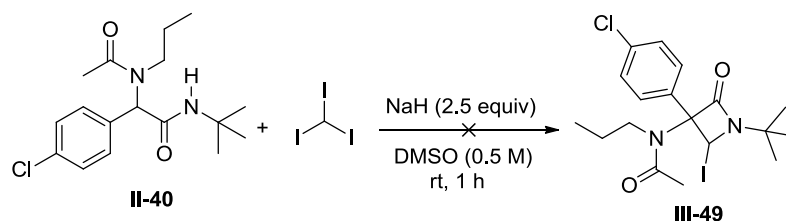


Scheme III.42. Proposed mechanism for [3+1] Ugi/diiodomethane cycloaddition.

Next, the reactivity of several diiodomethane derivatives in the intermolecular [3+1] cycloaddition was examined.

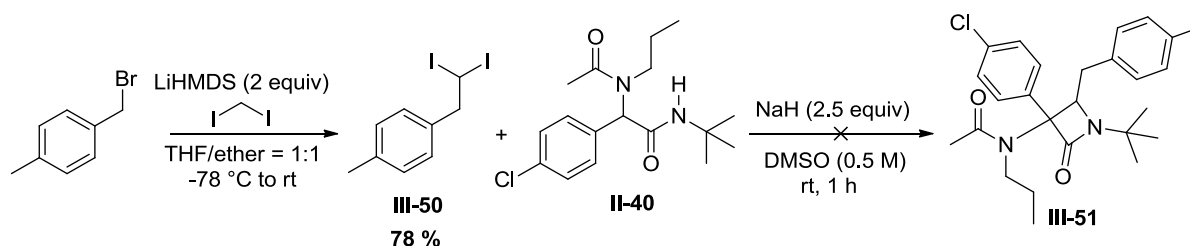
### III.10 Scope of diiodomethane derivatives

Different categories of substituted diiodomethane have been subjected to our reaction conditions. Starting with iodoform, Ugi adduct **II-40** was stirred with 2.5 equiv. of NaH in DMSO (0.5 M) for 10 min, followed by the addition of 1.5 equiv. of iodoform (Scheme III.43). A sudden increase in the reaction temperature occurred, but the target product **III-49** was not formed and the crude mixture only included the starting material. This is probably due to the highly acidic proton of the iodoform that could be abstracted by the Ugi dianion intermediate, regenerating the Ugi starting material.



Scheme III.43. Intermolecular [3+1] Ugi/iodoform cycloaddition.

The second trial was done using 1-(2,2-diiodoethyl)-4-methylbenzene **III-50**. The latter was prepared according to the described procedure in the literature.<sup>305</sup> It was obtained with a 78 % yield from the reaction of *p*-methylbenzyl bromide with diiodomethane in presence of 2.0 equiv of LiHMDS in a mixture of solvents (THF:ether = 1:1) at -78 °C to room temperature for 12 hours. Following the aforementioned reaction conditions, the reagent **III-50** failed to deliver the corresponding  $\beta$ -lactam **III-51** (Scheme III.44). This could be attributed to the probable hydrogen iodide elimination from the diiodo derivative affording styrene, although no side products were separated.



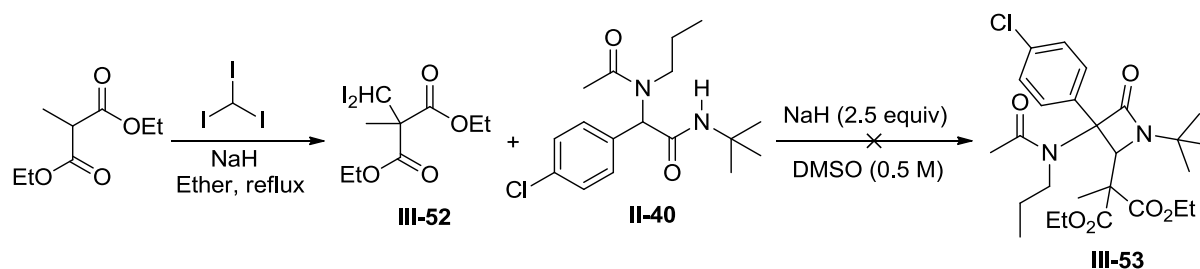
Scheme III.44. Intermolecular [3+1] Ugi/(diiodomethyl)benzene cycloaddition.

The last attempt was performed with diethyl 2-(diiodomethyl)-2-methylmalonate **III-52**. This derivative was prepared following the reported procedure in the literature.<sup>306</sup> It was obtained in quantitative yield using diethyl methylmalonate and iodoform in presence of 1.2 equiv. of NaH in diethyl ether under reflux for 12 hours. This diiodo reagent **III-52** failed as well to give the  $\beta$ -lactam **III-53** even after raising the temperature till 130 °C and heating the reaction for 24 hours (Scheme III.45). This is probably due to the steric bulkiness of the reagent.

<sup>305</sup> Bull, J. A.; Charette, A. B. *J. Org. Chem.* **2008**, 73, 8097.

<sup>306</sup> Mailhol, D.; Willwacher, J.; Kausch-Busies, N.; Rubitski, E. E.; Sobol, Z.; Schuler, M.; Lam, M.- H.; Musto, S.; Loganzo, F.; Maderna, II A.; Furstner, A. *J. Am. Chem. Soc.* **2014**, 136 (44), 15719.



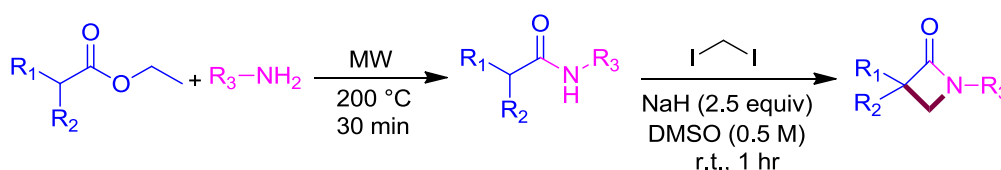


**Scheme III.45.** Intermolecular [3+1] Ugi/diethyl 2-(diiodomethyl)-2-methylmalonate cycloaddition.

Hence, all the employed diiodomethane derivatives were incompatible with our protocol to provide the target  $\beta$ -lactams and the reaction scope was only limited to the diiodomethane.

### III.11 General $\beta$ -lactam synthesis procedure

The success of the diiodomethane application in the [3+1] cycloaddition towards the 4-component  $\beta$ -lactams encouraged us to extend the protocol to different precursors other than Ugi adducts. For such purpose, a series of malonic ester amide starting materials were prepared. In view of Hirari's study,<sup>272</sup> the importance of having  $R_1$  and  $R_2$  substituents other than hydrogen is highlighted. This will help in suppressing the formation of side products, resulting in selectively  $\beta$ -lactams with high yields. Thus, the [3+1] cycloaddition reaction was carried out through the generation of the 1,3-amide dianion species from the malonate derivatives and their subsequent addition onto diiodomethane (Scheme III.46).

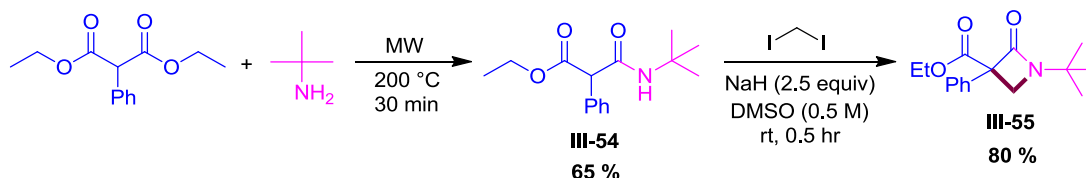


**Scheme III.46.** General [3+1] cycloaddition towards  $\beta$ -lactams.

#### Early trial

The first trial performed was using the previously optimized condition applied for Ugi adducts. Thus, we used the malonic ester amide **III-54** which was obtained in a 65 % yield upon the neat condensation of diethyl 2-phenylmalonate and *tert*-butylamine under microwave irradiation at 200 °C for 30 min. We allowed the latter **III-54** to react with 2.5 equiv. of NaH in DMF at room temperature for 10 minutes till a homogenous solution was

obtained, followed by the addition of 1.5 equiv. of diiodomethane. The resulting mixture was stirred at room temperature for further 30 min where the reaction completion was detected through TLC. A single new product was formed, which upon purification and identification, proved to be the target  $\beta$ -lactam **III-55** isolated with an 80 % yield (Scheme III.47).



Scheme III.47. First trial for [3+1] cycloaddition using malonic ester amide towards  $\beta$ -lactam.

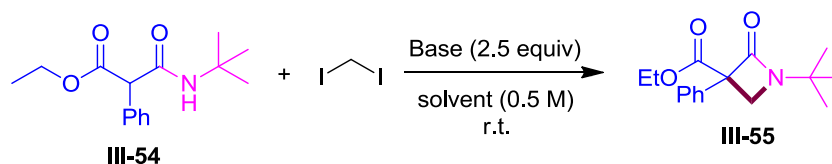
### Optimization of the reaction conditions

In order to make sure that the previously mentioned condition is the best for such precursors, a rapid optimization was carried out changing the base and solvent combination.

#### (1) Base-Solvent combination

The effect of using strong bases in various solvents on the generation of 1,3-amide dianion intermediate from malonic ester amide **III-54** was studied. Thus, KHMDS and LiHMDS were selected as powerful bases in addition to NaH to be tested in a group of solvents such as: THF,  $\text{CH}_3\text{CN}$  and DMF together with DMSO. A number of trials were performed using the same amide **III-54**, 2.5 equiv. of base and 1.5 equiv. of diiodomethane (see Table III-4). The reaction time was determined according to the reaction progress checked by TLC.

Table III-4. Optimization of Base/Solvent combination.



Entry	Base	Solvent	Time	Yield
1	NaH	DMF	1 h	44 %
2	NaH	CH <sub>3</sub> CN	12 h	36 %
3	NaH	THF	12 h	0 % (SM)
4	KHMDS	THF	12 h	traces
5	LiHMDS	THF	1 h	-*
6	LiHMDS	CH <sub>3</sub> CN	1 h	-*
7	NaH	DMSO	0.5 h	80 %

\*Decomposition of starting material.

The use of NaH in CH<sub>3</sub>CN or DMF didn't improve the reaction yield (affording 36 % and 44 % respectively). In THF, no product was isolated even after stirring for 12 hours, the reaction mixture included only starting material. Trying KHMDS in THF resulted in only traces of the corresponding  $\beta$ -lactam **III-55**. Whereas, using LiHMDS in either THF or CH<sub>3</sub>CN lead to the decomposition of the starting material after one hour with no product. The results are presented above in Table III-4.

Consequently, NaH in DMSO was kept as the optimum base/solvent combination for the reaction as it allowed the synthesis of the target  $\beta$ -lactam **III-55** at room temperature in 80 % yield after 30 min.

In order to affirm the necessity of the presence of excess amount of base, a control experiment was run using 1.0 equiv. of NaH. In this case, no product was obtained since the resulting carbanion is highly stabilized (compared to the Ugi monoanion) thus not nucleophilic enough to react with CH<sub>2</sub>I<sub>2</sub>.

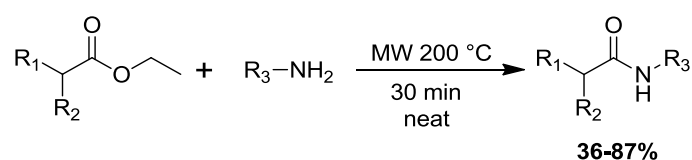
### III.12 Synthesis of Malonic ester amide

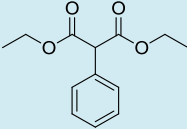

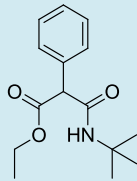
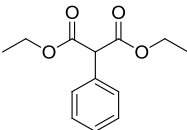
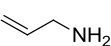
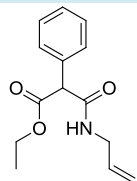
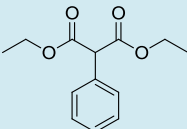
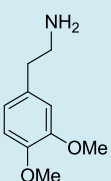
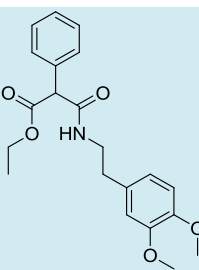
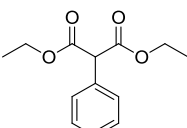
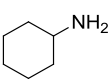
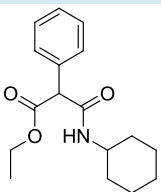
The malonic ester amide synthesis involves the condensation of a malonate derivative with various amines. There are several known conditions for such amidation reaction including conventional heating for prolonged time, microwave-assisted reaction or using catalysts.<sup>307</sup> We selected among them the simple microwave procedure, thus, the condensation

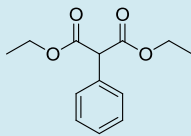
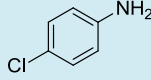
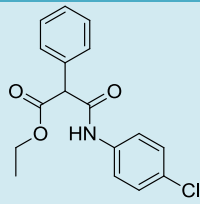
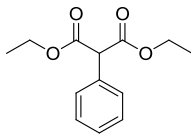
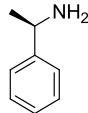
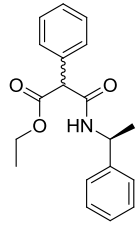
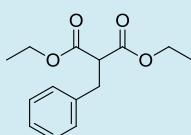

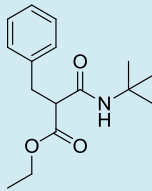
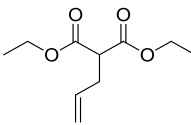

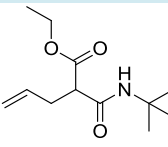
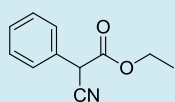

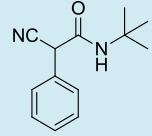
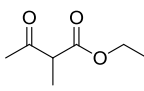

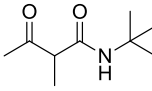
<sup>307</sup> See for example: (a) Mahajan, P. S.; Mahajan, J. P.; Mhaske, S. B. *Synth. Commun.* **2013**, 43, 2508. (b) Allen, C. L.; Williams, J. M. J. *Chem. Soc. Rev.* **2011**, 40, 3405. (c) Kim, B. R.; Lee, H.-G.; Kang, S.-B.; Sung, G. H.;

was carried out under microwave irradiation at 200 °C for 30 min without solvent. Consequently, we prepared a set of malonic ester amides and related derivatives with moderate to excellent yields (36 % to 87 %). The different results are presented below in Table III-5.

Table III-5. Synthesis of malonic ester amides.



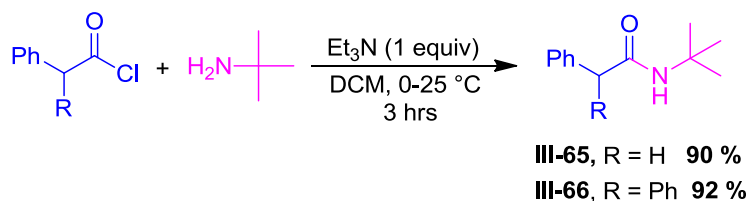
Entry	Ester	Amine	Prepared Amide	Yield
1			 <b>III-54</b>	65%
2			 <b>III-56</b>	46%
3			 <b>III-57</b>	53%
4			 <b>III-58</b>	54%

5			 <b>III-59</b>	73%
6			 <b>III-60</b>	51% (1:1)
7			 <b>III-61</b>	68%
8			 <b>III-62</b>	46%
9			 <b>III-63</b>	87%
10			 <b>III-64</b>	36%

Generally, this reaction allowed us to prepare a set of amides with moderate to excellent yields from 36 to 87 %.

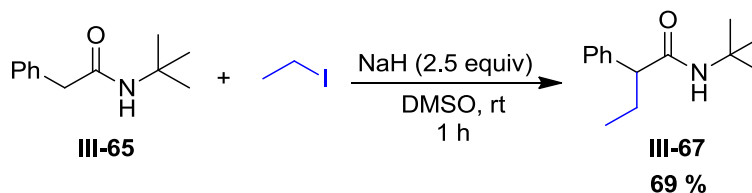
Additionally, other simple amides were prepared following the commonly used amide synthesis procedure. Thus, the amide **III-65** was obtained in 90 % yield from equimolar of 2-phenylacetyl chloride and *tert*-butylamine using triethylamine as base in DCM at 0 to 25 °C

for 3 hours (Scheme III.48). Whereas, the amide **III-66** was obtained in 92 % yield using diphenylacetyl chloride and *tert*-butylamine.



**Scheme III.48. Synthesis of different simple amides.**

The C-alkylation of the amide **III-65** provided the new amide **III-67**. The latter was isolated in 69 % yield from the reaction of ethyl iodide with the amide **III-65** in presence of 2.5 equiv of NaH as a base in DMSO at room temperature for 1 hour (Scheme III.49).

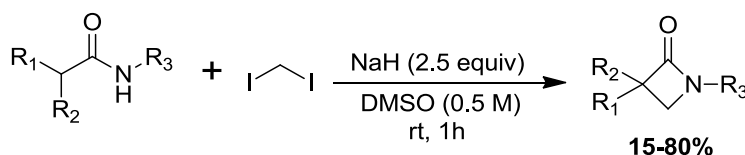



**Scheme III.49. C-Alkylation of the amide III-65 to prepare the amide III-67.**

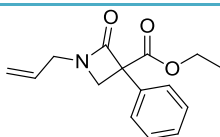
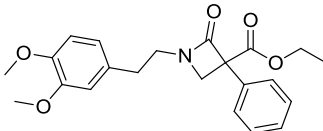
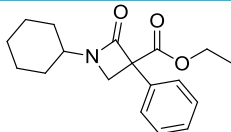
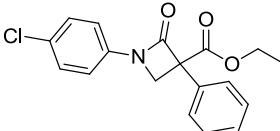
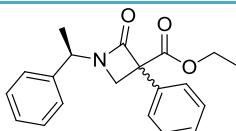
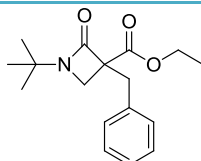
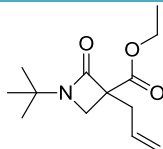
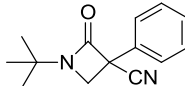
### III.13 Scope of $\beta$ -lactam synthesis from malonate ester amides

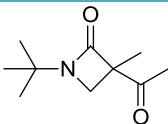
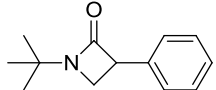
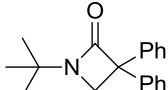
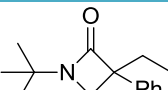
The prepared set of amides was then subjected to the reaction with NaH (2.5 equiv.) and diiodomethane (1.5 equiv.) in DMSO (0.5 M) at room temperature for one hour. This cycloaddition reaction provided a series of  $\beta$ -lactams with moderate to good yields. The different results are displayed in Table III-6.

**Table III-6. The scope of  $\beta$ -lactam synthesis from diverse amides.**



Entry	Amide	$\beta$ -lactam	Yield
1	III-54		80%

III-55			
2	III-56		65%
III-68			
3	III-57		53%
III-69			
4	III-58		66%
III-70			
5	III-59		38%
III-71			
6	III-60		62% (2:1)
III-72			
7	III-61		66%
III-73			
8	III-62		58%
III-74			
9	III-63		80%
III-75			

10	III-64	 III-76	43%
11	III-65	 III-77	15%
12	III-66	 III-78	0% (SM)
13	III-67	 III-79	0% (SM)

In general, the synthesized  $\beta$ -lactams were obtained with moderate to good yields from 15 to 80 % (see Table III-6).

The reaction proceeded well with amides derived from aliphatic amines. The tertiary amines proved to be the best partners affording  $\beta$ -lactam **III-55** in 80 % yield, followed by the secondary amines providing  $\beta$ -lactam **III-70** in 66 % and finally comes the primary one giving **III-69** in 53 % yield. Such results are congruent with those obtained using Ugi adducts. However, using aromatic amines like: *p*-chloroaniline, the corresponding  $\beta$ -lactam **III-71** was separated with only 38 % yield. This low yield could be attributed to the decreased nucleophilicity of the amide due to its conjugation with the aryl group.

The selectivity of the cycloaddition reaction was examined using a mixture of 1:1 diastereomers of the amide **III-60**. It yielded the  $\beta$ -lactam **III-72** in 62 % yield with 2:1 diastereomeric ratio which was detected from the  $^1\text{H-NMR}$ . Thus, the selectivity was slightly enhanced. Working at lower temperature using a mixture of solvents (DMSO : DCM = 1:1) did not improve the reaction selectivity.

The substitution at the peptidyl C-H position in the malonate ester amide affected greatly the reaction yield. The presence of aromatic groups like the phenyl group afforded the  $\beta$ -lactam **III-55** with a high yield (80 %). While, the benzyl substituent gave the  $\beta$ -lactam **III-**

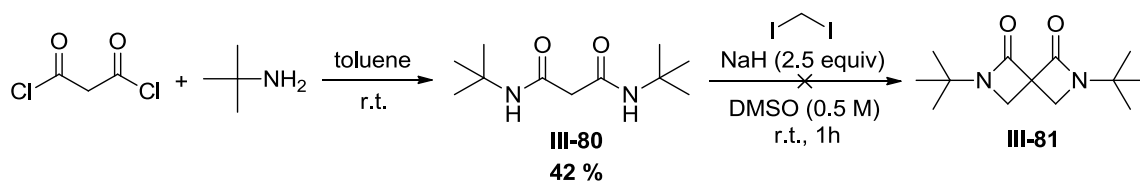


**73** in moderate 66 % yield and the allyl substituent provided the  $\beta$ -lactam **III-74** with 58 % yield. This is probably due to enhancing the acidity of the peptidyl C-H using aromatic substituent more than benzylic or allylic ones.

Other related compounds having groups other than the ester group like: cyano (**III-63**) or acetyl substituents (**III-64**), could successfully participate as the source of amide dianions in the reaction. The amide **III-63** afforded the corresponding  $\beta$ -lactam **III-75** in 80 % yield due to the high electron-withdrawing nature of the cyano group that is comparable with the ester one. Whereas, the amide **III-64** yielded the  $\beta$ -lactam **III-76** in relatively low 43 % yield due to the absence of aromatic groups.

The lowest yield obtained was using the amide **III-65** with a secondary peptidyl carbon. It afforded the  $\beta$ -lactam **III-77** in only 15 % yield. This is due to the presence of the  $\text{CH}_2$  group which enhances the possibility for various side reactions like double intermolecular addition or elimination leading to methylene intermediates. The poorly activated amide **III-67** failed to give the corresponding  $\beta$ -lactam **III-79**. Surprisingly, the amide **III-66** did not deliver the corresponding  $\beta$ -lactam **III-78**, which might be attributed to the non-planarity of the bulky amide **III-66** dianion intermediate.

An interesting trial towards spiro  $\beta$ -lactams was carried out using the malonamide **III-80**. The latter was prepared using 1.0 equiv. of malonyl chloride with 2.5 equiv. of *tert*-butylamine in toluene at room temperature in 42 % yield. When it was subjected to the reaction conditions, neither the expected product **III-81** nor the dimer were obtained (Scheme III.50). Instead, a new compound was formed that could not be identified at this stage. The  $^1\text{H}$ -NMR showed the presence of 1 NH, 5 H at the range from 3 to 4 ppm and 3 *t*-Bu groups. The  $^{13}\text{C}$ -NMR showed the presence of 3 CO and 4 different types of C beside the 3 *t*-Bu groups.



Scheme III.50. spiro  $\beta$ -lactam synthesis using malonamide.

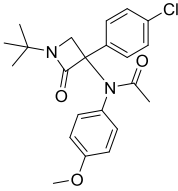
### III.14 Biological activity of the synthesized $\beta$ -lactams

In order to wrap up our study, the newly synthesized  $\beta$ -lactams were assayed in vitro for their antimicrobial activity in the “Biology Center” at Faculty of Pharmacy (Mansoura University, Egypt). The activity was determined against one gram negative bacteria (*Escherichia coli*), one gram positive bacteria (*Staphylococcus aureus*) in addition to the fungal species (*Candida albicans*).<sup>308</sup> The widely used bactericides *Ampicillin* and the fungicide *Colitrimazole* were selected as references to evaluate the potency of the examined compounds using a solution of 1 mg/ml in DMSO for each sample. The antimicrobial effect was determined through two main parameters, the values for the diameter of the inhibition zone in mm and the percentage of activity index. Where the diameter of the inhibition zone signifies the effectiveness of the antibiotic: the larger the diameter, the greater the sensitivity of the microorganism to the antibiotic. The inhibition zone denotes the area of inhibiting the microorganism growth by the antibiotic effect and does not necessarily indicate that it has been killed. While, the percentage of activity index signifies the activity of the investigated compound as antimicrobial agent and is calculated using the following equation:

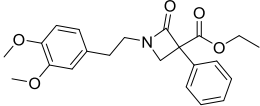
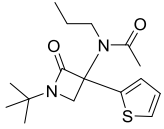
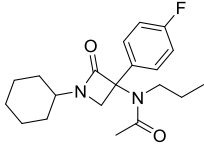
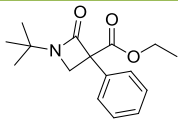
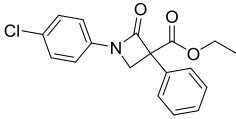
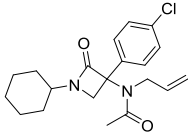
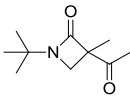
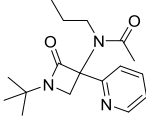
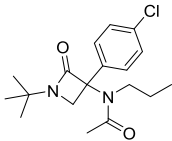
$$\% \text{Activity Index} = \frac{\text{Diameter of inhibition zone by examined structure (mm)}}{\text{Diameter of inhibition zone by standard (mm)}} \times 100$$

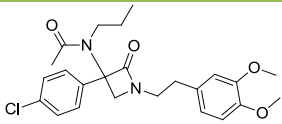
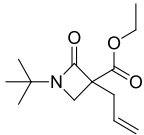
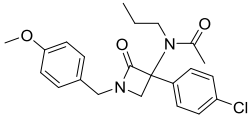
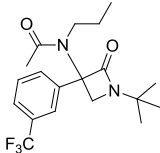
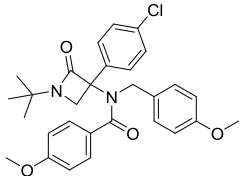
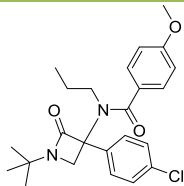
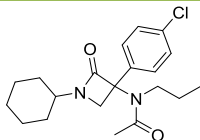
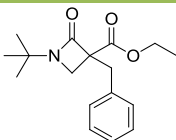
The various results obtained are illustrated in Table III-7.

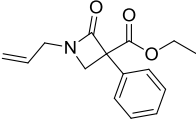
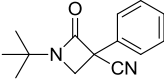
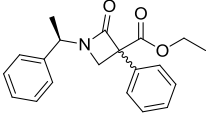
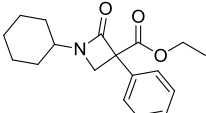
**Table III-7. The antimicrobial activity of the synthesized  $\beta$ -lactams**

Compound	Diameter of inhibition zone in mm [% Activity index]		
	<i>Escherichia coli</i>	<i>Staphylococcus aureus</i>	<i>Candida albicans</i>
 <b>III-44</b>	<b>25 [96.1]</b>	<b>24 [100.0]</b>	<b>26 [96.3]</b>

<sup>308</sup> Stylianakis, A.; Kolocouris, N.; Kolocouris, G.; Fytas, G. B.; Foscolos, E.; Padalko, J.; Neyts, D.; Clerq, E. *Bioorg. Med. Chem. Lett.* **2003**, 13, 1699.

 <p><b>III-30</b></p>	<b>23 [88.5]</b>	<b>23 [95.8]</b>	<b>24 [88.9]</b>
 <p><b>III-34</b></p>	<b>21 [80.8]</b>	<b>23 [95.8]</b>	<b>19 [70.4]</b>
 <p><b>III-39</b></p>	<b>19 [73.1]</b>	<b>22 [91.7]</b>	<b>23 [85.2]</b>
 <p><b>III-55</b></p>	<b>17 [65.4]</b>	<b>21 [87.5]</b>	<b>23 [85.2]</b>
 <p><b>III-71</b></p>	<b>16 [61.6]</b>	<b>19 [79.2]</b>	<b>21 [77.8]</b>
 <p><b>III-37</b></p>	<b>14 [53.8]</b>	<b>20 [83.3]</b>	<b>22 [81.5]</b>
 <p><b>III-76</b></p>	<b>13 [50.0]</b>	<b>18 [75.0]</b>	<b>19 [70.4]</b>
 <p><b>III-36</b></p>	<b>13 [50.0]</b>	<b>19 [79.2]</b>	<b>20 [74.1]</b>
 <p><b>III-25</b></p>	<b>11 [42.3]</b>	<b>16 [66.7]</b>	<b>15 [55.5]</b>

 <p><b>III-30</b></p>	10 [38.5]	17 [70.8]	19 [70.4]
 <p><b>III-74</b></p>	9 [34.6]	14 [58.3]	17 [63.0]
 <p><b>III-28</b></p>	6 [23.1]	11 [45.8]	10 [37.0]
 <p><b>III-32</b></p>	5 [19.2]	9 [37.5]	8 [29.6]
 <p><b>III-46</b></p>	4 [15.4]	8 [33.3]	5 [18.5]
 <p><b>III-43</b></p>	4 [15.4]	8 [33.3]	7 [25.9]
 <p><b>III-27</b></p>	2 [7.7]	6 [25.0]	4 [14.8]
 <p><b>III-73</b></p>	2 [7.7]	5 [20.8]	2 [7.4]

 <b>III-68</b>	NA	3 [12.5]	NA
 <b>III-75</b>	NA	2 [8.3]	NA
 <b>III-72</b>	NA	NA	NA
 <b>III-70</b>	NA	NA	NA
<b>Ampicillin</b>	26 [100.0]	24 [100.0]	NA
<b>Colitrimazole</b>	NA	NA	27 [100.0]

\*NA: No activity

The above results clarified that the  $\beta$ -lactams **III-30**, **III-34** and **III-44** possessed a highly promising antibacterial and antifungal activities against *Escherichia coli*, *Staphylococcus aureus* and *Candida albicans* compared to the reference drugs. Moreover, the  $\beta$ -lactam **III-44** in particular, showed exactly the same resistance to *Staphylococcus aureus* as the Ampicillin as well as a very close activity against *Candida albicans* and *Escherichia coli* compared with the Colitrimazole and the Ampicillin respectively. While the  $\beta$ -lactams **III-37**, **III-39**, **III-55** and **III-71**, exerted strong inhibition compared to the references. The  $\beta$ -lactams **III-25**, **III-30**, **III-36**, **III-74** and **III-76** exhibited moderate activity, while the  $\beta$ -lactams **III-27**, **III-28**, **III-32**, **III-43**, **III-46** and **III-73**, displayed low influence. However, the  $\beta$ -lactams **III-68**, **III-70**, **III-72** and **III-75** were almost inactive against the tested microorganisms.

It is worth mentioning that the reactivity of the  $\beta$ -lactams **III-30**, **III-34** and **III-44** is close to that of the Ampicillin (Figure III.11). However they are synthesized in two simple steps compared with the more complex ones required for the synthesis of Ampicillin with the proper enantioselectivity.

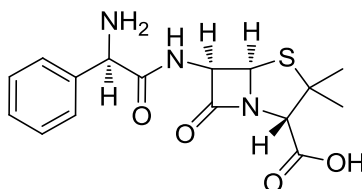


Figure III.11. Structure of Ampicillin.

In order to have a clearer picture for the comparison between the antimicrobial activities of all the examined  $\beta$ -lactams, a graphical representation has been depicted (Figure III.12).

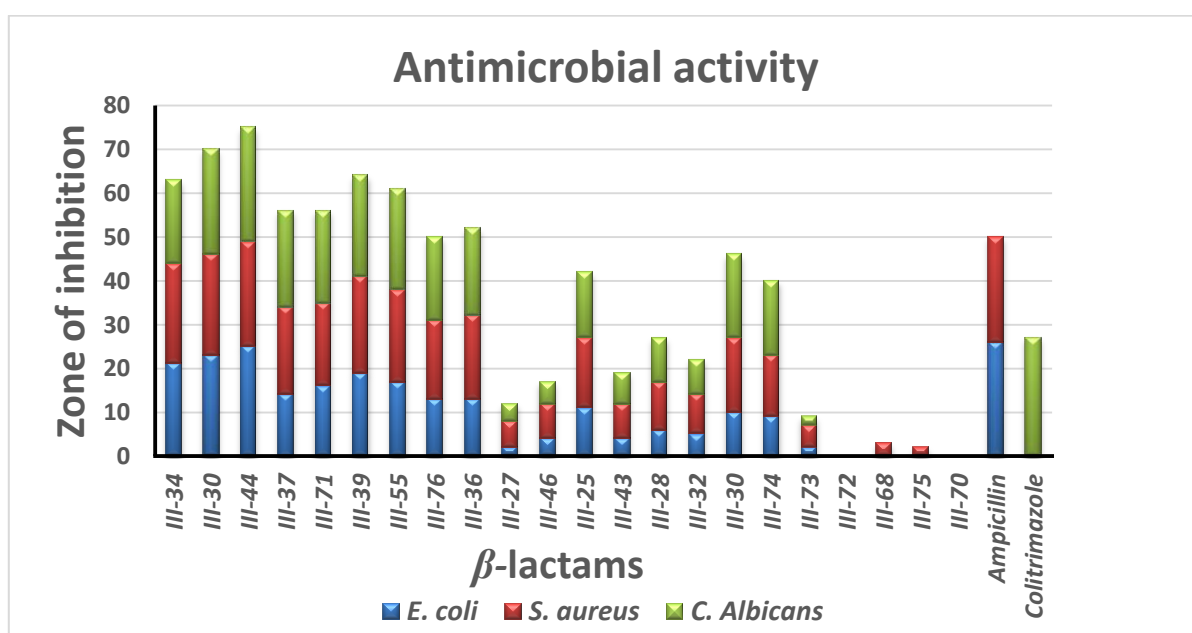


Figure III.12. A graphical representation of the antimicrobial activity of the examined  $\beta$ -lactams.

The results obtained are considered as preliminary signals to guide us afterwards in choosing the properly substituted  $\beta$ -lactams with high antibacterial effects to be entirely examined as antibiotics.

### III.15 Conclusion

In the context of this chapter, we reported an efficient intermolecular [3+1] cycloaddition reaction for the  $\beta$ -lactam synthesis. This methodology has been suggested before by Hirari, but it suffered from many limitations that rendered it unexploited by chemists thenceforth. Despite the simplicity of the procedure, only four examples were

reported with low yields and the reaction was limited to the thioether derivatives only. Furthermore, working in a concentrated medium resulted in undesired side products.

Our proposed strategy involved adding 2.5 equiv. of NaH to various amides in DMSO in order to generate 1,3-amide dianion intermediates. Such intermediates, as powerful nucleophiles, attacked in return the biselectrophile, diiodomethane, forming the cyclic adduct. The reaction proceeded smoothly at room temperature to completion in almost 1 hour for most of the examples.

Employing the multicomponent Ugi adducts in this reaction raised the diversity of the prepared  $\beta$ -lactams. This fulfilled an important criterion from the drug-discovery point of view. Since the process of finding a new drug usually involves a high-throughput screening (HTS), in which a large library of products is tested for their ability to fight a certain disease in order to reach the appropriate substitutions in the drug. Multicomponent reactions serve as an excellent tool for such purpose.

Moreover, the methodology was successfully extended as well to several malonic ester amides and their related derivatives. Accordingly, it could be considered as a general methodology for  $\beta$ -lactam synthesis and not limited only to Ugi adducts.

More interestingly, the newly synthesized  $\beta$ -lactams were subjected to biological tests as antibacterial and antifungal agents. The results showed that almost half of the prepared  $\beta$ -lactams possessed moderate to high inhibition activity against the selected gram positive, gram negative bacteria and fungus. Some of the  $\beta$ -lactams showed promising results, thus they could be fully examined later on to deliver new antibiotics to the market.

## **Chapter IV : Ugi amide dianion based synthesis of pyrrolidinones and benzoindolizidines.**

The chemistry described in this chapter has been published in:

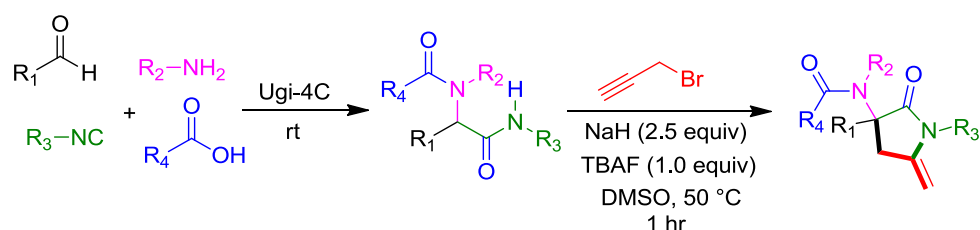
Zidan, A.; Cordier, M.; El-Naggar, A. M.; Abd El-Sattar, N. E. A.; Ali, A. K.; Hassan, M. A.; El Kaïm, L. *Org. Lett.* **2018**, DOI:10.1021/acs.orglett.8b00687.





## IV.1 Outline

In this chapter we report an approach towards pyrrolidin-2-ones, based on the already discussed Ugi amide dianion reactivity towards biselectrophiles disclosed in chapter III. Thus, Ugi adducts were allowed to react with propargyl bromide in presence of 2.5 equiv. of NaH and 1.0 equiv. of TBAF for 1 hour in DMSO at 50 °C (Scheme IV.1). This reaction delivered a set of 5-methylene-pyrrolidin-2-one derivatives through a sequence of C-alkylation followed by a 5-*exo-dig* hydroamidation cyclization.

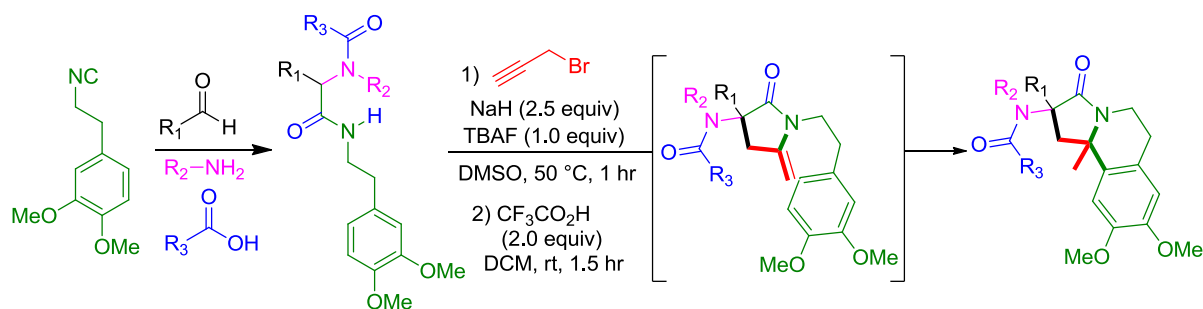


**Scheme IV.1.** An Ugi/Intermolecular propargylation sequence towards pyrrolidinones.

A series of Ugi reaction followed by two consecutive post-condensation modifications is gathering great interest nowadays. Such synthetic strategy has the advantage of increasing the molecular complexity and diversity. Wherein the starting materials shall be chosen so that the first ring obtained will still possess additional functional groups, that can further cyclize either via a carbon-carbon or carbon-heteroatom bond providing a more complex structure.<sup>309</sup> In this context, we present a synthetic protocol involving Ugi/double post-condensation reactions.

The enamine functional group in the synthesized 5-methylene-pyrrolidin-2-ones could be further exploited in a Pictet-Spengler type cyclization to prepare benzoindolizidine alkaloids analogues. For such purpose, an electron-rich  $\beta$ -arylethyl isocyanide was involved in the synthesis of Ugi adducts. Moreover the two post-condensations could be carried out in a one-pot reaction without the need for the isolation or the purification of the intermediates. Hence, Ugi adducts were allowed to react with propargyl bromide in presence of 2.5 equiv. of NaH and 1.0 equiv. of TBAF in DMSO at 50 °C for 1 hour. An extraction was then carried out to replace the solvent by dichloromethane, to which 2.0 equiv. of trifluoroacetic acid was added. Stirring the reaction for 1.5 hours at room temperature afforded the target benzoindolizidine derivatives (Scheme IV.2).

<sup>309</sup> Sunderhaus, J. D.; Martin, S. F. *Chemistry* **2009**, *15*, 1300.



Scheme IV.2. An Ugi/propargylation/Pictet-Spengler sequence towards benzoindolizidines.

Before presenting the results obtained, a brief introduction about pyrrolidin-2-ones, their synthesis and reactivity is displayed.

## IV.2 General aspects

Pyrrolidin-2-one is a five-membered cyclic amide ring ( $\gamma$ -lactam). It is the parent compound of the  $\gamma$ -lactam class of organic compounds (Figure IV.1).

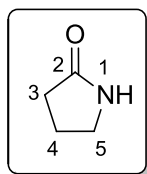


Figure IV.1. The simplest  $\gamma$ -Lactam "Pyrrolidin-2-one".

It is an active moiety in the core structure of various drugs. For example; Doxapram which is used as a respiratory stimulant,<sup>310</sup> Piracetam<sup>311</sup> that is prescribed for myoclonus (involuntary trembling of muscles) as well as Cotinine which is an alkaloid found in tobacco and used as a treatment for Alzheimer's disease and as an antidepressant<sup>312</sup> (Figure IV.2).

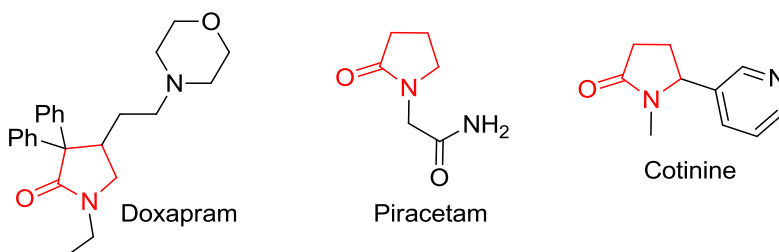


Figure IV.2. Structures of drugs containing pyrrolidin-2-one nucleus.

<sup>310</sup> Singh, P.; Dimitriou, V.; Mahajan, R. P.; Crossley, A. W. *Br. J. Anaesth.* **1993**, 71, 685.

<sup>311</sup> Winblad, B. *CNS Drug Rev.* **2005**, 11, 169.

<sup>312</sup> Grizzell, J. A.; Echeverria, V. *Neurochem. Res.* **2015**, 40, 2032.

It is used as well as a precursor for several polymers such as: polyvinylpyrrolidinone (PVP) which has wide range of applications for instance, it is used as a lubricant in eye drops and in contact lenses<sup>313</sup> (Figure IV.3).

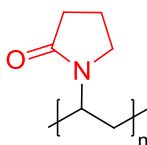


Figure IV.3. The structure of PVP.

### 5-Exo-methylene-2-pyrrolidinones

It is a 5-membered cyclic enamide ring. It is an important functionality for the synthesis of natural products such as: chlorins, isobacteriochlorins and corrins (Figure IV.4).<sup>314</sup> These products act as: vitamins, co-factors and light absorbing pigments.<sup>315</sup>

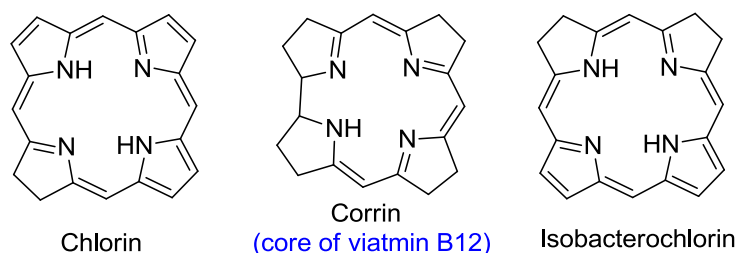


Figure IV.4. The Structures of naturally occurring chlorin, isobacteriochlorins and corrin.

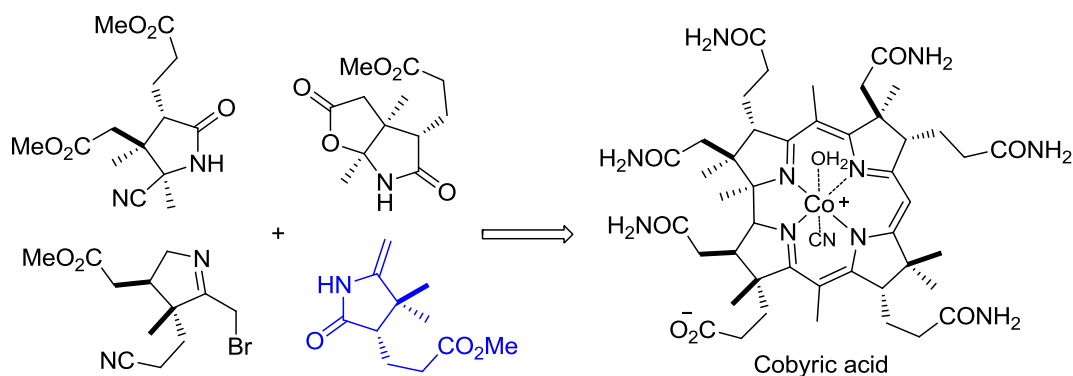
Eschenmoser and Wintner<sup>316</sup> used the 5-methylene-2-pyrrolidinone synthon in the total synthesis of cobyrinic acid which is the precursor to synthesize vitamin B12 (Scheme IV.3).

<sup>313</sup> Kading, D. L. *Contact Lens Spectrum* **2014**, 29, 19.

<sup>314</sup> Jacobi, P. A.; Briemann, H. L.; Hauck, S. I. *Tetrahedron Lett.* **1995**, 36, 1193.

<sup>315</sup> Flitsch, W. in *Advances in Heterocyclic Chemistry*, Katritzky, A. R., Ed., Academic Press, Inc.: San Diego, California, **1988**; Vol. 43, p.74 (Hydrogenated Porphyrin Derivatives: Hydroporphyrins).

<sup>316</sup> Eschenmoser, A.; Wintner, C. E. *Science* **1977**, 196, 1410.



Scheme IV.3. Synthesis of vitamin B12 precursor “cobyric acid” using 5-methylene-2-pyrrolidinones.

### (1) Ring construction

There are several reported protocols for the construction of the cyclic enamide ring in the literature,<sup>317</sup> among which the intramolecular hydroamidation of alkynes is remarkable.<sup>318</sup> The amide nucleophilic attack across the triple bond is slightly exothermic or thermo neutral,<sup>319</sup> however, it is kinetically less favored due to the repulsion between the nucleophile and  $\pi$ -electrons of the alkyne triple bond. Accordingly non-catalytic hydroamidations should involve either strong acids to protonate the triple bond, hence facilitate the nucleophilic attack, or strong bases to generate nucleophilic metal amides thus enhancing their addition onto the alkyne. While in case of catalytic hydroamidations, the metal usually coordinates to the triple bond, reducing its electron density, thus enabling the nucleophilic addition.

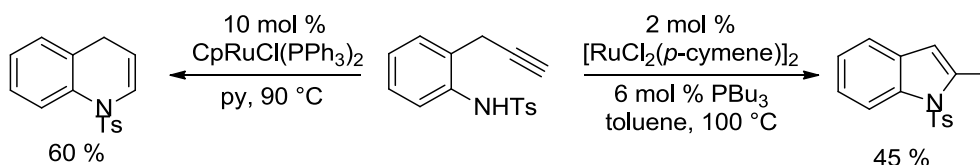
The selectivity between *exo*- and *endo*-cyclization products is affected by several factors. The electronic nature of the substrate, its steric bulkiness in addition to the metal catalyst which can also affect whether the cyclization occurs through the amide nitrogen or oxygen, are the main factors that affect the regioselectivity of the reaction. For instance the cyclization of alkynyl anilides can afford different products depending on the ruthenium

<sup>317</sup> See for example: (a) Sheiman, B. M.; Denisova, L. Y.; Dymova, S. F.; Shereshevskii, A. A.; Kustanovich, I. M.; Berezovskii, V. M. *Chem. Heterocycl. Compd.* **1971**, 7, 1119. (b) Cannizzo, L. F.; Grubbs, R. H. *J. Org. Chem.* **1985**, 50, 2316. (c) Cid, M. M.; Dominguez, D.; Castedo, L.; Vazquez-Lopez, E. M. *Tetrahedron* **1999**, 55, 5599. (d) Habib-Zahmani, H.; Viala, J.; Hacini, S.; Rodriguez, J. *Synlett* **2007**, 7, 1037. (e) Wong, Y.-C.; Parthasarathy, K.; Cheng, C.-H. *J. Am. Chem. Soc.* **2009**, 131, 18252. (f) Cao, H.; McNamee, L.; Alper, H. *Org. Lett.* **2008**, 10, 5281.

<sup>318</sup> For review on hydroamidation of alkynes see: (a) Huang, L.; Arndt, M.; Goossen, K.; Heydt, H.; Goossen, L. *J. Chem. Rev.* **2015**, 115, 2596.

<sup>319</sup> (a) Müller, T. E.; Hultsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, 108, 3795. (b) Pohlki, F.; Doye, S. *Chem. Soc. Rev.* **2003**, 32, 104.

catalyst employed.<sup>320</sup> Using  $\text{CpRuCl}(\text{PPh}_3)_2$ , the 6-*endo* product 1,4-dihydroquinoline is obtained while using  $[\text{RuCl}_2(p\text{-cymene})]_2$ , the 5-*exo* cyclization 2-methylindole is formed (Scheme IV.4).

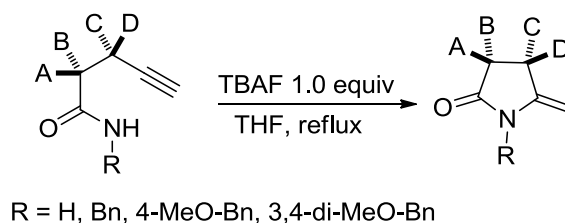


Scheme IV.4. Ru-catalyzed selective 5-*exo* and 6-*endo* cyclization products.

However we will present briefly the strategies involving the intramolecular 5-*exo-dig* hydroamidation of alkynes, which are related to our project.

### ➤ TBAF triggered 5-*exo-dig* cyclization

Jacobi *et al.*<sup>321</sup> reported a powerful protocol for the synthesis of 5-methylene-pyrrolidin-2-ones through a TBAF activated 5-*exo-dig* cyclization (Scheme IV.5). They observed that the use of primary amides gave only traces of the corresponding  $\gamma$ -lactams (5 % to 20 %), while using secondary amides improved the reaction yields (50 % to 98 %).



Scheme IV.5. TBAF catalyzed 5-*exo-dig* cyclization of acetylenic amides.

### ➤ Base-catalyzed 5-*exo-dig* cyclization

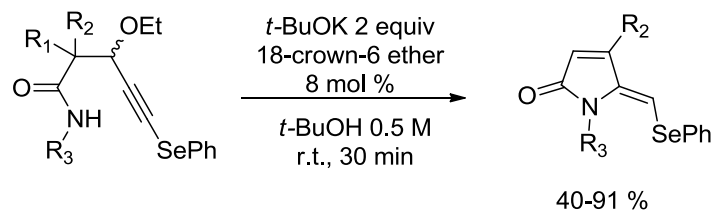
In 1996, a base-catalyzed intramolecular cyclization of alkynylamides stabilized by a selenium atom with subsequent dehydroalkoxylation was presented.<sup>322</sup> The authors used 2.0 equiv. of *t*-BuOK in *t*-BuOH in presence of catalytic amount of 18-crown-6 ether as a ligand for potassium cation, to catalyze the aforementioned 5-*exo-dig* cyclization (Scheme IV.6).

<sup>320</sup> (a) Varela-Fernández, A.; Varela, J. A.; Saá, C. *Adv. Synth. Catal.* **2011**, 353, 1933. (b) Varela-Fernández, A.; Varela, J. A.; Saá, C. *Synthesis* **2012**, 44, 3285.

<sup>321</sup> (a) Jacobi, P. A.; Briemann, H. L.; Hauck, S. I. *Tetrahedron Lett.* **1995**, 36, 1193. (b) Jacobi, P. A.; Briemann, H. L.; Hauck, S. I. *J. Org. Chem.* **1996**, 61, 5013. (c) Jacobi, P. A.; Guo, J.; Rajeswari, S.; Zheng, W. *J. Org. Chem.* **1997**, 62, 2907.

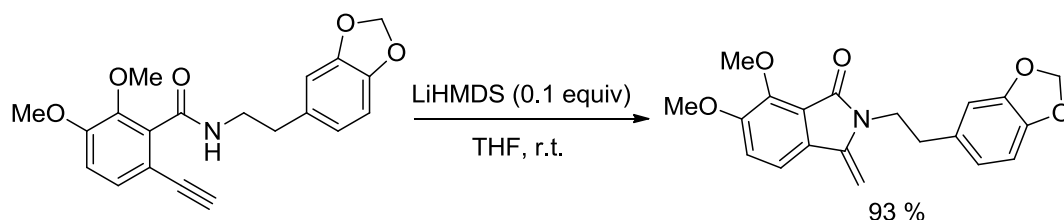
<sup>322</sup> Yoshimatsu, M.; Machida, K.; Fuseya, T.; Shimizu, H.; Kataoka, T. *J. Chem., Perkin Trans. 1* **1996**, 1839.

This protocol delivers in most examples selectively the *cis*-isomer (except when R<sub>3</sub> = Bn), however, it is limited to the alkynylselenium derivatives.



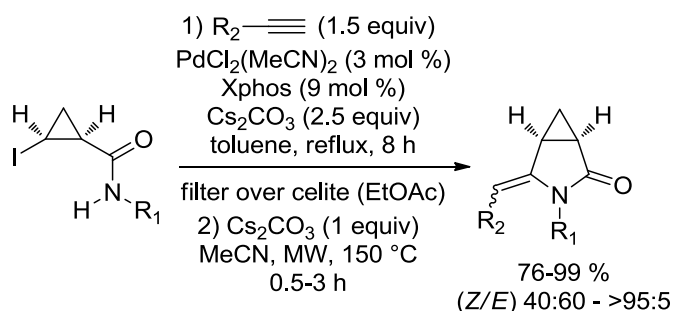
Scheme IV.6. Base-catalyzed cyclization of alkynylamides.

Nevertheless, the use of catalytic amount of LiHMDS is found to be equally effective as the used stoichiometric amount, in the intramolecular cyclization of *ortho*-ethynylbenzamide (Scheme IV.7).<sup>323</sup>



Scheme IV.7. base-catalyzed intramolecular cyclization of *o*-ethynylbenzamide.

Recently, a copper-free Sonogashira cross-coupling/*5-exo-dig* cyclization sequence was reported to prepare 4-substitued-3-azabicyclo[3.1.0]hexan-2-ones.<sup>324</sup> The intramolecular cyclization is performed using 1.0 equiv of Cs<sub>2</sub>CO<sub>3</sub> in acetonitrile, under microwave irradiation at 150 °C (Scheme IV.8). The bicyclic products are obtained with high yields and good diastereoselectivity.



Scheme IV.8. A Sonogashira cross-coupling/*5-exo-dig* cyclization cascade to prepare bicyclic enamides.

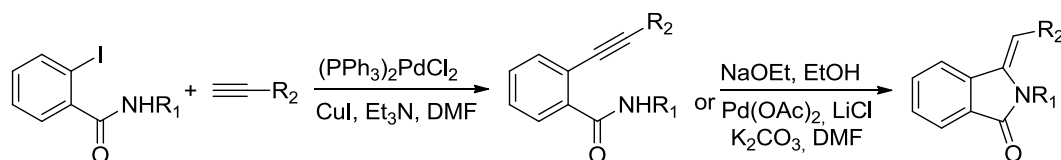
<sup>323</sup> (a) Koseki, Y.; Kusano, S.; Ichi, D.; Sakata, H.; Nagasaka, T. *Tetrahedron Lett.* **1999**, 40, 2169. (b) Koseki, Y.; Nagasaka, T. *Chem. Pharm. Bull.* **1995**, 43, 1604.

<sup>324</sup> de Carné-Caravalet, B.; Meyer, C.; Cossy, J.; Folléas, B.; Brayer, J.-L.; Demoute, J.-P. *J. Org. Chem.* **2013**, 78, 5794.

### ➤ Metal-catalyzed 5-*exo-dig* cyclization

Several transition metals are used to catalyze the 5-*exo-dig* *N*-cyclization of alkynlamides. Usually the metal catalyst activates the triple bond through  $\pi$ -coordination, thus reducing the alkyne electron density and allowing the C-N bond formation. Such  $\pi$ -coordination is not strong enough to inhibit the nucleophilic attack of the amide. Hereinafter we will present some of the reported examples in literature.

In 1997, Kundu and his coworker<sup>325</sup> introduced a palladium-catalyzed intramolecular cyclization of terminal alkynes towards 3-aryl(alkyl)idene-isoindolin-1-ones. They showed that the cyclization could be carried out by refluxing with 1.2 equiv. of sodium ethoxide in ethanol for 4 hrs. However, they also performed one cyclization trial using 5 mol % of Pd(OAc)<sub>2</sub>, 1.0 equiv. of LiCl and 2.5 equiv of K<sub>2</sub>CO<sub>3</sub> in DMF at 100 °C for 16 hrs affording 60 % of the product (R<sub>1</sub> = 4-Me-C<sub>6</sub>H<sub>4</sub>, R<sub>2</sub> = CMe<sub>2</sub>OH) (Scheme IV.9).



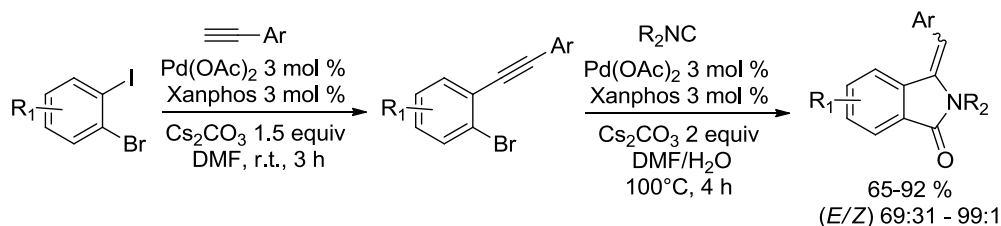
**Scheme IV.9.** Pd-catalyzed synthesis of isoindolin-1-ones from terminal alkynes.

Recently, using isocyanides as amide source, a synthesis of isoindolin-1-ones via a palladium-catalyzed carboxamidation/hydroamidation cascade was reported (Scheme IV.10).<sup>326</sup> The mechanistic studies showed that the carboxamidation step requires the presence of both Pd catalyst/ligand and the base, while the hydroamidation step is catalyzed by the base and can proceed smoothly in absence of the Pd source. Furthermore, the alkenyl and alkyl substituted alkynes failed to deliver the corresponding cyclic product and only the alkynylamide intermediates were isolated in such cases. This is attributed to the lack of electrophilicity of such alkynes as well as the absence of the anion stabilization by aromatic substituent.

<sup>325</sup> Khan, M. W.; Kundu, N. G. *Synlett* **1997**, 1435.

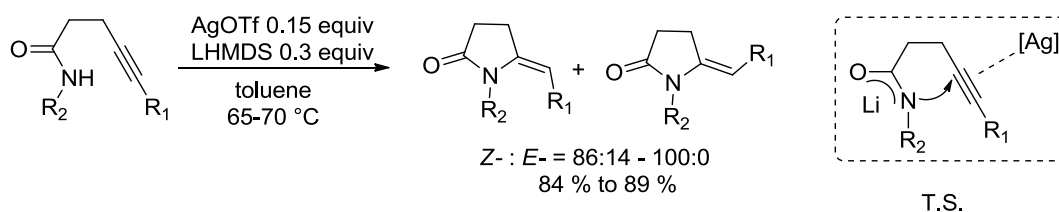
<sup>326</sup> Pathare, R. S.; Sharma, S.; Elagandhula, S.; Saini, V. Sawant, D. M. Yadav, M.; Sharon, A.; Khan, S.; Pardasani, R. T. *Eur. J. Org. Chem.* **2016**, 5579.





Scheme IV.10. Pd-catalyzed carboxamidation/hydroamidation cascade towards isoindolin-1-ones.

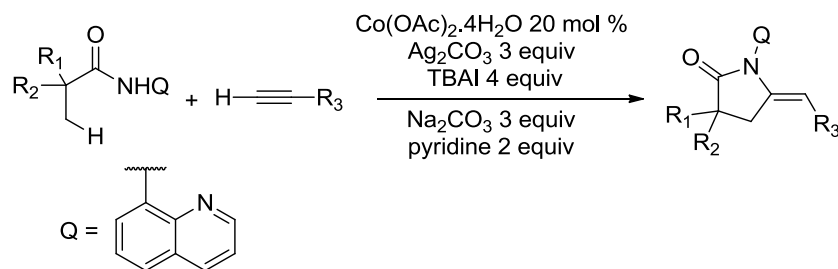
In 2000, Koseki and his colleagues<sup>327</sup> devised a catalyzed intramolecular cyclization for substituted  $\beta$ -alkynylamides to synthesize 5-alkylidene-pyrrolidin-2-ones. They used LiHMDS/AgOTf in the ratio 2:1, as a catalytic system in toluene at 70 °C to yield the *Z*-isomer with high stereoselectivity (Scheme IV.11).

Scheme IV.11. Intramolecular cyclization of  $\beta$ -alkynylamides using LiHMDS/AgOTf catalytic system.

In 2015, a cobalt-catalyzed cyclization of aliphatic amides with terminal alkynes using silver co-catalyst to prepare pyrrolidinones was described.<sup>328</sup> The reaction involves a C-H functionalization of unactivated  $sp^3$  carbons by terminal alkynes. Such activation proceeds by the Co (III) species, which results from the oxidation of Co (II) using  $Ag_2CO_3$ . The subsequent 5-*exo-dig* cyclization is facilitated by using TBAI, which acts as a phase transfer catalyst, to provide 5-aryl(alkyl)idene-pyrrolidin-2-ones with selectively *E*-configuration (Scheme IV.12). They observed that the *Z*-isomer is formed at the beginning, and gradually converted into the *E*-isomer under the reaction conditions. In this case, both electron-rich and electron-poor alkynes succeed to give the corresponding cyclic enamides.

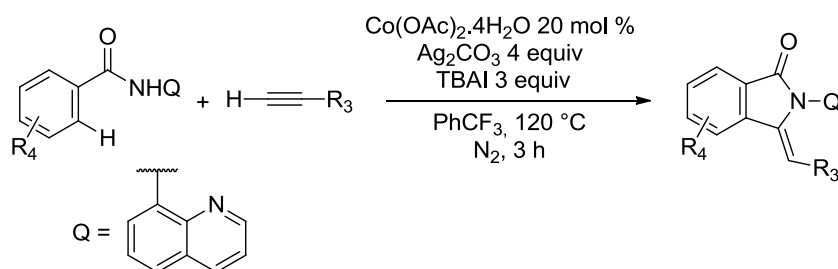
<sup>327</sup> Koseki, Y.; Kusano, S.; Ichi, D.; Yoshida, K.; Nagasaka, T. *Tetrahedron* **2000**, 56, 8855.

<sup>328</sup> Zhang, J.; Chen, H.; Lin, C.; Liu, Z.; Wang, C.; Zhang, Y. *J. Am. Chem. Soc.* **2015**, 137, 12990.



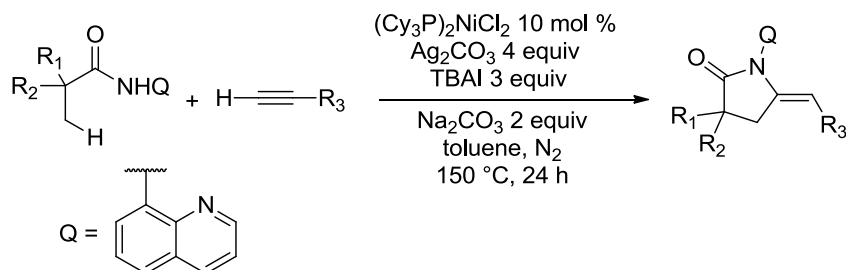
Scheme IV.12. Co/Ag-catalyzed cyclization of aliphatic amides and alkynes to prepare pyrrolidinones.

This strategy was extended successfully to the aromatic amides affording various isoindolinones with absolute *Z*-configuration (Scheme IV.13).



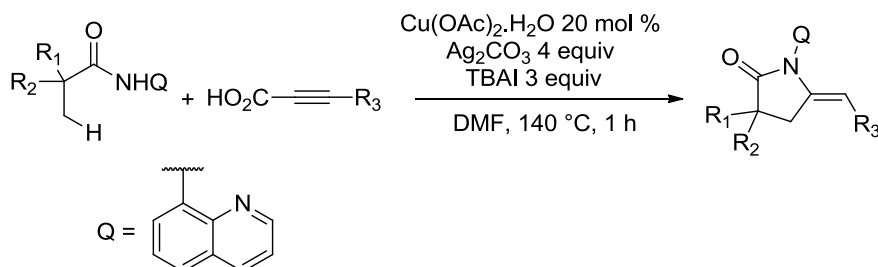
Scheme IV.13. Co/Ag-catalyzed cyclization of aromatic amides and alkynes to prepare isoindolinones.

More recently, they introduced a nickel-catalyzed synthesis of  $\gamma$ -lactams from aliphatic amides and terminal alkynes (Scheme IV.14). They selected nickel since it is less expensive and more durable transition metal.<sup>329</sup> The reaction proceeds via  $sp^3$  C-H activation followed by a 5-*exo-dig* cyclization. From the control experiments, they found that the nickel catalyst catalyzes only the alkynyl amide formation. However, the cyclization is promoted by a combination of the silver salt and TBAI. When they performed the cyclization reaction using silver salt only, trace of the corresponding  $\gamma$ -lactam was obtained which proves the key role of TBAI in the cyclization reaction.

Scheme IV.14. Ni/Ag-catalyzed cyclization of aliphatic amides and alkynes to prepare  $\gamma$ -lactams.

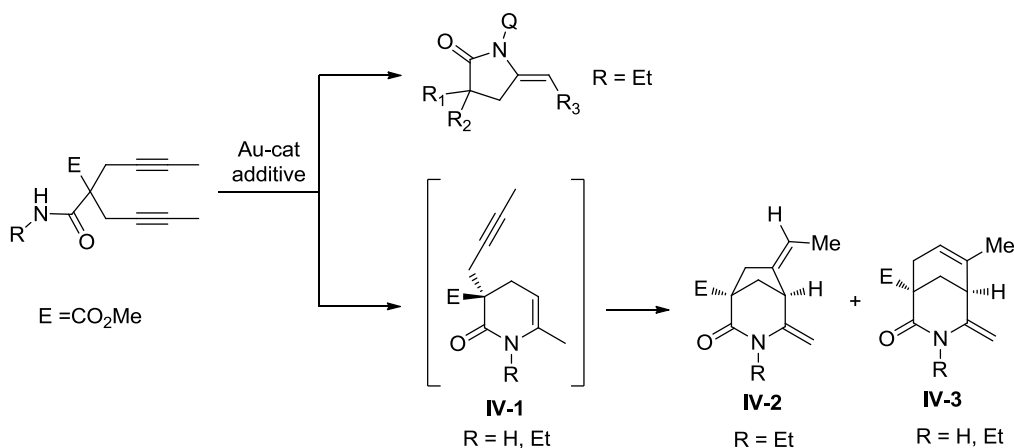
<sup>329</sup> Lin, C.; Zhang, J.; Chen, Z.; Liu, Y.; Liu, Z.; Zhang, Y. *Adv. Synth. Catal.* **2016**, 358, 1793.

Meanwhile, they provided a copper-catalyzed cyclization of aliphatic amines and alkynyl carboxylic acids using silver co-catalyst to synthesize pyrrolidinones.<sup>330</sup> In this case, the reaction involved a catalytic tandem decarboxylative cross-coupling/cyclization (Scheme IV.15). They found that the addition of TBAI was crucial, since in its absence, a trace of the cyclic product was separated.



**Scheme IV.15.** Cu/Ag-catalyzed cyclization of amides and alkynyl acids to prepare pyrrolidinones.

Gold catalysts are employed as well to catalyze the intramolecular *N*-nucleophilic ring closure of propargylic amides. For example, the cyclization of the bispropargylic amides reported by Sperger and Fiksdahl.<sup>331</sup> In this case, there are three possible products; *E*-pyrrolidinone that results from 5-*exo-dig* cyclization and two tandem bicyclic products **IV-2** and **IV-3** which result from 5-*exo-dig* and 6-*endo-dig* cyclizations of the intermediate lactam **IV-1**, respectively (Scheme IV.16). The pyrrolidinone is strongly favored using 5 mol % of triethylamine, in addition to the catalytic system AuCl(PPh<sub>3</sub>)/Ag salts such as: AgOTf, AgSbF<sub>6</sub> and AgNTf<sub>2</sub> (2.5–5 mol %).

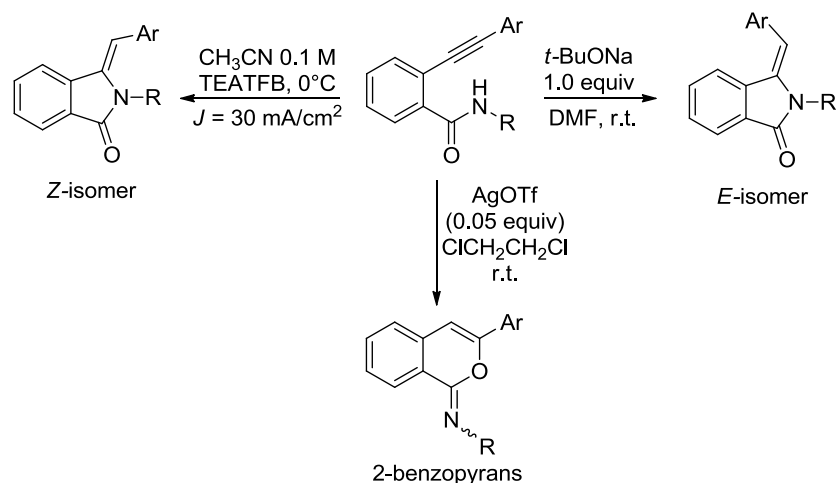


**Scheme IV.16.** Au-catalyzed cyclizations of bispropargylic amides.

<sup>330</sup> Zhang, J.; Li, D.; Chen, H.; Wang, B.; Liu, Z.; Zhang, Y. *Adv. Synth. Catal.* **2016**, 358, 792.

<sup>331</sup> Sperger, C. A.; Fiksdahl, A. *J. Org. Chem.* **2010**, 75, 4542.

In 2010, Bianchi *et al.*<sup>332</sup> presented a study to control the selectivity of the heteroannulation of *o*-(1-alkynyl)benzamides. By the suitable choice of bases and silver catalysts, they can obtain selectively either *Z*- or *E*-isoindolones or 2-benzopyran derivatives (Scheme IV.17). The electrolysis of acetonitrile in a divided electrochemical cell equipped with platinum electrodes under galvanostatic control ( $J = 30.0 \text{ mA/cm}^2$ ) generated cyanomethyl anion. The latter is employed as an efficient alternative for common bases, affording chemo- and stereo-selectively 5-*exo-dig* cyclization *Z*-isoindolones, regardless the nature of the substituent on the aromatic ring. While, the *E*-isoindolone derivatives are selectively obtained using *t*-BuONa in DMF.



Scheme IV.17. Catalyzed-cyclization reactions of *o*-(1-alkynyl)benzamides.

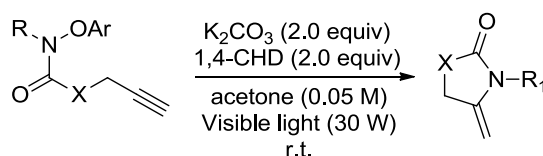
### ➤ Radical 5-*exo-dig* cyclization

Very recently, the first 5-*exo-dig* cyclization of amidyl radicals towards 5-methylene-pyrrolidinones was developed.<sup>333</sup> The authors used visible-light irradiation to generate the amidyl radical from electron-poor aryloxyamides, in presence of 2.0 equiv. of  $\text{K}_2\text{CO}_3$  and 2.0 equiv of 1,4-cyclohexadiene, in acetone at room temperature (Scheme IV.18). They justified the low yields obtained during their course of study by DFT calculations, which demonstrated that the 5-*exo-dig* cyclization of amidyl radicals had higher energy barrier, compared to their former 5-*exo-trig* cyclization approach.<sup>334</sup>

<sup>332</sup> Bianchi, G.; Chiarini, M.; Marinelli, F.; Rossi, L.; Arcadi, A. *Adv. Synth. Catal.* **2010**, 352, 136.

<sup>333</sup> Reina, D. F.; Dauncey, E. M.; Morcillo, S. P.; Svejstrup, T. D.; Popescu, M. V.; Douglas, J. J.; Sheikh, N. S.; Leonori, D. *Eur. J. Org. Chem.* **2017**, 2108.

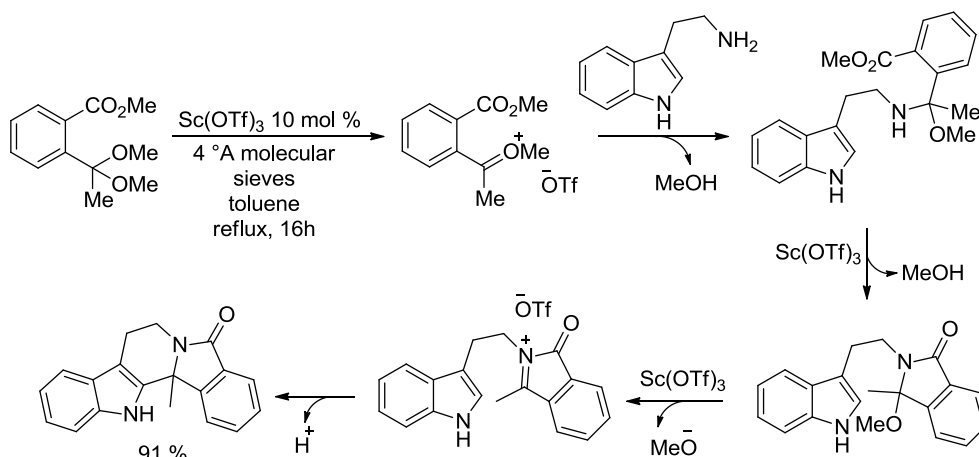
<sup>334</sup> Davies, J.; Svejstrup, T. D.; Reina, D. F.; Popescu, M. V.; Sheikh, N. S.; Leonori, D. *J. Am. Chem. Soc.* **2016**, 138, 8092.



Scheme IV.18. Visible light catalyzed 5-exo-dig cyclization of amidyl radicals towards cyclic amides.

## 2) Reactivity

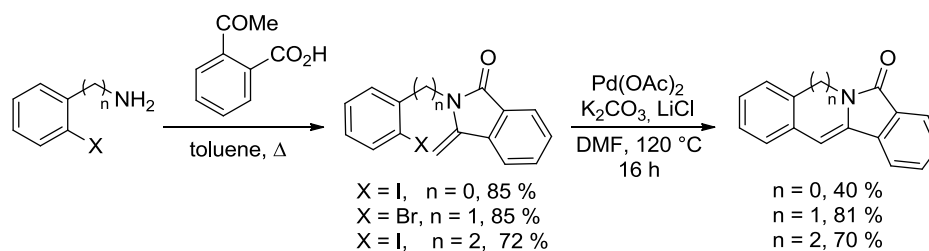
The cyclic enamide functionality serves as versatile building block in the synthesis of complex molecules. It is involved as an intermediate in a scandium triflate catalyzed reaction to afford  $\beta$ -carboline derivative through a sequence of reactions involving a hindered acetal and tryptamine (Scheme IV.19).<sup>335</sup> The lewis acid is used to promote the imine formation from the hindered unreactive ketone as well as to catalyze the subsequent cyclizations.

Scheme IV.19. Sc-catalyzed synthesis of  $\beta$ -carboline derivative through cyclic enamide intermediates.

Similarly, the synthesis of isoindolobenazepine alkaloids proceeded via cyclic enamide intermediate.<sup>336</sup> The condensation between 2-haloarylamines and aryl keto-ester affords the cyclic enamide, which is followed by a subsequent Heck reaction, delivering the target alkaloid-like structure (Scheme IV.20).

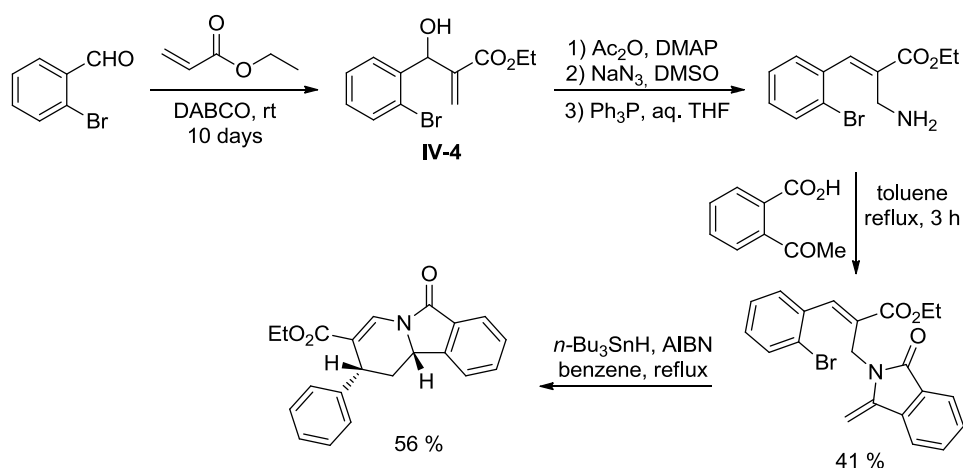
<sup>335</sup> Heaney, H.; Simcox, M. T. Slawin, A. M. Z.; Giles, R. G. *Synlett*. **1998**, 640.

<sup>336</sup> Kim, G.; Kim, J. H.; Kim, W.-J.; Kim, Y. A. *Tetrahedron Lett.* **2003**, 44, 8207.

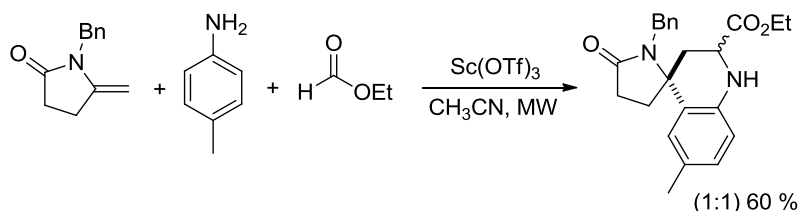


Scheme IV.20. Synthesis of isoindolobenazepine alkaloids through cyclic enamide intermediates.

In 2007, the same research group reported another approach involving a radical mechanism.<sup>337</sup> In this case, the cyclicenamide is prepared starting from the Baylis-Hillman product **IV-4** in four-steps. Thereafter, the enamide undergo a subsequent radical cyclization yielding dihydropyrido[2,1-*a*]isoindolone derivatives (Scheme IV.21).

Scheme IV.21. Synthesis of dihydropyrido[2,1-*a*]isoindolone by radical cyclization of enamides.

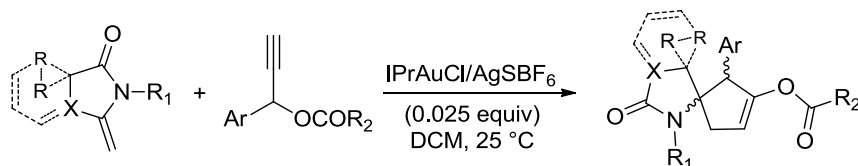
In 2010, 5-*exo*-methylene-2-pyrrolidinones were employed as electron-rich olefin precursors for Povarov-type multicomponent reactions.<sup>338</sup> The authors used scandium triflate as Lewis acid in acetonitrile under microwave irradiations, to prepare spiro-Povarov adduct (Scheme IV.22).

Scheme IV.22. Povarov MCR using unsaturated  $\gamma$ -lactam.

<sup>337</sup> Gowrisankar, S.; Kim, S. J.; Lee, J.-E.; Kim, J. N. *Tetrahedron Lett.* **2007**, 48, 4419.

<sup>338</sup> Vicente-García, E.; Catti, F.; Ramón, R.; Lavilla, R. *Org. Lett.* **2010**, 12, 860.

Recently, Fan *et al.*<sup>339</sup> presented Au-catalyzed [2+3] annulations of cyclic enamides with propargyl esters. The reaction is carried out using IPrAuCl/AgSbF<sub>6</sub> as a catalyst in dichloromethane at room temperature, giving a mixture of *cis*- and *trans*-spiro products (Scheme IV.23). Based on this key annulation step, followed by a Witkop cyclization, the total syntheses of cephalotaxine and cephalozomine H are developed.



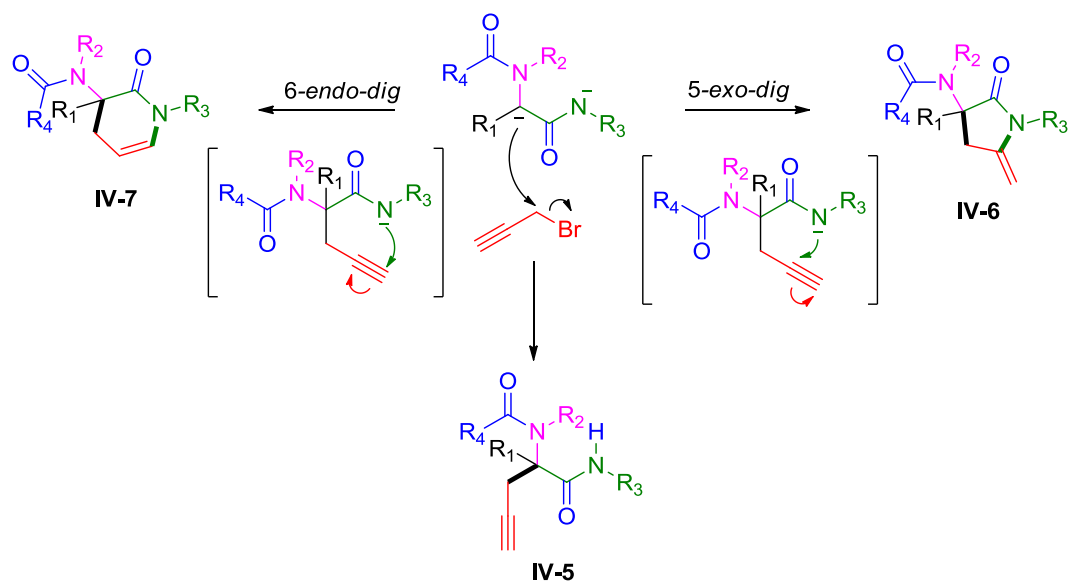
Scheme IV.23. Au-catalyzed [2+3] annulations of cyclic enamides with propargyl esters.

### IV.3 Ugi/Intermolecular cyclization towards pyrrolidinones

#### Overview of the Strategy

We explored the reactivity of the 1,3-amide dianion intermediates of Ugi adducts towards the propargyl bromide as an electrophile. There are several possible reaction pathways, some of them are presented in Scheme IV.24. The first involves the nucleophilic attack ( $S_N^1$  mechanism) of the peptidyl carbanion onto the propargyl bromide affording the open form  $\beta$ -alkynylamide derivative **IV-5**. The second arises from the nucleophilic attack of the peptidyl carbanion onto the propargyl bromide followed by a subsequent 5-*exo-dig* *N*-cyclization providing 5-*exo*-methylene-pyrrolidin-2-ones **IV-6**. Nevertheless, the nucleophilic attack could be followed by a 6-*endo-dig* *N*-cyclization yielding 3,4-dihydropyridin-2-ones **IV-7**.

<sup>339</sup> Ma, X.-Y.; An, X.-T.; Zhao, X.-H.; Du, J.-Y.; Deng, Y.-H.; Zhang, X.-Z.; Fan, C.-A. *Org. Lett.* **2017**, *19*, 2965.



Scheme IV.24. Three possible pathways for the propargylation of Ugi dianions.

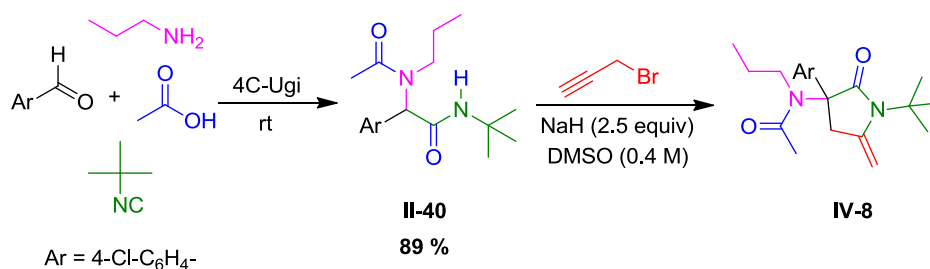
Our target was to search for the reaction conditions that would furnish the 5-*exo*-methylene-pyrrolidin-2-ones **IV-6** with high selectivity.

### Early attempts

The first attempt was performed using the Ugi adduct **II-40** isolated in 89 % yield. We adopted our optimum conditions applied in chapters II and III. Thus, we allowed this Ugi **II-40** to react with 2.5 equiv. of NaH in DMSO at room temperature for 10 minutes till a homogenous solution was obtained. Thereafter, 1.5 equiv. of propargyl bromide was added. The resulting mixture was stirred at room temperature for four hours, where the TLC indicated the formation of a new product with a complete consumption of the starting Ugi adduct. After purification and identification, we obtained selectively the desired 5-*exo*-methylene-pyrrolidin-2-one derivative **IV-8** in 54 % yield (Table IV-1). Moreover, carrying out the reaction at 50 °C, decreased the reaction time to one hour, but did not improve the reaction yield (52 %).



Table IV-1. Early propargylation/cyclization attempts.



Entry	Temp.	Time (h)	Yield (%)
1	room temperature	4	54
2	50 °C	1	52

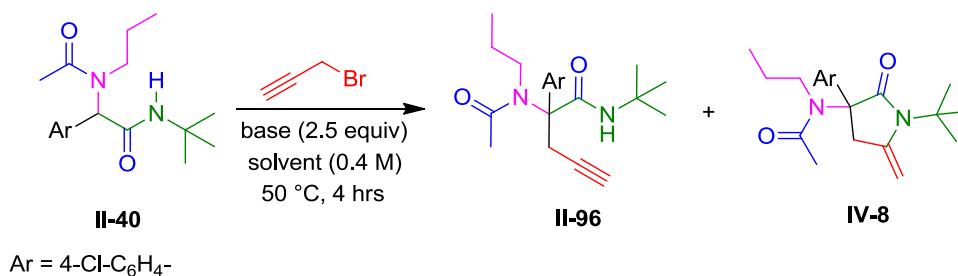
### Optimization of the reaction conditions

Such preliminary results motivated us to study the effect of changing the base-solvent combination in addition to employing various Lewis acids and phase transfer catalysts, in order to reach the optimum reaction condition.

#### (1) Base-Solvent combination

After the isolation of **IV-8** with a moderate yield (54 %) using NaH in DMSO, two further trials including the change of base and solvent were performed. The use of 2.5 equiv. of NaH in THF at 50 °C for four hours afforded a mixture of the unreacted starting Ugi, the alkynylamide intermediate **II-96** and the desired product **IV-8** with 42 %, 25 % and 15 % yields, respectively. Whereas using 2.5 equiv of LiHMDS in THF at 50 °C for four hours, resulted in a sluggish reaction with 15 % yield of the intermediate **II-96** and 40 % of the recovered starting material, however, the target product **IV-8** was not detected (Table IV-2).

Table IV-2. Optimization of Base/Solvent combination.



Entry	Base	Solvent	Recovered SM	Yield (II-96)	Yield (IV-8)
1	NaH	THF	42 %	25 %	15 %
2	LiHMDS	THF	40 %	15 %	0 %

The above-mentioned results demonstrated that changing the base-solvent combination lowered both the reaction efficiency and selectivity; therefore we decided to keep the NaH/DMSO combination working at 50 °C.

In order to visualize the nucleophilicity of the monoanion intermediate at 50 °C (the new reaction temperature), two control experiments were performed. The first was carried out using 1.0 equiv. of NaH in DMSO and delivered 51 % yield of **II-96** together with 32 % of recovered Ugi **II-40** after four hours. While using 1.4 equiv. of NaH in DMSO for four hours resulted in a mixture of 65 % of **II-96** and 8 % of **IV-8**, in addition to 20 % of unreacted Ugi adduct (Table IV-3). Such results indicated that the reactivity of the monoanion in this case differs from that in case of mono allylation reaction (presented in chapter II), which is performed at room temperature. This could be due to the enhanced nucleophilicity of the monoanion towards the mono alkylation reaction by raising the temperature.

Table IV-3. Changing the number of base equivalents.

Entry	No of base equiv.	Recovered SM	Yield (II-96)	Yield (IV-8)
1	1.0	32 %	51 %	0 %
2	1.4	20 %	65 %	8 %

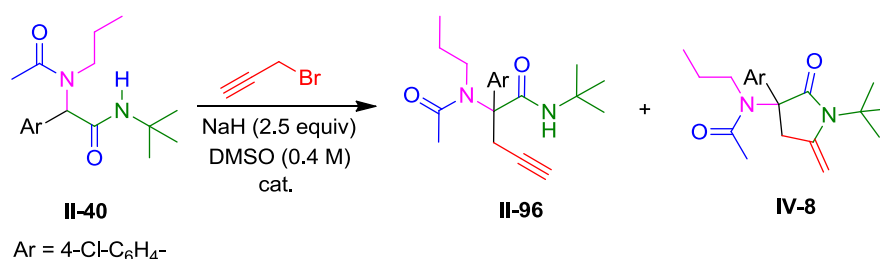
## (2) Catalytic Effect

In order to improve the reaction yield, different catalysts which are known to catalyze the hydroamidation reaction through  $\pi$ -coordination to alkynes were employed. The effect of some silver, zinc, ytterbium and gold catalysts on the reaction progression was investigated. The various trials were carried out using Ugi adduct **II-40** and 2.5 equiv. of NaH in DMSO at room temperature, followed by adding 1.5 equiv. of propargyl bromide and finally the catalyst (10 to 20 mol %). The different results obtained are displayed in Table IV-4. Among the

different triflates employed, 10 mol % of Ag(OTf) proved to be the best Lewis acid, affording selectively the 5-*exo* product **IV-8** with 65 % yield after four hours, working at room temperature. Both Zn(OTf)<sub>2</sub> and Yb(OTf)<sub>3</sub> (10 mol %) gave a mixture of the intermediate **II-96** and cyclic adduct **IV-8** (Table IV-4, entries 2 and 3). The result obtained using Zn(OTf)<sub>2</sub> was surprising, due to its effect in inhibiting the cyclization reaction. Using 1 mol % of the gold catalyst (SPhosAuNTf<sub>2</sub>) resulted as well in a mixture of products (Table IV-4, entry 4).

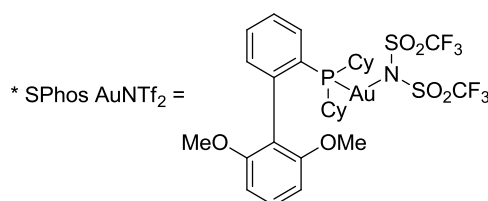
Therefore, we focused on the silver salts. The use of 10 mol % of Ag<sub>2</sub>CO<sub>3</sub> at room temperature for five hours, afforded 21 % yield of **II-96** together with 61 % yield of **IV-8**. Hence, the overall reaction yield increased using Ag<sub>2</sub>CO<sub>3</sub> while, the selectivity decreased. Using 20 mol % of Ag<sub>2</sub>CO<sub>3</sub> at room temperature for four hours afforded trace of **II-96** and 70 % yield of **IV-8**. The use of 20 mol % of Ag(OTf) did not improve the reaction yield (Table IV-4, entry 7). Consequently, we decided to maintain the Ag<sub>2</sub>CO<sub>3</sub>, varying the reaction temperature. Using 10 mol % of Ag<sub>2</sub>CO<sub>3</sub> at 50 °C for one hour yielded selectively the pyrrolidin-one **IV-8** with 68 % yield. Thus, raising the temperature to 50 °C helped in decreasing the amount of catalyst (from 20 to 10 mol %) and the reaction time to one hour, providing comparable yields (Table IV-4, entries 6 and 8). Subsequently, the last condition was selected as the best one at this stage of the study (Table IV-4, entry 8).

Table IV-4. The effect of using different catalysts.



Entry	Catalyst	Catalyst load	Temp	Time (h)	Yield (II-96)	Yield (IV-8)
1	Ag(OTf)	10 mol %	r.t.	4	0 %	65 %
2	Zn(OTf) <sub>2</sub>	10 mol %	r.t.	4	48 %	24 %
3	Yb(OTf) <sub>3</sub>	10 mol %	r.t.	5	17 %	51 %
4*	SPhosAuNTf <sub>2</sub>	1 mol %	r.t.	4	22 %	47 %
5	Ag <sub>2</sub> CO <sub>3</sub>	10 mol %	r.t.	5	21 %	61 %
6	Ag <sub>2</sub> CO <sub>3</sub>	20 mol %	r.t.	4	trace	70 %

<b>7</b>	Ag(OTf)	20 mol %	r.t.	4	0 %	45 %
<b>8</b>	Ag <sub>2</sub> CO <sub>3</sub>	10 mol %	50 °C	1	0 %	68 %



### (3) Phase transfer catalysts

After examining the effect of Lewis acids in enhancing the electrophilicity of the alkyne via  $\pi$ -activation, the effect of phase transfer catalysts (PTC) on enhancing the nucleophilicity of the amides was examined (Table IV-5). Using the previously optimized conditions, 2.5 equiv. of NaH was added to Ugi adduct **II-40** in DMSO at room temperature followed by 1.5 equiv. of propargyl bromide and 10 mol % of Ag<sub>2</sub>CO<sub>3</sub>. Then, 1.0 equiv. of TBAI was added and the reaction mixture was heated at 50 °C for one hour. In this case, 78 % of the cyclic enamide **IV-8** was isolated as a single product. Changing the amount of TBAI used into 0.5 and 2 equiv. did not affect greatly the reaction yield (Table IV-5, entries 1, 2 and 3). Thereafter, we decided to carry out the reaction without the silver catalyst in order to compare the effect of using Ag<sub>2</sub>CO<sub>3</sub> and TBAI separately on the reaction progress. Interestingly, using 1.0 equiv. of TBAI (without silver catalyst), we obtained 77 % of the cyclic enamide **IV-8** as a sole product. This trial showed that the ammonium salts are more effective in enhancing our intramolecular hydroamidation reaction compared to Lewis acids.

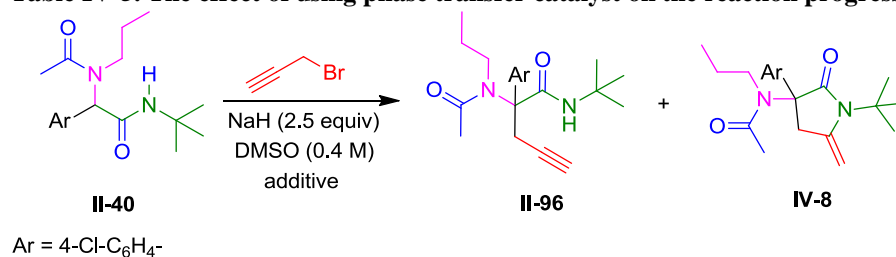
Afterwards, the effect of different ammonium salts (varying the counter anion) on the reaction progress was examined. The experiments showed that the TBAF afforded the highest yield of the desired product **IV-8** (81 %) among the employed ammonium salts (Table IV-5, entries 4, 5, 6 and 7). Carrying out the reaction with 1.0 equiv. of TBAF at room temperature, afforded a mixture of the open form **II-96** (7 % yield) and the cyclic form **IV-8** (52 % yield) after three hours. Using 0.5 equiv of TBAF at 50 °C for one hour resulted in a slight lower of the overall reaction yield (74 %).

Lastly, a final trial using 1.0 equiv of NaH and 1.0 equiv of TBAF was performed to indicate whether the second equiv. of base is necessary in case of using TBAF for the

subsequent hydroamidation cyclization step (Table IV-5). In this case, the cyclic product **IV-8** was not formed and 52 % of the alkynylamide **II-96** was isolated in addition to 32 % of unreacted starting Ugi **II-40**. This behavior was not expected, due to the familiar effect of TBAF in activating the hydroamidation of alkynes.<sup>321</sup> However, it can be explained by the conversion of TBAF into the less efficient TBABr, which shows the importance of using at least 2.0 equiv of NaH. Thus, based on all the above-mentioned attempts, we selected 2.5 equiv. of NaH in DMSO (0.4 M) in presence of 1.0 equiv of TBAF using 1.5 equiv. of propargyl bromide at 50 °C for one hour as the optimal reaction condition.

It is worth mentioning that during the whole course of study the 6-*endo-dig* cyclization product was not observed. This is in agreement with the early experimental work<sup>340</sup> which suggested that in case of electronically unbiased acetylenes, *exo-dig* cyclizations are favoured.

Table IV-5. The effect of using phase transfer catalyst on the reaction progress.



Entry	Catalyst	PTC	PTC load	Temp	Time (h)	Yield (II-96)	Yield (IV-8)
1	Ag <sub>2</sub> CO <sub>3</sub>	TBAI	1 equiv.	50 °C	1	0 %	78 %
2	Ag <sub>2</sub> CO <sub>3</sub>	TBAI	2 equiv.	50 °C	1	0 %	76 %
3	Ag <sub>2</sub> CO <sub>3</sub>	TBAI	0.5 equiv.	50 °C	1	0 %	72 %
4	-	TBAI	1 equiv.	50 °C	1	0 %	77 %
5	-	TBAF	1 equiv.	50 °C	1	0 %	81 %
6	-	TBABr	1 equiv.	50 °C	1	0 %	57 %
7	-	TBACl	1 equiv.	50 °C	1	0 %	66 %
8	-	TBAF	1 equiv.	r.t.	3	7 %	52 %
9	-	TBAF	0.5 equiv.	50 °C	1	0 %	74 %
10*	-	TBAF	1 equiv.	50 °C	1	52 %	0 %

\* The reaction was carried out using 1 equiv. of NaH, 32 % of starting Ugi was recovered.

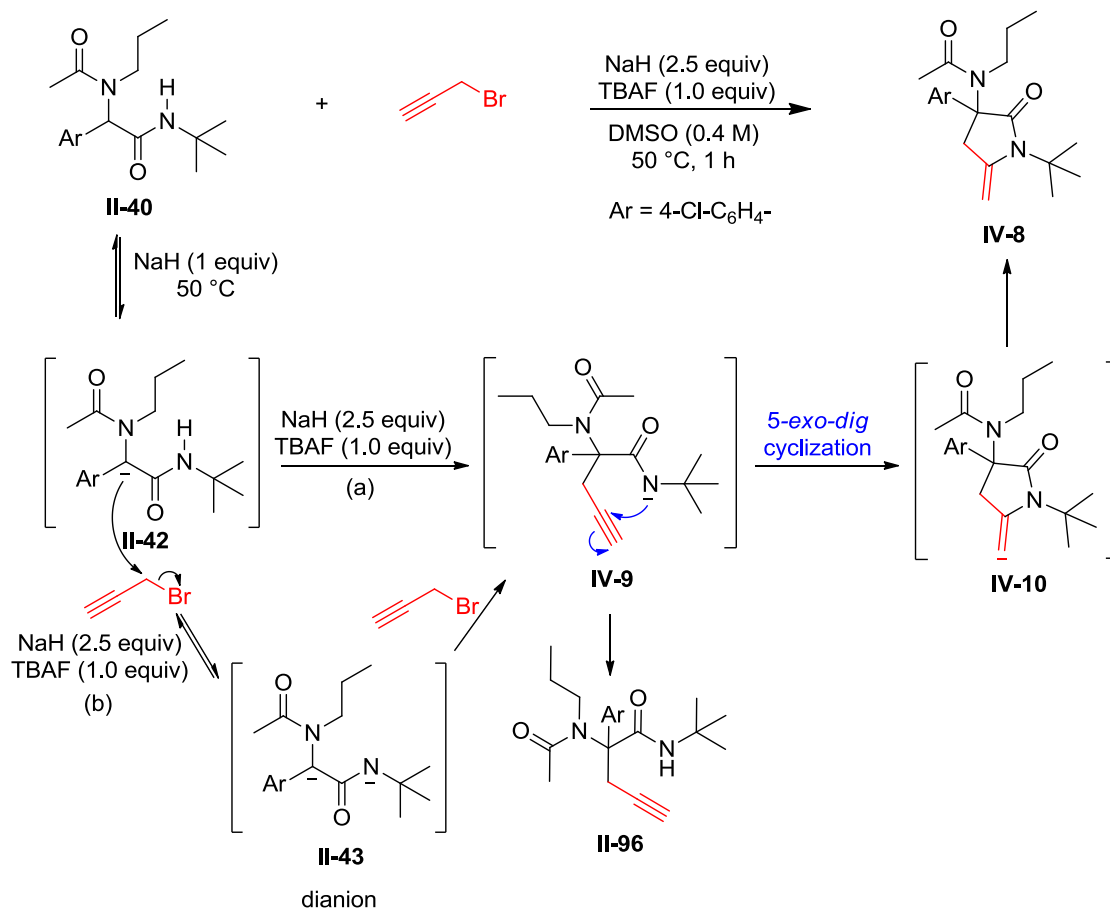
<sup>340</sup> (a) Mellor, M.; Santos, A.; Swrell, E. G.; Sutherland, J. K. *J. Chem. Soc., Chem. Commun.* **1978**, 528. (b) Evans, C. M.; Kirby, A. J. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1269. (c) Garcia, H.; Iborra, S.; Primo, J.; Miranda, M. A. *J. Org. Chem.* **1986**, 51, 4432.

## **IV.4 Reaction mechanism**

On the basis of the optimization results, using 1.0 equiv. of NaH at 50 °C, 51 % of the alkynylamide derivative **II-96** was obtained while the cyclic product **IV-8** was not formed. In this case, the reaction was not complete and 32 % of the starting Ugi **II-40** was recovered. This demonstrates that the monoanion intermediate at 50 °C starts to be nucleophilic enough to attack the propargyl bromide affording the open form **II-96**. However, using 2.5 equiv of base, it is difficult to address which is the effective nucleophile between the peptidyl monoanions and amide dianions in the propargylation reaction.

About the role of TBAF in the reaction mechanism, probably it promotes the propargylation by raising the nucleophilicity of the peptidyl anions but it may also trigger the following cyclization.

Basically, the mechanism starts with deprotonation at the peptidyl C-H position in Ugi adduct **II-40** providing monoanion intermediate **II-42**. The latter working at 50 °C can attack the propargyl bromide forming the intermediate **IV-9** (pathway a). Meanwhile, the monoanion could undergo as well second deprotonation affording the dianion intermediate **II-43** (pathway b). The latter upon attacking the propargyl bromide, results in the intermediate **IV-9**. In general, the second deprotonation enhances the nucleophilicity towards the propargylation reaction as well as allowing the *5-exo-dig* *N*-cyclization, affording the cyclic intermediate **IV-10**. The latter upon protonation delivers the final cyclic product **IV-8**. Several factors such as: the use of insufficient amount of base will lead to the isolation of the intermediate alkynylamide **II-96** (Scheme IV.25).

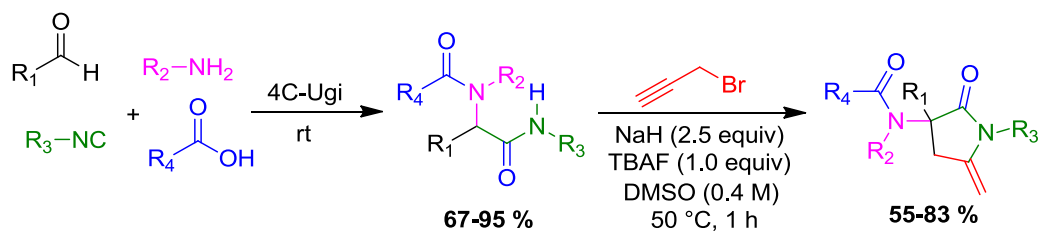


Scheme IV.25. Proposed mechanism for the propargylation/cyclization sequence.

## IV.5 Results & Discussion

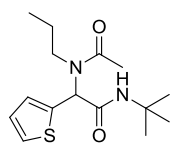
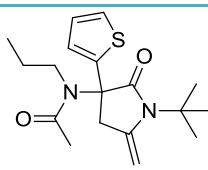
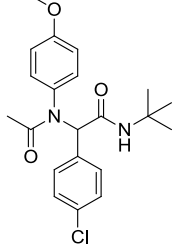
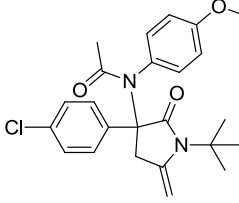
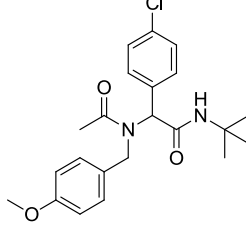
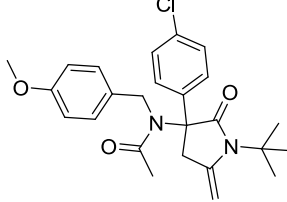
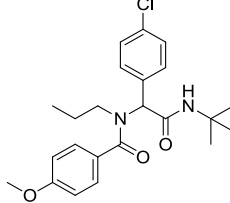
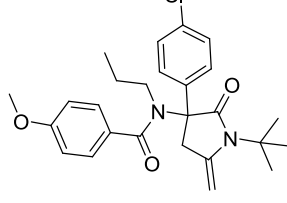
### (a) Results

A series of Ugi adducts was prepared varying the four reaction components with good to excellent yields from 67 to 95 % (the Ugi reaction has already been described in chapter II, section II.9). This series was subjected to the reaction with NaH (2.5 equiv.) and propargyl bromide (1.5 equiv.) in presence of TBAF (1.0 equiv.) in DMSO (0.4 M) at 50 °C for one hour. The propargylation/5-*exo-dig* cyclization sequence afforded an array of 5-*exo*-methylene-pyrrolidin-2-ones. The various results are presented thereafter in Table IV-6.

Table IV-6. The scope of 5-*exo*-methylene-pyrrolidin-2-ones synthesis from Ugi products.

Entry	Ugi adduct	Yield	Pyrrolidin-2-ones	Yield
1	 II-40	89 %	 IV-8	81 %
2	 II-46	85 %	 IV-11	78 %
3	 IV-12	93 %	 IV-13	59 %
4	 III-31	83 %	 IV-14	70 %
5	 IV-15	89 %	 IV-16	72 %
6	 II-53	84 %		83 %



7	 <p><b>III-33</b></p>	67 %	 <p><b>IV-17</b></p>	70 %
8	 <p><b>II-55</b></p>	95 %	 <p><b>IV-18</b></p>	69 %
9	 <p><b>II-56</b></p>	95 %	 <p><b>IV-19</b></p>	55 %
10	 <p><b>III-42</b></p>	77 %	 <p><b>IV-20</b></p>	78 %

### (b) Discussion

Broadly, various functional groups in Ugi adducts were compatible with the adopted protocol affording the corresponding cyclic enamides with good to high yields from 55 to 83 % (see Table IV-6). Thus, it is considered an efficient metal-free synthesis of 5-*exo*-methylene-pyrrolidin-2-ones from Ugi products.

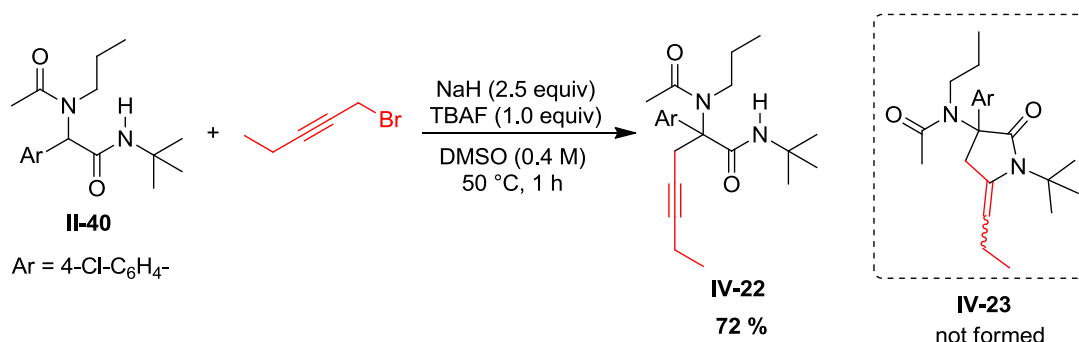
The reaction proceeded well with Ugi adducts derived from different isocyanides, where the highest yield was obtained using *tert*-butyl isocyanide **IV-8** (81 %) and a comparable yield was obtained using cyclohexyl isocyanide **IV-11** (78 %). While, the lowest one was obtained using *p*-methylbenzyl isocyanide **IV-13** (59 %). This goes along with the results obtained in case of alkylation and  $\beta$ -lactam synthesis.

Various aldehydes were submitted to the reaction to study the scope of the pyrrolidinones formation. Electron-rich and electron-poor aromatic and heterocyclic aldehydes were employed resulting in overall good yields. Hence, the use of *m*-(trifluoromethyl)benzaldehyde and *m*-anisaldehyde furnished **IV-14** and **IV-16** with 70 % and 72 % yields, respectively. Whereas, the use of pyridine-2-carboxaldehyde and thiophene-2-carboxaldehyde gave pyrrolidinones **IV-17** and **IV-18** in 83 % and 70 % yields, respectively.

Ugi precursors derived from both aliphatic and aromatic amines were submitted successfully to the reaction giving the target products in moderate to good yields. Thus using *p*-anisidine delivered **IV-19** with 69 % yield, while using 4-methoxybenzylamine afforded **IV-20** in 55 % yield.

Both aliphatic and aromatic acids were compatible with the reaction conditions and gave approximately similar yields. Using acetic acid, the pyrrolidinone **IV-8** was obtained with 81 % yield, while using *p*-methoxybenzoic acid provided **IV-21** in 78 % yield.

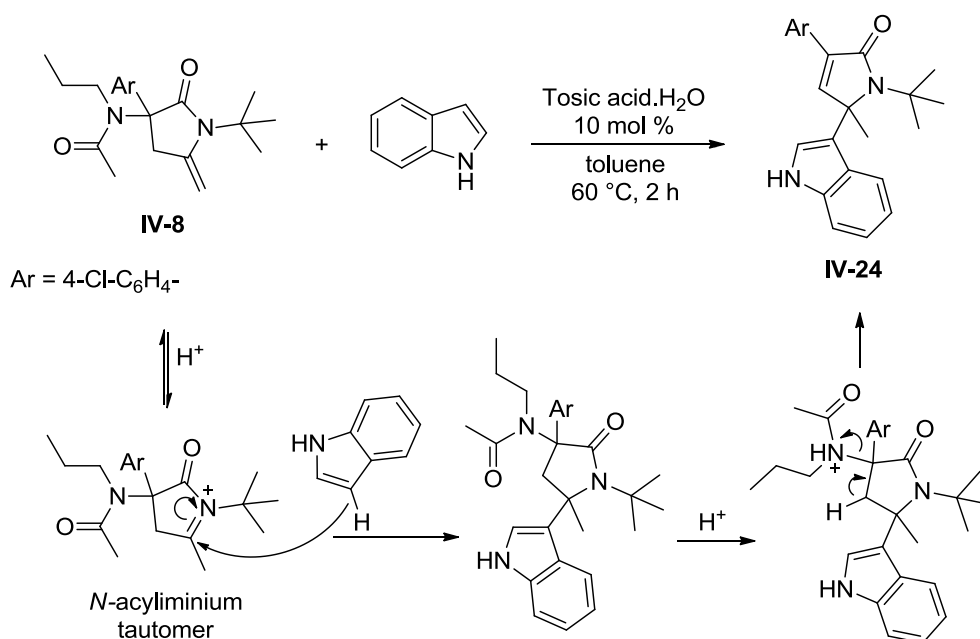
In order to examine the scope of propargyl bromide derivatives, a trial was performed using 1-bromopent-2-yne. In this case, only the corresponding  $\beta$ -alkynyl amide **IV-22** was isolated in 72 % yield (Scheme IV.26). Carrying out the same reaction using 10 mol % of Ag<sub>2</sub>CO<sub>3</sub> instead of TBAF, did not afford the desired product **IV-23** (only **IV-22** was obtained as well). This could be due to the relative decreased electrophilicity of such alkyne, which is considered the driving force for the cyclization process.



Scheme IV.26. Reaction of Ugi adduct with 1-bromopent-2-yne.

## IV.6 Reactivity of the synthesized cyclic enamides

Afterwards, the synthetic utility of the cyclic enamide functionality was evaluated. It is known that the enamide exists in equilibrium with its *N*-acyliminium tautomer under acidic conditions which could be trapped with nucleophiles. In this context, the pyrrolidin-2-one **IV-8** was allowed to react with 1.0 equiv. of indole in presence of 10 mol % of TsOH.H<sub>2</sub>O in toluene at 60 °C for 2 hours (Scheme IV.27). The addition product **IV-24** was obtained in 71 % yield. In this case, the nucleophilic addition of indole was accompanied by an elimination of the *N*-propylacetamide group. Thus, the reaction proceeds via the addition of the indole onto the *N*-acyliminium tautomer with an elimination of the amide moiety at position 3 affording the 5-(indol-3-yl)-pyrrol-2-one derivative **IV-24**. The potential of the newly obtained scaffold having a cyclic  $\alpha,\beta$ -unsaturated carbonyl group, could be further exploited in other reactions as Michael additions.



Scheme IV.27. Addition of indole onto the cyclic enamide under acidic conditions.

Accordingly, we decided to explore the reactivity of the newly synthesized Ugi derived pyrrolidinones in Pictet-Spengler reaction involving the *N*-acyliminium ions<sup>341</sup> generated under acidic conditions. Whether in this case, the reaction would result in the nucleophilic addition adduct only or will be associated with an elimination.

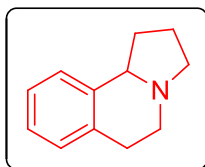
<sup>341</sup> For review on cyclization of *N*-acyliminium ions, see: Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431.

Before presenting the results obtained, a brief introduction concerning Pictet-Spengler reaction and the construction of the benzoindolizidine fused-ring is displayed.

## IV.7 Pictet-Spengler reaction

It is an acid-catalyzed reaction involving a condensation between a  $\beta$ -arylethylamine (such as: tryptamine) and an aldehyde or ketone forming an iminium ion which then undergoes ring closure.<sup>342</sup> It can be considered as a special case of Mannich reaction.

### Benzoindolizidineskeleton



The benzoindolizidine structural motif forms the core of many alkaloids of significant biological and pharmacological properties, such as; (S)-(-)-trolline, (R)-(+)-oleracein E and (R)-(+)-crispine A (their structures are presented in Scheme IV.28).<sup>343</sup> (S)-(-)-Trolline<sup>344</sup> is isolated from the flowers of *Trollius chinensis* and possess antibacterial effect against respiratory bacteria and antiviral effect against influenza viruses A and B. While (R)-(+)-oleracein E<sup>345</sup> is isolated from *Portulaca oleracea* L and has DPPH-radical scavenging activity. However crispine A<sup>346</sup> is isolated from *Carduus crispus* and has cytotoxic effect against Hela human cancer cell lines.

It is found as well in the structure of erythrina alkaloids such as: erysotramidine and erythrosotidienone (Scheme IV.28).<sup>347</sup> They are isolated from wide variety of tropical plants. They are well known for their curare-like effect as well as hypersensitive, sedative and CNS antidepressant properties.

<sup>342</sup> (a) Pictet, A.; Spengler, T. *Eur. J. Inorg. Chem.* **1911**, 44, 2030. (b) Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, 6, 74.

<sup>343</sup> Passlerand, U.; Knolker, H. J. *Alkaloids Chem. Biol.* **2011**, 70, 79.

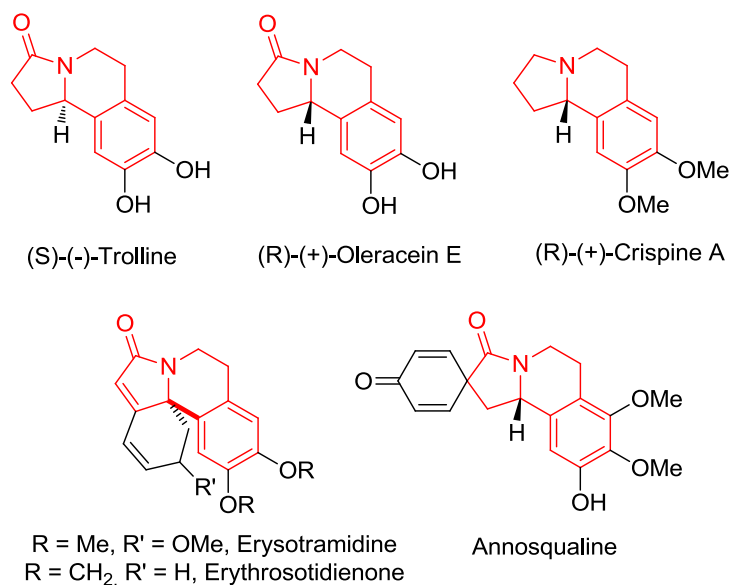
<sup>344</sup> Wang, R. F.; Yang, X. W.; Ma, C. M.; Cai, S. Q.; Nong, J. J.; Shoyama, Y. *Heterocycles* **2004**, 63, 1443.

<sup>345</sup> Xiang, L.; Xing, D.; Wang, W.; Wang, R.; Ding, Y.; Du, L. *Phytochemistry* **2005**, 66, 2595.

<sup>346</sup> Zhang, Q.; Tu, G.; Zhao, Y.; Cheng, T. *Tetrahedron* **2002**, 58, 6795.

<sup>347</sup> (a) Tsuda, Y.; Sano, T. in *The Alkaloids*, Vol. 48 (Ed.: Cordell, G. A.), Academic Press, San Diego, CA, **1996**, pp. 249–337. (b) Parsons, A. F.; Palframan, M. J. in *The Alkaloids*, Vol. 68 (Ed.: Cordell, G. A.), Academic Press, Amsterdam, **2010**, pp. 39–81.

It occurs also in annosequaline natural product which was isolated from the stems of *Annona squamosa* as a minor component (Scheme IV.28).<sup>348</sup> Its biological activity is not studied yet.



Scheme IV.28. Structures of benzoindolizidine alkaloids.

## Synthesis

There are several methodologies that deal with the synthesis of the benzoindolizidine skeleton in the literature.<sup>349</sup> However, we will present only the previous studies involving a 5-*exo-dig* cyclization/Pictet-Spengler sequence using a 5-membered cyclic enamide.

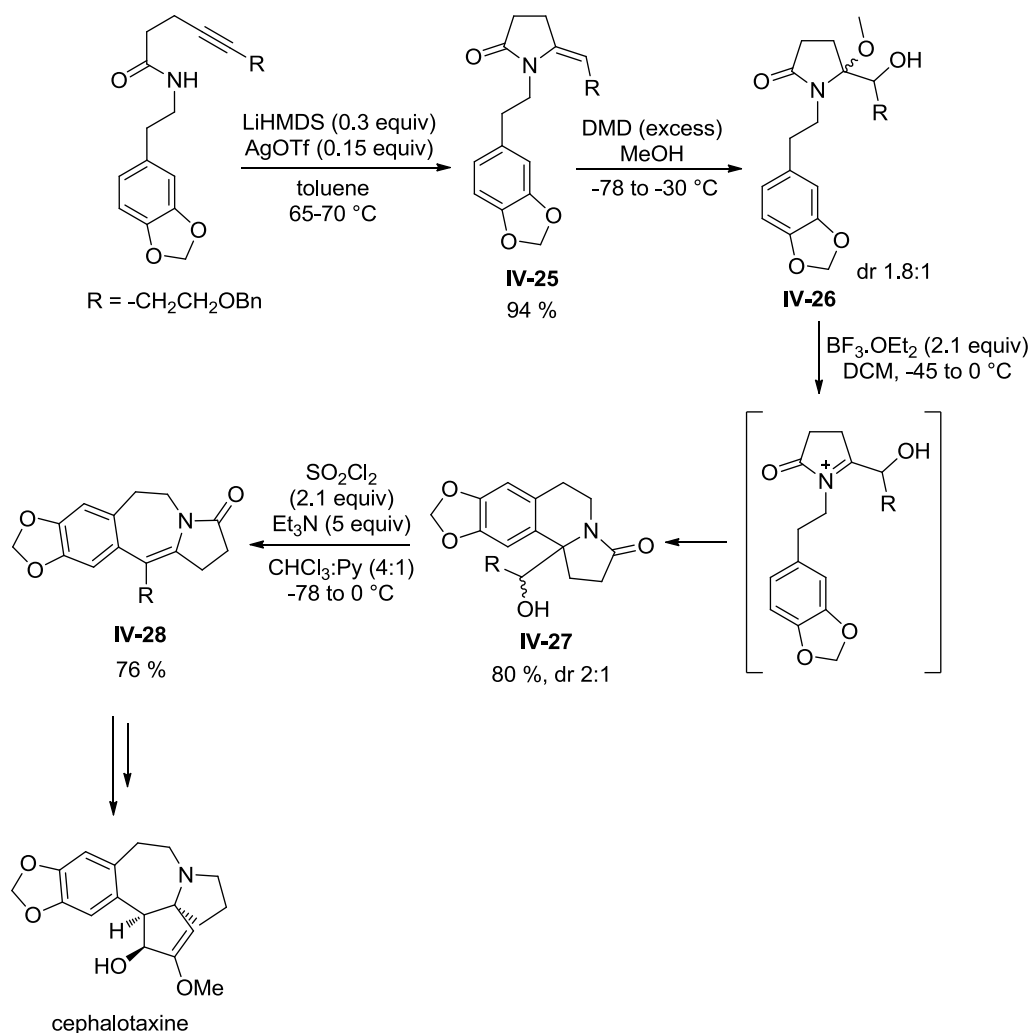
In 2002, a formal total synthesis of Cephalotaxine alkaloid was reported.<sup>350</sup> The synthesis key steps involved the hydroamidation/Pictet-Spengler sequence to prepare the benzoindolizidine structure, which underwent ring expansion afterwards affording the pyrrolobenzazepine **IV-28** (Scheme IV.29). The hydroamidation step was carried out using the aforementioned procedure (LiHMDS/AgOTf in the ratio 2:1, in toluene at 70 °C) yielding selectively the *Z*-form. The resulting enamide **IV-25** was oxidized using excess of DMD in methanol affording the unstable methoxylactam **IV-26** as a diastereomeric mixture. The latter

<sup>348</sup> (a) Yang, Y.-L.; Chang, F.-R.; Wu, Y.-C. *Helv. Chim. Acta* **2004**, *87*, 1392. (b) Shigehisa, H.; Takayama, J.; Honda, T. *Tetrahedron Lett.* **2006**, *47*, 7301.

<sup>349</sup> See for example: (a) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341. (b) Huang, H.; Ji, X.; Wu, W.; Jiang, H. *Chem. Commun.* **2013**, *49*, 3351. (c) Kalaitzakis, D.; Montagnon, T.; Antonatou, E.; Vassilikogiannakis, G. *Org. Lett.* **2013**, *15*, 3714. (d) Kalaitzakis, D.; Montagnon, T.; Antonatou, E.; Bardaji, N.; Vassilikogiannakis, G. *Chem. Eur. J.* **2013**, *19*, 10119. (e) Xu, X.-M.; Zhao, L.; Zhu, J.; Wang, M.-X. *Angew. Chem. Int. Ed.* **2016**, *55*, 3799.

<sup>350</sup> Koseki, Y.; Sato, H.; Watanabe, Y.; Nagasaka, T. *Org. Lett.* **2002**, *4*, 885.

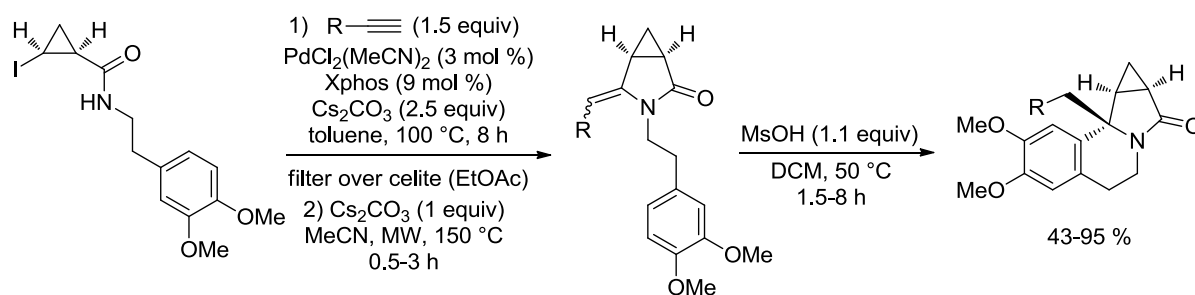
was submitted without purification to Pictet-Spengler reaction using 2.1 equiv. of  $\text{BF}_3 \cdot \text{OEt}_2$  in DCM resulting in the benzoindolizidinone structure **IV-27** as a diastereomeric mixture (2:1) via the *N*-acyliminium ion intermediate.



**Scheme IV.29. Total synthesis of cephalotaxine alkaloid.**

In 2012, Meyer and Cossy *et al.*<sup>351</sup> accounted for the Pictet-Spengler cyclization of 4-methylene-3-azabicyclo-[3.1.0]hexan-2-ones. The latter was synthesized using a copper-free Sonogashira/5-*exo-dig* cyclization cascade of *cis*-2-iodocyclopropanecarboxamides under basic conditions. They performed the Pictet-Spengler step using 1.1 equiv. of methanesulfonic acid in DCM at  $50^\circ\text{C}$  which afforded the corresponding product with high diastereoselectivity (Scheme IV.30).

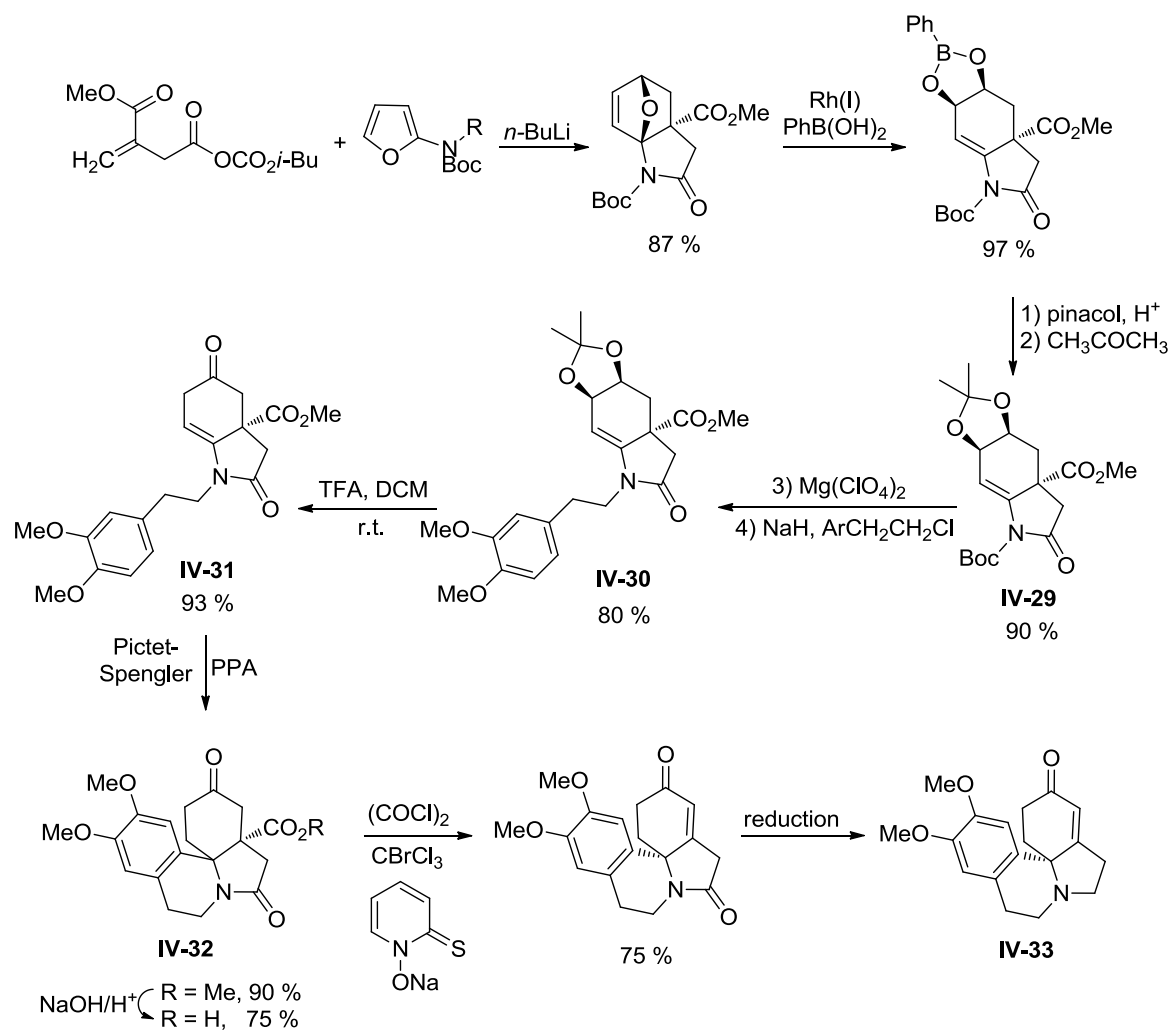
<sup>351</sup> de Carné-Carnavalet, B.; Archambeau, A.; Meyer, C.; Cossy, J.; Folléas, B.; Brayer, J.-L.; Demoute, J.-P. *Chem. Eur. J.* **2012**, *18*, 16716.



Scheme IV.30. Sonogashira coupling/5-*exo-dig* cyclization/Pictet-Spengler sequence.

In 2006, a novel synthesis of the erythrina alkaloid family was developed.<sup>352</sup> It proceeds via the intramolecular Diels-Alder reaction of a 2-imido-substituted furan followed by a Rh(I)-catalyzed ring opening of the oxabicyclic adduct yielding hexahydroindolinone derivative. The later was converted to its corresponding diol using pinacol and acetic acid, which was followed by the reaction with acetone to give the acetonide **IV-29**. The Boc group was removed using  $\text{Mg}(\text{ClO}_4)_2$  and *N*-alkylation was performed delivering the lactam **IV-30**. The treatment with trifluoroacetic acid in DCM, afforded the target compound **IV-31** for the Pictet-Spengler cyclization. The latter was achieved using polyphosphoric acid in refluxing DCM delivering the tetracyclic erythrinane structure **IV-32**. The desired alkaloid 3-demethoxyerythratidinone **IV-33** was obtained after a sequence of Barton decarboxylation and reduction reactions (Scheme IV.31).

<sup>352</sup> Wang, Q.; Padwa, A. *Org. Lett.* **2006**, 8, 601.

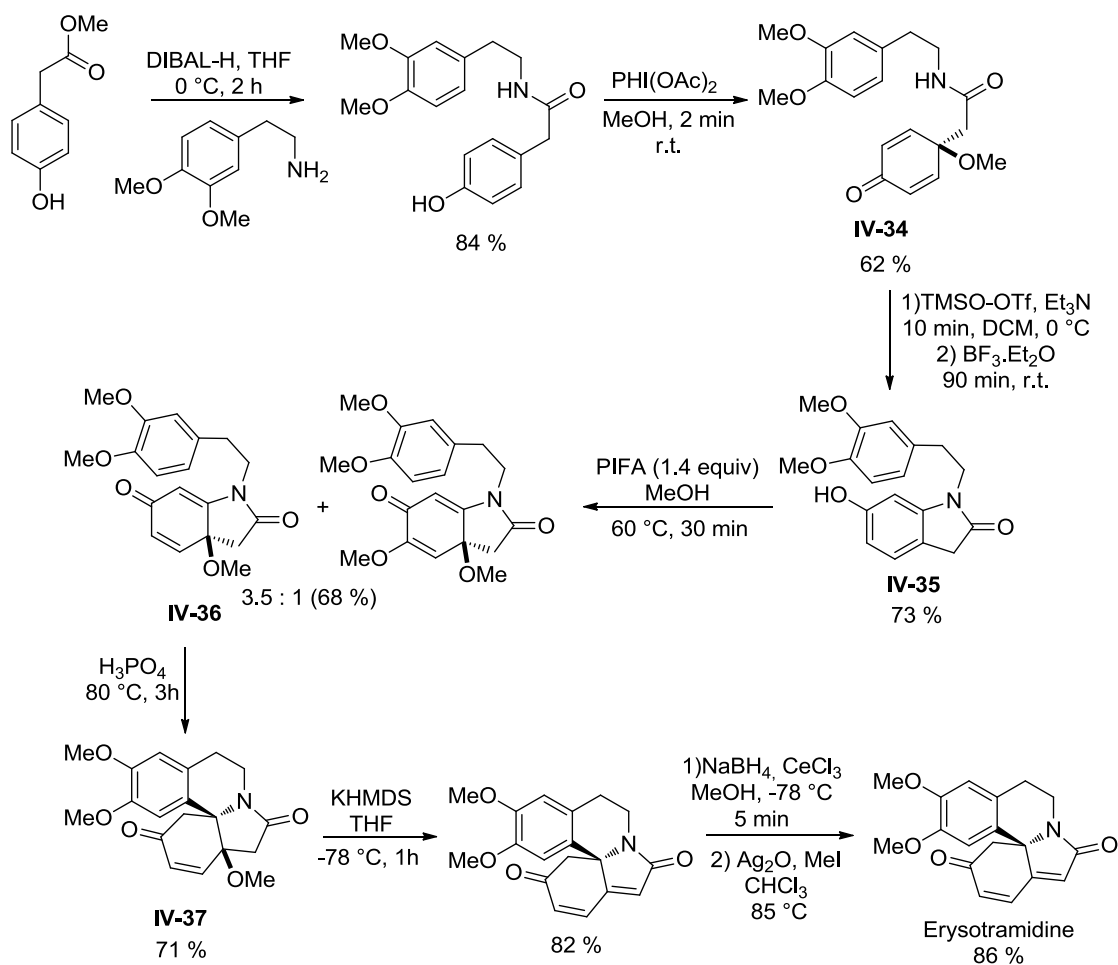


Scheme IV.31. Total synthesis of 3-demethoxyerythratinone alkaloid.

Another total synthesis strategy of the erythrina alkaloid “Erysotramidine” involving Pictet-Spengler reaction was reported in 2014.<sup>353</sup> The first step of the synthesis is an aluminium-catalyzed amide bond formation from phenol and amine, which was treated with DIB in methanol to afford **IV-34** via an oxidative dearomatization reaction. Then the product **IV-34** was treated with  $\text{TMS-OTf}$  followed by  $\text{BF}_3\cdot\text{Et}_2\text{O}$  yielding the indolinone **IV-35**. A second oxidative dearomatization reaction was achieved using PIFA, which led to a mixture of the target product **IV-36** with a side product in the ratio 3.5:1. The tetracyclic core structure of erythrina alkaloid was then obtained through Pictet-Spengler cyclization using phosphoric acid. The formed product **IV-37** was subjected afterwards to a series of reduction and methylation reactions delivering the target erysotramidine alkaloid (Scheme IV.32).

<sup>353</sup> L’Homme, C.; Ménard, M.-A.; Canesi, S. *J. Org. Chem.* **2014**, 79, 8481.

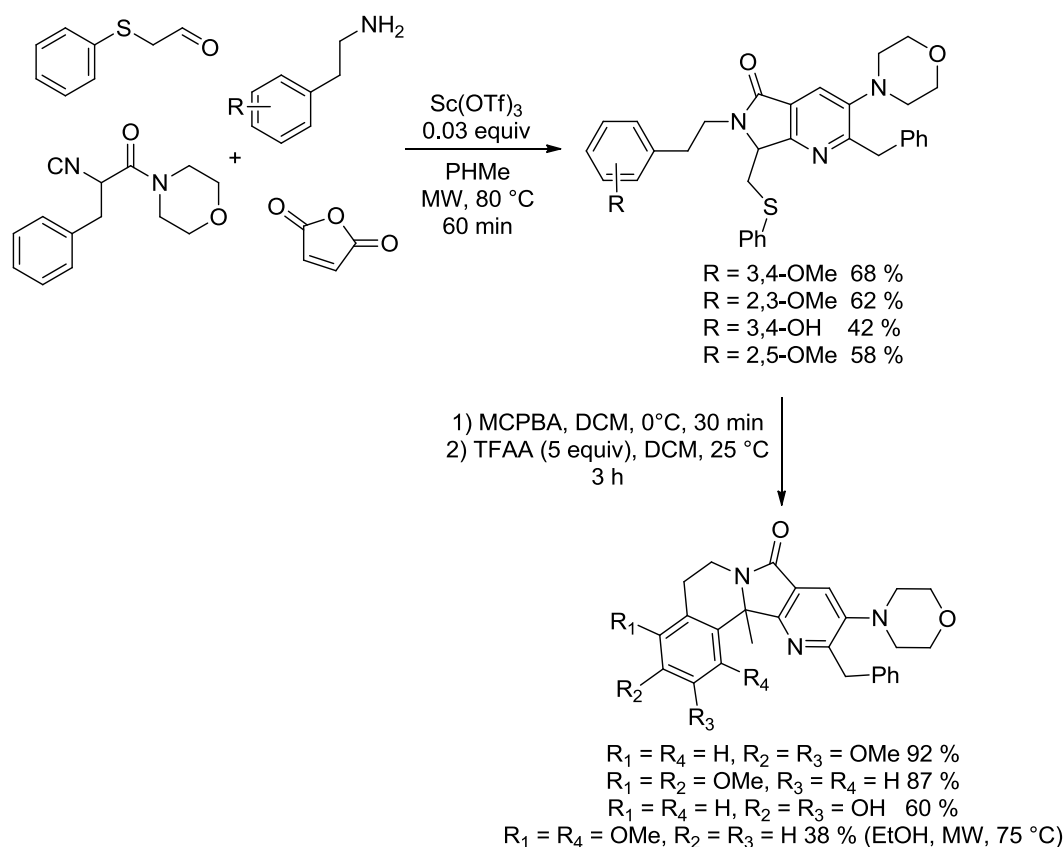




Scheme IV.32. Total synthesis of erysotramidine alkaloid.

In 2012, Islas-Jácome and his coworkers<sup>354</sup> presented the synthesis of nuevamine aza-analogues via I-MCR/Aza-Diels-Alder/Pictet-Spengler sequence of reactions. Their strategy was based on the preparation of pyrrole[3,4-*b*]pyridine-5-ones through a one pot I-MCR followed by subsequent aza-Diels-Alder reaction. The synthesized bicyclic compound was used as a key intermediate in the Pictet-Spengler reaction affording the desired alkaloid analogues (Scheme IV.33). It underwent *S*-oxidation using MCPBA, followed by *S*-oxide activation using trifluoroacetic anhydride to promote the cyclization process.

<sup>354</sup> Islas-Jácome, A.; Cárdenas-Galindo, L. E.; Jerezano, A. V.; Tamariz, J.; González-Zamora, E.; Gámez-Montañó, R. *Synlett* **2012**, 23, 2951.

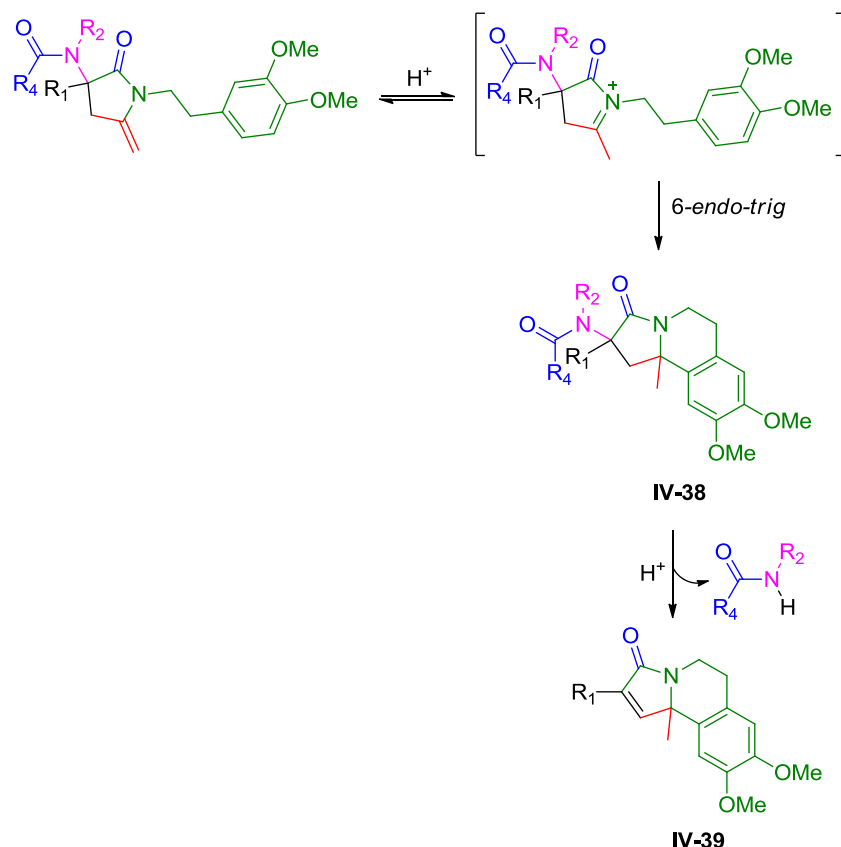


Scheme IV.33. Synthesis of nuevamine aza-analogues.

## IV.8 Ugi/Propargylation/Pictet-Spengler cascade

### Presentation of the protocol

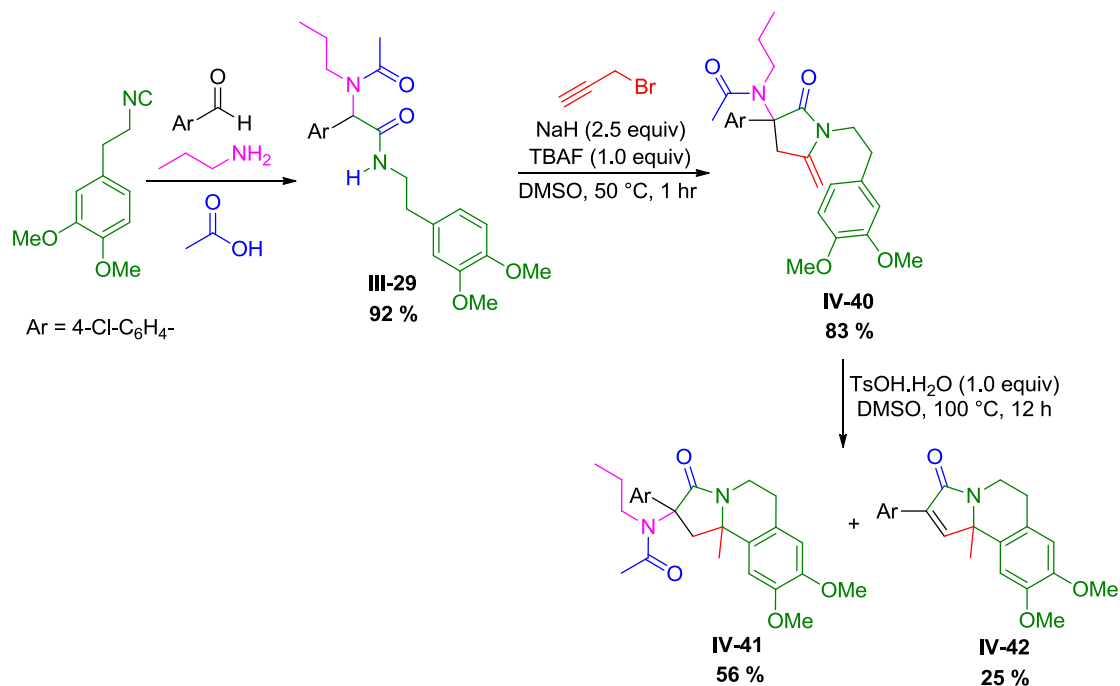
In the forthcoming part of this chapter, we present an Ugi multicomponent reaction based synthesis of benzoindolizinone alkaloid like structure. We examined the possibility of a diastereoselective cyclization of *N*-acyliminium ions generated from Ugi derived cyclic enamides through a Pictet-Spengler 6-*exo-trig* cyclization. We also described the potential of obtaining selectively, either the Pictet-Spengler cyclization adduct **IV-38** or that accompanied with an elimination reaction **IV-39** (Scheme IV.34).



Scheme IV.34. Possible pathways for Ugi  $N$ -acyliminium ions Pictet-Spengler cyclization.

### First trial

We began our study using the Ugi adduct **III-29**, obtained from the condensation between 4-chlorobenzaldehyde, propylamine, acetic acid and homoveratryl amine isocyanide in 92 % yield. Following the aforementioned procedure, the Ugi adduct **III-29** was allowed to react with 2.5 equiv. of NaH in DMSO at room temperature for 10 min. Then, 1.5 equiv. of propargyl bromide and 1.0 equiv of TBAF were added respectively and the resulting mixture was heated at 50 °C for one hour. This procedure delivered the corresponding pyrrolidin-2-one derivative **IV-40** in 83 % yield. The obtained cyclic enamide **IV-40** was then subjected to the reaction with 1.0 equiv. of TsOH.H<sub>2</sub>O in DMSO at 100°C for 12 hours. DMSO was selected as the reaction solvent as to enable the one-pot procedure of both steps afterwards. This reaction resulted in the desired benzoindolizidinone derivative **IV-41** as a single diastereomer with 56 % yield, together with the elimination product **IV-42** in 25 % yield (Scheme IV.35).



Scheme IV.35. First trial for the Pictet-Spengler cyclization towards benzoindolizidinones.

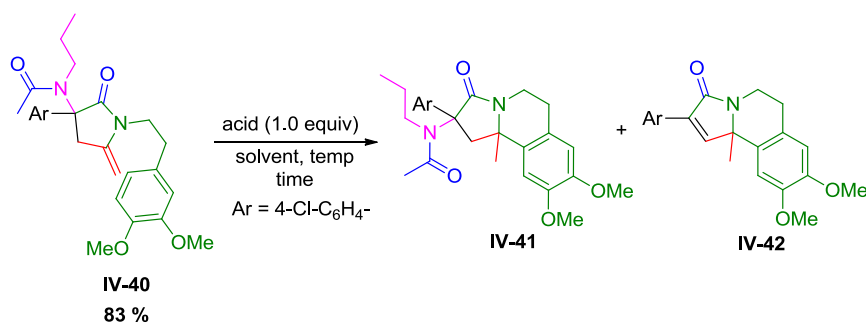
### Optimization of the reaction conditions

This initiatory result encouraged us to study the effect of different bronsted acids and solvents on the Pictet-Spengler reaction progression towards the target benzoindolizidinones.

#### Bronsted acid-Solvent combination

After the isolation of the desired product **IV-41** in 56 % yield, using TsOH.H<sub>2</sub>O in DMSO, we then decided to examine the effect of using non-polar solvent, such as: toluene. In this case, better selectivity was obtained in shorter reaction time, thus after 1.5 hours, 60 % of the target compound **IV-41** was isolated together with 18 % of the side product **IV-42**. However, the formation of the side product **IV-42** in both cases constituted unsatisfactory results for us. Consequently, we decided to examine the influence of using trifluoroacetic acid instead of tosic acid on the reaction progress and selectivity. The use of 1.0 equiv. of TFA in DMSO at room temperature for 12 hours resulted in 16 % yield of **IV-41** as a single product together with remaining unreacted starting Ugi. Changing the solvent from DMSO to DCM afforded the best results, where the target compound **IV-41** was isolated with 79 % yield as a single product and single isomer after 1.5 hours. All the results obtained are displayed in Table IV-7.

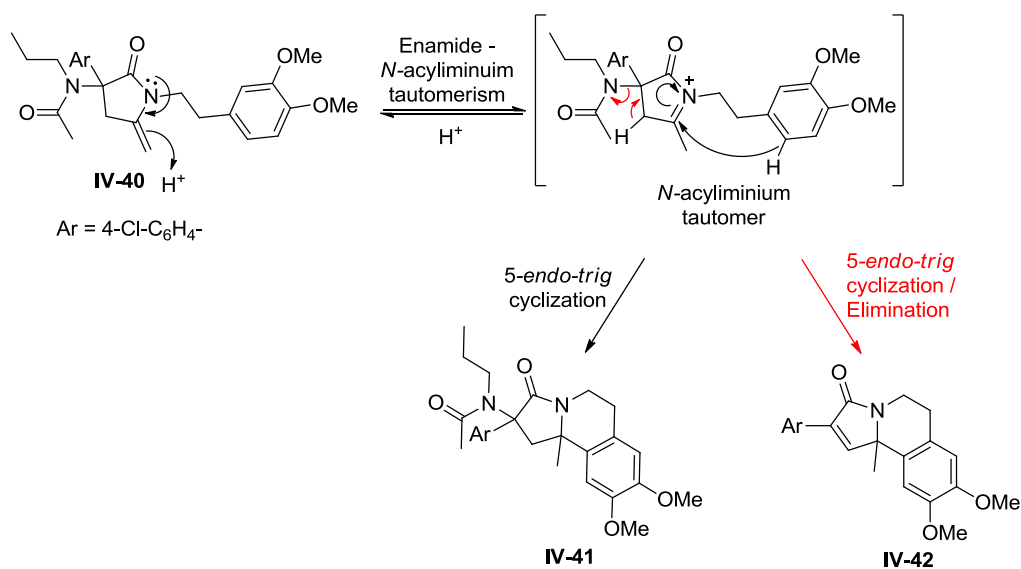
Table IV-7. Optimization of the Acid-Solvent combination.



Entry	Acid	Solvent	Temp.	Time (h)	Yield (IV-41)	Yield (IV-42)
1	TsOH.H <sub>2</sub> O	DMSO	100 °C	12	56 %	25 %
2	TsOH.H <sub>2</sub> O	Toluene	80 °C	1.5	60 %	18 %
3	TFA	DMSO	r.t.	12	16 %	0 %
4	TFA	DCM	r.t.	1.5	79 %	0 %

## IV.9 Reaction mechanism

The reaction mechanism starts with equilibrium between the enamide and its *N*-acyliminium tautomer under acidic conditions. Using electron rich aryl group attached to the isocyanide partner in Ugi adduct, the acyliminium intermediate could be trapped affording the desired benzoindolizidinone **IV-41**. The latter reaction proceeds via a Pictet-Spengler 6-*endo-trig* cyclization. In case of heating in presence of tosic acid, the Pictet-spengler cyclization is associated with an amide elimination affording the side product **IV-42** (Scheme IV.36).



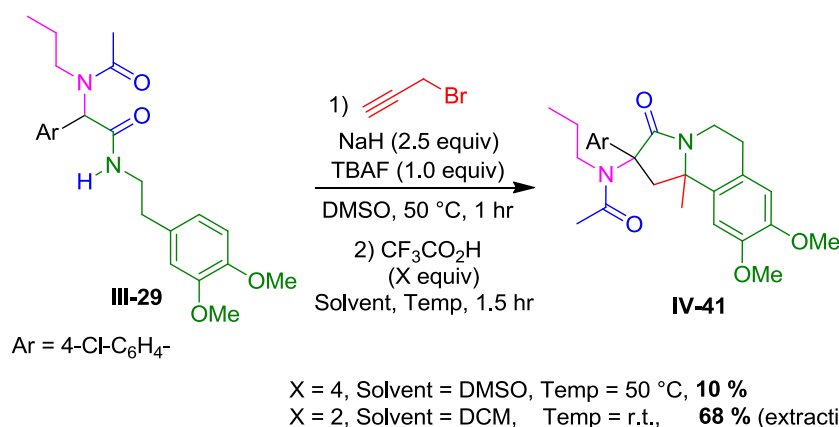
Scheme IV.36. Suggested mechanism for the Pictet-Spengler cyclization and the elimination products.

## IV.10 Results & Discussion

### (a) One-Pot procedure

Reaching the Pictet-Spengler reaction optimal condition (TFA in DCM at room temperature), we examined the possibility of performing both propargylation and Pictet-Spengler reactions in one step. In the first trial, we decided to keep the DMSO as the reaction solvent for the two steps and raise the temperature to 50 °C for the Pictet-Spengler step, hoping that such raise in temperature would enhance the reaction progression. Thus, the Ugi adduct **III-29** was allowed to react with 2.5 equiv. of NaH in DMSO (0.4 M) for 10 min, followed by the addition of 1.5 equiv. of propargyl bromide and 1.0 equiv. of TBAF. Then the reaction mixture was heated for 1 hour at 50 °C. This was followed by adding 4.0 equiv. of TFA and heating at 50 °C for further 1.5 hours. Using this protocol, only 10 % of the desired product **IV-41** was obtained (Scheme IV.37). This is probably due to the possible interaction between TFA and DMSO.

Accordingly, we decided to modify a little bit the protocol by carrying out an extraction after the propargylation reaction in order to permit switching the reaction solvent to DCM. Hence, after the reaction of Ugi dianion with the propargyl bromide for 1 hour at 50 °C, an extraction was carried out using citric acid/DCM. Then the solvent was evaporated and the crude mixture was dissolved in DCM (0.4 M) to which 2.0 equiv. of TFA was added. The reaction was stirred at room temperature for further 1.5 hours. Following this modified protocol, 68 % of the desired product **IV-41** was isolated as a single diastereomer.



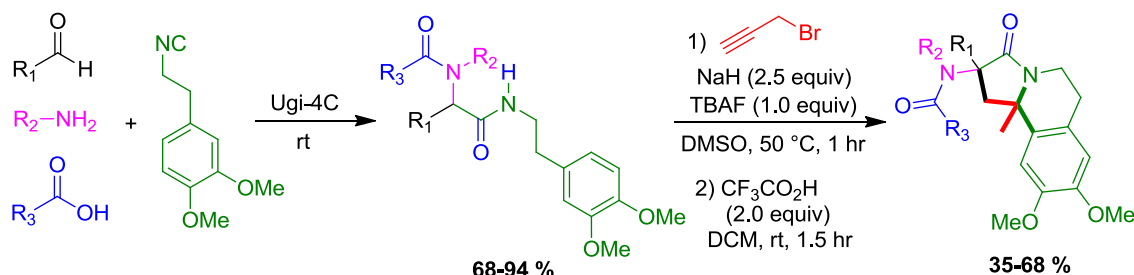
**Scheme IV.37. One pot procedure for benzoindolizidinone synthesis from Ugi adducts.**

It is worth mentioning that decreasing the amount of TFA below 2.0 equiv in this procedure, results in decreasing the overall reaction yield.

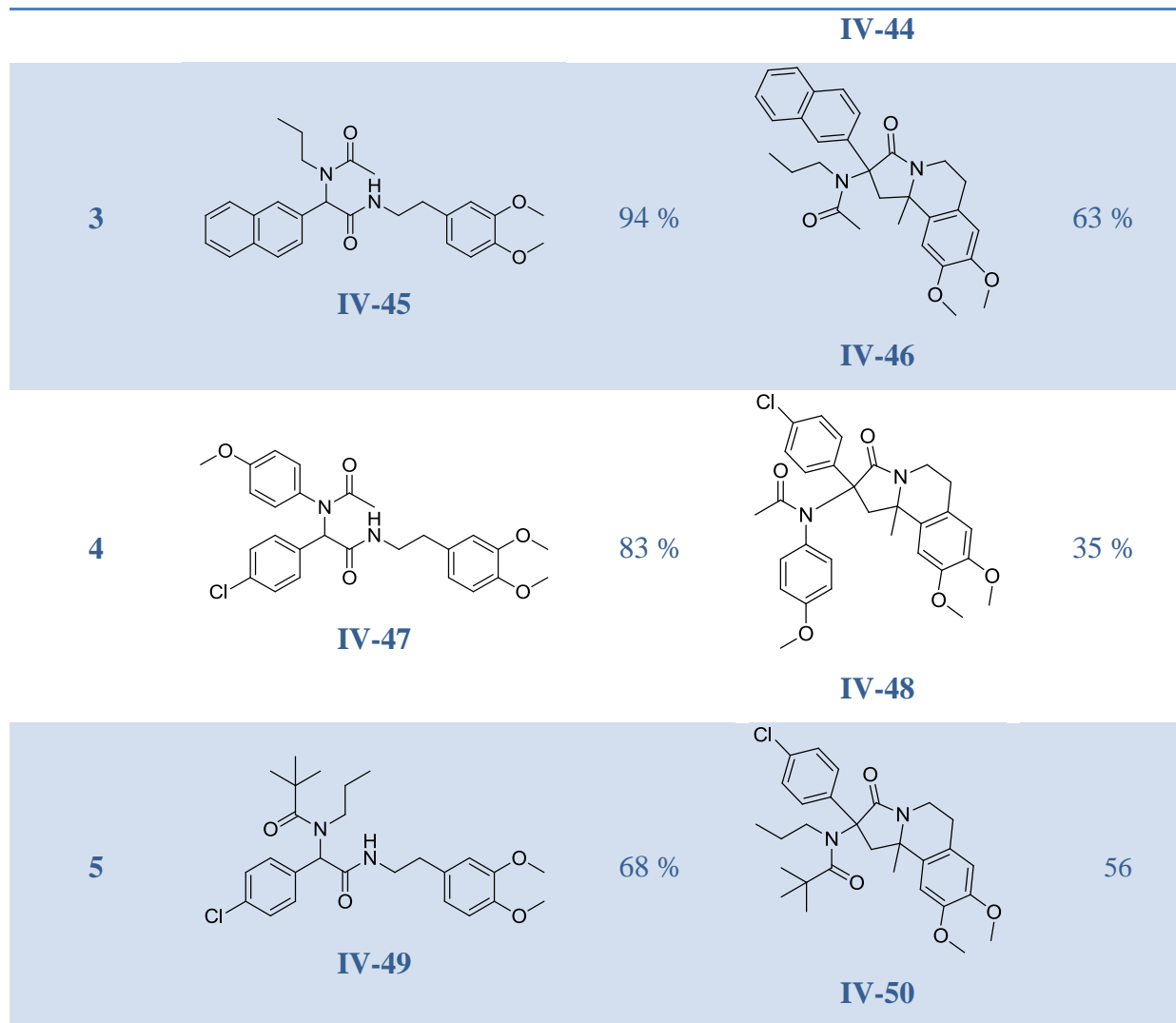
### (b) Results

A series of Ugi adducts was prepared fixing the isocyanide partner to 4-(2-isocyanoethyl)-1,2-dimethoxybenzene, with good to excellent yields from 68 to 94 % (the Ugi reaction has been already described in chapter II, section II.9). This series was subjected to the reaction with NaH (2.5 equiv.) and propargyl bromide (1.5 equiv.) in presence of TBAF (1.0 equiv.) in DMSO (0.4 M) at 50 °C for one hour. Then, an extraction was carried out to enable the solvent change to DCM (0.4 M), to which, trifluoroacetic acid (2.0 equiv.) was added and allowed to react at room temperature for 1.5 hour. Hence, the propargylation/5-*exo-dig* cyclization/Pictet-Spenglercascade afforded a series of benzoindolizidinone alkaloid like structures. The various results are displayed thereafter in Table IV-8.

Table IV-8. The scope of benzoindolizidinones synthesis from Ugi adducts.



Entry	Ugi adduct	Yield	Benzoindolizidinones	Yield
1	 III-29	92 %	 IV-41	68 %
2	 IV-43	94 %	 IV-43	51 %



### (c) Discussion

Generally, this reaction allowed us to prepare a set of benzoindolizidinone alkaloid like structures with moderate to good yields from 35 to 68 %. There are two possible diastereomers for such cyclization; however the products were obtained selectively as single diastereomers.

Changing the aldehyde partner didn't affect greatly the overall reaction yield. Thus using 4-chlorobenzaldehyde, the corresponding product **IV-41** was isolated in 68 % yield. While using pyridine-2-carboxaldehyde afforded the tricyclic structure **IV-44** in 51 % yield. Whereas the use of naphthalene-2-carboxaldehyde provided the target compound **IV-46** with 63 % yield.



Pivalic acid was submitted successfully as the acidic partner in Ugi adducts giving the corresponding benzoindolizidinone **IV-50** in 56 % yield. The employment of aromatic amines in Ugi adduct resulted in a dramatic decrease in the overall reaction yield. Thus, using *p*-anisidine derived Ugi **IV-47** resulted in only 35 % of the corresponding product **IV-48**. Despite the fact that the elimination product could not be isolated in this case, it still could account for the low isolated yield.

The relative positions of the substituents in the previous examples could not be identified through NMR. However, the benzoindolizidinone **IV-50** was crystallized from toluene by slow evaporation at room temperature affording single-crystals. The analysis of the crystals obtained using X-ray clarified the relative positions of the substituents in the single diastereomer obtained to be 50 % RR: 50 % SS (Figure IV.5). The stereochemistry of the other examples was proposed by analogy with the product **IV-50**.

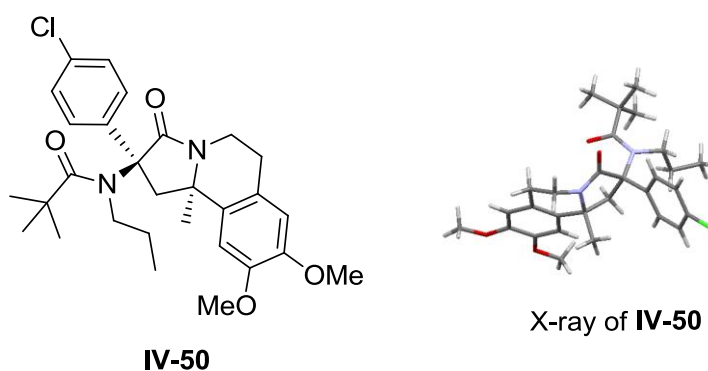


Figure IV.5. X-ray structure of benzoindolizidinone **IV-50**.

More interestingly, the reaction was carried out using 1.0 mmol scale in order to confirm its reproducibility. Hence, 1.0 mmol of Ugi adduct **III-29** was subjected to the propargylation/*5-exo-dig* cyclization/Pictet-Spengler cascade following the previously mentioned methodology in a one-pot reaction. The corresponding benzoindolizidinone **IV-41** was obtained in this case with 70 % yield (68 % was isolated using 0.4 mmol scale).

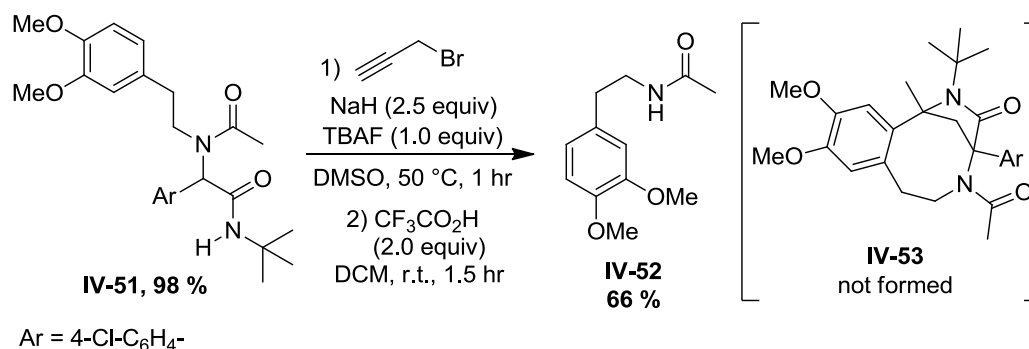
Furthermore, the conversion of the benzoindolizidinone **IV-41** into the corresponding elimination product **IV-42** could be achieved by refluxing in toluene, in presence of 1.0 equiv. of tosic acid, for 24 hours. In this case the product **IV-42** was obtained in 87 % yield (Scheme IV.38).



Scheme IV.38. Dehydroamidation of benzoindolizidinone under acidic conditions.

### (d) Other Pictet-Spengler attempts

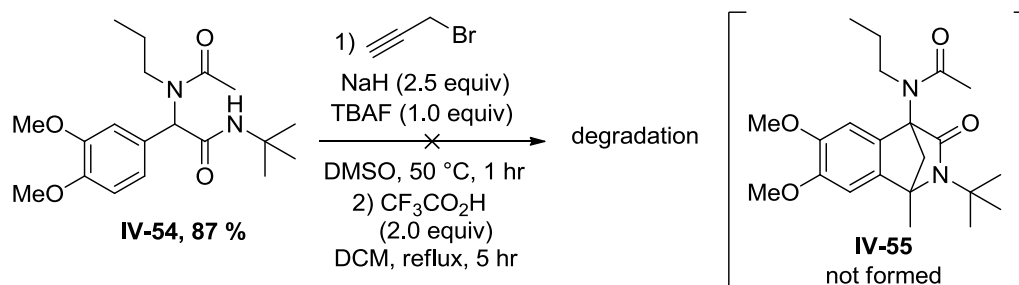
We tried to extend the Pictet-Spengler cyclization to deliver different scaffolds. Thus we decided to use the electron-rich aryl group, the nucleophile which traps the *N*-acyliminium ion, linked to other starting partners in Ugi adducts. Therefore, we prepared the Ugi adduct **IV-51** in 98 % yield from the condensation between 4-chlorobenzaldehyde, homoveratryl amine, acetic acid and *tert*-butyl isocyanide. The latter was subjected to reaction with propargyl bromide followed by treatment with TFA following the aforementioned general procedure. In this case, the expected product **IV-53** was not detected, only the amide **IV-52**, resulting from a decomposition process, was isolated in 66 % yield (Scheme IV.39). This goes along with the low yield obtained using *p*-anisidine. It could be rationalized by the steric hinderance that promotes the elimination reaction as well as the difficulties of constructing the 8-membered ring cycle.



Scheme IV.39. Propargylation/Pictet-Spengler cascade of homoveratryl amine derived Ugi adduct.

Finally, an-electron rich aldehyde derived Ugi adduct was synthesized and submitted to the cascade reaction. Thus, the Ugi adduct **IV-54** was prepared from the condensation between 3,4-dimethoxybenzaldehyde, propylamine, acetic acid and *tert*-butyl isocyanide in 87 % yield. Upon its reaction with propargylamide and TFA, only the pyrrolidinone intermediate

could be detected by TLC after 1.5 hrs at room temperature. Refluxing the reaction mixture resulted in degradation, while the expected product **IV-55** was not formed (Scheme IV.40). This is probably due to the difficulties of constructing the strained bicyclic system.



Scheme IV.40. Propargylation/Pictet-Spengler cascade of 3,4-dimethoxybenzaldehyde derived Ugi adduct.

## IV.11 Conclusion

In order to sum up, we have described a new versatile route towards pyrrolidin-2-ones starting from Ugi adducts. The protocol involved a propargylation of the Ugi amide dianions, attained under strongly basic conditions, followed by a 5-*exo-dig* hydroamidation cyclization. TBAF was used as a phase transfer catalyst to promote the cyclization reaction. Thus, the sequence of propargylation/cyclization processes was carried out in a one pot reaction at 50 °C for 1 hour, delivering the target pyrrolidin-2-one derivatives in moderate to good yields.

The synthetic potential of such pyrrolidin-2-ones derivatives was demonstrated by the equilibrium with their *N*-acyliminium ions under acidic conditions. The latter was successfully trapped in an intermolecular fashion using nucleophiles such as: indole as well as intramolecular fashion using electron-rich aryl group tethered to the isocyanide in the Ugi starting materials. Hence, the interest of such novel multicomponent access to pyrrolidin-2-ones was highlighted with a subsequent Pictet-Spengler cyclization involving *N*-acyliminium ions, generated from Ugi derived cyclic enamides.

Moreover, the construction of the tricyclic skeleton of crispine alkaloids can be directly achieved starting from acyclic Ugi adducts by a series of propargylation/5-*exo-dig* cyclization/Pictet-Spengler reactions in one step. Despite the fact that this sequence has been widely employed in the construction of the benzoindolizinone skeleton, herein, we disclosed the first approach starting from Ugi adducts conducting the three processes in one-pot

reaction. The interest of using Ugi adducts in this cascade is clearly demonstrated by raising the diversity of the synthesized alkaloid like structures. The target benzoindolizidinone compounds were isolated with moderate to good yields as single diastereomers.



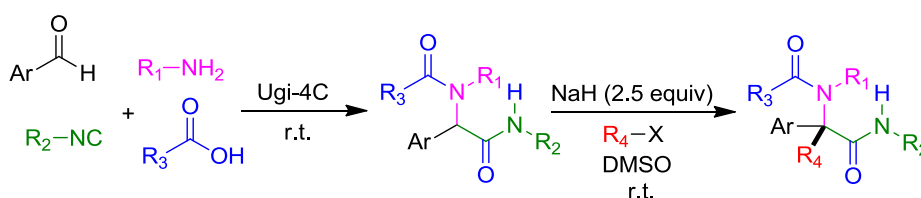
## Conclusion

## Conclusion

## General Conclusion and Perspectives

In the frame of this thesis, we presented a novel strategy for the Ugi-post condensation reactions affording valuable heterocycles by means of 1,3-amide dianion intermediates. The formation of the latter allows efficient room temperature intermolecular alkylation of Ugi adducts in spite of their rather hindered chemical environment.

The overall process (Ugi + alkylation) represent a formal Ugi reaction of aromatic ketones, compounds known for their poor reactivity in Ugi reactions (Scheme 1). The addition of a fifth component further raises the diversity of Ugi reaction and allows building more complex cascades as shown in our work.



**Scheme 1**

One of the future challenges for us in this context is to carry out the alkylation reaction in an enantioselective fashion, delivering enantiomerically pure Ugi-5C adducts.

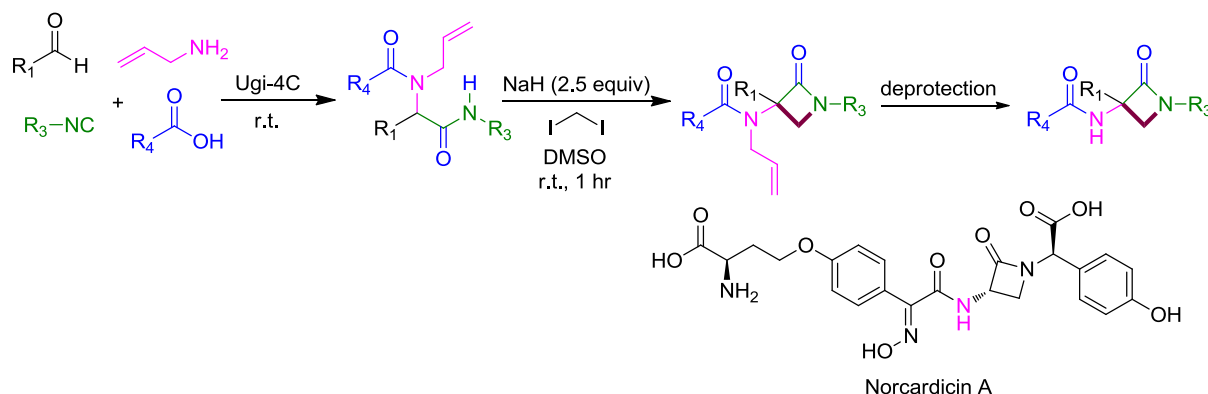
The dianionic Ugi intermediates were trapped as well using biselectrophiles. Diiodomethane was chosen as a biselectrophile to deliver  $\beta$ -lactams. Similar strategy was previously reported by Hirari in 1979 employing different scaffolds, but it suffered from several drawbacks such as: low yields, narrow scope, side products and few examples. During our course of study, we managed to overcome all of those drawbacks synthesizing a wide library of four component  $\beta$ -lactams. This protocol was successfully extended to malonic ester amide and their derivatives turning the strategy into a general methodology for the synthesis of  $\beta$ -lactams.

The biological tests performed on the synthesized  $\beta$ -lactams demonstrated that some of them have a comparable antibacterial effect with Ampicillin. This is considered as a very promising result, if we compare the simplicity of obtaining our scaffolds with respect to the complex total synthesis of the enantiomerically pure ampicillin.



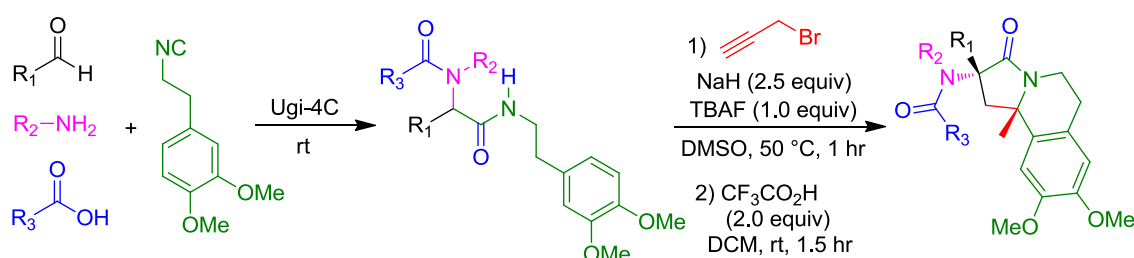
## Conclusion

One of our future projects concerning this subject is to try to prepare  $\beta$ -lactams with free amide in the side chain so as to resemble the structure of various  $\beta$ -lactam antibiotics in order to achieve better antibiotic activities (Scheme 2). Norcardicin A is presented as an example for the biologically active  $\beta$ -lactams with free amide in the side chain.



Scheme 2

This strategy was further extended to a propargylation/Pictet-Spengler cascade (Scheme 3).



Scheme 3

One of the extensions we are aiming to fulfill is to expand the scope of the propargylation reaction to include several propargyl bromide derivatives.

In general, this strategy could be applied to many biselectrophiles such as: bromo ketones, delivering different sized heterocycles. We are aiming as well to explore the reactivity of the Ugi amide dianions in single electron transfer reactions.

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## References

## Experimental part



## General Aspects

$^1\text{H}$ -NMR spectra are recorded at 400 MHz, using a Bruker Avance 400 MHz spectrometer.  $^{13}\text{C}$ -NMR spectra are recorded at 100.6 MHz, using a Bruker Avance 400 MHz spectrometer. The  $^1\text{H}$  and  $^{13}\text{C}$  chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS), using the residual solvent signal as an internal reference. Complete assignment of all NMR signals is carried out using a combination of DEPT, COSY, HSQC and HMBC experiments. Coupling constant ' $J$ ' is calculated in hertz Hz. Splitting patterns are abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad band).

The infrared 'IR' spectra are conducted on a Bruker IFS 66 spectrophotometer by thin-film technique as 5 % solution in  $\text{CHCl}_3$ , using PerkinElmer spectrum two FT-IR spectrometer. Wavelengths are presented in  $\text{cm}^{-1}$ .

High-resolution mass spectra (HRMS) are performed with JEOL JMS-Gcmate II spectrometer. Melting points (m.p.) are measured using Stuart SMP3 melting point apparatus in an open capillary tube and are left uncorrected. All the experiments involving microwave irradiation were performed on Anton Paar Monowave 300 device in sealed microwave tubes.

Reactions are followed by thin layer chromatography (TLC) using silica gel 60 F254 plates and was visualized using UV-Light or by staining with CAM (Cerium-ammoniummolybdate: mixture of ammonium molybdate, cerium (IV) sulfate, sulfuric acid and water) or potassium permanganate (a mixture of  $\text{KMnO}_4$ ,  $\text{K}_2\text{CO}_3$  and NaOH in water). Flash chromatography is performed using silicagel 60 (40-63  $\mu\text{m}$ ) obtained from Merck.

All commercially available reagents are purchased from Aldrich, Alfa-Aesar and are used without further purification. Solvents were thoroughly dried prior to the reactions. All volatile solvents are removed, in *vacuo*, under reduced pressure using a Büchi rotary evaporator. THF, DCM and toluene solvents are dried using MBraun Solvent Purification System (model MB-SPS 800) equipped with alumina drying columns.

### Experimental part

Reactions requiring anhydrous conditions or inert atmosphere were conducted either under argon or nitrogen atmosphere in dried glassware.

All the isocyanides used in the experimental part were synthesized from their corresponding amines according to the carbylamines procedure.<sup>355</sup>

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## **Experimental part for Chapter II**





## Experimental Part for Chapter II

### *General Procedures*

#### ➤ **General procedure II-A for Ugi products**

To a 1.0 M solution of aldehyde in methanol were added successively 1.0 equiv. of amine, 1.0 equiv. of acid and 1.0 equiv. of isocyanide. The resulting mixture was stirred at room temperature for 1 day. The solvent was removed under reduced pressure and the crude was purified by flash column chromatography on silica gel to afford Ugi product.

#### ➤ **General procedure II-B for Tsuji-Trost reaction**

A solution of Ugi adduct (1.0 equiv.) and sodium hydride (2.5 equiv.) in DMSO (0.5 M) was stirred at room temperature under Argon for 5 min., followed by the addition of allyl acetate derivative (1.5 equiv.), Pd(dba)<sub>2</sub> (0.05 equiv.) and PPh<sub>3</sub> (0.1 equiv.) respectively. The resulting solution was stirred at room temperature for 1 to 2 hours depending on the reaction progress checked by TLC. After the completion of the reaction, it was diluted with CH<sub>2</sub>Cl<sub>2</sub> and extracted with water. The organic phase was dried over MgSO<sub>4</sub> and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel to give the desired allylated product.

#### ➤ **General procedure II-C for alkylation reaction**

A solution of Ugi adducts (1.0 equiv.) and sodium hydride (2.5 equiv.) in DMSO (0.5 M) was stirred at room temperature under Argon for 5 min., followed by the addition of alkyl halide derivative (1.5 equiv.). The resulting solution was stirred at room temp for 1 to 4 hours depending on the reaction progress checked by TLC. After the completion of the reaction, it was diluted with CH<sub>2</sub>Cl<sub>2</sub> and extracted with water. The organic phase was dried over MgSO<sub>4</sub> and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel to give the target compound.

➤ **General procedure II-D for Ugi/alkylation cascade reaction**

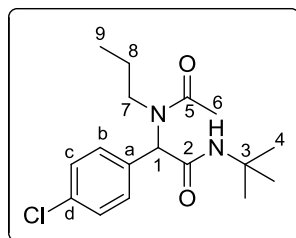
To a 1.0 M solution of aldehyde in methanol were added successively 1.0 equiv. of amine, 1.0 equiv. of acid and 1.0 equiv. of isocyanide. The resulting mixture was stirred at room temperature for 1 day. Then methanol was removed under reduced pressure and replaced by 0.5 M DMSO, sodium hydride (2.5 equiv.) was added and the resulting solution was stirred at room temperature under Argon for 5 min., followed by the addition of allyl bromide (1.5 equiv.), stirring was then continued at room temperature for extra 2 to 4 hours depending on the reaction progress checked by TLC. After the completion of the reaction, it was diluted with CH<sub>2</sub>Cl<sub>2</sub> and extracted with water. The organic phase was dried over MgSO<sub>4</sub> and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel to give the desired product.

➤ **General procedure II-E for Ring Closure Metathesis (RCM)**

A solution of allylated Ugi product (1.0 equiv.) and Hoveyda-Grubbs catalyst 2<sup>nd</sup> generation (2.5 mol %) in toluene (0.4 M) were stirred at 60 °C for 4 hours. The resulting mixture was filtered then the solvent was evaporated under reduced pressure. The crude residue was purified by flash chromatography on silica gel to afford the corresponding cyclic product.

**II-40**

**N-(*tert*-butyl)-2-(4-chlorophenyl)-2-(N-propylacetamido)acetamide**



Mol. Wt.: 324.161 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-A**, using 4-chlorobenzaldehyde (141 mg, 1.0 mmol), propylamine (0.08 ml, 1.0 mmol), acetic acid (0.06 ml, 1.0 mmol) and *tert*-butyl isocyanide (0.11 ml, 1.0 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : PE = 70 : 30) gave the desired product in 89 % isolated yield (288 mg, 0.89 mmol).

**Nature:** White solid.

**M.P.** = 173-175 °C.

**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 7 : 3) = 0.3.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.27 (br s, 4H, H-Ar), 5.83 (br s, 1H, NH), 5.70 (s, 1H, H-1), 3.18 (t, *J* = 8.2 Hz, 2H, H-7), 2.11 (s, 3H, H-6), 1.43-1.36 (m, 1H, H-8), 1.26 (s, 9H, H-4), 1.02-0.92 (m, 1H, H-8), 0.64 (t, *J* = 7.4 Hz, 3H, H-9).

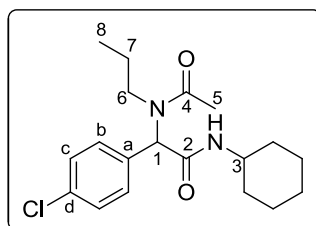
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.6 (C-5), 168.9 (C-2), 134.5 (C-a), 134.2 (C-d), 130.6 (C-Ar), 128.9 (C-Ar), 61.8 (C-1), 51.6 (C-3), 49.5 (C-7), 28.6 (C-4), 23.0 (C-8), 21.9 (C-6), 11.2 (C-9).

**HRMS:** Calculated for C<sub>17</sub>H<sub>25</sub>ClN<sub>2</sub>O<sub>2</sub>: 324.1605, Found: 324.1603.

**I.R.** (thin film): ν 3426, 2970, 2935, 2877, 1679, 1633, 1514, 1252, 1140, 1094 and 1016 cm<sup>-1</sup>.

## II-46

### 2-(4-chlorophenyl)-N-cyclohexyl-2-(N-propylacetamido)acetamide



Mol. Wt.: 350.176 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-A**, using 4-chlorobenzaldehyde (141 mg, 1.0 mmol), propylamine (0.08 ml, 1.0 mmol), acetic acid (0.06 ml, 1.0 mmol) and cyclohexylisocyanide (109 mg, 1.0 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : PE = 90 : 10) gave the desired product in 85 % isolated yield (320 mg, 0.85 mmol).

**Nature:** White solid.

**M.P.** = 189-191°C.

**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 9 : 1) = 0.39.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.26 (br s, 4H, H-Ar), 6.06 (br s, 1H, NH), 5.73 (s, 1H, H-1), 3.74-3.67 (m, 1H, H-3), 3.19 (t, *J* = 8.0 Hz, 2H, H-6), 2.10 (s, 3H, H-5), 1.82-1.80 (m, 2H, H), 1.61-1.49 (m, 3H), 1.44-1.36 (m, 1H), 1.31-1.22 (m, 2H), 1.13-1.01 (m, 4H), 0.66 (t, *J* = 7.3 Hz, 3H, H-8).

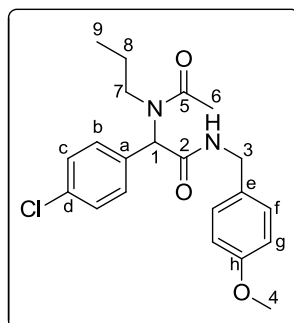
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.6 (C-4), 168.6 (C-2), 134.4 (C-a), 134.2 (C-d), 130.5 (C-b), 128.9 (C-c), 61.6 (C-1), 49.7 (C-6), 48.5 (C-3), 32.8 (C-Cy), 32.7 (C-Cy), 25.5 (C-Cy), 24.8 (C-Cy), 24.7 (C-Cy), 22.9 (C-7), 21.9 (C-5), 11.2 (C-8).

**HRMS:** Calculated for C<sub>19</sub>H<sub>27</sub>ClN<sub>2</sub>O<sub>2</sub>: 350.1761, Found: 350.1678.

**I.R.** (thin film): ν 3425, 2936, 2857, 1677, 1630, 1514, 1491, 1416, 1251 and 1094 cm<sup>-1</sup>.

**II-47**

**2-(4-chlorophenyl)-N-(4-methoxybenzyl)-2-(N-propylacetamido)acetamide**



Mol. Wt.: 388.155 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-A**, using 4-chlorobenzaldehyde (141 mg, 1.0 mmol), propylamine (0.08 ml, 1.0 mmol), acetic acid (0.06 ml, 1.0 mmol) and 1-(isocyanomethyl)-4-methoxybenzene (147 mg, 1.0 mmol). Purification by flash chromatography using (EtOAc : DCM = 20 : 80) gave the desired product in 90 % isolated yield (350 mg, 0.9 mmol).

**Nature:** White solid.

**M.P.** = 95-97 °C.

**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 9:1) = 0.29.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.23 (br s, 4H, H-b,c), 7.08 (d, *J* = 8.5 Hz, 2H, H-f), 6.74 (d, *J* = 8.6 Hz, 2H, H-g), 6.59 (br s, 1H, NH), 5.79 (s, 1H, H-1), 4.29 (dd, ABX system, *J*<sub>ab</sub> = 14.6, *J*<sub>ax</sub> = 5.5, *J*<sub>bx</sub> = 5.8 Hz, 2H, H-3), 3.69 (s, 3H, H-4), 3.20-3.15 (m, 2H, H-7), 2.04 (s, 3H, H-6), 1.4-1.3 (m, 1H, H-8), 1.01-0.90 (m, 1H, H-8), 0.62 (t, *J* = 7.4 Hz, 3H, H-9).

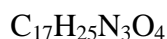
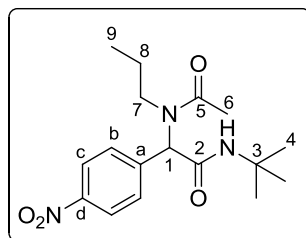
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.7 (C-5), 169.5 (C-2), 158.9 (C-h), 134.4 (C-a), 134.2 (C-d), 130.7 (C-b), 130.1 (C-e), 129.1 (C-f), 128.9 (C-c), 114.0 (C-g), 61.5 (C-1), 55.3 (C-4), 49.6 (C-7), 43.1 (C-3), 23.0 (C-8), 21.8 (C-6), 11.2 (C-9).

**HRMS:** Calculated for C<sub>21</sub>H<sub>25</sub>ClN<sub>2</sub>O<sub>3</sub>: 388.1554, Found: 388.1569.

**I.R.** (thin film): ν 3433, 3067, 3035, 3004, 2967, 2935, 2878, 2839, 1676, 1631, 1513, 1301, 1250, 1176, 1094 and 1035 cm<sup>-1</sup>.

## II-48

### N-(*tert*-butyl)-2-(4-nitrophenyl)-2-(N-propylacetamido)acetamide



Mol. Wt.: 335.185 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-A**, using 4-nitrobenzaldehyde (151 mg, 1.0mmol), propylamine (0.08 ml, 1.0mmol), acetic acid (0.06 ml, 1.0mmol) and *tert*-butyl isocyanide (0.11 ml, 1.0mmol). Purification by flash chromatography using (EtOAc : PE = 50 : 50) gave the desired product in 89 % isolated yield (297 mg, 0.89 mmol).

**Nature:** White solid.

**M.P.** = 96-98 °C.

**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 9:1) = 0.37.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 8.14 (d, *J* = 8.7 Hz, 2H, H-c), 7.48 (d, *J* = 8.6 Hz, 2H, H-b), 6.27 (br s, 1H, NH), 5.69 (s, 1H, H-1), 3.26 (t, *J* = 8.1 Hz, 2H, H-7), 2.15 (s, 3H, H-6), 1.52-1.44 (m, 1H, H-8), 1.29 (s, 9H, H-4), 1.19-1.13 (m, 1H, H-8), 0.71 (t, *J* = 7.4 Hz, 3H, H-9).

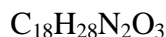
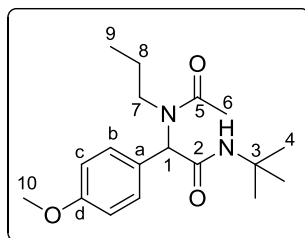
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.8 (C-5), 168.2 (C-2), 147.5 (C-d), 143.5 (C-a), 129.4 (C-b), 123.7 (C-c), 62.9 (C-1), 51.8 (C-3), 50.4 (C-7), 28.6 (C-4), 22.9 (C-8), 21.9 (C-6), 11.2 (C-9).

**HRMS:** Calculated for C<sub>17</sub>H<sub>25</sub>N<sub>3</sub>O<sub>4</sub>: 335.1845, Found: 335.1837.

**I.R.** (thin film): ν 3426, 2970, 2935, 2877, 1674, 1633, 1607, 1524, 1350, 1252 and 1222 cm<sup>-1</sup>.

**II-49**

**N-(*tert*-butyl)-2-(4-methoxyphenyl)-2-(N-propylacetamido)acetamide**



Mol. Wt.: 320.21 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-A**, using 4-methoxybenzaldehyde (0.12 ml, 1.0 mmol), propylamine (0.08 ml, 1.0mmol), acetic acid (0.06 ml, 1.0mmol) and *tert*-butyl isocyanide (0.11 ml, 1.0mmol). Purification by flash chromatography using (EtOAc : PE = 60 : 40) gave the desired product in 93 % isolated yield (298 mg, 0.93 mmol).

**Nature:** White solid.

**M.P.** = 170-172 °C.

**R<sub>f</sub>**: (Et<sub>2</sub>O : PE = 9:1) = 0.34.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.25 (d, *J* = 8.6 Hz, 2H, H-b), 6.81 (d, *J* = 8.7 Hz, 2H, H-c), 5.73 (s, 1H, H-1), 5.61 (br s, 1H, NH), 3.75 (s, 3H, H-10), 3.16 (t, *J* = 8.2 Hz, 2H, H-7), 2.10 (s, 3H, H-6), 1.34-1.28 (m, 1H, H-8), 1.26 (s, 9H, H-4), 0.91-0.81 (m, 1H, H-8), 0.59 (t, *J* = 7.4 Hz, 3H, H-9).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.4 (C-5), 169.5 (C-2), 159.6 (C-d), 130.8 (C-b), 127.9 (C-a), 114.1 (C-c), 61.6 (C-1), 55.3 (C-10), 51.5 (C-3), 49.1 (C-7), 28.7 (C-4), 23.1 (C-8), 21.9 (C-6), 11.3 (C-9).

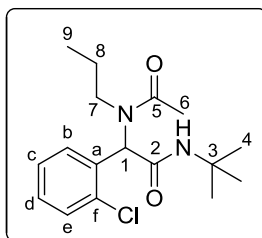
**HRMS:** Calculated for C<sub>18</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub>: 320.2100, Found: 320.2099.

**I.R.** (thin film): ν 3425, 2969, 2935, 2876, 1683, 1625, 1512, 1251, 1180 and 1035 cm<sup>-1</sup>.



## II-50

### N-(*tert*-butyl)-2-(2-chlorophenyl)-2-(N-propylacetamido)acetamide



Mol. Wt.: 324.161 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-A**, using 2-chlorobenzaldehyde (141 mg, 1.0 mmol), propylamine (0.08 ml, 1.0mmol), acetic acid (0.06 ml, 1.0mmol) and *tert*-butyl isocyanide (0.11 ml, 1.0 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 15 : 85) gave the desired product in 80 % isolated yield (261 mg, 0.8 mmol).

**Nature:** White solid.

**M.P.** = 187-189°C.

**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 7 : 3) = 0.3.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.68-7.66 (m, 1H, H-d), 7.47-7.45 (m, 1H, H-c), 7.37-7.34 (m, 2H, H-b,e), 6.08 (s, 1H, H-1), 5.69 (br s, 1H, NH), 3.26 (dt, ABX<sub>2</sub> system,  $J_{ab} = 10.4$ ,  $J_{ax} = J_{bx} = 5.6$  Hz, 2H, H-7), 2.23 (s, 3H, H-6), 1.52-1.47 (m, 1H, H-8), 1.39 (s, 9H, H-4), 1.00-0.91 (m, 1H, H-8), 0.68 (t,  $J = 7.4$  Hz, 3H, H-9).

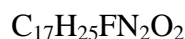
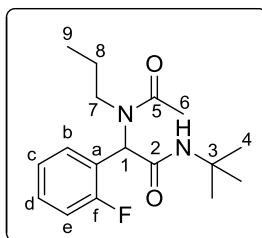
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.3 (C-5), 168.8 (C-2), 135.8 (C-a), 133.7 (C-f), 130.8 (C-b), 129.9 (C-d,e), 127.1 (C-c), 59.9 (C-1), 51.7 (C-3), 49.3 (C-7), 28.6 (C-4), 22.7 (C-8), 21.8 (C-6), 11.2 (C-9).

**HRMS:** Calculated for C<sub>17</sub>H<sub>25</sub>ClN<sub>2</sub>O<sub>2</sub>: 324.1605, Found: 324.1614.

**I.R.** (thin film): ν 3426, 2970, 2935, 2877, 1679, 1633, 1514, 1252, 1140, 1094 and 1016 cm<sup>-1</sup>.

## II-51

### N-(*tert*-butyl)-2-(2-fluorophenyl)-2-(N-propylacetamido)acetamide



Mol. Wt.: 308.19 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-A**, using 2-fluorobenzaldehyde (0.11 ml, 1.0 mmol), propylamine (0.08 ml, 1.0mmol), acetic acid (0.06 ml, 1.0mmol) and *tert*-butyl isocyanide (0.11 ml, 1.0 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 15 : 85) gave the desired product in 95% isolated yield (294 mg, 0.95 mmol).

**Nature:** White solid.

**M.P.** = 155-157°C.

**R<sub>f</sub>** (Et<sub>2</sub>O : DCM = 1.5 : 8.5) = 0.26.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.59 (td, *J* = 7.6, 1.3 Hz, 1H, H-d), 7.37 (td, *J* = 7.4, 1.6 Hz, 1H, H-b), 7.18 (t, *J* = 7.3 Hz, 1H, H-e), 7.12-7.06 (m, 1H, H-c), 6.05 (s, 1H, H-1), 5.95 (br s, 1H, NH), 3.29 (dd, *J* = 16.7, 8.6 Hz, 2H, H-7), 2.19 (s, 3H, H-6), 1.53 – 1.44 (m, 1H, H-8), 1.36 (s, 9H, H-4), 1.05-1.02 (m, 1H, H-8), 0.70 (t, *J* = 7.4 Hz, 3H, H-9).

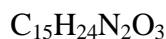
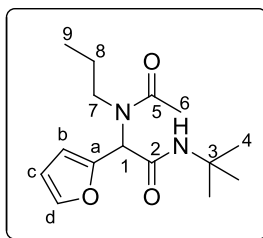
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.3 (C-5), 168.6 (C-2), 161.3 (d, *J* = 248.9 Hz, C-f), 130.8 (d, *J* = 2.8 Hz, C-d), 130.4 (d, *J* = 8.3 Hz, C-b), 124.3 (d, *J* = 3.5 Hz, C-e), 123.4 (d, *J* = 13.7 Hz, C-a), 115.6 (d, *J* = 21.9 Hz, C-c), 56.4 (C-1), 51.6 (C-3), 49.5 (C-7), 28.6 (C-4), 22.9 (C-8), 21.8 (C-6), 11.2 (C-9).

**HRMS:** Calculated for [M-CONH*t*-Bu] C<sub>12</sub>H<sub>16</sub>FNO: 209.1216, Found: 209.1213.

**I.R.** (thin film): ν 3308, 3070, 2965, 2933, 2874, 1680, 1626, 1549, 1453, 1363, 1224, 1097, 1033, 921 and 728 cm<sup>-1</sup>.

**II-52**

**N-(*tert*-butyl)-2-(furan-2-yl)-2-(N-propylacetamido)acetamide**



Mol. Wt.: 280.179 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-A**, using 2-furaldehyde (0.08 ml, 1.0mmol), propylamine (0.08 ml, 1.0mmol), acetic acid (0.06 ml, 1.0mmol) and *tert*-butyl isocyanide (0.11 ml, 1.0mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 10 : 90) gave the desired product in 88 % isolated yield (248 mg, 0.88 mmol).

**Nature:** White solid.

**M.P.** = 113-115 °C.

**R<sub>f</sub>:** (Et<sub>2</sub>O : PE = 9:1) = 0.42.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.45 (d, *J* = 1.2 Hz, 1H, H-d), 6.68 (d, *J* = 3.2 Hz, 1H, H-c), 6.43 (dd, *J* = 1.9, 3.2 Hz, 1H, H-b), 6.06 (br s, 1H, NH), 6.02 (s, 1H, H-1), 3.34 (ddd, ABX<sub>2</sub> system, *J* = 15.6, 10.8, 5.6 Hz, 1H, H-7), 3.21 (ddd, ABX<sub>2</sub> system, *J* = 15.6, 10.8, 5.2 Hz, 1H, H-7), 2.21 (s, 3H, H-6), 1.54-1.45 (m, 1H, H-8), 1.37 (s, 9H, H-4), 1.10-0.99 (m, 1H, H-8), 0.78 (t, *J* = 7.4 Hz, 3H, H-9).

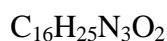
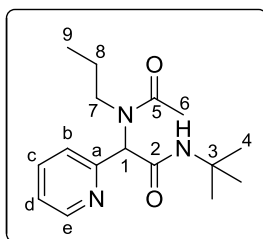
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.4 (C-5), 167.2 (C-2), 148.9 (C-a), 142.7 (C-d), 111.6 (C-b), 110.8 (C-c), 55.8 (C-1), 51.5 (C-3), 48.9 (C-7), 28.6 (C-4), 22.5 (C-8), 21.7 (C-6), 11.2 (C-9).

**HRMS:** Calculated for [M-CONH*t*-Bu] C<sub>10</sub>H<sub>14</sub>NO<sub>2</sub><sup>+</sup>: 180.1019, Found: 180.1022.

**I.R.** (thin film): ν 3425, 2970, 2934, 2877, 1687, 1627, 1517, 1419, 1223 and 1015 cm<sup>-1</sup>.

## II-53

### N-(*tert*-butyl)-2-(N-propylacetamido)-2-(pyridin-2-yl)acetamide



Mol. Wt.: 291.195 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-A**, using pyridine-2-carboxaldehyde (0.1 ml, 1.0 mmol), propylamine (0.08 ml, 1.0 mmol), acetic acid (0.06 ml, 1.0 mmol) and *tert*-butyl isocyanide (0.11 ml, 1.0 mmol). Purification by flash chromatography using pure EtOAc gave the desired product in 84 % isolated yield (244 mg, 0.84 mmol).

**Nature:** Yellow solid.

**M.P.** = 129-131 °C.

**R<sub>f</sub>** (pure EtOAc) = 0.33.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 8.60 (d, *J* = 4.4 Hz, 1H, H-e), 7.72 (td, *J* = 8.0, 1.6 Hz, 1H, H-c), 7.47 (d, *J* = 8.0 Hz, 1H, H-b), 7.37 (br s, 1H, NH), 7.26 (dd, *J* = 7.2, 5.2 Hz, 1H, H-d), 5.65 (s, 1H, H-1), 3.43 (t, *J* = 8.2 Hz, 2H, H-7), 2.24 (s, 3H, H-6), 1.65-1.56 (m, 1H, H-8), 1.40-1.33 (m, 10H, H-4,8), 0.84 (t, *J* = 7.4 Hz, 3H, H-9).

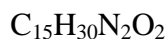
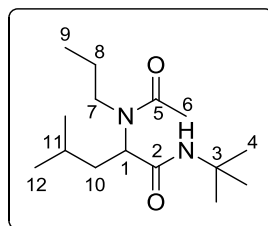
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.4 (C-5), 167.7 (C-2), 156.6 (C-a), 148.7 (C-e), 137.0 (C-c), 123.6 (C-b), 122.6 (C-d), 66.7 (C-1), 51.3 (C-3), 51.2 (C-7), 28.7 (C-9), 22.8 (C-8), 21.9 (C-6), 11.3 (C-9).

**HRMS:** Calculated for C<sub>16</sub>H<sub>25</sub>N<sub>3</sub>O<sub>2</sub>: 291.1947, Found: 291.1954.

**I.R.** (thin film): ν 3427, 3061, 2969, 2934, 2877, 1655, 1592, 1573, 1550, 1516, 1253, 1224, 1140, 1036 cm<sup>-1</sup>.

**II-54**

**N-(*tert*-butyl)-4-methyl-2-(N-propylacetamido)pentanamide**



Mol. Wt.: 270.231 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-A**, using 3-methylbutanal (0.11 ml, 1.0 mmol), propylamine (0.08 ml, 1.0 mmol), acetic acid (0.06 ml, 1.0 mmol) and *tert*-butyl isocyanide (0.11 ml, 1.0 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 10 : 90) gave the desired product in 73 % isolated yield (197 mg, 0.73 mmol).

**Nature:** Colorless oil.

**R<sub>f</sub>:** (Et<sub>2</sub>O : DCM = 1 : 9) = 0.28.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 6.37 (br s, 1H, NH), 4.78 (t, *J* = 7.6 Hz, 1H, H-1), 3.16-3.08 (m, 2H, H-7), 2.08 (s, 3H, H-6), 1.72-1.65 (m, 1H, H-10), 1.61-1.55 (m, 1H, H-10), 1.51-1.38 (m, 3H, H-11,12), 1.23 (s, 9H, H-4), 0.83 (2d, *J* = 6.4, 6.8 Hz, 1t, *J* = 7.6 Hz, 9H, H-12,9).

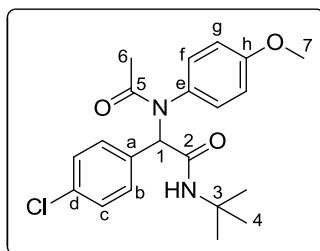
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 172.1 (C-5), 170.8 (C-2), 55.6 (C-1), 50.9 (C-3), 47.4 (C-7), 36.6 (C-10), 28.6 (C-4), 24.9 (C-11), 22.9 (C-8), 22.4 (C-12), 21.9 (C-6), 11.5 (C-9).

**HRMS:** Calculated for C<sub>15</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub>: 270.2307, Found: 270.1915.

**I.R.** (thin film): ν 3425, 2965, 2935, 2874, 1679, 1620, 1530, 1455, 1367, 1253, 1129 and 1024 cm<sup>-1</sup>.

## II-55

### N-(tert-butyl)-2-(4-chlorophenyl)-2-(N-(4-methoxyphenyl)acetamido)acetamide



Mol. Wt.: 388.155 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-A**, using 4-chlorobenzaldehyde (141 mg, 1.0 mmol), 4-methoxyaniline (0.12 ml, 1.0 mmol), acetic acid (0.06 ml, 1.0 mmol) and *tert*-butyl isocyanide (0.11 ml, 1.0 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : PE = 80 : 20) gave the desired product in 95 % isolated yield (371 mg, 0.95 mmol).

**Nature:** White solid.

**M.P.** = 214-216 °C.

**R<sub>f</sub>** (EtOAc : PE = 4 : 6) = 0.29.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.19 (d, *J* = 8.4 Hz, 2H, H-c), 7.10 (d, *J* = 8.5 Hz, 2H, H-b), 6.75 (br s, 4H, H-f,g), 6.00 (s, 1H, H-1), 5.75 (br s, 1H, NH), 3.80 (s, 3H, H-7), 1.89 (s, 3H, H-6), 1.38 (s, 9H, H-4).

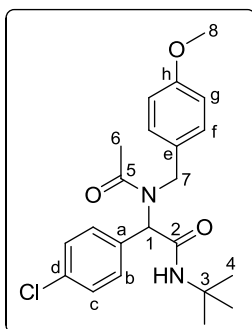
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.8 (C-5), 168.7 (C-2), 159.1 (C-h), 134.3 (C-a), 133.4 (C-d), 132.9 (C-e), 131.8 (C-b), 131.3 (C-c), 128.5 (C-f), 114.1 (C-g), 64.0 (C-1), 55.4 (C-7), 51.6 (C-3), 28.7 (C-4), 23.2 (C-6).

**HRMS:** Calculated for C<sub>21</sub>H<sub>25</sub>ClN<sub>2</sub>O<sub>3</sub>: 388.1554, Found: 388.1543.

**I.R.** (thin film): ν 3427, 3043, 2968, 2936, 2872, 2840, 1661, 1597, 1511, 1248, 1169, 1093, 1017 cm<sup>-1</sup>.

## II-56

### N-(tert-butyl)-2-(4-chlorophenyl)-2-(N-(4-methoxybenzyl)acetamido)acetamide



Mol. Wt.: 402.171 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-A**, using 4-chlorobenzaldehyde (141 mg, 1.0 mmol), 4-methoxybenzylamine (0.13 ml, 1.0 mmol), acetic acid (0.06 ml, 1.0 mmol) and *tert*-butyl isocyanide (0.11 ml, 1.0 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : PE = 70 : 30) gave the desired product in 95 % isolated yield (384 mg, 0.95 mmol).

**Nature:** White solid.

**M.P.** = 124-126 °C.

**R<sub>f</sub>**: (EtOAc : PE = 4 : 6) = 0.26.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.30 (d, *J* = 9.2 Hz, 2H, H-b), 7.24 (d, *J* = 8.4 Hz, 2H, H-c), 6.89 (d, *J* = 8.4 Hz, 2H, H-f), 6.75 (d, *J* = 8.4 Hz, 2H, H-g), 5.90 (m, 2H, NH, H-1), 4.61 (d, AB system, *J*<sub>ab</sub> = 17.6 Hz, 1H, H-7), 4.52 (d, AB system, *J*<sub>ab</sub> = 17.2 Hz, 1H, H-7), 3.78 (s, 3H, H-8), 2.12 (s, 3H, H-6), 1.35 (s, 9H, H-4).

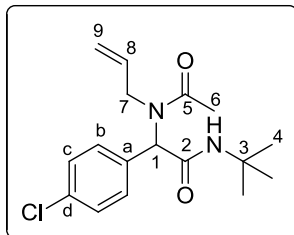
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 172.6 (C-5), 168.7 (C-2), 158.6 (C-h), 134.3 (C-a), 134.1 (C-d), 130.9 (C-c), 129.4 (C-e), 128.8 (C-f), 127.3 (C-b), 113.9 (C-g), 61.9 (C-1), 55.3 (C-8), 51.7 (C-3), 50.2 (C-7), 28.6 (C-4), 22.6 (C-6).

**HRMS:** Calculated for [M-CON*t*-Bu] C<sub>17</sub>H<sub>18</sub>ClNO<sub>2</sub>: 303.1026, Found: 303.1024.

**I.R.** (thin film): ν 3426, 2968, 2936, 2873, 2839, 1684, 1645, 1513, 1409, 1248, 1176, 1094, 1035 cm<sup>-1</sup>.

**II-57**

**2-(N-allylacetamido)-N-(*tert*-butyl)-2-(4-chlorophenyl)acetamide**



Mol. Wt.: 322.145 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-A**, using 4-chlorobenzaldehyde (141 mg, 1.0 mmol), allylamine (0.075 ml, 1.0mmol), acetic acid (0.06 ml, 1.0 mmol) and *tert*-butyl isocyanide (0.11 ml, 1.0mmol). Purification by flash chromatography using (Et<sub>2</sub>O : PE = 70 : 30) gave the desired product in 70 % isolated yield (226 mg, 0.7 mmol).

**Nature:** White solid.

**M.P.** = 140-142 °C.

**R<sub>f</sub>**: (Et<sub>2</sub>O : PE = 7 : 3) = 0.43.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 7.36 (br s, 4H, H-b,c), 6.05 (s, 1H, H-1), 5.81 (br s, 1H, NH), 5.50-5.41 (m, 1H, H-8), 5.02-4.96 (m, 2H, H-9), 4.02 (2dd, ABX system,  $J_{ab} = 17.8$ ,  $J_{ax} = 5.2$ ,  $J_{bx} = 4.8$  Hz, 2H, H-7), 2.18 (s, 3H, H-6), 1.38 (s, 9H, H-4).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz):  $\delta$  (ppm) 172.2 (C-5), 168.7 (C-2), 134.4 (C-a), 134.3 (C-d), 134.1 (C-8), 130.9 (C-c), 128.9 (C-b), 116.6 (C-9), 60.6 (C-1), 51.7 (C-3), 49.2 (C-7), 28.6 (C-4), 22.2 (C-6).

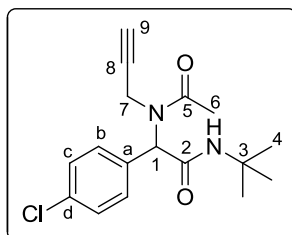
**HRMS:** Calculated for C<sub>17</sub>H<sub>23</sub>ClN<sub>2</sub>O<sub>3</sub>: 322.1448, Found: 322.1456.

**I.R.** (thin film):  $\nu$  3426, 3086, 2970, 2935, 2873, 1655, 1598, 1515, 1409, 1254, 1193, 1092 cm<sup>-1</sup>.



## II-58

### N-(*tert*-butyl)-2-(4-chlorophenyl)-2-(N-(prop-2-yn-1-yl)acetamido)acetamide



Mol. Wt.: 320.129 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-A**, using 4-chlorobenzaldehyde (141 mg, 1.0 mmol), propargylamine (0.07 ml, 1.0 mmol), acetic acid (0.06 ml, 1.0 mmol) and *tert*-butyl isocyanide (0.11 ml, 1.0 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : PE = 70 : 30) gave the desired product in 90 % isolated yield (289 mg, 0.9 mmol).

**Nature:** Yellow solid.

**M.P.** = 157-159 °C.

**R<sub>f</sub>**: (Et<sub>2</sub>O : PE = 7 : 3) = 0.31.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.26 (s, 4H, H-b,c), 6.06 (s, 1H, H-1), 5.72 (br s, 1H, NH), 4.10 – 3.96 (m, 2H, H-7), 2.23 (s, 3H, H-6), 1.96 (s, 1H, H-9), 1.29 (s, 9H, H-4).

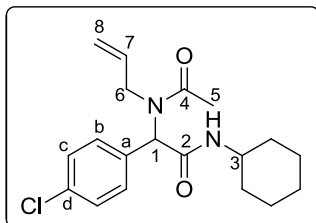
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.9 (C-5), 168.5 (C-2), 134.5 (C-a), 133.6 (C-d), 130.8 (C-c), 129.0 (C-b), 79.3 (C-8), 71.9 (C-9), 59.7 (C-1), 51.9 (C-3), 35.9 (C-7), 28.6 (C-4), 22.1 (C-6).

**HRMS:** Calculated for C<sub>17</sub>H<sub>21</sub>ClN<sub>2</sub>O<sub>2</sub>: 320.1292, Found: 320.1279.

**I.R.** (thin film): ν 3424, 3004, 2969, 1681, 1651, 1517, 1455, 1367, 1252, 1193 and 1016 cm<sup>-1</sup>.

## II-59

### 2-(N-allylacetamido)-2-(4-chlorophenyl)-N-cyclohexylacetamide



Mol. Wt.: 348.161 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-A**, using 4-chlorobenzaldehyde (141 mg, 1.0 mmol), allylamine (0.075 ml, 1.0 mmol), acetic acid (0.06 ml, 1.0 mmol) and cyclohexylisocyanide (109 mg, 1.0 mmol). Purification by flash chromatography using gradient (Et<sub>2</sub>O : DCM = 7 : 93 – 30 : 70) gave the desired product in 97 % isolated yield (340 mg, 0.97 mmol).

**Nature:** White solid.

**M.P.** = 174-176 °C.

**R<sub>f</sub>** (EtOAc : PE = 4 : 6) = 0.23.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.25 (br s, 4H, H-b,c), 5.96 (s, 1H, H-1), 5.82 (br s, 1H, NH), 5.39 (ddt, *J* = 17.6, 10.3, 5.3 Hz, 1H, H-7), 4.94-4.90 (m, 2H, H-8), 3.96-3.85 (m, 2H, H-6), 3.76-3.66 (m, 1H, H-3), 2.08 (s, 3H, H-5), 1.84-1.81 (m, 2H, H-Cy), 1.63-1.50 (m, 3H, H-Cy), 1.32-1.22 (m, 2H, H-Cy), 1.11- 0.97 (m, 3H, H-Cy).

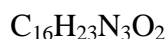
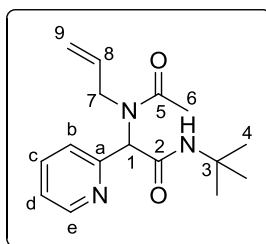
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 172.3 (C-4), 168.3 (C-2), 134.4 (C-a), 134.1 (C-d), 133.9 (C-7), 130.9 (C-c), 128.9 (C-b), 116.7 (C-8), 60.4 (C-1), 49.4 (C-6), 48.6 (C-3), 32.8 (C-Cy), 25.5 (C-Cy), 24.8 (C-Cy), 24.8 (C-Cy), 22.2 (C-5).

**HRMS:** Calculated for C<sub>19</sub>H<sub>25</sub>ClN<sub>2</sub>O<sub>2</sub>: 348.1605, Found: 348.1614.

**I.R.** (thin film): ν 3424, 3086, 2936, 2857, 1711, 1676, 1640, 1513, 1409, 1258 and 1094 cm<sup>-1</sup>.

**II-60**

**2-(N-allylacetamido)-N-(tert-butyl)-2-(pyridin-2-yl)acetamide**



Mol. Wt.: 289.179 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-A**, using pyridine-2-carboxaldehyde (0.1 ml, 1.0 mmol), allylamine (0.075 ml, 1.0 mmol), acetic acid (0.06 ml, 1.0 mmol) and *tert*-butyl isocyanide (0.11 ml, 1.0 mmol). Purification by flash chromatography using pure EtOAc gave the desired product in 97 % isolated yield (281 mg, 0.97 mmol).

**Nature:** Yellow solid.

**M.P.** = 79-81 °C.

**R<sub>f</sub>**: (pure EtOAc) = 0.3.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 8.48 (d, *J* = 4.2 Hz, 1H, H-e), 7.61 (t, *J* = 7.7 Hz, 1H, H-c), 7.35 (d, *J* = 7.9 Hz, 1H, H-b), 7.16 (dd, *J* = 7.2, 5.1 Hz, 1H, H-d), 6.94 (br s, 1H, NH), 5.95 (s, 1H, H-1), 5.50 (ddd, *J* = 22.4, 10.5, 5.4 Hz, 1H, H-8), 4.92 (2d, *J*<sub>trans-1,3</sub> = 12.4, *J*<sub>cis-1,3</sub> = 5.2 Hz, 2H, H-9), 4.04 (d, *J* = 5.3 Hz, 2H, H-7), 2.10 (s, 3H, H-6), 1.29 (s, 9H, H-4).

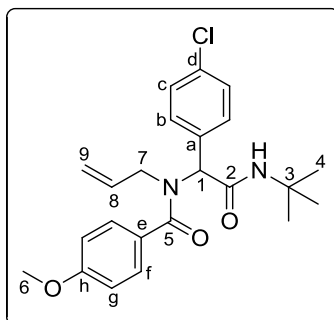
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 172.1 (C-5), 167.6 (C-2), 156.3 (C-a), 148.9 (C-e), 137.0 (C-c), 134.1 (C-8), 124.3 (C-b), 122.8 (C-d), 116.6 (C-9), 63.1 (C-1), 51.5 (C-3), 50.5 (C-7), 28.7 (C-4), 22.1 (C-6).

**HRMS:** Calculated for C<sub>16</sub>H<sub>23</sub>N<sub>3</sub>O<sub>2</sub>: 289.1790, Found: 289.1783.

**I.R.** (thin film): ν 3427, 3062, 2970, 2933, 2874, 1649, 1592, 1469, 1259, 1224 and 1053 cm<sup>-1</sup>.

## II-61

### N-(2-(*tert*-butylamino)-1-(4-chlorophenyl)-2-oxoethyl)-4-methoxy-N-propylbenzamide



Mol. Wt.: 416.187 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-A**, using 4-chlorobenzaldehyde (141 mg, 1.0 mmol), allylamine (0.075 ml, 1.0 mmol), 4-methoxybenzoic acid (152 mg, 1.0 mmol) and *tert*-butyl isocyanide (0.11 ml, 1.0 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 5 : 95) gave the desired product in 70 % isolated yield (292 mg, 0.7 mmol).

**Nature:** White solid.

**M.P.** = 138-140 °C.

**R<sub>f</sub>**: (EtOAc : PE = 4 : 6) = 0.43.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.39 (d, *J* = 8.4 Hz, 2H, H-f), 7.34-7.25 (m, 4H, H-b,c), 6.82 (d, *J* = 8.5 Hz, 2H, H-g), 5.93 (br s, 1H, NH), 5.50 (br s, 1H, H-8), 5.43 (s, 1H, H-1), 4.93-4.87 (m, 2H, H-9), 3.89 (2dd, ABX system, *J*<sub>ab</sub> = 16.8, *J*<sub>ax</sub> = *J*<sub>bx</sub> = 5.6 Hz, 2H, H-7), 3.75 (s, 3H, H-6), 1.29 (s, 9H, H-4).

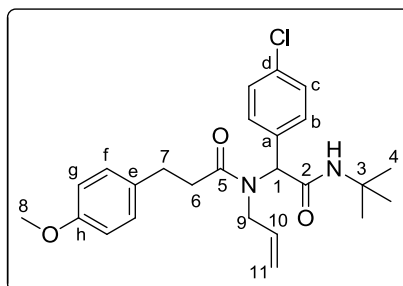
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 172.9 (C-5), 168.4 (C-2), 161.1 (C-h), 134.3 (C-a), 134.3 (C-d), 133.8 (C-8), 130.7 (C-f), 128.9 (C-b,c), 128.0 (C-e), 117.6 (C-9), 113.8 (C-g), 64.3 (C-1), 55.4 (C-6), 51.7 (C-7), 28.7 (C-4).

**HRMS:** Calculated for C<sub>23</sub>H<sub>27</sub>ClN<sub>2</sub>O<sub>3</sub>:414.1710, Found: 414.1701.

**I.R.** (thin film): ν 3426, 3084, 2968, 2936, 2841, 1681, 1621, 1576, 1513, 1252, 1175 and 1033 cm<sup>-1</sup>.

**II-62**

**N-allyl-N-(2-(*tert*-butylamino)-1-(4-chlorophenyl)-2-oxoethyl)-3-(4-methoxyphenyl)propanamide**



Mol. Wt.: 416.187 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-A**, using 4-chlorobenzaldehyde (141 mg, 1.0 mmol), allylamine (0.075 ml, 1.0 mmol), (4-methoxybenzyl)acetic acid (180 mg, 1.0 mmol) and *tert*-butyl isocyanide (0.11 ml, 1.0 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 7 : 93) gave the desired product in 68 % isolated yield (302 mg, 0.68 mmol).

**Nature:** White solid.

**M.P.** =121-123°C.

**R<sub>f</sub>:** (Et<sub>2</sub>O : PE = 7 : 3) = 0.47.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.23 (d, *J* = 8.5 Hz, 2H, H-c), 7.18 (d, *J* = 8.6 Hz, 2H, H-b), 7.03 (d, *J* = 8.5 Hz, 2H, H-f), 6.74 (d, *J* = 8.6 Hz, 2H, H-g), 5.89 (s, 1H, H-1), 5.68 (br s, 1H, NH), 5.33 (ddd, *J* = 22.1, 10.3, 5.1 Hz, 1H, H-10), 4.88-4.80 (m, 2H, H-11), 3.84 (dd, ABX system, *J*<sub>ab</sub> = 17.6, *J*<sub>ax</sub> = 4.8, *J*<sub>bx</sub> = 5.2 Hz, 2H, H-9), 3.71 (s, 3H, H-8), 2.85 (td, ABX<sub>2</sub> system, *J* = 6.8, 3.2 Hz, 2H, H-7), 2.58 (td, ABX<sub>2</sub> system, *J* = 7.2, 2.4 Hz, 2H, H-6), 1.26 (s, 9H, H-4).

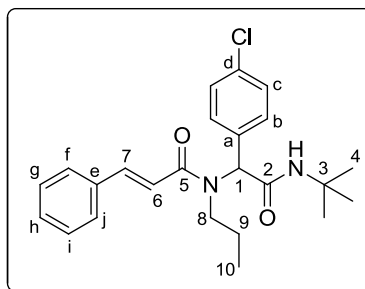
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 174.0 (C-5), 168.7 (C-2), 158.0 (C-h), 134.3 (C-a), 134.2 (C-10), 133.1 (C-e), 130.9 (C-c), 129.4 (C-f), 128.9 (C-b), 116.6 (C-11), 113.9 (C-g), 61.0 (C-1), 55.3 (C-8), 51.7 (C-3), 48.6 (C-9), 35.7 (C-6), 30.5 (C-7), 28.6 (C-4).

**HRMS:** Calculated for C<sub>25</sub>H<sub>31</sub>ClN<sub>2</sub>O<sub>3</sub>: 422.2023, Found: 442.2023.

**I.R.** (thin film): ν 3426, 3086, 3069, 2968, 2936, 2912, 2838, 1683, 1641, 1513, 1411, 1367, 1301, 1247, 1179 and 1094 cm<sup>-1</sup>.

## II-63

### N-(2-(*tert*-butylamino)-1-(4-chlorophenyl)-2-oxoethyl)-N-propylcinnamamide



Mol. Wt.: 412.192 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-A**, using 4-chlorobenzaldehyde (141 mg, 1.0 mmol), propylamine (0.08 ml, 1.0mmol), cinnamic acid (148 mg, 1.0 mmol) and *tert*-butyl isocyanide (0.11 ml, 1.0 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 4 : 96) gave the desired product in 85 % isolated yield (349 mg, 0.85 mmol).

**Nature:** White solid.

**M.P.** = 194-196 °C.

**R<sub>f</sub>:** (Et<sub>2</sub>O : DCM = 0.4 : 9.6) = 0.28.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.70 (d, *J* = 15.4 Hz, 1H, H-7), 7.45 (d, *J* = 5.4 Hz, 2H, H-Ar), 7.32-7.26 (m, 7H, H-Ar), 6.78 (d, *J* = 15.2 Hz, 1H, H-6), 5.97 (br s, 1H, NH), 5.90 (s, 1H, H-1), 3.43-3.30 (m, 2H, H-8), 1.54-1.45 (m, 1H, H-9), 1.29 (s, 9H, H-4), 1.14-1.02 (m, 1H, H-9), 0.70 (t, *J* = 7.4 Hz, 3H, H-10).

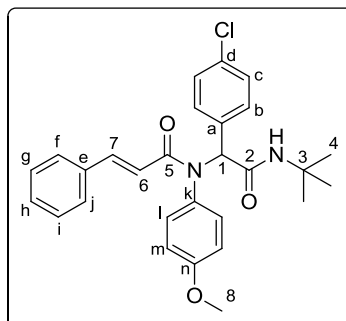
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 168.8 (C-2), 167.3 (C-5), 143.8 (C-7), 135.1 (C-Ar), 134.5 (C-Ar), 134.2 (C-Ar), 130.5 (C-Ar), 129.9 (C-Ar), 128.9 (C-Ar), 128.8 (C-Ar), 128.0 (C-Ar), 117.4 (C-6), 62.0 (C-1), 51.7 (C-3), 48.5 (C-8), 28.7 (C-4), 24.0 (C-9), 11.4 (C-10).

**HRMS:** Calculated for [M-CONHCMe<sub>3</sub>] C<sub>19</sub>H<sub>19</sub>ClNO: 312.1161, Found: 312.1156.

**I.R.** (thin film): ν 3426, 2969, 2933, 2877, 1684, 1646, 1598, 1513, 1493, 1453, 1418, 1367, 1220, 1128, 1094, 1016 and 977 cm<sup>-1</sup>.

## II-64

### N-(2-(*tert*-butylamino)-1-(4-chlorophenyl)-2-oxoethyl)-N-(4-methoxyphenyl)cinnamamide



Mol. Wt.: 476.187 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-A**, using 4-chlorobenzaldehyde (141 mg, 1.0 mmol), 4-methoxyaniline (0.12 ml, 1.0 mmol), cinnamic acid (148 mg, 1.0 mmol) and *tert*-butyl isocyanide (0.11 ml, 1.0 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 2 : 98) gave the desired product in 83 % isolated yield (393 mg, 0.83 mmol).

**Nature:** White solid.

**M.P.** = 156-158 °C.

**R<sub>f</sub>**: (Et<sub>2</sub>O : DCM = 0.2 : 9.8) = 0.28.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.71 (d, *J* = 15.6 Hz, 1H, H-7), 7.30 (s, 5H, H-f,g,h,i,j), 7.22 (d, *J* = 8.7 Hz, 2H, H-c), 7.18 (d, *J* = 8.7 Hz, 2H, H-b), 6.79 (br s, 4H, H-l,m), 6.27 (d, *J* = 15.6 Hz, 1H, H-6), 6.17 (s, 1H, H-1), 6.12 (br s, 1H, NH), 3.82 (s, 3H, H-8), 1.40 (s, 9H, H-4).

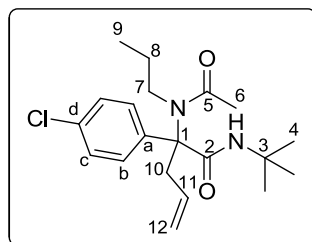
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 168.7 (C-5), 167.0 (C-2), 159.1 (C-n), 142.7 (C-7), 135.1 (C-e), 134.3 (C-a), 133.5 (C-d), 131.9 (C-Ar), 131.7 (C-Ar), 129.7 (C-k), 128.7 (C-c), 128.5 (C-Ar), 127.9 (C-b), 118.7 (C-6), 114.1 (C-Ar), 64.6 (C-1), 55.4 (C-8), 51.6 (C-3), 28.7 (C-4).

**HRMS:** Calculated for [M-CONHMe<sub>3</sub>] C<sub>23</sub>H<sub>20</sub>ClNO<sub>2</sub>: 377.1178, Found: 377.1167.

**I.R.** (thin film): ν 3310, 2968, 2928, 2901, 1655, 1614, 1543, 1508, 1449, 1355, 1234, 1185, 1033 and 761 cm<sup>-1</sup>.

## II-41

### N-(*tert*-butyl)-2-(4-chlorophenyl)-2-(*N*-propylacetamido)pent-4-enamide



Mol. Wt.: 364.192 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-B**, using Ugi product **II-40** (163 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol), allylacetate (0.08 ml, 0.75 mmol), Pd(dba)<sub>2</sub> (14 mg, 0.025 mmol) and PPh<sub>3</sub> (13 mg, 0.05 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 10 : 90) gave the desired product in 96 % isolated yield (175 mg, 0.48 mmol).

**Nature:** Yellow oil.

**R<sub>f</sub>:** (Et<sub>2</sub>O : PE = 6 : 4) = 0.43.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.25 (br s, 1H, NH), 7.17 (d, *J* = 8.8 Hz, 2H, H-c), 7.04 (d, *J* = 8.0 Hz, 2H, H-b), 5.48 (ddt, *J* = 10.3, 7.2, 6.5 Hz, 1H, H-11), 4.85 (2dd, *J*<sub>1,2</sub> = 1.2, *J*<sub>cis-1,3</sub> = 9.2, *J*<sub>trans-1,3</sub> = 16.8 Hz, 2H, H-12), 3.38-3.30 (m, 2H, H-7), 2.95 (dd, ABX system, *J*<sub>ab</sub> = 14.6, *J*<sub>ax</sub> = 6.2 Hz, 1H, H-10), 2.78 (dd, ABX system, *J*<sub>ba</sub> = 14.6, *J*<sub>bx</sub> = 7.4 Hz, 1H, H-10), 2.12 (s, 3H, H-6), 1.76-1.67 (m, 1H, H-8), 1.52-1.43 (m, 1H, H-8), 1.24 (s, 9H, H-4), 0.79 (t, *J* = 7.4 Hz, 3H, H-9).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 173.0 (C-5), 171.2 (C-2), 139.2 (C-a), 133.5 (C-11), 132.5 (C-d), 127.9 (C-c), 127.8 (C-b), 118.9 (C-12), 71.2 (C-1), 51.2 (C-3), 48.8 (C-7), 42.7 (C-10), 28.4 (C-4), 24.3 (C-6), 23.5 (C-8), 11.4 (C-9).

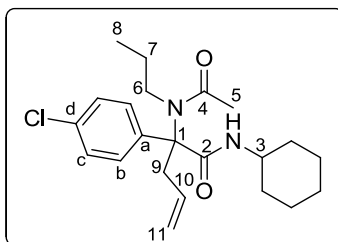
**HRMS:** Calculated for C<sub>20</sub>H<sub>29</sub>ClN<sub>2</sub>O<sub>2</sub>: 364.1918, Found: 364.1911.

**I.R.** (thin film): ν 3428, 3080, 2969, 2934, 2877, 1670, 1631, 1547, 1404, 1367, 1097 and 1014 cm<sup>-1</sup>.



## II-65

### 2-(4-chlorophenyl)-N-cyclohexyl-2-(N-propylacetamido)pent-4-enamide



Mol. Wt.: 390.207 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-B**, using Ugi product **II-46** (175 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol), allylacetate (0.08 ml, 0.75 mmol), Pd(dba)<sub>2</sub> (14 mg, 0.025 mmol) and PPh<sub>3</sub> (13 mg, 0.05 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 15 : 85) gave the desired product in 81 % isolated yield (159 mg, 0.41 mmol).

**Nature:** Yellow oil.

**R<sub>f</sub>:** (Et<sub>2</sub>O : PE = 7 : 3) = 0.33.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.17 (d, *J* = 8.7 Hz, 2H, H-c, NH), 7.06 (d, *J* = 8.2 Hz, 2H, H-b), 5.48 (ddt, *J* = 10.5, 7.2, 6.5 Hz, 1H, H-10), 4.91 – 4.82 (m, 2H, H-11), 3.77-3.68 (m, 1H, H-3), 3.39-3.29 (m, 2H, H-6), 3.02 (dd, ABX system, *J*<sub>ab</sub> = 14.5, *J*<sub>ax</sub> = 6.3 Hz, 1H, H-9), 2.79 (dd, ABX system, *J*<sub>ba</sub> = 14.5, *J*<sub>bx</sub> = 7.4 Hz, 1H, H-9), 2.11 (s, 3H, H-5), 1.85 – 1.65 (m, 3H, H-Cy, H-4), 1.65-1.45 (m, 4H, H-Cy, H-4), 1.32-1.22 (m, 2H, H-Cy), 1.15 – 0.97 (m, 3H, H-Cy), 0.78 (t, *J* = 7.4 Hz, 3H, H-8).

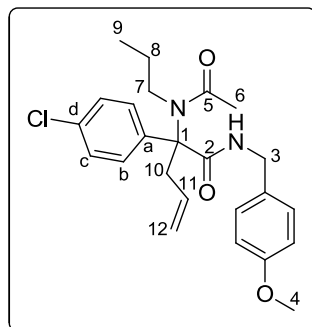
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 173.1 (C-4), 171.3 (C-2), 139.0 (C-a), 133.4 (C-10), 132.6 (C-d), 128.0 (C-c), 127.9 (C-b), 119.0 (C-11), 70.8 (C-1), 48.8 (C-6), 48.3 (C-3), 42.6 (C-9), 32.5 (C-Cy), 32.4 (C-Cy), 25.8 (C-Cy), 24.6 (C-Cy), 24.3 (C-5), 23.5 (C-7), 11.4 (C-8).

**HRMS:** Calculated for C<sub>22</sub>H<sub>31</sub>ClN<sub>2</sub>O<sub>2</sub>: 390.2074, Found: 390.2088.

**I.R.** (thin film): ν 3428, 3081, 2934, 2877, 2857, 1650, 1538, 1352, 1245, 1153, 1098, 1014 cm<sup>-1</sup>.

## II-66

### 2-(4-chlorophenyl)-N-(4-methoxybenzyl)-2-(N-propylacetamido)pent-4-enamide



Mol. Wt.: 428.187 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-B**, using Ugi product **II-47** (194 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol), allylacetate (0.08 ml, 0.75 mmol), Pd(dba)<sub>2</sub> (14 mg, 0.025 mmol) and PPh<sub>3</sub> (13 mg, 0.05 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : PE = 70 : 30) gave the desired product in 55% isolated yield (108 mg, 0.276 mmol).

**Nature:** Yellow oil. **R<sub>f</sub>**: (Et<sub>2</sub>O : PE = 8 : 2) = 0.35.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.39 (br s, 1H, NH), 7.15 (d, *J* = 8.8 Hz, 2H, H-c), 7.09 (d, *J* = 8.7 Hz, 2H, H-b), 7.05 (d, *J* = 8.6 Hz, 2H, H-f), 6.76 (d, *J* = 8.7 Hz, 2H, H-g), 5.48 (dddd, *J* = 16.9, 10.9, 7.4, 6.3 Hz, 1H, H-11), 4.92 – 4.83 (m, 2H, H-12), 4.29 (dd, ABX system, *J<sub>ab</sub>* = 5.7, *J<sub>ax</sub>* = *J<sub>bx</sub>* = 1.2 Hz, 2H, H-3), 3.72 (s, 3H, H-4), 3.33-3.19 (m, 2H, H-7), 3.04 (dd, ABX system, *J<sub>ab</sub>* = 14.6, *J<sub>ax</sub>* = 6.2 Hz, 1H, H-10), 2.84 (dd, ABX system, *J<sub>ba</sub>* = 14.5, *J<sub>bx</sub>* = 7.4 Hz, 1H, H-10), 2.09 (s, 3H, H-6), 1.64-1.55 (m, 1H, H-8), 1.41-1.31 (m, 1H, H-8), 0.72 (t, *J* = 7.4 Hz, 3H, H-9).

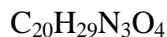
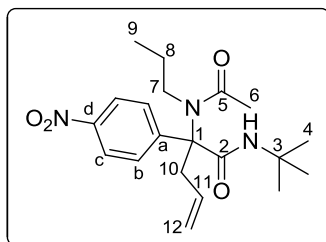
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 173.1 (C-5), 172.1 (C-2), 158.8 (C-h), 138.6 (C-a), 133.3 (C-11), 132.8 (C-d), 130.4 (C-e), 129.2 (C-f), 128.2 (C-c), 128.0 (C-b), 119.1 (C-12), 113.9 (C-g), 70.8 (C-1), 55.3 (C-4), 48.9 (C-7), 43.4 (C-3), 42.4 (C-10), 24.1 (C-6), 23.6 (C-8), 11.3 (C-9).

**HRMS:** Calculated for C<sub>24</sub>H<sub>29</sub>ClN<sub>2</sub>O<sub>3</sub>: 428.1867, Found: 428.1859.

**I.R.** (thin film): ν 3438, 3081, 2963, 2935, 2877, 2839, 1667, 1636, 1514, 1404, 1248, 1176, 1097, 1035, 1015 cm<sup>-1</sup>.

**II-67**

**N-(*tert*-butyl)-2-(4-nitrophenyl)-2-(N-propylacetamido)pent-4-enamide**



Mol. Wt.: 375.216 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-B**, using Ugi product **II-48** (168 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol), allylacetate (0.08 ml, 0.75 mmol), Pd(dba)<sub>2</sub> (14 mg, 0.025 mmol) and PPh<sub>3</sub> (13 mg, 0.05 mmol). Purification by flash chromatography using (EtOAc : PE = 20 : 80) gave the desired product in 75 % isolated yield (140 mg, 0.37 mmol).

**Nature:** Yellow oil.

**R<sub>f</sub>:** (Et<sub>2</sub>O : PE = 7 : 3) = 0.43.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 8.05 (d, *J* = 8.8 Hz, 2H, H-c), 7.63 (br s, 1H, NH), 7.15 (d, *J* = 8.4 Hz, 2H, H-b), 5.45 (ddt, *J* = 16.8, 10.2, 6.9 Hz, 1H, H-11), 4.82 (d, *J* = 10.0 Hz, 1H, H-12), 4.68 (d, *J* = 16.8 Hz, 1H, H-12), 3.49-3.43 (m, 2H, H-7), 2.93 (dd, ABX system, *J<sub>ab</sub>* = 14.4, *J<sub>ax</sub>* = 6.2 Hz, 1H, H-10), 2.68 (dd, ABX system, *J<sub>ba</sub>* = 14.4, *J<sub>bx</sub>* = 7.7 Hz, 1H, H-10), 2.16 (s, 3H, H-6), 1.85-1.76 (m, 1H, H-8), 1.55-1.46 (m, 1H, H-8), 1.26 (s, 9H, H-4), 0.87 (t, *J* = 7.4 Hz, 3H, H-).

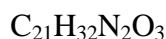
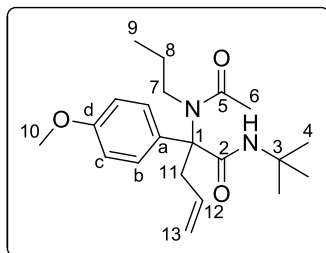
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 173.6 (C-5), 170.7 (C-2), 148.8 (C-d), 146.2 (C-11), 132.4 (C-a), 126.6 (C-b), 122.8 (C-c), 119.7 (C-12), 71.3 (C-1), 51.3 (C-3), 48.8 (C-7), 42.9 (C-10), 28.4 (C-4), 24.4 (C-6), 23.4 (C-8), 11.5 (C-9).

**HRMS:** Calculated for C<sub>20</sub>H<sub>29</sub>N<sub>3</sub>O<sub>4</sub>: 375.2158, Found: 375.2173.

**I.R.** (thin film): ν 3288, 3082, 2968, 2934, 2877, 1673, 1630, 1605, 1520, 1399, 1350, 1244 cm<sup>-1</sup>.

## II-68

### N-(*tert*-butyl)-2-(4-methoxyphenyl)-2-(*N*-propylacetamido)pent-4-enamide



Mol. Wt.: 360.241 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-B**, using Ugi product **II-49** (160 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol), allylacetate (0.08 ml, 0.75 mmol), Pd(dba)<sub>2</sub> (14 mg, 0.025 mmol) and PPh<sub>3</sub> (13 mg, 0.05 mmol). Purification by flash chromatography using (EtOAc : PE = 40 : 60) gave the desired product in 70 % isolated yield (127 mg, 0.35 mmol).

**Nature:** Yellow oil.

**R<sub>f</sub>:** (Et<sub>2</sub>O : PE = 7 : 3) = 0.3.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 7.16 (d,  $J$  = 8.4 Hz, 2H, H-b), 6.76 (d,  $J$  = 8.8 Hz, 3H, H-c, NH), 5.57 (ddt,  $J$  = 17.0, 10.2, 6.8 Hz, 1H, H-12), 4.95 (2d,  $J_{cis-1,3}$  = 10.4,  $J_{trans-1,3}$  = 17.2 Hz, 2H, H-13), 3.73 (s, 3H, H-10), 3.19 (dd,  $J$  = 10.1, 5.6 Hz, 2H, H-7), 3.10 (dd, ABX system,  $J_{ab}$  = 14.8,  $J_{ax}$  = 6.3 Hz, 1H, H-11), 2.92 (dd, ABX system,  $J_{ba}$  = 14.8,  $J_{bx}$  = 7.0 Hz, 1H, H-11), 2.10 (s, 3H, H-6), 1.64-1.57 (m, 1H, H-8), 1.51-1.40 (m, 1H, H-8), 1.24 (s, 9H, H-4), 0.71 (t,  $J$  = 7.3 Hz, 3H, H-9).

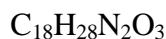
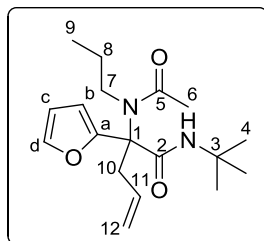
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz):  $\delta$  (ppm) 172.5 (C-5), 171.6 (C-2), 158.5 (C-d), 134.6 (C-12), 131.9 (C-a), 128.5 (C-b), 118.5 (C-13), 113.3 (C-c), 71.2 (C-1), 55.2 (C-10), 51.2 (C-3), 48.9 (C-7), 42.0 (C-11), 28.5 (C-4), 24.1 (C-6), 23.7 (C-8), 11.4 (C-9).

**HRMS:** Calculated for C<sub>21</sub>H<sub>32</sub>N<sub>2</sub>O<sub>3</sub>: 360.2413, Found: 360.2420.

**I.R.** (thin film):  $\nu$  3410, 3079, 2968, 2935, 2876, 2839, 1669, 1637, 1611, 1512, 1402, 1366, 1250, 1183, 1036 cm<sup>-1</sup>.

## II-71

### N-(*tert*-butyl)-2-(furan-2-yl)-2-(*N*-propylacetamido)pent-4-enamide



Mol. Wt.: 320.21 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-B**, using Ugi product **II-52** (140 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol), allylacetate (0.08 ml, 0.75 mmol), Pd(dba)<sub>2</sub> (14 mg, 0.025 mmol) and PPh<sub>3</sub> (13 mg, 0.05 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 10 : 90) gave the desired product in 77 % isolated yield (123 mg, 0.38 mmol).

**Nature:** Yellow oil.

**R<sub>f</sub>:** (Et<sub>2</sub>O : PE = 7 : 3) = 0.33.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.37 (dd, *J* = 1.8, 0.7 Hz, 1H, H-d), 6.43 (dd, *J* = 3.3, 0.6 Hz, 1H, H-c), 6.31 (dd, *J* = 3.3, 1.8 Hz, 1H, H-b), 5.97 (br s, 1H, NH), 5.74-5.64 (ddt, *J* = 17.2, 10.1, 7.1 Hz, 1H, H-11), 5.12 (dd, *J*<sub>trans-1,3</sub> = 17.1, *J*<sub>1,2</sub> = 1.8 Hz, 1H, H-12), 5.01 (dd, *J*<sub>cis-1,3</sub> = 10.0, *J*<sub>1,2</sub> = 1.6 Hz, 1H, H-12), 3.14 (dd, ABX system, *J*<sub>ab</sub> = 14.0, *J*<sub>ax</sub> = 6.8, *J*<sub>bx</sub> = 7.6 Hz, 2H, H-10), 3.02-2.94 (m, 1H, H-7), 2.81 (ddd, ABXY system, *J* = 16.4, 11.2, 5.6 Hz, 1H, H-7), 2.05 (s, 3H, H-6), 1.55-1.44 (m, 2H, H-8), 1.26 (s, 9H, H-4), 0.64 (t, *J* = 7.4 Hz, 3H, H-9).

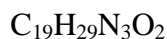
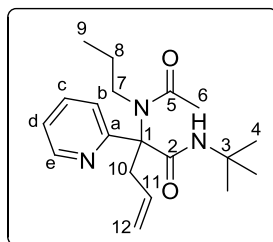
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.0 (C-5), 168.8 (C-2), 152.3 (C-a), 142.4 (C-d), 134.8 (C-11), 118.9 (C-12), 111.5 (C-c), 110.8 (C-b), 68.2 (C-1), 51.4 (C-3), 49.6 (C-7), 38.6 (C-10), 28.5 (C-4), 23.8 (C-8), 23.1 (C-6), 11.4 (C-9).

**HRMS:** Calculated for C<sub>18</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub>: 320.2100, Found: 320.2090.

**I.R.** (thin film): ν 3415, 3081, 2971, 2933, 2876, 1679, 1643, 1515, 1407, 1366, 1250, 1222, 1144, 1022 cm<sup>-1</sup>.

## II-72

### N-(*tert*-butyl)-2-(N-propylacetamido)-2-(pyridin-2-yl)pent-4-enamide



Mol. Wt.: 331.226 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-B**, using Ugi product **II-53** (146 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol), allylacetate (0.08 ml, 0.75 mmol), Pd(dba)<sub>2</sub> (14 mg, 0.025 mmol) and PPh<sub>3</sub> (13 mg, 0.05 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 20 : 80) gave the desired product in 92 % isolated yield (152 mg, 0.46 mmol).

**Nature:** Yellow oil.

**R<sub>f</sub>:** (Et<sub>2</sub>O : PE = 9 : 1) = 0.26.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 9.65 (br s, 1H, NH), 8.39 (d, *J* = 4.4 Hz, 1H, H-e), 7.55 (t, *J* = 7.5 Hz, 1H, H-c), 7.17 (d, *J* = 8.0 Hz, 1H, H-b), 7.05 (t, *J* = 5.6 Hz, 1H, H-d), 5.47-5.37 (ddt, *J* = 16.8, 10.8, 7.2 Hz, 1H, H-11), 4.89 – 4.79 (m, 2H, H-12), 3.55 – 3.40 (m, 2H, H-7), 2.96 (dd, ABX system, *J*<sub>ab</sub> = 14.0, *J*<sub>ax</sub> = 6.5 Hz, 1H, H-10), 2.70 (dd, ABX system, *J*<sub>ba</sub> = 13.9, *J*<sub>bx</sub> = 7.2 Hz, 1H, H-10), 2.09 (s, 3H, H-6), 1.94-1.85 (m, 1H, H-8), 1.77-1.68 (m, 1H, H-8), 1.30 (s, 9H, H-4), 0.86 (t, *J* = 7.4 Hz, 3H, H-9).

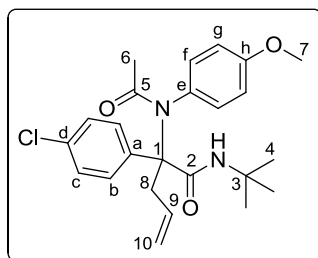
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.9 (C-5), 170.0 (C-2), 162.6 (C-a), 146.5 (C-e), 136.9 (C-c), 133.0 (C-11), 121.3 (C-d), 120.7 (C-b), 118.2 (C-12), 71.0 (C-1), 50.9 (C-3), 48.7 (C-7), 43.6 (C-10), 28.7 (C-4), 24.7 (C-8), 23.1 (C-6), 11.2 (C-9).

**HRMS:** Calculated for [M-CONHMe<sub>3</sub>] C<sub>14</sub>H<sub>19</sub>N<sub>2</sub>O: 231.1497, Found: 231.1494.

**I.R.** (thin film): ν 3401, 3061, 2970, 2933, 2876, 1667, 1651, 1574, 1431, 1405, 1365, 1247, 1224 and 1008 cm<sup>-1</sup>.

## II-74

### N-(*tert*-butyl)-2-(4-chlorophenyl)-2-(N-(4-methoxyphenyl)acetamido)pent-4-enamide



Mol. Wt.: 428.187 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-B**, using Ugi product **II-55** (151 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol), allylacetate (0.08 ml, 0.75 mmol), Pd(dba)<sub>2</sub> (14 mg, 0.025 mmol) and PPh<sub>3</sub> (13 mg, 0.05 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 5 : 95) gave the desired product in 60 % isolated yield (128 mg, 0.30 mmol).

**Nature:** Yellow oil.

**R<sub>f</sub>:** (Et<sub>2</sub>O : DCM = 5 : 95) = 0.43.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 7.37-7.31 (m, 4H, H-b,c), 7.27 (dd,  $J$  = 8.6, 2.6 Hz, 1H, H-f), 7.11 (dd,  $J$  = 8.7, 2.6 Hz, 1H, H-f), 7.02 (br s, 1H, NH), 6.96 (dd,  $J$  = 8.7, 2.9 Hz, 1H, H-g), 6.89 (dd,  $J$  = 8.7, 2.9 Hz, 1H, H-g), 5.44 (ddt,  $J$  = 17.2, 10.4, 6.4 Hz, 1H, H-9), 4.80 (dd,  $J_{cis-1,3}$  = 10.3,  $J_{1,2}$  = 1.4 Hz, 1H, H-10), 4.69 (dd,  $J_{trans-1,3}$  = 17.1,  $J_{1,2}$  = 1.4, 1H, H-10), 3.87 (s, 3H, H-7), 2.80 (dd, ABX system,  $J_{ab}$  = 13.9,  $J_{ax}$  = 6.2 Hz, 1H, H-8), 2.25 (dd, ABX system,  $J_{ba}$  = 13.9,  $J_{bx}$  = 7.6 Hz, 1H, H-8), 1.82 (s, 3H, H-6), 1.43 (s, 9H, H-4).

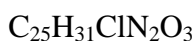
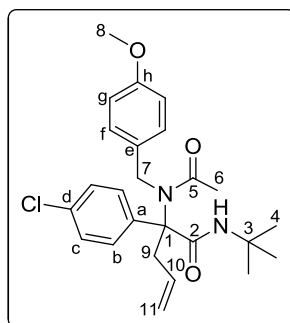
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz):  $\delta$  (ppm) 172.3 (C-5), 170.0 (C-2), 159.5 (C-h), 138.6 (C-a), 133.5 (C-9), 133.4 (C-d), 132.8 (C-e), 131.4 (C-f), 131.2 (C-f), 128.7 (C-c), 128.1 (C-b), 118.1 (C-10), 114.6 (C-g), 114.4 (C-g), 72.2 (C-1), 55.5 (C-7), 51.5 (C-3), 44.6 (C-8), 28.6 (C-4), 25.5 (C-6).

**HRMS:** Calculated for C<sub>24</sub>H<sub>29</sub>ClN<sub>2</sub>O<sub>3</sub>: 428.1867, Found: 428.1885.

**I.R.** (thin film):  $\nu$  3428, 3080, 3041, 2967, 2935, 2873, 2841, 1672, 1606, 1543, 1457, 1375, 1249, 1170, 1098, 1035, 1014 cm<sup>-1</sup>.

## II-75

### N-(*tert*-butyl)-2-(4-chlorophenyl)-2-(N-(4-methoxybenzyl)acetamido)pent-4-enamide



Mol. Wt.: 442.202 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-B**, using Ugi product **II-56** (202 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol), allylacetate (0.08 ml, 0.75 mmol), Pd(dba)<sub>2</sub> (14 mg, 0.025 mmol) and PPh<sub>3</sub> (13 mg, 0.05 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 10 : 90) gave the desired product in 56 % isolated yield (123 mg, 0.28 mmol).

**Nature:** Yellow oil.

**R<sub>f</sub>:** (Et<sub>2</sub>O : DCM = 1 : 9) = 0.32.

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, 400 MHz): δ (ppm) 7.44 (d, *J* = 8.8 Hz, 2H, H-c), 7.25 (d, *J* = 8.8 Hz, 4H, H-b,f), 6.91 (d, *J* = 8.7 Hz, 2H, H-g), 6.53 (br s, 1H, NH), 5.82-5.69 (m, 1H, H-10), 5.06 (dd, *J* = 11.3, 6.4 Hz, 2H, H-11), 4.61-4.41 (m, 2H, H-7), 3.80 (s, 3H, H-8), 2.22 (2 dd, ABX system, *J*<sub>ab</sub> = 14.4, *J*<sub>ax</sub> = 6.4 Hz, 1H, H-9), 2.15 (s, 3H, H-6), 1.31 (s, 9H, H-4).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, 100.6 MHz): δ (ppm) 175.7 (C-5), 172.2 (C-2), 160.4 (C-h), 138.5 (C-a), 135.1 (C-d), 134.9 (C-10), 131.2 (C-e), 131.0 (C-c), 129.1 (C-b), 128.5 (C-f), 119.9 (C-11), 115.2 (C-g), 73.3 (C-1), 55.8 (C-8), 52.7 (C-3), 51.4 (C-7), 41.4 (C-9), 28.8 (C-4), 24.0 (C-6).

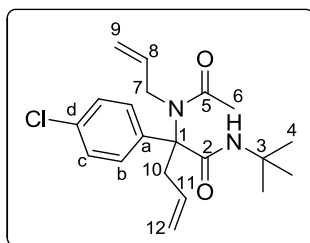
**HRMS:** Calculated for [M-CONHCMe<sub>3</sub>] C<sub>20</sub>H<sub>21</sub>ClNO<sub>2</sub>: 342.1261, Found: 342.1254.

**I.R.** (thin film): ν 3429, 3080, 3000, 2967, 2935, 2911, 2839, 1672, 1614, 1513, 1393, 1248, 1176, 1098, 1035, 1014 cm<sup>-1</sup>.



## II-76

### 2-(N-allylacetamido)-N-(*tert*-butyl)-2-(4-chlorophenyl)pent-4-enamide



Mol. Wt.: 362.176 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-B**, using Ugi product **II-57** (161 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol), allylacetate (0.08 ml, 0.75 mmol), Pd(dba)<sub>2</sub> (14 mg, 0.025 mmol) and PPh<sub>3</sub> (13 mg, 0.05 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 7 : 93) gave the desired product in 91 % isolated yield (166 mg, 0.46 mmol).

**Nature:** Yellow oil.

**R<sub>f</sub>** : (Et<sub>2</sub>O : DCM = 0.7 : 9.3) = 0.38.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.20 (br s, 4H, H-b,c), 6.48 (br s, 1H, NH), 5.82-5.73 (m, 1H, H-8), 5.56-5.46 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H, H-11), 5.29 (dd, *J*<sub>trans-1,3</sub> = 17.2, *J*<sub>1,2</sub> = 1.0 Hz, 1H, H-9), 5.18 (dd, *J*<sub>cis-1,3</sub> = 10.5, *J*<sub>1,2</sub> = 1.0 Hz, 1H, H-9), 5.01 – 4.91 (m, 2H, H-12), 3.94-3.83 (m, 2H, H-7), 3.15 (dd, ABX system, *J*<sub>ab</sub> = 14.6, *J*<sub>ax</sub> = 6.3 Hz, 1H, H-10), 2.90 (dd, ABX system, *J*<sub>ab</sub> = 14.6, *J*<sub>ax</sub> = 7.3 Hz, 1H, H-10), 2.08 (s, 3H, H-6), 1.24 (s, 9H, H-4).

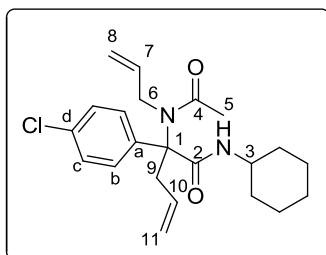
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 173.3 (C-5), 170.4 (C-2), 138.2 (C-a), 134.5 (C-8), 133.8 (C-11), 133.2 (C-d), 128.8 (C-c), 128.2 (C-b), 119.2 (C-12), 117.3 (C-9), 71.8 (C-1), 51.4 (C-3), 49.4 (C-7), 41.8 (C-10), 28.5 (C-4), 24.0 (C-6).

**HRMS:** Calculated for C<sub>20</sub>H<sub>27</sub>ClN<sub>2</sub>O<sub>2</sub>: 362.1761, Found: 362.1749.

**I.R.** (thin film): ν 3428, 3083, 2969, 2932, 2874, 1671, 1595, 1543, 1493, 1392, 1243, 1223, 1098, 1014 cm<sup>-1</sup>.

## II-78

### 2-(N-allylacetamido)-2-(4-chlorophenyl)-N-cyclohexylpent-4-enamide



Mol. Wt.: 388.192 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-B**, using Ugi product **II-59** (175 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol), allylacetate (0.08 ml, 0.75 mmol), Pd(dba)<sub>2</sub> (14 mg, 0.025 mmol) and PPh<sub>3</sub> (13 mg, 0.05 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 15 : 85) gave the desired product in 82 % isolated yield (159 mg, 0.41 mmol).

**Nature:** Yellow oil.

**R<sub>f</sub>:** (Et<sub>2</sub>O : DCM = 1.5 : 8.5) = 0.45.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.22 (br s, 4H, H-b,c), 6.41 (d, *J* = 7.0 Hz, 1H, NH), 5.81-5.72 (m, 1H, H-7), 5.56-5.46 (ddt, *J* = 16.8, 10.0, 6.8 Hz, 1H, H-10), 5.33 (dd, *J*<sub>trans-1,3</sub> = 17.3, *J*<sub>1,2</sub> = 1.0 Hz, 1H, H-8), 5.19 (dd, *J*<sub>cis-1,3</sub> = 10.5, *J*<sub>1,2</sub> = 0.8 Hz, 1H, H-8), 4.97 (2 dd, *J*<sub>trans-1,3</sub> = 16.8, *J*<sub>cis-1,3</sub> = 10.0, *J*<sub>1,2</sub> = 1.2 Hz, 2H, H-11), 3.87 (br s, 2H, H-6), 3.75-3.67 (m, 1H, H-3), 3.17 (dd, ABX system, *J*<sub>ab</sub> = 14.5, *J*<sub>ax</sub> = 6.2 Hz, 1H, H-9), 2.94 (dd, ABX system, *J*<sub>ba</sub> = 14.6, *J*<sub>bx</sub> = 7.4 Hz, 1H, H-9), 2.08 (s, 3H, H-5), 1.84-1.75 (m, 2H, H-Cy), 1.59-1.46 (m, 3H, H-Cy), 1.32-1.22 (m, 2H, H-Cy), 1.12-0.98 (m, 3H, H-Cy).

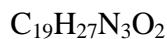
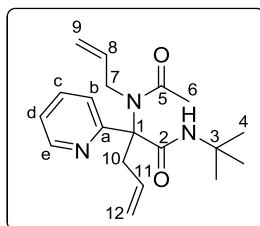
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 173.3 (C-4), 170.5 (C-2), 137.9 (C-a), 134.4 (C-7), 133.7 (C-d), 133.4 (C-10), 128.9 (C-c), 128.3 (C-b), 119.2 (C-11), 117.3 (C-8), 71.3 (C-1), 49.4 (C-6), 48.5 (C-3), 41.5 (C-9), 32.7 (C-Cy), 32.6 (C-Cy), 25.6 (C-Cy), 24.6 (C-Cy), 23.9 (C-5).

**HRMS:** Calculated for C<sub>22</sub>H<sub>29</sub>ClN<sub>2</sub>O<sub>2</sub>: 388.1918, Found: 388.1913.

**I.R.** (thin film): ν 3427, 3083, 3015, 2983, 2934, 2857, 1655, 1603, 1533, 1451, 1395, 1253, 1098, 1015 cm<sup>-1</sup>.

## II-79

### 2-(N-allylacetamido)-N-(*tert*-butyl)-2-(pyridin-2-yl)pent-4-enamide



Mol. Wt.: 329.21 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-B**, using Ugi product **II-60** (145 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol), allylacetate (0.08 ml, 0.75 mmol), Pd(dba)<sub>2</sub> (14 mg, 0.025 mmol) and PPh<sub>3</sub> (13 mg, 0.05 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 30 : 70) gave the desired product in 83 % isolated yield (136 mg, 0.41 mmol).

**Nature:** Yellow oil.

**R<sub>f</sub>:** (Et<sub>2</sub>O : DCM = 3 : 7) = 0.39.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 9.41 (br s, 1H, NH), 8.41 (d, *J* = 4.3 Hz, 1H, H-e), 7.57 (t, *J* = 7.5 Hz, 1H, H-c), 7.22 (d, *J* = 8.0 Hz, 1H, H-b), 7.08-7.06 (m, 1H, H-d), 6.12-6.03 (m, 1H, H-8), 5.51-5.35 (m, 2H, H-9,11), 5.21 (d, *J*<sub>cis-1,3</sub> = 10.4 Hz, 1H, H-9), 4.88-4.83 (m, 2H, H-12), 4.18 (br s, 2H, H-7), 2.99 (dd, ABX system, *J*<sub>ab</sub> = 13.9, *J*<sub>ax</sub> = 6.8 Hz, 1H, H-10), 2.79 (dd, ABX system, *J*<sub>ba</sub> = 14.0, *J*<sub>bx</sub> = 7.1 Hz, 1H, H-10), 2.07 (s, 3H, H-6), 1.28 (s, 9H, H-4).

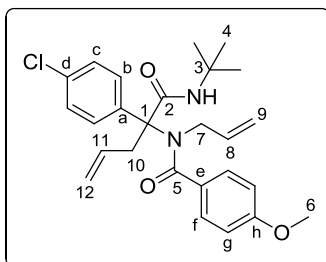
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 172.4 (C-5), 169.7 (C-2), 162.2 (C-a), 146.8 (C-e), 137.0 (C-c), 136.0 (C-8), 133.1 (C-11), 121.5 (C-d), 120.9 (C-b), 118.5 (C-12), 116.9 (C-9), 71.6 (C-1), 50.9 (C-3), 49.5 (C-7), 43.0 (C-10), 28.6 (C-4), 23.5 (C-6).

**HRMS:** Calculated for C<sub>19</sub>H<sub>27</sub>N<sub>3</sub>O<sub>2</sub>: 329.2103, Found: 329.2098.

**I.R.** (thin film): ν 3221, 3061, 2975, 2930, 1659, 1592, 1533, 1432, 1395, 1365, 1246, 1224 and 992 cm<sup>-1</sup>.

## II-80

### N-allyl-N-(1-(tert-butylamino)-2-(4-chlorophenyl)-1-oxopent-4-en-2-yl)-4-methoxybenzamide



Mol. Wt.: 454.202 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-B**, using Ugi product **II-61** (208 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol), allylacetate (0.08 ml, 0.75 mmol), Pd(dba)<sub>2</sub> (14 mg, 0.025 mmol) and PPh<sub>3</sub> (13 mg, 0.05 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 2 : 98) gave the desired product in 64% isolated yield (146 mg, 0.32mmol).

**Nature:** Yellow oil.

**R<sub>f</sub>:** (Et<sub>2</sub>O : DCM = 0.2 : 9.8) = 0.46.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 8.10 (br s, 1H, NH), 7.44 (d, *J* = 8.7 Hz, 2H, H-f), 7.14 (d, *J* = 8.7 Hz, 2H, H-c), 7.07 (d, *J* = 8.7 Hz, 2H, H-b), 6.86 (d, *J* = 8.7 Hz, 2H, H-g), 5.77-5.58 (m, 2H, H-8,11), 4.96 (dd, *J*<sub>cis-1,3</sub> = 10.2, *J*<sub>1,2</sub> = 4.5 Hz, 2H, H-9), 4.90 (d, *J*<sub>trans-1,3</sub> = 17.1 Hz, 2H, H-12), 4.27 (dd, ABX system, *J*<sub>ab</sub> = 16.4, *J*<sub>ax</sub> = 6.4 Hz, 1H, H-7), 4.05 (dd, ABX system, *J*<sub>ba</sub> = 16.4, *J*<sub>bx</sub> = 6.8 Hz, 1H, H-7), 3.78 (s, 3H, H-6), 3.00 (dd, ABX system, *J*<sub>ab</sub> = 15.0, *J*<sub>ax</sub> = 7.6 Hz, 1H, H-10), 2.86 (dd, ABX system, *J*<sub>ba</sub> = 15.0, *J*<sub>bx</sub> = 6.4 Hz, 1H, H-10), 1.29 (s, 9H, H-4).

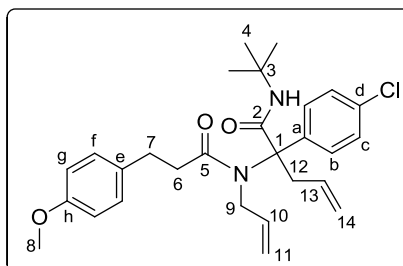
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 175.5 (C-5), 171.5 (C-2), 161.8 (C-h), 139.1 (C-a), 134.1 (C-8), 133.0 (C-11), 132.5 (C-d), 130.1 (C-f), 128.9 (C-e), 127.8 (C-c), 127.6 (C-b), 119.2 (C-9), 118.4 (C-12), 113.9 (C-g), 71.6 (C-1), 55.5 (C-6), 52.2 (C-7), 51.1 (C-3), 42.8 (C-10), 28.4 (C-4).

**HRMS:** Calculated for [M-CONHMe<sub>3</sub>] C<sub>21</sub>H<sub>21</sub>ClNO<sub>2</sub>: 354.1261, Found: 354.1262.

**I.R.** (thin film): ν 3429, 3079, 2968, 2936, 2841, 1672, 1623, 1551, 1511, 1379, 1252, 1172, 1097, 1032, 1014 cm<sup>-1</sup>.

## II-81

### 2-(N-allyl-3-(4-methoxyphenyl)propanamido)-N-(tert-butyl)-2-(4-chlorophenyl)pent-4-enamide



Mol. Wt.: 482.234 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-B**, using Ugi product **II-62** (222 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol), allylacetate (0.08 ml, 0.75 mmol), Pd(dba)<sub>2</sub> (14 mg, 0.025 mmol) and PPh<sub>3</sub> (13 mg, 0.05 mmol). Purification by flash chromatography using (EtOAc : DCM = 4 : 96) gave the desired product in 66 % isolated yield (160 mg, 0.33 mmol).

**Nature:** Yellow oil.

**R<sub>f</sub>:** (EtOAc : DCM = 0.4 : 9.6) = 0.35.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.17 (m, 2H, H-c), 7.09 (d, *J* = 8.0 Hz, 2H, H-b), 7.02 (d, *J* = 7.7 Hz, 2H, H-f), 6.75 (d, *J* = 8.4 Hz, 2H, H-g), 6.55 (br s, 1H, NH), 5.77-5.70 (m, 1H, H-10), 5.51-5.41 (m, 1H, H-13), 5.18 (2d, *J* = 16.8, 10.8 Hz, 2H, H-11), 4.93-4.88 (m, 2H, H-14), 3.92-3.77 (m, 2H, H-9), 3.72 (s, 3H, H-8), 3.13 (dd, ABX system, *J<sub>ab</sub>* = 14.5, *J<sub>ax</sub>* = 5.9 Hz, 1H, H-12), 2.86-2.79 (m, 3H, H-7,9), 2.65-2.55 (m, 2H, H-6), 1.22 (s, 9H, H-4).

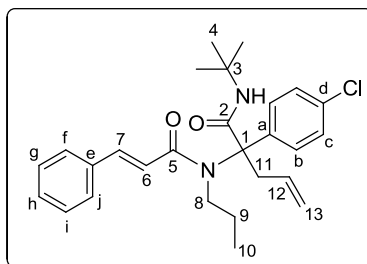
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 175.0 (C-5), 170.4 (C-2), 158.0 (C-h), 138.3 (C-a), 134.8 (C-10), 133.8 (C-13), 133.1 (C-d), 133.0 (C-f), 129.5 (C-b), 128.6 (C-e), 128.2 (C-c), 119.1 (C-14), 117.3 (C-11), 113.9 (C-g), 72.0 (C-1), 55.3 (C-8), 51.4 (C-3), 48.5 (C-9), 41.9 (C-12), 37.2 (C-6), 30.4 (C-7), 28.5 (C-4).

**HRMS:** Calculated for [M-CONHMe<sub>3</sub>] C<sub>23</sub>H<sub>25</sub>ClNO<sub>2</sub>: 382.1579, Found: 382.1579.

**I.R.** (thin film): ν 3407, 3082, 2967, 2935, 2838, 1671, 1612, 1513, 1456, 1393, 1366, 1247, 1098, 1036 and 1014 cm<sup>-1</sup>.

## II-82

### N-(*tert*-butyl)-2-(4-chlorophenyl)-2-(3-(4-methoxyphenyl)-N-propylacrylamido)pent-4-enamide



Mol. Wt.: 452.223 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-B**, using Ugi product **II-63** (206 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol), allylacetate (0.08 ml, 0.75 mmol), Pd(dba)<sub>2</sub> (14 mg, 0.025 mmol) and PPh<sub>3</sub> (13 mg, 0.05 mmol). Purification by flash chromatography using (pure DCM) gave the desired product in 49 % isolated yield (110 mg, 0.24 mmol).

**Nature:** Yellow oil.

**R<sub>f</sub>:** (DCM) = 0.38.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.64 (br s, 1H, NH), 7.55 (d, *J* = 15.3 Hz, 1H, H-7), 7.42 (d, *J* = 3.7 Hz, 2H, H-g), 7.30 (dd, *J* = 5.0, 1.8 Hz, 3H, H-f,h), 7.17 (d, *J* = 8.7 Hz, 2H, H-b), 7.06 (d, *J* = 7.3 Hz, 2H, H-c), 6.82 (d, *J* = 14.7 Hz, 1H, H-6), 5.57 – 5.46 (m, 1H, H-12), 4.86 (2d, *J*<sub>cis-1,3</sub> = 10.4, *J*<sub>trans-1,3</sub> = 17.2 Hz, 2H, H-13), 3.64 – 3.52 (m, 1H, H-8), 3.47 (ddd, ABXY system, *J*<sub>ab</sub> = 15.6, *J*<sub>ax</sub> = 10.6, *J*<sub>ay</sub> = 4.9 Hz, 1H, H-8), 2.97 (dd, ABX system, *J*<sub>ab</sub> = 14.6, *J*<sub>ax</sub> = 6.2 Hz, 1H, H-11), 2.84 (dd, ABX system, *J*<sub>ba</sub> = 14.6, *J*<sub>bx</sub> = 7.5 Hz, 1H, H-11), 1.82 – 1.70 (m, 1H, H-9), 1.67 – 1.55 (m, 1H, H-9), 1.26 (s, 9H, H-4), 0.84 (t, *J* = 7.4 Hz, 3H, H-10).

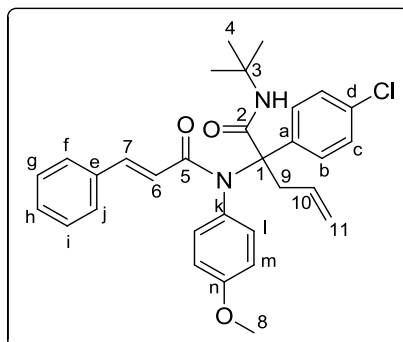
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.4 (C-2), 169.7 (C-5), 143.9 (C-7), 139.4 (C-a), 134.9 (C-e), 133.2 (C-12), 132.5 (C-d), 130.0 (C-h), 128.9 (C-f), 128.0 (C-b), 127.9 (C-c), 127.8 (C-g), 119.4 (C-6), 119.0 (C-13), 71.7 (C-1), 51.2 (C-3), 48.2 (C-8), 43.0 (C-11), 28.5 (C-4), 24.3 (C-9), 11.6 (C-10).

**HRMS:** Calculated for C<sub>27</sub>H<sub>33</sub>ClN<sub>2</sub>O<sub>2</sub>: 452.2231, Found: 452.2228.

**I.R.** (thin film): ν 3410, 3076, 2969, 2922, 2843, 1668, 1615, 1512, 1455, 1396, 1367, 1253, 1089, 1032 and 1013 cm<sup>-1</sup>.

## II-83

### N-*tert*-butyl-2-(4-chlorophenyl)-2-(N-(4-methoxyphenyl)cinnamamido)pent-4-enamide



Mol. Wt.: 516.218 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-B**, using Ugi product **II-64** (238 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol), allylacetate (0.08 ml, 0.75 mmol), Pd(dba)<sub>2</sub> (14 mg, 0.025 mmol) and PPh<sub>3</sub> (13 mg, 0.05 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 5 : 95) gave the desired product in 63 % isolated yield (163 mg, 0.32 mmol).

**Nature:** Yellow oil.

**R<sub>f</sub>:** (Et<sub>2</sub>O : DCM = 0.5 : 9.5) = 0.27.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.33 (d, *J* = 14.7 Hz, 1H, H-7), 7.11-7.05 (m, 8H, H-Ar, H-b, NH), 6.79-6.71 (m, 7H, H-6,c,m,l), 5.10 (br s, 1H, H-10), 4.87 (dd, *J* = 12.7, 8.2 Hz, 2H, H-11), 3.69 (s, 3H, H-8), 2.78 – 2.56 (m, 2H, H-9), 0.92 (s, 9H, H-4).

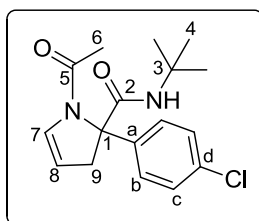
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 174.8 (C-2), 166.7 (C-5), 158.7 (C-n), 135.9 (C-7), 135.2 (C-a), 135.1 (C-e), 134.5 (C-d), 133.6 (C-10), 130.6 (C-b), 130.2 (C-k), 129.8 (C-c), 128.9 (C-Ar), 128.2 (C-Ar), 128.1 (C-Ar), 127.9 (C-l), 127.8 (C-6), 127.7 (C-11), 114.4 (C-m), 80.4 (C-1), 55.6 (C-8), 51.8 (C-3), 33.6 (C-9), 27.9 (C-4).

**HRMS:** Calculated for [M-CONHCMe<sub>3</sub>] C<sub>23</sub>H<sub>19</sub>ClNO<sub>2</sub>: 376.1099, Found: 376.1097.

**I.R.** (thin film): ν 3425, 3057, 3033, 2966, 2931, 2836, 1699, 1680, 1607, 1510, 1454, 1364, 1248, 1093, 1033, 1010, 827, 728 and 697 cm<sup>-1</sup>.

## II-85

### 1-Acetyl-N-*tert*-butyl-2-(4-chlorophenyl)-2,3-dihydro-1H-pyrrole-2-carboxamide



Mol. Wt.: 516.218 g.mol<sup>-1</sup>

This compound was synthesized using Ugi product **II-40** (161 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol) in DMSO (0.5 M) for 1 hour. Purification by flash chromatography using gradient eluent (Et<sub>2</sub>O : DCM = 6 : 94 – 10 : 90) gave the desired product in 79 % isolated yield (127 mg, 0.4 mmol).

**Nature:** White solid.

**M.P.** = 153-155 °C.

**R<sub>f</sub>:** (Et<sub>2</sub>O : DCM) = 0.25.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 8.12 (br s, 1H, NH), 7.21 (d, *J* = 7.9 Hz, 2H, H-c), 7.06 (d, *J* = 8.3 Hz, 2H, H-b), 5.90 (d, *J* = 6.3 Hz, 1H, H-7), 5.75 (d, *J* = 5.6 Hz, 1H, H-8), 4.43 (br s, 2H, H-9), 2.13 (s, 3H, H-6), 1.28 (s, 9H, H-4).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 170.5 (C-5), 170.2 (C-2), 138.1 (C-a), 135.1 (C-7), 133.3 (C-d), 128.7 (C-c), 127.1 (C-b), 121.3 (C-8), 81.0 (C-1), 57.1 (C-9), 51.3 (C-3), 28.6 (C-4), 24.0 (C-6).

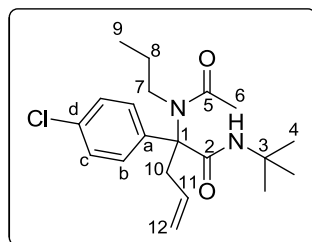
**HRMS:** Calculated for C<sub>17</sub>H<sub>21</sub>ClN<sub>2</sub>O<sub>2</sub>: 320.1292, Found: 320.1926.

**I.R.** (thin film): ν 3275, 3007, 2931, 1673, 1626, 1554, 1493, 1403, 1363, 1290, 1237, 1096, 1015 and 977 cm<sup>-1</sup>.



**II-41**

**N-(*tert*-butyl)-2-(4-chlorophenyl)-2-(N-propylacetamido)pent-4-enamide**

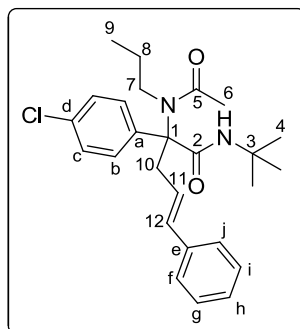


Mol. Wt.: 364.192 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-C**, using Ugi product **II-40** (163 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol), allyl bromide (0.06 ml, 0.75 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 10 : 90) gave the desired product in 83 % isolated yield (121 mg, 0.33 mmol) as yellow oil.

## **II-91**

### **N-tert-butyl-2-(4-chlorophenyl)-5-phenyl-2-(N-propylacetamido)pent-4-enamide**



Mol. Wt.: 440.223 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-C**, using Ugi product **II-40** (163 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol), cinnamyl bromide (148 mg, 0.75 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 7 : 93) gave the desired product in 88 % isolated yield (193 mg, 0.44 mmol).

**Nature:** Colourless oil.

**R<sub>f</sub>:** (Et<sub>2</sub>O : DCM = 0.7 : 9.3) = 0.41.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.43 – 6.46 (m, 9H, H-Ar), 6.13 (d, *J* = 15.6 Hz, 1H, H-12), 5.84 (dt, *J* = 16.0, 7.2 Hz, 1H, H-11), 3.44 – 3.28 (m, 2H, H-7), 3.10 (dd, ABX system, *J*<sub>ab</sub> = 14.4, *J*<sub>ax</sub> = 6.4 Hz, 1H, H-10), 2.92 (dd, ABX system, *J*<sub>ba</sub> = 14.4, *J*<sub>bx</sub> = 7.4 Hz, 1H, H-10), 2.14 (s, 3H, H-6), 1.78 – 1.67 (m, 1H, H-8), 1.58-1.43 (m, 1H, H-8), 1.24 (s, 9H, H-4), 0.80 (t, *J* = 7.2 Hz, 3H, H-9).

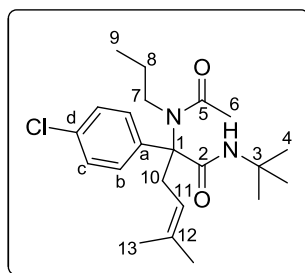
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 173.0 (C-5), 171.2 (C-2), 139.3 (C-a), 137.2 (C-d), 134.0 (C-12), 132.6 (C-e), 128.5 (C-c), 127.9 (C-Ar), 127.4 (C-Ar), 126.4 (C-b), 126.1 (C-Ar), 125.0 (C-11), 71.6 (C-1), 51.2 (C-3), 48.9 (C-7), 41.8 (C-10), 28.4 (C-4), 24.3 (C-6), 23.6 (C-8), 11.5 (C-9).

**HRMS:** Calculated for C<sub>26</sub>H<sub>33</sub>ClN<sub>2</sub>O<sub>2</sub>: 440.2231, Found: 440.2229.

**I.R.** (thin film): ν 3428, 3083, 3062, 3028, 2969, 2934, 2877, 1670, 1633, 1547, 1493, 1404, 1366, 1243, 1224, 1098 and 1014 cm<sup>-1</sup>.

## II-92

### N-tert-butyl-2-(4-chlorophenyl)-5-methyl-2-(N-propylacetamido)hex-4-enamide



Mol. Wt.: 392.223 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-C**, using Ugi product **II-40** (163 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol), 2-methyl-4-bromo-2-butene (0.09 ml, 0.75 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 10 : 90) gave the desired product in 74 % isolated yield (146 mg, 0.37 mmol).

**Nature:** Light yellow oil.

**R<sub>f</sub>:** (Et<sub>2</sub>O : DCM = 1 : 9) = 0.35.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.28 (br s, 1H, NH), 7.15 (d, *J* = 8.6 Hz, 2H, H-c), 7.03 (d, *J* = 6.7 Hz, 2H, H-b), 4.84 (t, *J* = 5.6 Hz, 1H, H-11), 3.26 (t, *J* = 8.4 Hz, 2H, H-7), 2.81 (d, *J* = 6.4 Hz, 2H, H-10), 2.14 (s, 3H, H-6), 1.73-1.65 (m, 1H, H-8), 1.52 (s, 3H, H-13), 1.45-1.36 (m, 1H, H-8), 1.28 (s, 3H, H-13), 1.23 (s, 9H, H-4), 0.76 (t, *J* = 7.3 Hz, 3H, H-9).

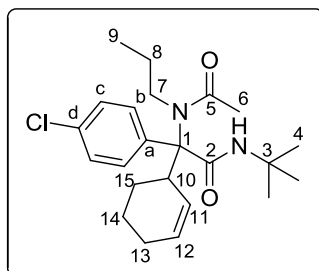
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 173.0 (C-5), 171.8 (C-2), 138.8 (C-a), 136.0 (C-12), 132.4 (C-d), 128.3 (C-c), 127.6 (C-b), 118.5 (C-11), 71.5 (C-1), 51.0 (C-3), 49.0 (C-7), 36.3 (C-10), 28.4 (C-4), 26.0 (C-13), 24.4 (C-6), 23.5 (C-8), 17.9 (C-13), 11.5 (C-9).

**HRMS:** Calculated for [M-CONHMe<sub>3</sub>] C<sub>17</sub>H<sub>23</sub>ClNO: 292.1474, Found: 292.1475.

**I.R.** (thin film): ν 3430, 3059, 2969, 2933, 2877, 1668, 1631, 1547, 1492, 1405, 1366, 1244, 1224, 1097 and 1015 cm<sup>-1</sup>.

## II-93

### N-(*tert*-butyl)-2-(4-chlorophenyl)-2-(cyclohex-2-en-1-yl)-2-(N-propylacetamido)acetamide



Mol. Wt.: 404.223 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-C**, using Ugi product **II-40** (163 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol), 3-bromocyclohexene (0.09 ml, 0.75 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 5 : 95) gave the desired product in 30% isolated yield (60 mg, 0.15 mmol).

**Nature:** Light yellow oil.

**R<sub>f</sub>:** (Et<sub>2</sub>O : DCM = 0.5 : 9.5) = 0.45.

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, 400 MHz): δ (ppm) 7.21-7.13 (m, 4H, H-b,c), 6.82 (br s, 1H, NH), 5.60 – 5.45 (m, 2H, H-11,12), 3.50 – 3.27 (m, 3H, H-7,10), 2.11 (s, 3H, H-6), 1.90 – 1.77 (m, 3H, H-8,13), 1.74 – 1.60 (m, 1H, H-14), 1.49 – 1.30 (m, 3H, H-8,15), 1.21 (br s, 10H, H-4,14), 0.75 (t, *J* = 7.3 Hz, 3H, H-9).

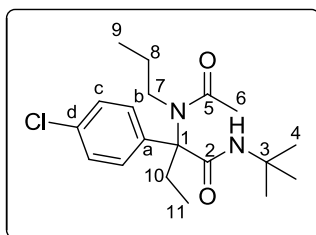
**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, 100.6 MHz): δ (ppm) 176.0 (C-5), 172.0 (C-2), 138.1 (C-a), 133.8 (C-d), 131.3 (C-11), 129.8 (C-12), 129.4 (C-c), 128.0 (C-b), 75.4 (C-1), 52.5 (C-3), 41.5 (C-7), 28.8 (C-10), 26.4 (C-4), 26.1 (C-13), 24.5 (C-15), 24.2 (C-6), 23.0 (C-14), 11.7 (C-9).

**HRMS:** Calculated for [M-CONHMe<sub>3</sub>] C<sub>18</sub>H<sub>23</sub>ClNO: 304.1474, Found: 304.1472.

**I.R.** (thin film): ν 3426, 3037, 2967, 2935, 2877, 2839, 1669, 1635, 1544, 1492, 1456, 1394, 1367, 1243, 1224, 1097 and 1014 cm<sup>-1</sup>.

## II-94

### N-(*tert*-butyl)-2-(4-chlorophenyl)-2-(N-propylacetamido)butanamide



Mol. Wt.: 352.192 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-C**, using Ugi product **II-40** (163 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol), ethyl iodide (0.06 ml, 0.75 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 7 : 93) gave the desired product in 94 % isolated yield (165 mg, 0.47 mmol).

**Nature:** Colourless oil.

**R<sub>f</sub>:** (Et<sub>2</sub>O : DCM = 0.6 : 9.4) = 0.25.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.59 (br s, 1H, NH), 7.16 (d, *J* = 8.3 Hz, 2H, H-c), 7.01 (br s, 2H, H-c), 3.44 – 3.27 (m, 2H, H-7), 2.18-2.12 (m, 4H, H-6,10), 1.89 (dq, *J* = 13.8, 7.0 Hz, 1H, H-10), 1.79-1.70 (m, 1H, H-8), 1.54-1.40 (m, 1H, H-8), 1.24 (s, 9H, H-4), 0.84 (t, *J* = 7.3 Hz, 3H, H-9), 0.56 (t, *J* = 6.4 Hz, 3H, H-11).

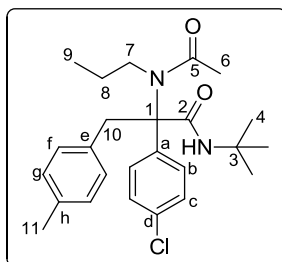
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 173.2 (C-5), 171.5 (C-2), 139.7 (C-a), 132.0 (C-d), 127.7 (C-c), 127.4 (C-b), 71.5 (C-1), 50.9 (C-3), 48.4 (C-7), 30.9 (C-10), 28.4 (C-4), 24.5 (C-6), 23.5 (C-8), 11.6 (C-9), 9.4 (C-11).

**HRMS:** Calculated for [M-CONHMe<sub>3</sub>] C<sub>14</sub>H<sub>19</sub>ClNO: 252.1161, Found: 252.1153.

**I.R.** (thin film): ν 3436, 3061, 2971, 2935, 2878, 1668, 1630, 1547, 1490, 1404, 1366, 1225, 1098 and 1014 cm<sup>-1</sup>.

## II-95

### N-(*tert*-butyl)-2-(4-chlorophenyl)-2-(N-propylacetamido)-3-(*p*-tolyl)propanamide



Mol. Wt.: 428.223 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-C**, using Ugi product **II-40** (163 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol), 4-methylbenzyl bromide (139 mg, 0.75 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 5 : 95) gave the desired product in 79 % isolated yield (170 mg, 0.40 mmol).

**Nature:** Colourless oil.

**R<sub>f</sub>:** (Et<sub>2</sub>O : DCM = 0.5 : 9.5) = 0.25.

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, 400 MHz): δ (ppm) 7.04 (d, *J* = 8.7 Hz, 2H, H-c), 6.92 (d, *J* = 8.3 Hz, 2H, H-b), 6.79 (d, *J* = 7.9 Hz, 2H, H-g), 6.64 (d, *J* = 8.0 Hz, 2H, H-f), 3.80 (d, AB system, *J*<sub>ab</sub> = 12.6 Hz, 1H, H-10), 3.38 (dt, *J* = 10.6, 5.7 Hz, 2H, H-7), 3.02 (d, AB system, *J*<sub>ba</sub> = 12.5 Hz, 1H, H-10), 2.13 (s, 3H, H-6), 2.09 (s, 3H, H-11), 1.87-1.75 (m, 1H, H-8), 1.63-1.54 (m, 1H, H-8), 1.18 (s, 9H, H-4), 0.80 (t, *J* = 7.4 Hz, 3H, H-9).

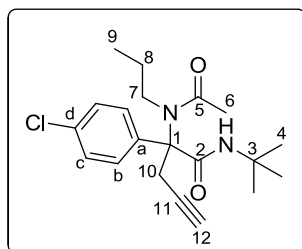
**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, 100.6 MHz): δ (ppm) 175.2 (C-5), 171.7 (C-2), 140.4 (C-a), 137.4 (C-h), 134.0 (C-d), 133.5 (C-e), 132.4 (C-c), 130.0 (C-g), 129.4 (C-f), 128.4 (C-b), 74.5 (C-1), 52.5 (C-3), 43.5 (C-7), 29.9 (C-10), 28.7 (C-4), 24.9 (C-6), 24.1 (C-8), 21.1 (C-11), 11.5 (C-9).

**HRMS:** Calculated for [M-CONHMe<sub>3</sub>] C<sub>20</sub>H<sub>23</sub>ClNO: 328.1474, Found: 328.1480.

**I.R.** (thin film): ν 3424, 2970, 2933, 2877, 1669, 1634, 1543, 1491, 1394, 1366, 1224, 1096 and 1015 cm<sup>-1</sup>.

## II-96

### N-tert-butyl-2-(4-chlorophenyl)-2-(N-propylacetamido)pent-4-ynamide



Mol. Wt.: 362.176 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-C**, using Ugi product **II-40** (163 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol), 2,3-dibromoprop-1-ene (0.07 ml, 0.75 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 2 : 98) gave the desired product in 27 % isolated yield (49 mg, 0.14 mmol).

**Nature:** Yellow oil.

**R<sub>f</sub>:** (Et<sub>2</sub>O : DCM = 0.2 : 9.8) = 0.23.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.35 (br s, 1H, NH), 7.20 (s, 4H, H-b,c), 3.41 (ddd, *J* = 15.7, 10.7, 4.9 Hz, 1H, H-7), 3.29 (ddd, *J* = 16.8, 10.8, 5.4 Hz, 1H, H-7), 3.21 (dd, ABX system, *J<sub>ax</sub>* = 17.9, *J<sub>ab</sub>* = 2.6 Hz, 1H, H-10), 2.95 (dd, ABX system, *J<sub>bx</sub>* = 17.9, *J<sub>ba</sub>* = 2.6 Hz, 1H, H-10), 2.16 (s, 3H, H-6), 1.96 (t, *J* = 2.6 Hz, 1H, H-12), 1.65 – 1.55 (m, 1H, H-8), 1.46–1.38 (m, 1H, H-8), 1.25 (s, 9H, H-4), 0.76 (t, *J* = 7.4 Hz, 3H, H-9).

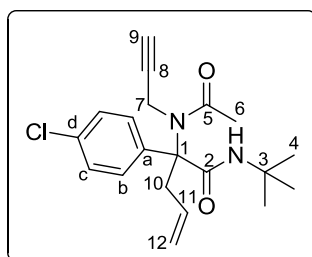
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 173.1 (C-5), 170.7 (C-2), 137.7 (C-a), 133.3 (C-d), 128.2 (C-b), 127.9 (C-c), 80.4 (C-11), 73.3 (C-12), 70.5 (C-1), 51.3 (C-3), 49.5 (C-7), 28.7 (C-10), 28.4 (C-4), 24.2 (C-6), 23.6 (C-8), 11.4 (C-9).

**HRMS:** Calculated for C<sub>20</sub>H<sub>27</sub>ClN<sub>2</sub>O<sub>2</sub>: 362.1761, Found: 362.1772.

**I.R.** (thin film): ν 3307, 2969, 2934, 2877, 1671, 1632, 1549, 1494, 1405, 1367, 1245, 1097 and 1015 cm<sup>-1</sup>.

## II-77

### **N-(*tert*-butyl)-2-(4-chlorophenyl)-2-(N-(prop-2-yn-1-yl)acetamido)pent-4-enamide**



Mol. Wt.: 360.161 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-C**, using Ugi product **II-58** (160 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol), allyl bromide (0.06 ml, 0.75 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 5 : 95) gave the desired product in 58 % isolated yield (105 mg, 0.29 mmol).

**Nature:** Light yellow oil.

**R<sub>f</sub>:** (Et<sub>2</sub>O : DCM = 0.5 : 9.5) = 0.19.

**<sup>1</sup>H-NMR** (DMSO-d<sub>6</sub>, 400 MHz): δ (ppm) 7.50 (d, *J* = 8.7 Hz, 2H, H-c), 7.33 (d, *J* = 8.8 Hz, 2H, H-b), 6.44 (br s, 1H, NH), 5.63 (ddt, *J* = 17.0, 10.3, 6.8 Hz, 1H, H-11), 5.05 – 4.96 (m, 2H, H-12), 4.26 (dd, *J* = 8.4, 2.2 Hz, 2H, H-7), 3.37 (t, *J* = 2.3 Hz, 1H, H-9), 3.1-3.05 (m, 2H, H-10), 2.15 (s, 3H, H-6), 1.26 (s, 9H, H-4).

**<sup>13</sup>C-NMR** (DMSO-d<sub>6</sub>, 100.6 MHz): δ (ppm) 171.9 (C-5), 169.7 (C-2), 139.8 (C-a), 134.1 (C-11), 132.0 (C-d), 123.0 (C-c), 127.7 (C-b), 118.8 (C-12), 81.4 (C-8), 76.0 (C-9), 71.3 (C-1), 51.1 (C-3), 41.9 (C-10), 36.6 (C-7), 28.7 (C-4), 23.9 (C-6).

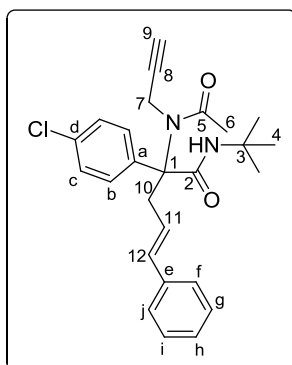
**HRMS:** Calculated for [M-CONH*t*-Bu] C<sub>15</sub>H<sub>16</sub>ClNO: 260.0848, Found: 260.0844.

**I.R.** (thin film): ν 3299, 3077, 2971, 2901, 1666, 1511, 1492, 1391, 1364, 1241, 1076, 1013, 920 and 733 cm<sup>-1</sup>.



## II-97

### N-tert-butyl-2-(4-chlorophenyl)-5-phenyl-2-(N-(prop-2-ynyl)acetamido)pent-4-enamide



Mol. Wt.: 436.192 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-C**, using Ugi product **II-58** (160 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol), cinnamyl bromide (148 mg, 0.75 mmol). Purification by flash chromatography using (EtOAc : P.E. = 40 : 60) gave the desired product in 44 % isolated yield (96 mg, 0.22 mmol).

**Nature:** Yellow oil.

**R<sub>f</sub>** (EtOAc :P.E. = 4 : 6) = 0.45.

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, 400 MHz):  $\delta$  7.61 (d,  $J$  = 8.7 Hz, 2H, H-b), 7.39 (d,  $J$  = 8.8 Hz, 2H, H-c), 7.32 – 7.26 (m, 4H, H-Ar), 7.21 (ddd,  $J$  = 8.5, 5.3, 2.7 Hz, 1H, H-Ar), 6.61 (br s, 1H, NH), 6.46 (d,  $J$  = 15.8 Hz, 1H, H-12), 6.19 – 6.08 (m, 1H, H-11), 4.24-4.15 (m, 2H, H-7), 3.33 (t,  $J$  = 3.3 Hz, 2H, H-10), 3.01 (s, 1H, H-9), 2.32 (s, 3H, H-6), 1.32 (s, 9H, H-4).

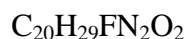
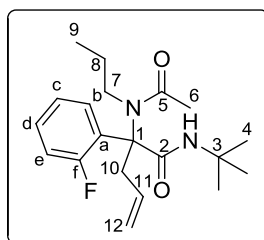
**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, 100.6 MHz):  $\delta$  174.9 (C-2), 172.0 (C-5), 138.5 (C-a), 135.5 (C-d), 134.8 (C-12), 130.9 (C-c), 129.6 (C-b), 129.2 (C-Ar), 128.6 (C-Ar), 128.4 (C-e), 127.2 (C-Ar), 111.7 (C-11), 81.0 (C-8), 75.6 (C-1), 73.5 (C-9), 52.7 (C-3), 46.7 (C-10), 38.4 (C-7), 28.7 (C-4), 23.8 (C-6).

**HRMS:** Calculated for C<sub>26</sub>H<sub>29</sub>ClN<sub>2</sub>O<sub>2</sub>: 436.1918, Found: 436.1925.

**I.R.** (thin film):  $\nu$  3404, 3298, 3056, 3026, 2968, 2931, 1667, 1511, 1491, 1390, 1364, 1265, 1223, 1095, 1013, 967 and 733 cm<sup>-1</sup>.

## II-70

### N-tert-butyl-2-(2-fluorophenyl)-2-(N-propylacetamido)pent-4-enamide



Mol. Wt.: 348.221 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-C**, using Ugi product **II-51** (154 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol), allyl bromide (0.06 ml, 0.75 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 5 : 95) gave the desired product in 40 % isolated yield (70 mg, 0.2 mmol).

**Nature:** Light yellow oil.

**R<sub>f</sub>:** (Et<sub>2</sub>O : DCM = 0.5 : 9.5) = 0.38.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.93 (br s, 1H, NH), 7.26 – 7.18 (m, 1H, H-c), 7.16 – 7.05 (m, 2H, H-b,d), 6.97 (dd, *J* = 12.7, 8.0 Hz, 1H, H-e), 5.70-5.59 (m, 1H, H-11), 4.92 – 4.81 (m, 2H, H-12), 3.50 (2 ddd, ABXY system, *J* = 15.6, 10.6, 4.9 Hz, 2H, H-7), 3.13 (dd, ABX system, *J<sub>ab</sub>* = 14.4, *J<sub>ax</sub>* = 6.2 Hz, 1H, H-10), 2.92 (dd, ABX system, *J<sub>ba</sub>* = 14.4, *J<sub>bx</sub>* = 7.6 Hz, 1H, H-10), 2.24 (s, 3H, H-6), 1.91-1.82 (m, 1H, H-8), 1.67 – 1.51 (m, 1H, H-8), 1.37 (s, 9H, H-4), 0.93 (t, *J* = 7.4 Hz, 3H, H-9).

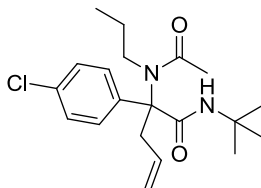
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 173.0 (C-5), 171.1 (C-2), 159.4 (d, *J* = 246.6 Hz, C-f), 133.9 (C-11), 128.4 (d, *J* = 3.4 Hz, C-c), 128.3 (d, *J* = 5.1 Hz, C-d), 123.4 (d, *J* = 3.3 Hz, C-b), 118.23 (C-12), 115.7 (d, *J* = 23.7 Hz, C-e), 70.09 (d, *J* = 2.6 Hz, C-1), 51.0 (C-3), 48.5 (C-7), 41.1 (C-10), 28.4 (C-4), 24.1 (C-8), 23.3 (C-6), 11.5 (C-9).

**HRMS:** Calculated for [M-CONH*t*-Bu] C<sub>15</sub>H<sub>19</sub>FNO: 248.1496, Found: 248.1507.

**I.R.** (thin film): ν 3269, 3075, 2963, 2931, 2875, 1674, 1627, 1544, 1489, 1402, 1363, 1219, 914 and 754 cm<sup>-1</sup>.

**II-41**

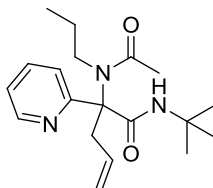
**N-(*tert*-butyl)-2-(4-chlorophenyl)-2-(N-propylacetamido)pent-4-enamide**



This compound was synthesized according to the general procedure **II-D**, using 4-chlorobenzaldehyde (141 mg, 1.0 mmol), propylamine (0.08 ml, 1.0 mmol), acetic acid (0.06 ml, 1.0 mmol) and *tert*-butyl isocyanide (0.11 ml, 1.0 mmol), sodium hydride (100 mg, 2.5 mmol) and allylbromide (0.13 ml, 1.5 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 10 : 90) gave the desired product in 81 % isolated yield (297 mg, 0.81 mmol) as yellow oil.

**II-72**

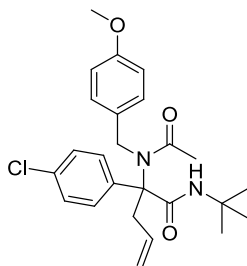
**N-(*tert*-butyl)-2-(N-propylacetamido)-2-(pyridin-2-yl)pent-4-enamide**



This compound was synthesized according to the general procedure **II-D**, using pyridine-2-carboxaldehyde (0.1 ml, 1.0 mmol), propylamine (0.08 ml, 1.0 mmol), acetic acid (0.06 ml, 1.0 mmol) and *tert*-butyl isocyanide (0.11 ml, 1.0 mmol), sodium hydride (100 mg, 2.5 mmol) and allylbromide (0.13 ml, 1.5 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 20 : 80) gave the desired product in 78 % isolated yield (257 mg, 0.78 mmol) as yellow oil.

## **II-75**

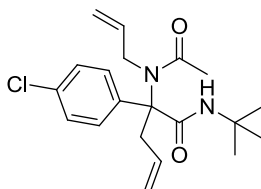
### **N-(*tert*-butyl)-2-(4-chlorophenyl)-2-(N-(4-methoxybenzyl)acetamido)pent-4-enamide**



This compound was synthesized according to the general procedure **II-D**, using 4-chlorobenzaldehyde (141 mg, 1.0 mmol), 4-methoxybenzylamine (0.13 ml, 1.0 mmol), acetic acid (0.06 ml, 1.0 mmol) and *tert*-butyl isocyanide (0.11 ml, 1.0 mmol), sodium hydride (100 mg, 2.5 mmol) and allylbromide (0.13 ml, 1.5 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 10 : 90) gave the desired product in 64 % isolated yield (282 mg, 0.64 mmol) as yellow oil.

## **II-76**

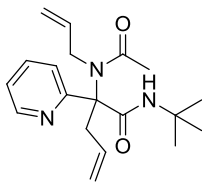
### **2-(N-allylacetamido)-N-(*tert*-butyl)-2-(4-chlorophenyl)pent-4-enamide**



This compound was synthesized according to the general procedure **II-D**, using 4-chlorobenzaldehyde (141 mg, 1.0 mmol), allylamine (0.075 ml, 1.0 mmol), acetic acid (0.06 ml, 1.0 mmol) and *tert*-butyl isocyanide (0.11 ml, 1.0 mmol), sodium hydride (100 mg, 2.5 mmol) and allylbromide (0.13 ml, 1.5 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 7 : 93) gave the desired product in 88 % isolated yield (320 mg, 0.88 mmol) as yellow oil.

**II-79**

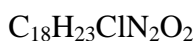
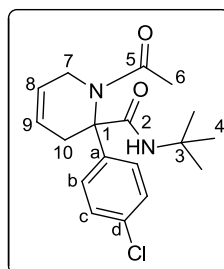
**2-(N-allylacetamido)-N-(*tert*-butyl)-2-(pyridin-2-yl)pent-4-enamide**



This compound was synthesized according to the general procedure **II-D**, using pyridine-2-carboxaldehyde (0.1 ml, 1.0 mmol), allylamine (0.075 ml, 1.0 mmol), acetic acid (0.06 ml, 1.0 mmol) and *tert*-butyl isocyanide (0.11 ml, 1.0 mmol), sodium hydride (100 mg, 2.5 mmol) and allylbromide (0.13 ml, 1.5 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 30 : 70) gave the desired product in 87 % isolated yield (287 mg, 0.87 mmol) as yellow oil.

## II-100

### 1-Acetyl-N-*tert*-butyl-2-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine-2-carboxamide



Mol. Wt.: 334.145 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-E**, using allylated Ugi product **II-76** (145 mg, 0.4 mmol) and Hoveyda-Grubbs catalyst 2<sup>nd</sup> Generation (6 mg, 0.01 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 20 : 80) gave the desired product in 89 % isolated yield (119 mg, 0.36 mmol).

**Nature:** Light brown oil.

**R<sub>f</sub>**: (Et<sub>2</sub>O : DCM = 1.5 : 8.5) = 0.23.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.21 (d, *J* = 8.7 Hz, 2H, H-b), 7.11 (d, *J* = 8.2 Hz, 2H, H-c), 6.42 (br s, 1H, NH), 5.97-5.93 (m, 1H, H-9), 5.77-5.65 (m, 1H, H-8), 4.07-4.04 (m, 1H, H-7), 3.91 (dd, ABX system, *J*<sub>ab</sub> = 16.3, *J*<sub>ax</sub> = 1.5 Hz, 1H, H-7), 2.99 (dd, ABX system, *J*<sub>ab</sub> = 16.3, *J*<sub>ax</sub> = 3.2 Hz, 1H, H-10), 2.38 (dd, ABX system, *J*<sub>ba</sub> = 16.3, *J*<sub>bx</sub> = 3.6 Hz, 1H, H-10), 2.14 (s, 3H, H-6), 1.22 (s, 9H, H-4).

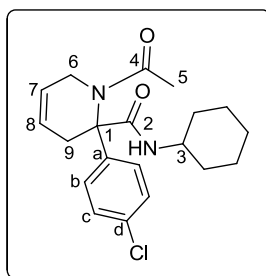
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 172.7 (C-5), 170.6 (C-2), 139.9 (C-a), 133.0 (C-d), 128.6 (C-b), 127.6 (C-c), 127.2 (C-9), 122.6 (C-8), 68.8 (C-1), 51.2 (C-3), 45.6 (C-7), 36.7 (C-10), 28.5 (C-4), 24.1 (C-6).

**HRMS:** Calculated for [M-CONHMe<sub>3</sub>] C<sub>13</sub>H<sub>13</sub>ClNO: 234.0691, Found: 234.0887.

**I.R.** (thin film): ν 3428, 3061, 2970, 2931, 1677, 1601, 1513, 1493, 1369, 1269, 1221, 1098 and 1015 cm<sup>-1</sup>.

## II-101

### 1-Acetyl-2-(4-chlorophenyl)-N-cyclohexyl-1,2,3,6-tetrahydropyridine-2-carboxamide



Mol. Wt.: 360.161 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-E**, using allylated Ugi product **II-78** (156 mg, 0.4 mmol) and Hoveyda-Grubbs catalyst 2<sup>nd</sup> Generation (6 mg, 0.01 mmol). Purification by flash chromatography using (pure Et<sub>2</sub>O) gave the desired product in 64 % isolated yield (89 mg, 0.26 mmol).

**Nature:** Light brown oil.

**R<sub>f</sub>:** (Et<sub>2</sub>O) = 0.32.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.22 (d, *J* = 8.7 Hz, 2H, H-c), 7.13 (d, *J* = 8.2 Hz, 2H, H-b), 6.25 (br s, 1H, NH), 5.96-5.91 (m, 1H, H-8), 5.75-5.62 (m, 1H, H-7), 4.10-4.06 (m, 1H, H-6), 3.87 (dd, ABX system, *J<sub>ab</sub>* = 16.4, *J<sub>ax</sub>* = 1.3 Hz, 1H, H-6), 3.73-3.64 (m, 1H, H-3), 3.04 (dd, ABX system, *J<sub>ab</sub>* = 16.3, *J<sub>ax</sub>* = 2.1 Hz, 1H, H-9), 2.45 (dd, ABX system, *J<sub>ba</sub>* = 16.3, *J<sub>bx</sub>* = 4.5 Hz, 1H, H-9), 2.14 (s, 3H, H-5), 1.79-1.75 (m, 2H, H-Cy), 1.55-1.44 (m, 3H, H-Cy), 1.31-1.18 (m, 2H, H-Cy), 1.09-0.94 (m, 3H, H-Cy).

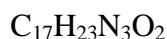
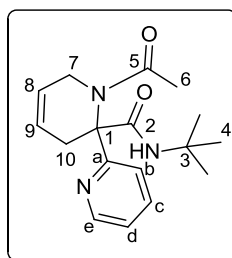
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 172.7 (C-4), 170.8 (C-2), 139.2 (C-a), 133.2 (C-d), 128.7 (C-c), 127.9 (C-b), 126.9 (C-8), 122.9 (C-7), 68.1 (C-1), 48.5 (C-3), 45.6 (C-6), 36.4 (C-9), 32.6 (C-Cy), 25.7 (C-Cy), 24.7 (C-Cy), 24.0 (C-5).

**HRMS:** Calculated for C<sub>20</sub>H<sub>25</sub>ClN<sub>2</sub>O<sub>2</sub>: 360.1605, Found: 360.1613.

**I.R.** (thin film): ν 3427, 3055, 2935, 2857, 1659, 1511, 1493, 1406, 1345, 1253, 1221, 1098 and 1015 cm<sup>-1</sup>.

## II-102

### 1-Acetyl-N-*tert*-butyl-2-(pyridin-2-yl)-1,2,3,6-tetrahydropyridine-2-carboxamide



Mol. Wt.: 301.179 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-E**, using allylated UGI product **II-79** (132 mg, 0.4 mmol) and Hoveyda-Grubbs catalyst 2<sup>nd</sup> Generation (6 mg, 0.01 mmol). Purification by flash chromatography using (EtOAc : DCM = 20 : 80) gave the desired product in 72 % isolated yield (87 mg, 0.29 mmol).

**Nature:** Light brown oil.

**R<sub>f</sub>:** (EtOAc : DCM = 1 : 9) = 0.22.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 8.64 (br s, 1H, NH), 8.45 (br s, 1H, H-e), 7.65-7.49 (m, 1H, H-c), 7.15– 7.00 (m, 2H, H-b,d), 6.04 – 5.82 (m, 1H, H-9), 5.71-5.55 (m, 1H, H-8), 4.13 (br s, 2H, H-7), 2.85-2.73 (m, 2H, H-10), 2.18 (s, 3H, H-6), 1.29 (s, 9H, H-4).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.5 (C-5), 170.2 (C-2), 161.4 (C-a), 153.1 (C-e), 147.7 (C-c), 136.8 (C-b), 126.2 (C-d), 124.8 (C-9), 121.7 (C-8), 68.5 (C-1), 50.9 (C-3), 45.2 (C-7), 36.8 (C-10), 28.6 (C-4), 23.5 (C-6).

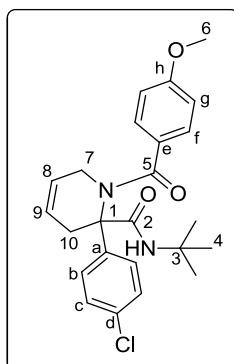
**HRMS:** Calculated for C<sub>17</sub>H<sub>23</sub>N<sub>3</sub>O<sub>2</sub>: 301.179, Found: 301.1801.

**I.R.** (thin film): ν 3235, 3060, 2971, 2931, 2876, 1677, 1604, 1591, 1434, 1367, 1279, 1224 and 1021cm<sup>-1</sup>.



## II-103

### N-tert-butyl-2-(4-chlorophenyl)-1-(4-methoxybenzoyl)-1,2,3,6-tetrahydropyridine-2-carboxamide



Mol. Wt.: 426.171 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-E**, using allylated Ugi product **II-80** (182 mg, 0.4 mmol) and Hoveyda-Grubbs catalyst 2<sup>nd</sup> Generation (6 mg, 0.01 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 4 : 96) gave the desired product in 68 % isolated yield (116 mg, 0.27 mmol).

**Nature:** Light brown oil.

**R<sub>f</sub>:** (Et<sub>2</sub>O : DCM = 0.4 : 9.6) = 0.32.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.55 (d, *J* = 8.8 Hz, 2H, H-f), 7.28 (d, *J* = 8.7 Hz, 2H, H-c), 7.21 (d, *J* = 9.0 Hz, 2H, H-b), 6.88 (d, *J* = 8.8 Hz, 2H, H-g), 6.78 (br s, 1H, NH), 5.90-5.85 (m, 1H, H-9), 5.50-5.46 (m, 1H, H-8), 3.98-3.84 (m, 2H, H-7), 3.79 (s, 3H, H-6), 3.15 (ddd, ABXY system, *J*<sub>ab</sub> = 17.1, *J*<sub>ax</sub> = 4.1, *J*<sub>ay</sub> = 1.9 Hz, 1H, H-10), 2.55 (ddd, ABXY system, *J*<sub>ba</sub> = 17.1, *J*<sub>bx</sub> = 3.8, *J*<sub>by</sub> = 2.0 Hz, 1H, H-10), 1.23 (s, 9H, H-4).

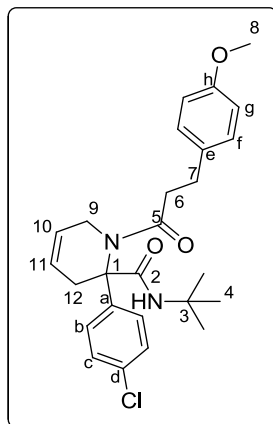
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 175.2 (C-5), 170.2 (C-2), 162.2 (C-h), 140.0 (C-a), 132.9 (C-d), 130.5 (C-f), 128.5 (C-c), 128.0 (C-e), 127.3 (C-b), 126.1 (C-9), 123.0 (C-8), 114.0 (C-g), 68.1 (C-1), 55.5 (C-6), 51.2 (C-3), 48.3 (C-7), 34.4 (C-10), 28.6 (C-4).

**HRMS:** Calculated for C<sub>24</sub>H<sub>27</sub>ClN<sub>2</sub>O<sub>3</sub>: 426.171, Found: 426.1729.

**I.R.** (thin film): ν 3432, 3046, 2967, 2935, 2870, 2841, 1676, 1636, 1607, 1548, 1510, 1394, 1255, 1171, 1096 and 1032 cm<sup>-1</sup>.

## II-104

### N-*tert*-butyl-2-(4-chlorophenyl)-1-(3-(4-methoxyphenyl)propanoyl)-1,2,3,6-tetrahydropyridine-2-carboxamide



Mol. Wt.: 454.203g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-E**, using allylated Ugi product **II-81** (193 mg, 0.4 mmol) and Hoveyda-Grubbs catalyst 2<sup>nd</sup> Generation (6 mg, 0.01 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : PE = 50 : 50) gave the desired product in 72 % isolated yield (131 mg, 0.288 mmol).

**Nature:** Light brown oil.

**R<sub>f</sub>:** (Et<sub>2</sub>O : PE = 5 : 5) = 0.22.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.15 (d, *J* = 8.7 Hz, 2H, H-c), 7.05 (d, *J* = 8.4 Hz, 2H, H-f), 7.01 (d, *J* = 8.5 Hz, 2H, H-b), 6.76 (d, *J* = 8.7 Hz, 2H, H-g), 6.63 (br s, 1H, NH), 5.96-5.92 (m, 1H, H-11), 5.70 – 5.61 (m, 1H, H-10), 4.01-3.88 (m, 2H, H-9), 3.72 (s, 3H, H-8), 2.96 (dd, ABX system, *J*<sub>ab</sub> = 16.2, *J*<sub>ax</sub> = 4.9 Hz, 1H, H-12), 2.83 (t, *J* = 7.4 Hz, 2H, H-7), 2.67-2.63 (m, 2H, H-6), 2.29 (dd, ABX system, *J*<sub>ba</sub> = 16.2, *J*<sub>bx</sub> = 2.7 Hz, 1H, H-12), 1.21 (s, 9H, H-4).

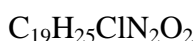
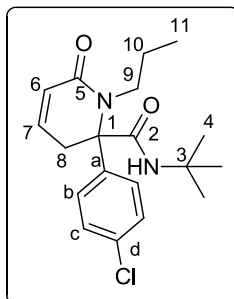
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 174.5 (C-5), 170.7 (C-2), 158.1 (C-h), 140.2 (C-a), 133.1 (C-e), 132.7 (C-d), 129.5 (C-c), 128.5 (C-f), 127.6 (C-b), 127.3 (C-11), 122.7 (C-10), 113.9 (C-g), 69.1 (C-1), 55.3 (C-8), 51.2 (C-3), 44.8 (C-9), 37.5 (C-6), 37.0 (C-12), 30.0 (C-7), 28.5 (C-4).

**HRMS:** Calculated for C<sub>26</sub>H<sub>31</sub>ClN<sub>2</sub>O<sub>3</sub>: 454.2033, Found: 454.2012.

**I.R.** (thin film): ν 3429, 2967, 2935, 2873, 2838, 1673, 1611, 1513, 1492, 1405, 1367, 1247, 1097, 1036 and 1015 cm<sup>-1</sup>.

## II-109

### N-(*tert*-butyl)-2-(4-chlorophenyl)-6-oxo-1-propyl-1,2,3,6-tetrahydropyridine-2-carboxamide



Mol. Wt.: 348.161 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-E**, using allylated Ugi product **II-82** (181 mg, 0.4 mmol) and Hoveyda-Grubbs catalyst 2<sup>nd</sup> Generation (6 mg, 0.01mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 10 : 90) gave the desired product in 72 % isolated yield (100 mg, 0.29 mmol).

**Nature:** Light brown oil.

**R<sub>f</sub>:** (Et<sub>2</sub>O : DCM = 1 : 9) = 0.3.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 7.30 (d,  $J$  = 8.8 Hz, 2H, H-c), 7.23 (d,  $J$  = 8.8 Hz, 2H, H-b), 6.43 (ddd,  $J$  = 9.8, 5.2, 3.3 Hz, 1H, H-7), 5.90 (dd,  $J$  = 9.8, 1.0 Hz, 1H, H-6), 5.64 (br s, 1H, NH), 3.30 (ddd, ABXY system,  $J_{ab}$  = 17.7,  $J_{ax}$  = 5.2,  $J_{ay}$  = 1.0 Hz, 1H, H-8), 3.15 (ddd, ABXY system,  $J_{ab}$  = 12.9,  $J_{ax}$  = 11.1,  $J_{ay}$  = 4.9 Hz, 1H, H-9), 2.86 (ddd, ABXY system,  $J_{ba}$  = 12.9,  $J_{bx}$  = 11.3,  $J_{by}$  = 5.0 Hz, 1H, H-9), 2.79 (ddd, ABXY system,  $J_{ba}$  = 17.7,  $J_{bx}$  = 3.0,  $J_{by}$  = 2.6 Hz, 1H, H-8), 1.60-1.50 (m, 1H, H-10), 1.29 (br s, 10H, H-4,10), 0.62 (t,  $J$  = 7.4 Hz, 3H, H-11).

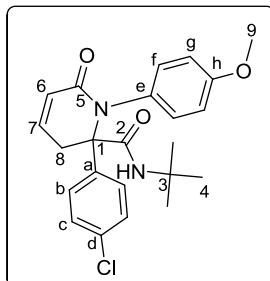
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz):  $\delta$  (ppm) 170.0 (C-5), 165.5 (C-2), 138.6 (C-7), 137.3 (C-a), 134.6 (C-d), 129.6 (C-c), 128.9 (C-b), 125.1 (C-6), 72.7 (C-1), 52.3 (C-3), 47.4 (C-9), 36.6 (C-8), 28.5 (C-4), 22.4 (C-10), 11.5 (C-11).

**HRMS:** Calculated for [M-CONHMe<sub>3</sub>] C<sub>14</sub>H<sub>15</sub>ClNO: 248.0843, Found: 248.0831.

**I.R.** (thin layer):  $\nu$  3449, 3058, 2971, 2934, 2876, 1667, 1612, 1510, 1455, 1403, 1368, 1221, 1098 and 1016 cm<sup>-1</sup>.

## **II-110**

### **N-tert-butyl-2-(4-chlorophenyl)-1-(4-methoxyphenyl)-6-oxo-1,2,3,6-tetrahydropyridine-2-carboxamide**



Mol. Wt.: 412.155 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-E**, using allylated Ugi product **II-83** (207 mg, 0.4 mmol) and Hoveyda-Grubbs catalyst 2<sup>nd</sup> Generation (6 mg, 0.01mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 5 : 95) gave the desired product in 82 % isolated yield (135 mg, 0.33 mmol).

**Nature:** Light brown oil.

**R<sub>f</sub>:** (Et<sub>2</sub>O : DCM = 0.5 : 9.5) = 0.23.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 7.08 (d,  $J$  = 8.5 Hz, 4H, H-c,b), 6.78 (dd,  $J$  = 8.8, 6.3 Hz, 4H, H-f,g), 6.72 (d,  $J$  = 7.1 Hz, 1H, H-6), 5.10 (br s, 1H, NH), 4.87 (dd,  $J$  = 12.9, 8.1 Hz, 1H, H-7), 3.70 (s, 3H, H-9), 2.69 (qd,  $J$  = 16.6, 10.5 Hz, 2H, H-8), 0.92 (s, 9H, H-4).

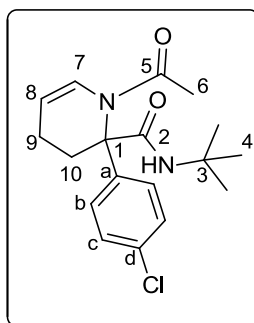
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz):  $\delta$  (ppm) 174.8 (C-2), 166.7 (C-5), 158.7 (C-h), 135.9 (C-a), 134.5 (C-d), 133.6 (C-7), 129.1 (C-c), 128.3 (C-b), 128.2 (C-e), 127.7 (C-6), 125.3 (C-f), 114.4 (C-g), 80.4 (C-1), 55.6 (C-9), 51.8 (C-3), 48.3 (C-7), 33.6 (C-8), 27.9 (C-4).

**HRMS:** Calculated for [M-CONHCMe<sub>3</sub>] C<sub>18</sub>H<sub>16</sub>ClNO<sub>2</sub>: 313.0869, Found: 313.0856.

**I.R.** (thin layer):  $\nu$  3432, 3035, 2983, 2922, 2874, 1665, 1615, 1513, 1445, 1409, 1375, 1225, 1097 and 1013 cm<sup>-1</sup>.

## **II-111**

### **1-Acetyl-N-*tert*-butyl-2-(4-chlorophenyl)-1,2,3,4-tetrahydropyridine-2-carboxamide**



Mol. Wt.: 334.145 g.mol<sup>-1</sup>

A solution of 1-acetyl-N-*tert*-butyl-2-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine-2-carboxamide **II-100** (101 mg, 0.3 mmol) and carbonylchlorohydridotris(triphenylphosphine)ruthenium (II) (14 mg, 0.015 mmol) in toluene (0.3 M) were refluxed for 1.5 hrs. The resulting mixture was filtered then the solvent was evaporated under reduced pressure. The crude residue obtained was purified by flash chromatography using (Et<sub>2</sub>O : DCM = 10 : 90) affording the desired product in 81 % isolated yield (82 mg, 0.25 mmol).

**Nature:** Yellow oil.

**R<sub>f</sub>:** (Et<sub>2</sub>O : PE = 1 : 9) = 0.31.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.25 (d, *J* = 8.8 Hz, 2H, H-c), 7.06 (d, *J* = 8.2 Hz, 2H, H-b), 6.61 (br s, 1H, H-7), 5.68 (br s, 1H, NH), 4.96-4.87 (m, 1H, H-8), 2.47 – 2.40 (m, 1H, H-10), 2.23 (s, 3H, H-6), 2.14 (dt, ABX<sub>2</sub> system, *J*<sub>ab</sub> = 13.7, *J*<sub>ax</sub> = 4.5 Hz, 1H, H-10), 2.02-1.97 (m, 1H, H-9), 1.55-1.46 (m, 1H, H-9), 1.22 (s, 9H, H-4).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 170.3 (C-5), 169.5 (C-2), 137.1 (C-a), 133.4 (C-d), 128.9 (C-c), 128.4 (C-b), 125.6 (C-7), 108.1 (C-8), 68.2 (C-1), 51.3 (C-3), 34.7 (C-10), 28.5 (C-4), 23.1 (C-6), 19.2 (C-9).

**HRMS:** Calculated for C<sub>18</sub>H<sub>23</sub>ClN<sub>2</sub>O<sub>2</sub>: 334.1448, Found: 334.1444.

**I.R.** (thin film): ν 3431, 3073, 2971, 2931, 2848, 1676, 1650, 1513, 1493, 1455, 1374, 1341, 1275, 1221, 1099 and 1013 cm<sup>-1</sup>.

## **Experimental part for Chapter III**



## Experimental Part for Chapter III

### *General Procedures*

#### ➤ **General procedure III-A for $\beta$ -lactam Synthesis from Ugi adducts**

To a solution of Ugi adduct (1.0 equiv.) in DMSO (0.5 M) was added sodium hydride 60% (2.5 equiv.), the resulting mixture was stirred at room temperature under Argon till a homogenous solution was obtained, followed by the addition of diiodomethane (1.5 equiv.). The resulting solution was stirred at room temperature for 1 to 4 hours depending on the reaction progress checked by TLC. After the completion of the reaction, it was diluted with  $\text{CH}_2\text{Cl}_2$  and extracted with water. The organic phase was dried over  $\text{MgSO}_4$  and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel to give the target  $\beta$ -lactam.

#### ➤ **General procedure III-B for Aminolysis of malonate esters**

A mixture of 1.0 equiv. of amine and 1.3 equiv. of malonate ester was heated without solvent at 200 °C for 30 min. under microwave radiations using Anton Paar Monowave 300. The reaction mixture was extracted with  $\text{CH}_2\text{Cl}_2$  and the crude was purified by flash column chromatography on silica gel to afford the desired product.

#### ➤ **General procedure III-C for $\beta$ -lactam Synthesis from malonate amide esters**

To a solution of malonate amide ester (1.0 equiv.) in DMSO (0.5 M) was added sodium hydride 60 % (2.5 equiv.), the resulting mixture was stirred at room temperature under Argon till a homogenous solution was obtained, followed by the addition of diiodomethane (1.5 equiv.). The resulting solution was stirred at room temperature for 1 to 2 hours depending on the reaction progress checked by TLC. After the completion of the reaction, it was diluted with  $\text{CH}_2\text{Cl}_2$  and extracted with water. The organic phase was dried over  $\text{MgSO}_4$  and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel to give the corresponding  $\beta$ -lactam.

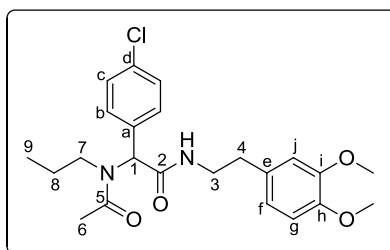


➤ **Biological assay**

Chemical compounds were individually tested against a panel of one Gram-positive bacteria (*Staphylococcus aureus*) and one Gram-negative bacteria (*Escherichia coli*) using Muller Hinton agar medium (Oxoid). The anti-fungal activities of the compounds were tested against one fungi (*Candida albicans*) using Sabouraud dextrose agar medium (Oxoid). Each of the compounds was dissolved in DMSO and solution of the concentration 1 mg /mL was prepared. Separately paper discs of Whatman filter paper were prepared with standard size (5 cm), were cut and sterilized in an autoclave. The paper discs soaked in the desired concentration of the complex solution were placed aseptically in the petri dishes containing Muller Hinton agar medium (Oxoid) seeded with *Staphylococcus aureus*, *E. coli* and *Candida albicans* using Sabouraud dextrose agar medium (Oxoid). The petri dishes were incubated at 36 °C and the inhibition zones were recorded after 24 h of incubation. Each treatment was replicated three times. The antibacterial activity of a common standard antibiotic *ampicillin* and antifungal *Colitrimazole* was also recorded using the same procedure with the same concentration and solvents.

### III-29

#### 2-(4-chlorophenyl)-N-(3,4-dimethoxyphenethyl)-2-(N-propylacetamido)acetamide



Mol. Wt.: 432.182 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-A**, using 4-chlorobenzaldehyde (141 mg, 1.0 mmol), propylamine (0.08 ml, 1.0 mmol), acetic acid (0.06 ml, 1.0 mmol) and 4-(2-isocyanoethyl)-1,2-dimethoxybenzene (191 mg, 1.0 mmol). Purification by flash chromatography using (pure EtOAc) gave the desired product in 92 % isolated yield (400 mg, 0.92 mmol).

**Nature:** White solid.

**M.P.** = 137-139 °C.

**R<sub>f</sub>** (EtOAc) = 0.32.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.31 (2d, *J* = 8.4 Hz, 4H, H-b,c), 6.79 (d, *J* = 8.0 Hz, 1H, H-g), 6.73 – 6.67 (m, 2H, H-f,j), 6.22 (br s, 1H, NH), 5.68 (s, 1H, H-1), 3.89 (s, 3H, OMe), 3.86 (s, 3H, OMe), 3.64-3.56 (m, 1H, H-3), 3.53-3.45 (m, 1H, H-3), 3.25 (t, *J* = 8.1 Hz, 2H, H-7), 2.78 (t, *J* = 6.9 Hz, 2H, H-4), 2.18 (s, 3H, H-6), 1.51-1.42 (m, 1H, H-8), 1.16-1.07 (m, 1H, H-8), 0.75 (t, *J* = 7.3 Hz, 3H, H-9).

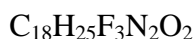
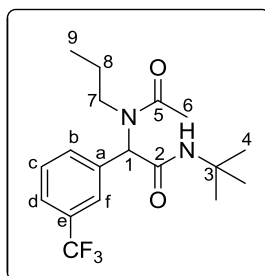
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.5 (C-5), 169.5 (C-2), 148.9 (C-i), 147.6 (C-h), 134.3 (C-a), 134.1 (C-d), 131.2 (C-e), 130.5 (C-b), 128.9 (C-c), 120.7 (C-f), 111.9 (C-j), 111.2 (C-g), 62.3 (C-1), 55.9 (C-OMe), 55.8 (C-OMe), 50.0 (C-7), 40.8 (C-3), 35.1 (C-4), 22.9 (C-8), 21.9 (C-6), 11.2 (C-9).

**HRMS:** Calculated for C<sub>23</sub>H<sub>29</sub>ClN<sub>2</sub>O<sub>4</sub>: 432.1816, Found: 432.1827.

**I.R.** (thin film): ν 3435, 3008, 2965, 2937, 2877, 2839, 1679, 1632, 1515, 1492, 1465, 1364, 1262, 1237, 1157, 1094 and 1029 cm<sup>-1</sup>.

### III-31

#### N-(*tert*-butyl)-2-(N-propylacetamido)-2-(3-(trifluoromethyl)phenyl)acetamide



Mol. Wt.: 358.187 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-A**, using 3-trifluoromethyl benzaldehyde (0.13 ml, 1.0 mmol), propylamine (0.08 ml, 1.0 mmol), acetic acid (0.06 ml, 1.0 mmol) and *tert*-butyl isocyanide (0.11 ml, 1.0 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 10 : 90) gave the desired product in 83 % isolated yield (298 mg, 0.83 mmol).

**Nature:** Colourless oil.

**R<sub>f</sub>** (Et<sub>2</sub>O : DCM = 1 : 9) = 0.2.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 7.59 – 7.50 (m, 3H, H-c,d,f), 7.42 (t,  $J$  = 7.6 Hz, 1H, H-b), 6.06 (br s, 1H, NH), 5.81 (s, 1H, H-1), 3.22 (t,  $J$  = 8.0 Hz, 2H, H-7), 2.12 (s, 3H, H-6), 1.46-1.37 (m, 1H, H-8), 1.28 (s, 9H, H-4), 0.99-0.89 (m, 1H, H-8), 0.63 (t,  $J$  = 7.3 Hz, 3H, H-9).

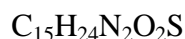
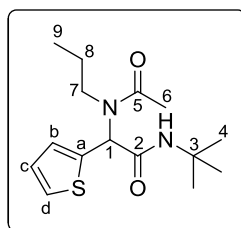
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz):  $\delta$  (ppm) 171.7 (C-5), 168.6 (C-2), 137.1 (C-a), 132.4 (C-f), 131.1 (q,  $J$  = 32.3 Hz, C-CF<sub>3</sub>), 129.1 (C-b), 125.8 (C-c), 125.0 (C-d), 122.5 (C-e), 61.9 (C-1), 51.7 (C-3), 49.6 (C-7), 28.6 (C-4), 22.9 (C-8), 21.9 (C-6), 11.2 (C-9).

**HRMS:** Calculated for [M-CONHMe<sub>3</sub>] C<sub>13</sub>H<sub>16</sub>F<sub>3</sub>NO: 259.1184, Found: 259.1189.

**I.R.** (thin film):  $\nu$  3426, 2970, 2935, 2877, 1684, 1630, 1515, 1455, 1331, 1251, 1169 and 1077 cm<sup>-1</sup>.

### III-33

#### N-(*tert*-butyl)-2-(N-propylacetamido)-2-(thiophen-2-yl)acetamide



Mol. Wt.: 296.156 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-A**, using thiophene-2-carboxaldehyde (0.09 ml, 1.0 mmol), propylamine (0.08 ml, 1.0 mmol), acetic acid (0.06 ml, 1.0 mmol) and *tert*-butyl isocyanide (0.11 ml, 1.0 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 15 : 85) gave the desired product in 67 % isolated yield (199 mg, 0.67 mmol).

**Nature:** White solid.

**M.P.** = 121-123 °C.

**R<sub>f</sub>** (Et<sub>2</sub>O : DCM = 1.5 : 8.5) = 0.23.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.27 (d, *J* = 5.1 Hz, 1H, H-d), 7.08 (d, *J* = 3.2 Hz, 1H, H-b), 6.93 (t, *J* = 4.2 Hz, 1H, H-c), 6.08 (br s, 1H, NH), 5.99 (s, 1H, H-1), 3.26 – 3.09 (m, 2H, H-7), 2.10 (s, 3H, H-6), 1.51 – 1.39 (m, 1H, H-8), 1.26 (s, 9H, H-4), 1.11-1.01 (m, 1H, H-8), 0.68 (t, *J* = 7.4 Hz, 3H, H-9).

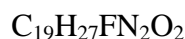
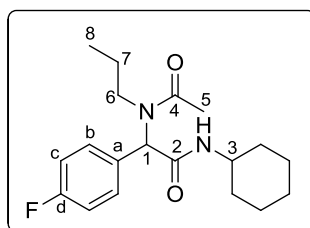
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.3 (C-5), 168.4 (C-2), 137.2 (C-a), 128.9 (C-b), 127.4 (C-d), 126.4 (C-c), 57.3 (C-1), 51.5 (C-3), 48.9 (C-7), 28.6 (C-4), 22.9 (C-8), 21.8 (C-6), 11.3 (C-9).

**HRMS:** Calculated for C<sub>15</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>S: 296.1558, Found: 296.1554.

**I.R.** (thin film): ν 3421, 2970, 2934, 2876, 1683, 1623, 1517, 1455, 1418, 1367, 1257, 1138 and 1035 cm<sup>-1</sup>.

### III-38

#### N-cyclohexyl-2-(4-fluorophenyl)-2-(N-propylacetamido)acetamide



Mol. Wt.: 334.206 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-A**, using 4-fluorobenzaldehyde (0.11 ml, 1.0 mmol), propylamine (0.08 ml, 1.0 mmol), acetic acid (0.06 ml, 1.0 mmol) and cyclohexylisocyanide (109 mg, 1.0 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 20 : 80) gave the desired product in 81 % isolated yield (271 mg, 0.81 mmol).

**Nature:** White solid.

**M.P.** = 150-152 °C.

**R<sub>f</sub>** (Et<sub>2</sub>O : DCM = 2 : 8) = 0.26.

**<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz):** δ (ppm) 7.44-7.37 (m, 2H, H-c), 7.08 (t, *J* = 7.8 Hz, 2H, H-b), 6.03 (d, *J* = 6.7 Hz, 1H, NH), 5.86 (s, 1H, H-1), 3.88-3.76 (m, 1H, H-3), 3.29 (t, *J* = 7.9 Hz, 2H, H-6), 2.21 (s, 3H, H-5), 1.94-1.91 (m, 2H, H-Cy), 1.71-1.61 (m, 3H, H-Cy), 1.55-1.46 (m, 1H, H-7), 1.42-1.36 (m, 2H, H-Cy), 1.22 – 1.06 (m, 4H, H-7,Cy), 0.75 (t, *J* = 6.9 Hz, 3H, H-8).

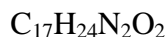
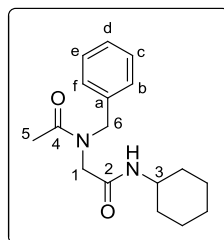
**<sup>13</sup>C-NMR (CDCl<sub>3</sub>, 100.6 MHz):** δ (ppm) 171.6 (C-4), 168.8 (C-2), 162.6 (d, *J* = 248.1 Hz, C-d), 131.6 (C-a), 131.1 (C-b), 115.8 (C-c), 61.4 (C-1), 49.5 (C-6), 48.5 (C-3), 32.8 (C-Cy), 32.8 (C-Cy), 25.5 (C-Cy), 24.7 (C-Cy), 22.9 (C-7), 21.9 (C-5), 11.2 (C-8).

**HRMS:** Calculated for C<sub>19</sub>H<sub>27</sub>FN<sub>2</sub>O<sub>2</sub>: 334.2057, Found: 334.2067.

**I.R. (thin film):** ν 3425, 2936, 2857, 1677, 1629, 1510, 1451, 1417, 1228 and 1162 cm<sup>-1</sup>.

### III-40

#### N-benzyl-N-(2-(cyclohexylamino)-2-oxoethyl)acetamide



Mol. Wt.: 288.184 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-A**, using formaldehyde (0.08 ml, 1.0 mmol), benzylamine (0.11 ml, 1.0 mmol) that were stirred together for 1 hr at RT then acetic acid (0.06 ml, 1.0 mmol) and cyclohexylisocyanide (109 mg, 1.0 mmol) were added. Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 40 : 60) gave the desired product in 81 % isolated yield (234 mg, 0.81 mmol).

**Nature:** White solid.

**M.P.** = 122-124 °C.

**R<sub>f</sub>**: (Et<sub>2</sub>O : PE = 4 : 6) = 0.25.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) (mixture of rotamers) δ 7.39-7.31 (m, 6H, H-Ar), 7.21 (d, *J* = 6.3 Hz, 2H, H-Ar), 6.30 (d, *J* = 6.7 Hz, 1H, NH), 5.69 (s, 1H, NH), 4.68 (s, 2H, H-6), 4.64 (s, 1H, H-6), 3.96 (s, 2H, H-1), 3.92 (s, 1H, H-1), 3.80 – 3.63 (m, 2H, H-3), 2.23 (s, 3H, H-5), 2.15 (s, 2H, H-5), 1.90-1.87 (m, 2H, H-Cy), 1.76-1.60 (m, 7H, H-Cy), 1.45-1.28 (m, 4H, H-Cy), 1.24-1.10 (m, 4H, H-Cy), 0.98-0.89 (m, 1H, H-Cy).

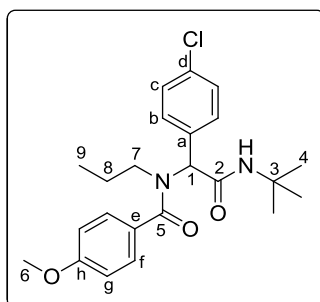
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) (mixture of rotamers) 171.9 (C-4), 171.5 (C-4), 167.9 (C-2), 166.9 (C-2), 137.0 (C-a), 135.8 (C-a), 129.1 (C-Ar), 129.0 (C-Ar), 128.6 (C-Ar), 128.1 (C-Ar), 127.9 (C-Ar), 126.6 (C-Ar), 53.4 (C-6), 52.5 (C-6), 50.7 (C-1), 50.5 (C-1), 48.3 (C-3), 48.2 (C-3), 32.9 (C-Cy), 32.8 (C-Cy), 25.5 (C-Cy), 25.4 (C-Cy), 24.8 (C-Cy), 24.7 (C-Cy), 21.8 (C-5), 21.5 (C-5).

**HRMS:** Calculated for C<sub>17</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>: 288.1838, Found: 288.1825.

**I.R.** (thin film): ν 3436, 3061, 2971, 2935, 2878, 1668, 1630, 1547, 1490, 1404, 1225, 1098 and 1014 cm<sup>-1</sup>.

### III-42

#### N-(2-(*tert*-butylamino)-1-(4-chlorophenyl)-2-oxoethyl)-4-methoxy-N-propylbenzamide



Mol. Wt.: 416.187 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-A**, using 4-chlorobenzaldehyde (141 mg, 1.0 mmol), propylamine (0.08 ml, 1.0 mmol), 4-methoxybenzoic acid (152 mg, 1.0 mmol) and *tert*-butyl isocyanide (0.11 ml, 1.0 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 5 : 95) gave the desired product in 77 % isolated yield (320 mg, 0.77 mmol).

**Nature:** Light yellow oil.

**R<sub>f</sub>** (Et<sub>2</sub>O : DCM = 0.5 : 9.5) = 0.28.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 7.38 – 7.24 (m, 6H, H-b,c,f), 6.84 (d,  $J$  = 8.8 Hz, 2H, H-g), 6.35 (br s, 1H, NH), 5.47 (s, 1H, H-1), 3.76 (s, 3H, H-6), 3.31 – 3.15 (m, 2H, H-7), 1.46-1.35 (m, 1H, H-8), 1.30 (s, 9H, H-4), 1.13 – 1.01 (m, 1H, H-8), 0.52 (t,  $J$  = 7.2 Hz, 3H, H-9).

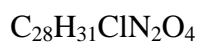
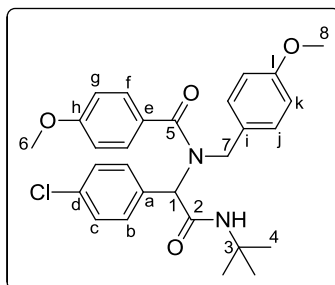
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz):  $\delta$  (ppm) 172.7 (C-5), 168.8 (C-2), 160.8 (C-h), 134.5 (C-a), 134.1 (C-d), 130.2 (C-c), 128.9 (C-b), 128.6 (C-f), 128.5 (C-e), 113.8 (C-g), 64.4 (C-1), 55.4 (C-6), 51.6 (C-3), 50.9 (C-7), 28.6 (C-4), 22.6 (C-8), 11.2 (C-9).

**HRMS:** Calculated for [M-CONHMe<sub>3</sub>] C<sub>18</sub>H<sub>19</sub>ClNO<sub>2</sub>: 316.1105, Found: 316.1106.

**I.R.** (thin film):  $\nu$  3425, 2968, 2936, 2876, 2840, 1683, 1610, 1513, 1457, 1409, 1367, 1251, 1173, 1095 and 1033 cm<sup>-1</sup>.

### III-45

#### N-(2-(*tert*-butylamino)-1-(4-chlorophenyl)-2-oxoethyl)-4-methoxy-N-(4-methoxybenzyl)benzamide



Mol. Wt.: 494.197 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-A**, using 4-chlorobenzaldehyde (141 mg, 1.0 mmol), 4-methoxybenzyl amine (0.13 ml, 1.0 mmol), 4-methoxybenzoic acid (152 mg, 1.0 mmol) and *tert*-butyl isocyanide (0.11 ml, 1.0 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : PE = 70 : 30) gave the desired product in 96 % isolated yield (475 mg, 0.96 mmol).

**Nature:** White solid.

**M.P.** = 145-147 °C.

**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 7 : 3) = 0.35.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.40 (d, *J* = 8.8 Hz, 2H, H-f), 7.26-7.17 (m, 4H, H-b,c), 6.93 (d, *J* = 8.5 Hz, 2H, H-j), 6.79 (d, *J* = 8.7 Hz, 2H, H-g), 6.67 (d, *J* = 8.7 Hz, 2H, H-k), 5.75 (br s, 1H, NH), 5.23 (s, 1H, H-1), 4.58 (d, AB system, *J<sub>ab</sub>* = 15.6 Hz, 1H, H-7), 4.36 (d, AB system, *J<sub>ab</sub>* = 16.1 Hz, 1H, H-7), 3.72 (s, 3H, H-6), 3.68 (s, 3H, H-8), 1.22 (s, 9H, H-4).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 173.1 (C-5), 168.2 (C-2), 161.1 (C-h), 158.8 (C-l), 134.3 (C-a), 134.2 (C-d), 130.8 (C-c), 129.3 (C-b), 128.9 (C-f), 128.8 (C-j), 128.5 (C-i), 128.1 (C-e), 113.9 (C-g), 113.8 (C-k), 65.4 (C-1), 55.4 (C-6), 55.3 (C-8), 53.5 (C-7), 51.6 (C-3), 28.6 (C-4).

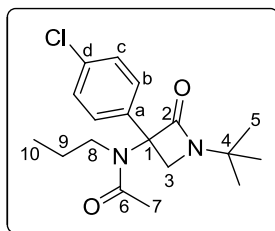
**HRMS:** Calculated for [M-4-ClPh-CHCONHCMe<sub>3</sub>] C<sub>16</sub>H<sub>16</sub>NO<sub>3</sub>: 270.1136, Found: 270.1121.

**I.R.** (thin film): ν 3426, 3003, 2967, 2937, 2911, 2839, 1679, 1610, 1513, 1457, 1394, 1250, 1175 and 1034 cm<sup>-1</sup>.



### III-25

#### N-(1-(*tert*-butyl)-3-(4-chlorophenyl)-2-oxoazetidin-3-yl)-N-propylacetamide



Mol. Wt.: 336.160 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **III-A**, using Ugi adduct **II-40** (162 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol) and diiodomethane (0.06 ml, 0.75 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 5 : 95) gave the desired product in 72 % isolated yield (122 mg, 0.36 mmol).

**Nature:** White solid.

**M.P.** = 172-172 °C.

**R<sub>f</sub>** (Et<sub>2</sub>O : DCM = 0.5 : 9.5) = 0.31.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.25 (2d, *J* = 8.6 Hz, 4H, H-b,c), 3.74, 3.64 (d, AB system, *J<sub>ab</sub>* = 6.8 Hz, 2H, H-3), 3.62 – 3.54 (m, 1H, H-8), 3.39 – 3.30 (m, 1H, H-8), 2.08 (s, 3H, H-7), 1.61-1.50 (m, 2H, H-9), 1.30 (s, 9H, H-5), 0.85 (t, *J* = 7.4 Hz, 3H, H-10).

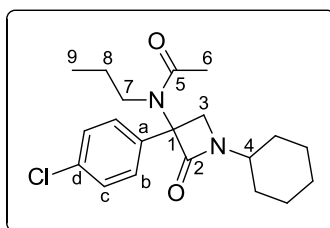
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.2 (C-6), 164.3 (C-2), 135.9 (C-a), 133.7 (C-d), 128.8 (C-c), 127.6 (C-b), 71.6 (C-1), 53.5 (C-4), 53.0 (C-3), 49.2 (C-8), 27.6 (C-5), 24.2 (C-9), 22.0 (C-7), 11.1 (C-10).

**HRMS:** Calculated for [M-CONCMe<sub>3</sub>] C<sub>13</sub>H<sub>16</sub>ClNO: 237.0920, Found: 237.0922.

**I.R.** (thin film): ν 2974, 2935, 2907, 2877, 1747, 1639, 1492, 1414, 1369, 1249, 1096 and 1014 cm<sup>-1</sup>.

### III-27

#### N-(3-(4-chlorophenyl)-1-cyclohexyl-2-oxoazetidin-3-yl)-N-propylacetamide



Mol. Wt.: 362.176 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **III-A**, using Ugi product **II-46** (175 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol) and diiodomethane (0.06 ml, 0.75 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 5 : 95) gave the desired product in 71 % isolated yield (128 mg, 0.35 mmol).

**Nature:** White solid.

**M.P.** = 122-124 °C.

**R<sub>f</sub>** (Et<sub>2</sub>O : DCM = 0.5 : 9.5) = 0.33.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.24 (2d, *J* = 8.4, 7.6 Hz, 4H, H-b,c), 3.77, 3.67 (d, AB system, *J<sub>ab</sub>* = 6.8 Hz, 2H, H-3), 3.63 – 3.52 (m, 2H, H-4,7), 3.39-3.31 (m, 1H, H-7), 2.08 (s, 3H, H-6), 1.83-1.80 (m, 2H, H-Cy), 1.74-1.70 (m, 2H, H-Cy), 1.59-1.55 (m, 3H, H-Cy,8), 1.38-1.20 (m, 4H, H-Cy,8), 1.12-1.03 (m, 1H, H-Cy), 0.84 (t, *J* = 7.3 Hz, 3H, H-9).

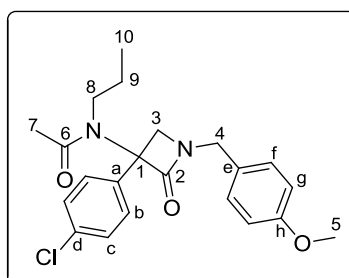
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.1 (C-5), 164.8 (C-2), 135.6 (C-a), 133.8 (C-d), 128.8 (C-c), 127.6 (C-b), 72.5 (C-1), 53.2 (C-3), 50.9 (C-4), 49.3 (C-7), 30.5 (C-Cy), 25.2 (C-Cy), 24.8 (C-Cy), 24.2 (C-8), 22.0 (C-6), 11.0 (C-9).

**HRMS:** Calculated for [M-CONCy] C<sub>13</sub>H<sub>15</sub>ClNO: 237.0831, Found: 237.0738.

**I.R.** (thin film): ν 2968, 2936, 2859, 1747, 1638, 1493, 1411, 1370, 1236, 1096 and 1013 cm<sup>-1</sup>.

### III-28

#### N-(3-(4-chlorophenyl)-1-(4-methoxybenzyl)-2-oxoazetidin-3-yl)-N-propylacetamide



Mol. Wt.: 400.155 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **III-A**, using Ugi product **II-47** (194 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol) and diiodomethane (0.06 ml, 0.75 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 5 : 95) gave the desired product in 51 % isolated yield (102 mg, 0.25 mmol).

**Nature:** Deep yellow oil.

**R<sub>f</sub>** (Et<sub>2</sub>O : DCM = 0.5 : 9.5) = 0.32.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.22 (2d, *J* = 8.8 Hz, 4H, H-b,c), 7.10 (d, *J* = 8.4 Hz, 2H, H-f), 6.81 (d, *J* = 8.5 Hz, 2H, H-g), 4.37 (d, AX system, *J<sub>ax</sub>* = 14.6 Hz, 1H, H-4), 4.27 (d, AX system, *J<sub>ax</sub>* = 14.7 Hz, 1H, H-4), 3.74 (s, 3H, H-5), 3.67 (d, AB system, *J<sub>ab</sub>* = 6.9 Hz, 1H, H-3), 3.63-3.55 (m, 2H, H-3,8), 3.37-3.30 (m, 1H, H-8), 2.04 (s, 3H, H-7), 1.59-1.44 (m, 2H, H-9), 0.83 (t, *J* = 7.4 Hz, 3H, H-10).

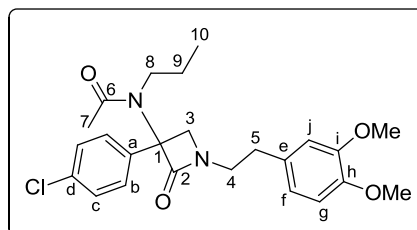
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.0 (C-6), 165.4 (C-2), 159.5 (C-h), 135.6 (C-a), 133.9 (C-d), 129.9 (C-f), 128.8 (C-c), 127.8 (C-b), 126.7 (C-e), 114.4 (C-g), 73.8 (C-1), 55.4 (C-5), 54.9 (C-3), 49.3 (C-8), 45.6 (C-4), 24.1 (C-9), 21.9 (C-7), 11.1 (C-10).

**HRMS:** Calculated for [M-CONCH<sub>2</sub>Ph-4-OMe] C<sub>13</sub>H<sub>16</sub>ClNO: 237.0920, Found: 237.0930.

**I.R.** (thin film): ν 3005, 2968, 2936, 2877, 2839, 1753, 1640, 1514, 1476, 1411, 1249, 1176, 1097 and 1035 cm<sup>-1</sup>.

### III-30

#### N-(3-(4-chlorophenyl)-1-(3,4-dimethoxyphenethyl)-2-oxoazetidin-3-yl)-N-propylacetamide



Mol. Wt.: 444.182 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **III-A**, using Ugi product **III-29** (217 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol) and diiodomethane (0.06 ml, 0.75 mmol). Purification by flash chromatography using (EtOAc : PE = 70 : 30) gave the desired product in 61 % isolated yield (136 mg, 0.31 mmol).

**Nature:** Light brown oil.

**R<sub>f</sub>** (EtOAc : PE = 7 : 3) = 0.26.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.24 (2d, *J* = 8.2 Hz, 4H, H-b,c), 6.81-6.76 (m, 3H, H-f,g,h), 3.91 (s, 3H, OMe), 3.87 (s, 3H, OMe), 3.77 (s, 2H, H-3), 3.71 (dt, ABX<sub>2</sub> system, *J*<sub>ab</sub> = 13.5, *J*<sub>ax</sub> = *J*<sub>bx</sub> = 6.7 Hz, 1H, H-4), 3.63-3.55 (m, 2H, H-4,8), 3.43 – 3.33 (m, 1H, H-8), 2.90 (t, *J* = 6.2 Hz, 2H, H-5), 2.16 (s, 3H, H-7), 1.63 – 1.51 (m, 1H, H-9), 1.48-1.39 (m, 1H, H-9), 0.90 (t, *J* = 7.3 Hz, 3H, H-10).

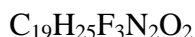
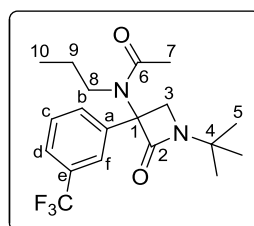
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.0 (C-6), 165.6 (C-2), 149.1 (C-i), 147.9 (C-h), 135.3 (C-a), 133.8 (C-d), 130.1 (C-e), 128.7 (C-c), 127.8 (C-b), 120.6 (C-f), 111.5 (C-g), 111.3 (C-j), 73.8 (C-1), 55.9 (C-OMe), 55.8 (C-OMe), 55.7 (C-3), 49.3 (C-8), 42.4 (C-4), 33.1 (C-5), 24.0 (C-9), 21.9 (C-7), 11.0 (C-10).

**HRMS:** Calculated for [M-CON(CH<sub>2</sub>)Ph(OMe)<sub>2</sub>] C<sub>13</sub>H<sub>16</sub>ClNO: 237.0915, Found: 237.0913.

**I.R.** (thin film): ν 3009, 2966, 2936, 2877, 2839, 1753, 1640, 1516, 1456, 1416, 1263, 1158, 1096 and 1029 cm<sup>-1</sup>.

### III-32

#### N-(1-(*tert*-butyl)-2-oxo-3-(3-(trifluoromethyl)phenyl)azetidin-3-yl)-N-propylacetamide



Mol. Wt.: 370.187 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **III-A**, using Ugi adduct **III-31** (179 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol) and diiodomethane (0.06 ml, 0.75 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : PE = 70 : 30) gave the desired product in 65 % isolated yield (121 mg, 0.33 mmol).

**Nature:** White solid.

**M.P.** = 146-148 °C.

**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 7 : 3) = 0.36.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.53 (s, 1H, H-f), 7.50 – 7.44 (m, 2H, H-b,d), 7.39 (t, *J* = 7.5 Hz, 1H, H-c), 3.80 (d, AB system, *J<sub>ab</sub>* = 6.9 Hz, 1H, H-3), 3.69 – 3.59 (m, 2H, H-3,8), 3.44 – 3.34 (m, 1H, H-8), 2.11 (s, 3H, H-7), 1.65 – 1.52 (m, 2H, H-9), 1.33 (s, 9H, H-5), 0.87 (t, *J* = 7.3 Hz, 3H, H-10).

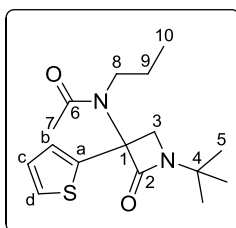
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.2 (C-6), 164.0 (C-2), 138.3 (C-a), 131.0 (q, *J* = 32.19 Hz, C-CF<sub>3</sub>), 129.3 (C-b), 129.2 (C-d), 125.4 (C-e), 124.7 (C-c), 122.7 (C-f), 71.8 (C-1), 53.6 (C-4), 53.2 (C-3), 49.2 (C-8), 27.6 (C-5), 24.2 (C-9), 21.9 (C-7), 11.0 (C-10).

**HRMS:** Calculated for [M-CONCMe<sub>3</sub>] C<sub>14</sub>H<sub>16</sub>F<sub>3</sub>NO: 271.1184, Found: 271.1176.

**I.R.** (thin film): ν 2974, 2935, 2907, 2877, 1749, 1639, 1476, 1413, 1383, 1330, 1232, 1133 and 1080 cm<sup>-1</sup>.

**III-34**

**N-(1-(*tert*-butyl)-2-oxo-3-(thiophen-2-yl)azetidin-3-yl)-N-propylacetamide**

Mol. Wt.: 308.156 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **III-A**, Ugi adduct **III-33** (148 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol) and diiodomethane (0.06 ml, 0.75 mmol). Purification by flash chromatography using gradient (Et<sub>2</sub>O : PE = 50 : 50 – 70 : 30) gave the desired product in 44 % isolated yield (68 mg, 0.22 mmol).

**Nature:** Yellow oil.

$$R_f (\text{Et}_2\text{O} : \text{PE} = 7 : 3) = 0.43.$$

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.16 (d, *J* = 5.0 Hz, 2H, H-b,d), 6.89 – 6.83 (dd, *J* = 4.0, 4.7 Hz 1H, H-c), 3.71 (s, 2H, H-3), 3.57 (ddd, ABX<sub>2</sub> system, *J* = 16.4, 10.8, 6.0 Hz, 1H, H-8), 3.29 (ddd, ABX<sub>2</sub> system, *J* = 15.6, 10.4, 6.0 Hz, 1H, H-8), 2.05 (s, 3H, H-7), 1.58-1.48 (m, 2H, H-9), 1.27 (s, 9H, H-5), 0.83 (t, *J* = 7.4 Hz, 3H, H-10).

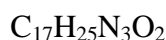
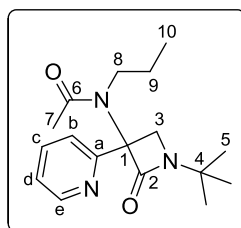
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.2 (C-6), 163.4 (C-2), 141.0 (C-a), 126.1 (C-b), 125.8 (C-c), 125.7 (C-d), 68.9 (C-1), 54.0 (C-3), 53.4 (C-4), 48.7 (C-8), 27.5 (C-5), 24.0 (C-9), 21.9 (C-7), 11.0 (C-10).

**HRMS:** Calculated for [M-CONCMe<sub>3</sub>] C<sub>11</sub>H<sub>15</sub>NOS: 209.0874, Found: 209.0864.

**I.R.** (thin film):  $\nu$  2974, 2935, 2905, 2877, 1747, 1639, 1461, 1413, 1256, 1148 and 1011  $\text{cm}^{-1}$

### III-36

#### N-(1-(*tert*-butyl)-2-oxo-3-(pyridin-2-yl)azetidin-3-yl)-N-propylacetamide



Mol. Wt.: 303.195 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **III-A**, using Ugi adduct **II-53** (146 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol) and diiodomethane (0.06 ml, 0.75 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 25 : 75) gave the desired product in 44 % isolated yield (66 mg, 0.22 mmol).

**Nature:** Dark yellow oil.

**R<sub>f</sub>** (Et<sub>2</sub>O : DCM = 2.5 : 7.5) = 0.29.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 8.49 (d, *J* = 4.2 Hz, 1H, H-e), 7.54 (td, *J* = 7.7, 1.4 Hz, 1H, H-c), 7.08-7.05 (m, 2H, H-b,d), 4.24, 3.41 (d, AX system, *J*<sub>ax</sub> = 5.9 Hz, 2H, H-3), 3.74 (ddd, ABX<sub>2</sub> system, *J* = 15.2, 10.0, 5.6 Hz, 1H, H-8), 3.46 (ddd, ABX<sub>2</sub> system, *J* = 15.6, 9.6, 6.4 Hz, 1H, H-8), 2.13 (s, 3H, H-7), 1.69-1.60 (m, 2H, H-9), 1.33 (s, 9H, H-5), 0.87 (d, *J* = 7.4 Hz, 3H, H-10).

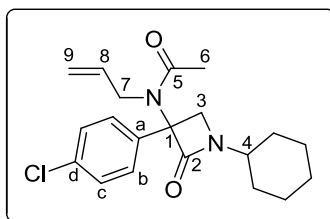
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.3 (C-6), 164.2 (C-2), 156.1 (C-a), 149.7 (C-e), 136.6 (C-c), 122.3 (C-b), 119.5 (C-d), 74.2 (C-1), 53.5 (C-4), 52.0 (C-3), 49.6 (C-8), 27.6 (C-5), 24.3 (C-9), 21.9 (C-7), 11.1 (C-10).

**HRMS:** Calculated for C<sub>17</sub>H<sub>25</sub>N<sub>3</sub>O<sub>2</sub>: 303.1947, Found: 303.1941.

**I.R.** (thin film): ν 3058, 2974, 2935, 2907, 2877, 1747, 1639, 1589, 1464, 1415, 1381, 1247, 1152 and 1011 cm<sup>-1</sup>.

### III-37

#### N-allyl-N-(3-(4-chlorophenyl)-1-cyclohexyl-2-oxoazetidin-3-yl)acetamide



Mol. Wt.: 360.160 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **III-A**, Ugi adduct **II-59** (174 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol) and diiodomethane (0.06 ml, 0.75 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 5 : 95) gave the desired product in 71% isolated yield (129 mg, 0.36 mmol).

**Nature:** Yellow solid.

**M.P.** = 131-133 °C.

**R<sub>f</sub>** (Et<sub>2</sub>O : DCM = 0.5 : 9.5) = 0.35.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.42 (d, *J* = 7.7 Hz, 2H, H-c), 7.35 (d, *J* = 7.9 Hz, 2H, H-b), 5.97 – 5.85 (m, 1H, H-8), 5.24 (2d, *J*<sub>cis-1,3</sub> = 10.8, *J*<sub>trans-1,3</sub> = 17.2 Hz, 2H, H-9), 4.51 (d, ABX system, *J*<sub>ax</sub> = 17.9 Hz, 1H, H-7), 4.16 (d, ABX system, *J*<sub>ax</sub> = 17.9 Hz, 1H, H-7), 3.91 (2d, AB system, *J*<sub>ab</sub> = 6.6 Hz, 2H, H-3), 3.68-3.63 (m, 1H, H-4), 2.16 (s, 3H, H-6), 1.91-1.80 (m, 4H, H-Cy), 1.70-1.66 (m, 1H H-Cy), 1.47 – 1.29 (m, 4H H-Cy), 1.22-1.14 (m, 1H H-Cy).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.8 (C-5), 164.4 (C-2), 135.4 (C-a), 134.1 (C-8), 133.9 (C-d), 128.9 (C-c), 127.8 (C-b), 115.5 (C-9), 72.3 (C-1), 52.9 (C-3), 50.9 (C-4), 49.3 (C-7), 30.5 (C-Cy), 30.4 (C-Cy), 25.2 (C-Cy), 24.8 (C-Cy), 22.0 (C-6).

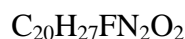
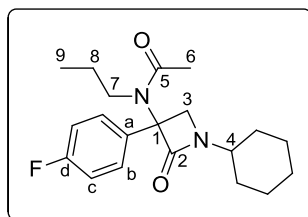
**HRMS:** Calculated for [M-CONCy] C<sub>13</sub>H<sub>14</sub>ClNO: 235.0764, Found: 235.0771.

**I.R.** (thin film): ν 3089, 2937, 2858, 1747, 1651, 1639, 1493, 1405, 1350, 1264, 1096 and 1013 cm<sup>-1</sup>.



### III-39

#### N-(1-cyclohexyl-3-(4-fluorophenyl)-2-oxoazetidin-3-yl)-N-propylacetamide



Mol. Wt.: 346.206 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **III-A**, using Ugi adduct **III-38** (167 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol) and diiodomethane (0.06 ml, 0.75 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : PE = 70 : 30) gave the desired product in 65 % isolated yield (112 mg, 0.32 mmol).

**Nature:** Light yellow oil.

**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 7 : 3) = 0.33.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.43 (2d, *J* = 6.0, 5.6 Hz, 2H, H-c), 7.05 (t, *J* = 8.5 Hz, 2H, H-b), 3.88 (d, AB system, *J<sub>ab</sub>* = 6.8 Hz, 1H, H-3), 3.79 (d, AB system, *J<sub>ab</sub>* = 6.7 Hz, 1H, H-3), 3.76 – 3.64 (m, 2H, H-4,7), 3.51 – 3.39 (m, 1H, H-7), 2.19 (s, 3H, H-6), 1.96 – 1.79 (m, 4H, H-Cy), 1.70-1.63 (m, 3H, H-Cy,8), 1.49 – 1.31 (m, 4H, H-Cy,8), 1.25 – 1.14 (m, 1H, H-Cy), 0.95 (t, *J* = 7.4 Hz, 3H, H-9).

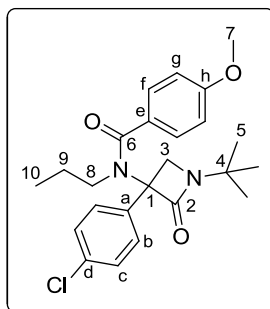
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.1 (C-5), 165.0 (C-2), 163.3 (d, *J* = 247.48 Hz, C-d), 132.9 (C-a), 128.1 (C-b), 115.6 (d, *J* = 21.13 Hz, C-c), 72.4 (C-1), 53.3 (C-3), 50.9 (C-4), 49.2 (C-7), 30.5 (C-Cy), 25.2 (C-Cy), 24.8 (C-Cy), 24.2 (C-8), 22.0 (C-6), 11.0 (C-9).

**HRMS:** Calculated for [M-CONCy] C<sub>13</sub>H<sub>16</sub>FNO: 221.1211, Found: 221.1208.

**I.R.** (thin film): ν 2968, 2936, 2859, 1746, 1639, 1605, 1510, 1412, 1370, 1236, 1163 and 1014 cm<sup>-1</sup>.

### III-43

#### N-(1-(*tert*-butyl)-3-(4-chlorophenyl)-2-oxoazetidin-3-yl)-4-methoxy-N-propylbenzamide



Mol. Wt.: 428.187 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **III-A**, using Ugi adduct **III-42** (209 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol) and diiodomethane (0.06 ml, 0.75 mmol). Purification by flash chromatography using gradient (Et<sub>2</sub>O : PE = 30 : 70 – 50 : 50) gave the desired product in 47 % isolated yield (100 mg, 0.23 mmol).

**Nature:** Light yellow oil.

**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 4 : 6) = 0.16.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.42 (d, *J* = 8.6 Hz, 2H, H-c), 7.29 (2d, *J* = 8.8 Hz, 4H, H-f,b), 6.84 (d, *J* = 8.7 Hz, 2H, H-g), 3.83, 3.75 (d, AB system, *J<sub>ab</sub>* = 6.8 Hz, 2H, H-3), 3.76 (s, 3H, H-7), 3.58-3.51 (m, 1H, H-8), 3.48 – 3.39 (m, 1H, H-8), 1.44 – 1.38 (m, 2H, H-9), 1.33 (s, 9H, H-5), 0.60 (t, *J* = 7.3 Hz, 3H, H-10).

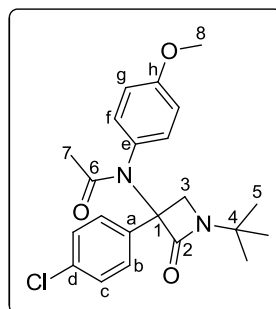
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 172.5 (C-6), 164.4 (C-2), 160.8 (C-h), 136.2 (C-a), 133.8 (C-d), 128.8 (C-b), 128.6 (C-c), 128.3 (C-e), 127.9 (C-f), 113.8 (C-g), 72.1 (C-1), 55.4 (C-7), 53.6 (C-4), 52.7 (C-3), 50.4 (C-8), 27.6 (C-5), 24.3 (C-9), 11.0 (C-10).

**HRMS:** Calculated for [M-CONCMe<sub>3</sub>] C<sub>19</sub>H<sub>20</sub>ClNO<sub>2</sub>: 329.1178, Found: 329.1175.

**I.R.** (thin film): ν 2973, 2936, 2907, 2877, 1741, 1711, 1627, 1513, 1459, 1368, 1252, 1174, 1096 and 1032 cm<sup>-1</sup>.

### III-44

#### N-(1-(*tert*-butyl)-3-(4-chlorophenyl)-2-oxoazetidin-3-yl)-N-(4-methoxyphenyl)acetamide



Mol. Wt.: 400.155 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **III-A**, using Ugi adduct **II-55** (194 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol) and diiodomethane (0.06 ml, 0.75 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 5 : 95) gave the desired product in 34 % isolated yield (68 mg, 0.17 mmol).

**Nature:** Yellow oil.

**R<sub>f</sub>** (Et<sub>2</sub>O : DCM = 0.5 : 9.5) = 0.17.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.46 (d, *J* = 8.6 Hz, 2H, H-c), 7.21 (d, *J* = 8.6 Hz, 2H, H-b), 6.90 (br s, 2H, H-f), 6.77 (d, *J* = 7.8 Hz, 2H, H-g), 3.93, 3.85 (d, AB system, *J<sub>ab</sub>* = 6.3 Hz, 2H, H-3), 3.73 (s, 3H, H-8), 1.72 (s, 3H, H-7), 1.25 (s, 9H, H-5).

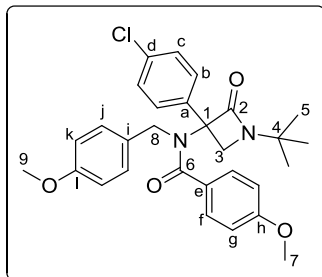
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.9 (C-6), 163.8 (C-2), 159.4 (C-h), 135.7 (C-a), 133.9 (C-d), 133.4 (C-e), 130.5 (C-f), 129.5 (C-b), 128.4 (C-c), 114.4 (C-g), 73.1 (C-1), 55.4 (C-8), 53.3 (C-4), 51.7 (C-3), 27.5 (C-5), 23.8 (C-7).

**HRMS:** Calculated for [M-CONCMe<sub>3</sub>] C<sub>17</sub>H<sub>16</sub>ClNO<sub>2</sub>: 301.0875, Found: 301.0865.

**I.R.** (thin film): ν 2975, 2936, 2907, 2840, 1750, 1657, 1510, 1443, 1379, 1249 1094 and 1033 cm<sup>-1</sup>.

### III-46

#### N-(1-(tert-butyl)-3-(4-chlorophenyl)-2-oxoazetidin-3-yl)-4-methoxy-N-(4-methoxybenzyl)benzamide



Mol. Wt.: 506.197 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **III-A**, using Ugi adduct **III-45** (248 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol) and diiodomethane (0.06 ml, 0.75 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 4 : 96) gave the desired product in 50 % isolated yield (126 mg, 0.25 mmol).

**Nature:** Light yellow solid.

**M.P.** = 184-186 °C.

**R<sub>f</sub>** (Et<sub>2</sub>O : DCM = 0.4 : 9.6) = 0.26.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.51 (d, *J* = 8.6 Hz, 2H, H-c), 7.48 (d, *J* = 8.8 Hz, 2H, H-f), 7.37 (d, *J* = 8.7 Hz, 2H, H-b), 7.11 (d, *J* = 8.7 Hz, 2H, H-j), 6.90 (d, *J* = 8.8 Hz, 2H, H-k), 6.86 (d, *J* = 8.7 Hz, 2H, H-g), 4.99 (s, 2H, H-8), 3.98, 3.81 (d, AB system, *J<sub>ab</sub>* = 6.8 Hz, 2H, H-3), 3.84 (s, 3H, H-7), 3.83 (s, 3H, H-9), 1.21 (s, 9H, H-5).

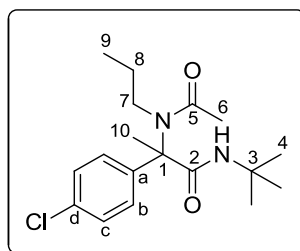
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 172.7 (C-6), 163.9 (C-2), 161.2 (C-h), 158.9 (C-l), 135.8 (C-a), 133.7 (C-d), 130.2 (C-i), 129.3 (C-f), 128.8 (C-b), 128.1 (C-j), 127.8 (C-c), 127.6 (C-e), 113.9 (C-g), 113.8 (C-k), 71.9 (C-1), 55.4 (C-7), 55.3 (C-9), 53.4 (C-4), 51.5 (C-3), 51.4 (C-8), 27.4 (C-5).

**HRMS:** Calculated for [M-CONCMe<sub>3</sub>, -4-OMe-PhCH<sub>2</sub>] C<sub>16</sub>H<sub>13</sub>ClNO<sub>2</sub>: 286.0651, Found: 286.0405.

**I.R.** (thin film): ν 2973, 2937, 2907, 2840, 1748, 1630, 1513, 1464, 1384, 1251, 1174 and 1034 cm<sup>-1</sup>.

### III-26

#### N-(*tert*-butyl)-2-(4-chlorophenyl)-3-iodo-2-(N-propylacetamido)propanamide



Mol. Wt.: 338.176 g.mol<sup>-1</sup>

This compound was separated during the reaction of Ugi adduct **II-40** (162 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol) and diiodomethane (0.06 ml, 0.75 mmol) in DMF according to the general procedure **III-A** during one of the optimization trials. Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 10 : 90) gave the intermediate in 29 % isolated yield (49 mg, 0.14 mmol).

**Nature:** White solid.

**M.P.** = 120-122 °C.

**R<sub>f</sub>** (Et<sub>2</sub>O : DCM = 1 : 9) = 0.17.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.19 (d, *J* = 8.8 Hz, 2H, H-c), 7.09 (d, *J* = 8.6 Hz, 2H, H-b), 6.96 (br s, 1H, NH), 3.39 – 3.24 (m, 2H, H-7), 2.13 (s, 3H, H-6), 1.68 – 1.57 (m, 4H, H-8,10), 1.52-1.43 (m, 1H, H-8), 1.24 (s, 9H, H-4), 0.81 (t, *J* = 7.4 Hz, 3H, H-9).

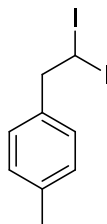
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 172.4 (C-5), 171.8 (C-2), 142.0 (C-a), 132.6 (C-d), 128.4 (C-b), 126.9 (C-c), 68.9 (C-1), 51.0 (C-3), 48.5 (C-7), 28.5 (C-4), 27.7 (C-10), 24.1 (C-6), 23.7 (C-8), 11.4 (C-9).

**HRMS:** Calculated for [M-CONHMe<sub>3</sub>] C<sub>13</sub>H<sub>18</sub>ClNO: 239.1077, Found: 239.1044.

**I.R.** (thin film): ν 3431, 2969, 2935, 2877, 1670, 1632, 1548, 1493, 1407, 1225, 1099 and 1014 cm<sup>-1</sup>.

**III-50**

**1-(2,2-Diiodoethyl)-4-methylbenzene**



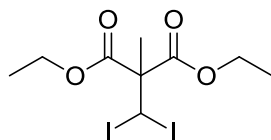
A solution of  $\text{CH}_2\text{I}_2$  (0.49 ml, 6.15 mmol) in THF was added dropwise to a solution of LiHMDS 20 % (5.6 ml, 6.0 mmol) in a mixture of THF and ether (1 : 1) at  $-78^\circ\text{C}$ . After 20 min, a solution of 4-methylbenzyl bromide (555 mg, 3 mmol) in THF was added dropwise. The reaction mixture was allowed to warm slowly to room temperature overnight in the dark. The crude was then extracted with water and  $\text{Et}_2\text{O}$  and dried over  $\text{MgSO}_4$ . The solvent was evaporated and purification of the crude mixture by flash chromatography using pure P.E. afforded the desired product in 78 % yield (876 mg, 2.35 mmol).

**Nature:** Dark red liquid.

**$^1\text{H-NMR}$**  ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  (ppm) 7.25 – 7.13 (m, 4H), 5.12 (t,  $J = 7.4$  Hz, 1H), 3.75 (d,  $J = 7.4$  Hz, 2H), 2.37 (s, 3H).

**III-52**

**Diethyl 2-(iodomethyl)-2-methylmalonate**

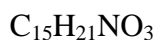
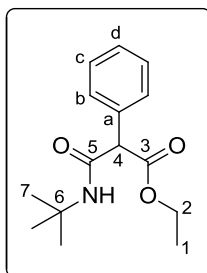


$\text{NaH}$  60 % (240 mg, 6 mmol) was stirred in diethyl ether (5 ml) for 30 min, followed by the addition of diethyl methylmalonate (0.86 ml, 5 mmol). Stirring was continued for 1.5 h and then iodoform was added (1.968 g, 5 mmol). The resulting mixture was refluxed in diethyl ether for 12 h. After extraction and evaporation of solvent, the desired product was obtained in quantitative yield (2200 mg, 5 mmol) and was used without further purification.

**$^1\text{H-NMR}$**  ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  (ppm) 5.71 (s, 1H), 4.16 (ddd,  $J = 14.2, 7.0, 1.5$  Hz, 4H), 1.73 (s, 3H), 1.23 (t,  $J = 7.1$  Hz, 6H).

**III-54**

**Ethyl 3-(*tert*-butylamino)-3-oxo-2-phenylpropanoate**



Mol. Wt.: 263.152 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **III-B**, using *tert*-butyl amine (0.21 ml, 2.0 mmol) and diethyl 2-phenylmalonate (0.56 ml, 2.6 mmol). Purification by flash chromatography using gradient eluent (EtOAc : PE = 10 : 90 – 20 : 80) gave the desired product in 64 % isolated yield (337 mg, 1.28 mmol).

**Nature:** White solid.

**M.P.** = 134-136 °C.

**R<sub>f</sub>** (EtOAc : PE = 2 : 8) = 0.45.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.45-7.36 (m, 5H, H-Ar), 6.75 (br s, 1H, NH), 4.46 (s, 1H, H-4), 4.24 (dq, ABX<sub>3</sub> system,  $J_{ab} = 10.8$ ,  $J_{ax} = J_{bx} = 7.2$  Hz, 2H, H-2), 1.38 (s, 9H, H-7), 1.30 (t,  $J = 7.1$  Hz, 3H, H-1).

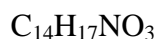
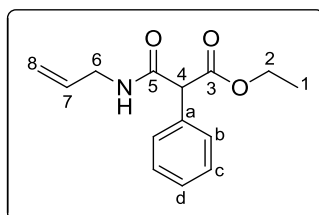
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.2 (C-3), 166.2 (C-5), 134.7 (C-a), 129.0 (C-c), 128.2 (C-b), 128.1 (C-d), 61.8 (C-2), 59.4 (C-4), 51.5 (C-6), 28.6 (C-7), 14.0 (C-1).

**HRMS:** Calculated for [M-CONHMe<sub>3</sub>] C<sub>10</sub>H<sub>12</sub>O: 164.0837, Found: 164.0825.

**I.R.** (thin film): ν 3421, 3362, 3068, 3033, 2980, 2936, 2907, 2874, 1715, 1673, 1539, 1456, 1368, 1318, 1221, 1189 and 1032 cm<sup>-1</sup>.

### III-56

#### Ethyl 3-(allylamino)-3-oxo-2-phenylpropanoate



Mol. Wt.: 247.121 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **III-B**, using allyl amine (0.15 ml, 2.0 mmol) and diethyl 2-phenylmalonate (0.56 ml, 2.6 mmol). Purification by flash chromatography using gradient eluent (DCM : PE = 70 : 30 - 100 : 0) gave the desired product in 46 % isolated yield (226 mg, 0.91 mmol).

**Nature:** White solid.

**M.P.** = 74-76 °C.

**R<sub>f</sub>** (pure DCM) = 0.17.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.36-7.24 (m, 5H, H-Ar), 6.88 (brs, 1H, NH), 5.74 (ddt,  $J = 17.1, 10.3, 5.4$  Hz, 1H, H-7), 5.05 (2 dd,  $J_{1,2} = 1.4, J_{cis-1,3} = 7.0, J_{trans-1,3} = 13.7$  Hz, 2H, H-8), 4.47 (s, 1H, H-4), 4.14 (dq, ABX<sub>3</sub> system,  $J_{ab} = 10.8, J_{ax} = J_{bx} = 7.1$  Hz, 2H, H-2), 3.84-3.81 (m, 2H, H-6), 1.19 (t,  $J = 7.1$  Hz, 3H, H-1).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 170.9 (C-3), 167.2 (C-5), 134.1 (C-7), 133.7 (C-a), 129.1 (C-c), 128.3 (C-b), 128.2 (C-d), 116.3 (C-8), 62.0 (C-2), 58.6 (C-4), 42.0 (C-6), 14.0 (C-1).

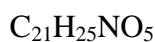
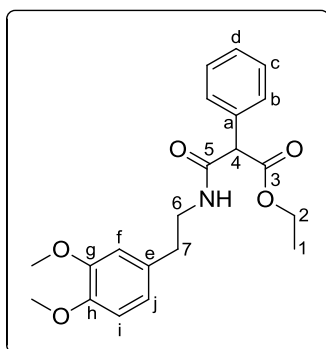
**HRMS:** Calculated for C<sub>14</sub>H<sub>17</sub>NO<sub>3</sub>: 247.1208, Found: 247.1205.

**I.R.** (thin film): ν 3432, 3376, 3089, 3069, 3033, 2987, 2931, 1720, 1671, 1530, 1455, 1320, 1264, 1191, 1027 cm<sup>-1</sup>.



### III-57

#### Ethyl 3-(3,4-dimethoxyphenethylamino)-3-oxo-2-phenylpropanoate



Mol. Wt.: 371.173 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **III-B**, using 2-(3,4-dimethoxyphenyl)ethylamine (0.34 ml, 2.0 mmol) and diethyl 2-phenylmalonate (0.56 ml, 2.6 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : PE = 80 : 20) gave the desired product in 53 % isolated yield (392 mg, 1.06 mmol).

**Nature:** Yellow oil.

**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 8 : 2) = 0.26.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 7.23 (br s, 5H, H-b, H-c, H-d), 6.76 (br s, 1H, NH), 6.69 (d,  $J$  = 8.0 Hz, 1H, H-i), 6.61 – 6.55 (m, 2H, H-f, H-j), 4.40 (s, 1H, H-4), 4.10 (dq, ABX<sub>3</sub> system,  $J_{ab}$  = 10.8,  $J_{ax}$  =  $J_{bx}$  = 7.2 Hz, 2H, H-2), 3.79 (s, 3H, OCH<sub>3</sub>), 3.76 (s, 3H, OCH<sub>3</sub>), 3.43 (q,  $J$  = 6.4 Hz, 2H, H-6), 2.67 (t,  $J$  = 6.9 Hz, 2H, H-7), 1.16 (t,  $J$  = 7.1 Hz, 3H, H-1).

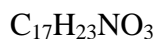
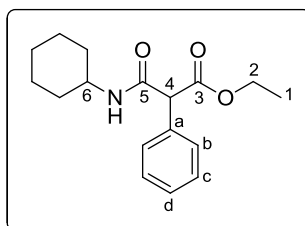
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz):  $\delta$  (ppm) 170.8 (C-3), 167.2 (C-5), 149.0 (C-h), 147.6 (C-g), 134.1 (C-a), 131.2 (C-e), 129.0 (C-c), 128.8 (C-d), 128.2 (C-b), 120.7 (C-j), 111.9 (C-f), 111.3 (C-i), 61.9 (C-4), 58.6 (C-2), 55.9 (C-OCH<sub>3</sub>), 55.8 (C-OCH<sub>3</sub>), 41.05 (C-6), 35.0 (C-7), 14.0 (C-1).

**HRMS:** Calculated for C<sub>21</sub>H<sub>25</sub>NO<sub>5</sub>: 371.1733, Found: 371.1747.

**I.R.** (thin film):  $\nu$  3430, 3375, 3066, 3033, 2962, 2939, 2839, 1721, 1667, 1593, 1516, 1466, 1322, 1237, 1190, 1028 cm<sup>-1</sup>.

### III-58

#### Ethyl 3-(cyclohexylamino)-3-oxo-2-phenylpropanoate



Mol. Wt.: 289.168 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **III-B**, using cyclohexylamine (0.23 ml, 2.0 mmol) and diethyl 2-phenylmalonate (0.56 ml, 2.6 mmol). Purification by flash chromatography using gradient eluent (DCM : Et<sub>2</sub>O = 100 : 0 - 98 : 2) gave the desired product in 54 % isolated yield (314 mg, 1.09 mmol).

**Nature:** White solid.

**M.P.** = 95-97 °C.

**R<sub>f</sub>** (Et<sub>2</sub>O : DCM = 0.2 : 9.8) = 0.36.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.34-7.24 (m, 5H, H-Ar), 6.74 (d, *J* = 6.7 Hz, 1H, NH), 4.41 (s, 1H, H-4), 4.12 (dq, ABX<sub>3</sub> system, *J<sub>ab</sub>* = 10.8, *J<sub>ax</sub>* = *J<sub>bx</sub>* = 7.1 Hz, 2H, H-2), 3.75-3.66 (m, 1H, H-6), 1.83-1.75 (m, 2H, H-Cy), 1.62-1.48 (m, 3H, H-Cy), 1.34-1.22 (m, 2H, H-Cy), 1.18 (t, *J* = 7.2 Hz, 3H, H-1), 1.15-1.03 (m, 3H, H-Cy).

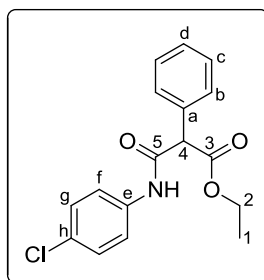
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.1 (C-3), 166.2 (C-5), 134.5 (C-a), 129.0 (C-c), 128.8 (C-d), 128.2 (C-b), 61.8 (C-2), 58.6 (C-4), 48.3 (C-6), 32.7 (C-Cy), 25.5 (C-Cy), 24.6 (C-Cy), 14.0 (C-1).

**HRMS:** Calculated for C<sub>17</sub>H<sub>23</sub>NO<sub>3</sub>: 289.1678, Found: 289.1676.

**I.R.** (thin film): ν 3420, 3366, 3068, 3033, 2985, 2937, 2857, 1718, 1663, 1532, 1454, 1372, 1317, 1190, 1163 and 1030 cm<sup>-1</sup>.

### III-59

#### Ethyl 3-((4-chlorophenyl)amino)-3-oxo-2-phenylpropanoate



Mol. Wt.: 317.082 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **III-B**, using 4-chloroaniline (255 mg, 2.0 mmol) and diethyl 2-phenylmalonate (0.56 ml, 2.6 mmol). Purification by flash chromatography using gradient eluent (DCM : PE = 40 : 60 – 70 : 30) gave the desired product in 73 % isolated yield (462 mg, 1.45 mmol).

**Nature:** Yellow oil.

**R<sub>f</sub>** (DCM : PE = 6 : 4) = 0.25.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 9.12 (br s, 1H, NH), 7.39 (d, *J* = 8.8 Hz, 2H, H-f), 7.36 (dd, *J* = 8.0, 1.6 Hz, 2H, H-c), 7.31-7.26 (m, 3H, H-b, H-d), 7.17 (d, *J* = 8.8 Hz, 2H, H-g), 4.54 (s, 1H, H-4), 4.17 (dq, ABX<sub>3</sub> system, *J*<sub>ab</sub> = 10.8, *J*<sub>ax</sub> = 7.2, *J*<sub>bx</sub> = 6.8 Hz, 2H, H-2), 1.19 (t, *J* = 7.1 Hz, 3H, H-1).

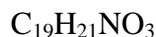
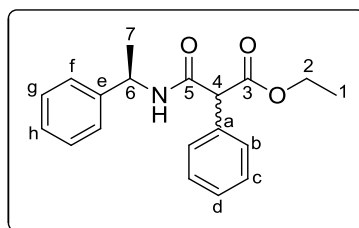
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.3 (C-3), 165.3 (C-5), 136.1 (C-e), 133.9 (C-a), 129.6 (C-h), 129.3 (C-c), 129.0 (C-g), 128.6 (C-d), 128.1 (C-b), 121.3 (C-f), 62.4 (C-2), 58.8 (C-4), 14.0 (C-1).

**HRMS:** Calculated for C<sub>17</sub>H<sub>16</sub>ClNO<sub>3</sub>: 317.0819, Found: 317.0831.

**I.R.** (thin film): ν 3407, 3334, 3302, 3068, 3035, 2986, 2940, 2908, 2874, 1717, 1686, 1596, 1537, 1493, 1400, 1374, 1322, 1252, 1190, 1094 and 1029 cm<sup>-1</sup>.

**III-60**

**Ethyl 3-oxo-2-phenyl-3-((1-phenylethyl)amino)propanoate**



Mol. Wt.: 311.152 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **III-B**, using (R)-1-phenylethyl amine (0.26 ml, 2.0 mmol) and diethyl 2-phenylmalonate (0.56 ml, 2.6 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : PE = 50 : 50) gave the desired product in 51 % isolated yield (317 mg, 1.02 mmol).

**Nature:** White solid.

**M.P.** = 82-84 °C.

**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 5 : 5) = 0.32.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) (mixture of diastereomers 1:1) 7.48-7.28 (m, 10H, H-Ar), 5.17 (2q, *J* = 7.0 Hz, 1H, H-6), 4.58, 4.57 (2s, 1H, H-4), 4.33 – 4.17 (2dq, ABX<sub>3</sub> system, *J*<sub>ab</sub> = 10.8, *J*<sub>ax</sub> = *J*<sub>bx</sub> = 7.2 Hz, 2H, H-2), 1.52 (2d, *J* = 6.8 Hz, 3H, H-7), 1.30 (2t, *J* = 7.1 Hz, 3H, H-1).

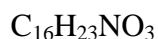
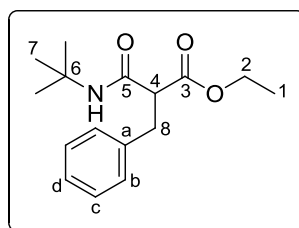
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) (mixture of diastereomers 1:1) 171.0 (C-3), 166.3 (C-5), 166.3 (C-5), 143.0 (C-e), 142.9 (C-e), 134.3 (C-a), 134.2 (C-a), 129.1 (C-c), 129.0 (C-c), 128.7 (C-g), 128.6 (C-g), 128.3 (C-d), 128.3 (C-b), 128.2 (C-b), 127.4 (C-h), 127.3 (C-h), 126.1 (C-f), 126.0 (C-f), 62.0 (C-2), 58.5 (C-4), 58.4 (C-4), 49.0 (C-6), 48.9 (C-6), 22.0 (C-7), 21.9 (C-7), 14.0 (C-1), 13.9 (C-1).

**HRMS:** Calculated for C<sub>19</sub>H<sub>21</sub>NO<sub>3</sub>: 311.1521, Found: 311.1533.

**I.R.** (thin film): ν 3423, 3089, 3067, 3033, 2984, 2933, 2874, 1720, 1668, 1525, 1455, 1373, 1318, 1190, 1164 and 1030 cm<sup>-1</sup>.

**III-61**

**Ethyl 2-benzyl-3-(*tert*-butylamino)-3-oxopropanoate**



Mol. Wt.: 277.168 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **III-B**, using *tert*-butyl amine (0.21 ml, 2.0 mmol) and diethyl 2-benzylmalonate (0.61 ml, 2.6 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 2 : 98) gave the desired product in 68 % isolated yield (379 mg, 1.37 mmol).

**Nature:** White solid.

**M.P.** = 64-66 °C.

**R<sub>f</sub>** (Et<sub>2</sub>O : DCM = 0.2 : 9.8) = 0.27.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.32-7.21 (m, 5H, H-Ar), 6.20 (br s, 1H, NH), 4.20-4.10 (m, 2H, H-2), 3.39 (td, *J* = 7.6, 1.6 Hz, 1H, H-4), 3.22 (dd, ABX system, *J<sub>ab</sub>* = 13.6, *J<sub>ax</sub>* = 6.8, *J<sub>bx</sub>* = 8.6 Hz, 2H, H-8), 1.33 (s, 9H, H-7), 1.19 (t, *J* = 7.1, 3H, H-1).

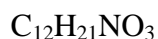
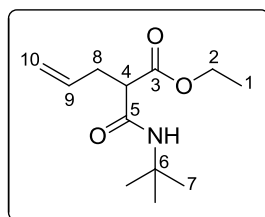
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.4 (C-3), 166.7 (C-5), 138.1 (C-a), 129.0 (C-c), 128.4 (C-b), 126.7 (C-d), 61.3 (C-2), 55.7 (C-4), 51.4 (C-6), 36.4 (C-8), 28.6 (C-7), 14.0 (C-1).

**HRMS:** Calculated for C<sub>16</sub>H<sub>23</sub>NO<sub>3</sub>: 277.1678, Found: 277.1669.

**I.R.** (thin film): ν 3438, 3088, 3066, 3031, 2979, 2935, 2908, 2873, 1741, 1716, 1681, 1604, 1516, 1455, 1367, 1254, 1221 and 1032 cm<sup>-1</sup>.

**III-62**

**Ethyl 2-(*tert*-butylcarbamoyl)pent-4-enoate**



Mol. Wt.: 227.152 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **III-B**, using *tert*-butyl amine (0.21 ml, 2.0 mmol) and diethyl 2-allylmalonate (0.52 ml, 2.6 mmol). Purification by flash chromatography using gradient eluent (Et<sub>2</sub>O : PE = 10 : 90 – 30 : 70) gave the desired product in 46 % isolated yield (210 mg, 0.92 mmol).

**Nature:** White solid.

**M.P.** = 70-72 °C.

**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 3 : 7) = 0.31.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 6.38 (br s, 1H, NH), 5.78 (ddt, *J* = 17.1, 10.1, 7.0 Hz, 1H, H-9), 5.19 – 5.06 (m, 2H, H-10), 4.22 (q, *J* = 7.1 Hz, 2H, H-2), 3.20 (t, *J* = 7.3 Hz, 1H, H-4), 2.65 (t, *J* = 7.1 Hz, 2H, H-8), 1.38 (s, 9H, H-7), 1.31 (t, *J* = 7.1 Hz, 3H, H-1).

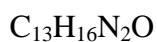
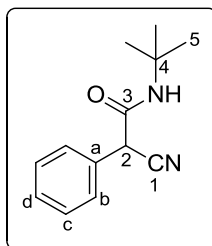
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.8 (C-3), 166.8 (C-5), 134.2 (C-9), 117.6 (C-10), 61.4 (C-2), 53.4 (C-4), 51.4 (C-6), 34.8 (C-8), 28.7 (C-7), 14.2 (C-1).

**HRMS:** Calculated for C<sub>12</sub>H<sub>21</sub>NO<sub>3</sub>: 227.1521, Found: 227.1524.

**I.R.** (thin film): ν 3436, 3083, 2980, 2933, 2909, 2873, 1718, 1677, 1535, 1456, 1393, 1367, 1253 and 1032 cm<sup>-1</sup>.

**III-63**

**N-(*tert*-butyl)-2-cyano-2-phenylacetamide**



Mol. Wt.: 216.126 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **III-B**, using *tert*-butyl amine (0.21 ml, 2.0 mmol) and ethyl 2-cyano-2-phenylacetate (0.45 ml, 2.6 mmol). Purification by flash chromatography using gradient eluent (Et<sub>2</sub>O : PE = 20 : 80 – 50 : 50) gave the desired product in 87 % isolated yield (376 mg, 1.74 mmol).

**Nature:** White solid.

**M.P.** = 129-131 °C.

**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 5 : 5) = 0.23.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.47 (br s, 5H, H-Ar), 5.81 (br s, 1H, NH), 4.61 (s, 1H, H-2), 1.36 (s, 9H, H-5).

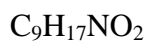
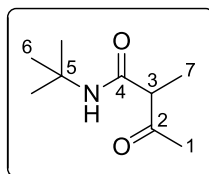
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 162.6 (C-3), 131.1 (C-a), 129.5 (C-c), 129.2 (C-d), 127.8 (C-b), 117.3 (C-1), 52.6 (C-4), 45.8 (C-2), 28.4 (C-5).

**HRMS:** Calculated for [M-CONH] C<sub>12</sub>H<sub>15</sub>N: 173.1204, Found: 173.1232.

**I.R.** (thin film): ν 3421, 3069, 3035, 2973, 2935, 2874, 2264, 1694, 1516, 1496, 1456 and 1217 cm<sup>-1</sup>.

**III-64**

**N-(*tert*-butyl)-2-methyl-3-oxobutanamide**



Mol. Wt.: 171.126 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **III-B**, using *tert*-butyl amine (0.21 ml, 2.0 mmol) and ethyl 2-acetyl-2-methylacetate (0.37 ml, 2.6 mmol). Purification by flash chromatography using gradient eluent (Et<sub>2</sub>O : PE = 30 : 70 – 60 : 40) gave the desired product in 36 % isolated yield (125 mg, 0.72 mmol).

**Nature:** White solid.

**M.P.** = 111-113 °C.

**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 6 : 4) = 0.24.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 5.80 (br s, 1H, NH), 3.20 (q, *J* = 7.1 Hz, 1H, H-3), 2.16 (s, 3H, H-1), 1.28 (d, *J* = 7.2 Hz, 3H, H-7), 1.27 (s, 9H, H-6).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 207.9 (C-2), 168.4 (C-4), 56.2 (C-3), 51.4 (C-5), 28.62 (C-6), 28.3 (C-1), 14.6 (C-7).

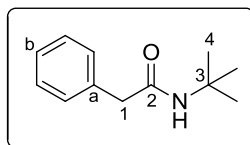
**HRMS:** Calculated for C<sub>9</sub>H<sub>17</sub>NO<sub>2</sub>: 171.1259, Found: 171.1255.

**I.R.** (thin film): ν 3436, 2971, 2938, 2876, 1706, 1679, 1513, 1456, 1366, 1221 and 1169 cm<sup>-1</sup>.



**III-65**

**N-*tert*-butyl-2-phenylacetamide**



Mol. Wt.: 191.131 g.mol<sup>-1</sup>

A solution of *tert*-butyl amine (0.21 ml, 2.0 mmol) and triethylamine (0.28 ml, 2.0 mmol) in dichloromethane (2 ml) at 0 °C was treated with 2-phenylacetyl chloride (0.27 ml, 2.0 mmol) drop wise under argon and the resulting mixture was stirred at 0 °C for 30 min then at room temperature for 3 hours. The reaction was then quenched with saturated aqueous ammonium chloride and extracted with dichloromethane. The organic phase was dried over magnesium sulfate, filtered and concentrated under vacuum. The residue was purified by flash chromatography using (Et<sub>2</sub>O : PE = 50 : 50) to afford the desired product in 90 % isolated yield (344 mg, 1.8 mmol).

**Nature:** White solid.

**M.P.** = 113-115 °C.

**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 5 : 5) = 0.37.

**<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz):** δ (ppm) 7.42-7.38 (m, 2H, H-Ar), 7.34-7.28 (m, 3H, H-Ar), 5.27 (br s, 1H, NH), 3.53 (s, 2H, H-1), 1.33 (s, 9H, H-4).

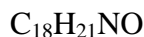
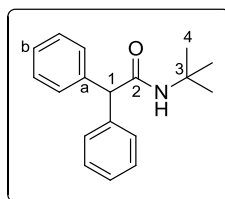
**<sup>13</sup>C-NMR (CDCl<sub>3</sub>, 100.6 MHz):** δ (ppm) 170.3 (C-2), 135.5 (C-a), 129.3 (C-Ar), 128.9 (C-Ar), 127.2 (C-d), 51.3 (C-3), 44.9 (C-1), 28.7 (C-4).

**HRMS:** Calculated for C<sub>12</sub>H<sub>17</sub>NO: 191.1310, Found: 191.1303.

**I.R. (thin film):** ν 3419, 3088, 3066, 3031, 2969, 2932, 2872, 1666, 1516, 1454, 1366, 1220 and 1031 cm<sup>-1</sup>.

**III-66**

**N-*tert*-butyl-2,2-diphenylacetamide**



Mol. Wt.: 267.162 g.mol<sup>-1</sup>

A solution of *tert*-butyl amine (0.21 ml, 2.0 mmol) and triethylamine (0.28 ml, 2.0 mmol) in dichloromethane (2 ml) at 0 °C was treated with 2,2'-diphenylacetyl chloride (461mg, 2.0 mmol) drop wise under argon and the resulting mixture was stirred at 0 °C for 30 min then at room temperature for 3 hours. The reaction was then quenched with saturated aqueous ammonium chloride and extracted with dichloromethane. The organic phase was dried over magnesium sulfate, filtered and concentrated under vacuum. The residue was purified by flash chromatography using (Et<sub>2</sub>O : PE = 50 : 50) to afford the desired product in 90 % isolated yield (482 mg, 1.8 mmol).

**Nature:** White solid.

**M.P.** = 206-208 °C.

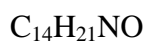
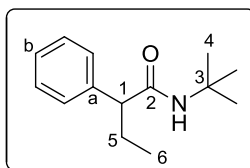
**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 5 : 5) = 0.23.

**<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz):** δ (ppm) 7.33-7.09 (m, 10H, H-Ar), 5.34 (br s, 1H, NH), 4.69 (s, 1H, H-1), 1.24 (s, 9H, H-4).

**<sup>13</sup>C-NMR (CDCl<sub>3</sub>, 100.6 MHz):** δ (ppm) 171.0 (C-2), 139.9 (C-a), 128.38 (C-Ar), 128.7 (C-Ar), 127.1 (C-b), 59.9 (C-1), 51.6 (C-3), 28.7 (C-4).

**III-66**

**N-*tert*-butyl-2-phenylbutanamide**



Mol. Wt.: 219.162 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-C**, using product **III-65** (191 mg, 1.0 mmol), sodium hydride (100 mg, 2.5 mmol), ethyl iodide (0.12 ml, 1.5 mmol). Purification by flash chromatography using (Et<sub>2</sub>O :P.E. = 6 : 4) gave the desired product in 69 % isolated yield (151 mg, 0.69 mmol).

**Nature:** Colourless oil.

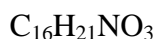
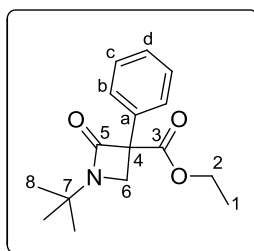
**R<sub>f</sub>:** (Et<sub>2</sub>O :P.E. = 6 : 4) = 0.25.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.28 – 7.14 (m, 5H, H-Ar), 5.15 (br s, 1H, NH), 3.03 (t, *J* = 7.6 Hz, 1H, H-1), 2.13 – 1.99 (m, 1H, H-5), 1.73 – 1.60 (m, 1H, H-5), 1.20 (s, 9H, H-4), 0.80 (t, *J* = 7.4 Hz, 3H, H-6).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 172.8 (C-2), 140.6 (C-a), 128.7 (C-Ar), 128.4 (C-Ar), 127.8 (C-Ar), 55.9 (C-1), 51.2 (C-3), 28.9 (C-4), 26.7 (C-5), 12.4 (C-6).

### III-55

#### Ethyl 1-(*tert*-butyl)-2-oxo-3-phenylazetidine-3-carboxylate



Mol. Wt.: 275.152 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **III-C**, using ethyl 3-(*tert*-butylamino)-3-oxo-2-phenylpropanoate **III-54** (132 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol) and diiodomethane (0.06 ml, 0.75 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : PE = 20 : 80) gave the desired product in 80 % isolated yield (110 mg, 0.4 mmol).

**Nature:** Colorless oil.

**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 2 : 8) = 0.18.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.52 (d, *J* = 7.3 Hz, 2H, H-b), 7.43-7.35 (m, 3H, H-c, H-d), 4.25 (q, *J* = 7.1 Hz, 2H, H-2), 4.08, 3.45 (d, AX system, *J*<sub>ax</sub> = 5.2 Hz, 2H, H-6), 1.40 (s, 9H, H-8), 1.27 (t, *J* = 7.1 Hz, 3H, H-1).

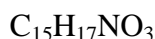
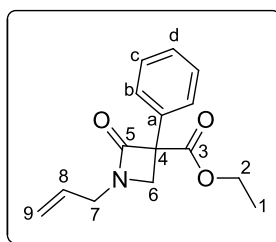
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 169.1 (C-3), 162.9 (C-5), 135.6 (C-a), 128.6 (C-b), 127.9 (C-d), 127.3 (C-c), 65.5 (C-4), 62.1 (C-2), 53.7 (C-7), 47.7 (C-6), 27.6 (C-8), 14.0 (C-1).

**HRMS:** Calculated for [M-NCOCMe<sub>3</sub>] C<sub>11</sub>H<sub>12</sub>O<sub>2</sub>: 176.0848, Found: 176.0829.

**I.R.** (thin film): ν 3090, 3066, 3030, 2979, 2906, 2874, 1751, 1601, 1498, 1449, 1380, 1227, 1146 and 1100 cm<sup>-1</sup>.

### III-68

#### Ethyl 1-allyl-2-oxo-3-phenylazetidine-3-carboxylate



Mol. Wt.: 259.121 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **III-C**, using ethyl 3-(allylamino)-3-oxo-2-phenylpropanoate **III-56** (124 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol) and diiodomethane (0.06 ml, 0.75 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : PE = 40 : 60) gave the desired product in 65 % isolated yield (84 mg, 0.32 mmol).

**Nature:** Light yellow oil.

**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 4 : 6) = 0.29.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 7.41 (d,  $J = 7.5$  Hz, 2H, H-b), 7.32-7.23 (m, 3H, H-c, H-d), 5.68 (ddt,  $J = 17.0, 10.3, 5.9$  Hz, 1H, H-8), 5.16 (2 dd,  $J_{1,2} = 0.8$ ,  $J_{cis-1,3} = 4.6$ ,  $J_{trans-1,3} = 11.7$  Hz, 2H, H-9), 4.14 (q,  $J = 7.1$  Hz, 2H, H-2), 4.01, 3.42 (d, AX system,  $J_{ax} = 5.5$  Hz, 2H, H-6), 3.83 (dd, ABX system,  $J_{ab} = 15.7$ ,  $J_{ax} = J_{bx} = 5.9$  Hz, 2H, H-7), 1.16 (t,  $J = 7.1$  Hz, 3H, H-1, H-1).

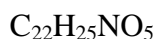
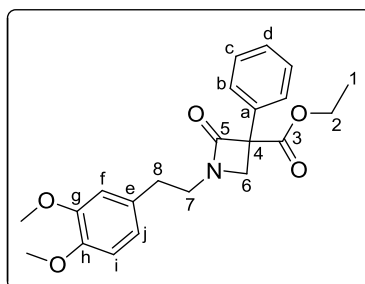
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz):  $\delta$  (ppm) 168.7 (C-3), 164.1 (C-5), 135.2 (C-a), 131.1 (C-8), 128.7 (C-b), 128.1 (C-d), 127.2 (C-c), 118.9 (C-9), 67.8 (C-4), 62.2 (C-2), 50.4 (C-6), 44.7 (C-6), 14.0 (C-1).

**HRMS:** Calculated for C<sub>15</sub>H<sub>17</sub>NO<sub>3</sub>: 259.1208, Found: 259.1209.

**I.R.** (thin film):  $\nu$  3089, 3067, 2985, 2909, 1761, 1726, 1646, 1602, 1476, 1408, 1254, 1221, 1141 and 1027 cm<sup>-1</sup>.

### III-69

#### Ethyl 1-(3,4-dimethoxyphenethyl)-2-oxo-3-phenylazetidine-3-carboxylate



Mol. Wt.: 383.173 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **III-C**, using ethyl 3-((3,4-dimethoxyphenethyl)amino)-3-oxo-2-phenylpropanoate **III-57** (186 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol) and diiodomethane (0.06 ml, 0.75 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : PE = 70 : 30) gave the desired product in 53 % isolated yield (102 mg, 0.27 mmol).

**Nature:** Yellow oil.

**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 7 : 3) = 0.24.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.31-7.21 (m, 5H, H-b, H-c, H-d), 6.67 – 6.58 (m, 3H, H-f, H-g, H-j), 4.11 (q, *J* = 7.1 Hz, 2H, H-2), 3.89, 3.24 (d, AX system, *J<sub>ax</sub>* = 5.3 Hz, 2H, H-6), 3.77 (s, 3H, OMe), 3.70 (s, 3H, OMe), 3.51, 3.41 (dt, ABX<sub>2</sub> system, *J<sub>ab</sub>* = 14.2, *J<sub>ax</sub>* = *J<sub>bx</sub>* = 7.1 Hz, 2H, H-7), 2.82 – 2.69 (dt, ABX<sub>2</sub> system, *J<sub>ab</sub>* = 14.0, *J<sub>ax</sub>* = *J<sub>bx</sub>* = 7.2 Hz, 2H, H-8), 1.13 (t, *J* = 7.1 Hz, 3H, H-1).

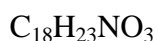
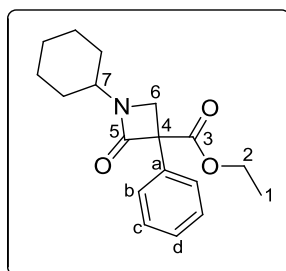
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 168.7 (C-3), 164.2 (C-5), 149.0 (C-i), 147.7 (C-h), 135.2 (C-a), 130.5 (C-e), 128.6 (C-b), 128.1 (C-d), 127.1 (C-c), 120.6 (C-j), 111.6 (C-f), 111.3 (C-g), 67.7 (C-4), 62.1 (C-2), 55.9 (C-OMe), 55.8 (C-OMe), 51.2 (C-6), 43.5 (C-7), 33.7 (C-8), 14.0 (C-1).

**HRMS:** Calculated for C<sub>22</sub>H<sub>25</sub>NO<sub>5</sub>: 383.1733, Found: 383.1728.

**I.R.** (thin film): ν 3064, 2963, 2908, 2839, 1760, 1725, 1593, 1516, 1466, 1417, 1367, 1261, 1143 and 1095 cm<sup>-1</sup>.

### **III-70**

#### **Ethyl 1-cyclohexyl-2-oxo-3-phenylazetidine-3-carboxylate**



Mol. Wt.: 301.168 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **III-C**, using ethyl 3-(cyclohexylamino)-3-oxo-2-phenylpropanoate **III-58** (145 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol) and diiodomethane (0.06 ml, 0.75 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : PE = 30 : 70) gave the desired product in 66 % isolated yield (100 mg, 0.33 mmol).

**Nature:** Yellow oil.

**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 3 : 7) = 0.26.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 7.41-7.38 (m, 2H, H-b), 7.32-7.25 (m, 3H, H-c, H-d), 4.14 (q,  $J$  = 7.1 Hz, 2H, H-2, H-2), 3.99, 3.36 (d, AX system,  $J_{ax}$  = 5.3 Hz, 2H, H-6), 3.58-3.51 (m, 1H, H-7), 1.88-1.84 (m, 1H H-Cy), 1.78-1.66 (m, 3H, H-Cy), 1.58-1.55 (m, 1H, H-Cy), 1.40-1.33 (m, 1H, H-Cy), 1.31-1.21 (m, 3H, H-Cy), 1.16 (t,  $J$  = 7.1 Hz, 3H, H-1), 1.12-1.01 (m, 1H, H-Cy).

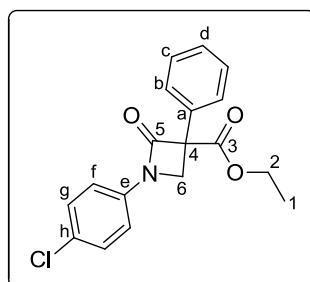
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz):  $\delta$  (ppm) 169.0 (C-3), 163.4 (C-5), 135.5 (C-a), 128.7 (C-b), 128.0 (C-d), 127.2 (C-c), 66.3 (C-4), 62.1 (C-2), 51.4 (C-7), 48.2 (C-6), 30.6 (C-Cy), 30.5 (C-Cy), 25.3 (C-Cy), 24.8 (C-Cy), 14.1 (C-1).

**HRMS:** Calculated for C<sub>18</sub>H<sub>23</sub>NO<sub>3</sub>: 301.1678, Found: 301.1669.

**I.R.** (thin film):  $\nu$  2938, 2859, 1752, 1725, 1602, 1497, 1475, 1449, 1406, 1261, 1220, 1099 and 1027 cm<sup>-1</sup>.

### III-71

#### Ethyl 1-(4-chlorophenyl)-2-oxo-3-phenylazetidine-3-carboxylate



Mol. Wt.: 329.082 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **III-C**, using ethyl 3-((4-chlorophenyl)amino)-3-oxo-2-phenylpropanoate **III-59** (159 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol) and diiodomethane (0.06 ml, 0.75 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : PE = 15 : 85) gave the desired product in 38 % isolated yield (62 mg, 0.19 mmol).

**Nature:** Yellow oil.

**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 1.5 : 8.5) = 0.19.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.49 – 7.45 (m, 2H, H-b), 7.35 – 7.23 (m, 8H, H-c, H-d, H-f, H-g), 4.42, 3.83 (d, AB system, *J*<sub>ab</sub> = 5.7 Hz, 2H, H-6), 4.17 (qd, ABX<sub>3</sub> system, *J*<sub>ab</sub> = 7.1, *J*<sub>ax</sub> = *J*<sub>bx</sub> = 1.1 Hz, 2H, H-2), 1.18 (d, *J* = 7.1 Hz, 3H, H-1).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 168.1 (C-3), 160.9 (C-5), 136.3 (C-e), 134.6 (C-a), 129.6 (C-h), 129.4 (C-b), 128.9 (C-c), 128.5 (C-d), 127.0 (C-f), 117.8 (C-g), 67.1 (C-4), 62.6 (C-2), 50.0 (C-6), 14.1 (C-1).

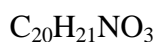
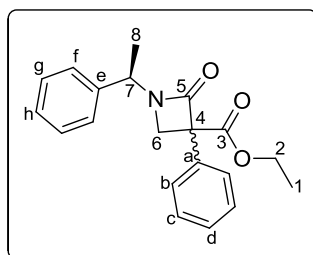
**HRMS:** Calculated for C<sub>18</sub>H<sub>16</sub>ClNO<sub>3</sub>: 329.0819, Found: 329.0833.

**I.R.** (thin film): ν 3067, 3033, 2984, 2901, 1753, 1599, 1496, 1384, 1252, 1095 and 1012 cm<sup>-1</sup>.



### III-72

#### Ethyl 2-oxo-3-phenyl-1-(1-phenylethyl)azetidine-3-carboxylate



Mol. Wt.: 323.152 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **III-C**, using ethyl 3-oxo-2-phenyl-3-((1-phenylethyl)amino)propanoate **III-60** (156 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol) and diiodomethane (0.06 ml, 0.75 mmol). Purification by flash chromatography using gradient eluent (pure DCM) gave the desired product in 62 % isolated yield (100 mg, 0.31 mmol).

**Nature:** Yellow oil.

**R<sub>f</sub>** (DCM) = 0.48.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) (mixture of diastereomers 2:1) 7.55-7.53 (m, 2H, H-Ar), 7.49-7.32 (m, 13H, H-Ar), 5.08 (q,  $J = 7.1$  Hz, 1H, H-7), 5.01 (q,  $J = 7.0$  Hz, 1H, H-7), 4.25 (2q,  $J = 7.2, 6.8$  Hz, 3H, H-2), 4.08, 3.32 (d, AX system,  $J_{ax} = 5.4$  Hz, 1H, H-6), 3.93, 3.51 (d, AX system,  $J_{ax} = 5.4$  Hz, 2H, H-6), 1.73 (d,  $J = 7.1$  Hz, 1H, H-8), 1.63 (d,  $J = 7.1$  Hz, 3H, H-8), 1.30 (t,  $J = 7.1$  Hz, 1H, H-1), 1.25 (t,  $J = 7.1$  Hz, 3H, H-1).

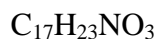
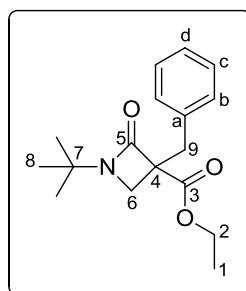
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz):  $\delta$  (ppm) (mixture of diastereomers 2:1) 168.9 (C-3), 168.8 (C-3), 163.7 (C-5), 163.6 (C-5), 139.9 (C-e), 139.8 (C-e), 135.2 (C-a), 135.1 (C-a), 128.9 (C-Ar), 128.8 (C-Ar), 128.7 (C-Ar), 128.6 (C-Ar), 128.1 (C-Ar), 128.0 (C-Ar), 127.8 (C-Ar), 127.3 (C-Ar), 127.2 (C-Ar), 126.7 (C-Ar), 66.6 (C-4), 66.5 (C-4), 62.2 (C-2), 62.1 (C-2), 52.3 (C-7), 51.7 (C-7), 48.5 (C-6), 18.7 (C-8), 18.6 (C-8), 14.1 (C-1), 14.0 (C-1).

**HRMS:** Calculated for C<sub>20</sub>H<sub>21</sub>NO<sub>3</sub>: 323.1521, Found: 323.1526.

**I.R.** (thin film):  $\nu$  3066, 3033, 2983, 2938, 2906, 2876, 1744, 1603, 1495, 1449, 1399, 1254 and 1025 cm<sup>-1</sup>.

### III-73

#### Ethyl 3-benzyl-1-(*tert*-butyl)-2-oxoazetidine-3-carboxylate



Mol. Wt.: 289.168 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **III-C**, using ethyl 2-benzyl-3-(*tert*-butylamino)-3-oxopropanoate **III-61** (139 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol) and diiodomethane (0.06 ml, 0.75 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : PE = 30 : 70) gave the desired product in 66 % isolated yield (95 mg, 0.33 mmol).

**Nature:** Yellow oil.

**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 3 : 7) = 0.26.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.35-7.28 (m, 5H, H-Ar), 4.34-4.23 (m, 2H, H-2), 3.55, 3.04 (d, AX system, *J*<sub>ax</sub> = 5.4 Hz, 2H, H-6), 3.38, 3.19 (d, AB system, *J*<sub>ab</sub> = 14 Hz, 2H, H-9), 1.33 (td, *J* = 7.1, 1.2 Hz, 3H, H-1), 1.13 (d, *J* = 1.2 Hz, 9H, H-8).

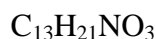
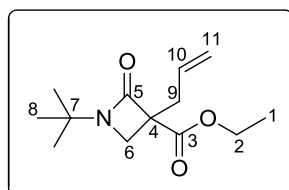
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 169.7 (C-3), 163.8 (C-5), 135.7 (C-a), 130.1 (C-b), 128.4 (C-c), 127.0 (C-d), 61.9 (C-4), 61.7 (C-2), 53.2 (C-7), 43.2 (C-6), 35.8 (C-9), 27.3 (C-8), 14.1 (C-1).

**HRMS:** Calculated for C<sub>17</sub>H<sub>23</sub>NO<sub>3</sub>: 289.1678, Found: 289.1668.

**I.R. (thin film):** ν 3066, 3031, 2978, 2935, 2905, 1751, 1604, 1496, 1456, 1368, 1249, 1100 and 1022 cm<sup>-1</sup>.

### III-74

#### Ethyl 3-allyl-1-(*tert*-butyl)-2-oxoazetidine-3-carboxylate



Mol. Wt.: 239.152 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **III-C**, using ethyl 2-(*tert*-butylcarbamoyl)pent-4-enoate **III-62** (114 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol) and diiodomethane (0.06 ml, 0.75 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : PE = 30 : 70) gave the desired product in 58 % isolated yield (69 mg, 0.29 mmol).

**Nature:** Colorless oil.

**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 3 : 7) = 0.23.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 5.87 – 5.75 (m, 1H, H-10), 5.22-5.15 (m, 2H, H-11), 4.33 – 4.19 (m, 2H, H-2), 3.60, 3.11 (d, AX system, *J*<sub>ax</sub> = 5.4 Hz, 2H, H-6), 2.77, 2.66 (dd, ABX system *J*<sub>ab</sub> = 14.5, *J*<sub>ax</sub> = 7.6, *J*<sub>bx</sub> = 6.4 Hz, 2H, H-9), 1.35 (s, 9H, H-8), 1.32 (t, *J* = 7.1, 3H, H-1).

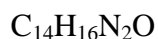
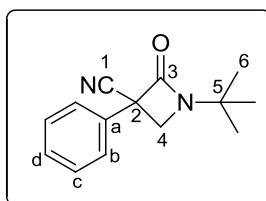
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 169.5 (C-3), 163.9 (C-5), 132.3 (C-10), 119.0 (C-11), 61.6 (C-2), 60.7 (C-4), 53.5 (C-7), 44.0 (C-6), 34.8 (C-9), 27.6 (C-8), 14.1 (C-1).

**HRMS:** Calculated for C<sub>13</sub>H<sub>21</sub>NO<sub>3</sub>: 239.1521, Found: 239.1521.

**I.R.** (thin film): ν 3083, 2979, 2936, 2906, 2874, 1738, 1642, 1464, 1368, 1324, 1246, 1099 and 1022 cm<sup>-1</sup>.

**III-75**

**1-(*tert*-butyl)-2-oxo-3-phenylazetidine-3-carbonitrile**



Mol. Wt.: 228.126 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **III-C**, using N-(*tert*-butyl)-2-cyano-2-phenylacetamide **III-63** (108 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol) and diiodomethane (0.06 ml, 0.75 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : PE = 30 : 70) gave the desired product in 80 % isolated yield (75 mg, 0.4 mmol).

**Nature:** Light yellow oil.

**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 3 : 7) = 0.25.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 7.40-7.31 (m, 5H, H-Ar), 3.84, 3.43 (d, AX system,  $J_{ax}$  = 5.8 Hz, 2H, H-4), 1.35 (s, 9H, H-6).

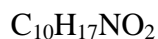
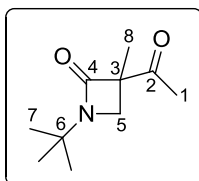
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz):  $\delta$  (ppm) 159.0 (C-3), 131.8 (C-a), 129.5 (C-b), 129.2 (C-d), 126.0 (C-c), 117.1 (C-1), 54.6 (C-5), 52.4 (C-2), 50.4 (C-4), 27.6 (C-6).

**HRMS:** Calculated for [M-CONCMe<sub>3</sub>] C<sub>9</sub>H<sub>7</sub>N: 129.0589, Found: 129.0593.

**I.R.** (thin film):  $\nu$  3068, 3034, 2977, 2937, 2902, 2248, 1772, 1712, 1602, 1498, 1451, 1377, 1270, 1163, 1119 and 1048 cm<sup>-1</sup>.

**III-76**

**3-Acetyl-1-(*tert*-butyl)-3-methylazetidin-2-one**



Mol. Wt.: 183.126 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **III-C**, using N-(*tert*-butyl)-2-methyl-3-oxobutanamide **III-64** (86 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol) and diiodomethane (0.06 ml, 0.75 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : PE = 50 : 50) gave the desired product in 43 % isolated yield (39 mg, 0.21 mmol).

**Nature:** Colorless oil.

**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 5 : 5) = 0.25.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 3.62, 2.83 (d, AX system,  $J_{ax}$  = 5.6 Hz, 1H, H-5), 2.21 (s, 3H, H-1), 1.45 (s, 3H, H-8), 1.26 (s, 9H, H-7).

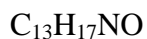
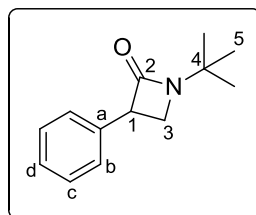
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz):  $\delta$  (ppm) 204.5 (C-2), 166.3 (C-4), 64.5 (C-3), 53.4 (C-6), 46.1 (C-5), 27.6 (C-7), 26.6 (C-1), 17.1 (C-8).

**HRMS:** Calculated for C<sub>10</sub>H<sub>17</sub>NO<sub>2</sub>: 183.1259, Found: 183.1255.

**I.R.** (thin film):  $\nu$  2976, 2933, 2874, 1744, 1708, 1457, 1387, 1367, 1239 and 1140 cm<sup>-1</sup>.

**III-77**

**1-(*Tert*-butyl)-3-phenylazetidin-2-one**



Mol. Wt.: 203.131 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **III-C**, using N-(*tert*-butyl)-2-phenylacetamide (96 mg, 0.5 mmol), sodium hydride (50 mg, 1.25 mmol) and diiodomethane (0.06 ml, 0.75 mmol). Purification by flash chromatography using gradient eluent (Et<sub>2</sub>O : PE = 10 : 90 – 20 : 80) gave the desired product in 15 % isolated yield (15 mg, 0.074 mmol).

**Nature:** Yellow oil.

**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 2 : 8) = 0.14.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.29-7.25 (m, 2H, H-b), 7.21-7.18 (m, 3H, H-c, H-d), 4.09, 3.12 (dd, ABX system,  $J_{ab} = 5.6$ ,  $J_{ax} = J_{bx} = 2.4$  Hz, 2H, H-3), 3.54 (t,  $J = 5.5$  Hz, 1H, H-1), 1.31 (s, 9H, H-5).

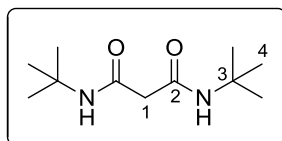
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 167.2 (C-2), 136.4 (C-a), 128.8 (C-b), 127.3 (C-d), 127.3 (C-c), 53.3 (C-4), 52.3 (C-1), 44.8 (C-3), 27.8 (C-5).

**HRMS:** Calculated for [M-CONCMe<sub>3</sub>] C<sub>8</sub>H<sub>8</sub>: 104.0621, Found: 104.0627.

**I.R.** (thin film): ν 3066, 3032, 2975, 2936, 2895, 1733, 1604, 1497, 1455, 1379 and 1240 cm<sup>-1</sup>.

**III-80**

**N<sup>1</sup>,N<sup>3</sup>-di-*tert*-butylmalonamide**



To a solution of *tert*-butyl amine (0.53 ml, 5.0 mmol) in toluene (5 ml) at 0 °C was treated with malonyl chloride (0.19ml, 2.0 mmol) drop wise under argon and the resulting mixture was stirred at 0 °C for 30 min then at room temperature overnight. The reaction was then quenched with saturated aqueous ammonium chloride and extracted with dichloromethane. The organic phase was dried over magnesium sulfate, filtered and concentrated under vacuum. The residue was purified by flash chromatography using (EtOAc : PE = 50 : 50) to afford the desired product in 42 % isolated yield (182 mg, 0.85 mmol).

**Nature:** White solid.

**M.P.** = 114-115 °C.

**R<sub>f</sub>** (EtOAc : PE = 50 : 50) = 0.4.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 6.80 (br s, 2H, NH), 2.95 (s, 2H, H-1), 1.32 (s, 18H, H-4).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 167.0 (C-2), 51.4 (C-3), 45.1 (C-1), 28.6 (C-4).

## **Experimental part for Chapter IV**





## Experimental Part for Chapter IV

### *General Procedures*

#### ➤ **General procedure IV-A for Ugi cyclic enamide Synthesis**

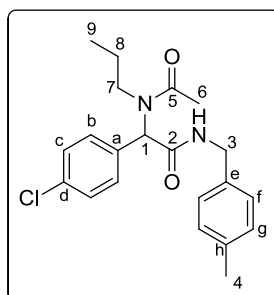
To a solution of Ugi adduct (1.0 equiv.) in DMSO (0.4 M) was added sodium hydride 60% (2.5 equiv.), the resulting mixture was stirred at room temp under Argon for 10 min, followed by the addition of propargyl bromide 80 wt % (1.5 equiv.) and TBAF 1.0 M (1.0 equiv.). The resulting solution was stirred at 50 °C for 1 hr. After the completion of the reaction, it was diluted with CH<sub>2</sub>Cl<sub>2</sub> and extracted with water/citric acid. The organic phase was washed with water 2 times and dried over MgSO<sub>4</sub> and the solvent was removed under reduced pressure. The crude residue was then purified by flash chromatography on silica gel to provide a pure product.

#### ➤ **General procedure IV-B for the one pot synthesis of benzoindolizine**

To a solution of Ugi product (1.0 equiv) in DMSO (0.4 M) was added sodium hydride 60 % (2.5 equiv.), the resulting mixture was stirred at room temp under Argon for 10 min, followed by the addition of propargyl bromide 80 wt % (1.5 equiv.) and TBAF 1.0 M (1.0 equiv.). The resulting solution was stirred at 50 °C for 1 hr. After the completion of the reaction, it was diluted with CH<sub>2</sub>Cl<sub>2</sub> and extracted with a solution of citric acid. The organic phase was washed with water 2 times and dried over MgSO<sub>4</sub> and the solvent was removed under reduced pressure. Without further purification, the crude product was dissolved in DCM (0.4 M) and trifluoroacetic acid (2.0 equiv.) was added. The resulting mixture was stirred at room temp under Argon for extra 1.5 hr. After the completion of the reaction, it was diluted with CH<sub>2</sub>Cl<sub>2</sub> and extracted with a solution of sodium bicarbonate. The organic phase was washed with water 2 times and dried over MgSO<sub>4</sub> and the solvent was removed under reduced pressure. The obtained crude residue was then purified by flash chromatography on silica gel to afford a pure product.

## IV-11

### 2-(4-Chlorophenyl)-N-(4-methylbenzyl)-2-(N-propylacetamido)acetamide



Mol. Wt.: 372.161 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-A**, using 4-chlorobenzaldehyde (141 mg, 1.0 mmol), propylamine (0.08 ml, 1.0 mmol), acetic acid (0.06 ml, 1.0 mmol) and 1-(isocyanomethyl)-4-methylbenzene (131 mg, 1.0 mmol). Purification by flash chromatography using gradient eluent (Et<sub>2</sub>O : PE = 80 : 20 – 100 : 0) gave the desired product in 93 % isolated yield (346 mg, 0.93 mmol).

**Nature:** Yellow solid.

**M.P.** = 120-122 °C.

**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 8 : 2) = 0.28.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.36 (br s, 4H, H-b,c), 7.16 (br s, 4H, H-f,g), 6.71 (br s, 1H, NH), 5.92 (s, 1H, H-1), 4.45 (dd, ABX system, *J*<sub>ab</sub> = 14.0, *J*<sub>ax</sub> = 6.0, *J*<sub>bx</sub> = 5.6 Hz, 2H, H-3), 3.30 (ddd, *J* = 9.8, 5.9, 3.6 Hz, 2H, H-7), 2.36 (s, 3H, H-4), 2.16 (s, 3H, H-6), 1.52-1.41 (m, 1H, H-8), 1.14-1.04 (m, 1H, H-8), 0.75 (t, *J* = 7.4 Hz, 3H, H-9).

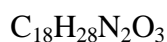
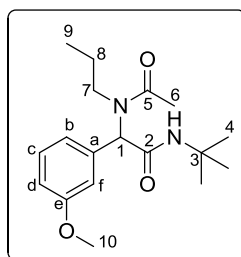
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.7 (C-5), 169.5 (C-2), 137.1 (C-h), 134.9 (C-e), 134.4 (C-d), 134.2 (C-a), 130.7 (C-b), 129.3 (C-g), 128.9 (C-c), 127.7 (C-f), 61.5 (C-1), 49.6 (C-7), 43.4 (C-3), 23.0 (C-8), 21.8 (C-6), 21.1 (C-4), 11.2 (C-9).

**HRMS:** Calculated for C<sub>21</sub>H<sub>25</sub>ClN<sub>2</sub>O<sub>2</sub>: 372.1605, Found: 372.1596.

**I.R.** (thin film): ν 3433, 3026, 2971, 2934, 2877, 1681, 1630, 1517, 1415, 1363, 1253, 1140, 1094 and 1016 cm<sup>-1</sup>.

IV-15

**N-(tert-butyl)-2-(3-methoxyphenyl)-2-(N-propylacetamido)acetamide**

Mol. Wt.: 320.21 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-A**, using 3-methoxybenzaldehyde (0.12 ml, 1.0 mmol), propylamine (0.08 ml, 1.0 mmol), acetic acid (0.06 ml, 1.0 mmol) and tert-butyl isocyanide (0.11 ml, 1.0 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 20 : 80) gave the desired product in 89 % isolated yield (286 mg, 0.89 mmol).

**Nature:** White solid.

**M.P.** = 119-121 °C.

$$\mathbf{R}_f \text{ (Et}_2\text{O : DCM = 2 : 8)} = 0.37.$$

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.20 (t, *J* = 7.9 Hz, 1H, H-c), 6.90 (d, *J* = 7.7 Hz, 1H, H-b), 6.86 (br s, 1H, H-f), 6.80 (dd, *J* = 8.2, 2.2 Hz, 1H, H-d), 5.73 (br s, 2H, NH, H-1), 3.72 (s, 3H, H-10), 3.19 (ddd, *J* = 9.6, 6.4, 2.4 Hz, 2H, H-7), 2.11 (s, 3H, H-6), 1.43 – 1.33 (m, 1H, H-8), 1.27 (s, 9H, H-4), 0.98 – 0.84 (m, 1H, H-8), 0.60 (t, *J* = 7.4 Hz, 3H, H-9).

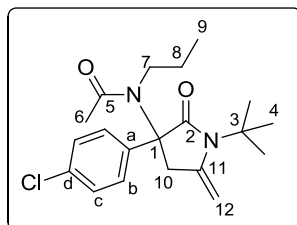
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.5 (C-5), 169.1 (C-2), 159.8 (C-e), 137.5 (C-a), 129.7 (C-c), 121.6 (C-b), 114.8 (C-f), 113.9 (C-d), 62.4 (C-1), 55.3 (C-10), 51.5 (C-3), 49.4 (C-7), 28.6 (C-4), 23.1 (C-8), 21.9 (C-6), 11.3 (C-9).

**HRMS:** Calculated for [M-CONHMe<sub>3</sub>] C<sub>13</sub>H<sub>19</sub>NO<sub>2</sub>: 221.1411, Found: 221.1417.

**I.R.** (thin film):  $\nu$  3425, 2969, 2935, 2876, 2838, 1684, 1626, 1515, 1454, 1367, 1266, 1223, 1141 and 1041  $\text{cm}^{-1}$ .

## IV-8

### N-(1-(*tert*-butyl)-3-(4-chlorophenyl)-5-methylene-2-oxopyrrolidin-3-yl)-N-propylacetamide



Mol. Wt.: 362.176 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **IV-A**, using N-(*tert*-butyl)-2-(4-chlorophenyl)-2-(N-propylacetamido)acetamide **II-40** (130 mg, 0.4 mmol), sodium hydride (40 mg, 1.0 mmol), propargyl bromide (0.07 ml, 0.6 mmol) and TBAF (0.4 ml, 0.4 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : PE = 70 : 30) gave the desired product in 81 % isolated yield (118 mg, 0.33 mmol).

**Nature:** Yellow solid.

**M.P.** = 150-152 °C.

**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 7 : 3) = 0.28.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.46 (d, *J* = 8.7 Hz, 2H, H-b), 7.26 (d, *J* = 8.8 Hz, 2H, H-c), 4.40 (s, 1H, H-12), 4.27 (s, 1H, H-12), 3.30 – 3.11 (m, 3H, H-7,10), 2.84 (ddd, *J* = 15.5, 10.1, 5.7 Hz, 1H, H-7), 2.10 (s, 3H, H-6), 1.44 (s, 9H, H-4), 1.34 – 1.23 (m, 2H, H-8), 0.63 (t, *J* = 7.4 Hz, 3H, H-9).

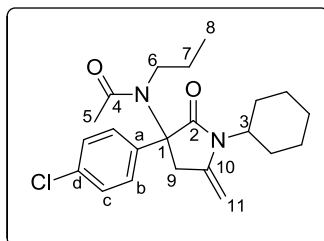
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 173.1 (C-2), 171.6 (C-5), 142.6 (C-11), 135.0 (C-a), 134.3 (C-d), 128.7 (C-b), 128.6 (C-c), 90.0 (C-12), 66.7 (C-1), 57.6 (C-3), 48.6 (C-7), 39.9 (C-10), 28.6 (C-4), 23.6 (C-8), 23.3 (C-6), 11.2 (C-9).

**HRMS:** Calculated for C<sub>20</sub>H<sub>27</sub>ClN<sub>2</sub>O<sub>2</sub>: 362.1761, Found: 362.1763.

**I.R.** (thin film): ν 2974, 2935, 2877, 1722, 1688, 1493, 1407, 1341, 1259, 1214, 1096 and 1015 cm<sup>-1</sup>.

## IV-11

### N-(3-(4-chlorophenyl)-1-cyclohexyl-5-methylene-2-oxopyrrolidin-3-yl)-N-propylacetamide



Mol. Wt.: 388.192 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **IV-A**, using 2-(4-chlorophenyl)-N-cyclohexyl-2-(N-propylacetamido)acetamide **II-46** (140 mg, 0.4 mmol), sodium hydride (40 mg, 1.0 mmol), propargyl bromide (0.07 ml, 0.6 mmol) and TBAF (0.4 ml, 0.4 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : PE = 70 : 30) gave the desired product in 78 % isolated yield (121 mg, 0.31 mmol).

**Nature:** Yellow solid.

**M.P.** = 129-131 °C.

**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 7 : 3) = 0.25.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.42 (d, *J* = 8.7 Hz, 2H, H-b), 7.24 (d, *J* = 8.8 Hz, 2H, H-c), 4.28 (s, 1H, H-11), 4.15 (s, 1H, H-11), 3.64 (tt, *J* = 12.3, 3.6 Hz, 1H, H-3), 3.33-3.24 (m, 2H, H-9), 3.19 (dt, *J* = 15.8, 2.3 Hz, 1H, H-6), 2.89 (ddd, *J* = 15.3, 9.8, 5.6 Hz, 1H, H-6), 2.10 (s, 3H, H-5), 2.01 – 1.86 (m, 2H, H-Cy), 1.70-1.67 (m, 2H, H-Cy), 1.54-1.43 (m, 2H, H-Cy), 1.36 – 0.98 (m, 6H, H-Cy,7), 0.63 (t, *J* = 7.4 Hz, 3H, H-8).

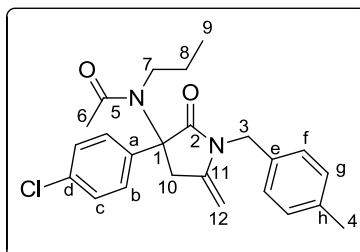
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 172.8 (C-2), 171.7 (C-4), 142.4 (C-10), 135.3 (C-a), 134.4 (C-d), 128.8 (C-b), 128.5 (C-c), 85.1 (C-11), 66.2 (C-1), 53.4 (C-3), 48.5 (C-6), 38.2 (C-9), 28.3 (C-Cy), 27.5 (C-Cy), 26.1 (C-Cy), 26.0 (C-Cy), 25.4 (C-Cy), 23.6 (C-7), 23.1 (C-5), 11.2 (C-8).

**HRMS:** Calculated for C<sub>22</sub>H<sub>29</sub>ClN<sub>2</sub>O<sub>2</sub>: 388.1918, Found: 388.1920.

**I.R.** (thin film): ν 2935, 2857, 1698, 1638, 1492, 1408, 1369, 1262, 1188, 1103 and 1015 cm<sup>-1</sup>.

### IV-13

#### N-(3-(4-chlorophenyl)-1-(4-methylbenzyl)-5-methylene-2-oxopyrrolidin-3-yl)-N-propylacetamide



Mol. Wt.: 410.176 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **IV-A**, using 2-(4-chlorophenyl)-N-(4-methylbenzyl)-2-(N-propylacetamido)acetamide **IV-12** (149 mg, 0.4 mmol), sodium hydride (40 mg, 1.0 mmol), propargyl bromide (0.07 ml, 0.6 mmol) and TBAF (0.4 ml, 0.4 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : PE = 80 : 20) gave the desired product in 59 % isolated yield (97 mg, 0.24 mmol).

**Nature:** Yellow solid.

**M.P.** = 96-98 °C.

**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 8 : 2) = 0.33.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.61 (d, *J* = 8.6 Hz, 2H, H-c), 7.41 (d, *J* = 8.6 Hz, 2H, H-b), 7.06 (d, *J* = 7.8 Hz, 2H, H-f), 6.96 (d, *J* = 7.9 Hz, 2H, H-g), 4.62 (d, AB system, *J*<sub>ab</sub> = 15.6 Hz, 2H, H-3), 4.22 (s, 1H, H-12), 4.16 (s, 1H, H-12), 3.50-3.36 (m, 3H, H-7,10), 3.04 (ddd, *J* = 15.4, 9.8, 5.6 Hz, 1H, H-7), 2.32 (s, 3H, H-4), 2.28 (s, 3H, H-6), 1.46-1.34 (m, 2H, H-8), 0.77 (t, *J* = 7.4 Hz, 3H, H-9).

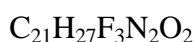
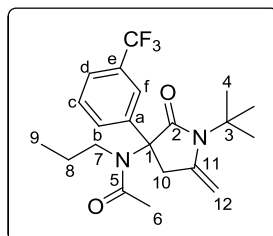
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 173.1 (C-2), 171.9 (C-5), 141.9 (C-11), 136.7 (C-h), 134.8 (C-a), 134.5 (C-d), 132.9 (C-e), 129.2 (C-b), 128.9 (C-c), 128.8 (C-g), 126.9 (C-f), 85.7 (C-12), 66.6 (C-1), 48.5 (C-7), 43.8 (C-3), 36.9 (C-10), 23.6 (C-8), 23.1 (C-6), 21.1 (C-4), 11.2 (C-9).

**HRMS:** Calculated for C<sub>24</sub>H<sub>27</sub>ClN<sub>2</sub>O<sub>2</sub>: 410.1761, Found: 410.1749.

**I.R.** (thin film): ν 2971, 2933, 2877, 1719, 1674, 1644, 1493, 1403, 1353, 1251, 1096 and 1015 cm<sup>-1</sup>.

## IV-14

### N-(1-(*tert*-butyl)-5-methylene-2-oxo-3-(3-(trifluoromethyl)phenyl)pyrrolidin-3-yl)-N-propylacetamide



Mol. Wt.: 396.203 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **IV-A**, using N-(*tert*-butyl)-2-(N-propylacetamido)-2-(3-(trifluoromethyl)phenyl)acetamide **III-31** (143 mg, 0.4 mmol), sodium hydride (40 mg, 1.0 mmol), propargyl bromide (0.07 ml, 0.6 mmol) and TBAF (0.4 ml, 0.4 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : PE = 60 : 40) gave the desired product in 70 % isolated yield (101 mg, 0.28 mmol).

**Nature:** Yellow solid.

**M.P.** = 95-97 °C.

**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 6 : 4) = 0.46.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.72-7.70 (m, 2H, H-d,f), 7.51 (d, *J* = 7.7 Hz, 1H, H-b), 7.41 (t, *J* = 7.8 Hz, 1H, H-c), 4.44 (s, 1H, H-12), 4.33 (s, 1H, H-12), 3.38 – 3.22 (m, 3H, H-7,10), 2.86 (ddd, *J* = 15.7, 10.4, 5.5 Hz, 1H, H-7), 2.11 (s, 3H, H-6), 1.44 (s, 9H, H-4), 1.38-1.28 (m, 2H, H-8), 0.64 (t, *J* = 7.4 Hz, 3H, H-9).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 172.7 (C-2), 171.6 (C-5), 142.4 (C-11), 138.4 (C-a), 130.7 (q, *J* = 31.3 Hz, C-CF<sub>3</sub>), 130.3 (C-f), 128.9 (C-c), 125.0 (C-b), 123.6 (C-d), 122.7 (C-e), 90.5 (C-12), 67.0 (C-1), 57.7 (C-3), 48.7 (C-7), 40.4 (C-10), 28.5 (C-4), 23.6 (C-8), 23.2 (C-6), 11.1 (C-9).

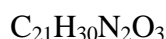
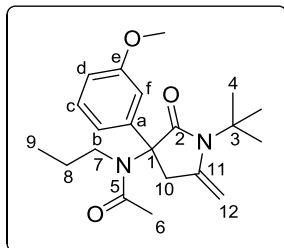
**HRMS:** Calculated for C<sub>21</sub>H<sub>27</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>: 396.2025, Found: 396.2018.

**I.R.** (thin film): ν 2975, 2935, 2877, 1721, 1639, 1406, 1329, 1260, 1171, 1133 and 1079 cm<sup>-1</sup>.



## IV-16

### N-(1-(*tert*-butyl)-3-(3-methoxyphenyl)-5-methylene-2-oxopyrrolidin-3-yl)-N-propylacetamide



Mol. Wt.: 358.226 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **IV-A**, using N-(*tert*-butyl)-2-(3-methoxyphenyl)-2-(N-propylacetamido)acetamide **IV-15** (128 mg, 0.4 mmol), sodium hydride (40 mg, 1.0 mmol), propargyl bromide (0.07 ml, 0.6 mmol) and TBAF (0.4 ml, 0.4 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : PE = 90 : 10) gave the desired product in 72 % isolated yield (103 mg, 0.29 mmol).

**Nature:** Yellow oil.

**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 9 : 1) = 0.3.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.31 (t, *J* = 8.2 Hz, 1H, H-c), 7.24 – 7.19 (m, 2H, H-f,b), 6.90 (ddd, *J* = 8.2, 2.4, 0.9 Hz, 1H, H-d), 4.49 (s, 1H, H-12), 4.35 (s, 1H, H-12), 3.85 (s, 3H, OMe), 3.39-3.25 (m, 3H, H-7,10), 3.03 – 2.93 (m, 1H, H-7), 2.22 (s, 3H, H-6), 1.56 (s, 9H, H-4), 1.45-1.37 (m, 2H, H-8), 0.71 (t, *J* = 7.4 Hz, 3H, H-9).

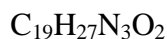
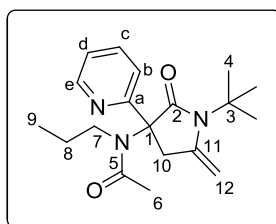
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 173.4 (C-2), 171.6 (C-5), 159.5 (C-e), 143.0 (C-11), 137.8 (C-a), 129.3 (C-c), 119.9 (C-b), 113.7 (C-d), 113.5 (C-f), 89.5 (C-12), 67.1 (C-1), 57.4 (C-3), 55.3 (C-OMe), 48.6 (C-7), 40.0 (C-10), 28.6 (C-4), 23.8 (C-8), 23.3 (C-6), 11.2 (C-9).

**HRMS:** Calculated for C<sub>21</sub>H<sub>30</sub>N<sub>2</sub>O<sub>3</sub>: 358.2256, Found: 358.2243.

**I.R.** (thin film): ν 2972, 2936, 2877, 2838, 1719, 1635, 1600, 1488, 1465, 1408, 1341, 1260, 1215, 1150 and 1037 cm<sup>-1</sup>.

## IV-17

### N-(1-(*tert*-butyl)-5-methylene-2-oxo-3-(pyridin-2-yl)pyrrolidin-3-yl)-N-propylacetamide



Mol. Wt.: 329.21 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **IV-A**, using N-(*tert*-butyl)-2-(N-propylacetamido)-2-(pyridin-2-yl)acetamide **II-53** (117 mg, 0.4 mmol), sodium hydride (40 mg, 1.0 mmol), propargyl bromide (0.07 ml, 0.6 mmol) and TBAF (0.4 ml, 0.4 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : PE = 70 : 30) gave the desired product in 83 % isolated yield (109 mg, 0.33 mmol).

**Nature:** Yellow oil.

**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 7 : 3) = 0.23.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 8.61 (d, *J* = 4.8 Hz, 1H, H-e), 7.77 (d, *J* = 7.9 Hz, 1H, H-b), 7.71 (td, *J* = 7.7, 1.8 Hz, 1H, H-c), 7.25 (ddd, *J* = 7.2, 4.9, 1.2 Hz, 1H, H-d), 4.52 (s, 1H, H-12), 4.37 (s, 1H, H-12), 4.19 (d, AB system, *J<sub>ab</sub>* = 14.7 Hz, 1H, H-10), 3.42 – 3.30 (m, 1H, H-7), 3.07 (d, AB system, *J<sub>ba</sub>* = 14.6 Hz, 1H, H-10), 2.93 – 2.80 (m, 1H, H-7), 2.20 (s, 3H, H-6), 1.58 (br s, 10H, H-4,8), 1.45-1.35 (m, 1H, H-8), 0.72 (t, *J* = 7.2 Hz, 3H, H-9).

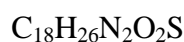
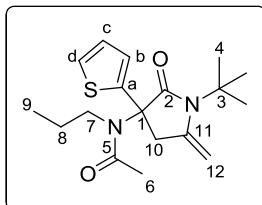
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 173.3 (C-2), 171.3 (C-5), 156.2 (C-a), 148.5 (C-e), 143.7 (C-11), 136.5 (C-c), 123.3 (C-b), 122.9 (C-d), 90.1 (C-12), 69.8 (C-1), 57.6 (C-3), 49.0 (C-7), 38.5 (C-10), 28.6 (C-4), 23.4 (C-8), 23.1 (C-6), 11.1 (C-9).

**HRMS:** Calculated for C<sub>19</sub>H<sub>27</sub>N<sub>3</sub>O<sub>2</sub>: 329.2103, Found: 329.2109.

**I.R.** (thin film): ν 3142, 3059, 2973, 2934, 2877, 1714, 1683, 1638, 1587, 1469, 1410, 1260 and 1153 cm<sup>-1</sup>.

## IV-18

### N-(1-(*tert*-butyl)-5-methylene-2-oxo-3-(thiophen-2-yl)pyrrolidin-3-yl)-N-propylacetamide



Mol. Wt.: 334.172 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **IV-A**, using N-(*tert*-butyl)-2-(N-propylacetamido)-2-(thiophen-2-yl)acetamide **III-33** (119 mg, 0.4 mmol), sodium hydride (40 mg, 1.0 mmol), propargyl bromide (0.07 ml, 0.6 mmol) and TBAF (0.4 ml, 0.4 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : PE = 70 : 30) gave the desired product in 70 % isolated yield (94 mg, 0.28 mmol).

**Nature:** Deep yellow solid.

**M.P.** = 132-134 °C.

**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 7 : 3) = 0.26.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.40 (dd, *J* = 5.2, 1.2 Hz, 1H, H-d), 7.32 (dd, *J* = 3.7, 1.2 Hz, 1H, H-c), 7.05 (dd, *J* = 5.1, 3.7 Hz, 1H, H-b), 4.46 (t, *J* = 2.0 Hz, 1H, H-12), 4.30 (br s, 1H, H-12), 3.45 (dt, *J* = 14.1, 2.3 Hz, 1H, H-10), 3.20-3.10 (m, 2H, H-7,10), 2.77 (ddd, *J* = 15.7, 10.3, 5.6 Hz, 1H, H-7), 2.20 (s, 3H, H-6), 1.58 (s, 9H, H-4), 1.50 – 1.42 (m, 2H, H-8), 0.70 (t, *J* = 7.4 Hz, 3H, H-9).

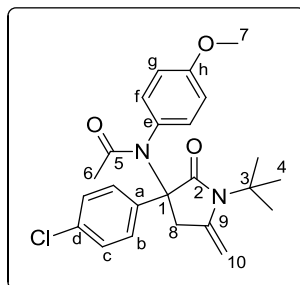
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 173.2 (C-2), 170.9 (C-5), 142.5 (C-11), 139.3 (C-a), 128.2 (C-c), 127.4 (C-d), 126.8 (C-b), 89.9 (C-12), 65.3 (C-1), 57.5 (C-3), 48.4 (C-7), 41.6 (C-10), 28.5 (C-4), 24.2 (C-8), 23.2 (C-6), 11.1 (C-9).

**HRMS:** Calculated for C<sub>18</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub>S: 334.1715, Found: 334.1725.

**I.R.** (thin film): ν 2973, 2934, 2877, 1721, 1635, 1460, 1408, 1345, 1260, 1214 and 1148 cm<sup>-1</sup>.

## IV-19

### N-(1-(tert-butyl)-3-(4-chlorophenyl)-5-methylene-2-oxopyrrolidin-3-yl)-N-(4-methoxyphenyl)acetamide



Mol. Wt.: 426.171 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **IV-A**, using N-(tert-butyl)-2-(4-chlorophenyl)-2-(N-(4-methoxyphenyl)acetamido)acetamide **II-55** (156 mg, 0.4 mmol), sodium hydride (40 mg, 1.0 mmol), propargyl bromide (0.07 ml, 0.6 mmol) and TBAF (0.4 ml, 0.4 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : PE = 60 : 40) gave the desired product in 69 % isolated yield (117 mg, 0.27 mmol).

**Nature:** Yellow oil.

**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 6 : 4) = 0.25.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.38 (d, *J* = 8.8 Hz, 2H, H-c), 7.14 (d, *J* = 8.8 Hz, 2H, H-b), 6.99 (br s, 2H, H-f), 6.70 (br s, 2H, H-g), 4.51 (t, *J* = 1.6 Hz, 1H, H-10), 4.35 (br s, 1H, H-10), 3.83 – 3.76 (m, 4H, H-7,8), 3.29 (d, *J* = 14.2 Hz, 1H, H-8), 1.84 (s, 3H, H-6), 1.59 (s, 9H, H-4).

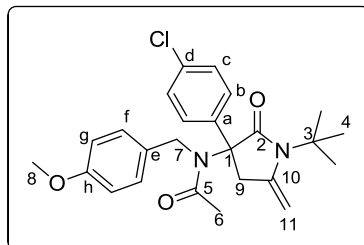
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 173.2 (C-2), 172.0 (C-5), 158.8 (C-h), 142.6 (C-9), 135.2 (C-a), 133.9 (C-e), 133.7 (C-d), 129.9 (C-c), 128.1 (C-b), 114.0 (C-g), 90.6 (C-10), 69.4 (C-1), 57.7 (C-3), 55.4 (C-7), 40.5 (C-8), 28.6 (C-4), 24.6 (C-6).

**HRMS:** Calculated for C<sub>24</sub>H<sub>27</sub>ClN<sub>2</sub>O<sub>3</sub>: 426.1710, Found: 426.2392.

**I.R.** (thin film): ν 3008, 2971, 2937, 2840, 1719, 1655, 1510, 1465, 1373, 1250, 1096 and 1015 cm<sup>-1</sup>.

## IV-20

### N-(1-(tert-butyl)-3-(4-chlorophenyl)-5-methylene-2-oxopyrrolidin-3-yl)-N-(4-methoxybenzyl)acetamide



Mol. Wt.: 426.171 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **IV-A**, using N-(tert-butyl)-2-(4-chlorophenyl)-2-(N-(4-methoxybenzyl)acetamido)acetamide **II-56** (161 mg, 0.4 mmol), sodium hydride (40 mg, 1.0 mmol), propargyl bromide (0.07 ml, 0.6 mmol) and TBAF (0.4 ml, 0.4 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : PE = 70 : 30) gave the desired product in 55 % isolated yield (97 mg, 0.22 mmol).

**Nature:** Yellow oil.

**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 7 : 3) = 0.26.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.42 (d, *J* = 8.7 Hz, 2H, H-c), 7.28 (d, *J* = 8.7 Hz, 2H, H-b), 6.85 (s, 4H, H-f,g), 4.67 (d, *J* = 17.1 Hz, 1H, H-7), 4.42 (s, 1H, H-11), 4.26 (s, 1H, H-11), 4.14 (d, *J* = 17.1 Hz, 1H, H-7), 3.84 (s, 3H, H-8), 3.39 (d, *J* = 14.5 Hz, 1H, H-9), 2.86 (d, *J* = 14.5 Hz, 1H, H-9), 2.30 (s, 3H, H-6), 1.51 (s, 9H, H-4).

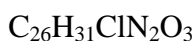
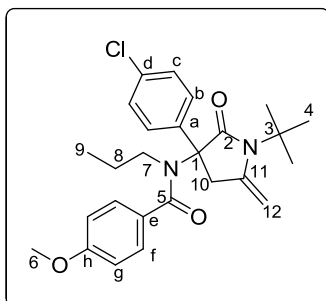
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 173.1 (C-2), 171.9 (C-5), 159.0 (C-h), 142.6 (C-10), 134.5 (C-a), 129.3 (C-c), 129.1 (C-e), 128.4 (C-b), 128.0 (C-f), 113.9 (C-g), 90.1 (C-11), 67.0 (C-1), 57.5 (C-3), 55.3 (C-8), 50.0 (C-7), 39.5 (C-9), 28.6 (C-4), 23.7 (C-6).

**HRMS:** Calculated for C<sub>25</sub>H<sub>29</sub>ClN<sub>2</sub>O<sub>3</sub>: 440.1867, Found: 440.1868.

**I.R.** (thin film): ν 2971, 2937, 2839, 1721, 1639, 1513, 1400, 1342, 1250, 1176, 1096 and 1015 cm<sup>-1</sup>.

## IV-21

### N-(1-(*tert*-butyl)-3-(4-chlorophenyl)-5-methylene-2-oxopyrrolidin-3-yl)-4-methoxy-N-propylbenzamide



Mol. Wt.: 454.202 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **IV-A**, using N-(2-(*tert*-butylamino)-1-(4-chlorophenyl)-2-oxoethyl)-4-methoxy-N-propylbenzamide **III-42** (167 mg, 0.4 mmol), sodium hydride (40 mg, 1.0 mmol), propargyl bromide (0.07 ml, 0.6 mmol) and TBAF (0.4 ml, 0.4 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : PE = 40 : 60) gave the desired product in 78 % isolated yield (142 mg, 0.31 mmol).

**Nature:** Yellow solid.

**M.P.** = 147-149 °C.

**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 4 : 6) = 0.27.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.70 (d, *J* = 8.7 Hz, 2H, H-c), 7.55 (d, *J* = 8.8 Hz, 2H, H-f), 7.40 (d, *J* = 8.7 Hz, 2H, H-b), 6.95 (d, *J* = 8.8 Hz, 2H, H-g), 4.58 (t, *J* = 2.0 Hz, 1H, H-12), 4.46 (s, 1H, H-12), 3.87 (s, 3H, H-6), 3.69 (dt, *J* = 14.5, 2.3 Hz, 1H, H-10), 3.49 (ddd, *J* = 15.1, 8.9, 7.5 Hz, 1H, H-7), 3.33 (d, *J* = 14.6 Hz, 1H, H-10), 2.97 – 2.89 (m, 1H, H-7), 1.55 (s, 9H, H-4), 1.25-1.16 (m, 2H, H-8), 0.56 (t, *J* = 7.3 Hz, 3H, H-9).

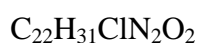
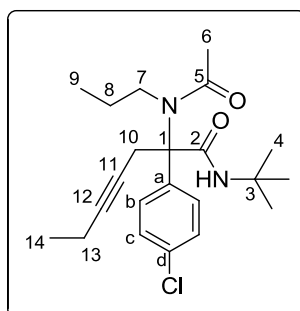
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 174.0 (C-2), 173.2 (C-5), 161.0 (C-h), 142.8 (C-11), 134.9 (C-a), 134.4 (C-d), 129.6 (C-b), 129.0 (C-e), 128.7 (C-f), 128.6 (C-c), 113.7 (C-g), 89.9 (C-12), 66.3 (C-1), 57.7 (C-3), 55.4 (C-6), 50.2 (C-7), 39.4 (C-10), 28.6 (C-4), 23.5 (C-8), 11.1 (C-9).

**HRMS:** Calculated for C<sub>26</sub>H<sub>31</sub>ClN<sub>2</sub>O<sub>3</sub>: 454.2023, Found: 454.2013.

**I.R.** (thin film): ν 2968, 2937, 2877, 2840, 1724, 1631, 1609, 1512, 1465, 1396, 1251, 1095 and 1014 cm<sup>-1</sup>.

## IV-22

### N-*tert*-butyl-2-(4-chlorophenyl)-2-(N-propylacetamido)hept-4-ynamide



Mol. Wt.: 390.207 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **IV-A**, using N-(*tert*-butyl)-2-(4-chlorophenyl)-2-(N-propylacetamido)acetamide **II-40** (130 mg, 0.4 mmol), sodium hydride (40 mg, 1.0 mmol), 1-bromopent-2-yne (0.06 ml, 0.6 mmol) and TBAF (0.4 ml, 0.4 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : PE = 50 : 50) gave the product in 72 % isolated yield (112 mg, 0.29 mmol).

**Nature:** Yellow oil.

**R<sub>f</sub>** (Et<sub>2</sub>O : PE = 5 : 5) = 0.44.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.48 (s, 1H, NH), 7.30 (s, 4H, H-b,c), 3.48 (ddd, *J* = 15.7, 10.7, 4.9 Hz, 1H, H-7), 3.39 – 3.29 (m, 1H, H-7), 3.21 (dt, *J* = 17.7, 2.1 Hz, 1H, H-10), 3.07 (dt, *J* = 17.7, 2.1 Hz, 1H, H-10), 2.26 (s, 3H, H-6), 2.12 (dddd, *J* = 9.8, 7.5, 4.9, 2.3 Hz, 2H, H-13), 1.75 – 1.62 (m, 1H, H-8), 1.58 – 1.49 (m, 1H, H-8), 1.36 (s, 9H, H-4), 1.06 (d, *J* = 7.5 Hz, 2H, H-14), 0.84 (t, *J* = 7.4 Hz, 3H, H-9).

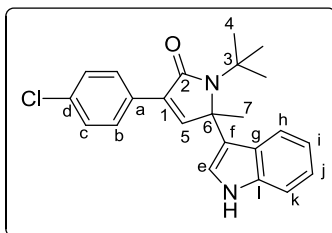
**<sup>13</sup>C-NMR** ((CDCl<sub>3</sub>, 400 MHz): δ (ppm) 172.9 (C-5), 170.9 (C-2), 137.9 (C-a), 133.1 (C-d), 128.5 (C-b), 127.6 (C-c), 86.7 (C-12), 75.38 (C-11), 70.7 (C-1), 51.2 (C-3), 49.4 (C-7), 28.6 (C-10), 28.4 (C-4), 24.2 (C-6), 23.6 (C-8), 13.9 (C-14), 12.4 (C-13), 11.5 (C-9).

**HRMS:** Calculated for C<sub>17</sub>H<sub>21</sub>ClNO[M-CONH*t*-Bu]: 290.1308, Found: 290.1306.

**I.R.** (thin film): ν 3379, 3275, 2976, 2936, 2877, 1670, 1631, 1548, 1493, 1457, 1405, 1366, 1223, 1097 and 1015 cm<sup>-1</sup>.

## IV-24

### 1-(*tert*-butyl)-3-(4-chlorophenyl)-5-(1H-indol-3-yl)-1H-pyrrol-2(5H)-one



Mol. Wt.: 378.15 g.mol<sup>-1</sup>

This compound was obtained upon heating a mixture of N-(1-(*tert*-butyl)-3-(4-chlorophenyl)-5-methylene-2-oxopyrrolidin-3-yl)-N-propylacetamide **IV-8** (109 mg, 0.3 mmol) with 1.0 equivalent of indole (35 mg, 0.3 mmol) in presence of 10 mol % of tosic acid.monohydrate (6 mg, 0.1 mmol) in toluene (0.3M) at 60 °C for 2 hours. After the completion of the reaction, the solvent was removed under reduced pressure. Purification by flash chromatography using (Et<sub>2</sub>O : PE = 50 : 50) gave the desired product in 71% isolated yield (81 mg, 0.21 mmol).

**Nature:** Yellow solid.

**M.P.** = 238-240 °C.

**R<sub>f</sub>** (Et<sub>2</sub>O : DCM = 1 : 1) = 0.21.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 8.35 (br s, 1H, NH), 7.76 (d, *J* = 8.6 Hz, 2H, H-c), 7.30 – 7.23 (m, 4H, H-b,h,k), 7.11 – 7.06 (m, 1H, H-j), 7.04 (d, *J* = 2.5 Hz, 1H, H-e), 6.93 – 6.87 (m, 1H, H-i), 6.77 (s, 1H, H-5), 1.99 (s, 3H, H-7), 1.33 (s, 9H, H-4).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 170.3 (C-2), 148.5 (C-5), 136.9 (C-l), 134.1 (C-a), 131.9 (C-d), 130.3 (C-1), 128.8 (C-b), 128.5 (C-c), 125.1 (C-g), 122.5 (C-j), 121.9 (C-e), 120.6 (C-h), 120.0 (C-i), 115.7 (C-f), 111.3 (C-k), 64.8 (C-6), 57.2 (C-3), 28.6 (C-4), 25.3 (C-7).

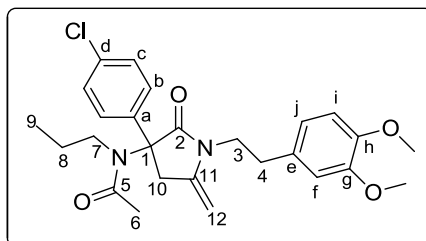
**HRMS:** Calculated for C<sub>23</sub>H<sub>23</sub>ClN<sub>2</sub>O: 378.1499, Found: 378.1482.

**I.R.** (thin film): ν 3273, 2969, 2923, 1656, 1637, 1490, 1361, 1270, 1202, 1090, 1013, 834 and 740 cm<sup>-1</sup>.



#### IV-40

### N-(3-(4-chlorophenyl)-1-(3,4-dimethoxyphenethyl)-5-methylene-2-oxopyrrolidin-3-yl)-N-propylacetamide



Mol. Wt.: 470.197 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **IV-A**, using 2-(4-chlorophenyl)-N-(3,4-dimethoxyphenethyl)-2-(N-propylacetamido)acetamide **III-29** (173 mg, 0.4 mmol), sodium hydride (40 mg, 1.0 mmol), propargyl bromide (0.07 ml, 0.6 mmol) and TBAF (0.4 ml, 0.4 mmol). Purification by flash chromatography using (Et<sub>2</sub>O) gave the desired product in 83 % isolated yield (156 mg, 0.33 mmol).

**Nature:** Yellow oil.

**R<sub>f</sub>** (Et<sub>2</sub>O) = 0.33.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.41 (d, *J* = 8.6 Hz, 2H, H-c), 7.25 (d, *J* = 8.6 Hz, 2H, H-b), 6.64 (d, *J* = 1.4 Hz, 1H, H-f), 6.61 (d, *J* = 8.1 Hz, 1H, H-i), 6.54 (dd, *J* = 8.1, 1.4 Hz, 1H, H-j), 4.18 (d, *J* = 8.7 Hz, 2H, H-12), 3.76 (s, 3H, OMe), 3.75 (s, 3H, OMe), 3.63-3.46 (m, 2H, H-3), 3.38 (d, AB system, *J<sub>ab</sub>* = 16.0 Hz, 1H, H-10), 3.28-3.17 (m, 2H, H-7,10), 2.83 (ddd, *J* = 15.4, 10.0, 5.5 Hz, 1H, H-7), 2.67 (t, *J* = 7.8 Hz, 2H, H-4), 2.12 (s, 3H, H-6), 1.31-1.20 (m, 2H, H-8), 0.63 (t, *J* = 7.3 Hz, 3H, H-9).

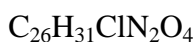
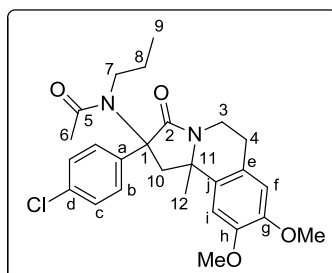
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) δ 172.6 (C-2), 171.9 (C-5), 148.8 (C-g), 147.5 (C-h), 142.3 (C-11), 134.7 (C-a), 131.0 (C-e), 128.8 (C-b), 128.7 (C-c), 120.6 (C-j), 111.9 (C-f), 111.0 (C-i), 84.0 (C-12), 66.4 (C-1), 55.9 (C-OMe), 55.8 (C-OMe), 48.5 (C-7), 41.9 (C-3), 37.3 (C-10), 31.7 (C-4), 23.6 (C-8), 23.0 (C-6), 11.2 (C-9).

**HRMS:** Calculated for C<sub>26</sub>H<sub>31</sub>ClN<sub>2</sub>O<sub>4</sub>: 470.1972, Found: 470.1971.

**I.R.** (thin film): ν 2965, 2937, 2877, 2838, 1702, 1633, 1516, 1465, 1409, 1262, 1157 and 1029 cm<sup>-1</sup>.

#### IV-41

**N-(2-(4-chlorophenyl)-8,9-dimethoxy-10b-methyl-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-2-yl)-N-propylacetamide**



Mol. Wt.: 470.197 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **IV-B**, using 2-(4-chlorophenyl)-N-(3,4-dimethoxyphenethyl)-2-(N-propylacetamido)acetamide **III-29** (173 mg, 0.4 mmol), sodium hydride (40 mg, 1.0 mmol), propargyl bromide (0.07 ml, 0.6 mmol), TBAF (0.4 ml, 0.4 mmol) and trifluoroacetic acid (0.06 ml, 0.8 mmol). Purification by flash chromatography using gradient eluent (EtOH : EtOAc = 0 : 100 – 5 : 95) gave the desired product in 68 % isolated yield (128 mg, 0.27 mmol).

**Nature:** White solid.

**M.P.** = 107-109 °C.

**R<sub>f</sub>** (EtOH : EtOAc = 0.5 : 9.5) = 0.22.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.78 (d, *J* = 8.7 Hz, 2H, H-c), 7.33 (d, *J* = 8.7 Hz, 2H, H-b), 6.50 (s, 1H, H-f), 6.46 (s, 1H, H-i), 4.24 (dd, *J* = 13.0, 5.1 Hz, 1H, H-3), 3.80 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.19 (d, AB system, *J<sub>ab</sub>* = 13.0 Hz, 1H, H-10), 3.15 – 2.98 (m, 2H, H-4,7), 2.91 (td, *J* = 12.7, 3.9 Hz, 1H, H-3), 2.80 (d, AB system, *J<sub>ba</sub>* = 13.0 Hz, 1H, H-10), 2.62 – 2.48 (m, 2H, H-4,7), 2.01 (s, 3H, H-6), 1.34 – 1.20 (m, 5H, H-8,12), 0.53 (t, *J* = 7.4 Hz, 3H, H-9).

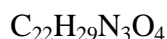
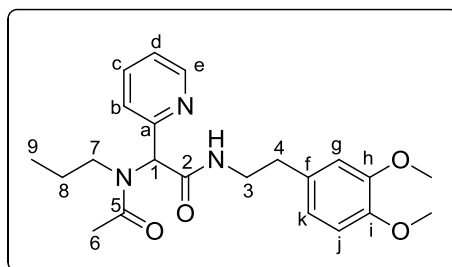
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.3 (C-5), 170.2 (C-2), 147.9 (C-h), 147.6 (C-g), 135.4 (C-a), 134.8 (C-d), 134.7 (C-j), 130.4 (C-c), 128.7 (C-b), 124.8 (C-e), 111.7 (C-f), 107.8 (C-i), 68.8 (C-1), 57.6 (C-11), 56.2 (C-OMe), 55.8 (C-OMe), 48.4 (C-7), 44.9 (C-10), 35.3 (C-3), 28.9 (C-12), 27.5 (C-4), 23.9 (C-8), 23.3 (C-6), 11.1 (C-9).

**HRMS:** Calculated for C<sub>26</sub>H<sub>31</sub>ClN<sub>2</sub>O<sub>4</sub>: 470.1972, Found: 470.1958.

**I.R.** (thin film): ν 3064, 3005, 2972, 2936, 2877, 2855, 2835, 1687, 1639, 1514, 1465, 1358, 1296, 1257, 1185, 1097 and 957 cm<sup>-1</sup>.

**IV-43**

**N-(3,4-dimethoxyphenethyl)-2-(N-propylacetamido)-2-(pyridin-2-yl)acetamide**



Mol. Wt.: 399.216 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-A**, using pyridine-2-carboxaldehyde (0.1 ml, 1.0 mmol), propylamine (0.08 ml, 1.0 mmol), acetic acid (0.06 ml, 1.0 mmol) and 4-(2-isocyanoethyl)-1,2-dimethoxybenzene (191 mg, 1.0 mmol). Purification by flash chromatography using (MeOH : DCM = 4 : 96) gave the desired product in 94 % isolated yield (377 mg, 0.94 mmol).

**Nature:** Deep yellow oil.

**R<sub>f</sub>** (MeOH : DCM = 0.4 : 9.6) = 0.17.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 8.48 (d,  $J$  = 4.1 Hz, 1H, H-e), 7.73 (t,  $J$  = 4.8 Hz, 1H, NH), 7.67 (td,  $J$  = 7.8, 1.6 Hz, 1H, H-c), 7.35 (d,  $J$  = 7.9 Hz, 1H, H-b), 7.22 (dd,  $J$  = 7.1, 5.1 Hz, 1H, H-d), 6.81-6.74 (m, 3H, H-g,j,k), 5.56 (s, 1H, H-1), 3.88 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.66 – 3.53 (m, 2H, H-3), 3.39 (t,  $J$  = 8.0 Hz, 2H, H-7), 2.81 (t,  $J$  = 7.0 Hz, 2H, H-4), 2.21 (s, 3H, H-6), 1.60-1.51 (m, 1H, H-8), 1.36-1.27 (m, 1H, H-8), 0.83 (t,  $J$  = 7.4 Hz, 3H, H-9).

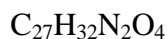
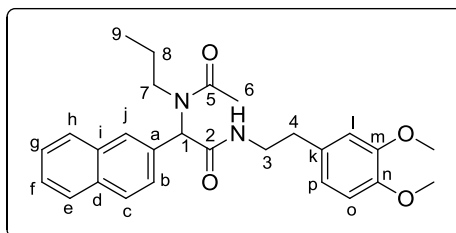
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz):  $\delta$  (ppm) 171.5 (C-5), 168.5 (C-2), 156.3 (C-a), 148.8 (C-h), 148.6 (C-e), 147.5 (C-i), 137.1 (C-c), 131.7 (C-f), 123.3 (C-b), 122.6 (C-d), 120.7 (C-k), 112.1 (C-g), 111.2 (C-j), 64.9 (C-1), 55.9 (C-OMe), 55.8 (C-OMe), 51.6 (C-7), 41.1 (C-3), 35.2 (C-4), 22.7 (C-8), 21.9 (C-6), 11.3 (C-9).

**HRMS:** Calculated for C<sub>22</sub>H<sub>29</sub>N<sub>3</sub>O<sub>4</sub>: 399.2158, Found: 399.2156.

**I.R.** (thin film):  $\nu$  3437, 3060, 2964, 2877, 2838, 1653, 1592, 1573, 1438, 1363, 1252, 1194 and 1030 cm<sup>-1</sup>.

**IV-45**

**N-(3,4-dimethoxyphenethyl)-2-(naphthalen-2-yl)-2-(N-propylacetamido)acetamide**



Mol. Wt.: 448.236 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-A**, using naphthalene-2-carboxaldehyde (156 mg, 1.0 mmol), propylamine (0.08 ml, 1.0 mmol), acetic acid (0.06 ml, 1.0 mmol) and 4-(2-isocyanoethyl)-1,2-dimethoxybenzene (191 mg, 1.0 mmol). Purification by flash chromatography using (pure EtOAc) gave the desired product in 94 % isolated yield (420 mg, 0.94 mmol).

**Nature:** Light yellow oil.

**R<sub>f</sub>** (pure EtOAc) = 0.3.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.89 – 7.81 (m, 4H, H-c,e,j,h), 7.54 (dd, *J* = 6.0, 3.1 Hz, 2H, H-f,g), 7.43 (d, *J* = 8.5 Hz, 1H, H-b), 6.66 (d, *J* = 5.7 Hz, 3H, H-l,o,p), 6.27 (t, *J* = 5.1 Hz, 1H, NH), 5.94 (s, 1H, H-1), 3.81 (s, 3H, OMe), 3.74 (s, 3H, OMe), 3.64 (td, *J* = 13.3, 6.7 Hz, 1H, H-3), 3.48 (td, *J* = 13.0, 6.7 Hz, 1H, H-3), 3.38 – 3.24 (m, 2H, H-7), 2.82 – 2.73 (m, 2H, H-4), 2.21 (s, 3H, H-6), 1.53 – 1.42 (m, 1H, H-8), 1.12-1.03 (m, 1H, H-8), 0.68 (t, *J* = 7.3 Hz, 3H, H-9).

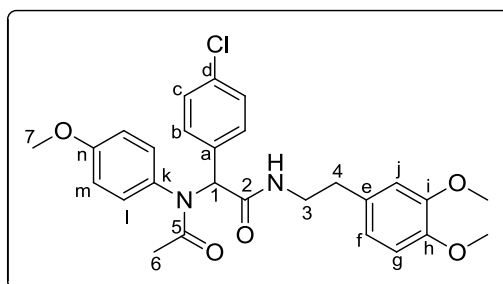
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.6 (C-5), 169.9 (C-2), 148.9 (C-m), 147.5 (C-n), 133.2 (C-i), 133.1 (C-a), 133.0 (C-d), 131.3 (C-k), 128.6 (C-h), 128.5 (C-e), 128.2 (C-c), 127.7 (C-j), 126.8 (C-b), 126.6 (C-f), 126.5 (C-g), 120.7 (C-p), 111.8 (C-l), 111.1 (C-o), 62.9 (C-1), 55.8 (C-OMe), 55.7 (C-OMe), 49.9 (C-7), 41.0 (C-3), 35.2 (C-4), 22.9 (C-8), 21.9 (C-6), 11.2 (C-9).

**HRMS:** Calculated for C<sub>27</sub>H<sub>32</sub>N<sub>2</sub>O<sub>4</sub>: 448.2362, Found: 448.2367.

**I.R.** (thin film): ν 3297, 3057, 2933, 2873, 2835, 1621, 1513, 1452, 1416, 1259, 1139, 1026, 908 and 725 cm<sup>-1</sup>.

**IV-47**

**2-(4-chlorophenyl)-N-(3,4-dimethoxyphenethyl)-2-(N-(4-methoxyphenyl)acetamido)acetamide**



Mol. Wt.: 496.177 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-A**, using 4-chlorobenzaldehyde (141 mg, 1.0 mmol), 4-methoxyaniline (123 mg, 1.0 mmol), acetic acid (0.06 ml, 1.0 mmol) and 4-(2-isocyanoethyl)-1,2-dimethoxybenzene (191 mg, 1.0 mmol). Purification by flash chromatography using (EtOAc : PE = 80 : 20) gave the desired product in 83 % isolated yield (413 mg, 0.83 mmol).

**Nature:** White solid.

**M.P.** = 71-73 °C.

**R<sub>f</sub>** (EtOAc : PE = 8 : 2) = 0.33.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.15 (d, *J* = 8.4 Hz, 2H, H-c), 7.02 (d, *J* = 8.4 Hz, 2H, H-b), 6.76-6.69 (m, 4H, H-Ar), 6.65 (dd, *J* = 8.1, 1.4 Hz, 1H, H-j), 6.04 (br s, 1H, NH), 5.98 (s, 1H, H-1), 3.86 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.78 (s, 3H, H-7), 3.60 (td, *J* = 13.2, 6.8 Hz, 1H, H-3), 3.50 (td, *J* = 13.0, 6.8 Hz, 1H, H-3), 2.82 – 2.70 (m, 2H, H-4), 1.85 (s, 3H, H-6).

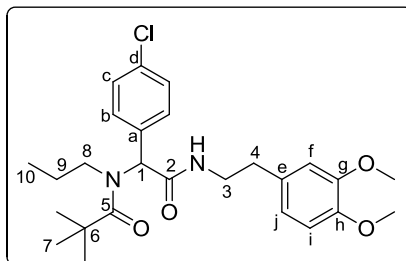
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.8 (C-5), 169.5 (C-2), 159.1 (C-n), 148.9 (C-i), 147.6 (C-h), 134.4 (C-k), 133.2 (C-a), 133.0 (C-e), 131.8 (C-d), 131.2 (C-b), 131.2 (C-l), 128.5 (C-c), 120.7 (C-f), 114.1 (C-m), 111.8 (C-g), 111.2 (C-j), 64.1 (C-1), 55.9 (C-OMe), 55.8 (C-OMe), 55.4 (C-7), 41.0 (C-3), 35.1 (C-4), 23.2 (C-6).

**HRMS:** Calculated for C<sub>27</sub>H<sub>29</sub>ClN<sub>2</sub>O<sub>5</sub>: 496.1765, Found: 496.2088.

**I.R.** (thin film): ν 3314, 3071, 2935, 2837, 1643, 1508, 1464, 1385, 1247, 1156, 1028, 906 and 724 cm<sup>-1</sup>.

**IV-49**

**N-(1-(4-chlorophenyl)-2-((3,4-dimethoxyphenethyl)amino)-2-oxoethyl)-N-propylpivalamide**



Mol. Wt.: 474.229 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-A**, using 4-chlorobenzaldehyde (141 mg, 1.0 mmol), propylamine (0.08 ml, 1.0 mmol), pivalic acid (102 mg, 1.0 mmol) and 4-(2-isocyanoethyl)-1,2-dimethoxybenzene (191 mg, 1.0 mmol). Purification by flash chromatography using (pure Et<sub>2</sub>O) gave the desired product in 68 % isolated yield (325 mg, 0.68 mmol).

**Nature:** Light yellow oil.

**R<sub>f</sub>** (pure Et<sub>2</sub>O) = 0.42.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.19 (d, *J* = 8.6 Hz, 2H, H-c), 7.08 (d, *J* = 8.5 Hz, 2H, H-b), 6.67 (d, *J* = 8.1 Hz, 1H, H-i), 6.63 (d, *J* = 1.9 Hz, 1H, H-f), 6.56 (dd, *J* = 8.1, 1.9 Hz, 1H, H-j), 6.29 (br s, 1H, NH), 4.89 (br s, 1H, H-1), 3.78 (s, 3H, OMe), 3.76 (s, 3H, OMe), 3.45 (q, *J* = 12.8, 6.8 Hz, 2H, H-3), 3.39-3.26 (m, 2H, H-8), 2.67 (t, *J* = 7.0 Hz, 2H, H-4), 1.47-1.31 (m, 2H, H-9), 1.20 (s, 9H, H-7), 0.70 (t, *J* = 7.3 Hz, 3H, H-10).

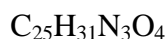
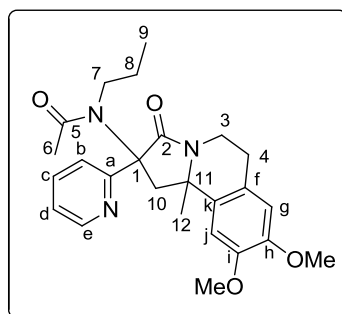
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 178.3 (C-5), 170.1 (C-2), 149.0 (C-h), 147.6 (C-g), 134.7 (C-a), 133.8 (C-d), 131.2 (C-e), 129.6 (C-b), 128.8 (C-c), 120.6 (C-j), 111.8 (C-f), 111.2 (C-i), 67.3 (C-1), 55.9 (C-OMe), 55.8 (C-OMe), 51.6 (C-8), 40.7 (C-6), 39.4 (C-3), 34.9 (C-4), 28.4 (C-7), 22.6 (C-9), 11.0 (C-10).

**HRMS:** Calculated for C<sub>26</sub>H<sub>35</sub>ClN<sub>2</sub>O<sub>4</sub>: 474.2285, Found: 474.2294.

**I.R.** (thin film): ν 3436, 2964, 2937, 2877, 2839, 1668, 1620, 1515, 1463, 1377, 1261, 1194, 1094 and 1028 cm<sup>-1</sup>.

#### IV-44

**N-(8,9-dimethoxy-10b-methyl-3-oxo-2-(pyridin-2-yl)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-2-yl)-N-propylacetamide**



Mol. Wt.: 437.232 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **IV-B**, using N-(3,4-dimethoxyphenethyl)-2-(N-propylacetamido)-2-(pyridin-2-yl)acetamide **IV-43** (160 mg, 0.4 mmol), sodium hydride (40 mg, 1.0 mmol), propargyl bromide (0.07 ml, 0.6 mmol), TBAF (0.4 ml, 0.4 mmol) and trifluoroacetic acid (0.06 ml, 0.8 mmol). Purification by flash chromatography using gradient eluent (EtOH : EtOAc = 2 : 98 – 8 : 92) gave the desired product in 51 % isolated yield (89 mg, 0.2 mmol).

**Nature:** Yellow oil.

**R<sub>f</sub>** (EtOH : EtOAc = 0.6 : 9.4) = 0.17.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 8.58 (d, *J* = 4.7 Hz, 1H, H-e), 8.01 (d, *J* = 8.0 Hz, 1H, H-b), 7.66 (td, *J* = 7.8, 1.8 Hz, 1H, H-c), 7.25 – 7.21 (m, 1H, H-d), 6.54 (s, 1H, H-j), 6.49 (s, 1H, H-g), 4.22 (dd, *J* = 12.9, 5.3 Hz, 1H, H-3), 4.12 (d, AB system, *J<sub>ab</sub>* = 12.3 Hz, 1H, H-10), 3.79 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.19-3.06 (m, 2H, H-4,7), 2.94 (td, *J* = 12.7, 3.8 Hz, 1H, H-3), 2.56 – 2.41 (m, 3H, H-4,7,10), 2.01 (s, 3H, H-6), 1.48-1.39 (m, 1H, H-8), 1.27 – 1.13 (m, 4H, H-8,12), 0.51 (t, *J* = 7.4 Hz, 3H, H-9).

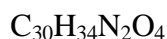
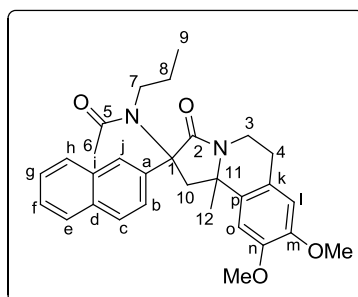
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.2 (C-5), 170.1 (C-2), 155.9 (C-a), 148.2 (C-e), 147.9 (C-i), 147.4 (C-h), 136.9 (C-c), 135.4 (C-k), 124.7 (C-b), 124.5 (C-f), 123.5 (C-d), 111.5 (C-g), 107.9 (C-j), 71.7 (C-1), 58.1 (C-11), 56.0 (C-OMe), 55.8 (C-OMe), 48.9 (C-7), 43.8 (C-10), 35.2 (C-3), 28.9 (C-12), 27.6 (C-4), 23.4 (C-8), 23.01 (C-6), 11.1 (C-9).

**HRMS:** Calculated for C<sub>25</sub>H<sub>31</sub>N<sub>3</sub>O<sub>4</sub>: 437.2315, Found: 437.2299.

**I.R.** (thin film): ν 3057, 2999, 2934, 2876, 2830, 1681, 1655, 1514, 1421, 1253, 1150, 1127, 1023, 927 and 722 cm<sup>-1</sup>.

#### IV-46

#### N-(8,9-dimethoxy-10b-methyl-2-(naphthalen-2-yl)-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-2-yl)-N-propylacetamide



Mol. Wt.: 486.252 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **IV-B**, using N-(3,4-dimethoxyphenethyl)-2-(naphthalen-2-yl)-2-(N-propylacetamido)acetamide **IV-45** (179 mg, 0.4 mmol), sodium hydride (40 mg, 1.0 mmol), propargyl bromide (0.07 ml, 0.6 mmol), TBAF (0.4 ml, 0.4 mmol) and trifluoroacetic acid (0.06 ml, 0.8 mmol). Purification by flash chromatography using gradient eluent (EtOH : EtOAc = 2 : 98 – 4 : 96) gave the desired product in 63 % isolated yield (123 mg, 0.25 mmol).

**Nature:** Yellow solid.

**M.P.** = 257-259 °C.

**R<sub>f</sub>** (EtOH : EtOAc = 0.4 : 9.6) = 0.17.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 8.36 (s, 1H, H-j), 8.07 (d, *J* = 8.7 Hz, 1H, H-b), 7.98-7.95 (m, 2H, H-h,e), 7.94 – 7.89 (m, 1H, H-c), 7.62 – 7.55 (m, 2H, H-g,f), 6.63 (d, *J* = 2.5 Hz, 2H, H-o,l), 4.40 (dd, *J* = 12.9, 5.8 Hz, 1H, H-3), 3.93 (s, 3H, OMe), 3.89 (s, 3H, OMe), 3.47 (d, AB system, *J<sub>ab</sub>* = 12.8 Hz, 1H, H-10), 3.32 – 3.21 (m, 1H, H-4), 3.19 – 3.09 (ddd, *J* = 16.0, 11.2, 5.6 Hz, 1H, H-7), 3.05-2.99 (m, 2H, H-3,10), 2.73 (ddd, *J* = 15.6, 10.8, 5.1 Hz, 1H, H-7), 2.63 (dd, *J* = 15.4, 2.9 Hz, 1H, H-4), 2.16 (s, 3H, H-6), 1.50 – 1.36 (m, 2H, H-8), 1.33 (s, 3H, H-12), 0.55 (t, *J* = 7.3 Hz, 3H, H-9).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.4 (C-5), 170.5 (C-2), 147.9 (C-n), 147.6 (C-m), 135.0 (C-p), 134.2 (C-a), 133.1 (C-i), 132.9 (C-d), 128.7 (C-h), 128.3 (C-e), 128.2 (C-j), 127.5 (C-c), 127.0 (C-f), 126.7 (C-b), 126.5 (C-g), 124.9 (C-k), 111.7 (C-l), 107.9 (C-o), 69.6 (C-1), 57.7 (C-3), 56.2 (C-OMe), 55.8 (C-OMe), 48.6 (C-7), 45.1 (C-10), 35.3 (C-3), 28.8 (C-12), 27.6 (C-4), 24.0 (C-8), 23.4 (C-6), 11.1 (C-9).

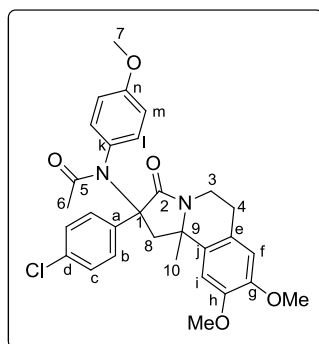
**HRMS:** Calculated for C<sub>30</sub>H<sub>34</sub>N<sub>2</sub>O<sub>4</sub>: 486.2519, Found: 486.2499.



**I.R.** (thin film):  $\nu$  3057, 2958, 2930, 2872, 2831, 1680, 1645, 1514, 1417, 1257, 1210, 1131, 1022, 825 and  $757\text{ cm}^{-1}$ .

#### **IV-48**

**N-(2-(4-chlorophenyl)-8,9-dimethoxy-10b-methyl-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-2-yl)-N-(4-methoxyphenyl)acetamide**



Mol. Wt.:  $534.192\text{ g.mol}^{-1}$

This compound was synthesized according to the general procedure **IV-B**, using 2-(4-chlorophenyl)-N-(3,4-dimethoxyphenethyl)-2-(N-(4-methoxyphenyl)acetamido)acetamide **IV-47** (199 mg, 0.4 mmol), sodium hydride (40 mg, 1.0 mmol), propargyl bromide (0.07 ml, 0.6 mmol), TBAF (0.4 ml, 0.4 mmol) and trifluoroacetic acid (0.06 ml, 0.8 mmol). Purification by flash chromatography using (pure EtOAc) gave the desired product in 35% isolated yield (75 mg, 0.14 mmol).

**Nature:** Yellow oil.  $R_f$  (pure EtOAc) = 0.18.

**$^1\text{H-NMR}$**  ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  (ppm) 7.37 (d,  $J = 8.3\text{ Hz}$ , 2H, H-c), 7.02 (d,  $J = 8.9\text{ Hz}$ , 2H, H-b), 6.81 (dd,  $J = 13.1, 8.7\text{ Hz}$ , 2H, H-l), 6.62 (dd,  $J = 8.4, 2.5\text{ Hz}$ , 1H, H-i), 6.53 (s, 1H, H-f), 6.49 – 6.43 (m, 2H, H-m), 4.36 (dd,  $J = 12.8, 5.1\text{ Hz}$ , 1H, H-3), 3.81 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.64 (s, 3H, H-7), 3.25 (d, AB system,  $J_{ab} = 12.4\text{ Hz}$ , 1H, H-8), 3.19-3.09 (m, 2H, H-4,8), 2.99 (td,  $J = 12.6, 3.7\text{ Hz}$ , 1H, H-3), 2.57 (dd,  $J = 15.5, 2.9\text{ Hz}$ , 1H, H-4), 1.63 (s, 3H, H-6), 1.09 (s, 3H, H-10).

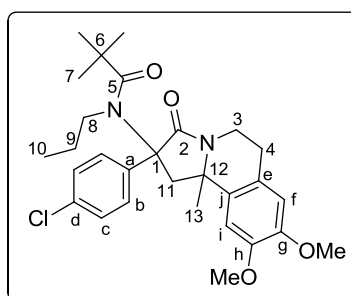
**$^{13}\text{C-NMR}$**  ( $\text{CDCl}_3$ , 100.6 MHz):  $\delta$  (ppm) 171.9 (C-5), 170.0 (C-2), 158.7 (C-n), 148.0 (C-h), 147.7 (C-g), 136.6 (C-a), 134.6 (C-j), 133.9 (C-d), 133.8 (C-k), 132.5 (C-l), 131.1 (C-c), 128.1 (C-b), 124.9 (C-e), 113.9 (C-m), 111.7 (C-i), 107.8 (C-f), 71.4 (C-1), 57.9 (C-9), 56.2 (C-OMe), 55.8 (C-OMe), 55.4 (C-7), 46.8 (C-8), 35.4 (C-3), 28.6 (C-10), 27.8 (C-6), 24.8 (C-4).

**HRMS:** Calculated for  $C_{30}H_{31}ClN_2O_5$ : 534.1921, Found: 534.1930.

**I.R.** (thin film):  $\nu$  2970, 2932, 2902, 1691, 1659, 1509, 1423, 1371, 1256, 1066, 1037, 910 and  $734\text{ cm}^{-1}$ .

#### **IV-50**

**N-(2-(4-chlorophenyl)-8,9-dimethoxy-10b-methyl-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-2-yl)-N-propylpivalamide**



Mol. Wt.:  $512.244\text{ g}\cdot\text{mol}^{-1}$

This compound was synthesized according to the general procedure **IV-B**, using N-(1-(4-chlorophenyl)-2-((3,4-dimethoxyphenethyl)amino)-2-oxoethyl)-N-propylpivalamide **IV-49** (190 mg, 0.4 mmol), sodium hydride (40 mg, 1.0 mmol), propargyl bromide (0.07 ml, 0.6 mmol), TBAF (0.4 ml, 0.4 mmol) and trifluoroacetic acid (0.06 ml, 0.8 mmol). Purification by flash chromatography using gradient eluent ( $\text{Et}_2\text{O} : \text{DCM} = 5 : 95 - 10 : 90$ ) gave the desired product in 56 % isolated yield (115 mg, 0.22 mmol).

**Nature:** Yellow solid.

**M.P.** = 220-222 °C.

**R<sub>f</sub>** ( $\text{Et}_2\text{O} : \text{DCM} = 1 : 9$ ) = 0.22.

**$^1\text{H-NMR}$**  ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  (ppm) 7.74 (d,  $J = 8.5\text{ Hz}$ , 2H, H-b), 7.29 (d,  $J = 8.9\text{ Hz}$ , 2H, H-c), 6.52 (s, 1H, H-i), 6.50 (s, 1H, H-f), 4.18 (dd,  $J = 13.0, 5.0\text{ Hz}$ , 1H, H-3), 3.83 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.59 – 3.48 (m, 1H, H-8), 3.38 (d, AB system,  $J_{ab} = 13.5\text{ Hz}$ , 1H, H-11), 3.06 (ddd,  $J = 15.3, 12.8, 6.0\text{ Hz}$ , 1H, H-4), 2.90 (td,  $J = 12.7, 3.8\text{ Hz}$ , 1H, H-3), 2.75 – 2.59 (m, 2H, H-8,11), 2.49 (dd,  $J = 15.5, 3.0\text{ Hz}$ , 1H, H-4), 1.39 (s, 3H, H-13), 1.25 – 1.09 (m, 11H, H-7,9), 0.53 (t,  $J = 7.3\text{ Hz}$ , 3H, H-10).

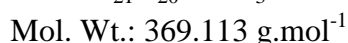
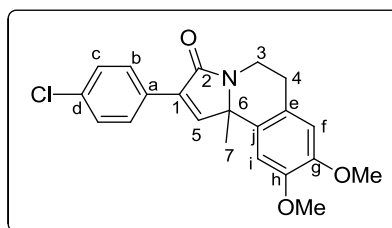
**$^{13}\text{C}$ -NMR** ( $\text{CDCl}_3$ , 100.6 MHz):  $\delta$  (ppm) 178.8 (C-5), 170.2 (C-2), 147.9 (C-h), 147.5 (C-g), 136.3 (C-a), 135.3 (C-j), 134.1 (C-d), 129.5 (C-b), 128.4 (C-c), 124.8 (C-e), 111.6 (C-f), 107.9 (C-i), 69.2 (C-1), 57.6 (C-12), 56.2 (C-OMe), 55.8 (C-OMe), 47.5 (C-8), 44.7 (C-11), 40.0 (C-6), 35.3 (C-3), 29.6 (C-13), 28.5 (C-7), 27.6 (C-4), 24.4 (C-9), 10.8 (C-10).

**HRMS:** Calculated for  $[\text{M}-\text{N}(\text{C}_3\text{H}_7)\text{COCMe}_3]$   $\text{C}_{21}\text{H}_{22}\text{ClNO}_3$ : 371.1288, Found: 371.1298.

**I.R.** (thin film):  $\nu$  2960, 2931, 1682, 1630, 1513, 1426, 1356, 1258, 1097, 1013, 850 and 749  $\text{cm}^{-1}$ .

**IV-42**

**2-(4-chlorophenyl)-8,9-dimethoxy-10b-methyl-5,6-dihydropyrrolo[2,1-a]isoquinolin-3(10bH)-one**



This compound was isolated upon the treatment of N-(2-(4-chlorophenyl)-8,9-dimethoxy-10b-methyl-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-2-yl)-N-propylacetamide **IV-41** (141 mg, 0.3 mmol) with 1 equiv. of tosic acid (57 mg, 0.3 mmol) in toluene (0.3 M) and refluxing the reaction mixture for 24 hours. After the completion of the reaction, it was diluted with  $\text{CH}_2\text{Cl}_2$  and extracted with a solution of sodium bicarbonate. The organic phase was washed with water 2 times and dried over  $\text{MgSO}_4$  and then solvent was removed under reduced pressure. Purification by flash chromatography using ( $\text{Et}_2\text{O} : \text{DCM} = 5 : 95$ ) gave the desired product in 87 % isolated yield (96 mg, 0.26 mmol)

**Nature:** Yellow oil.

**R<sub>f</sub>** ( $\text{Et}_2\text{O} : \text{DCM} = 0.5 : 9.5$ ) = 0.34.

**$^1\text{H-NMR}$**  ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  (ppm) 7.78 (d,  $J = 8.7$  Hz, 2H, H-c), 7.40 (s, 1H, H-5), 7.27 (d,  $J = 8.7$  Hz, 2H, H-b), 6.70 (s, 1H, H-i), 6.54 (s, 1H, H-f), 4.45 (dd,  $J = 13.4, 6.3$  Hz, 1H, H-3), 3.85 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.22 (ddd,  $J = 13.3, 12.1, 4.4$  Hz, 1H, H-3), 2.91 (ddd,  $J = 16.3, 12.1, 6.6$  Hz, 1H, H-4), 2.62 (dd,  $J = 16.1, 3.8$  Hz, 1H, H-4), 1.59 (s, 3H, H-7).

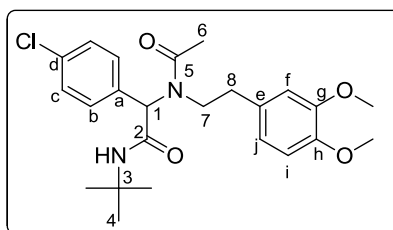
**$^{13}\text{C-NMR}$**  ( $\text{CDCl}_3$ , 100.6 MHz):  $\delta$  (ppm) 168.7 (C-2), 148.3 (C-g), 147.8 (C-h), 146.0 (C-5), 134.5 (C-a), 133.3 (C-d), 129.9 (C-1), 129.4 (C-e), 128.7 (C-b), 128.6 (C-c), 125.3 (C-j), 112.1 (C-f), 109.1 (C-i), 62.8 (C-6), 56.3 (C-OMe), 55.9 (C-OMe), 35.0 (C-3), 29.3 (C-4), 27.1 (C-7).

**HRMS:** Calculated for  $\text{C}_{21}\text{H}_{20}\text{ClNO}_3$ : 369.1132, Found: 369.0810.

**I.R.** (thin film):  $\nu$  3073, 3040, 3009, 2975, 2937, 2853, 1680, 1612, 1522, 1456, 1393, 1258, 1130, 1093 and  $1016 \text{ cm}^{-1}$ .

## IV-51

### N-(*tert*-butyl)-2-(4-chlorophenyl)-2-(N-(3,4-dimethoxyphenethyl)acetamido)acetamide



Mol. Wt.: 446.197 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-A**, using 4-chlorobenzaldehyde (141 mg, 1.0 mmol), 3,4-dimethoxyphenylethylamine (0.17 ml, 1.0 mmol), acetic acid (0.057 ml, 1.0 mmol) and *tert*-butyl isocyanide (0.11 ml, 1.0 mmol). Purification by flash chromatography using (Et<sub>2</sub>O : DCM = 20 : 80) gave the desired product in 98 % isolated yield (438 mg, 0.98 mmol).

**Nature:** White solid.

**M.P.** = 153-155 °C.

**R<sub>f</sub>:** (Et<sub>2</sub>O : DCM = 2 : 8) = 0.25.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.45 (d, *J* = 8.4 Hz, 4H, H-b,c), 6.76 (d, *J* = 8.1 Hz, 1H, H-i), 6.52 (dd, *J* = 8.1, 1.7 Hz, 1H, H-f), 6.38 (s, 1H, H-j), 5.92 (br s, 1H, NH), 5.87 (s, 1H, H-1), 3.87 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.52 (t, *J* = 8.3 Hz, 2H, H-7), 2.72-2.65 (m, 1H, H-8), 2.23 (s, 4H, H-6,8), 1.38 (s, 9H, H-4).

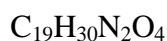
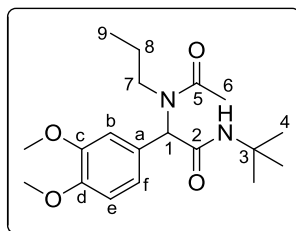
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.6 (C-5), 168.8 (C-2), 148.9 (C-g), 147.7 (C-h), 134.6 (C-a), 134.4 (C-d), 131.1 (C-c), 130.6 (C-e), 129.1 (C-b), 120.4 (C-i), 111.7 (C-f), 111.2 (C-j), 61.5 (C-1), 55.9 (C-OMe), 55.8 (C-OMe), 51.7 (C-3), 49.1 (C-7), 35.9 (C-8), 28.6 (C-4), 21.9 (C-6).

**HRMS:** Calculated for [M-NHCOCMe<sub>3</sub>] C<sub>19</sub>H<sub>21</sub>ClNO<sub>3</sub>: 346.1205, Found: 346.1211.

**I.R.** (thin film): ν 3426, 3086, 3069, 2968, 2936, 2912, 2838, 1683, 1641, 1513, 1411, 1367, 1301, 1247, 1179 and 1094 cm<sup>-1</sup>.

#### IV-54

#### N-(*tert*-butyl)-2-(3,4-dimethoxyphenyl)-2-(N-propylacetamido)acetamide



Mol. Wt.: 350.221 g.mol<sup>-1</sup>

This compound was synthesized according to the general procedure **II-A**, using 3,4-dimethoxybenzaldehyde (166 mg, 1.0 mmol), propylamine (0.082 ml, 1.0 mmol), acetic acid (0.057 ml, 1.0 mmol) and *tert*-butyl isocyanide (0.11 ml, 1.0 mmol). Purification by flash chromatography using (EtOAc : P.E. = 70 : 30) gave the desired product in 87 % isolated yield (305 mg, 0.87 mmol).

**Nature:** Yellow solid.

**M.P.** = 128-130 °C.

**R<sub>f</sub>**: (EtOAc : P.E. = 7 : 3) = 0.24.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 6.88 (d, *J* = 10.5 Hz, 2H, H-b,f), 6.77 (d, *J* = 8.1 Hz, 1H, H-e), 5.78 (s, 2H, NH, H-1), 3.81 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.17 (qt, *J* = 15.5, 7.7 Hz, 2H, H-7), 2.09 (s, 3H, H-6), 1.37 – 1.24 (m, 10H, H-4,8), 0.88-0.76 (m, 1H, H-8), 0.58 (t, *J* = 7.4 Hz, 3H, H-9).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, 100.6 MHz): δ (ppm) 171.4 (C-5), 169.4 (C-2), 148.9 (C-c), 148.9 (C-d), 128.3 (C-a), 122.1 (C-f), 112.5 (C-b), 110.9 (C-e), 61.5 (C-1), 55.9 (C-OMe), 55.8 (C-OMe), 51.4 (C-3), 48.9 (C-7), 28.6 (C-4), 23.1 (C-8), 21.8 (C-6), 11.3 (C-9).

**HRMS:** Calculated for C<sub>19</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub>: 350.2206, Found: 350.2212.

**I.R.** (thin film): ν 3425, 2968, 2936, 2876, 2840, 1683, 1624, 1592, 1516, 1477, 1367, 1301, 1264, 1144 and 1027 cm<sup>-1</sup>.



**Titre :** Réactions multicomposants pour la préparation de composés hétérocycliques azotés à haut potentiel biologique  
**Mots clés :** Réactions Multicomposants, Réaction Ugi, Réaction Tsuji-Trost,  $\beta$ -lactam, Pyrrolidinone

**Résumé :** Les réactions multicomposants représentent un axe de recherche important en chimie organique. La capacité de regrouper en une même réaction plus de trois produits de départ est la base de synthèse de molécules complexes proches de composés bioactifs. Par ailleurs, de par leur diversité, ces réactions sont des outils précieux pour la réalisation de bibliothèques dans la recherche pharmaceutique. Les réactions multicomposants à base d'isonitrile, particulièrement la réaction Ugi, sont largement utilisées. Malgré les nombreuses applications de cette réaction, elle souffre encore de nombreuses limitations notamment lorsque des fonctionnalisations des adduits de Ugi sont recherchées sur la nouvelle position peptidyle créée. Du fait de fort encombrement stérique autour de cette position, seules des réactions intramoléculaires étaient décrites dans la littérature. Ainsi nous avons développé des stratégies efficaces pour la réalisation d'addition intermoléculaires sur des adduits d'Ugi. Nous avons exploré la formation de dianions 1,3-amide permettant d'augmenter la nucléophilie de nos composés et de réaliser des alkylations avec différents agents électrophiles à température ambiante et avec d'excellents rendements. Une application très simple de cette approche a été réalisée en couplant l'alkylation de la position peptidyle à une réaction de métathèse cyclisante.

Ceci pourrait être réalisé en introduisant un fragment allylique dans les produits de départ d'Ugi, nécessaire pour la métathèse. Les piperidines et piperidones formées appartiennent à des classes de produits très exploitées dans le domaine pharmaceutique. Par ailleurs, poursuivant sur le potentiel de ces dianions 1,3-amides, nous avons voulu piéger ces intermédiaires par des électrophiles plus complexes nous permettant de former des dérivés cycliques. L'utilisation du diiodométhane en particulier, nous a permis d'ouvrir une voie très prometteuse dans la synthèse de  $\beta$ -lactames. Non limitée aux produits d'Ugi, des amides beaucoup plus simples issus d'esters maloniques ont pu être aussi transformés en  $\beta$ -lactames. En plus, les activités biologiques de ces  $\beta$ -lactames nouvellement synthétisés ont été examinées. Enfin, nous avons étendu cette approche à la formation de pyrrolidinones en une séquence monotopie d'alkylation/cyclisation en travaillant sur la propargylation de ces adduits d'Ugi. La fonction énamine des 5-méthylène-pyrrolidin-2-ones synthétisées a pu être exploitée dans la réaction de Pictet-Spengler permettant la synthèse de dérivés de benzoindolizidine proches de différents alcaloïdes naturels. Néanmoins, la cascade propargylation/Pictet-Spengler a pu être réalisée avec succès dans une seule étape avec de bons rendements.

**Title:** Multicomponent reactions for the synthesis of some nitrogenous heterocyclic compounds and studies of their biological activities

**Keywords:** Multicomponent Reactions, Ugi Reaction, Tsuji-Trost Reaction,  $\beta$ -lactam, Pyrrolidinone

**Abstract:** Multicomponent reactions represent an important line of research in organic chemistry. It permits the reaction between three or more starting materials, providing adducts which are considered as synthons for the syntheses of complex molecules close to bioactive compounds. As a result of their diversity, these reactions are considered as valuable tools for the preparation of libraries of organic structures in the pharmaceutical research field. The isonitrile-based multicomponent reactions, particularly the Ugi reaction, are the most frequently employed. Despite the wide applications of this reaction, it still suffers from numerous limitations, particularly when the newly formed peptidyl position is involved in the post-condensation reactions. Due to the steric hindrance around this position, only intramolecular reactions were described in the literature. Thus we have developed effective strategies for the intermolecular reactions involving Ugi adducts through the formation of 1,3-amide dianions to increase their nucleophilicity. Accordingly, such intermediates undergo alkylation reactions with different electrophilic agents at room temperature and with excellent yields. A very simple application of this approach has been attained by coupling the alkylation at the peptidyl position to a ring closure metathesis reaction.

This could be achieved by introducing an allylic fragment into the starting Ugi materials, necessary for metathesis. Such protocol allowed the synthesis of various piperidines and piperidones derivatives. Moreover, examining the potential of these 1,3-amide dianion intermediates by employing more complex electrophiles, allowed us to prepare cyclic derivatives. The use of diiodomethane in particular, has opened an access to a very promising way in the synthesis of  $\beta$ -lactams. Simpler malonic ester amides and their derivatives could also be converted to  $\beta$ -lactams following the same strategy, hence, it is not only limited to Ugi adducts. Additionally, the biological activities of such newly synthesized  $\beta$ -lactams were examined. Finally, we extended this approach to the preparation of pyrrolidinones through an alkylation/cyclization sequence via the propargylation of these Ugi adducts. The enamine functional group in the synthesized 5-methylene-pyrrolidin-2-ones could be exploited in a Pictet-Spengler reaction allowing the synthesis of benzoindolizidine derivatives, which are close in structure to natural alkaloids. Nevertheless, the propargylation/Pictet-Spengler cascade could be successfully performed in a one-pot reaction with good yields.