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Nouvelles opportunités pour la synthèse peptidique

Présentée par Eleonora TOSI

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Sous la direction de Renata MARCIA DE FIGUEIREDO et Jean-Marc CAMPAGNE

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« La sapienza è figliola della sperienza »

Leonardo da Vinci

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List of Abbreviations

AA: amino acid

ACN: acetonitrile

Act: activation

AOP: 7-(Azabenzotriazol-1-yl)oxy tris(dimethylamino)phosphonium hexafluorophosphate

Bn: benzyl

Boc: *tert*-butyloxycarbonyl

BOP: (benzotriazole-1-yl-oxy)tris(dimethylamino)-phosphonium hexafluorophosphate

Bu: butyl

Cbz: benzyloxycarbonyl

CDI: *N*,*N*′-carbonyldiimidazole

CDT: 1,1′-carbonyl-di-(1,2,4-triazole)

COD: cyclooctadiene

DCC: *N*,*N*′-dicyclohexylcarbodiimide

DCM: dichloromethane

DFT: density functional theory

DG: directing group

DIPEA: N,N-diisopropylethylamine

DMF: *N*,*N*-dimethylformamide

DMSO: dimethyl sulfoxide

DSC: *N*,*N*′-disuccinimidyl carbonate

Fmoc: fluorenylmethoxycarbonyl

EDC: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

Equiv: equivalent

ESI: electrospray ionization

EtOAc: ethyl acetate

HATU: 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate

HBTU: N,N,N′,N′-Tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate

HCTU: 1-[Bis(dimethylamino)methylen]-5-chlorobenzotriazolium 3-oxide hexafluorophosphate

HEPES: 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid

HFP: hexafluoroisopropanol

HMPA: hexamethylphosphoramide

HOBt: 1-Hydroxybenzotriazole

HPLC: high performance liquid chromatography

HRMS: high-resolution mass spectrometry

Hz: hertz

IR: infrared

J: coupling costant

KAHA: α-ketoacid-hydroxylamine

MI: mass intensity

Mp: melting point

MTBE: methyl *tert*-butyl ether

NCL: native chemical ligation

NIPS: new inverse peptide synthesis

NMP: 1-Methyl-2-pyrrolidone

NMR: nuclear magnetic resonance

NOPS: novel opportunities for peptide synthesis

P: protecting

PBS: Phosphate-buffered saline

PCS: protein chemical synthesis

Ph: phenyl

PTSA: p-toluenesulfonic acid

PyAOP: (7-Azabenzotriazol-1-yloxy)trispyrrolidinophosphonium hexafluorophosphate

PyBOP: benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate

Pytz: 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine

rt: room temperature

TFA: trifluoroacetic acid

TFE: 2,2,2-trifluoroethanol

THF: tetrahydrofuran

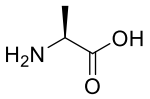
TLC: thin layer chromatography

TMS: trimethylsilyl

Ts: tosyl

UV: ultraviolet

List of α-amino acids



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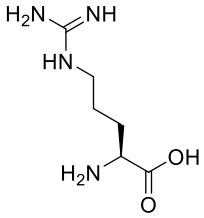

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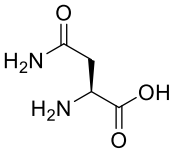

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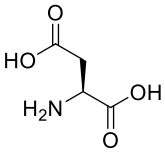

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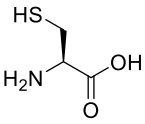

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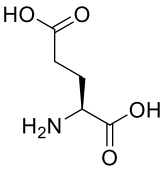

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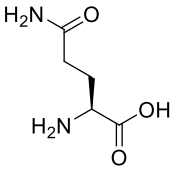

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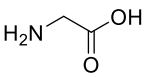

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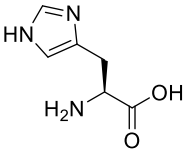

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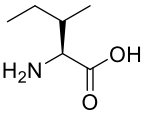

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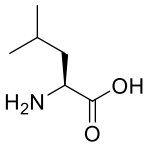

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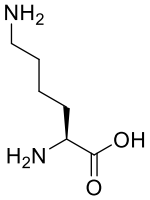

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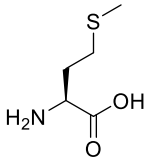

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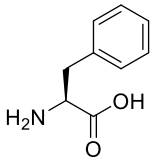

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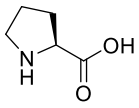

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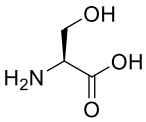

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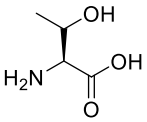

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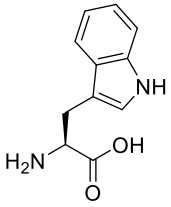

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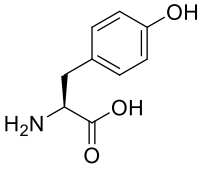

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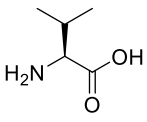

Val (V)

Table of Contents

General Introduction

Peptides and proteins are amongst the essential molecules in the everyday life. The backbone of these bioactive compounds is made of amino acids, bind together through peptide bonds (amide function). For this reason, researchers are making efforts to investigate thoroughly their synthesis and applications. These molecules are extensively used in different fields such as medical science (drugs, vaccines, biomarkers, etc.) as well as polymers and materials science (hydrogels, supported catalysts, etc.).

In the pharmaceutical industry, peptides come to prominence in the 1920s with the arrival of the insulin therapy. Nowadays, the number of peptide drugs under global clinical developments is currently more than 400 with over 60 already approved for clinical use in the United States, Europe and Japan.[1] This success can be explained due to their principal characteristics: (i) low toxicity, (ii) high specificity and (iii) high activity although some drawbacks are limiting their presence on the market such as (i) low bioavailability and (ii) the expensive cost of their synthesis.[2] In light of these considerations, researchers showed interest in the field of peptide synthesis, focusing their attention on novel atom-economic and greener methodologies to synthesise amides. In conclusion, peptides as well as their synthesis is one of the widest explored topic, where many progresses have been accomplished so far, and, still, many breakthroughs have yet to come.

The easiest way to synthesise the amide function is the direct reaction between a carboxylic acid and an amine with the formation of a water molecule as by-product (Scheme 1a).[3] However, this condensation process is only occurring under harsh conditions to sidestep the unreactive carboxylate-ammonium salt formation towards the desired amide function formation (Scheme 1b).

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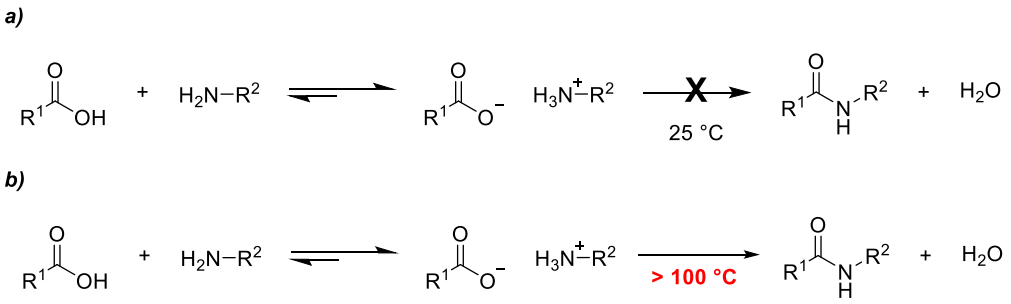
[1] a) J.L. Lau, M.K. Dunn *Bioorganic & Medicinal Chemistry* **2018**, *26*, 2700; b) A.C.-L. Lee, J.L. Harris, K.K. Khanna, J.-H. Hong *Int. J. Mol. Sci.* **2019**, *20*, 2383.

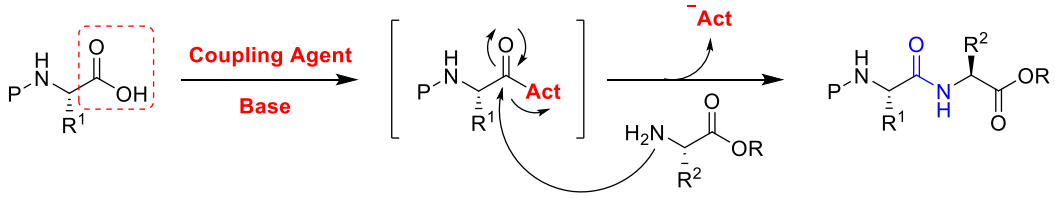
[2] A. Loffet *J. Peptide Sci.* **2002**, *8*, 1.

[3] a) G.H. Coleman, A.M. Alvarado *Org. Synth.* **1923**, *3*, 3; b) J. Cossy, C. Pale-Grosdemange *Tetrahedron Lett.* **1989**, *30*, 2771.



Scheme 1. Direct condensation of carboxylic acids and amines.

In consequence, when sensitive substrates like amino acids and peptides are employed, these procedures are incompatible. Hence, it is necessary to activate the carboxylic moiety of the first partner with a *pre* or *in-situ* activation to give a reactive intermediate which undergoes a nucleophilic attack by the second partner amine function (Scheme 2). Traditionally, the activation of carboxylic acids is achieved using the so-called "coupling reagents" in stoichiometric amounts making these procedures expensive and wasteful.[4]



Scheme 2. Classical activation of the carboxylic acid.

Despite their efficiency, the great molecular mass of the coupling agents makes these methodologies poor atom-economical processes.[5] In addition, the elongation of peptides is compulsory from the C-terminus to the N-terminus, adding amino acids one by one in order to avoid drawbacks associated with racemisation (while the biosynthesis of peptides and proteins occurs in the opposite direction).[6]

Hence, several non-conventional routes to amide bond were investigated and developed by many research's laboratories in order to avoid this "classical" activation of carboxylic acids. A

[4] a) A. El-Faham, F. Albericio *Chem. Rev.* **2011**, *111*, 6557; b) E. Valeur, M. Bradley *Chem. Soc. Rev*. **2009**, *38*, 606; c) K. Hollanders, B.U.W. Maes, S. Ballet *Synthesis* **2019**, *51*, 2261.

[5] a) B.M. Trost, Atom economy: a challenge for enhanced synthetic efficiency, Handbook of green chemistry volume 7: green synthesis. Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim; b) A.P. Dicks, A. Hent, (2015) Atom Economy and Reaction Mass Efficiency. In: Green Chemistry Metrics. SpringerBriefs in Molecular Science. Springer, Cham.

[6] Y. Yang *Side Reactions in Peptide Synthesis* **2016**.

non-exhaustive list of the more important and innovative methodologies for the amide synthesis will be introduced and briefly explored in this chapter. Our laboratory has also given its contribution developing a new alternative strategy to access peptides[7] based on the activation of the amino function paving the way to rethink peptide synthesis.

In this context, my PhD studies and this manuscript focus the attention on the efficiency of this new methodology (improve the kinetics of the reaction, study the mechanism) in order to provide a useful tool which could be transposed in the peptide field (such as SPPS or fragment couplings, etc…). Moreover, since the importance of the "amide function" in several domains such as pharmaceutical or agricultural industries, this approach will be extended to the synthesis of general amides as well. Eventually, in this manuscript another side-project in the field of the synthesis of small *N*-heterocyclic compounds starting from vinyl aziridines will be reported.

[7] J.-S. Suppo, G. Subra, M. Bergès, R.M. de Figueiredo, J.-M. Campagne *Angew. Chem. Int. Ed.* **2014**, *53*, 5389.

I. Peptide synthesis

At the beginning of the twentieth century, Fischer and Fourneau focused their attention on amino acids and proteins; in 1901 the first peptide synthesis was reported. The formation of the dipeptide glycyl-glycine was carried out by diketopiperazine opening.[8] We owe to them also the creation at that time of the term peptide, thereby defining the terminology of peptide chemistry up to date. Fischer exploited acyl chlorides reactivity in order to obtain peptide bond formation. He reported the synthesis of an octadecapeptide (Leu-$(Gly)_3$-Leu-$(Gly)_3$-Leu-$(Gly)_9$-OH) in 1907.[9]

Since then, the peptide science is constantly evolving; one of the most remarkable achievement is the solid-phase methodology to obtain long peptides, solving solubility's issues, developed by Bruce Merrifield in 1963 (awarded with Nobel Prize in 1984).[10] Therefore, the fastness of peptide synthesis was enhanced affording long chains of amino acids and small proteins in short reaction time.

Today, thanks to the pioneering works of Fischer, Merrifield and other chemists, it is possible to easily synthesise biologically active peptides and proteins.[11]

I.1 Principle of peptide synthesis

Peptide synthesis relies on two fundamentals: (i) selection of suitable protecting groups for amino acids and their orthogonal deprotection, and (ii) peptide bond formation.

A systematic procedure is required to synthesise peptides, each time coupling the amino group of one amino acid with the carboxylic acid of a second amino acid. Thereby, different parameters such as amino acids' nature (side chains), length of the desired molecules have to be taken into account in order to choose the most suitable methodology (solution phase, solid phase, ligation etc…).

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[8] E. Fischer, E. Fourneau *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 2868.

[9] G. Prabhu, Basavaprabhu, N. Narendra, T.M. Vishwanatha, V.V. Sureshbabu *Tetrahedron* **2015**, 71, 2785.

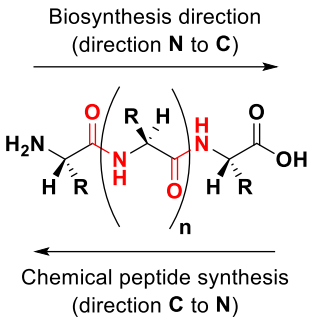
[10] R.B. Merrifield *J. Am. Chem. Soc.* **1963**, *85*, 2149.

[11] M. Goodman, W. Cai, N.D. Smith *J. Peptide Sci.* **2003**, *9*, 594.

Moreover, as above mentioned, it is important to consider amino acids and their protecting groups.[12] When a coupling reaction between two amino acids occurred, we have to be sure that no undesired products are obtained due to the presence of non-protected functional groups (e.g. side chains). A solution to this problem is to transform these functions in order to make them unreactive. For this reason, many efforts have been made to study in-depth protecting groups that allow these transformations. Protecting groups should be i) easy to introduce, ii) stable to a wide range of reaction conditions, and iii) easily removed when required. These protections should be, also, orthogonal[13] to the carboxylic and amine functions engaged in the peptide bond formation.

Before focusing on how peptide synthesis has been handled in laboratories, we will briefly see first how it occurs in nature.

I.2 N to C direction versus C to N direction



Peptides and proteins are naturally synthesised (ribosomal and non-ribosomal pathways) stepwise by polymerization of amino acids in a unidirectional manner, starting always from the N-terminus and ending at the C-terminus (see figure on the left).[14]

The twenty natural amino acids are incorporated when polypeptide chains are synthesised. Each one has a central carbon atom, known as the alpha carbon, surrounded by an amino group, a carboxyl group, a hydrogen atom, and a side chain or R-group, (except for glycine and proline). Amino acids are tied together by peptide bonds (amide functions). The first amino acid in the chain retains its free amino ($-NH_2$) group (N-terminus) of the polypeptide chain and the last amino acid to be added is left with a free carboxylic ($-COOH$) group, the so-called C-terminus.

Apart from glycine, amino acids have the alpha carbon atom connected to four different surrounding groups of atoms. The different spatial arrangement of these sets of atoms leads to two not superimposable mirror-image forming two stereoisomers, the so-called L- and D-forms. The amino acids found in proteins are all of the L-form. Although "L-amino acid" are mentioned

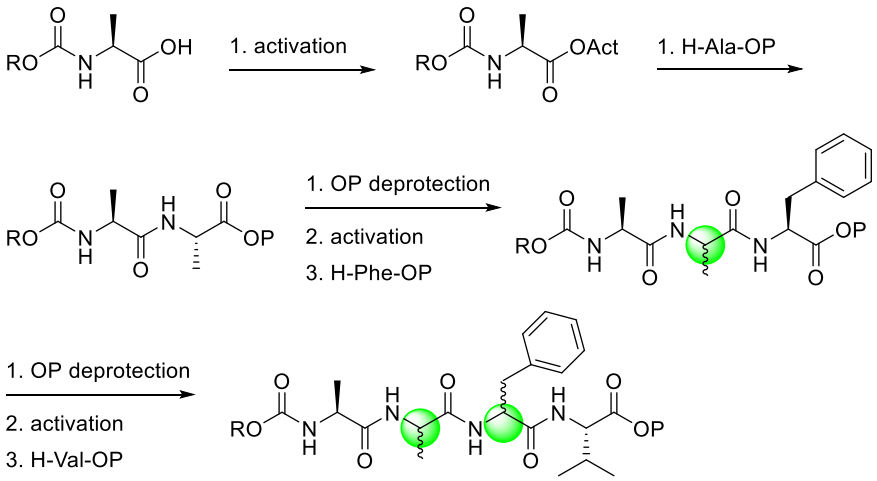
[12] A. Isidro-Llobet, M. Alvarez, F. Albericio *Chem. Rev.* **2009**, *109*, 2455.

[13] G. Barany, R. B. Merrifield *J. Am. Chem. Soc.* **1977**, *99*, 7363.

[14] a) J.H. Miller *Encyclopedia of Genetics* **2001**, 1567; b) M.A. Martínez-Núñez, V. E. López y López *Sustain. Chem. Process.* **2016**, *4*, 13.

as the "natural" isomers, D-amino acids do exist in nature. The peptidoglycan which is found in bacterial cell walls is an example of the presence in nature of D-amino acids. Moreover, when peptides are naturally synthesized they maintain the same stereochemistry and whenever an amide bond is formed racemisation never occurs.[15]

The same thing does not happen when the natural synthesis is reproduced in laboratories. In fact, when the couplings are performed in the N→C direction we will eventually have to face an important issue, the *racemisation*.



Scheme 3. Chemical N→C peptide synthesis.

I.3 Racemisation

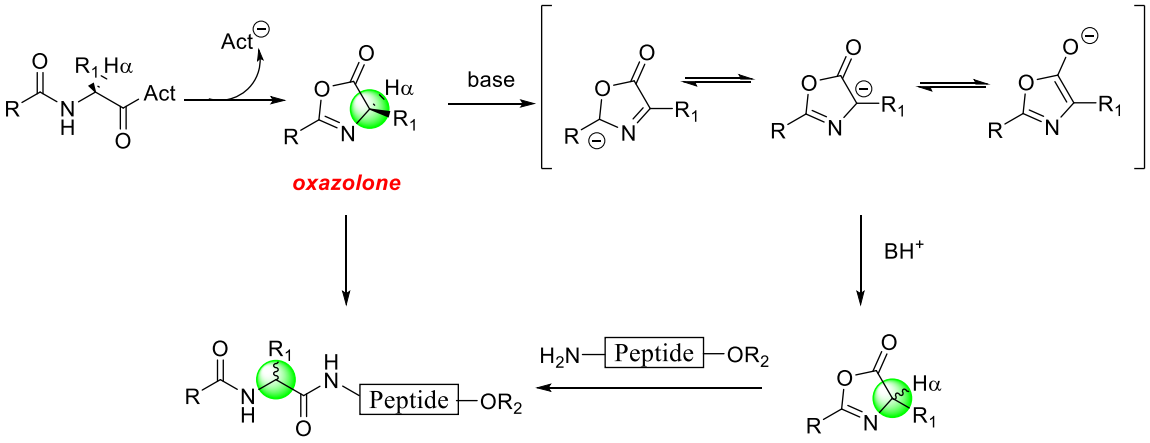
As shown in Scheme 3, the stepwise synthesis (except for the first coupling reaction) proceeds with deprotection, activation and coupling step for each amino acid. Each time a carboxylic function of amino acids is activated, it will undergo potential epimerisation allowing the formation of undesired peptide diastereomers. It can occur, mostly, through two mechanisms: the formation of the oxazolone,[16] and the direct proton abstraction.

In the first mechanism, peptide's carboxylate function is activated by the corresponding coupling reagent and converted in to an activated intermediate. If it does not undergo a rapid aminolysis with the incoming amino acid, the corresponding oxazol-5(4*H*)-one can be formed through an intramolecular process. Both the oxazolone intermediate and the activated intermediate, can react with the NH_2-free amino acid. Epimerisation proceeds through the

[15] D.P. Clark, N.J. Pazdernik, M.R. McGehee *Molecular Biology* **2019**, 397.

[16] M. Goodman, L. Levine *J. Am. Chem. Soc.* **1964**, *86*, 2918.

oxazolone formation in which the proton at the α position can be abstracted more easily due to the enhanced stability of the anion stabilised by the existence of mesomeric forms. Then, the anion itself could be reprotonated to give an epimerised oxazolone that could be subjected to further aminolysis by the amine partner to generate peptide diastereomers (Scheme 4).[6]

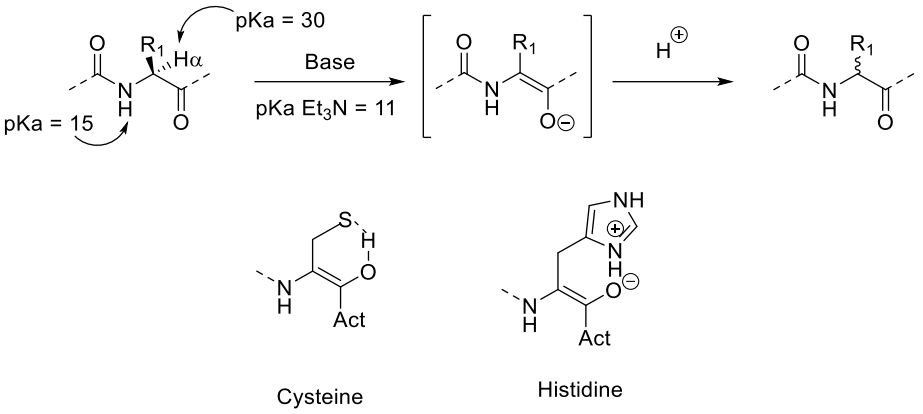


Scheme 4. Epimerisation through oxazolone formation.

The second epimerisation mechanism is the direct proton abstraction (Scheme 5). During the peptide synthesis, it happens especially when involved amino acids residues have relatively more acidic Hα. Compared with the oxazol-5(4*H*)-one formation mechanism, racemisation-induced by direct proton abstraction in peptide synthesis does not prevail. Normally, it only addresses the most susceptible amino acid residues (e.g., phenylglycine) since the engendered anion upon Hα abstraction could be stabilized by the aryl side chain group.[17] During the activation process, cysteine[18] and non-protected histidine are also prone to epimerisation when aminolysis is slow.

[17] M. Bodanszky, A. Bodanszky *Chem. Commun*. **1967**, 591.

[18] Y. Han, F. Albericio, G. Barany *J. Org. Chem.* **1997**, *62*, 4307.

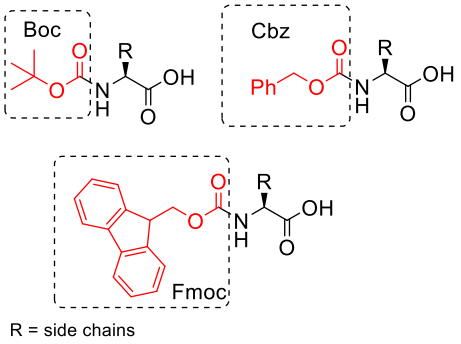


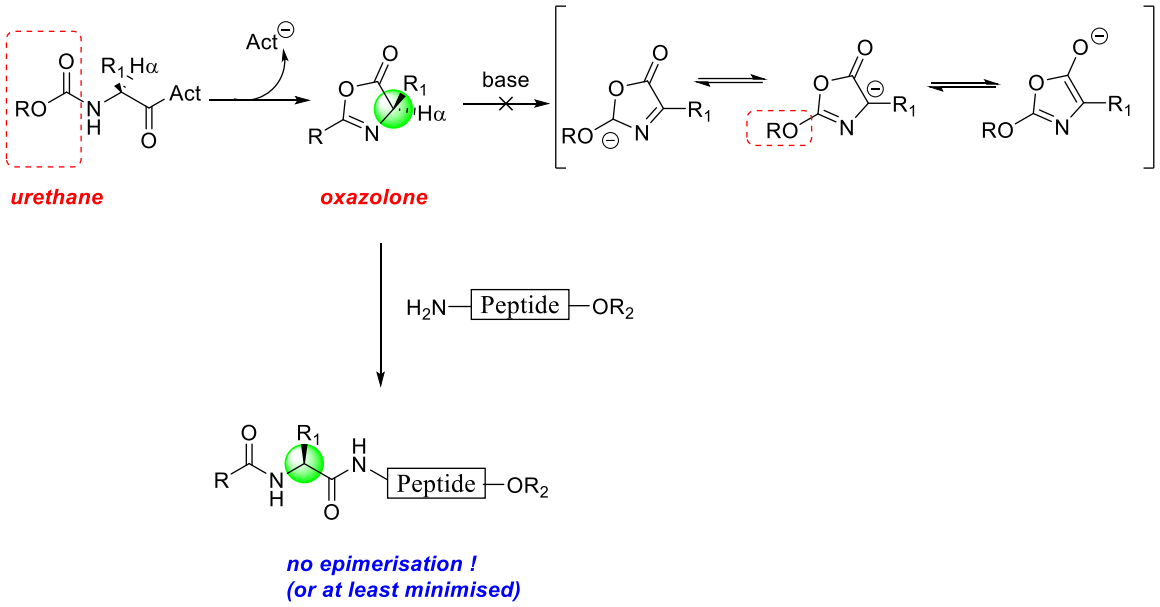
Scheme 5. Amino acid racemisation via direct Hα abstraction.

An intensive investigation of appropriate amino acid Nα-protecting groups has been conducted to reduce amino acid racemisation, and the library of the Nα-protecting groups has been remarkably enriched ever since. For instance, Nα-acyl protected amino acids are extremely prone to cyclize to the corresponding oxazolone intermediate during carboxylate activation. Therefore, with the disclosure of other protecting groups, the employment of Nα-acyl-type (e.g., formyl, acetyl and benzoyl) has been considered obsolete, and abandoned in peptide chemistry.

I.4 Nα-urethane protecting group

A milestone in the history of peptide science was, for sure, the application of manageable Nα-urethane protecting groups such as the *tert*-Butyloxycarbonyl protecting group (Boc), the carboxybenzyl group (Cbz) and the fluorenylmethyloxycarbonyl group (Fmoc) (see figure on the right). Their employment minimise the epimerisation of the concerned amino acids during the activation and coupling processes.[10]





Scheme 6. Mechanism of the coupling reaction in the presence of N-urethane protecting groups.

Indeed, if the oxazolone is formed, the presence of the alcoxy group destabilize the negative charge delocalised in the mesomeric forms influencing the acidity of the proton in α position, which becomes less acidic and the racemisation is, thus, inhibited or minimised (Scheme 6).

To avoid the racemisation it is also recommended to use:

a) weak and sterically hindered bases such as DIPEA
b) more concentrated solutions in order to favour the intermolecular reaction instead of the intramolecular reaction with the oxazolone formation
c) low temperature (from 0 °C to room temperature)

Moreover, three different orthogonal protecting strategies are widely-used in peptide chemistry:

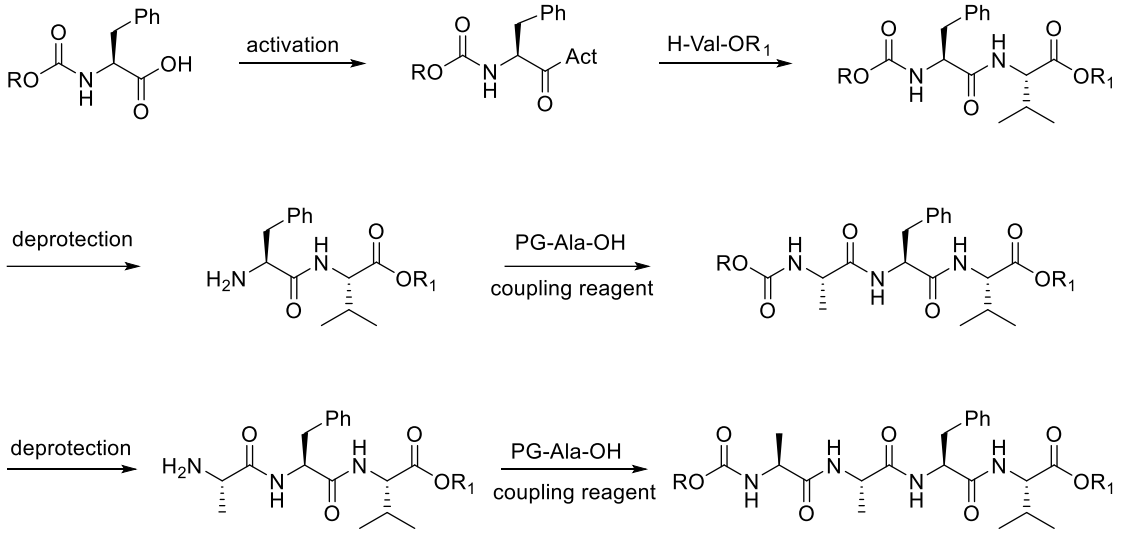
Protection permanent/temporary

a) O*t*Bu/Fmoc
b) Bn/Boc
c) O*t*Bu/Cbz

The first two are mostly used in both solution and solid-phase peptide synthesis. The different removal of Boc (acid conditions, TFA) and Fmoc (basic conditions, piperidine) allows the possibility to choose the right protection depending on the problems that have to be tackled during peptide synthesis.

Therefore, as already mentioned, C→N direction procedures were developed to prevent side reactions such as epimerisation (Scheme 7). These strategies follow three principles: (i)

activation of the carboxylic acid function, (ii) the use of Nα-urethane protecting groups, and (iii) step-wise procedure with the addition of one amino acid at the time.



Scheme 7. C→N direction chemical peptide synthesis.

I.5 Classical Methods in peptide synthesis

The activation of the carboxylic function, as already mentioned, relies on the conversion of the −OH group into a better leaving group (see Scheme 2). The coupling reagents used for the activation are extremely ubiquitous, exploited in both solution and solid-phase synthesis. Moreover, thank to R. B. Merrifield's revolutionary invention of SPPS[19] the idea of peptide synthesis was remarkably transformed giving rise to a more efficient procedure in terms of yield, purification and time.

I.5.1 The coupling agents

In this section, we will discuss briefly about some of the most important classes of coupling reagents.[4] In Figure 1 are presented the general structures of the most commonly applied ones.

[19] A.R. Mitchell *Pept. Sci.* **2008**, *90*, 175.

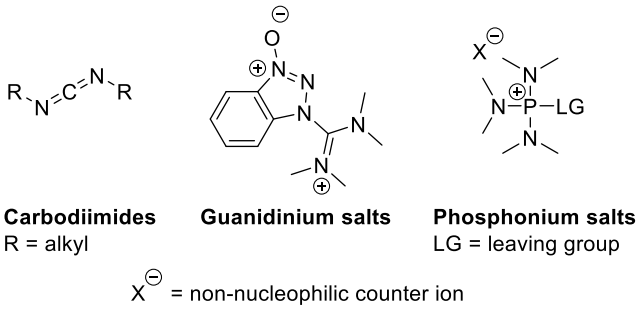


Figure 1. The major classes of coupling reagents.

Carbodiimides were the first generation of coupling reagents to be synthesized and the dicyclohexylcarbodiimide (DCC) has been used since 1955.[20] Nevertheless, when DCC is used epimerisation might occur. Hence, in order to reduce the level of racemisation some additives were added to the reaction. For instance, 1-hydroxy-1*H*-benzotriazole (HOBt) was introduced by Koenig and Geiger in 1970.[21] By using this additive, yields of coupling reactions were higher and epimerisation levels lower. Since then, efficient additives were currently adopted (Figure 2).[22]

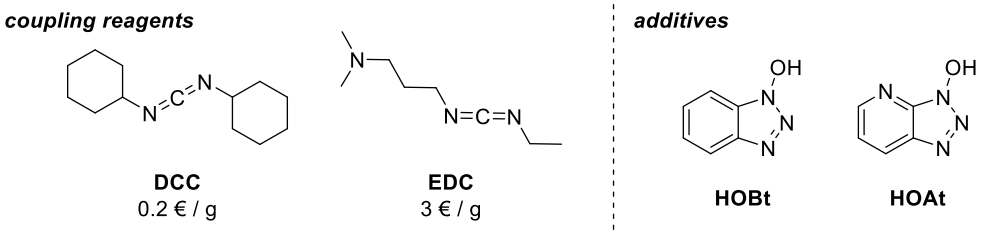


Figure 2. Carbodiimide class and HOBt as additive used in coupling reactions.

A more practical carbodiimide in terms of purification and solubility is the 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC).

Amongst the guanidinium salts (Figure 3) as activating agents, Carpino described in 1993[23] the HATU, which was more efficient compared to some derivatives of the same category (e.g.,

[20] J.C. Sheehan, G.P. Hess *J. Am. Chem. Soc.* **1955**, *77*, 1067.

[21] W. Koenig, R. Geiger *Chem. Ber.* **1970**, *103*, 788.

[22] a) L.A. Carpino *J. Am. Chem. Soc.* **1993**, *115*, 4397; b) R. Subirós-Funosas, S.N. Khattab, L. Nieto-Rodriguez, A. El-Faham, F. Albericio *Aldrichimica Acta* **2013**, *46*, 21; c) W. Van den Nest, S. Yuval, F. Albericio *J. Pept. Sci.* **2001**, *7*,115.

[23]L.A. Carpino *J. Am. Chem. Soc.* **1993**, *115*, 4397.

HBTU, HCTU). Still, one of the main drawbacks of using these agents as well as carbodiimides is that they are chemical sensitizers.[24]

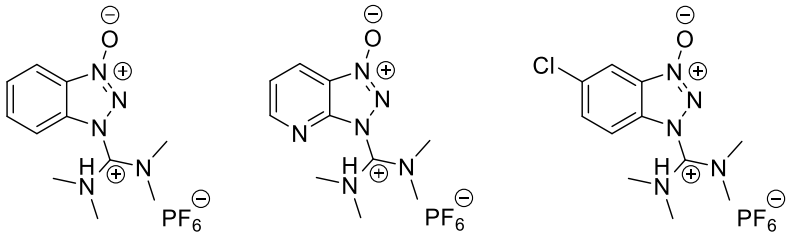


Figure 3. Common guanidinium salts.

Another family of coupling reagents that was largely investigated and used is the class of phosphonium salts (Figure 4). In 1975, Castro developed a new reagent called BOP.[25] Although its incredible reactivity, its use has been limited because of the formation of HMPA as by-product, which is known for its carcinogenicity and respiratory toxicity.[26] In order to avoid the formation of undesirable HMPA, PyBOP was introduced by Coste et al.[27] Furthermore, Carpino introduced AOP and PyAOP demonstrating that the aza-derivatives were more efficient compared to BOP and PyBOP.[28]

[24] K.J. McKnelly, W. Sokol, J.S. Nowick *J. Org. Chem.* **2020**, *85*, 1764.

[25] a) B. Castro, J.R. Dormoy *Bull. Soc. Chim. Fr.* **1973**, *12*, 3359; b) B. Castro, J.R. Dormoy, G. Evin, C. Selve *J. Chem. Res.* **1977**, *7*, 182.

[26] D. Hudson *J. Org. Chem.* **1988**, *53*, 617.

[27] J. Coste, D. Le-Nguyen, B. Castro *Tetrahedron Lett.* **1990**, *31*, 205.

[28] a) F. Albericio, M. Cases, J. Alsina, S.A. Triolo, L.A. Carpino, S.A. Kates *Tetrahedron Lett.* **1997**, *38*, 4853; b) F. Albericio, J.M. Bofill, A. El-faham, S.A. Kates *J. Org. Chem.* **1998**, *63*, 9678.

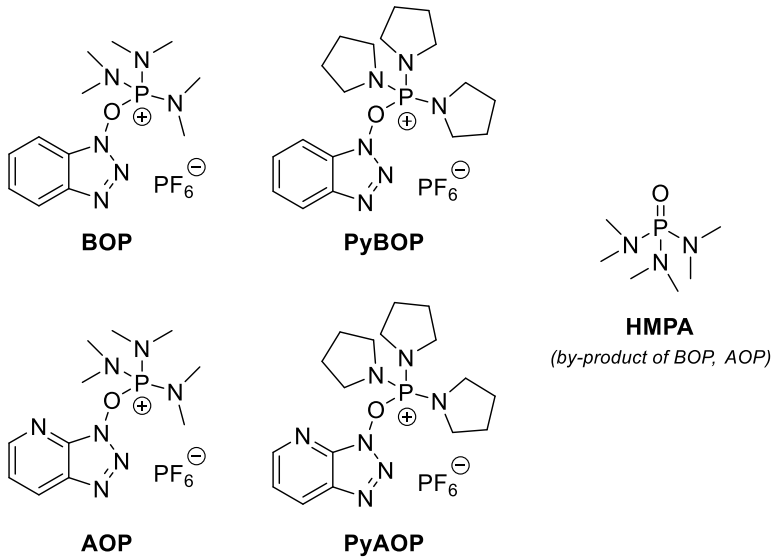
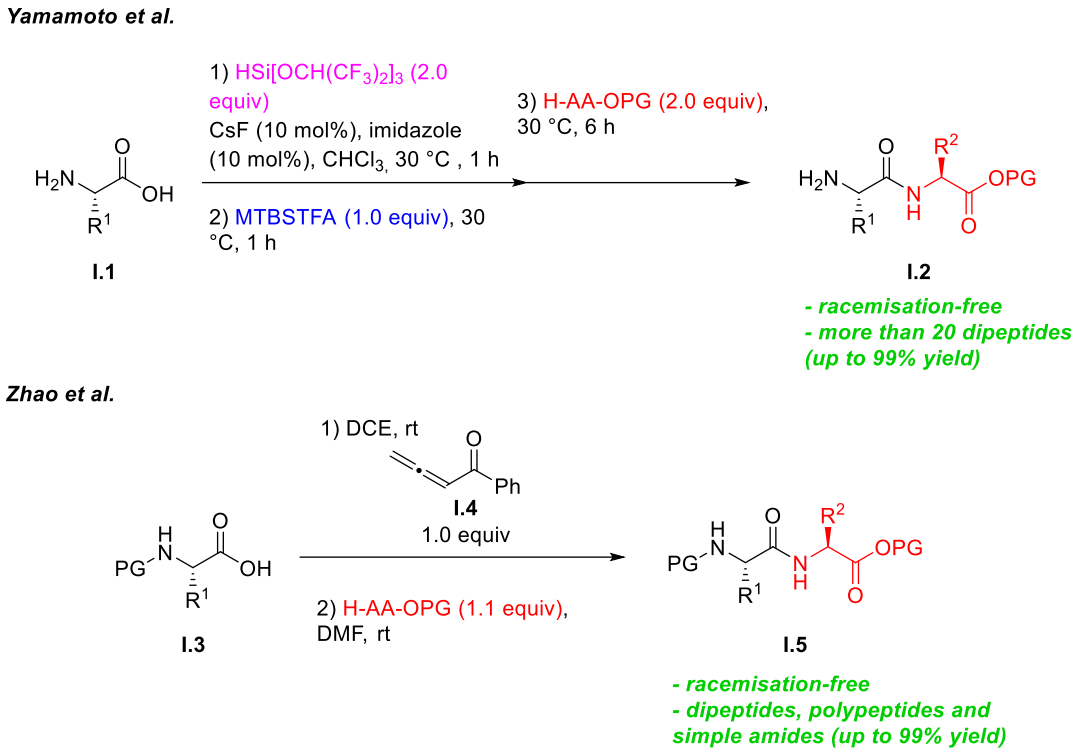


Figure 4. Family of phosphonium salts.

The amide bond-formation reactions in the pharmaceutical industry are very relevant and novel coupling reagents are in great demand. In 2021, Yamamoto et al. reported a one-pot peptide bond-forming using unprotected amino acids and peptides. In this case, a silylating reagent was used for the activation of the carboxylic acid.[29] This method provides up to >99% yields of corresponding peptides without racemisation. Some months later, Zhao et al. identified a new highly effective peptide coupling reagent, an allenone. The peptide bond is formed through a racemisation-free process and it has been proven to be also effective in peptide fragment condensation and solid-phase peptide synthesis [however no examples were reported with sensitive cysteine residues] (Scheme 8).[30]

[29] W. Muramatsu, H. Yamamoto *J. Am. Chem. Soc.* **2021**, 143, 6792.

[30] Z. Wang, X. Wang, P. Wang, J. Zhao *J. Am. Chem. Soc.* **2021**, 143, 10374.

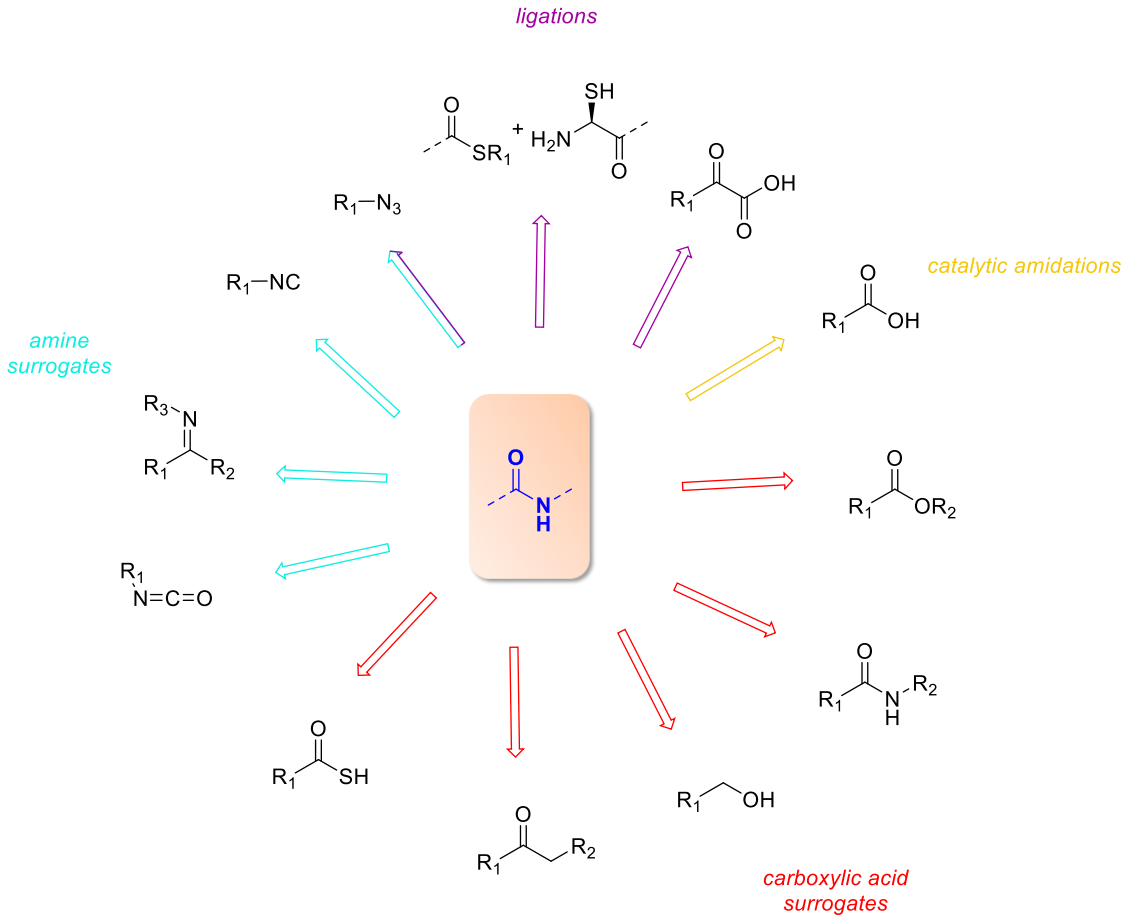


Scheme 8. Novel coupling reagents.

However, concerns regarding racemisation and potential health hazards still remain, when such coupling reagents have been employed. Hence, despite their success, novel efficient strategies, not based on the classical activation of the carboxylic acid and compatible with sensitive substrates such as amino acids and peptides, were demanded in order to sidestep (or at least to try to) drawbacks like racemisation and low-atom economy.

II. Non-conventional routes to amide function

New methodologies have been devised avoiding the classical activation of the carboxylic function (Scheme 9).



Scheme 9. New alternatives for amide function synthesis.

In 2016, our laboratory published a review on the *nonclassical routes for amide bond formation*[31] providing an exhaustive overview on the current state of non-conventional methodologies. Four sections are going to be presented herein, in which we will concisely take into account different types of amidation reactions, highlighting new strategies published after 2016. The last section will be focused on recent methodologies developed for the peptide synthesis in the N→C fashion.

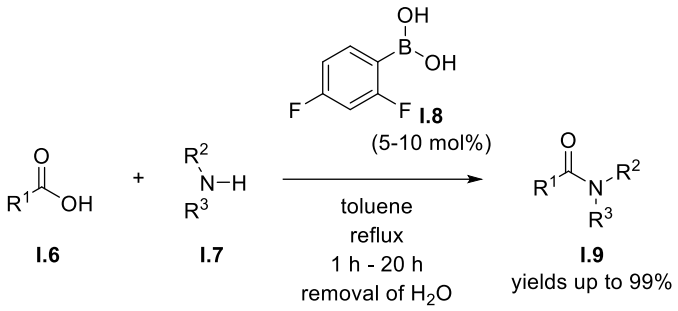
II.1 Catalytic amidation of carboxylic acids

During the past decades, despite the great interest in the development of amidation reactions, the uptake of catalytic amidations has been quite low. Nevertheless, interesting alternatives have emerged in recent years with the use of organoboron derivatives and metal catalytic systems.

[31] R.M. de Figueiredo, J.-S. Suppo, and J.-M. Campagne *Chem. Rev.* **2016**, *116*, 12029.

II.1.1 Organoboron Derivatives

In 1965, trisdialkylaminoborane derivatives were used for the first time as stoichiometric reagents for the amide synthesis.[32] 30 Years later, Yamamoto et al.[33] reported the use of organoboron derivatives for catalytic condensation processes between free carboxylic acids and amines (Scheme 10).



Scheme 10. Yamamoto's catalytic amidation.

Theoretical studies,[34] kinetic experiments, NMR and IR spectroscopies[35] allowed to propose a general mechanism to explain boron-catalysed amidation which relied on the formation of cyclic trimeric anhydrides (boroxines) as intermediates. In 2018, this mechanism was brought into question by a study of Whiting et al.[36] They demonstrated via NMR/X-ray cristollography and theoretical modelling that the more likely intermediates **A** and **B** happen to be dimeric forms B-X-B (where X = NR, O, Scheme 11). The carboxylic acid is thus extremely reactive and prompted to the amine's nucleophilic attack.

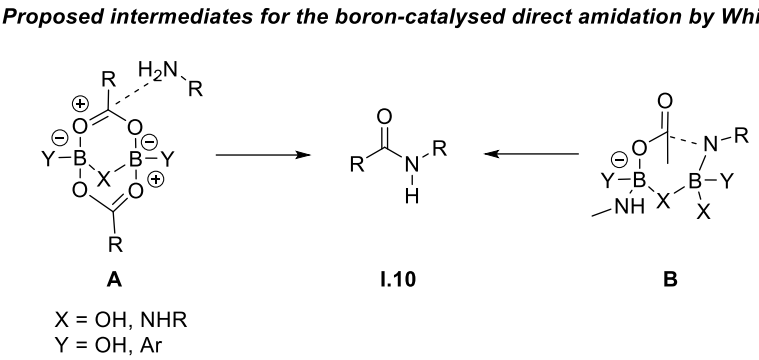
[32] P. Nelson, A. Pelter *J. Chem. Soc.*, **1965**, 5142.

[33] K. Ishihara, S. Ohara, H. Yamamoto *J. Org. Chem.*, **1996**, *61*, 4196.

[34] C. Wang, H.-Z. Yu, Y. Fu, Q.-X. Guo *Org. Biomol. Chem.* **2013**, *11*, 2140.

[35] K. Arnold, B. Davies, R.L. Giles, C. Grosjean, G.E. Smith, A. Whiting *Adv. Synth. Catal.* **2006**, 348, 813.

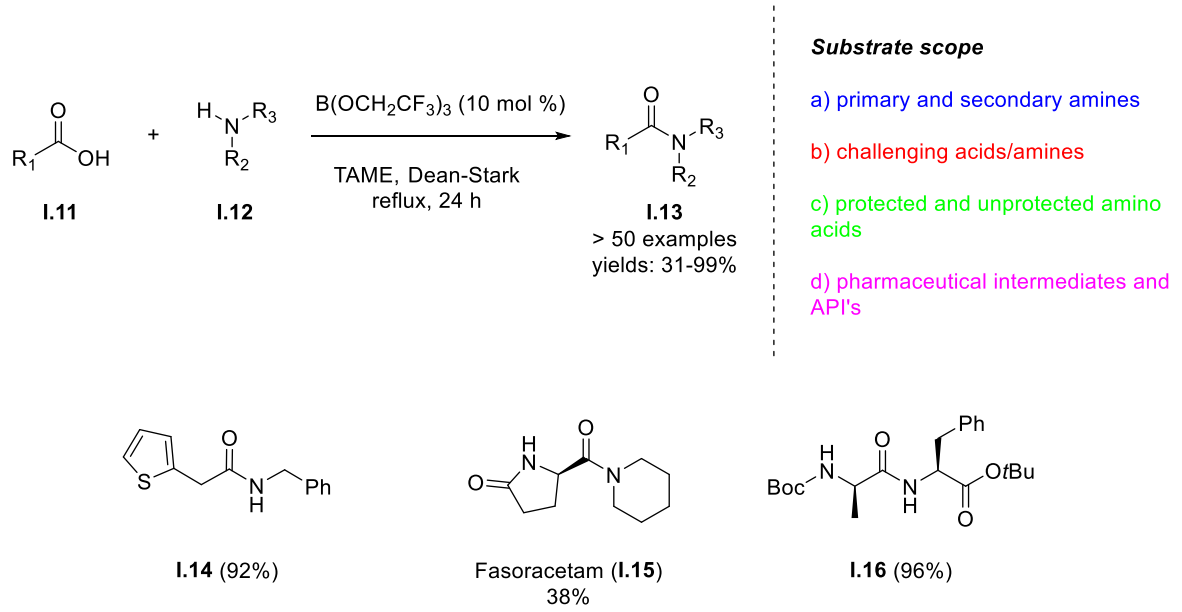
[36] S. Arkhipenko, M.T. Sabatini, A.S. Batsanov, V. Karaluka, T.D. Sheppard, H.S. Rzepad, A. Whiting *Chem. Sci.* **2018**, *9*, 1058.



Scheme 11. Boron-catalysed amide formation's intermediates proposed by Whiting.

Since the publication of this first examples of condensation, several arylboronic acid catalysts were developed in order to improve this strategy.

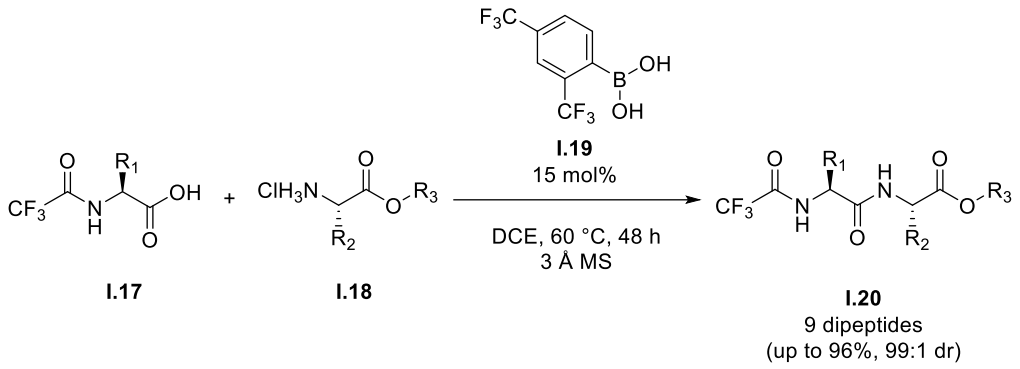
More recently, Sheppard et al. reported a novel more sustainable borate-ester catalytic process to synthesise complex amides.[37] This coupling reaction proves to have many advantages over the existing methods thanks to the use of a simple, commercially available catalyst, a low PMI value (process mass intensity), and a broad substrate scope. Multigram scale's reactions are also possible (Scheme 12).



Scheme 12. Borate-ester catalysed direct amidation. TAME: *tert*-amyl methyl ether.

[37] M.T. Sabatini, L.T. Boulton, T.D. Sheppard *Sci. Adv.* **2017**, *3*, e1701028.

Furthermore, in 2018 Ishihara et al. reported an efficient protocol via 2,4-bis(trifluoromethyl)phenylboronic acid (**I.19**) catalysis showing efficiency in dipeptide synthesis (Scheme 13).[38]



Scheme 13. Dipeptides synthesis via 2,4-bis(trifluoromethyl)phenylboronic acid catalysis.

II.2 Carboxylic acid surrogates

II.2.1 Catalytic amidation of unactivated esters

An alternative pathway for the amidation is the reaction between amines and unactivated esters.

In 1996, Yamamoto et al. reported a procedure[39] starting from various methyl esters and primary amines in the presence of $Sb(OEt)_3$ as catalyst (5-10 mol%) with azeotropical removal of methanol. Some examples of amides were obtained with moderate to excellent yields. In 2005, Porco et al. published the catalytic ester-amide exchange using group (IV) metal alkoxide combined with additives such as HOAt, HOBt and HYP.[40]

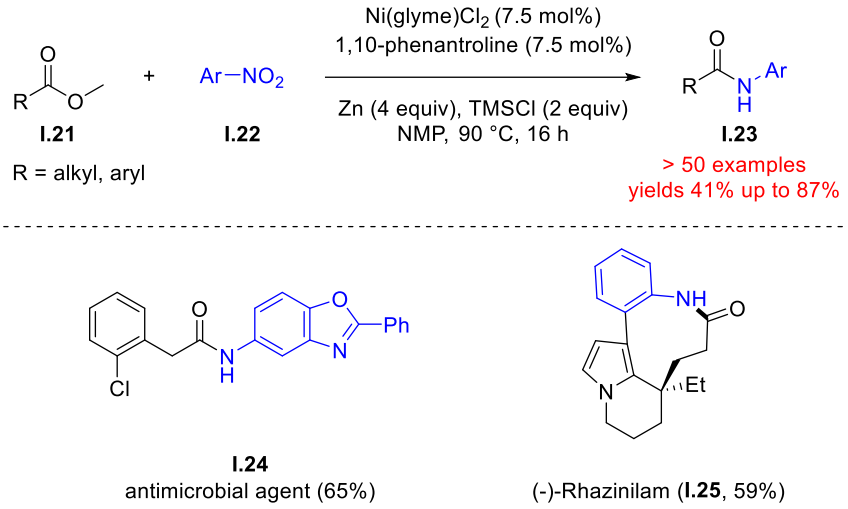
Lately, Hu et al. conducted some studies on iron-catalysed reductive coupling of nitroarenes with alkyl halide to form secondary amines. Afterward, they started to study the reactivity of nitroarenes with esters and in 2017 they reported an efficient nickel-catalysed reductive coupling to furnish, in a one-step method, a wide range of amides.[41] The synthesis of a handful of bio-active molecules, natural products, and agrochemicals has been accomplished giving robustness to this non-conventional protocol (Scheme 14).

[38] K. Wang, Y. Lu, K. Ishihara *Chem. Commun.* **2018**, *54*, 5410.

[39] K. Ishihara, Y. Kuroki, N. Hanaki, S. Ohara, H. Yamamoto *J. Am. Chem. Soc.* **1996**, *118*, 1569.

[40] C. Han, J.P. Lee, E. Lobkovsky, J.A. Porco *J. Am. Chem. Soc.* **2005**, *127*, 10039.

[41] C. W. Cheung, M. Leendert Ploeger, X. Hu *Nat. Commun.* **2017**, *8*, 14878.



Scheme 14. Direct amidation of unactivated esters with nitroarenes.

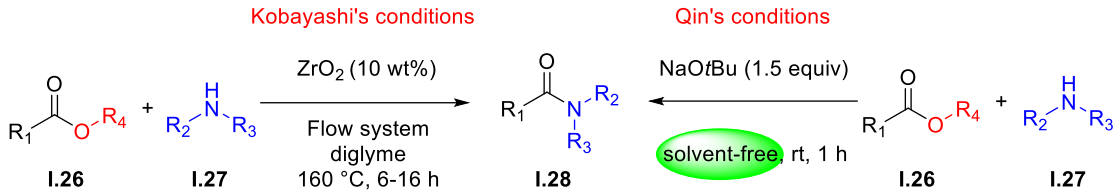
The syntheses of compounds **I.24** and **I.25** were achieved in one single-step from the nitroarenes and the esters.

Currently, the pharmaceutical and fine chemical industries have been focusing on continuous-flow systems rather than conventional batch production methods promoting greener and more sustainable manufacturing. The continuous-flow reaction has substantial advantages over the batch reaction in terms of its efficiency, easy handling, high selectivity, reproducibility, direct use of intermediates without any purification, and, its safety and environmental compatibility.[42] In 2021, Kobayashi et al. established a novel amidation reaction under flow conditions between unactivated esters and amines using a heterogeneous ZrO_2 catalyst.[43] The methodology does not require additives and it is highly tolerant towards a wide range of diverse ester and amine functionalities although the strategy was not tested on sensitive substrates such as amino acids. More than 25 compounds were obtained with moderate to good yields. The antidepressant drug moclobemide was synthesised in 80% yield demonstrating the potential of this alternative methodology (Scheme 15).

[42] M.B. Plutschack, B. Pieber, K. Gilmore, P.H. Seeberger *Chem. Rev.* **2017**, *117*, 11796.

[43] N. Rashed, K. Masuda, T. Ichitsuka, N. Koumura, K. Sato, S. Kobayashi *Adv. Synth. Catal.* **2021**, 363, 2529.

2021' reported works:



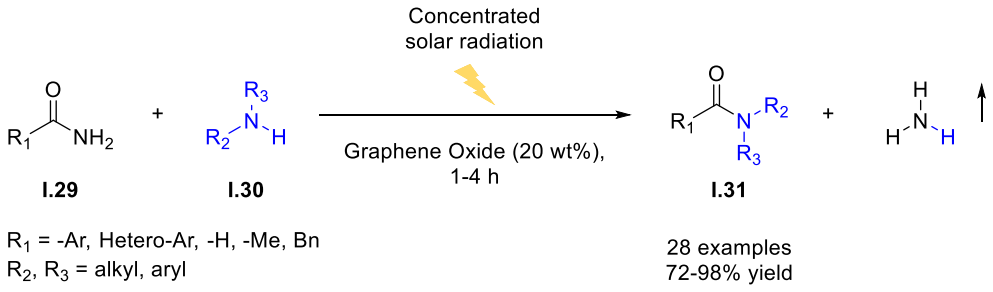
Scheme 15. Green and sustainable protocols of amidation.

In the meantime, Qin et al. proposed transition-metal- and solvent-free methodology using NaOtBu as a base promoter (Scheme 15). The gram-scale production of some products was efficiently realized as well as the synthesis of moclobemide, benodanil and fenfuram (two commercial agricultural fungicides).[44]

II.2.2 Catalytic Transamidation

Although less studied than catalytic amidation of unactivated esters, catalytic transamidation[45] has been investigated in the past decade.

During the last few years, more examples of catalytic transamidation have been flourishing. In 2020, Shankarling et al.[46] published a greener procedure catalysed by graphene oxide under concentrated solar radiation for the synthesis of various aromatic and aliphatic amides in 52-98% yield (Scheme 16).



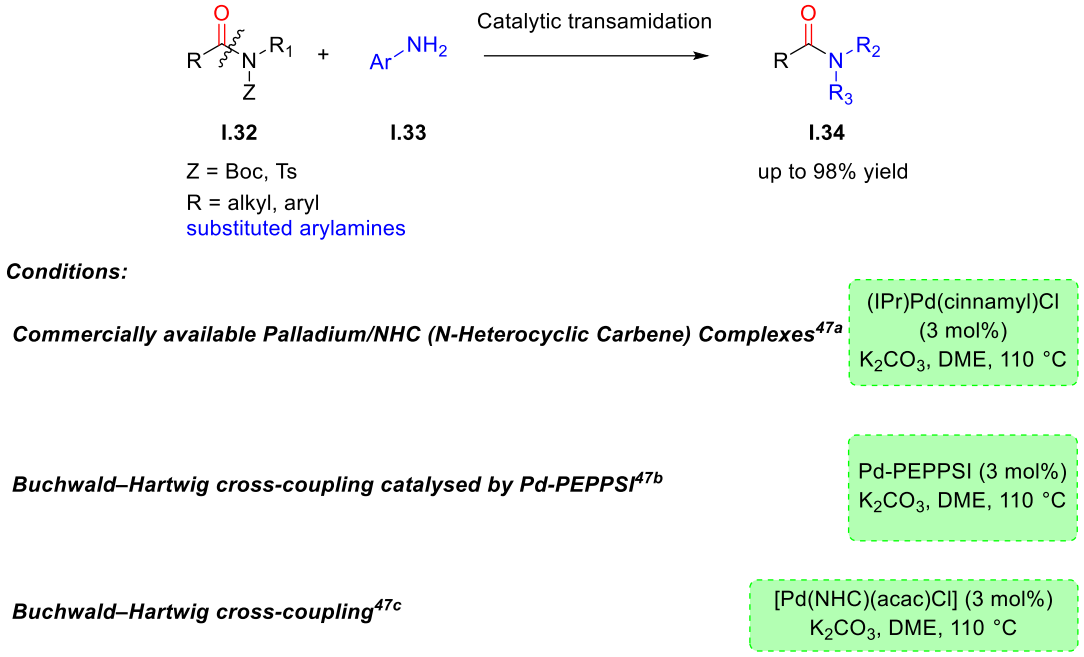
Scheme 16. Graphene oxide catalysed transamidation.

[44] R. Zhang, W.-Z. Yao, L. Qian, W. Sang, Y. Yuan, M.-C. Du, H. Cheng, C. Chen, X. Qin *Green Chem.* **2021**, *23*, 3972.

[45] a) S.E. Eldred, D.A. Stone, S.H. Gellman, S.S. Stahl *J. Am. Chem. Soc.* **2003**, *125*, 12, 3422; b) J.M. Hoerter, K.M. Otte, S.H. Gellman, Q. Cui, S. S. Stahl *J. Am. Chem. Soc.* **2008**, *130*, 647.

[46] K.P. Patel, S.S. Kamble, D.R. Boraste, G.S. Shankarling *Environ. Chem. Lett.* **2020**, *18*, 1731.

Since 2017, Szostak et al. has been publishing several works on transamidation under transition metal-catalytic conditions. Some examples are depicted in Scheme 17.[47]



Scheme 17. Examples of catalytic transamidations by Szostak.

II.2.3 Redox and Oxidative Amidations with Organo- and Metal-Catalysts

Redox and oxidative amidations with organo- and metal-catalysts have been considered as attractive atom economical transformations. General amides can be synthesised from reactions between amines and alcohol, aldehyde, ketone, nitrile derivatives and so on. Herein, we will report just few among the latest described methodologies.

In 2017, Milstein et al. reported a direct synthesis of amides by dehydrogenative coupling of amines with alcohols catalysed by a manganese pincer complex (MnP$^{t\text{Bu}}$NNH). The reaction is substrate-dependant and a poor reactivity was observed in the case of benzyl alcohols. For a direct amidation of benzyl alcohols and ammonia by a manganese pincer complex see ref. 48 A plausible mechanism is depicted on Scheme 18.[49] For the first time, an earth abundant metal complex has been used as catalyst to synthesise amides in a more sustainable way.

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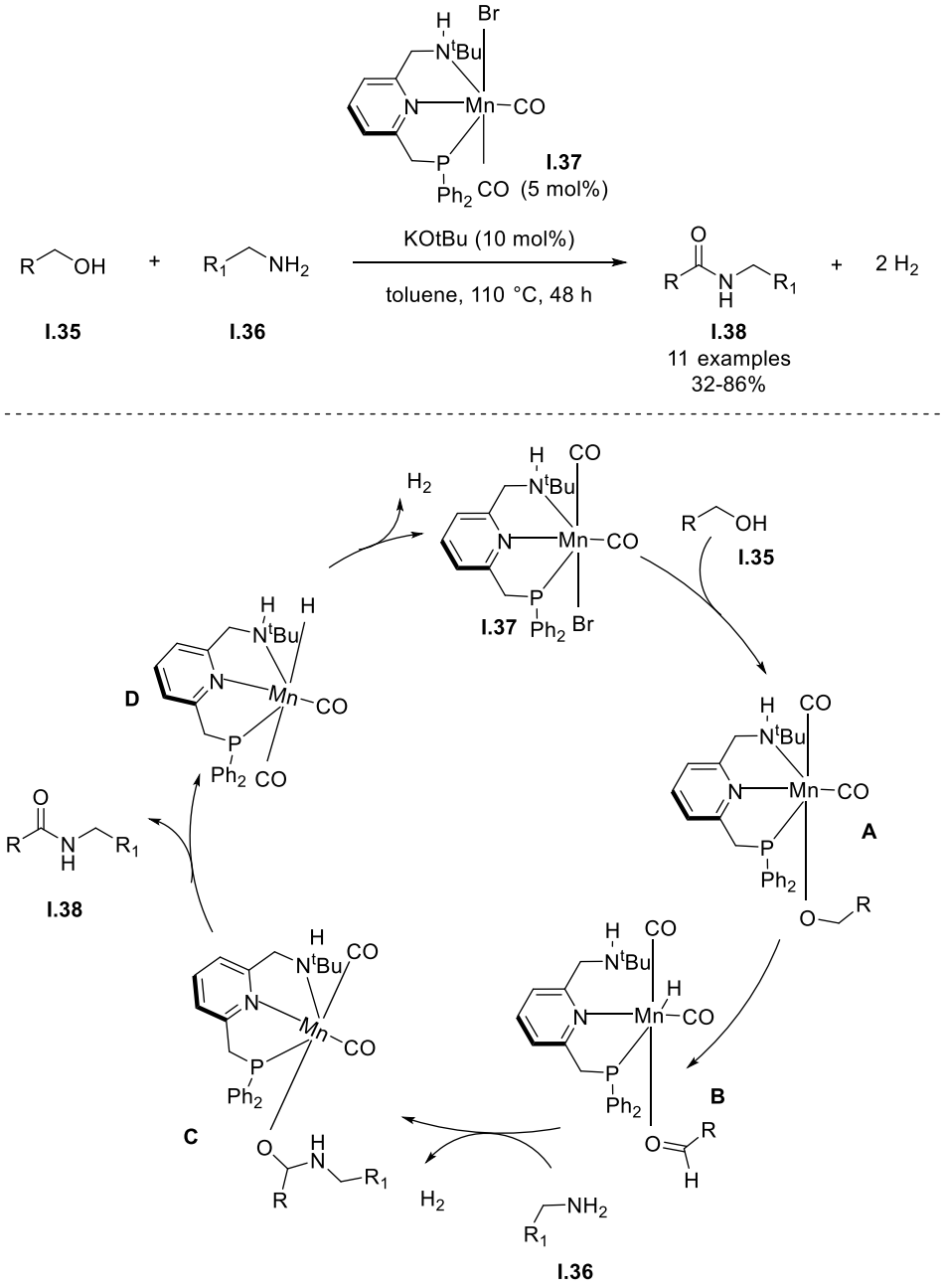
[47] a) G. Meng, P. Lei, M. Szostak *Org. Lett.* **2017**, *19*, 2158; b) S. Shi, M. Szostak *Chem. Commun.* **2017**, *53*, 10584; c) T. Zhou, G. Li, S.P. Nolan, M. Szostak *Org. Lett.* **2019**, 21, 3304.

[48] P. Daw, A. Kumar, N. A. Espinosa-Jalapa, Y. Ben-David, D. Milstein *J. Am. Chem. Soc.* **2019**, *141*, 12202.

[49] a) A. Kumar, N. A. Espinosa-Jalapa, G. Leitus, Y. Diskin-Posner, L. Avram, D. Milstein *Angew. Chem. Int. Ed.* **2017**, *56*, 14992; b) J. A. Luque-Urrutia, T. Pèlachs, M. Solà, and A. Poater *ACS Catal.* **2021**, *11*, 6155.



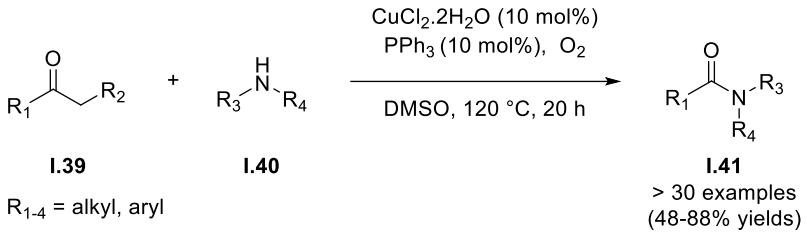
Scheme 18. Direct amidation by dehydrogenative coupling of amines with alcohols.

Copper-catalysed examples of amidations have also been developed. Liu reported a Cu-catalysed C-C bond cleavage of simple ketones and amines.[50] Alkyl- and arylamines have been employed (not only heterocyclic ones)[51] broadening the scope of the amidation. The reaction

[50] G.-P. Yang, K. Li, W. Liu, K. Zenga, Y.-F. Liu *Org. Biomol. Chem.* **2020**, *18*, 6958.

[51] a) P. Subramanian, S. Indu, K.P. Kaliappan *Org. Lett.* **2014**, *16*, 6212; b) W. Dinga, Q. Song *Org. Chem. Front.* **2015**, *2*, 765.

occurs in presence of 10 mol% of the inexpensive Cu-catalyst, 10 mol% of PPh_3 as ligand, in DMSO at 120 °C under O_2 atmosphere (Scheme 19).



Scheme 19. Copper-catalysed amide synthesis from ketones and amines.

II.2.4 Thioacids as carboxylic acid surrogates

Thioacids are a popular class of compounds and over the years they have become more attractive in the synthetic organic field, especially in ligation reactions. They have been extensively employed as mild reagents for the synthesis of peptides and peptidomimetics as well as for the chemoselective assembly of a variety of bio-conjugates.[52] The application of thioacids might be preferred to the use of carboxylic acid thanks to its powerful nucleophilicity and a low pKa value. Nevertheless, these compounds are unstable and not easily prepared. Anyway, thioacids as acyl sources to form amides under mild conditions have drawn increasing attention in the last decade.

Thioacids react with chemical reagents such as Sanger's or Mukaiyama's reagents,[53] organoisonitriles,[54] copper reagents[55] to form reactive intermediates which would then react with amines to give the desired products.

Guan et al. exploited the thiocarboxylic acids in a different way.[56] They disclosed a new catalyst-free approach for constructing amides. The reaction occurred through the formation of key disulfides as activated intermediates (proved by mechanistic studies) through the reaction between two molecules of thiocarboxylic acid. Both thiobenzoic and thioaliphatic acids were

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[52] N. Narendra, M. Vishwanatha Thimmalapura, B. Hosamani, G. Prabhu, L.R. Kumar, V.V. Sureshbabu *Org. Biomol. Chem.* **2018**, *16*, 3524.

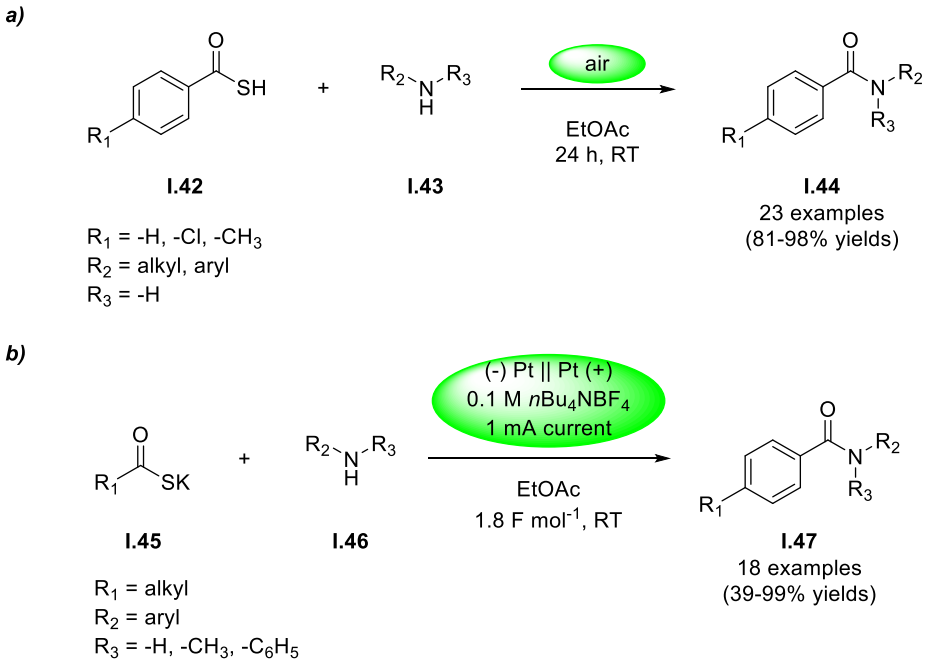
[53] D. Crich, I. Sharma *Angew. Chem. Int. Ed.* **2009**, *48*, 2355.

[54] a) Y. Rao, X. Li, S.J. Danishefsky *J. Am. Chem. Soc.***2009**, *131*, 12924; b) X. Wu, J.L. Stockdill, P.K. Park, S.J. Danishefsky **2012**, *134*, 2378.

[55] a) F.B. Dyer, C.M. Park, R. Joseph, P. Garner *J. Am. Chem. Soc.***2011**, *133*, 20033; b) S.M. Mali, S.V. Jadhav, H.N. Gopi *Chem. Commun.* **2012**, *48*, 7085.

[56] L. Tang, J.H. Matuska, Y.-H. Huang, Y.-H. He, Z. Guan *ChemSusChem* **2019**, *12*, 2570.

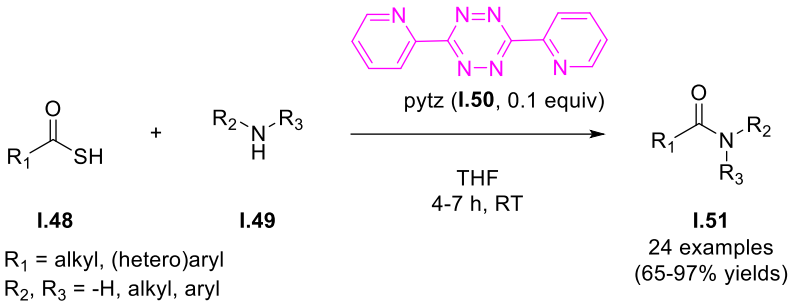
investigated. With these conditions on their hands, the first ones (Scheme 20a) showed better reactivity compared to the second ones. Thus for the thioaliphatic acids, the same authors proposed the formation of amides through an electrochemical process using potassium thioacids as substrates (Scheme 20b).



Scheme 20. Mild amide synthesis using thiocarboxylic acids as acyl source.

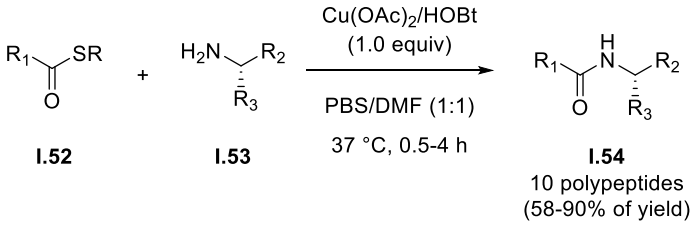
In 2020, a new organo-catalysed, mild and metal-free strategy has been reported by Samantaa et al.[57] They used pytz as the organocatalyst in order to oxidize thioacids into diacyl disulfides (unveiled as key intermediates via mechanistic studies). Both aliphatic and (hetero)aromatic compounds were suitable substrates. Electronic and steric effects appear to have a minimal impact on the yields (Scheme 21).

[57] S. Samantaa, S.R. Samanka, N.B. Partha, K. Samantaa, P. Biswas *Tetrahderon Lett.* **2020**, *61*, 152272.



Scheme 21. Organocatalysed strategy for amide bond synthesis.

Garner and Gopi groups reported a Cu(II)-promoted direct condensation of peptide thioacids and various amines under mild conditions.[58] In 2018, inspired by all previous works, Sun et al.[59] reported a novel Cu(II)/HOBt mediated conjugation approach to synthesise peptides under mild conditions (Scheme 22). Some dipeptides were obtained in good to excellent yields. Peptide-based fluorescent probes have also been efficiently constructed thanks to this methodology.



Scheme 22. Cu(II)/HOBt-mediated conjugation of thioesters to polypeptides. PBS phosphate-buffered saline.

II.3 Amine Surrogates

Herein, we will highlight selected novel strategies, published after 2016, using amine surrogates (isocyanates, isonitriles, acylnitrene, etc…) for the amide synthesis.

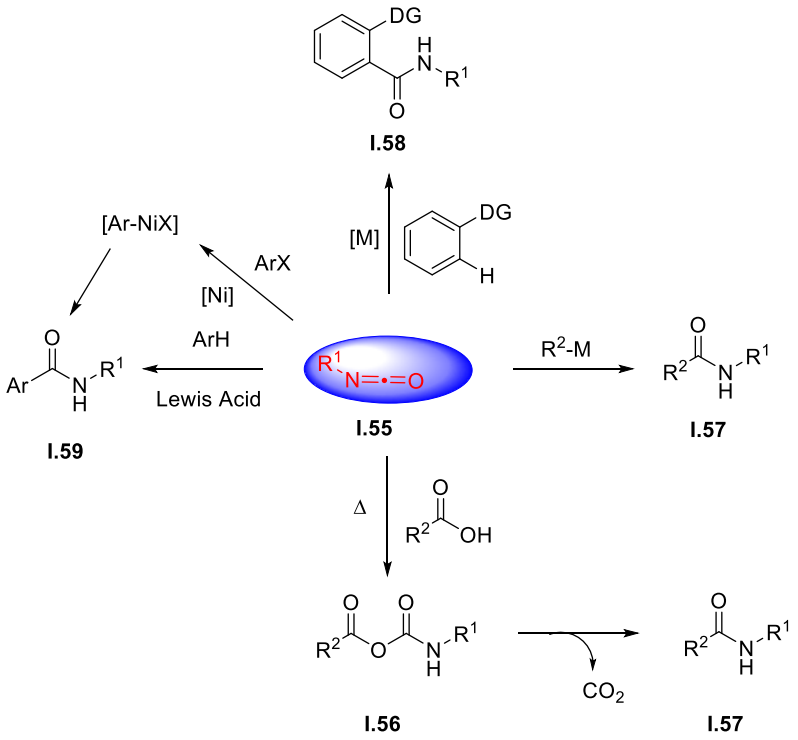
II.3.1 Isocyanate Derivatives

Isocyanates show a high electrophilicity even if the nitrogen and oxygen atoms are a priori nucleophilic. This makes isocyanates particularly reactive electrophilic partners in the presence of nucleophilic entities, including organometallic reagents, aromatics, and carboxylic acids.[32]

[58] a) S.M. Mali, S.V. Jadhav, H.N. Gopi *Chem. Commun.* **2012**, *48*, 7085; b) R. Joseph, F.B. Dyer, P. Garner *Org. Lett.* **2013**, *15*, 732.

[59] Y. Sun, Z. Lyu, Z. Wang, X. Zeng, H. Zhou, F. Xu, Z. Chen, Y. Xu, P. Xu, X. Hong *Org. Biomol. Chem.* **2018**, *16*, 3610.

Their synthesis is easily accomplished on a large scale through reaction with phosgene[60] providing access to a large number of isocyanates, many of which are commercially available.[61] Therefore, despite their toxicity, isocyanates represent an efficient and straightforward approach to the amidation processes (Scheme 23).



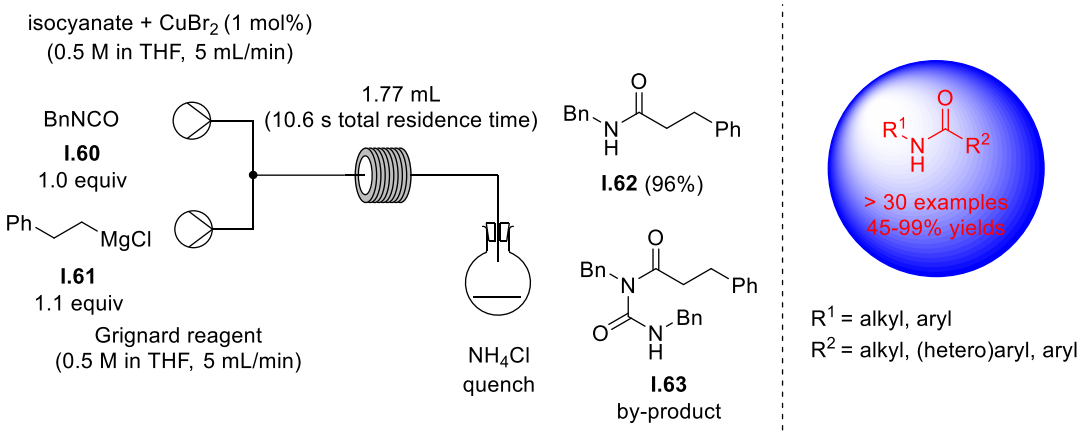
Scheme 23. Main routes to amide from isocyanate.

In 2018, a methodology based on isocyanates enabled the synthesis of amide using the flow chemistry technique.[62] Sterically hindered isocyanates and Grignard reagent gave promising results, unhindered substrates were more recalcitrant; acylurea was isolated as a side product in significant quantities. They decided to further screen several additives on a model reaction. It was found that in the presence of copper(II) bromide the product was obtained in 98% yield lowering the formation of the acylurea side-product. With the optimized conditions in hand, the scope of the reaction was explored giving excellent yields with a wide variety of isocyanates and Grignard reagents (Scheme 24).

[60] R.J. Slocombe, E.E. Hardy, J.H. Saunders, R.L. Jenkins *J. Am. Chem. Soc.* **1950**, *72*, 1888.

[61] E. Serrano, R. Martin *Eur. J. Org. Chem.* **2018**, 3051.

[62] J.D. Williams, W.J. Kerr, S.G. Leach, D.M. Lindsay *Angew. Chem. Int. Ed.* **2018**, *57*, 12126.

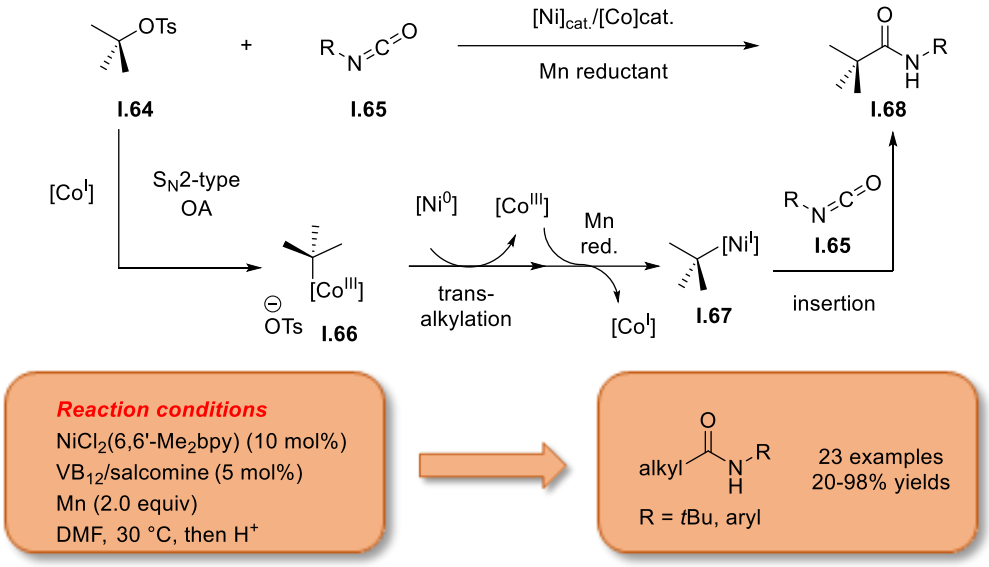


Scheme 24. General amidation method merging flow technology and isocyanates.

This protocol replaced the use of (stoichiometric) activating agents providing an efficient and productive formation of amide bonds from isocyanates.

Alkyl amides are common skeletons in a wide range of pharmaceutical and natural compounds. Komeyana et al. published an alternative method of amidation of alkyl metallic reagents with isocyanates. They used, instead of the classical alkyl halides, alkyl tosylates which are more easily prepared. Previous work on Ni-catalysed reductive amidation and Co-catalysed activation of alkyl tosylates paved the way to a novel methodology for amide synthesis. The reaction takes place under a Ni/Co dual-catalytic system, in DMF, at 30 °C giving the expected products in moderate to excellent yields (Scheme 25).[63]

[63] T. Michiyuki, I. Osaka, K. Komeyama *Chem. Commun.* **2020**, *56*, 1247.



Scheme 25. Reductive amidation of alkyl tosylates with isocyanates.

II.3.2 Umpolung Strategies

Umpolung amide synthesis (UmAS) has emerged as new alternative to conventional methods based on carbonyl electrophiles in a range of situations particularly when epimerization-prone substrates are prescribed. Johnston and Makley have explored the reactivity of α-bromo nitroalkanes as acyl anion equivalents and the amines as the electrophilic components. Simple reaction conditions enabled the synthesis of amide bonds under mild conditions.[64] Thanks to the development by the same group of an efficient access to enantiomerically enriched α-bromo nitroalkane derivatives, arylglycine compounds have been coupled with some amino acids to give dipeptides in moderate to good yields as single diastereomers.

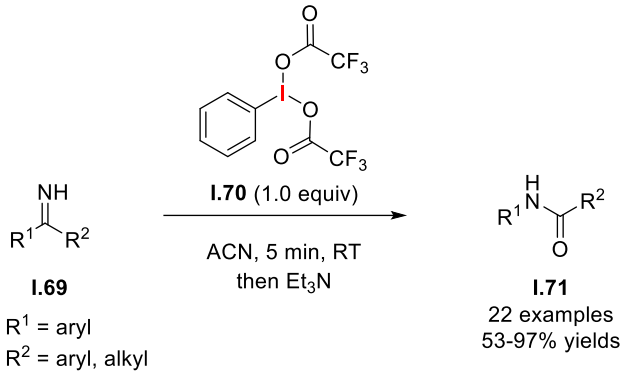
Following on this seminal work on the UmAS, Zhao et al. disclosed a new route to amides via hypervalent iodine-mediated oxidative rearrangement of N-H ketimines under mild conditions.[65] Inspired by the work of Danishefsky, which provided amides through Mumm rearrangement, they described an umpolung strategy to amide synthesis.[66] The reaction conditions were optimized with diphenyl methanimine as model substrate and several

[64] B. Shen, D.M. Makley, J.N. Johnston *Nature* **2010**, *465*, 1027.

[65] Z. Zhao, Z. Peng, Y. Zhao, H. Liu, C. Li, J. Zhao *J. Org. Chem.* **2017**, *82*, 11848.

[66] a) O. Mumm *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 886; b) X. Li, Y. Yuan, W.F. Berkowitz, L.J. Todaro, S.J. Danishefsky *J. Am. Chem. Soc.* **2008**, *130*, 13222.

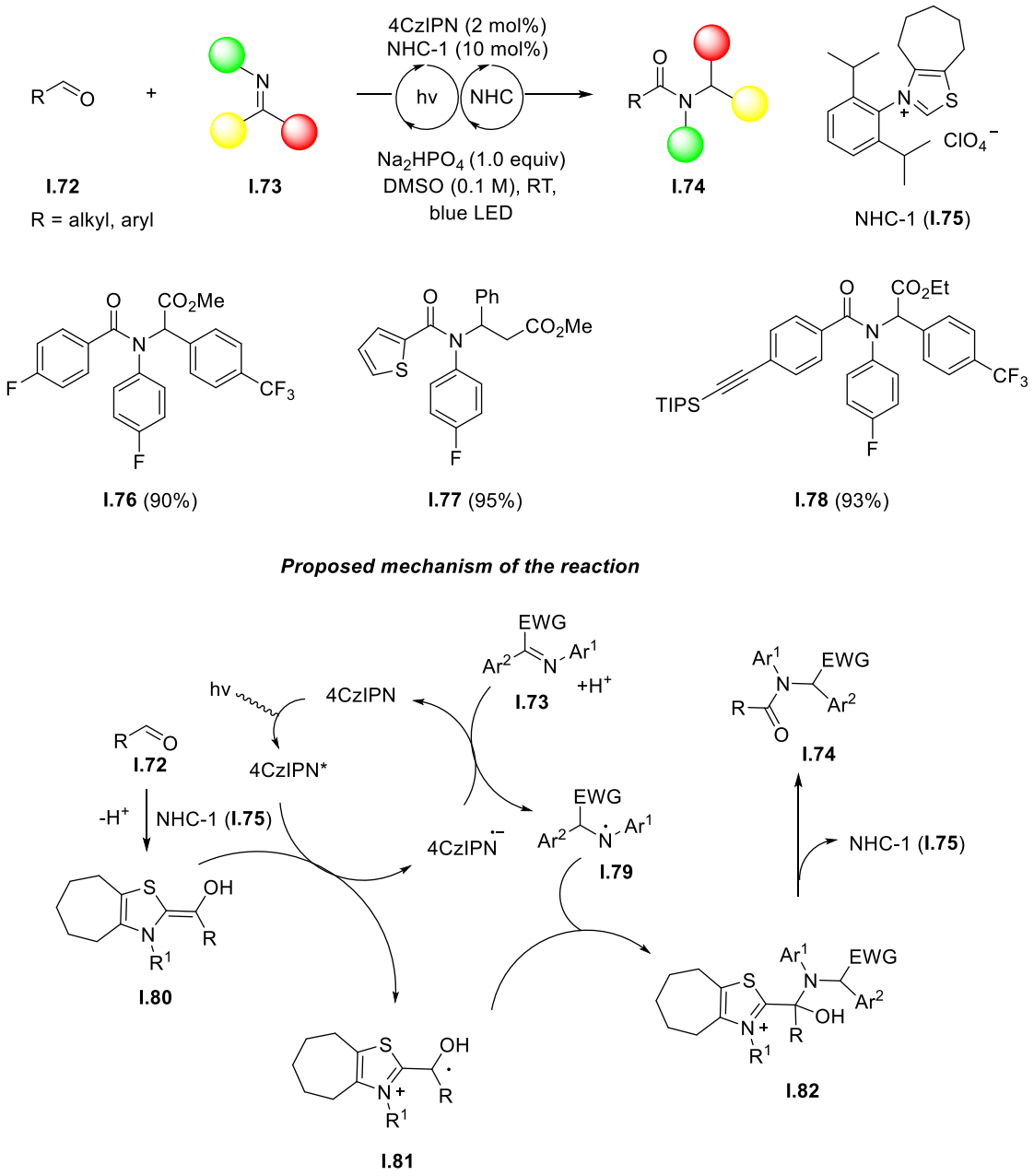
hypervalent iodine oxidants. $PhI(OCOCF_3)_2$ (**I.70**) was the best oxidant to obtain the desired product in 96% yield (Scheme 26).



Scheme 26. Hypervalent iodine-mediated amidation via umpolung approach.

A practical atom-economical direct synthesis of amide has been reported by Shu et al. from aldehydes and imines.[67] The combination of NHC and visible-light catalysis enables the access to a wide variety of amides (Scheme 27). Bromo-, chloro-, and fluorobenzaldehydes were converted to the corresponding amides in good yields. Several functional groups were well tolerated, such as alkynes and olefins, and the corresponding amides could undergo further functionalisation. This dual-catalytic metal free umpolung strategy was also applied to the late-stage functionalization of natural products. Adapalen, cholesterol, and oleanic acid derived aldehydes were transformed to the natural products in good yields showing the synthetic utility of this methodology.

[67] M.-S. Liu, W. Shu *ACS Catal*. **2020**, *10*, 12960.

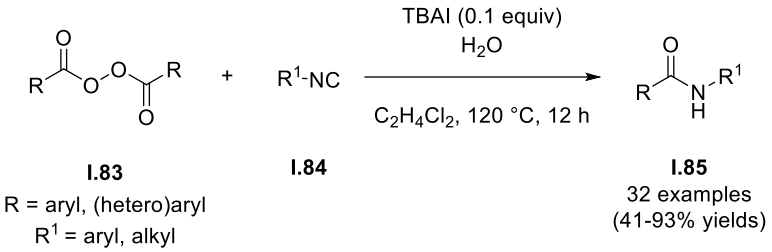


Scheme 27. Dual catalysed umpolung strategy for direct amide synthesis.

A plausible mechanism was proposed as shown in Scheme 27: the aldehyde **I.72** reacts with the NHC-1 (**I.75**) catalyst to give the corresponding Breslow intermediate (**I.80**) which could undergo single-electron oxidation by an excited photocatalyst. In the meanwhile, the imine **I.73** is reduced by the photocatalyst. The two radical intermediates undergo radical-radical cross-coupling to form the C-N bond. Once the new bond is formed, the NHC-catalyst is released to give the desired amide.

II.3.3 Isocyanides

Since the discovery of the Ugi reaction and related isocyanide-based multicomponent reaction, isocyanides are widely exploited in organic synthesis.[68] Concerning amides, Lei et al. presented a novel radical addition reaction between arylcarboxy radicals and isocyanides for the amidation via an intramolecular rearrangement in the presence of tetra-*n*-butylammonium iodide as catalyst (Scheme 28).[69] They combined arylcarboxy radicals, which are issued from acyl peroxides **I.83**, with isocyanides **I.84**, efficient traps for radicals. A wide range of substituents on the peroxide part was well-tolerated albeit alkyl-group-derived peroxides gave just traces of the products. The substrate scope was further explored with aliphatic and aromatic isocyanides and in both cases good yields were obtained.



Scheme 28. Synthesis of amides from isocyanides and acyl peroxides.

Aminocarbonylation reactions were performed through transition metal catalysis employing isocyanides as reagents.[70] Considering the cost of transition-metal catalysts and the requirement for removal of trace amounts of metal residues in pharmaceutical industries, the development of metal-free methodologies was desirable. The transition-metal free aminocarbonylation of diazonium salts, or azo sulfones, with isocyanides was next described under base or visible-light promoted conditions reaction.[71] More recently, direct C-H aminocarbonylation of electron-poor N-heteroarenes was described under oxidative conditions.[72] The reaction was

[68] a) T. Vlaar, E. Ruijter, B.U.W. Maes, R.V.A. Orru *Angew. Chem. Int. Ed.* **2013**, *52*, 7084; b) P. Patil, M. Ahmadian-Moghaddam, A. Dömling *Green. Chem.* **2020**, *22*, 6902.

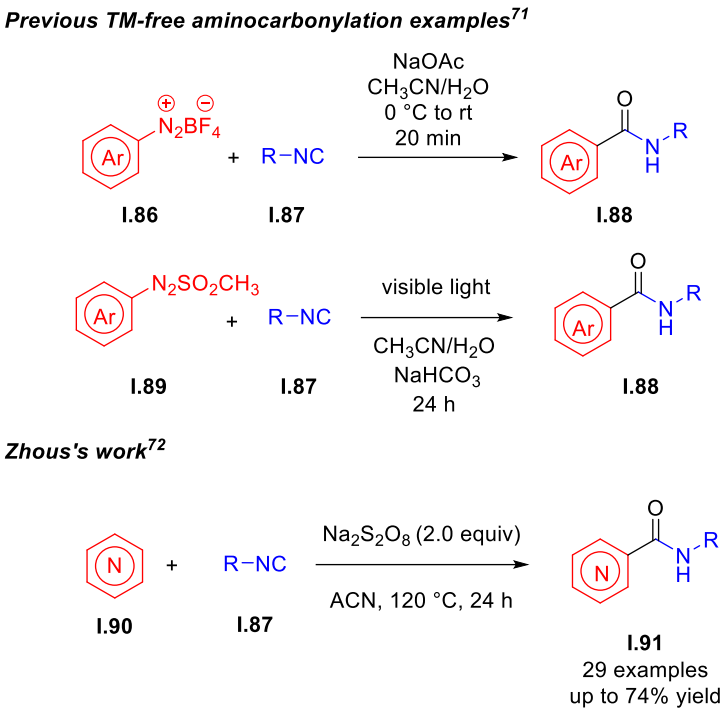
[69] M. Chen, Y. Li, H. Tang, H. Ding, K. Wang, L. Yang, C. Li, M. Gao, A. Lei *Org. Lett.* **2017**, *19*, 3147.

[70] See examples: a) H. Jiang, B. Liu, Y. Li, A. Wang, H. Huang *Org. Lett.* **2011**, *13*, 1028; b) J. Peng, L. Liu, Z. Hu, J. Huang, Q. Zhu *Chem. Commun.* **2012**, *48*, 377.

[71] See examples: a) U.M.V. Basavanag, A. Dos Santos, L. El Kaim, R. Gámez-Montaño, L. Grimaud *Angew. Chem. Int. Ed.* **2013**, *52*, 7194; b) M. Malacarne, S. Protti, M. Fagnoni *Adv. Synth. Catal.* **2017**, *359*, 3826.

[72] Z. Zhou, H. Ji, Q. Li, Q. Zhang, D. Li *Org. Biomol. Chem.* **2021**, *19*, 2917.

promoted by cheap, stable and readily available inorganic persulfate salt ($Na_2S_2O_8$, 2.0 equiv) and takes place in acetonitrile at 120 °C for 24 hours (Scheme 29).



Scheme 29. C-H aminocarbonylation under transition metal-free conditions.

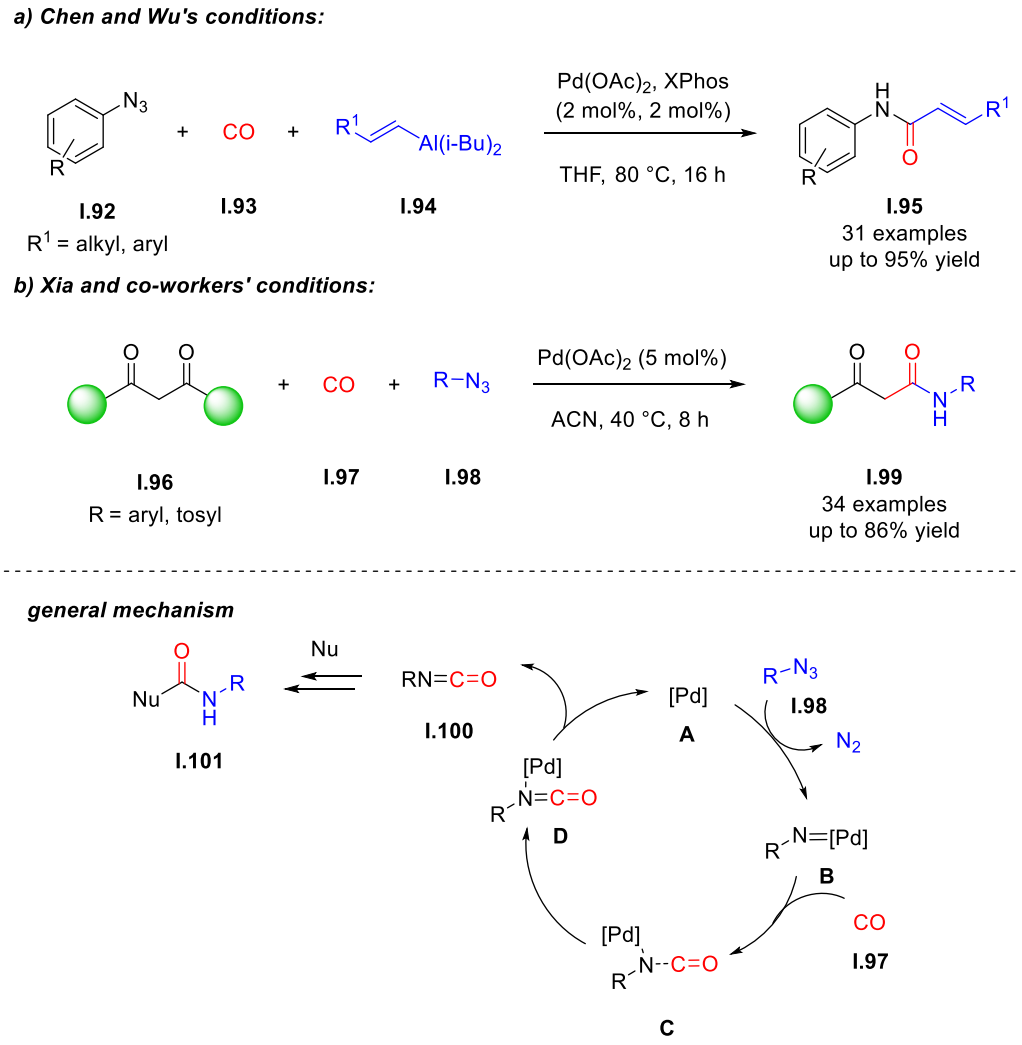
II.3.4 Azides

Azides can also be considered as useful amine-surrogates in amide synthesis. The first report was published by Hong et al. providing the amidation reaction from alcohols and benzyl azide through a dehydrogenative Ru-catalysed mechanism.[73] Since then, several works were published reporting Pd-catalysed carbonylative reactions to synthesise amides from azides (Scheme 30). Chen and Wu published the coupling between aryl azides and alkenylaluminum agents to afford α,β-unsaturated amides (**I.95**) in good to excellent yields. The authors proposed a plausible mechanism which occurred through an *in-situ* generated isocyanate intermediate.[74] Xia et al. published a Pd-catalysed amidation of 1,3 diketones (**I.96**) with azides (**I.98**) which follows the same general mechanism. This approach provides the access to β-ketoamides (**I.99**) from readily available compounds under mild conditions.[75]

[73] Z. Fu, J. Lee, B. Kang, S. Hong *Org. Lett.* **2012**, *14*, 6028.

[74] B. Chen, X.-F. Wu *Journal of Catalysis* **2020**, *383*, 160.

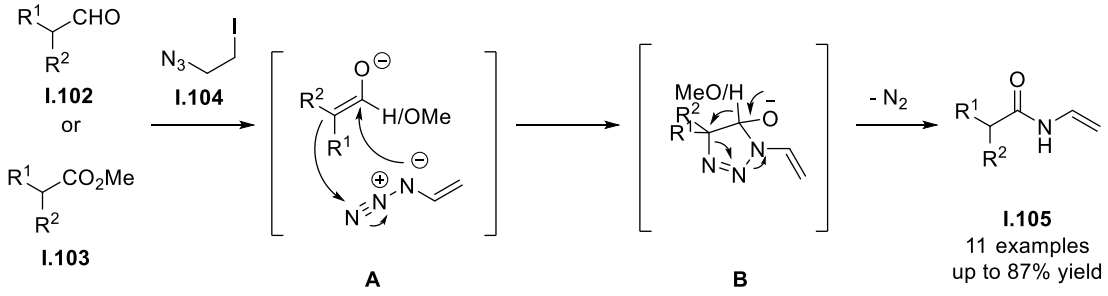
[75] Z.-Y. Gu, J. Chenbc, J.-B. Xia *Chem. Commun.* **2020**, *56*, 11437.



Scheme 30. Palladium-catalysed carbonylative amidation through isocyanate intermediate.

In 2017 Furkert et al. published preliminary results on a direct formation of N-vinyl amides through vinyl azide-enolate [3+2] cycloaddition.[76] They accomplished the synthesis of α,β-unsaturated N-vinyl amides from esters and N-vinyl amides from aldehydes (Scheme 31). The reaction proceeds through the *in-situ* formation of N-vinyl azide, which undergoes azido-enolate [3+2] cycloaddition followed by rearrangement and nitrogen extrusion according to both experimental data and DFT calculations.

[76] H. Choi, H.J. Shirley, P.A. Hume, M.A. Brimble, D.P. Furkert *Angew. Chem. Int. Ed.* **2017**, *56*, 7420.



Scheme 31. Vinyl azide-enolate [3+2] cycloaddition towards the synthesis of N-vinyl amides.

Furthermore, azides could be converted to amides through one-pot strategies with thioacids as reported by Just[77] and further explored by Rosen.[78] In 2017, Lovely showed also the interest of using thioacid-azide coupling reaction for application in the total synthesis of oroidin alkaloids (e.g. Nagelamide A and S) (Figure 5).[79]

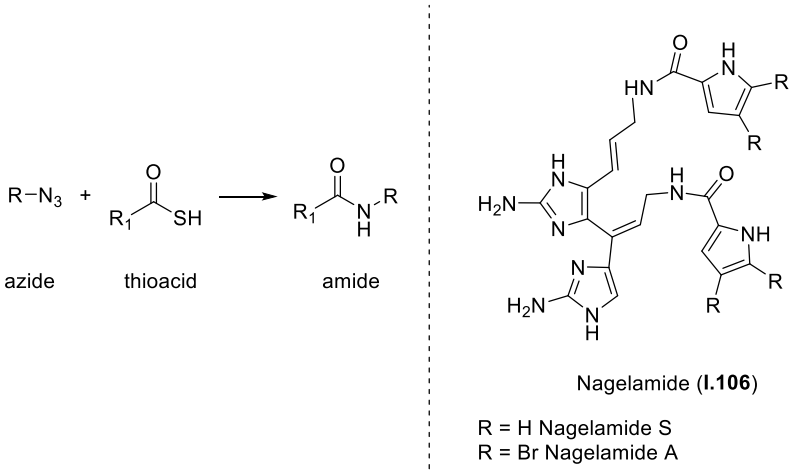


Figure 5. General structure of Nagelamide

II.3.5 Dioxazolones as Acylnitrene precursors

During the last few years an important breakthrough in catalytic amide reactions was the arising of C-H amidation; it is worthy to mention that in 2021 a highlight on this subject was published by our laboratory.[80] In 2015, Chang introduced dioxazolones **I.108** as acylnitrene precursors[81] giving a great impulse to the development of C-H amidations. If the earliest examples were

[77] G.H. Hakimelahi, G. Just *Tetrahedron Lett.*, **1980**, *21*, 2119.

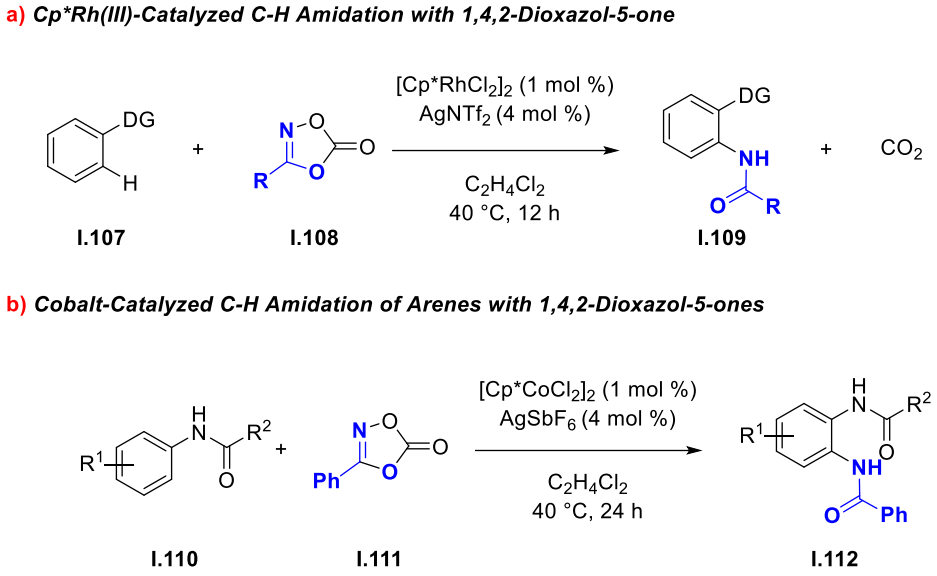
[78] T. Rosen, I.M. Lico, D.T.W. Chu *J. Org. Chem.* **1988**, *53*, 1580.

[79] A.K. Herath, M.R. Bhandari, D. Gout, M. Yousufuddin, C.J. Lovely *Tetrahedron Lett.* **2017**, *58*, 3913.

[80] E. Tosi, R.M. de Figueiredo, J.-M. Campagne *Catalysts* **2021**, *11*, 471.

[81] Y. Park, K.T. Park, J.G. Kim, S. Chang *J. Am. Chem. Soc.* **2015**, *137*, 4534.

carried out in the presence of noble and expensive metals,[82] the use of less toxic and cheap metals, such as cobalt and iron, has recently emerged (Scheme 32).[83]



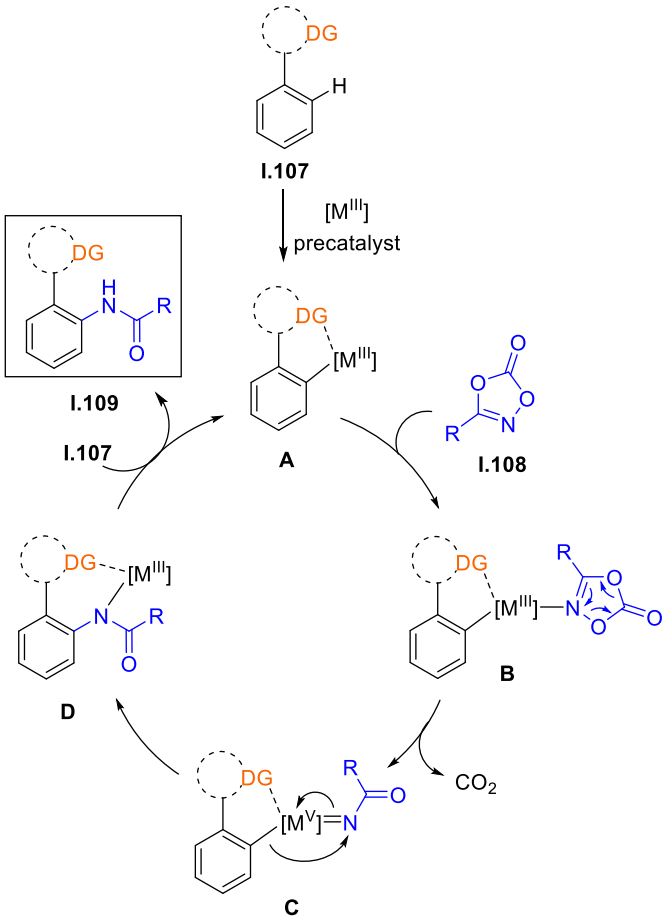
Scheme 32. C-H amidation seminal works.

A simplified general mechanism for the C(sp^2)-H amidation is illustrated in Scheme 33, although, important modifications exist depending on the metal used.[84]

[82] Y. Park, S. Jee, J.G. Kim, S. Chang *Org. Process Res. Dev.* **2015**, *19*, 1024.

[83] a) J. Park, S. Chang *Angew. Chem. Int. Ed.* **2015**, *54*, 14103; b) J. Kweon, S. Chang *Angew. Chem. Int. Ed.* **2021**, *60*, 2909.

[84] a) K.M. Van Vliet, B. De Bruin *ACS Catal.* **2020**, *10*, 4751; b) J. Kweon, S. Chang *Angew. Chem. Int. Ed.* **2021**, *60*, 2909; c) S. H. Park, J. Kwak, K. Shin, J. Ryu, Y. Park, S. Chang *J. Am. Chem. Soc.* **2014**, *136*, 2492.

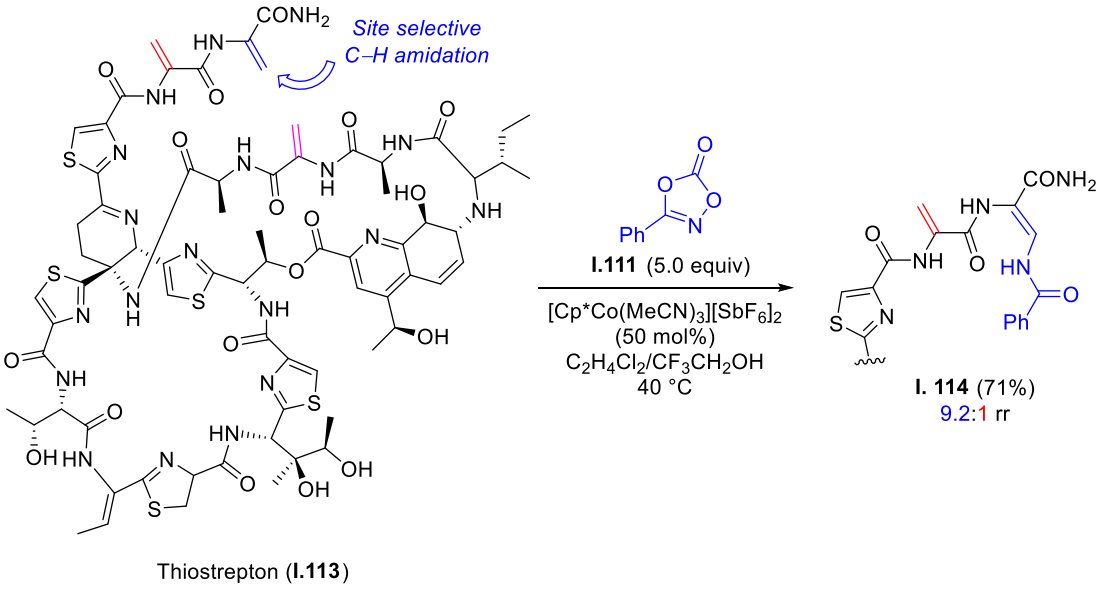


Scheme 33. Simplified mechanism of C(sp^2)-H amidation. DG: directing group.

In the C(sp^2)-H functionalizations, C-H amidations might be interesting especially in medicinal chemistry where amide bonds are strictly related to *N*-heterocyclic compounds which are abundant in drug candidates.[85] As a matter of fact, Ellman and Miller have already demonstrated the usefulness of C(sp^2)-H amidation in the functionalization of thiostrepton (**I.113**), a potent antibiotic peptide, leading to the synthesis of analogues with an increasing aqueous solubility (Scheme 34).[86]

[85] S.D. Roughley, A.M. Jordan *J. Med. Chem.* **2011**, *54*, 3451.

[86] R.J. Scamp, E. de Ramon, E.K. Paulson, S.J. Miller, J.A. Ellman *Angew. Chem. Int. Ed.* **2020**, *59*, 890.



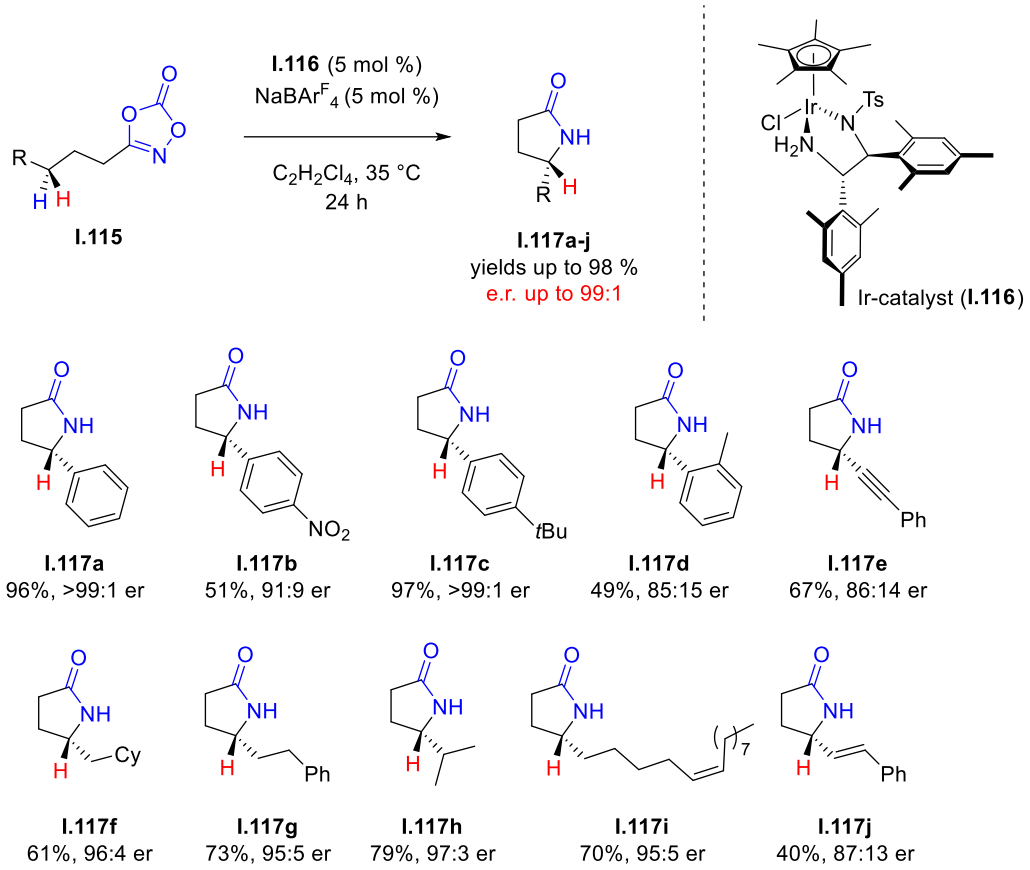
Scheme 34. C-H derivatisation of Thiostrepton.

C(sp^3)-H functionalizations have been investigated during the last two years thanks to the promising results obtained on branch-selective allylic C-H amidation of terminal double bonds via Ir-complex catalysis.[87] Several C(sp^3)-H reactions were developed using a variety of C-H substrates such as allylic, benzylic, propargylic and aliphatic as well as a wide range of metals (Co, Ir, Rh, Ru).

One of the first examples was published in 2019 by Chang, describing the Ir-catalysed enantioselective intramolecular benzylic C-H amidation allowing the synthesis of γ-lactams **I.117** in high yields and enantioselectivities (Scheme 35).[88] Allylic and propargylic substrates were also compatible.

[87] a) H. Lei, T. Rovis *J. Am. Chem. Soc.* **2019**, *141*, 2268; b) T. Knecht, S. Mondal, J.-H. Ye, M. Das, F. Glorius *Angew. Chem. Int. Ed.* **2019**, *58*, 7117; c) J.S. Burman, R.J. Harris, C.M.B. Farr, J. Bacsa, S.B. Blakey *ACS Catal.* **2019**, *9*, 5474.

[88] Y. Park, S. Chang *Nat. Catal.* **2019**, *2*, 219.



Scheme 35. Enantioselective C(sp^3)-H amidation. NaBAr$^F_4$ = sodium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate.

Thus, in the last 3 years, C-H amidations have known an incredible development providing a valuable tool for the construction of amide functions. If these reactions have been associated with a large range of metals (Co, Ru, Rh, Ir) and source of chirality (from classical chiral ligands or chiral carboxylic acids to chiral-at-metal complexes), challenges to be addressed now might be the use of Fe-catalysts,[89] the development of reusable chiral catalysts,[90] and the development of enantioselective C-H amidation in tandem processes.[91] To date, only dioxazolones have been reported as efficient substrates on these enantioselective transformations. Accordingly, alternative stable acylnitrene precursors warrant investigation. Another point that also deserves to be taken into consideration concerns the possibility to achieve C(sp^2)-H amidation reactions bypassing the need for directing groups.[92]

[89] J. Kweon, S. Chang *Angew. Chem. Int. Ed.* **2021**, *60*, 2909.

[90] H. Singh, C. Sen, E. Suresh, A.B. Panda, S.C. *J. Org. Chem.* **2021**, *86*, 3261.

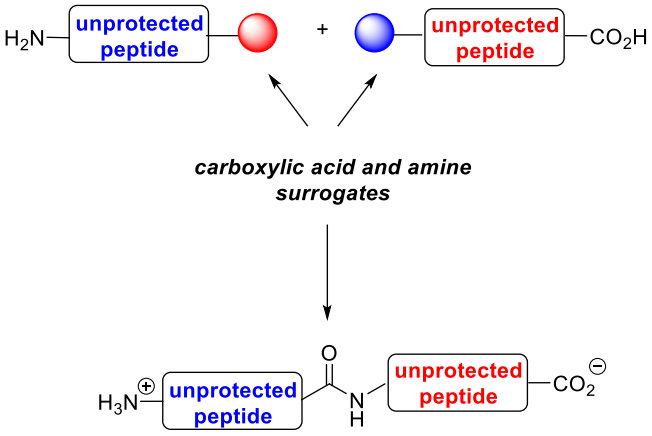
[91] C. Chen, C. Shi, Y. Yang, B. Zhou *Chem. Sci.* **2020**, *11*, 12124.

[92] J. Zhang, H; Xie, H. Zhu, S. Zhang, M.R. Lonka, H. Zou *ACS Catal.* **2019**, *9*, 10233.

II.4 Chemical Ligation

In chemistry, *Chemical Ligation* means an ensemble of procedures in order to create long chains of peptides and proteins (Scheme 36). It is the second step of a convergent approach. In fact, small chains containing 20-30 amino acids are synthesized by conventional methods and then they are coupled by chemoselective reaction to form longer peptide chains.

Ligation strategies are complementary to SPPS and offer the possibility to form an amide bond between two complex non-protected peptide fragments under physiological conditions.[31,93]



Scheme 36. Coupling fragments.

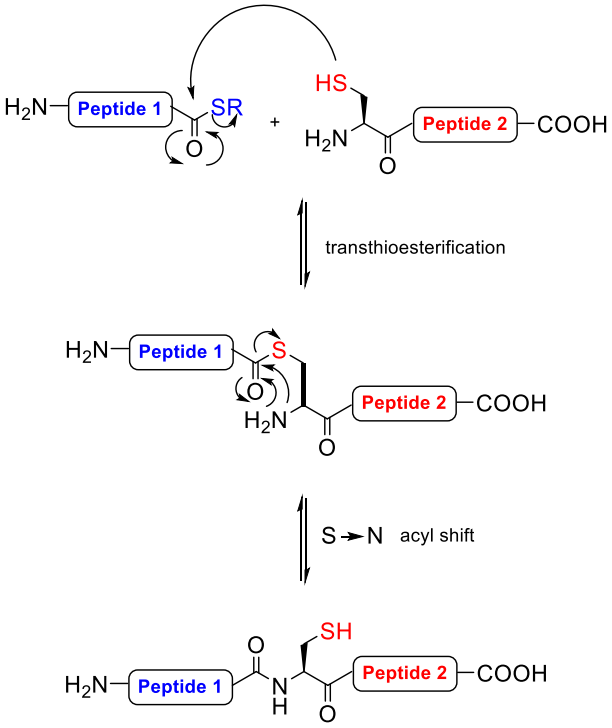
Herein, we will highlight the fundamentals of the principal ligation strategies such as the NCL (native chemical ligation), the Staudinger Ligation, and the KAHA (α-Ketoacid-Hydroxylamine amide-forming ligation).

II.4.1 Native Chemical Ligation

NCL has a privileged place among chemical strategies for peptides and proteins synthesis thanks to its wide utility and reliability.[2b] It allows the construction of chains longer than 50 amino acid residues through a covalent peptide bond formation. Kent and co-workers[94] initially explored this strategy in the early 1990s.

[93] E.M. Sletten, C.R. Bertozzi *Angew. Chem. Int. Ed.* **2009**, *48*, 6974.

[94] P.E. Dawson, T.W. Muir, I. Clarklewis, S.B.H. Kent *Science* **1994**, *266*, 776.



Scheme 37. General mechanism of Native Chemical Ligation.

The reaction first involves a reversible *trans*-thioesterification via nucleophilic attack on the C-terminal thioester-containing peptide by the N-terminal Cys-containing thiolate moiety, leading to the formation of a thioester linkage between two peptide segments. The thioester intermediate then undergoes a rapid S→N acyl shift to afford the native amide-linkage (Scheme 37). Moreover, it is noteworthy to underline its main advantage: the implication of unprotected AA side-chains in aqueous conditions.[28a]

Since 1994, NCL has found wide synthetic applications in chemical biology, medicinal chemistry, and material science. More specifically, NCL combined with SPPS have largely contributed to the chemical synthesis of peptides and proteins. According to the PCS database, over 700 proteins of biological relevance were synthesised. Continuous and significant advances in the field have culminated with the report of synthetic objects of exceptional size such as fully functional synthetic analogues of bacterial polymerases (~350 amino acids).[95] Many other biologically active targets were synthesized through the years via NCL[96] such as a variant of the 166-residue erythropoiesis protein,[97] the 203-residue covalent dimer of HIV1 protease,[98] and the 358-residue D-Dpo4 enzyme.[99]

However, this strategy shows important limitations: i) the need of N-terminal cysteine residue (Cysteine is relatively rare, 1,3% frequency in nature)[100] and ii) synthesis of C-terminal

---

[95] W. Xu, W. Jiang, J. Wang, L. Yu, J. Chen, X. Liu, L. Liu, T. F. Zhu *Cell Discov.* **2017**, *3*, 17008.

[96] a) S. Kulkarni, J. Sayers, B. Premdjee, R.J. Payne *Nat. Rev. Chem.* **2018**, *2*, 0122; b) A.C. Conibear, E.E. Watson, R.J. Payne, C.F.W. Becker *Chem. Rev.* **2018**, 47, 9046.

[97] G.G. Kochendoerfer et al. *Science* **2003**, *299*, 884.

[98] V.Y. Torbeev, S.B.H. Kent *Angew. Chem. Int. Ed.* **2007**, *46*, 1667.

[99] W. Jiang et al. *Cell Discov.* **2017**, *3*, 17037.

[100] H. Rohde, O. Seitz *Biopolymers* **2010**, *94*, 551.

thioesters (in particular by Fmoc solid-phase peptide synthesis). To circumvent these limitations, approaches have been developed for NCL with cysteine-like AA residues (such as alanine, phenylalanine and valine).

Often, the requirement of a Cys-containing peptide remains one of the main concern. In some proteins a cysteine is added just to ensure the ligation process, affecting also their initial biological activity. To sidestep this problem, the use of thiol auxiliaries was employed. These removable thiol-based auxiliaries (Figure 6) are attached to the α-amino group of a peptide fragment in order to mimic the Cys residue.[101] After the S,N-acyl shift (see Scheme 37), the auxiliaries are removed by application of a specific chemical treatment. These methods allowed to extend the limited scope of NCL to the synthesis of several peptides and proteins.

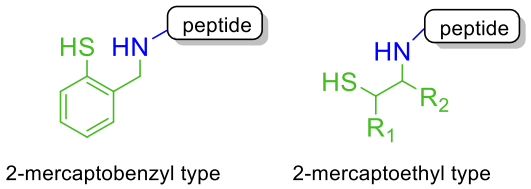


Figure 6. Thiol-based auxiliaries.

In addition, we should mention two other approaches for NCL which replace the Cys residue with the histidine and selenocysteine.[102] A detailed review has been recently published on Native Chemical Ligation and his extended methods. [103]

II.4.2 Staudinger Ligation

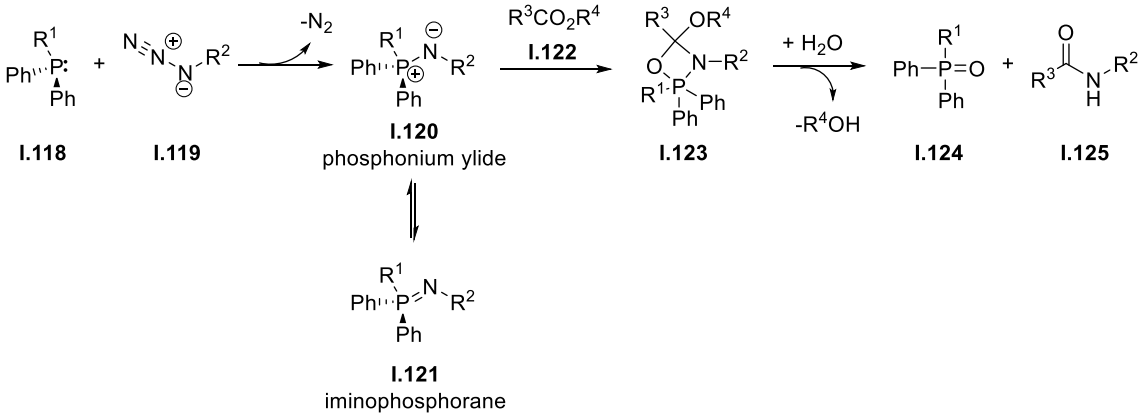
The Staudinger ligation, discovered by Staudinger and Meyer in 1919,[104] relies on a reaction between azides **I.119** and phophines **I.118** to give iminophosphorane-type intermediates which can further react with electrophiles (Scheme 38).

[101] S.F. Loibl, Z. Harpaz, O. Seitz *Angew. Chem. Int. Ed.* **2015**, *54*, 15055.

[102] a) M. Muttenthaler, P.F. Alewood *J. Pept. Sci.* **2008**, *14*, 1223; b) L. Zhang, J.P. Tam *Tetrahedron Lett.* **1997**, *38*, 3; c) S.S Kulkarni, E.E. Watson, B. Premdjee, K.W Conde-Frieboes, R.J Payne Nat. Protoc. **2019**, *14*, 2229.

[103] V. Agouridas, O. El Mahdi, V. Diemer, M. Cargoët, J.-C.M. Monbaliu, O. Melnyk *Chem. Rev.* **2019**, *119*, 7328.

[104] H. Staudinger, J. Meyer *Helv. Chim. Acta* **1919**, *2*, 635.

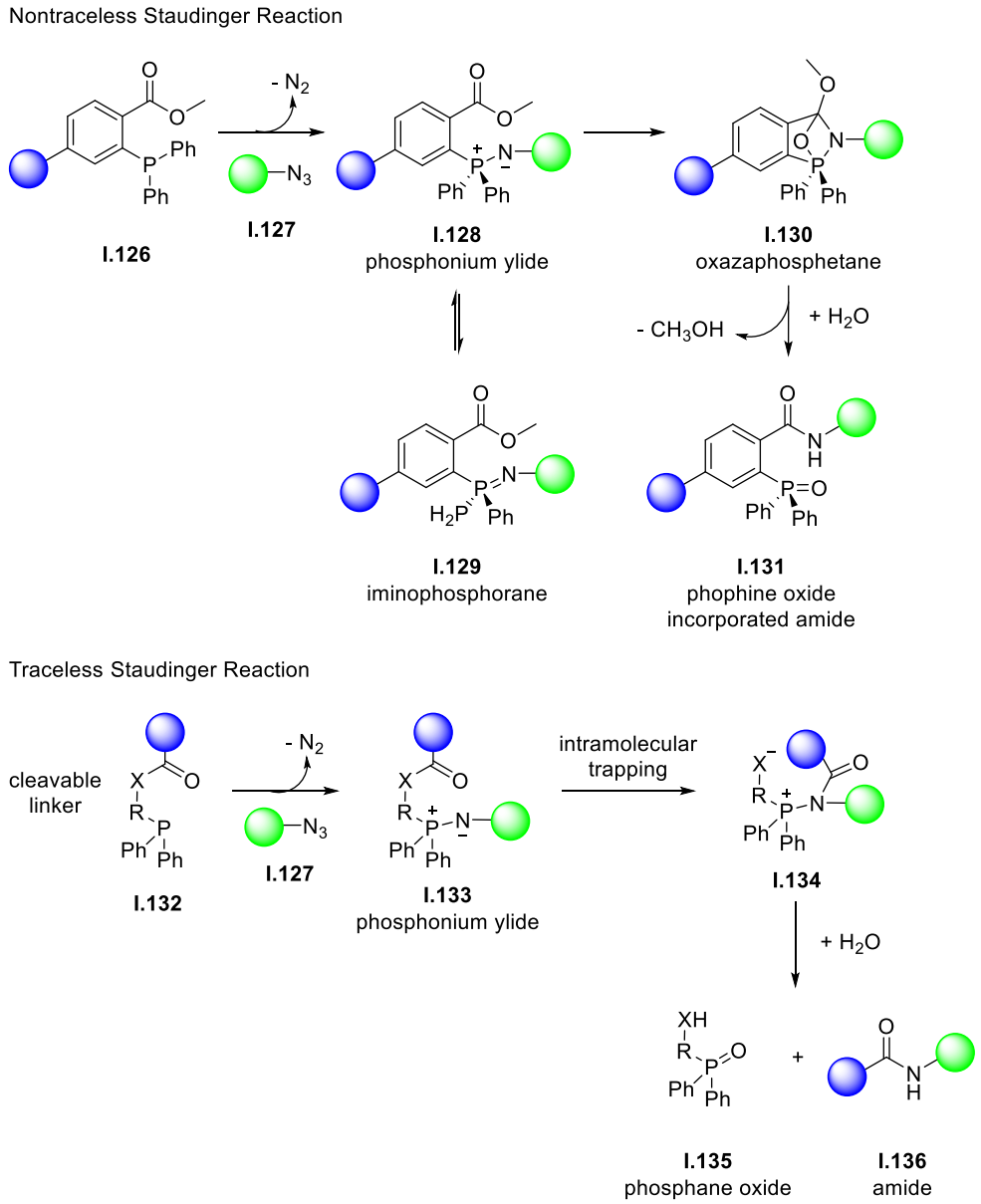


Scheme 38. Mechanism of the Staudinger Ligation.

Since then, a plethora of phosphorus derivatives have been used to obtain amides under mild conditions finding also applications in the peptide field.[105] There are two major conjugation variants regarding the Staudinger Ligation (Scheme 39): the nontraceless Staudinger Ligation and the traceless Staudinger Ligation.[106]

[105] J. Garcia, F. Urpì, J. Vilarrasa *Tetrahedron Lett.* **1984,** *25*, 4841.

[106] a) E. Saxon, C.R. Bertozzi *Science* **2000**, *287*, 2007; b) E. Saxon, J.I. Armstrong, C.R. Bertozzi *Org. Lett.* **2000**, *2*, 2141; c) B.L. Nilsson, L.L. Kiessling, R.T. Raines *Org. Lett.* **2000**, *2*, 1939; d) C. Bednarek, I. Wehl, N. Jung, U. Schepers, S. Bräse *Chem. Rev.* **2020**, *120*, 4301.



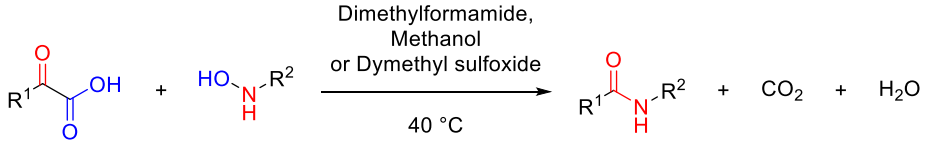
Scheme 39. Principal Staudinger Ligations.

The Staudinger ligation has become an important tool for chemists and biologists. Not only it is an alternative method for peptide ligation but also a well-established reaction used in the biorthogonal reactions, material science, organic synthesis, catalysis, synthesis of natural products...[28]

II.4.3 KAHA Ligation

In 2006, Bode et al. have identified the combination of C-terminal α-ketoacids and N-terminal hydroxylamine peptides as a remarkably selective and facile ligation reaction for the formation

of amides (Scheme 40).[107] It occurs in the presence of unprotected side chains, does not require any reagents or catalysts, and the by-products are only CO_2 and water. Efficient strategies to prepare the required starting materials (C-terminal peptide α-keto acids and N-terminal peptide hydroxylamine) were also developed improving the synthetic potential of this ligation strategy.[108] In 2011, the synthesis of a therapeutic peptide (30 AA residues),[109] without interference from unprotected side chain functional groups, has been reported. In addition to free hydroxyamines, O-substituted ones can be also employed.[100,110]



I.137 I.138 I.139

Scheme 40. KAHA ligation model.

In conclusion of this subsection, we reported selected non-conventional routes to amide synthesis, elucidating the latest updates for some of them. In the next subsection, an overview of non-conventional methodologies through amine activation towards the N→C direction will be given.

III. Inverse N→C Direction Peptide Synthesis

As previously mentioned, the peptide synthesis from N to C direction mimicking its biosynthesis encounter drawbacks, such as racemisation. For this reason, the chemical synthesis takes place on the opposite direction (C→N) via the carboxylic function activation. So far, to sidestep the limitations, inherently bounded to the coupling agents, non-conventional methodologies have emerged as highlighted in the previous section.

Some research's group started to show interest for a new type of activation: the activation of the amine function (Scheme 41).

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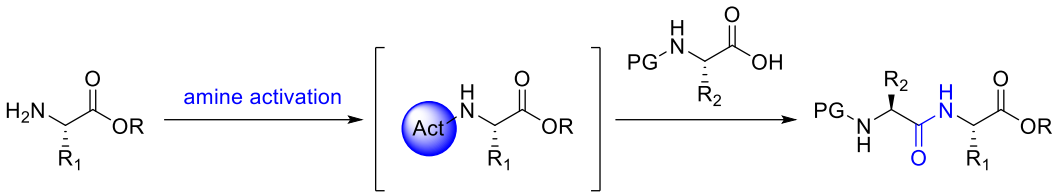
[107] J.W. Bode, R.M. Fox, K.D. Baucom *Angew. Chem. Int. Ed.* **2006**, *45*, 1248.

[108] a) L. Ju, A.R. Lippert, J.W. Bode *J. Am. Chem. Soc.* **2008**, *130*, 4253; b) L. Ju, J.W. Bode *Org. Biomol. Chem.* **2009**, *7*, 2259; c) T. Fukuzumi, J.W. Bode *J. Am. Chem. Soc.* **2009**, *131*, 3864.

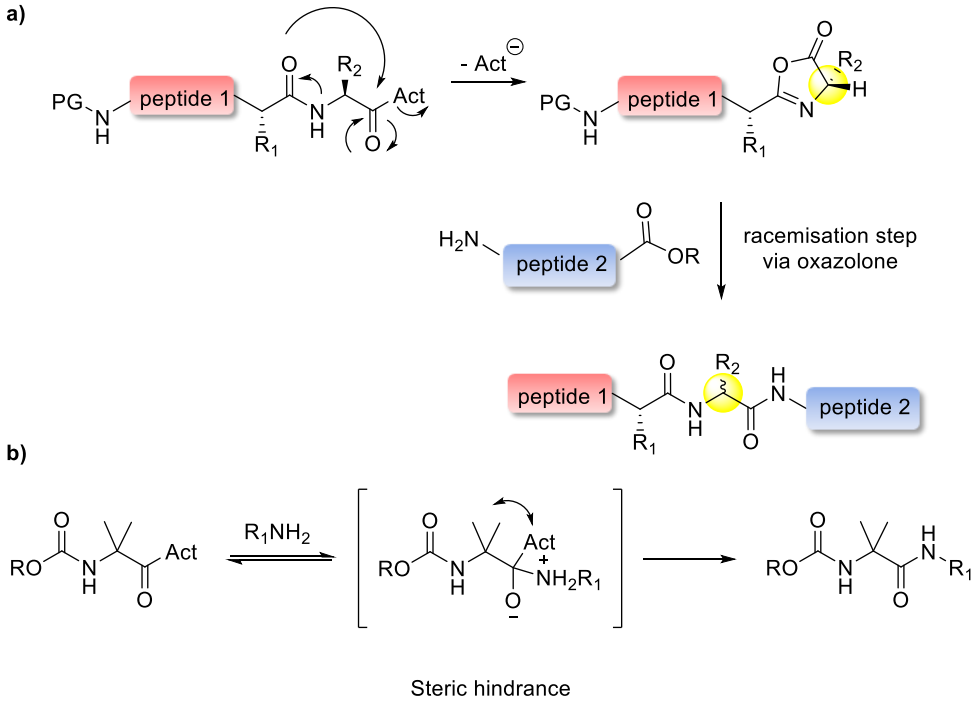
[109] J. Wu, J. Ruiz-Rodríguez, J.M. Comstock, J.Z. Dong, J.W. Bode *Chem. Sci.* **2011**, *2*, 1976.

[110] N. Carrillo, E.A. Davalos, J.A. Russak, J.W. Bode *J. Am. Chem. Soc.* **2006**, *128*, 1452.



Scheme 41. Activation of the amine group.

This type of activation can potentially solve, or at least minimise, racemisation issues (Scheme 42a). Besides, it might help when the introduction of sterically hindered amino acids in a peptide chain is quite difficult to accomplish (Scheme 42b).



Scheme 42. Racemisation and steric hindrance in classical activation.

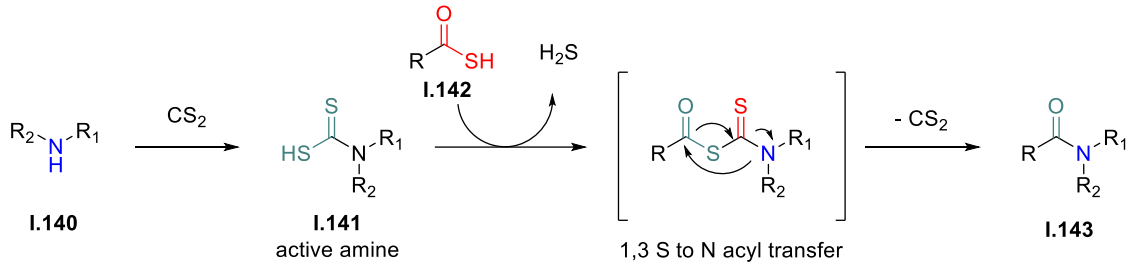
Up-to-date three strategies have been reported where the amino function is activated to afford the amide bond (N→C fashion).

III.1 Peptide and amide construction from *thioacids and dithiocarbamate*

In 2013, Yu and Houghten disclosed a methodology for peptide synthesis, by using thioacids, as acyl donors, and dithiocarbamates, as activated amines.[111]

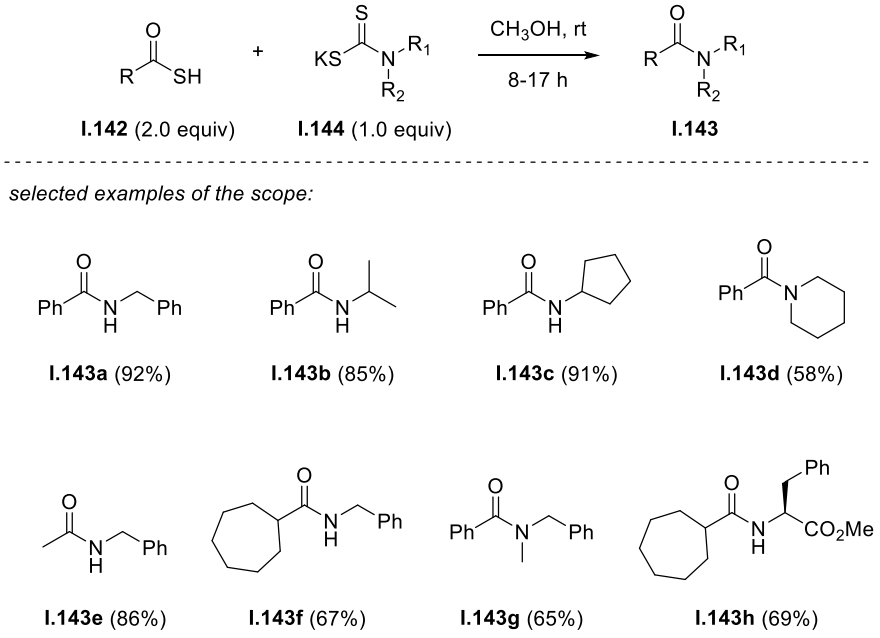
[111] W. Chen, J. Shao, M. Hu, W. Yu, M.A. Giulianotti, R.A. Houghten, Y. Yu *Chem. Sci.* **2013**, *4*, 970.

The dithiocarbamate was obtained from the reaction of the amine **I.140** with carbon disulfide (CS_2). Thereafter, the thioacid **I.142** reacted with the dithiocarbamate **I.141** to afford an amide bond by a traceless loss of a simple, volatile but extremely toxic byproduct, carbon disulfide. The mechanism of the reaction is shown in Scheme 43.



Scheme 43. Thioacid-dithiocarbamate strategy.

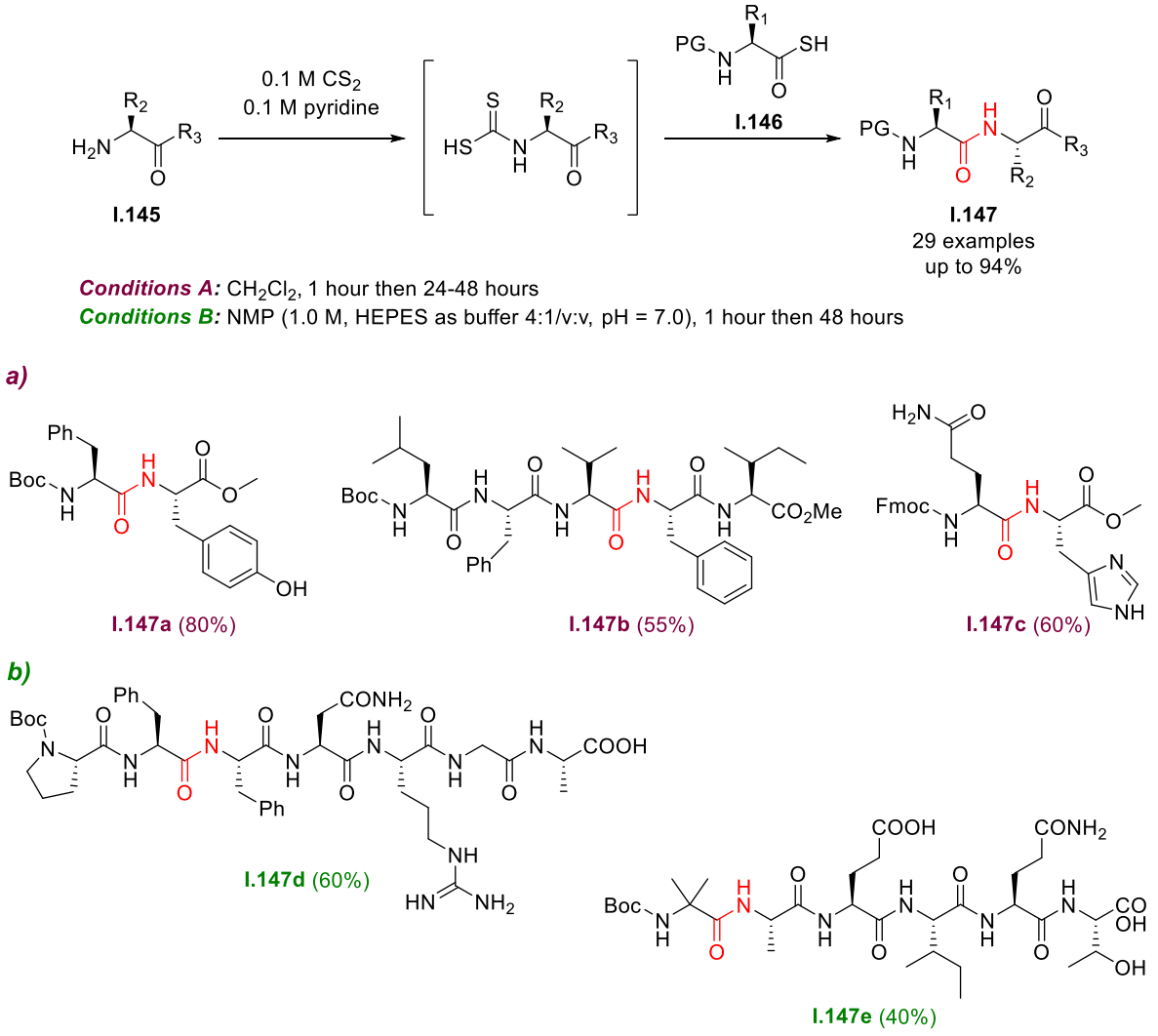
The reaction takes place in MeOH at room temperature. Some examples of the scope are depicted in Scheme 44; amines with aliphatic and aromatic substituents and with increasing steric hindrance performed well, delivering the desired amide in good to excellent yields. Lower yields were, however, observed using secondary amines (56-65%).



Scheme 44. Substrate scope of amide synthesis.

The method could be also extended to peptide chemistry after adjusting the reaction conditions. The corresponding dithiocarbamates were formed *in-situ* from the amino ester in the presence of pyridine and CS_2. A wide variety of dipeptides were synthesised. The reaction took place in dichloromethane at room temperature and the target molecules were obtained in good to

excellent yields. It is noteworthy to mention the high-tolerance for many amino thioacids (such as sterically hindred C-terminal Aib and Val). A range of diverse amino acid derived dithiocarbamates, including Phe, Trp, Val, Ile, Tyr and His, were efficiently prepared (Scheme 45a). This methodology was also applied to the coupling of short peptide fragments and the couplings were, in these cases, performed in a mixed organic/buffer system. No side-chain protecting groups were required (Scheme 45b).



Scheme 45. Substrate scope of peptide synthesis. NMP = N-Methyl-2-Pyrrolidone; HEPES = 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid

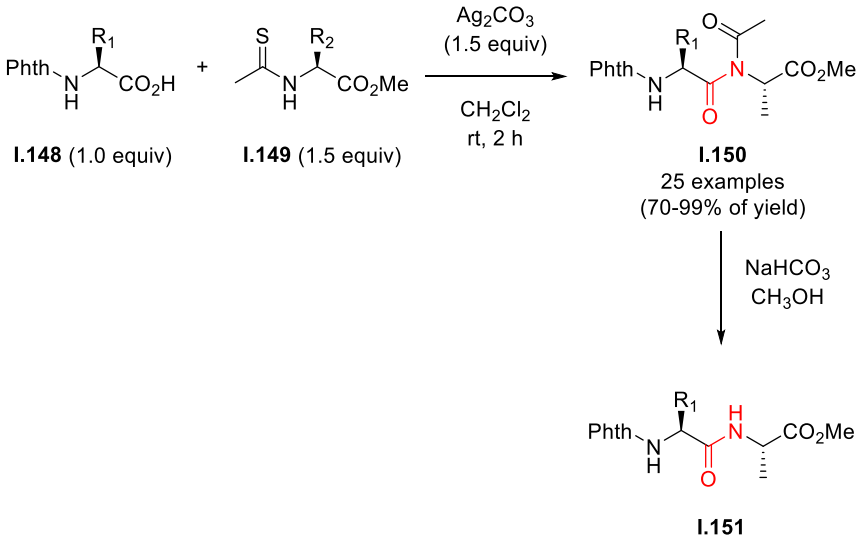
Finally, the synthesis of an endomorphin (EM) derivative was accomplished demonstrating the consistency of this alternative methodology. Important to mention, studies on the epimerisation were conducted showing that the couplings occurred (N- and C-terminal residue) without detection of racemisation.

The amine activation through dithiocarbamate enables the "left to right", (N→C) direction, peptide formation. The methodology is tolerant to a range of naturally occurring amino acid unprotected side chains, except lysine and cysteine, which must be protected. This strategy liberates, however, one equivalent each of CS_2 and H_2S which are harmful compounds.

III.2 Amide formation via silver-promoted reaction of thioamides

Hutton et al. proposed a coupling between thioamides and carboxylates in the presence of a thiophilic metal such as Ag(I).[112]

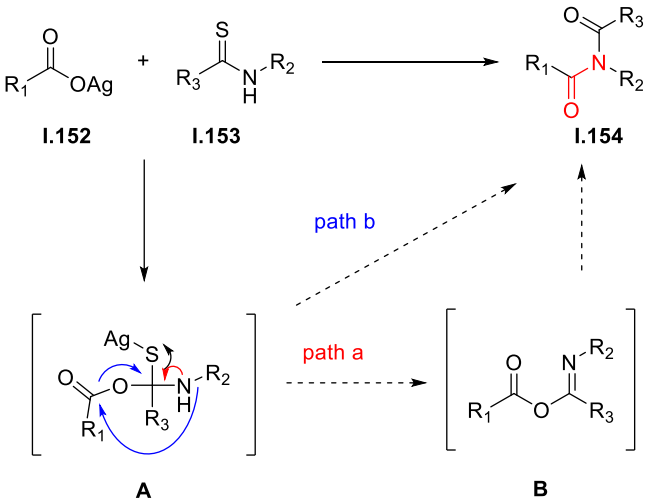
Optimisation of the reaction parameters identified Ag_2CO_3 in dichloromethane as the best conditions to afford the desired product. Then, a substrate scope was performed affording several imide products in good to excellent yields (71-100%), which can be hydrolysed to generate a native amide bond. Besides, sterically hindered amino acids such as Val and Leu were tolerated. The dipeptides were isolated as single stereoisomers showing no evidence of racemisation (Scheme 46).



Scheme 46. Synthesis of dipeptides.

A reaction mechanism was proposed and two pathways were hypothesised as shown in Scheme 47.

[112] A. Pourvali, J.R. Cochrane, C.A. Hutton *Chem. Commun.* **2014**, *50*, 15963.

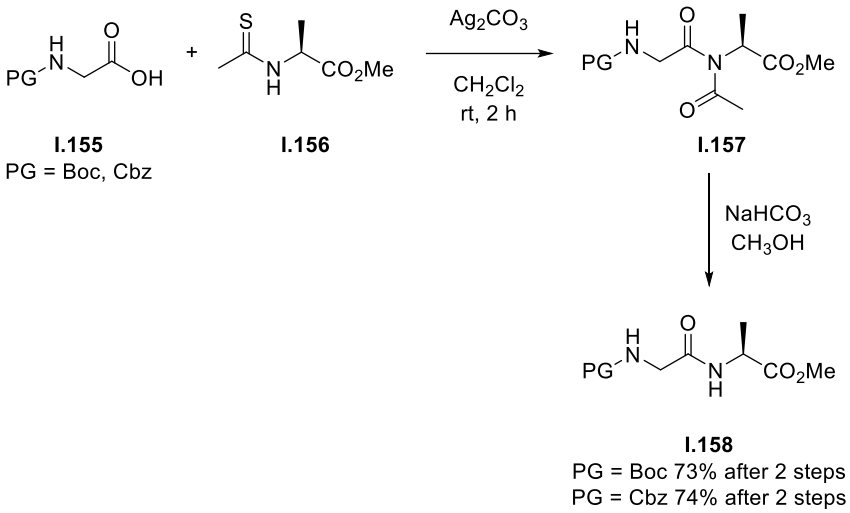


Scheme 47. Hypothesis for the reaction mechanism.

In the path a, the reaction proceeds through the formation of a tetrahedral intermediate **A**. Then, a mixed anhydride **B** gives, after rearrangement, the desired product. In path b the 1,3-acyl transfer occurs directly from the tetrahedral intermediate **A**, generating the imide with concomitant expulsion of the silver sulfide. According to the authors, the path b is more consistent with the experimental results. The mixed-anhydride intermediate **B** is usually observed at higher temperatures[113] and their couplings take place at room temperature. Moreover, the lack of epimerisation during the process suggests that the mechanism does not proceed through the formation of an epimerisation-prone intermediate such as **B**.

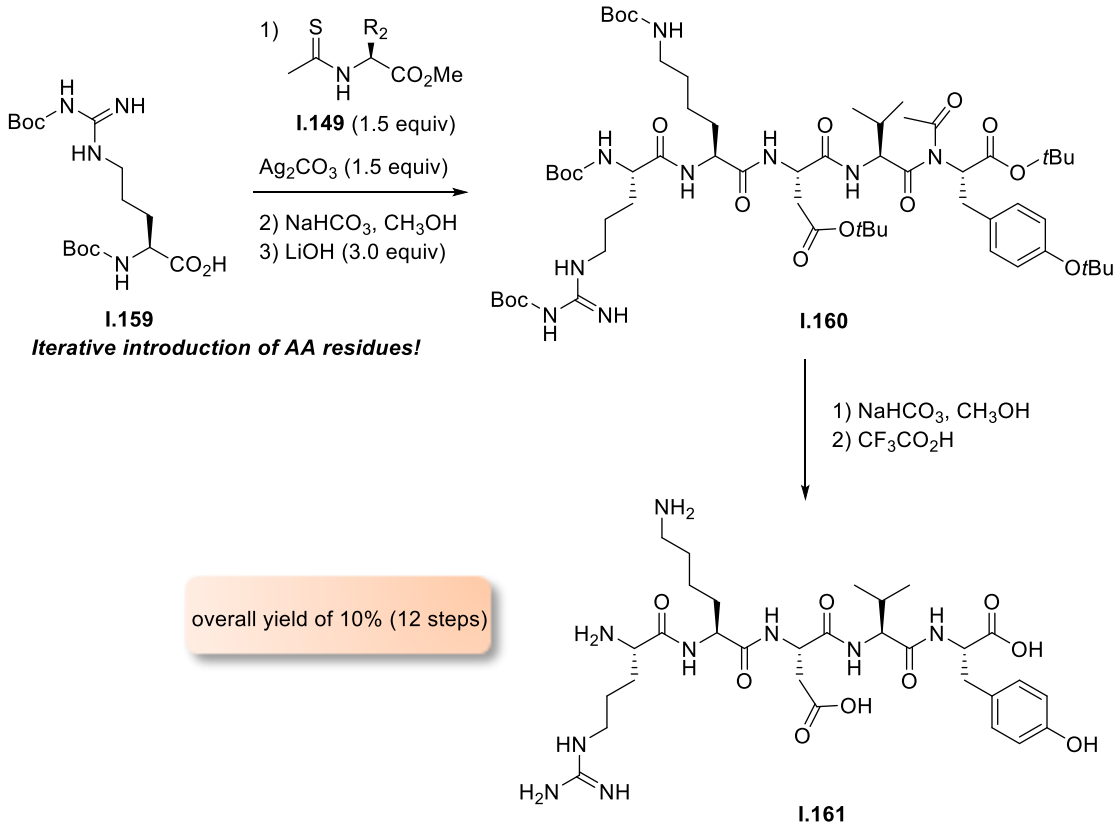
Treatment of Boc- and Cbz-protected dipeptide imides under mildly basic methanolysis conditions ($NaHCO_3/CH_3OH$) proceeded efficiently to give the desired amide bonds in good yield (Scheme 48). However, such basic conditions are not compatible with Fmoc-protected AA partners.

[113] X. Wu, X. Li, S.J. Danishefsky *Tetrahedron Lett.* **2009**, *50*, 1523.



Scheme 48. Hydrolysis of the peptide imides.

The biologically active pentapeptide Thymopentin (**I.161**) was synthesised via an iterative N→C coupling strategy, in order to exemplify the utility of the method. A Boc/methyl ester approach was chosen allowing a one-step concomitant imide hydrolysis/C-terminal deprotection. Each peptide coupling gave the expected imide which was transformed into the corresponding amide through the hydrolysis step. Successively, the methyl ester dipeptide was deprotected using LiOH to give the carboxylic acid, which was engaged in the following coupling reaction. After 12 steps, **I.161** was obtained in 10% overall yield with no evidence of epimerisation or other by-products (Scheme 49).



Scheme 49. N→C direction synthesis of Thymopentin (**I.161**).

In summary, a strategy for amino acid couplings was developed through the formation of imides, which are hydrolysed under mild conditions to form native amide bonds. A wide variety of Boc- and Cbz-protected amino acids could be employed although no coupling reaction was performed with amino acids containing sulfur in the side chain. Furthermore, this strategy proved to be suitable for N to C direction peptide synthesis. Afterwards, the same group was able to extend the applications of this methodology to ring expansions and macrolactonisations.[114]

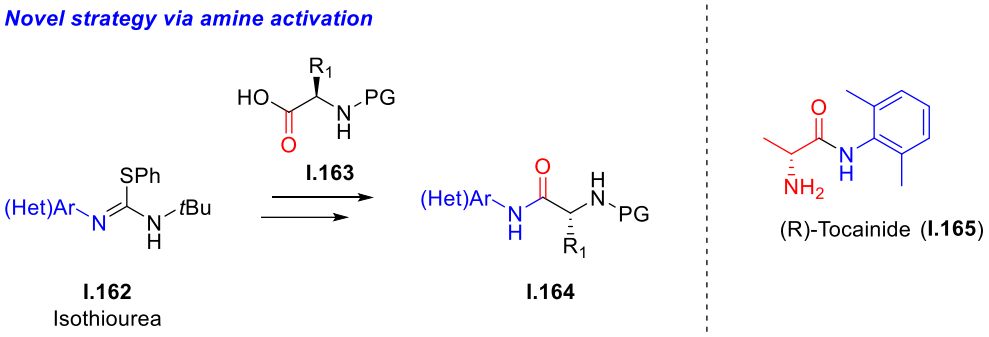
III.3 Isothioureas as amino activating reagents for coupling reaction

Maes et al. reported in 2017 the N-arylamino acid amide synthesis using isothioureas **I.162** and amino acids **I.163** (Scheme 50).[115] After seminal work on isothiourea as a new class of activated

[114] a) V.J. Thombare, C.A. Hutton *Angew. Chem. Int. Ed.* **2019**, *58*, 4998; b) J. Shang, V.J. Thombare, C.L. Charron, U. Wille, C.A. Hutton *Chem. Eur. J.* **2021**, *26*, 1620; c) S. Shabani, C.A. Hutton *Chem. Commun.* **2021**, *57*, 2081.

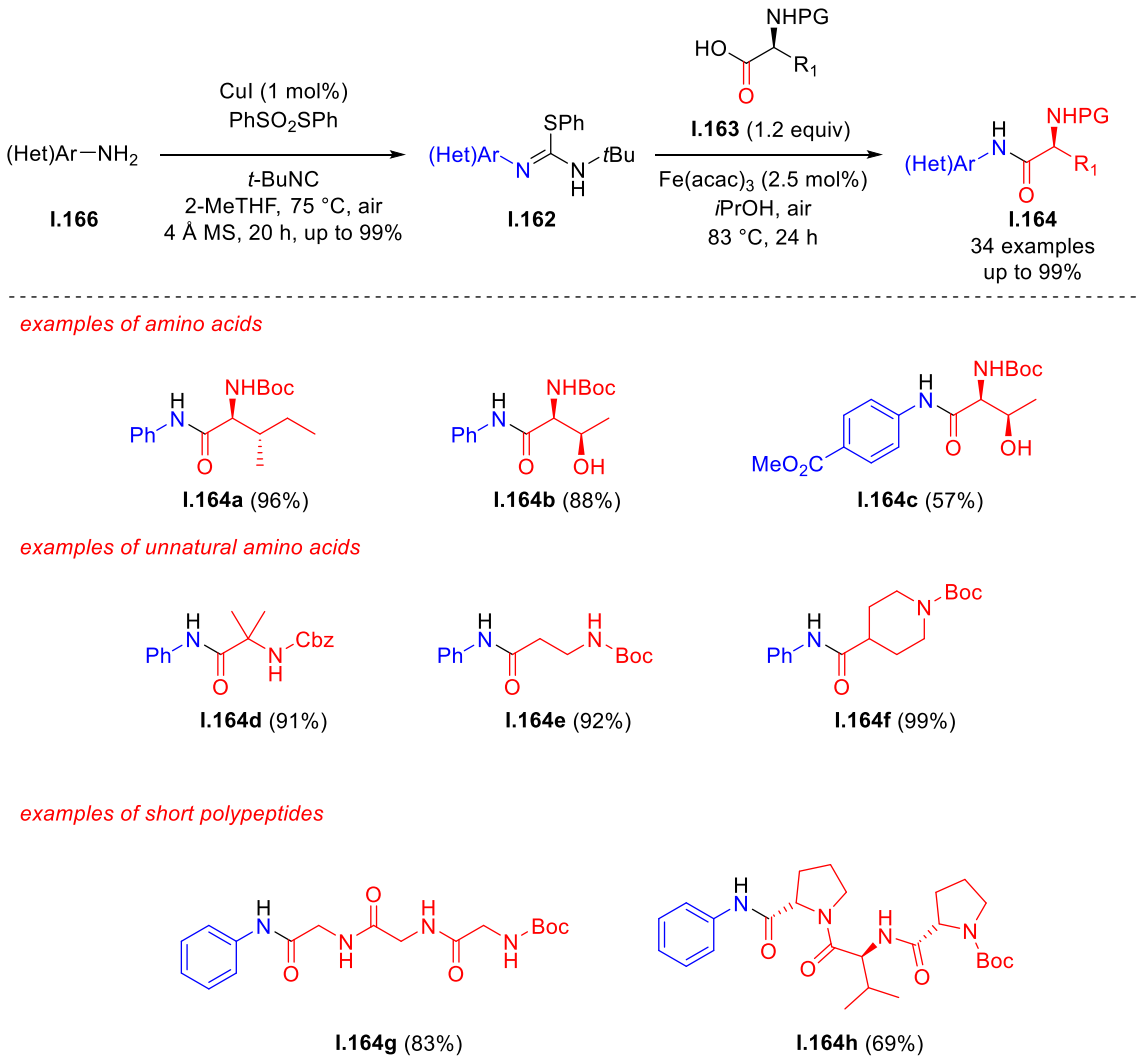
[115] Y.-P. Zhu, P. Mampuys, S. Sergeyev, S. Ballet, B.U.W. Maes *Adv. Synth. Catal.* **2017**, *359*, 2481.

amines suitable for N-(hetero)arylamide synthesis, the strategy was exploited for the synthesis of amino acid containing amides.



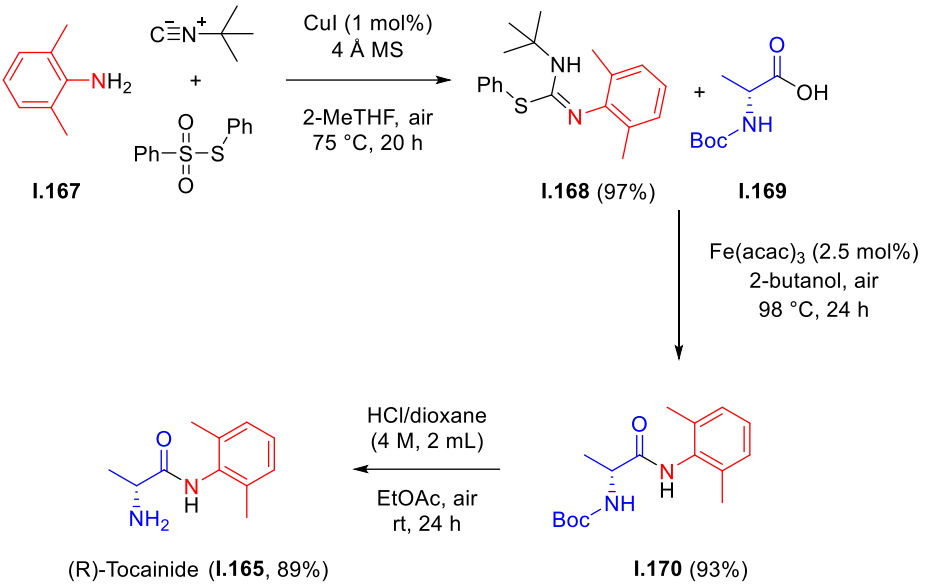
Scheme 50. New activated reagents for coupling reaction.

Reaction of L-amino acids with isothioureas gave the corresponding amides in moderate to excellent yields (57-97%) by using an iron catalyst, isopropanol as solvent at 83 °C for 24 hours (Scheme 51). The reaction proved to be fully compatible with the classical protecting groups at the N-terminus (Boc, Cbz, and Fmoc). Some amino acids containing nucleophilic group on the side chain can be used without requiring any protection (Boc-L-Tyr-OH, Boc-L-Thr-OH). Unnatural amino acids (Boc-β-Ala-OH, Cbz-Aib-OH, and Boc-Inp-OH) were also tested and excellent yields were obtained. Moreover, this is a free-racemisation method.



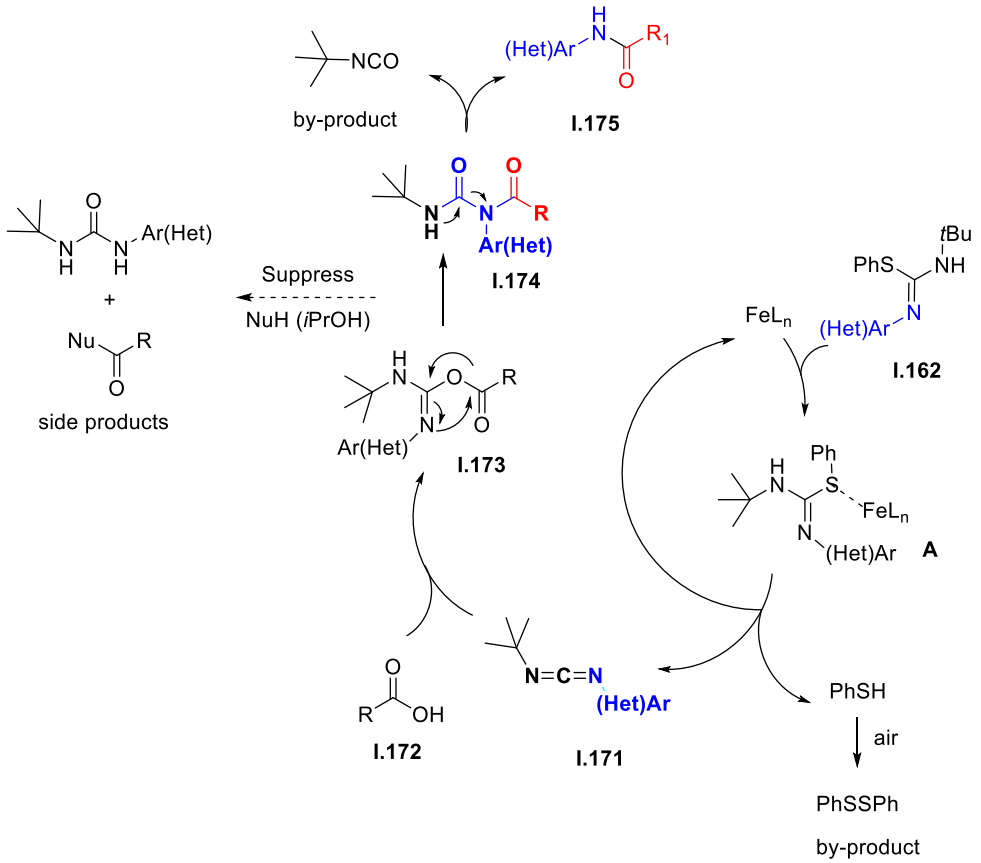
Scheme 51. Amino acids scope.

Eventually, amides were, as well, obtained from short polypeptides in good yield (69-87%). The potential of this methodology was, also, demonstrated through the synthesis of the antiarrythmic drug Tocainide (**I.165**) (Scheme 52). Although, this methodology is limited to the use of aromatic amines.



Scheme 52. Synthesis of (R)-Tocainide.

Insights on the mechanism were given on the basis of many control experiments results. Scheme 53 shows the formation of the isothiurea-Fe complex activating the substrate yielding the carbodiimide intermediate. The reaction of the intermediate with the carboxylic acid affords the *O*-acylisourea which undergoes an O→N acyl migration to form the corresponding urea. Finally, the urea intermediate eliminates isocyanate as by-product giving the formation of the expected amide. Additionally, the O→N acyl migration is consistent with the absence of epimerisation during the reaction.



Scheme 53. Proposed mechanism.

IV. Conclusion

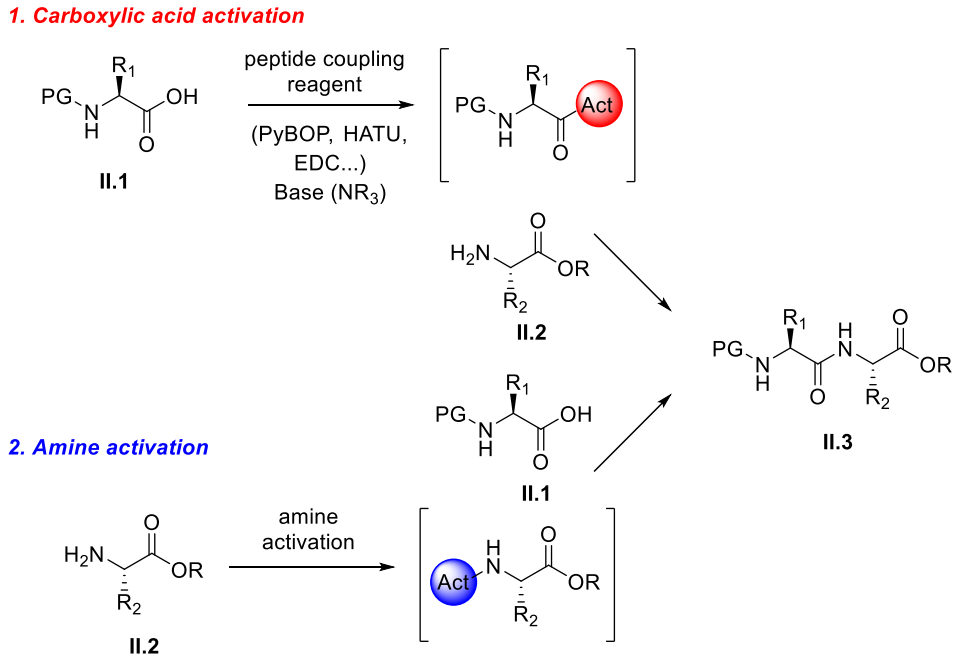
Peptide and amide synthesis are still of primary importance in life sciences, material, polymer and pharmaceutical industry. In the chemical synthesis, a lot of advances have been accomplished. The traditional methodologies to synthesise peptides are, still, broadly employed in the industries although, as previously mentioned, they have some limitations. For this reason, novel non-conventional methodologies (that are not related to COOH activation) have been developed paying attention, when possible, on being greener and more sustainable.

In the next two chapters, we will present the state of art and all recent developments on the methodology proposed by our laboratory based on the inverse activation (activation of the NH_2 function) of AA residues

II. State of art: New Inverse Peptide Synthesis

I.1 Concept of the project

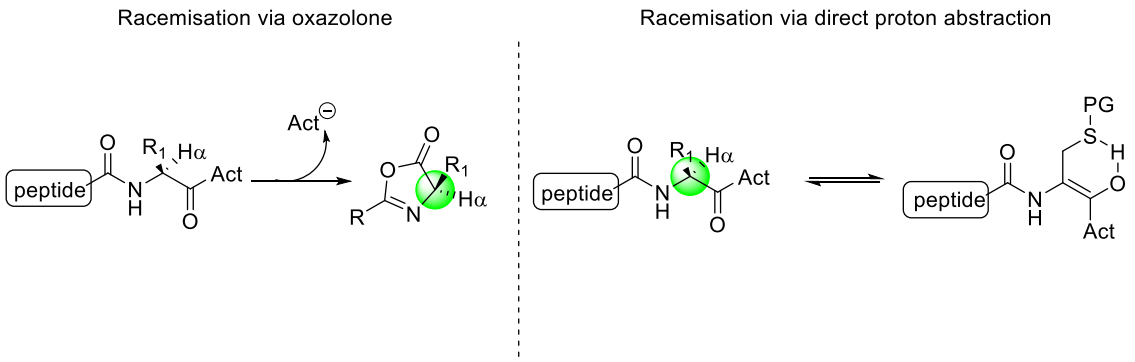
In 2012, we have initiated a program aiming at developing non-traditional strategies towards amide bond formation for application into peptide chemistry (ANR NIPS 2012 – PhD Thesis of Jean-Simon Suppo). Thus, the activation of the amine function was taking into account to generate an activated intermediate, which could react with a carboxylic acid. Indeed, this type of activation might offer for the peptide synthesis a valuable alternative to the traditional activation mimicking, also, the biosynthetic pathway (Schema 54).



Scheme 54. Inverse peptide activation.

I.2 The amine activation

Even though very efficient and widespread used in peptide synthesis, traditional activating agents suffers from several drawbacks related to their modus operandi. One major concern, as already discussed, is the epimerisation during the activation of the carboxylic acid. In fact, especially for some particular amino acids, like Cys, the racemisation occurs either via formation of the oxazolone or through the direct abstraction of the proton in α position (Scheme 55).



Scheme 55. Racemisation mechanisms.

Peptides are naturally synthesised from the N→C direction (Figure 7). However, when the chemical synthesis of a peptide takes place in the N→C direction a mixture of diastereoisomers will be obtained. Indeed, epimerisation proceeds mostly through the formation of the oxazolone (Scheme 55), in which the proton in the α position can be easily abstracted due to the enhanced stability of the corresponding anion through the existence of mesomeric forms. Thus, the chemical synthesis of peptides has been founded on the basis of the classical carboxylic activation, imposing the couplings of *N*-urethane protected amino acids (Boc, Fmoc, Cbz) one by one in the C→N direction in order to minimise racemisation issues. Alternatively, the N→C chemical synthesis might potentially occur when the amine function is activated, avoiding the epimerisation problem. Hence, the synthesis of peptides will be possible mimicking the natural pathway.

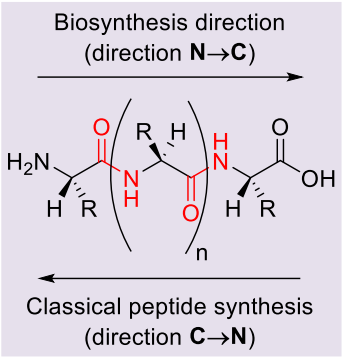
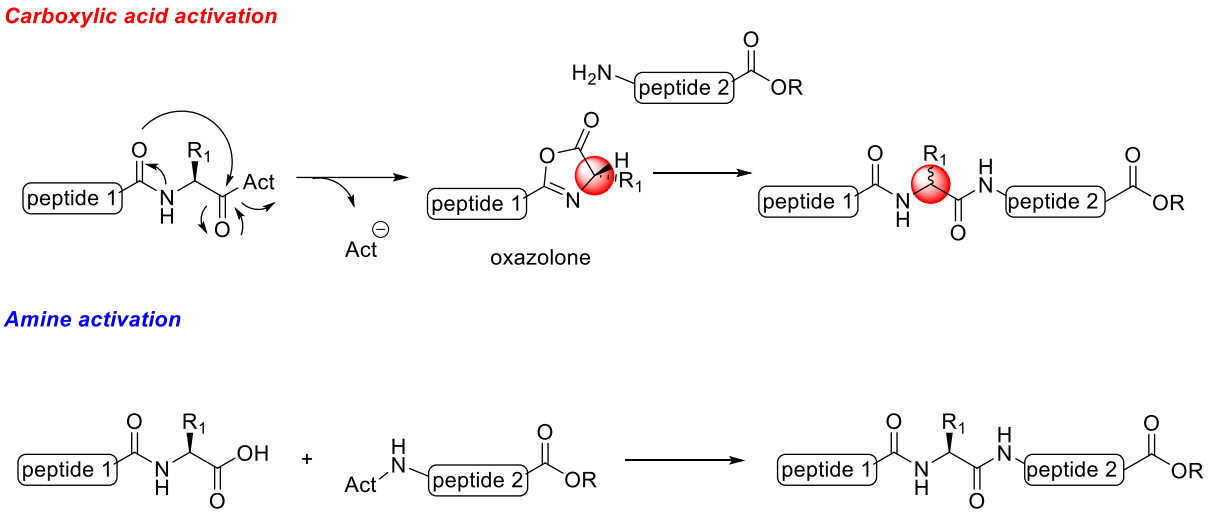


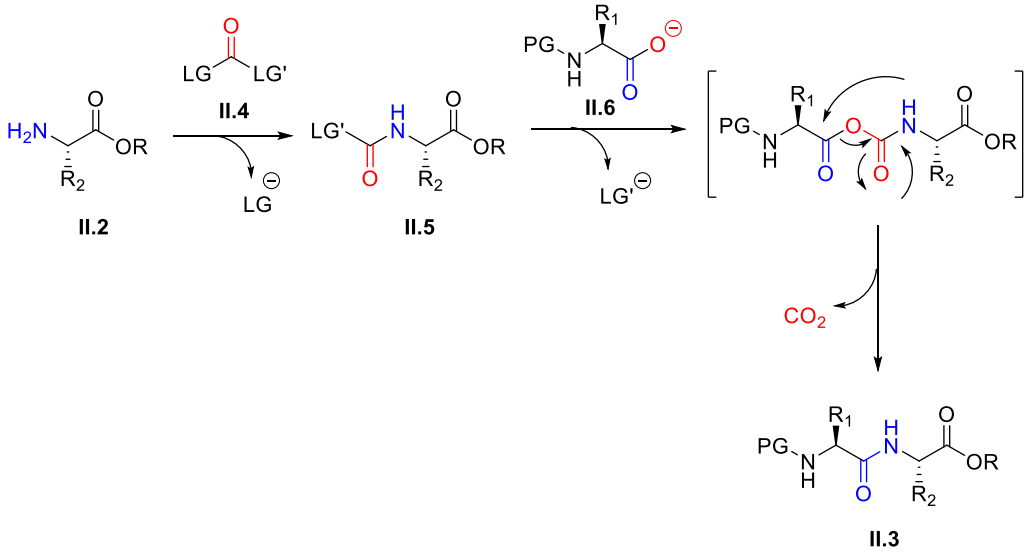
Figure 7. Natural and chemical peptide synthesis.

The racemisation problem does not only affect the peptide synthesis in solution or solid phase, but also the fragment couplings. In this case, the activation of the *C*-terminal extremity of the peptide could promote the formation of a transient oxazolone, favouring epimerisation and thus discouraging classical activation (except for Gly and Pro). By changing the activation mode, the amine activation should thus potentially suppress racemisation in peptide fragment couplings (Scheme 56).



Scheme 56. Racemisation: fragment couplings.

The first step for devising a good methodology based on the amine activation concerns the choice of a convenient and practical activating agent. The reagent should have two leaving groups. It should be able to react with the amine to form the activated intermediate and successively be electrophilic enough to react with the carboxylic acid of a second amino acid. The formation of an unstable carbamic anhydride will lead then to the formation of the amide bond after CO_2 extrusion (Scheme 57).

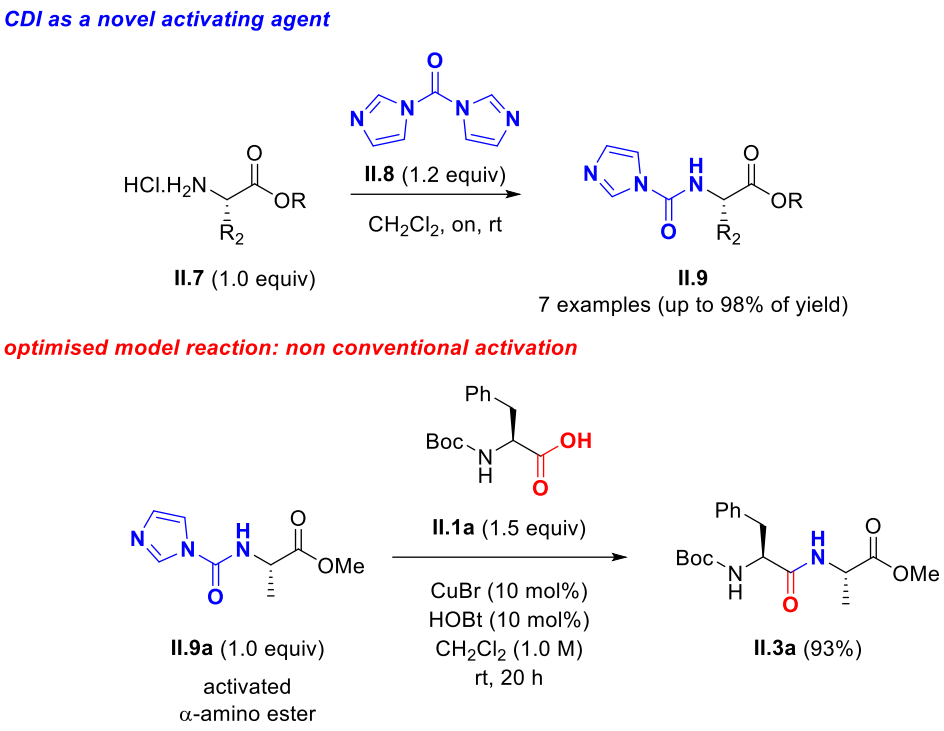


Scheme 57. Strategy for the amine activation.

I.3 New methodology for the peptide synthesis

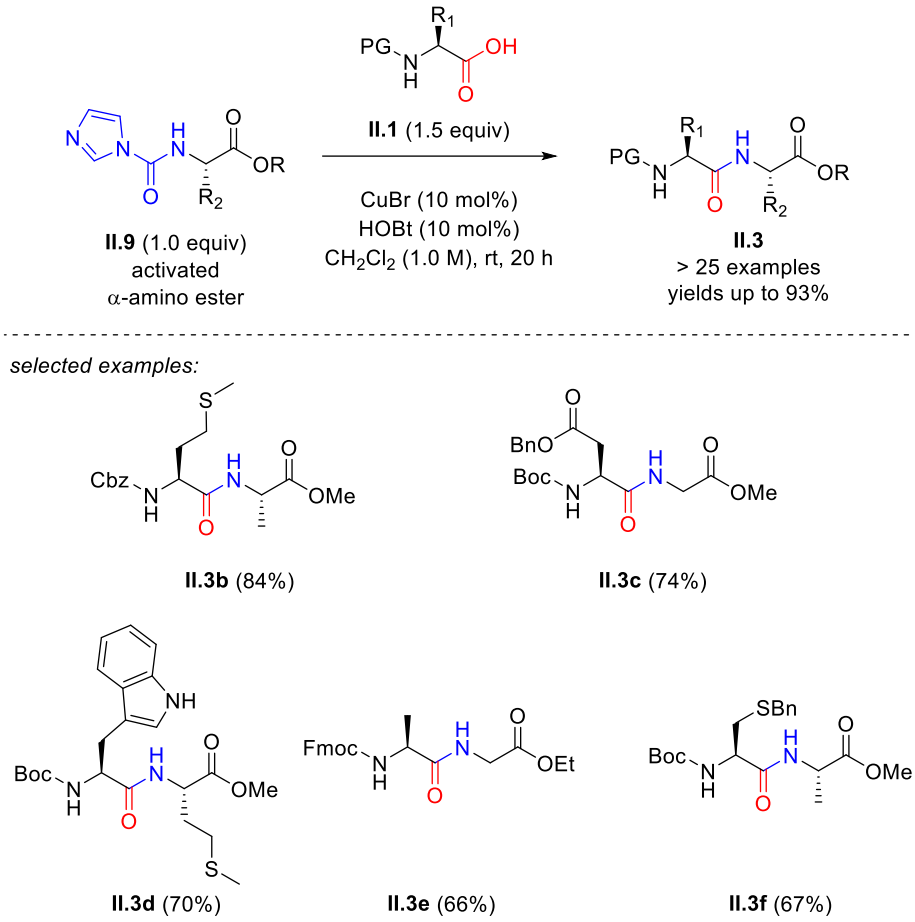
Based on these premises, an original procedure has been developed for the formation of amides (PhD thesis of Jean-Simon Suppo 2012-2015). In 2014, our laboratory published preliminary

results towards the dipeptide synthesis from readily available, bench-stable, activated α-aminoesters under mild conditions.[7] The starting point was to find a suitable activating agent, able to react with the amine function of the amino acids to give the activated amine intermediate. The commercially available *N,N'*-carbonyldiimidazole (CDI, **II.8**), which has been widely exploited as a carboxylic-activating agent, has proved its efficiency and suitability in the non-conventional activation to afford the synthesis of stable and easy-to-handle activated α-aminoesters (**II.9**). Thus, the reactivity of the activated intermediate was studied in a coupling reaction with Boc-Phe-OH (**II.11**) as a model amino acid to validate the inverse activation approach (Scheme 58).



Scheme 58. New route towards peptide synthesis.

Once established that amide-bond formation can take place when activated α-aminoesters are used instead of activated carboxylic acid, the scope of this reaction was conducted to synthesise a range of dipeptides. Under the optimised conditions, above depicted, all reactions proceeded cleanly, and the expected dipeptides were isolated in moderate-to-good yields. Interestingly, the reaction proved to be fully compatible with Boc-, Fmoc- and Cbz-protected amino acids. Slightly lower, but still respectable, yields were observed with Fmoc derivatives, mainly due to their lower solubility under these reaction conditions (Scheme 59).

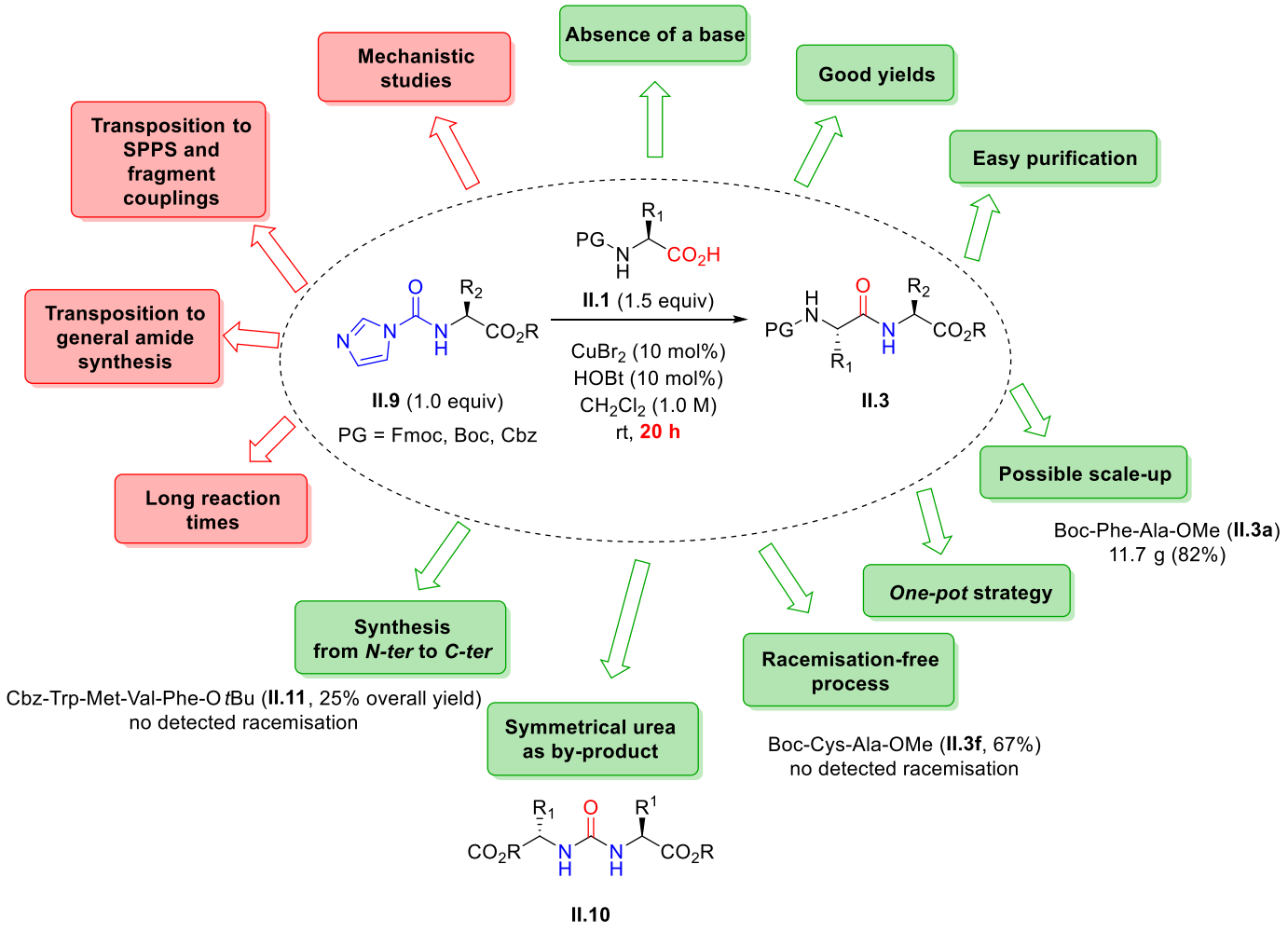


Scheme 59. Selected examples of dipeptides.

Normally, this new methodology does not imply the activation of the carboxylate function, thus, alleviating some side reactions commonly observed with the classical peptide reagents such as racemisation. For example, it is well-known that the activation of cysteine residues may occur with epimerisation as a result of the transient formation of a stabilised enol derivative.[116] Indeed, when Boc-Cys(Bn)-OH was coupled to Imi-Ala-OMe (**II.9a**) the expected dipeptide **II.3f** was obtained in 67% yield with no detectable epimerisation in the crude product.

[116] H. Li, X. Jiang, Y.-H. Ye, C. Fan, T. Romoff, M. Goodman *Org. Lett.* **1999**, *1*, 91.

I.3.1 Advances on the methodology



Scheme 60. From NIPS to NOPS project: advances on the methodology.

Once the methodology was proven to be a free-racemisation process it was interesting to investigate its application on longer peptides (Scheme 60). As a proof of concept, the synthesis of Cbz-Trp-Met-Val-Phe-OtBu tetrapeptide was performed in the N→C direction. As already mentioned, N→C peptide synthesis is not recommended, since the activation of the C-terminal carboxylic acid of an elongating peptide fragment is a source of potential epimerisation through oxazolone formation. To compare, the same tetrapeptide was assembled by PyBOP activation in the same N→C direction. The synthesis proceeded in five linear steps, the reactions were very easy to set up and, conveniently, after each peptide coupling, a classical workup of the crude material, followed by filtration through a short plug of silica gel, was carried out to eliminate excess of reagents and by-products. At the end of the synthesis, yields and HPLC profiles of the crude products were compared for the two methods, carboxylic acid activation with PyBOP and CDI-mediated α-aminoester activation. Purification of the product by

preparative HPLC gave the tetrapeptide target in 35 and 25% overall yield for the PyBOP and CDI strategies, respectively. The HPLC profiles were similar, but, a minor signal (resulting from epimerization) was observed in the PyBOP synthesis, whereas this product was absent in the CDI synthesis. Furthermore, due to the convenience and efficiency of this novel procedure, the possibility to scale up the protocol to afford the multi-grams dipeptide synthesis was investigated. Notably, the syntheses of model activated α-aminoester and dipeptide were accomplished in a 10 grams scale with comparable yields (Scheme 60).[117] The protocol offers several advantages compared to traditional strategies, such as less costly, more atom-economical, the absence of epimerization and the opportunity to realize the peptide couplings through the inverse and challenging N→C direction. Despite all these remarkable advantages, one drawback of this method is the need for a stepwise process with the prior synthesis and purification of the CDI-protected α-aminoesters followed by the coupling reaction with the amino acid bearing the free carboxylic acid function. Therefore, in 2017 our laboratory described an alternative pathway that offers a more practical, economical and straightforward access to dipeptides through a sequential one-pot protocol avoiding the purification of the activated α-aminoesters (Scheme 60).[118]

After establishing the optimized reaction conditions, the coupling of several commercially available amino acid residues in this sequential one-pot transformation was explored. Classical N-urethane (e. g. Fmoc, Cbz and Boc) and O-alkyl (e. g. Me, Et, *t*Bu) protecting groups were compatible with the one-pot process. Moreover, amino acid residues bearing protected functional groups were, also, well tolerated. In all cases, comparable yields for the prior stepwise method and this sequential one-pot procedure were obtained (Figure 8). The main advantage in the latter case was the final purification step with a simple column filtration on a short pad of silica gel after classical work-up. Moreover, avoiding the isolation of the intermediates makes this one-pot procedure much more convenient and less costly.

[117] J.-S. Suppo, R.M. de Figueiredo, J.-M. Campagne *Org. Synth.* **2015**, *92*, 296.

[118] R.M. de Figueiredo, J.-S. Suppo, C. Midrier, J.-M. Campagne *Adv. Synth. Catal.* **2017**, *359*, 1963.

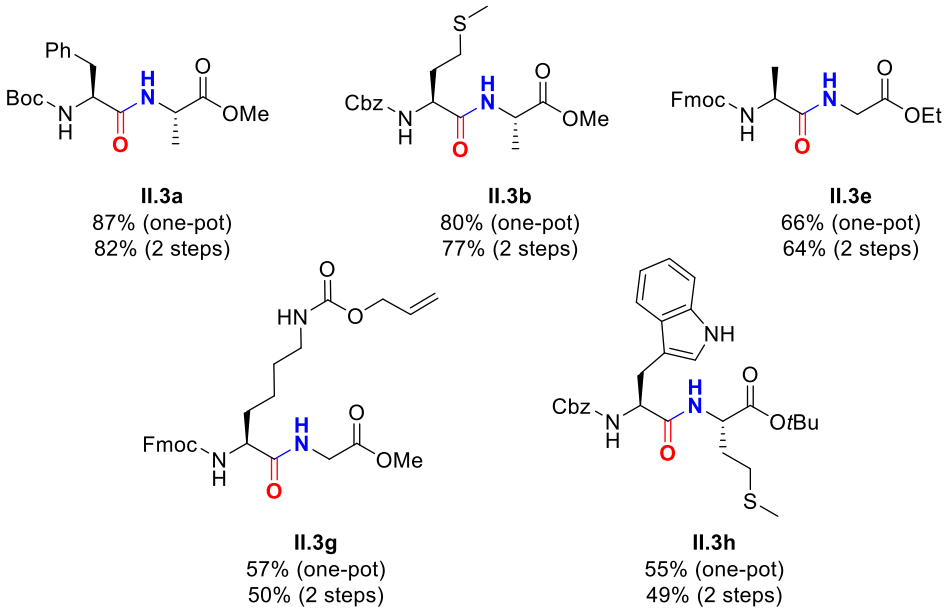


Figure 8. Selected examples of the sequential *one-pot* strategy.

II. From NIPS to New Opportunities for Peptide Synthesis (NOPS)

The project New Opportunities for Peptide Synthesis (NOPS) relies on this solid proof-of-concept and willing to explore and improve this new mode of activation. There are three main objectives which will be tackled in the NOPS project:

1. The improvement of the reaction efficiency, widening the scope and allowing the transposition to:
2. Fragment couplings and cyclizations
3. Inverse N→C solid phase peptide synthesis

In this context, in our laboratory, during my PhD work, our aim was to widely study how to improve the efficiency of the peptide coupling and to broaden the scope of the methodology as well, and to do so we examine different aspects of the reaction:

a) improve the reaction conditions analysing different parameters such as:
   - activating reagent
   - solvent
   - additives
   - time of the reaction

b) extend the method to the synthesis of general amides (no AA substrates)

c) improve the reaction kinetics (< 20 h)

d) elucidate the reaction mechanism

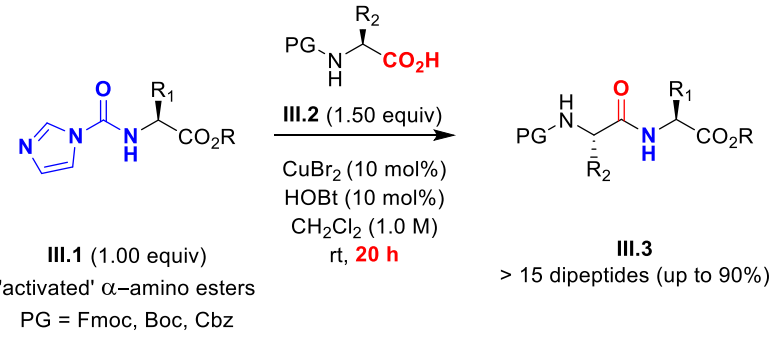
- NMR studies

A financial support allocated by the ANR (ANR PRC – Project NOPS – 2018-2022) gave us the opportunity to explore more in depth the possibilities to apply the methodology devised into peptide chemistry itself. In particular, a partnership was established with the groups of Dr. Vincent Aucagne (CBM-Orléans, expert for the development of innovative strategies dedicated to the simplification of the synthesis of "difficult" or long peptides and small proteins, through fragment-based solid-phase assembly of unprotected peptides) and Pr. Gilles Subra (IBMM-Montpellier, expert for peptide chemistry and solid phase synthesis).

In the next chapter we will discuss all the results obtained during my PhD thesis concerning the study in depth of the peptide coupling.

III. New Opportunities for Peptide Synthesis: Results and Discussion

During the NIPS project, an original procedure had been established for the synthesis of amides. As already mentioned, the novelty lies on the "inverse activation" (activation of the amine function of an amino acid instead of the carboxylic acid moiety) allowing the solution phase synthesis of several dipeptides. The reaction took place under very mild conditions, (in the absence of a base!) and moderate to good yields were obtained. Easy purifications were allowed, synthesis on multi-grams was possible and, above all it is a free-racemisation process, compatible with common N-urethane protecting groups. Up-to-date, the best conditions for the peptide coupling are depicted in the Scheme 61.



Scheme 61. State of art of the peptide coupling.

If these conditions work quite fine to afford several dipeptides, it might be mentioned that the reaction kinetic is still considerably slow (20 hours are necessary to reach yields > 80%). Consequently, one of the main objectives during my PhD studies was to improve the reaction efficiency in terms of kinetic (reducing the time of the reaction). A shorter reaction time would be desirable in order to envisage an application in solid phase peptide synthesis and fragment coupling (partnership with Pr. Gilles Subra and Dr. Vincent Aucagne, respectively). Therefore, we started to investigate in depth all the parameters of the reaction (Figure 9).

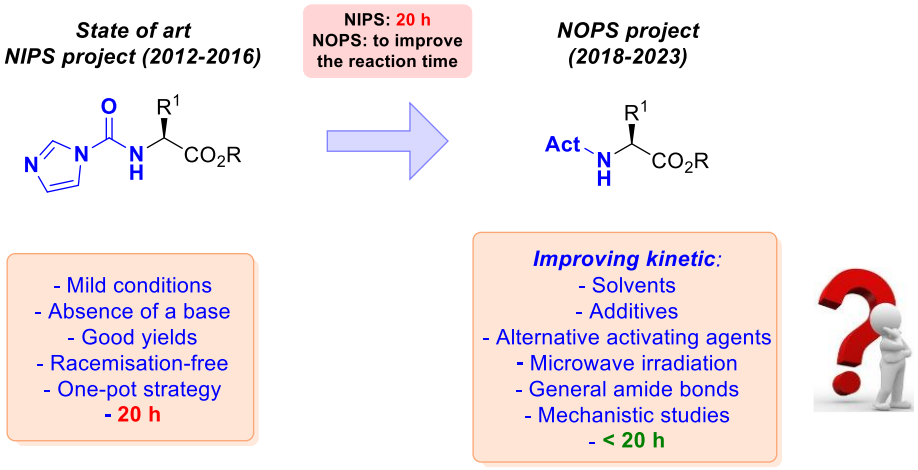


Figure 9. Main objectives in this PhD thesis.

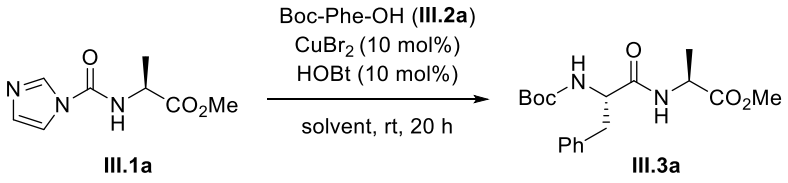
I.1 Optimisation of the methodology CDI-activated α-aminoesters

I.1.1 Solvent screening

We decided to investigate the solvent as first parameter. So far, the solvent for the coupling was dichloromethane, giving the best results in terms of yields. A broad set of solvents was tested in order to have an improvement in terms of reaction time (< 20 h) conserving similar yields (90% yield for the Boc-Phe-Ala-OMe model dipeptide). Other solvents, more apt to be exploited in peptide chemistry, such as NMP or DMF, were also considered in this study.

The reactions were performed in the same classical conditions (i.e. $CuBr_2$/HOBt 10 mol% each, room temperature, 20 hours and *C* 1.0 M), each time changing only the solvent. Results are shown in Table 1.

Table 1. Screening of solvents.



Solvent	Yield (%)
DCM	90
H_2O	<5
H_2O/CH_3CN 1:1	27
CH_3CN	76
NMP	5
HFP	<5
HFIP/DCM 1:1	7
TFE/DCM 1:1	16

TFE	8
DMF	16
CH_3NO_2	69
MTBE	47
(2 wt%)TPGS-750-M/H_2O	NR

NMP = N-methyl-2-pyrrolidone, HFP = hexafluoroisopropanol, MTBE = methyl *tert*-butyl ether, TPGS = DL-α-Tocopherol methoxypolyethylene glycol succinate solution, NR = no reaction.

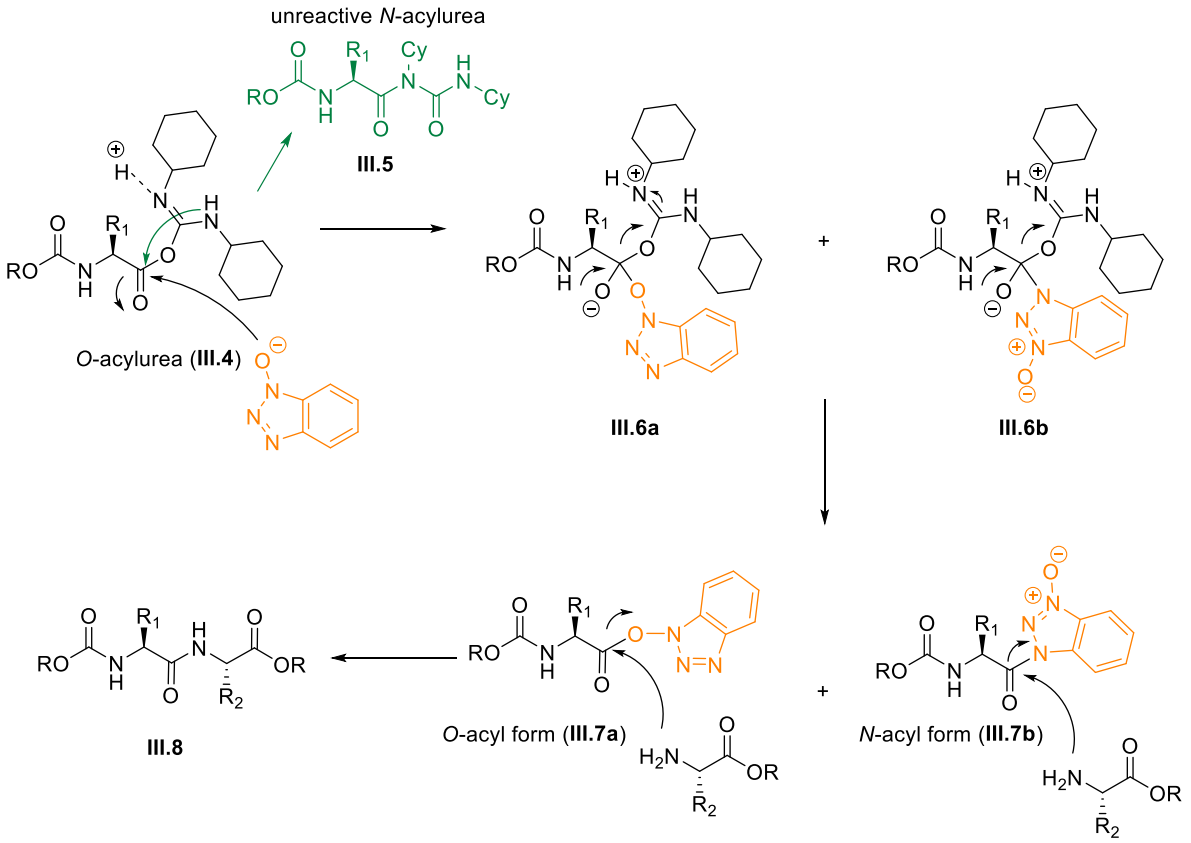
The use of different solvents or mixture of solvents on the previously devised conditions (in 20 h) did not lead to comparable yields (90% in dichloromethane). However, nitromethane and acetonitrile gave the product in good yields, respectively 69% and 76%. Based on these observations, we decided to go further in the optimization studies keeping dichloromethane as the solvent of choice for our couplings.

I.1.2 Additives optimization

The use of certain additives is well-known in the peptide synthesis. For example, to reduce the epimerisation level, when using carbodiimides (DCC, EDC etc…) as coupling reagents for the classical activation, Koenig and Geiger[119] introduced the 1-hydroxy-1*H*-benzotriazole (HOBt) as an additive showing that yields were higher and epimerisation levels lower. For example, when coupling Z-Gly-Phe-OH to H-Val-OMe, the epimerisation levels dropped from 35% to 1.5%. HOBt is believed to work by initially reacting with the O-acylurea to give the active ester (**III.7a**), which increase the reactivity of the "activated intermediate" (Scheme 62).[120]

[119] a) W. Koenig, R. Geiger *Chem. Ber.* **1970**, *103*, 788; b) W. Koenig, R. Geiger *Chem. Ber.* **1970**, *103*, 2024.

[120] a) E. Valeur, M. Bradley *Chem. Soc. Rev.* **2009**, *38*, 606; b) J. Coste, J.-M. Campagne *Tetrahedron Lett.* **1995**, *36*, 4253.



Scheme 62. Mechanism of action of HOBt as additive.

Moreover, several groups reported that copper(II) salts in peptide synthesis, both in solution and in solid phase,[121] are more effective in suppressing racemization than the compounds currently used for this purpose (like HOBt). In 2014, our laboratory published the combination of $CuBr_2$ and HOBt as additives on dipeptide synthesis, giving the best result in terms of yield with no detected racemisation. Nevertheless, the reaction time was set at 20 hours, still considered too long for a coupling reaction. Thus, to improve reaction kinetic we decided to evaluate other additives carrying out the experiments at 8 hours instead of 20 hours.

First, we were looking for a rapid qualitative response just to trace ideally the trend of the reaction, to have an insight on the behavior of the coupling. In our hands, we had the opportunity to observe the evolution of the experiments through the reverse phase HPLC, by sampling periodically. The sampling was effectuated each 2 hours during 8 hours of reaction. We performed 4 reactions; in each case we used different additives:

[121] a) T. Miyazawa, T. Otohlatsu, Y. Fukui, T. Yamada, S. Kuwata *Int. J. Peptide Protein Res.* **1992**, *39*, 237; b) W. Van den Nest, S. Yuval, F. Albericio *J. Pept. Sci.* **2001**, *7*, 115.

i) $CuBr_2$/HOBt (10 mol% each)

ii) PTSA/HOBt (10 mol% each)

iii) $CuBr_2$ (10 mol%)

iv) no additives

The trials were conducted in the presence of an internal standard (Boc-Phe-Val-OMe), which had a similar UV profile of the expected product Boc-Phe-Ala-OMe (**III.3a**). Thanks to the internal standard, we could estimate the conversion of the reaction and outline a qualitative tendency (Figure 10). For the 4 conditions monitored, and in 8 hours of couplings, we observed the formation of the product at a slow rate.

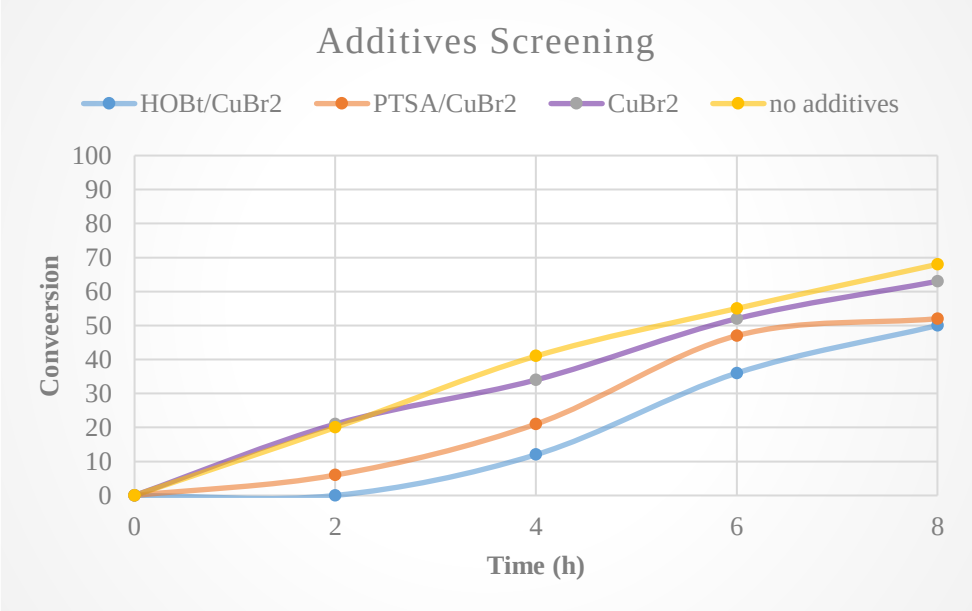


Figure 10. Additives screening followed by HPLC during 8 h of couplings.

Interesting to mention, a late sampling of reactions run in conditions i) $CuBr_2$/HOBt (10 mol% each) and iv) absence of additives at 24 h showed incomplete conversion (see in more detail in Chapter 3, Section III for the mechanistic aspects). However, we could outline some indications:

a) there was still the presence of the limiting reactant (Imi-Ala-OMe, **III.1a**)

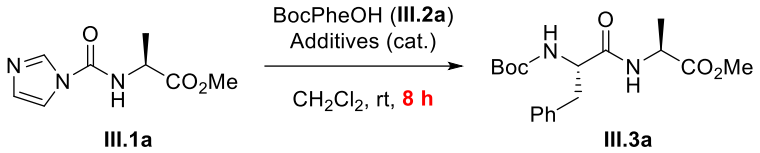
b) the complete conversion into the product was not achieved

c) no steep acceleration was observed after 8 h of reaction

d) a plateau was reached in the trend.

Afterwards, we considered to evaluate more precisely a set of additives and isolate the model dipeptide each time after 8 hours (work-up and purification by column chromatography for each reaction). Table 2 displays the results obtained.

*Table 2. Additive screening in a **8 hours** raction.*



Entry	Additives	Mol%	Yield (%)
1	**HOBt/$CuBr_2$**	10/10	62
2	–	–	56
3	**PTSA/$CuBr_2$**	10/10	60
4	**$CuBr_2$**	10	68
5	**HBr (48%)**	10	48
6	**CuCN**	10	67
7	**HOBt/$Mg(ClO_4)_2$**	10/10	70
8	**$Mg(ClO_4)_2$**	20	62
9	**$BF_3.OEt_2$**	10	64
10	**$BF_3.OEt_2$**	20	63
11	**$BF_3.OEt_2$**	50	67
12	**$BF_3.OEt_2$**	100	29
13	**Imidazole/$BF_3.OEt_2$**	10/50	69
14	**PTSA/$BF_3.OEt_2$**	10/10	64
15	**Phenylboronic acid**	20	49
16	**Phenylboronic acid**	50	71
17	**Phenylboronic acid**	100	75
18	**Phenylboronic acid**	150	78
19	***p*-Tolylboronic acid**	100	41
20	**4-Bromophenylboronic acid**	100	82

Experiment displayed in entry 1 was run using our devised conditions [$CuBr_2$/HOBt (10 mol% each)] in a reduced reaction time of 8 h. In this case, we obtained the target dipeptide (**III.3a**) in a reduced 62% yield (compared to 90% after 20 hours). We set this reaction as benchmark and then selected a set of novel additives to be tested. In entry 2, we evaluated the coupling reaction in the absence of additives and the product was obtained in 56% (63% in 20 hours). Then, HOBt was replaced by another Brønsted acid, the *p*-toluensulfonic acid, in the presence of the $CuBr_2$ (entry 3). The yield was comparable (entries 1-3). Interestingly, by using only $CuBr_2$ as additive, a slightly improved yield of 68% was observed (entry 4). We also studied the influence of a more acidic additive by using HBr (48 wt.% in H_2O) (entry 5). In this case, the yield decreased down to 48%. Moving from a Cu(II) to a Cu(I) salt, by using CuCN (10 mol%) without adding Brønsted acids, a yield of 67% was obtained (entry 6). This result is

comparable with the ones from entries 1-4. Amongst Lewis acids, magnesium perchlorate had emerged as an efficient catalyst in various organic transformations[122] thank to its high catalytic efficiency and availability, thus we tested its activity in the presence of a Brønsted acid (entry 7) and in the absence (entry 8). The results were comparable to the ones obtained with copper-based Lewis acids (entries 1, 2, 4 and 6). Afterwards, we evaluated the influence of boron-type Lewis acids. Boron reagents have a strong electrophilic nature granted by a vacant p-orbital into which electrons can be received.[123] Many neutral boranes have been synthesised and employed, such as trialkyl-, triaryl- and trihalo-boranes.[124] First, we performed some couplings with BF_3•OEt_2 as Lewis acid varying each time the molar percentage (entries 9-12). If from 10 to 50 mol% we were able to observe similar yields (respectively 64%, 63% and 67%), when a stoichiometric quantity was used the yield decreased to 29% yield and the starting material was not recovered, suggesting a possible degradation during the course of the reaction. By merging BF_3•OEt_2 with either imidazole or PTSA, no synergistic effect was observed and similar yields to the ones obtained when BF_3•OEt_2 was used alone were obtained (entries 13 and 14). Organoboron-type Lewis acids are effective to mediate amide bond formation. They have been used in stoichiometric amounts since 1965,[125] and some catalytic transformation have appeared since 1996.[126] Thus, we decided to investigate a few amongst many arylboronic acid into our peptide coupling. We started testing the phenylboronic acid (entries 15-18). The results were quite different from the ones obtained with BF_3•OEt_2. In fact, the best yields were attained when a stoichiometric amount or an excess was employed (75% and 78% respectively; entries 17 and 18). Substituted phenylboronic acids in the para position with an electron-donating and electron-withdrawing group were also tested (entries 19 and 20). Interestingly, when we used a stoichiometric amount of the 4-bromophenylboronic acid, we obtained the dipeptide in a good 82% yield (entry 20). A counter-proof reaction was performed demonstrating that even though a stoichiometric amount was required the amine function needed to be activated by CDI (Scheme 63). However, we did not explore more in depth its reactivity due to the stoichiometric

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[122] a) G. Bartoli, M. Bosco, R. Dalpozzo, E. Marcantoni, M. Massaccesi, S. Rinaldi, L. Sambri *Synlett* **2002**, *1*, 39; b) J. Wu, W. Sun, H.-G. Xiaa, X. Sun *Org. Biomol. Chem.* **2006**, *4*, 1663.

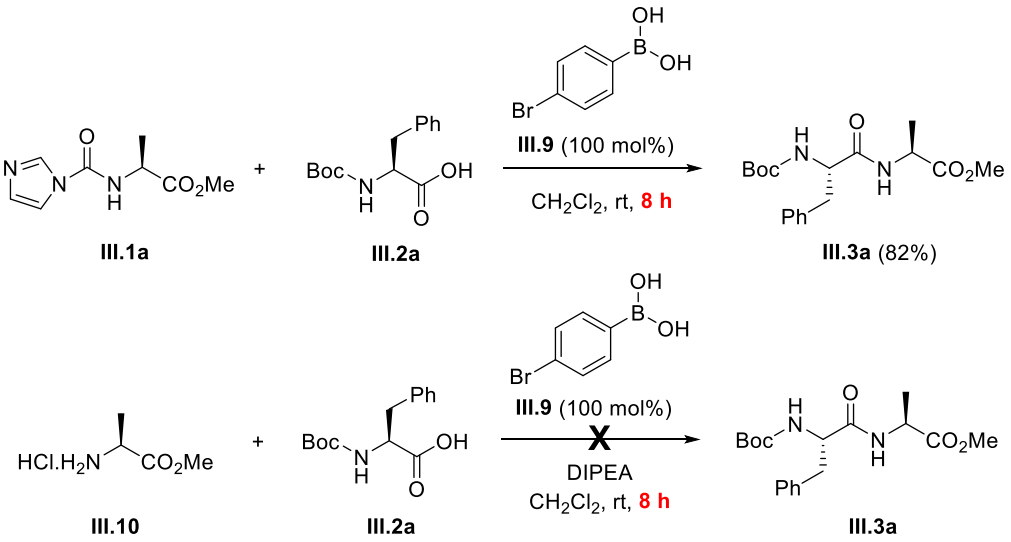
[123] J.R. Lawson, R.L. Melen *Organom. Chem.* **2017**, *41*, 1.

[124] E. Dimitrijević, M.S. Taylor *ACS Catal.* **2013**, *3*, 945.

[125] P. Nelson, A. Pelter *J. Chem. Soc.* **1965**, 5142.

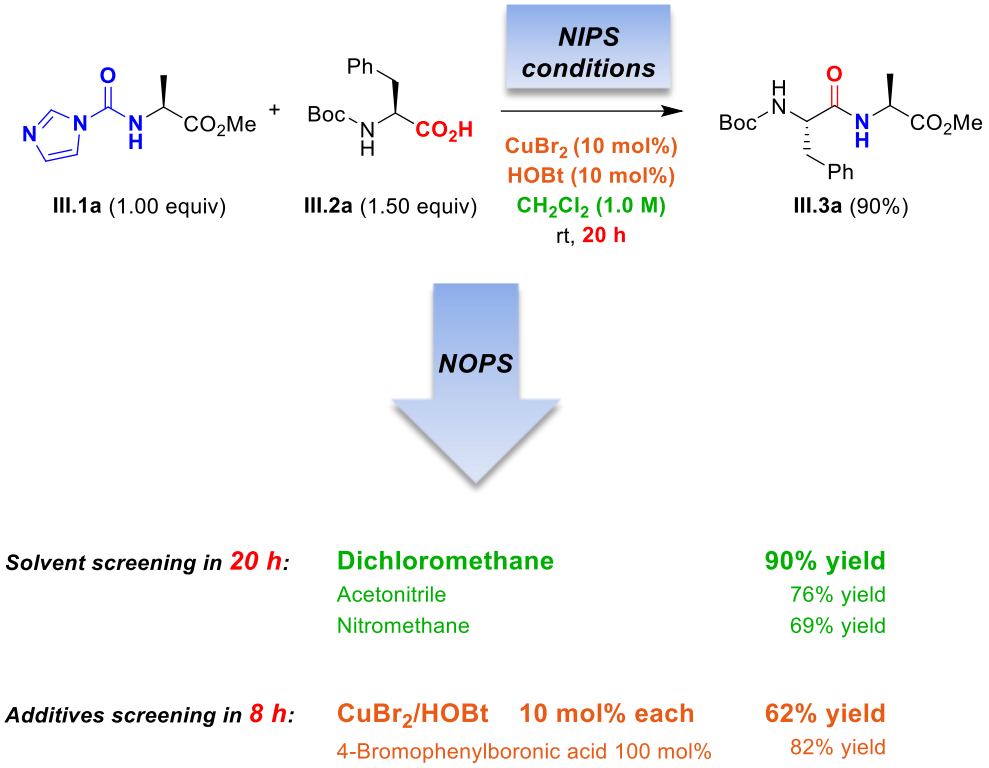
[126] a) K. Ishihara, S. Ohara, H. Yamamoto *J. Org. Chem.* **1996**, *61*, 4196; b) T.M. El Dine, W. Erb, Y. Berhault, J. Rouden, J. Blanchet *J. Org. Chem.* **2015**, *80*, 4532; c) T.M.E. Dine, D. Evans, J. Rouden, J. Blanchet *Chem. Eur. J.* **2016**, *22*, 5894.

amount demanded. Indeed, it was not considered more advantageous than our catalytic amount of additives in terms of both yield and cost.



Scheme 63. 4-Bromophenylboronic acid as additive.

From the screening of different solvents in 20 hours of reaction, we have observed that dichloromethane was still the best one as none of the other solvents tested was able to afford the expected dipeptide in comparable yield (> 80%). However, nitromethane and acetonitrile are both good alternative solvents for our couplings. Besides, concerning the additives or combination of additives tested, the reactions were performed in 8 hours instead of 20 hours. In most cases we were able to achieve good yields, acidic and/or basic additives being able to promote the couplings. Overall, almost all tested additives were able to give the dipeptide in an isolated yield superior than 60% after 8 h of reaction. If it can be seen as a positive point, it might be mentioned that these observations make difficult the reaction understanding and, consequently, the design or choice for further additives. However, we could isolate the desired dipeptide in a very good 82% yield (after 8 h of reaction) when a stoichiometric amount of 4-bromophenyl boronic acid was used. Even though the objective of reducing the reaction time of our couplings was reached (8 h vs 20 h), we choose to go ahead with our optimisation studies using the prior $CuBr_2$/HOBt combination seeking to attain better results (Scheme 64).

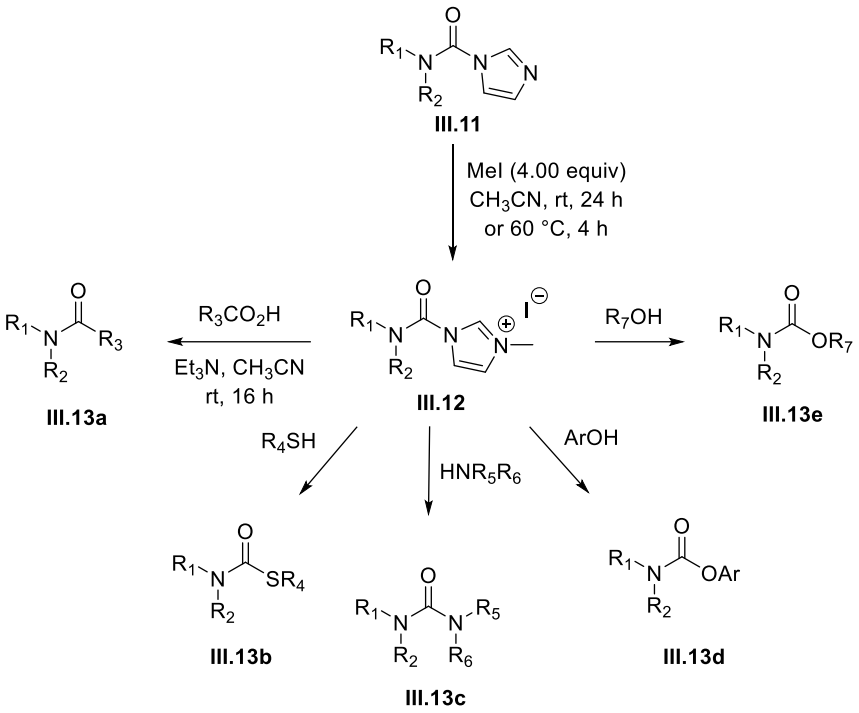


Scheme 64. Results after solvent and additives screenings.

I.1.3 Iodomethane: activation of the imidazole ring

Another idea to improve the coupling efficiency by decreasing the reaction time was to evaluate the possibility to render the imidazole ring on the Imi-AA-OR (**III.1**) partners a better leaving group. So far, Batey et al. reported studies exploiting iodomethane as an activating agent for the imidazole ring in the synthesis of ureas, thioureas, carbamates, thiocarbamates and amides (Scheme 65).[127] The cationic carbamoyl imidazolium intermediate was synthesised using a large excess of iodomethane (MeI; 4.00 equivalents) in 24 hours. In addition, the activation was possible only in the presence of secondary amines. For instance, when carboxylic acids were used the scope was limited to the formation of tertiary amides and no examples on peptide bond construction were reported.

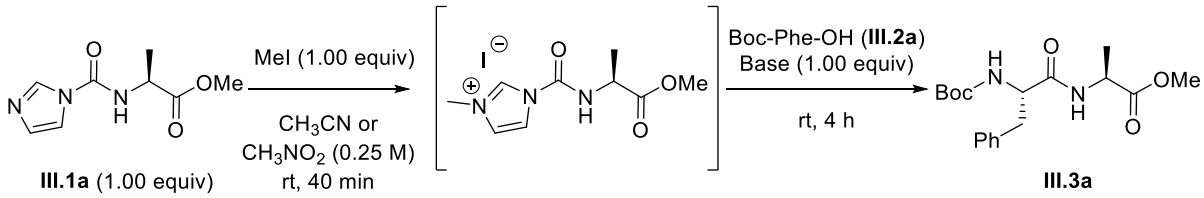
[127] R.A. Batey, V. Santhakumar, C. Yoshina-Ishii, S.D. Taylor *Tetrahedron Lett.* **1998**, *39*, 6267; b) R.A. Batey, C. Yoshina-Ishii, S.D. Taylor, V. Santhakumar *Tetrahedron Lett.* **1999**, *40*, 2669; c) J.A. Grzyb, R.A. Batey *Tetrahedron Lett.* **2003**, *44*, 7485; d) J. A. Grzyb, M. Shena, C. Yoshina-Ishii, W.Chi, R.S. Brown, R.A. Batey *Tetrahedron* **2005**, *61*, 7153.



Scheme 65. Carbamoyl imidazolium salts for the synthesis of carbamates, amides, ureas, esters and thiocarbamates reported by Batey.

Inspired by these results, we decided to explore the reactivity of carbamoyl imidazolium salts on our model reaction. If Batey's group used a large amount of (MeI) for preparing the imidazolium salts, our initial idea was to add to the model substrate (Imi-Ala-OMe) only 1.00 equivalent of MeI due to its high toxicity. After 40 minutes of 'activation' of substrate **III.1a** with MeI, the second amino acid (**III.2a**) was added, either in the presence or absence of a base, to allow the formation of the dipeptide as reported in Table 3.

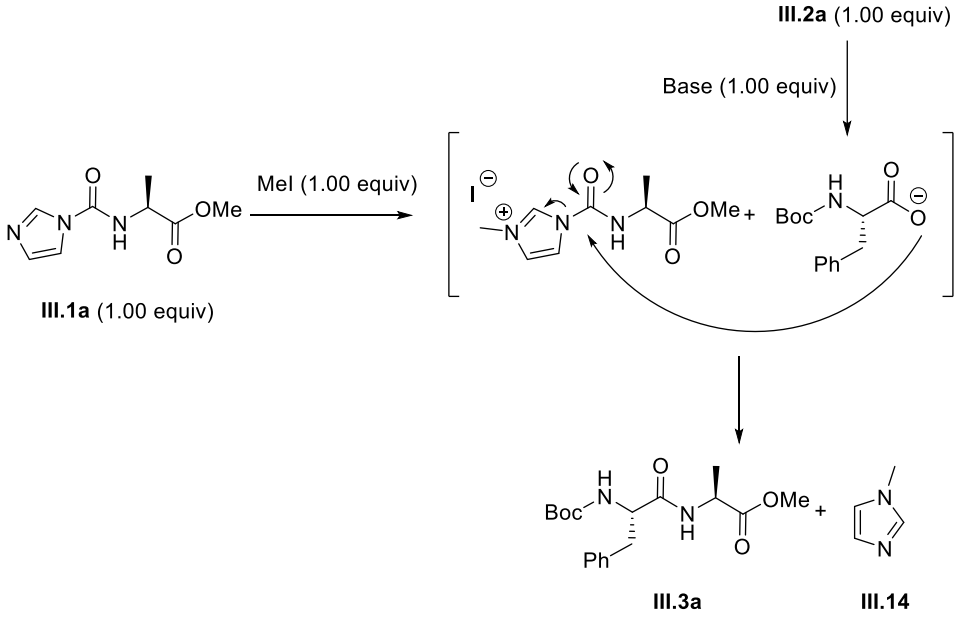
Table 3. Optimisation of the reaction with MeI.



Entry	Boc-Phe-OH	Base	Yield (%)
1	**1.00 equiv**	Et_3N	40
2	**1.00 equiv**	DIPEA	40
3	**1.00 equiv**	–	93
4	**1.30 equiv**	–	91

In the presence of a base (to form the carboxylate anion), the product was obtained in a disappointing 40% yield after 4 hours (entries 1 and 2). Interestingly, and quite surprisingly,

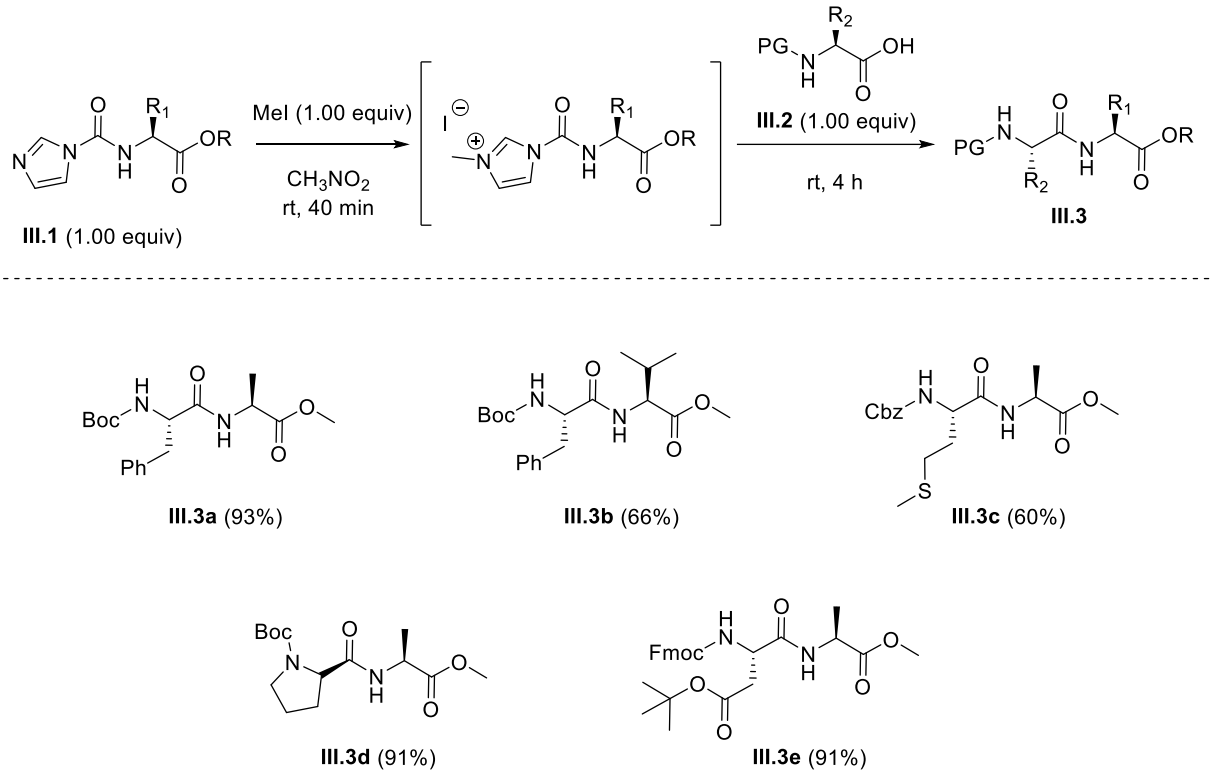
the dipeptide was isolated in excellent yields without adding a base (entries 3 and 4). Indeed, accordingly to our hypothesis, if one equivalent of imidazolium salt is formed by addition of one equivalent of MeI into Imi-AA-OR, the addition of the second amino acid partner (Boc-Phe-OH) might be done in the presence of a base to insure the carboxylate formation and, consequently, the nucleophilic displacement of the imidazolium salt (Scheme 66, for mechanistic aspects see Chapter 3, Section III).



Scheme 66. Supposed mechanism in the presence of MeI.

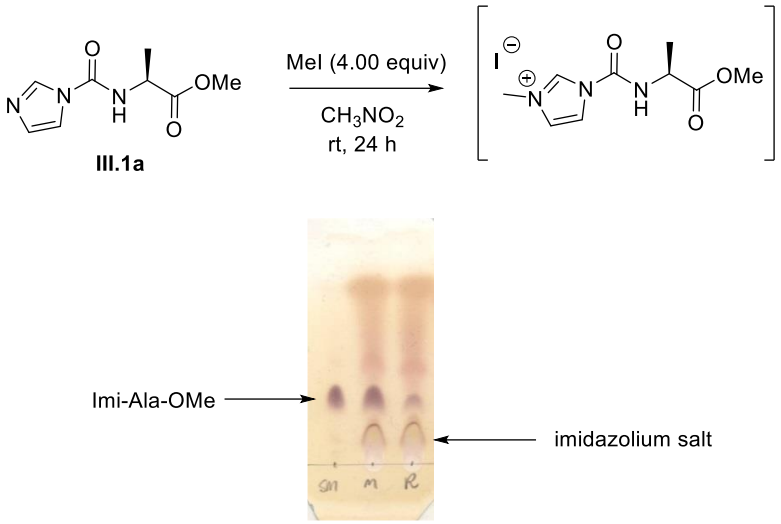
Even though not yet completely understood, this result was quite promising. In fact, without the addition of a base, in only 4 hours, the reaction was complete giving the dipeptide in an excellent isolated yield of 93%. A short reaction time and especially the absence of a base are advantageous in terms of atom economy and racemisation issues.

With the optimised conditions in hands, we were able to study the scope of the reaction. A few dipeptides were synthesised in moderate to good yields (Scheme 67). For the Fmoc protected dipeptide the yield was slightly lower (44%) but it is probably due to the scarce solubility of the Fmoc protected amino acid in the reaction medium.



Scheme 67. Scope of the reaction.

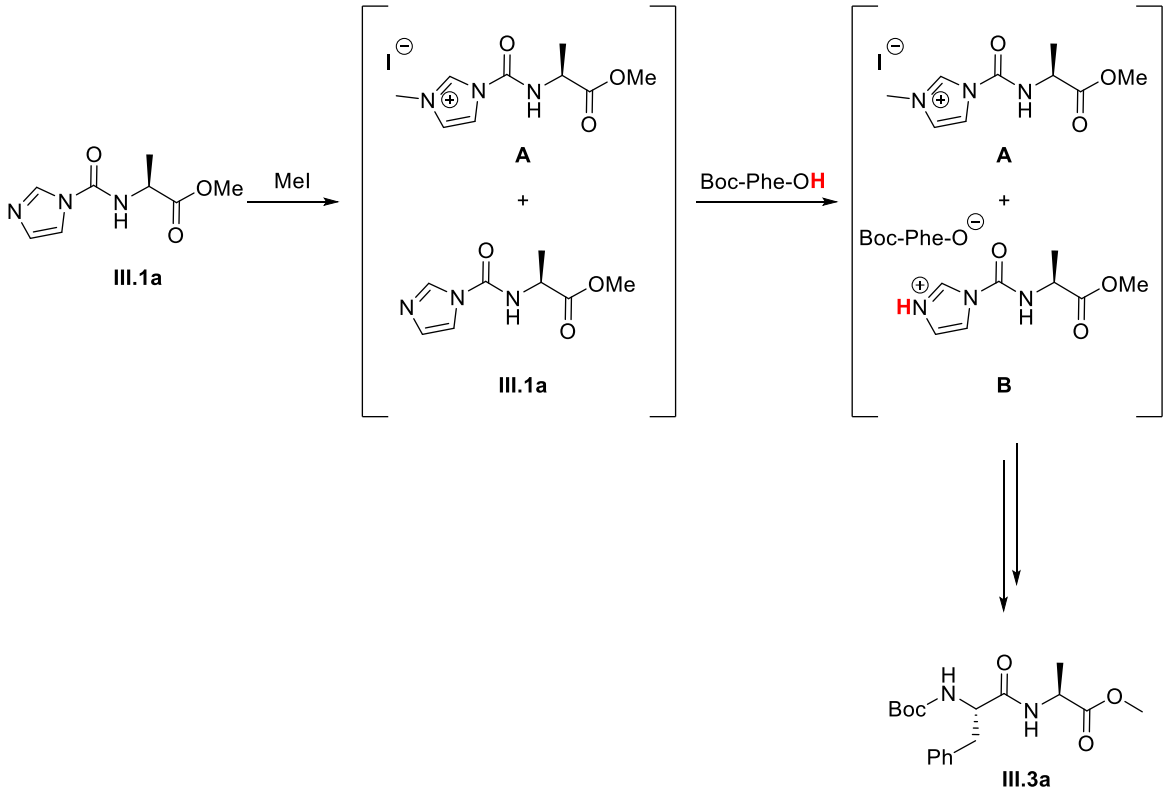
The results were quite encouraging, but better yields in the absence of a base were quite puzzling (see Table 3). Indeed, if the imidazolium (see Sceme 66) is completely formed, some base should be needed to generate the nucleophilic carboxylate partner and insure the amide formation. We thus decided to monitor the formation of the imidazolium intermediate. Under Batey's conditions, in the presence of an excess of MeI (4.00 equiv), the conversion to the N-Me imidazolium was not complete after 24 hours at rt, as one can judge by TLC monitoring (Scheme 68).



Scheme 68. TLC monitoring of the reaction with MeI for the imidazole to imidazolium transformation.

We could thus obtain evidence that the Imi-Ala-OMe was not completely transformed in the corresponding imidazolium salt when a large excess of iodomethane was employed. This observation corroborated our results showed in Table 3, in which only one equivalent of MeI was used, and also our hypothesis on the intermediates reactivity (Scheme 66). Indeed, in the best reaction conditions devised by using MeI (Table 3, entry 3), the complete conversion of imidazole into imidazolium salt was certainly unattained, justifying probably why there was no need for an additional base. In this case, the remaining imidazole could act as a base and deprotonate the carboxylic acid function.

In other words, we could suggest that MeI had the function to activate partially the substrate to give the intermediate **A**, bearing a better leaving group. The remaining Imi-Ala-OMe which was not transformed into the imidazolium salt could have had a different role. In fact, the imidazole ring of Imi-Ala-OMe (**III.1a**) could have also reacted as a base to deprotonate the carboxylic acid affording both the carboxylate anion and imidazolium salt (**B**) (Scheme 69). These mechanistic aspects will be also discussed more in depth in Chapter III, Section III.

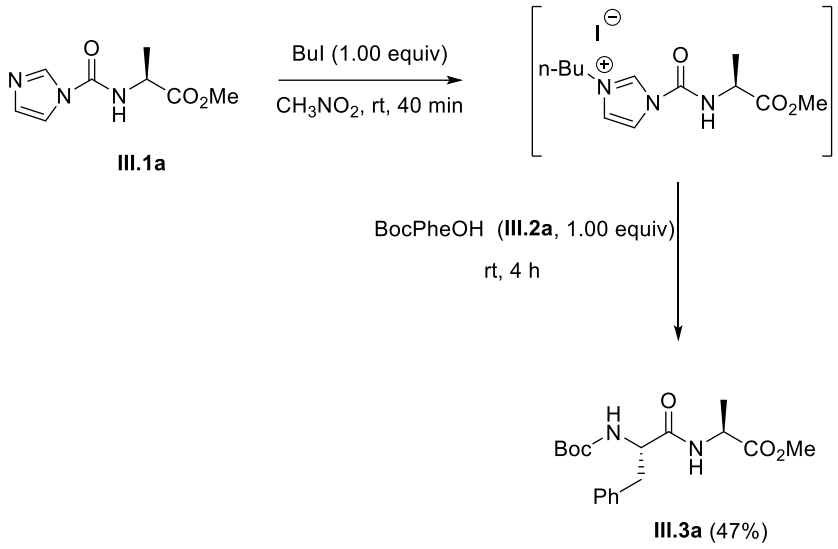


Scheme 69. Plausible mechanistic (competitive or simultaneous reactions) pathway with MeI.

I.1.4 New alternatives to activate the imidazole ring

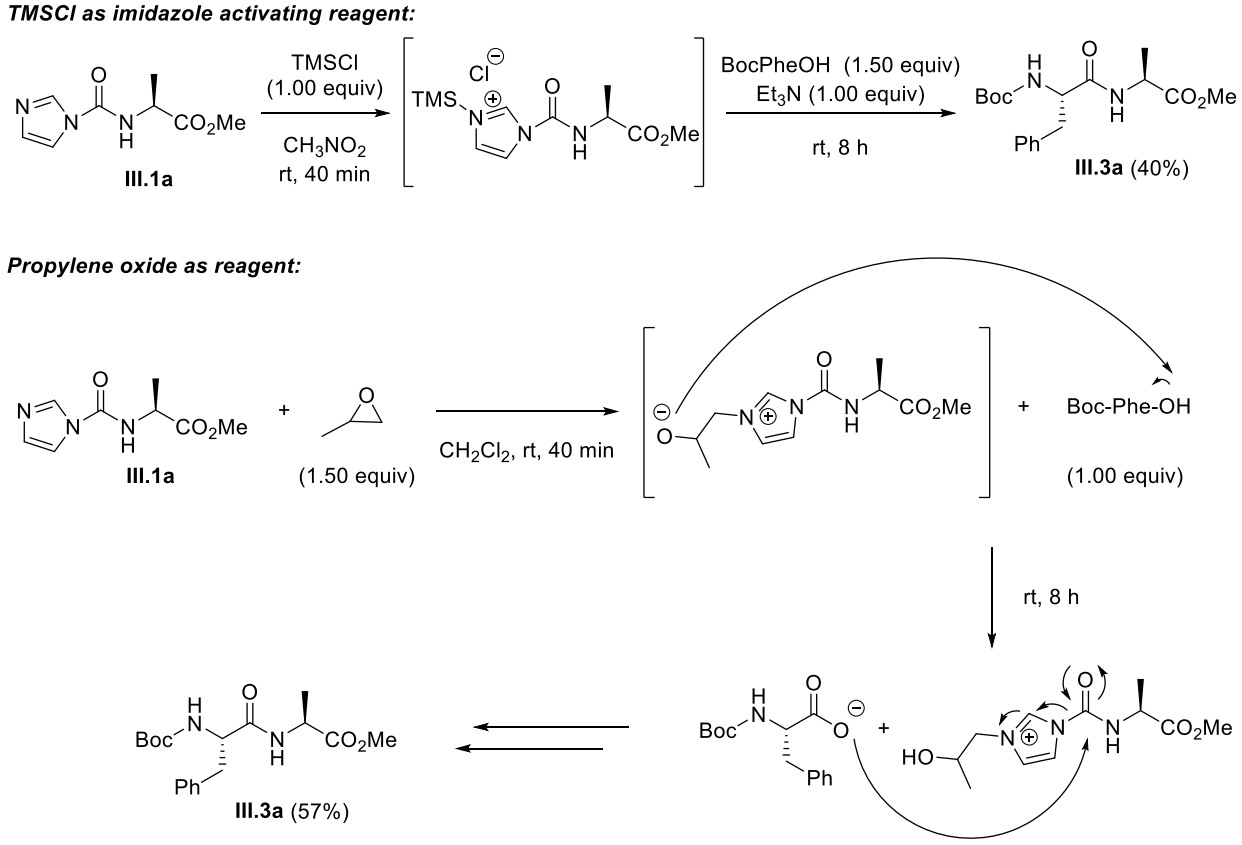
If the results were quite encouraging, we could not neglect the toxicity of MeI and the risk of a prolonged exposure.[128] We thus decided to investigate if less toxic compounds were able to replace it. The compounds chosen should have features similar to the ones of iodomethane: i) be able to transform the imidazole into a better leaving group and, consequently, ii) decrease the reaction time. Initially, we replaced the MeI with a less toxic alkylating agent such as the iodobutane (BuI), but unfortunately, the product was obtained in only 47% yield (Scheme 70).

[128] a) https://www.epa.gov/sites/default/files/2016-09/documents/methyl-iodide.pdf; b) M.P. Chamberlain, E.A. Lock, C.J. Reed *Toxicology*, **1998**, *129*, 169; c) M.P. Chamberlain, N.C. Sturgess, E.A. Lock, C.J. Reed *Toxicology*, **1999**, *139*, 27.



Scheme 70. BuI as activating agent for Imi-Ala-OMe.

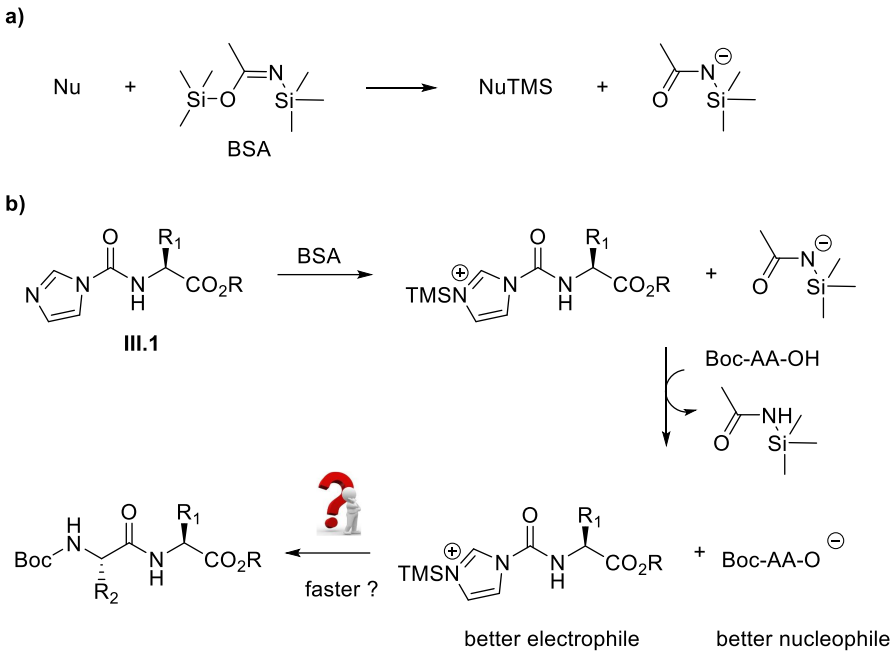
Afterwards, we moved on evaluating the reactivity of trimethylsilyl chloride (TMSCl) and propylene oxide as possible reaction promoters (Scheme 71). In these particular cases, the reaction mixtures were stirred for 8 hours. With TMSCl, it was important to add a stoichiometric quantity of a base to deprotonate the carboxylic acid of the Boc-Phe-OH, allowing the formation of the free carboxylate anion in order to have the nucleophilic attack. The reaction furnished the dipeptide in a moderate 40% yield. Meanwhile, in the reaction with propylene oxide there was no need of adding a base considering that the propylene oxide itself would have acted as both base and activating agent. In this case, the dipeptide was isolated in 57% yield.



Scheme 71. Novel additives to replace MeI.

After using TMSCl, we turn our attention to different silylating agents which, during the last decade, have been employing in a large number of synthetic applications. In 2011, Liebeskind et al. disclosed a novel, pH-neutral methodology for *in-situ* activation of the carboxyl function to afford amide and peptide bond in good yield.[129] This methodology relies on the employement of bistrimethylsilylacetamide (BSA) which can react as both the sylilating agent and the pro-base (Scheme 72a). Based on theses premises, in the presence of our intermediate **III.1** we supposed that such compound could act first as sylilating agent for the imidazole giving a better activated intermediate and successively the base could deprotonate the Boc-AA-OH, giving a better nucleophile for the coupling reaction (Scheme 72b).

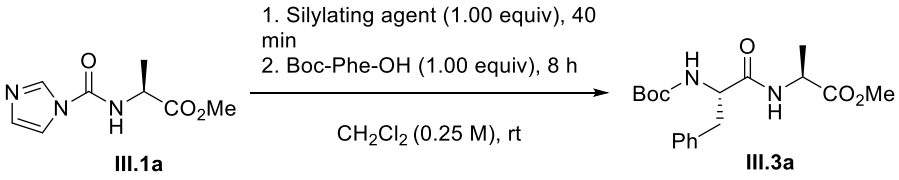
[129] W. Wu, Z. Zhang, L.S. Liebeskind *J. Am. Chem. Soc.* **2011**, *133*, 14256.

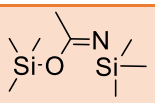
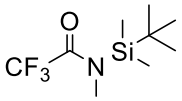


Scheme 72. a) BSA as sylilating agent and pro-base; b) BSA as reagent to improve the kinetics in our peptide coupling.

We, thus, engaged *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and *N*-Methyl-*N*-*tert*-butyldimethylsilyltrifluoroacetamide (MTBSTFA) as stoichiometric activating reagents in our strategy to afford the desired product (Table 4).

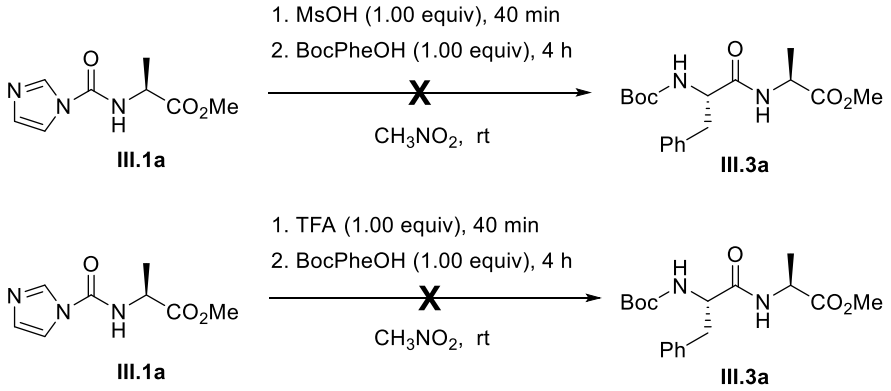
Table 4. Use of silylating agents as activating reagents for Imi-AA-OR.



Entry	Silylating compounds	Yield (%)
1	 BSA (**III.15**)	–
2	 MTBSTFA (**III.16**)	32

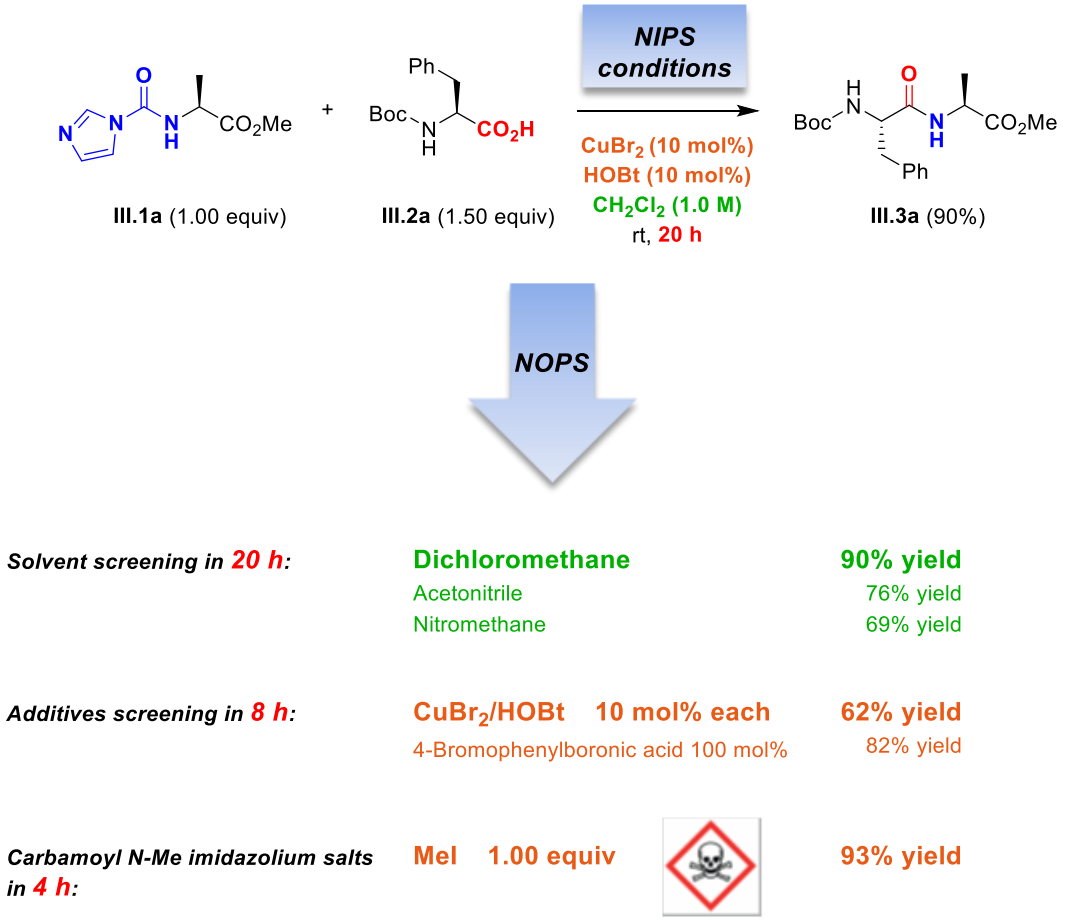
When BSA (**III.15**) was used (entry 1), the formation of the desired product after 8 hours was not attained and only the substrates were recovered. In the case of MTBSTFA (**III.16**) we isolated the target compound but only in 32% yield.

Previously, it has been shown that Brønsted acid like PTSA (Table 2, entry 3) could be efficient catalysts for this reaction-type. Thus, we tried two other different acids: the trifluoroacetic acid and the methanesulfonic acid seeking to obtain activated imidazolium salts intermediates (Scheme 73). Unfortunately, in both cases no coupling occurred.



Scheme 73. TFA and MsOH as activating agents for the transformation of the imidazole ring into imidazolium salts.

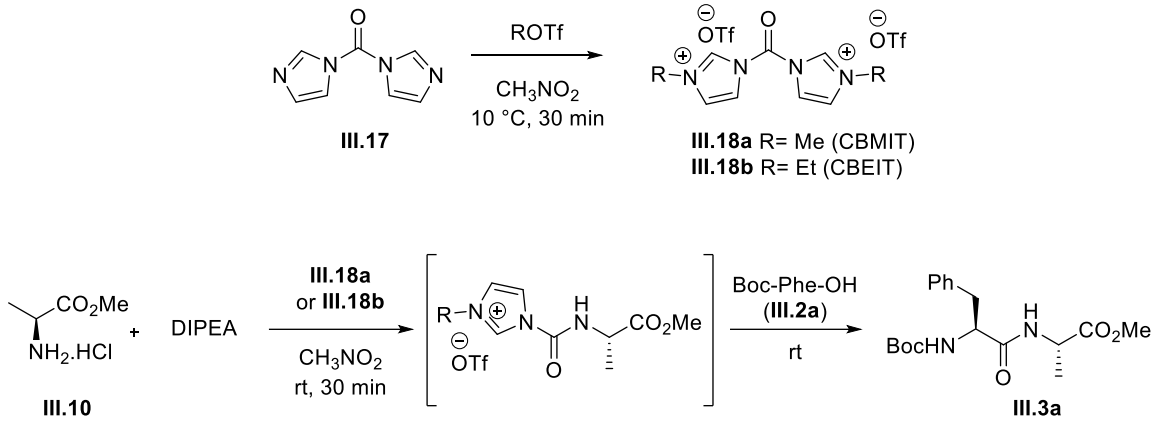
Our efforts to improve the kinetic through the use of other additives or by the transformation of the imidazole into an imidazolium salt allowed us to identify two possible issues: boronic acids, as alternative to $CuBr_2$/HOBt, and MeI as alkylating agent for the imidazole ring (Schema 74). Even though good yields (up to 82% with 4-bromophenylboronic acid in 8 hours and 93% with MeI in 4 hours) could be attained, the need for stoichiometric amounts of additives or the use of a toxic reagent were still required. Thus, we turned our attention to other activating agents for the amino group potentially able to replace the CDI.



Scheme 74. Results from all the screenings on the coupling reaction.

So far, the only activating agent for the amine function we took into account was the 1,1'-carbonyldiimidazole (CDI). This reagent is easy-to-handle and very economical (5 g = 24 €), rendering its use convenient for our purposes. First, we thought about using CDI-imidazolium salt derivatives that could be directly added into the coupling reactions without the need for a prior 'activation' with an alkylating agent (similarly to the previous studies with MeI and BuI addition).[130] For this purpose, compounds CBMIT and CBEIT were considered (Scheme 75).

[130] A.K. Saha, H. Rapoport, P. Schultz *J. Am. Chem. Soc.* **1989**, *111*, 4856.



Scheme 75. CBMIT and CBEIT as novel and more reactive activating agents.

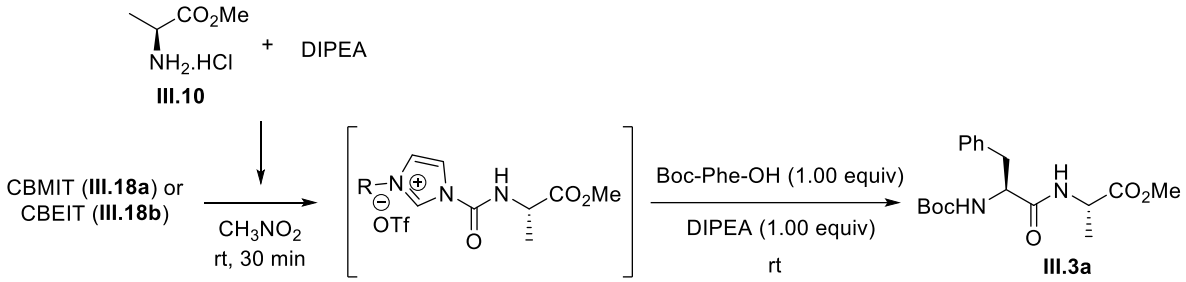
The first trials were performed adding strong activating agents, such as MeOTf and EtOTf, to a solution of CDI in nitromethane to form, respectively, the l,l'-Carbonylbis(3-methylimidazolium) triflate (CBMIT) and the l,l'-Carbonylbis(3-ethylimidazolium) triflate (CBEIT). The activated intermediates thus generated were added to a solution of L-alanine methyl ester hydrochloride in nitromethane. The mixture was then stirred for 30 minutes followed by the addition of the Boc-L-phenylalanine. The reactions were monitored by TLC. The results are reported in Table 5. When the product was observed, yields were low due to the formation of the symmetrical urea (Chapter 2, Scheme 60) and possible degradation. Indeed, we supposed that the enhanced reactivity of the activating agents favored side reactions and led not only to the formation of the desired dipeptide.

Table 5. Trials with CBMIT and CBEIT.

	Base (1.00 equiv)	Time (h)	Yield (%)
CBMIT	-	20	16
CBMIT	-	4	15
CBMIT	DIPEA	4	nd
CBEIT	DIPEA	20	9

It is noteworthy to mention that these activating agents are moisture and air sensitive. Their synthesis take place under anhydrous conditions and they might be engaged on coupling reactions immediately after their preparation. Therefore, after the earliest results obtained we thought to change the addition order to see if some improvement could have been observed (Table 6).

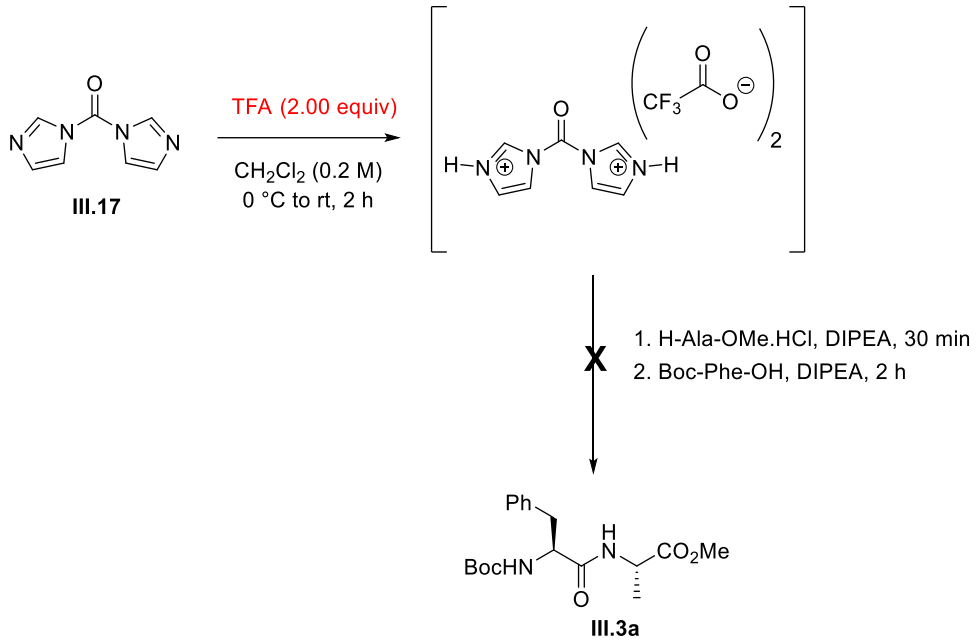
Table 6. One-pot reaction conditions.



	Time (h)	Yield (%)
CBMIT	20	nd
CBEIT	20	32

In this case, the activating agents were synthesized and then the substrate was added dropwise to the reaction mixture. The reactions were stirred for 30 minutes. By doing so, we believed that we could prevent, for instance, the formation of the symmetrical urea of the L-Alanine methyl ester. With CBMIT the expected product was not observed; for CBEIT the dipeptide was obtained in 32% yield. Due to the instability of such reagents, and also the fact that they are more difficult to handle than CDI, the idea of using them has been abandoned.

Besides, we also tried to activate CDI through the reaction with two equivalents of trifluoracetic acid as shown in Scheme 76. After the addition of TFA to the solution of CDI the reaction was stirred for two hours. To the mixture was, then; added a solution of the L-Alanine methyl ester and stirred for 30 minutes more. Afterwards, the carboxylate solution of Boc-L-phenylalanine was added to the reaction medium. The monitoring was effectuated by TLC and the formation of the dipeptide was not observed.



Scheme 76. TFA-mediated activation of CDI.

In conclusion, the idea of derivatizing CDI into CDI-imidazolium salts in order to improve the reaction kinetic did not lead to the expected results. These products are air and moisture sensitive and their synthesis would probably require more drastic anhydrous conditions not really compatible with the reaction conditions usually encountered in peptide synthesis (notably in SPPS). As we also want to propose practical conditions for couplings, these observations prompted us to abandon this strategy.

I.1.5 Exploring other activating reagents

Alternative activating agents to replace CDI (**III.17**) have also been envisaged and tested (Figure 11).

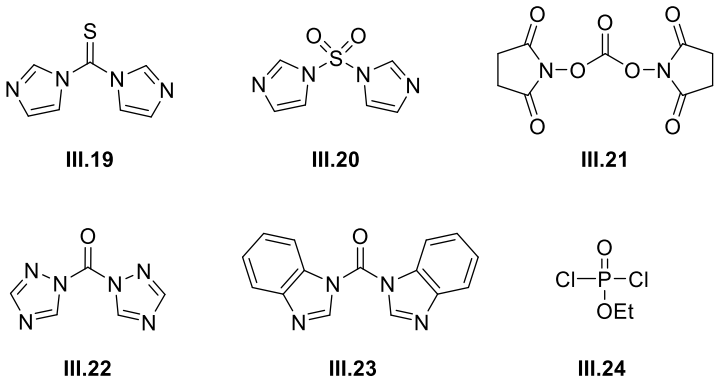


Figure 11. Novel activating reagents studied.

First, we studied the reactivity of the sulfur derivatives of the CDI: 1,1′-thiocarbonyldiimidazole (**III.19**) and 1,1′-sulfonyldiimidazole (**III.20**). For **III.19**, the crude ^{1}H NMR, issued from the activation of H-Ala-OMe, showed the signals which could have been attributed to the desired product but we were not able to isolate the activated intermediate by column chromatography (Figure 12).

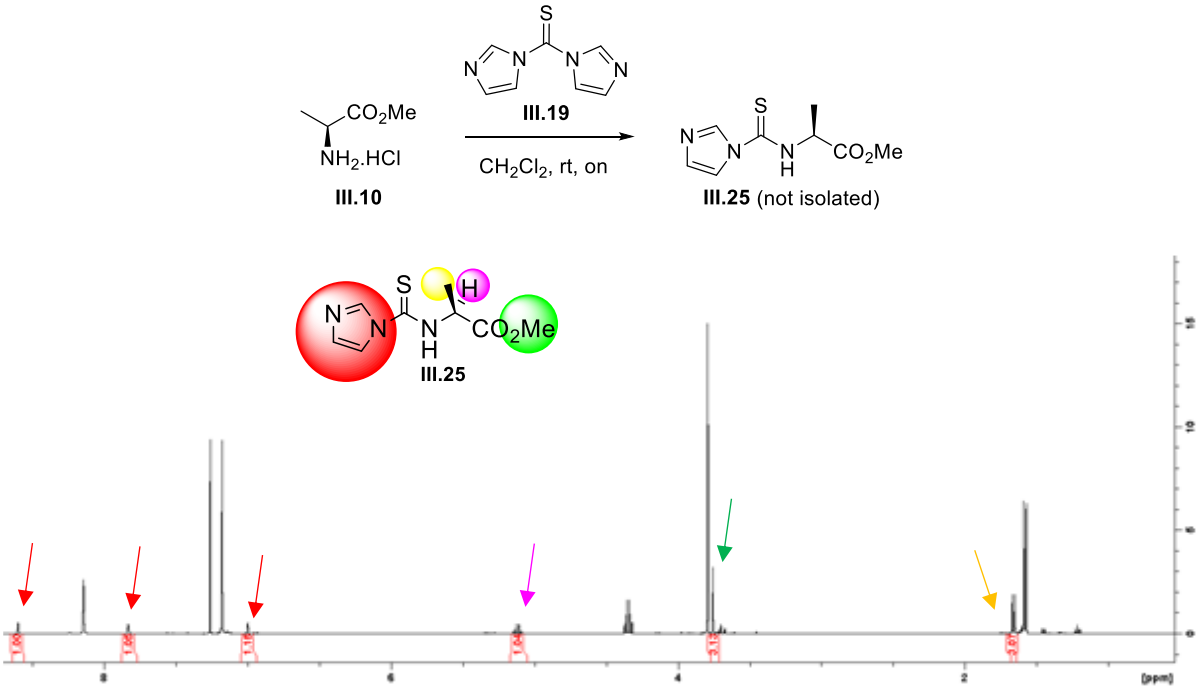
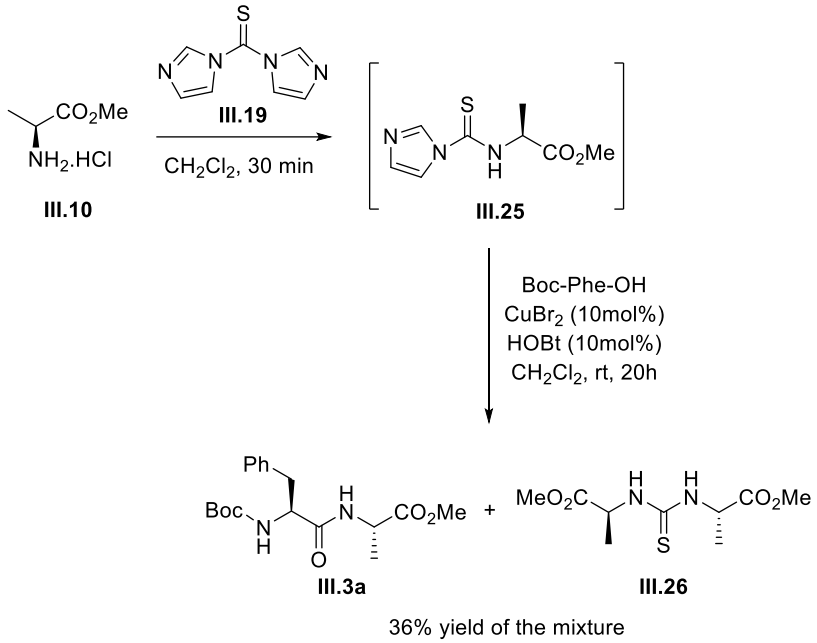


Figure 12. Reaction of L-alanine methyl ester hydrochloride with **III.19**; crude ^{1}H NMR.

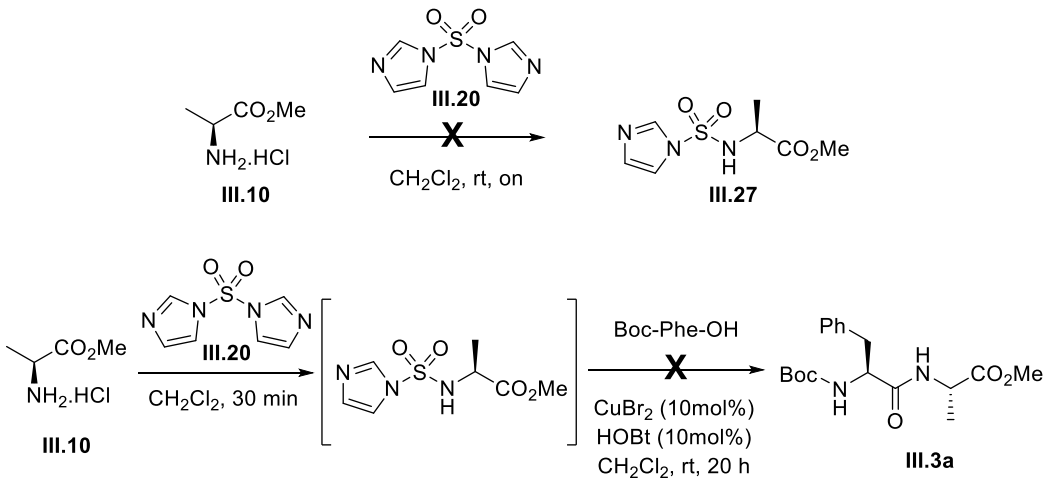
Thus, we employed the reagent **III.19** into a sequential one-pot reaction, without isolating the compound **III.25**, to see if we were able to form the dipeptide (Scheme 77).



Scheme 77. 1,1'-Thiocarbonyldiimidazole-mediated coupling.

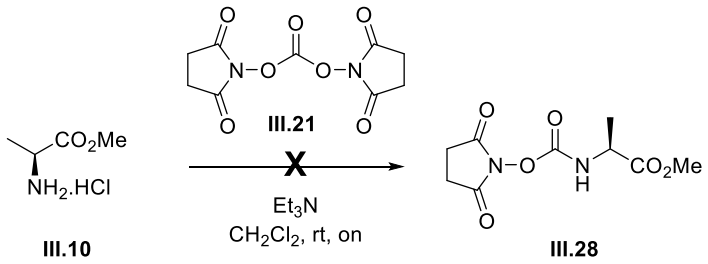
We obtained a mixture of the desired product and the symmetrical thiourea in 36% of yield. The crude ^{1}H NMR showed the presence of both compounds (ratio **III.3a:III.26** = 7:3) and it was not possible to separate them by column chromatography.

We, therefore, explored the reactivity of the compound **III.20**. In this case, **III.20** did not react with **III.10** in order to give the intermediate **III.27** neither via a two-step strategy nor via a sequential one-pot method (Scheme 78).



Scheme 78. 1,1′-Sulfonyldiimidazole as activating agent.

We pursued our studies with the *N*,*N*′-disuccinimidyl carbonate (DSC, **III.21**). Its application as a reagent to activate the carboxyl group is quite known in peptide chemistry.[131] Unfortunately, we were not able to observe the formation of the activated amine **III.28** either when the reaction was run in the classical conditions (i.e. CH_2Cl_2 at room temperature) or in the presence of a base (Et_3N) (Scheme 79).

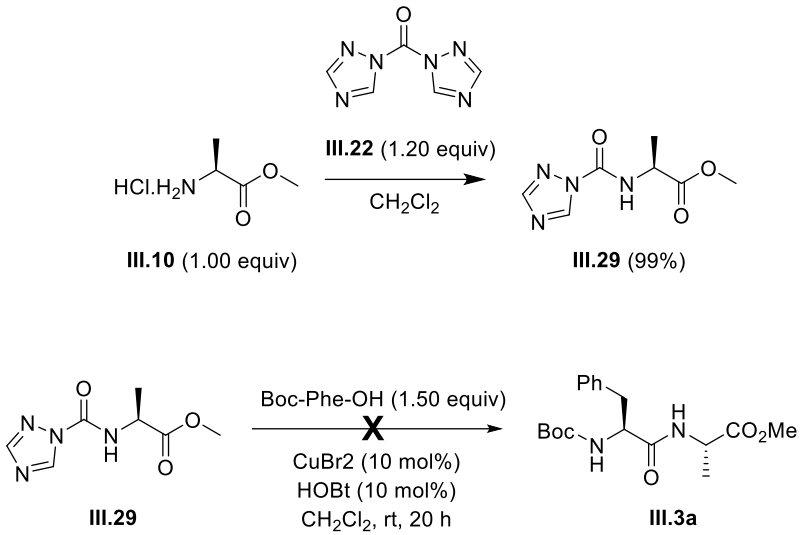


Scheme 79. DSC reactivity.

Afterwards, we tested was the 1,1′-carbonyl-di-(1,2,4-triazole) (CDT, **III.22**). Its reactivity was already described in the late sixties when Beyerman and Maassen van Den Brink reported their results showing that CDT was useful in peptide coupling reaction.[132] By using CDT to 'activate' the L-alanine methyl ester hydrochloride, the desired intermediate **III.29** was isolated in quantitative yield (Scheme 80). Unfortunately, intermediate **III.29** did not react with Boc-Phe-OH as, after 20 hours of coupling, no formation of the dipeptide was detected either by TLC monitoring or crude ^{1}H NMR.

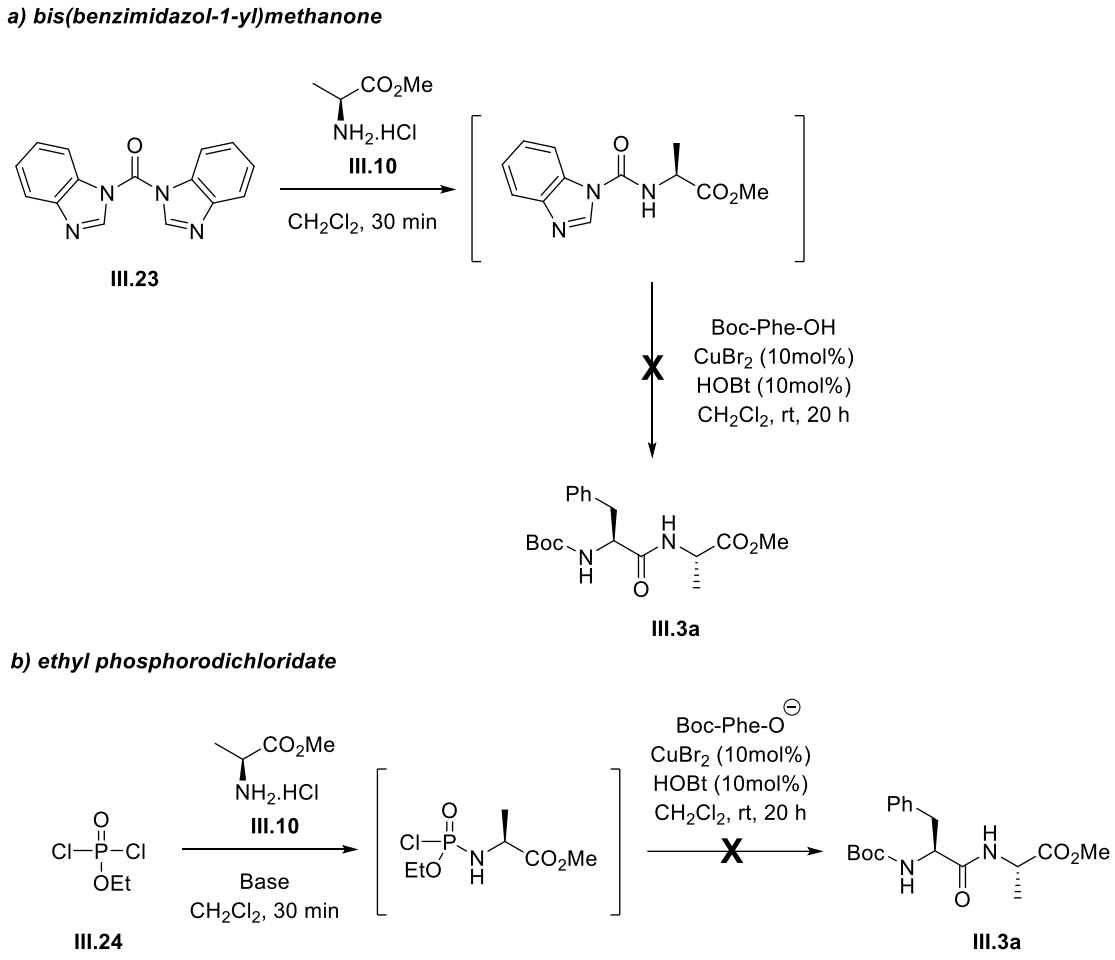
[131] a) J. Alsina, F. Rabanal, C. Chiva, E. Giralt, F. Albericio *Tetrahedron* **1998**, *54*, 10125; b) C.A.G.N. Montalbetti, V. Falque *Tetrahedron* **2005**, *61*, 10827; c) M.I. Meschaninova, D.S. Novopashina, O.A. Semikolenova, V.N. Silnikov, A.G. Venyaminova *Molecules* **2019**, *24*, 4266; d) H. Li, C. Chen, J. Balsells Padros *Synlett* **2011**, *10*, 1454.

[132] H.C. Beyerman, W. Maassen van Den Brink *Recueil* **1961**, *80*, 1372. See also for recent advances: S.D. Melton, M.S. Smith, D.M. Chenoweth *J. Org. Chem.* **2020**, *85*, 1706.



Scheme 80. CDT-mediated coupling.

Eventually, we also performed the one-pot strategy as shown in Scheme 81 with compounds **III.23** and **III.24** in order to see if we could have better reactivity compare with the CDI. In both cases, we were not able to observe the target product (**III.3a**).



Scheme 81. One-pot strategy with activating agents **III.23** and **III.24**.

Despite the variety of activating reagents investigated, none gave promising results. The CDI was still the best in terms of costs and yields.

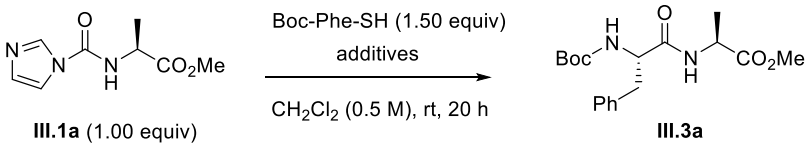
I.1.6 Thioacids

So far, we have analysed, in order to decrease the reaction time, different parameters such as solvents, additives and activating agents. We always used carboxylic acids as the nucleophilic counterpart but over the years thioacids have become a class of compounds very useful in synthetic organic chemistry. In particular, they have been extensively employed as mild reagents for the synthesis of peptide and peptidomimetics as well as for the chemoselective assembly of a variety of bio-conjugates. In fact, they have some favorable properties such as their enhanced nucleophilicity and low pK_a which have prompted several groups to explore the

full potential of thioacids.[133] Therefore, we studied the possibility to replace the carboxylic moiety in order to extend our methodology and also to improve the kinetic efficiency. We carried out some trials using the thio- equivalent of the Boc-Phe-OH. Indeed, as part of the project NOPS, a partnership with the group of Dr. Vincent Aucagne (CBM-Orléans) specialized on fragment couplings and cyclizations has been established. In this context, they furnished us the thio-derived compound (Dr. Vishwanatha Thimmalapura Marulappa) in order to explore its reactivity (Table 7).

The reactions were performed in the same conditions used for the carboxylic acids except for the solvent concentration. In fact, instead of a 1.0 M solution of dichloromethane, we used a 0.5 M solution to fully solubilize the thioacid. The reactions were monitored by TLC until completion.

Table 7. Thioacid peptide coupling.



Additives	Yield (%)
-	60
$CuBr_2$/HOBt (10 mol%)	52

By running the reaction in the absence of additives, the desired dipeptide was isolated in 60% yield. Additives ($CuBr_2$ and HOBt) were, in this case, somehow deleterious, as a slightly lower yield of 52% was obtained.

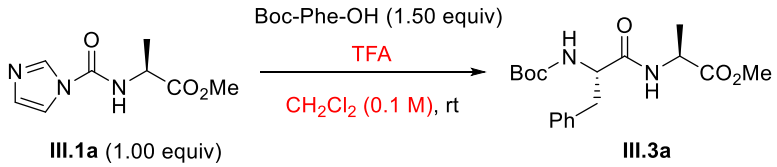
I.2 Investigating the trifluoroacetic acid as additive in peptide coupling

In this section, we are going to study the possibility of using a catalytic amount of TFA as additive to replace the $CuBr_2$/HOBt combination in our reaction conditions. Indeed, when investigating how to transpose the methodology to fragment couplings, Dr. V. Thimmalapura Marulappa (Post-doctoral fellow in the group of Dr. V. Aucagne) observed that the formation of a peptide bond could have been achieved using i) catalytic amounts of TFA and ii) by increasing the dilution of the reaction medium. Hence, this result prompted us to study the

[133]a) R.M. de Figueiredo, J.-S. Suppo, J.-M. Campagne *Chem. Rev.* **2016**, *116*, 12029; b) N. Narendra, V. Thimmalapura Marulappa, H. Basavaprabhu, P. Girish, L. Roopesh Kumar, V.V. Sureshbabu *Org. Biomol. Chem.* **2018**, *16*, 3524.

behavior of TFA in a diluted dichloromethane solution as an alternative in the model peptide coupling reaction (Table 8).

Table 8. Screening of TFA as additive.



Entry	TFA	Time (h)	Yield (%)
1	-	8	70%
2	-	24	85%
3	**(13 mol%)**	8	75%
4	**(13 mol%)**	24	90%

[a] Concentration of the DCM (1 M); [b] TFA is added dropwise during the time reaction.

First, we wanted to evaluate if only the dilution of the solvent from 1.0 M to 0.1 M could have changed the yield obtained (entries 1 and 2). Without additives, we obtained respectively in 24 hours the dipeptide in 85% of yield and in 8 hours in 70% (yield of 63% in 20 hours in DCM 1.0 M). Surprisingly, we achieved slightly enhanced yield compared to the model reaction demonstrating that the dilution affect the reactivity. As shown in entry 3, in the presence of 13 mol% of TFA, we obtained the desired product in 75% of yield after 8 hours (yield of 62% in 8 hours in the presence of $CuBr_2$/HOBt). The same coupling gave, in 24 hours, the product in 90% yield (entry 4) (yield of 90% in 20 hours with additives $CuBr_2$/HOBt). We also performed other trials, which are not mentioned in the table 8, tuning the addition sequence, the quantity of the additive and the concentration of the reaction. For example, we performed the reaction in the presence of a more concentrated solution or drop-wise addition of TFA. In all cases, no better results in terms of kinetics or yields were achieved.

These preliminary results are quite promising considering that we could avoid the use of $CuBr_2$ and HOBt; in addition HOBt is no more accepted on an industrial level due to his explosiveness.[134] Hence, it will be interesting to further study the role of TFA in peptide coupling as well as how much the concentration affects the reaction. Up-to-date, thanks to these

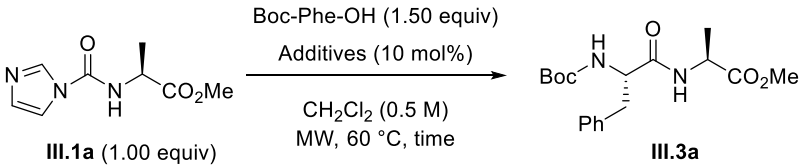
[134] K.D. Wehrstedt, P.A. Wandrey, D. Heitkamp *J. Hazard. Mater.* **2005**, *A126*, 1.

results, the classical conditions previously developed ($CuBr_2$/HOBt 10 mol% each) could also be replaced by a catalytic amount of TFA (13 mol%) in a more diluted reaction medium.

I.3 Investigating microwave as a tool to improve the reaction kinetics

Microwave chemistry is the science of applying microwave irradiation to heat and drive chemical reactions.[135] New and innovative applications of microwave energy prompted relevant advances in organic and peptide synthesis,[136] polymer chemistry,[137] material sciences,[138] nanotechnology and biochemical processes.[139] The application of microwave heating has been proven to dramatically reduce processing times, increase product yields and enhance product purities compared to conventional heating experiments.[14-18] In particular, in the organic and medicinal chemistry communities, this enabling technology has moved from laboratory curiosity to standard practice in just a few years. Since the growing importance of this tool, we took into account the possibility of applying microwave irradiation to our coupling conditions in order to see if some kinetic improvement could be reached. The results are summarized on Table 9:

Table 9. Optimisation of the conditions.



Additives	Reaction time	Yield (%)
–	60 minutes	67%
$CuBr_2$/HOBt	60 minutes	81%
$CuBr_2$/HOBt	30 minutes	78%
$CuBr_2$/HOBt	15 minutes	71%
TFA[a]	30 minutes	83%

[a] 13 mol% of TFA in CH_2Cl_2 (0.1 M), experiment conducted after the optimisation in order to see if TFA could replace the usual additives also when microwave irradiations were used.

[135] a) J.D. Moseley, C.O. Kappe *Green Chem.* **2011**, *13*, 794; b) S. Nain, R. Singh, S. Ravichandran *Adv. J. Chem. A* **2019**, *2*, 94; c) A.S. Grewal, K. Kumar, S. Redhu, S. Bhardwaj *Int. Res. J. Pharm. App. Sci.* **2013**; *3*, 278.

[136] a) C.O. Kappe, D. Dallinger *Mol. Diversity* **2009**, *13*, 71; b) S. Caddick, R. Fitzmaurice *Tetrahedron* **2009**, *65*, 3325; c) F. Rizzolo, G. Sabatino, M. Chelli, P. Rovero, A.M. Papini *Int. J. Pept. Res. Ther.* **2007**, *13*, 203; d) B. Bacsa, S. Bősze, C.O. Kappe *J. Org. Chem.* **2010**, 75, 2103.

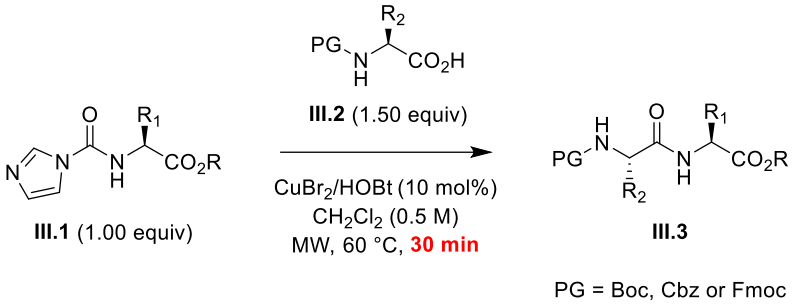
[137] M. Bardts, N. Gonsior, H. Ritter *Macromol. Chem. Phys.* **2008**, *209*, 25.

[138] S. Barlow, S. R. Marder *Adv. Funct. Mater.* **2003**, *13*, 517.

[139] a) J.G. Duque, M. Pasquali, H.K. Schmidt *J. Am. Chem. Soc.* **2008**, *130*, 15340; b) K.M. Rahman, D.E. Thurston *Chem. Commun.* **2009**, 2875.

Results were quite promising, in particular when after 30 minutes the target dipeptide was obtained in 78% yield. Moreover, diastereomers were not observed. Thus, the choice of exploring the coupling of several commercially available amino acids mediated by a microwave-assisted process was undertaken (Table 10).

Table 10. Scope of dipeptides[a] synthesised by MW-irradiation.



Entry	Imi-AA-OR	Dipeptides	Yield (%)[b]
1	Imi-Ala-OMe (**III.1a**)	Boc-Phe-Ala-OMe (**III.3a**)	78
2	**III.1a**	Cbz-Met-Ala-OMe (**III.3c**)	80
3	**III.1a**	Boc-Pro-Ala-OMe (**III.3d**)	47
4	**III.1a**	Fmoc-Lys(Alloc)-Ala-OMe (**III.3f**)	70
5	**III.1a**	Boc-Cys(Bn)-Ala-OMe (**III.3g**)	77
6	**III.1a**	Fmoc-Phe-Ala-OMe (**III.3h**)	73
7	Imi-Gly-OEt (**III.1b**)	Boc-Asp(OBn)-Gly-OEt (**III.3i**)	80
8	**III.1b**	Fmoc-Ala-Gly-OEt (**III.3j**)	77
9	**III.1b**	Cbz-Trp-Gly-OEt (**III.3k**)	66
10	Imi-Val-OMe (**III.1c**)	Boc-Phe-Val-OMe (**III.3b**)	70
11	Imi-Met-OMe (**III.1d**)	Cbz-Phe-Met-OMe (**III.3l**)	66
12	**III.1d**	Boc-Trp-Met-OMe (**III.3m**)	72
13	Imi-Met-O*t*Bu (**III.1e**)	Cbz-Trp-Met-O*t*Bu (**III.3n**)	66

[a] Reactions were performed on a 0.30 mmol scale; [b] Yield of the isolated products after purification by column chromatography.

Comparable or slightly improved results were obtained when the reactions were performed via microwave heating (30 min) instead of the room temperature (24 h) classical solution phase method. The coupling efficiency was not significantly affected by the different side chains (Table 10, entries 4, 5, 7, 9, 12 and 13). In addition, the reaction proved to be fully compatible with Boc-, Fmoc- and Cbz-protected amino acids, an important issue for the method to be applied in routine peptide synthesis. Slightly lower yield was observed when the Proline was used as carboxylic acid partner (Table 10, entry 3). Nonetheless, with this procedure it was possible to considerably reduce the reaction time (30 min vs 20 hours with traditional

$CuBr_2$/HOBt and 4 hours with MeI). NMR spectra did not display diastereomers for the dipeptide Boc-Phe-Ala-OMe, implying that microwave irradiation did not induce racemisation. Nevertheless, it is well-known that the activation of some sensitive amino acids like the cysteine might occur with some degree of epimerization as a result of the formation of a stabilized enol derivative. We thus analysed the crude dipeptide, Boc-Cys(Bn)-Ala-OMe, synthesized through MW irradiation, by chiral HPLC (Figure 13). Notably, epimerisation was not detected corroborating our mechanistic proposal through amine activation.

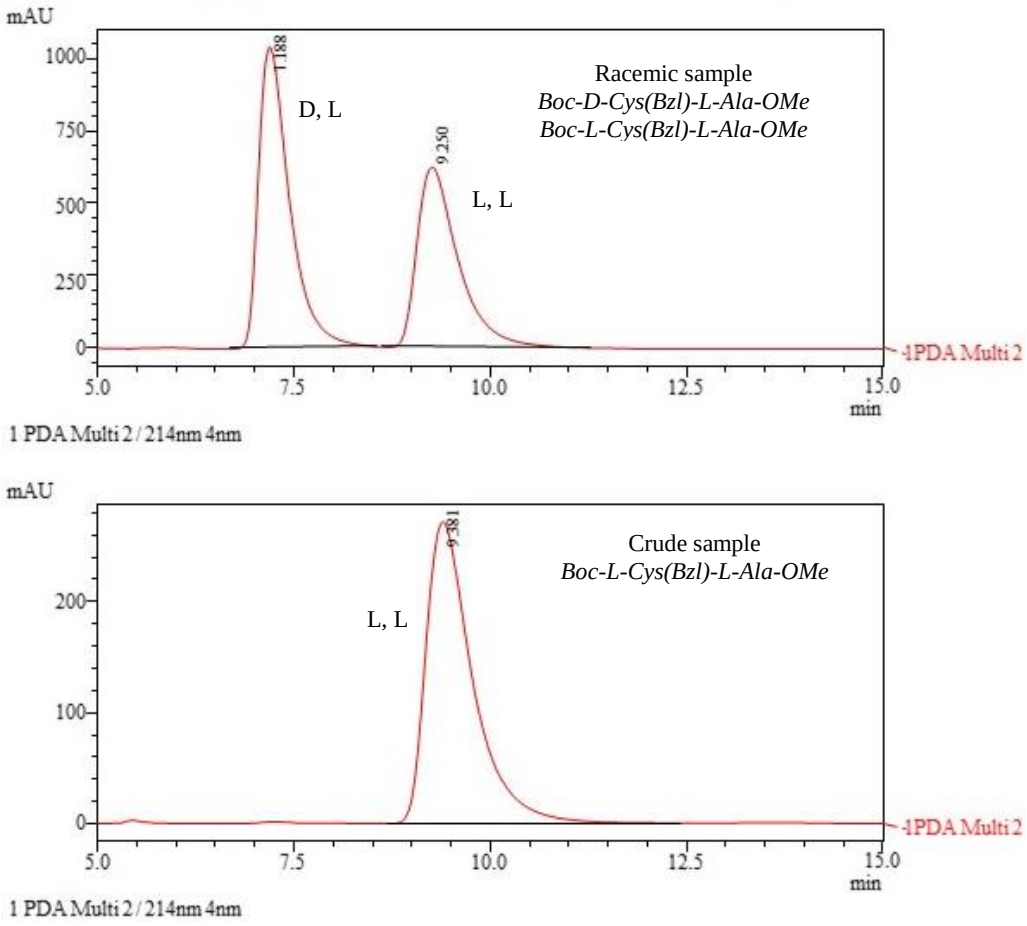


Figure 13. Chiral HPLC of Boc-Cys(Bn)-Ala-OMe prepared via microwave irradiation.

During the ANR program JCJC (project NIPS 2012-2016), our laboratory did propose an original procedure to synthesise dipeptides through the inverse activation of the amine function. The reaction took place under very mild conditions but one of the main drawbacks was the reaction kinetics (20 hours). So during my PhD work, one of the main goals was to improve the reaction efficiency by reducing the kinetic (e.g. to be able to propose alternative conditions where couplings were achieved within less than 20 hours of reaction in similar good yields) (Figure 14). By reducing the reaction time, we were seeking to transpose the methodology into

the SPPS (with Pr. Gilles Subra-IBMM/Montpellier) and fragment couplings (Dr. Vincent Aucagne-CBM/Orléans). After the evaluation of each parameter of the coupling reaction, some interesting results were obtained:

I. Boronic acids could be used as reaction promoters in **8 hours instead of 20 hours**, however in stoichiometric amounts;
II. The couplings could also be performed in solvents as nitromethane and acetonitrile;
III. The reaction could be performed from **20 hours to 4 hours** by using MeI (1.00 equivalent) as activating agent for Imi-AA-OR;
IV. The couplings can also take place in less concentrated solutions (from 1.0 M to 0.1 M) using a catalytic amount of TFA;
V. The couplings take place in **only 30 minutes** thanks to microwave irradiation.

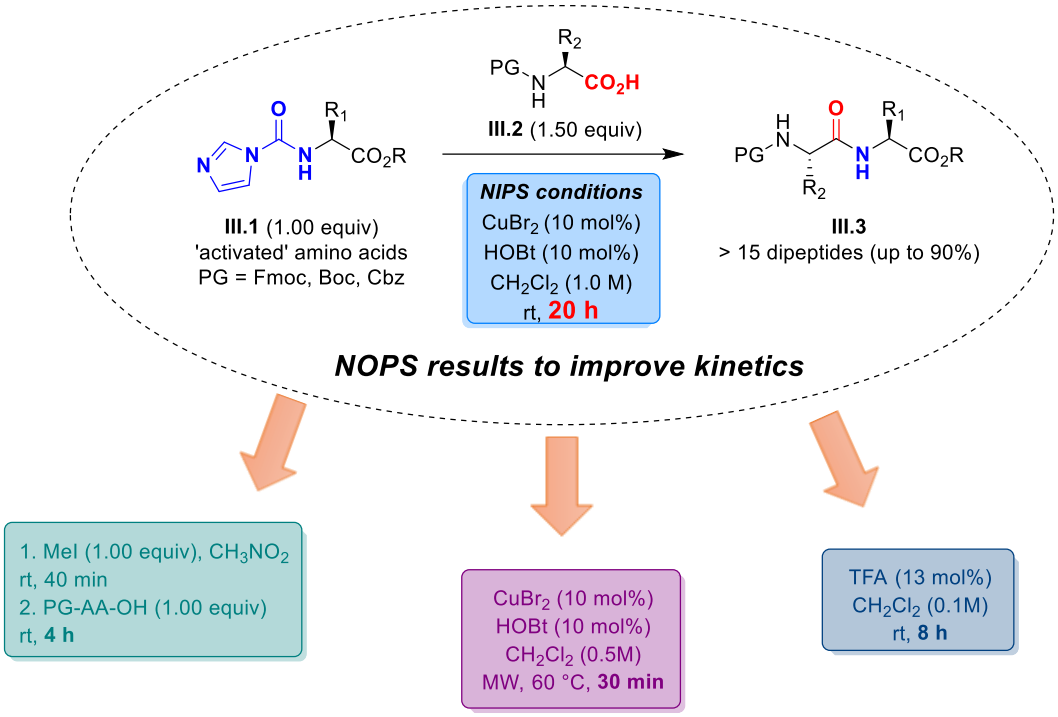


Figure 14. From NIPS to NOPS.

We thus decided to move forward and to see if there was the possibility to apply our methodology to the synthesis of general amides. Indeed, they are very important in medicinal chemistry, material sciences and so on.

II. From peptides to general amides

II.1 The amide function in drug candidates

In addition of improving the reaction efficiency by reducing the time of our couplings, we also envisaged to transpose the reaction conditions to the synthesis of general amides. Molecules bearing the amide function are ubiquitous not only in peptides but also in several natural and industrial products.[140] In 2011, an analysis of the most commonly used reactions in the pursuit of drug candidates development, reported by Roughley and Jordan,[141] showed that N-acylation to amide was ranked on the first position in the top 10 reactions most used (Figure 15).

Top 10 Reactions by Frequency in the 2008 Data Set

reaction	no. of reactions	% of all reactions
N-acylation to amide	1165	16.0
N-containing heterocycle formation	537	7.4
N-arylation with Ar-X	458	6.3
RCO_2H deprotection	395	5.4
N-subs with alkyl-X	390	5.3
reductive amination	386	5.3
N-Boc deprotection	357	4.9
Suzuki cross-coupling reaction	338	4.6
O-substitution	319	4.4
other NH deprotection	212	2.9

Figure 15. Top 10 reactions used in pharmaceutical industry. Data from 2011.

More recently in 2018, amongst the common chemical reactions in drug discovery and development, the amide function appears as one of the most used reaction type (Figure 16).[142]

[140] J.S. Carey, D. Laffan, C. Thomson, M.T. Williams *Org. Biomol. Chem.* **2006**, *4*, 2337.

[141] S.D. Roughley, A.M. Jordan *J. Med. Chem.* **2011**, *54*, 3451.

[142] J. Boström, D.G. Brown, R.J. Young, G.M. Keserü *Nat. Rev. Drug Discov.* **2018**, *17*, 922.

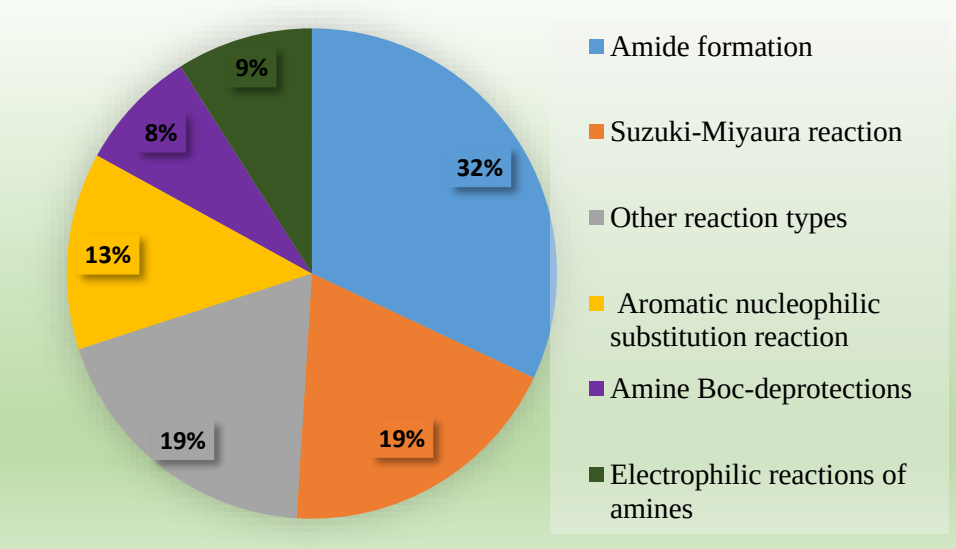


Figure 16. Common reactions in medicinal chemistry. Data from 2018.

Since their crucial importance in pharmaceutical industries, the amide synthesis have been the object of many discussions. For example, in 2005, the ACS Green Chemistry Institute (GCI) and the global pharmaceutical corporations (AstraZeneca, Eli Lilly & Company, GlaxoSmithKline, Johnson & Johnson, Merck & Co., Inc., Pfizer, Inc., and Schering–Plough Corporation) established the ACS GCI Pharmaceutical Roundtable to encourage the integration of green chemistry into the pharmaceutical industry.[143] The Roundtable made a list of key research areas, which resulted to have absolute priority in order to attain a more sustainable business and environment (Table 11).

Table 11. Key research areas suggested by ACS GCI Pharmaceutical Roundtable. Data from 2005.

Research Area	Roundtables companies voting for this research area as a priority
Amide formation avoiding poor atom aconomy reagents	**6 votes**
OH activation for nucleophilic substitution	5 votes
Reduction of amides without hydride reagents	4 votes
Oxidation/Epoxidation methods without the use of chlorinated solvents	4 votes

[143] D.J.C. Constable, P.J. Dunn, J.D. Hayler, G.R. Humphrey, J.L. Leazer, R.J. Linderman, K. Lorenz, J. Manley, B.A. Pearlman, A. Wells, A. Zaksh, T.Y. Zhang *Green Chem.* **2007**, *9*, 411.

Safer and more environmentally friendly Mitsunobu reactions	3 votes
Friedel-Crafts reaction on unactivated systems	2 votes
Nitrations	2 votes

The research area of primary importance was the amide formation avoiding poor atom economy reagents. In fact, from an analysis of drug candidates conducted by three leading pharmaceutical companies, it was found that amide bond formation was utilised in the synthesis of 65% of the candidates surveyed.[144] About 36% of the amide bond forming reactions were carried out by means of a coupling reagent such as N-ethyl-N'-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC), catalysed by HOBt or 1-propylphosphonic acid cyclic anhydride. These methods are less ‘‘atom economical’’ generating great quantities of waste as measured by their mass intensity factor (MI), (defined as the ratio of a total mass in a process divided by mass of product in kg). Amide bond formation using enzymatic catalysis eliminates some of the issues associated to poor atom economy as well as the potential hazards related to non-aqueous chemical based approaches, improving significantly the MI.[145]

It is well-known that the easiest way to form the amide bond could be the direct condensation of a carboxylic acid and an amine with the release of one equivalent of water. Nonetheless, due to the competing acid-base reaction, which occurs when the amine and the carboxylic acid are mixed (see chapter 1, section I), the amide bond can be only formed from the corresponding ammonium-carboxylate salt upon extensive heating, limiting the use of these procedures to robust substrates.[146] If we consider general amines and carboxylic acids as more robust substrates than amino acids, we could imagine to “easily” transpose our coupling conditions, devised for peptide synthesis purpose, to general amides formation. In health and material sciences, many researchers devoted their efforts to investigate alternative routes and master the synthesis of amides (Figure 17).

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[144]a) J.S. Carey, D. Laffan, C. Thomson, M.T. Williams *Org. Biomol. Chem.* **2006**, *4*, 2337; b) R.W. Dugger, J.A. Ragan, D.H.B. Ripin *Org. Process Res. Dev.* **2005**, *9*, 253.

[145] For a recent example of review on green amidations see: M.T. Sabatini, L.T. Boulton, H.F. Sneddon, T.D. Sheppard *Nat. Catal.* **2019**, *2*, 10.

[146] H. Lundberg, F. Tinnis, N. Selander, H. Adolfsson *Chem. Soc. Rev.* **2014**, *43*, 2714.

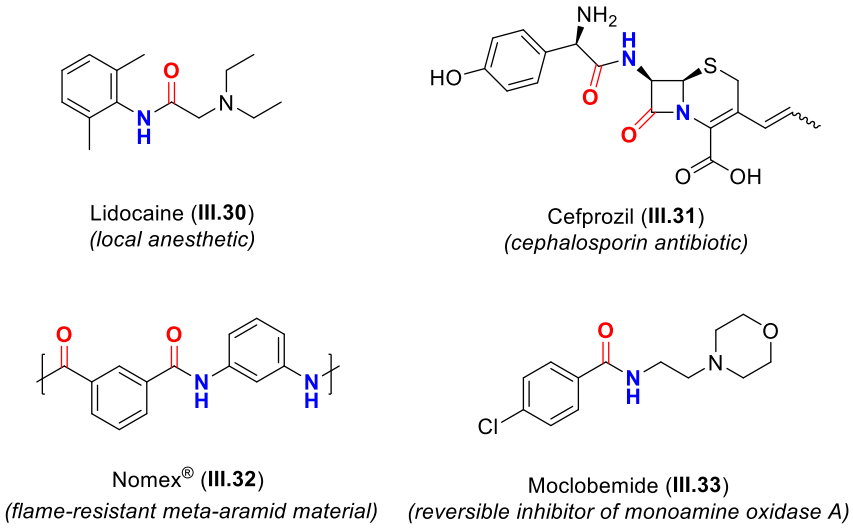


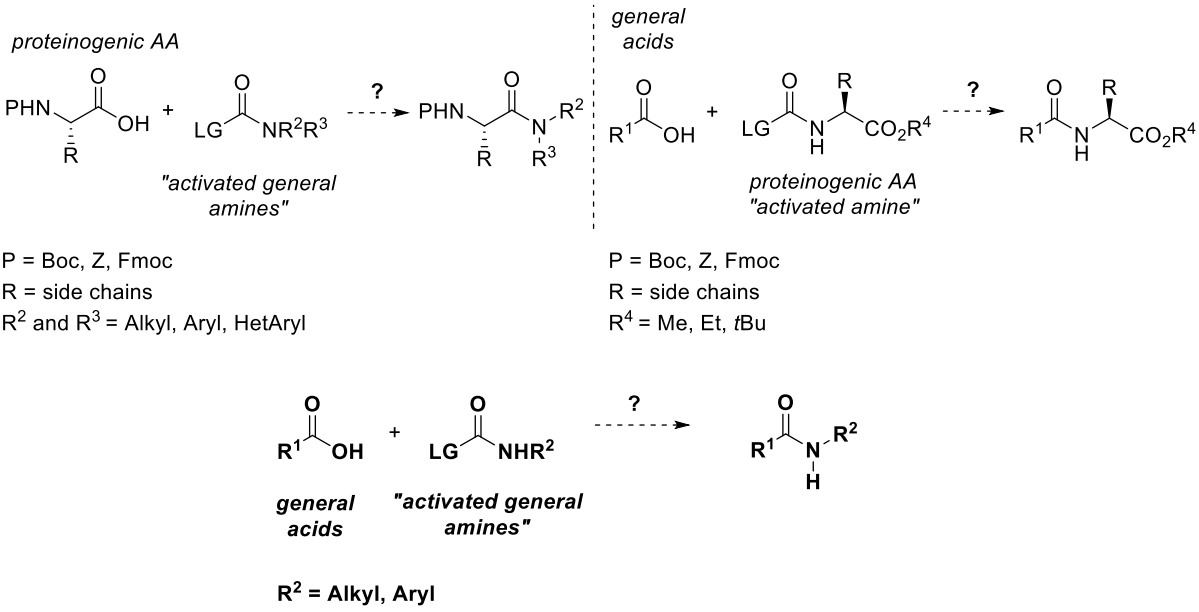
Figure 17. Amides in everyday life.

However, some issues deserve to be mentioned:

I. Are general amines and carboxylic acids reactive enough to afford general amides in such mild conditions?
II. Are the intermediates the same hypothesised for the amino acids?
III. Are the employed additives compatible with these substrates?

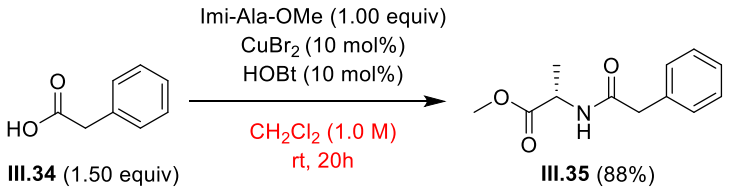
II.2 Transposition of our peptide coupling conditions to the general amide synthesis

With these questions in mind, we decided to explore the possibility to apply our methodology to the synthesis of general amides. The idea was first to evaluate the behaviour of each substrate, by using one amino acid partner with a simple carboxylic acid or amine derivative. Then in a second moment, we could use both general partners (Scheme 82).



Scheme 82. Synthesis of general amides.

Hence we conducted our first trials by combining our model intermediate Imi-Ala-OMe with a general acid, 2-phenylacetic acid, using our previous optimised conditions. Gratifyingly, after 20 hours, as shown in Scheme 83, we obtained the desired amide in 88% yield.



Scheme 83. Extension to mixed amides.

This encouraging preliminary result prompted us to validate our conditions on general carboxylic acid partners to afford hybrid amides (Figure 18).

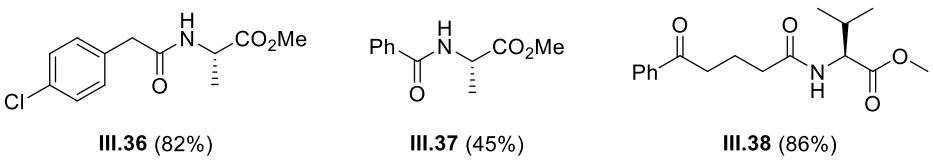
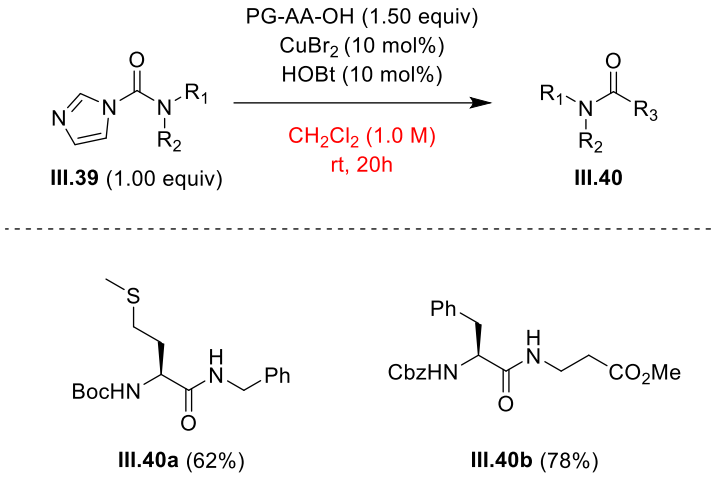


Figure 18. Examples of general acids with Imi-AA-OMe.

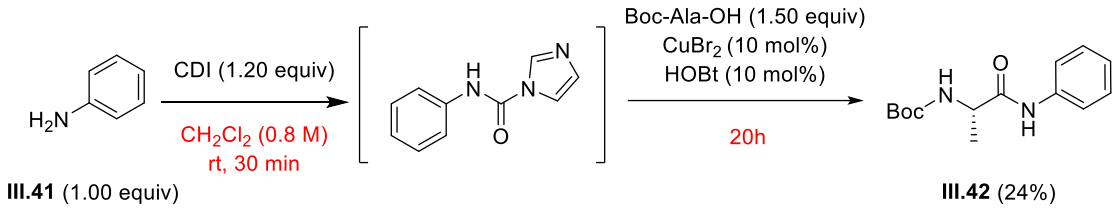
The products were isolated in good yields. A slightly lower yield was observed when benzoic acid was used as the acid partner (compound **III.37**, 45%). Its behaviour might be related to the steric hindrance of the phenyl group directly attached to the carboxylic moiety. After having

used general carboxylic acid partners, we did also test the behaviour of general amines throughout the activation with CDI and the further coupling with amino acids (Scheme 84).



Scheme 84. Coupling of activated general amines and carboxylic acids derived from amino acids.

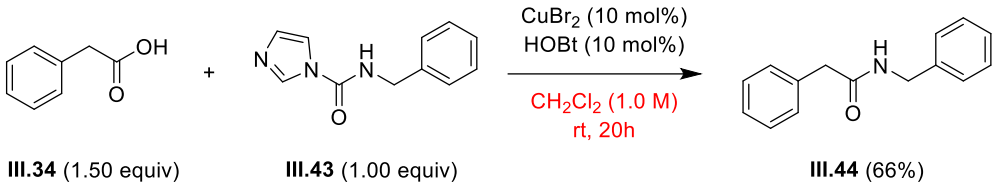
Additionally, it is important to note that, in the presence of particular substrates such as aniline, it was not possible to isolate the CDI-activated intermediate. However, the sequential one-pot procedure enabled the formation of the desired product in 24% yield (Scheme 85). We believe that with this particular substrate, the coupling goes through the intermediary formation of an isocyanate.



Scheme 85. Sequential one-pot procedure with aniline as the amino partner.

II.3 Optimisation of the reaction conditions and scope of the reaction

We, further, moved on to the synthesis of general amides. In the absence of sensitive substrates, we thought we could have adapted our parameters in order to improve the kinetics without modifying the efficiency of the reaction. After having chosen our model substrates, we performed the reaction with the classical conditions (Scheme 86).

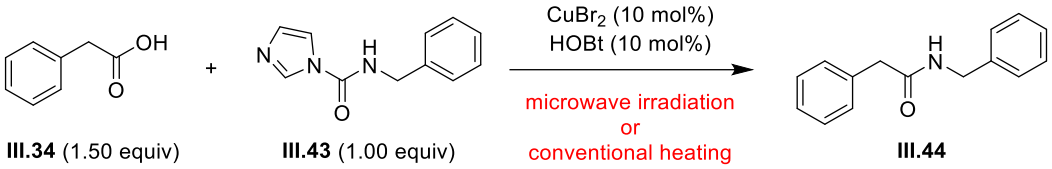


III.34 (1.50 equiv) **III.43** (1.00 equiv) **III.44** (66%)

Scheme 86. Classical conditions applied to general amides.

Encouraged by the yield obtained (66%), we decided to further investigate the reaction with microwave irradiation which gave us good results in reduced reaction times. For comparison, we conducted some experiments also by conventional heating. The results are presented in Table 12:

Table 12. Optimisation of the reaction conditions.



III.34 (1.50 equiv) **III.43** (1.00 equiv) **III.44**

Entry	Concentration	Time	Heating	Yield (%)
1	1.0 M	30 min	60 °C	58
2	0.5 M	30 min	60 °C	77
3	0.5 M	60 min	60 °C	77
4	0.5 M	30 min[a]	60 °C	72
5	**0.5 M**	**60 min[a]**	**60 °C**	**76**
6	0.5 M	12 hours[a]	60 °C	78

[a] Reactions performed with conventional heating.

Entry 1 shows that after 30 minutes, using the conditions in the presence of $CuBr_2$/HOBt, the dipeptide was obtained in 58% yield. Microwave irradiation did not improve the result as we had expected but the isolated yield of 58% is a quite good one for only 30 minutes of coupling. However, when the dichloromethane solution was more diluted, **III.44** was obtained in an improved 77% of yield (entry 2). In addition, varying the reaction time (30 min vs 60 min) did not have a remarkable impact on the efficiency (entry 3). Moreover, the comparison between microwave irradiation and conventional heating (entries 4-6) was made in order to prove if microwave irradiation had an impact on the efficiency of the reaction or if it was just increasing the temperature the key to improve the yield. The main factor that allows the couplings in such reduced reaction time (30 min vs 20 h) seems to be the heating and not a microwave effect as similar yields were obtained.

Given these observations, we pursued our studies by realising a scope of general amides (Figure 19). The conditions chosen were the ones reported in Table 12, entry 5.

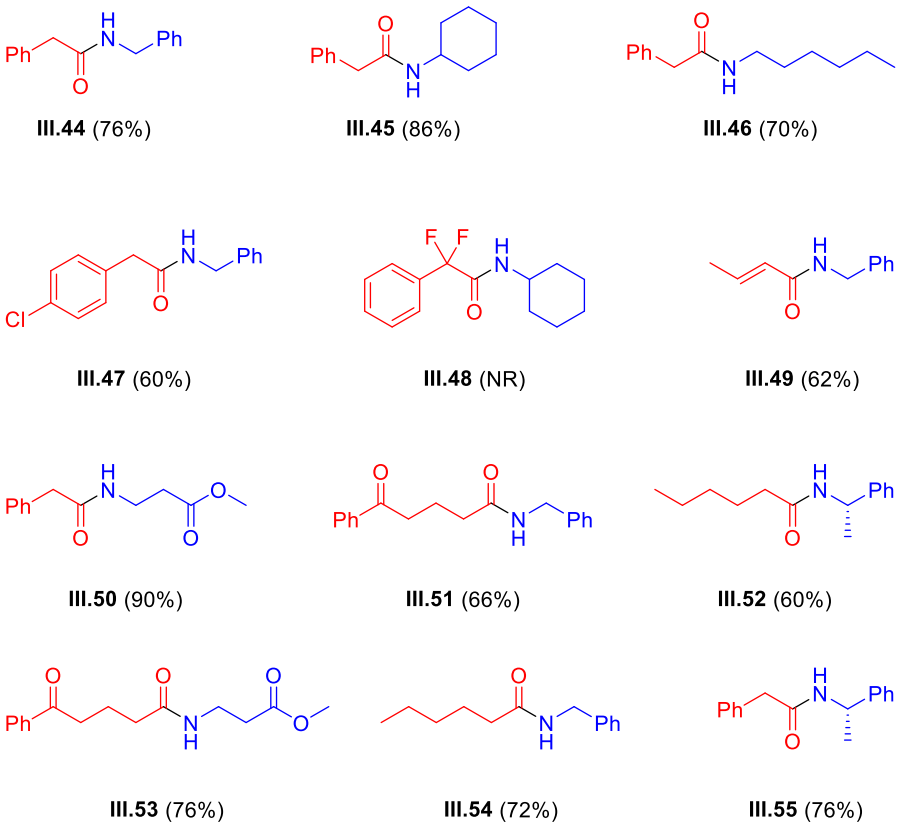


Figure 19. Scope of general amides.

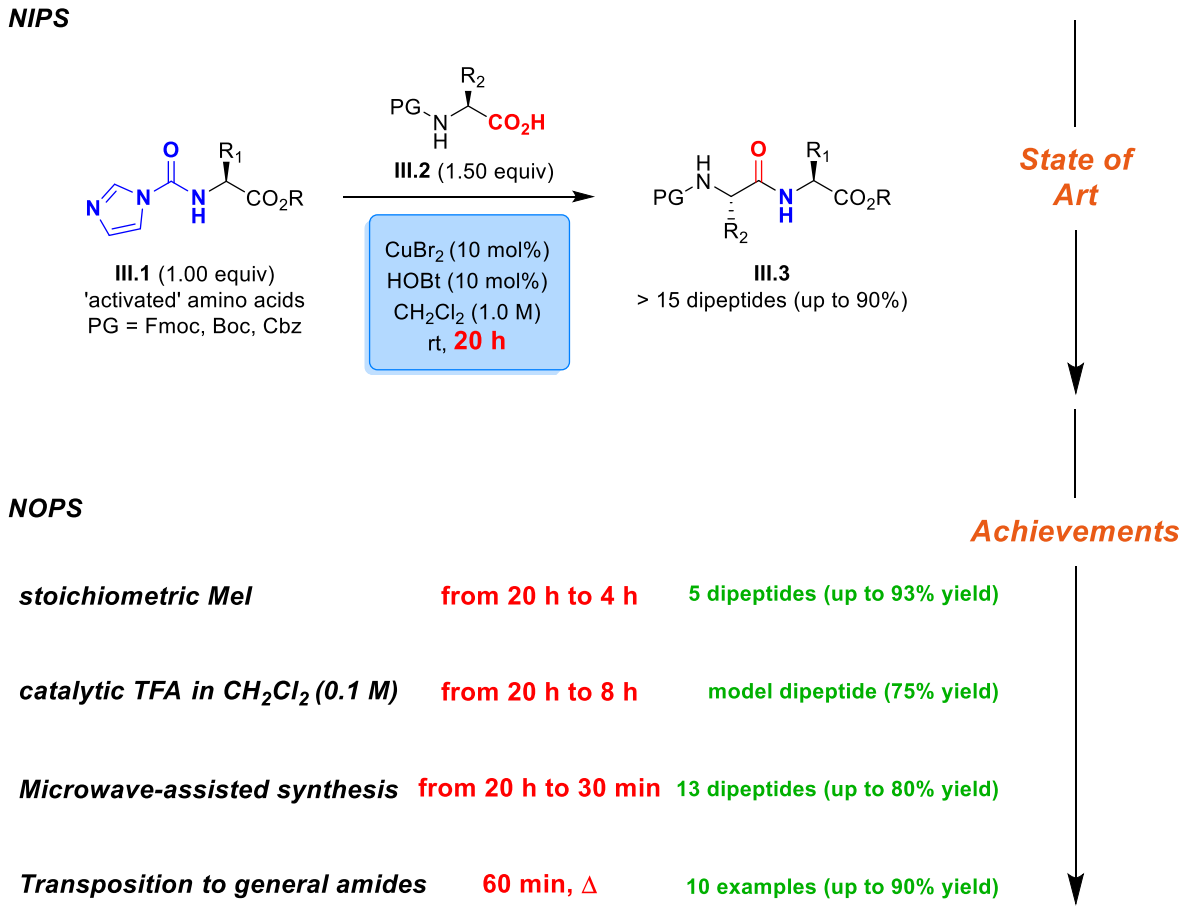
Moving from sensitive substrates, such as amino acids, to general carboxylic acids and amines lead us to believe that the coupling reaction could have been easier to handle. However, the amides studied were isolated in moderate to good yield, and the reaction was also substrate dependent. In particular, we observed in both, carboxylic and amine derivatives, that alkyl and benzyl chains were well tolerated. When α,β-unsaturated carboxylic acids were employed, the reaction did not give the expected product or it was isolated in low yields (such as **III.49**). In the presence of aryl chains (substrates such as benzoic acid), the corresponding amides were not obtained. Moreover, we might consider the influence of the pKa.[147] For example, this could be the explanation for the observed outcomes if we compare the results obtained with the

[147] see the table pKa Data Compiled by R. Williams
https://organicchemistrydata.org/hansreich/resources/pka/pka_data/pka-compilation-williams.pdf

phenylacetic acid (pKa value 4.31) and the more acidic α,α-difluorophenylacetic acid.[148] In the first case, we obtained the amide in 86% (compound **III.44**) and in the second, we did not detect the formation of the amide.

In conclusion (Scheme 87), we were able to transpose the conditions devised for dipeptide synthesis to the synthesis of general amides. By using either microwave irradiation or conventional heating, general amides were isolated in moderate to good yields in very short reactions time. Even though the reaction seems to be substrate dependent, we could propose an alternative strategy that is quite mild and practical to access such valuable structures. Indeed, in addition of short reaction times (only 1 hour), the couplings take place in a catalytic procedure that is base-free and quite atom economic (one equivalent of imidazole is the unique by-product formed in addition to the expected amides).

[148] pKa are not described but the correlation of pKa for CH_3COOH and CF_2HCOOH is 4.76 and 1.3, we can suppose the same correlation for the phenylacetic acid and the corresponding difluorinated compound (CHIMIE BIOORGANIQUE ET MÉDICINALE DU FLUOR, Jean-Pierre Bégué, Danièle Bonnet-Delpon, CNRS Editions, **2005**); Goss K.-U. *Environ. Sci. Technol.* **2008**, *42*, 456.



Scheme 87. From Nips to Nops: achievements.

III. Aspects mécanistiques de la réaction

L'ensemble des expériences menées et des résultats obtenus nous permettent de proposer une première hypothèse mécanistique (rendant compte globalement des résultats obtenus). Dans ce chapitre, différentes expériences de suivi (RMN; HPLC) et manipulations de contrôle seront décrites pour essayer d'affirmer cette hypothèse mécanistique.

III.1.1 Réaction en présence de base

La première observation est liée à la présence d'une base dans la réaction de couplage. En présence de 1,50 équivalent de N,N-diisopropyléthylamine (DIEA), aucune réaction n'est observée (Schéma 88a), alors que la même réaction en l'absence de base (Schéma 88b) conduit au dipeptide **III.3a** avec un bon rendement.

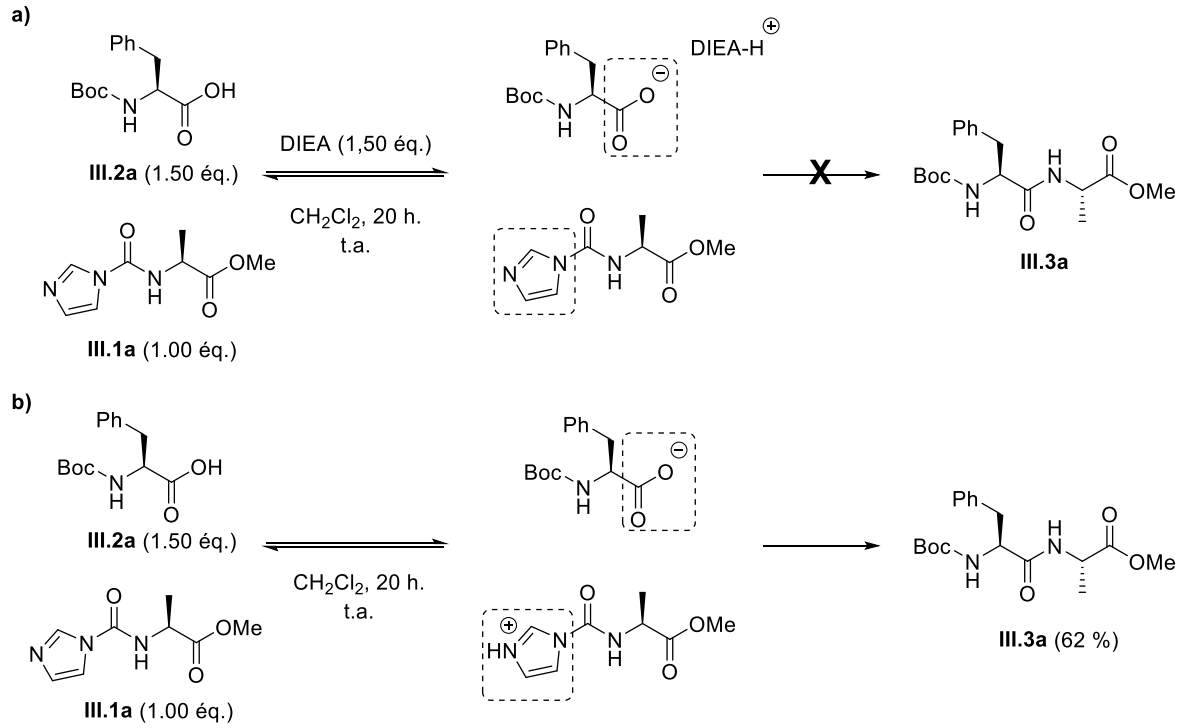


Schéma 88. Résultats de la réaction de couplage en présence et non d'une base.

Le proton de l'acide carboxylique semble donc avoir un rôle essentiel dans la réactivité. En présence de base (Schéma 88a), il semblerait que le carboxylate ne soit pas assez nucléophile, ou que l'imidazole ne soit pas un assez bon groupe partant pour permettre la réaction. Au contraire, en l'absence de base, la protonation réversible de l'imidazole permettrait de générer deux espèces plus réactives: un carboxylate nucléophile et un imidazolium meilleur groupement partant.

III.1.2 Réaction en présence d'iodométhane

La formation d'un imidazolium plus réactif est également attestée lors de l'utilisation d'iodomethane qui (voir section I.1.3) permet d'accélérer de façon significative la cinétique de réaction (4 h vs 20 h, Schéma 89).

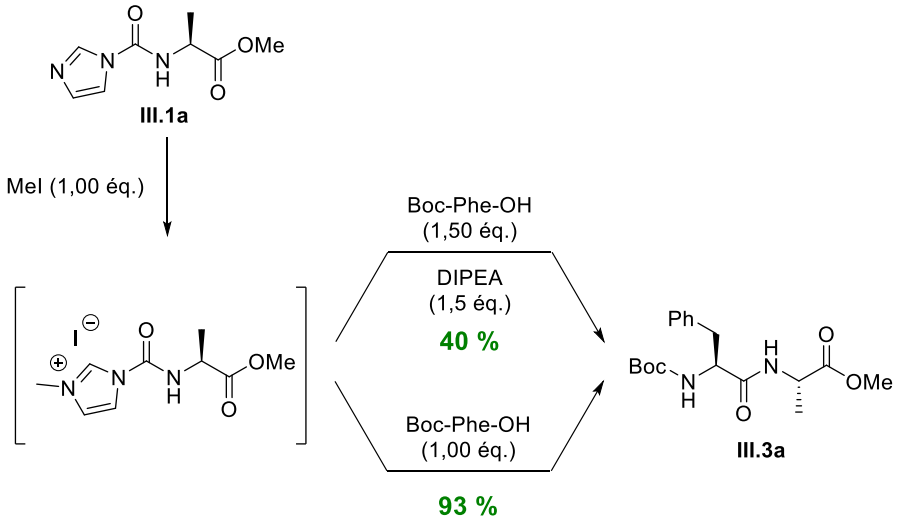


Schéma 89. Réactivité en présence d'iodomethane.

Nous avons pu toutefois montrer que la transformation en N-méthyl imadazolium n'était probablement pas complète comme en atteste le suivi CCM (voir Schéma 68, Section I.1.3). Comment donc expliquer une cinétique accrue si la conversion en N-méthyl imidazolium n'est pas complète? En présence d'iodométhane et de base, un rendement de 40 % est observé. Il semblerait que ce faible rendement provienne de la méthylation incomplète de l'imidazole, et que la réaction ne fonctionne qu'à hauteur de la quantité de N-méthyl imidazolium formé (Schéma 90).

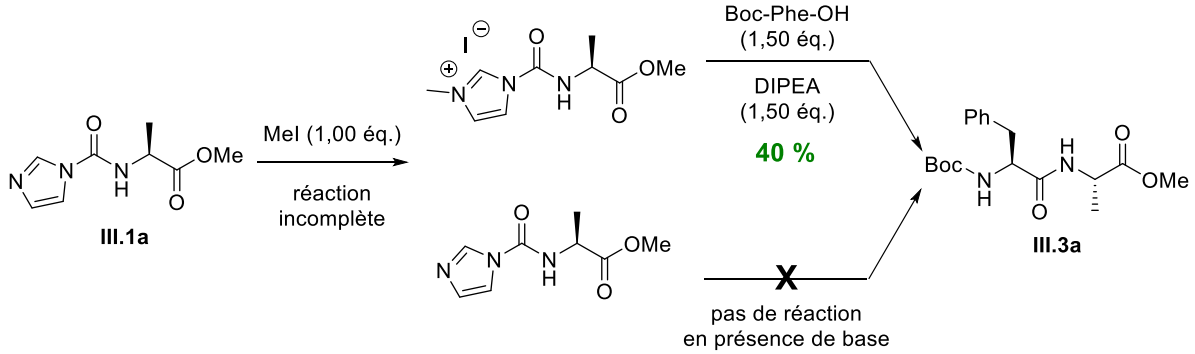


Schéma 90. Réactivité en présence de MeI et DIPEA.

La partie du Imi-Ala-OMe non méthylée ne réagit pas avec l'acide carboxylique en présence de base, et rend compte du rendement modéré observé (40 %). Lorsque la réaction est effectuée en l'absence de base, le dipeptide est isolé avec un rendement de 93 % (Schéma 91). Dans ces conditions, les deux formes activés **A** et **B** pourraient réagir de façon synergique et expliquer ainsi à la fois la cinétique (4 h vs 20 h) et le rendement accrus. En effet la formation incomplète du dérivé **A** va permettre l'occurrence d'un mécanisme parallèle via l'intermédiaire **B**. La formation via cet intermédiaire du dipeptide va permettre de libérer une molécule d'imidazole qui, à son tour va permettre, de déprotoner le Boc-Phe-OH pour générer un carboxylate suffisamment nucléophile pour substituer l'intermédiaire **A**. La combinaison de ces deux mécanismes fonctionnant en parallèle, permettrait ainsi d'expliquer le rendement excellent de 93 % en seulement 4 h (contre 20 h en l'absence de MeI) alors même que la formation de N-méthyl imidazolium n'est pas complète (comme attesté dans le suivi CCM).

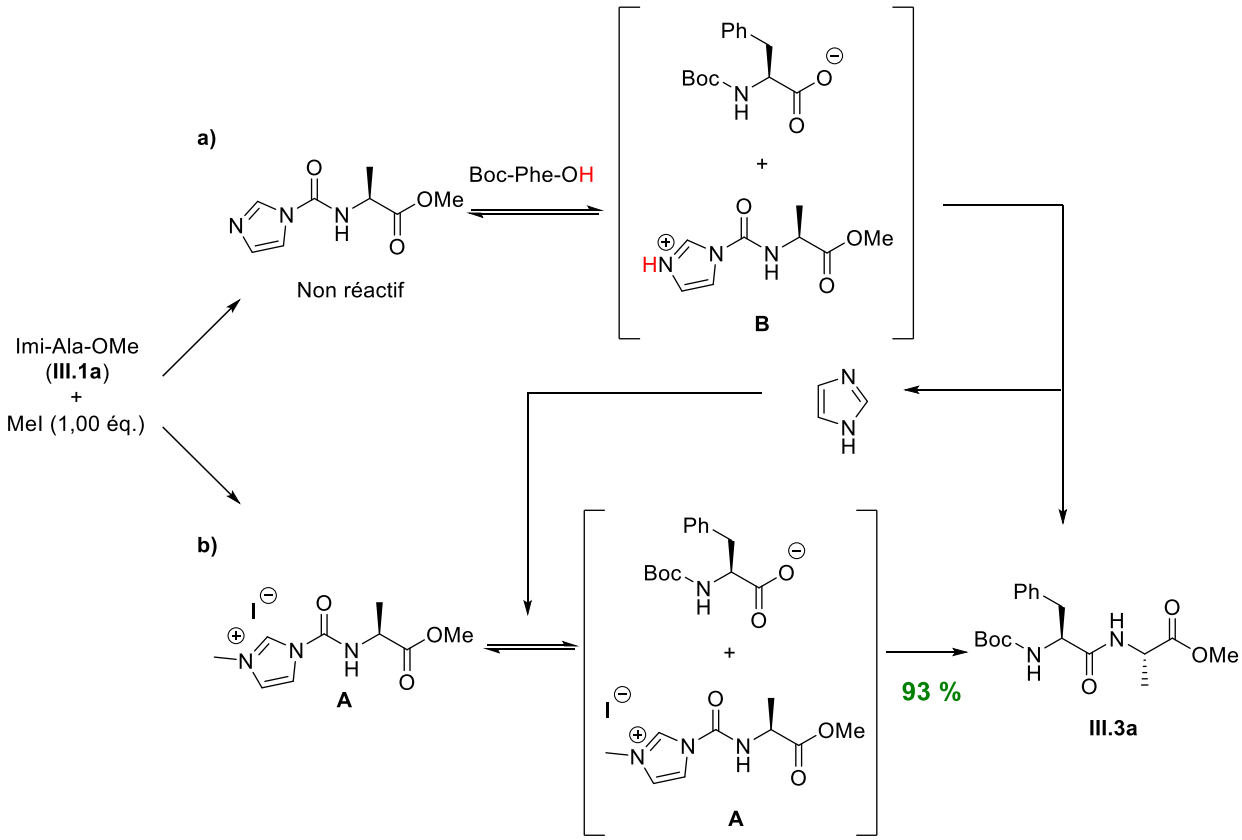


Schéma 91. Effet synergique des intermédiaires.

Si une conversion complète en N-méthyl imidazolium n'est peut-être pas nécessaire pour garantir un bon rendement, il aurait été intéressant de tester l'utilisation de quantités sous-stoichiometrique d'iodomethane (10, 50 mol %).

Quoi qu'il en soit, ces observations semblent indiquer que le mécanisme puisse passer dans un premier temps par la formation parallèle d'un sel d'imidazolium (plus électrophile que son équivalent imidazole) et d'un carboxylate nucléophile (Schéma 92).

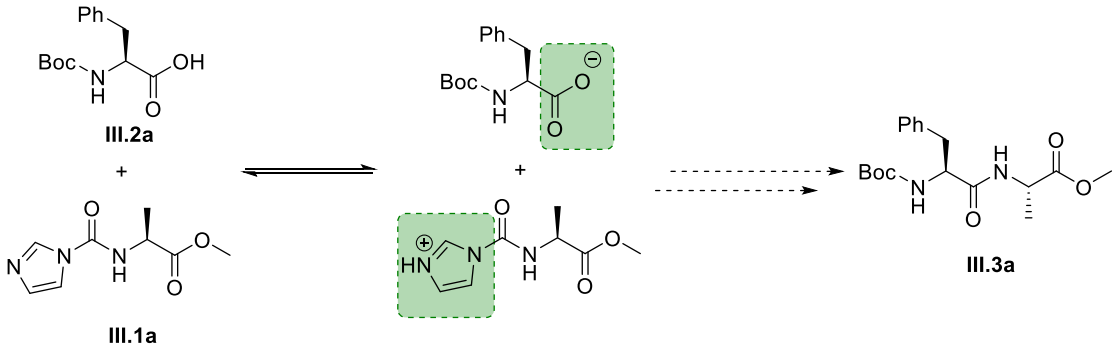


Schéma 92. Intermédiaires clés.

Néanmoins l'évolution de ces intermédiaires reste inconnue, et nous avons donc cherché à établir, corroborer certaines hypothèses permettant d'expliquer la formation du dipeptide final. En présence du carboxylate et de l'imidazolium, la formation d'un « anhydride carbamique » semble être l'hypothèse la plus solide (voir section suivante).

III.1.3 Hypothèses mécanistiques

Deux voies réactionnelles sont envisageables pour la formation d'un anhydride carbamique (**III.58**) comme intermédiaire clé (Schéma 93) :

- Voie bleue : addition directe du carboxylate sur l'imidazolium et expulsion de l'imidazole.
- Voie rouge : l'imidazolium pourrait être en équilibre avec la forme isocyanate (**III.57**). À ce stade, le carboxylate (Boc-AA-O^-) peut alors s'additionner pour conduire à la formation de l'anhydride carbamique (**III.58**).

L'évolution de cet intermédiaire vers la liaison amide pourrait également se faire via plusieurs chemins réactionnels :

- Voie a : une réaction intramoléculaire de transfert 1→3 d'acyle, avec dégagement de CO_2, peut permettre la formation directe de la liaison peptidique.
- Voie b : l'anhydride carbamique (**III.58**) peut réagir avec l'imidazole libéré et conduire à la formation d'un intermédiaire acyl-imidazole (**III.59**) avec dégagement de CO_2 et H-AA-OMe (**III.60**). Ce dernier peut à son tour réagir avec l'acyl-imidazole et conduire à la formation de la liaison peptidique.

- Voie c : l'intermédiaire anhydride carbamique (**III.58**) peut également évoluer, via une réaction intramoléculaire, vers une oxazolone (**III.61**). Cette dernière peut conduire au dipeptide par réaction avec H-AA-OMe libéré.

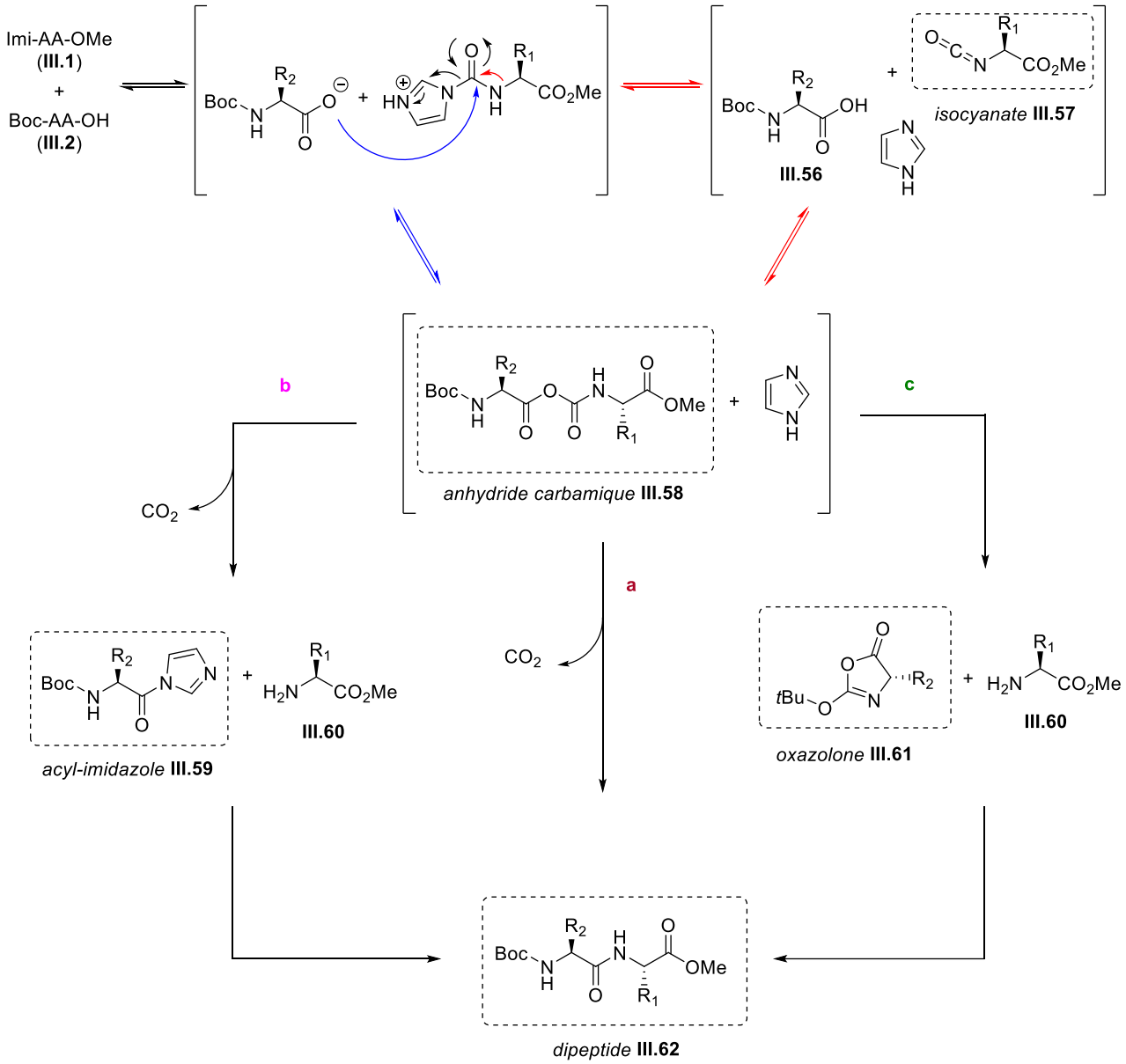


Schéma 93. Hypothèses mécanistiques et intermédiaires.

Dans la littérature, relativement peu de choses sont connues sur la synthèse et réactivité de ces anhydrides carbamiques. En 2004, R. Vaidyanathan et al.[149] ont décrit l'utilisation de CO_2 dans la réaction entre un acyl-imidazole et une amine (Schéma 94).

[149] R. Vaidyanathan, V.G. Kalthod, D.P. Ngo, J.M. Manley, S.P. Lapekas *J. Org. Chem.* **2004**, *69*, 2565.

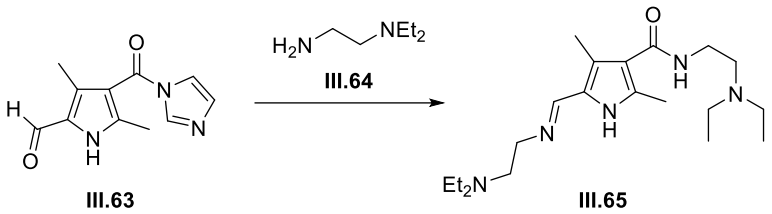


Schéma 94. Réactivité de l'acyl-imidazole avec une amine.

En l'absence de CO_2, la conversion est faible alors que l'ajout de CO_2 permet d'augmenter la cinétique de réaction (Figure 20).

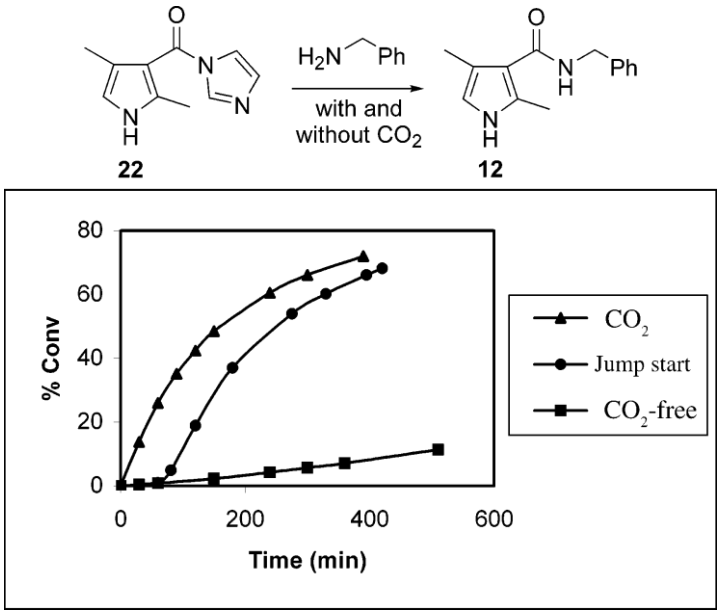


Figure 20. Cinétique de la réaction (copie de la publication originale).[29]

Pour expliquer ce résultat, les auteurs proposent que l'amine pourrait être carbonatée pour conduire au dérivé **III.68** (Schéma 95).

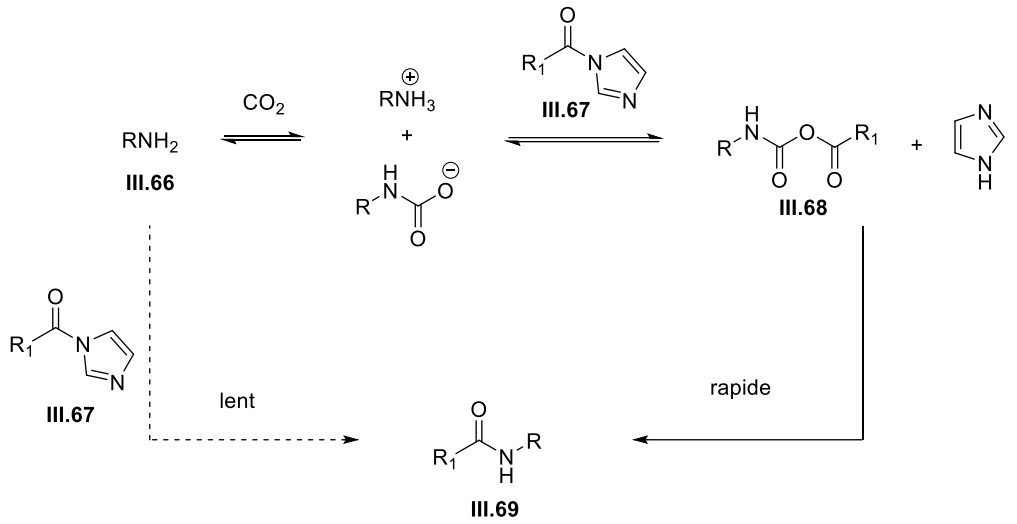


Schéma 95. Hypothèse de mécanisme en présence de CO_2.

Cette hypothèse d'un intermédiaire « anhydride carbamique » beaucoup plus réactif qu'un acyl-imidazole renforce notre hypothèse mécanistique (voie a, Schéma 93).

Plus récemment, et à la suite de la publication de notre premier article[116] sur la réactivité des N-acyl-imidazole, Jiang et Bi[150] ont étudié de façon systématique les différentes possibilités de transformation de l'anhydride carbamique (Schéma 96). Ils ont pu montrer que le transfert 1,3-acyle était favorisé dans tous les cas étudiés.

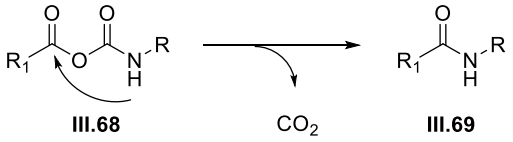


Schéma 96. 1,3 Transfert d'acyle proposé par Jiang et Bi.

III.1.4 Suivi de la cinétique de réaction par HPLC et RMN

Dans le but d'obtenir des informations sur la cinétique de la réaction et idéalement de pouvoir identifier les intermédiaires réactionnels, nous nous sommes attelés à suivre la réaction par HPLC, puis par RMN ^{1}H.

[150] Y.-Y. Jiang, T.-T. Liu, R.-X. Zhang, Z.-Y. Xu, X. Sun, S. Bi *J. Org. Chem.* **2018**, *83*, 2676.

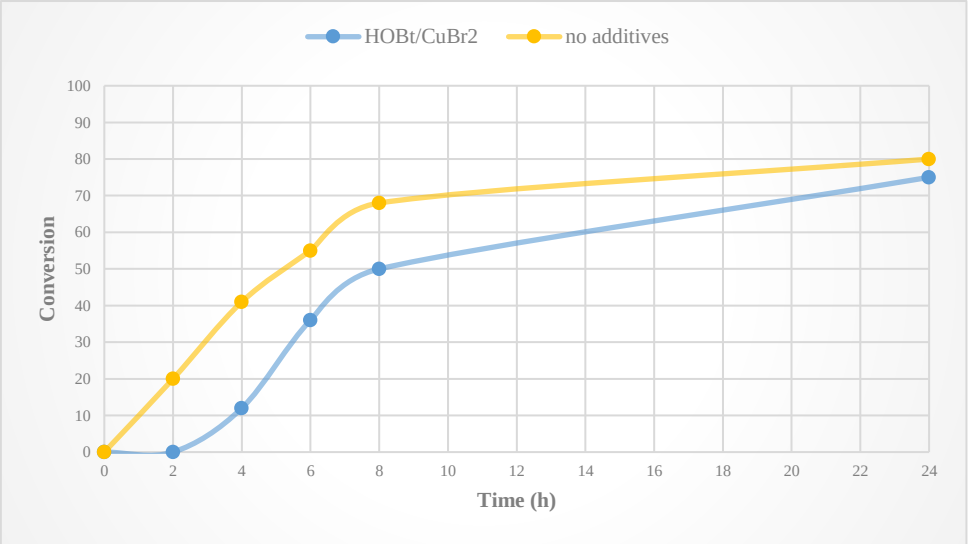


Figure 21. Suivi de la réaction par HPLC.

Comme précisé au début de ce chapitre (voir Figure 10), nous avons suivi par HPLC la transformation de Imi-Ala-OMe en présence de Boc-Phe-OH (Figure 21). La présence d'un étalon interne (Boc-Phe-Val-OMe, présentant un profil comparatif à celui de Boc-Phe-Ala-OMe) nous a permis de suivre la cinétique de réaction en l'absence ou en présence des additifs comme HOBt/$CuBr_2$. Comme préalablement observé expérimentalement, la réaction est relativement lente et n'évolue quasiment plus après 8 h. La réaction est (comme observé également en CCM) propre et nous n'avons pas pu identifier d'autres intermédiaires majeurs qui auraient pu s'accumuler dans le milieu réactionnel. Compte-tenu du peu d'information apportées par cette première analyse HPLC, nous n'avons pas pu juger opportun d'étudier cette réaction par LC-MS et nous nous sommes tournés vers la RMN ^{1}H. En collaboration avec A. Lebrun (L.M.P., Université de Montpellier) une réaction modèle entre l'Imi-Ala-OMe et l'acide 4-chlorophényl acétique a été choisie. Le choix hybride de ces deux partenaires a été fait pour minimiser le nombre de massifs et simplifier les spectres RMN, ainsi que pour éliminer la possibilité de rotamèrs autour de la liaison carbamate dans le cas de l'étude d'un dipeptide comme Boc-Phe-Ala-OMe. Pour des raisons de simplicité, les réactions ont également été menées en l'absence de HOBt/$CuBr_2$ (Schéma 97).

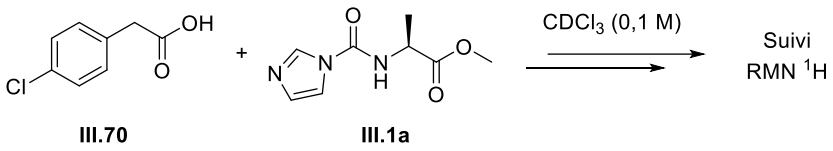


Schéma 97. Réaction modèle pour le suivi RMN ^{1}H.

D’un point de vue expérimental, les réactifs ont été rajoutés dans le tube RMN et la réaction suivie par une acquisition toutes les heures. Un premier suivi a été réalisé en mélangeant l’Imi-Ala-OMe (1,00 éq.) et l’acide 4-chlorophényl acétique (1,50 éq.) dans le $CDCl_3$ ([C] = 0,1 M). Ainsi un premier spectre a été enregistré au bout de 5 minutes (spectre noir en bas dans la figure 22) puis ensuite à 1 h (spectre rouge) pour arriver au spectre rouge (spectre en haut de la figure 22) après 24 h.

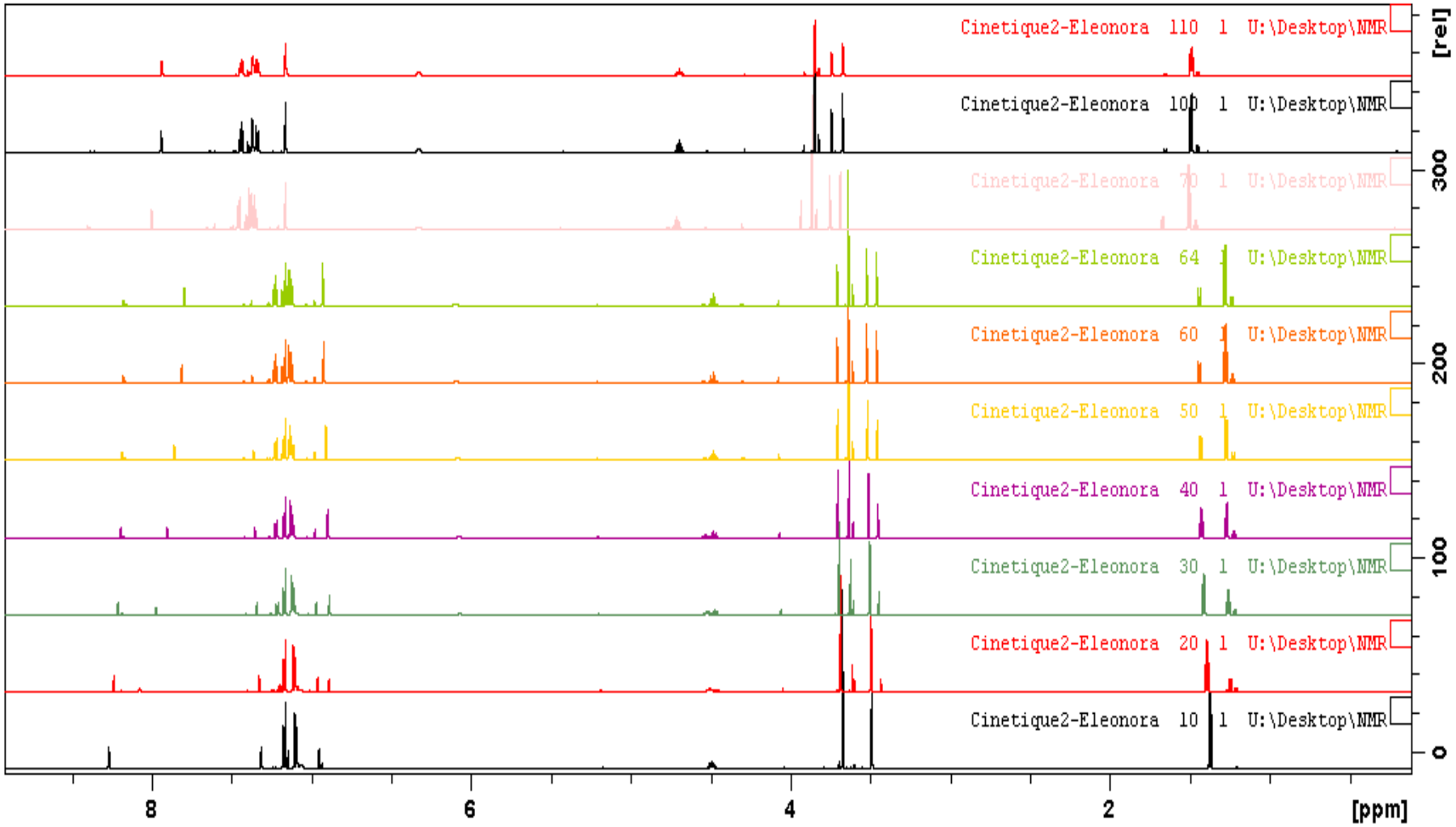


Figure 22. Superposition de spectres ^{1}H RMN.

Sur ces différents spectres, on peut observer l'évolution de différentes espèces notées A-F (Figure 23). Leurs pourcentages respectifs ont été qualitativement estimés par rapport à leurs intégrations respectives.

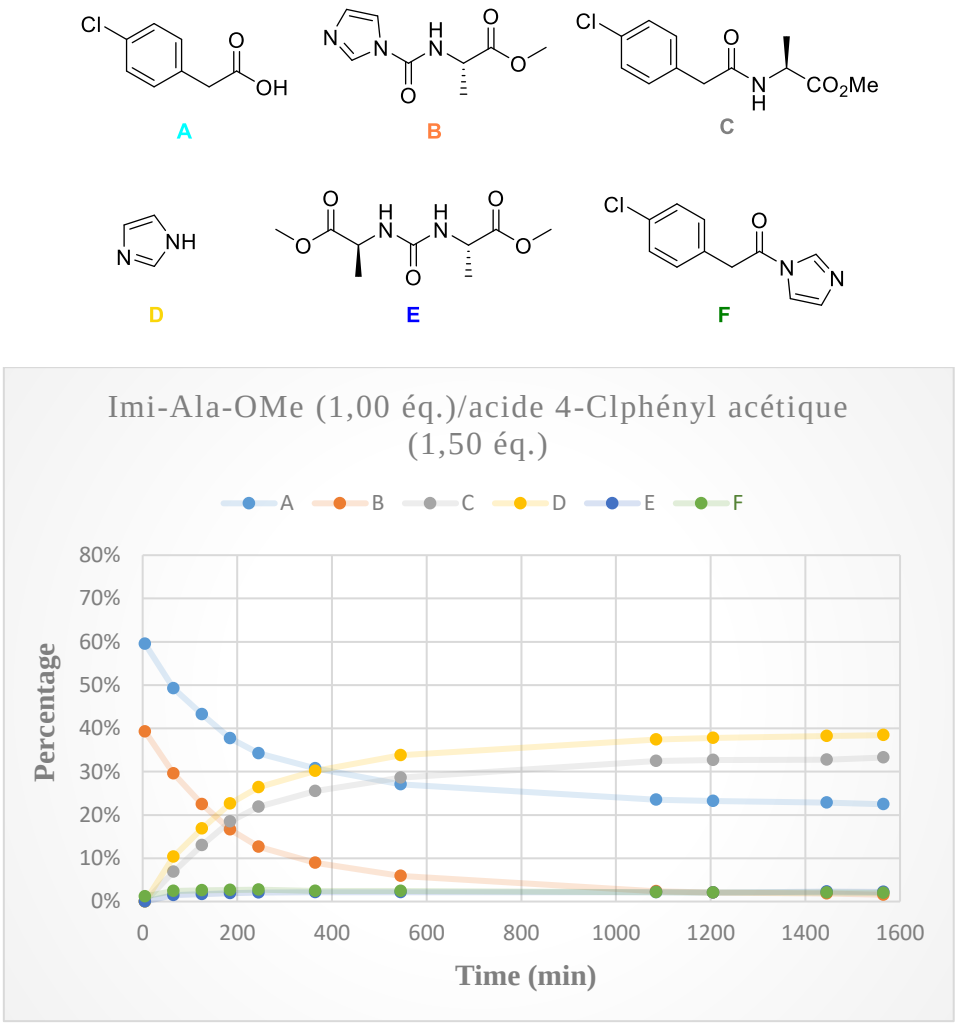


Figure 23. Composés observés (haut de la figure); RMN suivi de la réaction de couplage avec Imi-Ala-OMe (1,0 éq.) et l'acide carboxylique (1,5 éq.) (bas de la figure).

Comme cela avait pu être observé expérimentalement, et lors du suivi HPLC, la réaction est lente et semble atteindre un palier après 600 min (10 h). En effet à ce stade, l'Imi-Ala-OMe (**B**) semble avoir été totalement consommé. L'urée symétrique **E**, et le dérivé acyl-imidazole **F** qui sont formés dès le début de la réaction, mais dont la quantité ne semble pas évoluer au cours du temps sont également observés. L'urée symétrique **E** est le produit secondaire parfois observé dans nos réactions de couplage et peut provenir de la décomposition partielle de l'Imi-Ala-OMe.

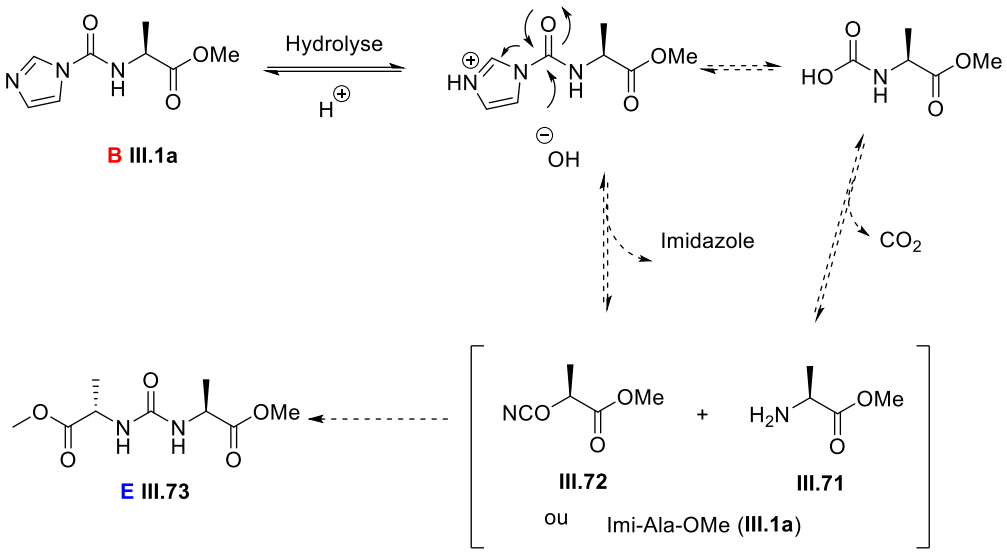


Schéma 98. Mécanisme plausible pour la formation de l'urée symétrique.

Cette urée symétrique est notamment visible lorsque les réactions sont menés en milieu acide fort. Cette réaction, même minime, doit être circonscrite car elle consomme deux équivalents de **B** qui est ici en défaut.

L'autre produit est l'acyl-imidazole **F** qui provient de l'activation de l'acide 4-chlorophényl acétique (**A**). Encore une fois ce produit est présent dès le début de la réaction mais sa proportion n'évolue pas au cours du temps.

Dans cette expérience de suivi RMN on n'observe pas l'isocyanate **G**, ni l'anhydride carbamique **H** (Figure 24). Soit qu'ils ne se forment pas, ou plus probablement dans le cas du composé **H** qu'il soit très rapidement consommé et ne s'accumule pas donc pour pouvoir être observé.

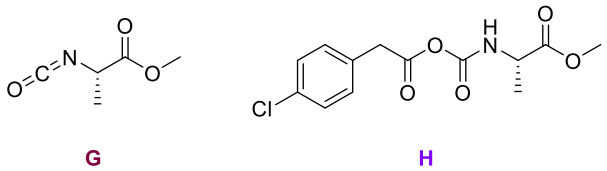


Figure 24. Intermédiaires non détectés par suivi RMN ^{1}H.

L'observation majeure après ce premier suivi RMN est qu'après 600 min l'Imi-Ala-OMe en défaut est quasiment tout consommé et que la réaction ne peut donc plus évoluer. Cela nous a donc conduit à étudier la même réaction avec un excès d'Imi-Ala-OMe (1,50 éq.) par rapport à l'acide 4-chlorophényl acétique (1,00 éq.). Les résultats, comme précédemment, sont exprimés en fonction des intégrations respectifs des différents signaux caractéristiques (Figure 25).

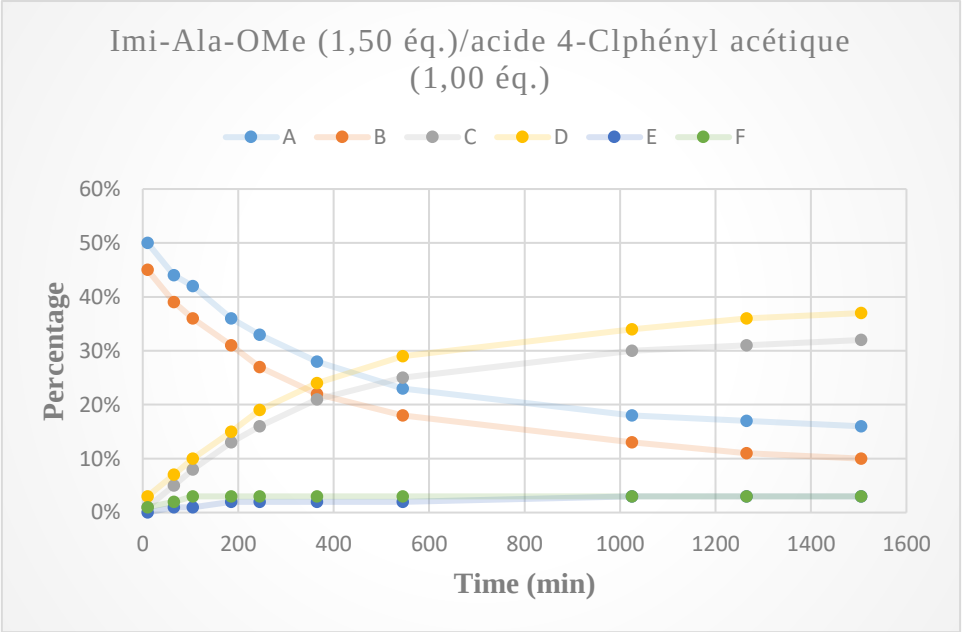


Figure 25. Suivi RMN de la réaction de couplage avec Imi-Ala-OMe (1,50 éq.) et l'acide 4-clorophényl acétique (1,00 éq.).

Dans ce cas on observe, comme préalablement, une cinétique lente et la formation minoritaire de l'urée symétrique **E** et de l'acyl-imidazole **F**. Toutefois, on observe toujours même après 24 h la présence d'**A** et **B** qui n'ont pas réagi.

Dans une troisième expérience, comme la réaction ne semble pas arriver à complétion avec un excès d'Imi-Ala-OMe, une réaction en présence de quantités équimolaires des deux substrats, **A** et **B**, a été étudiée (Figure 26).

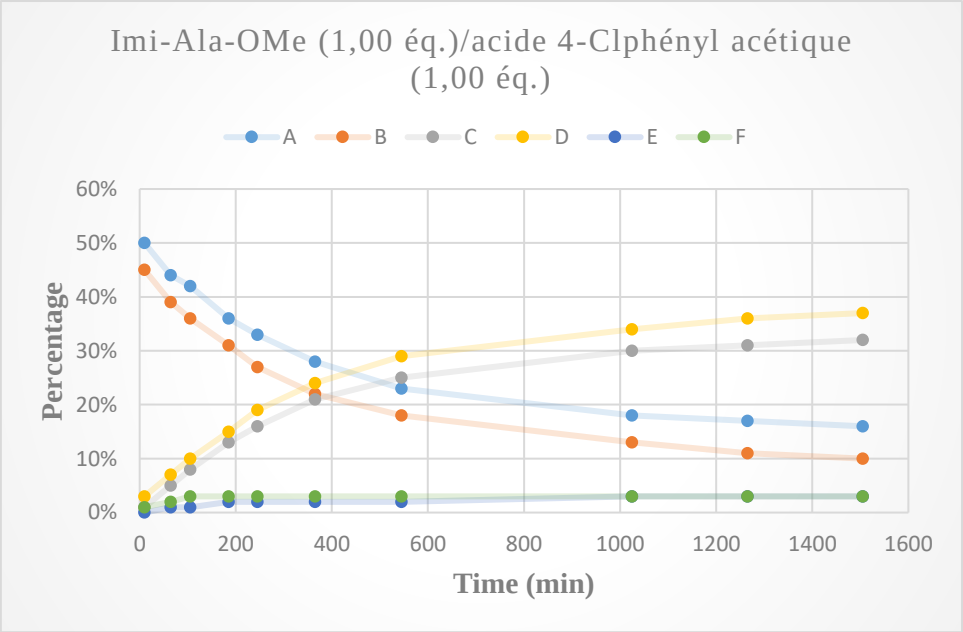


Figure 26. Suivi RMN de la réaction avec l'Imi-Ala-OMe (1,00 éq.) et l'acide 4-clorophényl acétique (1,00 éq.).

Comme précédemment, on observe au bout de 24 h, une réaction incomplète avec la présence des 2 réactifs **A** et **B** non complétement transformés.

En conclusion, ce suivi RMN ne nous a pas réellement permis de déterminer le mécanisme de la réaction tel que décrit dans le Schéma 93, et d'observer la formation de l'intermédiaire « anhydride carbamique ». Ces résultats néanmoins illustrent la « fragilité » de l'Imi-Ala-OMe de départ. En effet, sa dégradation peut conduire à la formation d'une urée symétrique **E** qui consomme 2,00 équivalents d'Imi-Ala-OMe ce qui peut être problématique si celui-ci est utilisé en défaut. Effectivement, d'un point de vue expérimentale, on retrouve cette tendance avec l'obtention de meilleurs rendements avec l'utilisation de 2,00 éq. de l'Imi-Ala-OMe (Schéma 99).

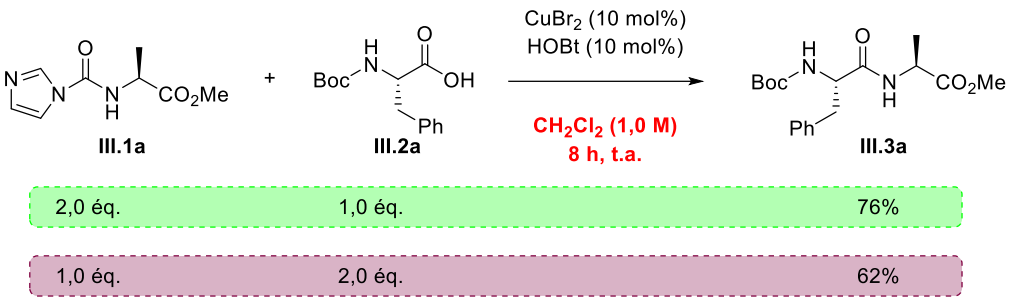


Schéma 99. Comparaison de la réaction de couplage modèle avec un excès et un défaut d'Imi-Ala-OMe.

Si ces conditions de réaction conduisent à de meilleurs rendements, elles sont synthétiquement moins intéressantes car l'Imi-Ala-OMe nécessite une étape supplémentaire de synthèse.

La conversion incomplète lors de l'utilisation d'un défaut (ou d'une quantité équimolaire) d'Imi-Ala-OMe pourrait s'expliquer de la façon suivante : après 50 % de conversion, si 50 % du dipeptide sont bien formés, 50 % d'imidazole seront aussi formés (Schéma 100).

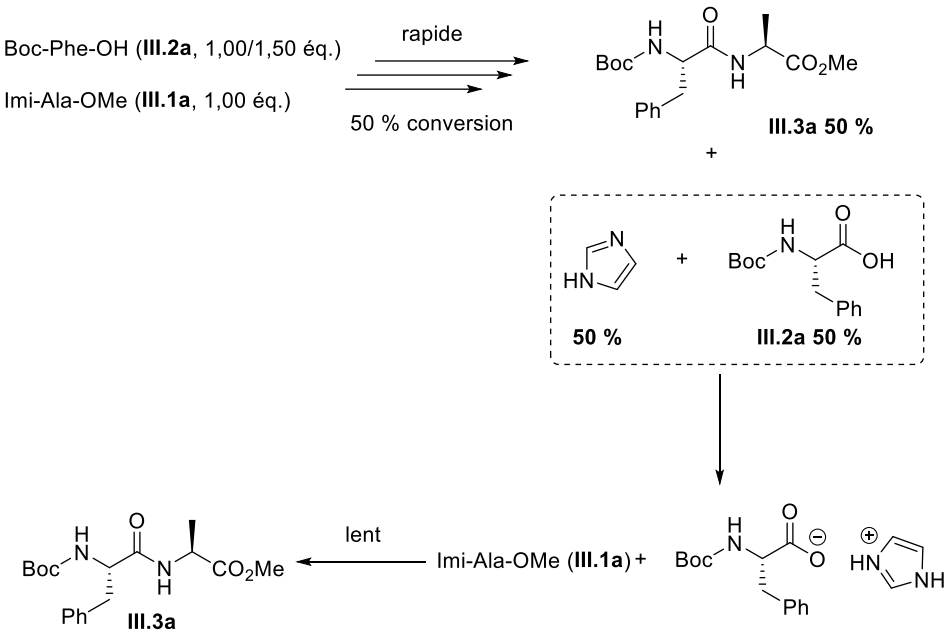


Schéma 100. Proposition de mécanisme lorsque l'Imi-Ala-OMe n'est pas utilisé en excès.

Dans ce cas, l'imidazole (0,5 éq.) ainsi formé pourra déprotoner l'acide carboxylique restant (0,5 éq.). Le carboxylate ainsi formé, l'imidazolium ne pourra donc pas être formé et la cinétique de synthèse de l'amide stoppée, ou tout du moins très ralentie.

III.1.5 Quelle stratégie utiliser pour accélérer la cinétique?

Piéger cet excès d'imidazole ainsi pourrait donc permettre d'avoir une conversion complète de Imi-Ala-OMe. Par exemple, comme décrit préalablement dans le manuscrit (voir Chapitre 3, section I.2), la réaction peut être effectuée en présence de TFA avec des résultats comparables à ceux observés avec HOBt/$CuBr_2$ (Schéma 101).

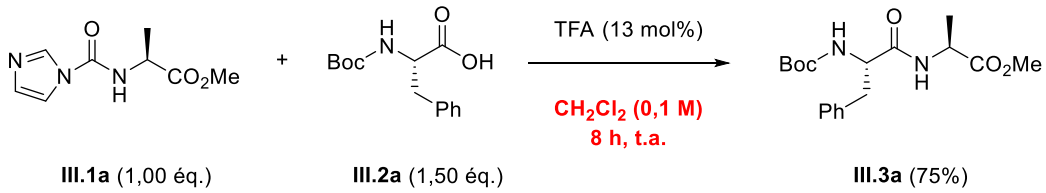
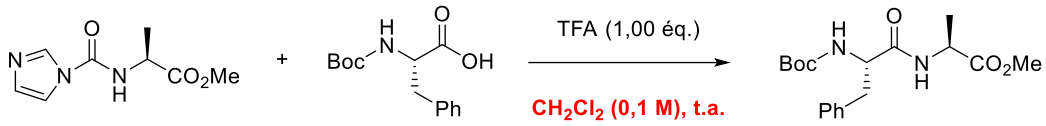


Schéma 101. Réaction de couplage avec TFA comme additif.

Toutefois aucune des conditions testées ne nous ont permis d'augmenter de façon significative la cinétique de la réaction.

Également, avec l'objectif de piéger l'imidazole au fur et à mesure de sa libération dans le milieu réactionnel, des essais ont été effectués avec un ajout lent (goutte à goutte) de TFA, sans qu'aucune amelioration du rendement n'ait pu être observée (Tableau 13).

Tableau 13. TFA pour réduire le temps de réaction : études préliminaires.



III.1a (1,00 éq.) **III.2a** (1,50 éq.) **III.3a**

Entry	Additives	Time (h)	Yield (%)
1	**TFA**[a]	4	66%
2	**TFA**[a]	8	80%

[a] Ajout de TFA effectué au fur et à mesure pendant tout le temps de réaction.

Ces essais concluent les travaux réalisés sur l'optimisation des conditions de couplage peptidique « inversé ». Un résumé de tous ce travaux d'optimisation et des perspectives associés sera donné dans la partie de conclusion générale et perspectives. Mais avant cela, comme décrit dans l'introduction de ce travail, nous allons montrer nos travaux paralléls dans le cadre de la synthèse de 3-pyrrolines à partir de vinyl aziridine.

IV. Synthesis of 3-Pyrrolines from Vinyl Aziridines

In the meantime, during my PhD thesis, we also focused our attention on a side-project based on the work conducted by Dr. Kim Spielmann, a former PhD student in our laboratory.

I. The importance of N-heterocycles

N-heterocyclic compounds are broadly distributed in nature, possess physiological and pharmacological properties and are constituents of many biologically important molecules, including many vitamins, nucleic acids, pharmaceuticals, antibiotics, dyes and agrochemicals amongst many others (Figure 27).[151] These molecules have thus received increasing attention over the past two decades. Many organic synthesis protocols have been published, increasing their applications in chemical and health sciences.[152]

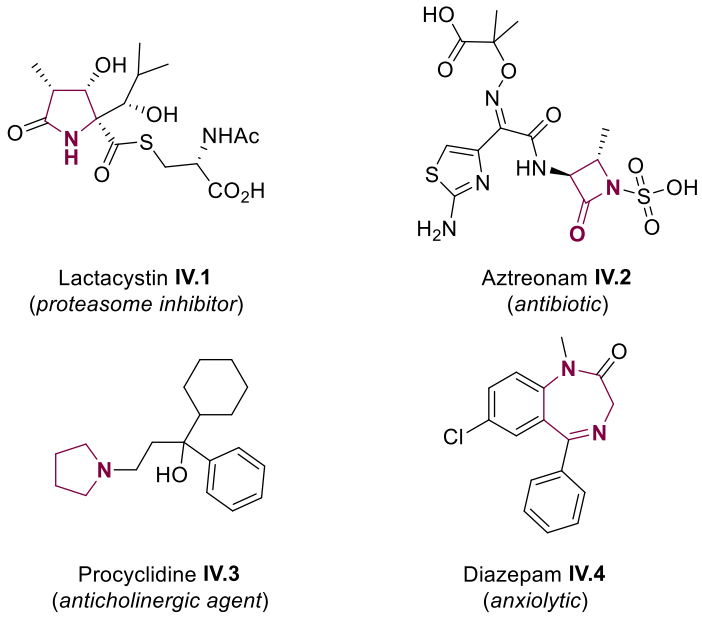


Figure 27. Examples of drugs-containing *N*-heterocycles.

According to the FDA databases, nearly 59% of unique small-molecule drugs that are approved contain a nitrogen heterocycle (Figure 28).[153]

---

[151] a) B. Eftekhari-Sis, M. Zirak, A. Akbari *Chem. Rev.* **2013**, *113*, 2958; b) Y. Ju, R.S. Varma *J. Org. Chem.* **2006**, *71*, 135; c) D.Z. Zarate, R. Aguilar,R.I. Hernandez-Benitez, E.M. Labarrios, F. Delgado, J. Tamariz *Tetrahedron* **2015**, *71*, 6961.

[152] N. Kerru, L. Gummidi, S. Maddila, K. Kumar Gangu, S.B. Jonnalagadda *Molecules*, **2020**, *25*, 1909.

[153] E. Vitaku, D.T. Smith, J.T. Njardarson *J. Med. Chem.* **2014**, *57*, 10257.

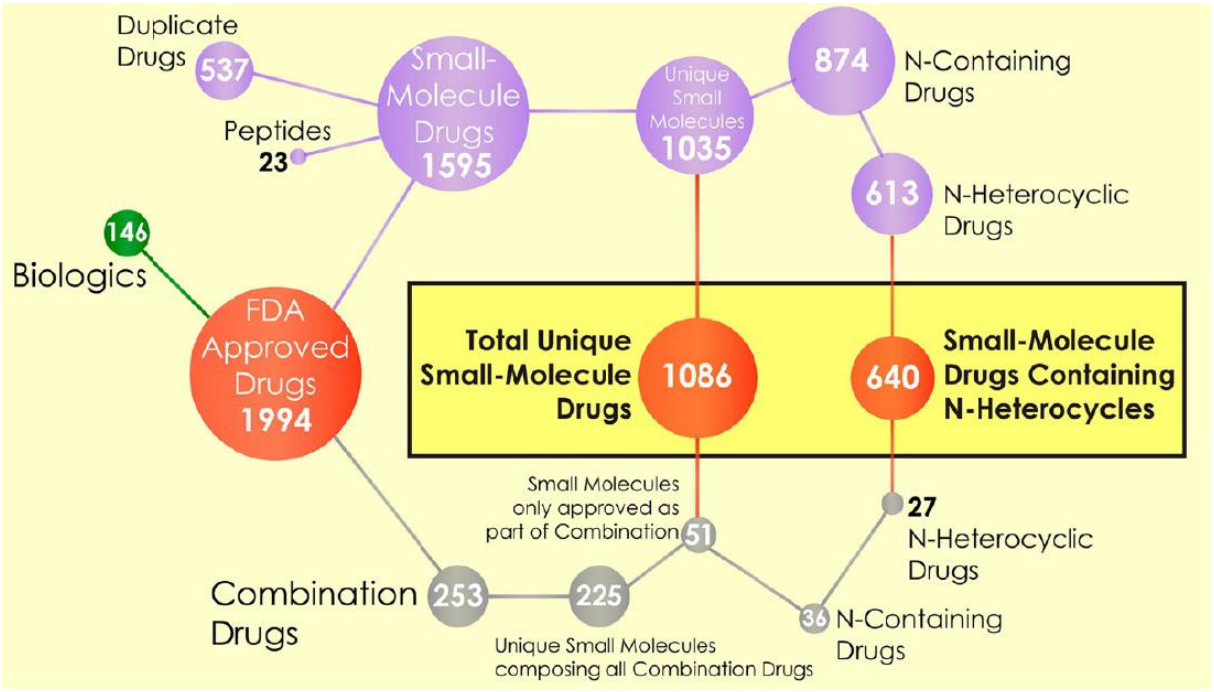


Figure 28. U.S. FDA approved drugs.

Electron-rich nitrogen heterocycles are not only able to readily accept or donate a proton; they can also easily establish weak interactions, such as hydrogen bonding formation, dipole-dipole interactions, hydrophobic effects, van der Waals forces and π-stacking interactions. These peculiar properties allowed these compounds to easily bind with a variety of enzymes and receptors in biological targets with higher affinity.

N-heterocyclic derivatives can be divided into two broad classes: aromatic and non-aromatic. Moreover, the reactivity varies if the systems are composed by three-, four-, five-, six-members etc...

Many different synthetic routes are readily available in order to synthesise *N*-heterocyclic compound.[154] In this chapter we will highlight five-membered rings, in particular 3-pyrrolines, their importance and synthesis.

[154] Selected reviews: a) C.-V.T. Vo, J.W. Bode *J. Org. Chem.* **2014**, *79*, 2809; b) J.-J; Feng, J. Zhang *ACS Catal.* **2016**, *6*, 6651; c) G. Pandey, P. Banerjee, S.R. Gadre *Chem. Rev.* **2006**, *106*, 4484; d) L. Jiao, Z.-X. Yu *J. Org. Chem.* **2013**, *78*, 6842.

II. 3-Pyrrolines

II.1 Five-membered ring in natural products and pharmaceutical molecules

Five-membered heterocycles are essential building blocks that are frequently used in the pharmaceutical and bulk chemical industry.[155] These products are very attractive building blocks *en route* to natural products, pharmaceuticals, materials and commodity chemicals. In particular, if we consider the class of pyrrolines, three isomeric groups are possible for the dihydro derivatives of pyrrole: 1-pyrrolines, 2-pyrrolines, and 3-pyrrolines.[156] Their unsaturated bonds are an attractive feature, as they enable straightforward access to reduced, oxidized and further functionalized members of these important structural family, such as pyrrolidines. Indeed, they are widely used as intermediates for the synthesis of five-membered nitrogen containing heterocyclic natural products and biologically active compounds.[157] We will next focus our attention on 3-pyrrolines. Among all the strategies devised for the construction of these compounds, we can non-exhaustively mention cycloaddition, metathesis, allene cyclization, and rearrangement reaction-type (Figure 29).

[155] M. Brichacek, J.T. Njardarson *Org. Biomol. Chem.* **2009**, *7*, 1761.

[156] F. Bellina, R. Rossi *Tetrahedron* **2006**, *62*, 7213.

[157] a) C. Cinquin, M. Bortolussi, R. Bloch *Tetrahedron: Asymmetry* **1996**, *7*, 3327; b) A.C.B. Montes de Oca, C.D.R. Vorreja, *ARKIVOC* **2003**, 390; c) R.A. Batey, P.D. Simonic, D. Lin, R.P. Smyj, A.J. Lough *Chem. Commun.* **1999**, 651.

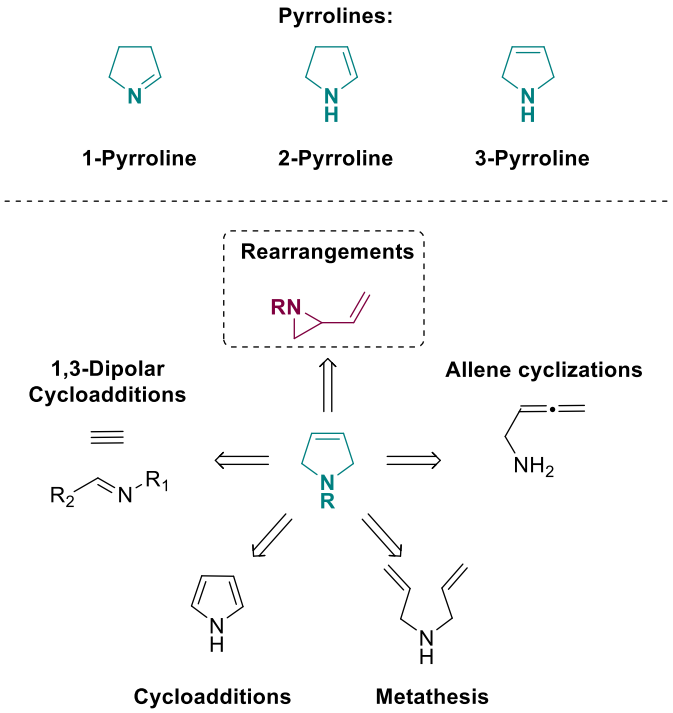
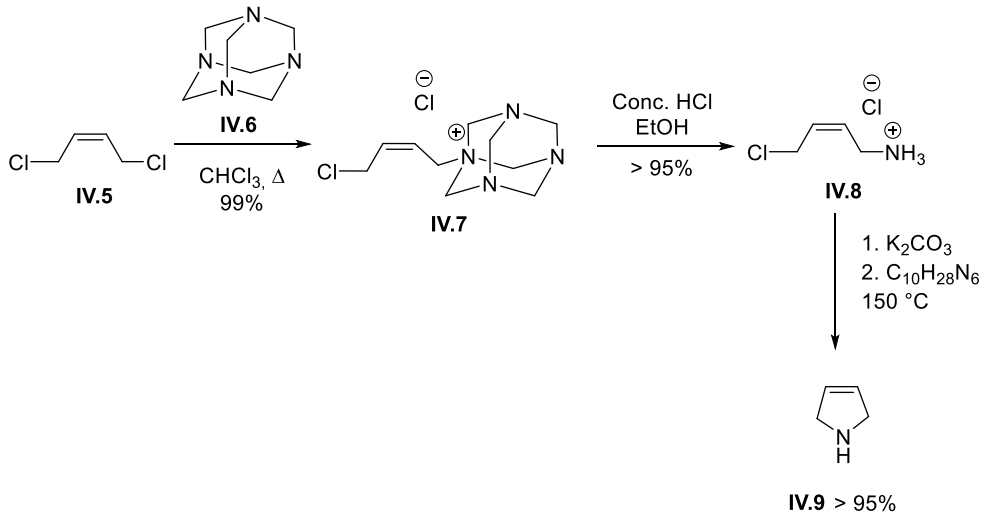


Figure 29. Strategies towards the synthesis of 3-pyrrolines.

II.2 Principal synthetic routes to 3-pyrrolines

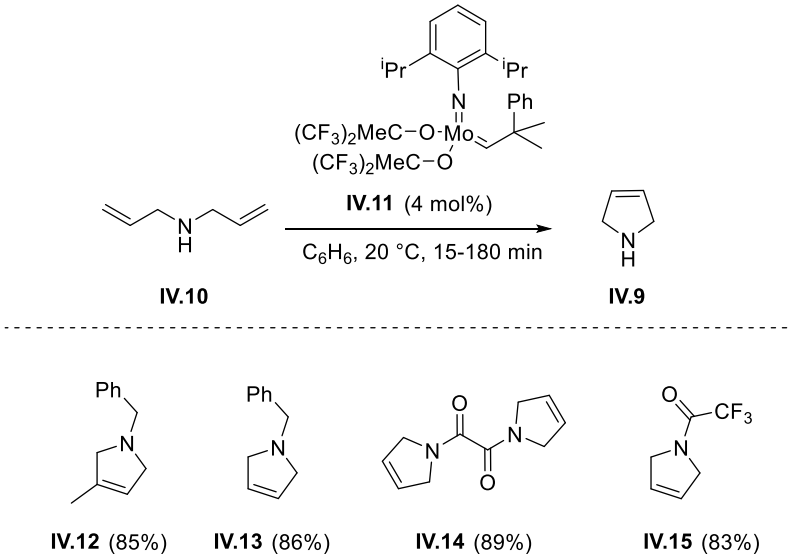
Herein, we will discuss just some of the strategies which give the possibility to synthesise 3-pyrrolines. One of the first example of 3-pyrroline synthesis, was reported in 1988 by Brandänge and Rodriguez.[158] During their studies on 1-acyl-3-pyrroline, the need for a practical synthesis of 3-pyrroline arose. In fact, at that period, this compound was commercially available as a mixture of the product itself and the corresponding pyrrolidine. The isolation of the 3-pyrroline was possible but with significant losses. Hence, they investigated a new method to have an easy access to this class of compounds. They were able to obtain the desired product in three steps: i) Delépine reaction (reaction of the haloalkene with hexamethylenetetramine and then acid hydrolysis of the quaternary ammonium salt), ii) ring-closing step with potassium carbonate and iii) further deprotonation with pentaethylenehexamine to afford the target molecule in good yields from the commercially available (*Z*)-1,4-dichlorobutene (Scheme 102).

[158] S. Brandänge, B. Rodriguez *Synthesis* **1988**, 347.



Scheme 102. Synthesis of 3-pyrroline by Brandänge and Rodriguez.

Since then, several new practical routes were proposed to synthesise 3-pyrroline scaffolds. In 1992, Grubbs et al. successfully applied the catalytic ring-closing olefin metathesis (RCM) strategy to the synthesis of a variety of nitrogen heterocycles.[159] Several substituted 3-pyrrolines were obtained in good yields (Scheme 103).

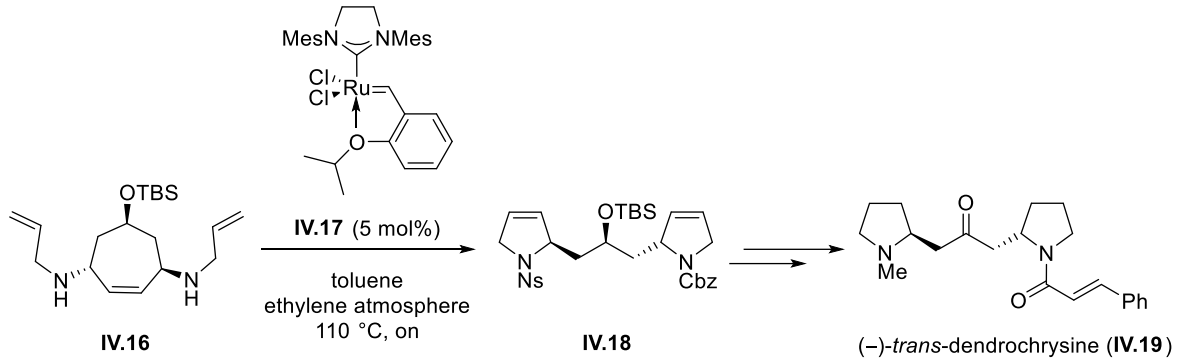


Scheme 103. Grubbs strategy for 3-pyrrolines.

A striking application of this RCM strategy was described by Blechert to access the natural product (−)-*trans*-dendrochrysine. In a cascade reaction, the ring rearrangement metathesis

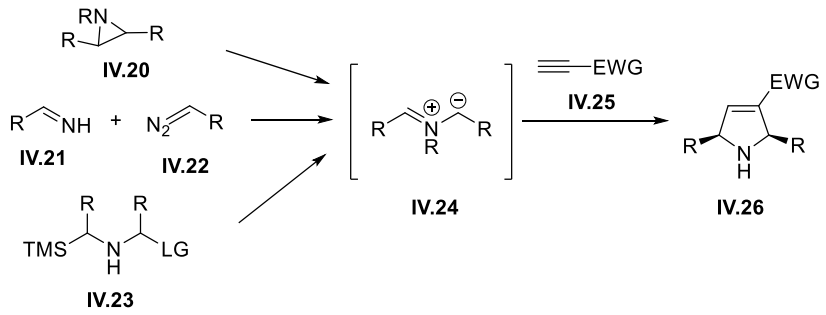
[159] G.C. Fu, R.H. Grubbs *J. Am. Chem. Soc.* **1992**, *114*, 7324.

(RRM) approach allows the formation of the two 3-pyrroline rings in a single step in 91% yield (Scheme 104).[160]



Scheme 104. Total synthesis of (−)-*trans*-dendrochrysine.

[3+2] Dipolar cycloadditions are a widely used strategy for the 3-pyrroline synthesis. 1,3-Dipoles when coupled with alkynes, provide an easy access to 3-pyrroline products. The formation of the required 1,3-dipole is one of the main challenges for this approach. Azomethine ylides (**IV.24**, Scheme 105) are the corresponding nitrogen-based 1,3-dipoles, mostly generated *in-situ* from sources like aziridines (**IV.20**), imines (**IV.21**), and secondary amines (**IV.23**). They are probably the commonly used intermediate in 1,3-dipolar cycloaddition reactions resulting to 5-member heterocycles like pyrrolines, and their employement in total synthesis, and formation of chiral ligands and pharmaceuticals, is quite important.[161]



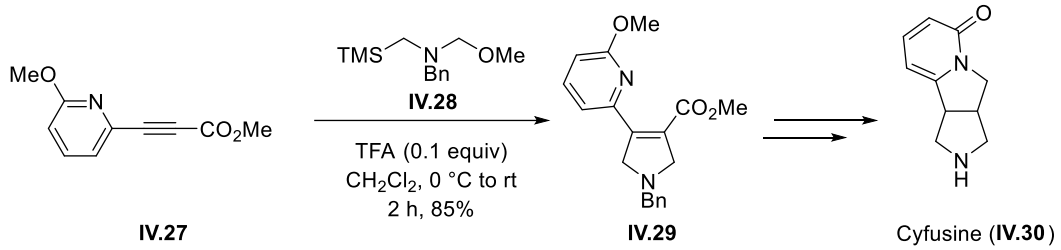
Scheme 105. General strategies for dipolar cycloadditions.

As an example, this approach with azomethine ylide has been used by Pfizer in the synthesis of a novel cytisine-inspired structure (cyfusine). The alkyne (**IV.27**) and the silyl aminal (**IV.28**)

[160] S. Blechert, M. Dochnahl, S. Schulz *Synlett*, **2007**, *16*, 2599.

[161] M.S. Singh, S. Chowdhury, S. Koley *Tetrahedron*, **2016**, *72*, 1603.

were coupled under acidic conditions to form the intermediate (**IV.29**), which was then converted, in four additional steps, into cyfusine (Scheme 106).[162]



Scheme 106. Road to Cyfusine by Pfizer.

Another important class of reactions that has been widely investigated in the synthesis of pyrrolines is the allene cyclization. In 1979, Claesson et al. demonstrated that 3-pyrrolines could be easily accessed towards silver tetrafluoroborate catalysis (Scheme 107a).[163] Since then, numerous pathways for the synthesis of substituted pyrrolines have been developed and much work was focused on metal-mediated cycloisomerisation of allenes. Metals such as Pd(0) or Pd(II),[164] Ag(I),[165] Hg(II)[166] have been used for this purpose. In 2004, this powerful transformation has been revisited by Krause et al. showing that Au(I) and Au(III) catalysts could be employed to afford 3-pyrrolines (Scheme 107b).[167] Moreover, Reissig et al. reported an efficient cyclization of an amino allene to a 3-pyrroline in the attempt of synthesising the strong immunosuppressant FR 901493.[168] In 2006, Tanaka et al. reported also the cyclization of unactivated allenes mediated by potassium carbonate in the absence of any transition-metal catalysis (Scheme 107c).[169] In 2021, Zhang et al. detailed an asymmetric gold-ligand catalysis which allows the transformation of chiral/achiral propargylic sulfonamides into chiral 3-pyrrolines (Scheme 107d).[170]

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[162] D. Yohannes, K. Procko, L.A. Lebel, C.B. Fox, B.T. O'Neill *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2316.

[163] A. Claesson, C. Sahlberg, K. Luthman, *Acta Chemica Scandinavica* **1979**, *B33*, 309.

[164] Selected examples: a) S. Ma, F. Yu, W. Gao *J. Org. Chem.* **2003**, *68*, 5943; b) R.K. Dieter, H. Yu *Org. Lett.* **2001**, *3*, 3855.

[165] M.O. Amombo, A. Hausherr, H.-U. Reissig *Synlett* **1999**, 1871.

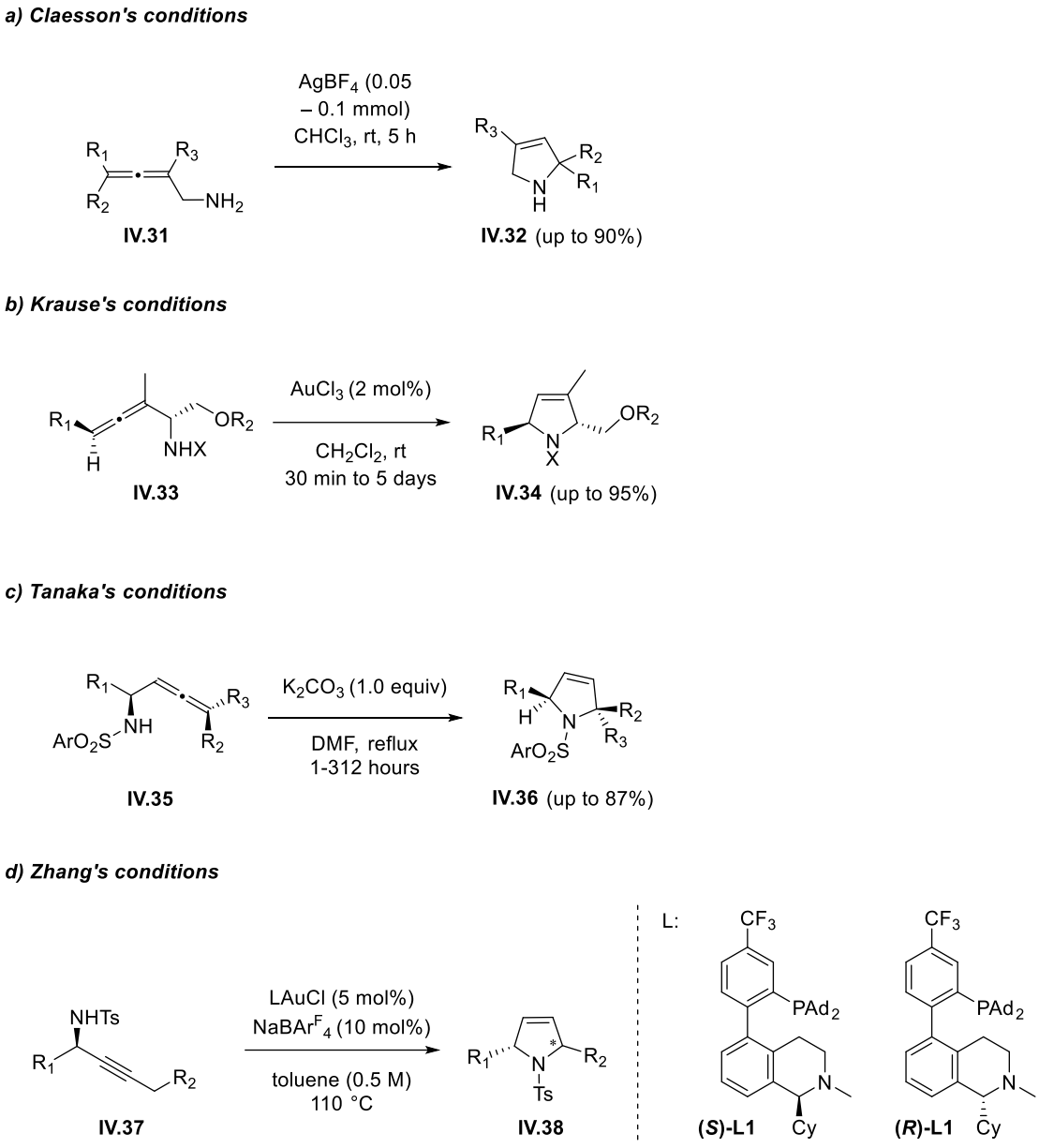
[166] D.N.A. Fox, D. Lathbury, M.F. Mahon, K.C. Molly, T. Gallagher *J. Chem. Soc., Chem. Commun.* **1989**, 1073.

[167] N. Morita, N. Krause *Org. Lett.* **2004**, *6*, 4121.

[168] S. Kaden, H.-U. Reissig *Org. Lett.* **2006**, *8*, 4763.

[169] H. Ohno, Y. Kadoh, N. Fujii, T. Tanaka *Org. Lett.* **2006**, *8*, 947.

[170] X. Cheng, L. Zhang *Org. Lett.* **2021**, *23*, 8194.



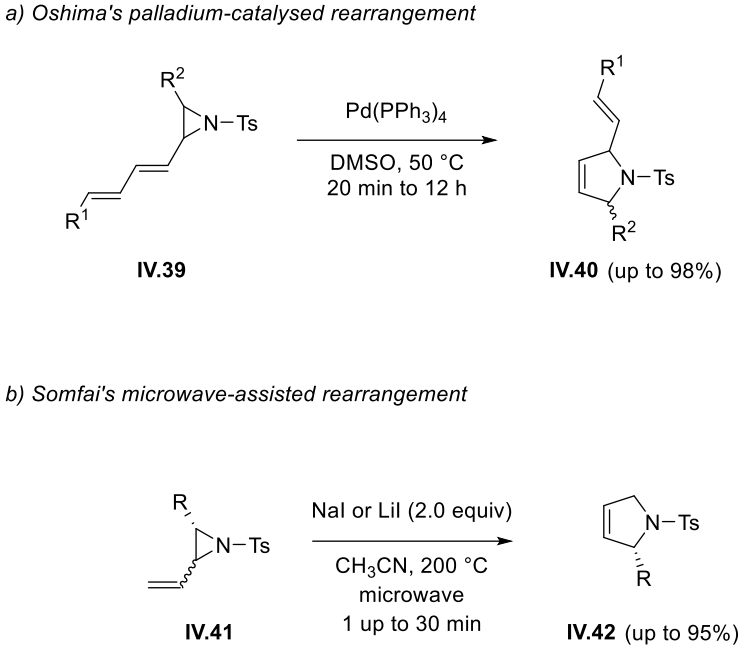
Scheme 107. Examples of allene cyclizations.

Furthermore, it has been known since the 1960's that some simple vinyl aziridines can be thermally rearranged[171] (e.g. refluxing acetone). Applications of this rearrangement are quite scarce, however i) in the 1980's Oshima et al. showed that triene monoaziridines can be rearranged in the presence of a palladium catalyst, while simple vinyl aziridines did not[172] (Scheme 108a) and ii) in 2005 Somfai et al. described a microwave-assisted rearrangement of activated vinyl aziridines to 3-pyrrolines mediated by NaI or LiI in ACN at elevated

[171] P. Scheiner *J. Org. Chem.* **1967**, *32*, 2628.

[172] K. Fugami, Y. Morizawa, K.Oshima, H. Nozaki *Tetrahedron Lett.*, **1985**, *26*, 857.

temperatures (Scheme 108b).[173] However, in 2008 Njardarson et al. proposed a practical Lewis acid rearrangement of vinyl aziridines, which will be discussed more in depth in the next section.



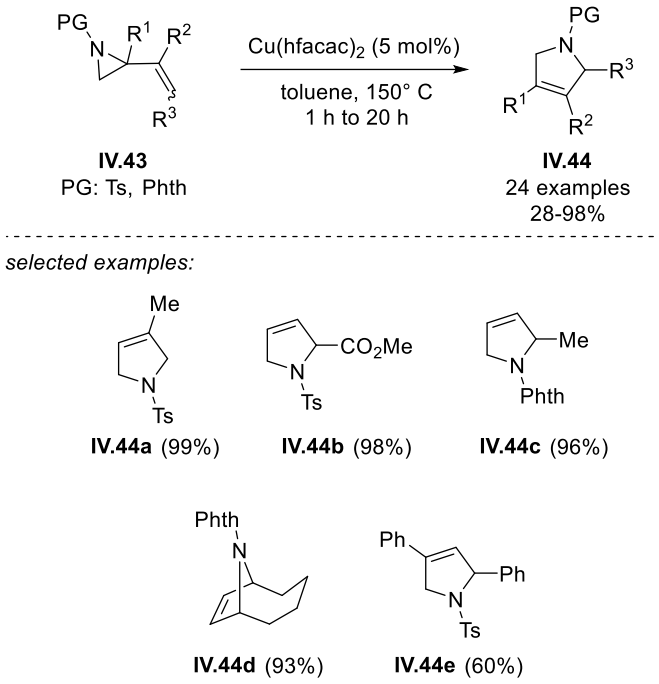
Scheme 108. Examples of vinyl aziridines rearrangement.

[173] S. Hirner, P. Somfai *Synlett* **2005**, 3099.

III. Cu-catalysed rearrangement of vinyl aziridines

In 2008, Njardarson et al. proposed a new efficient method towards the synthesis of 3-pyrrolines using commercially available copper(II) catalysts.[174]

On the basis of their previous work on the catalytic ring expansion of vinyl oxiranes and vinyl thiiranes,[175] the authors chosen vinyl aziridines bearing *p*-toluensulfonyl (Ts) or phtalimido (Phth) as protecting groups as substrates. More than 10 copper catalysts were tested during the optimisation of the reaction conditions. The more electrophilic copper(II) hexafluoroacetylacetonate proved to be superior to other commercially available and synthetic catalysts. Moreover, the reaction proceeds faster and with a higher yield when the $Cu(hfacac)_2$ hydrate is dried prior to use. Once the optimised conditions were found, a broad reaction scope was reported (Scheme 109).



Scheme 109. Njardarson's conditions and selected examples for the vinyl aziridine rearrangement.

More than 20 3-pyrrolines were obtained in moderate to good yields. The rearrangement proved to be quite functional group tolerant. These groups include enol ethers, esters, protected alcohols, sulfonamides, and imides. This compatibility is important because some of these

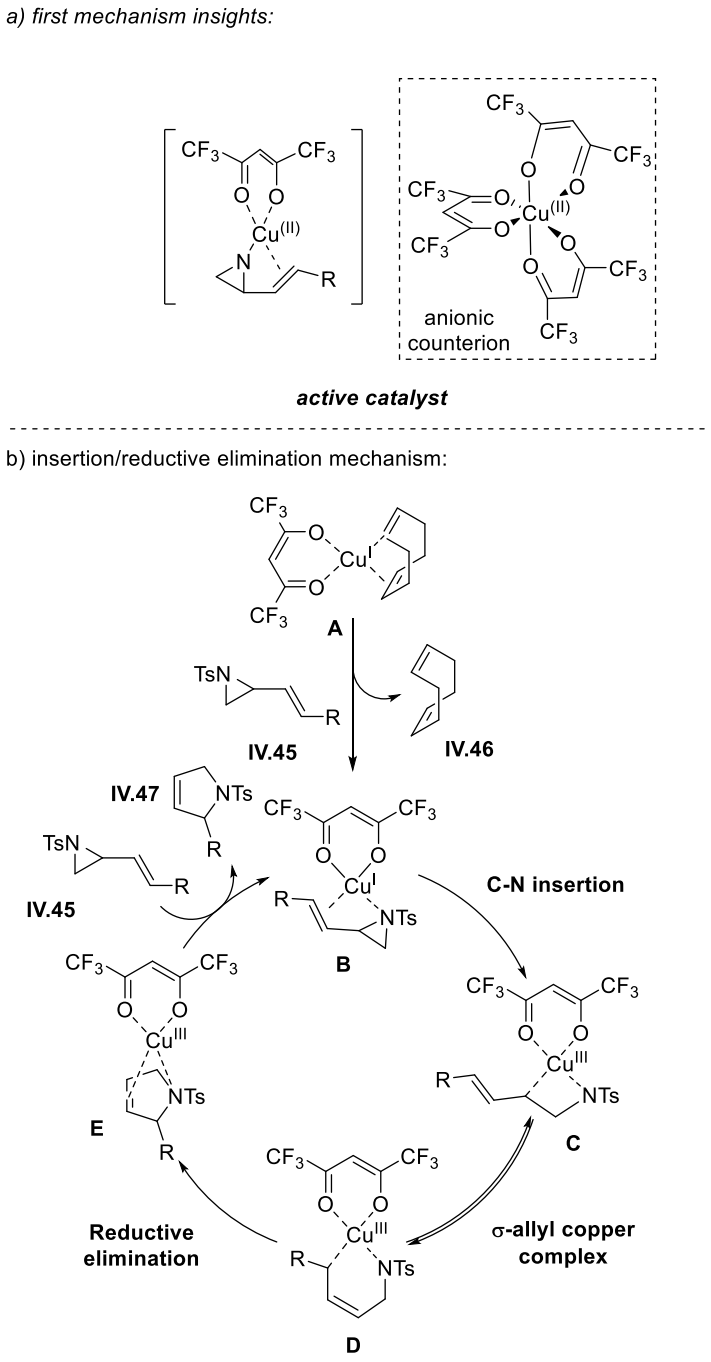
[174] M. Brichacek, D. Lee, J.T. Njardarson *Org. Lett.* **2008**, *10*, 5023.

[175] a) L.A. Batory, C.E. McInnis, J.T. Njardarson, *J. Am. Chem. Soc.* **2006**, *128*, 16054; b) Rogers, E.; Araki, H.; Batory, L. A.; McInnis, C. E.; J.T. Njardarson *J. Am. Chem. Soc.* **2007**, *129*, 2768.

functional groups likely coordinate to the electrophilic copper center and yet do not prevent the reaction from occurring. Fused and bridged bicyclic compounds were tolerated in order to furnish complex ring systems. More electron-rich phthalimide aziridines rearrange faster than the corresponding tosyl-protected aziridines.

Mechanistic investigations enabled the authors to initially propose a catalytic cycle involving an active cationic copper(II) catalyst (Scheme 110a) but later on the idea was abandoned for a different type of mechanism in which the ring expansion proceeds through a copper(I) mediated insertion/reductive elimination route (Scheme 110b).[176] This hypothesis was supported by performing mechanistic studies with a new catalytic system, Cu(hfacac)(cod) **A**. The catalyst undergoes an initial ligand exchange between 1,5-cyclooctadiene (cod) and the vinyl aziridine substrate to form **B**. Eventually, it will find itself in the tetrahedral chelate mode (nitrogen of aziridine and olefin chelated to the catalyst) prior to the critical C–N insertion step. The intermediate copper(III) σ-allyl four-membered ring metallocycle **C** then stereoselectively isomerizes to a six membered ring **D** that undergoes the final step of the catalytic cycle (reductive elimination) to form the 3-pyrroline **IV.47** and a copper(I) catalyst that is ready to bind to a new substrate. $Cu(hfacac)_2$ is reduced *in-situ* to a catalytically more active copper(I) species presumably due to a single electron transfer (SET) from the metal, ligand or substrate and it forms the active copper(I)(hfacac) catalyst.

[176] D.J. Mack, J.T. Njardarson *Chem. Sci*. **2012**, *3*, 3321.



Scheme 110. Proposed mechanism for the copper-catalysed vinyl aziridines rearrangement.

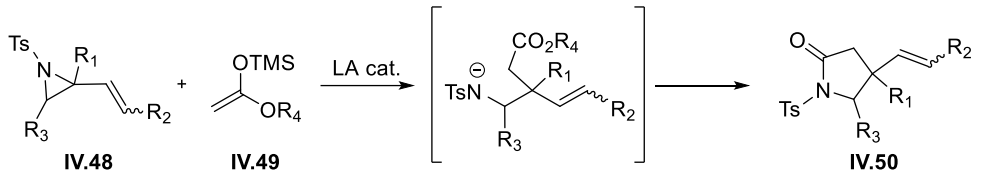
Although the copper-catalysed rearrangement appeared to be quite efficient, it is important to mention that the reaction takes place in the presence of a non-usual copper complex $Cu(hfacac)_2$ under relatively harsh conditions (150 °C in toluene). However, with these new insights on the mechanism they proved that the reaction could take place in the presence of Cu(hfacac)(cod) at 40 °C.

To the light of these results, while several studies were conducted in the area of palladium-catalyzed [3+2] cycloaddition of vinyl aziridines,[177] the synthesis of 3-pyrrolines drew the attention of our laboratory.

[177] a) K. Spielmann, A. van der Lee, R.M. de Figueiredo, J.-M. Campagne *Org. Lett.* **2018**, *20*, 1444; b) K. Spielmann, E. Tosi, A. Lebrun, G. Niel, A. van der Lee, R.M. de Figueiredo, J.-M. Campagne *Tetrahedron*, **2018**, *74*, 6497.

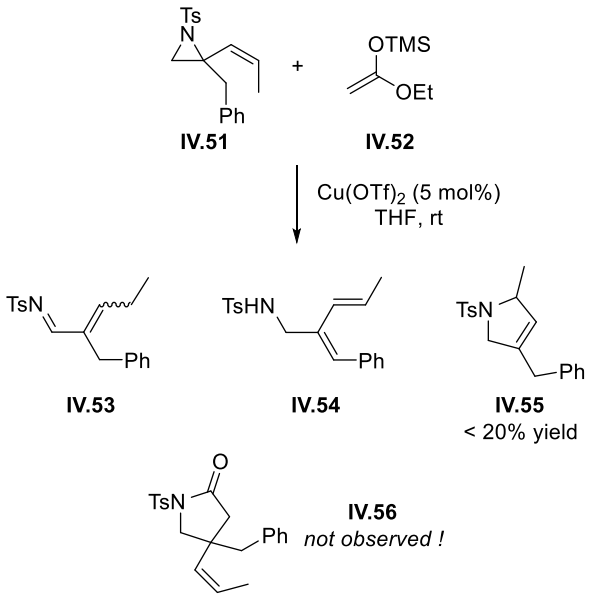
IV. Copper-catalysed ring-expansion of vinyl aziridines under mild conditions

In our laboratory, the formation of five-membered lactams bearing a quaternary center from silyl enol ethers and vinyl aziridines in the presence of Lewis acids was investigated (Scheme 111).



Scheme 111. Envisaged reaction between vinyl aziridine and silyl enol ether to afford δ-lactam.

When the reaction was attempted (Dr. Kim Spielmann, PhD in 2018) with model compound **IV.51** (R^1 = Bn; R^2 = Me; R^3 = H) and silyl enol ether **IV.52**, in the presence of 5 mol% of $Cu(OTf)_2$ at room temperature in tetrahydrofuran, the expected compound **IV.56** could not be observed in the crude material. Instead, along with the rather anticipated elimination compounds **IV.53** and **IV.54**, pyrroline **IV.55** could be also isolated albeit in low yield (10-20 %) (Scheme 112).



Scheme 112. First attempt towards the synthesis of δ-lactam under copper catalysis.

The very mild conditions in which the 3-pyrroline **IV.55** was formed prompted us to investigate the reaction conditions (Table 1) towards its exclusive, or at least, its main formation.

*Table 14. Optimisation studies for the synthesis of **IV.55**.*

Entry	Solvent	Cat (5 mol%)	Silyl enolate	IV.59 (%)
1	THF	$Cu(OTf)_2$	1.50 equiv	30%
2	THF	$Cu(OTf)_2$	–	NR
3	THF	[(*i*Pr)CuCl]	–	NR
4	THF	$[(PPh_3)_3CuF]$	–	NR
5	THF	CuTC	–	NR
6	THF	$Cu(OTf)_2$·Toluene	–	60%
7	THF	TFA	–	NR

a) Reactions were conducted using vinyl aziridine (0.05 mmol) and catalyst (5 mol%) under argon atmosphere in solvent (0.5 mL) at room temperature for 12 h; NR = No Reaction

Interestingly, in the absence of silyl enolate **IV.52**, the pyrroline **IV.55** was not observed (Table 1, entry 2). Suspecting an *in-situ* Cu(II) → Cu(I) reduction in the reaction process,[178] the use of Cu(I) salts was thus next investigated in the absence of **IV.52**. Whereas various Cu(I) salts proved unsuccessful to catalyze the reaction (entries 3-5), we were delighted to observe the clean formation of **IV.55** in the presence of 5 mol% of $(CuOTf)_2$·Toluene (entry 6) at room temperature in THF. In order to exclude the possibility of an organic acid-catalyzed transformation, a trial in the presence of 5 mol% of TFA has been performed and no reaction was observed.

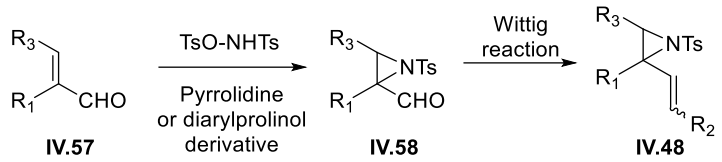
After optimization of the basic rearrangement reaction with vinyl aziridine **IV.51**, a scope was next envisaged. For this purpose, vinyl aziridines were prepared following a sequence involving an organocatalysed aziridination[179]/Wittig reaction which will be detailed in the next section.

[178] a) Y. Kobayashi, T. Taguchi, T. Morikwa, E. Tokuno, S. Sekiguchi *Chem. Pharm. Bull.* **1980**, *28*, 262; b) D. Ferraris, B. Young, C. Cox, W.J. Drury III, T. Dudding, T. Leckta *J. Org. Chem.* **1998**, *63*, 6090; c) B.L. Pagenkopf, J. Krüger, A. Stojanovic, E.M. Carreira *Angew. Chem. Int. Ed.* **1998**, *37*, 3124.

[179] A. Desmarchelier, D. Pereira de Sant'Ana, V. Terrasson, J.-M. Campagne, X. Moreau, C. Greck, R.M. de Figueiredo *Eur. J. Org. Chem.* **2011**, 4046.

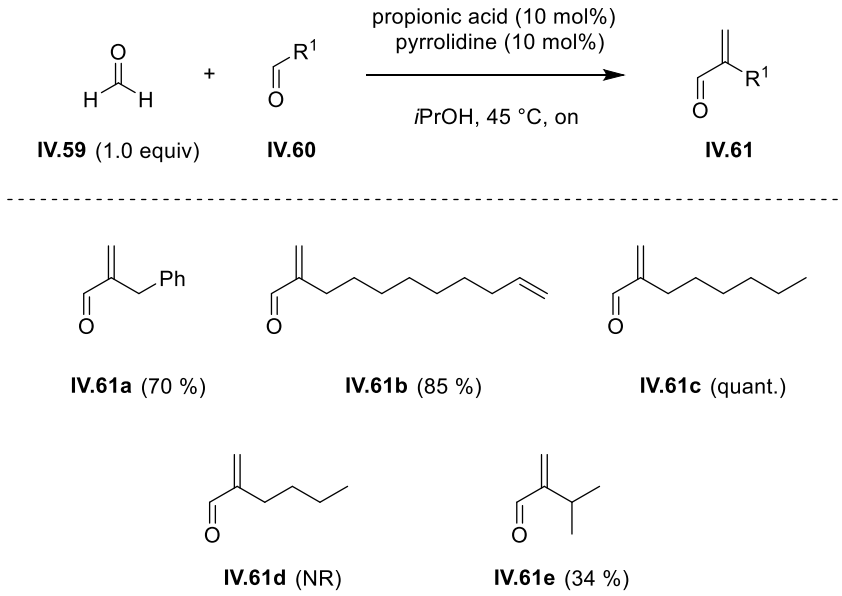
IV.1 Synthesis of vinyl aziridines

The synthesis of vinyl aziridines was accomplished through an organocatalyzed aziridination and a subsequent Wittig reaction giving the products in moderate-to-good yields (Scheme 113).



Scheme 113. Synthetic pathway for the vinyl aziridine formation.

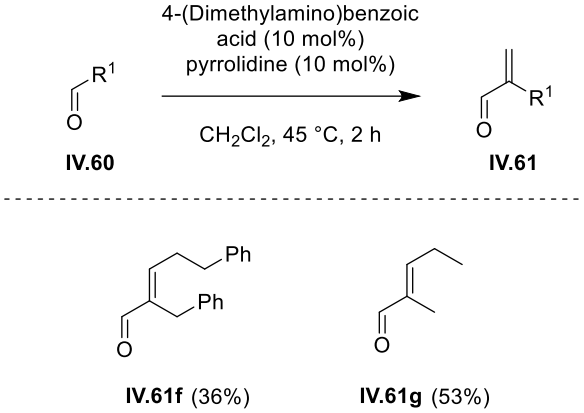
We started our synthesis from substituted-α,β-unsaturated aldehydes **IV.61** (Scheme 114). The majority of these substrates were not commercially available. However, a practical and rapid methodology for α-methylenation of aldehydes **IV.60** was described by Pihko et al. in 2006.[180] The reaction took place under mild conditions, with only one equivalent of aqueous formaldehyde **IV.59** and a pyrrolidine/propionic acid catalytic system to afford the desired products in good to excellent yields.



Scheme 114. Pihko's methylenation to afford α,β-unsaturated aldehydes.

[180] A Erkkila, P.M. Pihko *J. Org. Chem.* **2006**, *71*, 2538.

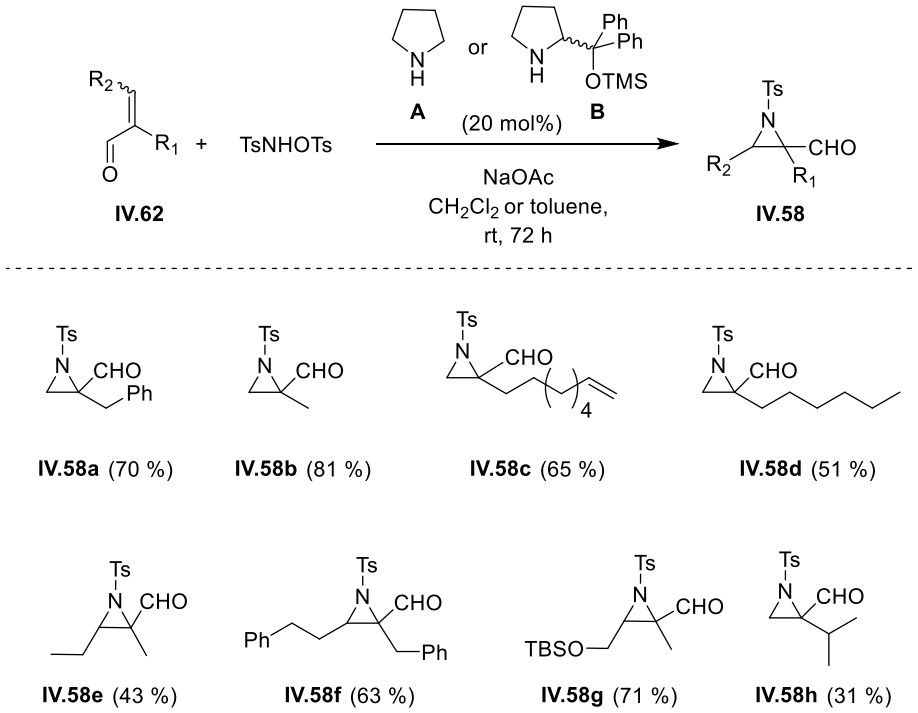
At our disposal, the same group reported in 2007 a procedure with similar conditions to promote the self-condensation of the aldehyde **IV.60**.[181] We were able to prepare two more substrates using this protocol (Scheme 115).



Scheme 115. Self-condensation reaction to afford α,β-substituted-α,β-unsaturated aldehydes.

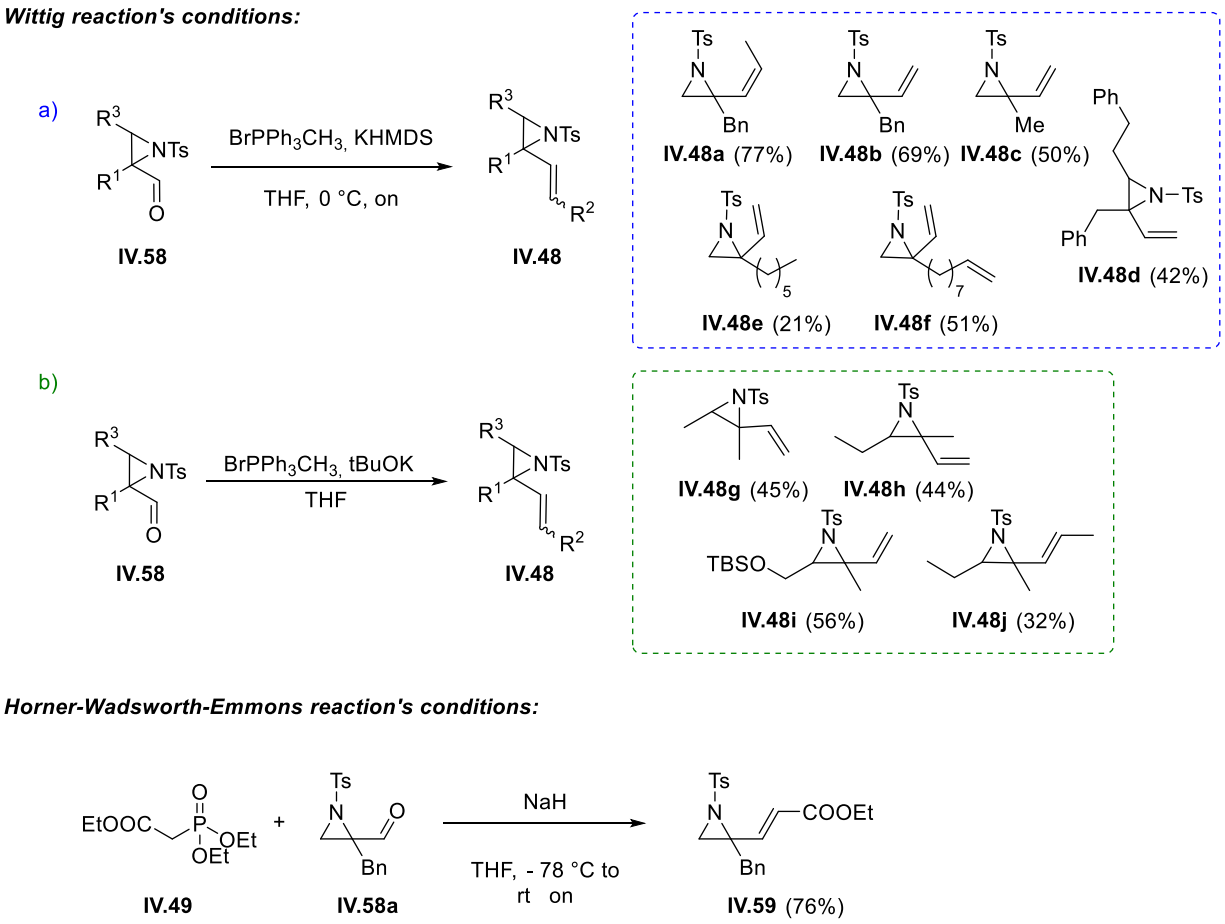
Once obtained, the aldehydes were readily transformed into the corresponding aziridines which thanks to an organocatalytic strategy developed by our laboratory in 2011.[179] The products were isolated in moderate-to-good yields. At this stage, we were not interested in obtaining enantioenriched aziridines, thus we used the asymmetric reaction conditions only when it was mandatory in order to obtain our targeted compounds (Scheme 116).

[181] A Erkkila, P.M. Pihko *Eur. J. Org. Chem.* **2007**, 4205.



Scheme 116. Organocatalytic strategy for the synthesis of *N*-tosylaziridine aldehydes.

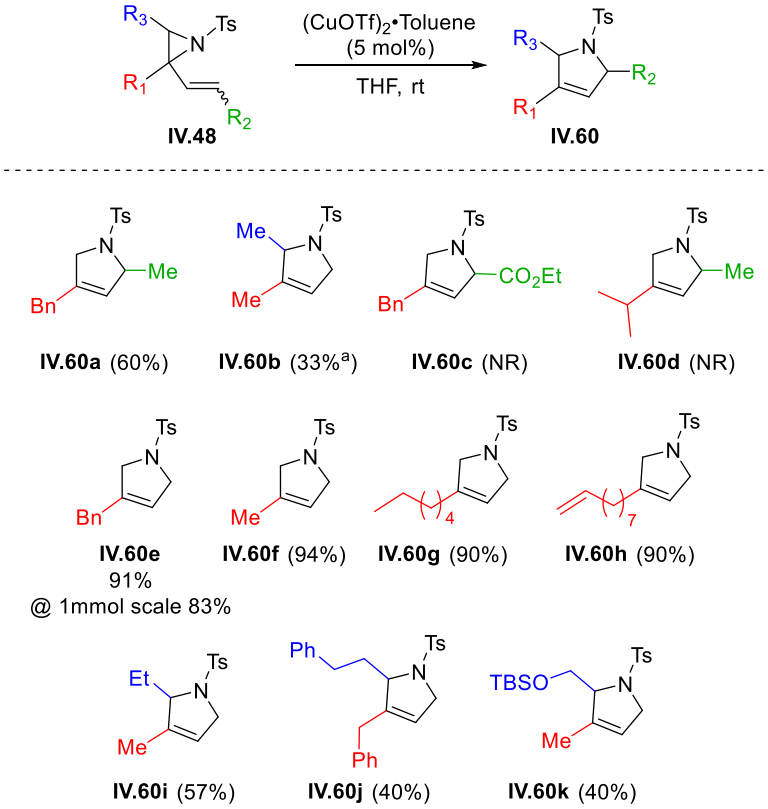
Afterwards, the Wittig reactions were performed in order to synthesise our substrates for the ring-opening strategy. The vinyl aziridines were obtained in moderate-to-good yields. However, it is important to mention that this last step to form a C-C bond was substrate-dependent and not always easily reproductible! For these reasons several procedures were employed to reach the desired compounds in optimised conditions (Scheme 117).



Scheme 117. Strategies towards the synthesis of vinyl aziridines.

IV.2 Scope of the ring-expansion of vinyl aziridines under mild conditions

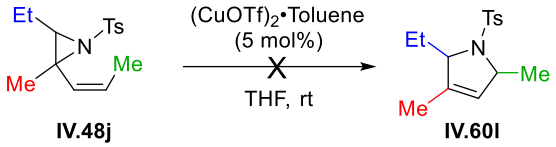
With mono- and di-substituted vinyl aziridines in hand, the copper(I)-catalysed rearrangements were explored (Scheme 118). Variously substituted pyrrolines **IV.60** were isolated in moderate-to-good yields.



Scheme 118. Scope of the ring-expansion of vinyl aziridines.

In the presence of R_2 or R_3 groups in the starting vinyl aziridines, pyrolines **IV.60a** and **IV.60b** were obtained respectively in 60% and 33% yield. Notably, no reaction was observed neither in the presence of an electron-withdrawing group (R^2 = CO_2Et; compound **IV.60c**) or an electron-donating group (R^2 = Me; compound **IV.60d**), for which the Njardarson's conditions are efficient.[174] From mono-substituted aziridines, the corresponding pyrrolines **IV.60e-h** have been obtained in 90-94% yield. In addition, the presence of functionalized side-chains are also well tolerated (see OTBS and double bond, **IV.60k** and **IV.60h**). The rearrangement of vinyl aziridine **IV.48b** was also performed at 1 mmol scale (vs 0.14 mmol) giving the expected pyrroline **IV.60e** in a comparable isolated yield (83%). The ring expansion of vinyl aziridines with substituents at the R_1 and R_3 positions were next investigated. In this case, pyrrolines **IV.60i-k** were formed in moderate to good yields (40-57%). From these results, we can deduct that the hindrance around the NTs functional group (R_2 and R_3 groups) has a deleterious effect

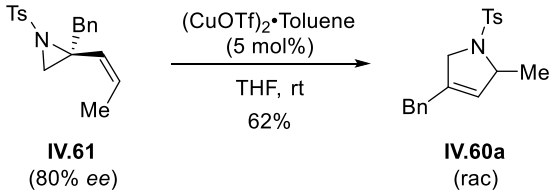
on the ring-expansion process as the expected compounds are isolated with lower yields (up to 60%). As a counterproof, we reinforced our hypothesis by submitting substrate **IV.48j** to the ring-expansion conditions and no formation of tri-substituted pyrroline **IV.60l** was observed (Scheme 119).



Scheme 119. Tri-substituted vinyl aziridine as substrate for the ring-expansion.

In contrast, R_1 mono-substituted pyrrolines are obtained in excellent yields (up to 94%, Scheme 118). Interesting to mention, $Cu(MeCN)_4 \cdot PF_6$ could also be used as catalyst for the synthesis of **IV.60b**,**e**,**k** affording similar yields (30%, 90% and 40% respectively).

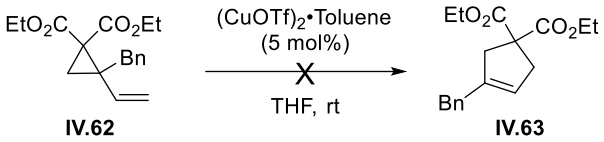
The mild conditions used for the rearrangement prompted us to investigate the stereospecificity of the reaction. Hence, we evaluated the reactivity of the enantiomerically enriched vinyl aziridine **IV.61** (80% ee); the corresponding pyrroline **IV.60a** was obtained in 60% yield in a racemic form showing no chirality transfer (Scheme 120).



Scheme 120. Rearrangement of the enantiomerically enriched compound **IV.61**.

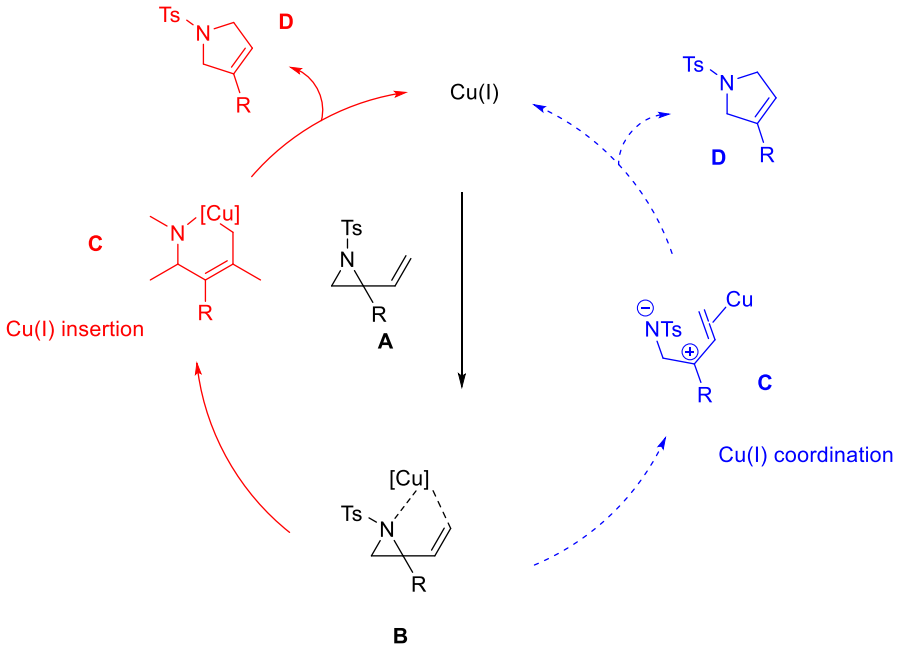
Thanks to an easy access to 2-substituted vinyl cyclopropanes,[182] a related reaction from compound **IV.62** was next attempted in the same reaction conditions to see if it was possible to widen our scope to the synthesis of substituted cyclopentenes (Scheme 121). However, the reaction did not occur.

[182] V. Terrasson, A. van der Lee, R.M. de Figueiredo J.-M. Campagne *Chem. Eur. J.* **2010**, *16*, 7875.



Scheme 121. Attempted copper-catalysed vinyl cyclopropane rearrangement.

In terms of mechanism, these results are in full accordance with Njardarson's observations[20] involving a copper(I) insertion into the C-N bond to give an allyl-copper intermediate **C**, ultimately leading, to the pyrroline after reductive elimination. However, an alternative mechanistic pathway involving copper coordination and subsequent heterolytic rupture of the C-N bond, followed by the attack of the *N*-tosyl anion, cannot be totally excluded under our reaction conditions.



Scheme 122. Proposed mechanistic scenarios.

In conclusion, we have developed a practical protocol for the synthesis of 3-substituted pyrrolines from accessible vinyl aziridines. The ring-expansion process takes place under Cu(I) catalysis. In particular, very mild conditions (THF, rt) are needed to accomplish the rearrangements. In the presence of R_2 and R_3 groups (steric hindrance around the NTs functionality) yields are ranging from 33% to 60% whereas 3-pyrrolines (R_2 and R_3 = H) are isolated in higher yields (> 90%).

V. Conclusions and Future Work

V.1 New Opportunities in Peptide Synthesis

As previously discussed in Chapter 1, section III, there are some research's laboratories that are currently rethinking the way of synthesizing peptides through a novel mode of activation ("inverse activation" of AA through amine function activation instead of classical carboxylate activation).

Since 2012, our laboratory has been working to develop a new efficient methodology using the commercially available CDI as activating agent of the amine function. The reaction takes place under very mild conditions in the absence of a base, using $CuBr_2$/HOBt (10 mol% each) as catalytic additives, at room temperature, and it is compatible with common *N*-urethane protecting groups (Figure 30). No racemization was detected when sensitive substrates, such as Cysteine, were engaged on the coupling conditions. Moreover, it was demonstrated that i) it was possible to obtain comparable results in terms of yields using a catalytic amount of TFA in a more diluted medium (0.1 M instead of 1.0 M); ii) iodomethane promoted the *N*-methylation of the imidazole ring of the CDI-activated amino acids shortening the coupling kinetics (4h vs. 20 h); iii) microwave irradiation could considerably improve the reaction kinetics affording the target dipeptides in only 30 minutes with better or at least comparable yields.

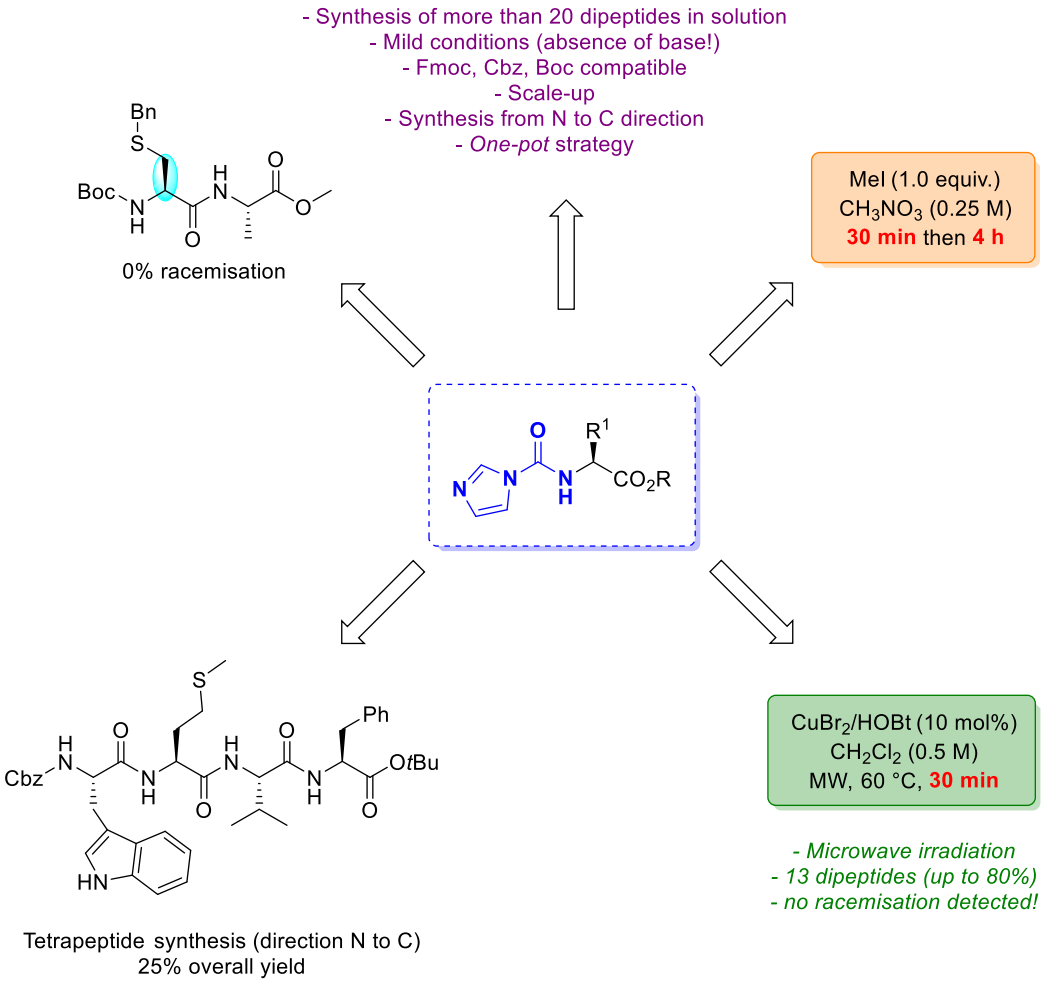


Figure 30. Imi-AA-OR on peptide synthesis.

In addition, having in mind the importance of the amide as functional group in the synthesis of bioactive compounds, we were able to transpose our coupling strategy to the synthesis of general amides (Figure 31).

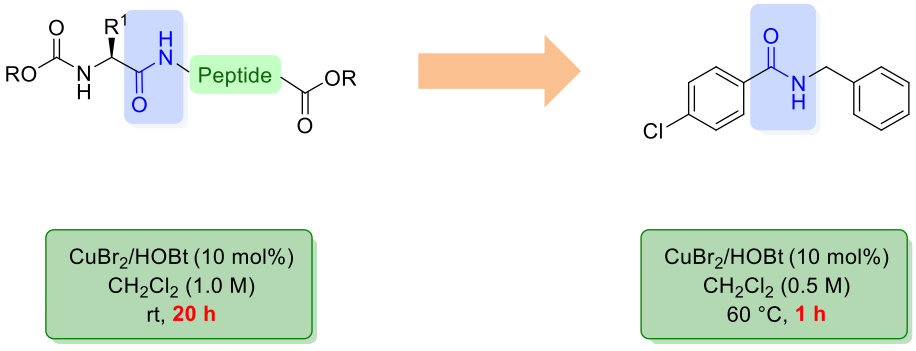


Figure 31. Transposition of the reaction conditions to general amides.

Even though we were not able to fully understand the reaction mechanism, NMR experiences combined with HPLC monitoring allowed us to identify some side compounds/intermediates,

such as the symmetrical urea, and consequently, giving some hints on novel directions to be taken in our studies.

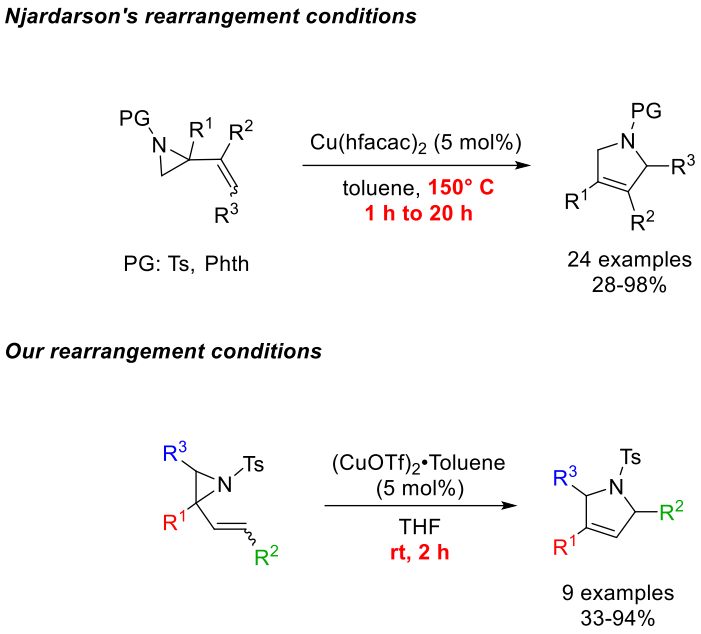
V.1.1 Future work

Although some important goals were reached, we still need to fully understand the mechanism of the reaction in order to further employ this tool in different fields of application. Future work will focus on:

- Mechanistic studies – for further studies and to improve the kinetic, the reaction pathway should be unveiled. To do so, we envisage to study the coupling model reaction (already used for the NMR experiments) with *in-situ* infrared studies (ReactIR®). We hope that, it will be easier to detect other intermediates involved in the reaction and its kinetic (e.g. when the reaction starts and when it finishes).
- Microwaves synthesis of small peptide models – once established the conditions to perform the peptide coupling in only 30 minutes (thanks to MW irradiation) it will be interesting to apply this strategy to the preparation of small peptide targets in solution, with minimisation of waste, time, and purification steps. In a first attempt the tetrapeptide Cbz-Gly-Leu-Phe-Ala-OMe will be synthesised (N→C direction) and then the synthesis of opioid peptides such as selected members of the enkephalin family could be envisaged (e.g. Met-enkephalin = H-Tyr-Gly-Gly-Phe-Met-OH).
- Transposition into SPPS and Fragment Couplings – next, the devised and unworked conditions will be studied for application into peptide chemistry (Pr. G. Subra and Dr. V. Aucagne). For the SPPS, to envisage the N→C strategy it will be important to choose convenient linkers, easy-to-handle C-terminal temporary protecting group, and a convenient set of side-chain protecting groups. For Fragment couplings, it will be interesting to investigate the activation of the N-terminal amine of a peptide fragment to afford the coupling reaction with a C-terminal peptide fragment without the formation of any side-products.

V.2 Ring-expansion of vinyl aziridines

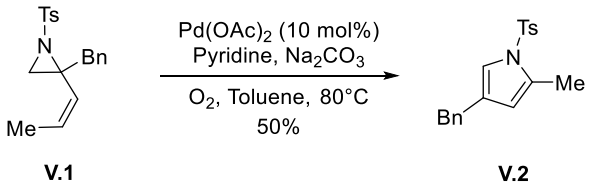
As discussed in Chapter 4, we coincidentally found out that vinyl aziridines could be subjected to a rearrangement in the presence of a catalytic amount of a Lewis acid affording the formation of substituted 3-pyrrolines in moderate-to-good yields. The reaction takes place under an argon atmosphere, in the presence of 5 mol% of $(CuOTf)_2$·Toluene complex, in THF, at room temperature, and for 2 hours (Scheme 123).



Scheme 123. Comparison between Cu-catalysed rearrangement performed by Njardarson's group and our laboratory.

V.2.1 Future work

The mechanistic insights on the copper-catalysed rearrangement for vinyl aziridines (Chapter 4, section IV.1.2, Scheme 122) encouraged us to test ring-opening aziridine reactions in the presence of palladium salts.[183] In a model reaction with (*Z*)-**V.1**, we discovered that, under aza-Wacker conditions, the corresponding pyrrole **V.2** could be obtained in an unoptimized 50% yield (Scheme 124). Further investigations will be carried out.



Scheme 124. Aza-Wacker type-rearrangement of vinyl aziridines.

[183] X. Bao, Q. Wang, J. Zhu *Angew. Chem. Int. Ed.* **2018**, *57*, 1995.

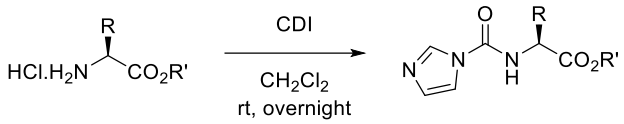
VI. Experimental Part

General informations

Reactions were carried out in round-bottom flasks and sealed tubes equipped with a magnetic stirring bar. Solutions for work-up are in water unless otherwise specified. Analytical thin-layer chromatography (TLC) of all reactions was performed on silica gel 60 F254 TLC plates. Visualization of the developed chromatogram was performed by UV absorbance (254 nm) and/or using potassium permanganate, ninhydrin, *p*-anisaldehyde stains. FT-IR spectra were recorded with Perkin-Elmer Spectrum 1000; absorptions are given in wave numbers (cm^{-1}). ^{1}H (400 MHz) and ^{13}C (100 MHz), NMR spectra were recorded by a Bruker Ultra Shield 400 Plus. ^{1}H and ^{13}C chemical shifts are reported in parts per million with the solvent resonance as the internal standard ($CDCl_3$, ^{1}H: δ 7.26 ppm, ^{13}C: δ 77.16 ppm). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sept, septet; m, multiplet; b, broad and combinations thereof. All coupling constants (*J* values) are reported in Hertz (Hz). Data are reported as follows: chemical shift (δ in ppm), multiplicity, coupling constants (Hz), and integration. HPLC analysis were performed on a Shimadzu® LC 20 A with a UV/visible detector PDA. Optical rotations were measured with a Bellingham + Stanley® ADP 440 Polarimeter or a Perkin Elmer® 341 Polarimeter with a sodium lamp at 589 nm. High resolution mass spectra were obtained using the mass spectrometers operated by the Laboratoire de Mesures Physique of the University of Montpellier.

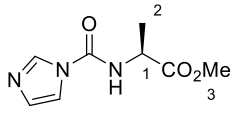
THF was dried by distillation over sodium and benzophenone under nitrogen. Nitromethane was dried by distillation over CaH_2 under nitrogen. KHMDS (0.50 M in Toluene) was purchased from Sigma-Aldrich® and used as received. Dichloromethane (≥ 99.5% stabilised with 0.002% of 2-methyl-2-butene, AnalR NORMAPUR® ACS, Reag. Ph. Eur. Analytical reagent) was purchased from VWR Chemicals®. Unless otherwise specified, all commercial substrates were used without further purification.

General Procedure A for the Preparation of Imi-AA-OR



To a solution of the corresponding H-AA-OR hydrochloric acid salt (1.00 equiv) in CH_2Cl_2 (*C* 0.2 M) at room temperature was added *N*,*N*'-carbonyldiimidazole (1.20 equiv). The obtained suspension was thus stirred at this temperature overnight. After reaction completion (TLC monitoring), the mixture was washed once with H_2O. The organic phase was separated and the aqueous phase was further extracted with CH_2Cl_2 (2×). The organic layers were combined, dried over $MgSO_4$ and evaporated. Purification was performed by column chromatography on a short silica gel pad to afford the desired compounds.

*(S)-Methyl 2-(1H-imidazole-1-carboxamido)propanoate (Imi-Ala-OMe) (**III.1a**)*



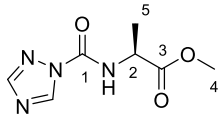
III.1a
$C_8H_{11}N_3O_3$
197,19

The title compound was isolated by short column chromatography (eluent: EtOAc 100%) as a white solid in 92% yield (0.99 g) from H_2N-Ala-OMe hydrochloric acid salt (0.76 g, 5.5 mmol) following the general procedure A.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (s, 1H, H_{ar}), 7.35 (s, 1H, H_{ar}), 7.11 (s, 1H, H_{ar}), 6.38 (bs, 1H, NH), 4.66 (quint, *J* = 7.1 Hz, 1H, H_1), 3.82 (s, 3H, H_3), 1.55 (d, *J* = 7.2 Hz, 3H, H_2) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[116]

*Methyl (1H-1,2,4-triazole-1-carbonyl)-L-alaninate (**III.29**)*



III.29
$C_7H_{10}N_4O_3$
198,18

The title compound was isolated by short column chromatography (eluent: EtOAc 100%) as a white solid in quantitative yield (0.19 g) from H_2N-Ala-OMe hydrochloric acid salt (0.14 g, 1.0 mmol) following the general procedure A replacing *N*,*N*'-carbonyldiimidazole with the N,N'-carbonyl-di-(1,2,4-triazole).

Mp: 73.6 – 77.1°C

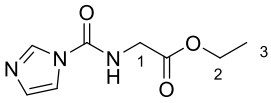
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (s, 1H, H_{ar}), 8.00 (s, 1H, H_{ar}), 7.47 (bs, 1H, NH), 4.65 (quint, *J* = 7.3 Hz, 1H, H_2), 3.81 (s, 3H, H_4), 1.57 (d, *J* = 7.3 Hz, 3H, H_5) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2 (C_3), 152.6 (C_1), 147.2 (C_{ar}), 143.7 (C_{ar}), 53.0 (C_4), 49.3 (C_2), 18.4 (C_5) ppm.

FTIR neat (cm^{-1}): 3141.9, 2937.4, 2871.2, 2849.1, 1730.9, 1699.7, 1513.1, 1480.1, 1420.2, 1376.9, 1291.8, 1240.3, 1197.2, 1139.6, 1104.0, 1058.6.

HRMS (ESI+) calculated for $C_7H_{11}N_4O_3$ (m/z): $[M+H]^+$: calculated : 199.0800, found: 199.0816.

*Ethyl 2-(1H-imidazole-1-carboxamido)acetate (Imi-Gly-OEt) (**III.1b**)*



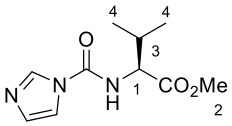
III.1b
$C_8H_{11}N_3O_3$
197,19

The title compound was isolated by short column chromatography (eluent: EtOAc 100%) as a white solid in 90% yield (0.53 g) from H_2N-Gly-OEt hydrochloric acid salt (0.42 g, 3.0 mmol) following the general procedure A.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (t, *J* = 1.1 Hz, 1H, H_{ar}), 7.35 (t, *J* = 1.5 Hz, 1H, H_{ar}), 7.10 (s, *J* = 0.8 Hz, 1H, H_{ar}), 6.43 (bs, 1H, NH), 4.27 (q, *J* = 7.1 Hz, 2H, H_2), 4.18 (d, *J* = 5.0 Hz, 2H, H_1), 1.31 (t, *J* = 7.1 Hz, 3H, H_3) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[116]

*(S)-Methyl 2-(1H-imidazole-1-carboxamido)-3-methylbutanoate (Imi-Val-OMe) (**III.1c**)*



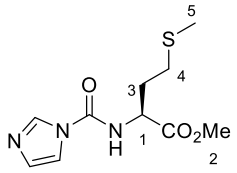
III.1c
$C_{10}H_{15}N_3O_3$
225,24

The title compound was isolated by short column chromatography (eluent: EtOAc 100%) as a pale yellow oil in 80% yield (0.35 g) from H_2N-Val-OMe hydrochloric acid salt (0.33 g, 2.0 mmol) following the general procedure A.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (s, 1H, H_{ar}), 7.39 (s, 1H, H_{ar}), 7.09 (s, 1H, H_{ar}), 6.60 (bs, 1H, NH), 4.60-4.56 (m, 1H, H_1), 3.79 (s, 3H, H_2), 2.29-2.24 (m, 1H, H_3), 1.00 (d, *J* = 6.8 Hz, 3H, H_4), 0.97 (d, *J* = 6.9 Hz, 3H, H_4) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[116]

*(S)-Methyl 2-(1H-imidazole-1-carboxamido)-4-(methylthio)butanoate (Imi-Met-OMe) (**III.1d**)*



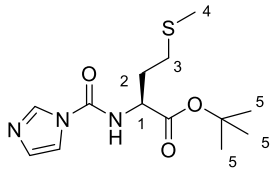
III.1d
$C_{10}H_{15}N_3O_3S$
257,30

The title compound was isolated by short column chromatography (eluent: EtOAc 100%) as a viscous pale yellow oil in 94% yield (0.48 g) from H_2N-Met-OMe hydrochloric acid salt (0.40 g, 2.0 mmol) following the general procedure A.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (s, 1H, H_{ar}), 7.39 (s, 1H, H_{ar}), 7.13 (bs, 1H, NH), 7.10 (s, 1H, H_{ar}), 4.81-4.76 (m, 1H, H_1), 3.81 (s, 3H, H_2), 2.65-2.55 (m, 2H, H_5), 2.31-2.24 (m, 1H, H_4), 2.20-2.14 (m, 1H, H_4), 2.12 (s, 3H, H_5) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[116]

*(S)-tert-Butyl 2-(1H-imidazole-1-carboxamido)-4-(methylthio)butanoate (Imi-Met-OtBu) (**III.1e**)*



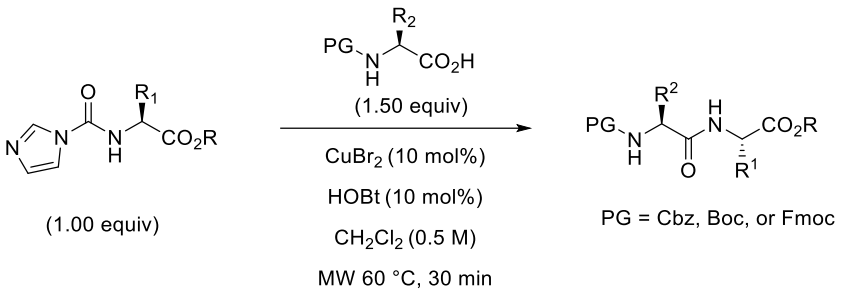
III.1e
$C_{13}H_{21}N_3O_3S$
299,38

The title compound was isolated by short column chromatography (eluent: EtOAc 100%) as a viscous pale yellow oil in quantitative yield (0.60 g) from H_2N-Met-O*t*Bu hydrochloric acid salt (0.48 g, 2.0 mmol) following the general procedure A.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (s, 1H, H_{ar}), 7.36 (s, 1H, H_{ar}), 7.10 (s, 1H, H_{ar}), 6.81 (d, *J* = 6.8 Hz, NH), 4.67-4.62 (m, 1H, H_1), 2.59 (t, *J* = 7.3 Hz, 2H, H_3), 2.29-2.20 (m, 1H, H_2), 2.16-2.07 (m, 1H, H_2), 2.12 (s, 3H, H_4), 1.50 (s, 9H, H_5) ppm.

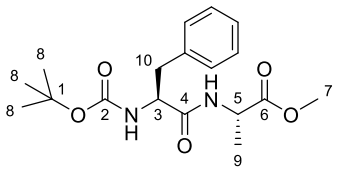
The analytical data were identical in all respects to those previously reported in the literature.[116]

General Procedure B for the microwave-assisted synthesis of dipeptides



In a 5 mL microwave vessel were successively added to a solution of the Imi-AA_1-OR derivative (1.00 equiv, 0.30 mmol) in CH_2Cl_2 (*C* 0.5 M): copper bromide (10 mol%), 1-hydroxybenzotriazole hydrate (10 mol%) and then P-AA_2-OH (1.50 equiv, 0.45 mmol). The suspension was then heated at 60 °C for 30 minutes with a microwave system (70 W). After reaction completion, the mixture was washed with aqueous HCl 0.5 N. Then, the aqueous phase was extracted with CH_2Cl_2 (1×). The organic layers were combined, washed with saturated aqueous $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$, and the solvent removed under vacuum. Purification was performed by column chromatography on silica gel to afford the products.

(S)-Methyl 2-((S)-2-((tert-butoxycarbonyl)amino)-3-phenylpropanamido)propanoate ***(III.3a)***



III.3a
$C_{18}H_{26}N_2O_5$
350,42

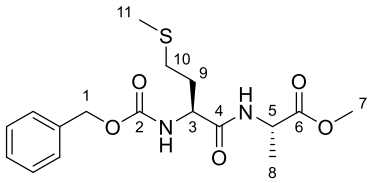
The title compound was isolated by short column chromatography (eluent: Pentane/EtOAc 7:3) as a white solid in 78% yield (82 mg) from Imi-Ala-OMe (59 mg, 0.30 mmol) and Boc-Phe-OH (119 mg, 0.45 mmol) following the general procedure B.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18-7.30 (m, 5H, H_{ar}), 6.54 (d, *J* = 7.0 Hz, 1H, NH), 5.06 (bs, 1H, NH), 4.51 (quin, *J* = 7.1 Hz, 1H, H_5), 4.37 (bd, *J* = 6.3 Hz, 1H, H_3), 3.70 (s, 3H, H_7), 3.05 (d, *J* = 6.6 Hz, 2H, H_{10}), 1.39 (s, 9H, H_8), 1.33 (d, *J* = 7.2 Hz, 3H, H_9) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0 (C_6), 170.9 (C_4), 155.5 (C_2), 136.7 (C_{ar}), 129.5 ($2C_{ar}$), 128.7 ($2C_{ar}$), 127.0 (C_{ar}), 80.3 (C_1), 55.7 (C_3), 52.5 (C_7), 48.2 (C_5), 38.5 (C_{10}), 28.4 ($3C_8$), 18.4 (C_9) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[116]

*(S)-Methyl 2-((2)-2(((benzyloxy)carbonyl)amino)-4-(methylthio)butanamido)propanoate (**III.3c**)*



III.3c
$C_{17}H_{24}N_2O_5S$
368,14

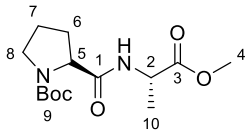
The title compound was isolated by short column chromatography (eluent: Pentane/EtOAc 7:3) as a white solid in 80% yield (87 mg) from Imi-Ala-OMe (59 mg, 0.30 mmol) and Cbz-Met-OH (128 mg, 0.45 mmol) following the general procedure B.

^{1}H NMR (400 MHz, CDCl3): δ 7.29-7.38 (m, 5H, H_{ar}), 6.60 (bd, *J* = 6.6 Hz, 1H, NH), 5.49 (bd, *J* = 7.7 Hz, 1H, NH), 5.11 (s, 2H, H_1), 4.57 (quin, *J* = 7.3 Hz, 1H, H_5), 4.37-4.42 (m, 1H, H_3), 3.75 (s, 3H, H_7), 2.61 (t, *J* = 7.2 Hz, 2H, H_{10}), 1.95-2.11 (m, 5H, $H_{9,11}$), 1.41 (d, *J* = 7.1 Hz, 3H, H_8) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1 (C_6), 170.7 (C_4), 156.1 (C_2), 136.3 (C_{ar}), 128.7 ($2C_{ar}$), 128.4 (C_{ar}), 128.2 ($2C_{ar}$), 67.0 (C_1), 53.5 (C_3), 52.7 (C_7), 48.2 (C_5), 31.8 (C_{10}), 30.0 (C_9), 18.3 (C_8), 15.2 (C_{11}) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[116]

*tert-Butyl (R)-2-(((S)-1-methoxy-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (**III.3d**)*



III.3d
$C_{14}H_{24}N_2O_5$
300,35

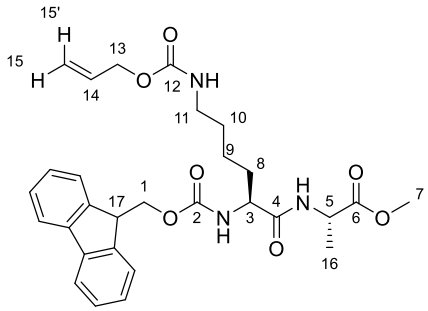
The title compound was isolated by short column chromatography (eluent: Pentane/EtOAc 7:3) as a white solid in 47% yield (42 mg) from Imi-Ala-OMe (59 mg, 0.30 mmol) and Boc-Pro-OH (97 mg, 0.45 mmol) following the general procedure B.

^{1}H NMR (400 MHz, CDCl3): δ 4.51 (bs, 1H, H_5), 4.19-4.31 (m, 1H, H_2), 3.72 (s, 3H, H_4), 3.31-3.43 (m, 2H, H_8), 1.84-2.26 (m, 4H, $H_{7,6}$), 1.45 (s, 9H, H_{Boc}), 1.37 (d, J = 7.1 Hz, 3H, H_{10}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.7 (C_3), 156.2 (C_1), 154.7 (C_{Boc}), 80.7 (C_{Boc}), 61.0 (C_4), 59.8 (C_2), 52.4 (C_5), 48.7 (C_8), 31.0 ($C_{7,6}$), 29.7 ($C_{7,6}$), 22.7 ($3C_{Boc}$), 18.8 (C_{10}) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[184]

*(S)-Methyl 2-((S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-6-(((allyloxy)carbonyl)amino)hexanamido)propanoate (**III.3f**)*



III.3f
$C_{29}H_{35}N_3O_7$
537,24

The title compound was isolated by short column chromatography (eluent: Pentane/EtOAc 7:3) as a white solid in 70% yield (114 mg) from Imi-Ala-OMe (59 mg, 0.30 mmol) and Fmoc-Lys(Alloc)-OH (204 mg, 0.45 mmol) following the general procedure B.

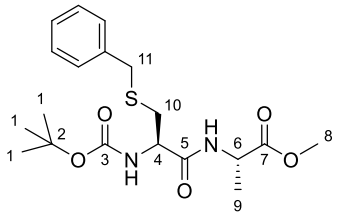
^{1}H NMR (400 MHz, CDCl3): δ 7.76 (d, J = 7.4 Hz, 2H, H_{ar}), 7.58 (d, J = 7.6 Hz, 2H, H_{ar}), 7.39 (td, J = 7.5, 0.5 Hz, 2H, H_{ar}), 7.30 (td, J = 7.5, 1.3 Hz, 2H, H_{ar}), 6.56 (d, J = 6.6 Hz, 1H, NH), 5.83-5.92 (m, 1H, H_{14}), 5.56 (d, J = 7.4 Hz, 1H, NH), 5.26 (d, J = 16.9 Hz, 1H, $H_{15'}$), 5.17 (d, J = 10.4 Hz, 1H, H_{15}), 4.97 (bs, 1H, H_{17}), 4.54-4.61 (m, 2H, H_{13}), 4.38 (d, J = 6.8 Hz, 2H, H_1), 4.17-4.23 (m, 2H, $H_{3,5}$), 3.74 (s, 3H, H_7), 3.16-3.24 (m, 2H, H_{11}), 1.83-1.92 (m, 1H, H_8), 1.65-1.71 (m, 1H, H_8), 1.49-1.58 (m, 2H, H_{10}), 1.40 (d, J = 7.2 Hz, 3H, H_{16}), 1.23-1.31 (m, 2H, H_9) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3 (C_6), 171.4 (C_4), 156.7 (C_{12}), 156.3 (C_2), 144.0 (C_{ar}), 143.9 (C_{ar}), 141.4 (2C_{ar}), 133.1 (C_{14}), 127.9 (2C_{ar}), 127.2 (2C_{ar}), 125.2 (2C_{ar}), 120.1 (2C_{ar}), 117.7 (C_{15}), 67.2 (C_1), 65.5 (C_{13}), 54.7 (C_7), 52.7 (C_3), 48.2 (C_5), 47.3 (C_{17}), 40.4 (C_{11}), 32.3 (C_{10}), 29.5 (C_8), 22.2 (C_9), 18.2 (C_{16}) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[116]

[184] A. Boruah, A.S. Devi, J. Iqbal, I. Rao, Y. Nageshwara; S.K. Kumar, R.K. Kunwar *J. Org. Chem.* **2004**, *69*, 2181.

(S)-Methyl 2-((S)-2-((tert-butoxycarbonyl)amino)-3-phenylpropanamido)propanoate ***(III.3g)***



III.3g
$C_{19}H_{28}N_2O_5S$
396,50

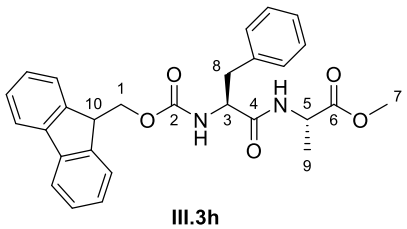
The title compound was isolated by short column chromatography (eluent: Pentane/EtOAc 7:3) as a white solid in 77% yield (82 mg) from Imi-Ala-OMe (59 mg, 0.30 mmol) and Boc-Cys(OBzl)-OH (119 mg, 0.45 mmol) following the general procedure B.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.36 (m, 5H, H_{ar}), 6.87 (d, *J* = 5.2 Hz, 1H, NH), 5.30 (bs, 1H, NH), 4.55 (quin, *J* = 7.2 Hz, 1H, H_4), 4.25 (bs, 1H, H_6), 3.75 (s, 3H, H_8), 3.74 (s, 2H, H_{11}) 2.88 (dd, *J* = 13.9, 5.7 Hz, 1H, H_{10}), 2.74 (dd, *J* = 14.0, 6.7 Hz, 1H, H_{10}), 1.46 (s, 9H, H_1), 1.40 (d, *J* = 7.2 Hz, 3H, H_9) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0 (C_7), 170.3 (C_5), 155.4 (C_3), 138.0 (C_{ar}), 129.2 ($2C_{ar}$), 128.7 ($2C_{ar}$), 127.4 (C_{ar}), 80.7 (C_2), 53.7 (C_4), 52.6 (C_8), 48.4 (C_6), 36.6 (C_{11}), 33.8 (C_{10}), 28.4 ($3C_1$), 18.5 (C_9) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[116]

(S)-Methyl 2-((S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-phenylpropanamido) propanoate ***(III.3h)***



III.3h
$C_{28}H_{28}N_2O_5$
472,54

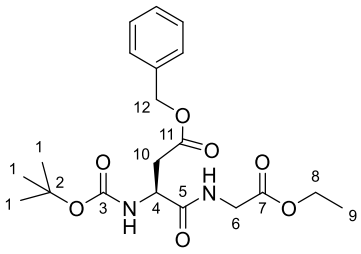
The title compound was isolated by short column chromatography (eluent: Pentane/EtOAc 7:3) as a white solid in 73% yield (105 mg) from Imi-Ala-OMe (59 mg, 0.30 mmol) and Fmoc-Phe-OH (174 mg, 0.45 mmol) following the general procedure B.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.5 Hz, 2H, H_{ar}), 7.54 (t, *J* = 6.9 Hz, 2H, H_{ar}), 7.40 (t, *J* = 7.3 Hz, 2H, H_{ar}), 7.19-7.33 (m, 7H, H_{ar}), 6.21 (bs, 1H, NH), 5.31 (bs, 1H, NH), 4.42-4.53 (m, 3H, $H_{1,10}$), 4.32-4.34 (m, 1H, H_3), 4.19 (t, *J* = 6.8 Hz, 1H, H_5), 3.71 (s, 3H, H_7), 3.12-3.15 (m, 1H, H_8), 3.01-3.06 (m, 1H, H_8), 1.34 (d, *J* = 7.0 Hz, 3H, H_9) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9 (C_6), 170.3 (C_4), 156.0 (C_2), 143.9 (C_{ar}), 143.8 (C_{ar}), 141.4 ($2C_{ar}$), 136.3 (C_{ar}), 129.5 ($2C_{ar}$), 128.9 ($2C_{ar}$), 127.9 ($2C_{ar}$), 127.3 (C_{ar}), 127.2 ($2C_{ar}$), 125.2 (C_{ar}), 125.1 ($2C_{ar}$), 120.1 (C_{ar}), 67.2 (C_1), 56.1 (C_3), 52.7 (C_7), 48.3 (C_8), 47.2 (C_{10}), 38.7 (C_8), 18.5 (C_9) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[116]

*Benzyl (S)-3-((tert-butoxycarbonyl)amino)-4-((2-ethoxy-2-oxoethyl)amino)-4-oxobutanoate (**III.3i**)*



III.3i
$C_{20}H_{28}N_2O_7$
408,4510

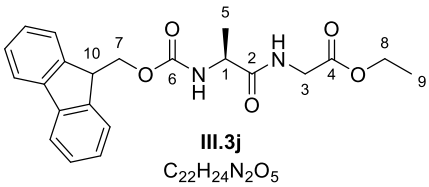
The title compound was isolated by short column chromatography (eluent: Pentane/EtOAc 7:3) as a white solid in 80% yield (100 mg) from Imi-Gly-OEt (59 mg, 0.30 mmol) and Boc-Asp(OBzl)-OH (146 mg, 0.45 mmol) following the general procedure B.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.34 (m, 5H, H_{ar}), 7.04 (t, *J* = 5.0 Hz, 1H, NH), 5.73 (d, *J* = 8.3 Hz, 1H, NH), 5.14 (d, *J* = 12.3 Hz, 1H, H_{12}), 5.09 (d, *J* = 12.3 Hz, 1H, H_{12}), 4.59 (bs, 1H, H_4), 4.18 (q, *J* = 7.1 Hz, 2H, H_8), 3.97 (d, *J* = 5.0 Hz, 2H, H_6), 3.03 (dd, *J* = 17.0 Hz, 3.7 Hz, 1H, H_{10}), 2.74 (dd, *J* = 17.0 Hz, 5.8 Hz, 1H, H_{10}), 1.43 (s, 9H, H_1), 1.25 (t, *J* = 7.1 Hz, 3H, H_9) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7 (C_5), 171.0 (C_7), 169.5 (C_{11}), 155.6 (C_3), 135.4 (C_{ar}), 128.6 ($2C_{ar}$), 128.4 (C_{ar}), 128.3 ($2C_{ar}$), 80.6 (C_2), 66.9 (C_{12}), 61.5 (C_8), 50.5 (C_4), 41.5 (C_6), 36.1 (C_{10}), 28.3 ($3C_1$), 14.2 (C_9) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[116]

*Ethyl (((9H-fluoren-9-yl)methoxy)carbonyl)-L-alanylglycinate (**III.3j**)*



III.3j
$C_{22}H_{24}N_2O_5$
396,44

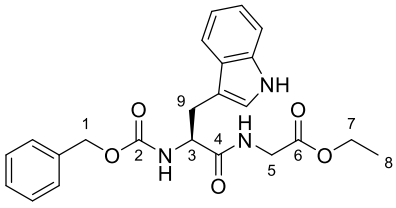
The title compound was isolated by short column chromatography (eluent: Pentane/EtOAc 7:3) as a white solid in 77% yield (92 mg) from Imi-Gly-OEt (59 mg, 0.30 mmol) and Fmoc-Ala-OH (140 mg, 0.45 mmol) following the general procedure B.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.5 Hz, 2H, H_{ar}), 7.59 (d, *J* = 7.6 Hz, 2H, H_{ar}), 7.41 (t, *J* = 7.5 Hz, 2H, H_{ar}), 7.31 (dt, *J* = 11.2, 0.6 Hz, 2H, H_{ar}), 6.44 (bs, 1H, NH), 5.30 (bs, 1H, NH), 4.42 (bs, 2H, H_7), 4.30 (bs, 1H, H_{10}), 4.22 (q, *J* = 7.1 Hz, 3H, $H_{1,8}$), 4.03 (d, *J* = 4.7 Hz, 2H, H_3), 1.42 (d, *J* = 6.2 Hz, 3H, H_5), 1.28 (t, *J* = 7.1 Hz, 3H, H_9) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5 (C_4), 169.7 (C_2), 156.1 (C_6), 143.9 ($2C_{ar}$), 141.4 ($2C_{ar}$), 127.9 ($2C_{ar}$), 127.2 ($2C_{ar}$), 125.2 ($2C_{ar}$), 120.1 ($2C_{ar}$), 67.3 (C_7), 61.8 (C_8), 50.4 (C_1), 47.3 (C_{10}), 41.5 (C_3), 18.6 (C_5), 14.3 (C_9) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[116]

*Ethyl ((benzyloxy)carbonyl)-L-tryptophylglycinate (**III.3k**)*



III.3k
$C_{23}H_{25}N_3O_5$
423,46

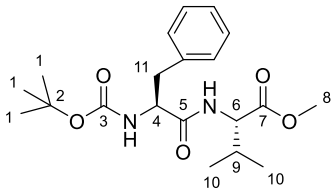
The title compound was isolated by short column chromatography (eluent: Pentane/EtOAc 7:3) as a white solid in 66% yield (86 mg) from Imi-Gly-OEt (59 mg, 0.30 mmol) and Cbz-Trp-OH (152 mg, 0.45 mmol) following the general procedure B.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 (bs, 1H, NH), 7.60 (bs, 1H, H_{ar}), 7.27-7.34 (m, 6H, H_{ar}), 7.16 (bt, *J* = 7.5 Hz, 1H, H_{ar}), 7.08 (bt, *J* = 7.3 Hz, 1H, H_{ar}), 7.01 (bs, 1H, H_{ar}), 6.51 (bs, 1H, NH), 5.66 (bs, 1H, NH), 5.03-5.11 (m, 2H, H_1), 4.57 (bs, 1H, H_3), 4.10 (q, *J* = 7.1 Hz, 2H, H_7), 3.79-3.90 (m, 2H, H_5), 3.19-3.30 (m, 2H, H_9), 1.22 (t, *J* = 7.1 Hz, 3H, H_8) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8 (C_4), 169.5 (C_6), 156.2 (C_2), 136.3 (C_{ar}), 128.6 ($2C_{ar}$), 128.2 ($2C_{ar}$), 128.1 ($2C_{ar}$), 127.5 (C_{ar}), 123.5 (C_{ar}), 122.2 (C_{ar}), 119.7 (C_{ar}), 118.7 (C_{ar}), 111.4 (C_{ar}), 110.2 (C_{ar}), 67.1 (C_1), 61.5 (C_7), 55.5 (C_3), 41.4 (C_5), 28.5 (C_9), 14.1 (C_8) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[185]

*Methyl (tert-butoxycarbonyl)-L-phenylalanyl-L-valinate (**III.3b**)*



III.3b
$C_{20}H_{30}N_2O_5$
378,46

The title compound was isolated by short column chromatography (eluent: Pentane/EtOAc 7:3) as a white solid in 70% yield (81 mg) from Imi-Val-OMe (68 mg, 0.30 mmol) and Boc-Phe-OH (119 mg, 0.45 mmol) following the general procedure B.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19-7.29 (m, 5H, H_{ar}), 6.42 (d, *J* = 7.8 Hz, 1H, NH), 5.07 (bs, 1H, NH), 4.45 (dd, *J* = 8.6, 5.1 Hz,

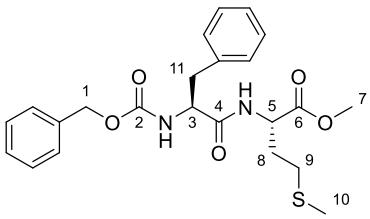
[185] H. Chen, M. He, Y. Wang, L. Zhai, Y. Cui, Y. Li, Y. Li, H. Zhou, X. Hong, Z. Denga *Green Chem.* **2011**, *13*, 2723.

1H, H_6), 4.33-4.38 (m, 1H, H_4), 3.67 (s, 3H, H_8), 3.06 (d, *J* = 6.8 Hz, 2H, H_{11}), 2.03-2.13 (m, 1H, H_9), 1.40 (s, 9H, H_1), 0.86 (d, *J* = 6.8 Hz, 3H, H_{10}), 0.83 (d, *J* = 6.9 Hz, 3H, H_{10}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8 (C_7), 171.2 (C_5), 155.5 (C_3), 136.7 (C_{ar}), 129.4 ($2C_{ar}$), 128.7 ($2C_{ar}$), 127.0 (C_{ar}), 80.2 (C_2), 57.3 (C_4), 55.9 (C_6), 52.1 (C_8), 38.1 (C_9), 31.3 (C_{11}), 28.3 ($3C_1$), 18.9 (C_{10}), 17.8 (C_{10}) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[116]

*Methyl ((benzyloxy)carbonyl)-L-phenylalanyl-L-methioninate (**III.3l**)*



III.3l
$C_{23}H_{28}N_2O_5S$
444,54

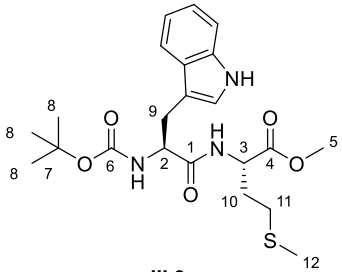
The title compound was isolated by short column chromatography (eluent: Pentane/EtOAc 7:3) as a white solid in 66% yield (88 mg) from Imi-Met-OMe (77 mg, 0.30 mmol) and Cbz-Phe-OH (135 mg, 0.45 mmol) following the general procedure B.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16-7.34 (m, 10H, H_{ar}), 6.58 (bs, 1H, NH), 5.42 (bs, 1H, NH), 5.08 (s, 2H, H_1), 4.63 (dt, *J* = 12.7, 3.7 Hz, 1H, H_3), 4.45 (q, J = 6.4 Hz, 1H, H_5), 3.70 (s, 3H, H_7), 3.02-3.13 (m, 2H, H_{11}), 2.39 (t, *J* = 7.3 Hz, 2H, H_9), 2.05-2.13 (m, 1H, H_8), 2.03 (s, 3H, H_{10}), 1.85-1.96 (m, 1H, H_8) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9 (C_4), 170.9 (C_6), 156.0 (C_2), 136.3 (C_{ar}), 136.2 (C_{ar}), 129.4 ($2C_{ar}$), 128.8 (C_{ar}), 128.6 ($2C_{ar}$), 128.3 ($2C_{ar}$), 128.1 ($2C_{ar}$), 127.2 (C_{ar}), 67.2 (C_1), 56.2 (C_3), 52.6 (C_5), 51.7 (C_7), 38.4 (C_{11}), 31.5 (C_9), 29.8 (C_8), 15.5 (C_{10}) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[116]

*Methyl (tert-butoxycarbonyl)-L-tryptophyl-L-methioninate (**III.3m**)*



III.3m
$C_{22}H_{31}N_3O_5S$
449,57

The title compound was isolated by short column chromatography (eluent: Pentane/EtOAc 7:3) as a white solid in 72% yield (97 mg) from Imi-Met-OMe (77 mg, 0.30 mmol) and Boc-Trp-OH (137 mg, 0.45 mmol) following the general procedure B.

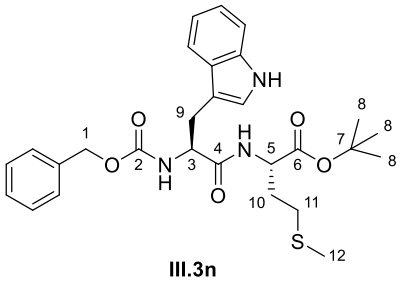
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (bs, 1H, NH), 7.64 (d, *J* = 7.8 Hz, 1H, H_{ar}), 7.36 (d, *J* = 8.0 Hz, 1H, H_{ar}), 7.17-7.21 (m, 1H, H_{ar}), 7.11-7.15 (m, 1H, H_{ar}), 7.09 (bs, 1H, NH), 6.45 (bs, 1H, H_{ar}), 5.16 (bs, 1H, NH), 4.55-4.60 (m, 1H, H_3), 4.44-4.47 (m, 1H, H_2), 3.65 (s, 3H, H_5), 3.35 (dd, *J* = 14.5,

5.4 Hz, 1H, H_9), 3.16 (dd, *J* = 14.5, 7.1 Hz, 1H, H_9), 2.23-2.27 (m, 2H, H_{11}), 1.99-2.04 (m, 4H, $H_{10,12}$), 1.82-1.89 (m, 1H, H_{10}), 1.43 (s, 9H, H_8) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7 (C_1), 171.5 (C_4), 155.4 (C_6), 136.2 (C_{ar}), 127.4 (C_{ar}), 123.3 (C_{ar}), 122.2 (C_{ar}), 119.7 (C_{ar}), 118.7 (C_{ar}), 111.2 (C_{ar}), 110.3 (C_{ar}), 80.1 (C_7), 55.3 (C_5), 52.4 (C_2), 51.5 (C_3), 31.4 (C_9), 29.5 (C_{12}), 28.2 ($3C_8$), 28.0 (C_{11}), 15.2 (C_{10}) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[116]

*tert-Butyl (S)-2-((S)-2-(((benzyloxy)carbonyl)amino)-3-(1H-indol-3-yl)propanamido)-4-(methylthio)butaneperoxoate (**III.3n**)*



III.3n
$C_{28}H_{35}N_3O_6S$
541,66

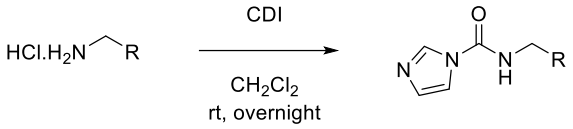
The title compound was isolated by short column chromatography (eluent: Pentane/EtOAc 7:3) as a white solid in 66% yield (107 mg) from Imi-Met-O*t*Bu (90 mg, 0.30 mmol) and Cbz-Trp-OH (152 mg, 0.45 mmol) following the general procedure B.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (bs, 1H, NH), 7.63 (d, *J* = 7.6 Hz, 1H, H_{ar}), 7.30-7.34 (m, 5H, H_{ar}), 7.18 (m, 1H, H_{ar}), 7.09-7.11 (m, 1H, H_{ar}), 7.01 (bs, 1H, NH), 6.57 (bs, 1H, H_{ar}), 5.52 (d, *J* = 6.7 Hz, 1H, H_{ar}), 5.10 (s, 2H, H_1), 4.56 (d, *J* = 6.4 Hz, 1H, H_3), 4.44-4.47 (m, 1H, H_5), 3.36 (dd, *J* = 14.6, 4.4 Hz, 1H, H_9), 3.19 (dd, *J* = 14.6, 6.8 Hz, 1H, H_9), 2.23-2.28 (m, 2H, H_{11}), 2.01-2.06 (m, 1H, H_{10}), 1.98 (s, 3H, H_{12}), 1.81-1.88 (m, 1H, H_{10}), 1.42 (s, 9H, H_8) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2 (C_4), 170.4 (C_6), 156.1 (C_2), 136.3 (C_{ar}), 128.6 ($2C_{ar}$), 128.2 ($2C_{ar}$), 128.1 ($2C_{ar}$), 127.5 (C_{ar}), 123.5 (C_{ar}), 122.3 (C_{ar}), 119.8 (C_{ar}), 118.8 (C_{ar}), 111.4 (C_{ar}), 110.1 (C_{ar}), 82.5 (C_7), 67.1 (C_1), 55.7 (C_5), 52.4 (C_3), 31.7 (C_{10}), 29.6 (C_{11}), 28.3 (C_9), 28.01 ($3C_8$), 15.4 (C_{12}) ppm.

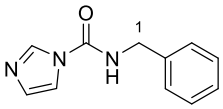
The analytical data were identical in all respects to those previously reported in the literature.[116]

General Procedure C for the Preparation of the "CDI-activated" general amines



To a solution of the corresponding amine (1.00 equiv) in CH_2Cl_2 (0.2 M) at room temperature was added *N*, *N*'-carbonyldiimidazole (1.20 equiv). The obtained suspension was thus stirred at this temperature overnight. After reaction completion (TLC monitoring), the mixture was washed once with H_2O. The organic phase was separated and the aqueous phase was further extracted with CH_2Cl_2 (2×). The organic layers were combined, dried over $MgSO_4$ and evaporated. Purification was performed by column chromatography on a short silica gel pad to afford the desired intermediates.

*N-(Benzyl)-1H-imidazole-1-carboxamide (**III.39a**)*



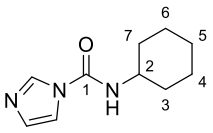
III.39a
$C_{11}H_{11}N_3O$
201,22

The title compound was isolated by short column chromatography (eluent: EtOAc 100%) as a white solid in 90% yield (0.54 g) from benzylamine (0.32 g, 3.00 mmol) following the general procedure C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (s, 1H, H_{ar}), 7.44 (s, 1H, H_{ar}), 7.38-7.22 (m, 5H, H_{ar}), 7.00 (s, 1H, H_{ar}) 6.69 (bs, 1H, NH), 4.59 (d, *J* = 5.6 Hz, 2H, H_1) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[186]

*N-Cyclohexyl-1H-imidazole-1-carboxamide (**III.39b**)*



III.39b
$C_{10}H_{15}N_3O$
193,25

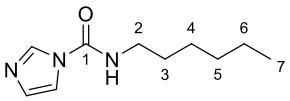
The title compound was isolated by short column chromatography (eluent: EtOAc 100%) as a white solid in 99% yield (0.58 g) from cyclohexylamine (0.30 g, 3.00 mmol) following the general procedure C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (s, 1H, H_{ar}), 7.58 (bs, 1H, NH), 7.48 (t, *J* = Hz, 1H, H_{ar}), 6.93 (s, 1H, H_{ar}), 3.70-3.77 (m, 1H, H_2), 1.94-2.06 (m, 2H, $H_{7\text{ or }3}$), 1.69-1.72 (m, 2H, $H_{7\text{ or }3}$), 1.58-1.61 (m, 1H, H_5), 1.16-1.34 (m, 4H, $H_{4,6}$), 0.99-1.10 (m, 1H, H_5) ppm.

[186] J. Nugent, S.G. Campbell, Y. Vo, B.D. Schwartz *Eur. J. Org. Chem.* **2017**, 5110.

The analytical data were identical in all respects to those previously reported in the literature.[184]

*N-Hexyl-1H-imidazole-1-carboxamide (**III.39c**)*



III.39c
$C_{10}H_{17}N_3O$
195,26

The title compound was isolated by short column chromatography (eluent: EtOAc 100%) as a viscous colourless oil in 89% yield (0.52 g) from hexylamine (0.30 g, 3.00 mmol) following the general procedure C.

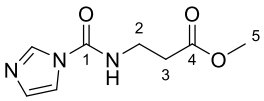
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (t, *J* = 5.6 Hz, 1H, NH), 8.20 (s, 1H, H_{ar}), 7.53 (t, *J* = 1.4 Hz, 1H, H_{ar}), 6.91-6.92 (m, 1H, H_{ar}), 3.29 (q, *J* = 6.7 Hz, 2H, H_2), 1.52 (quint, *J* = 7.3 Hz, 2H, H_3), 1.15-1.29 (m, 6H, $H_{4,5,6}$), 0.79 (t, *J* = 7.4 Hz, 3H, H_7) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.2 (C_1), 136.0 (C_{ar}), 129.3 (C_{ar}), 116.7 (C_{ar}), 41.0 (C_2), 31.3 (C_3), 29.3 (C_5), 26.5 (C_4), 22.4 (C_6), 13.9 (C_7) ppm.

FTIR neat (cm^{-1}): 3229, 2928, 2858, 1697, 1543, 1517, 1479, 1360, 1284, 1244, 1198, 1099, 1055, 911, 826, 748, 652.

HRMS (ESI+) calculated for $C_{10}H_{17}N_3O$ (m/z): $[M+H]^+$: calculated : 196.1444, found: 196.1449.

*Methyl 3-(imidazole-1-carbonylamino)propanoate (**III.39d**)*



III.39d
$C_8H_{11}N_3O_3$
197,19

The title compound was isolated by short column chromatography (eluent: EtOAc 100%) as a white solid in 63% yield (0.38 g) from β-alanine methyl ester hydrochloride (0.42 g, 3.00 mmol) following the general procedure C.

Mp: .80.7 – 82.7°C

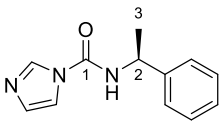
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 1H, H_{ar}), 7.29 (t, *J* = 1.5 Hz, 1H, H_{ar}), 7.09 (q, *J* = 2.5 Hz, 1H, H_{ar}), 6.55 (bs, 1H, NH), 3.73 (s, 3H, H_5), 3.69 (q, *J* = 5.9 Hz, 2H, H_2), 2.67 (t, *J* = 11.6 Hz, 2H, H_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.8 (C_4), 149.1 (C_1), 136.1 (C_{ar}), 130.1 (C_{ar}), 116.3 (C_{ar}), 52.0 (C_5), 36.5 (C_2), 33.5 (C_3) ppm.

FTIR neat (cm^{-1}): 3155, 3136, 2950, 1738, 1705, 1553, 1438, 1375, 1360, 1323, 1284, 1250, 1202, 1075, 1041, 1013, 916, 855, 794, 756, 716, 653

HRMS (ESI+) calculated for $C_8H_{11}N_3O_3$ (m/z): $[M+H]^+$: calculated : 198.0873, found: 198.0878

*(S)-N-(1-Phenylethyl)-1H-imidazole-1-carboxamide (**III.39e**)*



III.39e
$C_{12}H_{13}N_3O$
215,25

The title compound was isolated by short column chromatography (eluent: EtOAc 100%) as a viscous colourless oil in 80% yield (0.52 g) from 1-phenylethylamine (0.36 g, 3.00 mmol) following the general procedure C.

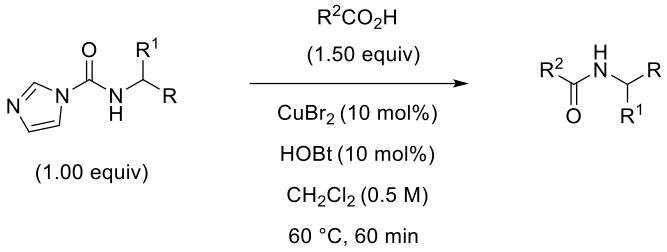
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (s, 1H, H_{ar}), 7.96 (d, *J* = 7.4 Hz, 1H, NH), 7.45 (t, *J* = 1.4 Hz, 1H, H_{ar}), 7.22-7.34 (m, 5H, H_{ar}), 6.87 (d, *J* = 0.5 Hz, 1H, H_{ar}), 5.13 (quint, *J* = 7.1 Hz, 1H, H_2), 1.55 (d, *J* = 7.1 Hz, 3H, H_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.5 (C_1), 142.3 (C_{ar}), 136.1 (C_{ar}), 129.5 (C_{ar}), 128.8 ($2C_{ar}$), 127.8 (C_{ar}), 126.4 ($2C_{ar}$), 116.8 (C_{ar}), 50.8 (C_2), 21.3 (C_3).

FTIR neat (cm^{-1}): 3213, 3029, 2978, 1694, 1538, 1517, 1479, 1449, 1368, 1321, 1276, 1241, 1096, 1073, 1059, 1016, 910, 837, 746, 696, 652.

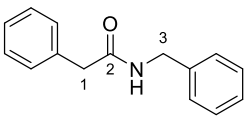
HRMS (ESI+) calculated for $C_{12}H_{13}N_3O$ (m/z): $[M+H]^-$: calculated : 214.0986, found: 214.0990.

General Procedure D for the synthesis of general amides



In a 4 mL screw top vial were successively added to a solution of the imidazole intermediate (1.00 equiv, 0.50 mmol) in CH_2Cl_2 (*C* 0.5 M): copper bromide (10 mol%), 1-hydroxybenzotriazole hydrate (10 mol%), and a carboxylic acid (1.50 equiv, 0.75 mmol). The suspension was then heated at 60 °C for 2 hours with conventional heating. After reaction completion, the mixture was washed with aqueous HCl 0.5 N. Then, the aqueous phase was extracted with CH_2Cl_2 (1×). The organic layers were combined, washed with saturated aqueous $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$, and the solvent removed under vacuum. Purification was performed by column chromatography on silica gel to afford general amides.

*N-Benzyl-2-phenylacetamide (**III.44**)*



III.44
$C_{15}H_{15}NO$
225,29

The title compound was isolated by short column chromatography (eluent: Pentane/EtOAc 6:4) as a white solid in 76% yield (87 mg) from *N*-(benzyl)-1*H*-imidazole-1-carboxamide (100 mg, 0.50 mmol) following the general procedure D.

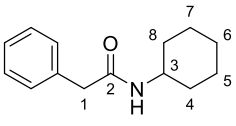
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17-7.37 (m, 10H, H_{ar}), 5.67 (bs, 1H, NH), 4.42 (d, *J* = 5.8 Hz, 2H, H_3), 3.63 (s, 2H, H_1) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0 (C_2), 138.3 (C_{ar}), 135.0 (C_{ar}), 129.6 ($2C_{ar}$), 129.1 ($2C_{ar}$), 128.7 ($2C_{ar}$), 127.6 ($2C_{ar}$), 127.5 (C_{ar}), 127.5 (C_{ar}), 43.9 (C_3), 43.6 (C_1) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[187]

[187] D.U. Nielsen, K. Neumann, R.H. Taaning, A.T. Lindhardt, A. Modvig, T. Skrydstrup *J. Org. Chem.* **2012**, *77*, 6155.

*N-Cyclohexyl-2-phenylacetamide (**III.45**)*



III.45
$C_{14}H_{19}NO$
217,31

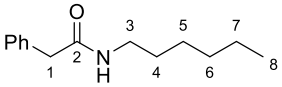
The title compound was isolated by short column chromatography (eluent: Pentane/EtOAc 6:4) as a white solid in 86% yield (93 mg) from *N*-cyclohexyl-1*H*-imidazole-1-carboxamide (97 mg, 0.50 mmol) following the general procedure D.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21-7.37 (m, 5H, H_{ar}), 5.19 (bs, 1H, NH), 3.70-3.80 (m, 1H, H_3), 3.54 (s, 2H, H_1), 1.80-1.84 (m, 2H, H_4), 1.53-1.63 (m, 3H, $H_{8,6}$), 1.25-1.37 (m, 2H, H_7), 0.95-1.13 (m, 3H, $H_{5,6}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1 (C_2), 135.3 (C_{ar}), 129.5 ($2C_{ar}$), 129.1 ($2C_{ar}$), 127.4 (C_{ar}), 48.3 (C_3), 44.1 (C_1), 33.0 ($2C_{4,8}$), 25.6 ($2C_{5,7}$), 24.8 (C_6) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[188]

*N-Hexyl-2-phenylacetamide (**III.46**)*



III.46
$C_{14}H_{21}NO$
219,32

The title compound was isolated by short column chromatography (eluent: Pentane/EtOAc 6:4) as a white solid in 70% yield (77 mg) from *N*-cyclohexyl-1*H*-imidazole-1-carboxamide (98 mg, 0.50 mmol) following the general procedure D.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24-7.37 (m, 5H, H_{ar}), 5.38 (bs, 1H, NH), 3.56 (s, 2H, H_1), 3.16-3.21 (m, 2H, H_3), 1.36-1.41 (m, 2H, H_4), 1.19-1.28 (m, 6H, $H_{5,6,7}$), 0.85 (t, J = 6.9 Hz, 3H, H_8) ppm.

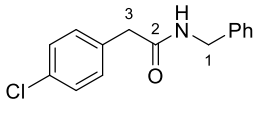
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9 (C_2), 135.2 (C_{ar}), 129.6 ($2C_{ar}$), 129.1 ($2C_{ar}$), 127.4 (C_{ar}), 44.0 (C_1), 39.8 (C_3), 31.5 (C_4), 29.5 (C_5), 26.5 (C_6), 22.6 (C_7), 14.1 (C_8) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[189]

188 A. Charvieux, L. Le Moigne, L.G. Borrego, N. Duguet, E. Métay *Eur. J. Org. Chem.* **2019**, 6842.

189 E.K.W. Tam, Rita, L.Y. Liu, A. Chen *Eur. J. Org. Chem.* **2015**, *5*, 1110.

*N-Benzyl-2-(4-chlorophenyl)acetamide (**III.47**)*



III.47
$C_{15}H_{14}ClNO$
259,73

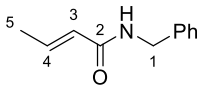
The title compound was isolated by short column chromatography (eluent: Pentane/EtOAc 6:4) as a white solid in 60% yield (79 mg) from *N*-(benzyl)-1*H*-imidazole-1-carboxamide (100 mg, 0.50 mmol) following the general procedure D.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.33 (m, 5H, H_{ar}), 7.18-7.22 (m, 4H, H_{ar}), 5.72 (bs, 1H, NH), 4.41 (d, *J* = 5.8 Hz, 2H, H_1), 3.57 (s, 2H, H_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4 (C_2), 138.1 (C_{ar}), 133.5 (C_{ar}), 133.4 (C_{ar}), 130.9 ($2C_{ar}$), 129.3 ($2C_{ar}$), 128.9 ($2C_{ar}$), 127.8 ($2C_{ar}$), 127.7 (C_{ar}), 43.9 (C_3), 43.2 (C_1) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[190]

*(E)-N-Benzylbut-2-enamide (**III.49**)*



III.49
$C_{11}H_{13}NO$
175,23

The title compound was isolated by short column chromatography (eluent: Pentane/EtOAc 6:4) as a white solid in 62% yield (54 mg) from *N*-(benzyl)-1*H*-imidazole-1-carboxamide (100 mg, 0.50 mmol) following the general procedure D.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.36 (m, 5H, H_{ar}), 6.89 (dq, *J* = 15.2, 6.8 Hz, 1H, H_4), 5.80 (dq, *J* = 15.2, 1.6 Hz, 1H, H_3), 5.64 (bs, 1H, NH), 4.51 (d, *J* = 5.7 Hz, 2H, H_1) 1.86 (dd, *J* = 6.8, 1.6 Hz, 3H, H_5) ppm.

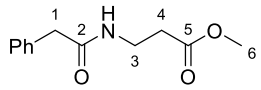
^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9 (C_2), 140.5 (C_4), 138.4 (C_{ar}), 128.8 ($2C_{ar}$), 128.0 ($2C_{ar}$), 127.6 (C_{ar}), 124.9 (C_3), 43.7 (C_1), 17.8 (C_5) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[191]

190 A.J.A. Watson, R.J. Wakeham, A.C. Maxwell, J.M.J. Williams *Tetrahedron* **2014**, *70*, 3683.

191 M.A. Ortega-Rojas, J.D. Rivera-Ramírez, C.G. Ávila-Ortiz, E. Juaristi, F. González-Muñoz, E. Castillo, J. Escalante *Molecules* **2017**, *22*, 2189.

*Methyl 3-(2-phenylacetamido)propanoate (**III.50**)*



III.50
$C_{12}H_{15}NO_3$
221,25

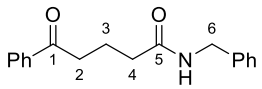
The title compound was isolated by short column chromatography (eluent: Pentane/EtOAc 6:4) as a pale-yellow oil in 90% yield (100 mg) from methyl 3-(imidazole-1-carbonylamino)propanoate (99 mg, 0.50 mmol) following the general procedure D.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23-7.37 (m, 5H, H_{ar}), 5.34 (bs, 1H, NH), 3.62 (s, 3H, H_6), 3.55 (s, 2H, H_1), 3.47 (q, *J* = 6.1 Hz, 2H, H_3) 2.50 (t, *J* = 6.0 Hz, 2H, H_4) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.7 (C_5), 171.1 (C_2), 134.9 (C_{ar}), 129.3 ($2C_{ar}$), 128.9 ($2C_{ar}$), 127.3 (C_{ar}), 51.7 (C_6), 43.8 (C_1), 35.1 (C_3), 33.8 (C_4) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[192]

*N-Benzyl-5-oxo-5-phenylpentanamide (**III.51**)*



III.51
$C_{18}H_{19}NO_2$
281,36

The title compound was isolated by short column chromatography (eluent: Pentane/EtOAc 6:4) as a white solid in 66% yield (74 mg) from *N*-(benzyl)-1*H*-imidazole-1-carboxamide (100 mg, 0.50 mmol) following the general procedure D.

Mp: 94.6 – 95.6°C

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96-7.93 (m, 2H, H_{ar}), 7.54-7.58 (m, 1H, H_{ar}), 7.43-7.47 (m, 2H, H_{ar}), 7.27-7.38 (m, 5H, H_{ar}), 5.85 (bs, 1H, NH), 4.44 (d, *J* = 5.7 Hz, 2H, H_6), 3.07 (t, *J* = 6.9 Hz, 2H, H_2), 2.34 (t, *J* = 7.2 Hz, 2H, H_4) 2.11 (quint, *J* = 7.1 Hz, 2H, H_3) ppm.

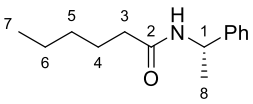
^{13}C NMR (100 MHz, $CDCl_3$): δ 200.0 (C_1), 172.4 (C_5), 138.4 (C_{ar}), 136.9 (C_{ar}), 133.3 (C_{ar}), 128.9 ($2C_{ar}$), 128.8 ($2C_{ar}$), 128.2 ($2C_{ar}$), 128.0 ($2C_{ar}$), 127.7 (C_{ar}), 43.8 (C_6), 37.5 (C_2), 35.6 (C_4), 20.4 (C_3) ppm.

FTIR neat (cm^{-1}): 3268, 3062, 2919, 1680, 1642, 1554, 1493, 1445, 1417, 1381, 1358, 1306, 1282, 1202, 1027, 977, 719, 699, 685, 656.

HRMS (ESI+) calculated for $C_{18}H_{19}NO_2$ (m/z): $[M+H]^+$: calculated : 282.1489, found: 282.1494.

192 A.M. Dumas, G.A. Molander, J.W. Bode *Angew. Chem. Int. Ed.* **2012**, *51*, 5683.

*(S)-N-(1-Phenylethyl)hexanamide (**III.52**)*



III.52
$C_{14}H_{21}NO$
219,32

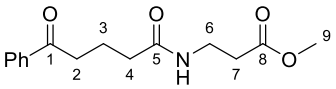
The title compound was isolated by short column chromatography (eluent: Pentane/EtOAc 6:4) as a white solid in 60% yield (65 mg) from (*S*)-*N*-(1-phenylethyl)-1*H*-imidazole-1-carboxamide (108 mg, 0.50 mmol) following the general procedure D.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23-7.35 (m, 5H, H_{ar}), 5.88 (bs, 1H, NH), 5.13 (quint, *J* = 7.2 Hz, 1H, H_1), 2.15 (t, *J* = 7.7 Hz, 2H, H_3), 1.62 (quint, *J* = 7.5 Hz, 2H, H_4) 1.47 (d, *J* = 6.9 Hz, 3H, H_8), 1.24-1.34 (m, 4H, $H_{5,6}$), 0.88 (t, *J* = 7.0 Hz, 3H, H_7) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3 (C_2), 143.5 (C_{ar}), 128.7 ($2C_{ar}$), 127.4 (C_{ar}), 126.3 ($2C_{ar}$), 48.6 (C_1), 36.9 (C_3), 31.5 (C_5), 25.5 (C_4), 22.5 (C_6), 21.8 (C_8), 14.0 (C_7) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[193]

*Methyl 3-(5-oxo-5-phenylpentanamido)propanoate (**III.53**)*



III.53
$C_{15}H_{19}NO_4$
277,32

The title compound was isolated by short column chromatography (eluent: Pentane/EtOAc 6:4) as a white solid in 76% yield (106 mg) from methyl 3-(imidazole-1-carbonylamino)propanoate (99 mg, 0.50 mmol) following the general procedure D.

Mp: 99.8 – 102.0°C

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94-7.97 (m, 2H, H_{ar}), 7.53-7.58 (m, 1H, H_{ar}), 7.43-7.47 (m, 2H, H_{ar}), 6.09 (bs, 1H, NH), 3.68 (s, 3H, H_9), 3.52 (q, *J* = 6.0 Hz, 2H, H_6), 3.05 (t, *J* = 7.0 Hz, 2H, H_4), 2.54 (t, *J* = 6.0 Hz, 2H, H_7), 2.28 (t, *J* = 7.2 Hz, 2H, H_2), 2.07 (quint, *J* = 7.0 Hz, 2H, H_3) ppm.

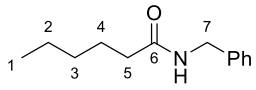
^{13}C NMR (100 MHz, $CDCl_3$): δ 199.9 (C_1), 173.2 (C_8), 172.5 (C_5), 136.9 (C_{ar}), 133.2 (C_{ar}), 128.7 ($2C_{ar}$), 128.2 ($2C_{ar}$), 51.9 (C_9), 37.5 (C_2), 35.6 (C_4), 34.9 (C_6), 34.0 (C_7), 20.2 (C_3) ppm.

FTIR neat (cm^{-1}): 3300, 2949, 1728, 1680, 1644, 1549, 1441, 1423, 1382, 1319, 1198, 1175, 1103, 1000, 947, 888, 738, 690, 657.

193 R.S.L. Chapman, J.D. Tibbetts, S.D. Bull *Tetrahedron* **2018**, *74*, 5330.

HRMS (ESI+) calculated for $C_{15}H_{19}NO_4$ (m/z): $[M-H]^-$: calculated : 276.1241, found: 276.1238.

*N-Benzylhexanamide (**III.54**)*



III.54
$C_{13}H_{19}NO$
205,30

The title compound was isolated by short column chromatography (eluent: Pentane/EtOAc 6:4) as a white solid in 72% yield (74 mg) from *N*-(benzyl)-1*H*-imidazole-1-carboxamide (100 mg, 0.50 mmol) following the general procedure D.

Mp: 53.8 – 54.7°C

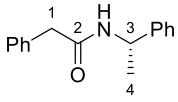
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.26 (m, 5H, H_{ar}), 5.66 (bs, 1H, NH), 4.44 (d, *J* = 5.7 Hz, 2H, H_7), 2.20 (t, *J* = 7.6 Hz, 2H, H_5), 1.62-1.70 (m, 2H, H_4) 1.28-1.34 (m, 4H, $H_{2,3}$), 0.89 (t, *J* = 7.0 Hz, 3H, H_1) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0 (C_6), 138.6 (C_{ar}), 128.8 ($2C_{ar}$), 128.0 ($2C_{ar}$), 127.6 (C_{ar}), 43.7 (C_7), 36.9 (C_5), 31.6 (C_3), 25.6 (C_4), 22.5 (C_2), 14.1 (C_1) ppm.

FTIR neat (cm^{-1}): 3288, 2955, 2930, 2856, 1631, 1548, 1492, 1453, 1430, 1355, 1284, 1260, 1235, 1217, 1190, 1080, 1025, 748, 724, 693.

HRMS (ESI+) calculated for $C_{13}H_{19}NO$ (m/z): $[M+H]^+$: calculated : 206.1500, found: 206.1500.

*(S)-2-Phenyl-N-(1-phenylethyl)acetamide (**III.55**)*



III.55
$C_{16}H_{17}NO$
239,31

The title compound was isolated by short column chromatography (eluent: Pentane/EtOAc 6:4) as a pale-yellow oil in 76% yield (92 mg) from (*S*)-*N*-(1-phenylethyl)-1*H*-imidazole-1-carboxamide (108 mg, 0.50 mmol) following the general procedure D.

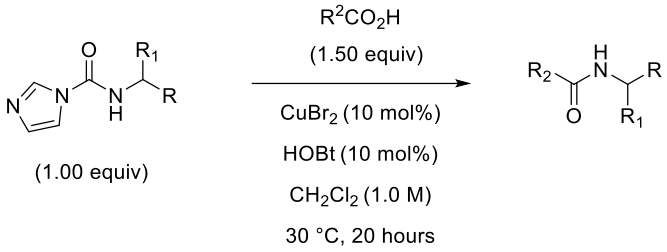
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.16 (m, 10H, H_{ar}), 5.62 (bd, *J* = 5.6 Hz 1H, NH), 5.12 (quint, *J* = 7.2 Hz, 1H, H_3), 3.58 (s, 2H, H_1), 1.40 (d, *J* = 7.2 Hz, 3H, H_4) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1 (C_2), 143.2 (C_{ar}), 135.0 (C_{ar}), 129.5 ($2C_{ar}$), 129.2 ($2C_{ar}$), 128.8 ($2C_{ar}$), 127.5 (C_{ar}), 127.4 (C_{ar}), 126.1 ($2C_{ar}$), 48.9 (C_3), 44.0 (C_1), 21.9 (C_4) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[194]

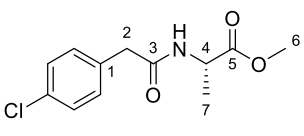
194 J. Bai, B.K. Zambron, P. Vogel *Org. Lett.* **2014**, *16*, 604.

General Procedure E for the synthesis of hybrid amides



In a 4 mL screw top vial were successively added to a solution of the imidazole intermediate (1.00 equiv, 0.50 mmol) in CH_2Cl_2 (C 1.0 M): copper bromide (10 mol%), 1-hydroxybenzotriazole hydrate (10 mol%), and a carboxylic acid (1.50 equiv, 0.75 mmol). The suspension was then stirred at 30 °C for 20 hour. After reaction completion, the mixture was washed with aqueous HCl 0.5 N. Then, the aqueous phase was extracted with CH_2Cl_2 (1x). The organic layers were combined, washed with saturated aqueous $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$, and the solvent removed under vacuum. Purification was performed by column chromatography on silica gel to afford the desired products.

*Methyl (2-(4-chlorophenyl)acetyl)-L-alaninate (**III.36**)*



III.36
$C_{12}H_{14}ClNO_3$
255,69

The title compound was isolated by short column chromatography (eluent: Pentane/EtOAc 7:3) as a white solid in 82% yield (108 mg) from Imi-Ala-OMe (99 mg, 0.50 mmol) following the general procedure E.

Mp: 103.7 – 104.9°C

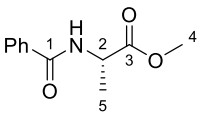
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.34 (m, 2H, H_{ar}), 7.20-7.23 (m, 2H, H_{ar}), 5.98 (bs, 1H, NH), 4.58 (quint, *J* = 7.2 Hz, 1H, H_4), 3.73 (s, 3H, H_6), 3.55 (s, 2H, H_2), 1.36 (d, *J* = 7.2 Hz, 3H, H_7) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5 (C_5), 170.0 (C_3), 133.4 (C_{ar}), 133.1 (C_{ar}), 130.8 ($2C_{ar}$), 129.2 ($2C_{ar}$), 52.6 (C_6), 48.3(C_4), 42.9 (C_2), 18.5 (C_7) ppm.

FTIR neat (cm^{-1}): 3272, 3070, 3009, 1730, 1653, 1543, 1491, 1445, 1361, 1332, 1304, 1260, 1217, 1108, 1088, 1013, 962, 856, 803, 734, 708, 677.

HRMS (ESI+) calculated for $C_{12}H_{14}ClNO_3$ (m/z): $[M+H]^+$: calculated : 256.0735, found: 256.0742.

*N-Benzoyl-L-alanine methyl ester **(III.37)***



III.37
$C_{11}H_{13}NO_3$
207,22

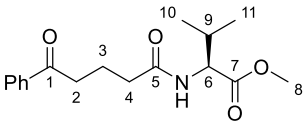
The title compound was isolated by short column chromatography (eluent: Pentane/EtOAc 7:3) as a white solid in 45% yield (47 mg) from Imi-Ala-OMe (99 mg, 0.50 mmol) following the general procedure E.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78-7.81 (m, 2H, H_{ar}), 7.47-7.51 (m, 1H, H_{ar}), 7.39-7.44 (m, 2H, H_{ar}), 6.85 (d, *J* = 6.0 Hz, 1H, NH), 4.79 (quint, *J* = 7.2 Hz, 1H, H_2), 3.77 (s, 3H, H_4), 1.51 (d, *J* = 7.2 Hz, 3H, H_5) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8 (C_3), 166.9 (C_1), 134.0 (C_{ar}), 131.8 (C_{ar}), 128.7 ($2C_{ar}$), 127.2 ($2C_{ar}$), 52.7 (C_4), 48.6 (C_2), 18.7 (C_5) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[195]

*Methyl (5-oxo-5-phenylpentanoyl)-L-valinate **(III.38)***



III.38
$C_{17}H_{23}NO_4$
305,37

The title compound was isolated by short column chromatography (eluent: Pentane/EtOAc 7:3) as a white solid in 86% yield (132 mg) from Imi-Val-OMe (113 mg, 0.50 mmol) following the general procedure E.

Mp: 72.5 – 73.7°C

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95-7.97 (m, 2H, H_{ar}), 7.50-37.57 (m, 1H, H_{ar}), 7.43-7.47 (m, 2H, H_{ar}), 6.02 (d, *J* = 8.6 Hz, 1H, NH), 4.57 (dd, *J* = 8.8, 4.9 Hz, 1H, H_6), 3.72 (s, 3H, H_8), 3.08 (t, *J* = 6.9 Hz, 2H, H_2), 2.35-2.39 (m, 2H, H_4), 2.06-2.19 (m, 3H, $H_{3,9}$), 0.93 (d, *J* = 6.8 Hz, 3H, $H_{10,11}$), 0.90 (d, *J* = 6.9 Hz, 3H, $H_{10,11}$) ppm.

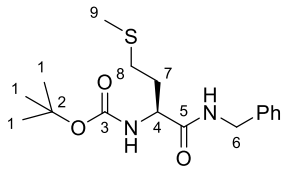
^{13}C NMR (100 MHz, $CDCl_3$): δ 200.0 (C_1), 172.7 (C_5), 172.6 (C_7), 136.9 (C_{ar}), 133.2 (C_{ar}), 128.7 ($2C_{ar}$), 128.2 ($2C_{ar}$), 57.1 (C_6), 52.2 (C_8), 37.4 (C_2), 35.5 (C_4), 31.3 (C_9), 20.3 (C_3), 19.1 ($C_{10,11}$), 18.0 ($C_{10,11}$) ppm.

FTIR neat (cm^{-1}): 3307, 2962, 1744, 1672, 1650, 1529, 1446, 1385, 1371, 1300, 1284, 1255, 1196, 1182, 1149, 1028, 994, 963, 734, 688, 659.

[195] Alandini, N.; Buzzetti, L.; Candish, L.; Collins, K. D.; Favi, G.; Melchiorre, P.; Schulte, T. *Angew. Chem. Int. Ed.* **2020**, *59*, 5248.

HRMS (ESI+) calculated for $C_{17}H_{23}NO_4$ (m/z): $[M-H]^-$: calculated : 304.1554, found: 304.1556.

*tert-Butyl (S)-(1-(benzylamino)-4-(methylthio)-1-oxobutan-2-yl)carbamate (**III.40a**)*



III.40a
$C_{17}H_{26}N_2O_3S$
338,46

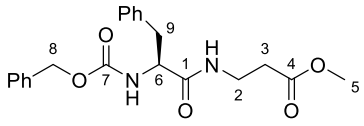
The title compound was isolated by short column chromatography (eluent: Pentane/EtOAc 7:3) as a white solid in 62% yield (104 mg) from *N*-(benzyl)-1*H*-imidazole-1-carboxamide (100 mg, 0.50 mmol) following the general procedure E.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24-7.33 (m, 5H, H_{ar}), 6.64 (bs, 1H, NH), 5.23 (bs, 1H, NH), 4.43 (s, 2H, H_6), 4.28 (d, *J* = 6.3 Hz, 1H, H_4), 2.47-2.60 (m, 2H, H_8), 2.08-2.15 (m, 1H, H_7), 2.07 (s, 3H, H_9), 1.89-1.98 (m, 1H, H_7), 1.41 (s, 9H, H_1) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5 (C_5), 155.8 (C_3), 138.0 (C_{ar}), 128.8 ($2C_{ar}$), 127.8 ($2C_{ar}$), 127.7 (C_{ar}), 80.4 (C_2), 53.7 (C_4), 43.6 (C_8), 31.7 (C_6), 30.4 (C_9), 28.4 ($3C_1$), 15.4 (C_7) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[196]

*Methyl (S)-3-(2-(((benzyloxy)carbonyl)amino)-3-phenylpropanamido)propanoate (**III.40b**)*



III.40b
$C_{21}H_{24}N_2O_5$
384,43

The title compound was isolated by short column chromatography (eluent: Pentane/EtOAc 7:3) as a white solid in 78% yield (148 mg) from methyl 3-(imidazole-1-carbonylamino)propanoate (99 mg, 0.50 mmol) following the general procedure E.

Mp: 116.8 – 118.6 °C

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.37 (m, 8H, H_{ar}), 7.15-7.17 (m, 2H, H_{ar}), 6.18 (bt, *J* = 5.8 Hz, 1H, NH), 5.37 (bd, *J* = 7.0 Hz, 1H, NH), 5.08 (s, 2H, H_8), 4.35 (bt, *J* = 6.3 Hz, 1H, H_6), 3.63 (s, 3H, H_5), 3.42-3.50 (m, 1H, H_9), 3.32-3.40 (m, 1H, H_9), 3.08-3.13 (m, 1H, H_2), 2.96-3.01 (m, 1H, H_2), 2.39-2.46 (m, 1H, H_3), 2.29-2.36 (m, 1H, H_3) ppm.

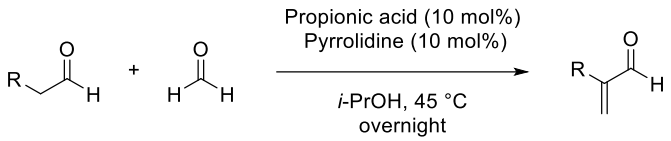
[196] Jimil, G.; Hun Young, K.; Kyungsoo, O. *Org. Lett.* **2017**, *19*, 628.

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.7 (C_4), 170.8 (C_1), 155.9 (C_7), 136.5 (C_{ar}), 136.3 (C_{ar}), 129.4 ($2C_{ar}$), 128.9 ($2C_{ar}$), 128.7 ($2C_{ar}$), 128.4 (C_{ar}), 128.2 ($2C_{ar}$), 127.2 (C_{ar}), 67.2 (C_8), 56.6 (C_5), 51.9 (C_6), 39.1 (C_9), 34.8 (C_3), 33.7 (C_2) ppm.

FTIR neat (cm^{-1}): 3284, 2956, 1734, 1688, 1644, 1535, 1495, 1435, 1372, 1329, 1253, 1230, 1199, 1136, 1086, 1039, 752, 697, 676.

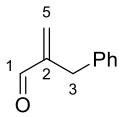
HRMS (ESI+) calculated for $C_{21}H_{24}N_2O_5$ (m/z): $[M+H]^+$: calculated : 385.1758, found: 385.1762.

General Procedure F for the α-Methylenation of aldehydes



To a mixture of aqueous formaldehyde solution (37% formaldehyde in water, 1.00 equiv) and aldehyde (1.00 equiv) in *i*-PrOH (*C* 10 M) were added propionic acid (0.10 equiv) and pyrrolidine (0.10 equiv). The reaction mixture was stirred at 45 °C overnight. $NaHCO_3$ was added, and the mixture was extracted with CH_2Cl_2 (3×). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The crude product thus obtained was purified by a passage through a short pad of silica gel using Pentane:Et_2O (90:10) as the eluent.

*2-Benzylacrylaldehyde (**IV.61a**)*



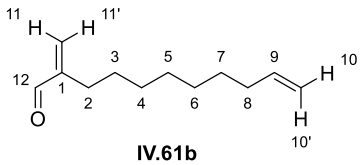
IV.61a
$C_{10}H_{10}O$
146,19

The title compound was isolated as a pale yellow oil in 68% yield (4.00 g) from 3-Phenylpropanal (5.37 g, 40.0 mmol) following the general procedure F.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.61 (s, 1H, CHO), 7.17-7.32 (m, 5H, H_{ar}), 6.10 (s, 1H, H_5), 6.07 (s, 1H, H_5), 3.57 (s, 2H, H_3) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[181]

*2-Methyleneundec-10-enal (**IV.61b**)*



IV.61b
$C_{12}H_{20}O$
180,29

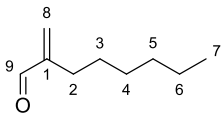
The title compound was isolated as a pale yellow oil in 85% yield (6.15 g) from 10-undecenal (6.73 g, 40.0 mmol) following the general procedure F.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.53 (s, 1H, CHO), 6.24 (s, 1H, $H_{11,11'}$), 5.98 (s, 1H, $H_{11,11'}$), 5.75-5.85 (m, 1H, H_9), 4.90-5.01 (m, 2H, $H_{10,10'}$), 2.23 (t, *J* = 7.7 Hz, 2H, H_2) 2.03 (q, *J* = 7.1 Hz, 2H, H_8), 1.30-1.47 (m, 10H, $H_{3,4,5,6,7}$) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[197]

[197] H. Nakahira, I. Ryu, M. Ikebe, Y. Oku, A. Ogawa et al. *J. Org. Chem.* **1992**, 57, 17.

*2-Methyleneoctanal (**IV.61c**)*



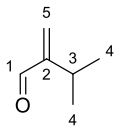
IV.61c
$C_9H_{16}O$
140,23

The title compound was isolated as a pale yellow oil in quantitative yield (5.60 g) from caprylic aldehyde (5.13 g, 40.0 mmol) following the general procedure F.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.54 (s, 1H, CHO), 6.24 (s, 1H, H_8), 5.98 (s, 1H, H_8), 2.23 (t, *J* = 7.7 Hz, 2H, H_2), 1.42-1.46 (m, 2H, H_3), 1.28-1.32 (m, 6H, $H_{4,5,6}$), 0.88 (t, *J* = 6.8 Hz, 3H, H_7) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[194]

*3-Methyl-2-methylenebutanal (**IV.61e**)*



IV.61e
$C_6H_{10}O$
98,15

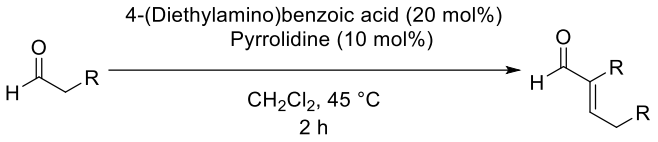
The title compound was isolated as a colourless oil in 34% yield (1.33 g) from isovaleraldehyde (3.45 g, 40.0 mmol) following the general procedure F.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.52 (s, 1H, CHO), 6.23 (d, *J* = 1.1 Hz, 1H, H_5), 5.94 (s, 1H, H_5), 2.79 (sept, *J* = 7.7, 1.1 Hz, 1H, H_3), 1.07 (quint, *J* = 6.9 Hz, 6H, H_4) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[198]

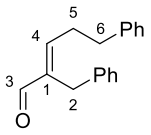
[198] A. Faulkner, J.S. Scott, J.F. Bower *J. Am. Chem. Soc.* **2015**, *137*, 7224.

General Procedure G for the self-condensations of aldehydes



To a mixture of 4-(diethylamino)benzoic acid (0.20 equiv) and pyrrolidine (0.10 equiv) in dichloromethane (*C* 1.0 M) was added the aldehyde (2.00 equiv). The reaction mixture was stirred at 45 °C for 2 hours. $NaHCO_3$ was added, and the mixture was extracted with CH_2Cl_2 (3×). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The crude product thus obtained was purified by a passage through a short pad of silica gel using Pentane:Et_2O (90:10) as the eluent.

*(E)-2-Benzyl-5-phenylpent-2-enal (**IV.61f**)*



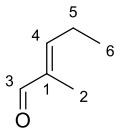
IV.61f
$C_{18}H_{18}O$
250,34

The title compound was isolated as a colourless oil in 36% yield (0.89 g) from 3-phenylpropanal (1.34 g, 10.0 mmol) following the general procedure G.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.45 (s, 1H, CHO), 7.10-7.32 (m, 10H, H_{ar}), 6.62 (t, *J* = 7.2 Hz, 1H, H_4), 3.59 (s, 2H, H_2), 2.74-2.77 (m, 4H, $H_{5,6}$) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[182]

*(E)-2-Methylpent-2-enal (**IV.61g**)*



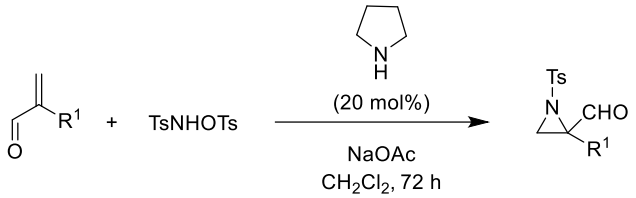
IV.61g
$C_6H_{10}O$
98,15

The title compound was isolated as a colourless oil in 53% yield (1.80 g) from acrolein (1.74 g, 30.0 mmol) following the general procedure G.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.39 (s, 1H, CHO), 6.47 (tq, *J* = 7.6, 1.3 Hz, 1H, H_4), 2.33-2.40 (m, 2H, H_5), 1.73-1.74 (m, 3H, H_2), 1.11 (t, *J* = 7.6 Hz, 3H, H_7) ppm.

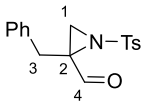
The analytical data were identical in all respects to those previously reported in the literature.[182]

General Procedure H for the aziridines



To a solution of α-substituted α,β-unsaturated aldehyde (2.00 equiv) in dichloromethane (*C* 0.2 M) was successively added TsNHOTs (1.00 equiv), NaOAc (3.00 equiv), and pyrrolidine (20 mol%). The reaction mixture was stirred for 72 h. The reaction mixture was then filtered through a pad of Celite (EtOAc), and the solvent was evaporated. Purification was performed by column chromatography on silica gel (pentane/EtOAc, 80:20) to afford aziridines.

*2-Benzyl-1-tosylaziridine-2-carbaldehyde (**IV.58a**)*



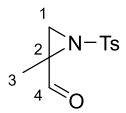
IV.58a
$C_{17}H_{17}NO_3S$
315,39

The title compound was prepared according to the general procedure H to give a colorless oil in 70% yield (377 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.46 (s, 1H, CHO), 7.78 (d, *J* = 8.3 Hz, 2H, H_{ArTs}), 7.31 (d, *J* = 8.1 Hz, 2H, H_{ArTs}), 7.25 -7.18 (m, 5H, H_{ar}), 3.28 (s, 2H, H_3), 3.19 (s, 1H, H_1), 2.63 (s, 1H, H_1), 2.45 (s, 3H, H_{meTs}) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[180]

*2-Methyl-1-tosylaziridine-2-carbaldehyde (**IV.58b**)*



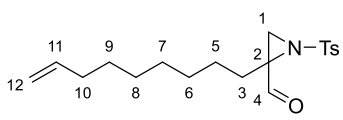
IV.58b
$C_{11}H_{13}NO_3S$
239,29

The title compound was prepared according to the general procedure H to give a colorless oil in 81% yield (660 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.10 (s, 1H, CHO), 7.83 (d, *J* = 8.2 Hz, 2H, H_{ArTs}), 7.35 (d, *J* = 8.2 Hz, 2H, H_{ArTs}), 2.88 (s, 1H, H_1), 2.82 (s, 1H, H_1), 2.42 (s, 3H, H_{meTs}), 1.69 (s, 3H, H_3) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[180]

*2-(Non-8-en-1-yl)-1-tosylaziridine-2-carbaldehyde (**IV.58c**)*



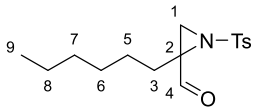
IV.58c
$C_{19}H_{27}NO_3S$
349,49

The title compound was prepared according to the general procedure H to give a colorless oil in 65% yield (430 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.34 (s, 1H, CHO), 7.84 (d, *J* = 8.3 Hz, 2H, H_{ArTs}), 7.35 (d, *J* = 8.1 Hz, 2H, H_{ArTs}), 5.75-5.85 (m, 1H, H_{11}), 4.90-5.01 (m, 2H, H_{12}), 3.12 (s, 1H, H_1), 2.68 (s, 1H, H_1), 2.45 (s, 3H, H_{meTs}), 1.99-2.08 (m, 3H, $H_{3,10}$), 1.66-1.73 (m, 1H, H_{10}), 1.25-1.43 (m, 10H, $H_{5,6,7,8,9}$) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[180]

*2-Hexyl-1-tosylaziridine-2-carbaldehyde (**IV.58d**)*



IV.58d
$C_{16}H_{23}NO_3S$
309,42

The title compound was prepared according to the general procedure H to give a colorless oil in 51% yield (298 mg).

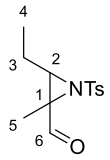
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.35 (s, 1H; CHO), 7.84 (d, *J* = 8.3 Hz, 2H, H_{ArTs}), 7.35 (d, *J* = 8.0 Hz, 2H, H_{ArTs}), 3.12 (s, 1H, H_1), 2.68 (s, 1H, H_1), 2.45 (s, 3H, H_{meTs}), 2.01-2.08 (m, 1H, H_3), 1.66-1.73 (m, 1H, H_3), 1.37-1.44 (m, 2H, H_5), 1.23-1.31 (m, 6H, $H_{6,7,8}$), 0.86 (t, *J* = 6.9 Hz, 3H, H_9) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.9 (C_4), 145 (C_{ArTs}), 136.3 (C_{ArTs}), 129.9 ($2C_{ArTs}$), 127.7 ($2C_{ArTs}$), 56.6 (C_2), 38.6 (C_1), 31.6 (C_3), 29.3 (C_5), 28.7 (C_6), 25.8 (C_7), 22.6 (C_8), 21.8 (C_{meTs}), 14.2 (C_9) ppm.

FTIR neat (cm^{-1}) 2924, 2868, 1721, 1323, 1309, 1291, 1267, 1160, 1122, 1093, 1084, 1033, 1019, 984, 949, 894, 874, 851, 817, 708, 681.

HRMS (ESI+) calculated for $C_{16}H_{24}NO_3S$ (m/z): $[M+H]^+$: calculated : 310.1471, found: 310.1474.

*3-Ethyl-2-methyl-1-tosylaziridine-2-carbaldehyde (**IV.58e**)*



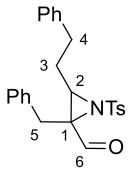
IV.58e
$C_{13}H_{17}NO_3S$
267,34

The title compound was prepared according to the methodology developed by Córdova et al.[199] to give an off-white solid in 43% yield (424 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.52 (s, 1H, CHO), 7.83 (d, *J* = 8.3 Hz, 2H, H_{ArTs}), 7.32 (d, *J* = 8.3 Hz, 2H, H_{ArTs}), 3.46 (dd, *J* = 7.8, 5.6 Hz, 1H, H_2), 2.45 (s, 3H, H_{meTs}), 1.45-1.63 (m, 2H, H_3), 1.39 (s, 3H, H_5), 0.92 (t, *J* = 7.5 Hz, 3H, H_4) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[200]

*2-Benzyl-3-phenethyl-1-tosylaziridine-2-carbaldehyde (**IV.58f**)*



IV.58f
$C_{25}H_{25}NO_3S$
419,54

The title compound was prepared according to the methodology developed by Córdova et al.[196] to give a yellow-brown oil in 63% yield (402 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.47 (s, 1H, CHO), 7.61 (d, *J* = 8.2 Hz, 2H, H_{ArTs}), 7.60-7.16 (m, 10H, H_{ar}), 7.11 (d, *J* = 6.8 Hz, 2H, H_{ArTs}), 3.64 (t, *J* = 6.6 Hz, 1H, H_2), 3.30 (d, *J* = 14.6 Hz, 1H, H_3), 2.64-2.68 (m, 3H, $H_{3,4}$), 2.43 (s, 3H, H_{meTs}), 1.90-1.96 (m, 2H, H_5) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.5 (C_6), 144.7 (C_{ArTs}), 140.1 (C_{ar}), 136.4 (C_{ArTs}), 136.2 (C_{ar}), 129.8 ($2C_{ArTs}$), 129.8 ($2C_{ar}$), 128.8 ($2C_{ar}$), 128.5 ($2C_{ArTs}$), 128.3 ($2C_{ar}$), 127.6 ($2C_{ar}$), 126.7 (C_{ar}), 126.7 (C_{ar}), 61.9 (C_1), 51.1 (C_2), 33.6 (C_5), 31.3 (C_3), 29.9 (C_4), 21.8 (C_{meTs}) ppm.

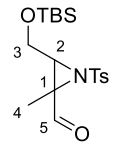
FTIR neat (cm^{-1}): 3029, 2931, 2862, 1721, 1597, 1495, 1454, 1327, 1154, 1089, 956, 874, 813, 750, 732, 687, 666.

HRMS (ESI-) calculated for $C_{25}H_{24}NO_3S$ (m/z): $[M-H]^-$: calculated : 418.1477, found: 418.1472.

[199] L. Deiana, P. Dziedzic, G.-L. Zhao, J. Vesely, I. Ibrahem, R. Rios, J. Sun, A. Córdova *Chem. Eur. J.* **2011**, *17*, 7904.

[200] A. Kulshrestha, N. Salehi Marzijarani, K. Dilip Ashtekar, R. Staples, B. Borhan *Org. Lett.* **2012**, *14*, 3592.

*3-(((tert-Butyldimethylsilyl)oxy)methyl)-2-methyl-1-tosylaziridine-2-carbaldehyde (**IV.58g**)*



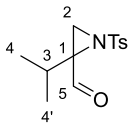
IV.58g
$C_{18}H_{29}NO_4SSi$
383,58

The title compound was prepared according to the procedure reported by Borhan et al.[201] to give a pale yellow oil in 71% yield (820 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.55 (s, 1H, CHO), 7.86 (d, *J* = 8.3 Hz, 2H, H_{ArTs}), 7.35 (d, *J* = 8.0 Hz, 2H, H_{ArTs}), 3.67-3.72 (m, 3H, $H_{2,3}$), 2.47 (s, 3H, H_{meTs}), 1.44 (s, 3H, H_4), 0.86 (s, 9H, H_{tBuTBS}), 0.01 (d, *J* = 6.6 Hz, 6H, H_{2meTBS}) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[196]

*2-Isopropyl-1-tosyl-2-vinylaziridine (**IV.58h**)*



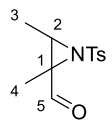
IV.58h
$C_{13}H_{17}NO_3S$
267,34

The title compound was prepared according to the general procedure H to give a pale yellow oil in 31% yield (157 mg).

^{1}H NMR (400 MHz, CDCl3): δ 9.51 (s, 1H, CHO), 7.85 (d, *J* = 8.3 Hz, 2H, H_{ArTs}), 7.36 (d, *J* = 8.6 Hz, 2H, H_{ArTs}), 3.21 (s, 1H, H_2), 2.66 (s, 1H, H_2), 2.46 (s, 3H, H_{meTs}), 2.37-2.45 (m, 1H, H_3), 1.02 (d, *J* = 6.8 Hz, 3H, $H_{4,4'}$), 0.89 (d, *J* = 6.8 Hz, 3H, $H_{4,4'}$) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[180]

*2,3-Dimethyl-1-tosylaziridine-2-carbaldehyde (**IV.a**)*



IV.a
$C_{12}H_{15}NO_3S$
253,32

The title compound was prepared according to the methodology developed by Sudalai et al.[202] to give a colorless oil in 9% yield (229 mg).

[201] A. Kulshrestha, N. Salehi Marzijarani, K. Dilip Ashtekar, R. Staples, B. Borhan *Angew. Chem. Int. Ed.* **2019**, *58*, 10110.

[202] S.I. Ali, M.D. Nikalje, A. Sudalai *Org. Lett.* **1999**, *1*, 705.

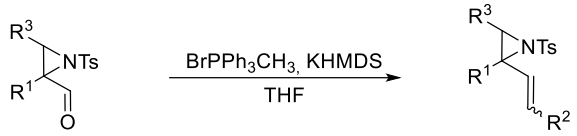
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.51 (s, 1H, CHO), 7.81 (d, *J* = 8.4 Hz, 2H, H_{ArTs}), 7.34 (d, *J* = 8.0 Hz, 2H, H_{ArTs}), 3.61 (q, *J* = 5.7 Hz, 1H, H_2), 2.45 (s, 3H, H_{meTs}), 1.38 (s, 3H, H_4), 1.29 (d, *J* = 5.8 Hz, 3H, H_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.3 (C_5), 144.7 (C_{ArTs}), 136.7 (C_{ArTs}), 129.9 ($2C_{ArTs}$), 127.4 ($2C_{ArTs}$), 57.9 (C_2), 46.5 (C_1), 21.8 (C_{meTs}), 12.7 (C_3), 11.6 (C_4) ppm.

FTIR neat (cm^{-1}): 2970, 2936, 1713, 1597, 1399, 1321, 1304, 1155, 1139, 1088, 1070, 1009, 985, 894, 823, 804, 787, 708, 683.

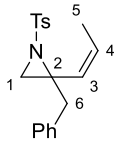
HRMS (ESI+): calculated for $C_{12}H_{16}NO_3S$ (m/z): $[M+H]^+$: calculated : 254.0851, found: 254.0858.

General Procedure I for the Wittig reaction



KHMDS in toluene (*C* 0.5 M, 2.00 equiv) was added to an ice-cooled (0 ˚C) solution of alkyl triphenylphosphonium bromide (1.80 equiv) in dry THF (*C* 0.33 M). After 30 min of stirring, a solution of the corresponding aldehyde (1.00 equiv) in dry THF (*C* 0.2 M) was added, and the mixture was stirred overnight at 0 °C. The reaction was quenched with saturated aqueous NH_4Cl (10 mL), and the resulting mixture was extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (15 mL), and dried over anhydrous $MgSO_4$. Filtration and evaporation under vacuum furnished the crude product, which was purified by column chromatography using Pentane/EtOAc (95:5 to 70:30) as eluent.

*(Z)-2-Benzyl-2-(prop-1-en-1-yl)-1-tosylaziridine (**IV.48a**)*



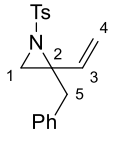
IV.48a
$C_{19}H_{21}NO_2S$
327,44

The title compound was prepared according to the general procedure I from the corresponding aldehyde to give a colorless oil in 77% yield (240 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82-7.84 (m, 2H, H_{ArTs}), 7.30-7.32 (m, 2H, H_{ArTs}), 7.17-7.25 (m, 5H, H_{ar}), 5.81 (dq, *J* = 11.1, 1.7 Hz, 1H, H_3), 5.81 (dq, *J* = 11.0, 7.0 Hz, 1H, H_4), 3.01-3.09 (m, 2H, H_6), 2.73 (s, 1H, H_1), 2.62 (s, 1H, H_1), 2.44 (s, 3H, H_{meTs}), 1.48 (dd, *J* = 7.0, 1.7 Hz, 3H, H_5) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[203]

*2-Benzyl-1-tosyl-2-vinyl aziridine (**IV.48b**)*



IV.48b
$C_{18}H_{19}NO_2S$
313,42

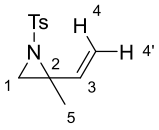
The title compound was prepared according to the general procedure I from the corresponding aldehyde to give a pale yellow oil in 69% yield (621 mg).

^{1}H NMR (400 MHz, CDCl3): δ 7.81-7.83 (m, 2H, H_{ArTs}), 7.20-7.32 (m, 7H, $H_{ArTs,ar}$), 6.14 (dd, J = 17.3, 10.7 Hz, 1H, H_3), 5.35-5.43 (m, 2H, H_4), 3.18-3.27 (m, 2H, H_5), 2.81 (s, 1H, H_1), 2.52 (s, 1H, H_1), 2.44 (s, 3H, H_{meTs}) ppm.

[203] K. Spielmann, A. van der Lee, R.M. de Figueiredo, J.-M. Campagne *Org. Lett.* **2018**, *20*, 1444.

The analytical data were identical in all respects to those previously reported in the literature.[199]

*2-Methyl-1-tosyl-2-vinyl aziridine (**IV.48c**)*



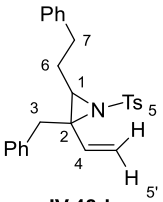
IV.48c
$C_{12}H_{15}NO_2S$
237,32

The title compound was prepared according to the general procedure I from the corresponding aldehyde to give a white solid in 50% yield (338 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82-7.84 (m, 2H, H_{ArTs}), 7.30-7.32 (m, 2H, H_{ArTs}), 5.97 (dd, *J* = 17.3, 10.7 Hz, 1H, H_3), 5.41 (d, *J* = 17.3 Hz, 1H, H_4), 5.32 (d, *J* = 10.7 Hz, 1H, $H_{4'}$), 2.64 (s, 1H, H_1), 2.62 (s, 1H, H_1), 2.43 (s, 3H, H_{meTs}), 1.66 (s, 3H, H_5) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[204]

*2-Benzyl-3-phenethyl-1-tosyl-2-vinyl aziridine (**IV.48d**)*



IV.48d
$C_{26}H_{27}NO_2S$
417,57

The title compound was prepared according to the general procedure I from the corresponding aldehyde to give a pale yellow oil in 42% yield (21 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.3 Hz, 2H, H_{ArTs}), 7.20-7.36 (m, 10H, H_{ar}) 7.10 (d, *J* = 6.9 Hz, 2H, H_{ArTs}), 6.20 (dd, *J* = 17.6, 11.2 Hz, 1H, H_4), 5.39 (d, *J* = 11.2, 1H, $H_{5'}$), 5.32 (d, *J* = 17.6 Hz, 1H, H_5), 3.33 (dd, J = 8.4, 5.2 Hz, 1H, H_1), 3.22 (d, *J* = 15.6 Hz, 1H, H_3), 2.90 (d, J = 15.6 Hz, 1H, H_3), 2.51-2.65 (m, 2H, H_6), 2.47 (s, 3H, H_{meTs}), 1.93-2.02 (m, 1H, H_7), 1.75-1.84 (m, 1H, H_7) ppm.

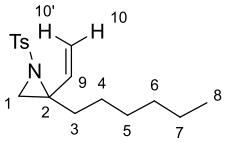
^{13}C NMR (100 MHz, $CDCl_3$): *δ* 144.1 (C_4), 140.9 (C_{ArTs}), 137.6 (C_{ArTs}), 136.7 (C_{ar}), 134.5 (C_{ar}), 129.6 ($2C_{ArTs}$), 129.1 ($2C_{ar}$), 128.6 ($2C_{ar}$), 128.5 ($2C_{ar}$), 128.4 ($2C_{ar}$), 127.9 ($2C_{ArTs}$), 126.5 (C_{ar}), 126.3 (C_{ar}), 120.7 (C_5), 57.6 (C_1), 51.4 (C_2), 37.5 (C_3), 33.8 (C_7), 30.3 (C_6), 21.7 (C_{meTs}) ppm.

FTIR neat (cm^{-1}): 2925, 2859, 1599, 1496, 1455, 1320, 1155, 1090, 905, 813, 725, 697.

HRMS (ESI+) calculated for $C_{26}H_{28}NO_2S$ (m/z): $[M+H]^+$: calculated : 418.1641, found: 418.1834.

[204] T. Hashimoto, K. Takino, K. Hato, K. Maruoka *Angew. Chem. Int. Ed.* **2016**, 55, 8081.

*2-Hexyl-1-tosyl-2-vinyl aziridine (**IV.48e**)*



IV.48e
$C_{17}H_{25}NO_2S$
307,45

The title compound was prepared according to the general procedure I from the corresponding aldehyde to give a colorless oil in 21% yield (39 mg).

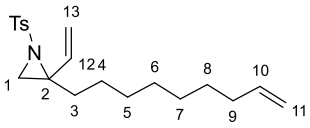
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.2 Hz, 2H, H_{ArTs}), 7.29-7.31 (m, 2H, H_{ArTs}), 6.12 (dd, *J* = 17.3, 10.7 Hz, 1H, H_9), 5.40 (dd, *J* = 17.3 and 0.9 Hz, 1H, $H_{10'}$), 5.37 (dd, *J* = 7.1, 0.9 Hz, 1H, H_{10}), 2.75 (s, 1H, H_1), 2.49 (s, 1H, H_1), 2.42 (s, 3H, H_{meTs}), 1.79-1.88 (m, 2H, H_3), 1.36-1.43 (m, 2H, H_4), 1.22-1.32 (m, 6H, $H_{5,6,7}$), 0.85-0.89 (m, 3H, H_8) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0 (C_9), 137.8 (C_{ArTs}), 134.5 (C_{ArTs}), 129.6 ($2C_{ArTs}$), 127.6 ($2C_{ArTs}$), 119.3 (C_{10}), 54.0 (C_2), 41.1 (C_1), 33.9 (C_3), 31.7 (C_7), 29.3 (C_4), 25.9 (C_5), 22.7 (C_6), 21.7 (C_{meTs}), 14.2 (C_8) ppm.

FTIR neat (cm^{-1}): 2924, 2870, 1323, 1320, 1299, 1256, 1135, 1093, 962, 894, 876, 832, 817, 756, 630.

HRMS (ESI+) calculated for $C_{17}H_{26}NO_2S$ (m/z): $[M+H]^+$: calculated : 308.1678, found: 308.1664.

*2-(Non-8-en-1-yl)-1-tosyl-2-vinyl aziridine (**IV.48f**)*



IV.48f
$C_{20}H_{29}NO_2S$
347,52

The title compound was prepared according to the general procedure I from the corresponding aldehyde to give a pale yellow oil in 51% yield (78 mg).

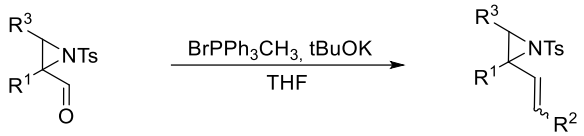
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.3 Hz, 2H, H_{ArTs}), 7.30 (d, *J* = 8.2 Hz, 2H, H_{ArTs}), 6.10 (dd, *J* = 17.3, 10.7, 1H, H_{12}), 5.74-5.85 (m, 1H, H_{10}), 5.35-5.41 (m, 2H, H_{13}), 4.90-5.01 (m, 2H, H_{11}), 2.74 (s, 1H, H_1), 2.48 (s, 1H, H_1), 2.42 (s, 3H, H_{meTs}), 1.99-2.05 (m, 2H, H_3), 1.75-1.89 (m, 2H, H_9), 1.35-1.42 (m, 3H, $H_{4,8}$), 1.25-1.34 (m, 7H, $H_{5,6,7,8}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.9 (C_{12}), 139.2 (C_{10}), 137.7 (C_{Ts}), 134.4 (C_{Ts}), 129.5 ($2C_{Ts}$), 127.5 ($2C_{Ts}$), 119.2 (C_{13}), 114.2 (C_{11}), 53.9 (C_1), 41.1 (C_2), 33.8 (C_3), 29.5 (C_9), 29.3 ($2C_{4,5}$), 29.0 (C_6), 28.9 (C_7), 25.9 (C_8), 21.6 (C_{Ts}) ppm.

FTIR neat (cm^{-1}): 2924, 2854, 1642, 1598, 1459, 1326, 1158, 814, 664, 564, 542, 510.

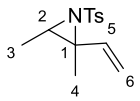
HRMS (ESI+) calculated for $C_{20}H_{30}NO_2S$ (m/z): $[M+H]^+$: calculated : 348.1991, found: 348.2005.

General Procedure J for the Wittig reaction



Alkyl triphenylphosphonium bromide (1.60 equiv) and potassium *tert*-butoxide (1.50 equiv) in dry THF (*C* 0.6 M) were stirred at 0 °C for 30 min. A solution of the above aldehyde (1.00 equiv) in dry THF (*C* 0.2 M) was added dropwise at 0 °C and the solution was stirred overnight at room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL), then extracted with EtOAc (2×15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude was purified via silica gel chromatography (Pentane/EtOAc 95:5 to 70:30) to afford the desired product.

*3-Methyl-2-methyl-1-tosyl-2-vinyl aziridine (**IV.48g**)*



IV.48g
$C_{13}H_{17}NO_2S$
251,34

The title compound was prepared according to the representative procedure J from the corresponding aldehyde to give a pale yellow solid in 45% yield (75 mg).

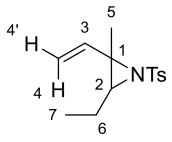
^{1}H NMR (400 MHz, $CDCl_3$): δ (2 diastereomers) 7.83 (d, *J* = 8.3 Hz, 2H, H_{ArTs}), 7.80 (d, *J* = 8.2 Hz, 2H, H_{ArTs}), 7.28-7.32 (m, 4H, H_{ArTs}), 6.26 (dd, *J* = 17.3, 10.8 Hz, 1H, H_5), 5.67 (dd, *J* = 17.3, 10.8 Hz, 1H; H_5), 5.25-5.37 (m, 4H, H_6), 3.19 (q, *J* = 5.8 Hz, 1H, H_2), 3.07 (q, *J* = 5.8 Hz, 1H, H_2), 2.43 (s, 3H, H_{meTs}), 2.43 (s, 3H, H_{meTs}), 1.81 (s, 3H, H_3) 1.40 (s, 3H, H_3), 1.22 (d, *J* = 5.8 Hz, 3H, H_4), 1.09 (d, *J* = 5.8 Hz, 3H, H_4) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.8 (C_5), 143.7 (C_5), 138.7 (C_{ArTs}), 138.2 (C_{ArTs}), 136.7 (C_{ArTs}), 135.7 (C_{ArTs}), 129.6 ($2C_{ArTs}$), 129.6 ($2C_{ArTs}$), 127.3 ($2C_{ArTs}$), 127.2 ($2C_{ArTs}$), 118.7 (C_6), 118.5 (C_6), 54.3 (C_1), 54.2 (C_1), 48.7 (C_2), 48.3 (C_2), 21.7 ($2C_{meTs}$), 18.4 (C_4), 15.9 (C_4), 13.0 (C_3), 12.8 (C_3) ppm.

FTIR neat (cm^{-1}): 3000, 2932, 2855, 1594, 1450, 1314, 1305, 1288, 1153, 1088, 1055, 1025, 987, 958, 929, 904, 814, 800, 730, 707, 685, 659.

HRMS (ESI+) calculated for $C_{13}H_{18}NO_2S$ (m/z): $[M+H]^+$: calculated : 252.1052, found: 252.1063.

*3-Ethyl-2-methyl-1-tosyl-2-vinyl aziridine (**IV.48h**)*



IV.89
$C_{14}H_{19}NO_2S$
265,37

The title compound was prepared according to the general procedure J from the corresponding aldehyde to give a pale yellow solid in 44% yield (94 mg).

Mp: 123.8 – 126.7°C

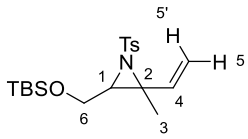
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, *J* = 8.2 Hz, 2H, H_{ArTs}), 7.28 (d, *J* = 7.9 Hz, 2H, H_{ArTs}), 6.27 (dd, *J* = 17.2, 10.8 Hz, 1H, H_3), 5.43 (dd, *J* = 17.2, 0.3 Hz, 1H, H_4), 5.37 (dd, *J* = 10.8 and 0.3 Hz, 1H, $H_{4'}$), 3.02 (dd, *J* = 7.8, 5.7 Hz, 1H, H_2), 2.42 (s, 3H, H_{meTs}), 1.39-1.61 (m, 2H, H_6), 1.41 (s, 3H, H_5), 0.83 (t, *J* = 7.8 Hz, 3H, H_7) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.8 (C_3), 137.8 (C_{ArTs}), 136.9 (C_{ArTs}), 129.5 ($2C_{ArTs}$), 127.7 ($2C_{ArTs}$), 118.6 (C_4), 54.6 (C_1), 54.5 (C_2), 21.7 (C_{ArTs}), 21.2 (C_6), 16.1 (C_5), 11.7 (C_7) ppm.

FTIR neat (cm^{-1}): 2968, 2926, 1458, 1313, 1304, 1285, 1153, 1086, 1059, 980, 933, 918, 908, 842, 767, 711, 659.

HRMS (ESI+) calculated for $C_{14}H_{20}NO_2S$ (m/z): $[M+H]^+$: calculated : 266.1209, found: 266.1208.

*(2R,3S)-3-(((tert-Butyldimethylsilyl)oxy)methyl)-2-methyl-1-tosyl-2-vinyl aziridine (**IV.48i**)*



IV.48i
$C_{19}H_{31}NO_3SSi$
381,61

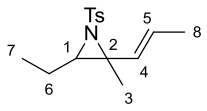
The title compound was prepared according to the general procedure J from the corresponding aldehyde to give an off-white solid in 56% yield (111 mg).

Mp: 43 – 45.3°C

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, *J* = 8.2 Hz, 2H, H_{ArTs}), 7.28 (d, *J* = 7.9 Hz, 2H, H_{ArTs}), 6.28 (dd, J = 17.2, 10.8 Hz, 1H, H_4), 5.47 (dd, *J* = 17.2, 0.6 Hz, 1H, $H_{5'}$), 5.42 (dd, *J* = 10.8, 0.6 Hz, 1H, H_5), 3.69 (dd, *J* = 11.2, 5.7 Hz, 1H, H_6), 3.62 (dd, *J* = 11.2, 5.7 Hz, 1H, H_6), 3.29 (t, *J* = 6.0 Hz, 1H, H_1), 2.42 (s, 3H, H_{meTs}), 1.44 (s, 3H, H_3), 0.83 (s, 9H, H_{tBuTBS}), -0.01 (s, 3H, H_{meTBS}), -0.03 (s, 3H, H_{meTBS}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.8 (C_4), 137.9 (C_{ArTs}), 136.4 (C_{ArTs}), 129.5 ($2C_{ArTs}$), 127.6 ($2C_{ArTs}$), 119.0 (C_5), 61.1 (C_6), 53.6 (C_1), 53.3 (C_2), 25.9 ($3C_{tBuTBS}$), 21.7 (C_{meTs}), 18.3 (C_5), 16.5 (C_3), -5.3 (C_{meTBS}), -5.4 (C_{meTBS}) ppm.

*3-Ethyl-2-methyl-1-tosyl-2-vinyl aziridine (**IV.48j**)*



IV.48j
$C_{15}H_{21}NO_2S$
279,40

The title compound was prepared according to the general procedure J from the corresponding aldehyde to give an off-white solid in 32% yield (89 mg).

Mp: 58.1 – 61.4°C

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* =7.9 Hz, 2H, H_{ArTs}), 7.28 (d, *J* = 8.6 Hz, 2H, H_{ArTs}), 6.11 (dd, *J* = 11.6, 0.7 Hz, 1H, H_4), 5.64-5.72 (m, 1H, H_5), 2.94 (dd, *J* = 8.3 5.2 Hz, 1H, H_1), 2.41 (s, 3H, H_{meTs}), 1.68-1.71 (m, 3H, H_8), 1.56-1.66 (m, 2H, H_6), 1.34 (s, 3H, H_{Ts}), 0.81 (t, *J* = 7.5 Hz, 3H, H_7) ppm.

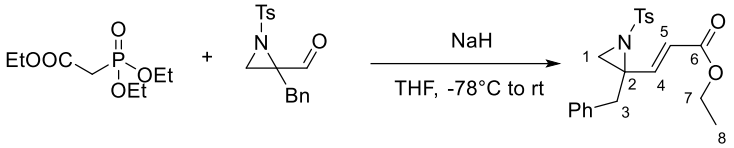
^{13}C NMR (100 MHz, $CDCl_3$): δ 143.8 (C_4), 138.0 (C_{ArTs}), 129.4 ($2C_{ArTs}$), 128.4 (C_{ArTs}), 127.8 (C_5), 127.7 ($2C_{ArTs}$), 54.2 (C_2), 52.4 (C_1), 21.7 (C_6), 21.2 (C_{meTs}), 20.0 (C_3), 14.2 (C_8), 11.8 (C_7) ppm.

FTIR neat (cm^{-1}): 2970, 2928, 1722, 1596, 1445, 1319, 1305, 1286, 1153, 1086, 1000, 944, 925, 847, 820, 717, 767, 670.

HRMS (ESI+) calculated for $C_{15}H_{22}NO_2S$ (m/z): $[M+H]^+$: calculated : 280.1371, found: 280.1374.

Procedure for the Horner-Wadsworth-Emmons reaction

*Ethyl (E)-3-(2-benzyl-1-tosylaziridin-2-yl)acrylate (**IV.59**)*



IV.59
$C_{21}H_{23}NO_4S$
385,48

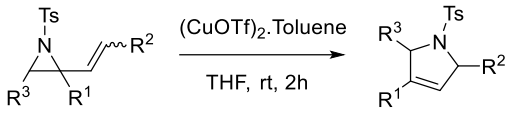
In a flame dried round bottom flask was charged the phosphonate (1.0 mL, 5.0 mmol) with 15 mL of dried THF. To this solution was poured the NaH portion wise (120 mg, 5.0 mmol). The mixture was cooled at –78 °C and a solution of the corresponding aldehyde (1.32 g, 4.20 mmol) in THF (13 mL plus 2×1 mL rinse) was added. The mixture was stirred for 1 h at –78 °C, then allowed to warm up to rt and stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl (5 mL), and the resulting mixture was extracted with AcOEt (3×20 mL). The combined organic layers were washed with brine (15 mL), and dried over anhydrous Na_2SO_4.

Filtration and evaporation under vacuum furnished the crude product, which was purified by column chromatography using Pentane/EtOAc (90:10 to 70:30) as eluent. The expected fractions were combined and the solvent was removed under vacuum to afford a white solid in 76% yield (1.48 g).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.1 Hz, 2H, H_{ArTs}), 7.17-7.31 (m, 7H, $H_{ar, ArTs}$), 7.04 (d, *J* = 15.7, 1H, H_5), 6.04 (d, *J* = 15.7, 1H, H_4), 4.15 (q, *J* = 7.1 Hz, 2H, H_7), 3.32 (d, *J* = 15.2 Hz, 1H, H_3), 3.26 (d, *J* = 15.2 Hz, 1H, H_3), 2.73 (s, 1H, H_1), 2.70 (s, 1H, H_1), 2.42 (s, 3H, H_{meTs}), 1.25 (t, *J* = 7.1 Hz, 3H, H_8) ppm.

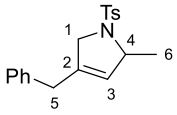
The analytical data were identical in all respects to those previously reported in the literature.[199]

General Procedure K for the Cu-catalysed ring expansion



A flame-dried 10 mL flask equipped with a stir bar was charged with substrate (0.14 mmol, 1.00 equiv) and $(CuOTf)_2$.Toluene (3.5 mg, 0.007 mmol, 0.05 equiv) in 0.7 mL THF (*C* 0.2 M). The mixture was stirred for 2 h under argon atmosphere. The solvent was removed by evaporation under reduced pressure. The crude was purified via silica gel chromatography using Pentane (100%) to Pentane/EtOAc (70:30) as eluent to afford the expected compound.

*4-Benzyl-2-methyl-1-tosyl-2,5-dihydro-1H-pyrrole (**IV.60a**)*



IV.60a
$C_{19}H_{21}NO_2S$
327,44

The title compound was prepared according to the general procedure K from the corresponding vinyl aziridine to give a pale yellow solid in 60% yield (28 mg).

Mp: 80 – 83 °C

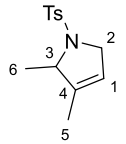
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63-7.65 (m, 2H, H_{ArTs}), 7.20-7.27 (m, 5H, H_{ar}), 6.99-7.01 (m, 2H, H_{ArTs}), 5.17-5.19 (m, 1H, H_3), 4.46-4.48 (m, 1H, H_1), 3.90-4.04 (m, 2H, H_5), 3.23-3.33 (m, 2H, H_1), 2.43 (s, 3H, H_{meTs}), 1.38 (d, *J* = 6.4 Hz, 3H, H_6) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.2 (C_{ArTs}), 137.6 (C_{ar}), 137.1 (C_{ar}), 134.8 (C_{ArTs}), 129.6 ($2C_{ArTs}$), 128.5 ($2C_{ArTs}$), 128.5 ($2C_{ar}$), 127.4 ($2C_{ar}$), 126.5 (C_2), 126.3 (C_3), 63.4 (C_1), 56.6 (C_4), 35.1 (C_5), 22.9 (C_6), 21.5 (C_{meTs}) ppm.

FTIR neat (cm^{-1}): 1402, 1355, 1178, 1163, 1090, 993, 945, 858, 840, 765, 664.

HRMS-ASAP (+) calculated for $C_{19}H_{22}NO_2S$ (m/z): $[M+H]^+$: calculated : 328.1371, found: 328.1381.

*2,3-Dimethyl-1-tosyl-2,5-dihydro-1H-pyrrole (**IV.60b**)*



IV.60b
$C_{13}H_{17}NO_2S$
251,34

The title compound was prepared according to the general procedure K from the corresponding vinyl aziridine to give a pale yellow oil in 33% yield (12 mg).

Mp: 63.7 – 65.4 °C

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.16 Hz, 2H, H_{ArTs}), 7.30 (d, *J* = 8.00 Hz, 2H, H_{ArTs}), 5.18-5.19 (m, 1H, H_1), 4.20-4.26 (m, 1H, H_3), 4.07-4.12 (m, 1H,

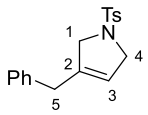
H_2), 3.97-4.02 (m, 1H, H_2), 2.43 (s, 3H, H_{meTs}), 1.59-1.61 (m, 3H, H_5), 1.42-1.43 (d, J = 6.40 Hz, 3H, H_6) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.2 (C_{ArTs}), 139.6 (C_4), 135.0 (C_1), 129.7 ($2C_{ArTs}$), 127.5 ($2C_{ArTs}$), 117.9 (C_{ArTs}), 65.1 (C_3), 54.6 (C_2), 21.6 (C_{ArTs}), 21.2 (C_5), 13.5 (C_6) ppm.

FTIR neat (cm^{-1}): 2921, 2851, 1740, 1598, 1445, 1341, 1161, 1097, 1046, 815, 708, 671.

HRMS-ASAP (+) calculated for $C_{13}H_{18}NO_2S$ (m/z): $[M+H]^+$: calculated : 251.0980, found: 252.1090.

*3-Benzyl-1-tosyl-2,5-dihydro-1H-pyrrole (**IV.60e**)*



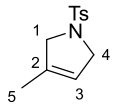
IV.60e
$C_{18}H_{19}NO_2S$
313,42

The title compound was prepared according to the general procedure K from the corresponding vinyl aziridine to give a pale yellow solid in 91% yield (40 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65-7.68 (m, 2H, H_{ArTs}), 7.21-7.31 (m, 5H, H_{ar}), 7.04-7.06 (m, 2H, H_{ArTs}), 5.24-5.26 (m, 1H, H_3), 4.08-4.11 (m, 2H, H_1), 3.95-3.99 (m, 2H, H_4), 3.31 (s, 2H, H_5), 2.43 (s, 3H, H_{meTs}) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[205]

*3-Methyl-1-tosyl-2,5-dihydro-1H-pyrrole (**IV.60f**)*



IV.60f
$C_{12}H_{15}NO_2S$
237,32

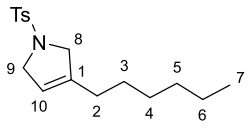
The title compound was prepared according to the general procedure K from the corresponding vinyl aziridine to give a white solid in 94% (31 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71-7.73 (m, 2H, H_{ArTs}), 7.31-7.33 (m, 2H, H_{ArTs}), 5.22-5.26 (m, 1H, H_3), 4.05-4.08 (m, 2H, H_1), 3.94-3.98 (m, 2H, H_4), 2.43 (s, 3H, H_{meTs}), 1.66 (brs, 3H, H_5) ppm.

The analytical data were identical in all respects to those previously reported in the literature.[175]

[205] J.J. Verendel, J.Q. Li, X. Quan, B. Peters, T. Zhou, O.R. Gautun, T. Govender, P.G. Andersson *Chem. Eur. J.* **2012**, 18, 6507.

*3-Hexyl-1-tosyl-2,5-dihydro-1H-pyrrole (**IV.60g**)*



IV.60g
$C_{17}H_{25}NO_2S$
307,45

The title compound was prepared according to the general procedure K from the corresponding vinyl aziridine to give a pale yellow solid in 90% yield (39 mg).

Mp: 58.7 – 60.8 °C

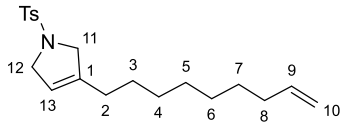
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.24 Hz, 2H, H_{ArTs}), 7.31 (d, *J* = 7.96 Hz, 2H, H_{ArTs}), 5.23-5.25 (m, 1H, H_{10}), 4.06-4.09 (m, 2H, H_8), 3.98-4.00 (m, 2H, H_9), 2.42 (s, 3H, H_{ArTs}), 1.93 (t, *J* = 7.93 Hz, 2H, H_2), 1.32-1.39 (m, 2H, H_6), 1.19-1.24 (m, 6H, $H_{3,4,5}$), 0.86 (t, *J* = 6.94 Hz, 3H, H_7) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.5 (C_{ArTs}), 140.0 (C_{10}), 134.5 (C_{ArTs}), 129.9 ($2C_{ArTs}$), 127.6 ($2C_{ArTs}$), 118.0 (C_1), 56.7 (C_8), 55.2 (C_9), 31.7 (C_2), 29.0 (C_6), 28.8 (C_{alk}), 27.3 (C_{alk}), 22.7 (C_{alk}), 21.7 (C_{meTs}), 14.2 (C_7) ppm.

FTIR neat (cm^{-1}): 2924, 2858, 1721, 1323, 1309, 1291, 1160, 1053, 1122, 1093, 1084, 1033, 1019, 949, 894, 874, 851, 817, 784, 708, 681.

HRMS (ESI+) calculated for $C_{17}H_{26}NO_2S$ (m/z): $[M+H]^+$: calculated : 308.1687, found: 308.1681.

*3-(Non-8-en-1-yl)-1-tosyl-2,5-dihydro-1H-pyrrole (**IV.60h**)*



IV.60h
$C_{20}H_{29}NO_2S$
347,52

The title compound was prepared according to the general procedure K from the corresponding vinyl aziridine to give a pale yellow solid in 90% (44 mg).

Mp: 51.0 – 52.8 °C

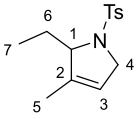
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.2 Hz, 2H, H_{ArTs}), 7.31 (d, *J* = 7.98 Hz, 2H, H_{ArTs}), 5.74-5.84 (m, 1H, H_{13}), 5.23 (t, *J* = 3.2 Hz, 1H, H_9), 4.91-5.00 (m, 2H, H_{10}), 4.06-4.09 (m, 2H, H_{11}), 3.98 (d, *J* = 3.2 Hz, 2H, H_{12}), 2.42 (s, 3H, H_{meTs}), 1.94-2.05 (m, 4H, H_{alk}), 1.32-1.39 (m, 4H, H_{alk}), 1.23-1.25 (m, 6H, H_{alk}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.4 (C_{ArTs}), 139.9 (C_1), 139.2 (C_{13}), 134.4 (C_{ArTs}), 129.8 ($2C_{ArTs}$), 127.5 ($2C_{ArTs}$), 117.9 (C_9), 114.3 (C_{10}), 56.6 (C_{12}), 55.1 (C_{11}), 33.8 (C_{alk}), 29.3 (C_{alk}), 29.2 (C_{alk}), 29.1 (C_{alk}), 28.9 (C_{alk}), 28.7 (C_{alk}), 27.3 (C_{alk}), 21.6 (C_{meTs}) ppm.

FTIR neat (cm^{-1}): 2923, 2848, 1641, 1595, 1465, 1338, 1301, 1100, 1158, 1070, 1015, 991, 906, 829, 816, 790, 726, 683, 664.

HRMS (ESI+) calculated for $C_{20}H_{30}NO_2S$ (m/z): $[M+H]^+$: calculated : 348.1991, found: 348.2023.

*2-Ethyl-3-methyl-1-tosyl-2,5-dihydro-1H-pyrrole (**IV.60i**)*



IV.60i
$C_{14}H_{19}NO_2S$
265,37

The title compound was prepared according to the general procedure K from the corresponding vinyl aziridine to give a pale yellow oil in 57% yield (21 mg).

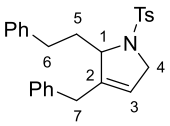
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.2 Hz, 2H, H_{ArTs}), 7.29 (d, *J* = 7.9 Hz, 2H, H_{ArTs}), 5.24-5.26 (m, 1H, H_3), 4.31-4.34 (m, 1H, H_1), 4.01-4.03 (m, 2H, H_4), 2.41 (s, 3H, H_{meTs}), 1.99-2.08 (m, 1H, H_6), 1.61-1.67 (m, 1H, H_6), 1.55-1.57 (m, 3H, H_5), 0.80 (t, *J* = 7.4 Hz, 3H, H_7) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.2 (C_{ArTs}), 137.2 (C_2), 135.1 (C_{ArTs}), 129.6 ($2C_{ArTs}$), 127.4 ($2C_{ArTs}$), 119.4 (C_3), 69.6 (C_1), 55.3 (C_4), 29.8 (C_6), 21.6 (C_{meTs}), 13.7 (C_5), 6.7 (C_7) ppm.

FTIR neat (cm^{-1}): 2922, 2855, 1457, 1342, 1162, 1094, 814, 672.

HRMS-ASAP (+) calculated for $C_{14}H_{20}NO_2S$ (m/z): $[M+H]^+$: calculated : 266.1209, found: 266.1216.

*3-Benzyl-2-phenethyl-1-tosyl-2,5-dihydro-1H-pyrrole (**IV.60j**)*



IV.60j
$C_{26}H_{27}NO_2S$
417,57

The title compound was prepared according to the general procedure K from the corresponding vinyl aziridine to give a pale yellow oil in 40% yield (24 mg).

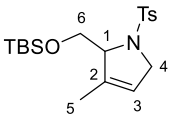
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.2 Hz, 2H, H_{ArTs}), 7.19-7.34 (m, 10H, H_{ar}), 6.95 (d, *J* = 7.1 Hz, 2H, H_{ArTs}), 5.29-5.31 (m, 1H, H_3), 4.42-4.45 (m, 1H, H_1), 4.15-4.18 (m, 2H, H_4), 3.42 (d, *J* = 16.0 Hz, 1H, H_7), 3.14 (d, *J* = 16.0 Hz, 1H, H_7), 2.80 (m, 1H, H_6), 2.57 (m, 1H, H_6), 2.48 (s, 3H, H_{meTs}), 2.26-2.35 (m, 1H, H_5), 1.89-1.97 (m, 1H, H_5) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.3 (C_{ArTs}), 142.1 (C_2), 141.4 (C_{ar}), 137.6 (C_{ar}), 134.9 (C_3), 129.8 ($2C_{ArTs}$), 128.8 ($2C_{ar}$), 128.6 ($2C_{ar}$), 128.6 ($2C_{ar}$), 128.5 ($2C_{ar}$), 127.5 ($2C_{ArTs}$), 126.7 (C_{ar}), 125.9 (C_{ar}), 121.1 (C_{ArTs}), 67.4 (C_1), 55.4 (C_4), 34.9 (C_7), 34.8 (C_6), 29.6 (C_5), 21.7 (C_{meTs}) ppm.

FTIR neat (cm^{-1}): 2921, 2852, 1599, 1494, 1454, 1341, 1159, 1092, 1061, 743, 700, 668.

HRMS-ASAP (+) calculated for $C_{26}H_{28}NO_2S$ (m/z): $[M+H]^+$: calculated : 418.1835, found: 418.1841.

2-(((tert-Butyldimethylsilyl)oxy)methyl)-3-methyl-1-tosyl-2,5-dihydro-1H-pyrrole ***(IV.60k)***



IV.60k
$C_{19}H_{31}NO_3SSi$
381,61

The title compound was prepared according to the general procedure K from the corresponding vinyl aziridine to give a colorless oil in 40% yield (22 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.20 Hz, 2H, H_{ArTs}), 7.29 (d, *J* = 8.90 Hz, 2H, H_{ArTs}), 5.25-5.27 (m, 1H, H_3), 4.18-4.20 (m, 1H, H_1), 4.00-4.02 (m, 2H, H_6), 3.89-3.91 (m, 2H, H_4), 2.41 (s, 3H, H_{meTs}), 1.65-1.68 (m, 3H, H_5), 0.86 (s, 9H, H_{tBuTBS}), 0.07 (s, 6H, H_{2meTBS}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.4 (C_{ArTs}), 137.3 (C_2), 135.3 (C_3), 129.8 ($2C_{ArTs}$), 127.5 ($2C_{ArTs}$), 119.9 (C_{ArTs}), 77.4 (C_{TBS}) 70.6 (C_6), 64.9 (C_1), 55.2 (C_4), 25.9 ($3C_{tBuTBS}$), 21.7 (C_{meTs}), 14.3 (C_5), -5.2 (C_{meTBS}), -5.4 (C_{meTBS}) ppm.

FTIR neat (cm^{-1}): 2958, 2928, 2885, 2857, 1342, 1254, 1160, 1139, 1096, 1045, 903, 832, 813, 775, 678.

HRMS (ESI+) calculated for $C_{19}H_{32}NO_3SSi$ (m/z): $[M+H]^+$: calculated : 381.1794, found: 382.1847.

Résumé

Les peptides et les protéines sont des biomolécules essentielles, impliquées dans des nombreux processus physiologiques. Au-delà de ces processus vitaux, ces molécules suscitent l'intérêt de la communauté scientifique dans des domaines variés, en particulier la chimie médicinale et la chimie des polymères. Ainsi, le développement de méthodes de voies d'accès à ces composés est essentiel.

Dans ce contexte, notre laboratoire a développé une méthode originale pour la synthèse de dipeptides, basée sur l'activation de la fonction amine au lieu de la fonction acide carboxylique. Elle présente aussi certains inconvénients, en particulier des temps de réaction très longs.

Ce projet de thèse a pour objectifs dans un premier temps l'amélioration de cette méthodologie, avec une attention particulière portée à la cinétique de la réaction et dans un second temps son extension à la synthèse d'amides non peptidiques (amides dites généraux). Entre autres, l'utilisation du micro-ondes nous a permis de réaliser la réaction en 30 minutes au lieu de 20 heures. Finalement, avec la mise au point des nouvelles conditions réactionnelles, nous avons pu appliquer cette méthode avec succès à la synthèse d'amides généraux.

En parallèle, nous nous sommes intéressés à l'expansion des petits cycles – plus spécifiquement au réarrangement des aziridines en 3-pyrrolines dans des conditions douces.

Mots clés : méthodologie de synthèse, peptides, fonction amide, petits hétérocycles

Abstract

Peptides and proteins are amongst the essential molecules in the everyday life. Consequently, they are widely investigated and used in several synthetic and natural-derived materials covering a broad range of applications. Hence, mastering their production, especially by chemical synthesis, is of utmost importance.

Our group has proposed an original procedure for the formation of amides on the basis of a novel mode of activation ("inverse activation" of AA through the amine function) affording the synthesis of several dipeptides. Nonetheless, this methodology presents some main drawbacks such as the long time to complete the reaction.

This PhD thesis work focuses on improving this methodology in terms of kinetics to synthesise peptide targets and to be able to extend the methodology to the synthesis of "general" (no-amino acids substrates) amides. For instance, we were delighted to observe that the reaction could take place in only 30 minutes instead of 20 hours using microwave irradiation. Then, we focus our attention on the synthesis of general amides. We explored the scope of the substrate obtaining the desired products in good yield showing the versatility of this methodology.

In parallel, we realised another project on the ring-expansion of the vinyl aziridines in order to afford the formation of 3-pyrrolines, interesting building blocks in organic synthesis

Keywords: methodology, peptides, amide function, small heterocycles