AtlanChim Pharma

N° 8 Scientific Letter

ATLANCHIM PHARMA : de nouveaux locaux en 2013

Après une année 2012 marquée par une croissance efficace, l'année 2013 s'est traduite par notre déménagement dans un nouveau bâtiment adapté en tout point à nos spécificités. En effet, nous avons quitté nos locaux de la Faculté de médecine pour nous installer en périphérie de Nantes, à Saint Herblain, dans un environnement biotech.

Cette nouvelle infrastructure, constituée de plus de 1200 m² de laboratoires de recherche (chimie – biologie), de bureaux commerciaux - administratifs et d'une animalerie répondant aux plus hautes exigences, permet de regrouper les équipes d'ATLANCHIM PHARMA et d'ATLANTIC BONE SCREEN sur un seul et même site.

Dans ces conditions, ATLANCHIM PHARMA a développé sa capacité de production et son pôle analytique. Grâce à cette nouvelle organisation, nous avons acquis de nouveaux équipements tels que UPLC-MS, HPLC semi-préparative etc… nous permettant de répondre efficacement aux demandes de nos clients avec une grande réactivité.

D'autre part, la qualité des services étant le fer de lance d'Atlanchim Pharma, nous avons recruté une nouvelle Responsable Assurance Qualité qui a intégré nos équipes en Juillet 2013.

De plus, vous trouverez sur le modèle des lettres scientifiques précédentes, le portrait d'un chef de projet en chimie : le Dr. Julien FARARD.

Enfin, nous sommes heureux de vous présenter la nouvelle édition de notre lettre scientifique dans laquelle nous vous faisons découvrir l'article scientifique sur la fonction amide hors du contexte de la synthèse peptidique intitulé « ***Amide Bond Formation beyond the Peptide Synthesis*** ».

Toute l'équipe d'ATLANCHIM PHARMA se joint à moi pour vous souhaiter une bonne lecture de notre lettre scientifique.

ATLANCHIM PHARMA – New premises for 2013

After a year of growth in 2012, ATLANCHIM PHARMA moved in 2013 into a new building corresponding to our specificities. Indeed, we left our offices in the Faculty of Medicine and we relocated ourselves in Saint-Herblain into a biotech environment.

This new premise represents more than 1200m² of laboratory in R&D (both chemistry and biology), commercial and administrative offices as well as animal facilities that fulfill the higher requirements of the applicable sanitary measure. In addition, we had the opportunity to bring together the research teams from ATLANCHIM PHARMA and ATLANTIC BONE SCREEN.

Consequently, ATLANCHIM PHARMA strengthened its production capacity and analytical services. Thanks to this new organization, we acquired new equipments such as UPLC-MS, HPLC semi-preparative … which enable us to respond efficiently to our customers.

On the other hand, attached to customers' satisfaction and quality, ATLANCHIM PHARMA increases its staff with the arrival of our new Quality Manager in July 2013.

In this new edition of our scientific letter, you will appreciate the presentation of one of our Project Managers, Dr. Julien FARARD.

*Finally, you will also be pleased to discover the scientific publication entitled « **Amide Bond Formation beyond the Peptide Synthesis** », written by our Scientific Director, Prof. Jacques LEBRETON.*

The ATLANCHIM PHARMA team joins me in wishing you an enjoyable read !

Ronan LE BOT
Directeur/*CEO*

SOMMAIRE / SUMMARY

Amide Bond Formation beyond the Peptide Synthesis

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Activation of carboxylic acids for the formation of amide bond is undoubtedly one of the most significant and widely used transformations in organic chemistry. The amide bond is ubiquitous throughout Nature in peptides and found in many biologically active compounds and drugs, as well as in their synthetic intermediates. A recent close examination carried out by pharmaceutical companies pointed out that amide bond formation was utilized in the preparation of 65% of the drug candidates surveyed.[1] It should be pointed out that the wide range of robust methodologies currently available for the formation of amide bonds are a result of the efforts made in the field of peptide synthesis. In fact, due to the growing interest in peptides, the arsenal of available highly efficient commercial reagents for solution and solid support synthesis has increased over the last two decades. These efforts have been covered in a number of valuable reviews.[2] Although a plethora of coupling agents has been developed, they all have advantages and limitations due to the structural diversity of the substrates. The search for new coupling reagents and conditions is still needed, in particular, for less nucleophilic and/or bulky amines. Also, the development of efficient low-cost reagents for large-scale production in the context of manufacturing drugs has become a great challenge.

Amide formation requires the activation of carboxylic acid partner by replacement of the hydroxyl group with a leaving group. So, this crucial activation could be carried out in the presence or not of the amine. In the two-step procedure, the carboxylic acid is first activated in a separate step prior to addition of the amine as a nucleophile. In this approach, the activated acyl could be isolated and purified. Of course, to resolve this issue, a more convenient one-step procedure is desired with activation of a carboxylic acid in the presence of an amine with the adequate coupling agent.

This letter focuses on major methodologies which have impacted the amide formation in the field of Medicinal Chemistry, including scale-up, through recent examples.

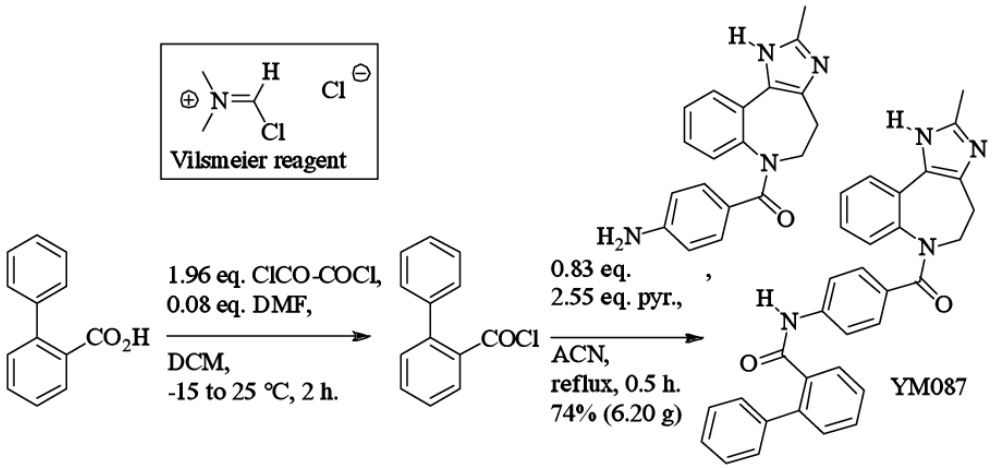
[1] S. D. Roughley, A. M. Jordan. *J. Med. Chem.* **2011**, 54, 3451-3479.
[2] (a) S.-Y. Han, Y.-A. Kim, *Tetrahedron*, **2004**, 60, 2447-2467. (b) C. A. G. N. Montalbetti, V. Falque, *Tetrahedron*, **2005**, 61, 10827-10852. (c) E. Valeur, M. Bradley, *Chem. Soc. Rev.*, **2009**, 38, 606-631. (d) A. El-Faham, F. Albericio, Chem. Rev., **2011**, *111*, 6557-6602.

Acid Halogenation Reagents

Despite its high reactivity and low cost, simple acid chloride activation for amide formation has been widely used since its introduction in peptide synthesis by Fischer in 1903. Nevertheless, there are a number of problems associated with the use of acid chlorides, such as their air-sensitivity and volatility. They are hydrolyzed by moisture to form acids and the HCl released could be a source of problems in the presence of acid-sensitive functionality. However, various protocols have been described to prepare acid chlorides. Thionyl and oxalic chloride are largely employed as the chlorinating agents, most of the time in the presence of a catalytic amounts of DMF. It is worth noting that the formation of the known carcinogen dimethylcarbamoyl chloride (DMCC) has been detected as the minor reaction by-product during the degradation of the Vilsmeier reagent (see Scheme 1) which is the chlorinating agent formed in situ.[3] The amount of DMCC, detected normally at a level of 0-20 ppm, is higher with thionyl chloride than oxalic chloride. Nevertheless, after standard aqueous workup no more than 3 ppm of DMCC could be detected in the final product.[4]

Due to the high cost of the acid partner (Scheme 1), a novel, reliable and cost-effective synthetic route to YM087, a potent Arginine vasopressin agonist, has been developed based on the formation of the amide at the final stage.[5] To carry out this condensation step, the acid chloride was treated, in the presence of pyridine to generate the more reactive *N*-acyl-pyridinium intermediate, with the aniline partner without the need to protect the imidazole moiety. The desired YM087 was obtained in good yield with an ideal protocol for large-scale productions.

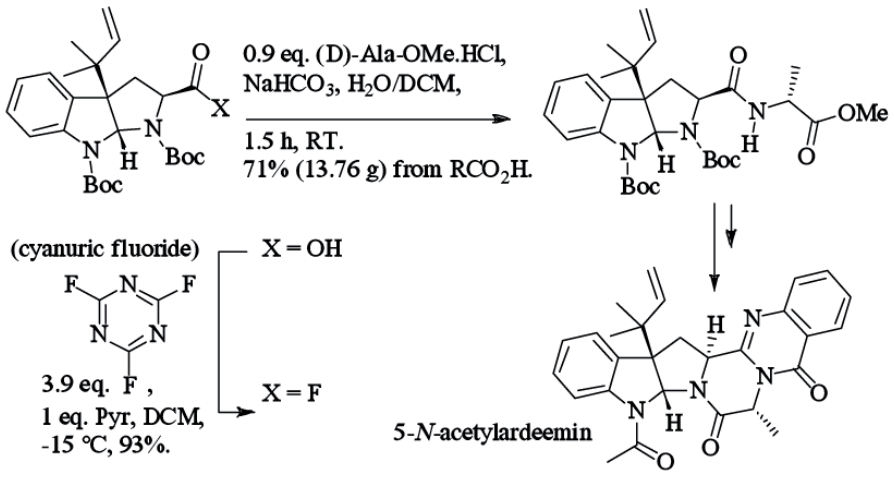
Scheme 1



[3] D. Levin, Org. *Process Res. Dev.*, **1997**, *1*, 182.
[4] W. Tian et *Coll., Org. Process Res. Dev.*, **2009**, *13*, 857-862.
[5] T. Tsunoda et *Coll., Org. Process Res. Dev.*, **2003**, *7*, 883-887.

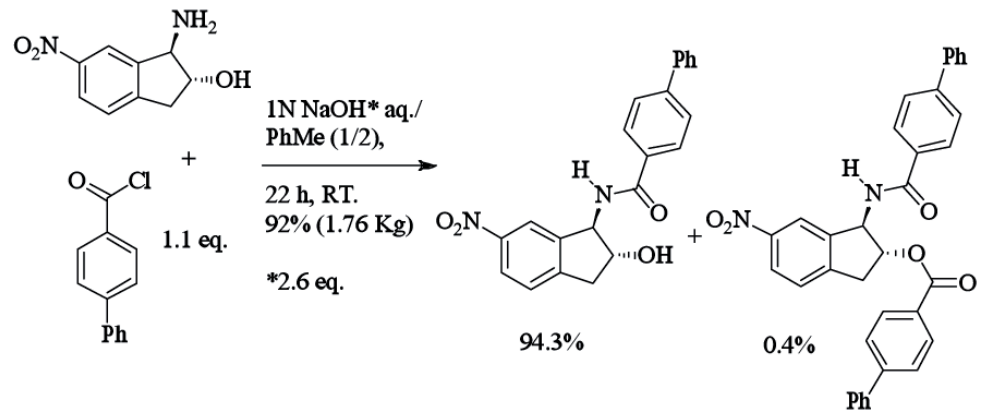
Since acid fluorides present a better stability toward moisture and oxygenated nucleophiles, with the same reactivity toward amines compared to their corresponding acid chlorides, several acid fluorinating reagents have been successfully developed. In this area, the most notable advance has been the introduction of cyanuric fluoride. In the total synthesis of 5-*N*-acetylardeemin, a potential MDR reversal agent, Danishefsky et *Coll.* successfully used cyanuric fluoride to generate the corresponding acid fluoride in the key chain-elongation step as depicted in Scheme 2. [6] It should be pointed out that attempts to carry out this crucial transformation with other coupling agents such as BOP-Cl, DCC (see Figures 1 and 4) with HOBt or DMAP (see Figure 2) failed due to partial racemization of the stereogenic centers C15b and/or C8 as noted after careful NMR analysis of the coupled peptide formed.

Scheme 2



In addition, the acid chlorides are often robust enough to react with amines under Schotten-Baumann conditions[7], under two-phase conditions in the presence of aqueous inorganic bases such as NaOH or K_2CO_3. Typical Schotten-Baumann acylation was successfully used on a kilo-lab scale to prepare the desired amide (Scheme 3) with low levels of the bis-acylated byproduct.[8]

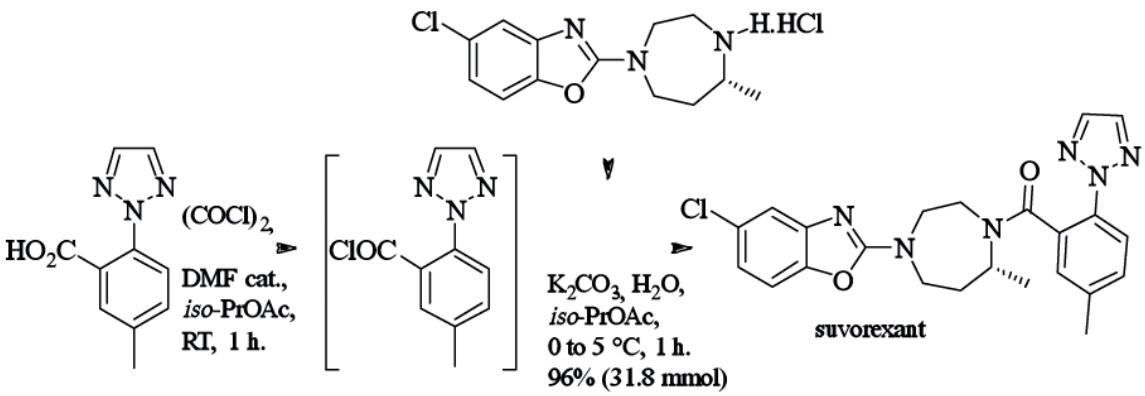
Scheme 3



[6] K. M. Depew, S. P. Marsden, D. ZatorskA, A. Zatorski, W. G. Bornmann, S. J. Danishefsky, J. *Am. Chem. Soc.*1999, *121*, 11953-11963.
[7] N. O. V. Sonntag, *Chem. Rev.*, **1953**, *52*, 237-416.
[8] M. M. Hansen et *Coll., Org. Process Res. Dev.*, **2009**, *13*, 198-208.

In the last step of the preparation of suvorexant, a potent brain penetrant dual orexin receptor antagonist developed by Merck and currently in phase III clinical trials, an amide bond formation was carried out. Thus, the amine partner as its HCl salt was directly treated with the acid chloride under Schotten-Baumann conditions to afford the target drug in 96% yield after crystallization (see Scheme 4).[9]

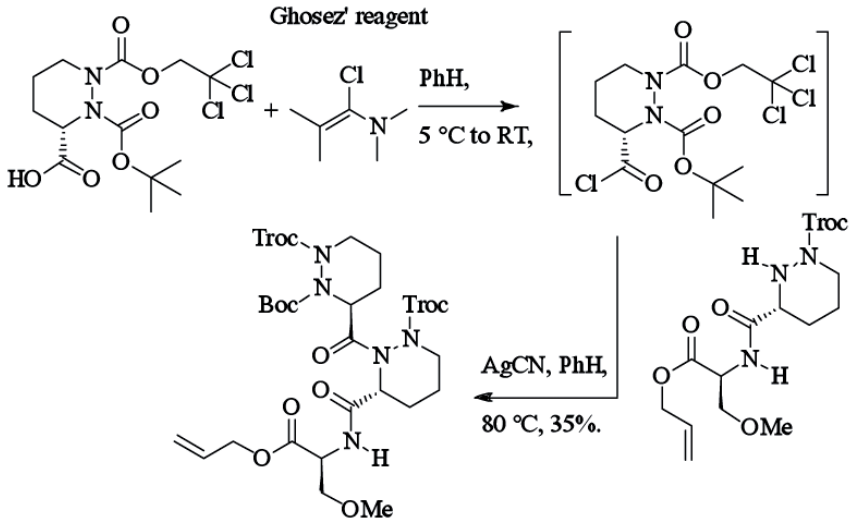
Scheme 4



To end this section, it is important to note that the commercially available Ghosez'reagent[10] is able to convert carboxylic acids into their corresponding acid chlorides under strictly neutral conditions, as exemplified in Scheme 5 [11]. All attempts to carry out this crucial coupling step between the two piperazinic partners under various standard peptide coupling conditions failed. Fortunately, this problem was solved using the Ghosez'reagent to generate the corresponding acid chloride followed by its activation with silver cyanide in the presence of the amine to provide the desired tripeptide in modest yield.

As reported in literature, samarium[12] - or zinc[13] -mediated formation of amide bonds by reaction of acyl chlorides and poorly nucleophilic and/or bulky amines has also been developed.

Scheme 5

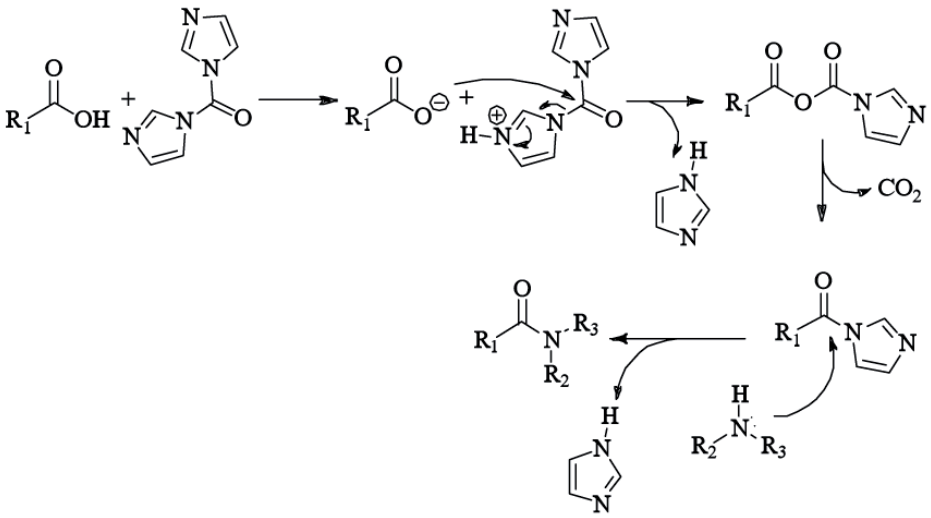


[9] I. K. Mangion, B. D. Sherry, J. Yin, F. J. Fleitz, *Org. Lett.*, **2012**, *14*, 3458-3461.
[10] A. Devos, J. Remion, A. M. Frisque-Hesbain, A. Colens, L. Ghosez, *J. Chem. Soc., Chem. Commun.*, **1979**, 1180-1181.
[11] A. J. Oelke, D. J. France, T. Hofmann, G. Wuitschike, S. V. Ley, *Chem. Eur. J.*, **2011**, 17, 4183-4194.
[12] F. Shi, J. Li, C. Li, X. Jia, *Tetrahedron Letters*, **2010**, 51, 6049-6051.
[13] H. M. Meshram, G. S. Reddy, M. M. Reddy, J. S. Yadav, *Tetrahedron Letters*, **1998**, 39, 4103-4106.

Acylimidazoles using CDI

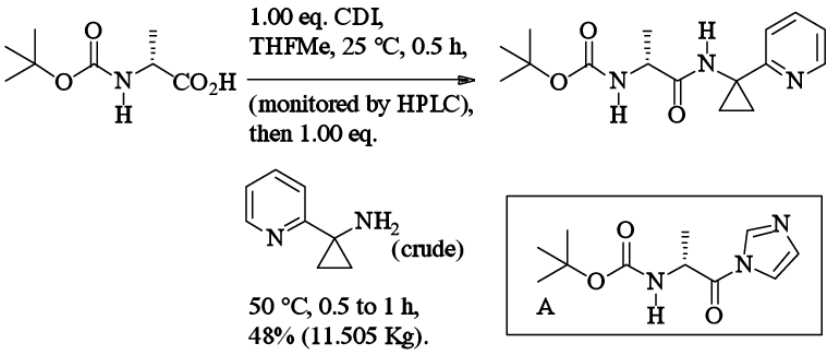
1,1'-Carbonyldiimidazole (CDI), a crystalline solid commercially available (around 8$ per mol), has been widely used as coupling agent. The activated species is the acylimidazole, which is formed as presented in the Scheme 6.[14] Practically, the acylimidazole is preformed and then the amine is added. Otherwise, the addition of the amine on CDI leads to the formation of the corresponding isocyanate, which could react with another molecule of amine to afford the symmetrical urea derivative.

Scheme 6



A multikilogram preparation of the dipeptide (see Scheme 7) in pilot-plant without column purification has been developed using CDI to form the amide linkage at the final stage. It should be noted that the formation of the acylimidazole A was monitored by GC analysis, and after 30 min. at 25 °C, the carboxylic acid was completely consumed. The resulting reaction mixture was then reacted with the 2-cyclopropylaminopyridine.

Scheme 7



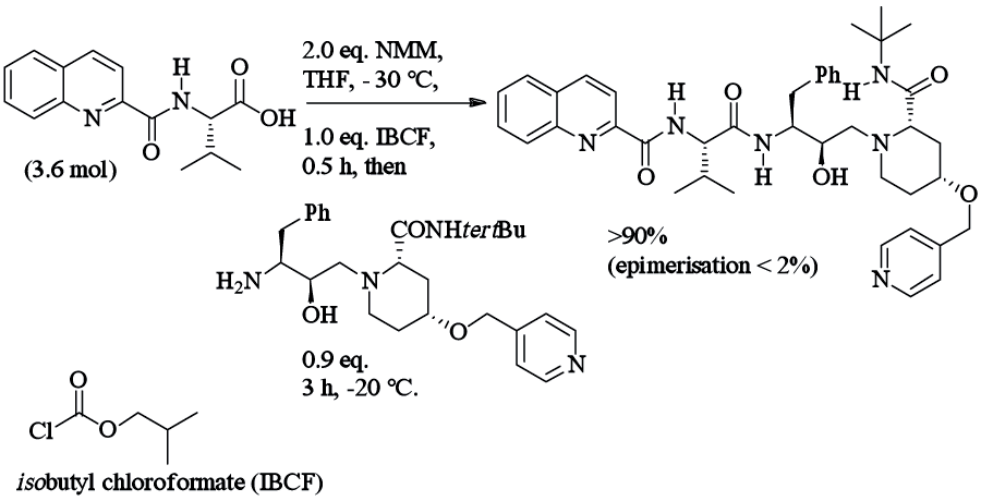
[14] M. Prashad, K. Prasad, O. Repic, T. J. Blacklock, *Org. Process Res. Dev.*, **1999**, *3*, 409-415.
[15] For a recent reference on this point, see: S. T. Heller, T. Fu, R. Sarpong, *Org. Lett.*, **2012**, *14*, 1970-1973.
[16] R. Vaidyanathan, V. G. Kalthod, D. P. Ngo, J. M. Manley, S. P. Lapekas, *J. Org. Chem.*, **2004**, *69*, 2565-2568.

More generally, acylimidazole intermediates could be also activated with various electrophiles (NBS), alkylating agents (MeI) and Brønsted acids.[15] Also, previous work established a substantial rate enhancement for the amide formation in the presence of the CO_2 released during the activation step.[16]

Mixed carbonic anhydrides

Chloroformates have also been used in peptide coupling reactions via the formation of mixed carbonic anhydride intermediates. Isobutyl chloroformate (IBCF), initially reported by Vaughan[17] more than sixty years ago, is still a popular reagent in the context of amide formation. In the course of the preparation of Palinavir (see Scheme 8), a potent peptidomimetic-based HIV protease inhibitor, the acid was reacted with IBCF in the presence of N-methylmorpholine (NMM) to form the corresponding mixed carbonic anhydride, which was treated with the amine, at -20 °C to give the target molecule in high yield.[18] This conversion proceeded smoothly with <2% of epimerization. Attempts to perform this transformation with other coupling reagents increased the level of epimerization (up to 30%).

Scheme 8

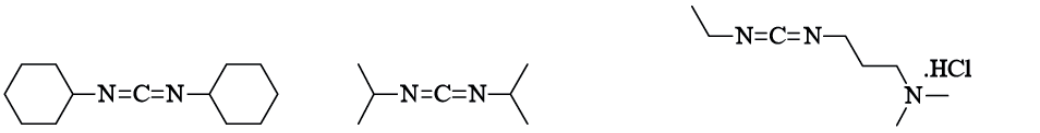


[17] J; R.Vaughan, J. Am. *Chem. Soc.*, **1951**, *73*, 3547-3547.
[18] P. L. Beaulieu et Coll., *J. Org. Chem.*, **1997**, *62*, 3440-3448.

Carbodiimides

Carbodiimides dominated this area during two decades. Dicyclohexylcarbodiimide (DCC), introduced by Sheehan in 1957, has been the first single most important reagent. Later, various other carbodiimides have been reported in the literature of which some are presented in Figure 1. The mechanism of the carbodiimide-mediated coupling is more complex than it appears: addition of the carboxylic group to the carbodiimide function afforded the *O*-acylisourea, a very reactive intermediate, which reacted with the amine to give the desired amide and the urea by-product. The formation of this later by-product is the driving force of this reaction. However, different side-reactions could be observed: the *O*-acylisourea could give the *N*-acylurea by intramolecular acyl transfer or may form the symmetrical anhydride by reaction with another carboxylic acid. With DCC, the low solubility of the dicyclohexylurea (DCU) by-product, in many solvents caused problems during the purification. The use of water soluble EDC as well as its corresponding urea greatly facilitated the removal of by-products by simple extraction in an acidic aqueous phase.

Figure 1. Commonly used carbodiimides.



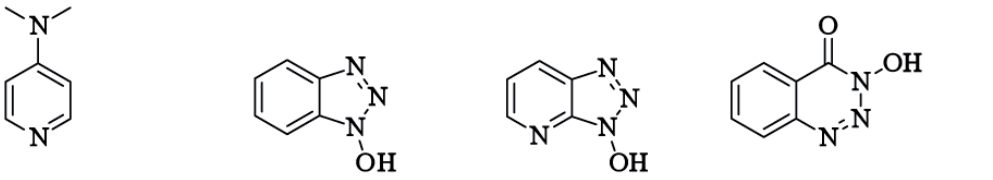
Dicyclohexylcarbodiimide (DCC)

Diisopropylcarbodiimide (DIC)

Ethyl-(*N'*,*N'*-dimethylamino)-propylcarbodiimide hydrochloride (EDC or WSC for Water Soluble Carbodiimide)

Addition of additives such as DMAP, HOBt, HOAt, and more recently HODhbt (see Figure 2) has dramatically expanded their scope by enhancing the coupling reaction rate. Reaction of these nucleophiles on the *O*-acylisourea generated a more reactive intermediate which also prevents the side-reactions. It is important to note that HOBt, HOAt and HOBhbt have been incorporated into stand-alone reagents such as phosphonium or uranium salts and neutral organophosphorus derivatives as discussed below. Nevertheless, it should be pointed out that HOBt, and more generally its triazole-based derivatives, have been classified as explosive compounds.[19]

Figure 2. Commonly used additives.



DMAP (4-(*N*,*N*-dimethylamino)-pyridine)

HOBt (1-hydroxy-benzotriazole)

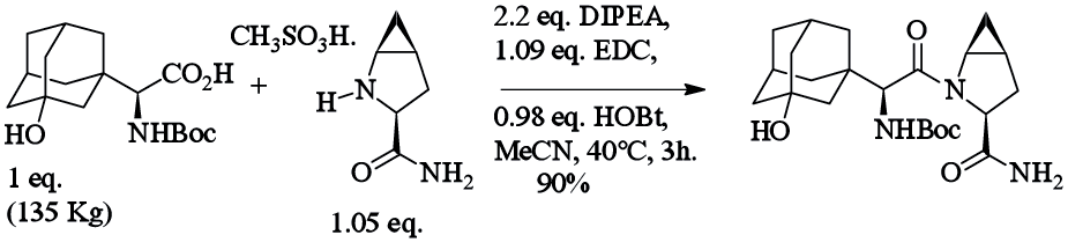
HOAt (1-hydroxy-7-aza benzotriazole)

HOBhbt (3-hydroxy-1, 2, 3-benzotriazin-4(3H)-one)

[19] P. J. Dunn et Coll., *Org. Process Res. Dev.*, **2005**, *9*, 956.

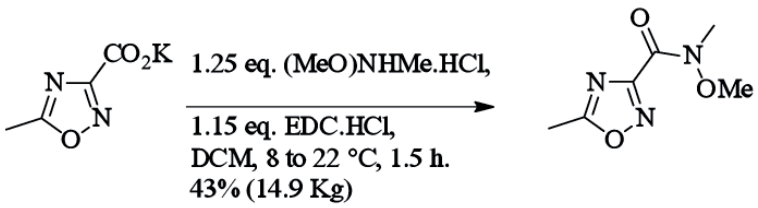
For the commercial-scale synthesis of saxagliptin, a novel inhibitor of dipeptidyl peptidase IV, the key amide intermediate was prepared as shown in Scheme 9.[20] An important and complete comparative evaluation of various coupling reagents showed the exceptional efficiency and robustness of the EDC/HOBt system. Interestingly, it was found that the best process was to load all four solids into the reactor prior to the sequential addition of acetonitrile (1.1 L/kg of total solids) and *N,N*-diisopropylethylamine (DIPEA).

Scheme 9



On multikilogram scale for the first GMP delivery of MK-4256, a somatostatin receptor antagonist, the oxadizole Weinreb amide was prepared from its corresponding potassium salt as presented in Scheme 10.[21] In the Medicinal Chemistry route, this oxadizole Weinreb amide was formed under Schotten-Bauman conditions from the acid chloride, which was prepared using oxalyl chloride in CH_2Cl_2. Unfortunately, on large scale, it was difficult to remove the excess of oxalyl chloride which led to the formation of the corresponding *bis*-Weinreb amide. This later by-product greatly complicated the subsequent ketone formation step.

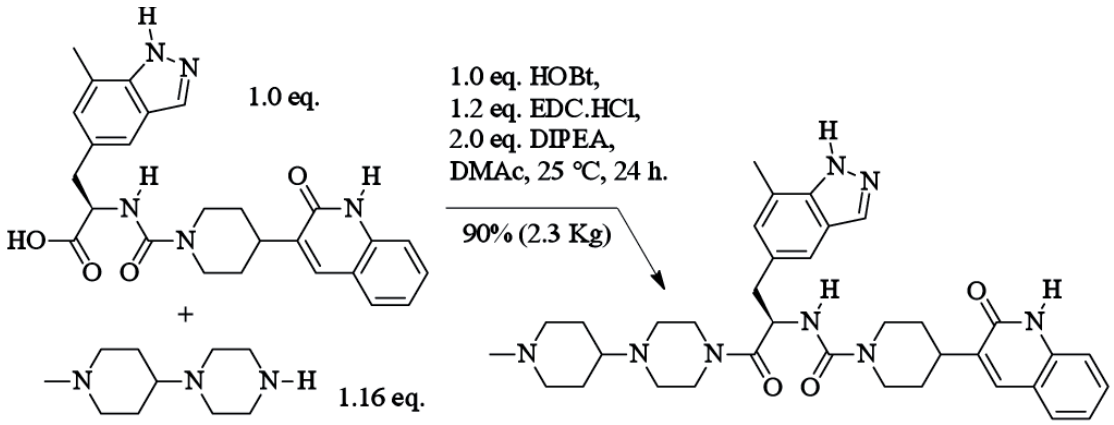
Scheme 10



[20] S. A. Savage et Coll., *Org. Process Res. Dev.*, **2009**, *13*, 1169–1176.
[21] R. T. Ruck et Coll., *Org. Process Res. Dev.*, **2012**, *16*, 1329-1337.

After screening several commercial coupling reagents, EDC/HOBt was identified as the most efficient system, in the development of a robust and practical route to a potent calcitonin gene-related peptide (CGRP) receptor antagonist for the long-term treatment of migraine headaches.[22] The last step of the synthesis is depicted in Scheme 11.

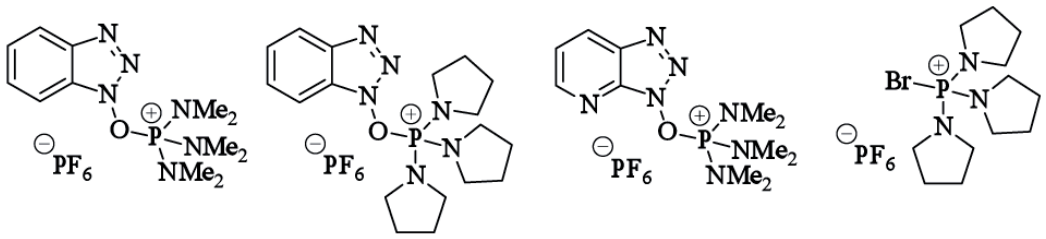
Scheme 11



Phosphonium reagents

Phosphonium-based coupling reagents are powerful and easy-to-use. The most popular agents are depicted in Figure 3. Unfortunately, the high cost of these reagents is one of the major obstacles for their use on large-scale synthesis.

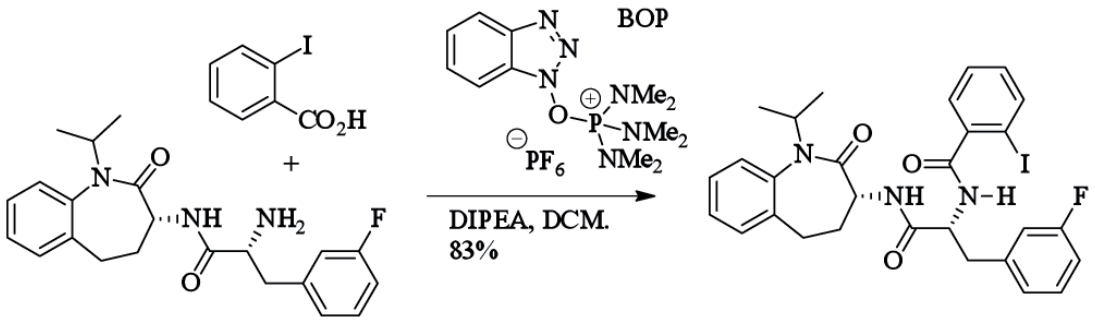
Figure 3. Commonly used phosphonium-based coupling reagents.



[22] R. O. Cann et Coll., *Org. Process Res. Dev.*, **2012**, *16*, 1953-1966.

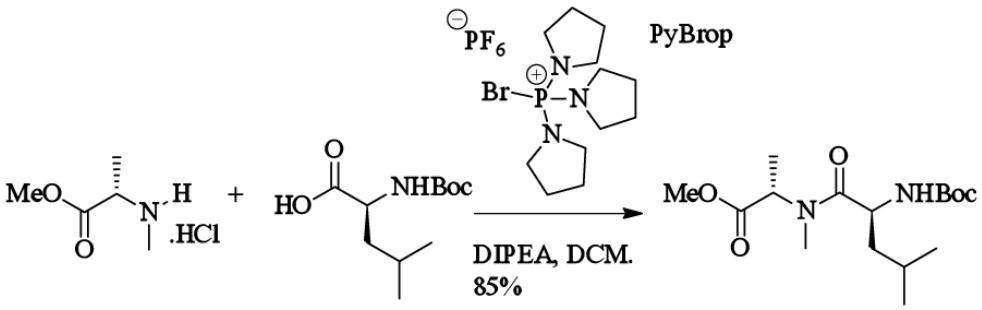
Introduced in 1975 by Castro, BOP is a non-hygroscopic crystalline reagent which has been largely used as depicted in the Scheme 12.[23] However, this later reagent generates HMPA as an extremely toxic by-product, so that PyBOP releasing less toxic 1,1",1"'-phosphoryltripyrrolidine has been developed later.

Scheme 12



Specifically, as illustrated in Scheme 13, PyBrop is a unique and very efficient coupling reagent with *N*-methylated amines.[24]

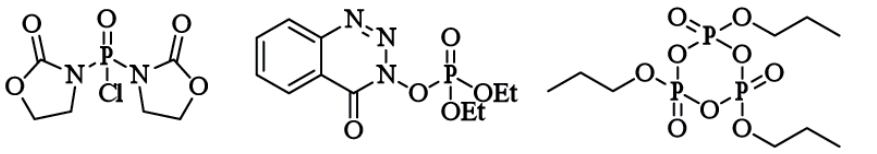
Scheme 13



Organophosphorus reagents

As depicted in Figure 4 various organophosphorus compounds have been also developed as peptide coupling reagents.

Figure 4. Commonly used organophosphorus coupling reagents.

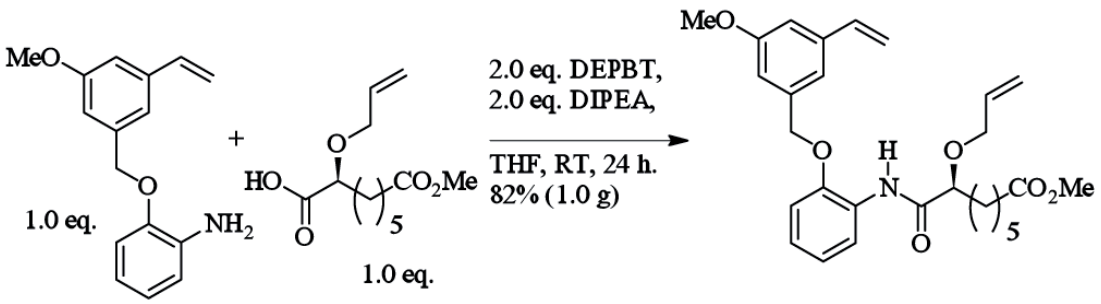


BOP-Cl | DEPBT | T3P® Propane Phosphonic Acid Anhydride

[23] C. Pérez-Medina, N. Patel, M. Robson, M. F. Lythgoe, E. Årstad, *Org. Biomol. Chem.*, **2012**, *10*, 9474-9480.
[24] K. Shimokawa, K. Yamada, D. Uemura, Bioorg. Med. *Chem. Lett.*, **2009**, *19*, 867-869.

During the synthesis of various nonpeptidic chiral macrocycles as inhibitors of histone deacetylases, DEPBT (known as Goodman's reagent) proved to be the most efficient coupling, compared to the EDC/HOBt system, to prepare some key anilide intermediates as outlined in Scheme 14.[25] It is worthwhile noting that DEPBT is more easy to handle and more stable than phosphonium and uranium activating agents, probably due to its existence as a neutral entity.

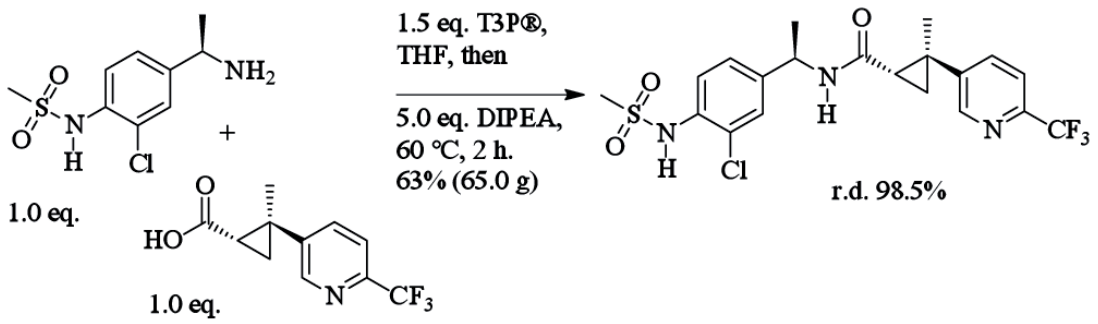
Scheme 14



Although 1-propanephosphonic acid cyclic anhydride (T3P®) was developed over 30 years ago[26], it is an exceptional coupling agent. T3P® combines several advantages over traditional reagents such as solubility, ease of workup, a broad variety of functional group tolerance. Furthermore, T3P®[27] reagent is nontoxic, non-allergenic and its salt by-products are non hazardous and completely water soluble, which greatly simplifies the workup and the purification of amide product, avoiding chromatography. T3R® is a registered trademark of Euticals which has an annual production capacity of several 100 tonnes. In addition, commercially available T3P® solutions (50% in various solvents) are easily handled and have a long shelf-life.

In the final coupling step for the preparation of the potential TRPV1 antagonist (see Scheme 15), T3P® was found to be superior to traditional methodologies used on large-scale synthesis, such as CDI or thionyl chloride activation via the acid chloride.[28]

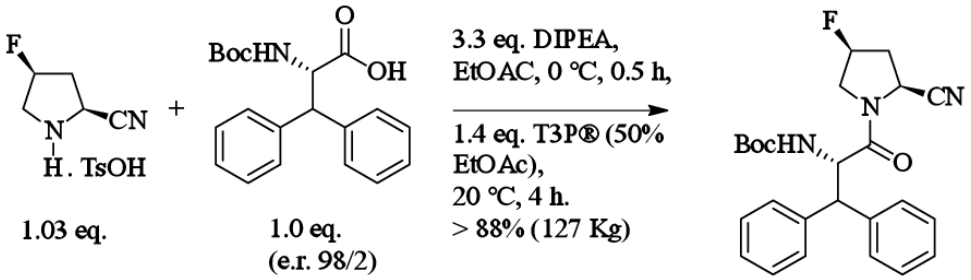
Scheme 15



[25] S. Hanessian et Coll., *J. Med. Chem.*, **2010**, *53*, 8387-8399.
[26] H. Wissmann, H.-J. Kleiner, *Angew. Chem.*, Int. Ed., **1980**, *19*, 133-135.
[27] A. L. Llanes Garcia, *Synlett*, **2007**, 1328-1329.
[28] B. A. Pibworth et Coll., *Org. Process Res. Dev.*, **2011**, *15*, 1192-1200.

An example of the potency of T3P® in the field of amide formation on large-scale synthesis is highlighted in Scheme 16.[29] During the development of a manufacturing process to synthesize Denagliptin tosylate, a dipeptidyl peptidase IV (DPPIV) inhibitor to treat type II diabetes, the formation of the amide bond was a challenging step. A number of common coupling reagents were screened including CDI, EDC and PyBOP, affording poor conversion and/or lower yields, and/or an increased level of impurities. In sharp contrast, the T3P®-mediated reaction proceeded cleanly without epimerization of the (*R*)-chiral center to furnish the desired amide in high yield (on 127 Kg scale) and in >98% purity.

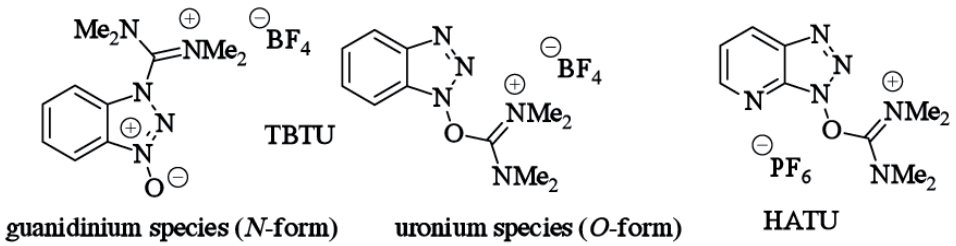
Scheme 16



Uronium-type reagents

Crystal and solution structure studies provided the evidence that uronium reagents have in fact a guanidinium *N*-oxide structure, as displayed in Figure 5.[30] Nevertheless, they are still called uronium-type reagents. It is worth noting that the nature of hexafluorophosphate or tetrafluoroborate counterions has no significant influence on the coupling rate. It is important to note that uronium reagents could directly react with amines to form undesired guanidinium by-products, so that pre-activation of the carboxylic acids is necessary to get the amides.

Figure 5. Commonly used uronium-type coupling reagents.

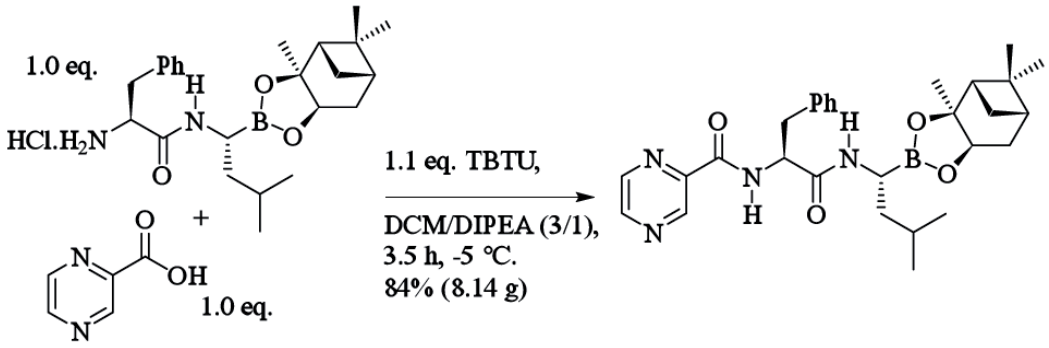


guanidinium species (*N*-form) uronium species (*O*-form) HATU

[29] D. E. Patterson et Coll., *Org. Process Res. Dev.*, **2009**, *13*, 900-906.
[30] L. A. Carpino et Coll., *Angew. Chem. Int. Ed.*, **2002**, *41*, 441-445.

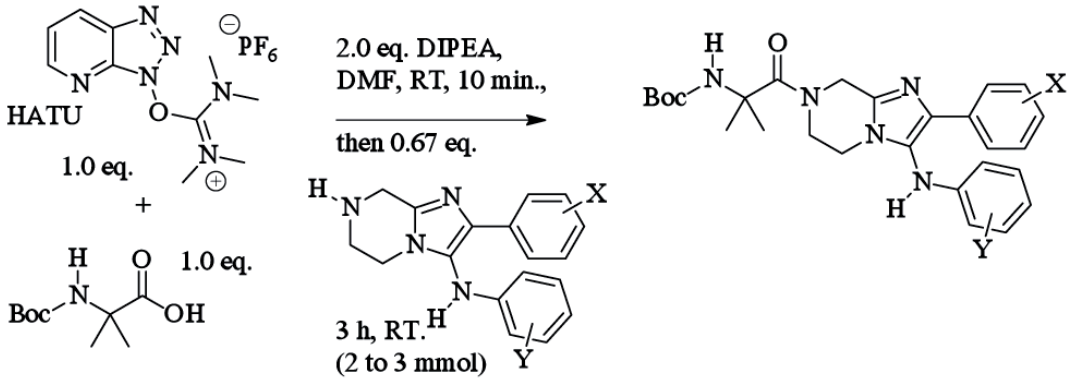
In the improved bench preparation of bortezomib, the first therapeutic proteasome inhibitor, marketed by Millennium Pharmaceuticals as Velcade, TBTU was found to be the most efficient reagent to suppress racemization in the coupling reaction (see Scheme 17).[31] Attempts to carry out the same coupling reaction using pre-activation of the carboxylic acid with CDI provided a 45/55 mixture of diastereoisomeric coupled products. The formation of an oxazolone intermediate, greatly promoted by the electronic-withdrawing nature of the $^{N\alpha}$-pyrazinoyl group in the activated species, explained the loss of chiral integrity of the coupled compound.

Scheme 17



As outlined in Scheme 18, HATU has been proven to be very efficient in difficult sterically hindered couplings (and gives a minimal level of racemization with α-chiral carboxylic acids).[32]

Scheme 18

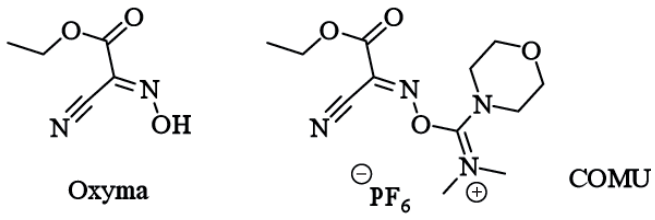


[31] A. S. Ivanov, A. A. Zhalnina, S. V. Shishkov, *Tetrahedron*, **2009**, *65*, 7105-7108.
[32] A. K. Chatterjee et Coll., *J. Med. Chem.*, **2011**, *54*, 5116-5130.

New coupling agents

A recent notable advance in this field was the development of Oxyma-(ethyl 2-cyano-2-(hydroxyimino)acetate)-based reagents (see Figure 6), which have been reported by El-Faham and Alberio.[33] Very recently, the same authors introduced the third generation of uronium-type reagent, named COMU (1-cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylaminomorpholino-carbenium hexafluorophosphate), based on Oxyma, as a safer and more efficient coupling reagent with very low or non-existent tendencies for racemization.[34]

Figure 6. Structures of Oxyma and COMU.



Conclusion

In the field of peptide chemistry, the development of a vast diversity of commercially available reagents has made many difficult couplings possible. However, although many of them are frequently used for early development, they could not be adapted to large-scale processes for economic reasons. It is not surprising, that in this context, acid halides are by far the most common acylating agents. These activated intermediates could be cleanly generated in situ, with inexpensive reagents such as thionyl and oxalic chloride, isolated and purified by recrystallization, or directly reacted with the amines. T3P® is also gaining popularity. As previously mentioned, this cost effective reagent (the cost of T3P® is around 10 times lower than HATU) offers several practical and experimental benefits.

The author would like to thank Dr. André Guingant and Dr. Samuel Golten for fruitful discussions and comments.

[19] P. J. Dunn et Coll., *Org. Process Res. Dev.*, **2005**, *9*, 956.

[33] A. El-Faham, F. Albericio, *J. Org. Chem.*, **2008**, *73*, 2731-2737.
[34] A. El-Faham, R. S. Funosas, R. Prohens, F. Albericio, *Chem. Eur. J.*, **2009**, *15*, 9404-9416.

Portrait Julien Farard

Le Dr. Julien FARARD, Chef de projet chez ATLANCHIM PHARMA depuis un peu plus d'un an, est titulaire d'un Doctorat en chimie organique avec une spécialité en chimie thérapeutique. Après avoir réalisé un post-doctorat en Belgique (Vrije Universiteit Brussel) avec une spécialisation en synthèse peptidique sur phase solide, il a intégré la société ATLANCHIM PHARMA en 2011. Il synthétise et optimise des contrats industriels de recherche en synthèse à façon de molécules complexes.

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