Amide bond formation: beyond the myth of coupling reagents

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Amide bond formation is a fundamentally important reaction in organic synthesis, and is typically mediated by one of a myriad of so-called coupling reagents. This critical review is focussed on the most recently developed coupling reagents with particular attention paid to the pros and cons of the plethora of "acronym" based reagents. It aims to demystify the process allowing the chemist to make a sensible and educated choice when carrying out an amide coupling reaction (179 references).

Introduction

Amide bonds play a major role in the elaboration and composition of biological systems, representing for example the main chemical bonds that link amino acid building blocks together to give proteins. Amide bonds are not limited to biological systems and are indeed present in a huge array of molecules, including major marketed drugs. For example, Atorvastatin **1**, the top selling drug worldwide since 2003, blocks the production of cholesterol and contains an amide bond (Fig. 1),[1] as do Lisinopril **2** (inhibitor of angiotensin converting enzyme),[2] Valsartan **3** (blockade of angiotensin-II receptors),[3] and Diltiazem **4** (calcium channel blocker used in the treatment of angina and hypertension).[4]

Amide bonds are typically synthesised from the union of carboxylic acids and amines; however, the unification of these two functional groups does not occur spontaneously at ambient temperature, with the necessary elimination of water only taking place at high temperatures (*e.g.* >200 °C),[5] conditions typically detrimental to the integrity of the substrates. For this reason, it is usually necessary to first activate the carboxylic acid, a process that usually takes place by converting the –OH of the acid into a good leaving group prior to treatment with the amine (Scheme 1). Enzymatic catalysis has also been investigated for the mild synthesis of amides and the organic chemist may find some of these methods useful as an alternative to traditional methods.[6,7]

In order to activate carboxylic acids, one can use so-called coupling reagents, which act as stand-alone reagents to generate compounds such as acid chlorides, (mixed) anhydrides, carbonic anhydrides or active esters. The choice of coupling reagent is however critical. For example, in medicinal chemistry library-based synthesis, amides are often generated using broad ranges of substrates with varying reactivities (*e.g.* anilines, secondary amines, bulky substrates). A coupling reagent needs to be able to cope with this whole portfolio of reactivity. Many reviews on coupling reagents have been published,[8–14] illustrating their importance in the synthetic armoury of the synthetic chemist, but these reviews have often failed to offer a critical view on the subject making the choice of reagent difficult. An important issue is that many of the coupling reagents reported have not been compared to others, making any real evaluation impossible. As many groups have reported "new" reagents as being wonderful and better than others, the chemist looking at the field of coupling reagent for

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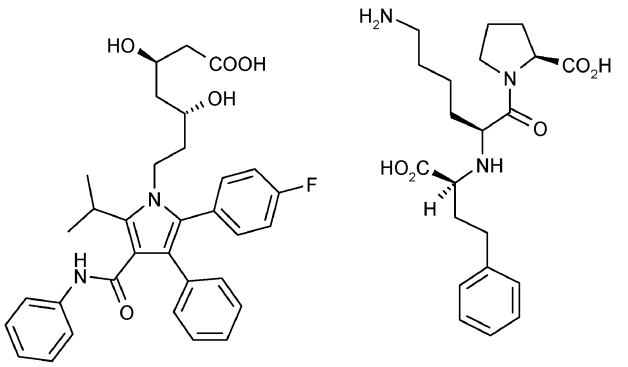
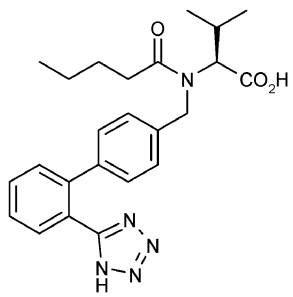
Professor Bradley's research interests are focused on the application of the tools and techniques of chemistry to address biological problems and needs, typically with a high-throughput twist. Two themes dominate at this time: the development of non-DNA based microarray platforms for cell and enzymatic based assays and the development of chemistries that enable efficient cellular delivery of proteins, nucleic acids, sensors and small molecules.

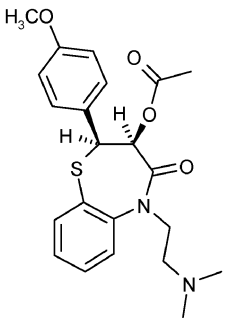


1 Atorvastatin

2 Lisinopril

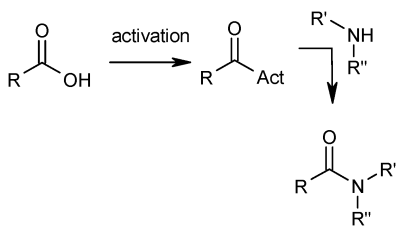


3 Valsartan



4 Diltiazem

Fig. 1 Examples of top drugs containing an amide bond. These examples are just a small selection of drugs containing amide bonds illustrating the importance of this functional group.



Scheme 1 Principle of the activation process for amide-bond formation.

the first time can be completely lost. The process can be made even more complicated as epimerisation, usually through an oxazoline intermediate, may take place during amide bond formation. Thus, when coupling reagents are evaluated, several tests that have been developed to assess the extent of epimerisation (see Table 1) should be carried out.

1. Coupling using carbodiimides

1.1 Dicyclohexylcarbodiimide

Carbodiimides were the first coupling reagents to be synthesised. Dicyclohexylcarbodiimide (DCC, **5**) has been used for coupling since 1955,[21] and the mechanism for coupling carboxylic acids to amines is shown in Scheme 2.

The first step involves the reaction of the carboxylic acid with DCC to form the *O*-acylurea **6**. This intermediate can then yield a number of different products:

- The amide *via* direct coupling with the amine (the by-product formed, dicyclohexylurea (DCU **7**), is usually insoluble in the reaction solvent and can be removed *via* filtration).
- Formation of an *N*-acylurea **8** by-product
- Formation of the carboxylic acid anhydride which subsequently yields the amide by reaction with the amine (needs 2 equiv. of acid).

When using DCC, oxazolone formation can take place after generation of the *O*-acylurea leading to epimerisation,[19] especially important when activating acid groups in the α position of an amide bond.

In addition to peptide synthesis, carbodiimides (often with *N*-hydroxysuccinimide as an additive) have been used extensively in nanotechnology for the functionalisation of monolayers on surfaces and nanoparticles.[22,23]

1.2 Use of additives

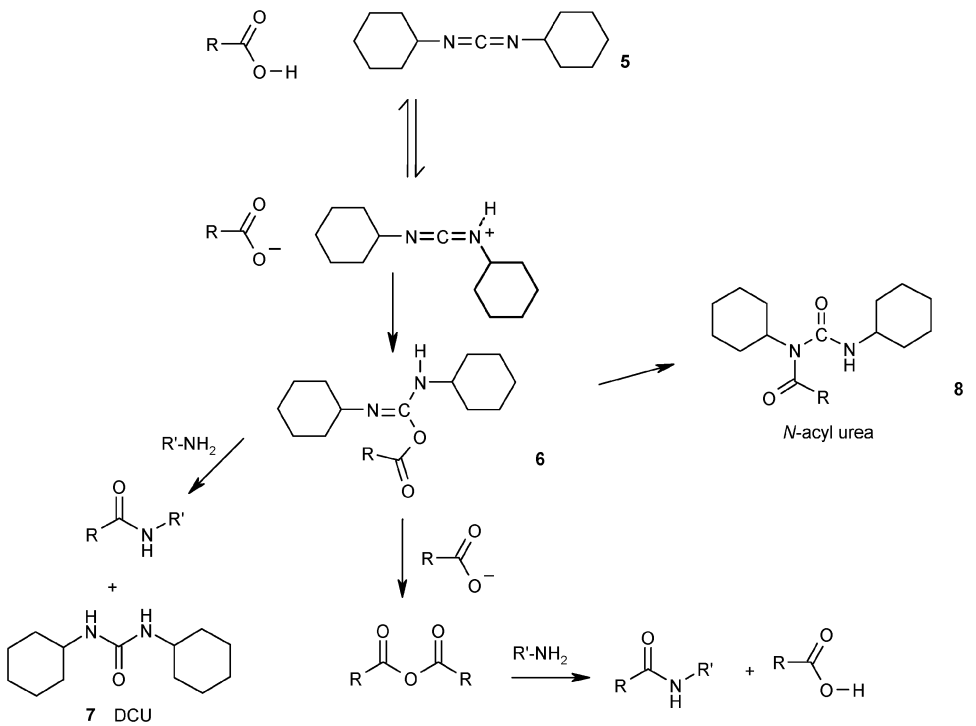
In order to reduce the epimerisation level when using carbodiimides as coupling reagents, Koenig and Geiger introduced 1-hydroxy-1*H*-benzotriazole (HOBt) **9** as an additive,[24,25] showing that, when using this additive, yields were higher and epimerisation levels lower. For example, when coupling Z-Gly-Phe-OH to H-Val-OMe, the epimerisation levels dropped from 35% to 1.5%.

HOBt **9** is believed to work by initially reacting with the *O*-acylurea **6** to give the OBt active ester **10**, which enhances the reactivity of the "activated ester" by encouraging/stabilising the approach of the amine *via* hydrogen bonding (Scheme 3). However, HOBt can yield by-products, thus it catalyses the formation of diazetidine **11** (Scheme 4).[26]

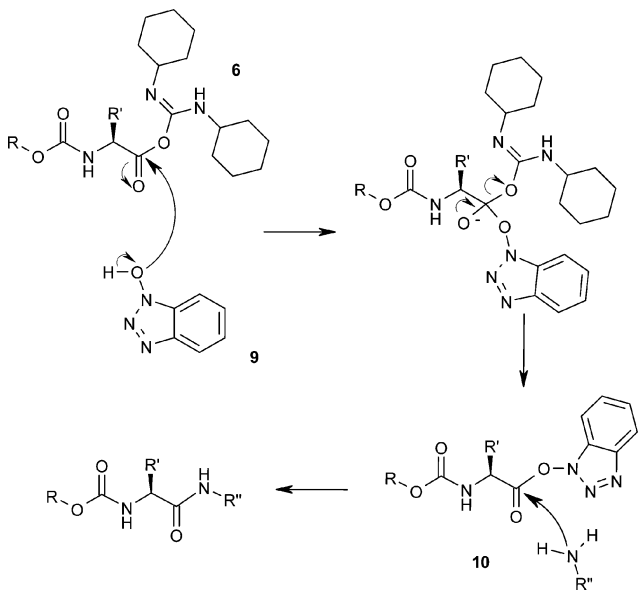
In 1994, Carpino reported a related additive, 1-hydroxy-7-azabenzotriazole (HOAt) **12** (Fig. 2), which was even more efficient than HOBt **9** in terms of yield, kinetics and reduced epimerisation levels.[27] For example epimerisation during coupling of Z-Val-OH and H-Val-OMe using DCC **5** dropped from 41.9% with HOBt **9** to 14.9% with HOAt **12**, while during the coupling of Z-PheVal-OH to H-Ala-OMe using

Table 1 Common epimerisation tests used for coupling reagent evaluation involving amino acids

Entry	Author	Acid	Amine	Analysis method
1	Young[15]	*Z*-Leu-OH	H-Gly-OEt	Optical rotation
2	Weinstein[16]	Ac-Phe-OH	H-Ala-OMe	NMR
3	Bodansky[17]	Ac-*iso*Leu-OH	H-Gly-OMe	Chiral HPLC
4	Anteunis[18]	Z-Gly-Phe-OH	H-Val-OMe	HPLC or NMR
5	Anderson[19]	Z-Gly-Phe-OH	H-Gly-OEt	Fractional crystallisation
6	Izumiya[20]	Z-Gly-Ala-OH	H-Leu-OBz	Hydrogenation followed by HPLC



Scheme 2 Coupling using DCC.



Scheme 3 Mechanism of activation by 1-hydroxy-1*H*-benzotriazole when used as an additive with DCC.

EDC, it dropped from 4.1% with HOBt **9** to under 2% with HOAt **12**.[27]

Much work has been carried out on the benefit of using additives. In particular, Carpino studied various isomers of HOAt concluding that the 7-isomer was the most efficient.[28] Albericio also showed that copper(II) complexes with HOAt **11** or HOBt **9** were efficient additives in lowering the epimerisation level.[29]

However, safety considerations when using benzotriazoles (and variants) need to be carefully considered as these compounds display explosive properties.[30,31]

1.3. Other carbodiimides

Since the application of DCC to amide bond formation, many carbodiimides, including DIC **13** (diisopropylcarbodiimide), have been reported and this field has been reviewed.[26] In particular, attention has focused on so-called water-soluble carbodiimides, as the ureas formed when using DCC **5** or the popular diisopropylcarbodiimide DIC **13** can sometimes be difficult to remove. Sheehan investigated several derivatives **14–17**, and concluded that coupling was more efficient when using tertiary amine carbodiimides rather than quaternary derivatives (*e.g.* **14** > **16**).[32,33]

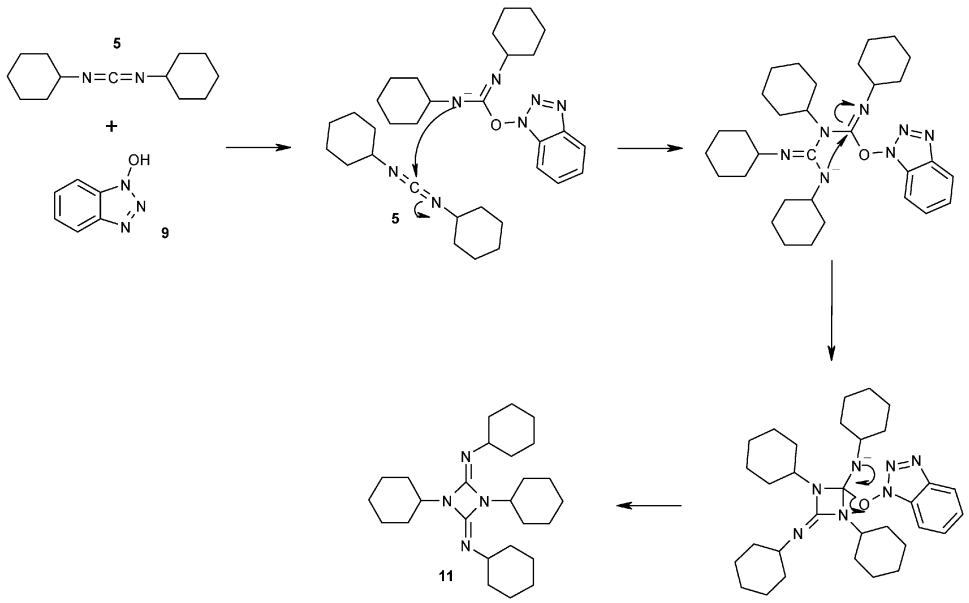
Carpino compared DIC **13** to EDC **20** and analogues **18–19**,[34] and also compared DIC **13** to some unsymmetrical alkyl/aryl carbodiimides such as phenyl ethyl carbodiimide (PEC **21**) and phenyl isopropyl carbodiimide (PIC **22**) (Fig. 3, Table 2). Overall, when using HOAt as an additive, DIC gave the best results for peptide segment coupling.

Other carbodiimides, BMC **23** and BEC **24** have been proposed by Izdebski, but these reagents showed no benefit over DIC **13**.[35]

Another so-called "water extractable" carbodiimide, BDDC **25** was synthesised and its efficiency was comparable to DCC **5** and EDC **20**.[36]

2. Coupling reagents based on 1*H*-benzotriazole

Several "salts" are often associated with reagents based on 1*H*-benzotriazoles, including uronium/aminium, phosphonium and immonium salts (Fig. 4).



Scheme 4 Formation of the diazetidine by-product when using DCC/HOBt.

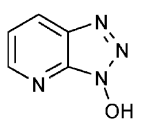


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Fig. 2 Structure of 1-hydroxy-7-azabenzotriazole.

2.1 Uronium/aminium salts

Many coupling reagents are based on the HOBt/HOAt system and uronium/aminium salts.[37] Uronium **26** and aminium **27** isomers of these reagents have been structurally identified and the true forms is probably a mater of debate depending on solvent, isolation method and counter anion *etc*. (Fig. 5).[38] Coupling reagents based on uronium salts were first reported as the *O*-isomer (**26**). However, Carpino showed by X-ray crystallography that HATU **28a** and HBTU **28b** were in fact the *N*-isomer (**27**).[38]

These reagents react with carboxylic acids to form OAt/OBt active esters, which then react with amines (Scheme 5).

A side-reaction can often take place with the amine reacting with the coupling reagent to form a guanidinium by-product **29** (Scheme 6),[14] thus order of addition and timing are crucial.

Comparative studies using HBTU[39] **28b** and TBTU[40] **30b** showed that the counter-anion had no practical influence on the outcome of coupling reactions using these reagents (Fig. 6). Carpino showed that the best results were obtained with HOAt, and many coupling reagents started to be based on this additive such as HATU **28a** and TATU **30a**.[27] It has been proven that coupling reagents based on HOAt (compared to HOBt) give faster, more efficient couplings with less epimerisation.[41] Much work has been carried out with variation of the substituents, yielding HAPyU **31** (also named BBC by Chen[42]) and TAPipU **32** with relatively little impact on the outcome of couplings.[43] Other modifications include HAPipU[37] **33a**, HBPipU[44] **33b**, HAMDU[37] **34a**, HBMDU[37] **34b** (also named BOI), and HAMTU[37] **35**. Overall the structural differences between these reagents did not appear to be based on rational considerations and were merely a screening of different substituents. Reagents **33–35** gave poor coupling results because the reagents were too reactive and degraded before coupling could take place.

Carpino modified the HOAt ring to form 5,6-benzo (**36**) and 4,5-benzo (**37**) derivatives,[45] which showed no real benefit over classical methods. In fact when used as additives with DIC, the epimerisation was higher than when using HOAt as additive.

More recently, derivatives HCTU **40a** and TCTU **40b** based on 6-chloro-HOBt were developed by Albericio,[46] but these reagents have not been directly compared to other coupling reagents.

Scientists at Argonaut also reported a 6-chloro-HOBt-based reagent, ACTU **40c**,[47] which was compared to DIC **13**. Some results were very disappointing as a simple, unhindered acid (phenylacetic acid) was only activated to 36%. This result was only improved to 70% when using an excess of acid, demonstrating that ACTU is a fairly poor coupling reagent.

Recently El-Faham developed some new reagents based on ''immonium salts''.[48] However, according to the terminology used in coupling reagents, these belong to the aminium/uronium salt-based class. Based on HOAt-/HOBt-rings, HAM_2PyU **41a**, HBM_2PyU **41b**, HAM_2PipU **42a**, HBM_2PipU **42b**, HAE_2PyU **43a**, HBE_2PyU **43b**, HAE_2PipU **44a**, HBE_2PipU **44b**, HATeU **45a** and HBTeU **45b** were synthesised. El-Faham firstly investigated the stability of these new reagents both in solution and in the solid state. Solids and solutions (in DMF) were stable for 3–4 weeks when kept under an inert atmosphere. However, like most coupling reagents, the reagents degraded rapidly when left in solution in the presence of a base. Thus, coupling involving hindered or poorly reactive substrates can be expected to be poor as longer reaction time are typically required for these substrates. Efficiency of the reagents was tested by measuring the

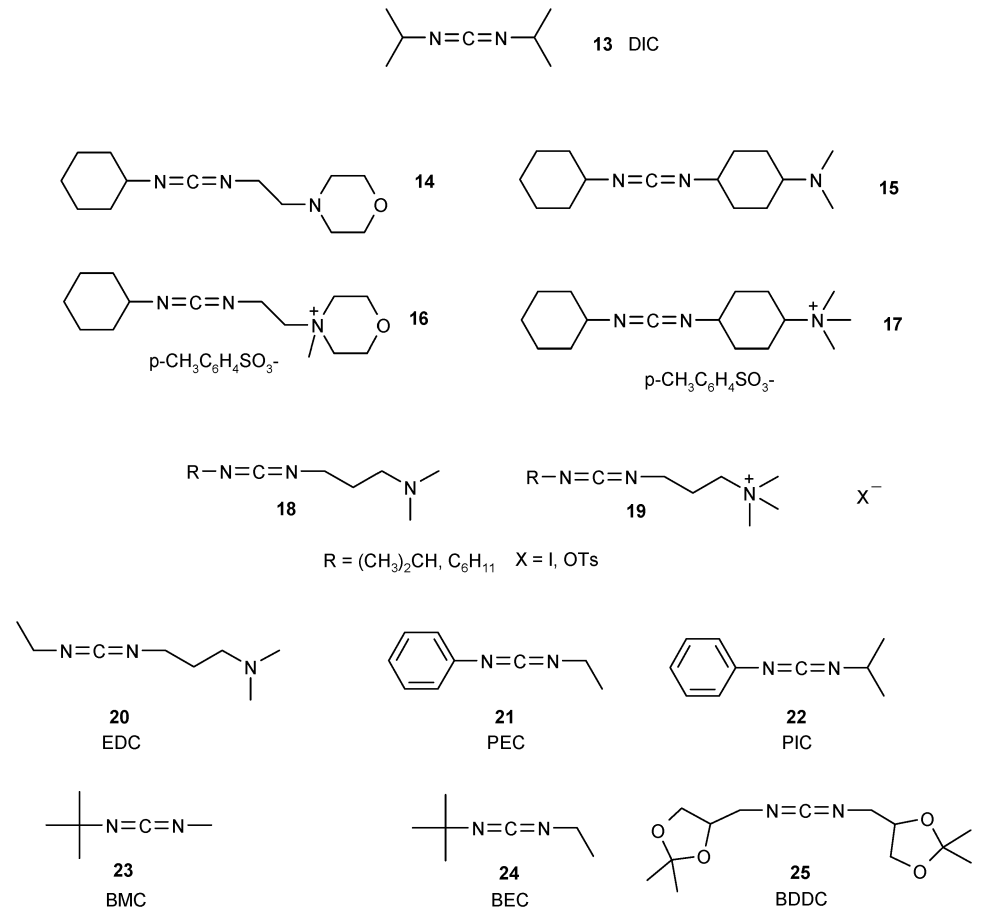
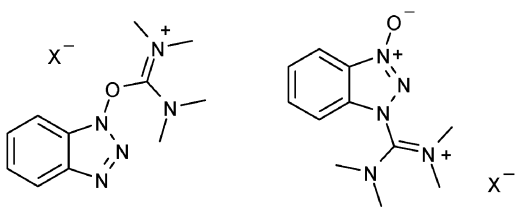


Fig. 3 Structure of some common carbodiimides.

Table 2 Results obtained when coupling Z-Phe-Val-OH to H-Pro-NH_2 with various carbodiimides and HOAt as an additive[34]

Entry	Coupling reagent	Yield (%)	LDL (%)
1	DIC	86	2.1
2	PEC	91	5.6
3	PIC	89	9.6
4	EDC	85	4.7
5	EDC·HCl	81	4.1



26 **27**

Fig. 5 Aminium and uronium isomers.

half-life of the activated esters of Z-Aib-OH in the presence of 4-chloroaniline. HOAt-based reagents HAM_2PyU **41a**, HAM_2PipU **42a**, HAE_2PyU **43a**, HAE_2PipU **44a**, HATeU **45a** reacted more quickly than the HOBt-based reagents HBM_2PyU **41b**, HBM_2PipU **42b**, HBE_2PyU **43b**, HBE_2PipU **44b**, HBTeU **45b**. However no yields were given, which makes the direct comparison of the reagents impossible. Indeed, the activated esters might be hydrolysed rather than coupled to the poorly nucleophilic 4-chloroaniline. Epimerisation was low (Anteunis test) when the reagents were used in the presence of collidine but was as high as 11.8% in the presence of DIPEA when using HBTeU **45b**. Overall it was not evident

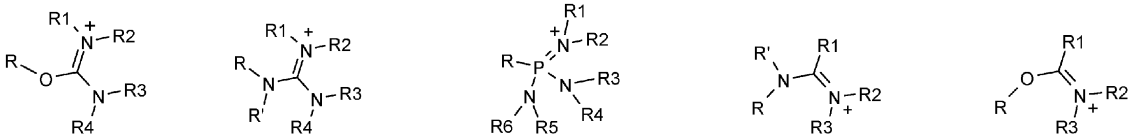
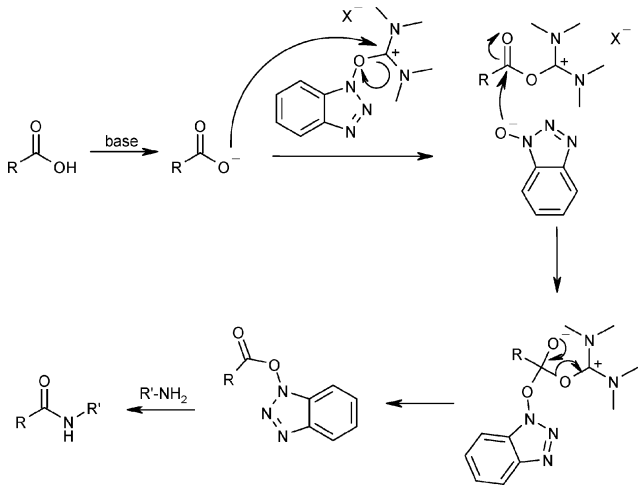
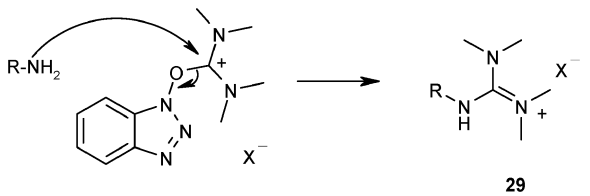


Fig. 4 Salts associated with reagents based on 1*H*-benzotriazole.



Scheme 5 Activation process using uronium/aminium type reagents.



Scheme 6 Guanidinium formation with aminium/uronium type coupling reagents.

that any of the new reagents reported were beneficial over a reagent like HATU **28a**.

Recently, El-Faham reported further development of such coupling reagents.[49] HDMA **46a**, HDMB **46b**, and 6-HDMCB **47** were evaluated and little variation on epimerisation levels was noticed, but HDMA **46a** proved to give higher yields for the synthesis of Fmoc-Val-Val-NH_2 compared to HATU **28a**. Other reagents such as 6-HDMFB **48**, 4-HDMA **49**, HDMTA **50a** and HDMTB **50b** were also synthesised.[50] Overall there was hardly any difference between the different reagents. HDMB **46b** displayed the best hydrolytic stability while having better solubility than HATU **28a**. Morpholino derivatives HDMA **46a** and HDMB **46b** showed better efficiency than their thio analogues HDMTA **50a** and HDMTB **50b**.

2.2 Phosphonium salts

Another family of coupling reagents based on HOBt/HOAt uses a phosphonium group. Phosphonium salts have the advantage of not yielding guanidinium by-products *via* reaction of the coupling reagent with amines. The first HOBt/HOAt-phosphonium salt introduced was BOP **51b**,[51] but its use has been limited due to the carcinogenicity and respiratory toxicity associated with HMPA generated when BOP **51b** is used in coupling reactions, leading to the development of the pyrrolidino derivative PyBOP **52b**.[52] Carpino prepared AOP[37] **51a** and PyAOP[37,53] **52a** and compared them to BOP **51b** and PyBOP **52b**, and showed that the aza-derivatives were more reactive.

For the synthesis of thioamides, Hoeg-Jensen developed phosphonium coupling reagents based on 6-nitro HOBt (Fig. 7).[54] PyNOP **53**, PyFOP **54** and NOP **55** were used successfully for the formation of thioamides, with good thioamide/amide selectivity but their solubility in organic solvents was poor. Moreover, the results obtained with PyBOP were very similar to PyNOP **53**, PyFOP **54** and NOP **55**.

In a recent patent, PyClock **56** was disclosed as a new coupling reagent.[55] However hydrolysis was shown to be worse than PyBOP **52b** in the absence of base after 6 h and this was also worse in the presence of a tertiary base as around 88% had been hydrolysed after 1 h compared to 81% for PyBOP **52b** under these conditions. The efficiency of PyClock **56** was evaluated *via* the solid-phase synthesis of three pentapeptides which incorporated hindered/*N*-methylated aminoacids (Table 3).

2.3 Immonium salts

Li designed and synthesised immonium/carbonium type coupling reagents,[56,57] such as BOMI **57**,[56,58–61] BDMP **58**,[56,60,61] BPMP **59**, BMMP **60**, and AOMP[56,59] **61** (Fig. 8). BOMI **57** and BDMP **58** showed the best results, achieving >90% conversion within 10 min during the coupling of Z-Gly-Phe-OH with H-Val-OMe (Anteunis test). In addition, epimerisation was low, BOMI **57** displaying 3.1% and BDMP **58** 2.3% of the DL-isomer. However, these reagents were not compared to classic reagents such as HATU **28a** or PyBOP **52b**. As an application, these reagents were used to carry out the total synthesis of Cyclosporine O, an immunosuppressive agent.[62]

2.4 Other reagents

DepOBt (originally called BDP) **62b** was reported by Kim (Fig. 9).[63] The reagent appeared to couple aniline to benzoic acid or phenylacetic acid in high yield, and also aminoacids (Phe, Val, Met, Ile) to other amino acids (Gly, Ser, Val) in high yield although *N*-Methylated substrates were not tested. Epimerisation was evaluated *via* Young's test and found to be low. The same group reported DpopOBt **63b** but epimerisation was high.[64]

Carpino reported DepOAt **62a**, DpopOAt **53a**, DmppOAt **64**, DtpOAt **65a** and DtpOBt **65b**.[65] Again, no real improvement was gained compared to HATU **33a**. For the synthesis of ACP(65-74), HATU **33a** outperformed any of these reagents. An epimerisation study for the coupling of Z-Phe-Val-OH and H-Pro-NH_2 showed that DmppOAt **64** (3.6% of LDL isomer) and DtpOAt **65a** (2.9%) gave less epimerisation than HATU **28a** (5.0%), while DtpOBt **65b** was worse (11.4%), but no explanation was given.

HAPyTU **66**, a thio-analogue of HAPyU **31**, was tested by Klose but proved to be unsuccessful as yields were lower and epimerisation higher than HAPyU **31**.[66]

Another type of reagent based on sulfonates was developed by Itoh.[67] These reagents **67–70** incorporated HOBt or HOCt (6-chloro-HOBt) with different substituents on the sulfonate. The best results were obtained with HCSCP **70**, the chlorine group enhancing the reactivity of the reagent. However, the reagents were not compared directly to each other. Compared to DCC **5** (without using HOBt), these reagents gave less side-reactions and the by-products were easily removed during aqueous workup. According to the authors, epimerisation was

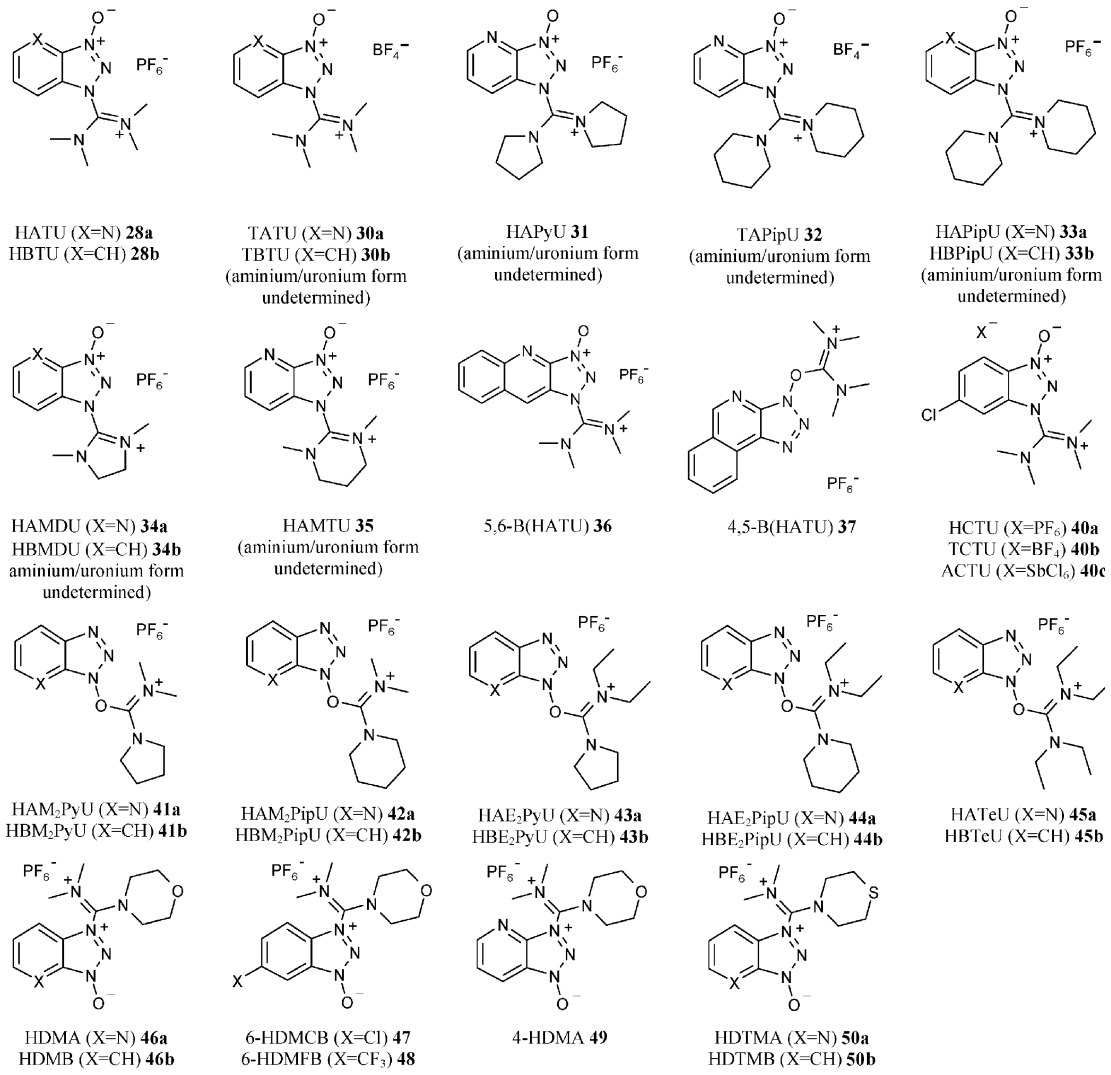


Fig. 6 Uronium/Aminium-based coupling reagents.

lower than with DCC **5**, but this was no surprise as DCC alone give very high levels of epimerisation.

2.5 Conclusion on 1*H*-benzotriazole-based reagents

1-*H*-benzotriazole-based reagents probably represent the widest class of coupling reagents. Although differences in reactivities have been reported by their authors, there is practically very little difference, as exemplified by Hachman,[68] and HBTU **28b** or TBTU **30b** are reagents which usually perform very well. Surprisingly, the potential explosive properties of these reagents is almost always disregarded.[30,31]

3. Reagents generating acid halides

3.1 General reagents used in organic chemistry and triazine-type reagents

Fischer reported the first synthesis of a dipeptide (Gly-Gly) in 1901 using acid chlorides for coupling.[69] The general approach consisted of using reagents such as thionyl chloride or phosphorus pentachloride to generate the acid chloride which reacted quickly with amines to form amides. This original method was quite harsh and not compatible with many protecting groups. It has however been adapted by Carpino to synthesise peptides *via* a Fmoc strategy.[70] Triphosgene has also been reported to generate amino-acid acid chlorides,[71] especially useful for hindered substrates.[72] Similarly, acid cyanides and azides have been used to synthesise amides.[73]

Cyanuric fluoride **71** can be used to synthesise acid fluorides,[74] which couple *N*-methylated amino-acids very efficiently. A variety of other reagents have been reported for the formation of acid fluorides, and include Deoxo-Fluor **72** and DAST **73** (Fig. 10).[75] However a side-reaction is observed when using Deoxo-Fluor **72** especially with hindered amines (Scheme 7), which limits the applicability of this reagent. In addition, Deoxo-Fluor **72** and DAST **73** are expensive and hazardous reagents, and purification by chromatography is required after reaction.

Part of this category of reagents is based on triazines (cyanuric fluoride, chloride and derivatives) and has been reviewed in details by Kaminski.[76] The mechanism of activation involves the generation of an acid halide moiety

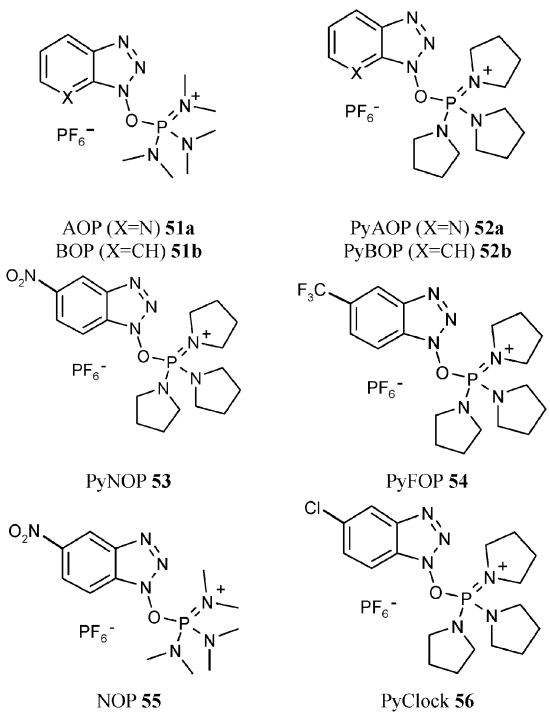


Fig. 7 Phosphonium type coupling reagents.

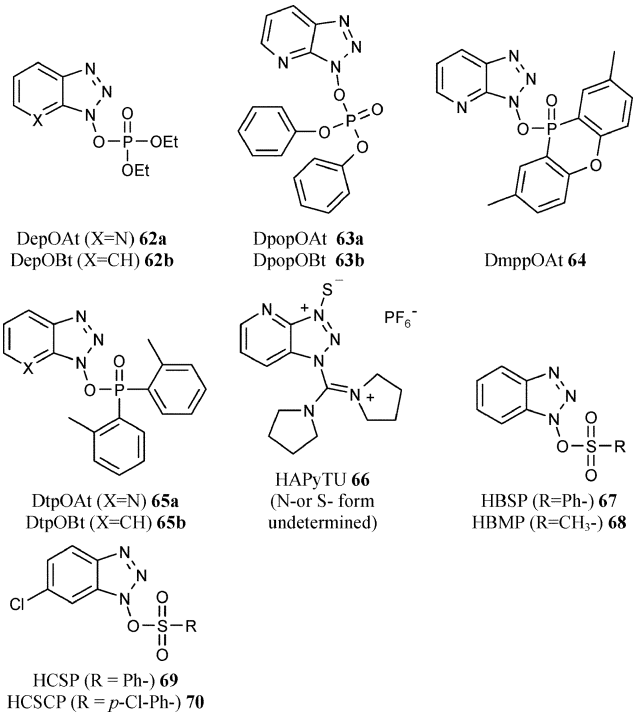


Fig. 9 Other coupling reagents based on 1-hydroxybenzotriazole and 1-hydroxy-7-azabenzotriazole.

Table 3 Comparison of pentapeptides yield when using PyClock **56** and PyBOP **52b**

		Yield (%)	
Entry	Amine	PyClock	PyBOP
1	H-Tyr-NMeVal-Phe-Leu-NH_2	11	0
2	H-Tyr-Aib-Aib-Phe-Leu-NH_2	97	83
3	H-Tyr-Arg-Arg-Phe-Leu-NH_2	85	75

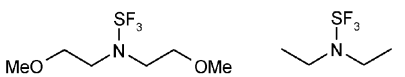


Fig. 10 Structure of Deoxo-Fluor **72** and DAST **73**.

(Scheme 8). Thus CDMT **74** and DCMT **75** (2,4-dichloro-6-methoxy-1,3,5-triazine) have been successfully applied in the synthesis of acid anhydrides (Fig. 11).[77]

3.2 Halo-uronium and halo-phosphonium type reagents (Fig. 12)

TFFH **76a**,[78] BTFFH **77**,[78,79] and DFIH[78] **78a** have been used to generate acid fluorides with amino acids such as histidine and arginine since the activated form of Fmoc-Arg-OH underwent deactivation *via* lactam formation when using cyanuric fluoride.[78] PyFloP **79a** did not yield any acid fluoride.[78] Interestingly, TFFH **76a** (100% coupling after 10 min) gave better results than the analogues TCFH **76b** (86%) and TBFH **76c** (79%), for the coupling of Fmoc-Val-OH to H-Ile-PEG-PS,[78] but overall, BTFFH **77** gave the best conversions.[79]

El-Faham synthesised three acid fluoride generating reagents: DMFFH **80**, DEFFH **81** and TEFFH **82**,[48] but these were poorly stable to hydrolysis in the presence of a base (most of the reagent hydrolysed within 1 h). The reactivity of these reagents was studied by monitoring acid fluoride formation for various hindered and unhindered amino acids, and all three reagents were shown to be less reactive than TFFH **76a** or BTFFH **77**.

Reagents aimed at generating acid chlorides or bromides under milder conditions than thionyl chloride have been targeted. BroP **83a** was first synthesised by Coste,[80] followed by PyBroP **79b** and PyCloP **79c**.[81] These reagents were shown

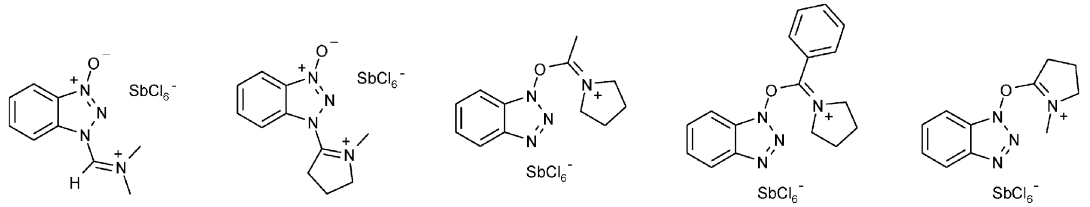
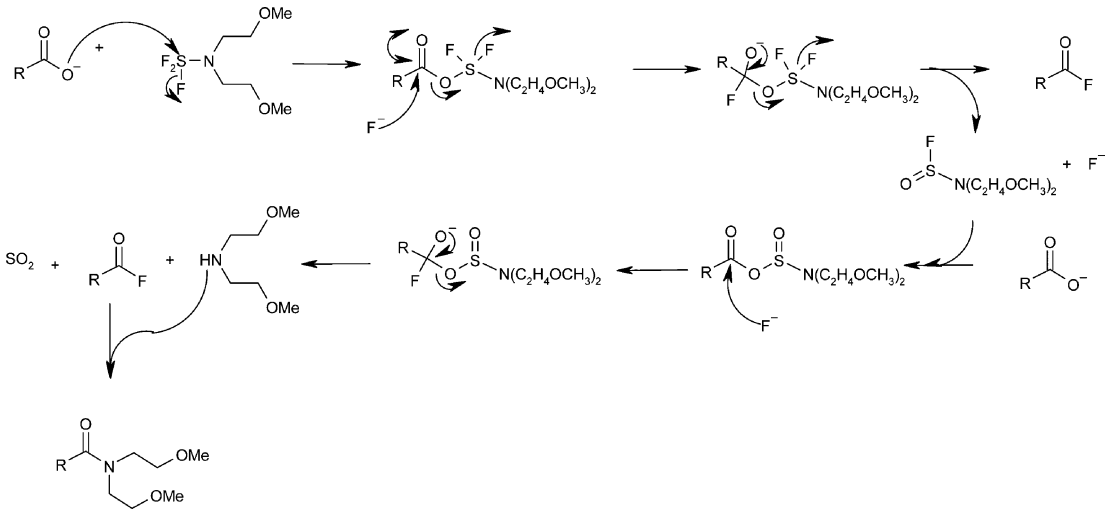
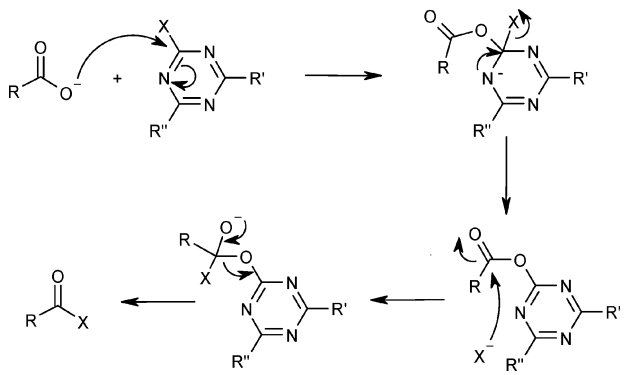


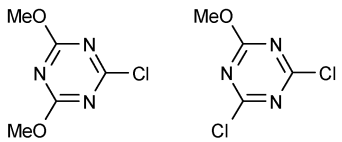
Fig. 8 Immonium type coupling reagents.



Scheme 7 Side-reaction observed during the activation process when using Deoxo-Fluor.



Scheme 8 Formation of acid halides when using triazines as coupling reagents.



CDMT **74** DCMT **75**

Fig. 11 Coupling reagents based on triazines.

to be more efficient that PyBOP **52b** in coupling *N*-methylamino acids. PyClU **84**, also synthesised by Coste, gave high yields when coupling hindered amino acids,[81] while DCIH **78b** (named CIP originally) gave comparable results to PyBroP **79b** and PyCloP **79c**.[82] One of the drawbacks of PyBroP **79b**, PyCloP **79c** and DCIH **78b** is the established formation oxazolones. CloP **83b** was reported by Castro and shown to give low levels of epimerisation *via* Young's test.[83]

PyClopP **85**, an analogue of PyCloP **79c**, was reported by Li in an attempt to increase reactivity by replacing a pyrrolidine ring with a phenyl group. The reagent was reported as being efficient for hindered peptide synthesis, but no results were given to illustrate this fact.[57]

BOP-Cl **86** is a reagent that has been widely used in peptide synthesis,[84] and was in particular reported as being suitable for coupling hindered substrates,[85] but it has the major drawback of capping primary amines.[86]

Other reagents include CDTP[87] **87** and CMMM[84] **88**, but these reagents, like PyBroP **79b** and PyCloP **79c**, usually give high epimerisation during coupling. CMMM **88** was also compared to other reagents such as FEP **96b**, and gave poor results with coupling times of over 2 h and epimerisation of over 30% (Anteunis test).[57]

DMC **89**, has been investigated as a coupling reagent.[88] It proved to be successful in the generation of some amides but questions of functional group compatibility are raised when considering its high reactivity. Recently, El-Faham tested DMFH **90a** and DMCH **90b**. DMFH **90a** was really efficient for coupling the hindered Aib amino acid to a tripeptide Aib-Phe-Leu. The tetrapeptide was synthesised on solid phase in 99% yield compared to 68% for HATU **28a**,[50] but complete scope of this reagent was not investigated. DMCH **90b** on the other hand performed poorly.

3.3 Halo-sulfonium, halo-dioxolium and halo-dithiolium coupling reagents

Li synthesised other types of coupling reagents, including CDMS **91**, CBDO **92** and CPDT **93** (Fig. 13).[57] However these reagents were far too reactive and decomposed in solution before activation could take place.

3.4 Halo-thiaziolium and halo-pyridinium type reagents

Li designed reagents based on thiazolium and 2-halopyridinium salts. Their design was based on the fact that, in halouronium type coupling reagents, the carbocation is well stabilised *via* the electron pairs on the amine groups. Therefore, the carbocation shares a relatively high electron density and the uronium salt demonstrates relatively low reactivity in the addition of the carboxylic acid. For this reason Li attempted to replace one nitrogen group with other groups without lone pairs or more electronegative groups with lone pairs to enhance the reactivity of the reaction-mediated carbocations. The first attempt to replace nitrogen with sulfur yielded thiazolium reagent, BEMT **94**.[89] The same type of

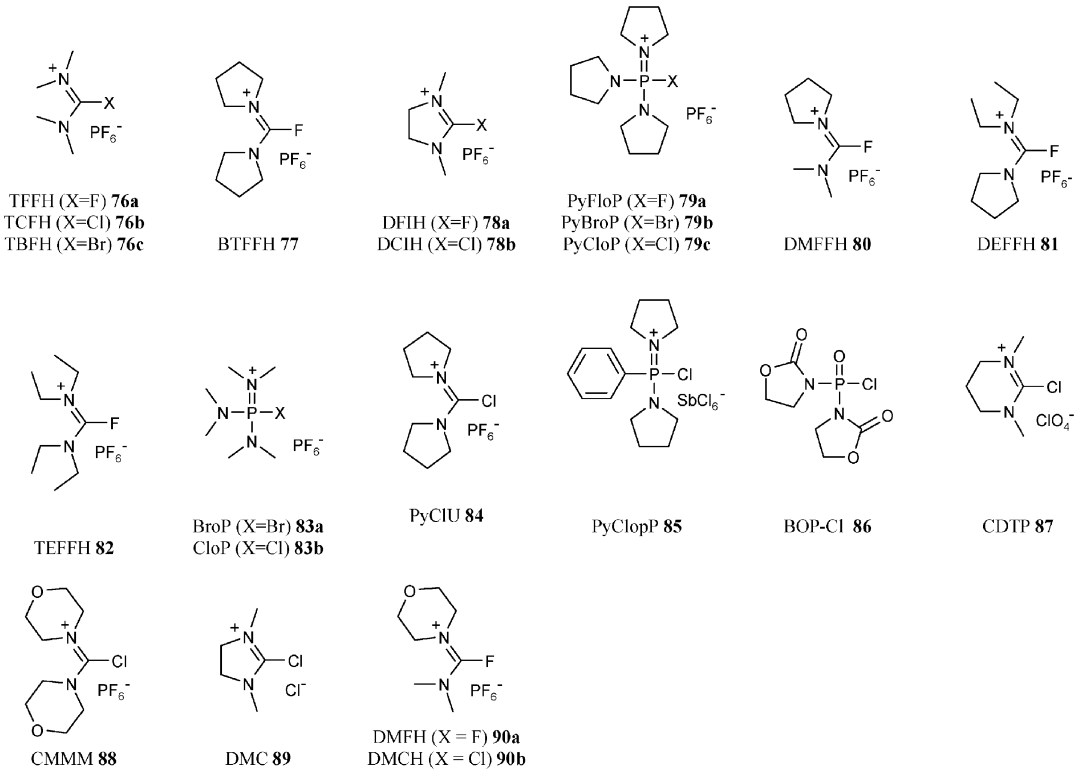


Fig. 12 Halo-uronium and halo-phosphonium type reagents.

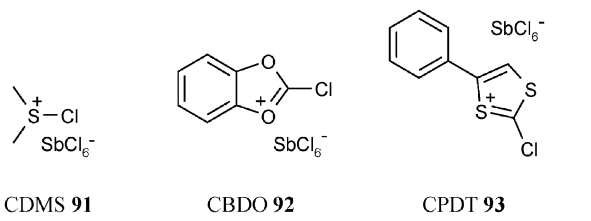
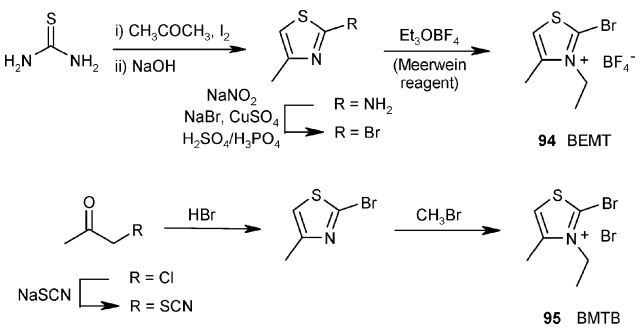


Fig. 13 Halo-sulfonium, halo-dioxolium and halo-dithiolium type reagents.



Scheme 9 Synthesis of BEMT and BMTB.

reagent, BMTB **95**, was proposed by Wischnat (Scheme 9).[90] BMTB **95** performed better than HATU **28a** in coupling Boc-*N*(Me)-Ile to *N*(Me)-Ile-OBn. However BMTB **95** was not compared to BEMT **94**.

Li reported 2-halopyridinium salts such as BEP **96a**, FEP **96b**, BEPH **97a** and FEPH **97b** (Fig. 14).[91] Mukaiyama has extensively used 2-chloro- and 2-bromo-pyridinium iodide **98**

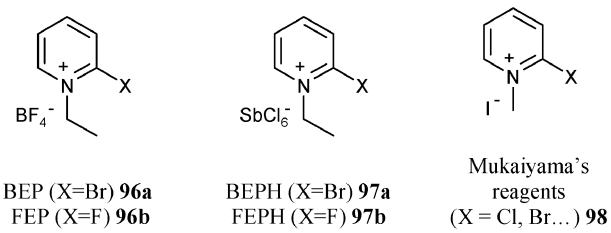


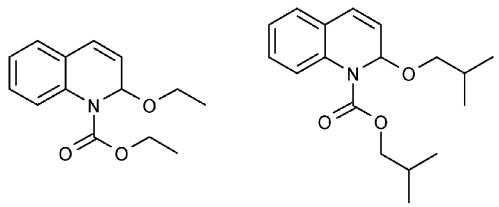
Fig. 14 Halo-pyridinium type reagents.

to synthesise esters, lactones and amides,[92] but the conditions used were not ideal for peptide synthesis, as reactions had to be performed at reflux in DCM due to the poor solubility of the reagents. For this reason Li used tetrafluoroborate and hexachloroantimonate counter anions to improve solubility, and chose the fluoro-analogues for higher reactivity. The efficiency of these reagents proved to be higher than BTFFH **77**, PyBrop **79b**, PyClU **84** or BOP-Cl **86**. However these reagents might be a bit too reactive as the base used during the coupling had to be added very slowly to avoid the coupling reagents reacting too violently. Thus side-reactions may be expected for some substrates.

4. Other coupling reagents

4.1 Reagents generating carbonic anhydrides (Fig. 15)

EEDQ **99**, was originally developed in 1967.[93] EEDQ **99** offers several advantages over most coupling reagents, as the reaction with an amine cannot yield a guanidinium salt, a typical side reaction observed with uronium type coupling



EEDQ **99** IIDQ **100**

Fig. 15 Structure of EEDQ and IIDQ.

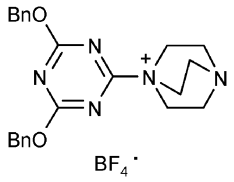


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Fig. 16 Structure of dibenzyloxytriazine **103**.

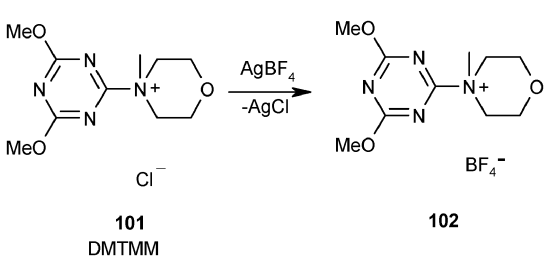
Table 4 Comparison of EEDQ and IIDQ

Entry	Amine	Acid	IIDQ yield	EEDQ yield
1	4-*tert*-Butylaniline	Phenylacetic acid	96	94
2	Benzylamine	Phenylacetic acid	91	87
3	Morpholine	Phenylacetic acid	38	32
4	4-*tert*-Butylaniline	Benzoic acid	88	85
5	Benzylamine	Benzoic acid	85	66
6	Morpholine	Benzoic acid	50	41
		Average	76	67

reagents. In addition, the carbonic anhydride is formed slowly but consumed rapidly, which avoids its accumulation and therefore minimises the possibility of side-reactions such as epimerisation, and it can also be used with unprotected hydroxy residues.[93] EEDQ **99** has thus been used for the synthesis of various amide derivatives.[94,95] Analogues of EEDQ **99** have also been successfully investigated such as IIDQ **100**, and a number of unsymmetrical reagents.[96] Not many comparison studies have been published, but IIDQ **100** proved, over a few examples, to perform slightly better than EEDQ **99** (Table 4).[97] Interestingly, when compared to other coupling reagents without activation, IIDQ **100** outperformed HATU **28a**, PyAOP **52a** and BOP-Cl **86**.[97]

4.2 Triazine-based reagents (not generating acid halides)

DMTMM **101** is a triazine derivative, which has the particular advantage of promoting amide synthesis in alcohols or aqueous media, without ester formation and with selectivity comparable to DCC **5** and EDC **20**.[98] Recently, a series of reagents based on DMTMM **101** was developed by Kaminski (Scheme 10).[99] *N*-Triazinylammonium salts were synthesised using different tertiary bases and the derivative incorporating



101 DMTMM **102**

Scheme 10 Exchange of counter anion on DMTMM **101**.

DABCO proved to give the best yield. However a full study was carried out on the *N*-methylmorpholine derivative **102**, because of its lower production cost. The reagent proved to be particularly efficient with high yields and low epimerisation levels. For the synthesis of the 65–74 segment of ACP, each coupling went faster (15 min.) than with TBTU **30b** (45 min) or HATU **28a** (30 min) and gave better purities (84%) than TBTU **30b** (69%).[99] Sulfonates of *N*-triazinylammonium salts were also synthesised, but a complete evaluation of these reagents was not reported.[100] The reagents were further optimised by replacing the methoxy groups by benzyloxy groups (Fig. 16).[101]

Remarkably, reagents such as triazine **103** proved to be stable in DMF with only 2.5% decomposition after 48 h. Comparison between the parent methoxy compounds (*e.g.* **97**) and the benzyloxy derivatives (*e.g.* **103**) showed that the later were more efficient for the synthesis of the 65–74 segment of ACP.

4.3 Pentafluorophenol (HOPfp)-based coupling reagents (Fig. 17)

These types of reagents are based on the traditional pentafluorophenol leaving group and the generation of active esters. They usually require the addition of HOAt as the level of epimerisation is quite high: when coupling Z-Phe-Val-OH to H-Pro-NH_2, 33.7% of the LDL isomer was observed in solution phase when using HPyOPfp **104a**, while epimerisation dropped to 1.7% when adding HOAt to the reaction mixture. The use of a thiophenol-analogue, HPySPfp **104b** did not change the outcome of the coupling reactions.[66] Like most reagents based on HOAt/HOBt, these reagents are not ideal for solution-phase chemistry as the use of an additive means that this has to be removed from the reaction mixture after coupling.

Li described a pentafluorophenyl immonium type reagent FOMP **105**,[56] but this reagent was not as efficient as the other immonium type reagents, based on HOBt/HOAt.

A reagent, PFNB **106**, was reported by Pudhom, but Boc-Gly-OH reacted slowly and incompletely and it was necessary to add HOBt to get good conversion.[102] In order to synthesise thioamides, Hoeg-Jensen synthesised PyPOP **107**, but this reagent was not as efficient as PyNOP **53** or PyFOP **54**.[54] Other reagents include FDPP **108**, which gave lower epimerisation levels than HBTU **28b**, BOP **51b** and DCC **5**.[103]

Recently, HDMPfp **109** was synthesised by El-Faham but the reagent proved to be outperformed by HATU **28a**.[50]

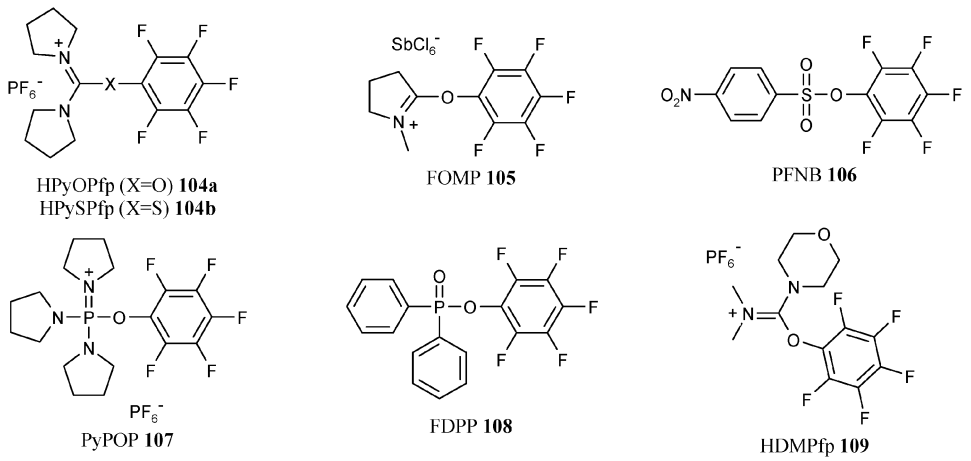
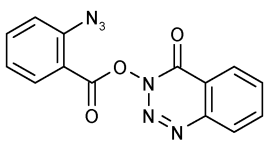


Fig. 17 Coupling reagents based on pentafluorophenol.



110

Fig. 18 Side-product formed when using HODhbt as additive.

4.4 Reagents based on 3,4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazine (HODhbt)

HODhbt was first mentioned in 1970 by Koenig who investigated over 30 *N*-hydroxy compounds as additives for peptide synthesis.[25] HOBt gave excellent results but HODhbt proved to be generally superior. However Koenig pointed out that the potential of HODhbt is limited due to inherent side reactions, in particular the formation of an azido-benzoyl derivative **110** (Fig. 18).

Knorr proposed the generation of a HODhbt based coupling reagent, synthesising TDBTU **111** (Fig. 19).[40] Although TDBTU **111** gave little epimerisation, its use was recommended only in critical cases because of the risk of side reactions. Indeed, ring opening of the 3,4-dihydro-4-oxo-1,2,3-benzotriazine ring can occur to form **110**, which can then react with amines. Another reagent, HDTU **112b**, where the counter ion of TDBTU **111** was replaced by hexafluorophosphate had similar efficiency to TBTU **30b**.[104] The disadvantage of HDTU **112b** has ever being its poor stability in DMF compared to classic reagents such as HATU **28a** as after 5 h HDTU **112b** had totally decomposed compared to less than 1% for HATU **28a**.[37]

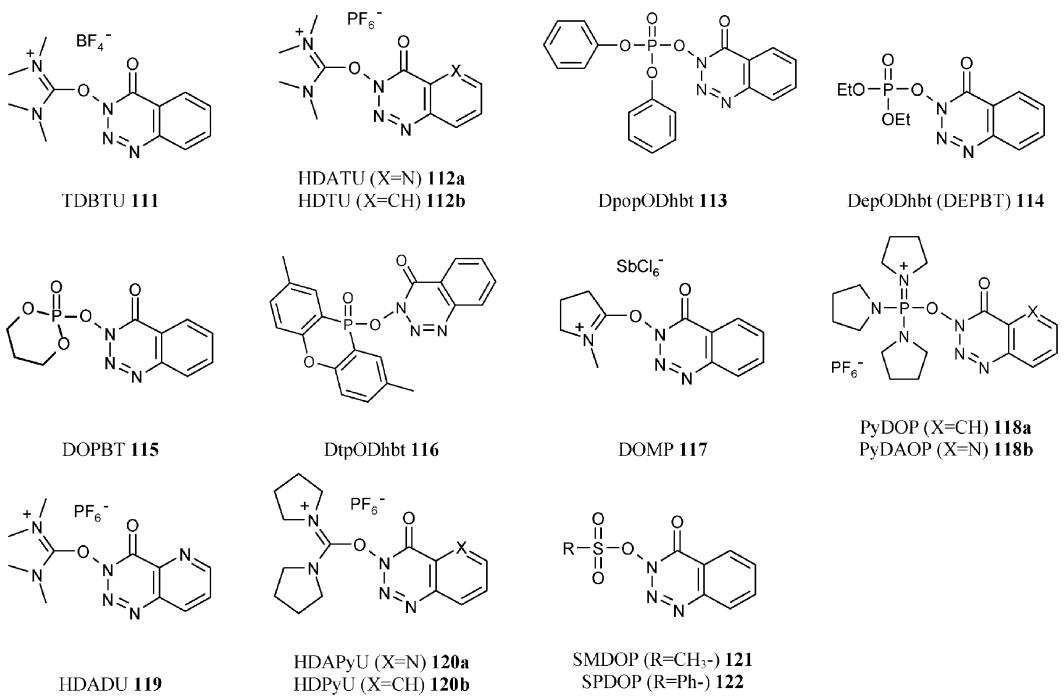


Fig. 19 Coupling reagents based on HODhbt.

Carpino compared some organophosphorus reagents to commonly used coupling reagents,[65] and showed that DpopODhbt **113** was comparable to HATU **28a** in terms of reaction times for the formation of the active ester of Z-Aib-OH (<2 min) but DepODhbt **114** (also named DEPBT by Ye[105,106]) was not as efficient (7–8 min). Similarly DOPBT **115** was poorer than DepODhbt **114**.[107] Another reagent, DtpODhbt **116** gave more epimerisation (4.3% of LDL isomer) than DepODhbt **114** (3.5%) but less than HATU **28a** (5.0%) when carrying out the coupling of Z-Phe-Val-OH and H-Pro-NH_2. The synthesis of the ACP decapeptide (H-Val-Gln-Ala-Ala-Ile-Asp-Tyr-Ile-Asn-Gly-NH_2) was used to show that DepODhbt **114** gave poor results (<1% yield) compared to HATU **28a** (85%).

Li also based immonium type reagents on HODhbt, but DOMP **117** showed very poor results for the coupling between Z-Gly-Phe-OH and H-Val-OMe with only 5.6% yield after 2 h compared to 95% for BDMP for example.[56] PyDOP **118a** was targeted for the synthesis of thioamides, but proved to be surpassed by PyNOP **53** or PyFOP **54**.[54]

More recently, Carpino developed coupling reagents based on aza-analogues of HODhbt,[65] and successfully synthesised HDATU **112a**, PyDAOP **118b**, HDADU **119**, HDAPyU **120a**, and HDPyU **120b**. As expected, derivatives of HODAhbt were more reactive than their HODhbt analogue. Thus, HDATU **112a** gave better results than HDTU **112b**, but was still less reactive than HATU **28a**. Moreover, results were more random for segment coupling as they depended on the system studied. However, in many cases, HDATU **112a** proved to be better than HATU **28a** for the solid-phase synthesis of ACP.

Itoh developed sulfonate reagents based on HODhbt.[67] The two reagents synthesised, SMDOP **121** and SPDOP **122** were however not as efficient as the other sulfonate reagents that this group synthesised, such as HCSCP **70**.

Overall, reagents based on 3,4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazine (HODhbt) do not appear to be more efficient that classical reagents like DIC **13**. Moreover, a critical issue regarding the safety of these materials has to be addressed due to the presence of the azide moiety.

4.5 Reagents based on 2-hydroxysuccinimide (HOSu) and 2-(5-norbornene–2,3-dicarboximide) (HONB) (Fig. 20)

Only a few reagents incorporating the hydroxysuccinimide leaving group have been synthesised. Knorr developed TSTU **123a** and its norbornene–dicarboximide analogue TNTU **124**, which showed high epimerisation levels without the use of additives.[40] Gruber reported HSTU (also called SbTMU) **123b**, but the reagent was not studied in detail as it was directly used for the preparation of thiol-reactive Cy5 derivatives.[108]

Other examples are SOMP[56] **125** and SOMI[57] **126** developed by Li, and similar other immonium type reagents, but they gave poor results.

Phosphate-based succinimide coupling reagents such as NDPP[109] **127** and SDPP[110] **128** have also been developed. The use of ENDPP **129** proved to be a better method than the isobutylchloroformate method because it could be performed

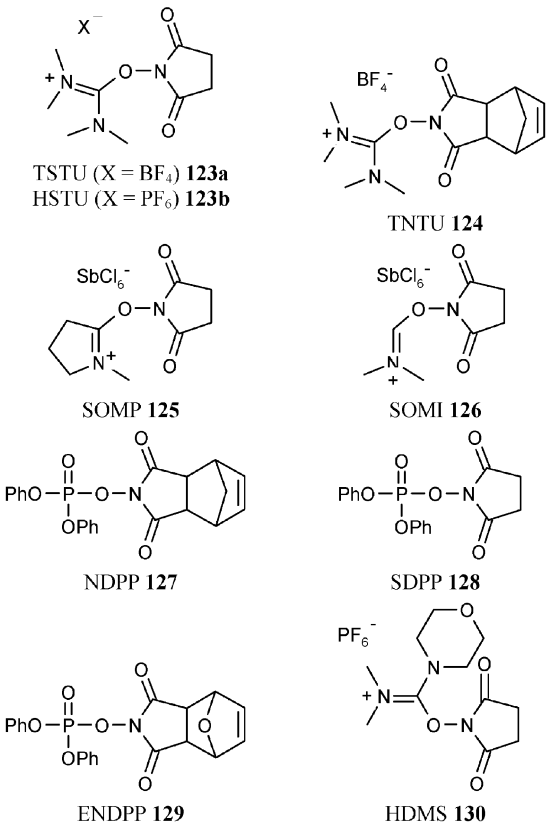


Fig. 20 Coupling reagents based on HOSu and HONB.

at room temperature, but no other comparison was reported. Similarly, SDPP **128** was only reported as being a "more convenient method" to use than DCC **5**.

El-Faham reported the use of HDMS **130**, which was based on a morpholino uronium salt.[50] The reagent proved to be less efficient than the HOAt/HOBt based analogues HDMA **46a** and HDMB **46b**.

4.6 Phosphorus-type reagents (not based on HOAt, HOBt, –OPfP, –OSu, and –ODhbt) (Fig. 21)

PyTOP **131** was developed by Hoeg-Jensen for the formation of thioamides but the reagent gave poorer selectivities than PyNOP **53** or PyFOP **54**.[54]

The possibility of using DPP-Cl **132** was first investigated with success by Jackson,[111] who claimed that NMR proved that no epimerisation was observed,[112] although this result is quite surprising, as epimerisation is usually high when acid chlorides are generated.

Other derivatives have also been synthesised and include the azide analogue DPPA **133a**,[113] and cyano analogue DECP **134**, which gave good coupling yields but with many side-reactions *via* the cyanide.[114] Dpop-Cl **133b** was also tested but poor results were observed without the use of an additive.[65] Similarly DEPC[115] **135a** and DEPB[116] **135b** typically give side reactions due to the release of the reactive halogen atom.

Reagents based on the same principle, Cpt-Cl[117] **136**, MPTA[118] **137a**, Mpt-Cl[119] **137b**, MPTO[118] **138**, and BMP-Cl[120] **139**, appeared overall to have similar efficiencies to reagents such as DPP-Cl **132**.

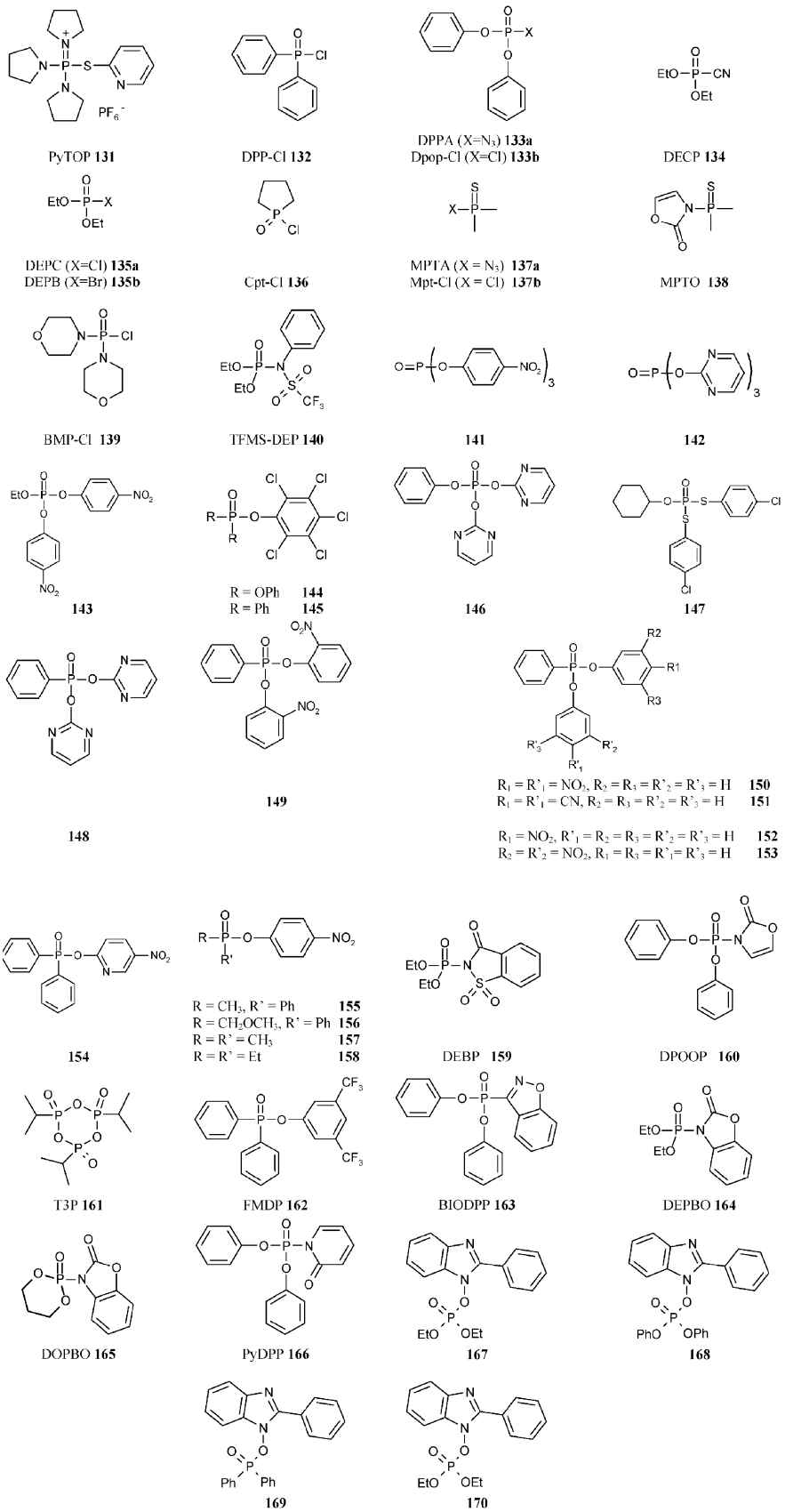


Fig. 21 Other phosphorus-based reagents.

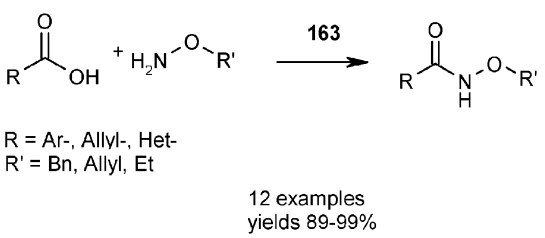
Another coupling reagent TFMS-DEP **140** was produced by activating diethylphosphate with trifluoromethanesulfonalide.[121] Using 1.2 equiv. of coupling reagent, hindered *tert*-butylamine was coupled in 89% yield to acetic acid. Other examples showed goods yields, typically over 80% yield, including a secondary amine (*N*-methylbenzylamine) and two anilines (*N*-methylaniline and aniline). Application for peptide synthesis was studied by carrying out Young's test, which showed 2% epimerisation. Also, the difficult synthesis of Z-Aib-Aib-OMe proved to be successful affording the product in a satisfactory 70% yield.

A wide range of phosphorus-based coupling reagents **141–153** were investigated by Mukaiyama.[122] Using Young's test as model reaction, it was concluded that the bis(nitrophenyl) phenylphosphonates **149** and **150** gave the best results. Further studies, using this time phosphinic esters **154–158** showed that (5-nitropyridyl)diphenylphosphinate **154** was an efficient coupling reagent, giving 92% of the expected dipeptide in Young's test, with less than 2% epimerisation.[123]

DEBP[124] **159** and DPOOP[125] **160** have been proposed as coupling reagents, but for both reagents, examples were limited to a few dipeptides and were not compared to any classical methods. T3P **161** was claimed to be more efficient than HAPyU **31** for head-to-tail cyclisation of hindered peptides.[126] However, the use of T3P may be limited as yields were lower and epimerisation higher than HAPyU when segment coupling studies were carried out.

Other reagents include FDMP **162**, which gave poor results (2% yield compared to 84% yield for BEMT when coupling Z-Gly-Phe-OH to H-Val-OMe),[57] BIODPP **163**, which gave amides in good yields but was not compared to any other coupling reagent,[127] and DEPBO **164** and DOPBO **165**, which proved to be not as efficient as DepODhbt **114**.[107] PyDPP **166** was reported as giving low epimerisation rates, but was not compared to other coupling reagents.[128]

Kokare reported three new reagents **166–169** based on phosphate derivatives of 1-hydroxy-2-phenylbenzimidazole.[129] The reagents gave in most cases similar results and yields over a wide range of substrates (*e.g.* 4-nitrobenzoic acid, cinnamic acid, anisic acid, piperidine, *tert*-butylamine) were excellent. However, one can wonder at the purity of the isolated products. The synthesis of the three reagents were reported (63–71% yields), but when used for amide bond formation, the reagents were generated *in situ* through the reaction of 2-phenylbenzimidazole with a chlorophosphate or phosphinic chloride. The acid and then amine were added to this mixture, and side-reactions were thus likely to occur. Kokare also used the diethylphosphate derivative **170** as a coupling reagent for the synthesis of *O*-alkyl hydroxamic acids (Scheme 11).[130] Yields were excellent for the 12 amides synthesised but comparison with other coupling reagents was not carried out.



Scheme 11 Synthesis of *O*-alkyl hydroxamic acids.

4.7 Miscellaneous reagents

CPMA **171**, a reagent based on a chloroimmonium salt (Fig. 22), mediated the esterification of carboxylic acids,[131] and in terms of amide bond formation, the reagent performed well (complete conversion) but only two examples were reported.

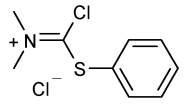
2-Mercaptopyridone-1-oxide **172** was used as a starting material to generate a cheaper and new type of uronium coupling reagent TOTT **173** and HOTT **174** (Scheme 12).[132] Both reagents gave better results that DCIH **78b** or PyBrop **79b** and were comparable to HATU **28a**, and the dipeptide Z-MeVal-Aib-OMe was obtained in 80% yield (89% for HATU **28a**). The epimerisation level was evaluated *via* Young's test and the use of TOTT **173** resulted in only 3.7% epimerisation compared to BOP **51b** (20%), PyBOP **52b** (15%), or HATU **28a** (20%). TOTT **173** and HOTT **174** have also been successfully used to synthesise primary amides from carboxylic acids and ammonium chloride.[133]

Najera synthesised two analogues of HOTT/TOTT, HODT **175** and TODT **176** (Fig. 23).[134] These two reagents gave higher yields in solid phase peptide synthesis, but associated with more epimerisation.

A reagent similar to the ones based on 2-mercaptopyridine oxide was proposed by Knorr but TPTU **177** (Fig. 24), based on 2-hydroxypyridine-*N*-oxide, gave high epimerisation level when used without an additive.[40]

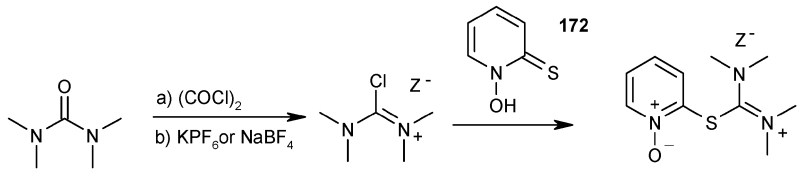
The possibility of using a 2-pyridinone based reagent, DPTC **178** (Fig. 25), for amide synthesis was investigated by Shiina.[135] Carboxylic acids were activated as 2-pyridyl esters using DPTC **178** and a catalytic amount of DMAP. However, a long pre-activation time was required (over 25 min) to limit the formation of an isothiocyanate specie (and probably a thiourea) upon addition of an amine. Thus the application of DPTC **178** is limited although simple amides can be obtained in good yield at room temperature. More hindered substrates imply carrying out the synthesis at higher temperature.

An original coupling reagent based on the rearrangement of carboxylic–sulfonic mixed anhydrides has been reported. Substituted *O*-hydroxybenzenesulfonyl chlorides **179** were used as condensation reagents *via* the mechanism suggested in Scheme 13.[136] Using this method various peptides were obtained in good yields. The epimerisation level was assessed through optical purity, but no comparison was made with any common coupling reagent. Itoh investigated the possibility of using sulfonate-based coupling reagents, and developed 2-methanesulfonyloximino-2-cyanoacetate **180** (Fig. 26), which proved however to be outperformed by HCSCP **69**.[67]

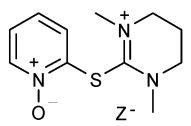


171

Fig. 22 Structure of CPMA.

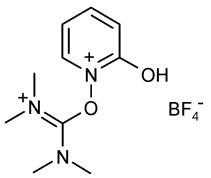


Scheme 12 Synthesis of HOTT and TOTT from 2-mercaptopyridone.



HODT (Z=PF_6) **175**
TODT (Z=BF_4) **176**

Fig. 23 Structure of HODT and TODT.



177

Fig. 24 Structure of TPTU.

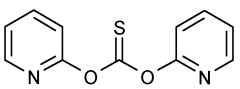


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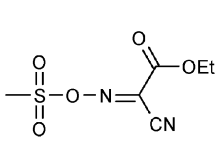
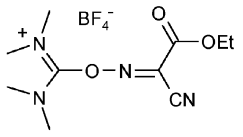
Fig. 25 Structure of DTPC.

A related reagent, also based on a cyanoacetate moiety, TOTU **181** was reported by König.[137]

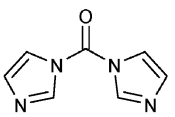
Carbonyl-diimidazole (CDI **182**) has been used to generate amide bonds.[138] Interestingly, Sharma showed that CDI **182**



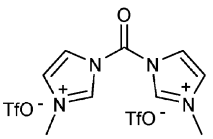
180



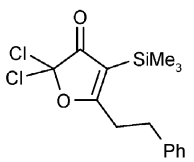
TOTU **181**



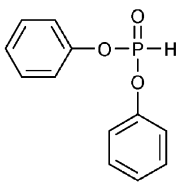
CDI **182**



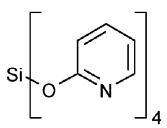
CBMIT **183**



DPTF **184**

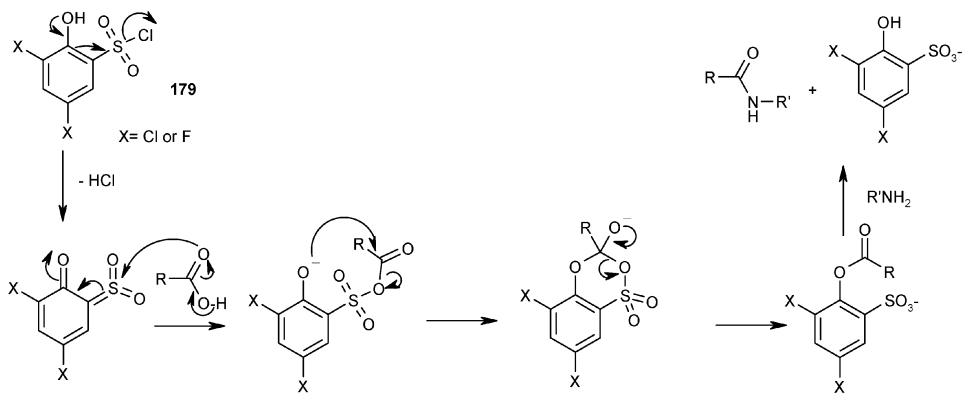


DPP **186**

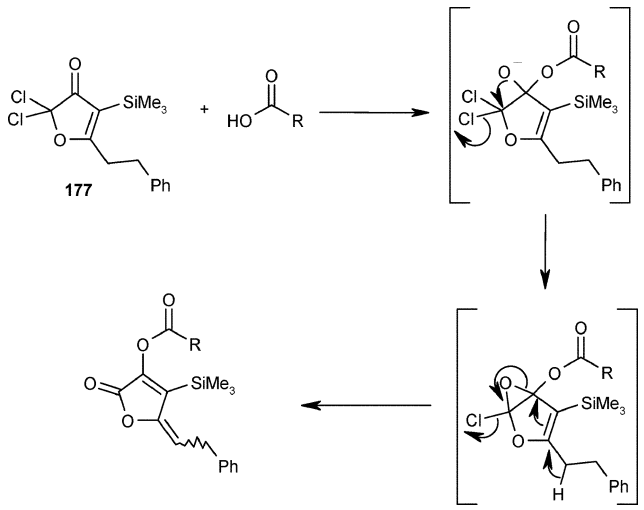


$Si(OPy)_4$ **187**

Fig. 26 Structure of other miscellaneous reagents.



Scheme 13 Mechanism of the coupling reagents using substituted *O*-hydroxybenzenesulfonyl chlorides.



Scheme 14 Suggested mechanism of DPTF.[141]

could be used to couple unprotected amino acids to amines in water.[139] The strategy however offers limited applicability as only primary amines were successfully coupled, while yields were moderate.

More recently, Saha proposed the use of an analogue, CBMIT **183**.[140] He obtained good yields and low epimerisation but these were not evaluated on standard tests and are therefore difficult to compare to classical reagents.

DPTF **184** was reported by Ito as a dehydrating reagent.[141] Its mechanism of action follows the active ester pathway to generate amides in good yields (Scheme 14). However hindered building blocks were not evaluated. One of the main advantages of DPTF **184** is its ability to activate a carboxylic acid in aqueous media.

In order to avoid the use of expensive reagents, Campagne suggested the use of ethyl propiolate **185** as coupling reagent, as described in Scheme 15.[142] Although being original, this route required a long pre-activation time (12 h) and the use of an additive (sodium bisulfite) was necessary to give good yields. Moreover, yields were typically lower than standard coupling reagents such as PyBOP **52b**.

Recently, diphenyl phosphite (DPP **186**),[143] and tetrakis-(pyridine-2-yloxy)silane **187**,[144] have been used to synthesise amides. DPP **186** forms a phosphonic-carboxylic mixed anhydride, while tetrakis(pyridine-2-yloxy)silane gives silyl esters **188** (Scheme 16). These reagents afforded amides in good yields but were not compared to other coupling reagents.

Phenylsilane $PhSiH_3$ **189** has been used in amide library formation.[145] The reagent was tested on seven carboxylic acids and 11 amines. Although amides were sometimes obtained in good yield, it was necessary to use reverse phase HPLC to purify the products, making the phenylsilane method unattractive for library generation. In addition, anilines and some secondary amines failed to couple with this reagent resulting in poor scope.

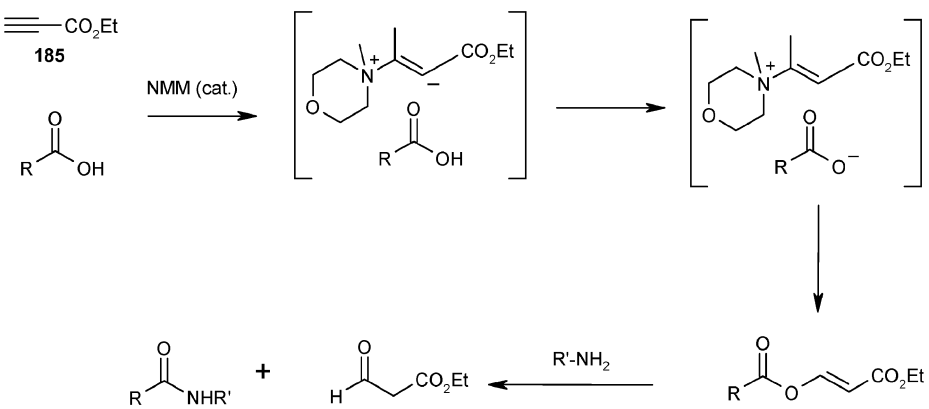
5. Other methods of *N*-acylation

5.1 Mixed anhydrides

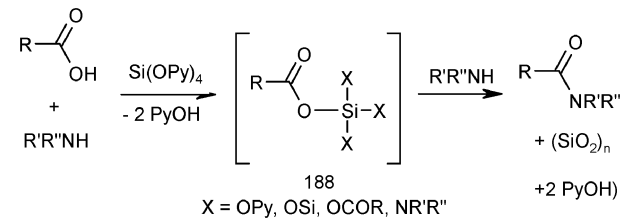
The formation of mixed anhydrides is a classic method of amide bond formation. It is important to note that many mixed anhydrides can be generated using some of the coupling reagents reported so far in this review. The mixed anhydride method was first reported by Vaughan,[146] who tested many acid chloride derivatives and concluded that the success of the amide-bond formation was governed by steric and inductive effects. Isovaleryl chloride proved to give the best results. However, as reported by many research groups, this method has a tendency to generate symmetrical anhydrides by reaction of a second carboxylic acid molecule on the mixed anhydride (Scheme 17). In addition regioselectivity is a major issue, as the amine can potentially react at either carbonyl group although this can be biased by using a bulky acid group. These drawbacks can sometimes be minimised by carrying out the coupling reactions at low temperature.

5.2 Chloroformates

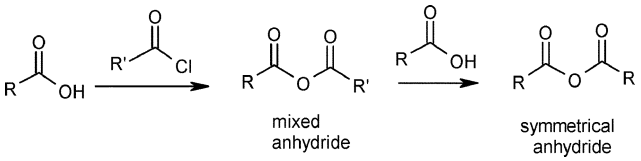
The use of chloroformates for amide-bond formation was first reported by Vaughan,[147] and was based on the mixed anhydride method. In the presence of a base, the reaction between a carboxylate and a chloroformate yields a mixed carbonic anhydride, which reacts quickly with amines to form amides. Vaughan's study highlighted slightly better results when using *sec*-butylchloroformate compared to isobutylchloroformate.[148] The method was "reinvestigated" by Anderson,[149] who tested several different chloroformates, and whose conclusions suggested that isobutylchloroformate was the most efficient reagent.



Scheme 15 Activation process when using ethyl propiolate as coupling reagent.



Scheme 16 Mechanism proposed by Tozawa for tetrakis(pyridine-2-yloxy)silane.



Scheme 17 Disproportionation issue with the mixed anhydride method.

5.3 Direct preparation of active esters

The direct formation of active esters has often attracted a lot of attention due to the stability of many of them, which allows storage. Many example of active esters have therefore been reported and include –*O*-succinimides,[150] –OBt and derivatives,[24] *p*-nitrophenol,[151] –OPfP,[152] –ODhbt,[153] and PTOC.[154] As this review focuses directly on coupling reagents, this useful method of amide-bond formation will not be discussed herein, but the reader is referred to Montalbetti's review for further details.[13]

5.4 Newer approaches to amide bond formation

Several alternatives to the use of coupling reagents have been reported. These interesting new methods were reviewed by Bode,[155] and include the so-called native chemical ligation and the Staudinger ligation (Scheme 18). Recently, Milstein reported another approach based on the ligation of amines to alcohols using a ruthenium complex as catalyst.[156] Molecular hydrogen was formed during the reaction and amides were obtained in high yield.

6. Polymer-supported coupling reagents

6.1 Immobilised carbodiimides

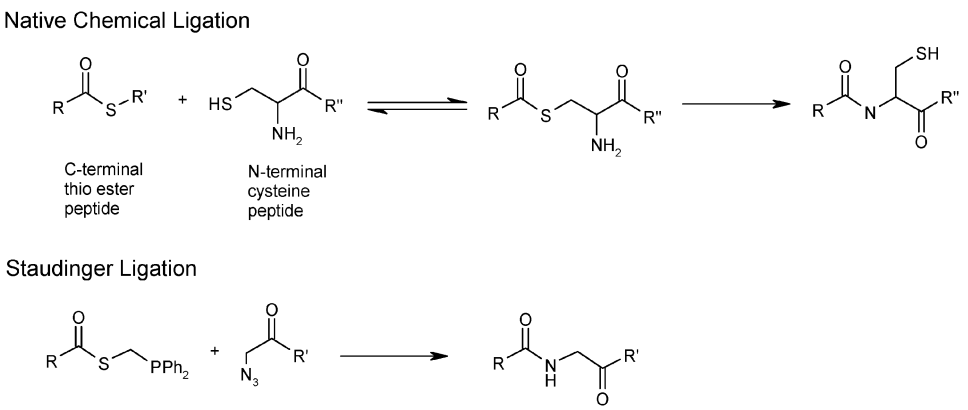
Only a few polymer-supported coupling reagents are available, probably because coupling reagents are mainly used in peptide synthesis, which is usually carried out on solid phase, the coupling reagent being in solution. Nevertheless, DCC **5**,[157] DIC **13**,[158] and EDC[159] **20** have been successfully immobilised and applied to the synthesis of amides.[160] However these carbodiimides maintain the same drawbacks as their solution-phase equivalents, in particular in terms of epimerisation in the absence of an additive. Furthermore, one can wonder at the interest of PS-EDC **190** (Fig. 27) in comparison to PS-DCC **191** as EDC **20** was originally designed and synthesised to be water soluble. Having the "extractable" moiety on a polystyrene support appears to be odd, especially as the ionic part of EDC **20** in solution-phase has proven to be counterproductive regarding the coupling reaction rate compared to DIC **13**.[34] A polyhexamethylene-carbodiimide has also been reported.[161]

Charette "attached" carbodiimides to tetraarylphosphonium salts as a means of "tagging" the reagent.[162] Reaction was carried out in solution phase, before precipitation of the salt with apolar solvents. Several carbodiimides derivatives **192** were synthesised (Fig. 28), and the ethyl and isopropyl derivatives based on a hexafluorophosphate salt were the most efficient, both in terms of yields and purities.

6.2 Immobilised additives and reagents based on HOBt

Some coupling reagents in solution can in rare cases be extracted after reaction (*e.g.* EDC **20**). However, the use of an additive is often required to limit epimerisation, and this additive has also to be separated from the reaction mixture. Therefore polymer-supported HOBt has been reported in different guises.[163,164] PS-HOBt **193** has also been used as a core for synthesising supported reagents for the preparation of *N*-hydroxysuccinimide active esters.[165]

The idea of using PS-HOBt **193** to form an immobilised HOBt-based coupling reagent was first exploited by Chinchilla, who synthesised polymer-supported TBTU **194**.[166] This idea was also applied by Filip for the synthesis of polymer-supported BOP **195**.[167] These reagents offer however the same



Scheme 18 Examples of newer methodologies for amide bond formation.

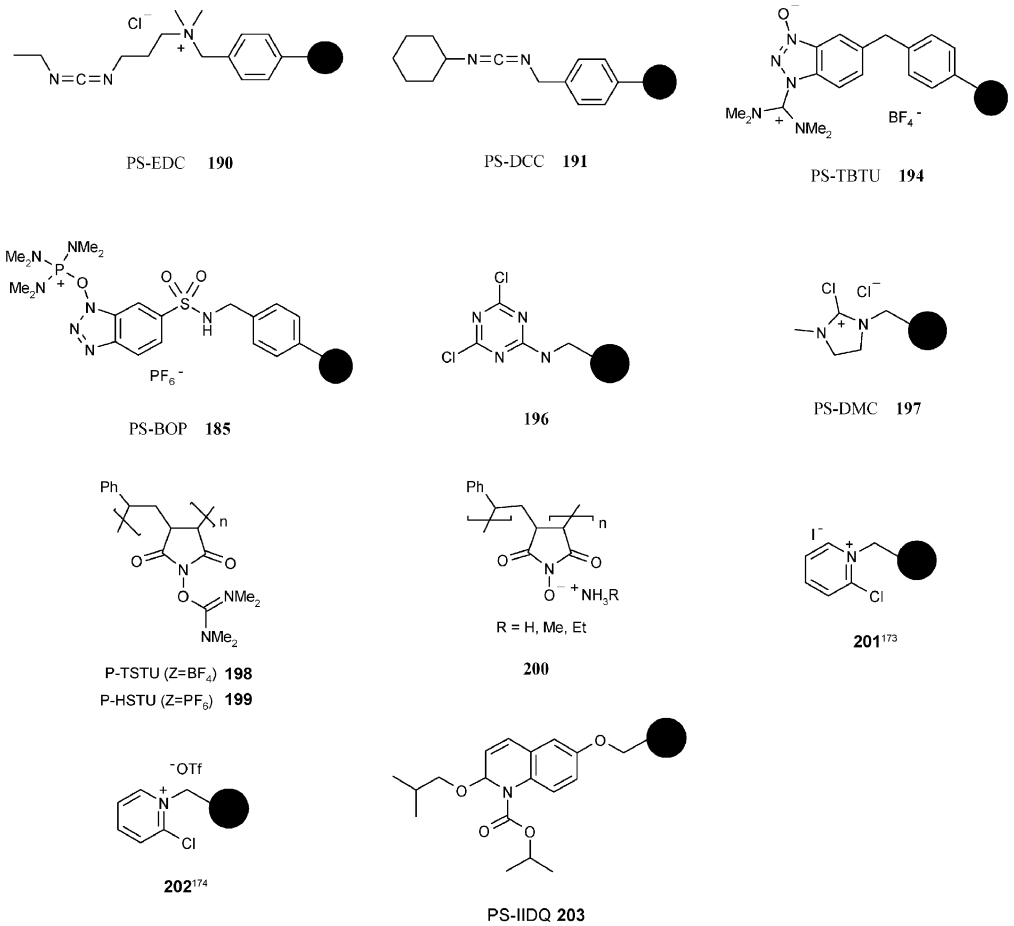


Fig. 27 Structure of polymer-supported reagents.

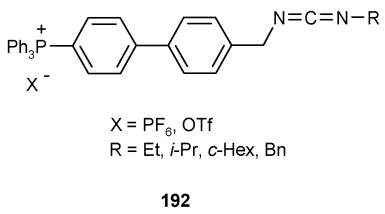


Fig. 28 Tetraarylphosphonium-supported carbodiimides.

drawbacks as TBTU **30b** and BOP **51b** in solution, while the structure of the reagent means that part of it will end up in solution after the coupling, clearly an undesirable occurrence for a supported reagent.

6.3 Other immobilised reagents

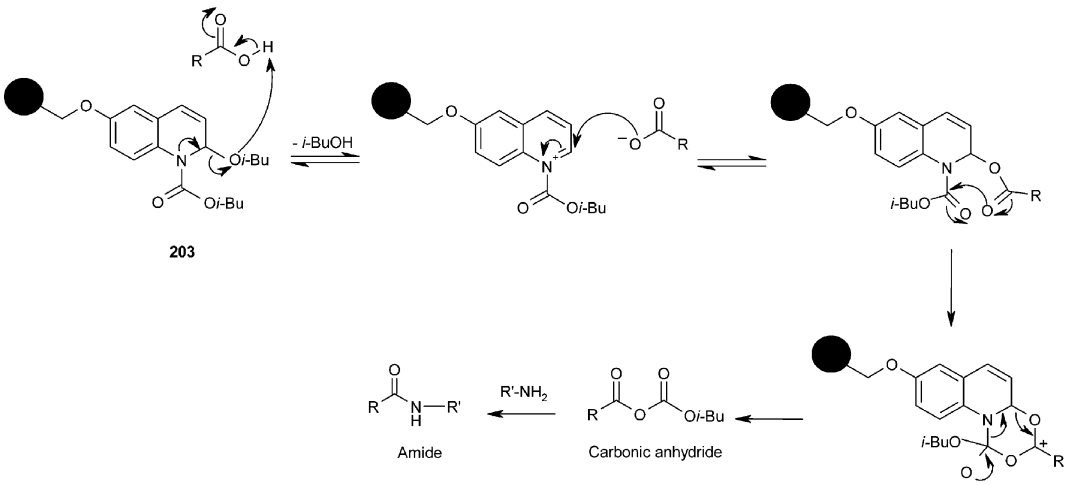
Triazine-based coupling reagents have been widely used in solution-phase. In 1999, Taddei reported polymer-supported chlorotriazine **196**.[168] Although amides were synthesised in moderate to good yield using this reagent, the ^{1}H NMR of the crude compounds revealed the presence of 5 to 10% of by-products. Hioki used another strategy to obtain polymeric triazine-type reagents.[169] Using a norbornene-derivatised triazine, they synthesised *via* ROMP an immobilised monomethoxychlorotriazine, which was tested on anilines and primary amines. Yields were good (nine examples, 80–98%), but no secondary amine was tested while the reagent was not compared to other classical amide bond formation methods.

PS-DMC **197**, a supported equivalent of DMC **89**, was reported by Ishikawa.[170] Yields over five examples were slightly lower for the polymer-supported version of the reagent, and the examples provided did no allow a full display of the scope and limitations of the reagent.

Chinchilla developed some reagents based on polymeric succinimides such as P-TSTU **198** and P-HSTU **199**,[171] and **200** (Fig. 27).[172] The results were good for classic amino acids but the yields were moderate to low when coupling hindered amino acids. Globally these reagents did not really add any benefit to the range of coupling reagents available, and, like PS-TBTU **194** and PS-BOP **195**, part of the reagent ended up in solution.

More recently, Convers reported an immobilised Mukaiyama reagent **201**.[173] However, Crosignani investigated this new reagent and concluded that the synthesis was poorly reproducible, and developed another route.[174] This reagent **202** appeared to work very efficiently for the synthesis of esters and amides including hindered substrates, secondary amines and anilines.[174,175]

Polymer-supported IIDQ **203** is an immobilised version of the solution-phase IIDQ **100** reagent.[97,176] It was synthesised in three steps from Merrifield resin and 6-hydroquinoline to provide a high loading reagent (>1.68 mmol/g). The main



Scheme 19 Activation process when using PS-IIDQ.

advantages of PS-IIDQ **203** are that no base is required during coupling, while the order of addition of amine, carboxylic acid and reagent do not influence the outcome of the reaction (Scheme 19).

This reagent was compared to other classically used and commercially available coupling reagents such as Polymer-supported EDC **190** and DCC **191**, as well as HATU **28a**. Interestingly, PS-IIDQ **203** performed better than any of these reagents on a set of three amines and three carboxylic acids, including anilines and bulky substrates (Table 5). Furthermore, PS-IIDQ **203** was evaluated on 9 amines and 5 carboxylic acids and gave an average yield of 73%. Epimerisation was low as Anteuni's test did not reveal any trace of the diastereo-isomer by NMR. PS-IIDQ **203** was stable under standard laboratory storage conditions and it was shown that the reagent could be advantageously recycled after any coupling reaction. Thus PS-IIDQ **203** appears to be a very versatile coupling reagent for the parallel synthesis of amides.

Very recently, Kakarla duplicated these studies to make PS-EEDQ **204**.[177] It was obtained using identical conditions for the transformation of PS-Quinoline into PS-EEDQ **204**, the only variation being the use of a Wang resin. However the loading of the so-called "high-loading" PS-EEDQ **204** was erroneous (starting from a 1.7 mmol/g Wang resin, the maximum physical loading of PS-EEDQ **204** would be 1.19 mmol/g assuming total conversion during synthesis, while the authors claimed 1.36 mmol/g loading), while a Wang linker was clearly of no use. When looking at the efficiency of EEDQ **99** and IIDQ **100** (Table 4),[97] the choice appears evident.

Table 5 Comparison of the yields and purities obtained over three amines (4-*tert*-butylaniline, benzylamine, H-PhG-OMe) and three carboxylic acids (Boc-Aib-OH, phenylacetic acid, benzoic acid)

Entry	Coupling reagent	Average yield (%)	Average purity (%)
1	PS-IIDQ	72	100
2	HATU	55	98
3	PS-EDC	41	96
4	PS-DCC	26	97

7. Conclusion on available coupling reagents

Although hundreds of coupling reagents have been reported, conclusions on their efficiency are in fact quick and simple. Most of these reagents are simply not efficient for a broad range of amide bond formation. Some reagents do perform well in general, but differences are typically small. Solid-phase peptide chemists may find useful reagents which display fast kinetics for coupling as the synthesis of long peptides has ideally to be rapid. However, for the general organic chemist, simple reagents are often the most appropriate allowing coupling reagents to be used on a large selection of substrates with varying reactivities.

This summary can be illustrated by the comparison of coupling reagents carried out by Hachman.[68] Very few comparisons of reagents have been published and the work by Hachman displayed the importance of a comparison system. Hachman compared classical reagents such as phosphonium salts, uronium salts, reagents generating acid halides and carbodiimides. During the synthesis of decapeptides, HBTU **28b** was the "fastest" reagent after 2 min while almost none of the expected amide was formed by DIC after this time. However, after 8 min, DIC **13** was comparable to HBTU **28b**. In addition very few side-reactions were observed with DIC **13** (in particular deletion) compared to BOP **51b** or HATU **28a**. This demonstrated that a simple reagent like DIC **13** (using HOBt as additive) performs well in many cases, and a compromise of speed/purity/by-products needs to be sought.

An important point is the way new coupling reagents are reported. As stated and demonstrated by Hachman: "the use of only one model sequence for evaluation of synthetic reagents [. . .] can be misleading." As such, unless new reagents are systematically tested against commonly considered "top coupling reagents", such as HATU **28a**, and traditional methods such as DIC/HOBt, it is likely that most new coupling reagents will have an application limited to the original publication by their authors.

Overall, keeping in mind all possible issues (side-reactions), HATU **28a** and HBTU **28b** offer generally excellent reactivity.

If quick coupling times are required, HATU **28a** probably represents the reagent of choice, providing the substrates are not hindered. Otherwise, the traditional method DCC **5** (or DIC **13**) /HOBt remains an excellent choice for many substrates. One has nevertheless to keep in mind potential hazards when using reagents based on 1*H*-benzotriazole due to the potential explosive properties of HOBt.[30,31]

For difficult couplings (*e.g.* secondary amines), our experience tells us that PyBrop **79b** is generally reliable.[178] Triazines can be an alternative for difficult coupling, although the most reactive reagents tend to give side-products. However, the recent developments by Kaminski are bringing new applications to this class of coupling reagents.

Finally, for library synthesis either the PS-Mukaiyama reagent **202** or polymer-supported IIDQ **203** are clearly the most suitable reagents,[179] and their efficiency has been confirmed by many groups. These reagents have the advantage of simplifying purification as the reagent is separated *via* simple filtration after reaction.

In conclusion, selecting suitable coupling reagents could be summarised by ''keep it simple'' as most reagents appear to be merely fancy and costly alternatives. Finding a universal coupling reagent remains elusive considering the wide portfolio of potential substrates and it is generally wise to avoid ''exotic'' reagents and not be mislead by ''fast'' coupling reagents. Efficiency is the key, with high conversions, low levels of epimerisation and limited by-products all being essential criteria.

List of abbreviations

General

ACP	acyl carrier protein decapeptide 65–74
DABCO	bicyclo[2,2,2]-1,4-diazaoctane
DCU	dicyclohexylurea
DMAP	4-dimethylaminopyridine
DMPU	dimethylpropyleneurea
HMPA	hexamethylphosphoramide
LHRH	Luteinising Hormone Releasing Hormone
NMM	*N*-methylmorpholine
ROMP	Ring Opening Metathesis Polymerisation

Coupling reagents and additives

ACTU	(2-(6-chloro-1-*H*-benzotriazol-1-yl)-1,1,3,3-tetramethylaminium) hexachloroantimonate
AOMP	5-(7-azabenzotriazol-1-yloxy)-3,4-dihydro-1-methyl-2*H*-pyrrolium hexachloroantimonate
AOP	(7-azabenzotriazol-1-yl)oxytris(dimethylamino)phosphonium hexafluorophosphate
BBC	benzotriazoloxy-bis(pyrrolidino)carbonium hexafluorophosphate
BDDC	bis[[4-(2,2-dimethyl-1,3-dioxolyl)]methyl]-carbodiimide
BDMP	5-(1*H*-benzotriazol-1-yloxy)-3,4-dihydro-1-methyl-2*H*-pyrrolium hexachloroantimonate
BDP	benzotriazol-1-yl diethylphosphate
BEC	*N*-*tert*-butyl-*N*′-ethylcarbodiimide
BEMT	2-bromo-3-ethyl-4-methylthiazolium tetrafluoroborate
BEP	2-bromo-1-ethylpyridinium tetrafluoroborate
BEPH	2-bromo-1-ethylpyridinium hexachloroantimonate
4,5-B(HATU)	*N*-[(dimethylamino)(3*H*-1,2,3-triazolo[4,5-*c*]-isoquinolin-3-yloxy)-*N*-methylmethanaminium hexafluorophosphate
5,6-B(HATU)	1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]quinolinium hexafluorophosphate-3-oxide
BIODPP	diphenyl benzo[*d*]isoxazol-3-ylphosphonate
BMC	*N*-*tert*-butyl-*N*′-methylcarbodiimide
BMMP	1-(1-(1*H*-benzo[*d*][1,2,3]triazol-1-yloxy)ethylidene)pyrrolidinium hexachloroantimonate
BMP-Cl	*N*,*N*′-bismorpholinophosphonic chloride
BMTB	2-bromo-3-methyl-4-methylthiazolium bromide
BOI	2-(benzotriazol-1-yl)oxy-1,3-dimethylimidazolidinium hexafluorophosphate
BOMI	benzotriazol-1-yloxy-*N*,*N*-dimethylmethaniminium hexachloroantimonate
BOP	benzotriazolyl-*N*-oxytrisdimethylaminophosphonium hexafluorophosphate
BOP-Cl	*N*,*N*′-bis(2-oxo-3-oxazolidinyl)phosphinic chloride
BPMP	1-(1*H*-benzotriazol-1-yloxy)phenylmethylene pyrrolidinium hexachloroantimonate
BroP	bromotris(dimethylamino)phosphonium hexafluorophosphate
BTFFH	bis(tetramethylene)fluoroformamidinium hexafluorophosphate
CBDO	2-chlorobenzo[*d*][1,3]dioxol-1-ium hexachloroantimonate
CBMIT	1,10-carbonylbis(3-methylimidazolium) triflate
CDI	carbonyldiimidazole
CDMS	chlorodimethylsulfonium hexachloroantimonate
CDMT	2-chloro-4,6-dimethoxy-1,3,5-triazine
CDTP	2-chloro-1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-1-ium perchlorate
CIP	2-chloro-1,3-dimethylimidazolidinium hexafluorophosphate
CloP	chlorotris(dimethylamino)phosphonium hexafluorophosphate
CMMM	chloro(4-morpholino)methylene morpholinium hexafluorophosphate
CPMA	(chlorophenylthiomethylene)dimethylammonium chloride
CPDT	2-chloro-5-phenyl-1,3-dithiol-1-ium hexachloroantimonate
Cpt-Cl	1-oxo-chlorophospholane
DAST	diethylaminosulfur trifluoride
DCC	dicyclohexylcarbodiimide
DCIH	1,3-dimethyl-2-chloro-4,5-dihydro-1*H*-imidazolium hexafluorophosphate
DCMT	2,4-dichloro-6-methoxy-1,3,5-triazine
DEBP	diethyl-2-(3-oxo-2,3-dihydro-1,2-benzisosulfonazolyl)phosphonate

DEFFH	1,2-diethyl-3,3-tetramethylenefluoroformamidinium hexafluorophosphate
DECP	diethylcyanophosphonate
DEPC	diethyl phosphorochloridate
DEPB	diethyl phosphorobromidate
DEPBO	*N*-diethoxyphosphorylbenzoxazolone
DEPBT	3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one
DepOAt	3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yldiethyl phosphate
DepOBt	diethoxyphosphinyloxybenzotriazole
DepODhbt	diethyl 4-oxobenzo[*d*][1,2,3]triazin-3(4*H*)-yl phosphate
DFIH	1,3-dimethyl-2-fluoro-4,5-dihydro-1*H*-imidazolium hexafluorophosphate
DIC	diisopropylcarbodiimide
DMC	2-chloro-1,3-dimethylimidazolinium chloride
DMCH	*N*-(chloro(morpholino)methylene)-*N*-methylmethanaminium hexafluorophosphate
DMFFH	1,2-dimethyl-3,3-tetramethylenefluoroformamidinium hexafluorophosphate
DMFH	*N*-(fluoro(morpholino)methylene)-*N*-methylmethanaminium hexafluorophosphate
DmppOAt	1-(2,8-dimethylphenoxaphosphinyloxy)-7-azabenzotriazole
DMTMM	4-(4,6-dimethoxy[1,3,5]triazin-2-yl)-4-methylmorpholinium chloride
DOMP	5-(3′,4′-dihydro-4′-oxo-1′,2′,3′-benzotriazin-3′-yloxy)-3,4-dihydro-1-methyl 2*H*-pyrrolium hexachloroantimonate
DOPBO	*N*-(2-oxo-1,2,3-dioxaphosphorinanyl)benzoxazolone
DOPBT	3-[*O*-(2-oxo-1,2,3-dioxaphosphorinanyl)oxy]-1,2,3-benzotriazin-4(3*H*)-one
DPOOP	diphenyl-2-oxo-3-oxazolinylphosphonate
Dpop-Cl	diphenyl phosphorochloridate
DpopOAt	1-(diphenoxyphosphoryloxy)-7-azabenzotriazole
DpopOBt	1-(diphenoxyphosphoryloxy)benzotriazole
DpopODhbt	3-(diphenoxyphosphinyloxy)-3,4-dihydro-4-oxo-1,2,3-benzotriazene
DPP	diphenylphosphite
DPPA	diphenylphosphoryl azide
Dpp-Cl	diphenylphosphinic chloride
DPTC	*O*,*O*′-di(2-pyridyl)thiocarbonate
DPTF	2,2-dichloro-5-(2-phenylethyl)-4-(trimethylsilyl)-3-furanone
DtpOAt	1-[di(*O*-tolyl)phosphinyloxy]-7-azabenzotriazole
DtpOBt	1-[di(*O*-tolyl)phosphinyloxy]benzotriazole
DtpODhbt	3-di(*O*-tolyl)phosphinyloxy]-3,4-dihydro-4-oxo-1,2,3-benzotriazine
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EEDQ	*N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline
ENDPP	phosphoric acid 3,5-dioxo-10-oxa-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-en-4-yl ester diphenyl ester
FDMP	3,5-bis(trifluoromethyl)phenyl diphenylphosphinate
FDPP	pentafluorophenyl diphenyl phosphinate
FEP	2-fluoro-1-ethylpyridinium tetrafluoroborate
FEPH	2-fluoro-1-ethylpyridinium hexachloroantimonate
FOMP	5-(pentafluorophenyloxy)-3,4-dihydro-1-methyl-2*H*-pyrrolium hexachloroantimonate
HAE_2PipU	*O*-(1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-yl)-1,1-diethyl-3,3-pentamethyleneuronium hexafluorophosphate
HAE_2PyU	*O*-(1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-yl)-1,1-diethyl-3,3-tetramethyleneuronium hexafluorophosphate
HAMDU	*O*-(7-azabenzotriazol-1-yl)-1,3-dimethyl-1,3-dimethyleneuronium hexafluorophosphate
HAM_2PipU	*O*-(1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-yl)-1,1-dimethyl-3,3-pentamethyleneuronium hexafluorophosphate
HAM_2PyU	*O*-(1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-yl)-1,1-dimethyl-3,3-tetramethyleneuronium hexafluorophosphate
HAMTU	*O*-(7-azabenzotriazol-1-yl)-1,1,3,3-bis(pentamethylene)uronium hexafluorophosphate
HAPipU	*O*-(7-azabenzotriazol-1-yl)-1,1,3,3-bis(pentamethylene)uronium hexafluorophosphate
HAPyTU	*S*-(7-azabenzotriazol-1-yl)-1,1,3,3-bis(tetramethylene)thiouronium hexafluorophosphate
HAPyU	1-(1-pyrrolidinyl-1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-ylmethylene)pyrrolidinium hexafluorophosphate *N*-oxide
HATeU	*O*-(1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-yl)-1,1,3,3-tetraethyluronium hexafluorophosphate
HATU	*O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HBE_2PipU	*O*-(1*H*-benzotriazol-1-yl)-1,1-diethyl-3,3-pentamethyleneuronium hexafluorophosphate
HBE_2PyU	*O*-(1*H*-benzotriazol-1-yl)-1,1-diethyl-3,3-tetramethyleneuronium hexafluorophosphate
HBMDU	*O*-(benzotriazol-l-yl)-l,3-dimethyl-l,3-dimethyleneuronium hexafluorophosphate
HBMP	1*H*-benzo[*d*][1,2,3]triazol-1-ylmethanesulfonate
HBM_2PipU	*O*-(1*H*-benzotriazol-1-yl)-1,1-dimethyl-3,3-pentamethyleneuronium hexafluorophosphate
HBM_2PyU	*O*-(1*H*-benzotriazol-1-yl)-1,1-dimethyl-3,3-tetramethyleneuronium hexafluorophosphate
HBPipU	*O*-(benzotriazol-1-yl)-1,1,3,3-bis(pentamethylene)-uronium hexafluorophosphate
HBSP	1*H*-benzo[*d*][1,2,3]triazol-1-ylbenzenesulfonate
HBTeU	*O*-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetraethyluronium hexafluorophosphate
HBTU	*O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HCTU	(2-(6-chloro-1-*H*-benzotriazol-1-yl)-1,1,3,3-tetramethylaminium) hexafluorophosphate
HCSCP	6-chloro-1*H*-benzo[*d*][1,2,3]triazol-1-yl-4-chlorobenzenesulfonate
HCSP	6-chloro-1*H*-benzo[*d*][1,2,3]triazol-1-ylbenzenesulfonate

HDATU	(bis(dimethylamino)methyl)(4-oxopyrido[3,2-*d*]-[1,2,3]triazin-3(4*H*)-yl)oxonium hexafluorophosphate
HDADU	(bis(dimethylamino)methyl)(4-oxopyrido[3,2-*d*]-pyrimidin-3(4*H*)-yl)oxonium hexafluorophosphate
HDAPyU	1-((4-oxopyrido[3,2-*d*][1,2,3]triazin-3(4*H*)-yloxy)-(pyrrolidin-1-yl)methylene)pyrrolidinium hexafluorophosphate
HDMA	1-((dimethylamino)(morpholino)methylene)-1*H*-[1,2,3]triazolo[4,5-*b*]pyridinium hexafluorophosphate 3-oxide
4-HDMA	3-((dimethylamino)(morpholino)methylene)-1*H*-[1,2,3]triazolo[4,5-*b*]pyridinium hexafluorophosphate 1-oxide
HDMB	1-((dimethylamino)(morpholino)methylene)-1*H*-benzotriazolium hexafluorophosphate 3-oxide
HDMCB	6-chloro-1-((dimethylamino)(morpholino)-methylene)-1*H*-benzotriazolium hexafluorophosphate 3-oxide
HDMFB	6-trifluoromethyl-1-((dimethylamino)-(morpholino)methylene)-1*H*-benzotriazolium hexafluorophosphate 3-oxide
HDMPfp	1-((dimethyamino)(morpholino))oxypenta-fluorophenyl metheniminium hexafluorophosphate
HDMS	1-((dimethyamino)(morpholino))oxypyrrolidine-2,5-dione methanaminium hexafluorophosphate
HDPyU	1-((4-oxobenzo[*d*][1,2,3]triazin-3(4*H*)-yloxy)-(pyrrolidin-1-yl)methylene)pyrrolidinium hexafluorophosphate
HDTMA	1-((dimethylamino)(thiomorpholino)methylene)-1*H*-[1,2,3]triazolo[4,5-*b*]pyridinium hexafluorophosphate 3-oxide
HDTMB	1-((dimethylamino)(thiomorpholino)methylene)-1*H*-benzotriazolium hexafluorophosphate 3-oxide
HDTU	*O*-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	1-hydroxy-1*H*-benzotriazole
HODhat	3-hydroxy-4-oxo-3,4-dihydro-5-azabenzo-1,2,3-triazine
HODhbt	3,4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazine
HODT	*S*-(1-oxido-2-pyridinyl)-1,3-dimethyl-1,3-trimethylenethiouronium
HONB	2-(5-norbornene-2,3-dicarboximide)
HOPfp	pentafluorophenol
HPyOPfp	*N*,*N*,*N*′,*N*′-bis(tetramethylene)-*O*-pentafluorophenyluronium hexafluorophosphate
HPySPfp	1-((perfluorophenylthio)(pyrrolidin-1-yl)-methylene)pyrrolidinium hexafluorophosphate
HOSu	*N*-hydroxysuccinimide
HOTT	*S*-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouronium hexafluorophosphate
HSTU	*O*-(*N*-succimidyl)-*N*,*N*,*N*′,*N*′-bis(tetramethylene)-uronium hexafluorophosphate
IDDQ	*N*-isobutoxycarbonyl-2-isobutoxy-1,2-dihydroquinoline
MPTA	dimethylphosphinothioyl azide
MPT-Cl	dimethylphosphinothioyl chloride
MPTO	3-dimethylphosphinothioyl-2(3*H*)-oxazolone
NDPP	norborn-5-ene-2,3-dicarboximidodiphenyl-phosphate
NOP	[(6-nitrobenzotriazol-1-yl)oxy]tris(dimethyl-aminop)phosphonium hexafluorophosphate
PEC	phenylethylcarbodiimide
PFNB	perfluorophenyl 4-nitrobenzenesulfonate
PIC	phenylisopropylcarbodiimide
PTOC	pyridine-2-thione-*N*-oxycarbonyl
PyAOP	[(7-azabenzotriazol-1-yl)oxy]tris(pyrrolidino)-phosphonium hexafluorophosphate
PyBOP	benzotriazol-1-yloxytri(pyrrolidino)-phosphonium hexafluorophosphate
PyBroP	bromotri(pyrrolidino)phosphonium hexafluorophosphate
PyClock	6-chloro-1-hydroxybenzotriazol-1-yl-*N*-oxy-tris(pyrrolidino)phosphonium hexafluorophosphate
PyCloP	chlorotri(pyrrolidino)phosphonium hexafluorophosphate
PyClopP	chlorobispyrrolidinophenylphosphonium hexachloroantimonate
PyFloP	fluorotri(pyrrolidino)phosphonium hexafluorophosphate
PyClU	chlorodipyrrolidinocarbenium hexafluorophosphate
PyDAOP	(4-oxopyrido[3,2-*d*][1,2,3]triazin-3(4*H*)-yloxy)-tripyrrolidin-1-ylphosphonium hexafluorophosphate
PyDOP	[(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-oxy]tris(pyrrolidino)phosphonium hexafluorophosphate
PyDPP	diphenyl 2-oxopyridin-1(2*H*)-ylphosphonate
PyFOP	[[6-(trifluoromethyl)benzotriazol-1-yl]oxy]tris-(pyrrolidino)phosphonium hexafluorophosphate
PyNOP	[(6-nitrobenzotriazol-1-yl)oxy]tris(pyrrolidino)-phosphonium hexafluorophosphate
PyPOP	(perfluorophenoxy)tripyrrolidin-1-ylphosphonium
PyTOP	(pyridyl-2-thio)tris(pyrrolidino)-phosphonium hexafluorophosphate
SbTMU	*O*-(*N*-succimidyl)-*N*,*N*,*N*′,*N*′-bis-(tetramethylene)-uronium hexafluorophosphate
SDPP	2,5-dioxopyrrolidin-1-yl diphenyl phosphate
SMDOP	4-oxobenzo[*d*][1,2,3]triazin-3(4*H*)-yl methanesulfonate
SPDOP	4-oxobenzo[*d*][1,2,3]triazin-3(4*H*)-yl benzenesulfonate
SOMI	5-(succinimidyloxy)-*N*,*N*-dimethylmethaniminium hexachloroantimonate
SOMP	5-(succinimidyloxy)-3,4-dihydro-1-methyl-2*H*-pyrrolium hexachloroantimonate
T3P	2-propanephosphonic acid anhydride
TATU	*O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate

TAPipU	1-(1-pyrrolidinyl-1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-ylmethylene)pyrrolidinium tetrafluoroborate *N*-oxide
TBFH	*N*,*N*,*N*′,*N*′-tetramethylbromoformamidinium hexafluorophosphate
TBTU	*O*-benzotriazol-1-yl-1,1,3,3-tetramethyluronium tetrafluoroborate
TCFH	*N*,*N*,*N*′,*N*′-tetramethylchloroformamidinium hexafluorophosphate
TCTU	(2-(6-chloro-1-*H*-benzotriazol-1-yl)-1,1,3,3-tetramethylaminium) tetrafluoroborate
TDBTU	2-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
TEFFH	tetraethylfluoroformamidinium hexafluorophosphate
TFMS-DEP	diethylphenyl(trifluoromethylsulfonyl)-phosphoramidate
TFFH	tetramethylfluoroformamidinium hexafluorophosphate
TNTU	2-(5-norbornene-2,3-dicarboximido)-1,1,3,3-tetramethyluronium tetrafluoroborate
TOTT	*S*-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouronium tetrafluoroborate
TODT	*S*-(1-oxido-2-pyridinyl)-1,3-dimethyl-1,3-trimethylenethiouronium tetrafluoroborate
TOTU	*O*-(cyano(ethoxycarbonyl)methylenamino)-1,1,3,3-tetramethyluronium tetrafluoroborate
TPTU	1-((dimethylamino)(dimethyliminio)methoxy)-2-hydroxypyridinium tetrafluoroborate
TSTU	2-succinimido-1,1,3,3-tetramethyluronium tetrafluoroborate

References

1 A. Graul and J. Castaner, *Drugs Future*, 1997, **22**, 956–968.
2 A. A. Patchett, *J. Med. Chem.*, 1993, **36**, 2051–2058.
3 M. de Gasparo and S. Whitebread, *Regul. Pept.*, 1995, **59**, 303–311.
4 V. S. Ananthanarayanan, S. Tetreault and A. Saint-Jean, *J. Med. Chem.*, 1993, **36**, 1324–1332.
5 B. S. Jursic and Z. Zdravkovdki, *Synth. Commun.*, 1993, **23**, 2761–2770.
6 V. Gotor, *Bioorg. Med. Chem.*, 1999, **7**, 2189–2197.
7 F. Van Rantwijk, M. A. P. J. Hacking and R. A. Sheldon, *Monatsh. Chem.*, 2000, **131**, 549–569.
8 M. Bodanszky, *Int. J. Pept. Protein Res.*, 1985, **25**, 449–474.
9 M. Bodanszky, *Peptide Res.*, 1992, **5**, 134–139.
10 S. Y. Han and Y. A. Kim, *Tetrahedron*, 2004, **60**, 2447–2467.
11 J. M. Humphrey and A. R. Chamberlin, *Chem. Rev.*, 1997, **97**, 2243–2266.
12 A. R. Katritzky, K. Suzuki and S. K. Singh, *Arkivoc*, 2004, 12–35.
13 C. A. G. N. Montalbetti and V. Falque, *Tetrahedron*, 2005, **61**, 10827–10852.
14 C. Najera, *Synlett*, 2002, 1388–1403.
15 M. W. Williams and G. T. Young, *J. Chem. Soc.*, 1963, 881–889.
16 B. Weinstein and A. E. Pritchard, *J. Chem. Soc., Perkin Trans. 1*, 1972, 1015–1020.
17 A. Bodanszky and L. E. Conklin, *Chem. Commun.*, 1967, 773–774.
18 C. Van der Auwera, S. Van Damme and M. J. O. Anteunis, *Int. J. Pept. Protein Res.*, 1987, **29**, 464–471.
19 G. W. Anderson and F. M. Callahan, *J. Am. Chem. Soc.*, 1958, **80**, 2902–2903.
20 N. Izumiya and M. Muraoka, *J. Am. Chem. Soc.*, 1969, **91**, 2391–2392.
21 J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, 1955, **77**, 1067–1068.
22 F. Meiser, C. Cortez and F. Caruso, *Angew. Chem., Int. Ed.*, 2004, **43**, 5954–5957.
23 A. Moraillon, A. C. Gouget-Laemmel, F. Ozanam and J.-N. Chazalviel, *J. Phys. Chem. C*, 2008, **112**, 7158–7167.
24 W. Koenig and R. Geiger, *Chem. Ber.*, 1970, **103**, 788–798.
25 W. Koenig and R. Geiger, *Chem. Ber.*, 1970, **103**, 2024–2033.
26 A. Williams and I. T. Ibrahim, *Chem. Rev.*, 1981, **81**, 589–636.
27 L. A. Carpino, *J. Am. Chem. Soc.*, 1993, **115**, 4397–4398.
28 L. A. Carpino, H. Imazumi, B. M. Foxman, M. J. Vela, P. Henklein, A. El-faham, J. Klose and M. Bienert, *Org. Lett.*, 2000, **2**, 2253–2256.
29 W. Van den Nest, S. Yuval and F. Albericio, *J. Pept. Sci.*, 2001, **7**, 115–120.
30 M. Malow, K. D. Wehrstedt and S. Neuenfeld, *Tetrahedron Lett.*, 2007, **48**, 1233–1235.
31 K. D. Wehrstedt, P. A. Wandrey and D. Heitkamp, *J. Hazard. Mater.*, 2005, **126**, 1–7.
32 J. C. Sheehan and J. J. Hlavka, *J. Org. Chem.*, 1955, **21**, 439–441.
33 J. C. Sheehan, P. A. Cruickshank and G. L. Boshart, *J. Org. Chem.*, 1961, **26**, 2525–2528.
34 L. A. Carpino and A. El-faham, *Tetrahedron*, 1999, **55**, 6813–6830.
35 J. Izdebski and D. Kunce, *J. Pept. Sci.*, 1997, **3**, 141–144.
36 F. S. Gibson, M. Sook Park and H. Rapoport, *J. Org. Chem.*, 1994, **59**, 7503–7507.
37 F. Albericio, J. M. Bofill, A. El-faham and S. A. Kates, *J. Org. Chem.*, 1998, **63**, 9678–9683.
38 L. A. Carpino, H. Imazumi, A. El-faham, F. J. Ferrer, C. W. Zhang, Y. S. Lee, B. M. Foxman, P. Henklein, C. Hanay, C. Mugge, H. Wenschuh, K. Klose, M. Beyermann and M. Bienert, *Angew. Chem., Int. Ed.*, 2002, **41**, 442–445.
39 V. Dourtoglou, J.-C. Z. and B. Gross, *Tetrahedron Lett.*, 1978, **15**, 1269–1272.
40 R. Knorr, A. Trzeciak, W. Bannwarth and D. Gillessen, *Tetrahedron Lett.*, 1989, **30**, 1927–1930.
41 L. A. Carpino, A. Elfaham and F. Albericio, *Tetrahedron Lett.*, 1994, **35**, 2279–2282.
42 S. Q. Chen and J. C. Xu, *Tetrahedron Lett.*, 1992, **33**, 647–650.
43 A. Ehrlich, S. Rothemund, M. Brudel, M. Beyermann, L. A. Carpino and M. Bienert, *Tetrahedron Lett.*, 1993, **34**, 4781–4784.
44 P. Henklein, M. B., M. B. and R. Knorr, *Pept. 1990, Proc. Eur. Pept. Symp., 21st*, eds. E. Giralt and D. Andreu, ESCOM, Leiden, 1991, pp. 67–68.
45 L. A. Carpino and F. J. Ferrer, *Org. Lett.*, 2001, **3**, 2793–2795.
46 O. Marder, Y. Shvo and F. Albericio, *Chim. Oggi: Chem. Today*, 2002, **20**, 37–41.
47 T. Parekh, S. Bhattacharyya, O. Gooding, T. J. Lindberg and J. W. Labadie, *225th ACS National Meeting*, New Orleans, 2003.
48 A. El-faham, S. N. Khattab, M. Abdul-Ghani and F. Albericio, *Eur. J. Org. Chem.*, 2006, **2006**, 1563–1573.
49 A. El-faham and F. Albericio, *Org. Lett.*, 2007, **9**, 4475–4477.
50 A. El-faham and F. Albericio, *J. Org. Chem.*, 2008, **73**, 2731–2737.
51 B. Castro, J. R. Dormoy, G. Evin and C. Selve, *Tetrahedron Lett.*, 1975, **14**, 1219–1222.
52 J. Coste, D. Lenguyen and B. Castro, *Tetrahedron Lett.*, 1990, **31**, 205–208.
53 F. Albericio, M. Cases, J. Alsina, S. A. Triolo, L. A. Carpino and S. A. Kates, *Tetrahedron Lett.*, 1997, **38**, 4853–4856.
54 T. Hoeg-Jensen, C. E. Olsen and A. Holm, *J. Org. Chem.*, 1994, **59**, 1257–1263.
55 Y. Luxembourg, Y. Shvo and A. Ewenson, *World Pat.*, 2007020620, 2007.
56 P. Li and J. C. Xu, *Tetrahedron*, 2000, **56**, 4437–4445.
57 P. Li and J. C. Xu, *J. Pept. Res.*, 2001, **58**, 129–139.
58 P. Li and J. C. Xu, *Tetrahedron Lett.*, 1999, **40**, 3605–3608.
59 P. Li and J. C. Xu, *J. Pept. Res.*, 2000, **55**, 110–119.
60 P. Li and J. C. Xu, *Tetrahedron Lett.*, 2000, **41**, 721–724.
61 P. Li and J. C. Xu, *J. Chem. Soc., Perkin Trans. 2*, 2001, 113–120.
62 P. Li and J. C. Xu, *J. Org. Chem.*, 2000, **65**, 2951–2958.
63 S. Kim, H. Chang and Y. K. Ko, *Tetrahedron Lett.*, 1985, **26**, 1341–1342.

64 S. Kim, H. Chang and Y. K. Ko, *Bull. Korean Chem. Soc.*, 1987, **8**, 471–475.
65 L. A. Carpino, J. S. Xia, C. W. Zhang and A. El-faham, *J. Org. Chem.*, 2004, **69**, 62–71.
66 J. Klose, A. El-faham, P. Henklein, L. A. Carpino and M. Bienert, *Tetrahedron Lett.*, 1999, **40**, 2045–2048.
67 M. Itoh, H. Nojima, J. Notani, D. Hagiwara and K. Takai, *Tetrahedron Lett.*, 1974, **35**, 3089–3092.
68 J. Hachmann and M. Lebl, *Biopolymers (Pept. Sci.)*, 2006, **84**, 340–347.
69 E. Fischer and E. Fourneau, *Ber. Dtsch. Chem. Ges.*, 1901, **34**, 2688–2877.
70 A. Oku, Y. Yamaura and T. Harada, *J. Org. Chem.*, 1986, **51**, 3732–3734.
71 E. Falb, T. Yechezkel, Y. Salitra and C. Gilon, *J. Pept. Res.*, 1999, **53**, 507–517.
72 B. Thern, J. Rudolph and G. Jung, *Tetrahedron Lett.*, 2002, **43**, 5013–5016.
73 Y. S. Klausner and M. Bodanszky, *Synthesis*, 1974, 549–559.
74 L. A. Carpino, D. Sadataalaee, H. G. Chao and R. H. Deselms, *J. Am. Chem. Soc.*, 1990, **112**, 9651–9652.
75 J. M. White, A. R. Tunoori, B. J. Turunen and G. I. Georg, *J. Org. Chem.*, 2004, **69**, 2573–2576.
76 Z. J. Kaminski, *Biopolymers (Pept. Sci.)*, 2000, **55**, 140–164.
77 Z. J. Kaminski, B. Kolesinska and M. Malgorzata, *Synth. Commun.*, 2004, **34**, 3349–3358.
78 L. A. Carpino and A. Elfaham, *J. Am. Chem. Soc.*, 1995, **117**, 5401–5402.
79 A. El-faham, *Chem. Lett.*, 1998, 671–672.
80 J. Coste, M. N. Dufour, A. Pantaloni and B. Castro, *Tetrahedron Lett.*, 1990, **31**, 669–672.
81 J. Coste, E. Frerot, P. Jouin and B. Castro, *Tetrahedron Lett.*, 1991, **32**, 1967–1970.
82 K. Akaji, N. Kuriyama and Y. Kiso, *Tetrahedron Lett.*, 1994, **35**, 3315–3318.
83 B. Castro and J. R. Dormoy, *Tetrahedron Lett.*, 1972, **47**, 4747–4750.
84 C. Van der Auwera and M. J. O. Anteunis, *Int. J. Pept. Protein Res.*, 1987, **29**, 574–588.
85 R. D. Tung and D. H. Rich, *J. Am. Chem. Soc.*, 1985, **107**, 4342–4343.
86 W. J. Colucci, R. D. Tung, J. A. Petri and D. H. Rich, *J. Org. Chem.*, 1990, **55**, 2895–2903.
87 J. Przybylski and K. Wasilewski, *PL19920296449*, 1993.
88 T. Isobe and T. Ishikawa, *J. Org. Chem.*, 1999, **64**, 6984–6988.
89 P. Li and J. C. Xu, *Tetrahedron Lett.*, 1999, **40**, 8301–8304.
90 R. Wischnat, J. Rudolph, R. Hanke, R. Kaese, A. May, H. Theisc and U. Zuther, *Tetrahedron Lett.*, 2003, **44**, 4393–4394.
91 P. Li and J. C. Xu, *Tetrahedron*, 2000, **56**, 8119–8131.
92 T. Mukaiyama, *Angew. Chem., Int. Ed.*, 1979, **18**, 707–721.
93 B. Belleau and G. Malek, *J. Am. Chem. Soc.*, 1968, **90**, 1651–1652.
94 M. H. Hyun, M. H. Kang and S. C. Han, *Tetrahedron Lett.*, 1999, **40**, 3435–3438.
95 J. B. Thomas, M. J. Fall, J. B. Cooper, J. P. Burgess and F. I. Carroll, *Tetrahedron Lett.*, 1997, **38**, 5099–5102.
96 Y. Kiso and H. Yajima, *J. Chem. Soc., Chem. Commun.*, 1972, 942–943.
97 E. Valeur and M. Bradley, *Tetrahedron*, 2007, **63**, 8855–8871.
98 M. Kunishima, C. Kawachi, J. Morita, K. Terao, F. Iwasaki and S. Tani, *Tetrahedron*, 1999, **55**, 13159–13170.
99 Z. J. Kaminski, B. Kolesinska, J. Kolesinska, G. Sabatino, M. Chelli, P. Rovero, M. Blaszcyk, M. L. Glowka and A. M. Papini, *J. Am. Chem. Soc.*, 2005, **127**, 16912–16920.
100 B. Kolesinska, J. Fraczyk, G. Sabatino, A. M. Papini and Z. J. Kaminski, *Chim. Oggi: Chem. Today*, 2007, **25**, 26–31.
101 K. Jastrzabek, B. Kolesinska, G. Sabatino, F. Rizzolo, A. M. Papini and Z. J. Kaminski, *Int. J. Pept. Res. Ther.*, 2007, **13**, 229–236.
102 K. Pudhom and T. Vilaivan, *Synth. Commun.*, 2001, **31**, 61–70.
103 S. Q. Chen and J. C. Xu, *Tetrahedron Lett.*, 1991, **32**, 6711–6714.
104 L. A. Carpino, A. Elfaham and F. Albericio, *J. Org. Chem.*, 1995, **60**, 3561–3564.
105 H. Li, X. Jiang, Y. Yun-hua, C. Fan, T. Romoff and M. Goodman, *Org. Lett.*, 1999, **1**, 91–93.
106 Y. H. Ye, H. Li and X. Jiang, *Biopolymers (Pept. Sci.)*, 2004, **80**, 172–178.
107 C.-X. Fan, X.-L. Hao and Y.-H. Ye, *Synth. Commun.*, 1986, **26**, 1455–1460.
108 H. J. Gruber, G. Kada, B. Pragl, C. Riener, C. D. Hahn, G. S. Harms, W. Ahrer, T. G. Dax, K. Hohenthanner and H.-G. Knaus, *Bioconjugate Chem.*, 2000, **11**, 161–166.
109 Y. Kiso, T. Miyazaki, M. Satomi, H. Hiraiwa and T. Akita, *J. Chem. Soc., Chem. Commun.*, 1980, 1029–1030.
110 H. Ogura, S. Nagai and K. Takeda, *Tetrahedron Lett.*, 1980, **21**, 1467–1468.
111 A. G. Jackson, G. W. Kenner, G. A. Moore, R. Ramage and W. D. Thorpe, *Tetrahedron Lett.*, 1976, **40**, 3627–3630.
112 I. J. Galpin, A. K. Mohammed and A. Patel, *Tetrahedron*, 1988, **44**, 1685–1690.
113 T. Shiori, K. Ninomiya and S. Yamada, *J. Am. Chem. Soc.*, 1972, **94**, 6203–6205.
114 S. Yamada, N. Ikota, T. Shiori and S. Tachibana, *J. Am. Chem. Soc.*, 1975, **97**, 7174–7175.
115 Y. Takeuchi and S. Yamada, *Chem. Pharm. Bull.*, 1974, **22**, 832–840.
116 A. Gorecka, M. Leplawy, J. Zabrocki and A. Zwierzak, *Synthesis*, 1978, 474–476.
117 R. Ramage, C. P. Ashton, D. Hopton and M. J. Parrott, *Tetrahedron Lett.*, 1984, **25**, 4825–4828.
118 T. Katoh and M. Ueki, *Int. J. Pept. Protein Res.*, 1993, **42**, 264–269.
119 M. Ueki and T. Inazu, *Chem. Lett.*, 1982, 45–48.
120 G. T. Panse and S. K. Kamat, *Indian J. Chem.*, 1989, 793–795.
121 T. Yasuhara, Y. Nagaoka and K. Tomioka, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2901–2902.
122 T. Mukaiyama, N. Morito and Y. Watanabe, *Chem. Lett.*, 1979, 1305–1308.
123 T. Mukaiyama, K. Kamekawa and Y. Watanabe, *Chem. Lett.*, 1981, 1367–1370.
124 M. Miyake, M. Kirisawa and N. Tokutake, *Chem. Lett.*, 1985, 123–126.
125 T. Kunieda, Y. Abe, T. Higuchi and M. Hirobe, *Tetrahedron Lett.*, 1981, **22**, 1257–1258.
126 J. Klose, M. Bienert, C. Mollenkopf, D. Wehle, C.-W. Zhang, L. A. Carpino and P. Henklein, *Chem. Commun.*, 1999, 1847–1848.
127 M. Ueda and H. Oikawa, *J. Org. Chem.*, 1985, **50**, 760–763.
128 S. Kim and S. S. Kim, *J. Chem. Soc., Chem. Commun.*, 1986, 719–720.
129 N. D. Kokare, R. R. Nagawade, V. P. Rane and D. B. Shinde, *Synthesis*, 2007, 766–772.
130 N. D. Kokare, R. R. Nagawade, V. P. Rane and D. B. Shinde, *Tetrahedron Lett.*, 2007, **48**, 4437–4440.
131 L. Gomez, S. Ngouela, F. Gellibert, A. Wagner and C. Mioskowski, *Tetrahedron Lett.*, 2002, **43**, 7597–7599.
132 M. A. Bailen, R. Chinchilla, D. J. Dodsworth and C. Najera, *J. Org. Chem.*, 1999, **64**, 8936–8939.
133 M. A. Bailen, R. Chinchilla, D. J. Dodsworth and C. Najera, *Tetrahedron Lett.*, 2000, **41**, 9809–9813.
134 F. Albericio, M. A. Bailen, R. Chinchilla, D. J. Dodsworth and C. Najera, *Tetrahedron*, 2001, **57**, 9607–9613.
135 I. Shiina, K. Saitoh, M. Nakano, Y. Suenaga and T. Mukaiyama, *Collect. Czech. Chem. Commun.*, 2000, **65**, 621–630.
136 D. Cabaret and M. Wakselman, *Tetrahedron Lett.*, 1994, **35**, 9561–9564.
137 W. König, G. Breipohl, P. Pokorny and M. Birkner, *Pept. Proc. Eur. Pept. Symp.*, 1991, **21**, 143–145.
138 R. Paul and G. W. Anderson, *J. Am. Chem. Soc.*, 1960, **82**, 4596–4600.
139 R. K. Sharma and R. Jain, *Synlett*, 2007, 603–606.
140 A. K. Saha, P. Schultz and H. Rapoport, *J. Am. Chem. Soc.*, 1989, **111**, 4856–4859.
141 M. Murakami, M. Hayashi, N. Tamura, Y. Hoshino and Y. Ito, *Tetrahedron Lett.*, 1996, **37**, 7541–7544.
142 B. Iorga and J. M. Campagne, *Synlett*, 2004, 1826–1828.
143 T. Yang, C. Lin, H. Fu, Y. Jiang and Y. F. Zhao, *Bioorg. Chem.*, 2005, **33**, 386–392.
144 T. Tozawa, Y. Yamane and T. Mukaiyama, *Chem. Lett.*, 2005, **34**, 1334–1335.
145 Z. Ruan, R. M. Lawrence and C. B. Cooper, *Tetrahedron Lett.*, 2006, **47**, 7649–7651.

146 J. Vaughan and R. L. Osato, *J. Am. Chem. Soc*., 1951, 5553–5555.
147 J. Vaughan, *J. Am. Chem. Soc*., 1951, 3547.
148 J. Vaughan and R. L. Osato, *J. Am. Chem. Soc*., 1952, **74**, 676–678.
149 G. W. Anderson, J. E. Zimmerman and F. M. Callahan, *J. Am. Chem. Soc*., 1967, **89**, 5012–5017.
150 G. W. Anderson, J. E. Zimmerman and F. M. Callahan, *J. Am. Chem. Soc*., 1963, **85**, 3039–3040.
151 N. F. Albertson, *Org. React*., 1962, **12**, 157–355.
152 J. Kovacs and A. Kapoor, *J. Am. Chem. Soc*., 1965, **87**, 118–119.
153 M. H. Jakobsen, O. Buchardt, T. Engdahl and A. Holm, *Tetrahedron Lett*., 1991, **32**, 6199–6202.
154 D. H. R. Barton and J. A. Ferreira, *Tetrahedron*, 1996, **52**, 9367–9386.
155 J. W. Bode, *Curr. Opin. Drug Discovery Development*, 2006, **9**, 765–775.
156 C. Gunanathan, Y. Ben-David and D. Milstein, *Science*, 2007, **317**, 790–792.
157 M. Zhang, P. Vedantham, D. L. Flynn and P. R. Hanson, *J. Org. Chem*., 2004, **69**, 8340–8344.
158 N. M. Weinshenker and C. M. Shen, *Tetrahedron Lett*., 1972, **13**, 3281–3284.
159 M. C. Desai and L. M. S. Stramiello, *Tetrahedron Lett*., 1993, **34**, 7685–7688.
160 M. Lannuzel, M. Lamothe and M. Perez, *Tetrahedron Lett*., 2001, **42**, 6703–6705.
161 Y. Wolman, S. Kivity and M. Frankel, *Chem. Commun*., 1967, 629–630.
162 M. Ginisty, M.-N. Roy and A. B. Charette, *J. Org. Chem*., 2008, **73**, 2542–2547.
163 I. E. Pop, B. P. Deprez and A. L. Tartar, *J. Org. Chem*., 1997, **62**, 2594–2603.
164 K. Dendrinos, J. Jeong, W. Huang and A. G. Kalivretenos, *Chem. Commun*., 1998, 499–500.
165 K. G. Dendrinos and A. G. Kalivretenos, *Tetrahedron Lett*., 1998, **39**, 1321–1324.
166 R. Chinchilla, D. J. Dodsworth, C. Najera and J. M. Soriano, *Tetrahedron Lett*., 2000, **41**, 2463–2466.
167 S. V. Filip, V. Lejeune, J. P. Vors, J. Martinez and F. Cavelier, *Eur. J. Org. Chem*., 2004, 1936–1939.
168 S. Masala and M. Taddei, *Org. Lett*., 1999, **1**, 1355–1357.
169 K. Hioki, S. Kameyama, S. Tani and M. Kunishima, *Chem. Pharm. Bull*., 2007, **55**, 825–828.
170 W. Disadee, T. Watanabe and T. Ishikawa, *Synlett*, 2003, 115–117.
171 R. Chinchilla, D. J. Dodsworth, C. Najera, J. M. Soriano and M. Yus, *Arkivoc*, 2003, 41–47.
172 R. Chinchilla, D. J. Dodsworth, C. Najera and J. M. Soriano, *Tetrahedron Lett*., 2003, **44**, 463–466.
173 E. Convers, H. Tye and M. Whittaker, *Tetrahedron Lett*., 2004, **45**, 3401–3404.
174 S. Crosignani, J. Gonzalez and D. Swinnen, *Org. Lett*., 2004, **6**, 4579–4582.
175 S. Crosignani and D. Swinnen, *J. Comb. Chem*., 2005, **7**, 688–696.
176 E. Valeur and M. Bradley, *Chem. Commun*., 2005, 1164–1167.
177 M. Kakarla, G. Li and S. W. Gerritz, *J. Comb. Chem*., 2007, **9**, 745–747.
178 L. Bialy, J. J. Diaz-Mochon, E. Specker, L. Keinicke and M. Bradley, *Tetrahedron*, 2005, **61**, 8295–8305.
179 P. A. Boguszewski, A. J. Mendonca, F. P. Warner and M. J. I. Williamson, *232nd ACS National Meeting San Francisco*, USA, 2006.