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# Recent development of peptide coupling reagents in organic synthesis

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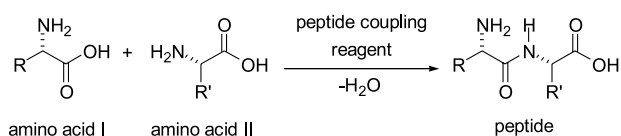
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## 1. Introduction

In recent years, peptide coupling reactions have been significantly advanced in accord with the development of new peptide coupling reagents in organic synthesis. Even though a number of valuable reviews have been published in this area,<sup>1</sup> the development of new peptide coupling reagents has been steadily accelerated in the past few years. Moreover, tremendously expanded applications have been possible to new and broad synthetic challenges. This report focuses on the major advances in coupling reagents that have had a great impact in the field. Among many, coupling reagents responsible for the formation of azide, mixed anhydride, and acid halide intermediates have gained substantial popularity in peptide coupling reactions. DCC as a peptide-coupling reagent has particularly attracted organic chemists in their synthesis of complex molecules. Moreover, the development of onium-type coupling reagents has made the incorporation of non-coded or sterically hindered amino acids including *N*-methylated and  $\alpha,\alpha$ -dialkylated amino acids smoothly into the corresponding peptides possible. In a typical peptide coupling reaction, the

carboxylic acid moiety of the amino acid I is first activated by an appropriate peptide coupling reagent, and then reacted with the amine moiety of the amino acid II to produce a desired peptide as illustrated in Scheme 1.

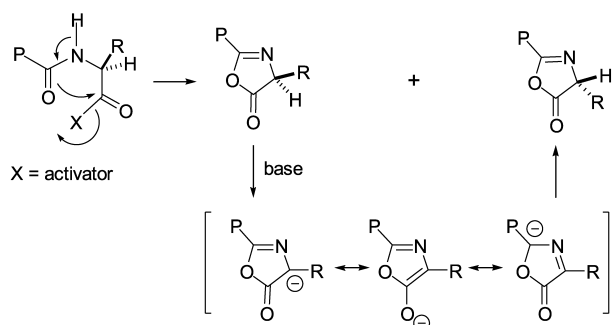


Scheme 1.

Another significant development in the field of peptide coupling reactions is the discovery of the racemisation suppressants. Racemisation can occur at the C-terminal amino acid residue in the course of a coupling reaction due to the ionisation of the  $\alpha$ -hydrogen and the formation of an oxazolone intermediate (Scheme 2). A peptide coupling reagent with an appropriate racemisation suppressing agent assures suppression of the undesired racemisation and other side reactions, and thus minimises the loss of the optical integrity at the chiral centre.<sup>2</sup> In some cases, racemisation suppressants are also used as additives to the peptide coupling reagent. In these examples, the additive plays a role as not only a racemisation suppressor but also as a rate enhancer.

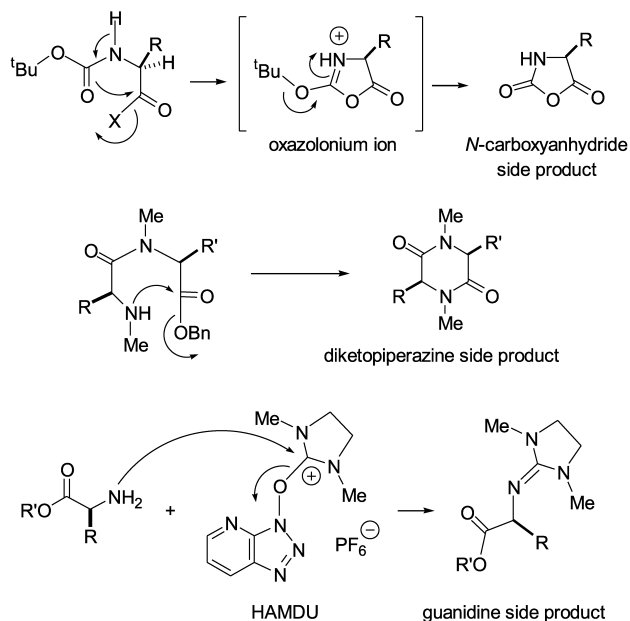
**Keywords:** Peptide coupling reagent; Amino acid; Racemisation suppressant; Enantiomeric excess.

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Scheme 2.

Immediate side reactions in peptide coupling reactions are the formation of *N*-carboxyanhydride, diketopiperazine and guanidine (Scheme 3).<sup>3,4</sup> A guanidine side product is often produced when the uronium coupling reagent is directly connected to the amine moiety of the amino acid residue.



Scheme 3.

Several techniques have been developed to overcome such side reactions during peptide coupling reactions. One aspect is the use of appropriate protecting groups (Fmoc, Trt, Cbz, etc.) on the nitrogen atom. Vedejs introduced arenesulfonyl protecting groups such as Bts and Ths in 1996 (Fig. 1). The *N*-Bts protected acid chloride gave a greater reactivity without any detectable racemisation than the *N*-Cbz protected acid fluoride (Bts-Phg-Aib-OCH<sub>3</sub>, 0.1% racemisation; Cbz-Phg-Aib-OCH<sub>3</sub>, <1% racemisation). Bts- and Ths-protected amines were easily deprotected by Zn/HOAc-EtOH or 50% H<sub>3</sub>PO<sub>2</sub>.<sup>5</sup>

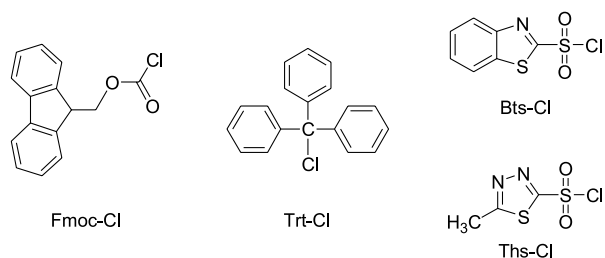
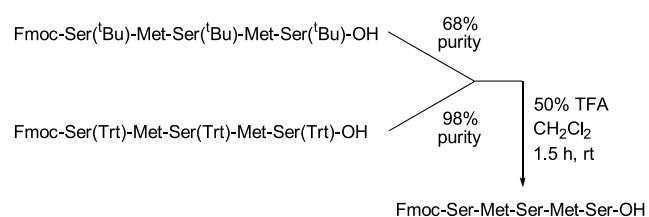


Figure 1.

Barlos showed that protecting groups influenced the purity of the peptides (Scheme 4).<sup>6</sup> For example, the purity of Fmoc-pentapeptide obtained from *N*-Fmoc-*O*-Trt protected peptide was 98%, while *N*-Fmoc-*O*-*t*Bu protected peptide gave only 68% due to the undesired *tert*-butylation of the nucleophilic side chain of Met and Trp. In addition, the Trt group of Fmoc-amino acids could be removed more easily than the *t*Bu group under very mild condition such as diluted TFA.

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Scheme 4.

The choice of base is also important in peptide coupling reactions (Fig. 2). Tertiary amines such as DIEA and NMM have been considered as practically useful bases in peptide synthesis due to the non-nucleophilic property of the base itself. More recently, collidine, TEMP, and DBDMAP were recommended by Carpino.<sup>7</sup> For example, coupling of Fmoc-Leu-OH with H-Pro-PAL-PEG-PS in DMF using TFFH/DIEA produced 0.8% of undesired epimer, while TFFH/DBDMAP reduced the epimerisation to 0.2%. The best result was obtained when collidine or TEMP was used as a base (0.1% of epimer).

This review evaluates advantages, disadvantages, and effectiveness of newly developed peptide coupling reagents. Each reagent is classified into one of eight types including phosphonium, uronium, immonium, carbodiimide, imidazolium, organophosphorous, acid halogenating and other coupling reagents, according to the structural similarity. Solid phase peptide synthesis is beyond the scope of this review.

## 2. Phosphonium reagents

In the early 1970s, Castro introduced CloP<sup>8</sup> and BroP<sup>9</sup> as peptide coupling reagents with noticeable racemisation in Young's test (Fig. 3). After HOBT was discovered as a

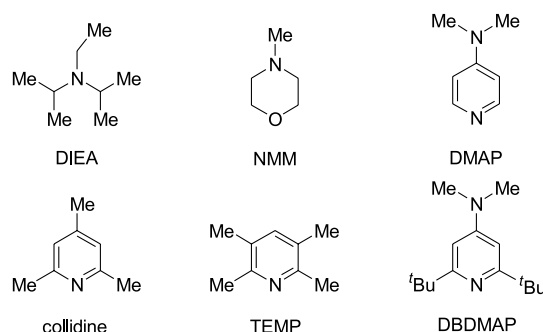


Figure 2.

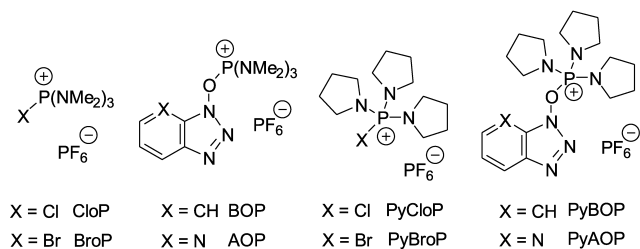
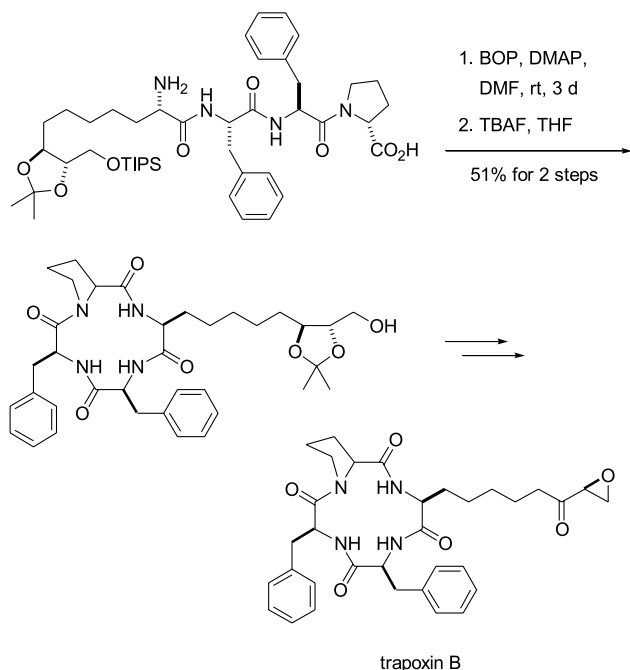


Figure 3.

racemisation suppressant, a new CloP-HOBt combined coupling reagent, known as BOP, was introduced in 1975.<sup>10</sup> BOP is a non-hygroscopic crystalline compound which can easily be prepared in large quantities.

Schreiber reported the use of BOP in the ring closure of 12-membered tetrapeptides such as trapoxin B. Schmidt's pentafluorophenyl ester protocol gave unsatisfactory results in this case (Scheme 5).<sup>11</sup>



Scheme 5.

Later, PyCloP, PyBroP, and PyBOP were introduced, where the dimethylamino moiety was replaced by pyrrolidine (Fig. 3).<sup>12</sup> These reagents could avoid the generation of poisonous hexamethylphosphoramide (HMPA) by-product.

In a following investigation, Coste reported that halogenophosphonium reagents often gave better results than other phosphonium-HOBt reagents in *N*-methylated amino acid cases.<sup>13</sup> For example, PyBroP and PyCloP gave 70–85% yields in the synthesis of Boc-Pro-MeVal-OMe and Cbz-Val-MeVal-OMe, whereas PyBOP gave only 11–26% yields. HBPyU and PyCIU uronium reagents also displayed a similar tendency. The formation of a stable benzotriazole activated ester intermediate lowered the reactivity and the yield. Similarly, the standard procedure such as the DCC/HOBt method gave a poor result due to the formation of

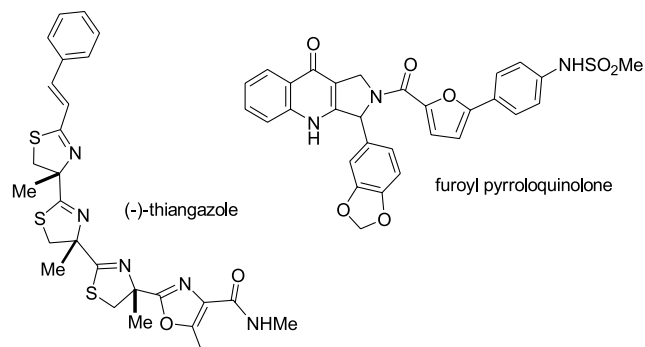
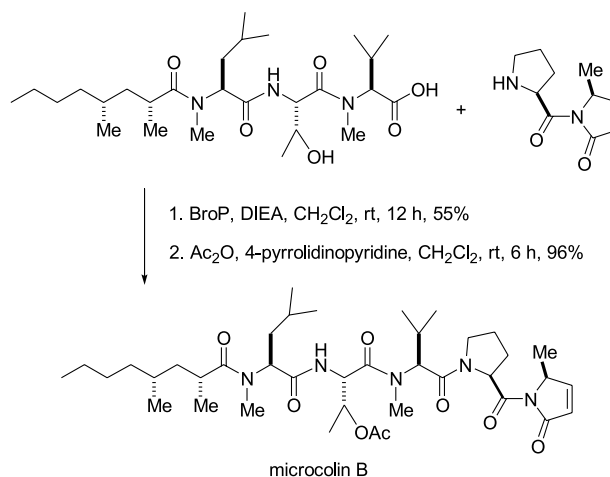


Figure 4.

HOBt ester and the *N*-acylurea as by-products. Coste also demonstrated that Fmoc or Cbz protected *N*-methyl amino acids were more prone to coupling reactions than Boc when PyBroP or PyCloP was used as the peptide coupling reagent. The loss of the *tert*-butyl cation caused the formation of *N*-carboxyanhydride through a Boc-oxazolium ion intermediate and lowered the reactivity (Scheme 3).<sup>14</sup> The efficiency of PyBroP was confirmed in the synthesis of (-)-thiangazole, destruxin B, and furoyl pyrroloquinolone (Fig. 4).<sup>15</sup>

Andrus reported the synthesis of a potent new immunosuppressant, microcolin B, using BroP as a peptide coupling reagent (Scheme 6).<sup>16</sup>



Scheme 6.

Since the discovery of HOBt-attached coupling reagents was successful, many racemisation suppressants have been exploited as a part of compositions of new peptide coupling reagents (Fig. 5). For example, AOP, PyAOP, PyTOP, and PyDOP (Figs. 3 and 5) were prepared in this regard. Additional electron-withdrawing substituents on the benzotriazole ring were introduced to form CF<sub>3</sub>-BOP, CF<sub>3</sub>-PyBOP, and CF<sub>3</sub>-NO<sub>2</sub>-PyBOP. They served as efficient peptide coupling reagents for the synthesis of dipeptides bearing *N*-methyl amino acids.<sup>17</sup>

Høeg-Jensen reported the formation of the thioamide as major and the amide as minor products when a monothio acid was reacted with an amine and phosphonium (BOP,

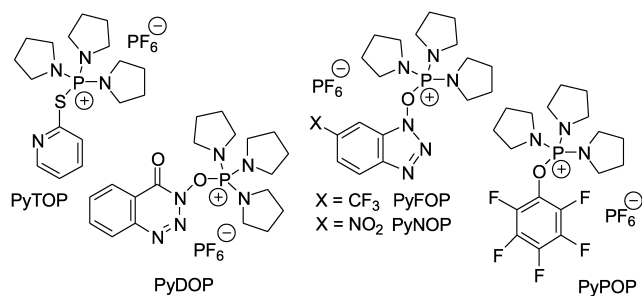
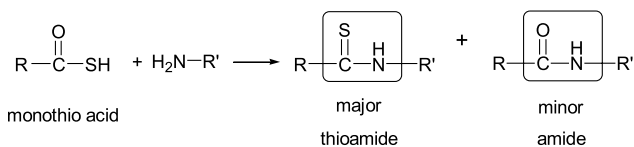


Figure 5.

NOP, PyBOP, PyNOP, PyBroP, PyCloP, PyFOP, PyTOP, PyPOP, and PyDOP) and organophosphorous reagents (BOP-Cl and ENDPP) as coupling reagents (Scheme 7). This was based upon the fact that phosphorus formed a stronger bond to oxygen than to sulfur for O/S-selectivity. PyNOP and PyFOP gave the best results for thioamide formation, while PyBroP gave the amide as the major product.<sup>18</sup>



Scheme 7.

### 3. Uronium reagents

Gross introduced HBTU as the progenitor of uronium reagents in 1978 (Fig. 6).<sup>19</sup> Since then, various analogues of HBTU have been prepared and investigated by Knorr.<sup>20</sup> The tetrafluoroborate or hexafluorophosphate anion is generally used as the non-nucleophilic counterion in uronium reagents. A comparison study between HBTU and TBTU showed that the counterion had no significant influence on the coupling rate or racemisation. Carpino disclosed the true structure of the active HBTU and its family as the *N*-guanidium rather than the *O*-uronium salt in his elegant study.<sup>21</sup>

TSTU and TNTU were recognised as useful peptide coupling reagents in aqueous reactions. The hematoregula-

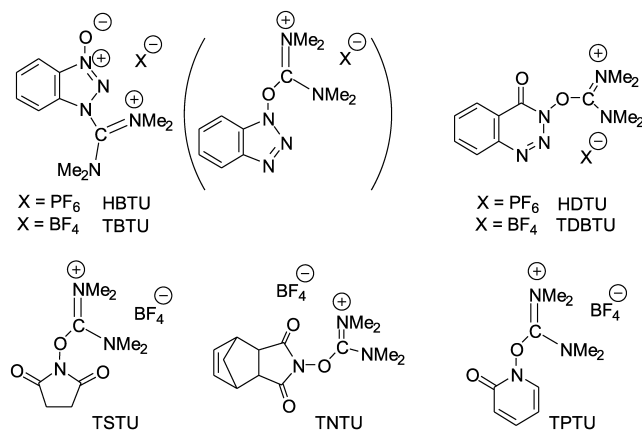
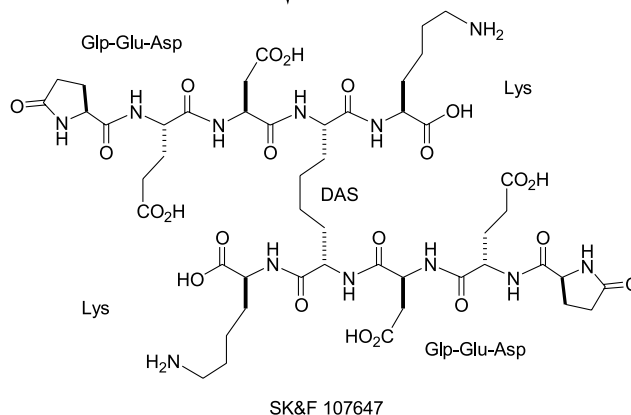
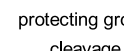
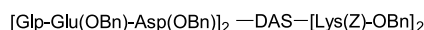
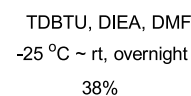
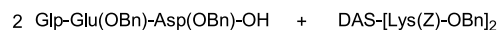


Figure 6.

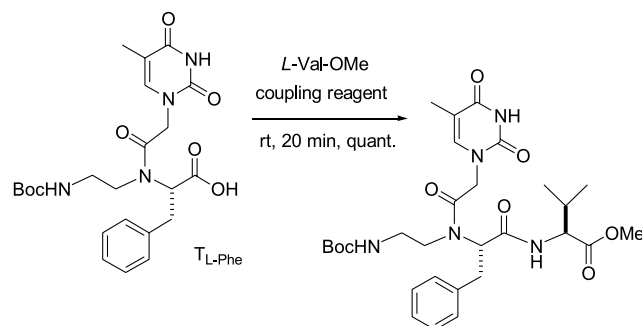


Scheme 8.

tory non-peptide SK&F 107647 was synthesised from the corresponding Glp-Glu(OBn)-Asp(OBn)-OH and DAS-[Lys(Z)-OBn]<sub>2</sub> by using TDBTU as the peptide coupling reagent in a purity of >97% in a Kg-scale synthesis (Scheme 8). Other coupling reagents were not as effective as TDBTU. DIEA was more efficient than NMM or collidine as a base in peptide coupling reactions.<sup>22</sup>

Since Nielsen first introduced PNA (peptide nucleic acid), in which the sugar-phosphate backbone was replaced by a polyamide chain composed of aminoethylglycine covalently linked to DNA bases,<sup>23</sup> several peptide coupling reagents have been employed in the synthesis of PNAs as DNA mimics.<sup>24</sup> As an example, the coupling reaction between T<sub>L</sub>-Phe and *L*-Val-OMe using TDBTU, DEPBT, HBTU, or HATU produced the chiral PNA monomer with good enantiomeric purity (DEPBT/DIEA, 95.8% ee; TDBTU/DIEA, 91.8% ee; HBTU/DIEA, 83.6% ee; HATU/DIEA, 77.2% ee) (Scheme 9).<sup>24a</sup>

The structural modification of HBTU provided several new peptide coupling reagents of same types with good activity.<sup>4,25</sup>



Scheme 9.

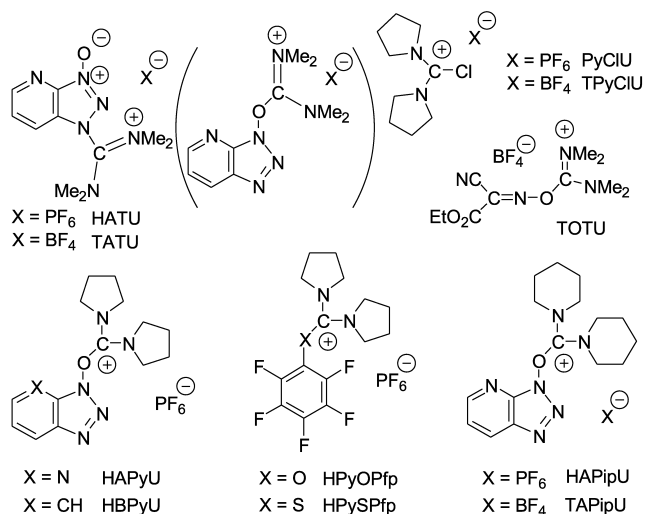
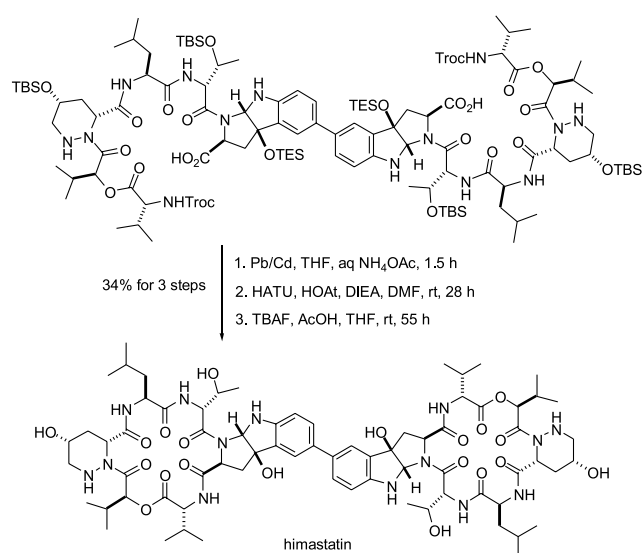


Figure 7.

Firstly, alteration on the HOBT moiety generated HATU, TATU, and TOTU (Fig. 7). Secondly, alteration on the *O*-uronium moiety gave HBPYU. Thirdly, alteration on both HOBT and *O*-uronium moieties resulted in PyCIU, TPyCIU, HAPyU, HPyOPfp, HPySPfp, HAPipU, and TAPipU.

HATU, the *N*-guanidium salt of HOAt, has been recently utilised in the macrocyclisation of complicated molecules.<sup>26</sup> For example, Danishefsky reported the total synthesis of himastatin, which structurally consisted of the biaryl linkage connecting the two identical subunits (Scheme 10).<sup>27</sup> Bismacrocyclisation on each end of the linear precursor was simultaneously achieved by the use of HATU/HOAt/DIEA.

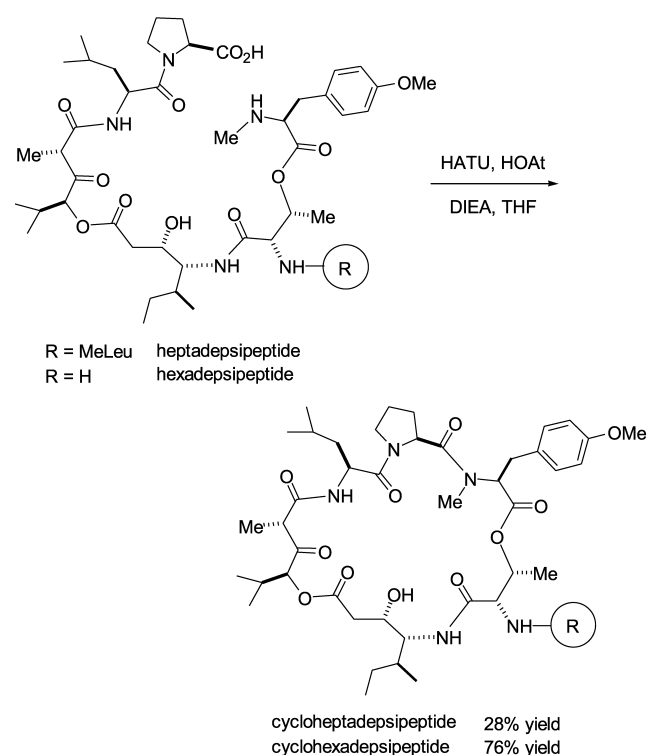
The cyclisation of all-*L*-tetrapeptides or all-*L*-pentapeptides was investigated by Ehrlich.<sup>26b</sup> It needed caution during the reaction to avoid side reactions such as cyclodimerisation or epimerisation at the C-terminal residue. HOAt-based reagents such as HATU, HAPyU, and TAPipU were more effective than TBTU or BOP. Notably,  $\alpha$ -configuration



Scheme 10.

alternation of the linear precursor ensured the efficient cyclisation. Marchelli reported a successful optimisation of the coupling condition using HATU/collidine in the synthesis of PNA analogues both in solution and in the solid phase.<sup>24b</sup>

Giralt and Lloyd-Williams applied HATU and improved the synthetic procedure of dehydrodidemnin B (Scheme 11), based on an earlier total synthesis of didemnins (Fig. 8).<sup>28</sup>



Scheme 11.

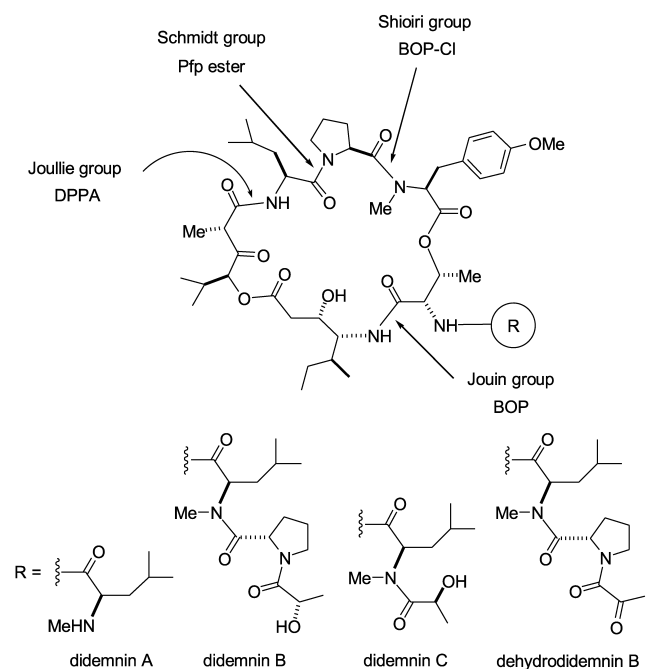
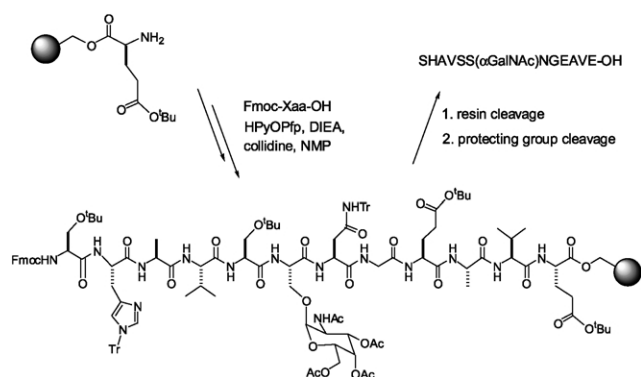


Figure 8.

Two routes were pursued for the synthesis of dehydridemnin B.<sup>29</sup> Firstly, the peptide coupling reaction with HATU/HOAt was undertaken between the carboxylic acid moiety of proline and the amine moiety of MeTyr-OMe, at the same cyclisation site with Shioiri's method in Figure 8, with the MeLeu side-chain already attached to the linear precursor to afford the desired macrocycle in 28% yield. The second route involved the synthesis of the macrocycle from the MeLeu side-chain-free linear hexadepsipeptide (HATU/HOAt, 76%; PyAOP/HOAt, 70%; PyBroP/HOAt, 37%). The side-chain was connected to the macrocycle afterwards in latter route.

More recently, Kunz introduced HPyOPfp (PfpPyU), which has a pentafluorophenyl (Pfp) residue as the leaving group, in 1998. HPyOPfp was first utilised in the synthesis of a glycopeptide from the homophilic recognition domain of mouse epithelial cadherin 1 in a solid-phase synthesis, and the result was compared with those of TBTU and Pfp-activated ester methods (Scheme 12).<sup>30</sup>



Scheme 12.

Carpino also investigated the ability of HPyOPfp to cyclise the linear Ala-Ala-MeAla-Ala-Ala peptide (0.001 M DMF, DIEA, 60 min). HPyOPfp (10%) and HPySPfp (11%) were less effective in yield compared with other reagents (HAPyU, 55%; HATU, 53%; PyAOP, 54%). However, when HOAt was applied together with HPyOPfp to the cyclisation, the product was obtained in much higher yield (56%) than with HPyOPfp alone. This result suggested that the racemisation suppressant could also take a part in the reaction rate enhancement.<sup>31</sup>

New thiouronium reagents were reported by Nájera (Fig. 9).<sup>32,33</sup> These reagents commonly consisted of 2-mercapto-pyridine-1-oxide which was also used as a racemisation suppressant. Structurally, HOTT and TOTT were derived from TMU (1,1,3,3-tetramethylurea), whereas HODT and TODT were derived from DMPU (1,3-dimethylpropyleneurea).

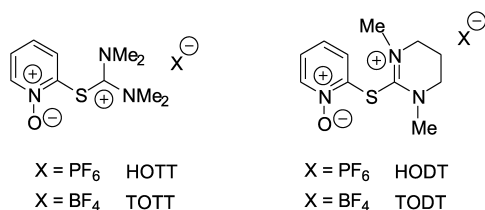
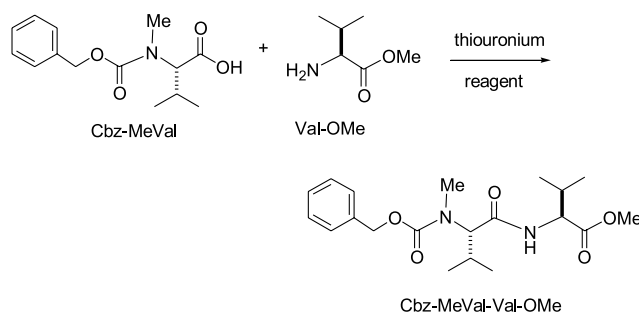


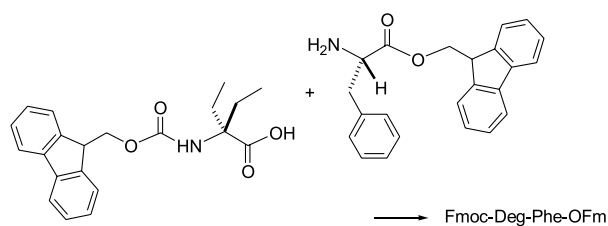
Figure 9.



Scheme 13.

When HOTT, TOTT, HODT, and TODT were applied to the solution synthesis of Cbz-MeVal-Val-OMe, similar yields were obtained (75–82%) (Scheme 13). In contrast, HODT and TODT showed a higher efficiency in both yield and racemisation inhibition in solid-phase synthesis, compared with HOTT and TOTT.

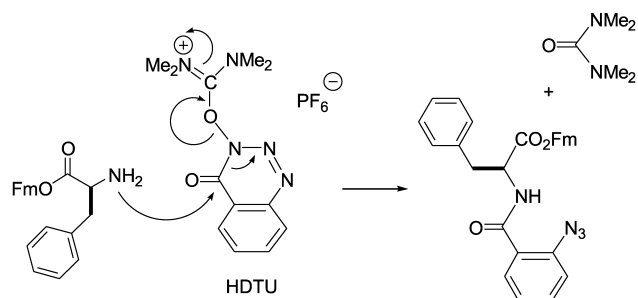
Albericio and Kates investigated the onium salt-based coupling reagents.<sup>4</sup> Uronium reagents were generally more stable than phosphonium reagents, while phosphonium reagents were more stable in the presence of base. It is particularly interesting to note that uronium and phosphonium reagents derived from HOAt were more efficient than the corresponding HOBt-based reagents. The difference in activities of these compounds could be explained by the hydrogen bond from the additional nitrogen atom of HOAt, stabilising the activated ester intermediate via the anchimeric assistance effect.<sup>34</sup> The reactivity pattern of these reagents was confirmed during the synthesis of a dipeptide, Fmoc-Deg-Phe-OFm (Scheme 14).



coupling reagent	HPLC yield (%)	coupling reagent	HPLC yield (%)
HATU	94	PyAOP	96
HBTU	85	PyBOP	89
HAPyU	92	AOP	94
HAMDU	57	BOP	85
HDTU	64		

Scheme 14.

HAMDU and HDTU are considered as inefficient reagents due to their instability by fast decomposition before achieving the activation of the carboxylic acid, as shown in Scheme 15. HAMDU decomposes to guanidine (Scheme 3), while HDTU decomposes to the side-product by the direct attack of the amine moiety of the amino acid on the carbonyl carbon of HDTU (Scheme 15).<sup>18,20</sup>



Scheme 15.

#### 4. Immonium reagents

Xu designed new immonium reagents by modifying known uronium reagents.<sup>35</sup> The structural distinction of immonium reagents is the replacement of the amino group of the central carbon atom in uronium reagents with a hydrogen, an alkyl, or an aryl group. BOMI was shown to be the *N*-guanidine derivative instead of the *O*-uronium compound by an X-ray single crystal analysis. Some representative immonium reagents are shown in Figure 10.

BOMI and BDMP showed a higher reactivity than other immonium reagents such as AOMP, FOMP, DOMP, BPMP, and SOMP for the synthesis of a tripeptide (Scheme 16).<sup>36</sup> Interestingly, immonium reagents gave better results than uronium compounds such as HAPyU and HBPpyU, presumably due to the fact that resonance stabilisation of uronium reagents from the amine substituent on the central carbon atom contributed to the retardation of reactivity and

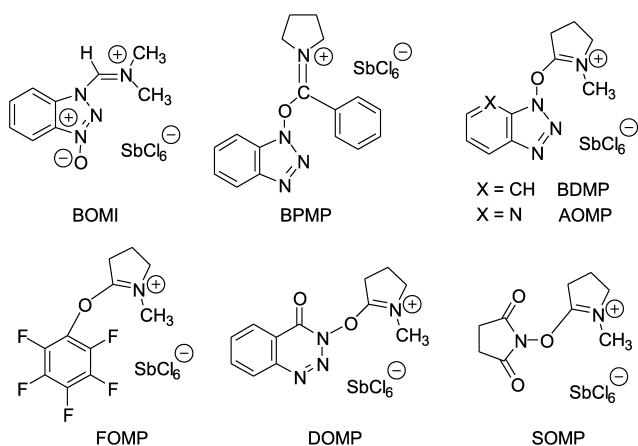
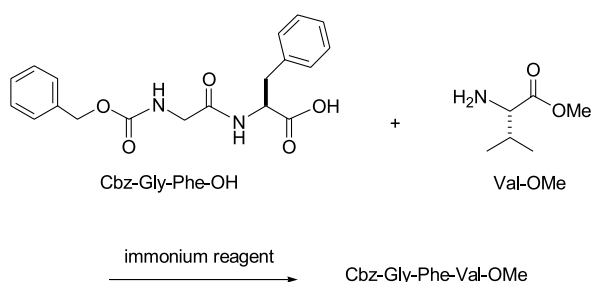


Figure 10.



Scheme 16.

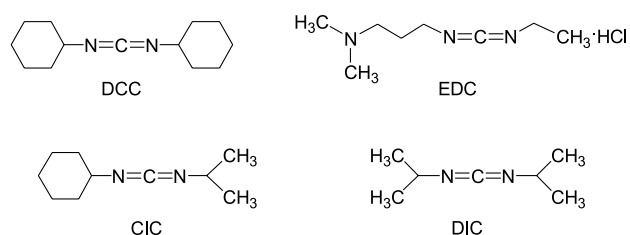


Figure 11.

such a nitrogen atom was not available in the immonium reagents.

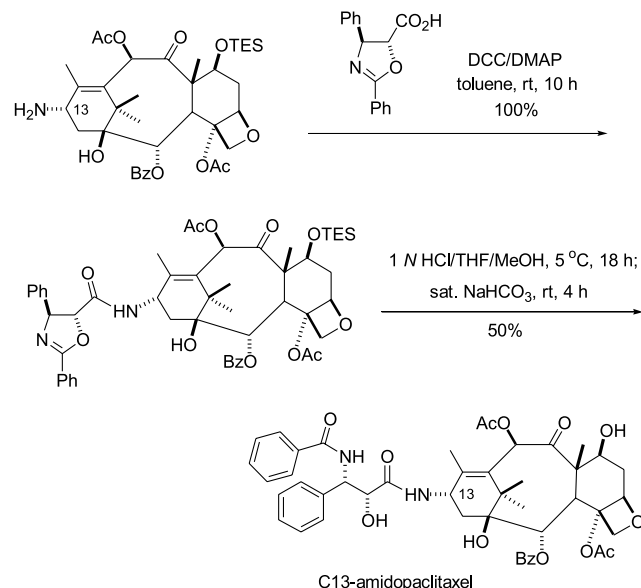
A suitable base for the immonium reagents was found to be 2,6-lutidine in THF or MeCN. BOMI was applied to the synthesis of an oligopeptide, Leu-enkephalin, both in solution and in the solid phase.<sup>36b</sup>

#### 5. Carbodiimide reagents

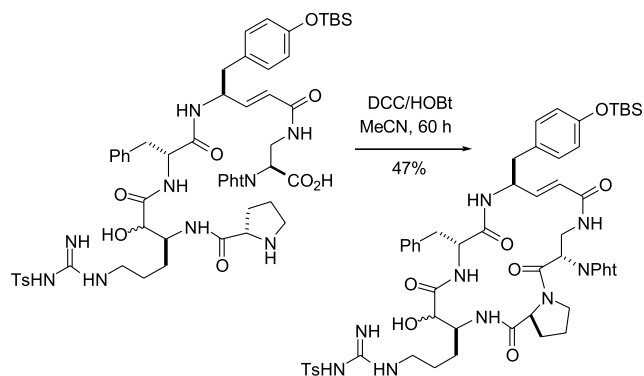
Carbodiimide reagents have been widely used in peptide synthesis because they show a moderate activity and they are reasonably cheap (Fig. 11). DCC was first reported by Sheehan in 1955.<sup>37</sup> The by-product was insoluble in most solvents and hence was easily separable from the product. Since the successful launch of DCC/HOBt in peptide synthesis,<sup>38</sup> carbodiimides have dramatically expanded their scope with the aid of various additives such as HOPO, HOAt, HODhbt and more recently HOCT. These additives have complemented the weakness of coupling reagents by enhancing the reaction rate and reducing the racemisation.

Chen reported the synthesis of C-13 amide-linked paclitaxel analogues (Scheme 17).<sup>39</sup> The coupling reaction between the C13-aminobaccatin and oxazoline was achieved by using DCC/DMAP to provide the desired product in good yield.

Maryanoff successfully constructed the macrocycle in a cyclic pentapeptide, cyclotheonamide A, employing



Scheme 17.

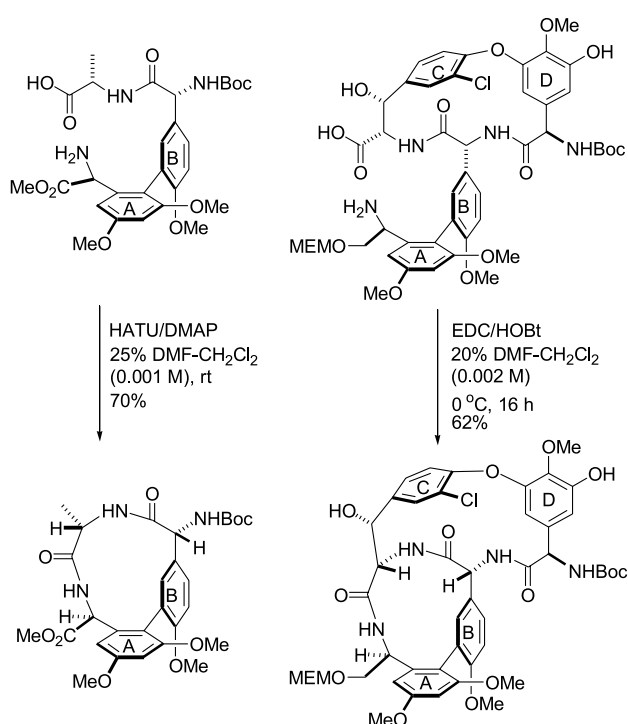


Scheme 18.

DCC/HOBt, in 47% yield (Scheme 18).<sup>40</sup> Cyclisation of the unprotected hydroxyl function produced the undesired 15-membered lactone as the side-product.

Some examples have been reported using EDC/HOBt, as compared to other types of reagents. Boger applied EDC/HOBt to the synthesis of the vancomycin aglycon AB ring system (Scheme 19).<sup>41a</sup> For the formation of the monocycle in a model study, HATU/DMAP gave a better result than PyBOP/DMAP or EDC/HOBt. However, the best condition in the natural bicyclo system of the vancomycin aglycon was EDC/HOBt for 16 h at 0 °C (62% yield). Joullié further adapted the same macrocyclisation condition elegantly for the synthesis of a cyclic depsipeptide containing a chiral tertiary-alkyl-aryl ether, ustiloxin D.<sup>41b</sup>

Carbodiimide reagents were designed to prevent the formation of the undesired *N*-acylurea and to facilitate easy separation from the by-products. The insolubility of the



Scheme 19.

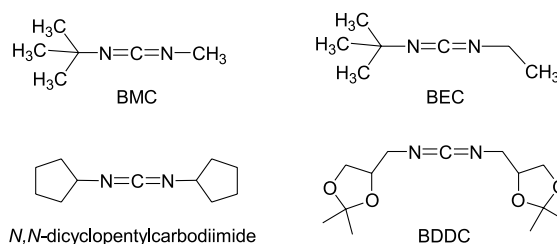


Figure 12.

by-product occasionally caused problems for the synthesis of polypeptides. Since the ureas from DIC and CIC were relatively soluble in  $\text{CH}_2\text{Cl}_2$ , these reagents were more suitable for solid-phase peptide synthesis than DCC. The solubilities of *N*-cyclohexyl-*N'*-isopropylurea, *N,N'*-diisopropylurea, and *N,N'*-dicyclohexylurea were 30, 5.2 and 1.5 g/L in  $\text{CH}_2\text{Cl}_2$ , respectively.<sup>42</sup> In Fmoc solid-phase peptide synthesis, the DIC/additive method was investigated in various conditions by changing the additive, base, and solvent. Carpino demonstrated that DIC/HOAt was superior to DIC/other additives.<sup>43</sup> Further variations of the carbodiimide such as BMC, BEC, and *N,N'*-dicyclopentylcarbodiimide were reported (Fig. 12).<sup>44</sup> Rapoport developed the hydrophilic side-chain-containing carbodiimide, BDDC, in 1994.<sup>45</sup> BDDC in THF, DMF, or toluene gave a reasonable yield for the coupling reaction with a Boc-protected amino acid and the by-product was easily removed by an acid wash.

A combination method using carbodiimides with appropriate activators has been widely applied in peptide coupling reactions since the pioneering work by Bodanszky with *p*-nitrophenol.<sup>46</sup> Active esters can be produced from activators such as *N*-hydroxyphthalimide,<sup>47</sup> and *N*-hydroxysuccinimide<sup>48</sup> (Fig. 13).

As an example, the HOSu/DCC method was used in the synthesis of the peptidyl nucleoside antibiotic, polyoxin J (Scheme 20). The polyoxamic acid derivative was converted to the *N*-hydroxysuccinimide active ester and then coupled with the unprotected thymine, polyoxin C, providing the sugar analogue in 58% yield.<sup>49</sup>

Kovacs and Balasubramanian have explored the electron-withdrawing effect of chlorine atoms in the pentachlorophenyl (Pcp) activated esters.<sup>50</sup> More recently, it was found that the Pfp activated ester was more reactive than the Pcp ester due to the steric hindrance of chlorine atoms. Although the Pfp ester should be isolated and purified prior to

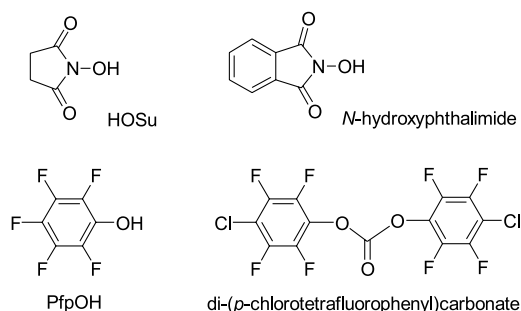
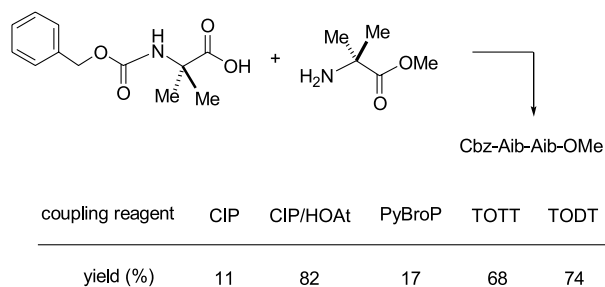


Figure 13.



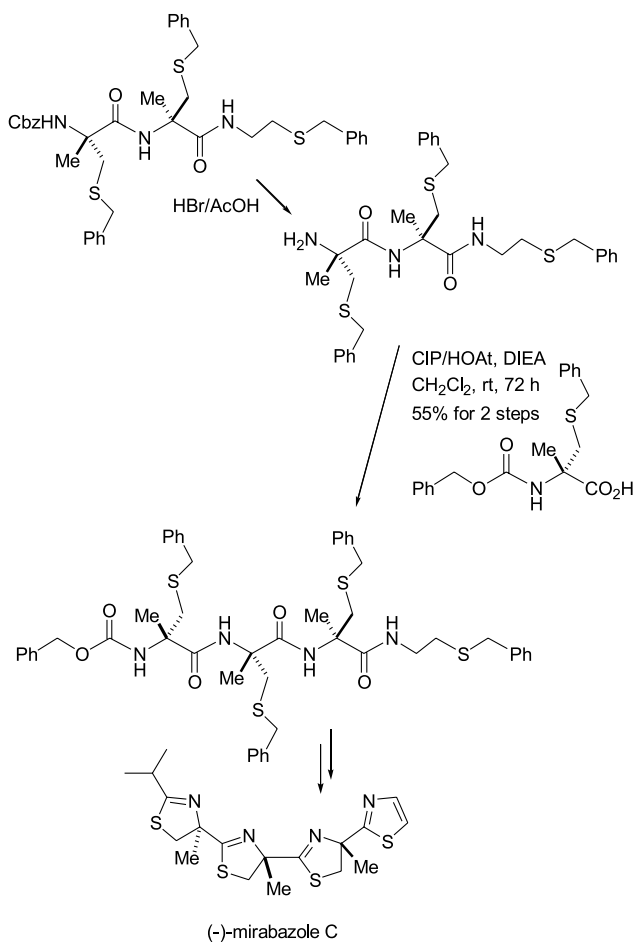




Scheme 23.

Kiso developed modified imidazolium reagents, BOI, and its precursor, CIP, as new peptide coupling reagents and, later, as new esterification reagents to avoid the toxic HMPA by-product of the BOP reagent.<sup>59</sup> The efficiency of CIP was also evaluated in peptide coupling reactions between sterically hindered  $\alpha,\alpha$ -dialkylated amino acids (Scheme 23). The CIP/HOAt combined coupling reagents showed the best result in the formation of a dipeptide, Cbz-Aib-Aib-OMe, compared with PyBroP, TODT, TOTT, and CIP alone.<sup>33</sup> HOAt as the additive to CIP gave the highest catalytic enhancement with the trend of activity in the order: HOAt > HODhbt > DMAP > HOBt.

In addition, Kiso successfully applied the CIP/HOAt combination to the synthesis of (-)-mirabazole C (Scheme 24).<sup>60</sup> After removal of the Cbz protecting group with HBr/



Scheme 24.

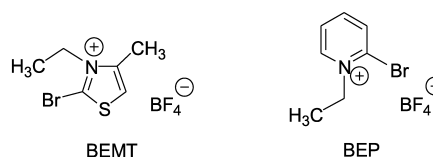


Figure 15.

AcOH, the resulting amine was coupled with *N*-Cbz-*S*-benzyl-(*R*)-2-methylcysteine using CIP/HOAt in 55% yield for 2 steps. The demasked tetrathiol unit of (*R*)-2-methylcysteine underwent  $\text{TiCl}_4$ -mediated cyclo-dehydration to establish the thiazole ring moiety in (-)-mirabazole C.

Recently, Xu developed CMBI (Fig. 14) a benzene ring-fused derivative of CIP, as a new peptide coupling reagent during the synthesis of a pentadepsipeptide intermediate of an anticancer drug, actinomycin D.<sup>61</sup>

Xu also introduced a thiazolium-type reagent, BEMT, as shown in Figure 15.<sup>62</sup> The mechanism of BEMT may involve the sequential conversion of a carboxylic acid of an amino acid into the corresponding acyloxythiazolium salt and then to the acid bromide, leaving *N*-ethyl-4-methylthiazolidone as the by-product. For the synthesis of the tripeptide, Z-Gly-Phe-Val-OMe, BEMT gave 46% yield and 2.7% racemisation, while a halogenouronium reagent, PyCIU, gave 12% yield and 25% racemisation after 2 min.

The efficacy of BEMT and BEP was elegantly demonstrated in fragment coupling reactions containing *N*-alkylated amino acids during the synthesis of the immunosuppressive cyclosporin O (Fig. 16).<sup>63</sup>

More recently, Wischnat has introduced the crystalline and non-hygroscopic BMTB as a new peptide coupling reagent (Scheme 25). BMTB was produced by alkylation of its

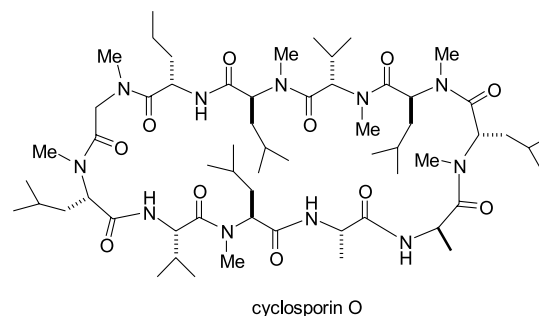
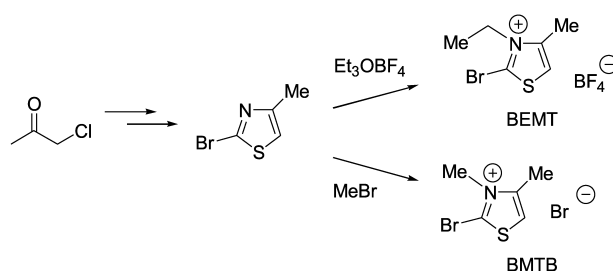


Figure 16.



Scheme 25.

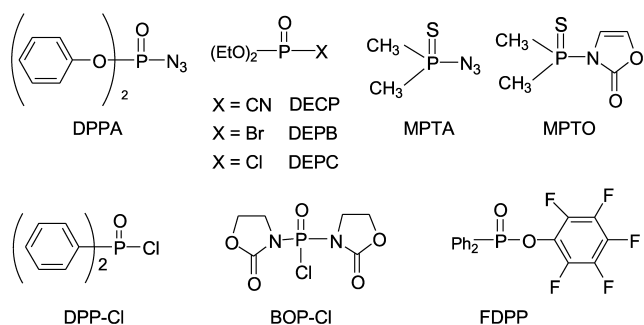


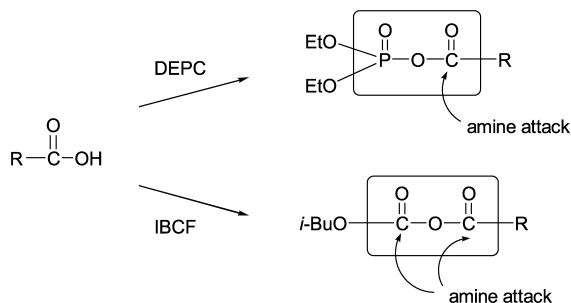
Figure 17.

precursor with methyl bromide (MeBr), while BEMT was prepared with triethyloxonium tetrafluoroborate ( $\text{Et}_3\text{OBF}_4$ ) from the common intermediate.<sup>64</sup>

## 7. Organophosphorous reagents

Since the mixed carboxylic-phosphoric anhydride method was first proposed in peptide chemistry by Yamada in 1972 using DPPA from diphenylphosphorochloridate and sodium azide,<sup>65</sup> various organophosphorous compounds have been developed as new peptide coupling reagents (Fig. 17).

This method usually gave a higher regioselectivity towards nucleophilic attack by the amine component than a mixed carbonic anhydride method (Scheme 26).<sup>66</sup>

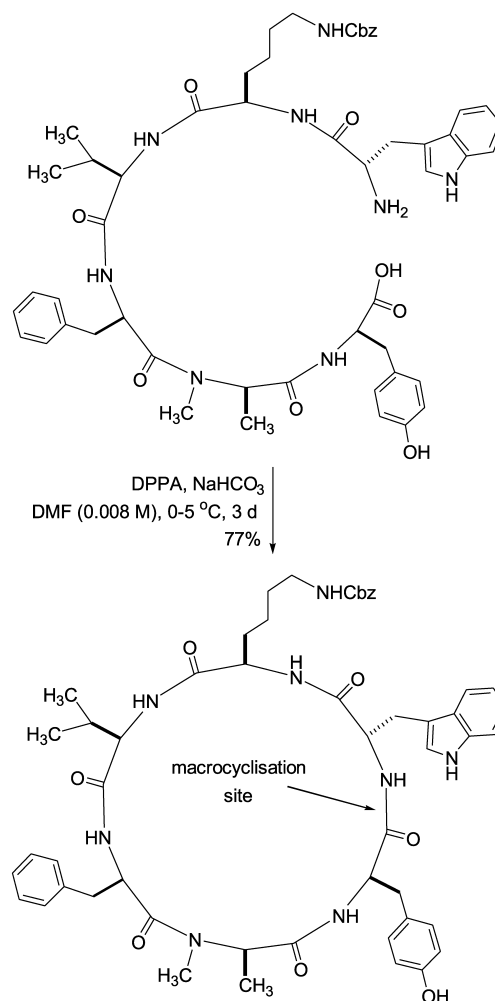


Scheme 26.

Brady applied an improved DPPA technique, in which the triethylamine base was replaced by sodium bicarbonate, in the macrocyclisation step during the synthesis of a cyclic hexapeptide analogue of somatostatin (DPPA/ $\text{NaHCO}_3$ , 90% monomer; DPPA/ $\text{Et}_3\text{N}$ , 75% monomer, as determined by analytical gel filtration) (Scheme 27).<sup>67</sup>

The DPPA/ $\text{NaHCO}_3$  method was also employed for the 32-membered macrocyclisation of (–)-sandramycin.<sup>68</sup> The key advantage of the use of this method relied on the insolubility of  $\text{NaHCO}_3$  in the reaction medium, where a mild reaction condition was required.

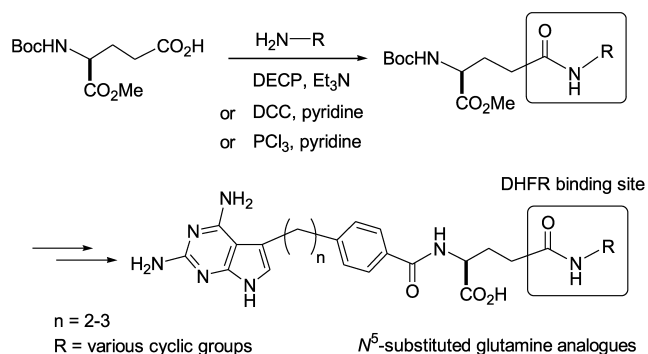
DECP (Fig. 17) was easily prepared by the reaction of triethyl phosphite with cyanogen bromide.<sup>69</sup> Itoh reported the synthesis of  $N^5$ -substituted glutamine analogues, which displayed potent antitumour activities against MTX-resistant tumours by inhibition of dihydrofolate reductase, using several coupling reagents including DECP and compared



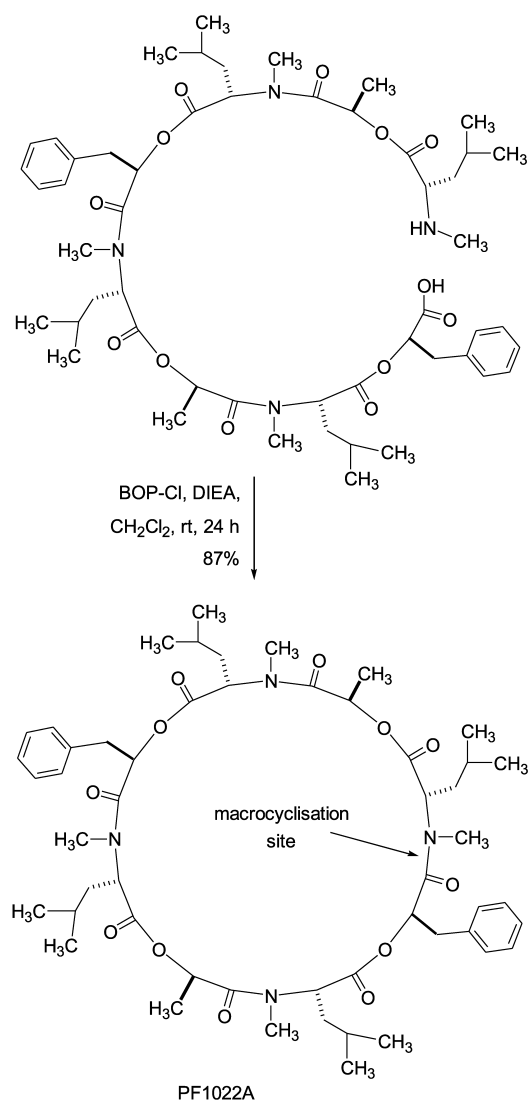
Scheme 27.

their results (Scheme 28).<sup>70</sup> The use of traditional carbodiimide reagents such as DCC was effective for coupling reactions between Boc-Glu-OMe and regular amines. On the other hand, DECP was useful for more nucleophilic amines containing electron-donating substituents in an aromatic ring, whereas phosphorus trichloride was effective for less nucleophilic amines.

One of the notable variations in organophosphorous reagents was the development of the phosphinic acid derivatives. DPP-Cl was first introduced in 1976.<sup>65b,71</sup>



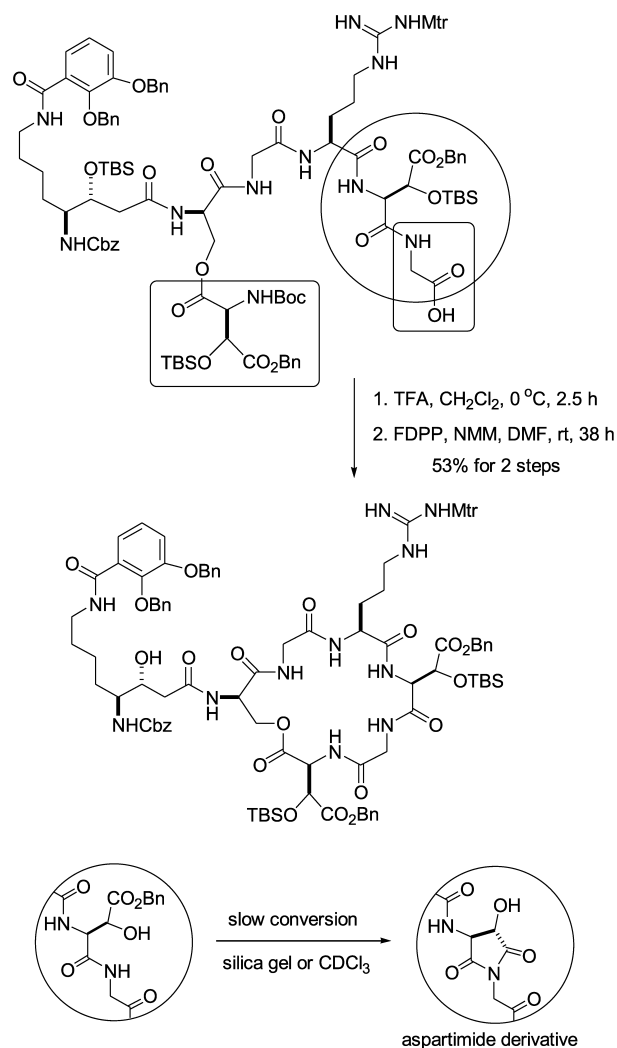
Scheme 28.



Scheme 29.

Shortly after, Palomo-Coll developed BOP-Cl (Fig. 17) in 1980<sup>72</sup> and it quickly became popular in practical applications. BOP-Cl was well known as a powerful reagent for peptide coupling reactions involving *N*-alkylamino acids. In the macrocyclisation step during the synthesis of the cyclooctadepsipeptide, PF1022A (Scheme 29), BOP-Cl gave a high yield (87%) with negligible racemisation, whereas the Pfp active ester or EDC/HOBt method gave only moderate yields (28 and 59%, respectively).<sup>73</sup>

FDPP has been widely used as a new coupling reagent in macrocyclisation since its development in 1991 (Fig. 17).<sup>74</sup> Shioiri employed FDPP for the synthesis of a cyclic depsipeptide, alterobactin A, containing two types of non-coded amino acids such as *L*-threo- $\beta$ -hydroxyaspartic acid and (3*R*,4*S*)-4,8-diamino-3-hydroxyoctanoic acid (Scheme 30). Cyclisation between Gly and  $\beta$ -OH-Asp was accomplished with FDPP in 53% yield for 2 steps. The choice of glycine as the C-terminal residue in the macrocyclisation gave the synthetic advantages of non-epimerisation and non-steric hindrance.<sup>75</sup> When the hydroxyl group of the eastern hemisphere was not protected prior to the macro-



Scheme 30.

cyclisation, an aspartimide derivative was formed as the by-product.

Modification of DPPA led to the development of thiophosphinic-type coupling reagents such as MPTA and MPTO (Fig. 17).<sup>76</sup> As DPPA is an oil, these reagents are crystalline and stable for long-term storage. Since MPTA generated a carbamoyl azide or urea derivative as the by-product, Ueki introduced MPTO, in which the azide group of MPTA was replaced by a 2-oxazolone group. When the coupling conditions were compared for the cyclisation of H-D-Trp-D-Glu(OBn)-Ala-D-Val-Leu-OH, MPTA/HOBt/DIEA gave 84% yield (<0.1% of epimer) in 8 h and MPTO/HOBt/DIEA gave 78% yield (<0.1% of epimer) in 3 h, whereas DPPA/HOBt/DIEA gave only 66% yield in 3 days (6.0% of epimer).

In addition to the earlier development of organophosphorous reagents, a great deal of effort has been focused on creating various coupling reagents of a similar kind. For example, NDPP,<sup>77</sup> Cpt-Cl,<sup>78</sup> BMP-Cl,<sup>79</sup> DEBP,<sup>80</sup> BDP,<sup>81</sup> bis(*o*-nitrophenyl)phenyl phosphonate,<sup>82</sup> (5-nitro-pyridyl)-diphenyl phosphinate,<sup>83</sup> diphenyl 2-oxo-3-oxazolonyl phosphonate,<sup>84</sup> and 1,2-benzisoxazol-3-yl diphenyl phosphate<sup>85</sup> were prepared by various research groups (Fig. 18).

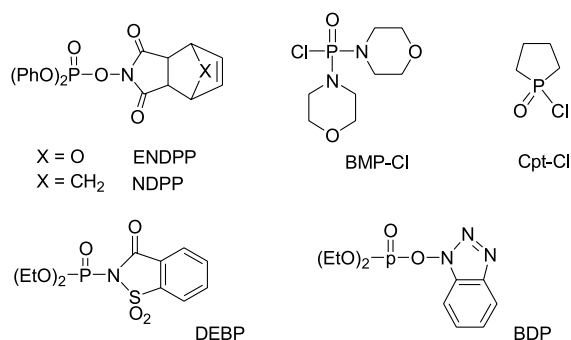


Figure 18.

More recently, Ye developed DEPBO, DOPBO, DOPBT, and DEPBT (Fig. 19).<sup>86</sup> DEPBT derived from DEPC and HODhbt was evaluated against other peptide coupling reagents and gave good results in segment coupling reactions.<sup>87</sup> Even though HODhbt was superior to HOBT for racemisation-suppressing ability, its utility was limited due to the side reactions. Thus, the reaction conditions were optimised to use 2 equivalents of DEPBT and DIEA in THF.

DEPBT was efficient for the synthesis of *N*-protected peptide alcohols and *N*-glycopeptides (Scheme 31).<sup>88</sup> When DEPBT was used as the coupling reagent, the carboxylic group selectively reacted with the amino group in the presence of unprotected hydroxyl functional groups.

### 8. Acid halogenating reagents

The acid halide technique is frequently recommended in

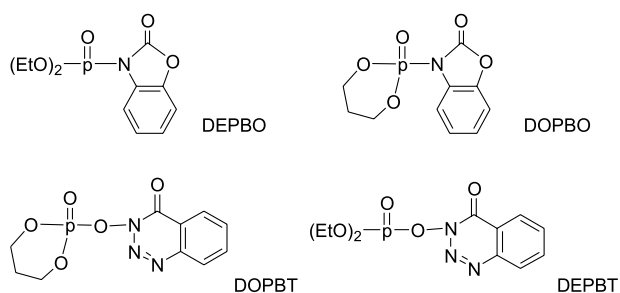
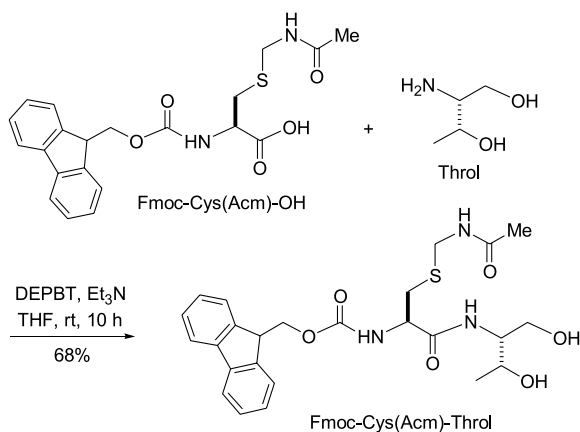


Figure 19.

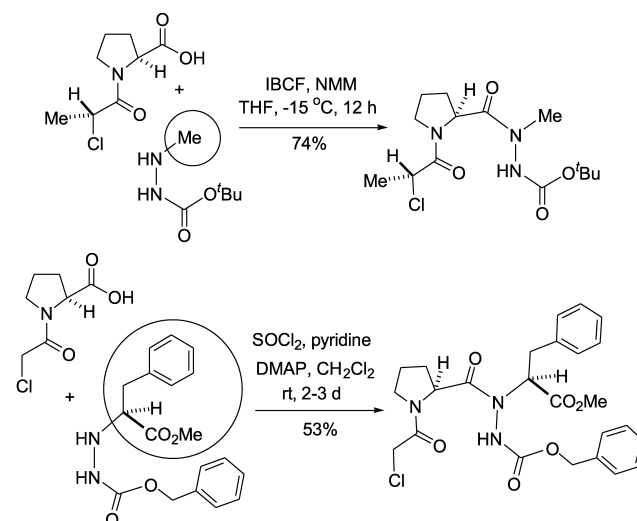


Scheme 31.

peptide coupling reactions of extremely hindered amino acids. Nonetheless, an amino acid chloride-bearing acid-labile protecting group can be easily racemised to the oxazolone so that the practical application of the acid chloride is restricted, despite its high reactivity and low cost.

The acid chloride method was first introduced to peptide chemistry by Fisher in 1903.<sup>89</sup> Since then, chlorination of amino acids was carried out with various chlorinating reagents such as pivaloyl chloride,<sup>90</sup> phthaloyl dichloride,<sup>91</sup> thionyl chloride,<sup>92</sup> oxalic chloride,<sup>93</sup> etc.

Gani reported the synthesis of *cis*-peptidyl prolyl peptide mimetics (Scheme 32). The coupling reaction between proline and methyl hydrazide was achieved with IBCF in 74% yield. However, when the steric bulkiness of the *N*-substituent in the hydrazide was increased, a more powerful activation of the carboxylic acid was required. Thionyl chloride in pyridine was applied to the coupling reactions for this purpose.<sup>92c</sup>



Scheme 32.

Other useful acid halogenating reagents are cyanuric chloride<sup>94</sup> and CDMT<sup>95</sup> (Fig. 20). Due to the weak basicity of the triazine moiety, the by-product and excess coupling reagent were easily removed by washing with dilute acid.

Gilon has recently reported the use of BTC (Fig. 20) as a chlorinating reagent in solid-phase peptide synthesis.<sup>96</sup> Coupling reactions mediated by BTC gave good results for Fmoc-amino acids containing acid-labile side-chains. Since NMP reacted with BTC to form the chloroiminium ion and led to racemisation, inert solvents such as THF or dioxane were required.

Since amino acid fluorides showed a better stability towards

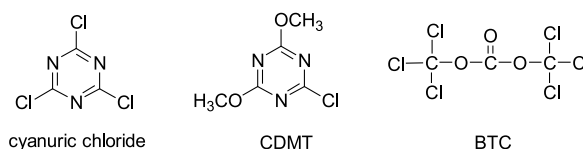


Figure 20.

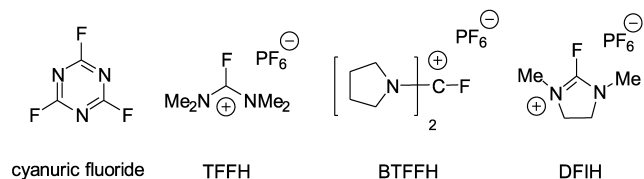
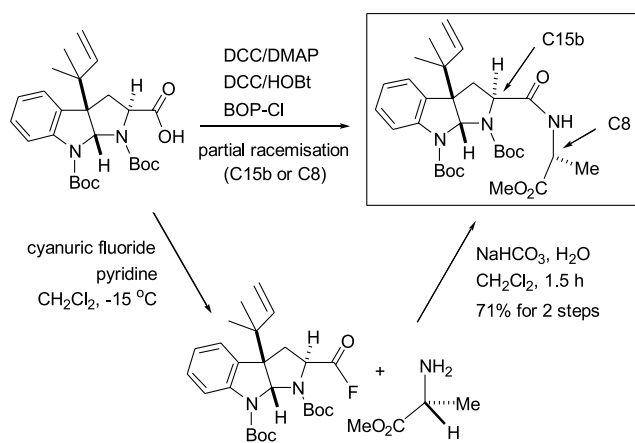


Figure 21.

moisture and acid-labile functional groups than amino acid chlorides, several acid fluorinating reagents were developed, as shown in Figure 21<sup>97</sup> Cyanuric fluoride easily converted amino acids into the corresponding acid fluorides.<sup>98</sup> For sterically hindered amino acids, such as Deg, MeAib and Iva, the acid fluoride method gave excellent yields in peptide coupling reactions.<sup>99</sup>

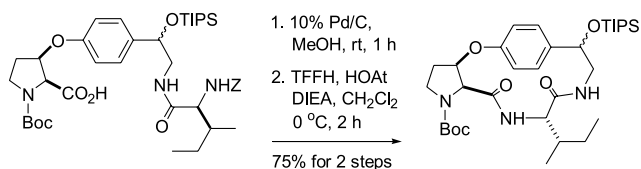
Danishefsky elegantly applied the acid fluoride method to the peptide coupling reaction in the crucial chain-elongation step during the synthesis of a potential MDR reversal agent, 5-*N*-acetylardeemin. Other attempts with BOP-Cl, DCC/HOBt and DCC/DMAP were inefficient, due to partial racemisation (Scheme 33).<sup>100</sup>



Scheme 33.

The most notable advance in acid halogenations has been the development of fluorotrimethylammonium salts. Carpino reported TFFH, BTFFH, and DFIH as new acid fluorinating reagents which act by in situ generating amino acid fluorides in peptide coupling reactions (Fig. 21).<sup>101</sup> These fluorinating reagents are especially useful for His and Arg because the corresponding amino acid fluoride intermediates are not stable on shelf storage. BTFFH may be more useful than TFFH due to its lack of toxic by-product forming ability.<sup>102</sup>

Han applied the acid fluoride method to the synthesis of a 14-membered cyclic enamide, the key intermediate of C3-epimaunitine D (Scheme 34).<sup>103</sup> The in situ-generated acid



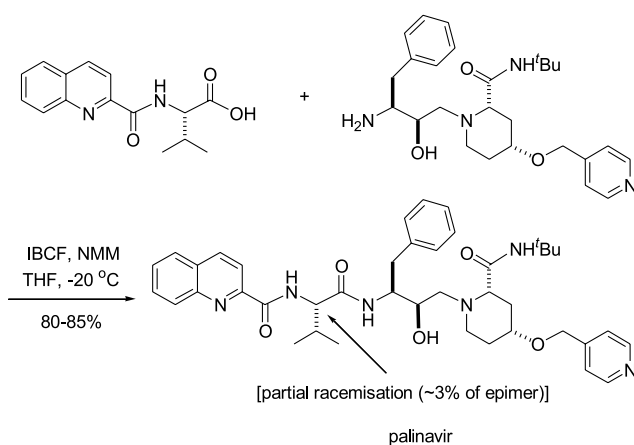
Scheme 34.

fluoride with TFFH in the presence of HOAt successfully afforded the desired macrolactam in 75% yield for 2 steps, while the corresponding Pfp activated ester gave none of the product.

## 9. Chloroformate, pyridinium and other coupling reagents

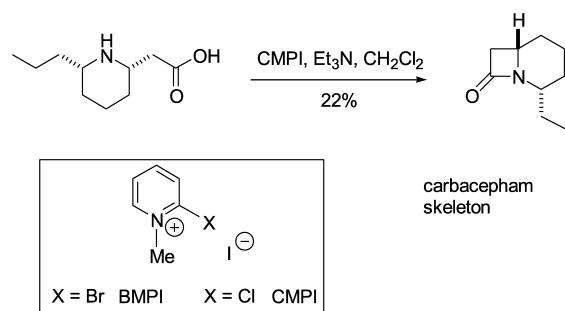
Chloroformates have been used in peptide coupling reactions via mixed carbonic anhydride intermediates. A well-known side reaction with chloroformate is the second acylation of the amine at the carbonate carbonyl carbon (Scheme 26). IBCF was mainly used in peptide synthesis among chloroformate reagents such as IPCF, <sup>i</sup>PrO<sub>2</sub>CCl, EtO<sub>2</sub>CCl, and PhO<sub>2</sub>CCl because the bulky *tert*-butyl group decreased the side reaction.<sup>104</sup>

Beaulieu applied IBCF to the synthesis of a peptidomimetic HIV protease inhibitor, palinavir (Scheme 35).<sup>104b</sup> The coupling reaction was successful by the use of IBCF/NMM with little racemisation. Lower temperatures (−20 °C) minimised the epimerisation compared with room temperature. Attempts to form palinavir using other coupling reagents such as BOP, TBTU, DCC/HOBt, or pivaloyl chloride gave poorer results.

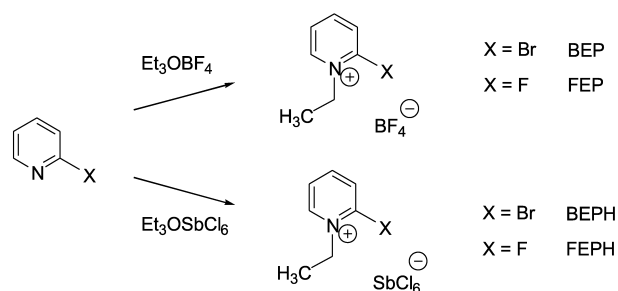


Scheme 35.

Mukaiyama introduced pyridinium reagents such as BMPI and CMPI to peptide chemistry in 1979.<sup>105</sup> CMPI was applied to the synthesis of a  $\beta$ -lactam carbacepham skeleton (Scheme 36).



Scheme 36.

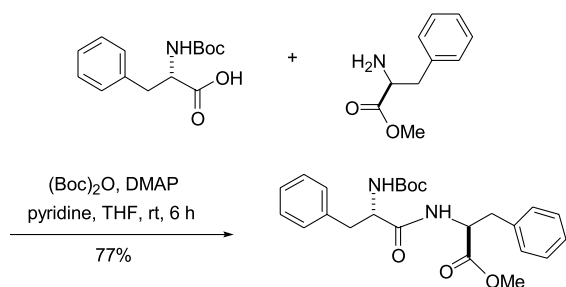


Scheme 37.

Recently, Xu reported novel pyridinium reagents such as BEP, FEP, BEPH, and FEPH (Scheme 37).<sup>106</sup> Tetrafluoroborate or hexachloroantimonate was chosen as the non-nucleophilic counterion to improve the solubility of the pyridinium reagents, compared to Mukaiyama's reagents.<sup>105</sup> BEP was applied in the synthesis of a tetrapeptide fragment of cyclosporin A and a pentapeptide moiety of dolastatin 15.

Datta applied (Boc)<sub>2</sub>O/DMAP to peptide coupling reactions in the presence of pyridine.<sup>107</sup> For the proposed mechanism, 1-*tert*-butoxycarbonyl-4-dimethylaminopyridinium *tert*-butyl carbonate (Fig. 22) was first induced by condensation between (Boc)<sub>2</sub>O and DMAP, and then attacked by an oxygen nucleophile of a carboxylic acid to form an activated ester species.

The (Boc)<sub>2</sub>O-mediated coupling reaction gave the dipeptide in good yield with very little racemisation comparable to DCC/HOBt method (Scheme 38). This method was efficient in terms of its low cost, non-toxicity, and stability on storage compared with other coupling reagents.



Scheme 38.

Taddei reported DMTMM (Fig. 22), which was derived from CDMT and NMM, as a new coupling reagent, and has applied it to solid-phase synthesis.<sup>108</sup>

Murakami and Ito reported a water-compatible reagent, DPTF. The coupling reaction was processed via step-wise

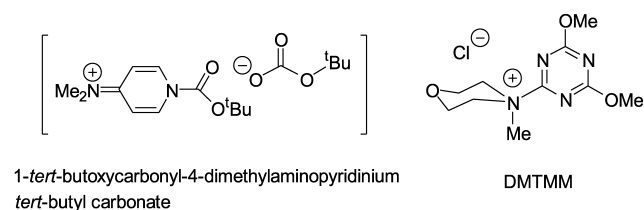
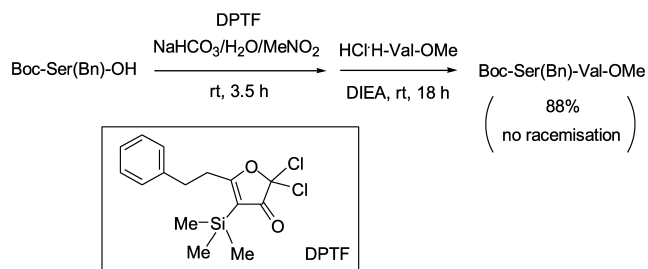


Figure 22.



Scheme 39.

dehydration in a multisolvent system composed of water and organic solvent (Scheme 39).<sup>109</sup>

## 10. Racemisation suppressants

In 1970, König and Geiger first reported the use of HOBt as a racemisation suppressant in peptide coupling reactions with carbodiimide coupling reagents (Fig. 23).<sup>38</sup> With this technique, additives such as HOBt, HOAt, HODhbt, *N*-hydroxytetrazole, HOCT, and PTF have roles in not only suppressing racemisation, but also enhancing the reactivity.

HODhbt has been limited in its widespread adoption due to the side reaction of ring opening. HOAt has been reported to be more efficient than HOBt because of an anchimeric assistance effect caused by the pyridine ring.<sup>34</sup> Later, *N*-hydroxytriazoles and *N*-hydroxytetrazoles were examined for their coupling efficiency.<sup>110a</sup> Ramage reported the coupling reaction of dipeptides with DIC and the newly designed HOCT for a racemisation study. Racemisation with DIC/HOCT activation was negligible for all amino acids except histidine.<sup>110b,c</sup> More recently, Carpino and Henklein reported polyhydrogen fluoride additives, Py(HF)<sub>*n*</sub>.<sup>111</sup> For example, the efficiency of the coupling reaction for HBTU combined with PTF (Fig. 23) was as good as HATU. Unfortunately, PTF was unsuitable for phosphonium or organophosphorous reagents due to the high strength of the P–F linkage.

For inorganic additives, the lowest level of racemisation was occasionally found in the presence of CuCl<sub>2</sub> combined with various coupling reagents.<sup>58,112</sup> However, the improvement in yield was not sufficient by addition of CuCl<sub>2</sub>. In addition, the Cu(II)-based complexes, Cu(OBt)<sub>2</sub> and Cu(OAt)<sub>2</sub> also showed the ability to function as racemisation suppressants.<sup>113</sup>

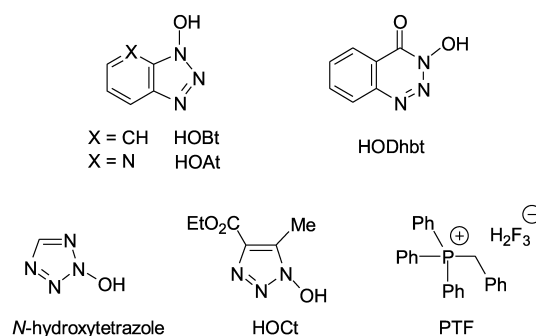


Figure 23.

## 11. Conclusions

This review has presented an overview of the recent development of peptide coupling reagents including racemisation suppressants. For coded amino acids, the standard coupling method using a carbodiimide/additive method produces peptides in good yield. However, a number of organic and natural products with interesting biological activities have been discovered and they usually contain highly functionalised or non-coded amino acids as building blocks, which may not be easily constructed by the traditional peptide coupling reagents. For this reason, the development of new peptide coupling reagents and reactions has become a most fascinating field of research for many organic chemists with various backgrounds.

Since Fischer introduced the acid chloride method into peptide coupling reactions in 1903, the development of diverse peptide coupling reagents has made many difficult peptide coupling reactions possible. Perhaps one of the most significant advances in peptide coupling reagents was the emergence of the onium or fluoroformamidinium salts. Moreover, the discovery of racemisation suppressants has reinforced the coupling reagents by enhancing the reactivity as well as reducing racemisation and side reactions. In addition, both difficult fragment coupling reactions and macrocyclisation are often influenced by other reaction parameters such as solvent systems, temperature, disconnection sites, etc. It is believed that this review presents a systematic overview of recent advances in peptide coupling reagents and serves as an excellent guideline for the organic synthesis of bioactive molecules bearing peptide linkages.

## Abbreviations

Aib	$\alpha$ -aminoisobutyric acid
AOMP	5-(7-azabenzotriazol-1-yloxy)-3,4-dihydro-1-methyl 2 <i>H</i> -pyrrolium hexachloroantimonate
AOP	(7-azabenzotriazol-1-yl)oxytris-(dimethylamino)phosphonium hexafluorophosphate
BDDC	bis[[4-(2,2-dimethyl-1,3-dioxolyl)]-methyl]carbodiimide
BDMP	5-(1 <i>H</i> -benzotriazol-1-yloxy)-3,4-dihydro-1-methyl 2 <i>H</i> -pyrrolium hexachloroantimonate
BDP	benzotriazol-1-yl diethylphosphate
BEC	<i>N</i> - <i>tert</i> -butyl- <i>N'</i> -ethylcarbodiimide
BEMT	2-bromo-3-ethyl-4-methyl thiazolium tetrafluoroborate
BEP	2-bromo-1-ethyl pyridinium tetrafluoroborate
BEPH	2-bromo-1-ethyl pyridinium hexachloroantimonate
BMC	<i>N</i> - <i>tert</i> -butyl- <i>N'</i> -methylcarbodiimide
BMP-Cl	<i>N,N'</i> -bismorpholinophosphinic chloride
BMPI	2-bromo-1-methylpyridinium iodide
BMTB	2-bromo-3-methyl-4-methyl thiazolium bromide
BOI	2-(benzotriazol-1-yl)oxy-1,3-dimethylimidazolidinium hexafluorophosphate

BOMI	benzotriazol-1-yloxy- <i>N,N</i> -dimethyl-methaniminium hexachloroantimonate
BOP	benzotriazol-1-yloxytris(dimethyl-amino)-phosphonium hexafluorophosphate
BOP-Cl	<i>N,N'</i> -bis(2-oxo-3-oxazolidinyl)-phosphinic chloride
BPMP	1-(1 <i>H</i> -benzotriazol-1-yloxy)phenyl-methylene pyrrolidinium hexachloroantimonate
BroP	bromotris(dimethylamino)phosphonium hexafluorophosphate
BTC	bis(trichloromethyl)carbonate
BTFFH	bis(tetramethylene)fluoroformamidinium hexafluorophosphate
Bts-Cl	benzothiazol-2-sulfonyl chloride
CBMIT	1,1'-carbonylbis(3-methyl-imidazolium)-triflate
CDI	1,1'-carbonyldiimidazole
CDMT	2-chloro-4,6-dimethoxy-1,3,5-triazine
CIC	<i>N</i> -cyclohexyl- <i>N'</i> -isopropylcarbodiimide
CIP	2-chloro-1,3-dimethylimidazolidinium hexafluorophosphate
CMBI	2-chloro-1,3-dimethyl 1 <i>H</i> -benzimidazolium hexafluorophosphate
CMPI	2-chloro-1-methylpyridinium iodide
Cpt-Cl	1-oxo-chlorophospholane
DBDMAP	2,6-di- <i>tert</i> -butyl-4-(dimethylamino)pyridine
DCC	<i>N,N'</i> -dicyclohexylcarbodiimide
DEBP	diethyl 2-(3-oxo-2,3-dihydro-1,2-benzisulfonazolyl)phosphonate
DECP	diethylcyanophosphonate
Deg	$\alpha,\alpha$ -diethylglycine
DEPB	diethyl phosphorobromidate
DEPBO	<i>N</i> -diethoxyphosphoryl benzoxazolone
DEPBT	3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3 <i>H</i> )-one
DEPC	diphenyl phosphorochloridate
DFIH	1,3-dimethyl-2-fluoro-4,5-dihydro-1 <i>H</i> -imidazolium hexafluorophosphate
DIC	<i>N,N'</i> -diisopropylcarbodiimide
DIEA(DIPEA)	diisopropylethylamine
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 <i>H</i> -pyrrolium hexachloroantimonate
DOPBO	<i>N</i> -(2-oxo-1,3,2-dioxaphosphorinanyl)-benzoxazolone
DOPBT	3-[ <i>O</i> -(2-oxo-1,3,2-dioxaphosphorinanyl)-oxy]-1,2,3-benzotriazin-4(3 <i>H</i> )-one
DPP-Cl	diphenylphosphinic chloride
DPPA	diphenylphosphoryl azide
DPTF	2,2-dichloro-5-(2-phenylethyl)-4-(trimethylsilyl)-3-furanone
EDC	1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride
FDPP	pentafluorophenyl diphenyl phosphinate
FEP	2-fluoro-1-ethyl pyridinium tetrafluoroborate
FEPH	2-fluoro-1-ethyl pyridinium hexachloroantimonate
FOMP	5-(pentafluorophenoxy)-3,4-dihydro-1-methyl 2 <i>H</i> pyrrolium hexachloroantimonate
HAMDU	<i>O</i> -(7-azabenzotriazol-1-yl)-1,3-dimethyl-



	1,3-dimethylenuronium hexafluorophosphate	TDBTU	2-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
HAPipU	<i>O</i> -(7-azabenzotriazol-1-yl)-1,1,3,3-bis(pentamethylene)uronium hexafluorophosphate	TEMP	2,3,5,6-tetramethylpyridine
HATU	<i>O</i> -(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate	TFFH	tetramethylfluoroformamidinium hexafluorophosphate
HBPyU	<i>O</i> -(benzotriazol-1-yl)oxybis-(pyrrolidino)uronium hexafluorophosphate	Ths-Cl	5-methyl-1,3,4-thiadiazole-2-sulfonyl chloride
HBTU	<i>O</i> -(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate	TNTU	2-(5-norbornene-2,3-dicarboximido)-1,1,3,3-tetramethyluronium tetrafluoroborate
HDTU	<i>O</i> -(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate	TODT	<i>S</i> -(1-oxido-2-pyridinyl)-1,3-dimethyl-1,3-trimethylenethiuronium tetrafluoroborate
HIP	$\alpha$ -( $\alpha$ -hydroxyisovaleryl)propionic acid	TOTT	<i>S</i> -(1-oxido-2-pyridinyl)-1,1,3,3-tetramethylthiuronium tetrafluoroborate
HOAt	1-hydroxy-7-azabenzotriazole	TOTU	<i>O</i> -[cyano(ethoxycarbonyl)methyleneamino]- <i>N,N,N',N'</i> -tetramethyluronium tetrafluoroborate
HOBt	1-hydroxybenzotriazole	TSTU	2-succinimido-1,1,3,3-tetramethyluronium tetrafluoroborate
HOCT	ethyl-1-hydroxy-1 <i>H</i> -1,2,3-triazole-4-carboxylate		
HODhbt	3,4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazine		
HODT	<i>S</i> -(1-oxido-2-pyridinyl)-1,3-dimethyl-1,3-trimethylenethiuronium hexafluorophosphate		
HOSu	<i>N</i> -hydroxysuccinimide		
HOTT	<i>S</i> -(1-oxido-2-pyridinyl)-1,1,3,3-tetramethylthiuronium hexafluorophosphate		
HPyOPfp	<i>N,N,N',N'</i> -bis(tetramethylene)- <i>O</i> -pentafluorophenyluronium hexafluorophosphate		
IBCF	isobutyl chloroformate		
Iva	isovaline		
MPTA	dimethylphosphinothioyl azide		
MPTO	3-dimethylphosphinothioyl-2(3 <i>H</i> )-oxazolone		
NDPP	norborn-5-ene-2,3-dicarboximidodiphenylphosphate		
PTF	benzyltriphenylphosphonium dihydrogen trifluoride		
PyAOP	[(7-azabenzotriazol-1-yl)oxy]tris-(pyrrolidino)phosphonium hexafluorophosphate		
PyBOP	benzotriazol-1-yloxytri(pyrrolidino)phosphonium hexafluorophosphate		
PyBroP	bromotri(pyrrolidino)phosphonium hexafluorophosphate		
PyCloP	chlorotri(pyrrolidino)phosphonium hexafluorophosphate		
PyCIU	chloro-1,1,3,3-bis(tetramethylene)-formamidinium hexafluorophosphate		
PyDOP	[(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)oxy]tris-(pyrrolidino)phosphonium hexafluorophosphate		
PyFOP	[[6-(trifluoromethyl)benzotriazol-1-yl]oxy]tris(pyrrolidino)phosphonium hexafluorophosphate		
PyNOP	[(6-nitrobenzotriazol-1-yl)oxy]tris-(pyrrolidino)phosphonium hexafluorophosphate		
PyTOP	(pyridyl-2-thio)tris(pyrrolidino)phosphonium hexafluorophosphate		
SOMP	5-(succinimidyloxy)-3,4-dihydro-1-methyl-2 <i>H</i> -pyrrolium hexachloroantimonate		
TATU	<i>O</i> -(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate		
TBTU	<i>O</i> -benzotriazol-1-yl-1,1,3,3-tetramethyluronium tetrafluoroborate		

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