CHEMICAL REVIEWS

REVIEW

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Peptide Coupling Reagents, More than a Letter Soup

Ayman El-Faham*[,†,‡] and Fernando Albericio*[,†,§,∥]

[†]Institute for Research in Biomedicine, Barcelona Science Park, Baldiri Reixac 10, 08028-Barcelona, Spain

[‡]Alexandria University, Faculty of Science, Department of Chemistry, P.O. Box 426, Ibrahimia, 21321 Alexandria, Egypt

[§]CIBER-BBN, Networking Centre on Bioengineering, Biomaterials and Nanomedicine, Barcelona Science Park, Baldiri Reixac 10, 08028-Barcelona, Spain.

[∥]Department of Organic Chemistry, University of Barcelona, Martí i Franqués 1-11, 08028-Barcelona, Spain

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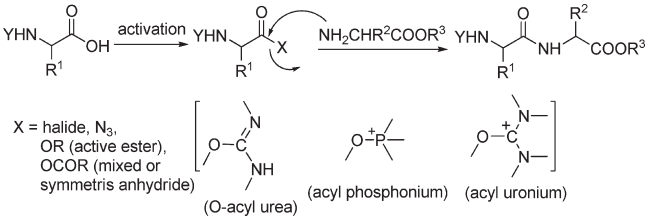
1. INTRODUCTION

In recent years, peptide-coupling reactions have significantly advanced in parallel with the development of new peptide-coupling reagents, which have been covered in a number of valuable reviews.[1−11]

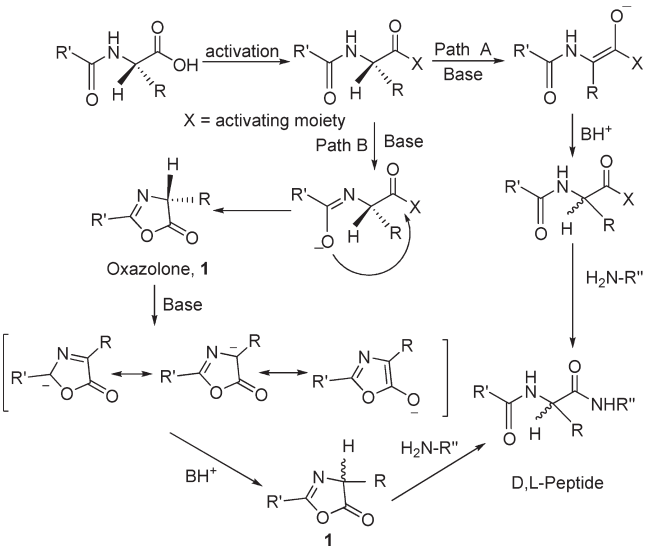
The procedures used to combine two amino acid residues to form a peptide are referred to as coupling methods. Coupling involves attack by the amino group of one residue at the carbonyl carbon atom of the carboxy-containing component that has been activated by the introduction of an electron-withdrawing group, X (Scheme 1).

The activated form may be a shelf-stable reagent, such as some active esters; a compound of intermediate stability, such as an acyl

Scheme 1. Peptide Bond Formation



Scheme 2. Racemization Mechanisms: (A) Direct Enolization; (B) Oxazolone Formation



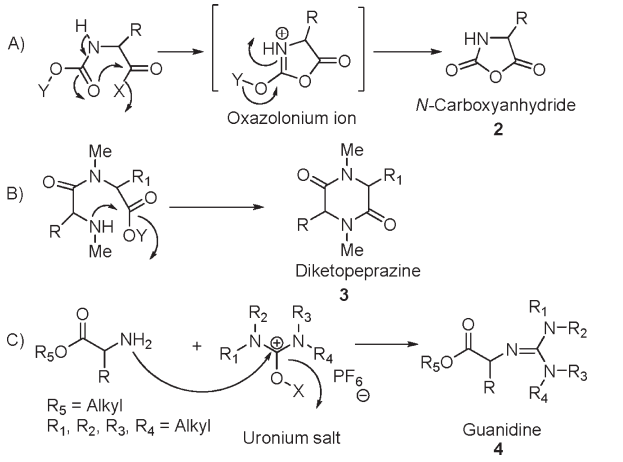
halide, azide, or a mixed or symmetrical anhydride, which may or may not be isolated; or a transient intermediate, indicated in Scheme 1 by brackets, which is neither isolable nor detectable. The latter immediately undergoes aminolysis to give the peptide, or it may react with a second nucleophile that originates from the reactants or that was added for the purpose to give the more stable active ester or symmetrical anhydride, whose aminolysis then generates the peptide.

Activation of one of the carboxylic groups is required before the reaction can occur. Unfortunately, this activation step, along with the next coupling reaction, poses a serious obstacle, namely, the potential loss of chiral integrity at the carboxyl residue undergoing activation. Therefore, a full understanding of racemization mechanisms is required in order to tackle this problem. Two major pathways for the loss of configuration, both base-catalyzed, have been recognized: (a) direct enolization (path A) and (b) 5(4*H*)-oxazolone (**1**) formation (path B) (Scheme 2).[12−15]

Several parameters are used to control racemization during peptide-coupling reactions. A key issue is the use of an appropriate *N*-protecting group. Carbamate decreases the likelihood of oxazolone formation, and groups containing electron-withdrawing moieties are more prone to enolization.[16−25] A further issue is the basicity and purity of the tertiary amines commonly used during the coupling reaction. Thus, those that are greatly hindered jeopardize H abstraction.[26]

In addition, some side reactions are intrinsically associated with the coupling step, namely, the formation of *N*-carboxyanhydrides (**2**) when the protection of the α-amino is a carbamate and of

Scheme 3. Side Reactions That May Occur during Coupling



diketopiperazines (DKP, **3**) when at least one dipeptide is present[27,28] (Scheme 3A,B). These two reactions are strongly favored by the presence of the leaving group in the carboxyl function (the C-terminal one in the case of DKP formation). Furthermore, the formation of DKP is also facilitated by the presence of *N*-methylamino acids (favoring the *cis* amide bond conformation) or amino acids of L- and D-configuration (more stable than the six-membered ring DKP). Finally, when an aminium/uronium salt is used as coupling reagent (see corresponding section), a guanidine side product (**4**) may arise when the reagent reacts directly with the amine moiety of the amino acid residue[29] (Scheme 3). This result is often due to the slow preactivation of the carboxylic acid or to the use of excess uronium reagent.

It is pertinent to remember that two types of acyl groups are involved in couplings, namely, those originating from an *N*-alkoxycarbonylamino acid and those from a peptide. All coupling reagents and methods are applicable to the coupling of *N*-protected amino acids, but not all are applicable to the coupling of peptides. Some approaches, such as the acyl halide and symmetrical anhydride methods, cannot be used for coupling peptides. In addition, the protocols used for coupling may not be the same for the two types of substrates. For these and other reasons, the techniques are discussed mostly in relation to peptide-bond formation of *N*-alkoxycarbonylamino acids.

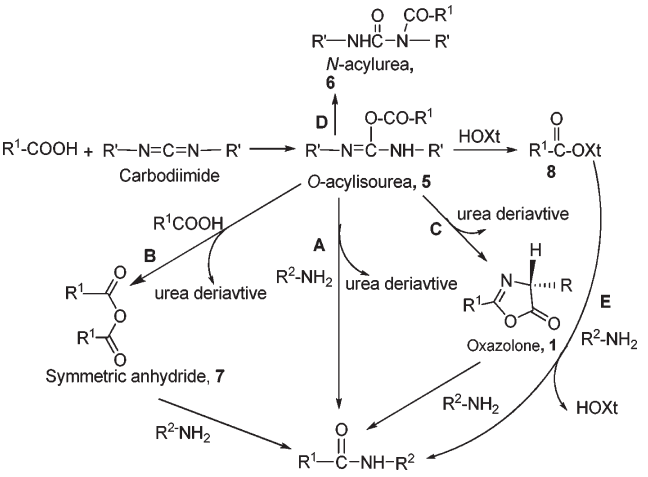
2. CARBODIIMIDE-MEDIATED REACTIONS

2.1. Carbodiimides

The most traditional approach used to form peptide bonds is the carbodiimide method, using dicyclohexylcarbodiimide (DCC, **9**). Carbodiimides contain two nitrogen atoms, which are weakly alkaline; this is sufficient to trigger a reaction between the carbodiimide and an acid to generate *O*-acylisourea (**5**) (Scheme 4).[30−37]

O-Acylisourea of an *N*-alkoxycarbonylamino acid or peptide is one of the most reactive active species and rapidly undergoes aminolysis in the presence of the amine component to yield the peptide (path A, Scheme 4). However, under excess carboxylic acid, *O*-acylisourea undergoes attack by a second molecule of the acid to give the symmetrical anhydride (**7**) (path B, Scheme 4). The latter is then aminolyzed to give the peptide. A third option is that some *O*-acylisourea cyclizes to the oxazolone (**1**)[33,38] (path C; Scheme 4), which also yields the peptide by aminolysis. However, oxazolone is less reactive than other derivatives and can

Scheme 4. Mechanism of Peptide Bond Formation from a Carbodiimide-Mediated Reaction



led to racemization, as shown above. A fourth reaction, which is undesirable, may occur because of the high reactivity of *O*-acylisourea. This reaction consists of its rearrangement (path D, Scheme 4) to the *N*-acylurea (**6**), a stable inert form of the incoming acid. The reaction, which is irreversible and consumes starting acid without generating peptide, is very fast in *N*,*N*-dimethylformamide (DMF) and much slower in dichloromethane (DCM).[33]

A copious precipitate of *N*,*N*′-dicyclohexylurea (DCU) separates within a few minutes in any reaction using DCC (**9**), which is soluble only in trifluoroacetic acid (TFA). Thus depite being compatible with solid-phase synthesis (SPS) using *tert*-butyloxycarbonyl (Boc) chemistry, DCC (**9**) is not compatible with fluorenylmethyloxycarbonyl (Fmoc). When DCC is used in solution, traces of DCU are difficult to remove, even after passage through a chromatographic column. Thus DCC has been replaced by the reagents diisopropylcarbodiimide (DIC, **10**), *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodimide (EDC, **11**), and *N*-cyclohexyl-*N*′-isopropylcarbodiimide (CIC, **12**),[39] which are all relatively soluble in DCM and are therefore more suitable for Fmoc-SPS. EDC (**11**) is highly suitable for use in solution because this reagent and its urea are soluble in aqueous solvents and can therefore be removed in the workup. A number of variations on carbodiimide, such as BMC (**13**), BEC (**14**),[40,41] *N*,*N*′-cyclopentyl carbodiimide (**15**), BDDC (**16**),[42] PEC (**17**), and PIC (**18**)[43] have been reported (Table 1). BDDC (**16**) gives a reasonable yield for the coupling reaction with Boc-amino acids, and the byproduct is easily removed by an acid wash.

2.2. Carbodiimides and Additives

The corresponding active esters of additives such as *N*-hydroxy derivatives (HOXt **19**−**42**, Table 2) are less reactive than *O*-acylisourea (**5**). However, these additives increase the efficiency of carbodiimide-mediated reactions. First of all, they suppress the formation of *N*-acylurea. The beneficial effect of HOXt is attributed to its capacity to protonate *O*-acylisourea, thus preventing the intramolecular reaction from occurring and shifting the reaction to form the corresponding active esters (**8**) (path E, Scheme 4) and thereby decreasing the degree of racemization in numerous cases.[38,44] The presence of a tertiary amine favors the formation of the active ester.[43] Compared with other additives, HOAt (**22**) forms superior active esters in terms of yield and degree of racemization in both solution and

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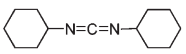
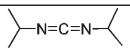
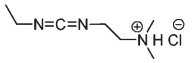
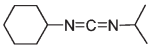
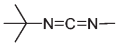
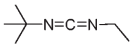
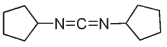
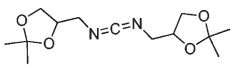
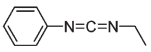
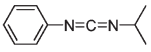
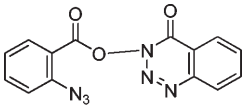
Table 1. Carbodiimide Coupling Reagents

Entry	Abbreviation	Name and Structure	Ref
9	DCC	*N,N′*-dicyclohexylcarbodimide 	30
10	DIPCDI, DIC	*N,N′*-diisopropylcarbodimide 	31
11	EDC, WSC	*N*-ethyl-*N′*(3-dimethylaminopropyl)carbodimidehydrochloride 	31
12	CIC	*N*-cyclohexyl, *N′*-isopropylcarbodiimide 	39
13	BMC	*N*-*tert*-butyl, *N′*-methylcarbodiimide 	40
14	BEC	*N*-*tert*-butyl, *N′*-ethylcarbodiimide 	40
15	CPC	*N,N′*-dicyclopentylcarbodiimide 	42
16	BDDC	*bis*[[4-(2,2-dimethyl-1,3-dioxolyl)]methyl]carbodiimide 	42
17	PEC	*N*-ethyl, *N*-phenylcarbodiimide 	43
18	PIC	*N*-phenyl, *N*-isopropylcarbodiimide 	43

solid-phase synthesis,[45] even when the coupling occurs with the hindered α-aminoisobutyric acid (Aib).[46] The key behind the outstanding behavior of HOAt (**22**) is the nitrogen atom located at position 7 of the benzotriazole, which provides a double effect.[44] First, the electron-withdrawing influence of a nitrogen atom (regardless of its position) improves the quality of the leaving group, thereby leading to greater reactivity. Second, placement of this nitrogen atom specifically at position 7 makes it feasible to achieve a classic neighboring group effect (Figure 1), which can increase reactivity and reduce the loss of configurational integrity.[44] Compared with HOBt (**19**), the corresponding 6-HOAt (**24**), 5-HOAt (**25**), and 4-HOAt (**26**) lack the capacity to participate in such a neighboring group effect and have little influence on the extent of stereomutation during segment coupling.[47,48]

6-Cl-HOBt (**23**) has also been introduced into solid-phase synthesis. This additive is a good compromise between HOAt and HOBt in terms of reactivity and price.[49]

1-Oxo-2-hydroxydihydrobenzotriazine (HODhbt, **27**)[38] gives highly reactive esters, but their *in situ* formation is accompanied by 3-(2-azidobenzyloxy)-4-oxo-3,4-dihydro-1,2,3-benzotriazine (**43**) as a byproduct, which can then react with the amino group to terminate chain growth.[38] Furthermore, the active esters can be prepared free of **43**.



43

The aza derivatives of HODhbt (HODhat, **28**, and HODhad, **29**) have been reported by Carpino et al.[50] Active esters of this additive (**8**) are slightly more reactive than OAt ones, which are considered the most reactive derivatives among these esters; however, the additive **28** gives the side product **43**, as occurs with HODhbt (**27**).[50]

Recently, *N*-hydroxy-5-norbornene-endo-2,3-dicarboxyimide (HONB, **31**) has been reported as the additive of choice for water solid-phase peptide synthesis (SPPS).[51]

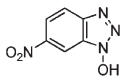
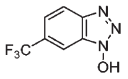
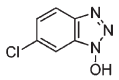
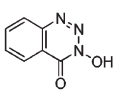
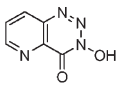
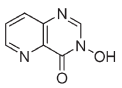
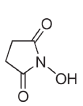
Several coupling additives with triazole and tetrazole structures (**32**−**37**) in the presence of DIC (**10**) have been evaluated in solid-phase Fmoc-based peptide synthesis.[52] These reagents show an advantage over others because they do not have absorption in the UV at 302 nm, thus allowing the monitoring of the coupling process, a feature incompatible with Fmoc methodology in the case of HOBt and HOAt. However, a disadvantage is that these reagents are highly explosive due to their low molecular weight and the presence of three or four consecutive nitrogen atoms.

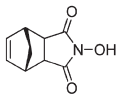
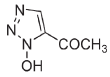
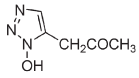
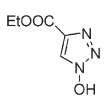
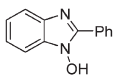
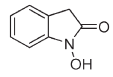
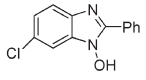
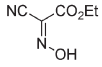
Very recently, El-Faham and Albericio[53,54] reported a safe and highly efficient additive, ethyl 2-cyano-2-(hydroxyimino)acetate (Oxyma, **42**) to be used mainly in the carbodiimide approach for peptide bond formation. Oxyma displays a remarkable capacity to suppress racemization and an impressive coupling efficiency in both automated and manual synthesis. These effects are superior to those shown by HOBt and comparable to those of HOAt. Stability assays show that there is no risk of capping the resin in standard coupling conditions when using Oxyma as an aditive. Finally, calorimetry assays (DSC and ARC) confirm the explosive potential of benzotriazole-based additives and demonstrate the lower risk of explosion induced by Oxyma.[54] This feature is highly relevant because all benzotriazole derivatives, such as HOBt and HOAt, exhibit explosive properties.[55]

Carbodiimide-mediated couplings are usually performed with preactivation of the protected amino acid at either 4 or 25 °C using DCM as a solvent. For Fmoc-amino acids that are not totally soluble in DCM, mixtures with DMF can be used.[56] The use of DCM is optimal for the solid-phase acylation of isolated nucleophiles.[57] However, for linear assembly, where interchain aggregation may occur, a more polar solvent to inhibit the formation of secondary structure is recommended. In these cases, if DCM is used as an initial solvent, a more effective procedure would involve filtration of the urea byproduct and evaporation, followed by addition of DMF to the coupling medium.[58,59]

For large-scale synthesis, preactivation at 4 °C is recommended because of the exothermic nature of the reaction. Carbodiimides, as well as other coupling reagents, are acute skin irritants and should be handled with great care. Thus, manipulation in a well-ventilated hood, using glasses, gloves, and, when possible, a face mask, is recommended. DCC, which has a low melting point (34 °C), can be handled as a liquid by gentle warming of the reagent container.[60] HOBt normally crystallizes with one molecule of water. Use of the

Table 2. Additive Used with Carbodiimides

Entry	Abbreviation	Name and Structure	Ref
19	HOBt	1-hydroxybenzotrialzole 	30
20	6-NO_2-HOBt	1-hydroxy-6-nitro benzotrialzole 	43
21	6-CF_3-HOBt	6-trifluoromethyl-1-hydroxy benzotrialzole 	43
22	HOAt	1-hydroxy-7-azabenzotriazole 	44
23	6-Cl-HOBt	6-chloro-1-hydroxy benzotrialzole 	49
24	6-HOAt	5-aza-1-hydroxybenzotriazole 	48
25	5-HOAt	6-aza-1-hydroxybenzotriazole 	48
26	4- HOAt	4-aza-1-hydroxybenzotriazole 	48
27	HODhbt	3,4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazine 	38
28	HODhat	3-|hydroxy-4-oxo-3,4-dihydro-5-azabenzo-1,2,3-triazene 	50
29	HODhad	3-hydroxy-4-oxo-3,4-dihydro-5-azabenzo-1,3-diazene 	50
30	HOSu	*N*-hydroxysuccinimide 	90

Entry	Abbreviation	Name and Structure	Ref
31	HONB	*N*-hydroxy-5-norborene-endo-2,3-dicarboxyimide 	51
32		1-hydroxy-1*H*-1,2,3-triazole 	52
33		5-chloro-1-hydroxy-1*H*-1,2,3-triazole 	52
34		5-acetyl-1-hydroxy-1*H*-1,2,3-triazole 	52
35		1-(1-hydroxy-1H-1,2,3-triazol-5-yl)propan-2-one 	52
36	HOCt	ethyl-1-hydroxy-1*H*-1,2,3-triazole-4-carboxylate 	52
37		1-hydroxy-1*H*-1,2,3,5-tetrazole 	52
38	HOPy	1-hydroxy-2-pyridinone 	53
39	HOBI	*N*-hydroxy-2-phenylbenzimidazole 	53
40	HOI	*N*-hydroxyindolin-2-one 	53
41	6-Cl-HOBI	6-chloro-*N*-hydroxy-2-phenylbenzimidazole 	53
42	Oxyma	ethyl 2-cyano-2-(hydroxyimino)acetate 	54

dx.doi.org/10.1021/cr100048w |*Chem. Rev.* 2011, 111, 6557–6602

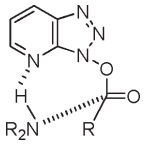


Figure 1. Neighboring group effect for HOAt.

hydrated form is highly satisfactory, but if anhydrous material is required, dehydration should be carried out with extreme care. Heating HOBt or HOAt above 180 °C can cause rapid exothermic decomposition. The uses of *N*-hydroxytetrazoles as trapping reagents are precluded because of their explosive nature.[55]

3. ANHYDRIDES

Anhydrides are species that readily react with a vast range of nucleophiles, such as amines, alcohols, and thiols. This strategy comprises the use of simple symmetric anhydrides and refined mixed anhydrides involving, for example, isoureas or phosphoric acid-derived species.

3.1. Symmetric Anhydrides

An alternative to the classical method of synthesis using carbodiimides is the symmetric anhydride- mediated reaction, in which the carbodiimide and acid are first allowed to react together in the absence of *N*-nucleophile. In this reaction, 0.5 equiv of carbodiimide is used; this generates 0.5 equiv of symmetrical anhydride (**7**) (Scheme 4, path B), the formation of which can be rationalized in the same way as the reaction of acid with carbodiimide, namely, protonation at the basic nitrogen atom of *O*-acylisourea by the acid, followed by attack at the activated carbonyl of the acyl group by the carboxylate anion. Aminolysis at either carbonyl of the anhydride yields peptide and 0.5 equiv of acid, which is recoverable. Recovery of the acid, however, is usually not cost- or time-effective. The symmetrical anhydride is less reactive and consequently more selective in its reactions than *O*-acylisourea. Although the latter acylates both *N*- and *O*-nucleophiles, the symmetrical anhydride acylates only *N*-nucleophiles. When the reagent is DCC (**9**), the reaction is carried out in dichloromethane, *N*,*N*′-dicyclohexylurea is removed by filtration after 15−30 min, the solvent is sometimes replaced by dimethylformamide, and the solution is then added to the second amino acid. The symmetrical anhydride is not prepared directly in the polar solvent because the latter suppresses its formation. Symmetrical anhydrides show sufficient stability to be isolated but not to be stored for future use. They can be purified by repeated crystallization or by washing a solution of the anhydride, obtained using a soluble carbodiimide, with aqueous solutions. Anhydrides are particularly effective for acylating secondary amines.[61,62]

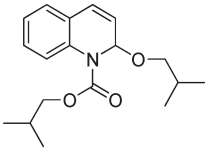
3.2. Mixed Anhydrides

The mixed anhydride technique, reported by Vaughan,[63] was the first general method available for peptide synthesis. This approach has the drawback of a lack of regioselectivity in the nucleophilic addition for one position over the second one.

3.2.1. Mixed Carbonic Anhydrides. *3.2.1.1. Chloroformate-Mediated Reaction.* The procedure involves separate preparation of the mixed anhydride by addition of the reagent chloroformate (**44**) to the *N*-alkoxycarbonylamino acid anion that is generated by deprotonation of the acid by a tertiary amine, such as NMM (Scheme 5).[64,65]

The activation is rapid. Reactants are usually left together for 1−2 min, and aminolysis is generally complete within 1 h. The activation cannot be carried out in the presence of the *N*-nucleophile because it also reacts with the chloroformate (Scheme 5, path B). All stages of the reaction are performed at low temperature to prevent side reactions. There is evidence that the tertiary amine used in the reaction is not merely a hydrogen chloride acceptor but also an active participant in the reaction. An explanation for this would be that the acylmorpholinium cation is formed first (Scheme 5, path C) and that it is the acceptor of the acid anion. The observation that diisopropylethylamine (DIEA) fails to generate any mixed anhydride when it is used as base in a reaction strongly supports the notion of a more elaborate mechanism. The reactivity of mixed anhydrides is similar to that of symmetrical anhydrides. Symmetrical and mixed anhydride reactions differ from those involving carbodiimides and other coupling reagents in that they can be used to acylate amino acid or peptide anions in partially aqueous solvent mixtures. The main side reaction associated with the mixed anhydride method is aminolysis at the carbonyl of the carbonate moiety (path B), thereby giving urethane. In most cases, the reaction is not of great significance, but it may reduce peptide yield by up to 10% for hindered residues. An additional minor source of urethane may result from the reaction of unconsumed reagent with the *N*-nucleophile. Aminolysis of chloroformate occurs when there is an excess of reagent or when the anhydride-forming reaction is incomplete. This side reaction can be prevented by limiting the amount of reagent and extending the time of activation. The success of mixed anhydride reactions is considered to be extremely dependent on the choice of conditions used. Much attention has been devoted to defining the conditions that minimize the epimerization that occurs during peptide coupling. It was concluded that superior results are achieved by carrying out the activation for only 1−2 min from −5 to −15 °C, using *N*-methylmorpholine as the base in anhydrous solvents other than chloroform and DCM.[66] Triethylamine or tri-*n*-butylamine had previously been used initially as base, but it was found that the weaker and less hindered cyclic amine leads to less isomerization.[63,67−70]

3.2.1.2. 2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EDDQ)-Mediated Reaction. The same occurs when 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EDDQ, **45**)[71] is used as a reagent (Scheme 6). In this reaction, ethanol is removed from EDDQ to generate a reactive ethyl formate quinolinium salt (**46**). This intermediate has a similar reactivity to pyridinium salts (discussed later in section 7.1.6, Coupling Reactions with Acyl Chlorides) and readily reacts with the desired carboxylate to form the required ethoxycarbonyl anhydride **47**. Analogs of EEDQ (**45**) have been successfully developed, such as IIDQ (**48**).[72] IIDQ showed better performance than EEDQ (**45**).[73]



IIDQ, **48**

3.2.2. Cyclic Anhydrides. *3.2.2.1. N-Carboxy Anhydrides or Leuch's Anhydrides.* The anhydride strategy was explored and further expanded in peptide synthesis by Leuch. Cyclic anhydrides or *N*-carboxy anhydrides (NCAs) can be readily prepared from unprotected amino acids and phosgene.[74,75]

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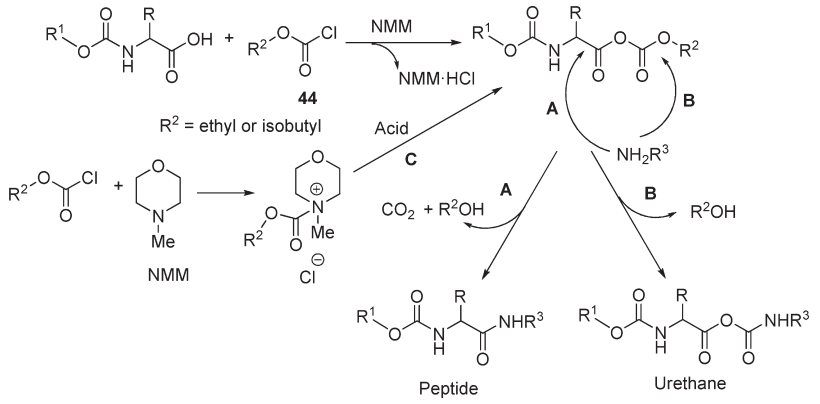
Scheme 5. Mechanism of Peptide Bond Formation from a Chloroformate-Mediated Reaction



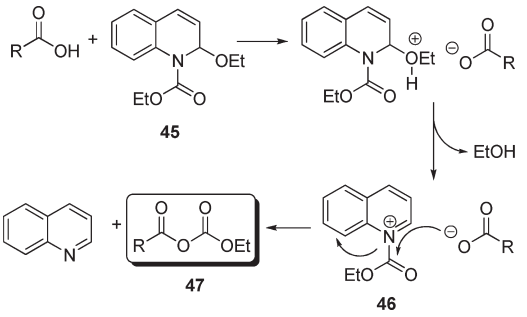
NCAs **49** can react in diverse manners. A catalytic amount of a nucleophile (e.g., primary or secondary amine) initiates a chain reaction that leads to the formation of homopoly(amino acid)s **50**. The ring opening followed by decarboxylation yields a new nucleophile that reacts on the next molecule of NCA **49** and so on (Scheme 7).

Under more carefully controlled conditions, however, NCAs (**49**) can be monocoupled to the nitrogen atom of an unprotected amino acid in high optical purity.[74] NCAs (**49**) are added to a basic aqueous solution of the selected amino acid at 0 °C (Scheme 7). The key factor of this activating method is the relative stability/instability of the intermediate carbamic acid that prevents the formation of the free amino dipeptide, while **49** is still present in the reaction mixture. This process can be repeated several times to form small oligopeptides in solution. Overcoupling is the main limitation of this method.

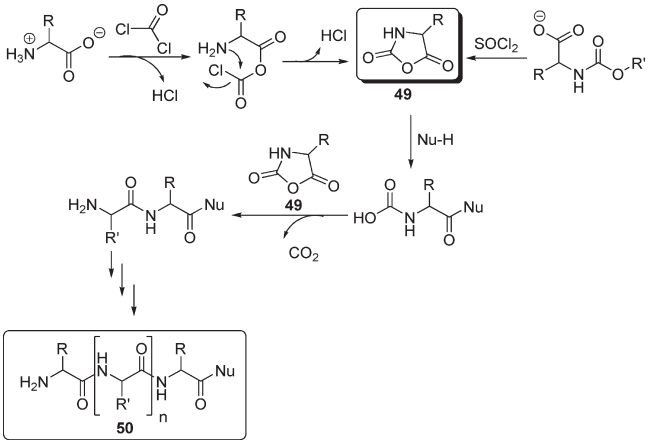
3.2.2.2. Urethane-Protected N-Carboxy Anhydrides (UNCAs). To overcome problems associated with the lack of control, urethane-protected *N*-carboxyanhydrides have been proposed.[76] Their synthesis first requires the preparation of the intermediate NCA (**49**) followed by *N*-protection by acylation in the presence of a non-nucleophilic base such as *N*-methylmorpholine (NMM), which is unable to inititate polymerization. From the byproduct point of view, NCAs and UNCAs are ideal peptide reagents because the only byproduct of the coupling is CO_2.

Fmoc-NCAs react smoothly with hydroxyl resins and with minimal racemization.[77] One of the clearest examples of the power of these derivatives for introducing the first residue is the loading of Fmoc-His(Trt)-NCA (Trt = trityl) on a Wang resin in toluene and in the presence on NMM (10%). This reaction proceeds with good yields and very low racemization (<0.3%).[78]

Scheme 6. Using EDDQ To Generate Ethoxycarbonyl Anhydride 45



Scheme 7. Peptide Synthesis Using NCAs



4. ACTIVE ESTERS

A unique approach to peptide synthesis is the preparation of a derivative of the *N*-alkoxycarbonylamino acid that is stable enough to be stored and yet reactive enough to combine with an amino group when the two are mixed. Such compounds are normally achieved by converting the acid to the active ester by reacting it with either a substituted phenol or a substituted hydroxylamine, HOXt, in the presence of carbodiimide (Scheme 8).

Active esters are in fact mixed anhydrides formed from a carboxylic acid and a phenolic or hydroxamic acid. Many types of active esters are available. The substituents Xt are designed to render the carbonyl of the acyl moiety susceptible to nucleophilic attack by an amine at room temperature. Active esters undergo aminolysis because of the electon-withdrawing property of the ester moiety. However, the esters formed from substituted hydroxamic acids are so highly activated that their reactivity cannot be explained on the basis of this property alone. An additional phenomenon is operative, namely, neighboring atoms assist in reaction of the two reactants. This neighboring group

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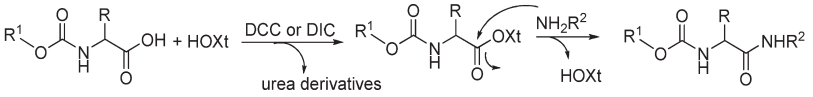
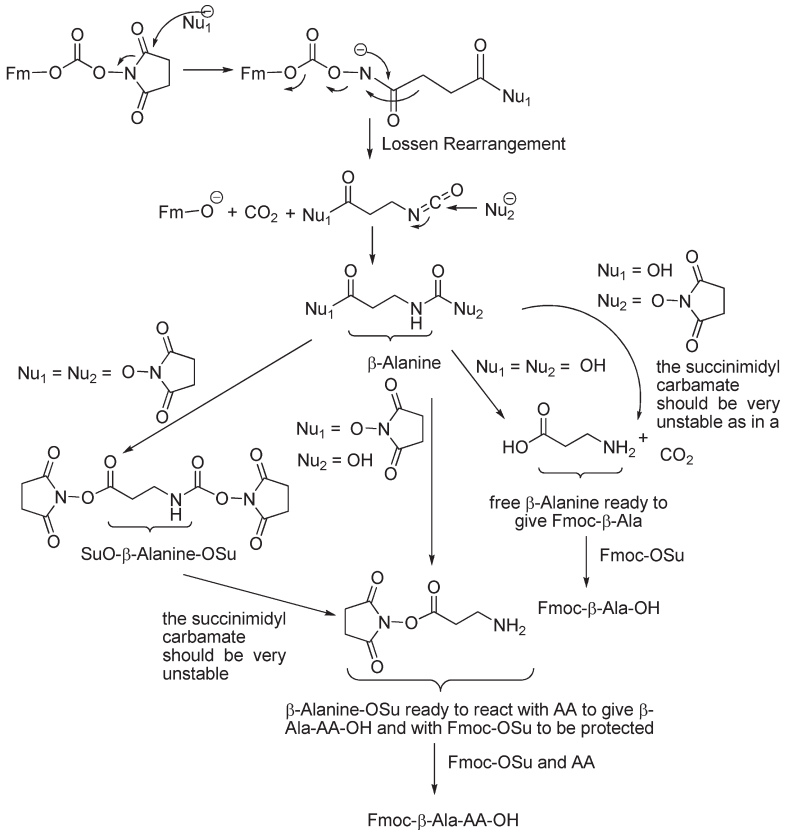
Scheme 8. Peptide Bond Formation via Preformed Active Ester



Scheme 9. Mechanism for the Formation of Fmoc-β-Ala-OH and Fmoc-β-Ala-AA-OH during the Fmoc Protection of Amino Acids with Fmoc-OSu[a]



[a] A similar reaction is obtained when OSu and ONB esters are used.

participation in the formation of a new chemical bond is referred to as anchimeric assistance. The reaction is, in fact, an intramolecular general base-catalyzed process.[38,79−81]

4.1. Procedure for the Preparation of Active Ester

Active esters can be prepared in advance, purified, and stored. Some amino acids are even commercially available as pentafluorophenyl (Pfp)[82] and 3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl (Dhbt or OOBt)[83] esters. Active esters are usually synthesized using standard ester-formation methods such as DCC (**9**), but more sophisticated procedures can be found in the literature.

4.1.1. Phenyl Active Ester Derivatives. The *p*-nitrophenyl (**51**),[84] 2,4,5-trichlorophenyl (**52**),[85] and later the more reactive Pfp esters[86] (**53**) emerged as the most popular derivatives. These compounds are activated by the electron-withdrawing nature of the substituted phenyl ring. The phenols released by aminolysis are not soluble in water, and they consequently make it difficult to purify the desired products. Although in all times, *p*-nitrophenyl esters were broadly be used, in the 1980s and 1990s, Pfp esters were clearly accepted due to their stability and crystallinity, which have made Pfp esters a very suitable coupling strategy for automatic solid-phase peptide synthesis.[87] On the other hand, although 2,4,5-trichlorophenyl has been used as protecting/activating group,[88] it is not used anymore because of the presence of Cl atoms. Pfp is being also as protecting/activating group, mainly in glycopeptide chemistry.[89]

4.1.2. *p*-Hydroxamic Active Ester. Active esters derived from hydroxamic acid have also found broad application. The first were the *o*-phthalimido (**54**)[90] esters, which release a water-insoluble side product. However, these were soon replaced by the more versatile succinimido esters (OSu) (**55**). The latter generate water-soluble *N*-hydroxysuccinimide,[91,92] which is straightforward to remove from target peptides. The use of HOSu and *N*-hydroxy-5-norbornene-*endo*-2,3-dicarboxyimide (HONB, **56**) esters[93,94] can lead to a side-product resulting from a Lossen rearrangement after the attack of a nucleophile at the carbonyl of the ester moiety.[63,95] This side reaction is more pronounced when Fmoc (and other) amino acids are prepared from Fmoc-OSu (Scheme 9).[96]

In addition to their use as activated forms of *N*-alkoxycarbonylamino acids, the esters derived from hydroxamic acids are

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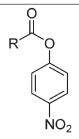
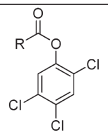
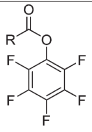
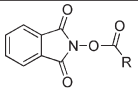
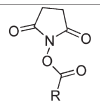
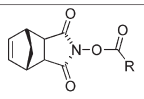
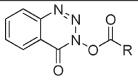
Table 3. Active Esters Used in Peptide Synthesis

Entry	Structure	Name	Ref
51		p-nitrophenyl active ester	84
52		2,4,5-trichlorophenyl active ester	85
53		pentafluoro active ester	86
54		o-phthalimido active ester	90
55		*N*-succinimide active ester	93
56		*N*-hydroxy-5-norbornene-endo-2,3-dicarboxyimide	93
57		4-oxo-3,4- dihydrobenzotriazinyl esters	86

implicated as intermediates in coupling reactions in which *N*-hydroxy compounds are added to promote efficiency in carbodiimide-based coupling (see section 4.1.2.). These derivatives are not very active due to the pK_a of the conjugate acid of the ester moiety. To enhance coupling effectivity, HOBt-related compounds can be added during the coupling. All the esters mentioned above are shelf-stable reagents.

DHbt/OOBt (**57**) esters can also be prepared and stored. During their work up, the benzotriazine (**43**) byproduct is removed. This byproduct can then react with the amino group to terminate chain growth.[38]

The aminolysis of active esters generally occurs more readily in polar solvents and is catalyzed by mild acid or 1-hydroxybenzotriazole. Active esters can also be obtained by transesterification and the mixed-anhydride approach (Table 3).[79,84,97−101]

4.2. Hexafluoroacetone (HFA) as Activating and Protecting Strategy

HFA reacts with α-amino, α-hydroxy, and α-mercapto acids to give five-membered lactones (2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-ones (**58**) for amino acids) (Scheme 10A). These lactones, which are activated esters, are cleaved by various *O*- and *N*-nucleophiles in solution and in solid-phase to give the corresponding unprotected derivatives in one step (Scheme 10B).[102] HFA derivatives can be considered bidentate protecting and activating reagents for α-functionalized carboxylic compounds, because the nucleophile attack releases HFA, thereby freeing the amino, hydroxyl, or mercapto function. In the case of α-amino acids, no additional α-amino protection is required, which is an advantage over NCAs.

In solid-phase mode, the HFA chemistry, which has been successfully used for the synthesis of depsipeptides, allows recovery of the excess of HFA monomers. Thus, after the solid-phase reaction has taken place, the filtrate containing the excess of HFA-hydoxy can be evaporated, redissolved, and reused (Scheme 11).[103] However, the use of HFA-amino acids for stepwise SPPS has some limitations.[103]

5. ACYLAZOLES AS COUPLING REAGENTS

5.1. Acylimidazoles Using CDI

Carbonyl diimidazole (CDI, **59**)[104] is a useful coupling reagent that allows one-pot amide formation. Acyl carboxy imidazole and imidazole are initially formed but readily react together to yield the activated species, such as the acylimidazole **60** (Scheme 12). The acylimidazole is preformed for 1 h, and the amine is then added. This reaction, which generates imidazole *in situ*, does not require an additional base and is even compatible with HCl salts of the amine.[105,106]

CDI (**59**) is commonly used on a large scale[107] in peptide chemistry, and its application can be extended to the formation of esters and thioesters. The reaction of secondary amines with *N*,*N*′-carbonyldiimidazole, followed by methylation with methyl iodide, has also been used for the efficient preparation of tertiary amides.

5.2. Acylbenzotriazoles

N-(Protected-α-aminoacyl)benzotriazoles are efficient intermediates for *N*- and *O*-aminoacylation. These intermediates allow rapid preparation of peptides in high yields and purity under mild reaction conditions with full retention of the original chirality. The developed methodology allows simple solution and solid-phase preparative techniques to generate complex peptides and peptide conjugates.[108]

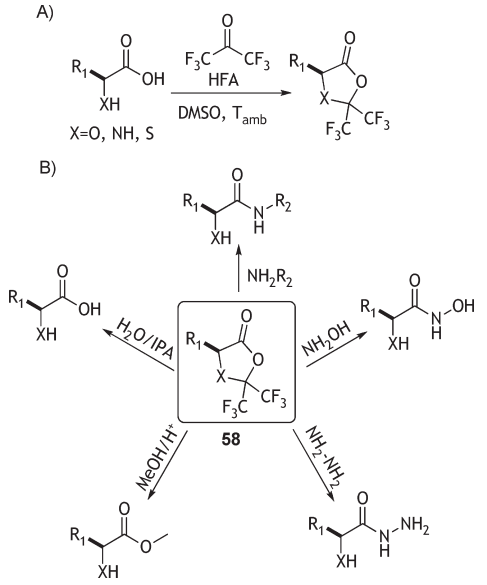
5.2.1. Preparation of *N*-(Protected-α-aminoacyl)benzotriazoles (61). Two methods have been developed recently to prepare a wide range of *N*-acylbenzotriazoles starting directly from carboxylic acids. The first method uses sulfonylbenzotriazoles as a "counter attack" reagent (Scheme 13A). In the presence of Et_3N, carboxylic acids are converted into the desired acylbenzotriazoles, possibly through intermediate formation of the mixed carboxylic sulfonic anhydride and benzotriazole anion, which is then acylated by the mixed anhydride.[109,110] The second method involves treatment of a carboxylic acid with BtSOBt prepared *in situ* from thionyl chloride and an excess of benzotriazole (Scheme 13B).[111]

The two methods allow the preparation of a wide range of *N*-acylbenzotriazoles. Carboxylic acids as starting materials include not only alkyl and aryl carboxylic acids but also a wide range of heterocyclic carboxylic acids, unsaturated carboxylic acids, and carboxylic acids with other functionalities.[109−111]

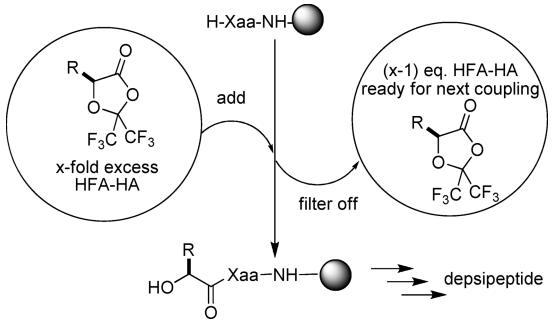
The methods of Scheme 13A,B have been applied to prepare Bt derivatives of *N*-protected-α-amino acids. Scheme 13A was used to prepare *N*-(Boc-α-aminoacyl)benzotriazoles,[112] while Scheme 13B was found to be more convenient for the preparation of *N*-(Z- and Fmoc-α-aminoacyl)benzotriazoles wherein 1 equiv of a carboxylic acid with 4 equiv of 1*H*-benzotriazole and 1−1.2 equiv of thionyl chloride in THF or CH_2Cl_2 were stirred at 20 °C for 2 h.[113−119]

Major advantages of *N*-acylbenzotriazoles over the corresponding acid chlorides include the following: (1) resistance to short periods of contact with water, thereby allowing compounds

Scheme 10. (A) Preparation of the HFA Derivatives and (B) Examples of the Reactivity of the HFA Derivatives



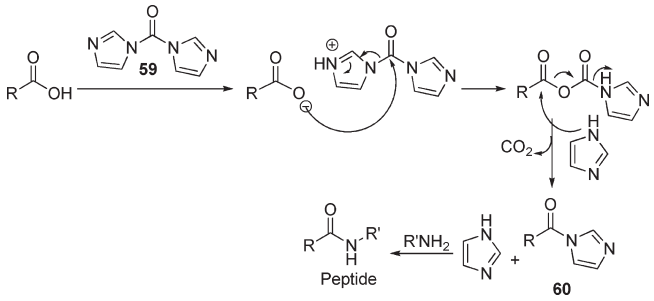
Scheme 11. HFA Monomers Are Reusable in Solid-Phase Mode



such as free amino acids (only soluble in water or mixed solvents containing a high proportion of water) to be reacted in solution with the acylbenzotriazoles; (2) *N*-(protected-α-aminoacyl)-benzotriazoles can be isolated, they are stable at room temperature for months, and they can be handled without special procedures to exclude air or moisture, with the exception of histidine. Another major advantage of this methodology is that it is compatbible with the use of functionalized *N*-protected-amino acids, such as tryptophan, tyrosine, serine, histidine, etc. without prior protection, thereby saving on additional steps required for protection and subsequent deprotection. For example, the indole-NH in tryptophan does not require prior protection, thus making its subsequent deprotection unnecessary. In addition, the reagents involved in the preparation are inexpensive, thereby offering an overall cost-effective methodology. These reagents are relatively insensitive to water and can be used in aqueous solution, thus allowing efficient peptide coupling.[113−118]

5.2.2. Peptide Coupling with Chiral *N*-(Protected-α-aminoacyl)benzotriazoles. Peptide coupling reactions are performed using chiral *N*-(protected-α-aminoacyl)benzotriazoles with the following: (i) nonfunctionalized amino acids (alanine, glycine,

Scheme 12. Mechanism of Peptide Bond Formation Using CDI



phenylalanine, valine, and leucine); (ii) amino acids with additional unprotected functionalization, hydroxyl (serine, tyrosine, and glutamine), sulfanyl (methionine and cysteine), and amino (tryptophan, proline); (iii) dicarboxylic acids (aspartic acid and glutamic acid); (iv) amino acids containing two amino groups (lysine); and (v) the guanidinium group (arginine).[113−118,120,121]

5.2.3. Preparation of Peptides Using *N*-(Protected-α-aminoacyl)benzotriazoles. Free amino acids are coupled with *N*-(protected-α-aminoacyl)benzotriazoles in aqueous acetonitrile (CH_3CN/H_2O = 2:1 v/v) in the presence of Et_3N during 1 h. The crude products are washed with 4 N HCl to remove BtH as byproduct. This procedure affords the dipeptide in high purity (>99%) and without the use of chromatography (Scheme 12).[113,115,120] Tripeptide syntheses can be achieved using fragment coupling procedures[113,115] or by stepwise coupling procedures.[113,120]

5.2.4. Tripeptides by the Fragment Coupling Procedure. *N*-Protected dipeptides are readily converted into their corresponding benzotriazole derivatives (Scheme 12).[113,115−119,122,123] The reactions are carried out at −10 °C until the starting dipeptide is completely consumed, following a simple procedure similar to that used for *N*-(protected-α-aminoacyl)benzotriazoles.

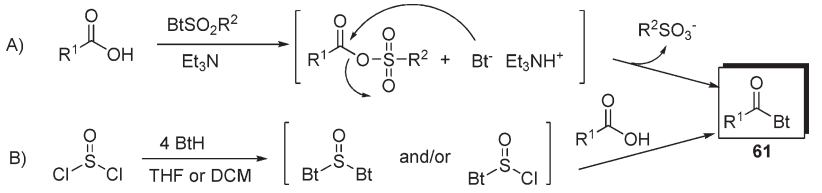
The coupling reactions between *N*-protected dipeptidoylbenzotriazoles and free amino acids are performed in aqueous acetonitrile at −10 °C. NMR and HPLC analyses show minimal racemization (<1%) (Scheme 14). However, some couplings performed under similar conditions but at 20 °C show significant racemization (30−50%).[115]

5.2.5. Stepwise Coupling Procedures. In stepwise coupling, the coupling reactions are achieved in good yields using the method described above, with minimal racemization (>99%), as observed by NMR and HPLC analysis (Scheme 14).[115]

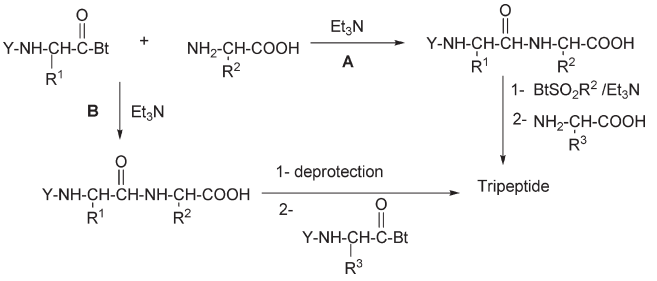
5.2.6. Preparation of Dipeptides Involving Sterically Hindered Amino Acids Using *N*-(Protected-α-aminoacyl)benzotriazoles. Peptide chain extensions are also performed using the following N- and C- terminal sterically hindered amino acids: (i) *N*-methyl amino acids [*N*-(Me)-Phe and *N*-(Me)-Gly]; and (ii) α,α-disubstituted amino acids (Aib).[121] The preparation of peptides involving sterically hindered amino acids requires different conditions from that of peptides containing only natural amino acids. The coupling conditions using *C*-activated hindered amino acids are the same as for dipeptides. However, coupling the NH_2 of sterically hindered amino acids such as Aib (i.e., with free CO_2H) under a variety of conditions (temperature, solvent systems, time) and reagents (base, additives) consistently results in extensive hydrolysis of the benzotriazole-activated amino acid. Consequently, hindered esters that are soluble in water-free media (dry acetonitrile or THF)

dx.doi.org/10.1021/cr100048w |*Chem. Rev.* 2011, 111, 6557–6602

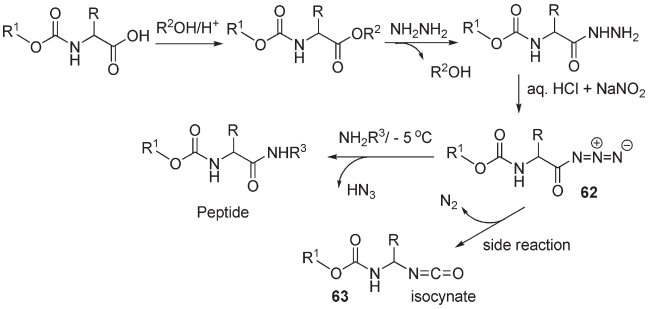
Scheme 13. Preparation of *N*-Acylbenzotriazole



Scheme 14. Preparation of Dipeptide and Tripeptide Using *N*-(Protected-α-aminoacyl)benzotriazoles



Scheme 15. Mechanism of Peptide Bond Formation from Acid Azide and Its Side Reaction



are coupled in the presence of Et_3N at 20 °C during 24−36 h. This process can be shortened to ca. 1 h by microwave irradiation.[124−126]

6. ACYL AZIDES

Although the acyl azide method of coupling was developed about 100 years ago, it is not attractive for routine use because it involves four distinct steps, including two stable intermediates that require purification.[127,128] In addition, aminolysis of the azide is slow. The first step involves preparation of the ester, which can be methyl, ethyl, or benzyl. The ester is converted to the hydrazide by reaction in alcohol with excess hydrazine at ambient or higher temperatures. The hydrazide often crystallizes out of solution or after removal of solvent. The purified hydrazide is transformed into the azide by the action of nitrous acid; this transformation is usually achieved by the addition of sodium nitrite to a cold solution of the hydrazide in a mixture of acetic and hydrochloric acids. The azide (**62**) is generated at low temperature because it readily decomposes with the release of nitrogen at ambient temperature. The azide is extracted into an organic solvent, and the peptide is obtained by leaving the dried solution in the presence of the amine nucleophile in the cold for several hours (Scheme 15).

An additional side reaction that occurs at higher temperature is rearrangement of the acyl azide **62** to the alkyl isocyanate (**63**), which can react with the nucleophile to yield a peptide urea that is difficult to remove from the product (Scheme 15).[127] The side product is neutral and not easy to remove from the peptide. The acyl azide method is time- and effort-consuming and is therefore not suitable for repetitive syntheses. However, it has two characteristic features that make it a popular option for coupling in selected cases. The first regards the strategy of minimum protection. This method can be used for the activation of serine, threonine, and histidine derivatives with unprotected side chains, the latter being unaffected by the reactions used. The second feature regards the coupling of segments. It is the method most likely to guarantee the preservation of chiral integrity during peptide-bond formation between segments. This is possible because the acyl azide does not generate oxazolone. Acyl azide is the only activated form of an *N*-acylamino acid or peptide that can be isolated for which cyclization to the oxazolone has not been demonstrated.

7. ACID HALIDES

7.1. Acid Chlorides

The most obvious method for activating the carboxyl group of an amino acid for peptide bond formation at room temperature or below is via a simple acid chloride.[129] The acid chloride method was first introduced into peptide chemistry by Fisher in 1903.[130] However, for many years, acid chlorides were rarely used because this method gained the reputation among peptide practitioners as being "over activated" and therefore prone to numerous side reactions including the loss of configuration.[12]

7.1.1. Acid Chloride Formation with "Simple" Chlorinating Agents. Chlorination of amino acids is performed usually with various chlorinating reagents, such as pivaloyl chloride,[131] phthaloyl dichloride,[132] thionyl chloride,[133,135] oxalyl chloride,[136,137] and others. Thionyl chloride in pyridine is perhaps the most used chlorinating agent.[134] Thus, Fmoc-amino acid chlorides are generated by reaction of the parent acid with thionyl chloride in hot DCM (Scheme 16).[134] These chlorides show sufficient stability to be purified by recrystallization.

Fmoc-amino acid chloride (**64**) acylates the amino group in the presence of a base, which is required to neutralize the hydrogen chloride released (Scheme 16). The base is necessary, but its presence complicates the process, converting the acid chloride to the 2-alkoxy-5(4*H*)-oxazolone (**65**) (Scheme 16, path A), which is aminolyzed at a slower rate. Aminolysis by acid chloride can also be carried out in a two-phase system of DCM−aqueous carbonate to minimize contact of acid chloride with the base. Another option that allows efficient coupling is the

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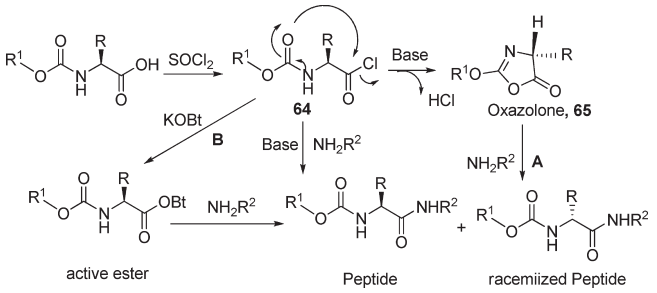
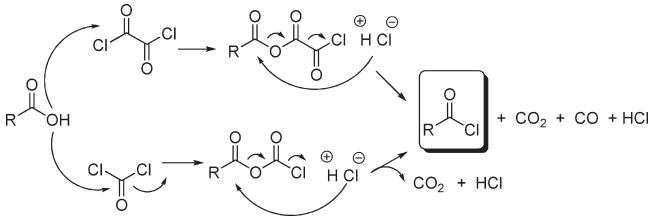
Scheme 16. Mechanism of Peptide Bond Formation from *N*-Protecting Amino Acid Chloride-Mediated Reaction



Scheme 17. Mechanism of Peptide Bond Formation from *N*-Protecting Amino Acid Chloride-Mediated Reaction Using a Phosgene or Oxalyl Chloride



use of the potassium salt of 1-hydroxybenzotriazole instead of tertiary amine for neutralizing the acid (Scheme 16, path B).

The acid chlorides of derivatives with *t*-butyl-based side chains are not accessible by the general procedures, but they can be made using a phosgene or triphosgene replacement and probably using oxalyl chloride[135,138−143] (Scheme 17).

7.1.2. Triazine Chlorinating Reagents. Cyanuric chloride (**66**)[144] and 2-chloro-4,6-dimethyl-1,3,5-triazine, DMCT (**67**),[145] are useful halogenating reagents (Scheme 18).

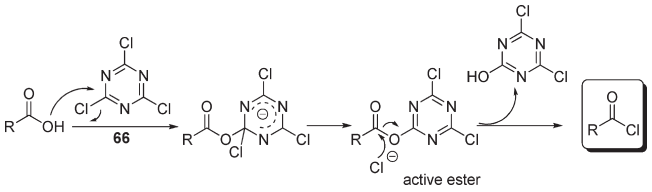
7.1.3. Triphenylphosphine−CCl_4. Triphenylphosphine (TPP, **68**) has been used under neutral conditions to provide conversion of carboxylic acid into acyl chloride,[146−148] analogously to the conversion of alkyl alcohols into alkyl chlorides.[149] It has been suggested that initial formation of triphenyltrichloromethyl phosphonium chloride (**69**) occurs with further reaction, yielding chloroform and triphenylacyloxyphosphonium chloride (Scheme 19). Difficulties to separate the product from the phosphorus-containing byproduct can be avoided by using a polymer-supported phosphine−carbon tetrachloride reagent.[150]

Villeneuve demonstrated that carboxylic acids are converted into the corresponding acyl chloride by hexachloroacetone and TPP at low temperature.[150] This method has also been applied to generate highly reactive formyl chloride. Alternatively, trichloroacetonitrile and TPP also provide mild and efficient conditions.[151]

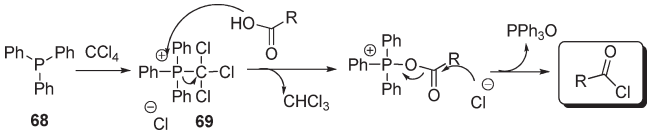
7.1.4. Tetramethyl-α-chloroenamine Chlorinating Reagents. Other neutral conditions using tetramethyl-α-chloroenamine **70** are described by Ghosez et al.[152] During this process, the formation of hydrogen halides is prevented. Thus, this method is extremely useful when acid-labile protecting groups are present (Scheme 20).

7.1.5. Bis(trichloromethyl)carbonate Chlorinating Reagents. In addition to using thiophosgene for the preparation of acyl chlorides, BTC (bis(trichloromethyl)carbonate) (**71**) (Table 4) has been used as an *in situ* chlorinating reagent in

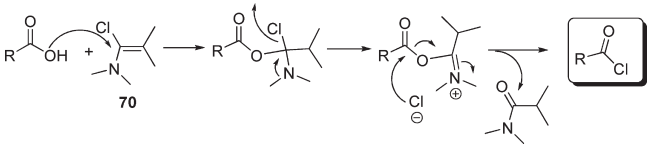
Scheme 18. Acyl Chloride Formation Using Cyanuric Chloride



Scheme 19. Acyl Chloride Formation Using TPP−CCl_4



Scheme 20. Acyl Chloride Formation Using Tetramethyl-α-chloroenamine



SPPS.[153] There is some question as to the nature of the exact intermediates involved in the process described by Gilon.[153] Coupling reactions mediated by BTC (**71**) give good results for Fmoc-amino acids containing acid-labile side chains.

7.1.6. Coupling Reactions with Acyl Chlorides. The amide bond is formed by reaction of the acyl chloride with the desired amine. Couplings are usually performed in inert dry solvents. An additional non-nucleophilic base, such as triethylamine, DIEA, or NMM, is usually required to trap the HCl formed. Sometimes acyl chlorides couple to amines under aqueous conditions, for example, in the presence of NaOH (Schotten−Baumann conditions).[154] These reactions can be accelerated with a catalytic amount of pyridine or *N*,*N*-dimethylaminopyridine (DMAP).[155] In some cases, pyridine is used as the solvent. The formation of an intermediate acylpyridinum salt **72** has been suggested (Scheme 21). The use of Zn can also accelerate coupling at room temperature. The method is applicable to alkyl, aryl, heterocycles, carbohydrates and amino acids and leads to high yields.[156]

7.2. Acid Fluorides

Acyl chlorides have limited value in peptide coupling because of the danger of hydrolysis, racemization, cleavage of protecting groups, and other side reactions (e.g., *N*-carboxy anhydride formation). However, because of their high reactivity, they can be used for highly hindered substrate, and under appropriate conditions, there is no loss of configuration. The main drawback of these systems is that acid-sensitive side chains, such as those derived from *t*-butyl residues, cannot be accommodated. Furthermore, acid fluorides are more stable to hydrolysis than acid chlorides, and in addition, their preparation is not subject to the limitation mentioned with regard to *t*-butyl-based side-chain

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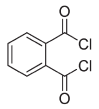
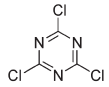
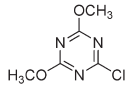
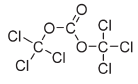
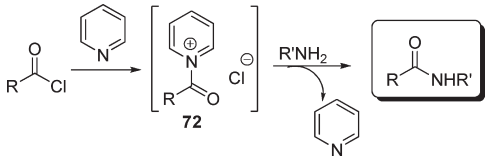
Table 4. Chlorinating Reagents

Entry	Abbreviation	Name and Stucture	Ref.
		pivaloyl chloride 	131
		phthaloyl chloride 	132
		thionyl chloride $SOCl_2$	134
		oxalyl chloride $(COCl)_2$	136
		phosgene $COCl_2$	138
66	CC	cyanuric chloride 	144
67	DMCT	2-chloro-4,6-dimethyl-1,3,5-triazine 	145
68	TPP	triphenylphosphine-carbon tetrachloride PPh_3/CCl_4	150
69		tetramethyl-α-chloroenamine 	152
71	BTC	triphosgene 	153

protection. Thus Fmoc-based SPPS can be performed easily via Fmoc amino acid fluorides.[157−162]

Thus, *N*-protecting amino acid fluorides have been shown to be useful for both solution and solid-phase synthesis and especially suited for the coupling of sterically hindered α,α-disubstituted amino acids, which are not easily handled by standard techniques.[163,164] Acyl fluorides are, indeed, less moisture-sensitive than acyl chlorides and more reactive toward amines. Another advantage is that they are compatible with Fmoc or Cbz N-protections and even with *t*-Bu esters or other acid-labile ester groups, and thus they are useful in peptide chemistry. Examples of the singular reactivity of these compounds include the first ever solid-phase syntheses of naturally occurring peptaibols, peptide alcohols of about 20 units, which are rich in such hindered amino acids.[165] For these syntheses, the Fmoc amino

Scheme 21. Role of Pyridine in Coupling with Acyl Chloride



acid fluorides are isolated and purified by recrystallization before use.

It is now possible to take advantage of the exceptional nature of amino acid fluorides without their isolation via utilization of a new reagent that effects clean *in situ* conversion of the acid to the fluoride under conditions similar to those common in the case of uronium and phosphonium reagents (discussed later).

7.2.1. Fluorinating Reagents. *7.2.1.1. Cyanuric Fluoride.* Cyanuric fluoride[162,166] (**73**) is the most commonly used reagent for the conversion of amino acids into the corresponding acid fluorides (Scheme 22).

7.2.1.2. Other Fluorinating Reagents. The following reagents can also be used: diethylaminosulfur trifluoride (DAST), which is an expensive and hazardous reagent and after reaction requires purification by chromatography;[167] 2-fluoro-1-ethylpyridinium tetrafluoroborate (FEP) (**75**); and 2-fluoro-1-ethylpyridinium hexachloro antimonate (FEPH) (**76**)[168−170] (Table 5).

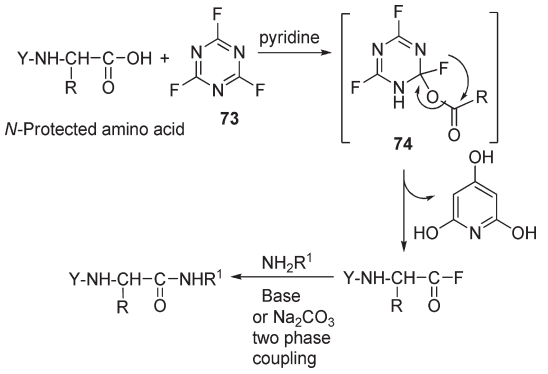
The conversion of the acids to the acid fluorides with all of these reagents follows a similar process. For example, the intermediate **74** is involved with cyanuric fluoride (Scheme 22). The presence of a base was found to be essential for formation of the carboxylic acid fluorides and for peptide bond formation. IR and UV spectroscopic measurements confirm this course of the reaction.[171−173]

7.2.1.3. Fluoroformamidinium Salts. A notable advance was the development of fluoroformamidinium salts. Carpino and El-Faham reported that the air-stable, nonhygroscopic solid TFFH (**77**) is a convenient *in situ* reagent for amino acid fluoride during peptide synthesis (Scheme 23).[174−176] TFFH is especially useful for the two amino acids histidine and arginine since the corresponding amino acid fluorides are not stable toward isolation or storage.

Other analogous reagents have also been synthesized (Table 5). BTFFH (**78**) has an advantage over TFFH in that toxic byproducts are generated upon work up of the reaction mixture.[175−177]

Fluorinating reagents BTFFH (**78**), TEFFH (**80**), DMFFH (**81**), DEFFH (**82**), and DMFH (**83**) behave in the same way as TFFH (**77**) in their capcity to provide routes to amino acid fluorides for both solution and solid-phase reactions.[175−177] DMFH (**83**), which has recently been introduced by El-Faham and Albericio,[178,179] has the advantage over the other fluorinating agents in that it gives convenient results with 1 equiv of base. This performance is the result of the presence of the oxygen atom in the carbon skeleton (morpholino moiety), which acts as a proton acceptor. Compound FIP (**79**) is more reactive but more sensitive to moisture and does not allow complete conversion to the acid fluoride. For some amino acids, for example, Fmoc-Aib-OH, the use of TFFH alone gives results that are less satisfactory than those obtained with isolated amino acid fluorides. The deficiency is traced to inefficient conversion to the acid fluoride, which, under the conditions used (2 equiv of DIEA), is accompanied by the corresponding symmetric anhydride and oxazolone (Scheme 24).[175,176,180,181]

Scheme 22. Synthesis of Amino Acid Fluoride and Coupling Using Cyanuric Fluoride



7.2.1.4. Complex Fluoride Additive. Interestingly, conversion of the acid to the acid fluoride is also observed via treatment with uronium salts such as HATU or HBTU (discussed later) in the presence of additive PTF (**84**). In this way, excellent syntheses have been achieved for difficult peptides for which HBTU gave poor results because of the sluggish reactivity of OBt esters.[182,183]

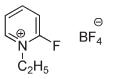
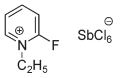
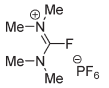
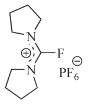
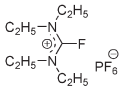
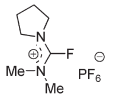
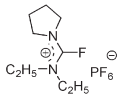
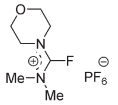
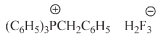
By this means, the relatively inexpensive reagents HBTU provide peptides of equal or greater quality than those obtained via HATU or isolated acid fluorides. Regardless of the kind of coupling reagents used in these reactions, a tertiary base, such as DIEA, is required in the activation step. In the case of systems that undergo facile loss of configuration, the presence of a base may be deleterious and is not required for the actual coupling step in the case of acid fluorides.[184] It is thus particularly significant that acid fluorides can be generated via carbodiimides in the absence of base.[185] The carbodiimide method of peptide activation is believed to involve transient formation of a labile *O*-acylisourea **85**. In the presence of a second equivalent of carboxylic acid, **85** is converted to the symmetric anhydride **86**, which represents the active coupling species.[186] It has now been found that in the presence of PTF (**84**) the putative *O*-acylisourea intermediate is diverted to the acid fluoride (Scheme 25).

8. PHOSPHONIUM SALTS

Kenner and co-workers[187] were the first to describe the use of acylphosphonium salts as coupling reagents. These species were widely adopted only after extensive studies by Castro and Coste,[188] who first introduced ClopP[189−191] (**91**) as peptide-coupling reagents with noticeable racemization.

Phosphonium salts react with the carboxylate, and therefore the presence of at least 1 equiv of base is essential. With regards to the mechanism, several authors[187,192−194] have proposed that the same acyloxyphosphonium salt is the active species. However, Castro and Dormoy[195−197] suggested that this salt is very reactive and even at low temperatures it will react immediately with carboxylate ions present in the medium to give the symmetrical anhydride. This pathway is supported by kinetic studies carried out by Hudson (Scheme 26).[198] Several years later, Kim and Patel[199] reported that this intermediate could be present at −20 °C when BOP (**85**) is used as a coupling reagent. However, Coste and Campagne[200] propound that this species is highly unstable and even at low temperatures undergoes conversion to an active ester. Despite this controversy, it is widely accepted that the active species is an active ester when phosphonium salts

Table 5. Fluorinating Reagents

Entry	Abbreviation	Name and Structure	Ref.
73	CF	cyanuric fluoride 	166
75	FEP	2-fluoro-1-ethyl pyridinium tetrafluoroborate 	168
76	FEPH	2-fluoro-1-ethyl pyridinium hexachloroantimonate 	168
77	TFFH	tetramethylfluoroformamidinium hexafluorophosphate 	174
78	BTFFH	*bis*(tetramethylene)fluoroformamidinium hexafluorophosphate 	174
79	FIP	2-fluoro-1,3-Dimethylimidazolidinium hexafluorophosphate 	174
80	HEFFH	tetraethylfluoroformamidinium hexafluorophosphate 	177
81	DMFFH	1-dimethyl-3,3-tetramethylene fluoroformamidiniumhexafluorophosphate 	177
82	DEFFH	1,1-diethyl-3,3-tetramethylene fluoroformamidinium hexafluorophosphate 	177
83	DMFH	*N*-(fluoro(morpholino)methylene)-*N*-methylmethanaminium hexafluorophosphate 	179
84	PTF	benzyltriphenylphosphonium dihydrogen trifluoride 	180

containing nucleophilic derivatives are used. These couplings are carried out with an excess of the base, usually 2 equiv of DIEA,

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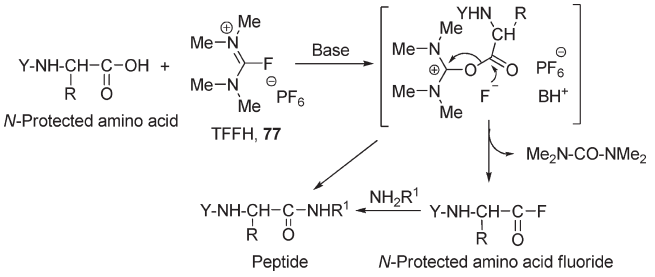
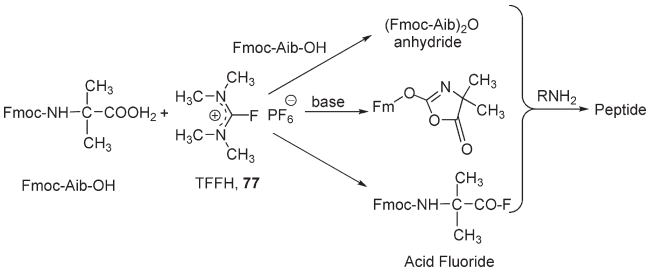
Scheme 23. Mechanism of Peptide Bond Formation Using TFFH-Mediated Reaction



Scheme 24. Mechansim of the Reaction of Fmoc-Aib-OH with TFFH and Coupling



and in the presence of 1 equiv of the hydroxylamine derivative, usually HOBt or HOAt. The active species detected during couplings with the chloro and bromo derivatives of phosphonium salts, BroP (**88**), PyCloP (**89**), and PyBroP (**90**), in the absence of HOBt are the symmetrical anhydride 5(4*H*)-oxazolone and for Boc-amino acids the unprotected *N*-carboxy-anhydride.[201]

A great advantage of phosphonium salts over aminium/uronium salts (see above) is that the phosphonium does not react with the amino function of the incoming moiety and therefore the phosphonium does not terminate the peptide chain. This is relevant in fragment coupling and cyclization when both reactants are in equimolar relation and an excess of the coupling reagent reacts with the amino component.[29]

8.1. HOBt Phosphonium Salt Derivatives

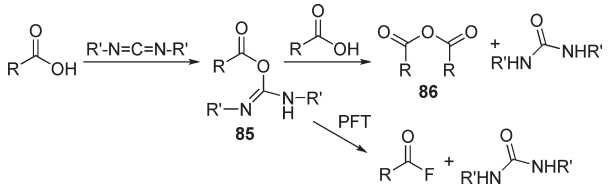
8.1.1. BOP Coupling Reagent. In 1975, Coste and Castro introduced[196,197] BOP (benzotriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate) (**85**), which contains the racemization suppressant HOBt. Although BOP is an excellent coupling reagent, hexamethylphosphoramide (HMPA, **87**), a toxic compound, is generated.[198]

8.1.2. PyBOP Coupling Reagent. In order to prevent the generation of the undesirable HMPA (**87**), Coste and co-workers introduced PyCloP (**89**), PyBroP (**90**), and PyBOP (**92**) (Table 6). In these compounds, the dimethylamine moiety is replaced by pyrrolidine[196,202,203] In a following study, Coste reported that halogenophosphonium reagents [PyCloP (**89**), PyBroP (**90**)] often give better results than other phosphonium-HOBt reagents for the coupling of *N*-methylated amino acid.[197]

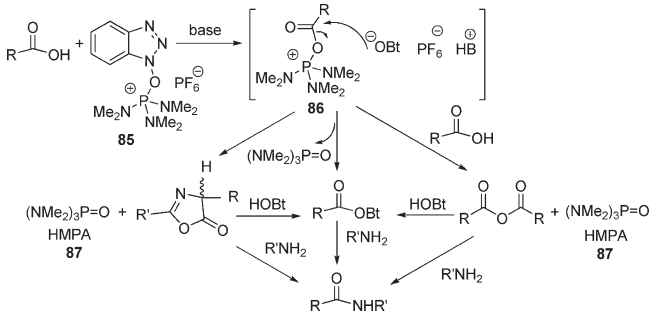
8.2. HOAt Phosphonium Salt Derivatives

Phosphonium salts derived from HOAt, such as (7-azabenzotriazol-1-yloxy)tris-(dimethylamino)phosphonium hexafluorophosphate (AOP, **93**) and (7-azabenzotriazol-1-yloxy)tris-(pyrrolidino)

Scheme 25. Reaction of Acid with Carbodiimide in Presence of PFT



Scheme 26. Mechanism of BOP-Mediated Reaction



phosphonium hexafluorophosphate (PyAOP, **94**), have also been prepared and are generally more efficient than BOP (**85**) and PyBOP (**92**) as coupling reagents[204−208]

The pyrrolidino derivative PyAOP is slightly more reactive than the dimethylamino derivative AOP, and it does not release HMPA (**87**) in the activation step.

8.3. Oxyma-Based Phosphonium Salts

Very recently, El-Faham and Albericio[209] reported the phosphonium salt of Oxyma, *O*-[(cyano-(ethoxycarbonyl)methyliden)-amino]yloxytripyrrolidinophosphonium hexafluorophosphate (PyOxm, **95**) (Table 6), as an efficient, racemization-suppressing coupling reagent for the assembly of hindered peptides. Oxyma performs better than classical benzotriazole. Similarly to the recently introduced uronium salt COMU (discussed later), **95** renders a higher percentage of cyclic peptides than other known phosphonium salts in cyclization models.

8.4. Other Phosphonium Salts

Since the discovery of HOBt-mediated coupling reagents, many racemization suppressants have been exploited as a part of the composition of new peptide-coupling reagents (Table 6). For example, PyNOP (**96**), PyFOP (**97**), PyFNOP (**98**), PyCloK (**99**), PyPOP (**100**), PyTOP (**101**), PyDOP (**102**), and PyDAOP (**103**)[50,204−208,210,211] were prepared in this regard and serve as efficient peptide-coupling reagents for the synthesis of dipeptides bearing *N*-methyl amino acids.

8.5. Preparation of Phosphonium Salts

Castro and Dormoy[212,213] isolated the chlorotris(dimethylamino)phosphonium cation in its perchlorate form (**104**) by reaction of tris(dimethylamino)phosphine with CCl_4 in ether, followed by addition of an aqueous solution of ammonium perchlorate (Scheme 27).

The corresponding bromo derivative **88** (BroP) is prepared in a similar way by using Br_2 in ether at 0 °C followed by anion exchange with KPF_6 (Scheme 27).[214] The tripyrrolidino derivatives

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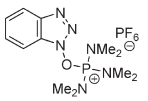
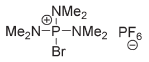
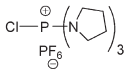
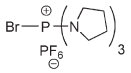
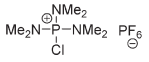
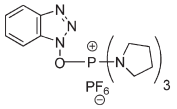
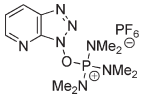
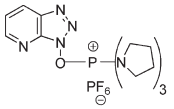
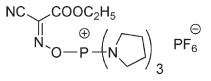
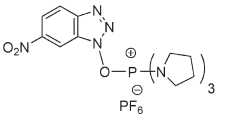
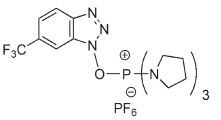
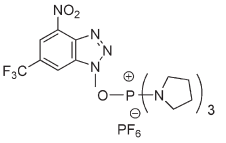
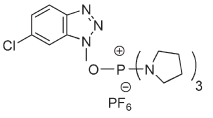
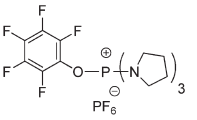
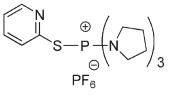
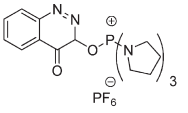
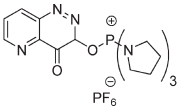
Table 6. Phosphonium Salt Coupling Reagents

Entry	Abbreviations	Names and Structure	Ref.
85	BOP	benzotriazol-1-yloxytris(dimethyl amino) phosphonium hexafluorophosphate 	187
88	BrOP	bromo*tris*(dimethylamino)phosphonium hexafluorophosphate 	201
89	PyCloP	chlorotri(pyrrolidino)phosphonium hexafluorophosphate 	201
90	PyBroP	bromotri(pyrrolidino)phosphonium hexafluorophosphate 	201
91	CloP	chloro-*tris*(dimethylamino)-phosphonium hexafluorophosphate) 	190
92	PyBOP	benzotriazol-1-yloxytri(pyrrolidino)- phosphonium hexafluorophosphate 	197
93	AOP	(7-azabenzotriazol-1-yl)oxytris-(dimethylamino) phosphonium hexafluorophosphate 	206
94	PyAOP	[(7-azabenzotriazol-1-yl)oxy]*tris*-(pyrrolidino) phosphonium hexafluorophosphate 	206
95	PyOxm	*O*-[(cyano-(ethoxycarbonyl)methyliden)-amino]-yloxytripyrrolidinophosphonium hexafluorophosphate 	209

Entry	Abbreviations	Names and Structure	Ref.
96	PyNOP	[(6-nitrobenzotriazol-1-yl)oxy]tris-(pyrrolidino) phosphonium hexafluorophosphate 	211
97	PyFOP	[[6-(trifluoromethyl)benzotriazol-1-yl]oxy]-*tris*(pyrrolidino)phosphonium hexafluorophosphate 	211
98	PyFNBOP	[4-nitro-6- (trifluoromethyl)benzotriazol-1-yl)oxy]*tris* (pyrrolidino)phosphonium hexafluorophosphate 	211
99	PyCloK	(6-chloro-benzotriazol-1-yloxy)*tris* (pyrrolidino)-phosphonium hexafluorophosphate 	209
100	PyPOP	*N*,*N*,*N*′,*N*′-*bis*(tetramethylene)-*O*-pentafluoro phenyluronium hexafluorophosphate 	210
101	PyTOP	(pyridyl-2-thio)tris(pyrrolidino)-phosphonium hexafluorophosphate 	210
102	PyDOP	[(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3- yl)oxy]tris-(pyrrolidino)phosphonium hexafluorophosphate 	50
103	PyDAOP	[(3,4-dihydro-4-oxo-5-azabenzo-1,2,3-triazin-3-yl]*tris*-(pyrrolidino)phosphonium hexafluorophosphate 	50

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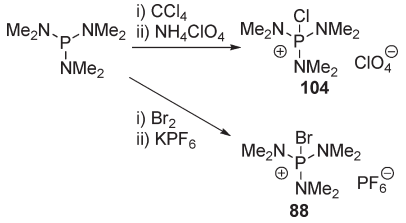
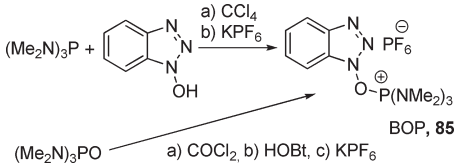
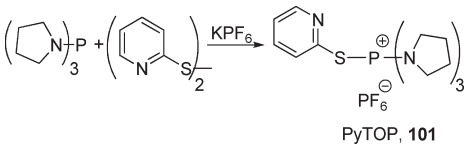
Scheme 27. Synthesis of Halophosphonium Salts



Scheme 28. Synthesis of BOP Reagent



Scheme 29. Synthesis of PyTOP



are prepared in a similar manner by substitution of the tris(dimethylamino) group by the tripyrrolidino, thereby affording PyCloP (**89**) and PyBroP(**90**).[194]

BOP (**85**), one of the first phosphonium salts to become commercially available, is prepared by reaction of tris(dimethylamino) phosphine with carbon tetrachloride in the presence of 1-hydroxybenzotriazole (HOBt) in tetrahydrofuran (THF) at −30 °C, followed by exchange of the chloride anion with the hexafluorophosphate anion (Scheme 28).[196]

A more economical method to prepare this reagent was described by Castro.[190] This involved the reaction of HMPA with $COCl_2$ in toluene, followed by reaction with HOBt in the presence of TEA and then final anion exchange (Scheme 23). Phosphoryl chloride can also be used to prepare the chlorophosphonium cation intermediate, which can be isolated as hexafluorophosphate or perchlorate in almost quantitative yield.[191] The pyrrolidine derivative **92** (PyBOP) is prepared under similar reaction conditions.[190]

Related HOBt-substituted reagents, such as PyFOP (**97**), are prepared[215] following the same protocol as for BOP (**85**) and PyBOP (**92**).[190] The preparation of PyNOP (**96**), PyFOP (**97**), and PyClok (**99**) has been carried out from the corresponding 6-nitro-, 6-trifluoromethyl-, or 6-chloro-substituted benzotriazoles, which are allowed to react with PyCloP (**89**). The disubstituted benzotriazole derivative PyFNOP (**98**) [4-nitro-6-(trifluoromethyl)benzotriazol-1-yl)oxy]tris-(pyrrolidino)phosphonium hexafluorophosphate[216] is prepared by reaction of PyBrOP (**89**) with the corresponding disubstituted hydroxybenzotriazole. The dimethylamine and pyrrolidine phosphoramide derivatives AOP (**93**) and PyAOP (**94**) are prepared in the same way,[217] as well as the phosphonium salt PyDOP (**96**) and PyDAOP (**103**), by reaction of the corresponding additive

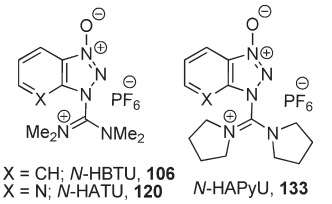
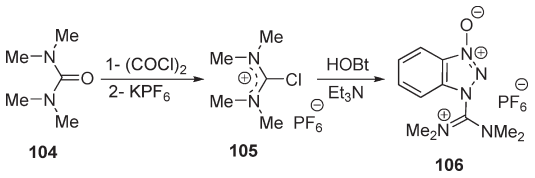


Figure 2. Structures of aminium salts.

Scheme 30. Synthesis of *N*-HBTU



with the phosphonium salt PyCloP (**89**) in the presence of TEA.[50] Pentafluorophenol (PyPOP, **100**) is also obtained by reaction of the corresponding phenol with PyCloP. The thiophosphonium salt (PyTOP, **101**) is prepared by treating tris(pyrrolidino)phosphine with 2,2′-dipyridyl disulfide followed by precipitation of the phosphonium salt as its hexafluorophosphate (Scheme 29).

9. AMINIUM/URONIUM SALTS

Aminium salts bear a positive carbon atom instead of the phosphonium residue and were at first assigned a uronium-type structure by analogy with the corresponding phosphonium salt. Initially, the product obtained by reaction of HOBt with tetramethylchlorouronium salt (TMUCl) was assigned to a uronium-type structure, presumably by analogy with the corresponding phosphonium salts, which bear a positive carbon atom instead of the phosphonium residue.[218]

Later,[219−221] it was shown by X-ray analysis that salts crystallize as aminium salts (guanidinium *N*-oxides) rather than the corresponding uronium salts. This occurs for *N*-[(1*H*-benzotriazol-1-yl)-(dimethylamino)methylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide (*N*-HBTU, **106**), *N*-[(dimethylamino)-1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide (*N*-HATU, **120**), and 1-(1-pyrrolidinyl-1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-ylmethylene) pyrrolidinium hexafluorophosphate *N*-oxide (HAPyU, **133**) (Figure 2).[176,222−227]

As mentioned in the Introduction (Scheme 3), aminium/uronium reacts directly with the amine moiety of the amino acid residue to give a guanidine side product (**4**), which terminates the peptide chain.[29] This result is often due to the slow preactivation of the carboxylic acid or to the use of excess uronium reagent. This should be taken into consideration during fragment coupling and cyclization, where both reactants are in equimolar relation. Furthermore, in stepwise SPPS use of a slight defect (0.95 equiv) of the aminium/uronium salt is recommended to prevent the reaction with the amino function.

9.1. Tetramethyl Aminium Salts

The preparation of these commercially available reagents is achieved by transformation of tetramethylurea (TMU, **104**) into the corresponding chlorouronium salt (chlorotetramethyluronium

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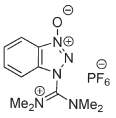
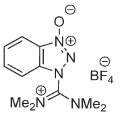
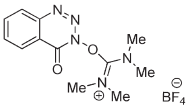
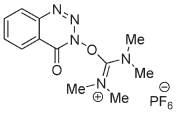
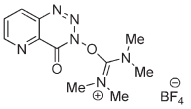
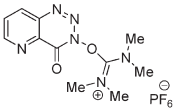
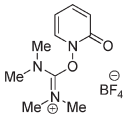
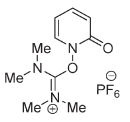
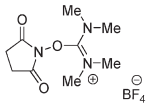
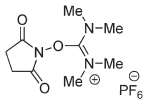
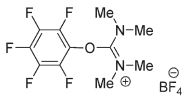
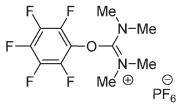
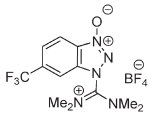
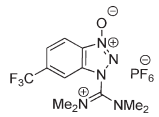
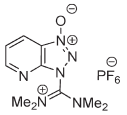
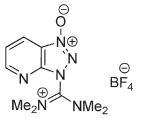
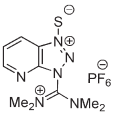
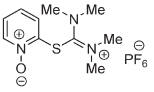
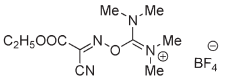
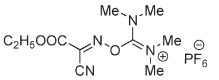
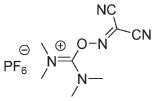
Table 7. Tetramethyl Aminium Salts

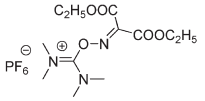
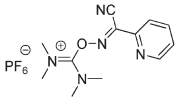
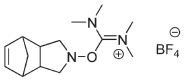
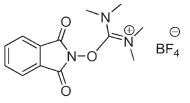
Entry	Abbreviation	Name and Structure	Ref
106	*N*-HBTU	*N*-[(1*H*-benzotriazol-1-yl)(dimethylamino)methylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide 	219
107	*N*-TBTU	*N*-[(1*H*-benzotriazol-1-yl)(dimethylamino)methylene]-*N*-methylmethanaminium tetrafluoroborate *N*-oxide 	219
108	TDTU	2-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyl uronium tetrafluoroborate 	227
109	HDTU	2-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate 	227
110	TDATU	*O*-(3,4-Dihydro-4-oxo-5-azabenzo-1,2,3-triazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate 	50
111	HDATU	*O*-(3,4-dihydro-4-oxo-5-azabenzo-1,2,3-triazin-3-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate 	50
112	TPTU	2-(2-oxo-1(2*H*)-pyridyl-1,1,3,3-tetramethyluronium tetrafluoroborate 	224
113	HPTU	2-(2-oxo-1(2*H*)-pyridyl-1,1,3,3-tetramethyluronium hexafluorophosphate 	224

Entry	Abbreviation	Name and Structure	Ref
114	TSTU	2-succinimido-1,1,3,3-tetramethyluronium tetrafluoroborate 	226
115	HSTU	2-succinimido-1,1,3,3-tetramethyluronium hexafluorophosphate 	226
116	TPFTU	*N*,*N*,*N*′,*N*′-*bis*(tetramethylene)-*O*-pentafluorophenyluronium tetrafluoroborate 	229
117	HPFTU	*N*,*N*,*N*′,*N*′-*bis*(tetramethylene)-*O*-pentafluorophenyluronium hexafluorophosphate 	229
118	*N*-CF_3-TBTU	*N*-[6-trifluoromethyl (1*H*-benzotriazol-1-yl)(dimethylamino) methylene]-*N*-methylmethanaminium tetrafluoroborate *N*-oxide 	210
119	*N*-CF_3-HBTU	*N*-[6-trifluoromethyl (1*H*-benzotriazol-1-yl)(dimethylamino) methylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide 	210
120	*N*-HATU	*N*-[(dimethylamino)-1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-yl methylene]-*N*-methyl methan aminium hexafluorophosphate *N*-oxide 	219
121	*N*-TATU	*N*-[(dimethylamino)-1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-yl methylene]-*N*-methylmethanaminium tetrafluoroborate *N*-oxide 	219

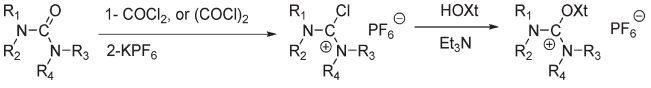
dx.doi.org/10.1021/cr100048w |*Chem. Rev.* 2011, 111, 6557–6602

Table 7. Continued

Entry	Abbreviation	Name and Structure	Ref
122	*N*-HATTU	*N*-[(dimethylamino)-1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-yl methylene]-*N*-methylmethanaminium hexafluorophosphate *N*-sulfide 	222
123	HOTT	*S*-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouronium hexafluorophosphate 	231
124	TOTU	*O*-[cyano(ethoxycarbonyl)methyleneamino]-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate 	234
125	HOTU	*O*-[cyano(ethoxycarbonyl)methyleneamino]-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate 	234
126	HTODC	O-[(dicyanomethylidene)-amino]-1,1,3,3-tetramethyluronium hexafluorophosphate 	234

Entry	Abbreviation	Name and Structure	Ref
127	HTODeC	O-[(diethoxycarbonylmethylidene)amino]-1,1,3,3-tetramethyluronium hexafluorophosphate 	234
128	HTOPC	*N*-[(cyano(pyridine-2-yl) methylene aminooxy)(dimethylamino) methylene)-*N*-methylmethanaminium hexafluorophosphate 	234
129	TNTU	2-(5-norbornene-2,3-dicarboximido)-1,1,3,3-tetramethyluronium tetrafluoroborate 	235
130	TPhTU	2-phthalimido-1,1,3,3- tetramethyluronium tetrafluoroborate 	235

Scheme 31. Synthesis of Uronium−Aminium Salts



chloride, TMUCl, **105**), by treatment with $COCl_2$ in toluene followed by exchange with NH_4PF_6 or KPF_6 and then reaction of **105** with HOBt to afford *N*-HBTU (**106**) (Scheme 30, Table 7).[224,225] Compound **106** is also prepared by replacement of the extremely toxic $COCl_2$ by oxalyl chloride[176,177] or $POCl_3$,[176] using a one-pot procedure in organic solvents, and also the analogous tetrafluoroborate reagent (TBTU, **107**, Table 7), which cannot be prepared by the previous procedure.

This one-pot method has also been applied to the preparation of the HODhbt derivative 2-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TDTU, **108**) and the corresponding hexafluorophosphate (HDTU, **109**); the HODhat derivatives, *O*-(3,4-dihydro-4-oxo-5-azabenzo-1,2,3-triazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TDATU, **110**) and the corresponding hexafluorophosphate (HDATU, **111**);[50] the pyridone derivative 2-(2-oxo-1(2*H*)-pyridyl-1,1,3,3-tetramethyluronium derivatives (TPTU, **112**, and HPTU, **113**); and the hydroxysuccinimide derivatives 2-succinimido-1,1,3,3-tetramethyluronium tetrafluoroborate (TSTU, **114**),[224] which are all commercially available. The hexafluorophosphate **115** is also been prepared following the same strategy.[226,227]

Other HOXt derivatives attached to the tetramethyluronium cation include the pentafluorophenol derivatives **116** (TPFTU) and **117** (HPFTU).[228,229]

In the case of 1-hydroxybenzotriazole derivatives containing electron-withdrawing groups, the 6-trifluoromethyl derivative (CF_3-TBTU, **118**, and CF_3-HBTU **119**) is prepared from tetrafluoromethylchloroformamidinium hexafluorophosphate.[210]

The corresponding HBTU and TBTU analogs, containing the HOAt structure instead of HOBt, are prepared from TMU-Cl salts to give the corresponding reagents *N*-[(dimethylamino)-1*H*-1,2,3-triazolo[4,5-*b*]pyridino-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate (HATU, **120**) and tetrafluoroborate **121** (TATU),[219] which have been shown to be *N*-oxides with aminium structures.[220−222] Two tetramethylurea-derived thiouronium reagents, the HOAt derivative **122** (HATTU)[230] and the *N*-hydroxy-2-pyridinethione derivatives **123** (HOTT),[231−233] are prepared, following Knorr's strategy.[226] The *O*-[(ethoxycarbonyl) cyanomethylene amino]-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TOTU **124** and HOTU **125**) are reported by Hoechst's group and recently developed with other derivatives (**126**−**128**) by El-Faham and Albericio.[234] TNTU (**129**)[226] and TPhTU (**130**)[235] are prepared using the same strategy as described above (Table 7).

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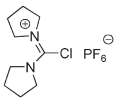
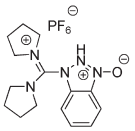
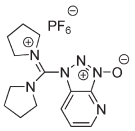
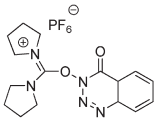
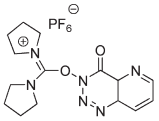
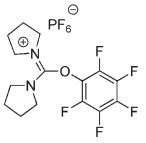
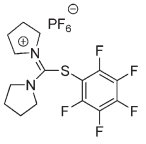
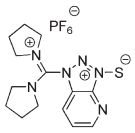
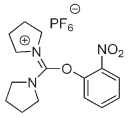
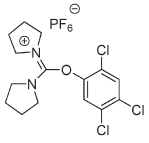
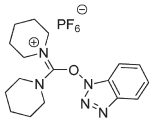
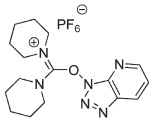
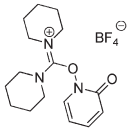
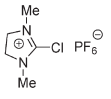
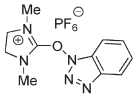
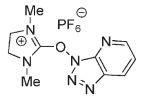
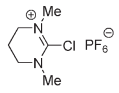
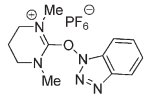
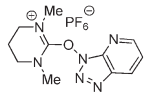
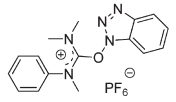
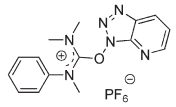
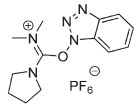
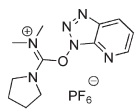
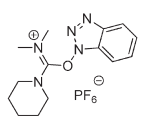
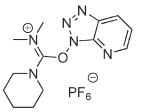
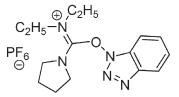
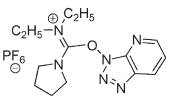
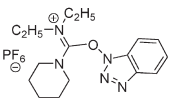
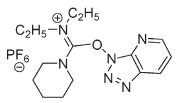
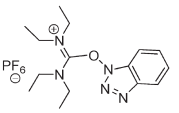
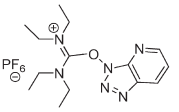
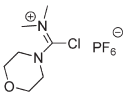
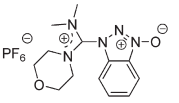
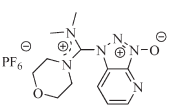
Table 8. Aminium Coupling Reagents

Entry	Abbreviation	Name and Structure	Ref.
131	BTCFH, PyClU	*bis*(tetramethylene)chlororformamidinium hexafluorophosphate 	175
132	HBPyU	(*1H*-benzotriazol-1-yl)(1-pyrrolidinylmethylene) pyrrolidinmium hexafluoro phosphate *N*-oxide 	175
133	HAPyU	1-(1-pyrrolidinyl-1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-ylmethylene) pyrrolidinmium hexafluoro phosphate *N*-oxide 	176
134	HDPyU	*O*-(3,4-Dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate 	50
135	HDAPyU	*O*-(3,4-dihydro-4-oxo-5-azabenzo-1,2,3-triazin-3-y)-1,1,3,3-*bis*(tetramethylene) uronium hexafluorophosphate 	50
136	HPyOPfp	*N*,*N*,*N*′,*N*′-*bis*(tetramethylene)-*O*-pentafluorophenyluronium hexafluorophosphate 	236
137	HPySPfp	*N*,*N*,*N*′,*N*′-*bis*(tetramethylene)-*S*-pentafluorothiophenyluronium hexafluorophosphate 	237

Entry	Abbreviation	Name and Structure	Ref.
138	HAPyTU	1-(1-pyrrolidinyl-1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-ylmethylene) pyrrolidinmium hexafluoro phosphate *N*-sulfide 	237
149	HPyONP	*N*,*N*,*N*′,*N*′-*bis*(tetramethylene)-*O*-2-nitrophenyluronium hexafluorophosphate 	238
140	HPyOTCp	*N*,*N*,*N*′,*N*′-*bis*(tetramethylene)-*O*-pentafluorophenyluronium hexafluorophosphate 	238
141	HBPipU	*O*-(benzotriazol-1-yl)-1,1,3,3-*bis*(pentamethylene) uronium hexafluorophosphate 	45
142	HAPipU	*O*-(7-azabenzotriazol-1-yl)- 1,1,3,3-*bis*(pentamethylene)- uronium hexafluorophosphate 	48
143	TOPPipU	2-[2-oxo-1(2*H*)-pyridyl]-1,1,3,3- *bis*(pentamethylene)uronium tetrafluoroborate 	239
145	CIP	2-chloro-1,3-dimethylimidazolidinium hexafluorophosphate 	176
146	HBMDU	*O*-(benzotriazol-1-yl)-1,3-dimethyl-1,3-dimethyleneuronium hexafluorophosphate 	176

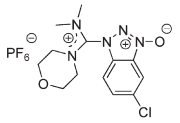
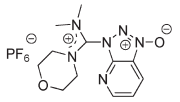
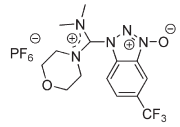
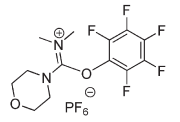
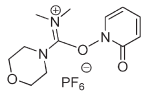
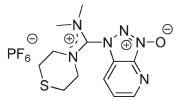
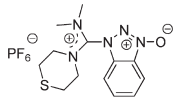
dx.doi.org/10.1021/cr100048w |*Chem. Rev.* 2011, 111, 6557–6602

Table 8. Continued

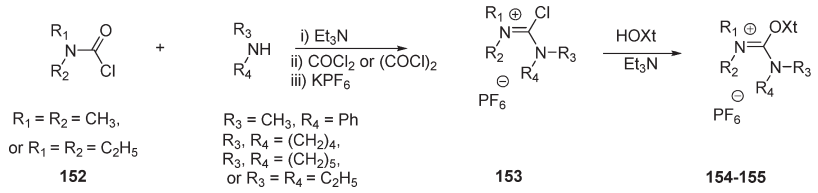
Entry	Abbreviation	Name and Structure	Ref.
147	HAMDU	*O*-(7-azabenzotriazol-1-yl)-1,3-dimethyl-1,3-dimethyleneuronium hexafluorophosphate 	176
148	CPP	2-chloro-1,3-dimethylpyrimidinium hexafluorophosphate 	177
149	HBMTU	*O*-(benzotriazol-1-yl)-1,3-dimethyl-1,3-trimethyleneuronium hexafluorophosphate 	177
150	HAMTU	*O*-(7-azabenzotriazol-1-yl)-1,3-dimethyl-1,3-trimethyleneuronium hexafluorophosphate 	177
154	HBPTU	(7-benzotriazol-yl)-1,1,3-trimethyl-1 phenyluronium hexafluorophosphate 	241
155	HAPTU	(7-azabenzotriazol-yl)-1,1,3-trimethyl-1-phenyluronium hexafluorophosphate 	241
156	HBM_2PyU	*O*-(1*H*-benzotriazol-1-yl)-1,1-dimethyl-3,3-tetramethylene uronium hexafluorophosphate 	182
157	HAM_2PyU	*O*-(1*H*-1,2,3-triazolo[4,5-b]pyridin-1-yl)-1,1-dimethyl-3,3-tetramethyleneuronium hexafluorophosphate 	182
158	HBM_2PipU	*O*-(1*H*-benzotriazol-1-yl)-1,1-dimethyl-3,3-pentamethylene uronium hexafluorophosphate 	182
159	HAM_2PipU	*O*-(1*H*-1,2,3-triazolo[4,5-b]pyridin-1-yl)-1,1-dimethyl-3,3-pentamethyleneuronium hexafluorophosphate 	183
160	HBE_2PyU	*O*-(1*H*-benzotriazol-1-yl)-1,1-diethyl-3,3-tetramethyleneuronium hexafluorophosphate 	182
161	HAE_2PyU	*O*-(1*H*-1,2,3-triazolo[4,5-b]pyridin-1-yl)-1,1-diethyl-3,3-tetramethyleneuronium hexafluorophosphate 	182
162	HBE_2PipU	*O*-(1*H*-benzotriazol-1-yl)-1,1-diethyl-3,3-pentamethyleneuronium hexafluorophosphate 	182
163	HAE_2PipU	*O*-(1*H*-1,2,3-triazolo[4,5-b]pyridin-1-yl)-1,1-diethyl-3,3-pentamethyleneuronium hexafluorophosphate 	182
164	HBTeU	*O*-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetraethyluronium hexafluorophosphate 	182
165	HATeU	*O*-(1*H*-1,2,3-triazolo[4,5-b]pyridin-1-yl)-1,1,3,3-tetraethyluronium hexafluorophosphate 	182
167	DMCH	*N*-(chloro(morpholino)methylene)-*N*-methylmethanaminium hexafluorophosphate 	179
168	HDMB	1-((dimethylamino)(morpholino)methylene)-1*H*-benzotriazoliumhexafluorophosphate-3 oxide 	179
169	HDMA	1-((dimethylamino)-(morpholino)methylene)-1*H* [1,2,3]triazolo[4,5-*b*]pyridinium hexafluorophosphate-3-oxide 	179

dx.doi.org/10.1021/cr100048w |*Chem. Rev.* 2011, 111, 6557–6602

Table 8. Continued

Entry	Abbreviation	Name and Structure	Ref.
170	HDMC	6-chloro-1 ((dimethylamino) (morpholino)methylene)-1*H*-benzotriazolium hexafluorophosphate-3 oxide 	179
171	4-HDMA	3-((dimethylamino)-(morpholino)methylene)-1*H*-[1,2,3]triazolo[4,5-*b*]pyridinium hexafluorophosphate 1-oxide 	179
172	6-HDMFB	6-trifluoromethyl-1-((dimethylamino)(morpholino)methylene)-1*H*-benzotriazoliumhexafluorophosphate -3-oxide 	179
173	HDMPfp	1-((dimethyamino)-(morpholino))oxypentafluorophenyl metheniminium hexafluorophosphate 	179
174	HDMP	1-((dimethyamino) (morpholino)) oxypyrrolidine-2,5-dione methanaminium hexafluorophosphate 	179
175	HDTMA	1-((dimethylamino)(thiomorpholino)methylene)-1*H*-[1,2,3]triazolo[4,5-*b*]pyridinium hexafluorophosphate 3-oxide 	179
176	HDTMB	1-((dimethylamino) (thiomorpholino)methylene)-1*H*-benzotriazolium hexafluorophosphate 3-oxide 	179

Scheme 32. Synthesis of Unsymmetric Aminium Salts



9.2. Bispyrrolidino Aminium Salts

9.2.1. HBPyU. The chlorouronium salts (BTCFH, **131**), derived from dipyrrolidinourea, are prepared by chlorination with phosgene,[174] oxalyl chloride,[175] or $POCl_3$,[176] followed by treatment with aqueous KPF_6. HOBt (**19**) is coupled with these chlorouronium reagents to give the corresponding aminium salt, HBPyU, **132** (Scheme 31).

9.2.2. HXPyU. The related HXPyU derived from HOAt, HODhbt, and HOADhbt are prepared by a similar method to that above to afford HAPyU (**133**), HDPyU (**134**), and HDAPyU (**135**). NMR spectral analysis showed that HBPyU and HAPyU are present in the *N*-form.[219,220] Although these derivatives have been shown to be more reactive that their tetramethyl derivatives,[29] they are not commercially available due mainly to their price.

9.2.3. HPyOPfp. The pentafluorophenyluronium salt **136** is prepared by treatment of the urea with $POCl_3$, followed by anion interc1hange and final reaction with potassium pentafluorophenolate.[236] The corresponding thiouronium reagent **137** (HPySPfp) has also been described as well as the reagent **138** (HAPyTU).[237]

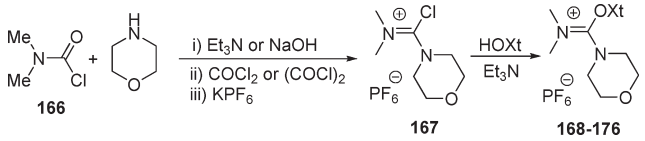
9.2.4. Phenol Derivatives. 2-Nitrophenol (HPyONP, **139**) and 2,4,5-trichlorophenol (HPyOTcP, **140**) are reacted with the chlorouronium salt **141** (BTCFH) to give the two new reagents **139** (HPyONp) and **140**(HPyOTcp).[238]

9.3. Bispiperidino Aminium Salts

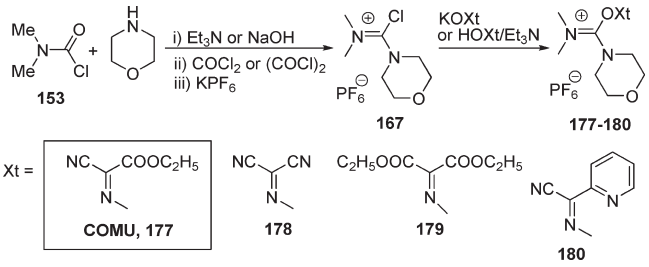
The chlorouronium salts derived from dipiperidinourea are prepared by chlorination with phosgene[174] or oxalyl chloride[175] or $POCl_3$,[176] followed by treatment with aqueous KPF_6. HOXt is coupled with these chlorouronium reagents to give the corresponding aminium salts HBPipU (**141**), HAPipU (**142**),[45,217] and TOPPipU (**143**).[239] Although the pyrrolidino derivatives are

dx.doi.org/10.1021/cr100048w |*Chem. Rev.* 2011, 111, 6557–6602

Scheme 33. Synthesis of Morpholino-Based Coupling Reagents



Scheme 34. Synthesis of Oxyma-Based Coupling Reagents



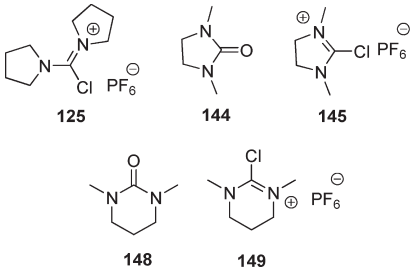
more reactive than the tetramethyl ones, the piperidino are less reactive than the parent tetramethyl derivatives.[29]

9.4. Imidazolium Uronium Salts

The chloroimidazolidinium salt (CIP,**145**) is obtained by chlorination of the commercial 1,3-dimethylimidazolidin-2-one (**144**) with phosgene or oxalyl chloride, followed by anion interchange with NH_4PF_6,[240] and reaction with HOXt to afford the corresponding uranium salts HBMDU (**146**) and HAMDU (**147**) (Scheme 31, Table 8).

9.5. Pyrimidinium Uronium Salts

The chloropyrimidinium salt (CPP, **149**) is obtained by chlorination of the commercial 1,3-dimethyltetrahydropyrimidin-2(1H)-one (**148**) with phosgene or oxalyl chloride, followed by anion interchange with KPF_6[239] and reaction with HOXt to afford the corresponding uronium salts HBMTU (**150**) and HAMTU (**151**) (Scheme 31, Table 8).



9.6. Unsymmetic Aminium/Uronium Salts

9.6.1. Uronium Salts Derived from *N,N,N′*-Trimethyl-*N′*-phenylurea. *N,N,N′*-Trimethyl-*N′*-phenylurea, prepared from commercially available *N,N*-dialkyl carbamoyl chloride (**152**), is transformed into the corresponding chlorouronium salt **153** by treatment with phosgene, followed by anionic interchange with KPF_6. Finally, reaction with HOBt or HOAt in the presence of triethylamine gives HBPTU (**154**) or HAPTU (**155**), respectively[241] (Scheme 32, Table 8).

9.6.2. Other Unsymmetic Aminium/Uronium Salts. Recently, El-Faham and Albericio described a new family of aminium-type coupling reagents that show differences in the carbocation skeletons of coupling reagents,[177] which correlate with differences in stability and reactivity. The unsymmetric tetra-substituted urea is prepared from commercially available *N,N*-dialkyl carbamoyl chloride to afford the corresponding urea. The urea derivatives are transformed into the corresponding chlorouronium salt by treatment with phosgene or oxalyl chloride, followed by anionic interchange with KPF_6. Finally, reaction with HOBt or HOAt in the presence of triethyl amine gives the corresponding aminium salt **156**−**165** (Scheme 32, Table 8).

9.7. Morpholino-Based Aminium/Uronium Coupling Reagents

Very recently,[178,179] El-Faham and Albericio described a new family of aminium/uronium-type coupling reagents derived from dimethylmorpholino urea. In addition to decreasing the racemization level, the morpholine moiety has a remarkable effect on the stability and reactivity of the reagent. The recent aminium-type reagents can be readily prepared by treating *N,N*-methylcarbamoyl chloride **166** with morpholine to give the corresponding urea derivatives (Scheme 31). The urea derivatives then react with oxalyl chloride to yield the corresponding chloro salts **167** (Scheme 33), which are stabilized by the formation of a PF_6 salt. Subsequent reaction with HOXt (HOBt, HOAt, or 6-Cl-HOBt) in the presence of a tertiary amine, such as Et_3N, affords the desired compounds **168**−**176** (Table 8) as crystalline and shelf-stable solids (Scheme 33). These derivatives have been shown to be the most soluble and the most reactive when compared with the previous analogues described above, which differ in the skeleton.[178,179]

9.8. Oxyma Uronium Salt Coupling Reagents

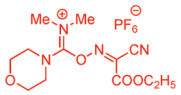
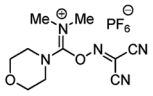
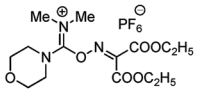
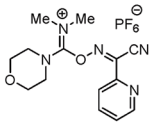
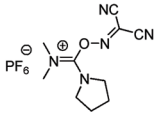
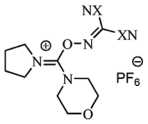
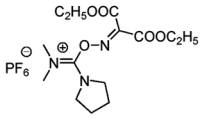
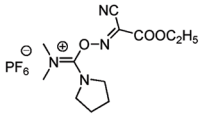
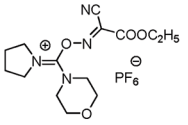
El-Faham and Albercio showed that Oxyma (**42**) is an excellent replacement for HOBt and its analogs.[54] Very recently,[234] they devised a third generation of uronium salt, COMU (**177**), which involves the combination of a morpholonium-based iminium moiety as proton acceptor,[178,179] and Oxyma (**42**) as leaving group to provide a superior and safe coupling reagent for amide formation (Scheme 34).

Although a typical protocol for the use of these reagents involves 2 equiv of base, usually DIEA, the presence of the morpholinium moiety also allows good results with COMU when only 1 equiv of DIEA is used. Alternatively, the less basic TMP (2 or even 1 equiv) can be used instead of DIEA and provides good yields and reduces racemization.[234]

Furthermore, COMU (**177**) is compatible with microwave-assisted peptide synthesizers.[242] Consistent with previous reports, COMU displays higher efficiency than HATU/HBTU in the demanding synthesis of the Aib derivative of the Leu-enkephalin pentapeptide and produces no Oxyma-based byproduct. Thus, the combination of microwave irradiation and COMU results in a similar performance to that observed by manual synthesis in

dx.doi.org/10.1021/cr100048w |*Chem. Rev.* 2011, 111, 6557–6602

Table 9. Oxyma Uronium Salts

Entry	Abbreviation	Name and Structure	Ref.
177	COMU	1-[(1-(cyano-2-ethoxy-2- oxoethylideneaminooxy)-dimethylamino-morpholinomethylene)] methanaminium hexafluorophosphate 	234
178	HDMODC	1-[(1-(dicyanomethyleneaminooxy) dimethylaminomorpholinomethylene)] methanaminium hexafluorophosphate 	234
179	HDMODeC	1-[(1,3-diethyoxy-1,3-dioxopropan-2-ylideneaminooxy)-dimethylamino-morpholinomethylene)] methanaminium hexafluorophosphate 	234
180	HDMOPC	*N*-[(cyano(pyridine-2-yl)methyleneaminooxy) (dimethylamino)methylene)-*N*-morpholinomethanaminiumhexafluorophosphate 	234
181	HDmPyODC	1-[(1-(cyano-2-ethoxy-2-oxoethylideneaminooxy)-dimethylamino-pyrrolodinomethylene)] methanaminium hexafluorophosphate 	234
182	HMPyODC	1-((dicyanomethyleneaminooxy) morpholinomethylene)pyrrolidinium hexafluorophosphoate 	234
183	HDmPyODeC	1-[(1,3-diethyoxy-1,3-dioxopropan-2-ylideneaminooxy)-dimethylamino-pyrrolodinomethylene)] methanaminium hexafluorophosphate 	234
184	HDmPyOC	1-[(1-(cyano-2-ethoxy-2-oxoethylideneaminooxy)-dimethylamino-pyrrolodinomethylene)] methanaminium hexafluorophosphate 	234
185	HMPyOC	1-((1-cyano-2-ethoxy-2-oxoethylideneaminooxy) (morpholino)methylene) pyrrolidinium hexafluorophosphate 	234

considerably shorter time. Also, Oxyma shows much better results than other oxime derivatives **178**−**185** (Scheme 34, Table 9).[234]

Extention to the Oxyma work, a new family of uronium salts (HTMU, **187**; HMMU, **188**; and HDmPyMU, **189**, Figure 3) based on isonitroso Meldrum's acid (HONM, **186**) were reported as stand-alone coupling reagents.[243] HONM[243] shows structural similarities to **42**, except for the presence of two carbonyl groups as electron-withdrawing substituents contained in the six-membered cyclic structure. This modification should enhance the reactivity of the oxime-based additive as a result of its more powerful electron-withdrawing effect compared with **42**. The cyclic structure of **186** may also be beneficial because the hydroxy function is more accessible.

9.9. Antimoniate Uronium Salts

Several iminium salts derived from carboxamides have been prepared.[244−246] Thus, *N*,*N*-dimethylformamide (DMF) is transformed into an iminium chloride by reaction with triphosgene followed by stabilization with $SbCl_5$. Subsequent reaction with HOBt gives benzotriazol-1-yl-oxy-*N*,*N*-dimethylmethaniminium hexachloroantimoniate **190** (BOMI) in 76% yield[244] (Scheme 35, Table 10). Its structure was determined by X-ray analysis. The same methodology has been used for the preparation of the iminium reagent **191** (BDMP) from *N*-methylpyrrolidine (NMP) and HOBt in 80% overall yield.[245] When HOBt is replaced by HOAt, the related reagent **192** (AOMP) is obtained. The HOBt-derived reagent **193** (BPMP) has also been prepared

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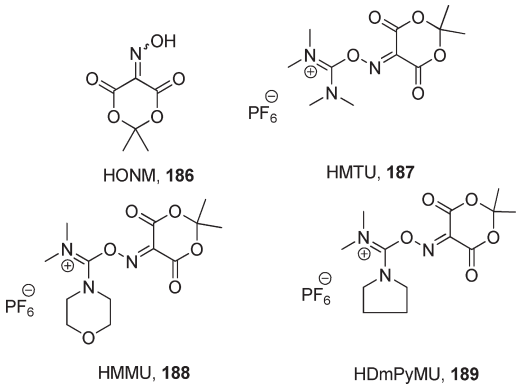


Figure 3. Structure of isonitroso Meldrum's acid uronium salts.

from the more highly substituted *N*,*N*-tetramethylenebenzamide.[246]

9.10. Reaction Mechanism of Aminium/Uronium Salts

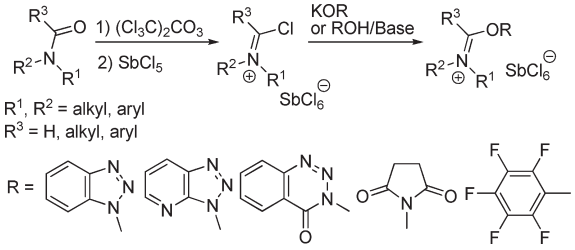
Mechanistically, aminium/uronium salts are thought to function in a manner similar to the phosphonium analogs (Scheme 36). Formation of carboxyl uronium salts, which generate an active ester, is achieved in the presence of 1 equiv of tertiary base, such as DIEA, NMM, or TMP,[26] and can be seen by NMR at −20 °C.[204,205] The presence of an extra equivalent of HOXt can accelerate coupling and reduce the loss of configuration.[204,205]

9.10.1. Stability of Aminium/Uronium Salts. DMF solutions of the uronium/aminium salts shown in Table 8 are stable under nitrogen at 25 °C for 3−4 weeks. The data reported showed that the aza derivatives are less stable and therefore more reactive than the benzotriazole analogs.[29,177] Furthermore, the nature of the carbon skeleton of a compound is of marked importance to the stability of the compound. Both dihydroimidazole [HBMDU (**146**), HAMDU (**147**)] derivatives are very unstable, whereas their corresponding dimethylamine salts are the most stable and the pyrrolidino derivatives are of intermediate stability. As expected, all the coupling reagents are more stable when their DMF solutions are stored under N_2.[177] The dimethylmorpholino uronium salts were less stable than the corresponding tetramethyl derivatives, whereas the dimethylpyrrolidino analogues displayed intermediate stability. All reagents showed stability greater than 90% in CH_3CN in a closed vial for 3−4 days.

The stability of these coupling reagents was also examined in the presence of DIEA[29,177] because peptide bond formation is usually carried out in the presence of at least one extra equivalent of base. Under these conditions, aza derivatives are more labile than the benzotriazole derivatives and pyrrolidino and morpholine derivatives are more labile than dimethylamino and diethylamino derivatives.

The presence of the oxygen atom in the carbon skeleton of compounds **168**−**174** is of marked importance for the solubility of the compound.[178,179] All morpholine derivatives were more soluble than the dimethyl pyrrolidine derivatives and the dimethylamine ones. The oxygen atom in the carbon skeleton is of marked relevance for the solubility of the compounds. Thus, all dimethyl-morpholino derivatives were more soluble than their tetramethyl counterparts. The compounds with a sulfur atom (dimethyl-thiomorpholino **175** and **176**) in the carbon skeleton gave less satisfactory results than the dimethyl-morpholino ones.

Scheme 35. Synthesis of Aminium/Uronium Salts



A characteristic of COMU (**177**) is that the course of reaction can be followed as a result of change of color, which depends on the type of base used.[234] Thus, 2 min after the addition of the coupling reagent, the solution turns orange-red when DIEA is used as a base and pink in the case of TMP. Once the reaction is complete, the solution becomes colorless and yellow, respectively. These results should be taken into account mainly when coupling reagents are placed in open vessels, such as in some automatic synthesizers.

Given that peptide bond formation is usually carried out in the presence of at least one extra equivalent of base, the stability of onium salts has also been examined in the presence of DIEA. Analysis of these results confirms that the various coupling reagents rapidly degrade in the absence of a carboxylic acid function. This observation has practical consequences for both solid-phase and solution strategies. Thus, if activation of a carboxylic acid is slow, the coupling reagents will be degraded and will no longer have the capacity to activate the carboxyl function. Under these conditions, aza derivatives are more labile than the benzotriazole derivatives, and pyrrolidino derivatives are more labile than morpholino, dimethylamino, and diethylamino derivatives. These observations are relevant for cyclization steps or in convergent strategies during fragment coupling because the yields tend to be lower than for other couplings.

10. ORGANOPHOSPHORUS REAGENTS

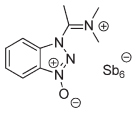
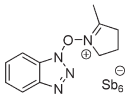
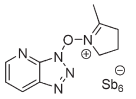
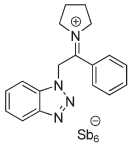
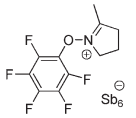
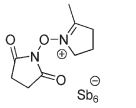
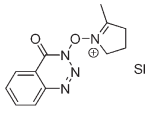
10.1. Phosphinic and Phosphoric Acid Derivatives

Since Yamada introduced the mixed carboxylic−phosphoric anhydride method to peptide chemistry[247,248] in 1972 using DPPA (**200**) synthesized from diphenylphosphorochloridate and sodium azide, various organophosphorus compounds have been developed as peptide-coupling reagents (Table 11). This method usually gives higher regioselectivity toward nucleophilic attack by the amine component than a mixed carbonic anhydride method.[249−251]

Modification of DPPA (**200**) has led to the development of thiophosphinic-type coupling reagents such as MPTA (**201**) and MPTO (**202**) (Table 11).[252] Since MPTA (**201**) generates a carbamoyl azide or urea derivative as the byproduct, Ueki introduced MPTO (**202**), in which the azide group of MTPA is replaced by a 2-oxazolone group. On the basis of the earlier development of organophosphorus reagents, a great amount of effort has been focused on developing various coupling reagents of a similar kind (Table 11). For example, NDPP (**204**), FNDPP (**205**),[253,254] Cpt-Cl (**206**),[255,256] BMP-Cl (**207**),[257] DEBP-(**208**),[258] BDP (**209**),[259] bis(*o*-nitrophenyl)phenyl phosphonate (**210**),[260] (5-nitro-pyridyl)-diphenyl phosphinate (**211**),[261] diphenyl 2-oxo-3-oxazolinyl phosphonate (DPOOP, **212**),[262] and 1,2-benzisoxazol-3-yl diphenyl phosphate (BIODPP, **213**)[263,264] have been prepared by several research groups.

dx.doi.org/10.1021/cr100048w |*Chem. Rev.* 2011, 111, 6557–6602

Table 10. Antimoniate Uronium Salts

Entry	Abbreviation	Name and Structure	Ref
190	BOMI	benzotriazol-1-yloxy-N,N-dimethyl-methaniminium hexachloroantimonate 	244
191	BDMP	5-(*1H*-benzotriazol-1-yloxy)-3,4-dihydro-1-methyl-*2H*-pyrroliumhexachloroantimonate 	245
192	AOMP	5-(7-azabenzotriazol-1-yloxy)-3,4-dihydro-1-methyl-*2H*-pyrrolium hexachloroantimonate 	246
193	BPMP	1-(*1H*-benzotriazol-1-yloxy)phenyl-methylene pyrrolidinium hexachloroantimonate 	246
194	FOMP	5-(pentafluorophenyloxy)-3,4-dihydro-1-methyl-2*H*- pyrrolium hexachloroantimonate 	246
195	SOMP	5-(succinimidyloxy)-3,4-dihydro-1-methyl *2H*-pyrrolium hexachloroantimonate 	246
196	DOMP	5-(3',4'-dihydro-4'-oxo-1',2',3'-benzotriazin-3'-yloxy)-3,4-dihydro-1-methyl -*2H*-pyrrolium hexachloroantimonate 	246

DppCl (**219**) is prepared by oxidation of diphenylchlorophosphine with oxygen.[265] The cyclic derivative 1-oxo-1-chlorophospholane **206** (Cpt-Cl) gives the best results when compared with other dialkylphosphinic chlorides. Reagent **206** is prepared by reacting butadiene with phosphorus trichloride to give 1,1,1-trichlorophospholene, which is then hydrolyzed to 1-oxo-1-hydroxyphospholene and subsequently hydrogenated and chlorinated with thionyl chloride (Scheme 37).

Pentafluorophenyl diphenylphosphinate **220** (FDPP) can be prepared quantitatively from DppCl (**219**) by treatment with pentafluorophenol and imidazole in dichloromethane at room temperature[263] (Scheme 38).

A wider variety of phosphorus reagents, DEBPO[266] (**221**), DOPBO[267] (**222**), DOPBT263 (**223**), and DEPBT[268] (**224**), are prepared following asimilar protocol.

DEPBT derived from DEPC and HODhbt has been evaluated against other peptide-coupling reagents and gives good results in segment coupling reactions. Although the racemization-suppressing capacity of HODhbt is greater than that of HOBt, its utility is limited due to side reactions.

Bis(2-oxo-3-oxazolidinyl)phosphorodiamidic chloride (BOP-Cl, **225**) is the most widely used peptide coupling reagent of this family of phosphorus derivatives.[268] BOP-Cl has shown excellent results for the coupling of *N*-methylamino acids in solution.[269] This reagent is commercially available and can be prepared by the reaction of 1,3-oxazolidin-2-one with phosphorus pentachloride in acetonitrile or nitromethane[268] (Scheme 39).

The only phosphonic acid derivative reported is 2-propanephosphonic acid anhydride **226** (PPAA, T3P), which is a commercially available trimeric reagent prepared by reaction of propanephosphonic acid dichloride with water.[270]

Carpino et al.[50] introduced new organophosphorus reagents (DEPAT, **227**, and DPPAT, **228**, Table 11 and Scheme 40). In this case, the neighboring group effects believed to be relevant to the properties of HOAt are superimposed on the effects that enhance the efficiency of the phosphorus moiety. On the basis of the results described, these effects are related to the greater speed with which protected amino acids are converted to their active esters by the phosphorus derivatives.

Recently,[271,272] phosphoric acid diethyl 2-phenylbenzimidazol-1-yl ester, diphenylphosphinic acid 2-phenylbenzimidazol-1-yl ester (Scheme 41, Table 11), phosphoric acid diphenyl ester, and 2-phenylbenzimidazol-1-yl ester (**230**−**232**) have been reported as highly efficient coupling reagents. Their efficiency was evaluated through the synthesis of a range of amides and peptides, and the extent of racemization was found to be negligible.[272]

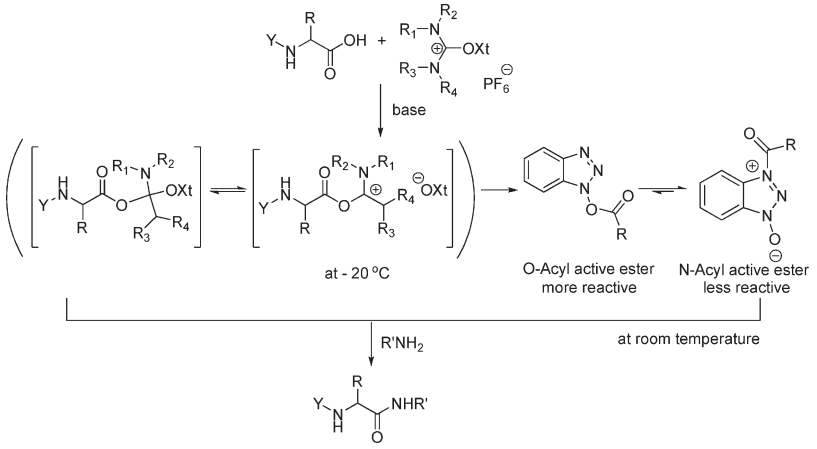
A wide range of phosphorus-based coupling reagents, **223**−**246** (Table 11), were examined by Mukaiyama.[273] Other reagents include FDMP (**247**), which gave poor results compared with 2-bromo-3-ethyl-4-methylthiazolium tetrafluoroborate (BEMT).[274] PyDPP (**248**) was reported to give low epimerization rates but was not compared with other coupling reagents.[275] Another coupling reagent, TFMS-DEP (**249**), was produced by activating diethylphosphate with trifluoromethanesulfonate to afford the peptide in a satisfactory yield.[276]

10.2. Coupling-Mediated Reaction by Phosphinic Acids

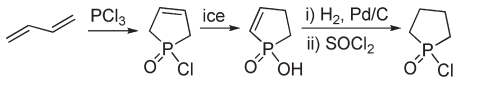
The mechanism of coupling mediated by phosphinic acids has been postulated to proceed through a carboxylic−phosphinic mixed anhydride.[277] The advantage of these mixed anhydride intermediates compared to the biscarboxylic derivatives is associated with the regioselectivity. Reactions of biscarboxylic mixed anhydrides are governed by electronic and steric factors, while carboxylic−phosphinic derivatives are dependent on the nature of the incoming nucleophile. Thus, ammonolysis and alcoholysis occur at the carboxylic and phosphinic sites, respectively (Scheme 42).[277,278]

The effectiveness of BOP-Cl (**225**), a phosphoric acid derivative, during the acylation of *N*-methyl amino acid derivatives is attributed to intramolecular base catalysis by the oxazolidinone

Scheme 36. Proposed Activation Mechanism of Aminium/Uronium Salts

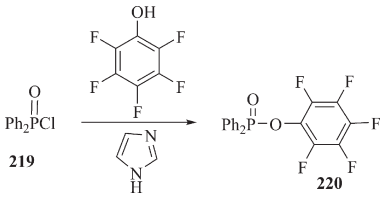


Scheme 37. Synthesis of Cpt-Cl



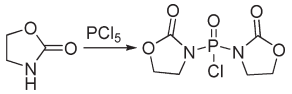
Cpt-Cl, **206**

Scheme 38. Synthesis of FDPP



219 **220**

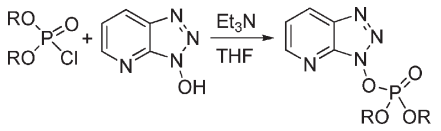
Scheme 39. Synthesis of BOP-Cl



BOP-Cl, **225**

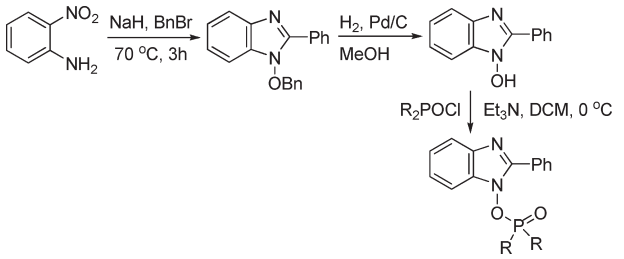
carbonyl of the mixed anhydride active species (Scheme 40).[279] A comparative study of the dimethyl derivatives of phosphinic chloride (Me_2POCl) and phosphochloridate [$(MeO)_2POCl$] indicate that the latter was less reactive toward oxygen nucleophiles than dimethylphosphinic chloride, which would suggest that phosphinic chloride derivatives should react with carboxylate anions to form mixed anhydrides more rapidly than phosphorochloridates.[278] Rapid formation of mixed anhydrides is an important consideration in coupling reactions. A further advantage of the use of phosphinic carboxylic mixed anhydrides lies in the potential elimination of the substitution of the OR groups.[278] The active species of the derivatives that contain nucleophiles other than Cl, such as HOBt, HOOBt, or pentafluorophenol, are presumably the corresponding active esters.

Scheme 40. Synthesis of DEPAT and DPPT



R = C_2H_5; DEPAT (**227**)
R = C_6H_5; DPPAT(**228**)

Scheme 41. Synthesis of Phosphorus Reagents of 1-Hydroxy-2-phenylbenzimidazole



11. ORGANOSULFUR REAGENTS

11.1. Sulfonic Acid Derivatives

Esters of sulfonic acids and HOBt related to those described for the phosphorus series are also used for peptide coupling.[280−285] The reactivity of such sulfonate esters is directly related to the presence of electron-withdrawing substituent in both the HOBt and the sulfonic acid moieties.[286−289]

This methodology has seen little practical application however, since, depending on the basicity or reactivity of the amino component of the coupling process, the use of such sulfonate esters (**250**−**265**) for *in situ* coupling via the formation of an active ester (Scheme 43) is often compromised by formation of a sulfonamide byproduct.[280,281] Byproduct formation, which is particularly prominent with proline derivatives among amino acid derivatives,[290] can be prevented by preactivation of the reactive carboxylic acid component. However, when applying these reagents for segment coupling, especially when such conversions

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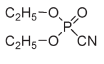
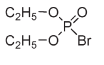
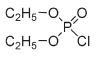
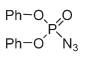
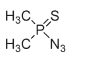
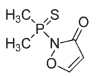
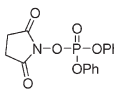
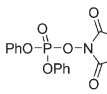
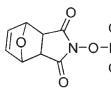
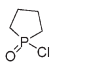
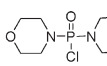
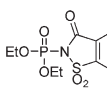
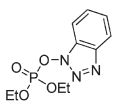
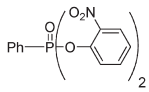
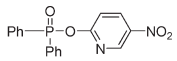
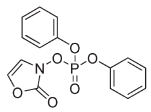
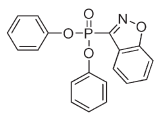
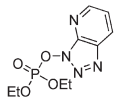
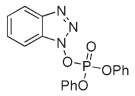
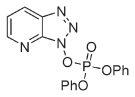
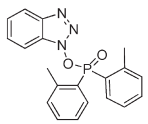
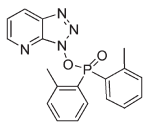
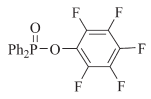
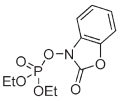
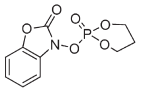
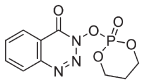
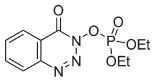
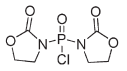
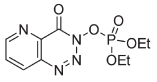
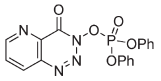
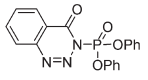
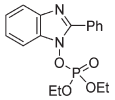
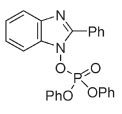
Table 11. Organophosphorous Reagents

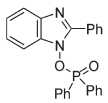
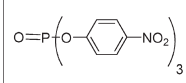
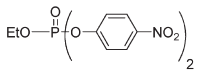
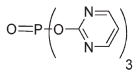
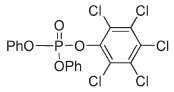
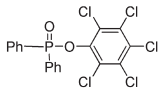
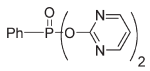
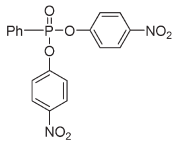
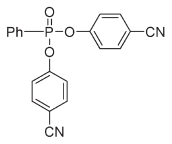
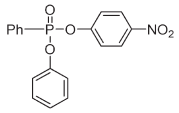
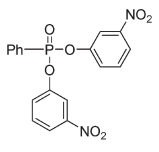
Entry	Abbreviation	Name and Structure	Ref
197	DECP	diethylcyanophosphonate 	248
198	DEPB	diethyl 2-(3-oxo-2,3-dihydro-1,2-benzisosulfonazolyl) phosphonate 	248
199	DEPC	diphenyl phosphorochloridate 	248
200	DPPA	diphenylphosphoryl azide 	252
201	MPTA	dimethylphosphinothioyl azide 	252
202	MPTO	3-dimethylphosphinothioyl-2(*3H*)-oxazolone 	252
203		2,5-dioxopyrrolidin-1-yl diphenyl phosphate 	253
204	NDPP	norborn-5-ene-2,3-dicarboximidodiphenylphosphate 	253
205	FNDPP	3,5-dioxo-10-oxo-4-azatricyclo[5.2.1.02,6] dec-8-en-4-yl diphenylphosphate 	253
206	Cpt-Cl	1-oxo-chlorophospholane 	253
207	BMP-Cl	*N,N'-bis*(morpholino)phosphinic chloride 	257
208	DEBP	diethyl 2-(3-oxo-2,3-dihydro-1,2-benzisosulfonazolyl) phosphonate 	258
209	BDP	benzotriazol-1-yl diethylphosphate 	259

Entry	Abbreviation	Name and Structure	Ref
210		*bis*(2-nitrophenyl) phenylphosphonate 	260
211		(5-nitro-pyridyl)diphenyl phosphinate 	261
212	DPOOP	diphenyl 2-oxo-3-oxazolinyl phosphonate 	262
213	BIODPP	1,2-benzisoxazol-3-yl diphenyl phosphate 	263
214	ADP	7-azabenzotriazol-1-yl diethylphosphate 	50
215	BDOP	benzotriazol-1-yl iphenylphosphate 	50
216	ADOP	7-azabenzotriazol-1-yl diphenylphosphate 	50
217	BDTP	*1H*-benzo[d][1,2,3]triazol-1-yl di-*o*-tolylphosphinate 	50
218	ADTP	*3H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl di-*o*-tolylphosphinate 	50
219	DPPCl	diphenylphosphinic chloride 	263
220	FDPP	pentafluorophenyl diphenyl phosphinate 	263

dx.doi.org/10.1021/cr100048w |*Chem. Rev.* 2011, 111, 6557–6602

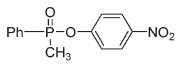
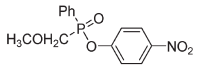
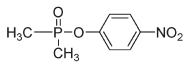
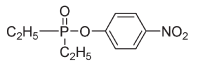
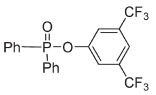
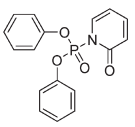
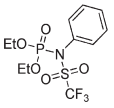
Table 11. Continued

Entry	Abbreviation	Name and Structure	Ref
221	DEBPO	*N*-diethoxyphosphorylbenzoxazolone 	263
222	DOBPO	*N*-(2-oxo-1,3,2-dioxaphosphorinanyl) benzoxazolone 	263
223	DOPBT	3-[*O*-(2-oxo-1,3,2-dioxaphosphorinanyl)-oxy]-1,2,3-benzotriazin-4(3*H*)- one 	263
224	DEPBT	3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4-(3*H*)-one 	268
225	BOP-Cl	*N,N'-bis*(2-oxo-3-oxazolidinyl)-phosphinic chloride 	269
226	T3P; PPAA	2-propanephosphonic acid anhydride 	270
227	DEPAT	3-(diethoxyphosphoryloxy)-1,2,3-pyridino[*b*]triazin-4-(3*H*)-one 	50
228	DPPAT	3-(diphenoxyphosphoryloxy)-1,2,3-pyridino[*b*]triazin-4-(3*H*)-one 	50
229		diphenyl 4-oxobenzo[d][1,2,3]triazin-3(4*H*)-ylphosphonate 	50
230	DOEPBI	phosphoric acid diethyl ester 2-phenylbenzimidazol-1-yl ester 	272
231	DOPPBI	phosphoric acid diphenyl ester and 2-phenylbenzimidazol-1-yl ester 	272

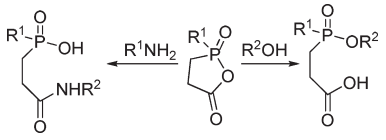
Entry	Abbreviation	Name and Structure	Ref
232	DPPBI	diphenylphosphinic acid 2-phenylbenzimidazol-1-yl ester 	272
233		*tris*(4-nitrophenyl) phosphonate 	273
234		ethyl-bis(2-nitrophenyl) phosphonate 	273
235		tripyrimidin-2-yl phosphate 	273
236	CDPOP	pentachlorophenyl diphenyl phosphate 	273
237	CDPP	pentachlorophenyl diphenyl phosphinate 	273
238		dipyrimidin-2-yl phenylphosphonate 	273
239		*bis*(4-nitrophenyl) phenylphosphonate 	273
240		*bis*(4-cyanophenyl) phenylphosphonate 	273
241		4-nitrophenyl phenyl phenylphosphonate 	273
242		3-nitrophenyl phenyl phenylphosphonate 	273

dx.doi.org/10.1021/cr100048w |*Chem. Rev.* 2011, 111, 6557–6602

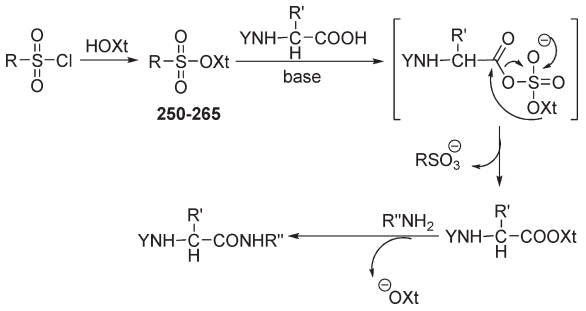
Table 11. Continued

Entry	Abbreviation	Name and Structure	Ref
243		4-nitrophenyl methyl(phenyl)phosphinate 	273
244		4-nitrophenyl methoxymethyl(phenyl)phosphinate 	273
245		4-nitrophenyl-dimethylphosphinate 	273
246		4-nitrophenyl diethylphosphinate 	273
247	FDMP	3,5-*bis*(trifluoromethylphenyl)phenyl diphenylphosphinate 	274
248	PyDPP	diphenyl-2-oxopyridin-1-(2H)-yl phosphonate 	275
249	TFMS-DEP	diphenyl(trifluoromethylsulfonyl)phosphoramidate 	276

Scheme 42. Aminolysis of Diphosphonic Acid



Scheme 43. Synthesis and Reaction of Organosulfur Reagents



are slow, use of a preactivation step is counterproductive since loss of configuration at the C-terminal carboxylic acid residue directly increases with preactivation time.[291] As demonstrated in other systems, the substitution of 1-hydroxy-7-azabenzotriazole (HOAt) for HOBt (Table 12) is expected to reduce the extent of configurational loss, although the advantages of HOAt are lost for long preactivation times. Itoh studied the possibility of using sulfonate-base coupling reagents and developed 2-methanesulfonyloximino-2-cyanoacetate (MSOXm, **265**), which is outperformed by HCSCP (**261**).[292] A drawback of the use of these reagents is the capacity of reacting with the amine function with the formation of the corresponding sulfonamide.

The sulfonate ester is prepared by reaction of HOXt with the sulfonyl chloride in presence of triethylamine (Scheme 43).[291]

12. TRIAZINE COUPLING REAGENT

12.1. 2-Chloro-4,6-dimethoxy-1,3,5-triazine

1,3,5-Triazines are also used as coupling reagents. Thus, 2-chloro-4,6-dimethoxy-1,3,5-triazine, **67** (DMCT), is a stable commercially available crystalline compound that is readily accessible from cyanuric chloride (Scheme 44).[293,294]

12.2. 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4 methylmorpholinium chloride

The related triazine, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4 methylmorpholinium chloride, **267** (DMTMM), is prepared from DMCT (**67**) by a simple reaction with *N*-methylmorpholine (NMM)[295] (Scheme 44).

12.3. 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4 methylmorpholinium Tetrafluoroborate

The synthetic procedure leading to the tetrafluoroborate salts of TBCRs **268**−**271** involves *in situ* formation of *N*-triazinylammonium chlorides **267** by treatment of the triazine with appropriate tertiary amines, followed by replacement of the chloride anion with the tetrafluoroborate anion by treatment with silver or lithium tetrafluoroborate (Scheme 45, Table 13).[296−299] However, a full study was performed on *N*-morpholino tetraborate derivative **268**, because of its lower production cost. The reagents were further optimized by replacing the methoxy groups of **270** by benzyloxy group (**271**).[300] The reagent **271** is stable in DMF and gives better results than its analog **270** in the synthesis of ACP (**65**−**74**).[300]

12.4. Activation by 1,3,5-Triazines

The activation of carboxylic acids by 2-chloro-4,6-dimethoxy-1,3,5-triazine (**67**, DMCT) requires the presence of a tertiary amine in the reaction medium. This reaction can be considered erratic because only a few of the amines, such as NMM and NMP, have the capacity to react. In addition, the capacity of the amines to participate in the reaction does not correlate with the basicity of the amines in polar solvents. This observation suggests the existence of an intermediate involving the amine as a part of a multistep process.[293] The rate of formation of this intermediate, a triazinylammonium salt such as **267** (Scheme 44), will depend strongly on the steric hindrance of the amine. Thus, the concourse of hindered amines, such as TEA, causes a loss of reactivity of **67**. Only amines prone to the formation of salts, such as NMM when treated with **67**, are useful in the activation of carboxylic functions. TEA, which does not form a quaternary ammonium salt at low temperature in the reaction with **67**, does not have the capacity to activate benzoic acid.[261] Thus, the activation of carboxylic

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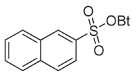
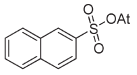
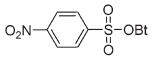
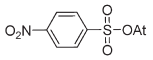
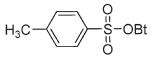
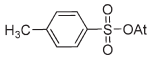
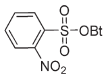
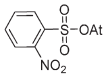
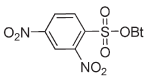
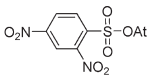
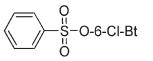
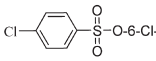
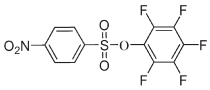
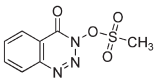
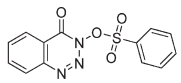
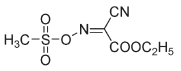
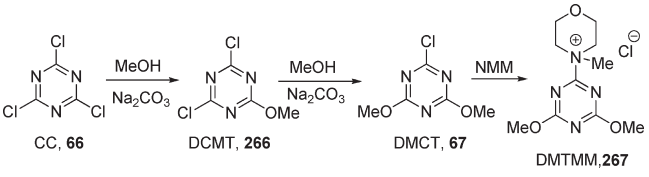
Table 12. Organosulfur Reagents

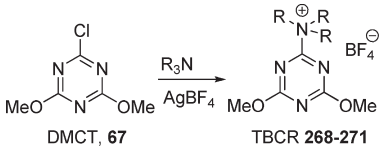
Entry	Abbreviation	Name and Structure	Ref
250	NBs	1-((naphthalen-2-ylsulfonyl)methyl)-1*H*-benzo[*d*][1,2,3]triazole 	287
251	NAs	3-((naphthalen-2-ylsulfonyl)methyl)-3*H*-[1,2,3]triazolo[4,5-*b*]pyridine 	287
252	4-NBs	*1H*-benzo[d][1,2,3]triazol-1-yl 4-nitrobenzenesulfonate 	281
253	4-NAs:	3*H*-[1,2,3]triazolo[4,5-b]pyridin-3-yl 4-nitrobenzenesulfonate 	281
254	TBs	1*H*-benzo[*d*][1,2,3]triazol-1-yl 4-methylbenzenesulfonate 	291
255	TAs	3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl 4-methylbenzenesulfonate 	291
256	2-NBs	1*H*-benzo[*d*][1,2,3]triazol-1-yl 2-nitrobenzenesulfonate 	292
257	2-NAs	3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl 2-nitrobenzenesulfonate 	292

Entry	Abbreviation	Name and Structure	Ref
258	DNBs	1*H*-benzo[*d*][1,2,3]triazol-1-yl 2,4-dinitrobenzenesulfonate 	292
259	DNAs	3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl 2,4-dinitrobenzenesulfonate 	292
260	HCSP	6-chloro-1*H*-benzo[*d*][1,2,3]triazol-1-yl benzenesulfonate 	292
261	HCSCP	6-chloro-1*H*-benzo[*d*][1,2,3]triazol-1-yl 4chlorobenzenesulfonate 	292
262	PFNB	pentafluorophenyl-4-nitrobenzenesulfonate 	
263	SMDOP	4-oxobenzo[*d*][1,2,3]triazin-3(*4H*)-yl methanesulfonate 	292
264	SPDOP	4-oxobenzo[*d*][1,2,3]triazin-3(*4H*)-yl benzeneesulfonate 	292
265	MSOxm	ethyl-2-cyano-2-(methylsulfonyloxyimino)acetate 	292

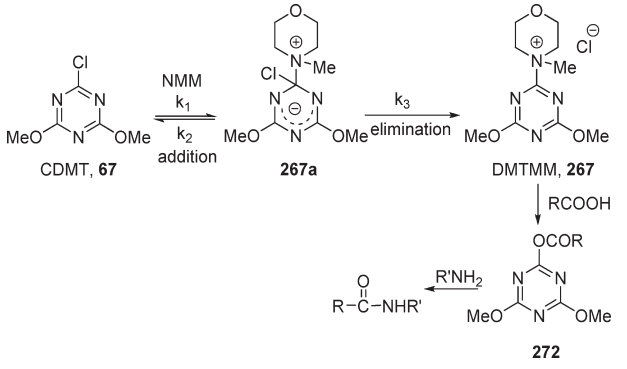
Scheme 44. Synthesis of DMTMM



Scheme 45. Synthesis of Triazinylammonium Tetrafluoroborates



Scheme 46. Coupling Using DMTMM



acids by **67** comprises two subsequent substitution reactions in the triazine ring. The first involves substitution of the chlorine atom by the amine with the formation of a quaternary ammonium salt. This step is extremely sensitive to steric hindrance of amine substituents. The second step, which is highly tolerant of the steric hindrance of the carboxylic acid, involves substitution of the amine leaving group by the carboxylate ion to afford the triazine "superactive esters" **272**. In this regard, the 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride **267** (DMTMM)

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prepared by reaction of **67** with NMM has been successfully applied to the synthesis of amides and esters (Scheme 46).[293,301]

The monitoring of the quaternization of NMM at low temperature provides evidence of the formation of the zwitterionic addition product **267a**, the key intermediate in the classic two-step process. Semiempirical modelings of the reaction, as well as measurements of nitrogen and chlorine kinetic isotope effects, also support this mechanism. Further data confirming this mechanism have been obtained during the enantioselective activation of carboxylic acids.[302,303]

13. PYRIDINIUM COUPLING REAGENTS

13.1. Mukaiyama's Reagent

Mukaiyama's reagent, 2-chloro-1-methylpyridinium iodide **273**, in the presence of a carboxylic acid and a tertiary amine, gives an activated pyridinium ester **274** that reacts with a range of nucleophiles (Scheme 47).[259]

This reagent is not commonly used in peptide synthesis owing to the poor solubility of the pyridinium iodides in conventional solvents. The reaction has therefore to be performed under reflux in DCM.

13.2. Pyridinium Tetrafluoroborate Coupling Reagents

Xu et al.[244] have recently published alternatives to Mukaiyama's reagent **273**. In order to improve the solubility of the pyridinium compounds, the tetrafluoroborate and hexachloroantimonate counterions are adopted (Table 14). 2-Bromo-3-ethyl-4-methylthiazolium tetrafluoroborate (BEMT) **274** has been successfully applied to the synthesis of peptides containing *N*-alkyl or α-*C*-dialkyl amino acids, and later, these authors developed other 2-halopyridinium salts, such as 2-bromo-1-ethylpyridinium tetrafluoroborate (BEP, **275**), 2-fluoro-1-ethylpyridinium tetrafluoroborate (FEP, **276**), 2-bromo-1-ethylpyridinium hexachloroantimonate (BEPH, **277**), and 2-fluoro-1-ethylpyridinium hexachloroantimonate (FEPH, **278**).[160,161] These α-halopyridinium-type coupling reagents have also been used in SPPS.

14. POLYMER-SUPPORTED REAGENTS

For the synthesis of peptides in solution-phase, a few polymer-supported coupling reagents have been described.

14.1. Polymer-Bound Carbodiimide

1-Ethyl-3-(3′-dimethylaminopropyl)carbodiimide (PS-EDC, **279**) is obtained by treating Merrifield resins with EDC in DMF at 100 °C or in refluxing acetonitrile for 15 h.[304] DCC[305] and DIC[306] have been successfully immobilized and applied to the synthesis of amide.[307] However, these reagents have the same drawbacks as their solution-phase synthesis, in terms of epimerization in the absence of an additive.[307]

14.2. Polymer-Bound TBTU

Polymer-bound TBTU, **281** (PS-TBTU),[308] is prepared by the coupling of chlorotetramethyluronium tetrafluoroborate with polymeric HOBt (PS-HOBt).[309]

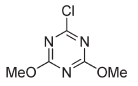
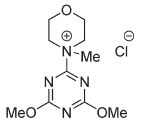
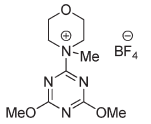
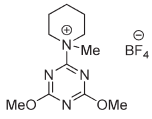
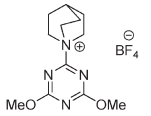
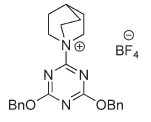
14.3. Polymer-Bound 2,4,6-Trichloro-1,3,5-triazine

2,4,6-Trichloro-1,3,5-triazine anchored to different aminated polystyrene resins, **282**, has recently been prepared by reaction of cyanuric chloride with the corresponding NH_2-functionalized resin.[310]

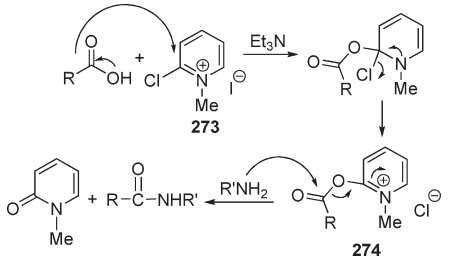
14.4. Polymer-Bound HOBt

Polymer-bound HOBt[311] (**283**) is used for the formation of medium ring lactams with DCC in the presence of resin-bound esters[312] and also for amides from primary and secondary amines.[313]

Table 13. Triazine Coupling Reagent

Entry	Abbreviation	Name and Structure	Ref.
67	DMCT	2-chloro-4,6-dimethoxy-1,3,5-triazine 	294
267	DMTMM	4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride 	296
268	$TBCR_1$	4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium tetrafluoroborate 	297
269	$TBCR_2$	1-(4,6-dimethoxy-1,3,5-triazin-2-yl)-1-methylpiperydinium tetrafluoroborate 	297
270	$TBCR_3$	1-(4,6-dimethoxy-1,3,5-triazin-2-yl)quinuclidinium tetrafluoroborate 	297
271	$TBCR_4$	1-(4,6-dimethoxy-1,3,5-triazin-2-yl)quinuclidinium tetrafluoroborate 	301

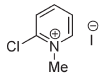
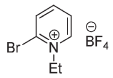
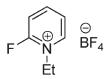
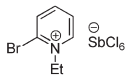
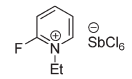
Scheme 47. One-Pot Coupling Using Mukaiyama's Reagent



14.5. Polymer-Bound HOBt Derivative

The polymer-supported HOBt derivative **284**, bonded by a sulfonamide group to polystyrene, reacts with carboxylic acids in

Table 14. Pyridinium Coupling Reagents

Entry	Abbreviation	Name and Structure	Ref.
273	Mukaiyama's Reagent	2-chloro-1-methylpyridinium iodide 	244
274	BEMT	2-bromo-3-ethyl-4-methylthiazolium tetrafluoroborate 	245
275	BEP	2-bromo-1-ethylpyridinium tetrafluoroborate 	245
276	FEP	2-fluoro-1-ethylpyridinium tetrafluoroborate 	245
277	BEPH	2-bromo-1-ethylpyridinium hexachloroantimonate 	160
278	FEPH	2-fluoro-1-ethylpyridinium hexachloroantimonate 	160

the presence of PyBroP (**90**) to give the corresponding active esters. Subsequent addition of amines affords the corresponding amides in an automated procedure.[314]

14.6. Polymer-Bound HOSu

N-Hydroxysuccinimide bound to Merrifield and Argopore TM resins (**285**) also gives resin-bound active esters, which are transformed into amides when reacted with primary, branched primary, and secondary amines.[315]

14.7. Polymer-Bound IIDQ and EEDQ

Polymer-supported IIDQ (**286**)[316] is synthesized in three steps from Merrifield resin and hydroquinoline derivative IIDQ to provide high loading reagents (>1.68 mmol/g). The main advantage of PS-IIDQ (**286**) is that no base is required during coupling (Scheme 48, Table 15). This reagent performs better than other commercially available reagents, such as PS-EDC and PS-DCC (**280**).[316] Very recently, Kakarla duplicated these studies to make PS-EEDQ **287**,[317] which was obtained using the same conditions, the only variation being the use of Wang resin. The loading was also high (1.7 mmol/g) and PS-IIDQ was preformed better than PS-EEDQ in most of the cases.[318]

15. GENERAL REMARKS

15.1. $Cu(OBt)_2$ and $Cu(OAt)_2$, Copper(II)-Based Reagent

Cu(II)-based complexes have recently been developed by Blodgett et al.[319] $Cu(OBt)_2$, $Cu(OAt)_2$, $Cu(OOBt)_2$, $Cu(OSu)_2$, and $Cu(OpNp)_2$) reduce racemization in solution peptide segment coupling involving DIC (**9**). Furthermore, $Cu(OBt)_2$ efficiently suppresses racemization in solid-phase peptide assembly in the reverse *N*−*C* direction using a Cl-trityl resin and an allyl ester as temporary protecting groups.[320] Synthesis of these compounds is straightforward.[320]

However, as far as the coupling efficiency is concerned, the new Cu complexes seem to result in lower yields than the commonly used reagents. This disadvantage can be easily overcome by performing double coupling protocols. These reagents show great promise for application in fully automated peptide syntheses together with phosphonium and aminium coupling reagents, such as HBTU (**106**), HATU (**120**), and BOP (**85**), for the synthesis of peptides containing residues such as cysteine and serine, which are particularly prone to racemization. The advantage in these cases is that even during the long preactivation times used in automated instruments, the degree of racemization is kept very low. The complex $Cu(OAt)_2$ performs slightly better than $Cu(OBt)_2$.[320]

Ryadnov et al.[321]reported an epimerization-free system for coupling *N*-protected peptides with free amino acids. A number of inorganic substances were tested as epimerization suppressant additives during the coupling by various methods (carbodiimide plus additives, uronium salts, Woodward's reagent-K, isobutylchloroformate, etc.). Some of them ($ZnCl_2$, $RbClO_4$, LiCl, $SnCl_4$, $AlCl_3$, etc.) were tested in combination with some coupling with minimal epimerization (D-epimer,1%). However, only simultaneous use of 1-hydroxybenzotriazole and Cu^{2+} ions as additives in carbodiimide-mediated peptide couplings appears to give a standard result (D-epimer, 0.1%). There is no epimerization even in the case of *N*-methyl amino acid, while in the absence of Cu^2+ ions an unacceptable level of epimerization is observed (D-epimer, 22% for carbodiimide with the 1-hydroxybenzotriazole method). So far, it has been considered that Cu^{2+} ions prevent obtaining peptides in high yields (90%) by various coupling methods. The use of 1-hydroxybenzotriazole, $CuCl_2$, and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide instead of DCC provides a method to obtain the desired peptides in 90 ± 99% yields without epimerization.

15.2. Thiaziolium-Based Coupling Reagents

2-Bromo-3-ethyl-4-methylthiazolinium tetrafluoroborate (**288**, BEMT) is an efficient peptide coupling reagent for hindered amino acids.[322] It is prepared from thiourea in three steps in 23% overall yield and is a stable crystalline solid (Scheme 49A). The same type of reagent, BMTB (**289**), was proposed by Wischnat (Scheme 49B).[323] BMTB (**289**) performs better than HATU (**120**) in coupling Boc-*N*(Me)-Ile to *N*(Me)-Ile-OBn. However, BMTB (**289**) has not been compared with BEMT (**284**).

The reaction mechanism was studied by carrying out the coupling reaction in $CDC1_3$ and monitoring by ^{1}H NMR and IR.[323] It is speculated that the first step is carboxylic acid activation by BEMT (**288**) involving the formation of an unstable acyloxythiazolium salt **I**, which in turn reacts directly with the amino component to give the product, or is competitively converted into the acid bromide, which is subsequently converted into the dipeptide by aminolysis. A small amount of the corresponding acid anhydride and 5(4*H*)-oxazolone is also formed from the acyloxythiaozolium salt or acid bromide (Scheme 50). The main byproduct of the reaction is *N*-ethyl-4-methyl thiazolidone **II**, which can be isolated from the reaction mixture and characterized by elemental analysis, ^{1}H NMR, EI-MS, and IR.

dx.doi.org/10.1021/cr100048w |*Chem. Rev.* 2011, 111, 6557–6602

Scheme 48. Activation and Coupling Using PS-IIDQ

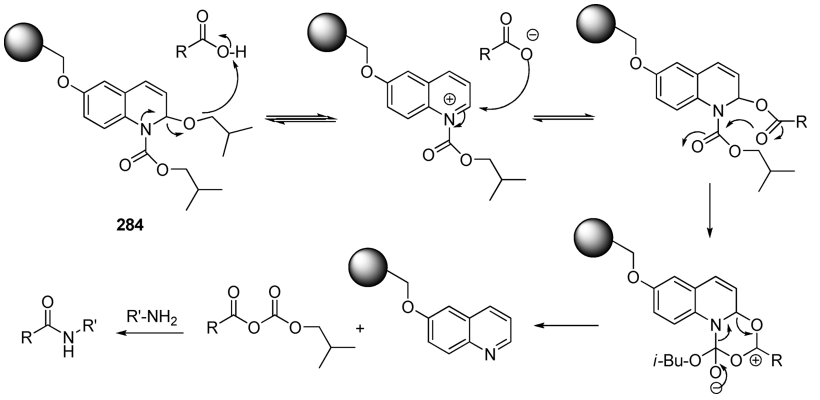
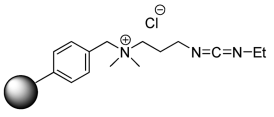
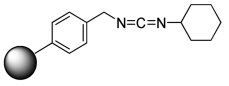
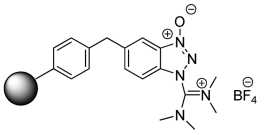
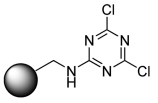
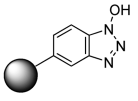
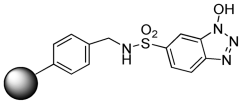
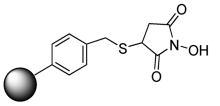
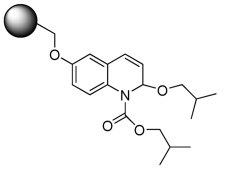
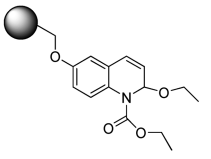
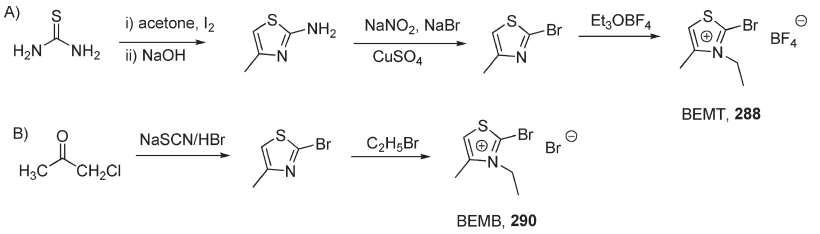


Table 15. Polymer-Supported Reagents

Entry	Abbreviation	Name and Structure	Ref
279	PS-EDC	polymer 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide 	305
280	PS-DCC	polymer cyclohexylcarbodiimide 	305
281	PS-TBTU	*N*-[(1*H*-benzotriazol-1-yl)(dimethylamino)methylene]-*N*-methylmethanaminium tetrafluoro- borate *N*-oxide 	308
282	PS-DCT	polymer supported 2,4-dichloro-1,3,5-triazine 	310
283	PS-HOBt	polymer supported 1-hydroxy benzotriazole 	311

Entry	Abbreviation	Name and Structure	Ref
284	PS-SO_2HOBt	polymer supported 1-hydroxy-6-disulfoxide benzotriazole 	315
285	PS-HOSu	polymer supported N-hydroxysuccinimide 	316
286	PS-IIDQ	polymer supported 1-isobutoxycarbonyl-2-isobutoxy-1,2-dihydroquinoline 	317
287	PS-EEDQ	polymer supported 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline 	318

Scheme 49. Synthesis of BEMT (A) and BEMB (B)



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15.3. Microwave Irradiation

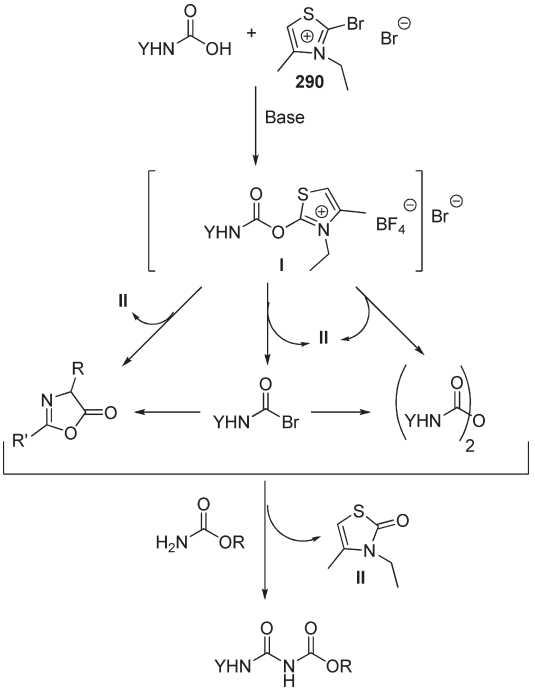
In several cases, microwave irradiation has been a successful alternative to conventional high temperatures to perform direct condensation of amines to carboxylic acids without prior activation. The use of direct microwave heating reduces the chemical reaction time, decreases side reactions, increases yields, and improves reproducibility.[324,325] Microwave irradiation can be run with or without catalyst.[326] Different kinds of catalysts, such as K-10 montmorillonite,[138,327] imidazole,[328] zeolite-HY,[329] polyphosphoric acid,[330] *p*-toluenesulfonic acid,[331] and $TaCl_5$−silica gel,[332] are used in this approach. Microwave irradiation is specially useful for the preparation of *N*-Me β-branched amino acid containing peptides.[333]

15.4. Native Chemical Ligation

Native chemical ligation is a reversible *trans* thioesterification, followed by amide formation. Intramolecular nucleophilic attack of α-amino group on the initial thioester product occurs only when the thiol is on the side chain of an N-terminal cysteine, thus regenerating the thiol functional group of the cysteine side chain and giving a final ligation product containing a native peptide bond at the site of ligation. The initial thiol−thioester exchange step is fully reversible, while the second amide-forming step is irreversible under the reaction conditions. Consequently, only the desired amide-containing product is formed, even in the presence of internal cysteine residues in either peptide segment. It is this reversible−irreversible two-step reaction mechanism that is the essence of the native chemical ligation method (Scheme 51).[334]

The main benefit of the native ligation strategy is the reduced solubility problems that commonly appear in fragment condensation strategy and the absence of reagents that require purification. In this approach, the side chain protecting groups of the fragments are removed before the fragment ligation. The reaction takes place in aqueous media in neutral pH, in order to give a native peptide bond at the ligation point. The limitation of this hybrid technology is the mandatory use of a cysteine residue at the N-terminus of the first fragment and the synthesis of an appropriate C-terminal thioester in the second fragment, which in some cases provides poor yields.[334] Advances in the field include, for example, the use of conformationally assisted ligation,[335] removable auxiliaries,[336] and Staudinger ligation.[337] Interestingly, a side-chain-assisted chemical ligation has been reported recently, with no limits to the amino acids assembled.[338] In view of the significantly increased demand for larger peptides, continuous improvement of ligation strategies provides an additive tool to peptide chemists to overcome the most immediate challenges.

Scheme 50. The Proposed Reaction Mechanism for the Coupling Reagent BEMT



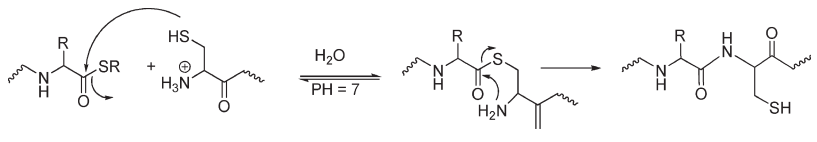
16. THERE IS MORE THAN ONE WAY TO SKIN A CAT

What is the best coupling reagent? Could just a single coupling reagent be used for all amide bond formations? These are recurrent questions very often proposed by students, conference attendees, and even self-questions. The answer is definitely no. Unfortunately, there is no coupling reagent that can be used for all coupling reactions, and even in a same synthesis different coupling reagents are used. In addition to the price, it is important to take into account several parameters, such as (i) chemistry in solution or in solid phase, (ii) manual or automatic synthesis, (iii) use of an excess or deficit of coupling reagents, and (iv) presence of other functional groups into the molecule(s) involved in the reaction.

The following example could perfectly illustrate that issue.

Oxa-thiocoraline is a member of a family of potent antitumoral bicyclic peptide antibiotics, all of marine origin but proceeding from distinct actinomycetes.[339] Its synthesis requires the concourse of a myriad of both protecting groups and coupling reagents (Scheme 52). Regarding the latter, peptide bond formation involving the presence of an *N*-Me amino acid requires the most powerful coupling reagents such as those derived from HOAt (**22**) as the aminium salt HATU (**120**). In this regard, it is important to highlight that while the use of HATU−HOAt should be mandatory for the coupling of *N*-Me amino acids, it is not necessary for the first coupling of pNZ-Ser(Trt)-OH onto Gly-resin, because the low hindrance of glycine allows it to be acylated with other cheaper and milder coupling reagents such as DIPCDI (**10**)−HOBt (**19**)/Oxyma (**42**), HBTU (**106**)−HOBt, or COMU (**177**)−Oxyma. These last ones can provoke the capping of the amino bond by formation of a guanidine moiety.[29] This side reaction takes place when the activation of the carboxlic group is slow or

Scheme 51. Principles of Chemical Native Ligation[a]



[a] Unprotected side chains favor the reaction in aqueous media.

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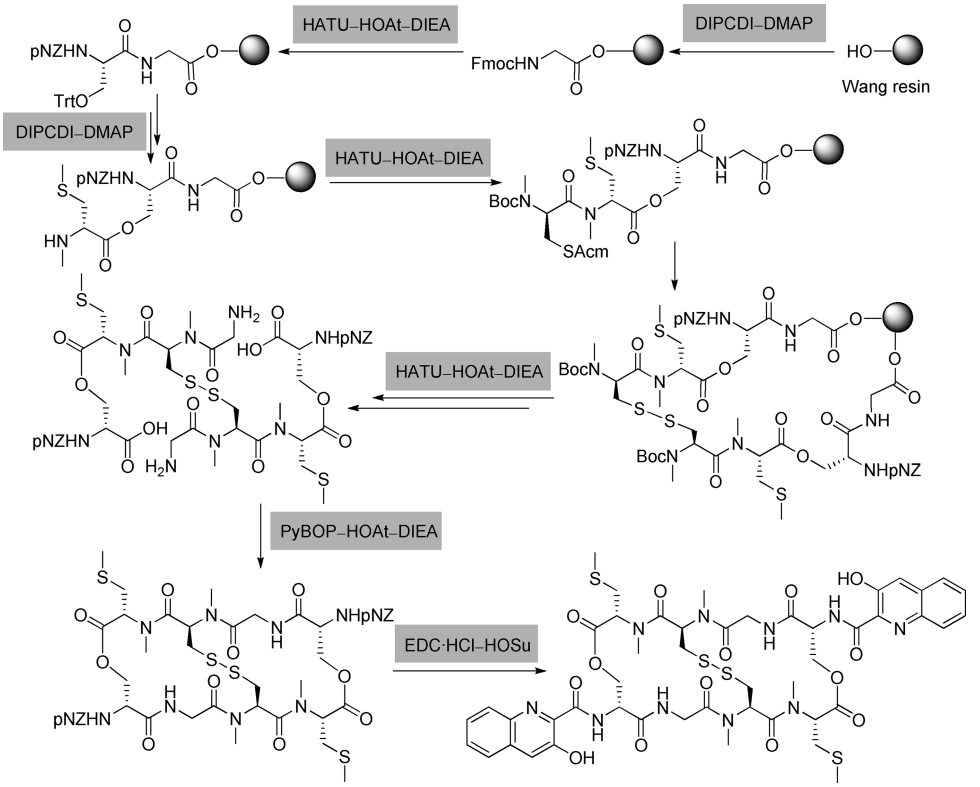
Scheme 52. Synthesis of Oxa-thiocoraline,[339] Indicating Just the Coupling Reagents Used



when the carboxylic function is not in excess withrespect to the amino one as in the case of cyclizations or fragment couplings.

Thus, the macrolactamization reaction requires the use phosphonium salts rather than iminium ones. Because macrolactamizations are demanding reactions, PyBOP (**92**)−HOAt is used. This has a similar behavior to PyAOP (**94**), which is the most powerful phosphonium derivative.[29] Formation of the depsipeptide bond (and the incorporation of the first amino acid on the resin) requires the catalyst of DMAP, which can be used together with DIPCDI. Finally, the acylation of the terminal amino group with the 3-hydroxyquinaldic acid, which takes place in solution, is carried out with EDC·HCl (**11**) in the presence of HOSu (**30**), which is a rather milder additive. The use of stronger additives such as HOBt or HOAt leads to an overincorporation of the quinaldic acid derivative on the hydroxyl function.[340] EDC·HCl is a soluble carbodiimide and therefore facilitates the purification, Thus, in the same synthesis of cyclic peptide, it has been used with a myriad of coupling regents: aminium and phosphonium salts, two differente carboddimides, three *N*-hydroxy additives, and a catalyst.

Another example of use of the same synthesis of phosphonium and aminium derivatives can be found in the solution synthesis of complex cyclic peptide dehydrodidemmin B, which is of marine origin.[341]

These trends can be found on the synthesis of other complex peptides. Thus in the solid-phase synthesis of backbone cyclic peptides, Gilon et al. used HBTU−HOBt for the acylation of primary amino acids and HATU−HOAt when *N*-Me residues should acylated.[342] Furthermore in the solution synthesis of plusbacin A_3, Van Nieuwenhze et al. used EDC·Cl with HOBt or HOAt depending of the difficulty of the coupling.[343]

For the solution synthesis of *N*-Me containing peptides, BOP-Cl (**225**) is also an excellent alternative to the HOAt derivatives.[269,344]

If the synthesis is carried out in automatic mode, more stable coupling reagents should be used to minimizes the decomposition of the coupling reagent becoming detrimental for the yield of the coupling reaction.

17. CONCLUSIONS

At the beginning of the last century, Emil Fisher proposed the use of acid chlorides for peptide synthesis and at the end of the century; as this review has related, acid halides, both chlorides and fluorides, were again coming into vogue for the same purpose. Since the middle of the 20th century, carbodiimides, azides, active esters, anhydrides, and stand-alone reagents, such as phosphonium or iminium salts, have been and continue to be extensively used. Approaches involving the most effective coupling reagents have allowed for a rapid and flourishing expansion of the field of peptide chemistry, which in turn has promoted an expansion of other areas of organic chemistry that work with the formation of amide bonds. Thus, not only is the synthesis of small linear peptides contain natural amino acids now routinely possible, but also the laboratory synthesis of large peptides containing 30−50 amino acid residues is achievable. Having said this, the reader could be given the impression that no challenges remain in this field. This is not the case. Many challenges still lie ahead, such as the stepwise solid-phase synthesis of small proteins containing up to 100 coded residues or the synthesis of peptides containing extremely hindered building blocks, such as α,α-dialkyl amino acids, *N*-alkyl amino acids, and the more difficult *N*-aryl amino acids. It is certain that these challenges will not be overcome through the use of new and more effective coupling methods alone. On the contrary, a proper combination of the coupling reagent, α-amino protecting group, solid support,

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solvent, temperature, and other experimental conditions will be mandatory. New stand-alone coupling reagents containing better leaving groups that enhance coupling rates and reduce the risk of racemization, in the same way as HOAt, are required. A highly efficient leaving group (Oxyma) is now available. Oxyma is safer and less hazardous than HOAt. Moreover, Oxyma shows the same efficiency as HOAt and greater performance than HOBt. As related in this review, the use of an acid chloride is an excellent coupling method, but its overall efficiency is not compatible with carbamate-based α-amino groups, such as Boc or Fmoc, because the method requires a base as hydrogen chloride acceptor and, under these conditions, the corresponding 5(4*H*)-oxazolone is formed. Although the latter can function as an acylating reagent, the oxazolone is much less reactive than the acid chloride. In this respect, the development of new non-carbamate-based α-amino protecting groups, such as Pbf, *o*NBS, or Bts, will be necessary. Furthermore, the nature of the carbon skeleton of a compound is of marked relevance to the stability of the compound. Dihydroimidazole [HBMDU (**146**) and HAMDU (**147**)] derivatives are highly unstable, whereas their corresponding morpholino and dimethylamine salts are the most stable of the series, and pyrrolidino derivatives are of intermediate stability. These results should be considered mainly for those syntheses performed in automatic synthesizers in which the coupling reagents are dispensed in open vessels. As expected, all the coupling reagents are more stable when DMF solutions are stored under N_2 atmosphere, conditions typically used in some automatic synthesizers.

In conclusion, the coupling methods currently available, together with a new generation of reagents, which will undoubtedly expand in the short term, in combination with improvements in other reagents and experimental conditions should allow for the facile and routine preparation of any desired peptide. Further progress in peptide coupling methodologies will greatly contribute to the introduction of peptides and peptidomimetics as drugs for the treatment of a broad range of diseases.

AUTHOR INFORMATION

Corresponding Author

*E-mail addresses: aymanel_faham@hotmail.com; albericio@irbbarcelona.org.

BIOGRAPHIES

Professor Ayman El-Faham received his B.Sc. degree in Chemistry in 1980 and his M.Sc. in 1985 in Physical Organic Chemistry from Faculty of Science, University of Alexandria, Egypt. In 1991, he received his Ph.D in organic chemistry as a joint project between the University of Alexandria and the University of Massachusetts, Amherst, MA, U.S.A. under the supervision of Prof. L. A. Carpino, where he worked on the synthesis of new protecting groups for both solution and solid-phase peptide synthesis. In 2010, he received his D.Sc. in chemistry, Faculty of Science, University of Alexandria, Egypt. In addition, Dr. El-Faham was involved in the development of new coupling reagents based on 1-hydroxy-7-azabenzotriazole. He continued working on these new coupling reagents during his postdoctoral work (1992−1999) at the University of Massachusetts in Prof. Carpino's Lab. He holds many patents in this field. He received the University of Alexandria award in Chemistry in 1999. He joined the Barcelona Science Park during the summers of 2006, 2007, 2008, and 2009 and worked with Prof. Fernando Albericio in the development of a new family of iminium/uronium-type coupling reagents. His research interests include the synthesis of peptides under solution and solid-phase conditions, natural products, heterocylic synthesis, and biologically active synthetic targets. Professor El-Faham acted as Head of the Chemistry Department, Beriut Arab University, Lebanon (2000−2004), and as a Professor of Organic Chemistry, Faculty of Science, and the Direct Manager of both the NMR Lab and the Central Lab at the Faculty of Science, Alexandria University, Egypt (2004−2008). He worked at King Saud University as a Professor of Organic Chemistry, College of Science, Chemistry Department, Saudi Arabia 2008−2010. Currently he is a professor of Organic Chemistry, Faculty of Science, Alexandria University, Egypt.

Professor Fernando Albericio was born in Barcelona, Spain, in 1953. He received his Ph.D. in Chemistry at the University of Barcelona in 1981. Following postdoctoral work at Tufts University (Boston), at the Université d'Aix-Marseille (France), and at the University of Minnesota (1981−1984), he returned to Barcelona as Associate Professor. During the 1992−1994 period, he was Director of Peptide Research with Milligen/Biosearch in Boston. He rejoined the University of Barcelona, where he was promoted to professor in 1995. Nowadays, he is holding various appointments: General Director of the Barcelona Science Park, Professor at the University of Barcelona, and Group Leader at the Institute for Research in Biomedicine. Professor Albericio is deeply involved in the development of the third mission of the University, the transference to knowledge and technology to the society. He has founded several biotech companies and is acting in the board of directors of several foundations and companies.

Furthermore, he is consultant for several companies in the chemical and pharmaceutical areas. Professor Albericio's major research interests cover practically all aspects of peptide synthesis and combinatorial chemistry methodologies, as well as synthesis of peptides and small molecules with therapeutic activities. He has published over 550 papers, several review articles, and more than 40 patents and has coauthored three books. He is editor of several scientific journals and sit on the editorial board of several others. Recently, Professor Albericio has been honored with a Doctorate Honoris Causa by the Universidad de Buenos Aires (Argentina) and the Vincent du Vigneaud Award (American Peptide Society).

18. ACKNOWLEDGMENT

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ABBREVIATIONS

AOMP	5-(7-azabenzotriazol-1-yloxy)-3,4-dihydro-1-methyl 2*H*-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*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-methyl thiazolium tetrafluoroborate
BEP	2-bromo-1-ethyl pyridinium tetrafluoroborate
BEPH	2-bromo-1-ethyl pyridinium hexachloroantimonate
BMP-Cl	*N*,*N*′-bismorpholinophosphinic chloride
Boc	*t*-butyloxycarbonyl
BOMP	2-(benzotriazol-1-yloxy)-1,3-dimethyl-2-pyrrolidin-1-yl-1,3,2-diazaphospholidinium hexafluorophosphate
BOP	benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate
BOP-Cl	*N*,*N*′-bis(2-oxo-3-oxazolidinyl)phosphinic chloride
BroP	bromotris(dimethylamino)phosphonium hexafluorophosphate
Bsmoc	1,1-dioxobenzo[*b*]thiophene-2-ylmethyloxycarbonyl
Bspoc, 8	2-(*tert*-butylsulfonyl)-2-propyloxycarbonyl
Bts-Fmoc	2,7-bis(trimethylsilyl)-9-fluorenylmethyloxycarbonyl
BTFFH	bis(tetramethylene)fluoroformamidinium hexafluorophosphate
BPMP	1-(1*H*-benzotriazol-1-yloxy)phenylmethylene pyrrolidinium hexachloroantimonate
BTC	triphosgene
BTCFH (PyClU)	bis(tetramethylene)chlororformamidinium hexafluorophosphate
Bts-Cl	benzothiazol-2-sulfonyl chloride
Cbz, Z	benzyloxycarbonyl
DCM	dichloromethane
CDMT	2-chloro-4,6-dimethoxy-1,3,5-triazine
DCMT	2,4-dichloro-6-methoxy-1,3,5-triazine
DECP	diethylcyanophosphonate
DEPAT	3-(diethoxyphosphoryloxy)-1,2,3-pyridino-[*b*]triazin-4-(3*H*)-one
DKP	diketopiperazine
DMCH	*N*-(chloro(morpholino)methylene)-*N*-methylmethanaminium hexafluorophosphate
DMF	*N*,*N*-dimethylformamide
DPPAT	3-(diphenoxyphosphoryloxy)-1,2,3-pyridino-[*b*]triazin-4-(3*H*)-one
DOEPBI	phosphoric acid diethyl ester 2-phenylbenzimidazol-1-yl ester
DOPPBI	phosphoric acid diphenyl-2-phenylbenzimidazol-1-yl ester
DPPBI	diphenylphosphinic acid 2-phenylbenzimidazol-1-yl ester
CC	cyanuric chloride
CDPOP	pentachlorophenyl diphenyl phosphate
CDPP	pentachlorophenyl diphenyl phosphinate
CF	cyanuric fluoride
CF_3-BOP	[6-(trifluoromethyl) benzotriazol- 1-yl]-*N*-oxy-tris(dimethylamino) phosphonium hexafluorophosphate
CF_3-HBTU	2-[6-(trifluoromethyl)- benzotriazol-1-yl]-1,1,3,3- tetramethyluronium hexafluorophosphate
CF_3-NO_2-PyBOP	[4-nitro-6-(trifluoromethyl)benzotriazol-1-yl)-oxy]tris(pyrrolidino)-
6-CF_3-HOBt	6-trifluoromethyl-1-hydroxy benzotrialzole
6-Cl-HOBI	6-chloro-*N*-hydroxy-2-phenylbenzimidazole phosphonium hexafluorophosphate
CF_3-PyBOP	[6-(trifluoromethyl)-benzotriazol-1-yl]-*N*-oxytris-(pyrrolidino)phosphonium hexafluorophosphate
6-Cl-HOBt	6-chloro-1-hydroxybenzotriazole
CIC	*N*-cyclohexyl,*N*′-isopropyl carbodiimide
CIP	2-chloro-1,3-dimethylimidazolidinium hexafluorophosphate
CloP	chloro-tris(dimethylamino)phosphonium hexafluorophosphate
CMBI	2-chloro-1,3-dimethyl 1*H*-benzimidazolium hexafluorophosphate
CMPI	2-chloro-1-methylpyridinium iodide
COMU	1-[(1-(cyano-2-ethoxy-2-oxoethylideneamino-oxy)-dimethylamino-morpholinomethylene)] methanaminium hexafluorophosphate
Cpt-Cl	1-oxo-chlorophospholane
CPC	*N*,*N*′-dicyclopentylcarbodiimide
CPP	2-chloro-1,3-dimethylpyrimidinium hexafluorophosphate
DBDMAP	2,6-di-*tert*-butyl-4-(dimethylamino)pyridine
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DEBP	diethyl 2-(3-oxo-2,3-dihydro-1,2-benzisosulfonazolyl) phosphonate
DEPB	diethyl phosphorobromidate
DEPBO	*N*-diethoxyphosphoryl benzoxazolone
DEPBT	3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one
DEPC	diphenyl phosphorochloridate
DFIH	1,3-dimethyl-2-fluoro-4,5-dihydro-1*H*-imidazolium hexafluorophosphate
DIC	*N*,*N*′-diisopropylcarbodiimide

DEFFH	1,2-diethyl-3,3-tetramethylene fluoroformamidinium hexafluorophosphate
DIEA (DIPEA)	diisopropylethylamine
DMCH	*N*-(chloro(morpholino)methylene)-N-methylmethanaminium hexafluorophosphate
DMCT	2-chloro-4,6-dimethyl-1,3,5-triazine
DMFFH	1,2-dimethyl-3,3-tetramethylene fluoroformamidinium hexafluorophosphate
DMFH	*N*-(fluoro(morpholino)methylene)-*N*-methylmethanaminium hexafluorophosphate
DMTMM	4-(4,6-dimethoxy[1,3,5]triazin-2-yl)-4-methylmorpholinium chloride
DNAs	3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl 2,4-dinitrobenzenesulfonate
DNBs	1*H*-benzo[*d*][1,2,3]triazol-1-yl 2,4-dinitrobenzenesulfonate
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-1,3,2-dioxaphosphorinanyl)-benzoxazolone
DOPBT	3-[*O*-(2-oxo-1,3,2-dioxaphosphorinanyl)-oxy]-1,2,3-benzotriazin-4(3*H*)-one
DPP-Cl	diphenylphosphinic chloride
DPPA	diphenylphosphoryl azide
Dtb-Fmoc	2,7-di-*tert*-butyl-9-fluorenylmethyloxycarbonyl
EDC	1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride
FDMP	3,5-bis(trifluoromethylphenyl)phenyl diphenylphosphinate
FDPP	pentafluorophenyl diphenyl phosphinate
FEP	2-fluoro-1-ethyl pyridinium tetrafluoroborate
FEPH	2-fluoro-1-ethyl pyridinium hexachloroantimonate
FIP	2-fluoro-1,3-dimethylimidazolidinium hexafluorophosphate
Fmoc	9-fluorenylmethyloxcarbonyl
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
HAE_2PyU	*O*-(1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-yl)-1,1-diethyl-3,3-tetramethyleneuronium 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)-1,3-dimethyl-1,3-trimethyleneuronium hexafluorophosphate hexafluorophosphate
HAMDU	*O*-(7-azabenzotriazol-1-yl)-1,3-dimethyl-1,3-dimethyleneuronium hexafluorophosphate
HAPipU	*O*-(7-azabenzotriazol-1-yl)-1,1,3,3-bis(pentamethylene) uronium hexafluorophosphate
HAPyU	1-(1-pyrrolidinyl-1*H*-1,2,3-triazolo[4,5-*b*]-pyridin-1-ylmethylene) pyrrolidinmium hexafluorophosphate *N*-oxide
HAPyTU	1-(1-pyrrolidinyl-1*H*-1,2,3-triazolo[4,5-*b*]-pyridin-1-ylmethylene) pyrrolidinmium hexafluorophosphate *N*-sulfide
HAPTU	(7-azabenzotriazol-yl)-1,1,3-trimethyl-1-phenyluronium hexafluorophosphate
HATTU	*S*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HATU	*O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HATeU	*O*-(1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-yl)-1,1,3,3-tetraethyluronium 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
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
HBMTU	*O*-(benzotriazol-1-yl)-1,3-dimethyl-1,3-trimethyleneuronium hexafluorophosphate
HBPTU	(7-benzotriazol-yl)-1,1,3-trimethyl-1-phenyluronium hexafluorophosphate
HBTeU	*O*-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetraethyluronium hexafluorophosphate
HBMDU	*O*-(benzotriazol-1-yl)-1,3-dimethyl-1,3-dimethyleneuronium hexafluorophosphate
HBPipU	*O*-(benzotriazol-1-yl)-1,1,3,3-bis(pentamethylene)uronium hexafluorophosphate
HBPyU	*O*-(benzotriazol-1-yl)oxybis(pyrrolidino)-uronium hexafluorophosphate
HBTU	*O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HDATU	*O*-(3,4-dihydro-4-oxo-5-azabenzo-1,2,3-triazin-3-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HDAPyU	*O*-(3,4-dihydro-4-oxo-5-azabenzo-1,2,3-triazin-3-yl)-1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate
HDTU	*O*-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HDATU	*O*-(3,4-dihydro-4-oxo-5-azabenzo-1,2,3-triazin-3-yl)-1,1,3,3-tetramethyluronium 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
HDMC	6-chloro-1-((dimethylamino)(morpholino)-methylene)-1*H*-benzotriazolium hexafluorophosphate-3-oxide
6-HDMFB	6-trifluoromethyl-1-((dimethylamino)(morpholino)methylene)-1*H*-benzotriazolium hexafluorophosphate-3-oxide
HDMODC	1-[(1-(dicyanomethyleneaminooxy)-dimethylaminomorpholinomethylene)] methanaminium hexafluorophosphate
HDMODeC	1-[(1,3-diethyoxy-1,3-dioxopropan-2-ylideneaminooxy)-dimethylamino-morpholinomethylene)] methanaminium hexafluorophosphate

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HDMOPC	*N*-[(cyano(pyridine-2-yl)methyleneaminooxy)-(dimethylamino)methylene]-*N*-morpholino-methanaminium hexafluorophosphate
HDMP	1-((dimethyamino)(morpholino))oxypyrrolidine-2,5-dione methanaminium hexafluorophosphate
HDMPfp	1-((dimethyamino)-(morpholino))oxypentafluorophenylmetheniminium hexafluorophosphate
HDmPyODC	1-[(1-(cyano-2-ethoxy-2-oxoethylideneamino-oxy)-dimethylaminopyrrolodino methylene)] methanaminium hexafluorophosphate
HDPyU	*O*-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-bis(tetramethylene)uronium 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
HDmPyODeC	1-[(1,3-diethyoxy-1,3-dioxopropan-2-ylideneaminooxy)-dimethylamino pyrrolodinomethylene)] methanaminium hexafluorophosphate
HDmPyOC	1-[(1-(cyano-2-ethoxy-2-oxoethylideneamino-oxy)-dimethylamino-pyrrolodinomethylene)] methanaminium hexafluorophosphate
HMPyODC	1-((dicyanomethyleneaminooxy) morpholino-methylene)pyrrolidinium hexafluorophosphoate
HMPA	hexamethylphosphoramide
HMPyOC	1-((1-cyano-2-ethoxy-2-oxoethylideneamino-oxy)(morpholino)methylene) pyrrolidinium hexafluorophosphate
HOAt	1-hydroxy-7-azabenzotriazole
4-HOAt	4-aza-1-hydroxybenzotriazole
5-HOAt	5-aza-1-hydroxybenzotriazole
6-HOAt	6-aza-1-hydroxybenzotriazole
HOBI	*N*-hydroxy-2-phenylbenzimidazole
HOBt	1-hydroxybenzotriazole
HOCt	ethyl-1-hydroxy-1*H*-1,2,3-triazole-4-carboxylate
HODhbt	3,4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazine
HODhad	3-hydroxy-4-oxo-3,4-dihydro-5-azabenzo-1,3-diazene
HODhat	3-hydroxy-4-oxo-3,4-dihydro-5-azabenzo-1,2,3-triazene
HODT	*S*-(1-oxido-2-pyridinyl)-1,3-dimethyl-1,3-trimethylenethiouronium hexafluorophosphate
HOSu	*N*-hydroxysuccinimide
HOI	*N*-hydroxyindolin-2-one
HONB	*N*-hydroxy-5-norbornene-*endo*-2,3-dicarboxyimide
HONP	*p*-nitrophenyl active ester
HOPy	1-hydroxy-2-pyridinone
HOTT	*S*-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouronium hexafluorophosphate
HOTT	*S*-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouronium hexafluorophosphate
HOTU	*O*-[cyano(ethoxycarbonyl)methyleneamino]-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate
HPyOPfp	*N*,*N*,*N*′,*N*′-bis(tetramethylene)-*O*-pentafluorophenyluronium hexafluorophosphate
HPFTU	*N*,*N*,*N*′,*N*′-bis(tetramethylene)-*O*-pentafluorophenyluronium hexafluorophosphate
HPTU	2-(2-oxo-1(2*H*)-pyridyl-1,1,3,3-tetramethyluronium hexafluorophosphate
HPyONP	*N*,*N*,*N*′,*N*′-bis(tetramethylene)-*O*-2-nitrophenyluronium hexafluorophosphate
HPyOTCp	*N*,*N*,*N*′,*N*′-bis(tetramethylene)-*O*-pentafluorophenyluronium hexafluorophosphate
HPySPfp	*N*,*N*,*N*′,*N*′-bis(tetramethylene)-*S*-pentafluorothiophenyluronium hexafluorophosphate
HSTU	2-succinimido-1,1,3,3-tetramethyluronium hexafluorophosphate
HTODC	*O*-[(dicyanomethylidene)-amino]-1,1,3,3-tetramethyluronium hexafluorophosphate
HTODeC	*O*-[(diethoxycarbonylmethylidene)amino]-1,1,3,3-tetramethyluronium hexafluorophosphate
HTOPC	*N*-[(cyano(pyridine-2-yl)methyleneaminooxy)-(dimethylamino)methylene)-*N*-methyl methanaminium hexafluorophosphate
NAs	3-((naphthalen-2-ylsulfonyl)methyl)-3*H*-[1,2,3]-triazolo[4,5-*b*]pyridine
2-NAs	3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl 2-nitrobenzenesulfonate
4-NAs	3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl 4-nitrobenzenesulfonate
NBs	1-((naphthalen-2-ylsulfonyl)methyl)-1*H*-benzo[*d*][1,2,3]triazole
2-NBs	1*H*-benzo[*d*][1,2,3]triazol-1-yl 2-nitrobenzenesulfonate
4-NBs	1*H*-benzo[*d*][1,2,3]triazol-1-yl 4-nitrobenzenesulfonate
NDPP	norborn-5-ene-2,3-dicarboximidodiphenylphosphate
N-HATU	*N*-[(dimethylamino)-1*H*-1,2,3-triazolo[4,5-*b*]-pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide
N-CF_3-HBTU	*N*-[6-trifluoromethyl(1*H*-benzotriazol-1-yl)-(dimethylamino)methylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide
N-CF_3-TBTU	*N*-[6-trifluoromethyl(1*H*-benzotriazol-1-yl)-(dimethylamino)methylene]-*N*-methylmethanaminium tetrafluoroborate *N*-oxide
N-HAPyU	1-(1-pyrrolidinyl-1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-ylmethylene) pyrrolidinium hexafluorophosphate *N*-oxide
N-HATTU	*N*-[(dimethylamino)-1*H*-1,2,3-triazolo[4,5-*b*]-pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-sulfide
N-HBPyU	(1*H*-benzotriazol-1-yl)(1-pyrrolidinylmethylene) pyrrolidinium hexafluorophosphate *N*-oxide
N-HBTU	*N*-[(1*H*-benzotriazol-1-yl)(dimethylamino)-methylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide
6-NO_2-HOBt	1-hydroxy-6-nitrobenzotrialzole
N-TATU	*N*-[(dimethylamino)-1*H*-1,2,3-triazolo[4,5-*b*]-pyridin-1-ylmethylene]-*N*-methylmethanaminium tetrafluoroborate *N*-oxide
N-TBTU	*N*-[(1*H*-benzotriazol-1-yl)(dimethylamino)-methylene]-*N*-methylmethanaminium tetrafluoroborate *N*-oxide
MPTA	dimethylphosphinothioyl azide
MPTO	3-dimethylphosphinothioyl-2(3*H*)-oxazolone

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Mspoc	2-methylsulfonyl-3-phenyl-1-prop-2-enyloxycarbonyl
Mukaiyama's reagent	2-chloro-1-methylpyridinium iodide
NDPP	norborn-5-ene-2,3-dicarboximidodiphenylphosphate
NMM	*N*-methylmorpholine
NO_2-PyBOP	(6-nitrobenzotriazol-1-yloxy)tris(pyrrolidino)-phosphonium hexafluorophosphate
Oxyma	ethyl 2-cyano-2-(hydroxyimino)acetate
PIC	*N*-phenyl,*N*-isopropylcarbodiimide
PS-DCC	polymer cyclohexylcarbodiimide
PS-DCT	polymer-supported 2,4-dichloro-1,3,5-triazine
PS-EDC	polymer 1-ethyl-3-(3′-dimethylaminopropyl)-carbodiimide
PEC	*N*-ethyl, *N*-phenylcarbodiimide
PS-HOSu	polymer-supported *N*-hydroxysuccinimide
PS- SO_2-HOBt	polymer-supported 1-hydroxy-6-disulfoxide benzotriazole
PS-TBTU	*N*-[(*1H*-benzotriazol-1-yl)(dimethylamino)-methylene]-*N*-methylmethanaminium tetrafluoroborate *N*-oxide
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
PyDOP	[(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)oxy]-tris(pyrrolidino) phosphonium hexafluorophosphate
PyCloK	(6-chloro-benzotriazol-1-yloxy)tris(pyrrolidino) phosphonium hexafluorophosphate
PyPOP	(pentafluorophenyloxy)tris(pyrrolidino) phosphonium hexafluorophosphate
PyDAOP	[(3,4-dihydro-4-oxo-5-azabenzo-1,2,3-triazin-3-yl]tris(pyrrolidino) phosphonium hexafluorophosphate
PyFOP	[[6-(trifluoromethyl)benzotriazol-1-yl]oxy]-tris(pyrrolidino) phosphonium hexafluorophosphate
PyFNBOP	[4-nitro-6-(trifluoromethyl)benzotriazol-1-yl)-oxy]tris(pyrrolidino) phosphonium hexafluorophosphate
PyNOP	[(6-nitrobenzotriazol-1-yl)oxy]tris(pyrrolidino) phosphonium hexafluorophosphate
PyOxm	*O*-[(cyano(ethoxycarbonyl)methyliden)-amino]-yloxytri(pyrrolidino) phosphonium hexafluorophosphate
PyTOP	(pyridyl-2-thio)tris(pyrrolidino) phosphonium hexafluorophosphate
SOMP	5-(succinimidyloxy)-3,4-dihydro-1-methyl 2*H*-pyrrolium hexachloroantimonate
TATU	*O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
TAs	3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl 4-methylbenzenesulfonate
TBs	1*H*-benzo[*d*][1,2,3]triazol-1-yl 4-methylbenzenesulfonate
$TBCR_1$	4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium tetrafluoroborate
$TBCR_2$	1-(4,6-dimethoxy-1,3,5-triazin-2-yl)-1-methylpiperydinium tetrafluoroborate
$TBCR_3$	1-(4,6-dimethoxy-1,3,5-triazin-2-yl)quinuclidinium tetrafluoroborate
TBTU	*O*-benzotriazol-1-yl-1,1,3,3-tetramethyluronium tetrafluoroborate
TDBTU	2-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
TCFH	tetramethylchloroformamidinium hexafluorophosphate
TCP	2,4,5-trichlorophenyl active ester
TDATU	*O*-(3,4-dihydro-4-oxo-5-azabenzo-1,2,3-triazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
TDTU	2-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
TEFFH	tetraethylfluoroformamidinium hexafluorophosphate
TEMP	2,3,5,6-tetramethylpyridine
TFMS-DEP	diphenyl(trifluoromethylsulfonyl)phosphoramidate
TFFH	tetramethylfluoroformamidinium hexafluorophosphate
TMP	collidine
TMU	tetramethylurea
TNTU	2-(5-norbornene-2,3-dicarboximido)-1,1,3,3-tetramethyluronium tetrafluoroborate
TODT	*S*-(1-oxido-2-pyridinyl)-1,3-dimethyl-1,3-trimethylenethiouronium tetrafluoroborate
TOTT	*S*-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouronium tetrafluoroborate
TOTU	*O*-[cyano(ethoxycarbonyl)methyleneamino]-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate
TPTU	2-(2-oxo-1(2*H*)-pyridyl-1,1,3,3-tetramethyluronium tetrafluoroborate
TSTU	2-succinimido-1,1,3,3-tetramethyluronium tetrafluoroborate
TOPPipU	2-[2-Oxo-1(2*H*)-pyridyl]-1,1,3,3-bis(pentamethylene)uranium tetrafluoroborate
T3P; PPAA	2-propanephosphonic acid anhydride
TPFTU	*N*,*N*,*N*′,*N*′-bis(tetramethylene)-*O*-pentafluorophenyluronium tetrafluoroborate
TPhTU	2-phthalimido-1,1,3,3-tetramethyluronium tetrafluoroborate
TPP	triphenylphosphine−carbon tetrachloride

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