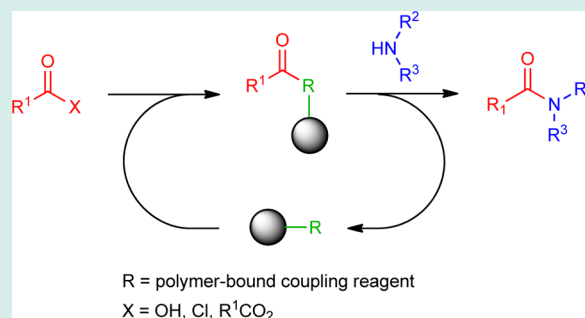


## Immobilized Coupling Reagents: Synthesis of Amides/Peptides

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**ABSTRACT:** The primary idea of using immobilized reagents in organic synthetic chemistry is to simplify the downstream process, product workup and isolation, and therefore avoiding time-consuming and expensive chromatographic separations, which are intrinsic to every synthetic process. Numerous polymer-bounded reagents are commercially available and applicable to almost all kinds of synthetic chemistry conversions. Herein, we have covered all known supported-coupling reagents and bases which have had a great impact in amide/peptide formation. These coupling reagents have been used for the activation of a carboxyl moiety; thus generating an active acylating species that is ready to couple with an amine nucleophile liberating the amide/peptide and polymeric support which can be regenerated for reuse. This also addresses a large variety of anchored coupling reagents, additives, and bases that have only been employed in amide/peptide syntheses during the last six decades.



**KEYWORDS:** *combinatorial chemistry, high-throughput organic synthesis, solid-phase synthesis, stand-alone coupling reagent, coupling additive*

## 1. INTRODUCTION

Although the first roots of immobilized chemistry can be traced back to the use of ionic-exchange resins as catalysts in 1947,<sup>1</sup> there is no doubt that the beginning of this splendid field only started off in 1963 when the Nobel Laureate R. Bruce Merrifield published the synthesis of a tetrapeptide on solid-phase.<sup>2</sup> The cornerstone of the so-called solid-phase method is to have one of the reactants covalently bound to a polymer, in the case of the Merrifield strategy a solid polymer. In his own words, “The advantages of the new method were speed and simplicity of operations”, characteristics that could be applied to all forms of immobilized chemistry. Once the first immobilized reaction has occurred to capitalize on the advantages of the method, successive reactions should occur in the same way. Thus, this strategy is particularly appealing for the preparation of polymers where a single reaction is key for all of the subsequent synthetic processes. Solid-phase is nowadays the method of choice for preparing peptides and related polymers, DNA, and carbohydrates. It was probably in the case of peptides where greater efforts have been invested, but also where the successes have been more spectacular. The last 50 years of continuous development is translated into the fact that almost any peptide of any size can be chemically synthesized with high purity. This has

been the determinant to fuel the development of peptides as therapeutics.<sup>3</sup>

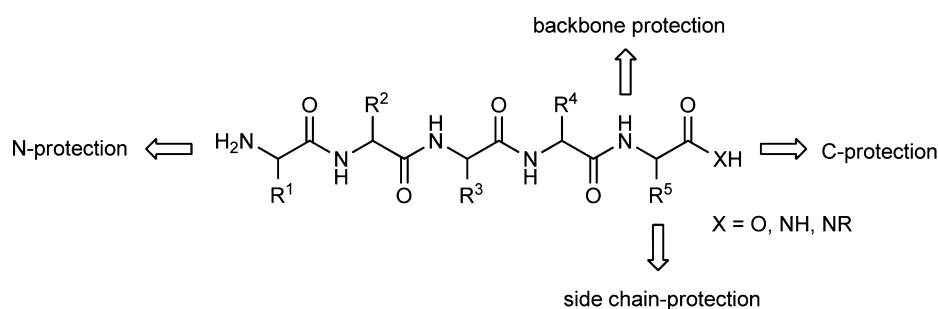
The construction of an amide/peptide bond involves the concurrence of a carboxylic acid, an amine, and some additives such as coupling reagents and bases. Additionally, the preparation of a peptide (more than one amide formation) will involve the removal of protecting groups, which prevents uncontrolled elongation reactions. Thus, the immobilization can be applied to the two main reactants, the carboxylic or the amine components, to the additives or to the reagents employed to remove the temporary protecting group. In the first case, the immobilization acts as a permanent protecting group, whose removal at the end of the synthesis is accompanied by the deimmobilization of the final product.<sup>4</sup>

This Review is divided into two parts; in the first, immobilized methods for the preparation of peptides and related biopolymers will be reviewed. The second will be devoted to immobilized additives and reagents.

**Received:** August 10, 2014

**Revised:** October 3, 2014

**Published:** October 20, 2014



**Figure 1.** Dissection of a peptide structure taking into account potential anchoring sites.

From a chemical point of view, “immobilization” can be defined as a system in which a compound is covalently attached to a stable matrix or material. For practical reasons and to fulfill the advantages outlined by Merrifield, this material is more convenient when it is a polymer with the idea of facilitating the separation of the elongated product at the end of the reaction. It is even more preferred, when the material is insoluble or heterogeneous.

Nowadays, solid-phase synthesis of peptides is normally accomplished using two types of resins, that is, polystyrene, and polyethylene glycol (ChemMatrix).<sup>5</sup> The latter is the support of choice for the preparation of difficult sequences and is compatible with solvents such as acetonitrile (ACN) and water thereby making it very useful for biological applications.<sup>6</sup> Peptides for several other purposes can be conveniently prepared from a broad range of materials, for example, libraries using cellulose membranes (SPOT method).<sup>7</sup>

Peptide synthesis on soluble supports was a technique developed in the early 1970s by Mutter and Bayer using polyethylene glycol as the polymer.<sup>8</sup> This was born from the idea of combining the advantages of both solid-phase and classical solution chemistry. At a glance, the reactions were performed in solution and then the polymer was precipitated. A major drawback of this is the removal of the remaining reagents and methods that were developed for avoiding the precipitation steps through microfiltration. In the 1990s, Janda and others revived the use of polyethylene glycol polymers for applications in combinatorial chemistry.<sup>9</sup>

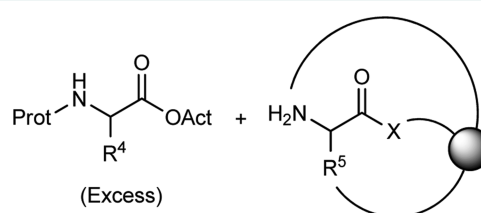
In this regard, the examples of this work will be centered on the use of insoluble polymeric materials. As such, the transformation process described herein is rather independent of the kind of polymer. As in the case of peptides, there are excellent reviews and books dealing with this subject, herein only the most important and frequently applied techniques have been outlined.

## 2. PEPTIDES AND RELATED POLYMERS

**2.1. Peptides.** Immobilized peptide synthesis involves the use of protecting groups that forms part of the polymeric material. This is based on the application of protecting groups (temporary groups are removed after each step and permanent ones are removed at the end of the synthesis) with the concurrence of the most appropriate coupling reagents for each case. Figure 1 shows a schematic representation of a peptide with the tentative protection sites useful for the anchoring of the polymer.

From a practical point of view, the majority of peptides are synthesized using C-anchoring but in some cases anchoring is also done through either the side-chain<sup>10</sup> or the backbone of the C-terminal amino acid ( $R^5$ ).<sup>11</sup> In the latter two cases, the C-terminal carboxylic group is blocked with a permanent protecting group. Thus, the three strategies which involve

anchoring to the polymeric support of the C-terminal amino acid are based on the successive incorporation of N-protected amino acids, through the activation of its carboxylic group, to an amino immobilized function (Figure 2).

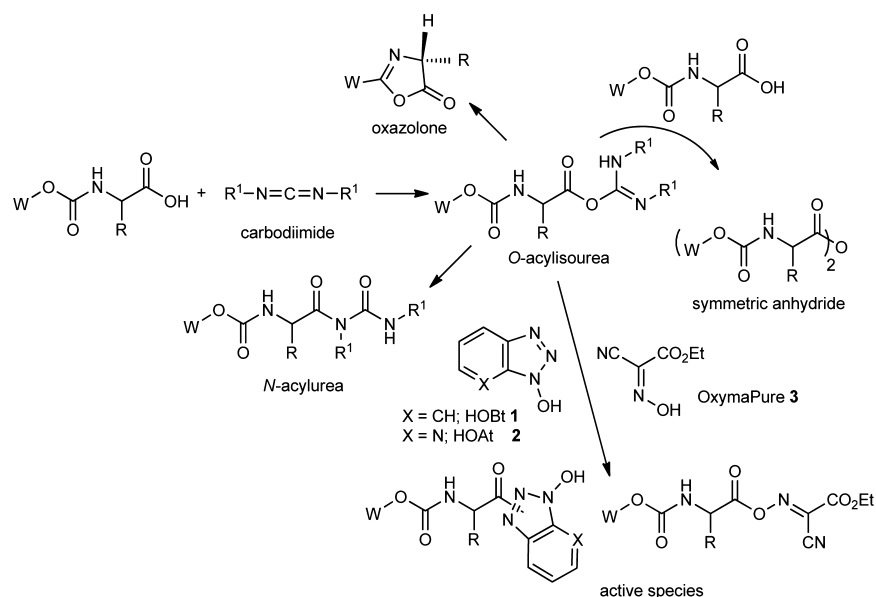


**Figure 2.** Basics on immobilized peptide bond formation.

Anchoring through the N-terminal has been assayed with rather poor results due to the activated carboxylic group being situated on the solid-phase and therefore the absence of the excess reagent approach to force the reaction to completion, leading to lower yields accompanied by several side-reactions.<sup>12</sup>

The two main strategies for N-protection are *tert*-butoxycarbonyl (Boc)/benzyl (Bzl) and fluorenylmethyloxycarbonyl (Fmoc)/*tert*-butyl (*t*Bu); both approaches utilize basically the same coupling reagents. Thus, for solid-phase peptide synthesis (SPPS), activation of the carboxylic group is usually achieved with carbodiimides, such as dicyclohexylcarbodiimide (DCC) or diisopropylcarbodiimide (DIC) in the presence of *N*-hydroxy additives, mainly 1-hydroxybenzotriazole (HOBT, 1), 1-hydroxy-7-azabenzotriazole (HOAt, 2), and ethyl 2-cyano-2-(hydroxyimino)acetate (OxymaPure, 3) (by increasing order of reactivity).<sup>4</sup> The purpose of these additives is to convert an *O*-acylisourea to the corresponding active species which are rather less reactive than *O*-acylisourea. Nevertheless, these additives increase the efficiency of carbodiimide-mediated reactions and suppress the formation of *N*-acylurea. The *O*-acylisourea can suffer rearrangement to the inactive *N*-acylurea or, in the case of carbamate protected amino acids, to the less reactive oxazolone, which is prone to racemization. The use of half an equivalent of the carbodiimide in the absence of the *N*-hydroxy additives leads to the formation of a symmetrical anhydride, which is also a highly reactive species (Scheme 1). As the dicyclohexylurea is only soluble in trifluoroacetic acid (TFA), which is the common agent for the removal of Boc protection, utilization of DCC is only practical in the Boc/Bzl strategy, while DIC is generally suited for Fmoc/*t*Bu synthesis.

Other coupling reagents of choice are the uronium salts, [1-[(1-(cyano-2-ethoxy-2-oxoethylideneaminoxy)-dimethylamino-morpholinomethylene)] methanaminium hexafluorophosphate] (COMU, 4), aminium *N*-[(1*H*-benzotriazol-1-yl)(dimethylamino)methylene]-*N*-methylmethanaminium

Scheme 1. Pathways for Peptide Bond Formation from a Carbodiimide-Mediated Reaction<sup>4</sup>

hexafluorophosphate *N*-oxide (HBTU, **5**), *N*-[(dimethylamino)-1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide (HATU, **6**), in the presence of diisopropylethylamine (DIEA) as base, which render a similar active species as above (Figure 3).<sup>4</sup>

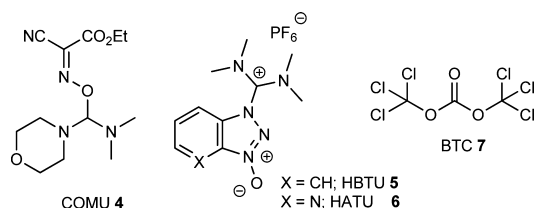


Figure 3. Structures of COMU, HBTU, HATU, and BTC.

The use of microwave heating accelerates this reaction without a substantial increase of side reactions.<sup>13</sup> In this case the use of DIC in combination with OxymaPure (**3**) is highly recommended since it is preferred over HOBT (**1**) in terms of absorbing microwave radiations and also does not pose a risk of explosion.<sup>14</sup> Racemization is not usually a threat in immobilized chemistry because of the presence of the electron withdrawing effect of the carbamate protecting groups which do not favor the formation of oxazolones (one of the causes of racemization). On the other hand, the use of a large excess of reagents favors faster reactions and also minimizes the chance of racemization. The only residue which is really prone to racemize is Cys and can be minimized by employing DIC-*N*-hydroxy additives with 5 min preactivation or uronium/aminium salts without preactivation.<sup>15</sup> As the racemization is a function of the side-chain SH group, it has recently been demonstrated that the dimethylphenyl (Dmp)

protected thiol group is easier to prepare and renders lower racemization.<sup>16</sup>

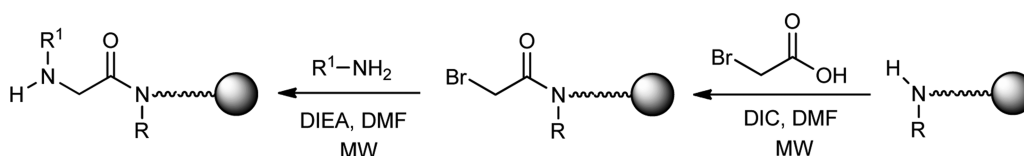
Acylation of *N*-Me residues can require stronger conditions such as HATU and microwave assistance.<sup>17</sup> For the acylation of larger *N*-alkyl derivatives, the use of triphosgene [*bis*(trichloromethyl)carbonate (BTC, **7**)],<sup>18</sup> which is totally compatible with *t*-butyl protecting groups, is the last resort. Although, dimethylformamide (DMF) has been the solvent of choice for most coupling conditions, acetonitrile (ACN) in conjunction with hydrophilic resins such as ChemMatrix or mixtures of ACN and DMF gave excellent results.<sup>19</sup>

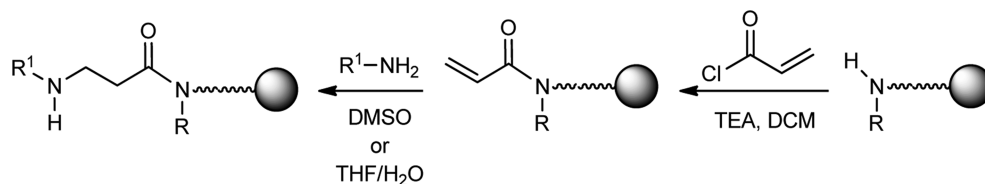
While other peptides formed from  $\beta$ - or  $\gamma$ -amino acids are synthesized on solid-phase utilizing similar techniques as for the  $\alpha$ -derivatives, the preparation of peptoids requires a significantly different strategy.

**2.2. Peptoids.**  $\alpha$ -Peptoids are constituted of poly-*N*-alkylglycines, which are more difficult to be acylated by the corresponding protected glycine monomers. However, taking advantage of the ease to convert bromoacetic acid to glycine, an elegant peptoid synthesis was developed with that as the monomer. After its introduction with DIC (the presence of **1** decrease dramatically the incorporation yield, confirming that OBT esters are less reactive than *O*-acylisoureas),<sup>20</sup> the *N*-side chain is introduced by reaction with a primary amine. Both reactions can be accelerated by the assistance of the microwave (Scheme 2).<sup>13</sup>

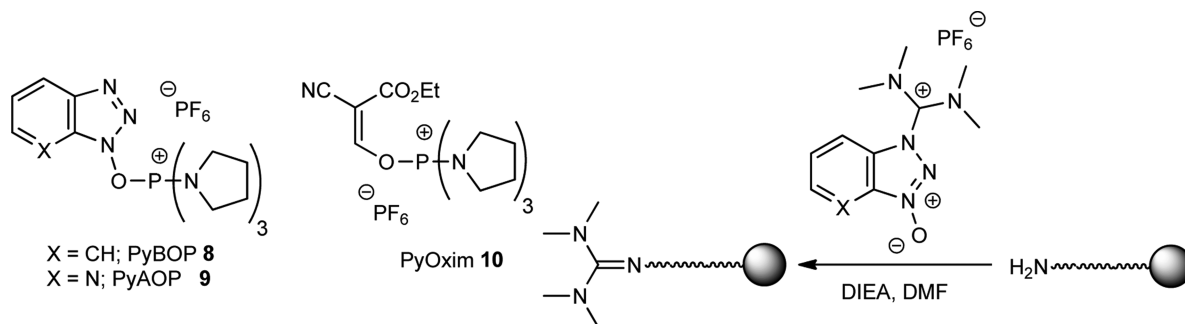
$\beta$ -Peptoids, which can be considered as poly- $\beta$ -alanines, are synthesized in solid-phase by the incorporation of acryloyl chloride followed by a conjugate aza-Michael addition of the next amine (Scheme 3).<sup>21</sup>

**2.3. Macrolactamization.** **2.3.1. Immobilized.** Immobilized chemistry is associated with the phenomenon of pseudodilution,

Scheme 2. Solid-Phase Synthesis of  $\alpha$ -Peptoids

Scheme 3. Solid-Phase Synthesis of  $\beta$ -Peptoids

Scheme 4. Structures of Phosphonium Salts and Formation of the Inactive Guanidine



which favors intramolecular over intermolecular reactions. In this regard, it is very attractive to prepare homodetic cyclic peptides by performing the macrolactamization while the protected peptide is resin bound. For the preparation of “head-to-tail” cyclic peptides, side-chain anchoring is essential since the free C-carboxyl group is required for the cyclization step. Although the same coupling methods as discussed earlier can be considered for this reaction, phosphonium salts [benzotriazol-1-yloxytris-(pyrrolidino)-phosphonium hexafluorophosphate (PyBOP, **8**); [(7-azabenzotriazol-1-yl)oxy]tris-(pyrrolidino) phosphonium hexafluorophosphate (PyAOP, **9**); O-[(cyano-(ethoxycarbonyl)-methylidene)-amino]-yloxytripyrrolidinophosphonium hexafluorophosphate (PyOxim, **10**), have proven to give the best results.<sup>4</sup> These reagents lead to similar active species as uronium/aminium species, but also have the advantage of not reacting with the free amine. On the other hand, uronium/aminium activators react with the amine to give the corresponding guanidines.<sup>22</sup> This side-reaction can be particularly detrimental in the cyclization step, since the carboxylic component is the limiting “reagent” and therefore a slight excess of the uronium/aminium salts can ruin the cyclization (Scheme 4).

**2.3.2. Cyclative Cleavage.** In this strategy, the macrolactamization and release of the freshly cyclized peptide from the support occurs simultaneously. This cannot be considered a general method as it works really well with very stable cyclic peptides such as diketopiperazines (DKP), but it fails with a large range of medium size peptides due to entropy reasons. As the peptide formation occurs through the nucleophilic attack of the amino function to an activated carboxyl group, in this strategy the first amino acid has to be linked to the support via a “kind” of activated bond. This very often precludes the use of the Fmoc/*t*Bu methodology for growing the linear peptide, because the bond formed between the first amino acid and the linker is susceptible to nucleophiles such as piperidine. Two main resins of choice are the Kaiser oxime resin (**11**) and the nitrobenzamido resin (NBB, **12**), mainly for the preparation of DKP. Alternatively, a “safety-catch resin”, such as the Kenner resin (**13**), which is activated at the end of the peptide elongation, can also be considered.

The Kaiser oxime resin has been employed for a so-called biomimetic synthesis of gramicidin S, cyclo(D-Phe-Pro-Val-Orn-Leu)<sub>2</sub>,

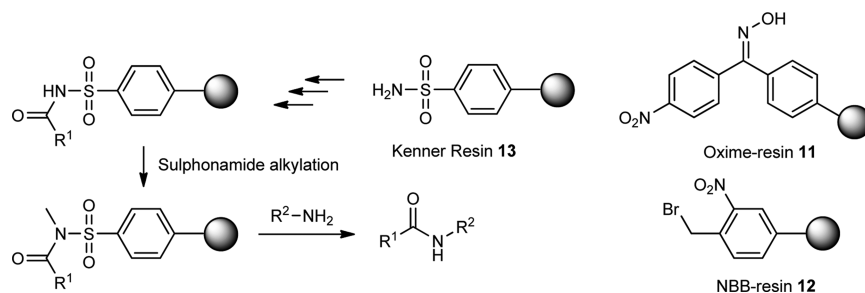
from the pentapeptide anchored to the resin.<sup>23</sup> Thus, H-D-Phe-Pro-Val-Orn-Leu-oxime resin was reacted for 24 h in the corresponding solvent containing 2 equiv of DIEA and AcOH (concentration of peptide in solution;  $3 \times 10^{-3}$  M) to simultaneously achieve dimerization and cyclative cleavage. The effect of the solvent and the loading of the resin were crucial and the conclusion was that dioxane was superior to pyridine, DMF, and dichloromethane (DCM); and a loading of 0.68 mmol/g afforded best results. To avoid the above-mentioned problems because of the presence or the use of amines during the stepwise synthesis, the key H-D-Phe-Pro-Val-Orn-Leu-oxime resin was prepared by coupling of Boc-D-Phe-Pro-Val-Orn(Boc)-OH onto H-Leu-oxime resin. Cyclative cleavage was achieved with the  $\delta$ -amino of the Orn showing the importance of the stability of the final product during the whole the process.

The Kaiser oxime resin (**11**) was conceptually designed for the preparation of linear peptides via a Boc/Bzl strategy and performing the cleavage by acid-catalyzed aminolysis with amino acid or peptide esters.<sup>24</sup> However, because of its lability in the presence of nucleophiles, the Kaiser oxime resin is only useful for specific synthesis such as peptide esters. In this case, the peptide is released from the resin with an amino acid ester.

The NBB resin (**12**) has been developed for the synthesis of protected peptides, because the release of the final products can be achieved by photolysis. One of the main drawbacks of this resin is its extreme propensity to afford the formation of DKP during the removal of the protecting group of the second residue. However, it is possible to take advantage of this side reaction for the effective preparation of such cyclic peptides.<sup>25</sup>

The sulfonamide Kenner resin (**13**) is totally stable to piperidine and TFA treatments; therefore compatible with the main two solid-phase synthetic strategies. At the end of the sequence elongation, sulfonamide alkylation (e.g., iodoacetonitrile) activates the peptide resin bond which becomes labile in the presence of amines such as the N-amino terminal; this activation of the Kenner resin provokes cyclative cleavage.<sup>26</sup> If the Fmoc strategy is chosen, it is important to realize that during the alkylation/activation step that the N-amino terminal should be protected as the Boc or trityl chloride (TrtCl) to avoid this

Scheme 5. Various Resins Employed for Cyclative Cleavage

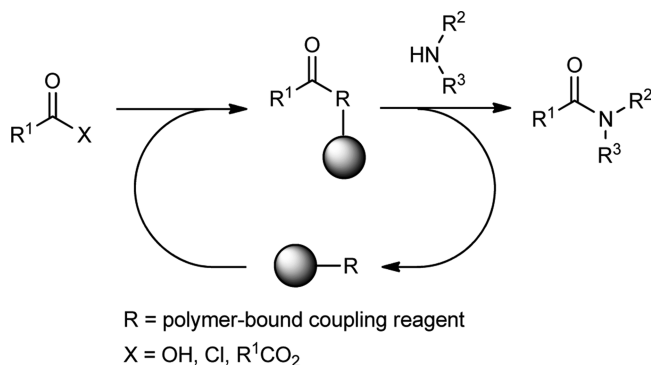


undesired alkylation. The structures of the above-discussed resins are presented in Scheme 5.

### 3. IMMOBILIZED COUPLING REAGENTS IN AMIDE (OR PEPTIDE) SYNTHESIS

As discussed earlier, amide/peptide formation is dependent on activating the carboxylic species with the assistance of reagents discussed in the previous section (coupling reagents, additives, bases). Polymer-supported coupling agents can facilitate the reaction by the “capture and release” technique. In this process, the polymer binds and activates a substrate that then reacts with another reagent, to release the products into the solution. In this technique, the “by-products” or catalyst remains attached to the insoluble polymer (Scheme 6). Furthermore, this method yields

Scheme 6. Basic Principle of Activation Process for Amide Bond Formation with Polymer-Bound Coupling Reagents



the products with very high purity and polymer-bound reagents can be regenerated for other synthetic transformations. Merrifield chloromethylated cross-linked polystyrene is the most commonly utilized insoluble support because of its commercial availability, but other supports such as polyglycerol, tentagel, macroporous, PEGA, and silica gel have also been utilized.<sup>27</sup>

A full range of soluble and high molecular weight coupling reagents and additives have also been developed from its monomer units via ring-opening metathesis polymerization (ROMP) method with Grubbs' catalyst.<sup>28</sup>

#### 3.1. Immobilized Carbodiimide Coupling Reagents.

Carbodiimides are the most classical and common coupling reagents to form peptide bonds. The supported versions of carbodiimides have the advantage that the side product urea remains bound to the support and is easily separated from the product in solution. A variety of polymer-bound carbodiimides are known, such as polyhexamethylenecarbodiimide (**14**),<sup>29</sup> isopropylcarbodiimide (PS-DIC, **15**),<sup>30</sup> cyclohexylcarbodiimides (PS-DCC, **16**<sup>31</sup> and **17**<sup>32</sup>), ethylcarbodiimides (PS-EDC or

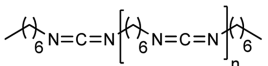
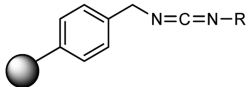
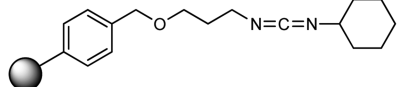
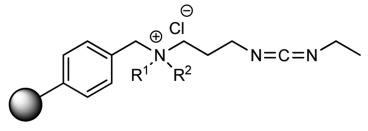
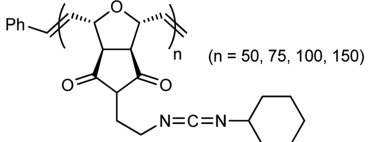
PS-EDCI, **18**, and PS-EPC, **19**),<sup>33</sup> and oligomeric alkyl cyclohexylcarbodiimide (OACC, **20**)<sup>34</sup> (Table 1). Except for a few cases such as **20**, polystyrene (PS) is the most accepted and convenient polymer for the preparation of these types of coupling resins. Recycling of these carbodiimide coupling reagents is a lengthy process because conversion of the byproduct “polymer-bound urea” into the supported carbodiimide form involves several experiments.

Although, isopropylcarbodiimide was the first reagent to be linked to these types of resins, it has not been successful for amide formation, probably because of a low quality of the commercialized reagent.<sup>30b</sup> However, the related PS-EDC or PS-EDCI (**18**) resins are commercially available and found to be appropriate for amide formation, without the presence of any additives in DCM/Chloroform as solvent.<sup>33b</sup> However, there are not much reports on PS-EPC (**19**) for amide bond formation.<sup>33d</sup> Polyhexamethylenecarbodiimide (**14**), which by itself is a polymer with film- and fiber-forming capabilities which has been employed for coupling of *N*-protected amino acids and amino acid ester hydrochlorides in the presence of triethylamine (TEA).<sup>29</sup>

PS-EDC (**18**) was employed for the formation of “Moshier amides” in CDCl<sub>3</sub> as solvent, and determination of the degree of racemization of the peptide product can be easily accomplished by direct NMR analysis after filtration.<sup>33c</sup> PS-EDC (**18**) has also been reported for the preparation of a (pyrazolyl-carbonyl-amino)benzamide library from (pyrazolyl-carbonyl-amino)-benzoic acids and amines (primary and secondary)<sup>33e</sup> and employed with sulphonamides to afford acylsulfonamide libraries, in the presence of DMAP as an additive.<sup>33f</sup> PS-EDC in the presence of a HOBt (**1**) additive was utilized for the synthesis of the antioxidative enzyme trypanothione reductase (TryR).<sup>33g</sup> The crucial cyclization step for the synthesis of Boc-amino-benzazepinones (lactam formation) was accomplished using **18**; subsequent Boc deprotection and acylation using the supported-reagent to give amido-benzazepinones in high yields (82–100%) and purities.<sup>33h</sup> The carbodiimide-mediated mechanism for the formation of an amide bond is outlined in Scheme 7.

Weinshenker and his co-workers have discussed the synthesis and reaction of PS-DIC (**15**) with various carboxylic acids. The side reaction of *N*-acyl ureas was problematic when carboxylic acids were treated with **15** to form anhydrides. PS-DIC could be recycled but the activity was generally less than the starting material due to blockage of some active sites by the *N*-acyl urea rearrangement product.<sup>30a</sup> The PS-cyclohexylcarbodiimides (**16** and **17**) are also commercially available and have been widely recommended as one of the most successful supported coupling reagents, particularly in the presence of additives to promote the coupling efficiencies and to evade racemizations. The *N*-propyloxymethyl backbone carbodiimide **17** (0.9–1.4 mmol g<sup>-1</sup>) was more favored than the *N*-methylene backbone carbodiimide

Table 1. Polymer-Supported Carbodiimide Coupling Reagents

Entry	Abbreviation	Name and Structure	Ref
14		Polymer-supported hexamethylenecarbodiimide 	[29]
15	PS-DIC	Polymer-supported <i>N</i> -isopropylcarbodiimide (R = <i>i</i> Pr)	[30]
16	PS-DCC	Polymer-supported <i>N</i> -cyclohexylcarbodiimide (R = Cyclohexyl) 	[31]
17	PS-DCC	Polymer-supported <i>N</i> -cyclohexyl- <i>N'</i> -propyloxymethylcarbodiimide 	[32]
18	PS-EDC	Polymer-supported <i>N</i> -ethyl- <i>N'</i> -(3-dimethylaminopropyl)carbodiimide R <sup>1</sup> , R <sup>2</sup> = Et	[33]
19	PS-EPC	Polymer-supported <i>N</i> -ethyl- <i>N'</i> -(3-pyrrolidinylpropyl)carbodiimide R <sup>1</sup> -R <sup>2</sup> = -[CH <sub>2</sub> ] <sub>4</sub> - 	[33d]
20	<sup>2G</sup> OACC <sub>n</sub>	Oligomeric alkyl cyclohexylcarbodiimides 	[34]

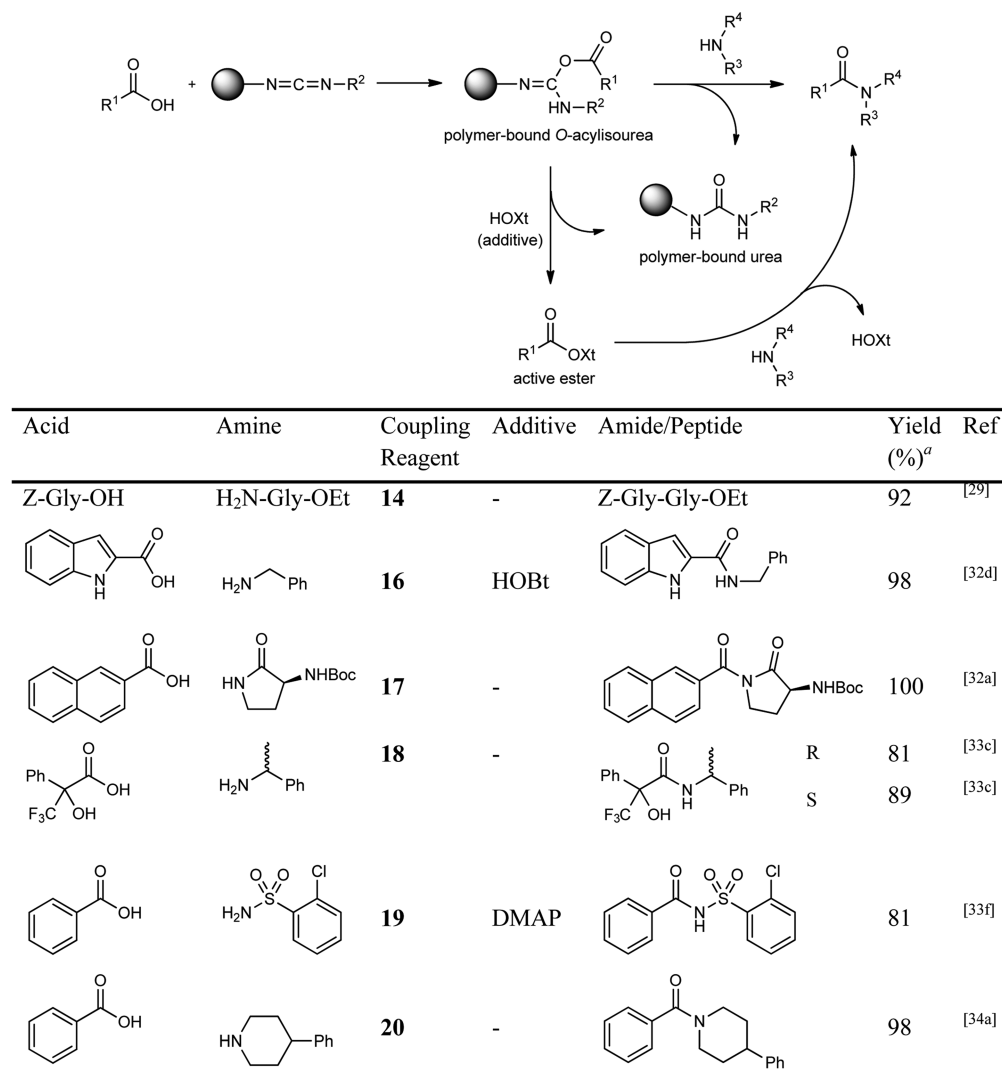
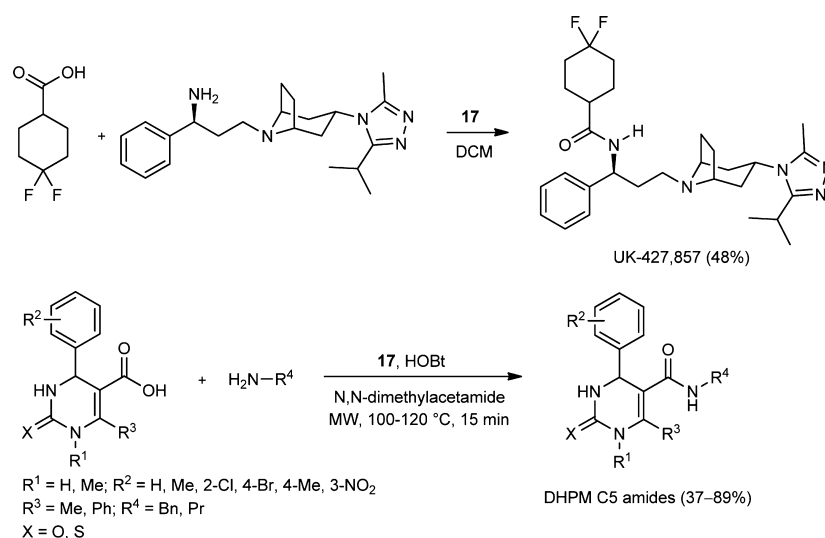
16 because of its higher reactivity. The PS-DCC (16) reagent has also been reported without additives in the amidation reaction of 2-(methylthio)-acetic acid to form an active intermediate, which reacts with amino-scaffolds to give trisubstituted 3,4-diaminocyclopentanol.<sup>31a</sup> There are some applications of supported carbodiimides for the formation of benzotriazole active esters from *N*-Boc protected amino acids and HOBt (1), which have been consequently utilized in coupling reactions to form dipeptide *p*-nitroanilides and dipeptide diphenyl phosphonates.<sup>31c,h</sup> A one-pot method was developed for the synthesis of an amide library using 16 by incorporating 1 to improve the reactivity of the supported reagent. The excess HOBt was then subsequently scavenged with a supported carbonate base.<sup>31b</sup> A single pot conversion of esters or lactones to amides was accomplished utilizing a resin-bound carbodiimide, in which, hydrolysis of the ester or lactone was initiated, followed by formation of the amide bond.<sup>31d</sup> This combination of reagents (16 and 1) have also been reported for amidation reactions in the parallel synthesis of pyrazinone-derivatives, substituted benzenes, benzoquinone analogs and  $\alpha$ -ketothiazoles, which are useful as tissue factor VIIa inhibitors.<sup>31e-g</sup>

The two-step library synthesis of  $\alpha$ -ketoamides involves an amide formation with a  $\alpha$ -hydroxy acid and an amine in the presence of PS-DCC (17) as coupling reagent.<sup>32b</sup> It has also been used in the presence of HOAt (2) additive for monoamidation of diphenyldiamines to provide *o*-amido-diphenylamines, which was further cyclodehydrated to prepare a benzimidazole library.<sup>32c</sup>

PS-DCC (17) was employed in the synthesis of pharmacologically interesting compound UK-427,857 (Maraviroc), a powerful antagonist of the CCR5 receptor for the treatment of HIV. It was used for amide bond formations of 4,4-difluorocyclohexanecarboxylic acid and triazole-containing amine templates (Scheme 8).<sup>32e</sup> Moreover, *N*-acylated derivatives of deoxy- and ribo purinenucleosides were synthesized utilizing 17 for the formation of active esters for further acylation with amines.<sup>32f</sup> The microwave heating technique for shortening the reaction times was optimized for a rapid and efficient amide formation protocol with PS-DCC (17) in the presence of HOBt (1) as an additive.<sup>32d</sup> Another example of using these reagents with microwave-assisted heating is for the synthesis of DHPM C5 amides from 3,4-dihydropyrimidin-2-(1*H*)-one 5-carboxylic acids (DHPM-acid) and primary amines (Scheme 8).<sup>32g</sup>

A new class of immobilized coupling agents are the high-load and soluble supported reagents such as oligomeric alkyl cyclohexylcarbodiimide (<sup>2G</sup>OACC<sub>n</sub>, 20), which was synthesized from the monomer unit, *N*-cyclohexyl-*N'*-(2-succinimidoethyl)-carbodiimide, through the ROMP method via Grubbs' second-generation catalyst [(IMesH<sub>2</sub>)(PCy<sub>3</sub>)(Cl)<sub>2</sub>Ru=CHPh].<sup>34a</sup> These ROMPgel-supported reagents are suitable for amide formation. With this family, the bound urea byproduct was removed by precipitation with an appropriate solvent (Et<sub>2</sub>O, MeOH, or EtOAc). Unfortunately, <sup>2G</sup>OACC<sub>n</sub> resins are not yet commercially accessible and thus their use has been limited. The immobilized carbodiimide <sup>2G</sup>OACC<sub>n</sub> was also applied in the

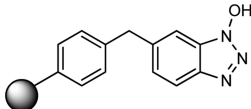
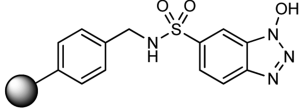
Scheme 7. General Mechanism of Amide Bond Formation Using Polymer-Bound Carbodiimide-Mediated Reactions

Scheme 8. Synthesis of UK-427,857 (Maraviroc) and DHPM C5 Amides Using **17**

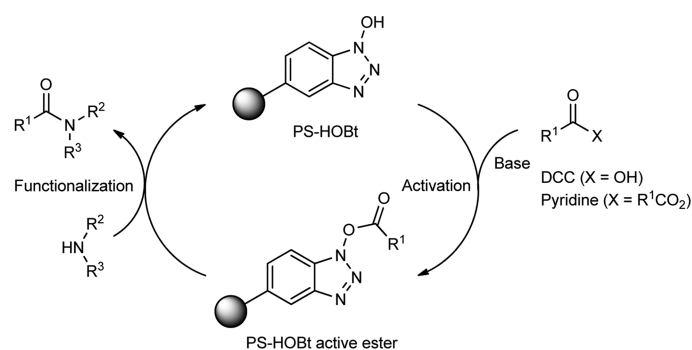
chromatography-free synthesis of various linear and heterocyclic amides in good to excellent yields (65–98%) with high purities (99%) from a variety of carboxylic acids (aliphatic, aromatic, and

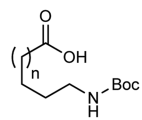
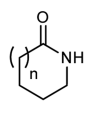
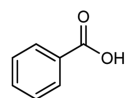

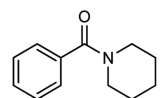
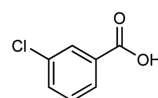
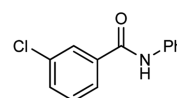
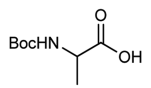
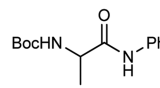
heterocyclic) and amines (aliphatic primary, secondary, benzylic, and aromatic/anilines). The addition of 4-(*N,N*-dimethylamino)pyridine (DMAP) in certain coupling reactions

Table 2. Polymer-Supported HOBt Additive and its Derivatives

Entry	Abbreviation	Name and Structure	Ref
21	PS-HOBt	Polymer-supported 1-hydroxybenzotriazole 	[35]
22	PS-SO <sub>2</sub> HOBt	1-Hydroxybenzotriazole-6-sulfonamidomethyl polystyrene 	[36]

Scheme 9. Synthesis of Amides/Peptides via PS-HOBt (21) Active Ester Methodology



Acid	Amine	Coupling Reagent	Additive	Amide/Peptide	Yield (%) <sup>a</sup>	Ref
Z-Phe-OH	H <sub>2</sub> N-Leu-OMe	DCC	21	Z-Phe-Leu-OMe	99	[35a]
	-	DCC	21		n = 2: 23 n = 8: 34	[35d] [35d]
		DIC	21		96	[35e]
	H <sub>2</sub> N-Ph	PyBrOP	22		79	[36a]
	H <sub>2</sub> N-Ph	DIC	22		61	[36b]

was essential, which was simply be removed either by an aqueous workup or by the use of a scavenger resin (Amberlyst A-15 resin).<sup>34a,c</sup> Another noteworthy example of a soluble supported reagent for amide formation is the dendritic polyglycerol-supported cyclohexylcarbodiimide (PG-DCC).<sup>34b</sup>

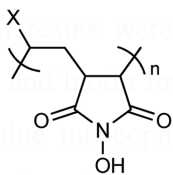
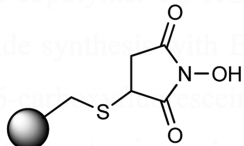
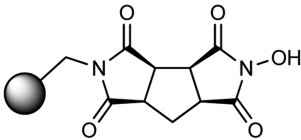
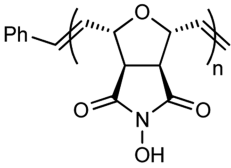
**3.2. Immobilized Hydroxy Additives.** Carbodiimides are very reactive and therefore relatively unstable, which can also be translated into poor yields, and provoke racemization of amino acids, because it makes the  $\alpha$ -proton more acidic and therefore prone to enolization. To increase the stability and minimize the formation of side-reactions, carbodiimide facilitated couplings

are carried out in the presence of *N*-hydroxy compounds, which largely neutralizes these side reactions.

**3.2.1. Immobilized HOBt Additives.** In recent years, a number of new stable and easily handled polymer-bound additives have been developed such as 1-hydroxybenzotriazoles (PS-HOBt, 21)<sup>35</sup> and 1-hydroxybenzotriazole-6-sulfonamidomethyl polystyrene (PS-SO<sub>2</sub>HOBt, 22), the structures of which are shown in Table 2.<sup>36</sup> Thus, immobilized-HOBt additives are also useful in a similar fashion as their soluble analogue HOBt (1), since it minimizes the workup processes. Moreover, 21 and 22 can be regenerated by relatively easy purification and reused without loss of activity.



Table 3. Polymer-Supported *N*-Hydroxysuccinimide (NHS) Coupling Reagents

Entry	Abbreviation	Name and Structure	Ref
23	PHMI	Poly(ethylene- <i>co</i> - <i>N</i> -hydroxymaleimide) (X = H)	[37a-c]
24	PS-HOSu	Polymer-supported <i>N</i> -hydroxysuccinimide (X = Ph) 	[37j-o]
25	PS-HOSu	Polymer-supported <i>N</i> -hydroxysuccinimide thiol derivative 	[37d-f]
26	PS-HOSu	Polymer-supported <i>N</i> -hydroxysuccinimide derivative 	[37h]
27	ROMPgel-HOSu	Ring-opening metathesis polymer gel-supported <i>N</i> -hydroxysuccinimide 	[37g, 37i, 37p-r]

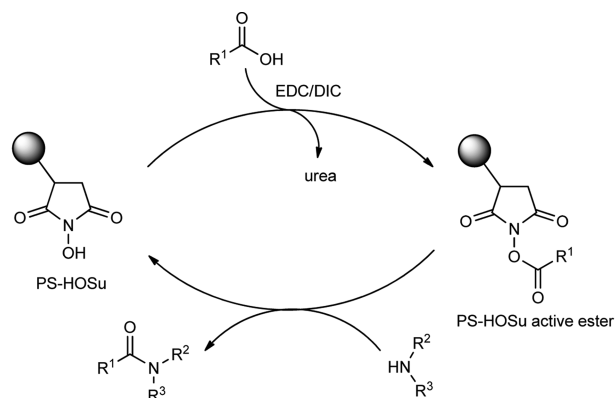
Reagents **21** and **22** are commercially available and are used in peptide couplings (Scheme 9) in the presence of activating reagents, such as DCC or bromo-tris-pyrrolidinophosphonium (PyBrOP). They react with *N*-blocked amino acids or anhydrides for in situ formation of supported active esters for the synthesis of peptides,<sup>35e,36</sup> including the tetrapeptide thyrotropin-releasing hormone,<sup>35a</sup> thymosin  $\alpha_1$  (15–28),<sup>35b</sup> immunostimulating peptides<sup>35c</sup> (chemically related to the bioactive peptides thymosin  $\alpha_1$  and thymopentin), and medium ring lactams (7–13 membered rings).<sup>35d</sup> In addition, a variety of primary and secondary amine moieties can be protected as carbamate derivatives (Boc, Cbz, and Fmoc) using polymer-supported reagents (PS-HOBt).<sup>35f</sup> Also, it has been reported for amide formation in the synthesis of Sildenafil (Viagra), a pharmaceutical drug treatment for male erectile dysfunction.<sup>35g</sup> The recently developed silica-anchored 1-hydroxybenzotriazole (Si-HOBt) displayed similar activity to **21**, and maintained its high performance even after numerous regenerations.<sup>35i</sup>

**3.2.2. Immobilized HOSu Additives.** PS-*N*-hydroxysuccinimide (HOSu)-derived active esters are less reactive than other active ester reagents, but they are more stable and can be stored for longer periods. Supported HOSu reagents facilitate the formation of a peptide bond through an isolated polymeric *N*-hydroxysuccinimidyl ester. The most conventional approach for one-pot amide bond formation with supported HOSu additives includes

the addition of carbodiimide-mediated initiators. Several common polymer supported HOSu additives<sup>37</sup> have been extensively applied as condensing agents for peptide synthesis (Table 3).

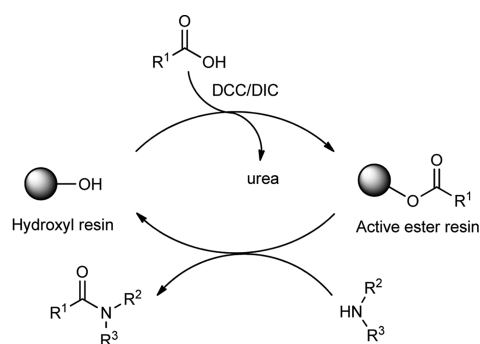
The first HOSu additive, poly(ethylene-*co*-*N*-hydroxymaleimide) (PHMI, **23**), was reported for peptide synthesis in the late 60s<sup>37a</sup> with Boc-protected amino acid derivatives in the presence of DCC and subsequent amidation with carboxy protected amino acids (Scheme 10).<sup>37a-c</sup> In addition, reports suggested that these PHMI additives are soluble in DMF and DMSO but not in water, alcohols (MeOH, EtOH or 2-PrOH), dimethoxyethane (DME) and ACN. To improve the insolubility of polymeric active esters for the synthesis of hexa- or higher peptides, PHMI was cross-linked by exposure to high-energy electrons during preparation.<sup>37a</sup> The PHMI was also cross-linked by reacting the starting poly(ethylene-*co*-maleicanhydride) with polyamines such as hydrazine, spermine or spermidine just prior to the reaction with hydroxylamine. Consequently, the spermidine cross-linked poly(ethylene-*co*-*N*-hydroxymaleimide) gave an average particle size of 200–300 mesh, enhanced its insoluble nature in H<sub>2</sub>O, MeOH, EtOH, CHCl<sub>3</sub>, ACN, DMF, and AcOH and increased the mechanical stability of the resin. This cross-linking polymer, together with various *N*-Boc-amino acids and DCC as the coupling agent, was successful in synthesizing the heptapeptide corresponding to residues 159–165 of bovine carboxypeptidase A.<sup>37b</sup>

Scheme 10. Formation of Peptide Bonds using Polymer-Bound HOSu Additive



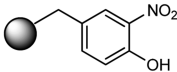
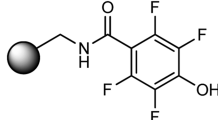
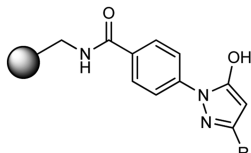
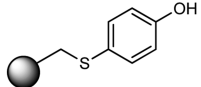
Acid	Amine	Coupling Reagent	Additive	Amide/Peptide	Yield (%) <sup>a</sup>	Ref
Boc-Ala-OH	H <sub>2</sub> N-Ala-OBz	DCC	<b>23</b>	Boc-Ala-Ala-OBz	86	[37a]
Boc-Gly-OH	H <sub>2</sub> N-Phe-OEt	DCC	<b>24</b>	Boc-Gly-Phe-OEt	98	[37i]
	H <sub>2</sub> N-Ph	EDC	<b>25</b>		99	[37d]
		EDC	<b>26</b>		81	[37h]
		DIC	<b>27</b>		91	[37i]

Scheme 11. Amidation Using Polymer-bound Hydroxyl-mediated Resins

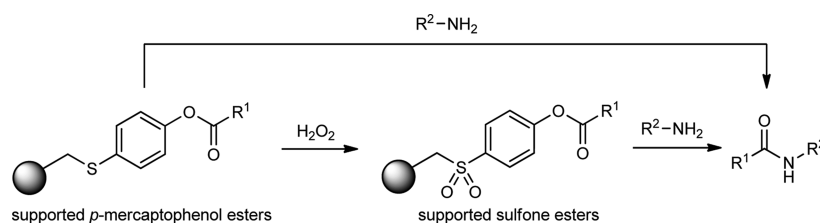


Acid	Amine	Coupling Reagent	Additive	Amide/Peptide	Yield (%) <sup>a</sup>	Ref
Z-Phe-OH	H <sub>2</sub> N-Gly-OBzl	DCC	<b>28</b>	Z-Phe-Gly-OBzl	99	[39b]
	H <sub>2</sub> N-Ph	DIC	<b>29</b>		96	[41a]
Boc-Leu-OH	H <sub>2</sub> N-Gly-OMe	DCC	<b>30</b>	Boc-Leu-Gly-OMe	98	[42]
		DIC	<b>31</b>		99	[43]
Bz-Leu-OH	H <sub>2</sub> N-Gly-OEt	DCC	<b>32</b>	Bz-Leu-Gly-OEt	38	[44b]

Table 4. Polymer-Supported Hydroxyl Coupling Reagents

Entry	Abbreviation	Name and Structure	Ref
28	PS-NP	Polymer-supported nitrophenol 	[38-40]
29	PS-TFP	Polymer-supported 4-hydroxy-2,3,5,6-tetrafluorobenzamide 	[41]
30	PS-CMPO	Polymeric 1-(4-carboxyphenyl)-3-methyl-2-pyrazolin-5-one (R = Me)	[42]
31	PS-CNPO	Polymeric 1-(4-carboxyphenyl)-3-(4-nitrophenyl)-2-pyrazolin-5-one (R = <i>p</i> -nitrophenyl)	[43]
			
32		Polymer-supported 4-(benzylthio)phenol 	[44]

Scheme 12. Synthesis of Amides through Sulfone Active Ester Resin Using Phenol-Sulfide Resin



Polymer supported HOSu-active esters are synthesized from *N*-hydroxymaleimide esters of *N*-protected amino acids and subsequent copolymerization of these esters with styrene, divinylbenzene and 4-chlorophenylmaleimide. These HOSu-active esters are popular for the synthesis of dipeptides in excellent yields (86–99%).<sup>37c</sup> The polymeric reagent, PS-HOSu (24), is obtained from the reaction of commercially available poly(styrene-*alt*-maleic anhydride) with 50% aqueous solution of hydroxylamine at 90 °C.<sup>37j</sup> This supported reagent was exploited as an additive for amide bond formations between Boc, Cbz and Fmoc-protected amino acids and amino acid esters with DCC as the coupling agent. The extent of racemization was studied with this additive utilizing the Anteunis test; the observed degree of epimerization in tripeptide synthesis without any additive was 9:1, whereas when the reaction was performed in the presence of 24, the level was reduced to 18:1. Also, 24 could be successfully reused without appreciable loss of activity.<sup>37j</sup> Moreover, 24 is established as a polymeric reagent for the protection of amino functionality with the Fmoc,<sup>37k</sup> 2,7-di-*tert*-butyl-9-fluorenylmethoxycarbonyl (Dtb-Fmoc),<sup>37m</sup> allyloxycarbonyl (Alloc) and propargyloxycarbonyl (Proc)<sup>37o</sup> groups. Furthermore, *N*-hydroxysuccinimido ammonium and alkylammonium salts derived from PS-HOSu (24) were also useful for

amide bond formation in the presence of EDC as the coupling reagent with easy recycling of the residual 24.<sup>37n</sup>

Supported-HOSu (25) resins were employed with labeling compounds, such as fluorescein, coumarin, acridinium, and biotin, for the formation of resin-bound active HOSu esters; followed by coupling with amine nucleophiles, such as estriol, thyroxine, phenytoin and desipramine haptens giving labeled conjugates without the need of further purification.<sup>37d,e</sup> A spacer-modified cross-linked copolymer PS-HOSu (similar to 25) that can be regenerated and reused was designed for amide synthesis with EDC as an initiator.<sup>37q</sup> Also, PS-HOSu-esters from 1-pyrenebutyric acid, 6-carboxyfluorescein diacetate, and biotin were efficiently prepared and further aminolysis with tryptamine, adamantamine and dehydroabietylamine in the presence of DCC affords the corresponding amides in excellent isolated yields (81–92%).<sup>37f</sup> Another HOSu-inducing polymer, *N*-hydroxysuccinimidyl resin (26), was reported for the formation of HOSu-active esters from carboxylic acids and EDC or DIC as coupling reagents which upon exposition to amines yielded the corresponding amides within 20 min. The authors did not mention the recyclability of this supported reagent.<sup>37h</sup>

The efficacy of a novel ring-opening metathesis polymer supported *N*-hydroxysuccinimide reagent (ROMPgel-HOSu, 27) for amide formations (including Mosher and Weinreb

Table 5. Polymer-Supported Uranium/Aminium Coupling Reagents

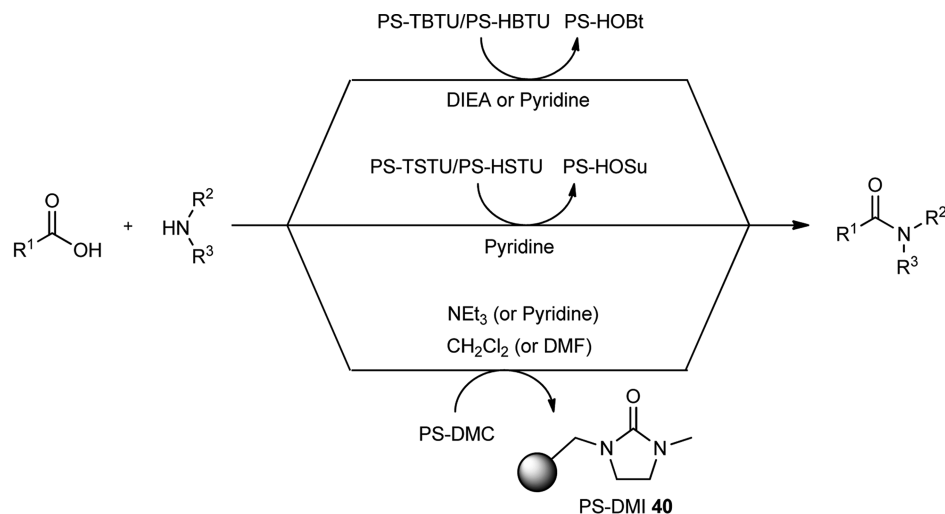
Entry	Abbreviation	Name and Structure	Ref
33	PS-TBTU	Polymer-supported 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (X = BF <sub>4</sub> )	[45a]
34	PS-HBTU	Polymer-supported 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexachloroantimonate (X = SbCl <sub>6</sub> )	[45c]
35	PS-TSTU	Polymer-supported 2-succinimido-1,1,3,3-tetramethyluronium tetrafluoroborate (X = BF <sub>4</sub> )	[45b]
36	PS-HSTU	Polymer-supported 2-succinimido-1,1,3,3-tetramethyluronium hexafluorophosphate (X = PF <sub>6</sub> )	[45b]
37	PS-DMC	Polymer-supported 2-chloro-1,3-dimethylimidazolium chloride	[46]
38		ROMPsphere-supported fluoroformamidinium hexafluorophosphate	[47]
39		ROMPsphere-supported 2-Bromo-1-ethylpyridinium tetrafluoroborate	[47]

amides) was reported. The polymer, **27**, is a recyclable acyl transfer reagent to appropriate amines with excellent isolated yields and purities and requiring little purification.<sup>37g,i</sup> IRORI Kan formatted ROMPgel-HOSu was developed and utilized as an acylating agent as well. Several amides have been prepared and yields are greatly improved in the presence of perfluorinated solvents as a nonparticipating cosolvent in the acylation process. The resin can be reused several times with no apparent loss of activity or purity.<sup>37p</sup> Another novel MicroGel-supported acylating reagent (MGAR) was prepared from two key

polymerization processes, namely, ring-opening metathesis polymerization (ROMP) and activators re-generated by electron transfer for atom transfer radical polymerization (ARGET ATRP). MGAR are reported as an excellent acylating agent for peptide synthesis with primary and secondary amines. Moreover, the microgels are recovered and the regenerated reagents showed almost similar acylation performance as the newly prepared counterparts.<sup>37r</sup>

**3.2.3. Immobilized Hydroxyl Coupling Reagents.** Polymer-supported nitrophenol (PS-NP, **28**) is an exceptional replacement

Scheme 13. Synthesis of Amide/Peptide using Uranium/Aminium Coupling Reagent



Acid	Amine	Coupling Reagent	Base	Amide/Peptide	Yield (%) <sup>a</sup>	Ref
Boc-Val-OH	H <sub>2</sub> N-Aib-OMe	<b>33</b>	Pyridine	Boc-Val-Aib-OMe	53 <sup>b</sup>	[45a]
Boc-Ala-OH	H <sub>2</sub> N-Phe-OEt	<b>35</b>	Pyridine	Boc-Ala-Phe-OEt	63	[45b]
Boc-Gly-OH	H <sub>2</sub> N-Phe-OEt	<b>36</b>	Pyridine	Boc-Gly-Phe-OEt	65	[45b]
Z-Phe-OH	H <sub>2</sub> N-Pro-OMe	<b>37</b>	Et <sub>3</sub> N	Z-Phe-Pro-OMe	77	[46]
Z-Trp-OH	H <sub>2</sub> N-Pro-OMe	<b>37</b>	Et <sub>3</sub> N	Z-Trp-Pro-OMe	86	[46]

for reagents, such as PS-HOBT, PS-HOSu, and their analogs, which was first developed in the mid 60s and applied for cyclic peptide synthesis in DMF.<sup>38</sup> Later, it was noticed that active esters from **28** can be stored at room temperature in the solid form without decomposition, it was also utilized for the synthesis of di-, tri-, including nonapeptide “Bradykinin hormone” and decapeptide ‘luteinizing hormone-releasing hormone’ in the presence of DCC as the coupling agent (Scheme 11).<sup>39</sup> On the other hand, it has also been applied in conjunction with a broad range of polymers (polystyrene, TentaGel, macroporous, PEGA, and silica gel). Thus, nitrophenol and sulfonate esters have been developed for the acylation of weakly nucleophilic heterocyclic amines giving amides and sulphonamides, respectively.<sup>27,40</sup> Additionally, the polymeric alcohol (PS-NP, **28**) is recyclable.<sup>39c</sup> The various polymer-bound hydroxyl coupling reagents are listed in Table 4.

Polymer-supported tetrafluorophenol (PS-TFP, **29**) is a useful tool for the synthesis of PS-TFP-acyl esters and novel PS-TFP-sulfonate esters from carboxylic acids and sulfonyl chlorides, respectively, in DMF as the solvent. These active resins are also utilized for the synthesis of a large variety of amides and sulphonamides.<sup>41</sup> Similar to PS-NP reagent, the PS-TFP could also be efficiently recycled. New polymer-bound pyrazolone active esters derived from polymeric 1-(4-carboxyphenyl)-3-methyl-2-pyrazolin-5-one (PS-CMPO, **30**) and polymeric 1-(4-carboxyphenyl)-3-(4-nitrophenyl)-2-pyrazolin-5-one (PS-CNPO, **31**) resins with acids (in the presence of DIC) or from acid chlorides (in the presence of TEA) in THF as solvent, are efficient acyl-translating agents over primary or secondary amines for the synthesis of amides and dipeptides within 20–30 min, with high reactivity and good recyclability.<sup>42,43</sup>

Chloromethylpolystyrene (Merrifield) resin treated with the *o*-carbonate ester of *p*-mercaptophenol gives the corresponding polymer-bound *p*-mercaptophenol *o*-carbonate ester, which upon ester hydrolysis results in supported 4-(benzylthio)phenol (**32**). The obtained resin has been employed to form *p*-mercaptophenol esters from *N*-protected amino acids via mixed anhydrides or DCC. The sulfide group is then oxidized to sulfone with H<sub>2</sub>O<sub>2</sub> to increase the electron-withdrawing nature of the aromatic ring (Scheme 12). The resulting sulfone species is very reactive toward amino groups to liberate amides and the polymer-supported sulfone resin as byproduct.<sup>44a,b</sup> Later on, studies have revealed that oxidation of the thioether is not necessary for effective cleavage even when utilizing limited amounts of the amine (Scheme 12). It is possible to recover and reuse this supported thiophenol reagent, **32**.<sup>44c</sup>

**3.3. Immobilized Uranium/Aminium Coupling Reagents.** Polymer-supported uranium/aminium salts such as PS-TBTU (**33**), PS-HBTU (**34**) and PS-HSTU (**35**), PS-TSTU (**36**) (Table 5) were prepared from commercially available PS-HOBT (**21**) and PS-HOSu (**26**), respectively.<sup>45</sup> Reagent **33** is recommended for synthesis of dipeptides from *N*-protected amino acids and amino acid ester hydrochlorides in the presence of an organic base like pyridine and TEA (Scheme 13). Interestingly, it was demonstrated to be more effective with wet solvents and in some cases heating is required to obtain the dipeptide products.<sup>45a</sup> For **34**, a hexachloroantimonate (SbCl<sub>6</sub>) related reagent was necessary for the formation of hydroxamic acid derivatives on automated solution phase synthesis.<sup>45c</sup> Reagents **33** and **34** were obtained in the form of **21** after the coupling process, which can be recovered by filtration and

Table 6. Polymer-Supported Phosphorous Containing Coupling Reagents

Entry	Abbreviation	Name and Structure	Ref
41	PS-BOP	Benzotriazol-1-yloxy-tris(dimethylamino) phosphonium hexafluorophosphate 6-sulfonamidomethyl polystyrene 	[48]
42	PS-PPh <sub>3</sub>	Polymer-supported triphenylphosphine with CCl <sub>4</sub> or CCl <sub>3</sub> CN or I <sub>2</sub> 	[49]
43		Polymer-supported triphenylphosphine ditriflate 	[50]
44		Polymer-supported 1,1,3,3-tetraphenyl-2-oxa-1,3-diphospholanium bistriflate 	[51]

recycled for preparation of the uranium/aminium salts (**33** and **34**). In addition, new polymeric *N*-hydroxysuccinimido mediated uranium/aminium salts such as **35** and **36** were developed as solid-supported coupling reagents for peptide synthesis from *N*-protected amino acids and amino acid ester hydrochlorides with pyridine as the organic base. PS-HOSu (**24**) was quantitatively recovered in a pure form and was reused for the preparation of new coupling reagents **35** and **36** (Scheme 13).<sup>45b</sup>

The polymer-supported chloroaminidinium chloride (PS-DMC, **37**), a heterogeneous dehydrating agent, was applied for amidation in dipeptide synthesis. The dipeptides were isolated from *N*-protected amino acids and amino acid esters with low levels of unwanted epimerization and the resulted supported urea byproduct (PS-DMI, **40**) was separated by filtration and recycled up to three times (Scheme 13).<sup>46</sup>

ROMP-originated reagents, ROMPsphere-supported fluoroformamidinium hexafluorophosphate (**38**) and ROMPsphere-supported 2-bromo-*N*-ethylpyridinium tetrafluoroborate (**39**) were prepared from formamidinium norbornene monomers by ROMP or graft copolymerized onto polystyrene cores. These reagents were successfully utilized for the synthesis of hindered amides and dipeptides containing sterically hindered Aib ( $\alpha$ -aminoisobutyric acid) residues. The main drawback of these reagents is the high levels of racemization and epimerization; therefore usage is very limited and only suitable for hindered peptides containing  $\alpha,\alpha$ -disubstituted amino acids. There was no information about the recyclability of these reagents.<sup>47</sup>

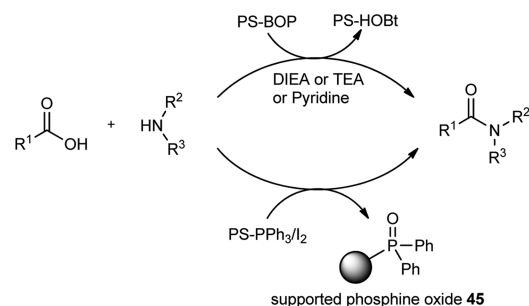
### 3.4. Immobilized Phosphorus Containing Reagents.

Supported phosphorus containing coupling reagents such as (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (PS-BOP, **41**) were prepared from commercially available **21** (Table 6) and is a suitable activating agent especially

for difficult peptide couplings involving sterically hindered  $\alpha,\alpha$ -dialkyl amino acids (e.g., Aib). Compared to unsupported BOP reagents, less racemization was observed. After coupling, the polymer **21** was obtained, which can be recovered by filtration and reused to make the phosphonium salts.<sup>48</sup>

The combination of polymer-supported triphenylphosphine (PS-PPh<sub>3</sub>, **42**) with carbon tetrachloride (CCl<sub>4</sub>), trichloroacetonitrile (CCl<sub>3</sub>CN) or iodine (I<sub>2</sub>) mixtures are considered as attractive condensing agents for amide formation (Scheme 14).<sup>49</sup> The coupling reaction strategy proceeds via formation of acid chlorides/iodides, which further reacts with amines to give amides and liberates polymer-bound phosphine oxide (**45**) as a byproduct. The PS-PPh<sub>3</sub> (**42**) and CCl<sub>4</sub> (or I<sub>2</sub>) mixture has been extensively employed for the synthesis of various dipeptides from *N*-protected (Cbz, Boc or Fmoc) amino acids and amino acid esters with high yields and negligible racemisation.<sup>49b,c</sup> The recipe for **42**/I<sub>2</sub> is also applicable for the synthesis of secondary, tertiary and Weinreb amides. In addition, this mixture was reported for amide formation in the total synthesis of natural products such as apocynin, pratiosine and hippadine.<sup>49e</sup> Polymer supported triphenylphosphine ditriflate (**43**) was easily generated from the polymer-supported phosphine with excess hydrogen peroxide and then subsequent treatment with triflic anhydride. This strategy was found to be useful as a general dehydrating reagent for amide formation from acids with an appropriate amine in the presence of DIEA as base and DCM as solvent.<sup>50</sup> Related anchored 1,1,3,3-tetraphenyl-2-oxa-1,3-diphospholanium bistriflate (**44**) was also employed for amide synthesis but was not explored further due to the number of steps required to synthesize it resulting in preference for reagent **43**.<sup>51</sup> Resins **42** and **43** were effective for amide formation and an extra

## Scheme 14. Peptide Synthesis Using Immobilized Phosphorous Containing Coupling Reagents



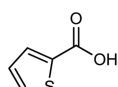

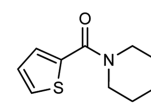
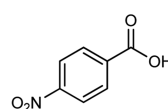
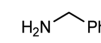
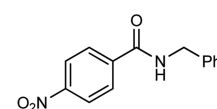
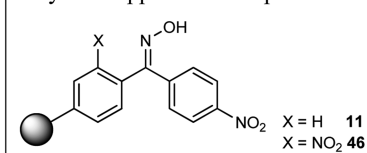
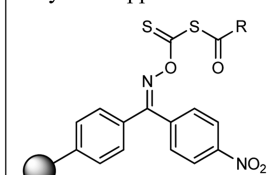
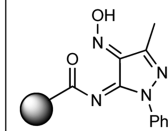
Acid	Amine	Coupling Reagent	Amide/Peptide	Yield (%) <sup>a</sup>	Ref
Z-Gly-Phe-OH	H <sub>2</sub> N-Val-OMe	<b>41</b>	Z-Gly-Phe-Val-OMe	80	[48]
Boc-Aib-OH	H <sub>2</sub> N-Val-OMe	<b>41</b>	Boc-Aib-Val-OMe	76	[48]
Boc-Aib-OH	H <sub>2</sub> N-Phe-OEt	<b>41</b>	Boc-Aib-Phe-OEt	75	[48]
Z-Met-OH	H <sub>2</sub> N-Ala-OMe	<b>42</b>	Z-Met-Ala-OMe	98	[49c]
		<b>42</b>		87	[49d]
		<b>43</b>		96	[50]

Table 7. Polymer-Supported Oxime Coupling Reagents

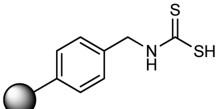
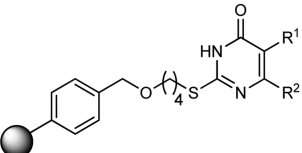
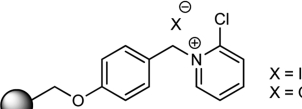
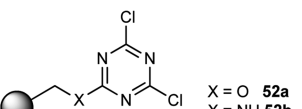
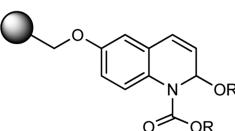
Entry	Name and Structure	Ref
<b>46</b>	Polymer-supported benzophenone oximes (Kaiser resin, X = NO <sub>2</sub> )  X = H <b>11</b> X = NO <sub>2</sub> <b>46</b>	[52-54]
<b>47</b>	Polymer-supported oximino dithiocarbonic anhydrides 	[55]
<b>48</b>	Polymer-supported 1-phenyl-3-methyl-4-oximino-5-iminopyrazole 	[56]

benefit was that the polymers were obtained mainly as the recyclable phosphine oxide, **45**, byproduct.

**3.5. Immobilized Oxime Coupling Reagents.** As discussed earlier, the polystyrene bound p-substituted benzophenone oximes (**11** and **46**) (Scheme 5, Kaiser resin)<sup>52</sup> have found some applications in stepwise Boc/Bzl peptide syntheses.<sup>52a,b</sup> Their applications were extended to other amide

formations, since the bond between the first amino acid and the resin can be considered as an active ester. Various amides have been prepared by aminolysis on polystyrene supported oximino esters via recyclable oximes without loss of its performance.<sup>52c</sup> Related oxime-based coupling reagents are shown in Table 7. Kaiser oximes were reported for amide bond formation in the synthesis of piperazinedione and diazepinedione

Table 8. Miscellaneous Polymer-Supported Coupling Reagents

Entry	Abbreviation	Name and Structure	Ref
49		Polymer-supported dithiocarbamic acid 	[57-58]
50		Polymer-supported pyrimidinone  $R^1, R^2 = H, H$ 50a $R^1, R^2 = H, Me$ 50b $R^1, R^2 = Me, Me$ 50c	[59]
51		Polymer-supported <i>N</i> -alkyl-2-chloro pyridinium triflate (Polymer-supported Mukaiyama Reagent)  $X = I$ 51a $X = OTf$ 51b	[60]
52	PS-DCT	Polymer-supported 2,4-dichloro(1,3,5)triazine  $X = O$ 52a $X = NH$ 52b	[61]
53	PS-EEDQ (R = Et)	Polymer-supported 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline	[62]
54	PS-IIDQ (R = <i>i</i> -Bu)	Polymer-supported 2-isobutoxy-1-isobutoxycarbonyl-1,2-dihydroquinoline 	[63]

libraries.<sup>52d</sup> Moreover, the Kaiser oxime active esters were modified and utilized as a fluorescence labeling method.<sup>53</sup> Several amides were prepared employing a resin-to-resin acyl transfer technique in which the oxime resin-derived active esters were reacted with Wang resin bearing an amine nucleophile in the presence of HOSu in DCM.<sup>54</sup>

Related to the Kaiser oxime resin, polystyrene attached oximino dithiocarbamic anhydride (47), is another class of supported coupling reagents particularly for aminolysis.<sup>55</sup> The reagent 47 was prepared from the Kaiser resin and carbon disulfide with aqueous NaOH to give oximino sodium dithiocarbonate intermediate resin; which upon further treatment with an acyl chloride yielded the final product. These mixed thioanhydrides reacted with amines (aliphatic or aromatic) to yield amides (46–70%) in solution and reusable oximino dithiocarbamic acid resin.<sup>55</sup>

Polymer-bound 1-phenyl-3-methyl-4-hydroxyiminoxyppyrazole (48) was synthesized via several steps from Merrifield's resin and numerous supported active esters of *N*-protected amino acids were prepared.<sup>56</sup> These active esters were established to be highly reactive for *N*-acylation reactions, which were examined for the preparation of several dipeptides that were obtained in good to excellent yields (52–98%) in shorter times (within 10 min) and progress of the reactions can be easily recognized by the color

change of the resin. The authors did not mention about the recyclability of this reagent.<sup>56</sup>

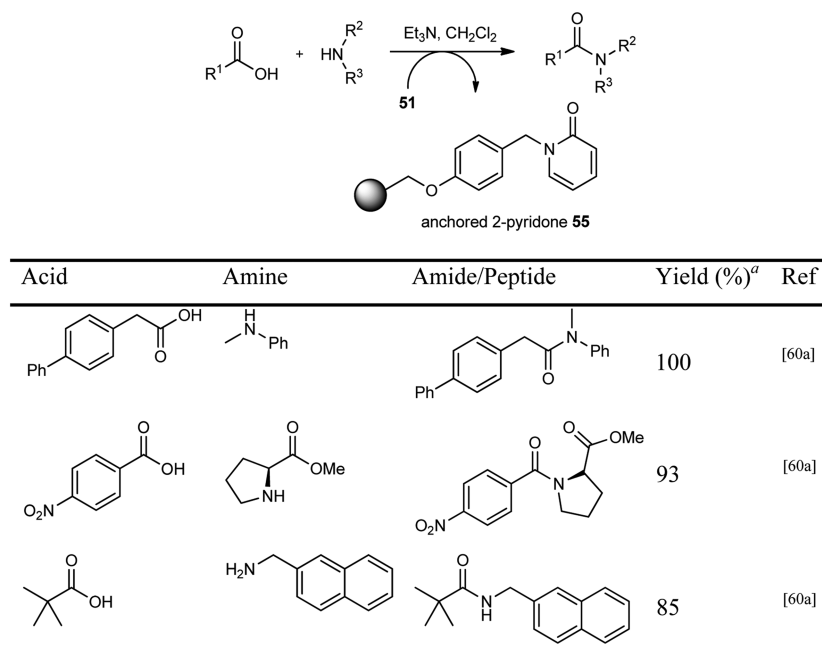
**3.6. Miscellaneous Immobilized Coupling Reagents.** A new class of regenerable polymer-supported dithiocarbamic acid (49) was applied for amide and peptide synthesis. This resin with *N*-protected amino acids in the presence of DCC gave *N*-protected amino acyl dithiocarbamic anhydrides, which subsequently reacted with amino acid esters to provide the corresponding dipeptides.<sup>57</sup> Similar to this reagent, polymer-bound hydroxamic dithiocarbamic anhydride was also used as an acylating agent for the preparation of amides.<sup>58</sup> Some of the miscellaneous polymer-bound coupling reagents are shown in Table 8.

Solid-supported pyrimidinones, 50, reacted with various acyl chlorides for the preparation of polymer-bound pyrimidines. The latter yield rapid and selective acylation of amines under microwave irradiation conditions to afford the corresponding amides in less than 3 min with high purity. In addition, the resulting polymer-bound pyrimidinone can be regenerated and reused for several coupling reaction cycles.<sup>59</sup>

*N*-Alkyl-2-halopyridinium salts (Mukaiyama reagents), such as *N*-methyl-2-chloropyridinium iodides, are familiar activating reagents for the conversion of carboxylic acids to esters and amides.<sup>64</sup> Thus, the supported version of this reagent, 51, has the



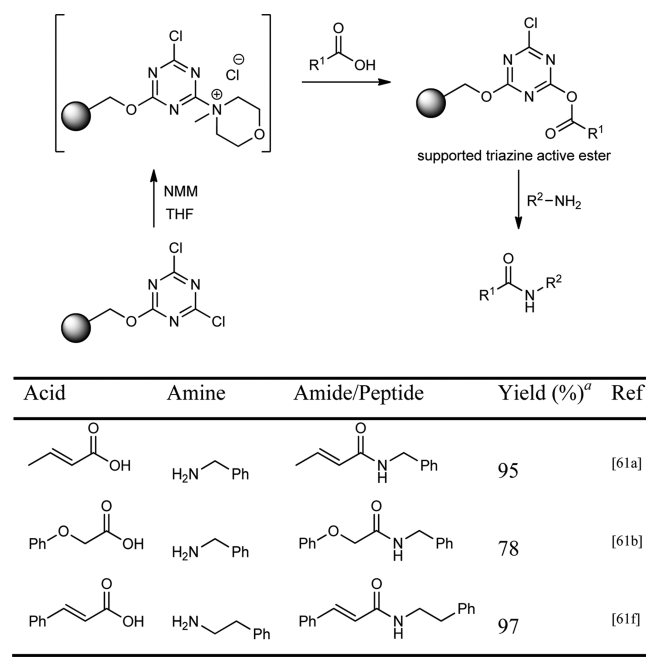
## Scheme 15. Amide Synthesis using Polymer-Bound Mukaiyama-Related Reagent



potential to reduce the purification processes and remove the polymer-supported 2-pyridone (**55**) byproduct by filtration (Scheme 15). This resin has proven to be a perfect coupling reagent for the synthesis of amides, even with poorly nucleophilic amines (*N*-methylaniline) in the presence of TEA or DIEA as base and DCM as solvent.<sup>60a</sup> The bound Mukaiyama reagents (2-chloro-1-methylpyridinium chloride/iodide) failed to form  $\beta$ -lactams via the “Staudinger” reaction, but the modified spacer anchored Mukaiyama reagent (*N*-methylpyridinium iodide salts) facilitated this under ultrasound conditions with TEA as base.<sup>60b</sup> The parallel synthesis of 2-oxazolines from  $\beta$ -hydroxy amides were achieved utilizing such Mukaiyama reagents in which chemoselective formation of  $\beta$ -hydroxy amides formed from carboxylic acids and amino-alcohols. It seems that this coupling reagent is nonrecyclable and requires several methods for purification and conversion of **55** into **51**.<sup>60c</sup>

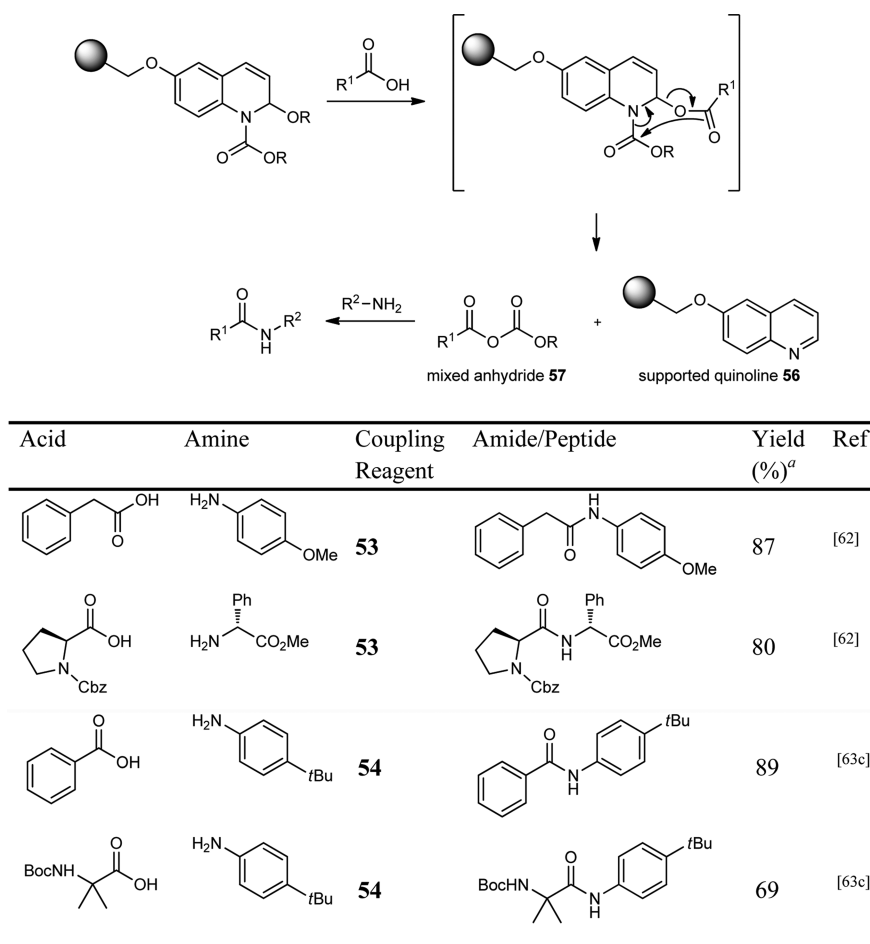
Triazines, such as 2,4,6-trichloro[1,3,5]triazine and 2-chloro-4,6-dimethoxy-[1,3,5]triazine, are well-known versatile and selective condensing agents for amide synthesis.<sup>65</sup> The first immobilized reagent of this type of family was the polymer-supported 2,4-trichloro[1,3,5]triazine **52**. Most commonly *N*-methylmorpholine (NMM) is utilized for the activation of chlorotriazines to give active morpholinium salts<sup>61a</sup> that are very reactive toward carboxylic acids, even in the absence of additives (HOBt, HOSu, etc.), to generate active esters (Scheme 16). These esters react with amine nucleophiles liberating high yields of the corresponding amides (60–87%), while being unreactive to oxygen nucleophiles. The best amide formation reactions yielded 90–95% of products (less than 5% racemization) with various resin supports (other than Wang resin), for example polystyrene-poly(ethylene glycol) cross-linked chlorotriazine. Although, the authors did not try to recycle the resin, they did mention that it would be possible.<sup>61a</sup> The PEG 4000-loaded 4,6-dichloro[1,3,5]triazine was employed on benzoic acid derivatives in the presence of NMM to give supported activated esters, followed by aminolysis with aliphatic and aromatic amines to produce the corresponding amides in good yields (66–91%).<sup>61c</sup> The resin bound dichlorotriazine group (DCT)

## Scheme 16. Amide Synthesis using Polymer-Supported Triazine Reagent



was utilized as a chlorinating agent of carboxylic acids to form acyl chlorides followed by condensation with a variety of amines to give the corresponding amides in good yields.<sup>61b</sup> Moreover, 2,4,6-trichloro[1,3,5]triazine was reacted with tetra(ethylene glycol) to form bis(dichlorotriazino)ether and further copolymerization with tris(2-aminoethyl)amine which resulted in the monochlorinated copolymer. This copolymer is insoluble in many common solvents and it has a high loading dehydrocondensing activity. This insoluble resin was employed for amide synthesis from dehydro-condensation of various carboxylic acids with amines by in situ formation of active morpholinium salts in the presence of NMM in DCM as solvent. Investigations and

Scheme 17. Amide Synthesis through Mixed Anhydride Using PS-EEDQ (53)/PS-IIDQ (54) Reagents



suitable methods are under process for recycling these copolymerized polymers.<sup>61d-f</sup>

2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (PS-EEDQ, 53) and 2-isobutoxy-1-isobutoxycarbonyl-1,2-dihydroquinoline (PS-IIDQ, 54) were more recently developed supported-coupling reagents for amidation. These resins retained their reactivities for several months when stored under laboratory conditions. PS-EEDQ (53) was applied to the peptide synthesis for both N- and O-protected amino acids and was capable of forming amide bonds without any additives or bases, from the selective coupling of acids with aliphatic amines even in the presence of aromatic amines. The amide bond formation occurs via a mixed anhydride (57) activation step (Scheme 17). The supported quinoline byproduct, 56, can be recycled up to 3–4 times.<sup>62</sup> Reagent PS-IIDQ (54) was found to be more efficient than other commercially available supported resins (PS-EDC, PS-DCC) and also superior than the popular HATU for amide synthesis with good yields and high purity without any preactivation process.<sup>63a,c</sup> There was no influence of the order of addition of the amine, acid or coupling reagent to form the amides. PS-IIDQ (54) was evaluated for the first time in the bioconjugation of hapten protein synthesis.<sup>63d</sup> Even sterically hindered amino acids such as phenylglycine or Aib gave higher yields with negligible amount of racemisation. It was also developed for a flow synthesis process, generating anhydrides from Fmoc-protected amino acids that subsequently passed through a column containing PS-HOBt (21), forming activated amino esters which are ready for the peptide coupling step.<sup>63b</sup>

**3.7. Polymer-Supported Bases.** Traditionally, peptide synthesis involves the addition of a base before or during coupling reactions. In the presence of a base, the amino acid converts to a carboxylate, which reacts with uronium/aminium salts to form active esters. 4-(*N,N*-Dialkylamino)pyridines such as 4-pyrrolidinopyridine or 4-(*N,N*-dimethylamino)pyridine (DMAP) are highly active mediums for the acylation of alcohols with carboxylic anhydrides or acyl halides.<sup>66</sup>

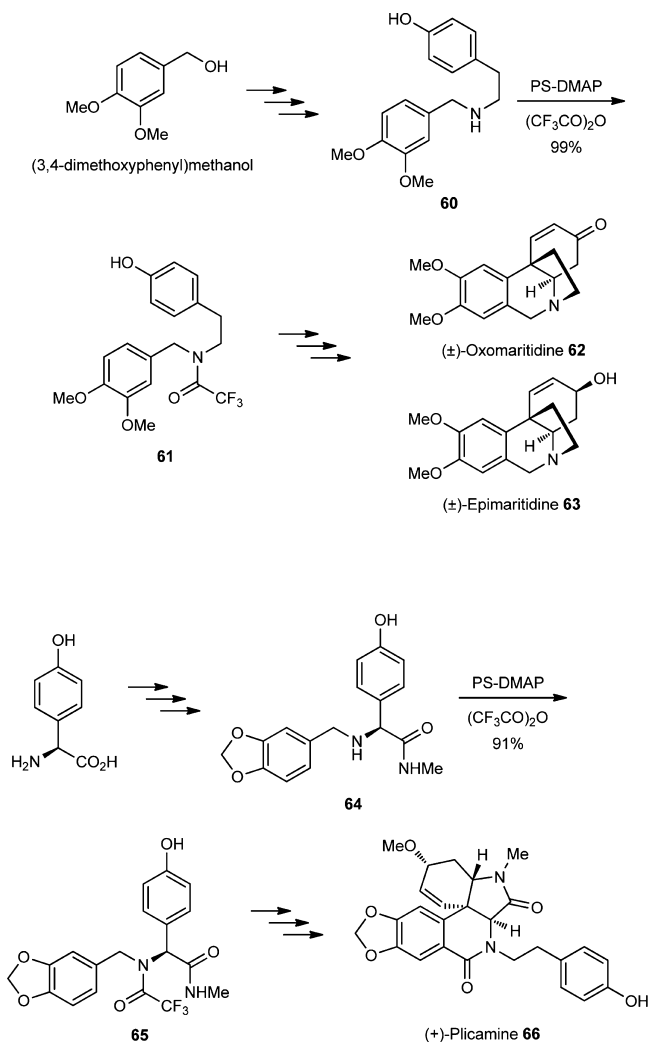
The polymer version of *N*-methylaminopyridine (PS-DMAP, 58) (Table 9) has been synthesized from chloromethylated

Table 9. Polymer-Supported Bases

Entry	Abbreviation	Name and Structure	Ref
58	PS-DMAP	Polymer-supported <i>N</i> -methylaminopyridine 	[66-68]
59		Polymer-supported morpholine 	[69]

polystyrene resins and the sodium salt of 4-(*N*-methylamino)pyridine. The polymer 58 could be recycled three times without a significant decrease in catalytic activity.<sup>66</sup> This reagent was for the first time employed as a mediator in two-polymeric systems

**Scheme 18. Trifluoroacetylation Using the PS-DMAP (**58**) Base for the Synthesis of ( $\pm$ )-Oxomaritidine, ( $\pm$ )-Epimaritidine, and (+)-Plicamine Alkaloids**



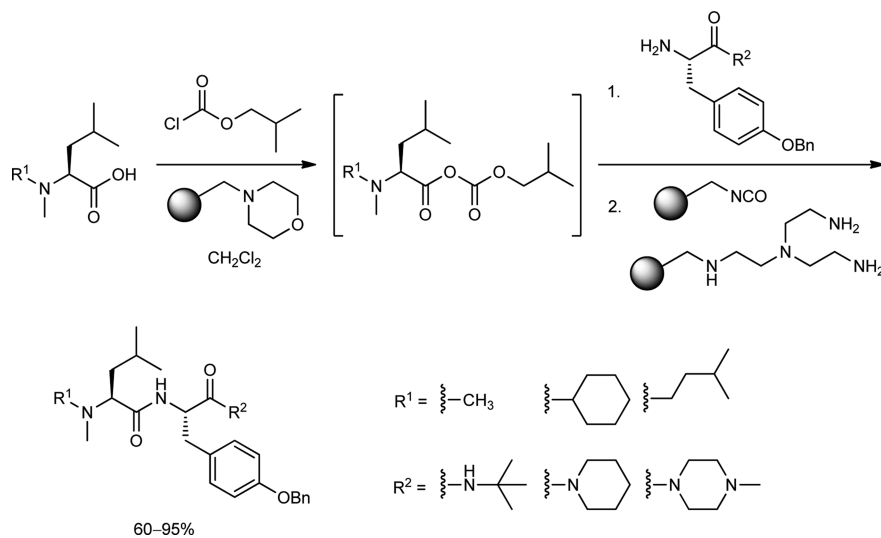
based on automated methodology for the preparation of peptides.<sup>67</sup> This method involves transferring the *N*-protected amino acid from one insoluble polymer (donor) such as a polymeric *o*-nitrophenyl ester (a “collection” of active ester) to an insoluble polymer-bound amino acid (acceptor), with the aid of a soluble mediator molecule (Shadchan). [Shadchan is the Hebrew term for a matchmaker, go-between, or agent.] Moreover, **58** was shown to be the polymer of choice and revealed that it was more reactive than the corresponding polymeric *o*-nitrophenyl esters. Treatment of **58** with acid chlorides (acetyl chloride, tosyl chloride, isobutyl chloroformate, and other electrophilic species) formed *N*-substituted pyridinium salts, which were subsequently transferred to a mediator (Shadchan) molecule. These salts with carboxylic acids released mixed carbonic-carboxylic anhydrides that reacted with amines to form the required peptides and a library of dipeptides were prepared in solution by this activation technique.<sup>67</sup>

Trifluoroacetylation of secondary amines (**60** and **64**) with trifluoroacetic anhydride in the presence of **58** rendered the amides (**61** and **65**) in 91–99% yields with high purities during the total synthesis of natural products such as ( $\pm$ )-oxomaritidine (**62**), ( $\pm$ )-epimaritidine (**63**),<sup>68a</sup> and (+)-plicamine alkaloids (**66**) (Scheme 18).<sup>68b</sup> PS-DMAP (**58**) was employed in a continuous flow process for releasing the free amine from its salt (amino acid ester hydrochloride), which was then passed through a HOBt-activated Boc or Cbz protected amino ester column for formation of the new amide bonds.<sup>63b</sup>

Polymer-supported morpholine **59** is a base that activates the *N,N*-disubstituted leucine acid for reaction with isobutyl chloroformate and subsequent formation of a mixed carbonic-carboxylic anhydride, followed by addition of tyrosine amine leading to the *N,N*-disubstituted-Leu-Tyr-OBn dipeptides in 60–95% yields and 80–98% purities. Excess starting materials were scavenged by the addition of polymer-supported isocyanate and tris(2-aminoethyl)amine resins (Scheme 19).<sup>69</sup>

3-Aminoimidazo[1,2-*a*]pyridines and pyrazines was derived from 2-aminopyridine, an aldehyde, and an isonitrile *via* a three-component condensation and could be further functionalized by reacting with an acid chloride in the presence of a polymer-supported morpholine resin as a catalyst. Removal of excess acid

**Scheme 19. Amide Synthesis Using Polymer-Supported Morpholine (**59**)**



chloride was achieved by treatment with polymer-supported tris(2-aminoethyl)amine.<sup>69b</sup>

**3.8. Conclusions.** Polymer-supported coupling reagents are extremely convenient for the synthesis of amides/peptides in solution. The resin activates a substrate which then affords the product into the solution and the byproduct remains attached to the insoluble polymer negating the need for chromatographic purification. Moreover, the cross-linked polystyrene reagent can be regenerated for reuse after the facile separation, or will lead to anchored residual products that, if the appropriate chemistry is available, could be recycled. In addition, polymer-bound reagents provide the possibility of automation in the case of repetitive stepwise syntheses and the facility of carrying out reactions in flow reactors on a commercial scale. In last six decades, a huge number of polymer-supported coupling reagents have been developed for amide/peptide bond formation and it will be no surprise that more immobilized coupling reagents will be developed and introduced in the near future.

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### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

The work carried out in the author laboratories is partially funded by the CICYT (CTQ2012-30930), the Generalitat de Catalunya (2014 SGR 137), and the Institute for Research in Biomedicine-Barcelona (IRB Barcelona) (Spain); the National Research Foundation (NRF), the University of KwaZulu Natal (South Africa); and SENESCYT (Ecuador)

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