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Review

Applications of Polymeric Reagents in Organic Synthesis

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Summary. Polymer supported reagents have found many applications in recent years. Scientists in research laboratories of agrochemical and pharmaceutical industries now routinely utilize these compounds to prepare ensembles of small organic molecules for screening. This review is aimed to highlight some of the most important applications of these promising materials in organic synthesis. Furthermore, an extensive listing of polymeric reagents that were recently used in organic synthesis is included.

Keywords. Synthesis; Polymeric reagent; Solid-supported reagent; Polymeric catalyst.

Introduction

The use of polymer-supported species in both syntheses and separations is steadily increasing and the applications in industry continue to grow [1–12]. Medicinal chemists in the pharmaceutical industry now routinely utilize polymer-supported reagents to prepare ensembles of small organic molecules [2, 8, 13]. Using polymeric materials as supports, solid supported reagents, or scavengers have had a great influence in organic synthesis, work-up, and purification of the products.

Until *Merrifield* introduced the concept of solid-phase peptide synthesis in 1963 all chemistry was performed in solution-phase [14]. In 1962, *Merrifield* utilized a functionalized and nitrated styrene-divinylbenzene copolymer for synthesizing a tetrapeptide (Scheme 1) [15]. This polymer was reacted with an amino acid with its amino group protected by a carbobenzoxy group. For deprotecting the amino group of the product, he utilized a HBr/HO*Ac* mixture. For chain extension, the product was reacted with another carbobenzoxy-protected aminoacid, and at the end of the reaction, the polymer linkage was cleaved by saponification. The manipulations required for the synthesis of a polypeptide chain consist simply of pumping the proper solvents or reagents into and out of the vessel containing the polymer in the proper sequence and timing. It was obvious to *Merrifield* that the simplicity of the steps involved in this process could be automated. Thus, he constructed an apparatus which performed all these operations automatically [16–18]. The ease of solid phase synthesis (SPS) compared with the labour and time to produce a tetrapeptide by conventional solution approaches was sufficient to attract considerable attention of the scientists.

Method A: Solid Phase Synthesis

In solid phase synthesis (*Merrifield*-type synthesis) (Scheme 2 [5]: method A) the substrate is the material which is attached to the support, and it is cleaved

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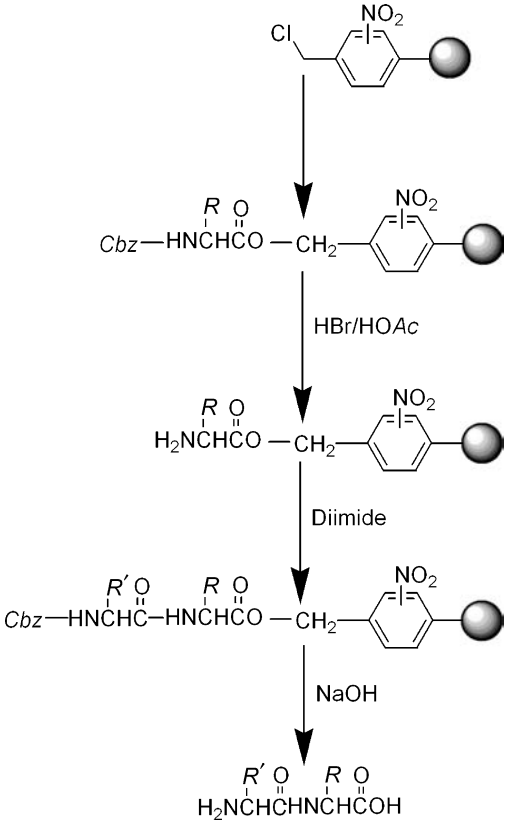


Scheme 1

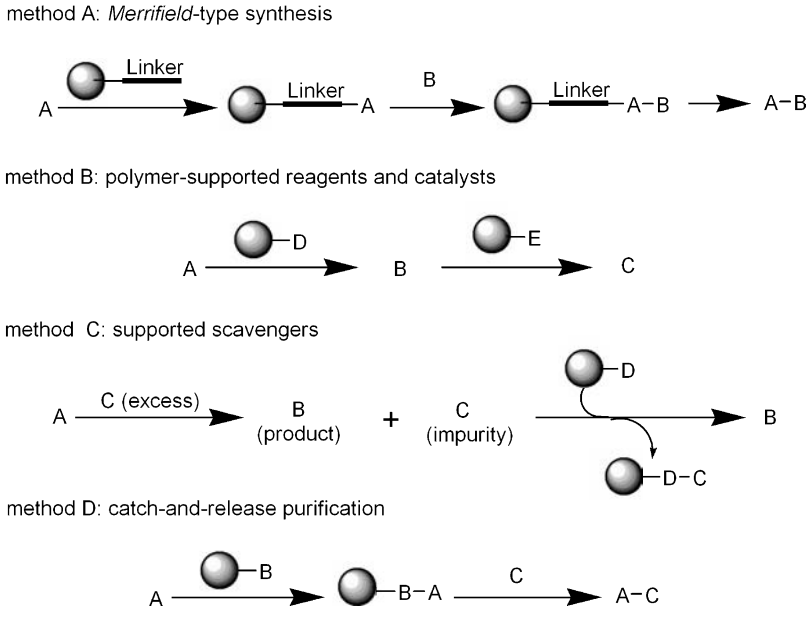
from the support in the final step. Although *Merrifield*-type synthesis has gained a lot of attention and success, the limitations of this method in comparison to solution phase techniques seem to be worth noting [2, 5]:

1. Monitoring the progress of the reactions is not an easy task even though advanced techniques have been employed in solid phase synthesis in recent years.
2. The need for two additional synthetic steps, *i.e.*, attaching the starting material to the resin and detaching the material from the resin.
3. Sometimes because of the poor loading and swelling features of the resin, it is necessary to make use of a solvent, which may not be optimal for the chemistry of the reactions involved.
4. The need to re-optimize solution phase chemistry on the solid support.
5. Convergent synthesis is not possible.
6. Every functional site needs to react.
7. The reactions can be slower than solution phase synthesis.

To overcome part of these problems and combine the desirable features of solution- and solid-phase synthesis, some promising innovative methods have been developed as shown in Scheme 2.

Method B: Polymer Supported Reagents and Catalysts

In this method the polymer supported reagent or catalyst causes a chemical transformation of the substrate



Scheme 2

which is present in solution. It should be emphasized that in contrast to method A, in this process substrate is not attached to the support.

Method C: Supported Scavengers

In this process, all reactions are completed in solution and at the final stage the desired product is purified *via* the polymeric reagent, which selectively reacts with by-products and impurities [2, 11].

Method D: Catch-and-Release Purification

In the catch–release method (D), in contrast to method C the product reacts or is absorbed selectively by the support, and is thus separated from impurities and a pure product is obtained [12].

Synthesis using solid supported reagents has emerged as one of the most promising approaches to drug discovery and is now a widely used technology. In most cases the separation of the supported materials from the reaction mixture is easy, and so robots can carry out all the manipulations required. Therefore, this method is attractive and suitable for ensemble generation and parallel synthesis. It has been subject of many review articles [1–12]. In summary, the advantages of this approach are as follows [2, 5]:

1. Supported reagents can be isolated from the reaction mixture without work-up using a simple filtration to yield a solution of the pure product. Thus, the chemistry is suitable for automation.
2. To drive the reaction to completion, it is possible to use an excess of reagent without complicating the work up procedure.
3. No residual functionality from bead attachment in the final product.
4. Supported catalysts and reagents are safer, less toxic, more stable, and easier to handle.
5. New (or better) selectivities.
6. The spent reagent can be potentially reused after recovery and regeneration.
7. The scale-up and optimization of the reaction is easy.
8. Monitoring the progress of the reactions is easy by using conventional techniques, such as TLC, LC-MS, GC-MS, etc.
9. Convergent synthesis is possible.
10. Polymer supported reagents can be used in flow systems [19–22].
11. Polymeric reagents (e.g. scavengers) can be used for purification of the reaction mixture from by-products and impurities.

The popularity of polymeric reagents is rapidly growing as based on the number of publications, presentations, and meetings demonstrating their vast potential. This review is aimed to highlight some recent applications and trends in polymer-assisted solution-phase synthesis.

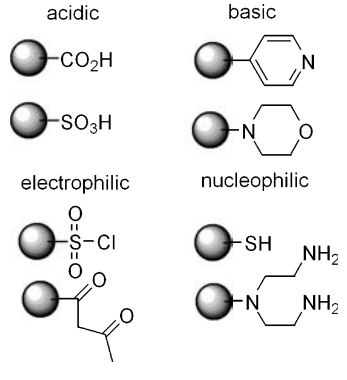
Polymer Supported Purification

The removal of an excess of a reagent, unreacted starting materials, or by-products in the end of the reaction is a critical step in every organic synthesis. Extraction and chromatographic purification are commonly used. These steps can be avoided by using polymer supported reagents. Some of the most widely used purification protocols are as follows: a) solid supported scavengers [2, 11], b) sequestration enabling reagents, c) tagging reagents [23], and d) catch and release purification [12].

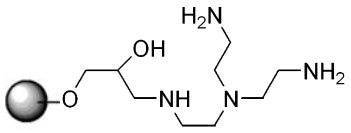
These methods are discussed in the following sections.

Solid Supported Scavengers

Many review articles have been published in this context in recent years [2, 11, 24–29]. Scavengers are functionalized resins and designed in such a way that they selectively react with impurities in the reaction mixture. After the reaction completion, polymer-bound impurities can be easily removed by filtration and pure products are obtained. Scavenging reagents



Scheme 3



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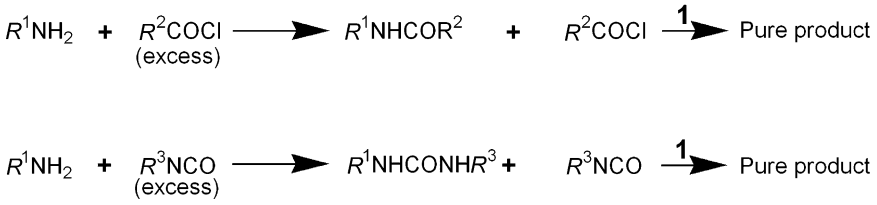


Scheme 4

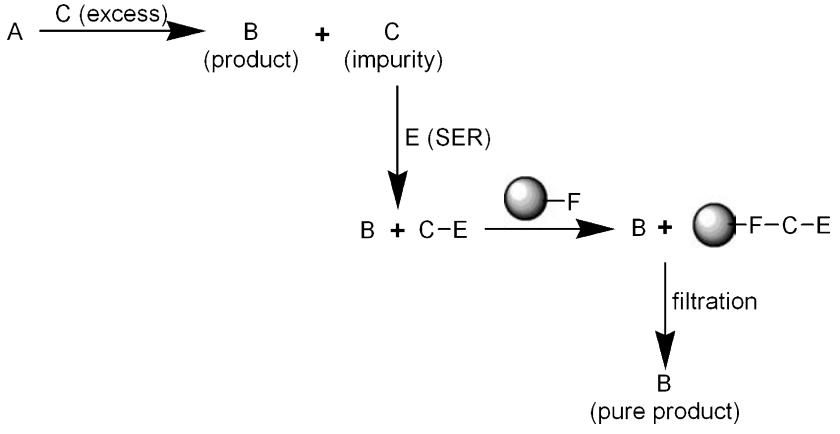
can be roughly divided into two categories [11]: ionic scavengers (acidic or basic reagents) and covalent scavengers (electrophilic or nucleophilic reagents) (Scheme 3).

Chesney et al. recently demonstrated that cellulose beads could be used in polymer assisted solution synthesis by examining the scavenging of excess electrophiles in simple well-established acylation reactions of several amines using the tris amino resin **1** (Scheme 4) [30]. In each case the amines were treated with an excess of the acylating reagent (both acid chlorides and isocyanates). After consumption of the amine was complete, the resin was added and the solution filtered and concentrated to afford the amide or urea in essentially pure form.

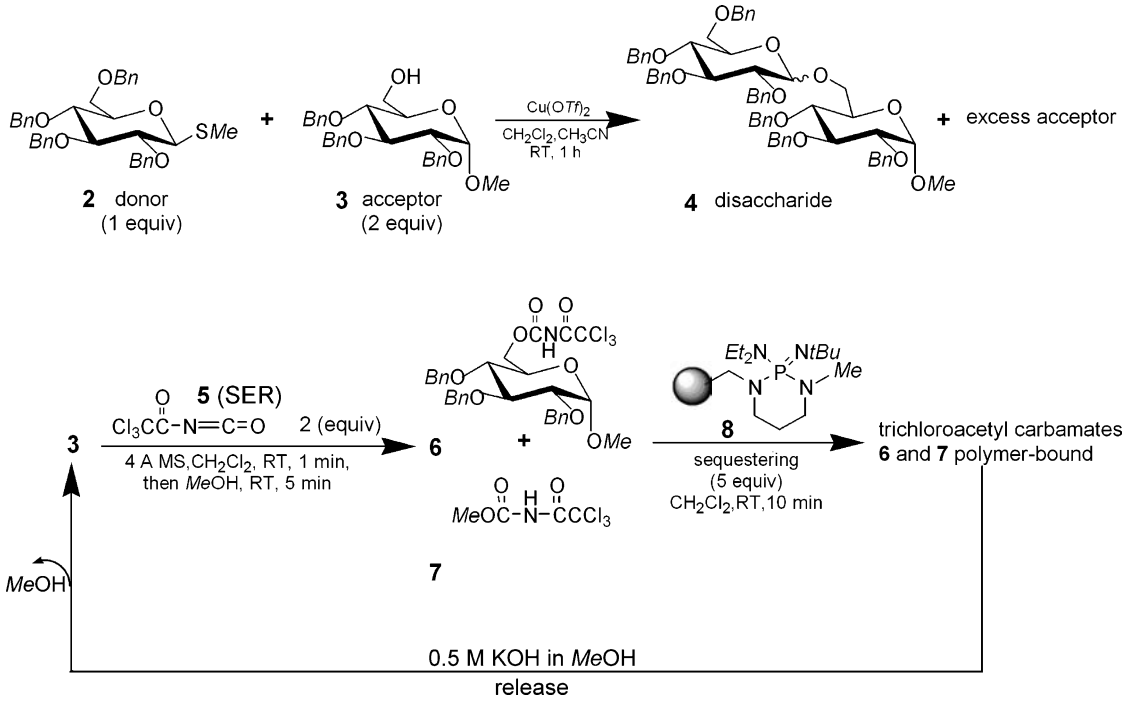
Sequestration Enabling Reagents (SERs)

These reagents are employed in cases that by-products are not reactive enough to be scavenged by functionalized polymeric scavengers. So, active bifunctional soluble compounds (SERs) are used to transform the poorly reactive molecule into an activated intermediate easily trapped by a scavenger (Scheme 5 [8]).

Dondoni et al. recently studied the synthesis of oligosaccharides by using trichloroacetyl isocyanate (**5**, TAI) as sequestration enabling reagent (SER) of sugar alcohols (Scheme 6) [31]. Once the glycosidation of the donor **2** was completed in the presence of a twofold excess of acceptor **3**, filtration of the reaction mixture was followed by aqueous workup and evaporation of the solvent to afford the target disaccharides **4** along with the unconverted acceptor **3** and other carbohydrate-containing by-products. The unconverted sugar alcohol **3** was scavenged by trichloroacetyl isocyanate **5** as SER. The urethane was obtained almost instantaneously under neutral conditions. Then, the reaction mixture was quenched with a large excess of *Me*OH that transformed unconverted TAI **5** into methyl urethane **7**. The solid-phase sequestration of **6** and **7** was carried out using the highly basic, non-nucleophilic polymer supported *BEMP*



Scheme 5



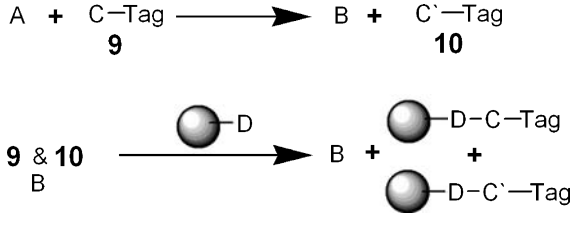
Scheme 6

8 to give urethanes bound to the polymer as ion pairs. So, the desired disaccharide was isolated as a mixture of anomers in high purity (80–95%).

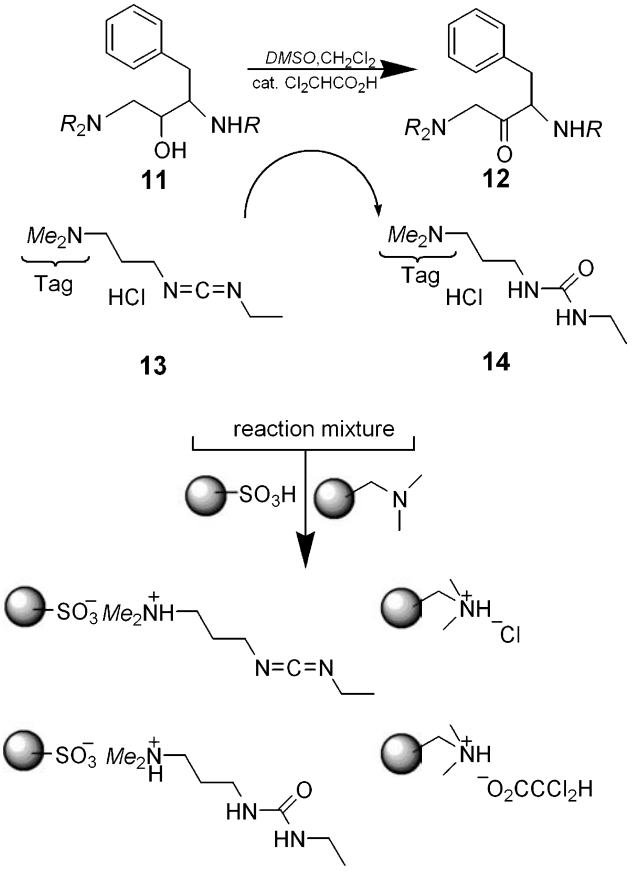
Tagging Reagents

Using tagged reagents is another approach in purification of the desired product [23]. Tagged reagents are soluble materials with a functional group that does not affect their reactivity. After the reaction completion, a polymeric scavenger is added to the reaction mixture to react with the functional group of the tagged reagent, which is preserved in the by-products (Scheme 7).

An example of a soluble, tagged reagent is given in Scheme 8 [32]. A tertiary amine tagged carbodiimide **13** was applied to the oxidation of alcohols. At the end of the reaction using a combination of both



Scheme 7



Scheme 8

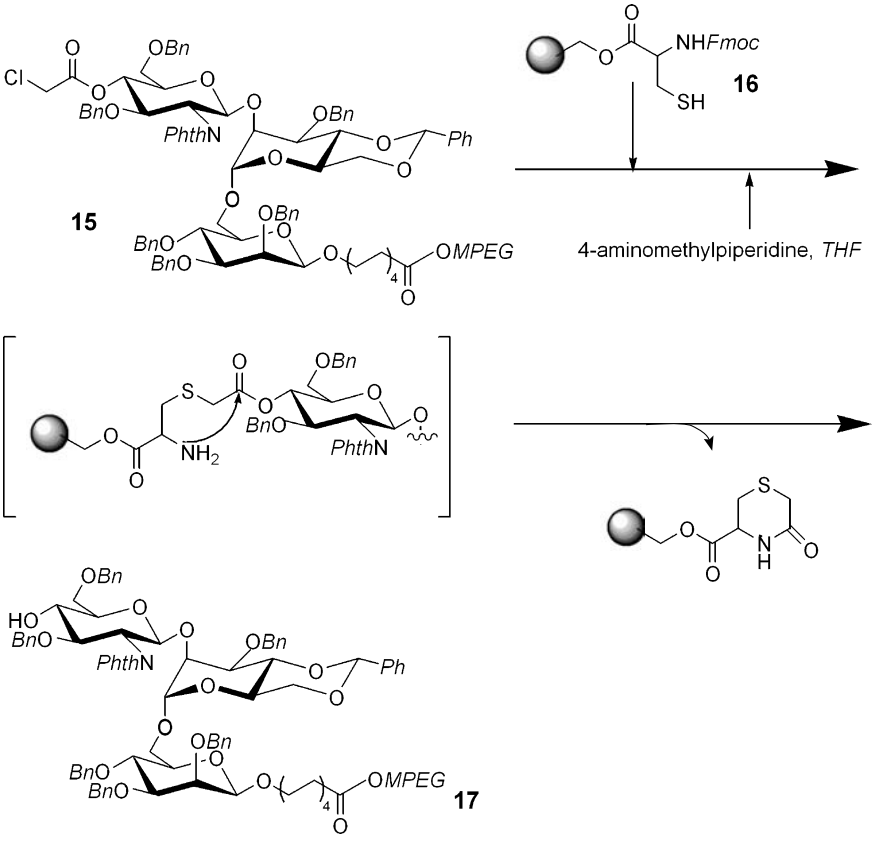
acidic and basic resins the tagged urea **14** and excess carbodiimide **13** was removed from the reaction mixture. The basic resin neutralizes the HCl and also removes the dicholoroacetic acid. A sulfonic acid resin scavenges the tagged urea **14** and unreacted tertiary amine tagged carbodiimide **13**. Because acidic resin and basic resin do not interfere with one another, both processes can be accomplished simultaneously by employing two ion-exchange resins.

Catch and Release Purification

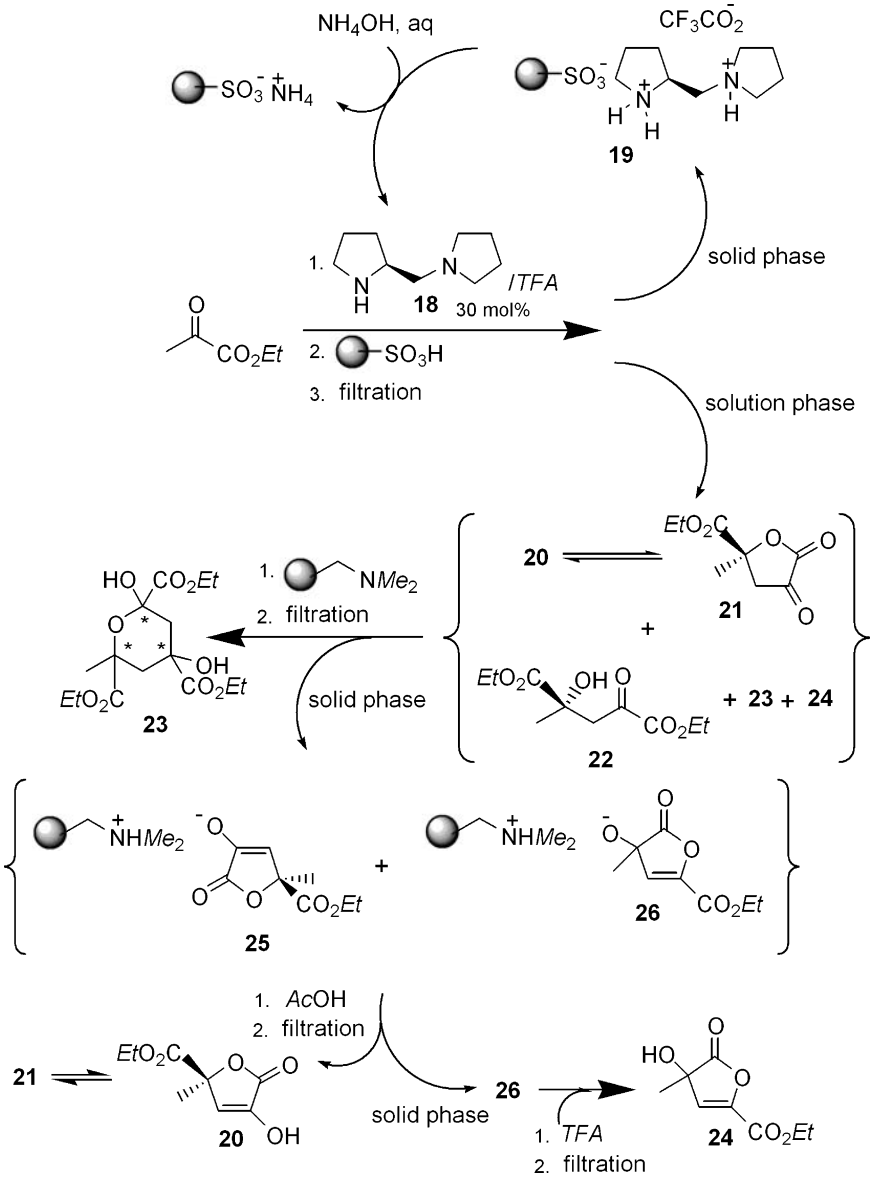
In this method, as mentioned in Scheme 2, the reactions are carried out in solution. After the reaction completion, a polymeric reagent is added to the reaction mixture, which selectively reacts with the product. After simple filtration and washing to remove soluble by-products, the polymer bound product is subjected to another transformation. As a consequence, the pure product is obtained [12].

This method has been used by *Ito et al.* in the synthesis of bisubstrate-type inhibitors of *N*-acetylglucosaminyltransferases [33]. The trisaccharide **15** was subjected to the catch-release purification. **15** was captured with cysteine-conjugated *Wang* resin **16** through a selective reaction between chloroacetyl and thiol groups. Liberation of an amino group by *Fmoc* deprotection with 4-aminomethylpiperidine initiated cyclization and the trisaccharide **17** was obtained (Scheme 9).

Synthesis of isotetronic acid, recently reported by *Dondoni et al.* [34], also clearly shows the high potential of these promising materials in organic synthesis (Scheme 10). To obtain a pure product, they used two strategies together, *i.e.* catch and release purification and purification by scavenging reagents. To separate the diamine **18** (catalyst), the crude reaction mixture was first treated with Amberlyst 15 (scavenger), and the mixture filtered to give a solid constituted of the sequestered catalyst **19**. This material when treated with aqueous ammonium hydroxide liberated the diamine **18**/*TFA* couple (70%) that remained in solution while the polymer-supported ammonium sulfonate was filtered off. After recovery of the catalyst, the solution containing the crude reaction mixture was treated with the basic resin



Scheme 9

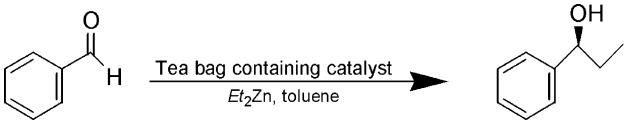


Scheme 10

Amberlyst 21 that induced the lactonization of the functionalized glutarate **22** to isotetronic acid **20**, and this was sequestered by the resin itself as the ammonium salt **25**. The same resin sequestered also the side product lactone **24** as the ammonium salt **26**. Filtration afforded a solution of the pure trimer **23**, which was recovered in 12% yield. The solid material containing **25** and **26** was then treated first with *Ac*OH that released exclusively the lactone **20** due to the weaker basic character of the conjugate base of **25** with respect to **26**. After filtration, the solution furnished the pure isotetronic acid derivative **20** in 55% yield and in the hydroxy free form as required for biological studies. The remaining solid material was treated with the stronger acid *TFA* to liberate the lactone **24** in less than 5% yield (catch-and-release strategy).

Tea Bags Technology

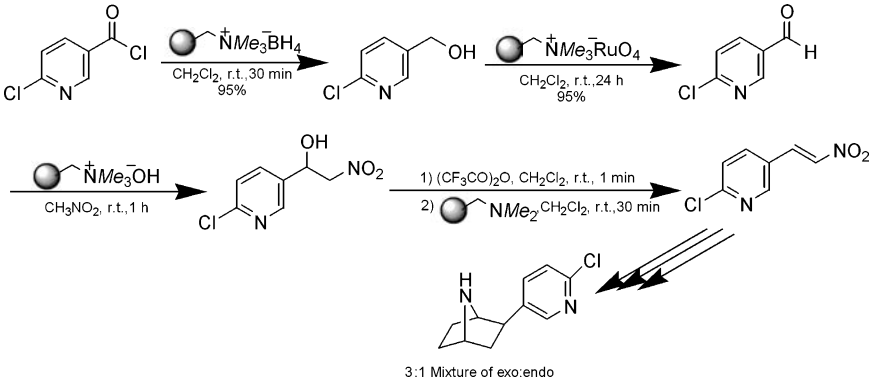
Reactions using polymer supported reagents can be carried out with the reagents in tea bags so that when the reaction is complete the tea bag is simply removed. *Seebach et al.* have devised a simple apparatus for this purpose [35]. The polymer supported reagent was contained within two circles of



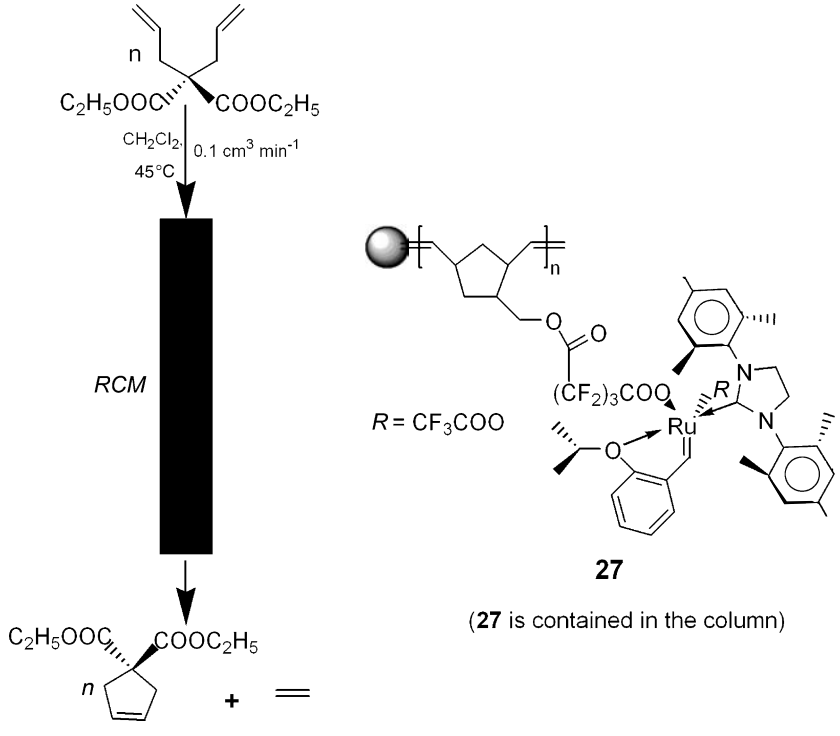
Scheme 11

polypropylene mesh (mesh size 0.1 mm) and sealed using nylon thread forming the tea bag. The tea bag was sandwiched between two glass grilles, and these in turn were placed into the apparatus, above a magnetic stirrer flea. A variety of enantioselective dialkylzink additions to aldehydes mediated by polymer-bound $\alpha,\alpha,\acute{\alpha},\acute{\alpha}$-tetraaryl-1,3-dioxolane-4,5-dimethanol titanates using this new apparatus have been carried out (Scheme 11). Although the polymer is held within a relatively small area of the apparatus, sufficient solvent circulation through the glass grilles and indeed through the tea bag is occurring. This catalyst can be used many times in successive reactions with excellent yields and minimal loss of activity or enantioselectivity.

Ley et al. employed this technique in the total synthesis of epibatidine (Scheme 12) [36]. The five-step reaction sequence of acid chloride to nitroal-



Scheme 12



Scheme 13

kene could be carried out in a one-pot procedure. When the reaction was judged to have reached completion the pouch was simply removed, washed, and replaced by the next, thus facilitating the filtrations between steps.

Flow Systems

This is a new area of study. In recent years several review articles have been published in this context [19–21]. The particle nature of polymer-supported reagents or catalysts makes it possible to let reactants flow through a bed continuously. In this technique, the solutions of the starting materials are introduced to the column including support, flow through it, and are then collected in a receiver. Three basic types of column system have been used; also, Pumping is usually necessary [19]. According to *Hodge* [20], advantages of flow systems are as follows: there is little or no reaction work-up, the supports suffered no physical damage in use, automation is relatively easy, and extension to continuous production, even on a large scale is possible.

Krause et al. [37] recently reported a long-term stable continuous flow system for ring-closing metathesis (RCM) with low leaching of ruthenium in the products (Scheme 13). Olefin metathesis and related reactions are among the most important C–C bond forming reactions. In order to avoid time-consuming and expensive cleaning issues related to catalyst removal, fixation of these catalysts is of prime importance. In this procedure, the reactant was dissolved in CH_2Cl_2. This solution was pumped through the column, and finally collected.

Automation

In the beginning of third millennium, humankind has encountered numerous obstacles. While we rebelled against many new diseases such as AIDS, there are many reports that obviously show that many organisms have resisted the common antibiotics. Thus, synthesis of novel drugs is of prime importance. On the other hand, considering the ever increasing activities in research laboratories of pharmaceutical and agricultural industries to synthesize new compounds, the necessity of designing new processes with greater time efficiency, which leads to more

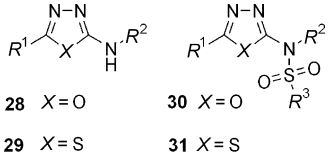


Fig. 1. 5-Substituted-2-amino-1,3,4-oxadiazoles **28**, 5-substituted-2-amino-1,3,4-thiodiazoles **29**, 2*N*,5-disubstituted 2-amino-1,3,4-oxadiazoles **30** and 2*N*,5-disubstituted-2-amino-1,3,4-thiodiazoles **31** [38]

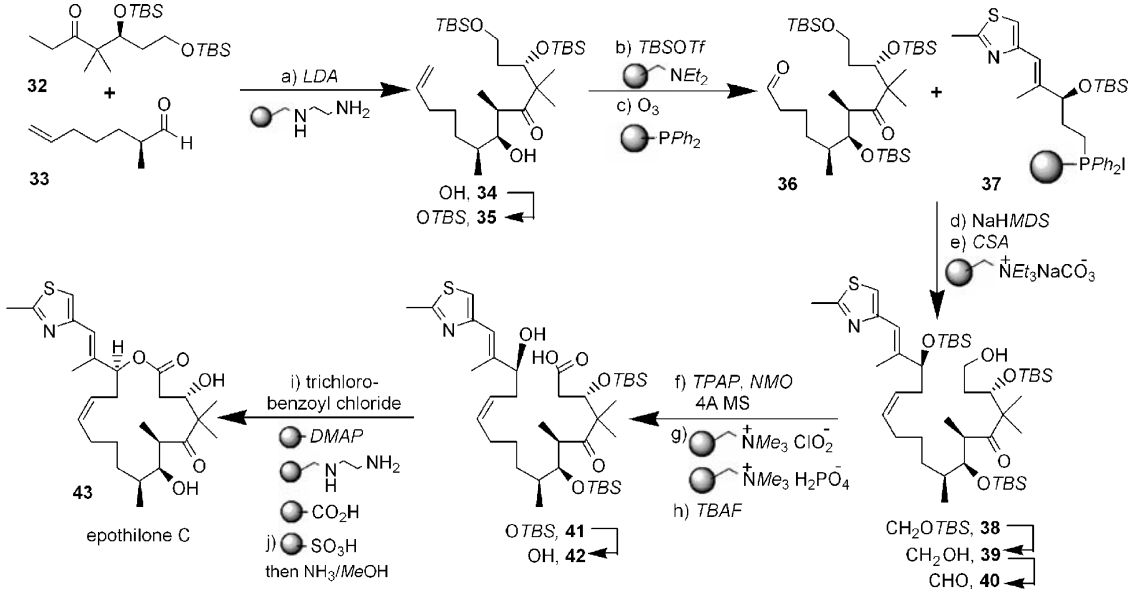
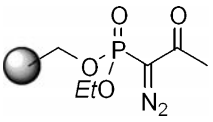
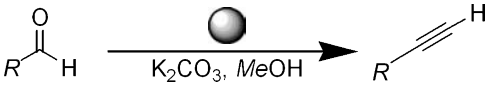
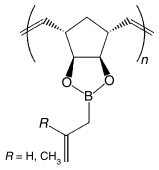
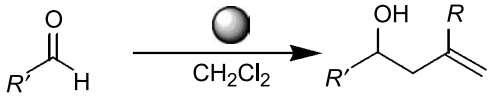
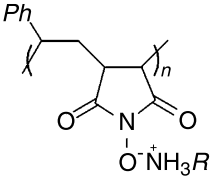
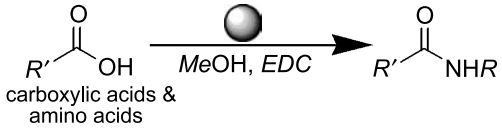
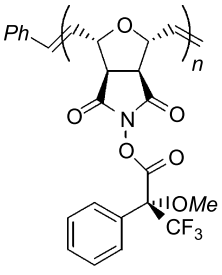
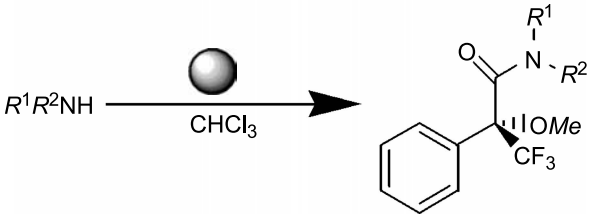
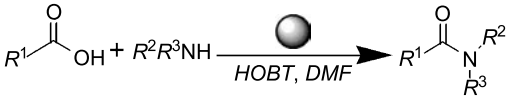
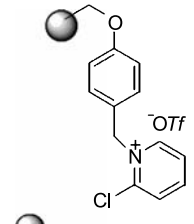
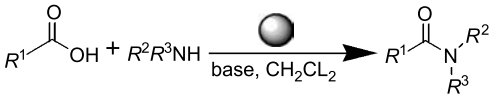
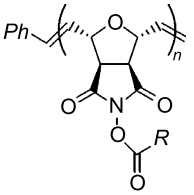
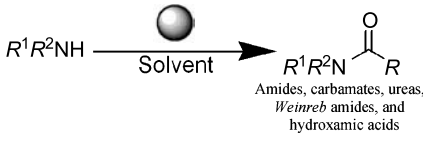


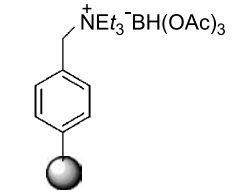
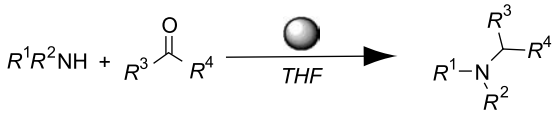
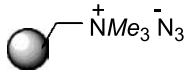
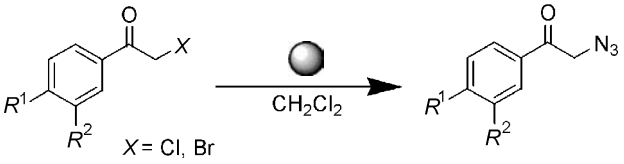
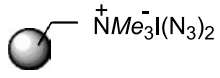
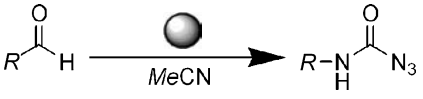
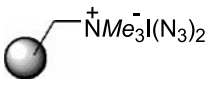
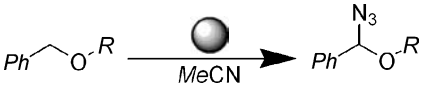
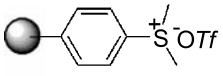
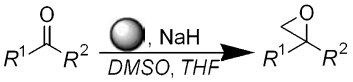
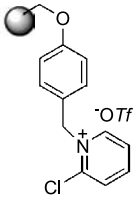
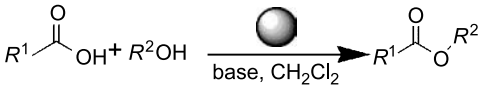
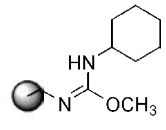
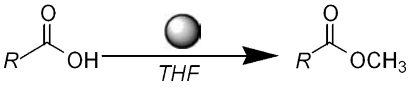
Fig. 2. *Ley*'s synthesis of the natural product epothilone C (three fragments **32**, **33**, and **37** also synthesized using polymeric reagents) [39]

Table 1. Representative examples

Polymeric reagent	Transformation	Yield %	Number of examples	Ref.
Alkynes				
 *ROMP*gel-supported ethyl 1-diazo-2-oxo-propylphosphonate		63–91	9	[40]
Allylboration of Aldehydes				
		49–96	18	[41]
Amidation				
	 carboxylic acids & amino acids	54–87	14	[42]
		80–94	12	[43]
PS-carbodiimide		81–100	11	[44]
 (= *Wang* resin)		15–100	14	[45]
	 Amides, carbamates, ureas, *Weinreb* amides, and hydroxamic acids	89–98	35	[46]

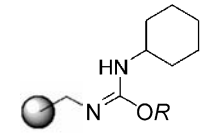
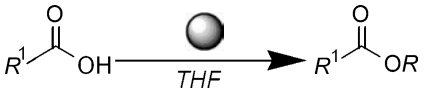
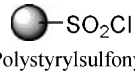
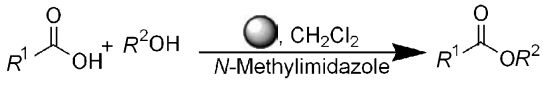
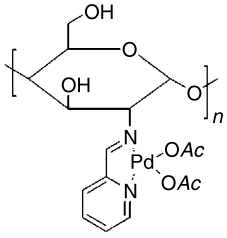
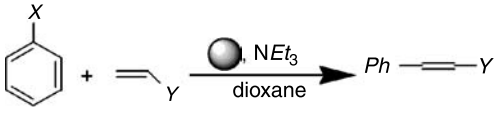
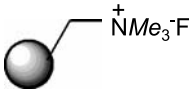
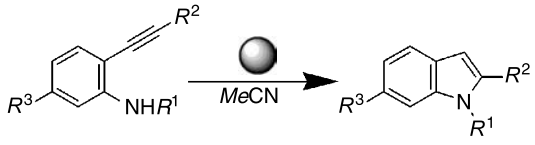
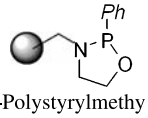
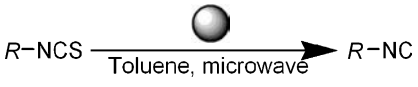
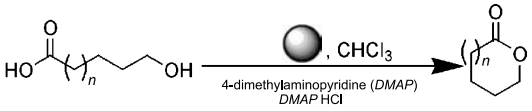
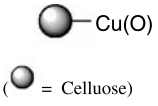
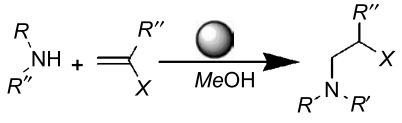
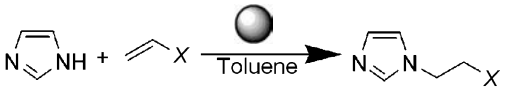
(*continued*)

Table 1 (*continued*)

Polymeric reagent	Transformation	Yield %	Number of examples	Ref.
Amination				
 *MP*-$BH(OAc)_3$		39–93	10	[47]
Azides				
 Amberlite IRA 900 Azide form		68–95	10	[48]
 Amberlyst A-26 Diazidoiodate form		87–96	5	[49]
 Amberlyst A-26 Diazidoiodate form		57–68	4	[49]
Epoxides				
 Sulfonium salt of copolymer of 4-vinylphenyl methyl sulfide and *JandaJel*		65–98	8	[50]
Esters				
 (= *Wang* resin)		45–100	15	[45]
 (= Polystyrene)		74–94	9	[51]

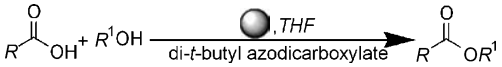
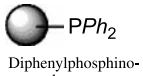
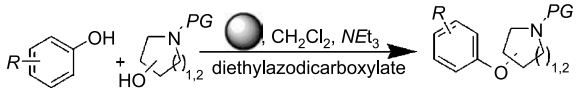
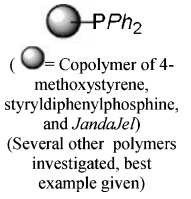
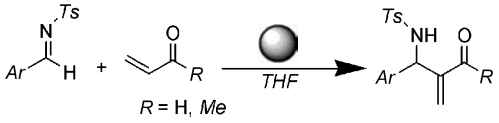
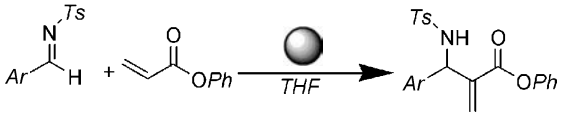
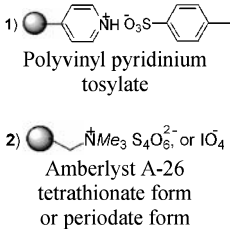
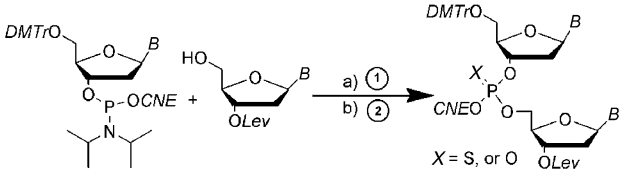
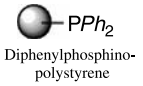
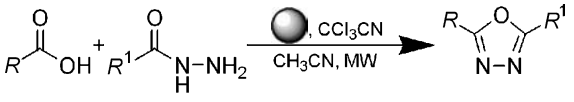
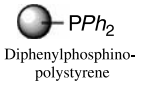
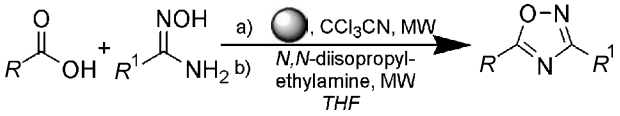
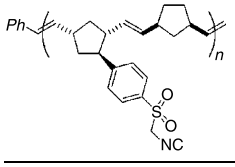
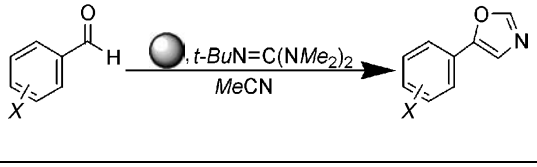
(*continued*)

Table 1 (*continued*)

Polymeric reagent	Transformation	Yield %	Number of examples	Ref.
 (*R* = allyl, benzyl, methyl) (= Polystyrene)		82–99	14	[52]
 Polystyrylsulfonyl chloride resin		87–100 (purity%)	13	[53]
Heck Reaction				
		87–88	2	[54]
Indoles				
 (Polystyrylmethyl)trimethylammonium fluoride		0–86	8	[55]
Isocyanides				
 3-Polystyrylmethy1-2-phenyl[1,3,2]oxazaphospholidine		54–96	6	[56]
Macrolactonization				
PS-carbodiimide		52–97	4	[57]
Michael Addition				
 (= Celluose)		90–98	24	[58]
		56–98	7	[58]

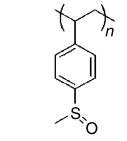
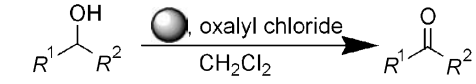
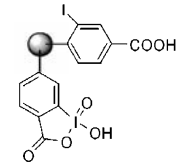
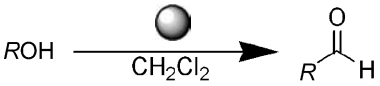
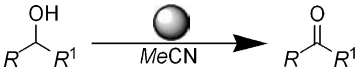
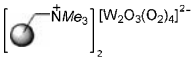
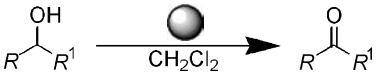
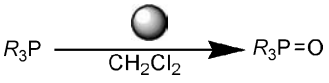
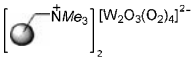
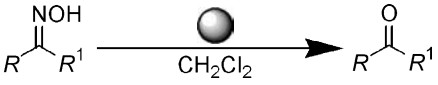
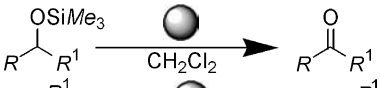
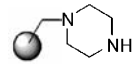
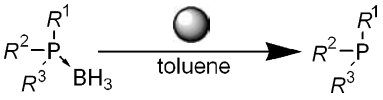
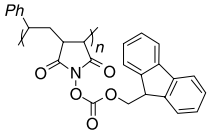
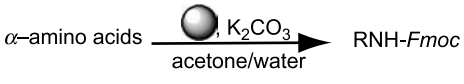
(*continued*)

Table 1 (*continued*)

Polymeric reagent	Transformation	Yield %	Number of examples	Ref.
Mitsunobu Reaction				
		78–91 (A resin synthesized from co-polymerised 4-bromopolystyrene compared with commercial one, best results given)	3	[59]
 Diphenylphosphino-polystyrene		61–99 (Several reaction conditions investigated, best conversions given)	8	[60]
Morita-Baylis-Hillman Reaction				
		0–97	6	[61]
		45–81	9	[61]
Oligonucleotides				
		73–96 (Yields for the overall procedure including detritylation or other reactions)	12	[62]
Oxadiazoles				
 Diphenylphosphino-polystyrene		80–99	11	[63]
 Diphenylphosphino-polystyrene		77–98	15	[64]
Oxazoles				
		46–90	12	[65]

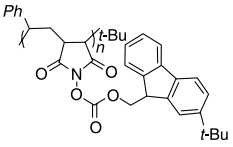
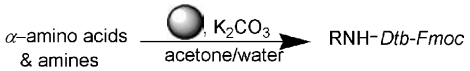
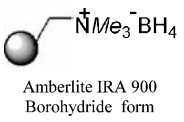
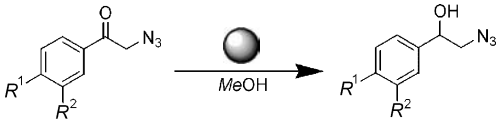
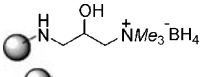
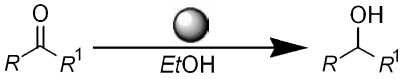
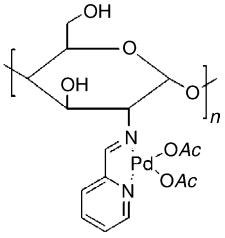
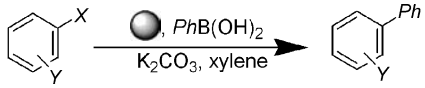
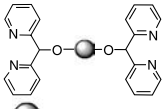
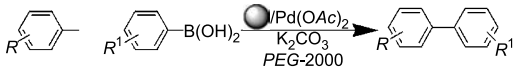
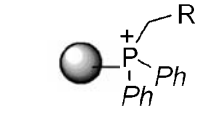
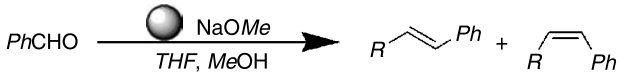
(*continued*)

Table 1 (*continued*)

Polymeric reagent	Transformation	Yield %	Number of examples	Ref.
Oxidation				
 Copolymer with *JandaJel*	 secondary alcohols	60–85	6	[50]
 (● = Copolymer of *p*-methylstyrene and divinylbenzene)		52–100 (Conversion %)	5	[66]
Amberlyst D-201 peroxodisulfate ($S_2O_8^{2-}$) form		65–97	9	[67]
 Amberlyst A-26 peroxotungestate form		80–97	21	[68]
		97–100	3	[68]
Protection and Deprotection				
Amberlyst D-201 peroxodisulfate ($S_2O_8^{2-}$) form		98–100	6	[67]
 Amberlyst A-26 peroxotungestate form		90	4	[68]
		90–95	4	[68]
 Piperazinomethyl polystyrene		68–100 (Several reaction conditions investigated, best conversions given)	10	[69]
		34–96	10	[70]

(*continued*)

Table 1 (*continued*)

Polymeric reagent	Transformation	Yelid %	Number of examples	Ref.
		76–96	8	[71]
Reduction				
 Amberlite IRA 900 Borohydride form		78–96	10	[48]
 (= Chitosan cross-linked with epichlorohydrin)		37–100	18	[72]
Suzuki Reaction				
		2–92	9	[54]
 (=Poly(ethylene glycol) (*PEG*))		45–98	15	[73]
Wittig Reaction				
 R=*Ph*, CO_2Et (= Copolymer of styrene and divinylbenzene)		48–61	2	[59]

structural variation seems more obvious. As a consequence, to discover active pharmaceutical compounds as well as agrochemicals, and other fine chemicals, generation of ensembles of compounds is of prime significance. However, parallel purification of products may be difficult. One of the most successful techniques to reduce the time spent for work-up or purification during organic synthesis is undoubtedly the use of polymer supported reagents. Extraction and chromatographic purification can be avoided by using these reagents, and so robots can carry out all the manipulations required. Therefore, these techniques have attracted the considerable interest of scientists, particularly in agricultural and pharmaceutical industries [2, 8, 13].

Recently, the *Ley* group described an efficient preparation of 5-substituted-2-amino-1,3,4-oxadiazoles and the corresponding thiadiazole analogues ensem-

bles (Fig. 1) [38]. These materials have attracted much attention in both agrochemical and pharmaceutical fields. To the rapid generation of combinatorial ensembles, two technologies were used together, *i.e.* solid supported reagents and microwave-assisted organic synthesis. Over 1500 compounds were produced during this program of work with high yield and purity. This example clearly shows the high potential of the method in medicinal research laboratories.

Natural Product Synthesis

An example will serve to illustrate the state-of-the-art with the polymeric reagents approach. This example is *Ley*'s synthesis of the cytotoxic antitumour natural product epothilone C (Fig. 2) that clearly shows the high potential of the methodology [39]. In this procedure, a series of polymer-supported reagents were used to effect the synthesis, including reagents, catalysts, and scavengers together with catch-and-release techniques to avoid frequent aqueous work-up and chromatographic purification. A key feature of this work is that a convergent synthetic strategy was applied. Moreover, the reactions involved in this process are stereoselective. This work paves the way to further developments in this area in the future.

Literature Survey

This section covers the most significant advancements during the period from January 2000–December 2006 on polymeric reagents and catalysts (Table 1). The most comprehensive review in this context was published in 2000 by *Ley et al.* [2]. Each reaction will be discussed briefly. Thus, the reader should consult the literature source for more detailed information.

Conclusion

Polymer assisted solution-phase synthesis is now a widely used technology both in academic and industrial context. It has become a prevalent method for the rapid generation and purification of solution-phase chemical libraries in the pharmaceutical or agrochemical industries in recent years. Polymeric reagents realize our wishes to reduce or even eliminate extraction and chromatographic purification steps since these are simply removed from the reaction mixtures by filtration. However, further applications in the future in industry is strongly depended on developing new high-loading, recyclable, and inexpensive supports. In this context, natural-based polymers, such as chitin, chitosan [74], cellulose, carrageenan, etc. can be of prime importance due to their biodegradability and non-toxicity. Therefore, the potential of these promising materials should be fully investigated.

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