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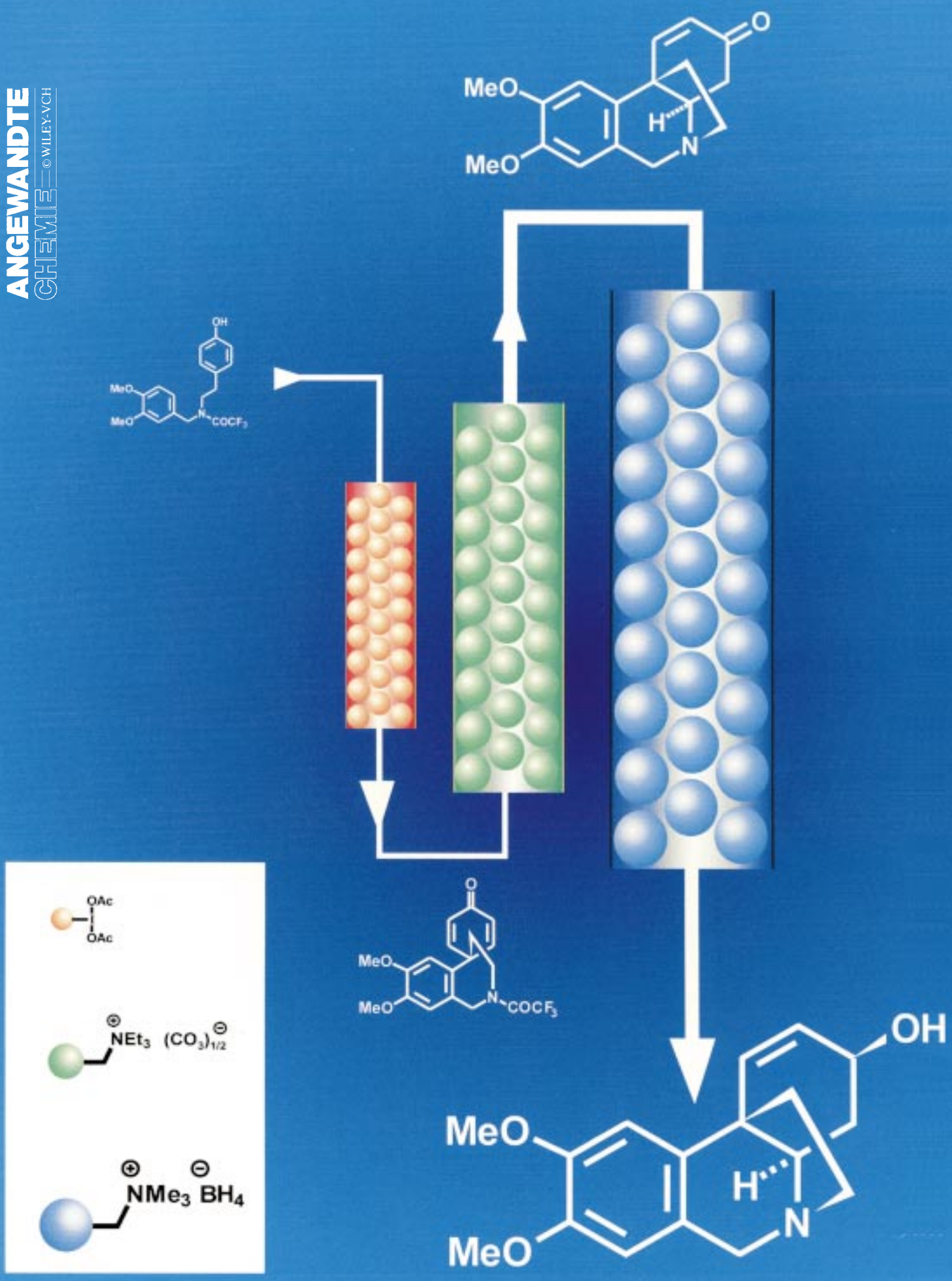

Functionalized Polymers—Emerging Versatile Tools for Solution-Phase Chemistry and Automated Parallel Synthesis

Andreas Kirschning,* Holger Monenschein, and Rüdiger Wittenberg

As part of the dramatic changes associated with the need for preparing compound libraries in pharmaceutical and agrochemical research laboratories, industry searches for new technologies that allow for the automation of synthetic processes. Since the pioneering work by Merrifield polymeric supports have been identified to play a key role in this field however, polymer-assisted solution-phase synthesis which utilizes immobilized reagents and catalysts has only recently begun to flourish. Polymer-assisted solution-phase synthesis has various advantages over conventional solution-phase chemistry, such as the ease of separation of the supported species from a reaction mixture by filtration and washing, the opportunity to use an excess of the reagent to force the reaction to completion without causing workup problems, and the adaptability to continuous-flow processes. Various strategies for employing functionalized polymers stoichiometrically have been developed. Apart from reagents that are covalently or ionically attached to the polymeric backbone and which are released into solution in the presence of a suitable substrate, scavenger reagents play an increasingly important role in purifying reaction mixtures. Employing functionalized polymers in solution-phase synthesis has been shown to be extremely useful in automated parallel synthesis and multistep sequences. So far, compound libraries containing as many as 88 members have been generated by using several polymer-bound reagents one after another. Furthermore, it has been demonstrated that complex natural products like the alkaloids (±)-oxomaritidine and (±)-epimaritidine can be prepared by a sequence of five and six consecutive polymer-assisted steps, respectively, and the potent analgesic compound (±)-epibatidine in twelve linear steps ten of which are based on functionalized polymers. These developments reveal the great future prospects of polymer-assisted solution-phase synthesis.

Keywords: automated synthesis · combinatorial chemistry · functionalized polymers · reagents

1. Introduction

Since the pioneering work by Merrifield[1] polymer supports have become the subject of considerable and increasing interest as insoluble matrices in organic synthesis.[2] This solid-phase technique revolutionized polypeptide and polynucleotide synthesis and, almost thirty years later, it set the stage for combinatorial chemistry. This conceptual revolution in organic synthesis was mainly governed by the need to generate rapidly libraries of compounds. In most cases, the development of new synthetic sequences on polymeric supports is regarded as the key for successfully generating these libraries (Scheme 1; method A).[3]

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In the shadow of these dramatic changes, the utilization of functional polymers as reagents and catalysts has developed only sluggishly.[4] In this process, the substrate does not remain attached to the solid support during a multistep synthesis until, in the final step, it is cleaved from the support, instead, the polymer-bound reagent or catalyst promotes a chemical transformation of a substrate which is present in solution. At first glance, it may be surprising that this approach has not been too popular, as this technique allows for the parallel solution-phase synthesis of organic compounds.[5–7] In fact, this approach is very familiar to organic chemists, as reactions can be monitored using known analytical techniques like thin layer chromatography.[8] In the seventies and eighties it was thought that the future of wide-scale use of polymeric reagents and catalysts lay in their adoption by industry for large-scale fine-chemical and pharmaceutical manufacturing. In fact, this restricted view hampered their use.[9] The dramatic developments in pharmaceutical and agrochemical industries resulting in the need for compound library preparation has finally removed functionalized polymers from an

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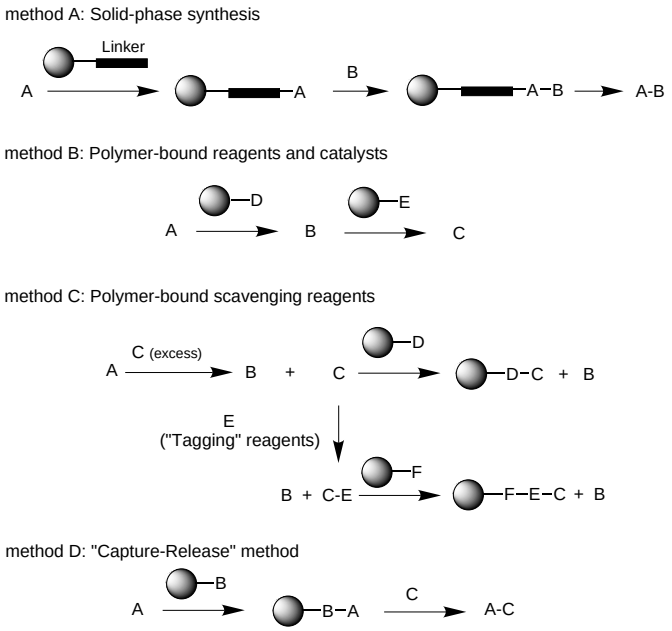


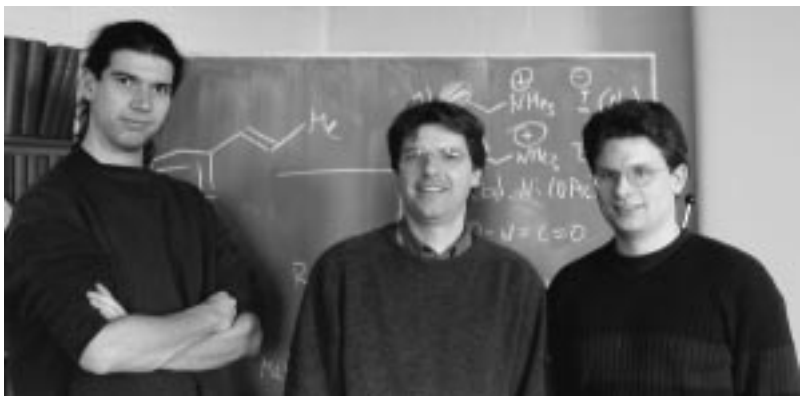
Scheme 1. Various uses of polymer supports in organic synthesis.

academic corner and helped them to be rediscovered for industrial applications.

This technique which in its most general form, and in this review, is termed polymer-assisted solution-phase synthesis has various advantages over conventional solution-phase chemistry: 1) the ease of separation of the supported species, from a reaction mixture, by filtration and washing, 2) the possibility to use an excess of reagent to force the reaction to completion without causing workup problems, 3) reuse of a catalyst or of a supported reagent after regeneration, 4) the ease of adaptation to continuous-flow processes and hence use in automated synthesis, 5) the reduced toxicity and odor of supported species compared with low molecular weight unsupported analogues, 6) chemical differences, such as prolonged activity or altered selectivity of a catalyst in supported form compared with its soluble analogue.

Furthermore, polymer-assisted solution-phase syntheses shows advantages over Merrifield-type syntheses, these are summarized in Scheme 1 (methods B – D). Such methods are in fact much less demanding since polymer-supported reagents are used in only one reaction and, because of the excess of reagent usually employed, not every functional site needs to react. It has been demonstrated in numerous examples that, compared to solid-phase synthesis, the development time for new polymer-supported reagents and their applications is much shorter.

Nevertheless, the high loadings are still necessary in cases of reagents used stoichiometrically. With polymer-supported catalysts not every site needs to react and lower loadings are acceptable. The recovered catalyst is often available for immediate reuse. A discussion on functionalized polymers should also include a brief listing of obstacles associated with their use, particular in comparison to their soluble analogues,



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Andreas Kirschning was born in 1960 in Hamburg. He studied chemistry at the University of Hamburg and at Southampton University (UK). In Hamburg, he joined the group of Prof. E. Schaumann and received his Ph.D. there in 1989 working in the field of organosilicon chemistry. After a postdoctoral stay at the University of Washington (Seattle) with Prof. H. G. Floss, he started his independent research at the Technical University of Clausthal (Germany) in 1991, where he finished his habilitation in 1996. In 1997, he held a position as guest professor at the Humboldt-University in Berlin and in 1998 as a visiting professor at the University of Wisconsin in Madison. Recently, he has accepted a position at the University of Hannover. During his career he has received DAAD, Fritz-Prosiegel, and Feodor Lynen scholarships. His prime research interests are preparative natural product chemistry, polymer-assisted synthesis, and the bioorganic chemistry of glycoconjugates.

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these are 1) higher costs, 2) lower reactivities because of diffusion limitations, 3) difficulty in structural analysis of the supported species, 4) the inability to separate polymer-bound impurities.

Until recently, polymer-bound reagents for stoichiometric use (Scheme 1; method B) have been the most important group of functionalized polymers. Now, additional techniques for polymer-assisted solution-phase synthesis are available. In this review the following terminology is used for these new functionalized polymers: polymer scavengers are resins which are added after a chemical reaction to remove excess reactants and by-products (Scheme 1; method C). The molecule to be removed can also be "tagged", that is, derivatized and functionalized to facilitate its removal by a polymer scavenger. There is a subset of functionalized polymers which allow the "capturing" of a small molecule as an activated polymer intermediate. After washing to remove soluble by-products, this intermediate is subjected to a second transformation to "release" the product back into solution (Scheme 1; method D). As this hybrid technique basically combines the concept of solid-phase synthesis (method A) with the idea of polymer-supported reagents (method B) it will not be discussed here whereas the description and applications of methods B and C will be.

Lately, several excellent reviews have appeared indicating the increased interest in functionalized polymers and in the synthetic techniques associated with them. Most of these reviews introduced the reader to the preparation and properties of immobilized reagents,[4] catalysts,[8] and scavenging techniques.[10] The true potential of functionalized polymers is reached when they are employed in multistep sequences and automated parallel syntheses leading to compound libraries. In multistep sequences polymer-supported reagents and catalysts along with the use of scavenging reagents and resin "capture – release" techniques can be mixed to generate ever more complex molecules. In an ideal synthesis of this kind, only filtration and washing is required for purification so that the process can be automated easily. Therefore, the discussion will focus on multistep sequences employing techniques B and C (Scheme 1).

As it becomes more and more evident that one key to the successful automation of organic synthesis is the development of altered or new polymeric backbones we include a brief discussion of various aspects in this field which are relevant for the functionalization of polymers. Recent trends in the rapidly developing field of inorganic supports will be covered as only a few examples of reagents attached to these promising supports have been published. To keep to a tractable length, polymer-supported catalysts are not covered in great detail mainly because they have not been employed in multistep sequences so far. The great initial hopes, particularly for polymer-bound transition metal catalysts, have, with few exceptions, not been fulfilled yet. One problem is that the transition metals are not bound irreversibly to the polymer support and transition metal complexes are not as stable as they were once thought to be. Still, we believe that the future prospects for polymer-anchored transition metal catalysts are bright, because they combine the best of both worlds: heterogenic and homogenic catalysis.

2. Polymer Supports

The attachment of a chemical functionality to a polymeric support has been realized by physical adsorption or by chemical bonding. The former technique is sometimes unsatisfactory, dissociation can occur too easily and hence this method is unsuitable for column or cyclic flow-reactor applications. Chemical attachment has been achieved through ionic or coordinative interactions, for example, with metal complexes and in an increasing number of cases by covalent bonding. The former mode of attachment is mainly found in ion-exchange resins and is highly attractive. These reagents are very easily regenerated, usually treatment with an excess of the ionic reactant is all that is required.

Two approaches exist for the preparation of functional polymers, the polymerization or copolymerization of monomers which carry the desired functionality, and the chemical modification of preformed polymers. It is mainly the second approach which has been exploited. In this respect, cross-linked poly(styrene-co-divinylbenzene) resins (1% or 2% cross-linking) are widely used as functionalized polymers because of their stability, reasonably high loading capacity (>1 mmol g^{-1}), and good swelling characteristics. Furthermore, they are compatible with a variety of non-protic solvents and many functionalized analogues in particular based on ion exchange resins are commercially available.

The alternate concept, the polymerization of prefunctionalized monomers was extensively tested in the "early days" of polymer-assisted syntheses, for example, in the preparation of polymers containing pyridine[11] or quinone[12] residues, and benzaldehyde[13] or phosphane[14] functionalities. Although this approach demands that the synthetic organic chemist acquires a profound knowledge of polymers and polymerization, this strategy will acquire increasing importance because most supports employed today are still far from ideal (see Section 7).

For successfully designing new polymer-supported reagents, particularly in the context of combinatorial chemistry and automation, it is important to consider the properties and the role of the polymeric support.[15, 16] In many cases, reactions carried out under homogeneous conditions are the same in terms of efficiency and selectivity as reactions of polymer-supported species. It must be remembered that up to 99% of functional groups of a polymer-supported system are within a polymer bead of diameter of about 100 μm. Thus, most of the reactants in solution have to enter the beads and react in a gel phase. The swelling of the polymers with organic solvents is one method of affording better access to the reactive sites of the polymer prior to its use. However, in this context it is important to recall that the extent of swelling decreases markedly as the percentage of cross-linking increases from 1% to 2% or more. The choice of reaction solvent is therefore crucial in polymer-supported reactions and the best solvent may not be the one commonly applied in the analogous reaction using low molecular mass reactants. The diffusion of the soluble substrate into the polymer beads is rate limiting and therefore, in some cases, can result in the supported reactant displaying a pronounced size selectivity. [15–17] The selectivity arises because a more bulky molecule diffuses

more slowly to the reactive sites in the beads. Another effect that needs consideration occurs when the polarity of the microenvironment within the beads differs significantly from that of the solvent outside. This difference can either facilitate or prevent a low molecular mass reactant from approaching the active sites. For example, polymer-supported *N*-bromosuccinimide (NBS) shows a reactivity pattern with cumene in which the dehydrobromination reaction is more favored than in the solution reaction with NBS.[18] The authors made the higher polarity in the beads around the active sites responsible for this behavior.[15]

Generally, it is believed that attaching reactive species to a polymer support leads to site isolation, but in fact, many examples are known which clearly indicate that functional groups on a bead do interact with each other.[15, 19] A typical loading of functional groups on a polystyrene-based support is around 1 mmol g^{-1}. This results in a concentration of reactive groups of around 0.33 mol dm^{-3} provided that the reaction solvent is able to swell the polymer by a factor of three. Indeed, site–site reactions can occur as, for example, was shown for polymer-supported Wittig reagents.[20] One strategy to circumvent the ease of site–site interaction is to increase the percentage of cross-linking which is expected to reduce chain mobility. Noteworthy is that the supported substrate molecule can act as a flexible spacer group facilitating the side reactions caused by site–site interactions. In this respect, the strategy of polymer supported reagents (Scheme 1; methods B–D) clearly has advantages over the construction of molecules on a polymer support (Scheme 1; method A), the reagents are commonly small and thus site–site interactions in the bead are not particularly significant, and can be overcome simply by using an excess of the reagent without necessarily creating impurities in solution.

The accessibility of the active sites may be improved by using macroporous or macroreticular polymers.[21] These polymers are usually prepared by suspension polymerization in the presence of a porogen to afford 20–40% cross-linked polystyrene beads. Typically, such beads have a rigid porous structure and normally do not swell in most organic solvents. Some commercial macroporous polymer supports, in particular certain anion-exchange resins, are ideally suited for making anions available for reactions in non-aqueous solvents.[22] For example, the periodiate form of such resins cleave diols in a wide range of different solvents such as ethanol, chloroform, diethyl ether, benzene, and even water.[23] Another advantage of macroporous resins is their dimensional stability which makes them ideally suited for column applications where better solvent flow rates can be achieved than would be the case with gel polymers.

Contrary to the use of cross-linked polystyrenes, and of macropores, non-cross-linked polystyrene copolymer supports have been introduced to overcome the restricted access to active sites.[24] These polymers are soluble in most organic solvents but precipitate in certain cooled solvents, for example, methanol.[25, 26] This development is in line with the use of other soluble polymers and in particular soluble poly(ethylene glycol) (PEG)[27] in polymer-supported synthesis. PEG was first studied by Bayer and Mutter and has recently been reintroduced by Janda and co-workers.[28] In many cases, these soluble supports behave like reactants in homogenous reactions.[29] However, only limited use of reagents or catalysts attached to soluble polymers has been made, which can be ascribed to problems associated with their handling. PEG–ethers are highly hygroscopic and typically have low loading capacities (0.2 mmol g^{-1}). Often, large amounts of solvent are required to precipitate soluble polymers quantitatively. In particular the latter drawback makes them very difficult to use in automated parallel synthesis. An important new soluble polymer was recently reported by Frey and Haag, they described the controlled synthesis of well-defined hyperbranched polyglycerols[30] which like related polymers[31] have a very high loading capacity (4–8.8 mmol g^{-1}) and are superior to dendrimers in terms of preparative accessibility. As the authors point out, reagents or catalysts attached to soluble polymeric supports may be used conveniently in continuous reactors using membrane techniques (see also Outlook, Section 7).

3. Stoichiometric Polymer-Supported Reagents

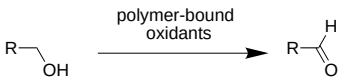
Despite the dramatic increase in applications of, and enthusiasm for, polymer-supported reagents and catalysts (Scheme 1; method B) in solution-phase synthesis it is of note that the foundations of this technique were laid at the beginning of the seventies and lot of the credit for today's successes ought to go to the pioneers of that time. However, for reasons mentioned above these contributions came well ahead of the time when efficiently creating compound libraries was a prime goal. Therefore, stoichiometric polymer-supported reagents, including some important contributions from the early days are discussed.

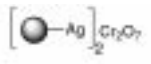
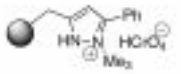
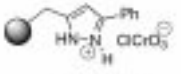
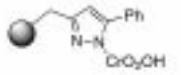
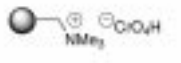
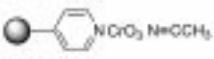
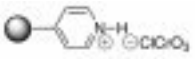
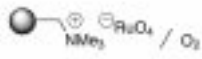
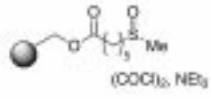
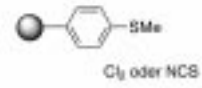
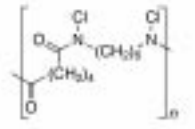
Among these reagents, a clear classification is not always possible, for example, in many cases polymer-bound bases will not only act by deprotonating soluble organic substrates but are associated with further transformations such as the immobilization of counterions (see above) which initiates the nucleophilic substitution of alkyl halides and sulfonic esters or the Horner–Wadsworth–Emmons olefination of aldehydes. In addition, they have been employed widely as scavenging reagents (Scheme 1; method C) and for the "capture-release" technique (Scheme 1; method D). Herein, we pursued a classification based on the type of reaction rather than the nature of reagent.

3.1 Oxidations

For at least thirty years it has been known that oxidations can be promoted by polymer-bound reagents.[32] Most of these oxidants were developed for the conversion of alcohols into carbonyl compounds. The number of polymers functionalized with $ClCrO_3^-$, $HCrO_4^-$, ClO^-, and RuO_4^- ions is still increasing, the most prominent examples are listed in Table 1. Typically, these oxidants are attached by different N-heterocycles, or simple quaternary ammonium cations as in Amberlyst A-26, to the polymeric backbone. Also polymer-supported versions of the Swern oxidation[33] (Table 1, entry 12) as

Table 1. Oxidation of alcohols.



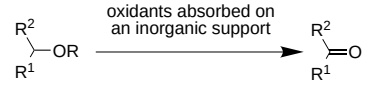
Entry	Reagent/co-oxidant	Polymeric backbone[a]	No.[b]	Yield [%]	Ref.
1		PEI	10	73 – 98	[35]
2		PS (2% DVB) PS (2% EGDMA)	10 10	70 – 86 72 – 87	[36]
3		PS (2% DVB) PS (2% EGDMA)	10 10	75 – 90 80 – 90	[36]
4		PS (2% DVB) PS (2% EGDMA)	10 10	75 – 86 75 – 86	[36]
5		Amberlyst A-26	15	73 – 98	[37]
6		PS (2% DVB)	13	0 – 89	[38]
7		PS (2% DVB)	13	0 – 82	[38]
8		P-4VP (copolymer PS)	10	5 – 80	[39]
9		P-4VP	15	94 – > 99	[40, 41]
10		Amberlyst IR 27	10	54 – 95	[42]
11		Amberlyst A-26	7	56 – 95	[43]
12		PEG/PS	7	91 – 99	[44]
13		Amberlite XE-305	5	53 – > 99	[45]
14		IRA-900	5	60 – 98	[46]
15		Nylon 66	11	5 – 97	[47]
16		PS	8	66 – 95	[48]

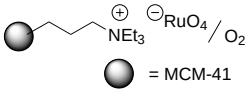
[a] PEI = polyethyleneimine, PS = polystyrene, DVB = divinyl benzene, EGDMA = ethylene-glycol dimethylacrylate, PEG = poly(ethylene glycol), P-4VP = poly(4-vinylpyridine); [b] number of examples.

well as the Corey oxidation[34] (Table 1, entry 13) were developed.

Suitable inorganic-based supports for chromium and other metal-based oxidants are silica gel and clays such as montmorillonite K10 (Table 2). These have served in numerous examples as excellent reagents for oxidizing alcohols of various types to the corresponding carbonyl compounds. More recently, the direct oxidative deprotection of trimethylsilyl and THP-ethers (THP = tetrahydropyranyl) with Cr^{IV} oxides absorbed on silica gel or wet alumina[49, 60] or with montmorillonite clay loaded with iron(III) nitrate[50] was achieved, which increased the number for immobilized oxidants available. Similarly, oximes, semicarbazones, and *p*-nitrophenylhydrazones were oxidatively cleaved to their parent carbonyl compounds using different metal-based oxidants immobilized on inorganic supports.[51]

Table 2. Oxidation of alcohols using silica-based oxidants.

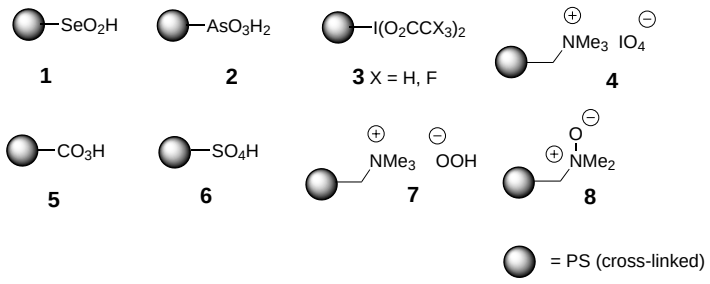


R	Oxidant	No.[a]	Yield [%]	Ref.
H	bis(trimethylsilyl)chromate/	22	71 – 99	[54]
$SiMe_3$	SiO_2 or	10	71 – 95	[49]
THP	Al_2O_3	18	72 – 90	[60]
H	ammoniumchlorochromate/SiO_2	16	70 – 95	[55]
H	chromium(VI)oxide/SiO_2	7	46 – 85	[56]
H	chromium(VI)oxide/SiO_2/$(SiMe_3)_2O$, microwave irradiation	10	72 – 99	[57]
$SiMe_3$	iron(III)nitrate/montmorillonite K10	8	70 – 95	[50]
H		10	> 99	[58]
H	CrO_2 (magtrieve)	7	61 – 95	[59]

[a] Number of examples.

Related to these applications montmorillonite clay,[52] molecular sieves,[61] bentonite,[61] alumina,[62] and in particular Kieselgur (82 – 97%)[63] have served as solid supports for potassium permanganate. Only recently, Ley and co-workers disclosed an oxidant anchored to the macroporous inorganic support MCM-41 (Table 2).[58] In the presence of oxygen, this immobilized catalyst is a very efficient oxidant for alcohol oxidation. Another remarkable oxidant, Magtrieve, created by Lee and Donald from Du Pont, is based on tetravalent CrO_2.[59a] The oxide is able to convert alcohols as well as less active compounds like acetals and alkanes into aldehydes (Table 2).[59] This reagent is produced in the commercial process for making magnetic-tape pigments but isolated prior to the reductive surface treatment. Since only the surface of the material is involved in the oxidation reaction the material remains ferromagnetic and can be readily removed by magnetic separation.

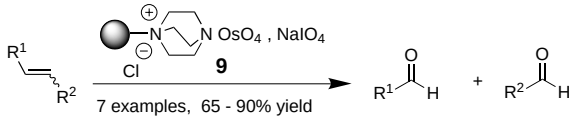
Furthermore, various polymer-anchored reagents **1** – **8** were developed for promoting diverse oxidations with functional groups other than alcohols. Thus, 1,2-*trans* diols (41 – 89%) are obtained from alkenes, and esters (71 – 98%) from the



corresponding ketones in a triphasic system composed of hydrogen peroxide, dichloromethane, and polymer-bound phenylselenic acid (**1**).[64] In the presence of *tert*-butyl hydroperoxide, **1** is able to effect selective oxidation of benzylic alcohols to the corresponding carbonyl species as well as the conversion of phenols to quinones.

A similar approach using arsenate polystyrenes **2** was reported by Jacobson et al.[65] Oxidation of ketones by **2** in the presence of hydrogen peroxide affords the Baeyer–Villiger oxidation products, namely lactones, usually in very good yields. Polymer-supported α-oxidation of ketones has been achieved using the versatile oxidant poly(styrene(iodosobenzene diacetate)) **3** (X = H; for X = F see also Scheme 44).[66, 67] Furthermore, **3** has been reported to promote oxidative 1,2-aryl migration of alkyl aryl ketones thus furnishing the corresponding α-aryl carboxylic esters.[68, 69]

The periodate anion was immobilized, either on an ion-exchange resin to yield reagent **4**[23, 70–72] or on inorganic supports,[73] and was used in different organic solvents to promote oxidative cleavage of 1,2-diols. Furthermore, with **4**, quinoles are transformed to quinones, sulfides are converted to sulfoxides, and triphenylphosphane is oxidized to triphenylphosphane oxide. Polymer-supported peracids **5** and **6** which are prepared from the parent polymer-bound carboxylic[74] or sulfonic acids[75] have been shown to oxidize thioethers and sulfoxides to the corresponding sulfones. In addition, alkenes are epoxidized and cyclic ketones are transformed to the ring-expanded lactones by means of the Baeyer–Villiger oxidation. Likewise, intermediate polymer-bound hydroperoxide **7** is able to promote epoxidation of alkenes including electron-deficient enones.[76] Amine oxides **8** derived from aminated polystyrene resins are reported to selectively oxidize primary alkyl halides, in particular iodides, to the corresponding aldehydes.[77] Various variants of polymer-supported osmium tetroxide have been disclosed. Although these reagents are used catalytically in the presence of cooxidants like trimethylamine-*N*-oxide (NMO) or *t*BuOOH[78] one application should be mentioned here. Reagent **9** in combination with sodium periodate can be used to carry out an oxidative cleavage of alkenes leading to carbonyl compounds (Scheme 2).[79] The continuous regeneration of the polymer-bound osmium tetroxide by periodate allows the use of catalytic amounts of reagent **9**. Finally, the epoxidation of alkenes has been carried out using a polystyrene- or tentagel-anchored dioxirane and its analogues derived from trifluoromethyl ketones.[80] The same reaction can be performed using the bromite anion attached to a macroporous anion-exchange resin (IRA-900), the active species can be regenerated electrochemically.[81]

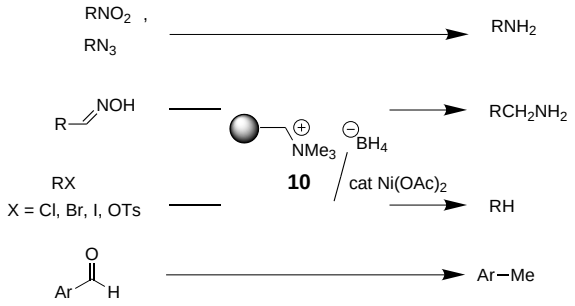


Scheme 2. Oxidative cleavage of alkenes by using polymer-supported osmium tetroxide.

3.2 Reductions

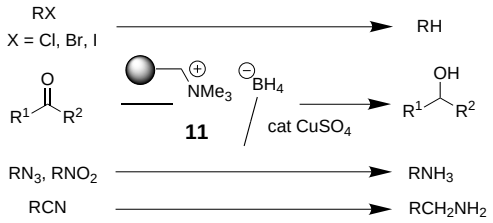
Polymeric supports are not only ideally suited for anchoring oxidants but have also been shown to immobilize reducing agents very effectively.[82] The chemical modification of quaternary ammonium type resins, such as Amberlyst A-26, with $NaBH_4$[83] and $NaCNBH_3$ (reported in the early seventies) gives highly efficient and chemoselective reducing agents.[84] Recently, the polymeric backbones of these functionalized ion-exchange resins have been optimized.[84b] In fact, these functionalized resins have been used in many organic transformations including the reduction of aldehydes and ketones,[85] α,β-unsaturated carbonyl-compounds,[86] benzyl and primary alkyl halides,[87] and aliphatic acid chlorides.[88] Even α,β-unsaturated cyanoacetates[89] and nitroalkenes[90] could be selectively reduced. Importantly, it was demonstrated that aryl azides and arylsulfonyl azides can be transformed to the corresponding aromatic amines and aryl sulfonamides, respectively, in up to 98% yield[91] and even the reductive amination of aldehydes and ketones in weakly acidic alcohol solvents has been achieved using these polymer-supported hydrides.[92] In Sections 5 and 6, many more applications of these reagents are mentioned.

An interesting modification of borohydride exchange resins (BER) is their combination with transition metal salts. Thus, cross-linked poly(4-vinylpyridine)-supported zinc borohydride was used to reduce aldehydes in high yields even in the presence of ketones.[93] When $Zr(BH_4)_4$ is used instead,[94] a polymer with enhanced reactivity is obtained which also reduces ketones, while conjugated double bonds are kept intact. The addition of a catalytic amount of nickel(II) acetate affords a very powerful and highly chemoselective[95] functionalized polymer **10** which allows reduction of nitro[96] and azido[97] groups as well as aryloximes[98] to the corresponding primary amines. Alkyl and aryl halides,[99, 100] tosylates,[99] and remarkably also benzaldehydes[101] are converted into alkanes by **10** in moderate to excellent yields (Scheme 3).



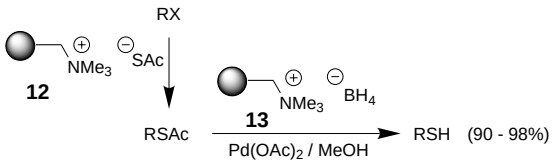
Scheme 3. Synthetic applications of BER and a catalytic amount of $Ni(OAc)_2$.

When borohydride is attached to Amberlite IRA 400 and treated with a catalytic amount of $CuSO_4$ a functionalized polymer **11** which is strong reducing towards different functional groups is obtained; these groups are listed in Scheme 4.[102] Reagent **11** is particular useful for the reduction of alkyl halides including aryl iodides, azides, aldehydes, and ketones. Nitriles and particularly esters and amides are poor substrates. Alkenic double bonds when in conjugation with aryl or carbonyl groups are readily hydrogenated.



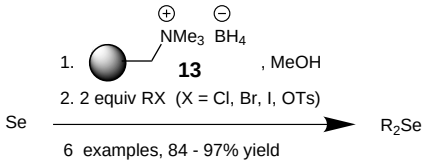
Scheme 4. Synthetic applications of BER and a catalytic amount of $CuSO_4$.

Recently, the synthesis of thiols by palladium-catalyzed methanolysis of thioacetates was reported.[103] Here reagent **13**, Amberlyst A-26 loaded with borohydride, served as the reductant. Prior to this step, alkyl halides were converted into the thioacetates using the appropriately loaded ion-exchange resin **12**. This two-step process can also be performed in a one-pot fashion (Scheme 5).[103]



Scheme 5. A synthetic equivalent for polymer-supported SH^-.

Borohydride exchange resin (BER) in methanol is also able to reduce selenium, probably to give an immobilized selenide which reacts with alkyl halides or tosylates to afford dialkyl selenides in high yield without forming toxic hydrogen selenide and/or foul-smelling selenol (Scheme 6).[104]

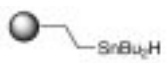
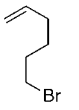
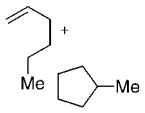
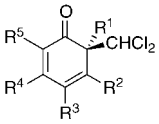
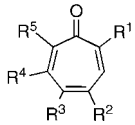
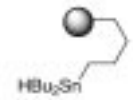


Scheme 6. BER-promoted preparation of dialkylselenides from selenium.

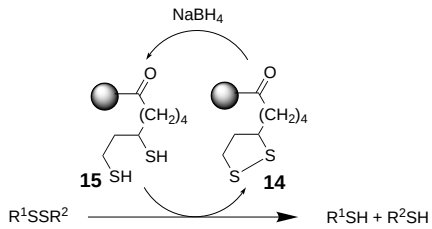
Another very important group of functionalized polymers with reductive properties are polymer-supported organotin reagents, especially tin hydrides.[105] The development of these polymers was associated with the need, particularly for pharmaceutical applications, to improve separation techniques and prevent contamination by tin by-products. Therefore, a whole family of these reagents was introduced which mainly differ in the length of the aliphatic linker and the nature of the polymeric backbone. All of these polymer-supported tin hydrides have been employed for the reduction of sulfonic esters, xanthates, or alkyl halides, including tertiary bromides like adamantyl bromide (Table 3). However, in some cases the radical-induced cyclization of unsaturated organic halides is difficult to suppress (see also Table 6).

Finally, a biomimetic tool for the reduction of disulfides was developed by Gorecki and Patchornik (Scheme 7).[112] Lipoic acid was coupled covalently to aminoethyl solid matrices. Treatment of this disulfide **14** with $NaBH_4$ gave the polymer-bound dithiol **15** which was shown to reduce oxidized glutathione and cystine.

Table 3. Reductions with polymer-supported tin hydrides.

Reagent	Polymeric backbone	Substrate	Product	No.[a]	Yield [%]	Ref.
1 	PS (5–7% DVB)			1	> 99	[106]
2 				12	29–99	[107]
3 	PS	RX[b]	RH	17	44–98	[108, 109]
4 	Amberlite XE 305			1	93	[110]
5 	Amberlite XE 305	3-iodo-5-cholesterene	5-cholesterene	1	60	[111]

[a] Number of examples; [b] X = Cl, Br, PhOC(S)O, MeSC(S)O.



Scheme 7. Biomimetic polymer-supported reduction of disulfides.

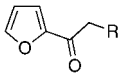
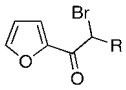
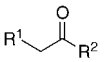
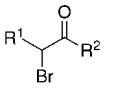
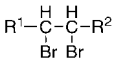
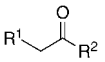
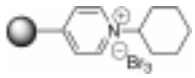
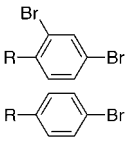
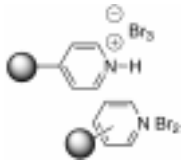
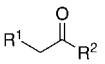
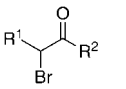
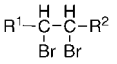
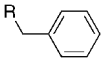
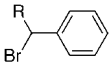
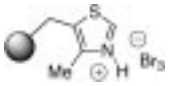
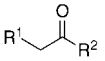
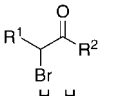
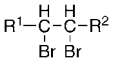
3.3 Halogenations

Halogenation of organic compounds is a crucial step in the preparation of various synthetic intermediates or products. Therefore, it is not surprising that several polymer-bound halogenization reagents were established more than 20 years ago in the early days of functionalized polymers.[11a, 18, 113, 114] Most of these reagents are based on ion-exchange resins[115] often loaded with perbromide making them well suited for bromination reactions (Table 4). Commonly, these highly reactive reagents are stable and therefore can conveniently be stored. They perform 1,2-addition reactions to alkenes and alkynes[116] as well as α-bromination of carbonyl compounds and acetals.[116]

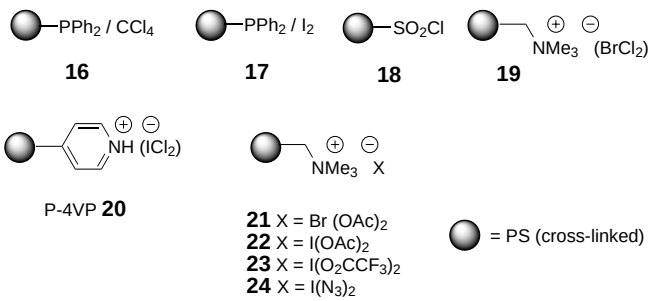
In contrast to the numerous examples of functionalized polymers that promote bromination, a general route for chlorination has not been worked out so far.[122] Polymer-supported phosphane (poly-TPP; TPP = triphenylphosphane) in CCl_4 **16** is suited for the chlorination of primary alcohols to the corresponding alkyl chlorides under essentially neutral conditions.[123, 124] The same reagent system and also a combination of poly-TPP and Cl_2[14d, 125] is able to convert carboxylic acids into acid chlorides. The analogous reagent, poly-TPP and I_2 **17** has been used to transform alcohols, including N-protected β-amino alcohols, to the corresponding alkyl iodides.[126] Furthermore, α-chlorination has been achieved using lithium diisopropylamide (LDA) and the immobilized chlorosulfonyl moiety **18**.[127] Additionally, anion-exchange resins such as Amberlyst A-26 have been utilized for the preparation of polymer-bound interhalogen compounds.[116] Reagents such as **19** perform chlorobromination of double- and also triple-bonds. Along this line, also polymer-bound dichloroiodate(I) **20** was developed for the iodochlorination of alkenes and alkynes as well as monoiodination of arenes.[128] The reagent system iodine and poly(styrene(iodoso)diacetate) **3** (X = H) also promotes efficient iodination of electron-rich aromatic compounds.[68, 69]

Recently, new halogenate(I)-complexes were developed in our group[129] which can conveniently be attached to anionic exchange resins. Reagents **21** – **24** promote Markovnikov-type 1,2-cohalogention-like iodoacetoxylation of alkenes in most cases in a 1,2-*trans* mode.[130] Furthermore, iodination of

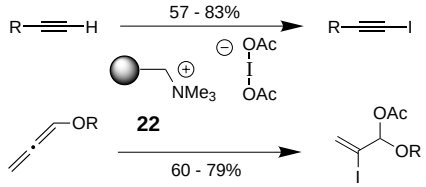
Table 4. Functionalized polymers for bromination.

Reagent	Polymeric backbone[a]	Substrate	Product	No.[b]	Yields [%]	Ref.
	Amberlyst A-162			9	60 – 98	[117]
	Amberlyst A-26			12	70 – 97	[116]
						
	Amberlyst A-26			5	55 – 78	[118]
	P-4VP			7	70 – 90	[119]
	P-4VP (copolymer with PS and DVB)			4	80 – > 99	[11a]
				9	55 – > 99	[11a, 113]
				9	63 – 85	[120]
	PM5VTHT			16	30 – > 99	[121]
						

[a] PM5VTHT = poly(4-methyl-5-vinylthiazol); [b] number of examples.

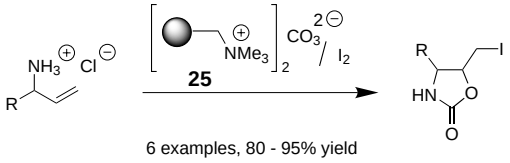


alkynes to the corresponding alkynyl iodides and chemo- and regioselective iodoacetoxylation of alkoxyallenes was achieved with functionalized resin **22** (Scheme 8). It is noteworthy that polymer-supported halogenate(I)-complex **24** is a stable and nonexplosive source for iodine azide, which indicates that on polymer supports a separation of active sites can be realized, thereby stabilizing a highly reactive species.



Scheme 8. Functionalization of alkynes and alkoxyallenes using polymer-bound iodate(I) complex **22**.[130c]

Carboxylation and iodine-induced cyclization of allyl amines to iodomethyl-substituted oxazolidinones was achieved with the bisfunctionalized ion-exchange resin **25** composed of the basic carbonate anion which is complexed with molecular iodine (Scheme 9).[131]

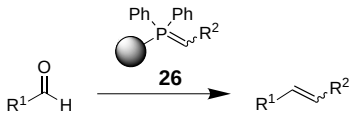


Scheme 9. Polymer-supported preparation of oxazolidinones from allyl amines.

A set of functionalized polymers was developed for the selective fluorination of organic compounds (Table 5). Primary and secondary alkyl fluorides are obtained from alkyl halides or organic sulfonates by using fluoride-loaded anion-exchange resin.[132] Likewise, the combination of anhydrous hydrogen fluoride and poly-4-vinylpyridine (P-4VP) affords P-4VP poly(hydrogen fluoride) an efficient functionalized resin for the fluorination of alcohols and the hydrofluorination of alkenes and alkynes.[133] Finally, polymeric aryliodine(III) difluoride is able to fluorinate several phenyl-substituted olefins to their geminal difluorides after rearrangement.[134]

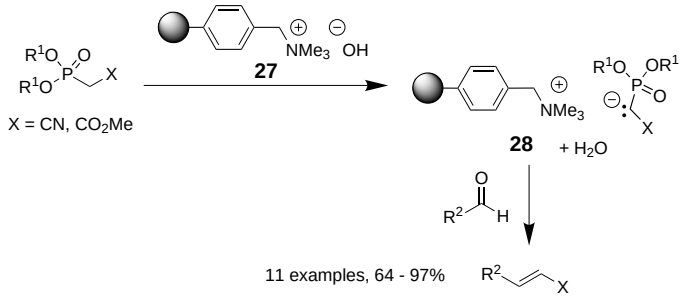
3.4 C–C Coupling reactions

The Wittig reaction and the organophosphorous chemistry derived from it[135] are the best studied examples of carbon–carbon coupling reactions promoted by functionalized polymers. Commonly, polymer-bound phosphorous ylides **26** are employed, often giving yields and selectivities equal to those of the corresponding solution chemistry (Scheme 10).[136] Highly cross-linked macroporous polystyrene supports (20% divinyl benzene (DVB)) has been shown to be particularly effective in this reaction.[14b, 137, 138]



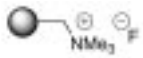
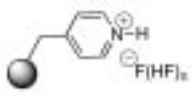
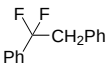
Scheme 10. Polymer-supported Wittig-olefinations. With R = alkyl: *Z* selectivity; with R = C(O)R²: *E* selectivity.

Polymer-supported Horner–Emmons olefination was first reported by Cainelli et al. (Scheme 11).[139] The anion-exchange resin Amberlyst A-26 (OH^- form) **27** is sufficiently basic to deprotonate phosphonates thereby generating polymer-bound phosphonate anions **28**. These functionalized resins were further treated with carbonyl compounds to furnish the corresponding alkenes. A two-step extension of this work utilized Amberlyst A-15 (H^+ form) prior to the olefination step. This ion-exchange resin promoted hydrolysis of a dioxolane affording the corresponding carbonyl compound which was further reacted to the corresponding alkene.



Scheme 11. Polymer-supported Horner–Emmons olefination using ion pair reagents.

Table 5. Polymer-supported fluorination.

	Reagent	Polymeric backbone	Substrate	Fluorinated Product	No.[a]	Yields [%]	Ref.
1		Amberlyst A-26	RX[b]	RF	13	20–>99	[132]
2		P-4VP	ROH	RF	13	56–94	[133]
3		PS			6	85–96	[134]

[a] Number of examples; [b] X = Br, Cl, OMs, OTs.

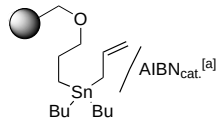
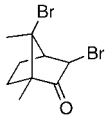
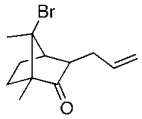
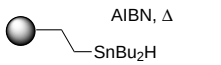
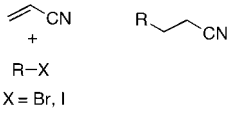
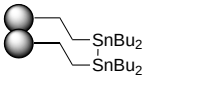
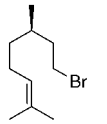
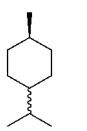
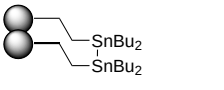
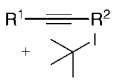
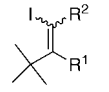
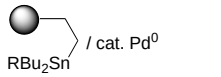
An alternative polymer-supported approach for the Horner–Emmons olefination was recently devised by Barrett et al. (Scheme 12).[140] They performed a ring opening metathesis (ROMP) with 2-norbornenemethanol phosphonates, the polymerization afforded an immobilized phosphonate **29** which in acetonitrile and in the presence of Barton's base (*N*-*tert*-butyl-*N*′-*N*′-*N*″-*N*″-tetramethylguanidine) as well as a carbonyl compound exclusively afforded (*E*)-configured α,β-unsaturated esters.

Likewise, sulfonium salts were also anchored to cross-linked polystyrene and sulfur ylides were generated, after use the sulfonium salts could be regenerated.[141] These functionalized polymers have successfully been employed in reactions with carbonyl compounds leading to homologated oxiranes.

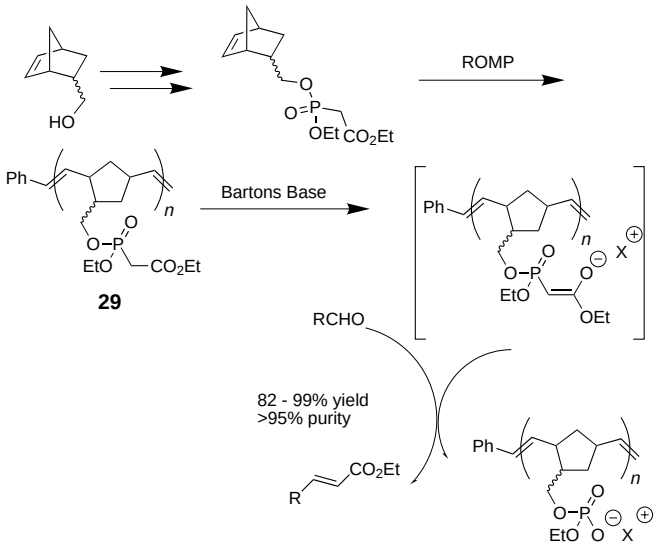
Polymer-bound organotin reagents are ideally suited for promoting free radical C–C coupling reactions (Table 6). Thus, allyl stannanes attached to soluble polymeric supports, namely non-cross-linked polystyrene, allow allyl transfer onto organohalides (five examples; 50–73% yield).[142] Accordingly, polymer-attached distannanes are able to promote cyclization of unsaturated alkylhalides as well as radical addition of alkyhalides to alkynes.[144] When polymer-anchored tin reagents are loaded with transferable functional groups like vinyl or aryl substitutents (R) the palladium-catalyzed Stille reaction becomes feasible.[145]

Nickel(II) boride BER **10** has proven to be a substitute for polymer-bound tributyltin hydride (see also Scheme 3), because it promotes the radical addition of alkyl iodides to electron-deficient alkenes (Scheme 13).[146] With α-bromo carboxylic acids **10** has been employed for generating C-radicals which react with aliphatic alkenes and vinyl ethers.[147]

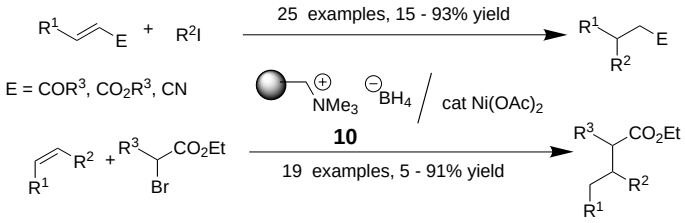
Table 6. C–C Coupling reactions using polymer-bound organotin reagents.

Reagent	Polymeric support	Substrate	C–C coupling product	Yield [%]	Ref.
	PS (non-cross-linked)			66	[142]
	PS			10–93	[106a, 110, 143]
	PS			89	[144]
	PS			66–78	[144]
	PS	R^1X	R^1R	51–96	[145]

[a] AIBN = azobisisobutyronitrile.



Scheme 12. Polymer-bound phosphonate **29** generated by ring-opening metathesis (ROMP).

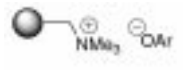
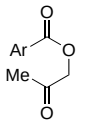
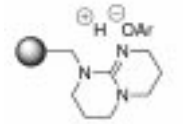
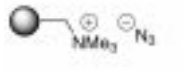
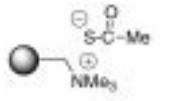
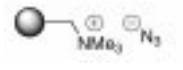
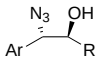
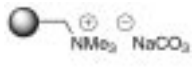


Scheme 13. C–C coupling reactions promoted by nickel boride BER **10**.

3.5 Nucleophilic Substitution Reactions

Basic ion-exchange resins, which are loaded with various inorganic and organic anions (see Table 1) are ideally suited for promoting substitution reactions with organic halides and sulfonic esters. Immobilized phenolates and thiophenolates as well as carboxylates exhibit excellent reactivity. It can be argued that these functionalized resins could also be classified as polymers suitable for the "capture–release" technique (Scheme 1; method D), as the anion is immobilized prior to release into solution. However, many immobilized nucleophiles useful for S_N reactions are of an inorganic nature for which the resin "capture–release" terminology would be stretched too far. For the purpose of conceptual homogeneity organic nucleophiles are also included in Table 7.

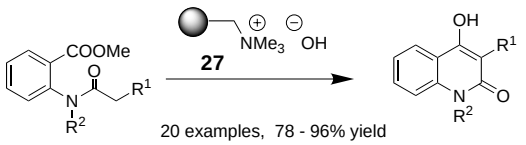
Table 7. Polymer-bound nucleophiles in S_N reactions.

Reagent	Polymeric backbone	Substrate	Product	No.[a]	Yield [%]	Ref.
	Amberlite IRA 900	RX, X = Cl, Br, I	ROAr	20	0 – > 99	[148]
	IRA 400	Me_2SO_4	MeOAr	11	40 – 92	[149]
	IRA 400	*t*BuMe$_2$SiCl	*t*BuMe$_2$SiOAr	7	65 – 96	[150]
	Amberlite IRA 400	MeC(O)CH$_2$Cl		8	89 – 96	[151]
	PS	RX, R = Acyl, Allyl, X = Cl, Br	ROAr	11	47 – 98	[152]
		Ar^{1}F	Ar^{1}OAr	2	73 – 75	[152]
	Amberlite IRA 400	RX, X = Cl, Br	ArSR	8	93 – 99	[153]
	Amberlite IRA 400	RX, X = Br	RCN	7	52 – 98	[154]
	Amberlite IRA 400	RX, X = Cl, Br, I, OTs	RN$_3$	16	60 – > 99	[155]
	Amberlyst A-26	RX, X = Cl, Br, OTs	CH$_3$COSR	11	80 – 95	[156]
	Amberlyst A-26	RX, X = Cl, Br	RSCN	4	49 – 91	[159]
	Amberlite IRA 400			3	68 – 86	[157]
	Amberlyst A-26	RCH$_2$X, X = Br, I	RCH$_2$OH	7	90 – 95	[158]
	Amberlite IRA 400	RX, X = Cl, Br	RNO$_2$	7	10 – > 99	[148]
	Amberlyst A-26	RX, X = Cl, Br		2	83 – 85	[159]
	Amberlyst A-26	RX, X = Cl, Br, I	RSePh	7	76 – > 99	[160]

[a] Number of examples.

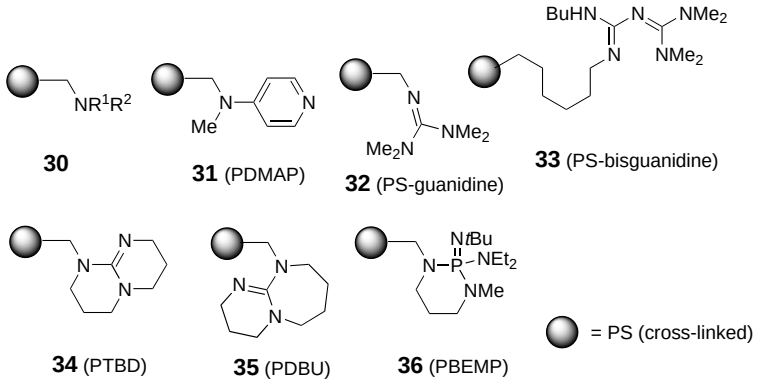
3.6 Polymer-Supported Deprotonation

Polymer-bound bases have been widely employed for the deprotonation of organic substrates, alkylation, and acylation reactions. Basic ion-exchange resins such as **27**[161] can be used for the preparation of 4-hydroxyquinolin-2(1*H*)-ones by an intramolecular Claisen-type condensation (Scheme 14).[162] During this reaction polymer-supported carbonate, a rather strong base in organic solvents, and the less-basic immobilized acetate (see Scheme 34) are produced. The reactivity differences of these bases allow for selective transformations.[163]

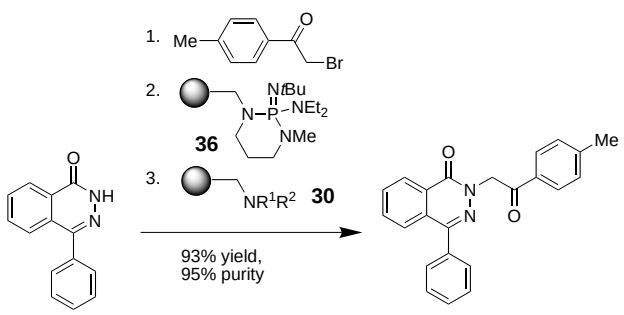


Scheme 14. Intramolecular Claisen-type condensation promoted by basic ion-exchange resin **27**.

In some cases, the polymer-support is directly deprotonated with strong bases like butyllithium or by radical anion induced reductive metallation of polymer-bound thioethers.[164] These procedures afford metallated polymers which show similar properties to LDA or the lithiated trityl group.[165] Further important polymer-anchored bases are readily obtained when Merrifield resin is treated with primary and secondary amines. By means of this substitution aminomethylpolystyrenes **30**, polymer-supported dimethylaminopyridine (PDMAP) **31**,[166] guanidines **32**[167] and **33**,[168] and particularly the cyclic analogues, such as 1,5,7-triazabicyclo[4.4.0]dec-5-ene[169] (PTBD) **34** and 1,8-diazabicyclo[5.4.0]undec-7-ene[169] (PDBU) **35** have become available. Even Schwesinger's phosphazene base, can be conveniently attached to a polymeric support P-BEMP (2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphonine) **36**[170] without loss of the strong basic character ($pK_B = 27.5$ in CH_3CN).

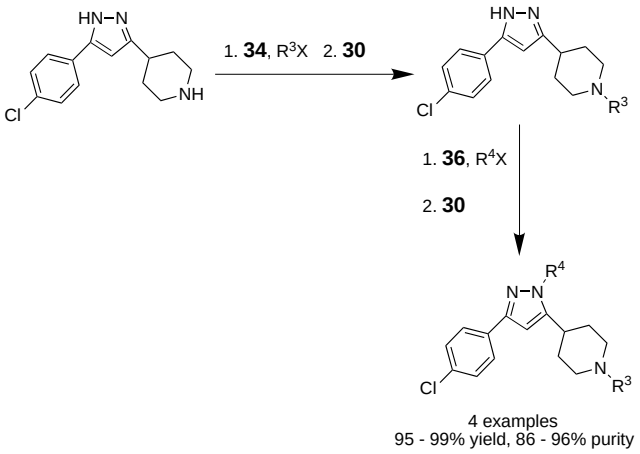


These bases have been utilized for N-benzylation of amines[171] as well as N-alkylation of weakly acidic aromatic N-heterocycles.[172] Treatment of 2*H*-phtalazin-1-one with α-bromo ketone in the presence of **36** efficiently yields an N-alkylated product with high purity (Scheme 15).[166] In addition, aminomethylpolystyrene **30** ($R^1 = R^2 = H$) was added to remove remaining excess of alkylating agent.



Scheme 15. Base-promoted alkylation of 4-phenyl-2*H*-phtalazin-1-one.

In comparison to PBEMP **36**, reagent PTBD **34** shows reduced basicity and has turned out to be an inefficient base for the deprotonation of aromatic N-heterocycles. Nevertheless, polymer-bound base **34** promotes alkylation of piperidines, this property was exploited in a two-step one-pot alkylation cascade leading to alkylated pyrazoles (Scheme 16).[173]



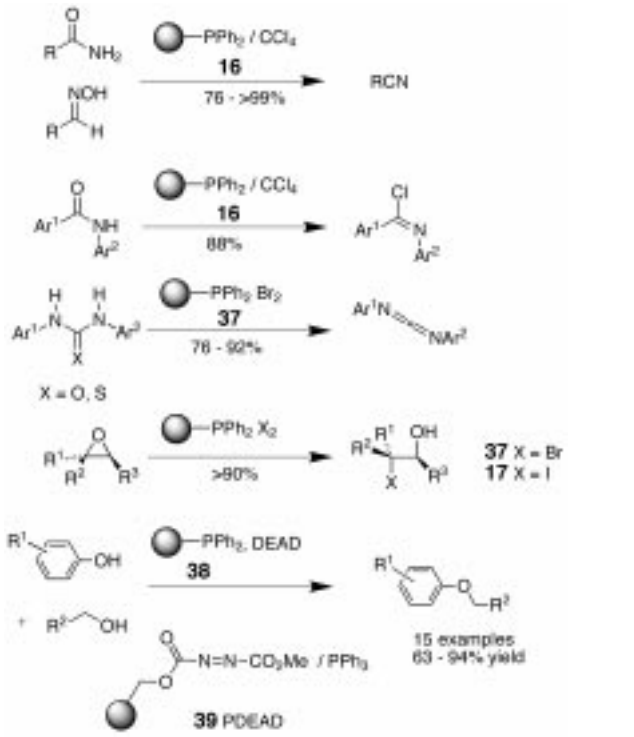
Scheme 16. Polymer-bound bases **30** ($R^1 = R^2 = H$), **34**, and **36** in a two-step one-pot alkylation of piperidinyl pyrazole.

3.7 Miscellaneous

Various functionalized polymers derived from triphenylphosphane are strongly dehydrating (Scheme 17).[174] Thus, the reagent system poly-TPP/CCl_4 **16** can be used to transform primary carboxamides and aryl oximes into nitriles;[175] imidoyl chlorides are generated when secondary amides are employed instead. Polymer-supported triphenylphosphane dibromide **37** is ideally suited for the preparation of unstable carbodiimides from ureas and thioureas.[176] Furthermore, poly-TPP-dihalides **17** and **37** promote esterifications of carboxylic acids,[177] acetalization of carbonyl compounds,[178a] and can be used for promoting ring opening of oxiranes to the corresponding halohydrines. The mild workup and simple removal of the phosphane from the reaction mixture enables the unstable products to be isolated in high yields.[178b]

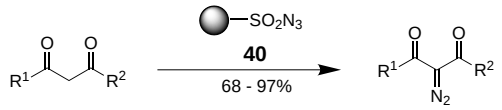
Another important use of polymer-bound triphenylphosphane **38** is the Mitsunobu-reaction, for example, by coupling phenols and alcohols to aryl ethers in the presence of diethyl azodicarboxylate (DEAD).[179] Alternatively, the polymer-assisted Mitsunobu reaction was achieved by immobilizing alkyl azodicarboxylates on polystyrene.[180] Reagents like **39** are able to replace hydroxy groups by oxygen, nitrogen, and carbon nucleophiles with an efficiency comparable to that of the solution methods. Furthermore, polymer-supported triphenylphosphane **38** promotes the isomerization of (*Z*)-nitro olefines to the corresponding (*E*)-isomers in high yield and with excellent selectivity.[181]

Polymer-bound tosyl azide **40** was prepared from Amberlite XE 305 by chlorination with chlorosulfonic acid followed by



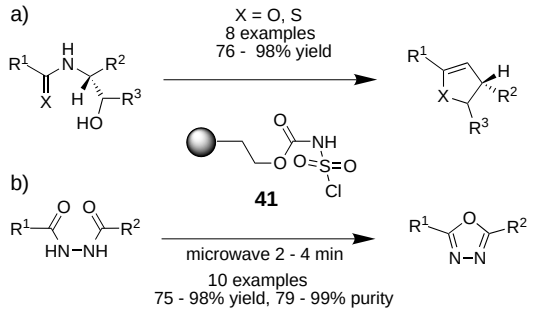
Scheme 17. Polymer-bound triphenylphosphane.

displacement of the chlorine in the intermediate polymer-supported sulfonyl chloride with azide. Reagent **40** is able to promote diazo transfer onto β-dicarbonyl compounds (Scheme 18).[182]



Scheme 18. Polymer-supported sulfonyl azide.

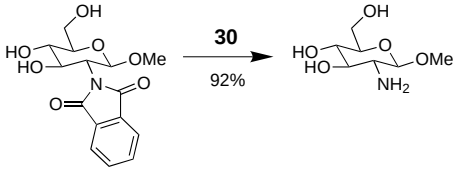
The first example of a soluble polymer-supported Burgess reagent was disclosed by Wipf and Venkatraman.[183] They employed **41** (attached to PEG) for the cyclodehydration of β-hydroxy amides and thioamides to oxazolines and thiazolines, respectively (Scheme 19). The utility of these reagents was further demonstrated in the synthesis of 1,3,4,-oxadiazoles



Scheme 19. Applications of polymer-bound Burgess reagent; a) PEG polymer, b) cross-linked PS.

starting from 1,2-diacylhydrazines with microwave radiation (**41** attached to Merrifield resin).[184]

The N-phtalimido and N-tetrachlorophtalimido groups on carbohydrate derivatives are removed using alkyl diamines immobilized on polystyrene, thereby leaving the protecting group on the resin while the free sugar remains in solution (Scheme 20).[185]



Scheme 20. Polymer-supported deprotection of the carbohydrate-bound phthalimido group ($R^1 = H$, $R^2 = CH_2NH_2$).

Finally, acylation including trifluoroacetylation[186] of amines, carboxylic acids,[187] and alcohols,[188] as well as the formation of internucleotide bonds[189] has been achieved with various polymer-bound reagents and some selected examples of these reagents are given in Section 5.

4. Polymer-Assisted Purification

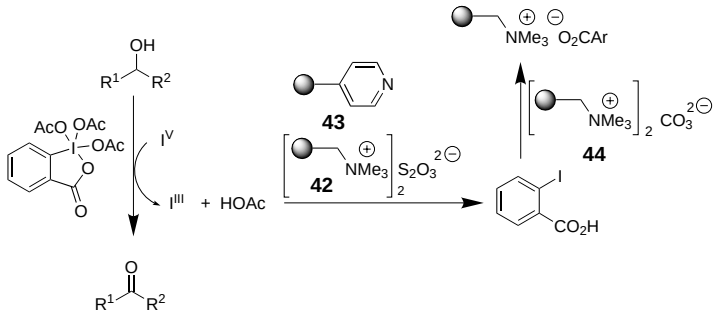
In automated parallel solution-phase chemistry each aqueous extractive workup requires the optimization of a new step and usually a need for chromatographic purification. Polymer-assisted purification techniques offer the chance to circumvent these extraction and chromatographic purification steps. Usually the removal of an excess of a reagent, unreacted starting materials, or by-products from reaction mixtures is achieved by employing polymer-supported reagents with complementary reactivities.[190] Three closely related variants of polymer-assisted purification protocols have been reported: 1) solid-supported scavengers, 2) sequestration by "tagging" the impurity with the help of sequestration enabling reagents (SER) prior to its polymer-assisted removal, and 3) sequestration by post polymerization. Each method will be briefly discussed.

4.1 Scavenging Reagents

In 1999 several review articles about polymer-supported scavenger reagents (Scheme 1, method C), the most widely utilized functionalized polymers for purification, were published[10, 190, 191] so that only selected examples are given in this report. These reagents can be roughly divided into scavengers for electrophiles and for nucleophiles. It is clear that the principle behind the standard scavenging protocols is the same: electrophiles react with polymer-bound nucleophiles and acids can be removed with polymer-bound bases and vice versa. This complementary reactivity has been used in nearly all carbon–heteroatom bond-forming reactions. Despite the wealth of methods for the removal of these functionalized compounds, there are few—if any—examples of the scaveng-

ing of reactants from C–C coupling reactions. This may be because of the lack of need as protocols for organometallic complexes in automated solution-phase parallel synthesis are rare.

Often ion-exchange resins have served as functionalized polymers for purification. They can either serve as acidic or basic catalysts in parallel solution chemistry or as scavenger reagents for by-products or reaction products. An advantage of ion-exchange resins is that they can be simply reactivated after the sequestration step. This property was exploited in the purification of molecules that can be protonated by ion-exchange chromatography with acidic resins, and has occasionally been combined with acid or base catalysis in preceding reactions.[148a, 192] An example of this method is the deprotection of *tert*-butoxycarbonyl (Boc) protected amines mediated by Amberlyst A-15 and their purification by ionic resin capture.[193] To enhance the use of ion-exchange resins they have been loaded with other counter ions which not only allow purification by neutralization but also by, for example, oxidation or reduction (for examples see Table 7). Even incompatible functionalities can be employed using mixed-bed reactors (Scheme 21). Excess Dess–Martin periodinane as well as its reduced iodine(III) form were removed

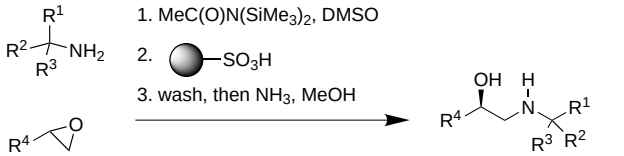


Ref. [194a] 8 examples; 68 - 97% yield
Ref. [194b] 28 examples; 9 - 94% yield, 68 - >99% LC-purity

Scheme 21. Polymer-supported purification of by-products formed in the Dess–Martin oxidation.

by Amberlyst A-26, loaded with thiosulfate **42**, to form *o*-iodobenzoic acid. In addition, acetic acid which was formed as a by-product was scavenged by poly(4-vinylpyridine) **43**. Finally, the third functionalized polymer, Amberlyst A-26 in the carbonate form **44**, or other polymer-supported bases such as **30** ($R^1 = R^2 = Me$) and **34** were used to remove the *o*-iodobenzoic acid from the reaction mixture. Remarkably, sequential purification was unnecessary.[194]

Ethanolamines were prepared by a highly optimized three component reaction using primary amines which were N-silylated in situ followed by nucleophilic addition to various oxiranes (Scheme 22).[195] Using this procedure, bisalkylation of the primary amines was avoided. Finally, the use of a cation-exchange resin allowed rapid purification of a library containing 48 compounds.



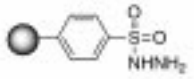
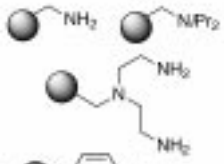
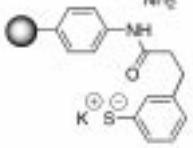
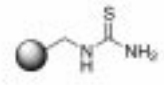
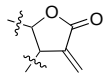
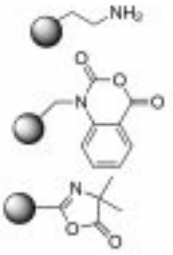
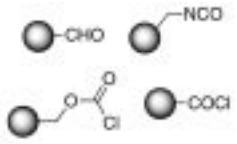
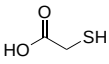
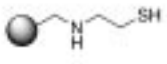
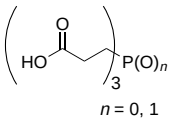
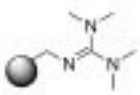
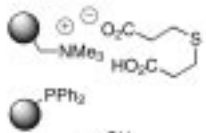
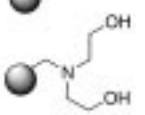
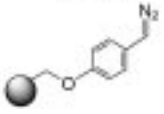
48 examples
14 - 99% yield, 67 - >99% purity

Scheme 22. Polymer-supported purification after aminolysis of oxiranes.

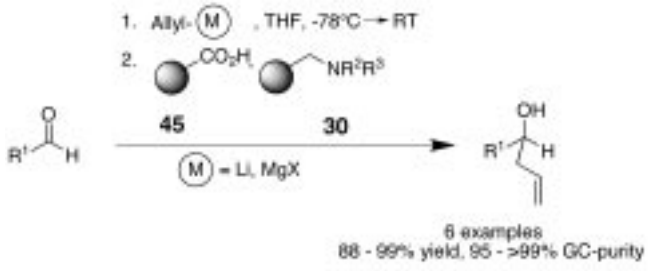
A large number of covalently bound reagents for scavenging certain functional groups are known of which only the most important examples are summarized in Table 8. One of the earliest examples of the purification of reaction mixtures by using polymeric scavengers was described by Fréchet and co-workers. in the early eighties.[196] They developed a methodology for removing allergenic α-methylene-γ-butyrolactones from natural oils by using aminated polystyrene resins (Table 8, entry 5). In their detailed study the influence of cross-linking, the chain length of the aminoalkyl residue, as well as the nature of the solvent on the efficiency of the scavenging process was addressed. Recently, Coppola[197a] along with Fréchet[197b] and co-workers disclosed a new scavenger reagent for amines (Table 8, entry 6). Thus, it is possible to attach isatoic anhydride to a Merrifield resin which then readily reacts with amines to form CO_2 as the only by-product.

Aldehydes and ketones are removed under mild conditions using polymer-supported *p*-toluenesulfonyl hydrazide (PS-Ts-$NHNH_2$; Table 8, entry 1).[198] In comparison with polymer-bound benzyl hydrazide the PS-Ts-$NHNH_2$ is better suited for storage and it shows superior scavenging properties. In thorough studies, it was shown by Dressman, Hahn, and co-workers [202] and by Booth and Hodges[204] that polymer-bound amines are efficient scavenger reagents for isocyanates, acid chlorides, and many other electrophilic functional groups after these substrates have been employed in solution-phase parallel synthesis (entry 2). Polystyrene-based benzaldehyde was used for removing various nucleophiles including amines, hydrazines, keto esters, reducing agents, C-nucleophiles such as Meldrum's acid, and organometallic reagents (entry 7).[199–202, 209] In this context, it is noteworthy that polymer-bound isocyanate, which behaves in a similar manner to formyl polystyrene, has been employed for distinguishing between secondary and tertiary amines.[204] For scavenging α-halogenated carbonyl compounds from complex reaction mixtures polymer-bound thiourea has served as a suitable reagent (entry 4).[208] Another scavenging reagent, namely polymer-supported guanidine, has been developed for removing remaining triscarboxyethyl phosphane, phosphane oxide, as well as HBr (entry 10).[210] Recently, *N*,*N*-diethanolaminomethyl polystyrene was prepared to accomplish purification of Suzuki cross-coupling products (Table 8, entry 12).[213] Nucleophilic addition of alkyl anions to carbonyl compounds affords intermediate alkoxides which are protonated by ion-exchange resin **45**. In addition, unreacted or excess aldehyde is sequestered as an imine by the polymeric amine **30** ($R^2 = H$, $R^3 = (CH_2)_2NH_2$; Scheme 23).[201]

Table 8. Covalently immobilized scavenging reagents.

Entry	Functional group to be scavenged	Reagent[a]	Ref.
1	RCHO, RCOR′		[198]
2	RCO_2H, RSO_3H, RCOCl, RSO_2Cl, RNCO, RNCS, $(RCO)_2O$, RCHO		[199 – 206]
3	RX		[207]
4			[208]
5			[196]
6	RNH_2		[197]
7	R^1R^2NH		[199 – 202, 209]
8	RLi, RMgX (X = Br, Cl)		[201]
9			[205]
10			[210]
11	reductive work-up of ozonolysis reaction		[211]
12			[212, 213]
13[b]	RCO_2H		[214]

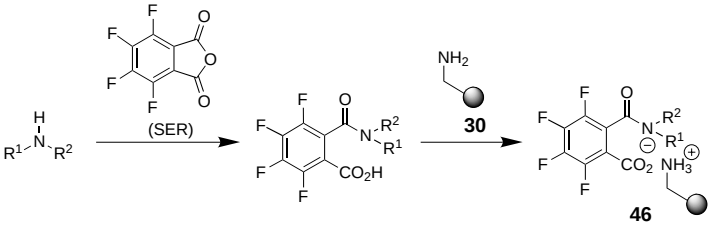
[a] Polystyrene (1 – 2 % cross-linked with DVB). [b] Wang-resin.



Scheme 23. Polymer-supported scavenging of by-products generated in the nucleophilic alkylation of aldehydes.

4.2 Purification by Using "Tagging" Reagents

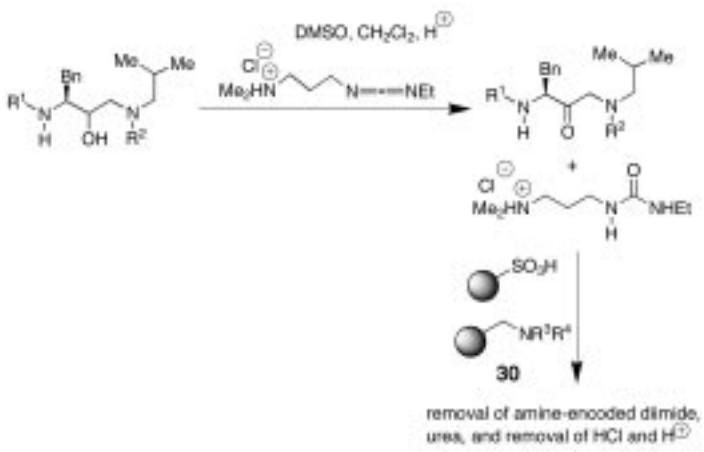
Sometimes by-products are not reactive enough to be scavenged quantitatively by functionalized polymers. For this reason, highly active bifunctional soluble compounds, termed "sequestration enabling reagents" (SERs), were developed. These reagents transform less-reactive functional groups, in solution, into easily scavenged species. Examples exist for both electrophilic and nucleophilic SERs.[215] The "tagging" of reactive functional groups is most often accomplished with amino groups. They play the active role in the sequestration process by reacting with the polymer-based scavenger reagents listed in Table 8, entry 7. Treatment of an excess of amine with the highly electrophilic tetrafluorophthalic anhydride leads to an addition product which then can be sequestered as polymer **46** with the help of the polymer-bound amine **30** (Scheme 24).[200, 216]



Scheme 24. Tetrafluorophthalic anhydride, a sequestration enabling reagent for amines.

The concept of scavenging enabling reagents is closely related to that of a second method, that is the tagging of soluble reagents or products. An example of a soluble, "tagged" reagent is presented in Scheme 25. Parlow and coworkers developed an elegant purification strategy for the Pfitzner – Moffat oxidation of alcohols to the corresponding carbonyl compounds.[201] The parallel oxidation of hydroxyethyl amines was effected by a tertiary-amine-tagged carbodiimide in combination with DMSO and a catalytic amount of acid. The tagged urea and carbodiimide resulting from this process as well as acids were then scavenged by employing two ion-exchange resins.

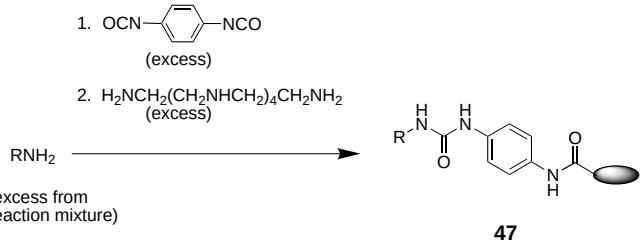
Only in a few cases has the product been tagged. Crown-ether-tagged peptides were readily separated from the reaction mixture by affinity chromatography using aminomethylated (in CF_3CO_2H form) polystyrene columns.[217]



Scheme 25. "Tagged" carbodiimide in Pfitzner–Moffat oxidations and purification by ion-exchange resins ($R^3 = R^4 =$ methyl).

4.3 Purification by Post Polymerization

Barrett, Smith, and Zecri added the latest method to the growing number of purification techniques based on insoluble materials which they named "impurity annihilation" (Scheme 26).[218] This method, in fact, does not rely on



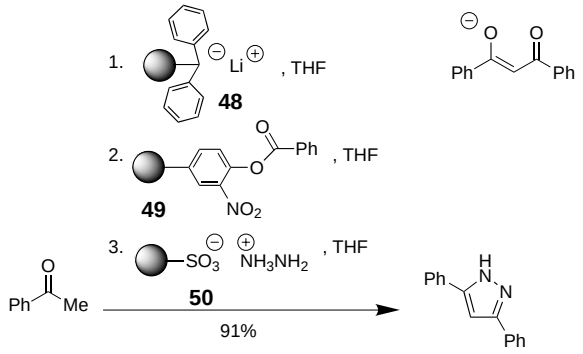
Scheme 26. Removal of amines by incorporation into a polyurethane matrix.

polymer-bound reagents. Instead, a soluble polyamine is added to the reaction mixture and the insoluble polymer support is formed during the process of scavenging. Thus, after performing amide or sulfonamide bond-forming reactions excess amines were treated with excess 1,4-phenylene diisocyanate and then with pentaethylenehexamine affording the insoluble polyurea **47** which can easily be removed by filtration. This strategy requires very careful optimization of the reaction conditions to avoid the creation of soluble impurities by the reaction of the diisocyanate with two equivalents of the amine to be scavenged. Furthermore, yields for the product could be reduced by trapping during the polymerization process. However, "impurity annihilation" shows promise because only solutions are employed, which allows automation through liquid-handling robots.

Despite the fact that only selected examples have been listed here, it is evident that, with the sheer number of possibilities of functionalizing polymers as well as tagging soluble reagents, purification based on scavenging techniques will play an increasing role in automated solution-phase synthesis in the future.

5 Polymer-Assisted Multistep Solution-Phase Syntheses

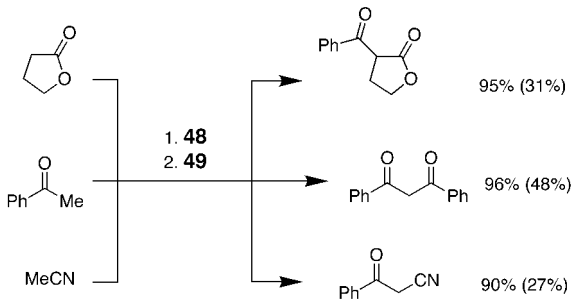
The renewed interest in functionalized polymers whether employed stoichiometrically or as catalysts will only prevail and be sustained if they prove to be powerful tools in automated parallel synthesis and multistep sequences. For this purpose, all the synthetic techniques that were presented in Sections 3 and 4 and in addition the emerging polymer-supported catalysts need to be combined in an intelligent and creative way. Much evidence has already been collected, particularly by applying scavenger reagents and in employing "capture–release" technology, which shows that functionalized polymers can be employed conveniently in automated parallel synthesis by using conventional automation facilities such as liquid-handling devices. As shown in Scheme 32 compound libraries with up to 88 members were generated using this solid-phase technique. However, up to now multistep syntheses promoted by functionalized polymers have led to hardly any novel synthetic sequences. As long as the number of polymeric reagents is limited, this field can only follow known strategies by successively exchanging soluble reagents by their parent polymer-anchored counterparts. In this context, the Patchornik group [219] was the pioneer in this field. Unlike contemporary strategies, they initiated their studies by anchoring two different reactive groups, namely an enolizable and a nonenolizable ester to the same resin and studied the base-promoted "intrapolymeric" condensation, which proceeded in much better yields and with higher purity than the corresponding solution variant. As a continuation of their work, Cohen, Patchornik, and Kraus switched their attention to the development of the first multicomponent synthesis based on several reagents attached to different polymer supports, which they named "Wolf and Lamb" reactions (after Isaiah 11:6 in the Old Testament).[220] In the presence of acetophenone they employed two insoluble polymer-supported reagents **48** and **49** which are "antagonists" in solution. Immobilized, and thus spatially separated the functionalized polymers did not interact when mixed (Scheme 27). Polymer-attached triphenylmethyl lithium **48** promoted deprotonation while reagent **49** acted as an acylating agent.[221] The acylation product, the dibenzoylmethane anion, was directly treated with polymer-supported hydrazine **50** to afford a disubstituted pyrazole in excellent yield. In a



Scheme 27. The first three-step synthesis aided by polymer-bound reagents.

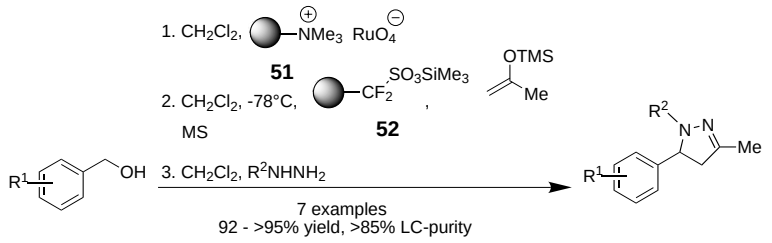
control experiment in solution the ketone formed in the first step was generated in reduced yield (48%), because it is more acidic than the starting ketone and thus protonates the starting enolate. The important message from this work was, that two reagents possessing high reactivity toward each other are rendered completely inactive by their attachment to two insoluble polymers. In such reactions both kinetic factors and equilibrium conditions differ from those prevailing in conventional reactions in solution, or in reactions utilizing a single polymeric reagent.[222]

In a later more detailed study, the use of strong bases such as **48** or polymer-supported LDA in conjunction with an acylating agent such as **49** was verified, using various CH-acidic organic substrates (Scheme 28).[165] A comparison of isolated yields for the final products was conducted and clearly revealed the superiority of the polymer-supported process over the pure solution variant.



Scheme 28. Polymer-supported α-acylation of CH-acidic compounds. The yields in parentheses are from the reaction in solution.

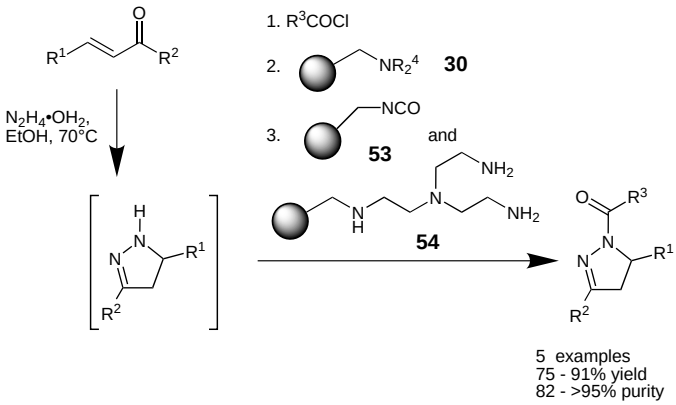
For the preparation of a library composed of 4,5-dihydro-1*H*-pyrazoles two polymer-supported reagents **51** and **52** were successfully employed (Scheme 29).[223] The sequence was initiated by oxidation of six different benzyl alcohols to the



Scheme 29. Polymer-supported synthesis of 4,5-dihydro-1*H*-pyrazoles (version 1). MS = Molecular sieve (4 Å).

corresponding benzaldehydes. Then a Mukaiyama aldol reaction was conducted by coupling these aldehydes with silyl enol ethers. This step was mediated by polymer-supported TMSOTf (TMS = trimethylsilyl; Nafion-TMS) **52** in the presence of 4 Å molecular sieves as a dehydrating agent, a reaction which is noteworthy, as it demonstrates that functionalized polymers may also be employed at low temperature. The synthesis was finally accomplished by treatment of the intermediate α,β-unsaturated ketones with hydrazine or methyl hydrazine to afford the target heterocycles in high yields after removal of volatile compounds.

An alternate polymer-assisted synthesis of pyrazoles was disclosed recently[224] in which the treatment of chalcones with hydrazine monohydrate resulted in unstable pyrazoline intermediates (Scheme 30). These intermediates were trapped in the presence of polymer-bound base **30** with electrophiles such as acid chlorides to provide N-acylated pyrazolines. A scavenging cocktail of polymer-supported isocyanate **53** and trisamine **54** was used to remove remaining pyrazoline and excess electrophile, respectively.

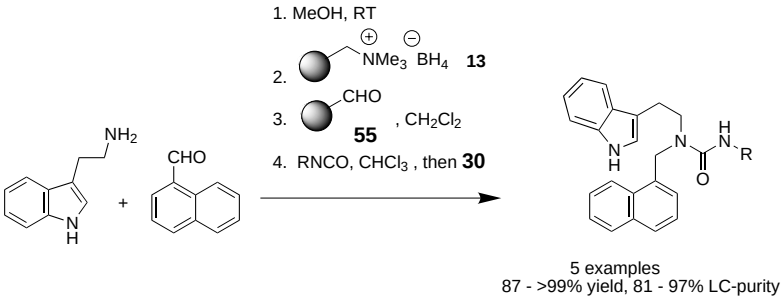


Scheme 30. Polymer-supported synthesis of pyrazoles (version 2; $R^2 = R^3 = 2$-propyl).

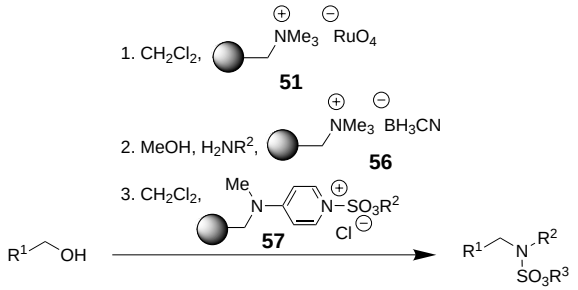
Trisubstituted ureas were prepared from three building blocks (Scheme 31).[199] Aldehydes and amines were coupled by means of reductive amination[225] with polymer-bound borohydride **13**. Excess of the starting amines was removed by polystyrene carboxaldehyde **55**. After filtration addition of a set of isocyanates gave a small library of ureas. Finally, the polymer-anchored amine **30** ($R^1 = R^2 = H$) removed excess of isocyanates.

Libraries of amines and sulfonamides were prepared by a three-step process fully controlled by polymer-supported reagents (Scheme 32).[226] A set of benzyl alcohols was oxidized to the corresponding aldehydes followed by reductive amination in the usual way using reagents **51** and **56** (see also Schemes 29 and 31). The authors point out that solution-phase synthesis using functionalized polymers can be conducted with the technical equipment used in combinatorial synthesis. The primary oxidation products were dispensed into 96 wells each containing the polymer-supported reducing agent. A robot was used to add various amines in methanol to the wells. Finally, the secondary amines were further functionalized using sulfonated amino pyridine polymers **57** which promoted sulfonation to sulfonamides. By using this technique, the preparation of a medium-sized compound library was achieved.

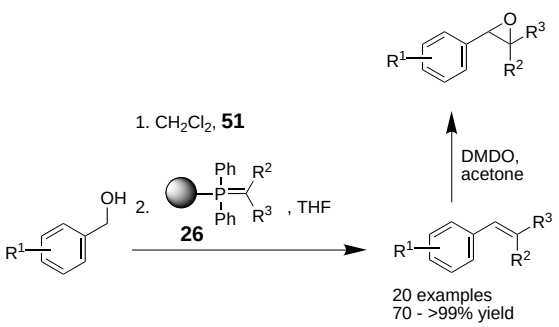
Another access to compound libraries based on polymer-supported reagents utilized polymer-bound phosphorous ylides **26** which were coupled with aldehydes, themselves prepared in the usual manner, to afford di- and trisubstituted alkenes (Scheme 33).[227] The *Z*/*E*-selectivity was moderate with the best ratios being 6:1. Finally, additional structural



Scheme 31. Polymer-supported synthesis of trisubstituted ureas $R^1 = R^2 = H$).



Scheme 32. Polymer-supported preparation of sulfonamides.

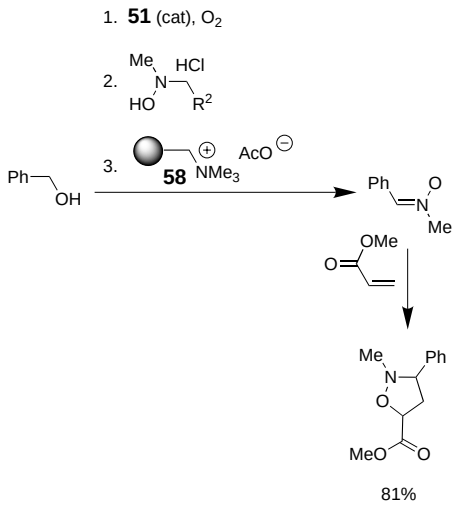


Scheme 33. Polymer-supported phosphorous ylides **26** in multistep syntheses (DMDO = dimethyldioxirane).

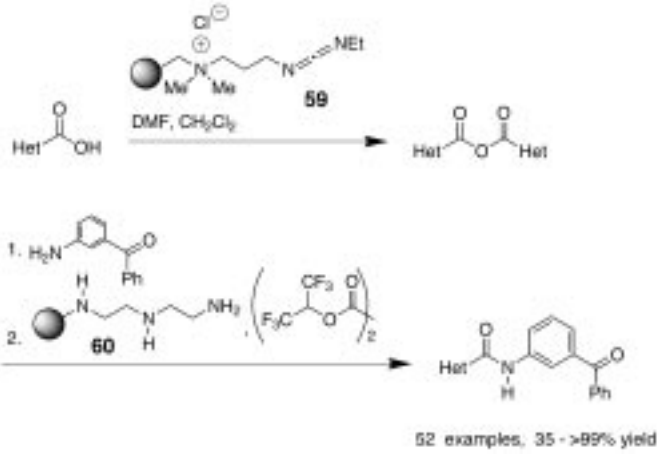
variation was achieved by dimethyldioxirane-promoted epoxidation, a suitable tool in this context, as reagent-derived by-products are commonly removed in vacuo.

Aldehydes prepared from the corresponding alcohols (c.f. Table 1, entry 10 and 11) were transformed into nitrones by condensation with primary hydroxylamines which were initially prepared in situ with the help of polymer-supported acetate **58** (Scheme 34).[228] Cycloaddition in the presence of methyl acrylate led to isoxazolidines like *N*-methyl-5-methoxycarbonyl-3-phenylisoxazolidine which was generated in a one-pot reaction in 81 % yield.

Another multistep synthesis takes advantage of the dehydrating power of polymer-bound carbodiimide **59** in the primary step which was used to prepare anhydrides from the respective heterocyclic substituted carboxylic acids (Scheme 35).[214c] These anhydrides were treated with a substituted aniline to afford a set of carboxamides. A well orchestrated mixture of additives was employed for removing both the acidic as well as the basic unreacted starting materials.



Scheme 34. Polymer-supported synthesis of isoxazolidines.

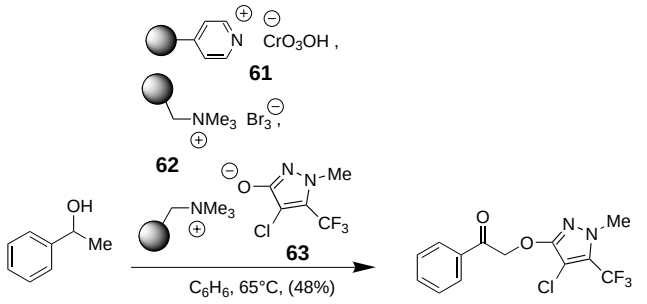


Scheme 35. Preparation of carboxamides involving the SER technique (Het = hetrocyclic residue).

Anhydrides and traces of the carboxylic acids were sequestered using polymer-supported amine **60**. In addition, hexafluoroisopropyl oxalate was used as a supporting sequestering reagent (see Section 4.2) to convert unreacted aniline into the monoamide. Both, the oxalate as well as the monoamide were then removed by **60**.

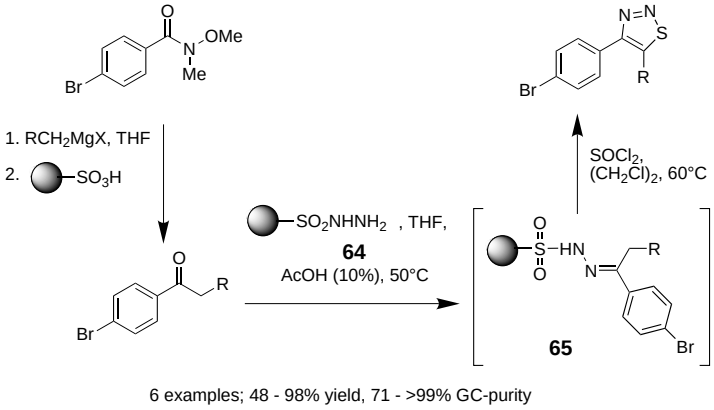
Parlow devised a three-step procedure based on polymer-supported dichromate **61**, perbromide on Amberlyst A-26 **62**, and Amberlite IRA-900 loaded with 4-chloro-1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-ol (**63**) to prepare substituted phenylethanone (Scheme 36).[229] Although only one compound was prepared the study clearly supports the view that different polymer-supported reagents can be handled simultaneously in one vessel under conditions that allow the soluble substrate to access all three polymers. In fact, when the reagents were employed successively, the substituted phenylethanone was prepared in only 42 % (instead of 48 %) yield underlying in this case the advantage of a one-pot multistep strategy.

1,2,3-Thiadiazoles were prepared, starting from a Weinreb amide which was alkylated with a variety of Grignard reagents to the corresponding ketones, using a sulfonic acid on a



Scheme 36. Polymer-supported synthesis of substituted phenylethanone.

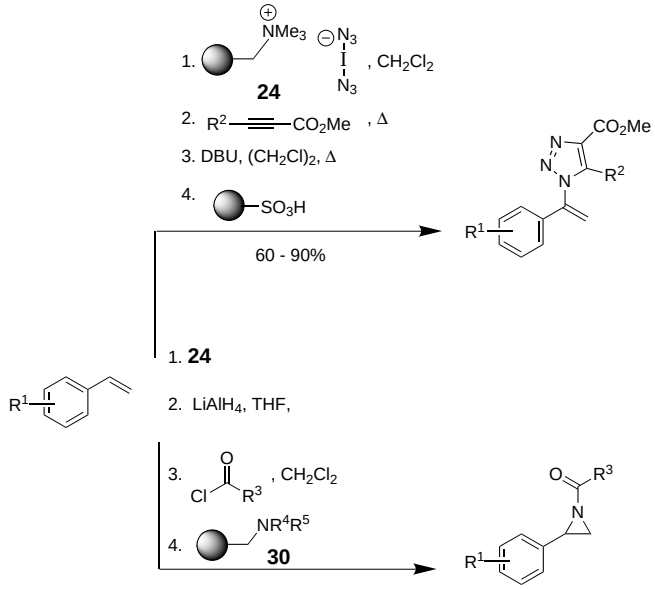
macroporous support. This led to decomposition of the tetrahedral intermediate (Scheme 37).[230] α-Methylene ketones are ideal starting materials for the Hurd – Mori cycliza-



Scheme 37. Polymer-supported synthesis of 1,2,3-thiadiazoles.

tion.[231] For this purpose, a gel-type polystyrene-sulfonyl hydrazide resin **64** was employed. Here, the polymeric reagent, which was originally designed for carbonyl scavenging applications (Section 4), was used in a resin capture – release strategy. After the keto group in **65** was trapped by **64** thionyl chloride mediated cleavage led to thiadiazoles in high yield and with good purity.

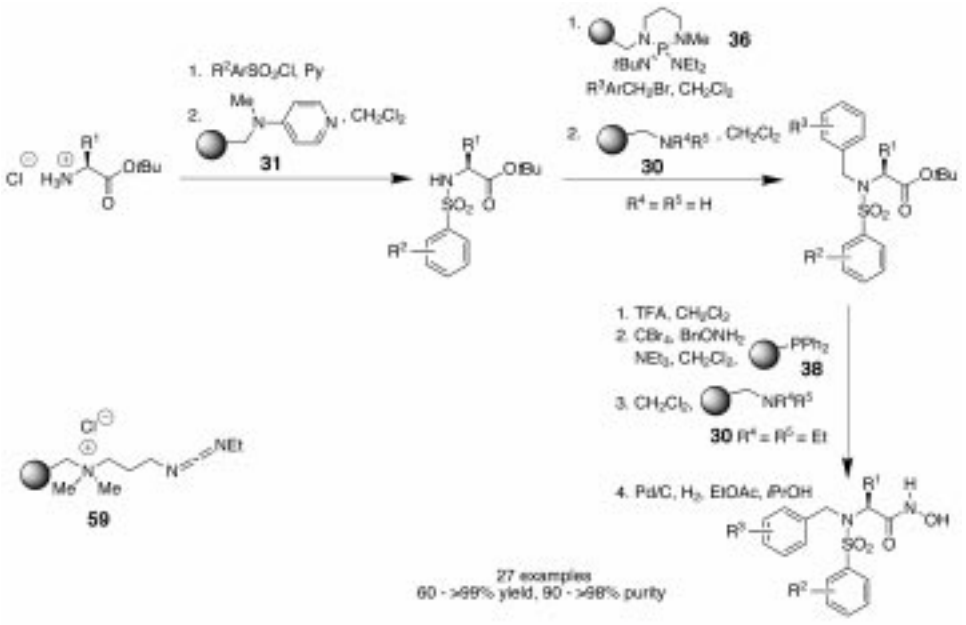
Azidoiodination of alkenes using novel polymer-based haloate(I) complex **24** provides a very useful entry to various nitrogen-containing heterocycles (Scheme 38).[130, 232] Thus, the primary addition products were used as 1,3-dipoles in a cycloaddition reaction with electron-deficient alkynes. After removal of excess alkyne in vacuo iodine was removed by elimination affording triazoles. The elimination was initiated with DBU which was finally removed by an acidic scavenging resin. Al-



Scheme 38. Polymer-supported synthesis of triazoles and acyl aziridines (DBU = 1,8-Diazabicyclo[5.4.0]undec-7-en, $R^4 = H$, $R^5 = CH_2CH_2NH_2$).

ternatively, α-iodo azides were transformed into the unprotected aziridines which are ideally suited for acylation. In this case, excess acylating agent was scavenged by the basic polymer **30** ($R^4 = H$, $R^5 = (CH_2CH_2NH_2)_2$)

Hydroxamic acids are known to exert an inhibitory effect on the matrix metalloproteins (MMP) class of enzymes. Polymer-supported reagents proved to be a very useful tool for constructing a small library of chiral hydroxamic acids (Scheme 39).[233] The *tert*-butyl ester hydrochlorides of glycine, valine, and phenylalanine were converted into aryl sulfonamides under classical conditions followed by using first aminomethyl polystyrene and then Amberlyst A-21 to desalt the solution by binding hydrogen chloride. Alternatively, this

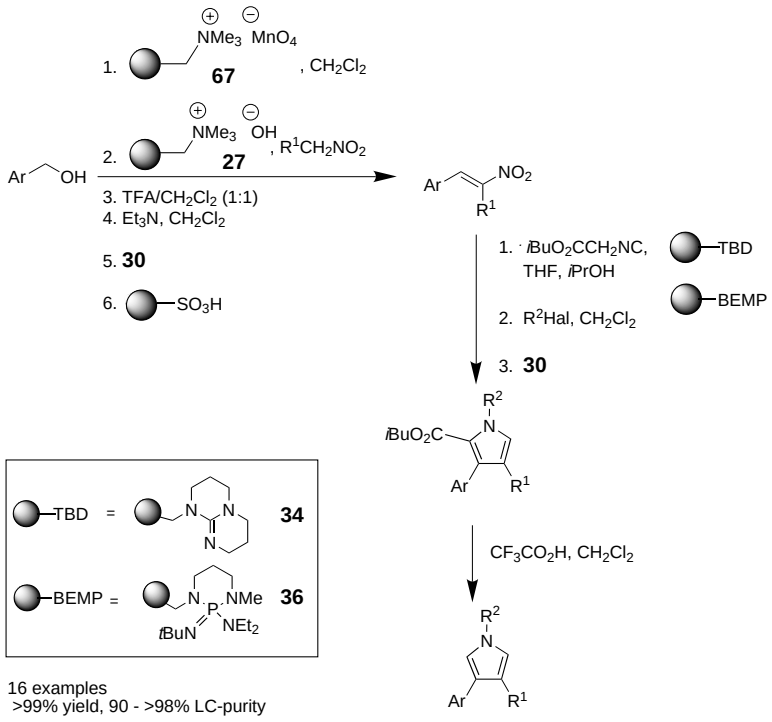


Scheme 39. Polymer-supported multistep synthesis of a hydroxamic acid library.

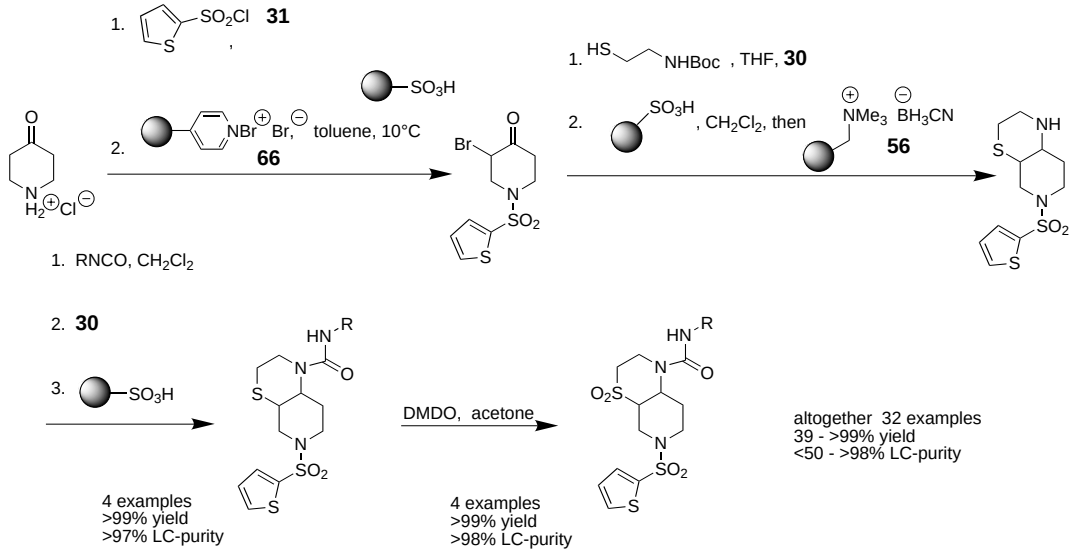
step can be achieved by activation of the amino group with polymer-supported dimethylaminopyridine **31**. Subsequently, benzylation of the nitrogen functionality was achieved using three equivalents of benzyl bromide and polymer-supported phosphazene base **36**. Excess of the alkylating agent was sequestered with aminomethyl polystyrene. Cleavage of the *tert*-butyl group and activation of the intermediate carboxylic acid in the presence of carbon tetrabromide and polymer-bound triphenylphosphane **38** afforded intermediate acyl bromides which were coupled with *O*-benzyl hydroxylamine to give the corresponding hydroxamic acid esters. For workup, aminomethyl polystyrene **30** was employed for sequestering acid anhydrides, the free acid, and remaining acyl bromides. The sequence was terminated by catalytic hydrogenation to furnish the target compounds. Remarkably, direct formation of hydroxamic acids from the carboxylic acids with *O*-benzyl hydroxylamine using polymer-supported cyclohexyl carbodiimide **59** was not successful.

Ley and co-workers developed a route to piperidino-thiomorpholines using a series of polymer-anchored reagents (Scheme 40).[234] The secondary amino functionality of 4-piperidino hydrochloride hydrate was transformed into various sulfonamides, promoted by polymer-supported (dimethylamino)pyridine **31** followed by the addition of acidic Amberlyst 15 as the sequestering agent. This allowed removal of the remaining amine. This step was followed by α-bromination of the keto functionality for which polymer-supported pyridinium bromide perbromide **66** was used. The α-bromoketone was then treated with *N*-Boc protected 1-amino-ethane-2-thiol aided by Amberlyst A-21 **30** ($R^1 = R^2 = Me$) as a base. This treatment effected substitution. After ion-exchange-mediated removal of the protection and imine formation polymer-supported reduction using cyanoborohydride **56** afforded thiomorpholine derivatives (*trans*:*cis* = 2:1). The amino function was further modified with different isocyanates, by-products, or excess reagent and was sequestered using two polymer-supported reagents. The resulting thiomorpholine derivatives were finally oxidized to the corresponding sulfones using dimethyldioxirane under standard conditions.

Also pyrroles can be prepared by a polymer-supported synthetic sequence (Scheme 41).[235] Here, the synthesis was initiated by the oxidation of a benzyl alcohol using polymer-supported permanganate **67**. This step was followed by the Henry reaction in which nitroalkanes were deprotonated with Amberlite IRA-420 **27**.[161] After trifluormethylacylation of the 1-hydroxy-2-nitro compounds elimination was effected by treatment with triethylamine. Final, desalting of the reaction



Scheme 41. Polymer-supported multistep synthesis of pyrroles ($R^3 = R^4 = H$).

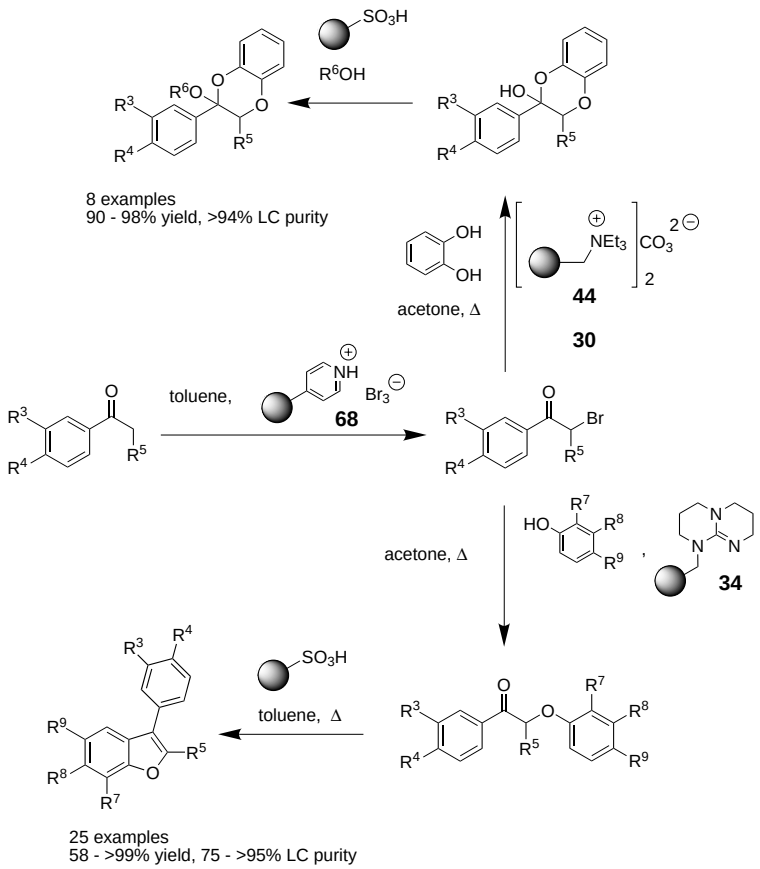


Scheme 40. Polymer-supported multistep synthesis of two piperidino-thiomorpholines.

mixture involved the use of two sequestering agents to afford various nitroalkenes. The pyrrole ring was then constructed by a 1,3-dipolar cycloaddition with *tert*-butyl isocyanoacetate in the presence of polymer-supported guanidine base (PTBD) **34**. Alkylation of the ring nitrogen was possible using the very strong polymer-supported Schwesinger's base **36** which yielded tetrasubstituted pyrroles. In conjunction with aminomethyl polystyrene **30** excess alkylating agent was sequestered, followed by decarboxylation by treatment with trifluoroacetic acid to furnish trisubstituted pyrroles.

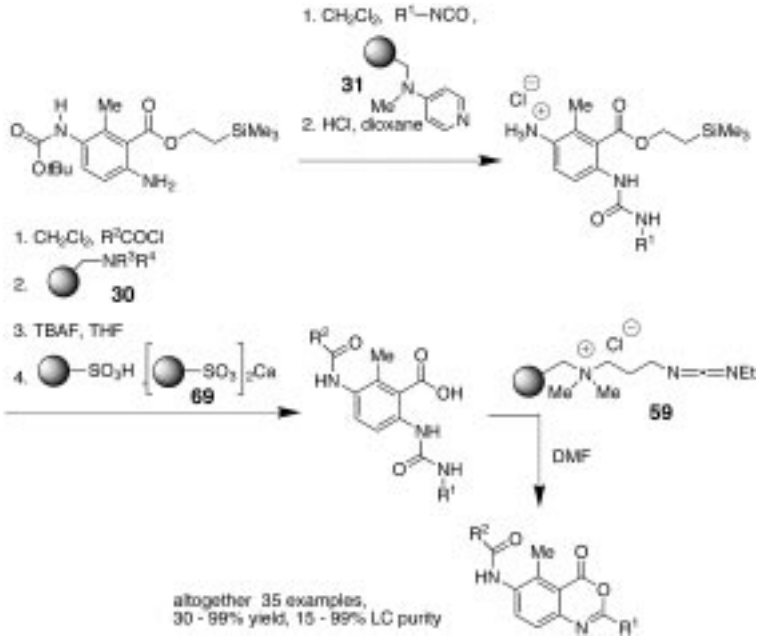
A three-step sequence was developed to synthesize an array of substituted benzodioxane derivatives (Scheme 42).[236, 237] Substituted acetophenones were initially α-brominated using polymer-attached pyridinium bromide perbromide **68**. Treatment with catechols in the presence of two equivalents of polymer-supported carbonate **44** afforded benzodioxanes as a mixture of the open-chain and ring-closed tautomers. Workup involved the addition of aminomethyl polystyrene **30** which captured unreacted catechol and traces of α-bromo ketones. Finally, a *trans*-acetalization reaction was effected in the presence of the acidic ion-exchange resin Dowex 50 in methanol or ethanol to afford 1,4-benzodioxanes.

In a similar manner, substituted 3-phenyl benzofurans were prepared in three steps from acetophenones by using polymer-supported pyridinium bromide perbromide **68**, triazabicyclodecene **34**, and Amberlyst 15 (Scheme 42). As for most polymer-based multistep syntheses developed no chromatographic purification was required in preparing a library of 25 compounds. When α-brominated acetophenones were treated with a strong polymer-bound base and thiourea 2-amino-1,3-thiazoles (four examples) were formed, again with high yields (47 – > 95 %) and excellent purities (> 95 %).[236]



Scheme 42. Synthetic routes to benzodioxanes and benzofurans promoted by polymer-supported reagents (**30**: $R^3 = R^4 = H$).

Finally, a five-step solution-phase synthesis of a benzoxazino library based on functionalized polymers accomplished by Parlow, Vazquez, and Flynn is worth mentioning (Scheme 43).[238] Suitably protected bisfunctionalized aniline served as a starting scaffold to allow for orthogonal deprotection. Acylation of the amino group was supported by polymer-bound dimethyl pyridinamine **31** which allowed the scavenging of excess acylating agents. Proton-induced removal of the Boc-group afforded aniline hydrochloride salts. This paved the way for acylating the second amino group and here again the product was purified with the help of a polymer-supported amine **30** ($R^3 = R^4 = Me$). Deprotection of the 2-(trimethylsilyl) ether under classical conditions (tetrabutyl ammonium fluoride (TBAF)) was followed by use of two polymer supported reagents which allowed efficient desalting of the reaction mixture. While polymer-bound sulfonic acid helped to remove the tetrabutyl ammonium cation from the corresponding acid by filtration, the immobilized calcium salt **69** trapped excess fluoride and led to the formation of insoluble calcium fluoride.[200] The final step involved ring closure using polymer-supported carbodiimide **59** to provide benzoxazinones. It is noteworthy that the five-step sequence



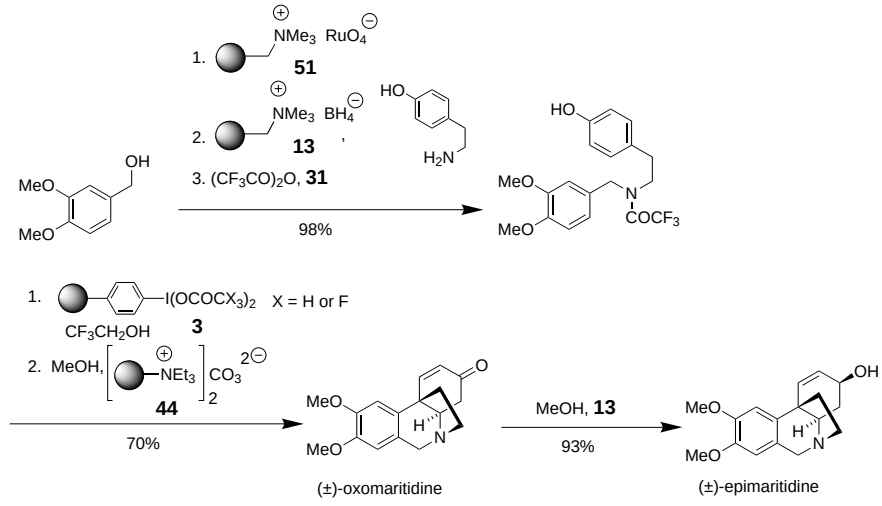
Scheme 43. Polymer-supported synthesis of a benzoxazino library ($R^3 = R^4 = Me$).

was performed in an automated parallel fashion using a commercial synthesizer.

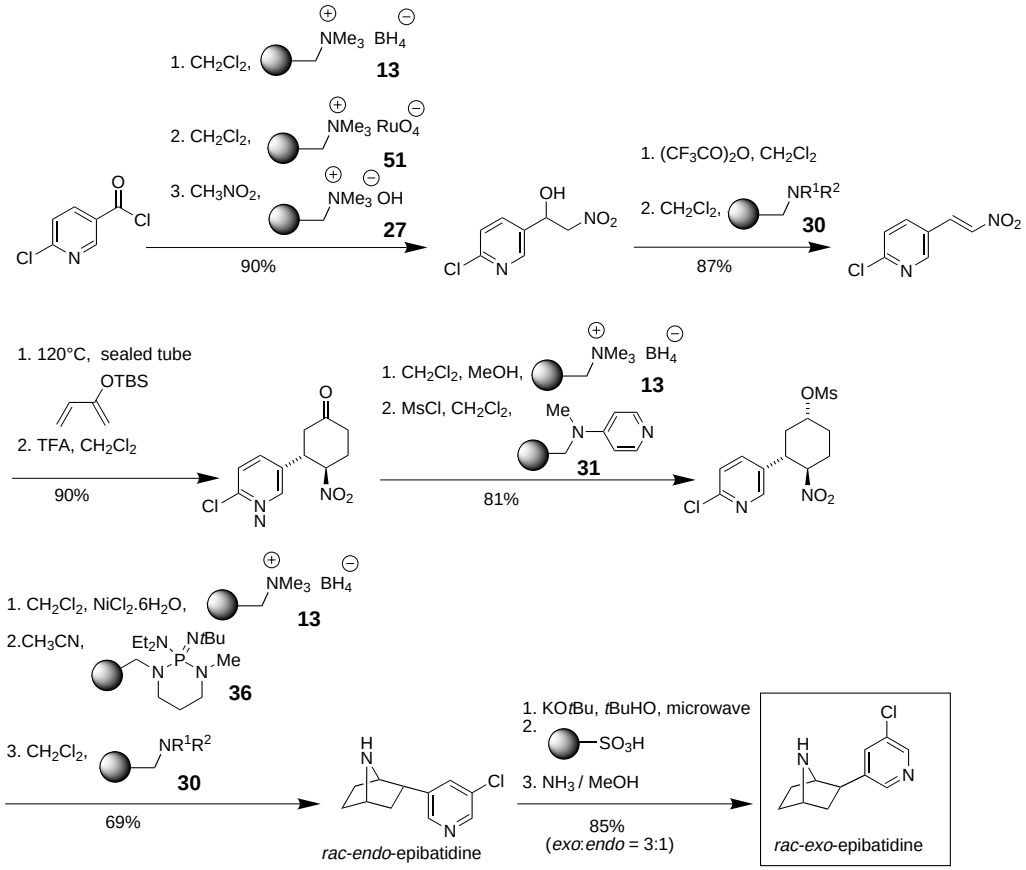
6. Natural Product Synthesis with Functionalized Polymers

Very recently, Ley and co-workers dramatically accelerated the pace in the field of solution-phase synthesis using functionalized resins. A set of new multistep sequences based on polymer-supported reagents allowed for the total synthesis of various natural products, in particularly alkaloids.

In this context, a concise syntheses of (±)-oxomaritidine and (±)-epimaritidine were achieved by sequences of five and six consecutive steps, respectively (Scheme 44).[239] In analogy to a strategy developed by Kita et al.[240] substituted benzyl alcohol was transformed into trifluoroacetyl amide (90%) in three steps using functionalized polymers **51**, **13**, and **31**. This set the stage for the intramolecular phenolic oxidative cyclization promoted by polymer-supported (diacetoxyiodo)benzene **3** (X = H) or by the trifluoroacetate analogue (X = F). Treatment of the *para*–*para* coupled intermediate product with polymer-supported carbonate **44** resulted in rapid deprotection and spontaneous intramolecular 1,4-addition of the intermediate amine to afford (±)-oxomaritidine in high yield. The sequence was terminated by reduction of the keto group by polymer-supported borohydride **13** and provided (±)-epimaritidine.



Scheme 44. Polymer-supported total synthesis of (±)-oxomaritidine and (±)-epimaritidine.



Scheme 45. Polymer-supported synthesis of (±)-epibatidine.

For the synthesis of the potent analgesic compound (±)-epibatidine, isolated from the Ecuadorian poison frog *Epipedobates tricolor*[241] an even longer synthetic sequence[242] (12 linear steps; 10 steps mediated by functionalized polymers) based on polymer-supported reagents was designed (Scheme 45).[243] Starting from an acid chloride, the synthesis was initiated with two polymer-supported functional-group manipulating steps based on functionalized polymers **13** and **51** (reduction to alcohol, oxidation to aldehyde) and one polymer-promoted Henry reaction using nitromethane and base **27** to provide unstable nitro alcohol. Derivatization with trifluoroacetic anhydride, one of the few synthetic steps which is not based on a polymer-supported reagent, followed by treatment with dimethylaminomethyl polystyrene resin **30** ($R^1 = R^2 = Me$) prompted elimination to furnish intermediate *trans* alkene. The thermal Diels–Alder reaction in an undried, sealed vial provided the intermediate silyl enol ether which after removal of excess of diene in vacuo was transformed exclusively into *trans*-

configured cyclohexanone. After this intermezzo without functionalized polymers the sequence was continued by the polymer-supported reduction of the ketone and mesylation using functionalized polymers **13** and **31**. The mesylate formed was further transformed by reduction of the nitro group using nickel-modified BER reagent **13**[244] followed by transannular cyclization using the polymer-supported version of Schwesinger's base **36** and sequestering of acidic impurities by use of basic aminomethyl polystyrene resin **30** ($R^1 = R^2 = H$). This sequence allowed for the preparation of the *endo* isomer of (±)-epibatidine (>85% purity by liquid chromatography–mass spectrometry; LC-MS). Final epimerization was achieved by using microwave irradiation. Again, an acidic scavenger resin helped to remove basic components and the products from the reaction mixture. The product was then displaced from the resin with the help of a methanolic solution of NH_3.

Analogous to the "tea-bag" technology which has been widely used in "split and combine" combinatorial chemistry, pouches filled with the various functionalized polymers were employed in this synthesis. Thus, when a reaction is judged to have gone to completion, the pouch can be removed, washed, and the next reagent-containing pouch can be added to the reaction vessel. The authors note that the syntheses were achieved without chromatographic purification, with excellent yields for most steps, and importantly with minimum optimization

The last two examples clearly reveal the advantages of stoichiometrically employed functionalized polymers and demonstrate their future prospects.

7. Outlook

Solid-supported reagents have been the subject of research for four decades. The interest shown by the chemical community has varied dramatically, partly because such reagents are relatively costly compared to reagents which are not attached to a polymeric support. Therefore, the ability to recycle stoichiometrically employed solid-supported reagents is a key factor for their wide use in the future. Still, the potential of these polymers was recently demonstrated in optimized solution-phase synthesis and compound-library generation. Therefore, it is reasonable to assume that polymer-supported reagents will be employed with increasing regularity to conduct one- to multistage synthetic sequences. They will routinely find use in automated parallel synthesis, in particular, for creating compound libraries which are difficult to construct on a polymeric support. To facilitate this use, the technique requires rapid development, in particular in the following areas: 1) the search for new functionalized polymers, 2) the development of new solid supports with properties specifically optimized for the synthetic procedure, 3) the development of new multistep sequences, 4) automation with improved "hardware" and subsequently 5) miniaturization as summarized below.

In fact, all the advantages of using polymers in organic synthesis can be exploited fully when the various techniques are mixed, not only those mentioned herein but also immobilized catalysts. These catalytically active polymers, in particular those based on transition metals, show great promise for future applications. Once some drawbacks, such as stability, recovery, and metal leaching, have been resolved, they will play an important role in multistep syntheses, particular in the key steps involving C–C bond forming processes. Many of these catalytic processes will be coupled with scavenging techniques (Section 4), which by then will be even more sophisticated. Indeed, the coupling of these two processes is essential when the removal of by-products or an excess of one reactant becomes necessary. Soon, hybrid techniques will become available that use both solid-phase organic synthesis followed by derivatization of the functional groups with polymer-supported reagents after the release and cleavage of the substrate from the polymer.[245] These developments will also enhance the utility of soluble polymers in automated parallel synthesis. Thus, soluble polymers may be loaded with substrates which are processed by polymer-anchored reagents or catalysts. At this stage, soluble impurities may be removed by polymer-bound scavenging reagents. Furthermore, prior to cleavage of the target molecule from the soluble resin, purification may be achieved by precipitation. More promising, however, is membrane filtration.

It is evident from the above discussion that the polymer supports used are still far from ideal in several respects and that there is considerable scope to prepare improved supports.[246] Indeed, this is already a very active interdisciplinary area of research. The goal is to develop functionalized polymers and supports that have a satisfactory physical shape that permits agitation during reactions and filtration without problems. A reasonably high load capacity (>1.0 to 1.5 $mmol\,g^{-1}$), and repeat units that, unless required to do so, will not react with the diverse range of reagents involved in a multistage combinatorial synthesis are required. One way forward is to investigate beads prepared using cross-linking agents that are longer and more flexible than divinyl benzene. Such networks are likely to be superior to the common polystyrene beads.[247] Related to this concept are tentagels which are a significant improvement. Here, the hydrophobic properties of cross-linked polystyrenes have been substantially offset by carrying out graft polymerization of ethylene oxide on the surface of the beads.[248] At present, however, most tentagels show loading capacities (about 0.2 $mmol\,g^{-1}$) that are too low for use in stoichiometric transformations. Interestingly, magnetic separation techniques are slowly emerging in the field of solid-assisted organic chemistry;[249] it has been shown that a ferromagnetic core can be encased in a highly cross-linked polymeric support. This technique gives beads which are enmeshed into larger composites composed of functionalized, 1–2% cross-linked polystyrene.[250]

However, the most dramatic improvements in the design of ideal supports for reagents and catalysts, we think, will be seen in the field of macroporous inorganic materials.[251] In general, inorganic supports do not tend to swell which makes them ideal supports for use in continuous reactors. Indeed, mesoporous phases based on zeolites, glass, and metal oxides, of which MCM-41 is the most prominent member, have appeared as highly promising supports in polymer-based synthesis,[252] mainly as catalysts.[253] These materials, prepared using surfactant micellar structures as templates, have a very

high surface area ($>1000\,m^2g^{-1}$). Techniques have been developed that allow construction of pores of highly defined size.[254] These materials are composed of an ordered pore structure which is mostly an hexagonally packed array of inorganic tubules ranging from 20–100 Å in diameter. Remarkably, they show an extremely narrow pore-size distribution and the pore diameter can be adjusted from 2 to 15 nm. Co-condensation of reactive species during the mesopore synthesis is a method to incorporate functional groups into the walls of the channel system.[255] Thus, organometallic complexes can be attached to the walls, which leads to the immobilization of catalysts originally designed for homogeneous catalysis.[256] Reactions[257] that have so far been conducted with these novel catalysts are the Heck-reaction,[258] epoxidations,[259] C–H activation,[260] and Ziegler–Natta polymerization.[261] This area develops ever faster, and recently the first stable organic analogue of a zeolite was prepared[262] which showed catalytic properties in the base-catalyzed Knoevenagel condensation. In this remarkable work the authors employed lyotropic liquid crystals, which in an aqueous environment are organized in hexagonal channels. Depending on the amount of water used an inverted supramolecular structure is formed with the polar carboxylates directed into the channel in which the countercations are densely packed. These conglomerates were cross-linked in the presence of divinyl benzene which "froze" the cylindrical hexagonal structure.

In addition to these improvements, microfabricated systems[263] will soon be used for combinatorial synthesis, including solution-phase synthesis promoted by functionalized polymers. The promise of miniaturization lies in the power of massive parallelization. Other potential benefits of miniaturization are automation, reduced waste streams, increased precision and accuracy, and disposability. Miniaturized reactors[264] should be ideally suited for prederivatization of analytical and diagnostic samples and for microscale alteration of drugs and precious pharmacologically active natural products.

While this review was under preparation, several other examples of polymer-bound reagents appeared in the literature. These include polymer-attached aminium/uronium salts for peptide synthesis[265] and polymer-supported thiophenol for removing excess alkylating agents from solution.[266] In addition a lot of recently published work on functionalized polymers can be found in two recent reviews.[267] We apologize to those investigators whose work could not be summarized herein.

Our contributions in this field were supported by the Fonds der Chemische Industrie. We are grateful to M. Ries for technical assistance and to M. Jesberger, G. Sourkouni-Argirusi, N. Merayo, and A. Schönberger (Clausthal) for expert preparative contributions. Furthermore, we thank Bayer AG (Leverkusen, Germany) as well as Novabiochem (Switzerland) for financial and technical assistance. We are indebted to Prof. S. L. Ley (Cambridge, UK) for providing unpublished results.

Received: March 9, 2000 [A 399]

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