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Polymer-Supported Organic Catalysts[†]

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1. Introduction

The expression “organic catalyst” has recently been introduced to define an organic compound (of relatively low molecular weight and simple structure) capable of promoting a given transformation in substoichiometric quantity. In this context, organic means metal-free, and it is used to differentiate this class of catalysts from that of metal-based catalytic species.

Implicitly, however, the term organic emphasizes the advantages of performing a catalytic reaction under metal-free conditions. These advantages might include, inter alia, the possibility of (i) working in wet solvents and under an aerobic atmosphere, (ii) dealing with a stable and robust catalyst, and (iii) avoiding from the outset the problem of the leaching of a (possibly toxic) metal into the organic product.

[†] Dedicated to professor Fernando Montanari, a pioneer in the field of polymer-supported catalysis.

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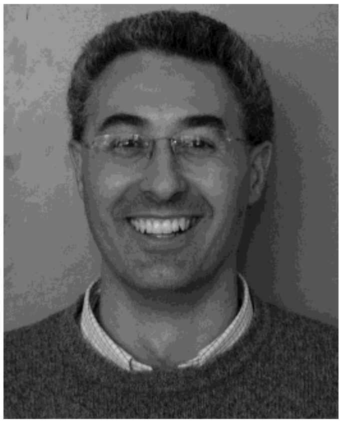
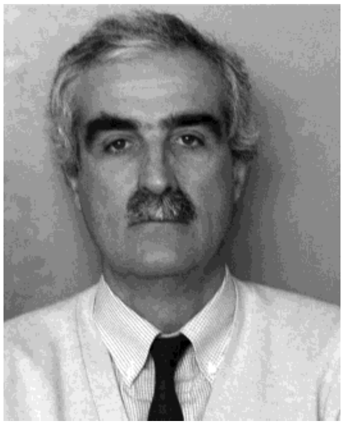


Maurizio Benaglia was born in Bergamo in 1966. He received his laurea in Chemistry at the University of Milano in 1991 and his PhD in 1994 working with professor Mauro Cinquini on the stereoselective synthesis of β-lactams. He then spent two years as a postdoctoral fellow with professor Jay Siegel at the University of California at San Diego working on the stereoselective synthesis of supramolecular structures. He is now research associate at the University of Milano. His research projects concern the development of new asymmetric catalysts, the immobilization of chiral catalysts on soluble polymeric supports, and the study of new supramolecular devices.

Alessandra Puglisi was born in Varese in 1976. She received her laurea in Industrial Chemistry in 2000 and is currently completing her PhD program under the supervision of professor Mauro Cinquini at the University of Milano working on the synthesis of polymer supported chiral organic catalysts.



Franco Cozzi was born in Milano in 1950. He graduated in Chemistry at the University of Milano in 1974. After two years with professor Kurt Mislow at Priceton University, he moved to the University of Cagliari and then came back as an associate professor to the University of Milano, where he is full professor of Organic Chemistry since 1994. The stereoselective synthesis of bioactive β-lactams, the study of the interaction between aromatic systems, and the synthesis of catalysts on soluble polymeric supports have been his recent research topics.

Organic catalysts can be seen as minimalistic versions of enzymes, from which they are conceptually derived and to which are often compared.[1] Even if only in some cases they display the remarkable selectivity peculiar of enzymes, organic catalysts generally are more stable, less expensive, and enjoy a wider application under a variety of conditions unsustainable by enzymes.

In addition, organic catalysts are also more readily amenable than both metal-based and biocatalysts to anchoring on a support with the aim of facilitating catalyst recovery and recycling. As far as enzyme supporting is concerned,[2,3] in principle one can expect the connection to a support to have a deeper impact on the complex structure of an enzyme (and, hence, on its properties) than on that of a simple organic derivative. Moreover, the introduction of several units of a catalyst on a polyvalent support (e.g., a polymer with many reactive sites) seems more feasible in the case of a small molecule than in that of a large biocatalyst. On the other hand, it has repeatedly been shown that immobilization of a metal-based catalyst on a support (generally achieved by anchoring an organic ligand followed by metal addition) is often affected by extensive metal leaching and often requires catalyst regeneration by metal replenishment before recycling.

The development of a polymer-supported version of an organic catalyst has quite timely followed that of the catalyst itself,[4] since the benefits of catalyst recovery and recycling [5] became compellingly evident to the very first researchers in the field. This “going-onto-polymer” tendency has exploded in recent years, which have witnessed a tremendous growth of chemists’ interest in synthetic methods based on supported reagents and catalysts.[6−11] It is worth mentioning, however, that while combinatorial chemistry is largely responsible for this phenomenon, it will be unfair to the ingenuity and insightfulness of the chemists of the 1970s and 1980s to state that polymer-supported chemistry was a mere scientific curiosity in the period between Merrifield’s invention and the advent of combichem.

This review will focus on the implementation of methodologies for polymer-supported organic catalysts[12−20] in organic synthesis appeared in the literature up until the year 2002. The use of organic catalysts bound to inorganic supports[21−24] will be considered only when these catalysts are particularly important, when they are the only existing examples of a supported organic catalyst, or when the comparison between systems immobilized onto inorganic and organic supports appears particularly relevant. The use of ion-exchange resins[25−28] and Nafion-type polymers[29] in catalytic quantity will not be considered. Excellent recent reviews on all of these topics are available.[4−11,21−29] Also, catalysis by molecularly imprinted polymers will not be considered here, since this has been the subject of an excellent recent review.[30]

Whenever possible, comparison between the behavior of supported versus nonsupported catalyst will be attempted. Particular attention will also be devoted to catalyst recovery and recycling. The discussion on the structure of the polymeric support will be limited to those examples for which its influence on the catalyst performance has clearly been demonstrated. The schemes show catalyst structures; the figures describe the reactions in which they are involved. Polymer structures will be explicitly indicated in the schemes only when they can clearly be deduced from the original articles.

2. Achiral Polymer-Supported Organic Catalysts

2.1. Phase-Transfer Catalysts Anchored to Insoluble Supports

2.1.1. Polystyrene-Supported Catalysts

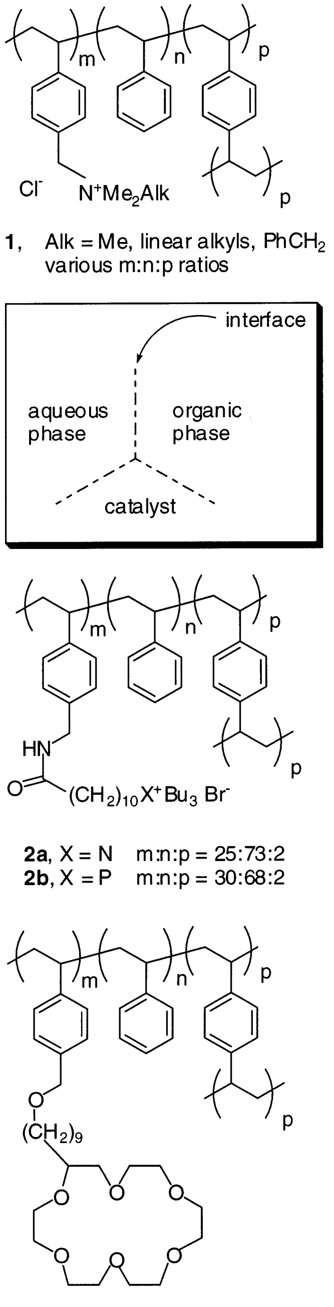
The multifaceted applications of phase-transfer catalysis[31] in organic synthesis decisively contributed to the establishment of organic catalysts as useful preparative tools. Regen[32] was the first to report the immobilization of quaternary ammonim salts on polystyrene cross-linked with 2% divinylbenzene (DVB) and the use of species as **1** (Scheme 1) to catalyze the 1-bromooctane to nonanitrile conversion (Figure 1, eq 1). The simultaneous presence of an insoluble catalyst and of immiscible aqueous and organic phases led the author to dub the process "triphase catalysis".[33,34]

Preliminary kinetic studies[33] demonstrated that the catalytic activity of chloromethylated polymers in which 1−21% of the chlorine atoms of Merrifield resin have been replaced by quaternary ammonium groups of different structures was directly related to the number of the catalytic sites. However, a further increase of the catalyst loading (the number of active catalytic sites per gram of polymer) up to 76% led to a sharp decrease in catalytic activity. This behavior was explained in terms of the much poorer swelling properties of the high-loaded than of the low-loaded support (that prevented easy access of the reagents to the catalytic sites), and of a reduced lipophilicity of the catalyst.

Several preparative applications of the supported catalysts **1** and related quaternary onium species, including nitrile and dichlorocyclopropane synthesis, ether and thioether formation, halogen exchange reactions on organic halides, dehalogenation of *vic*-dibromides, oxidation of alcohols, and nucleophilic ring opening of dioxiranes, were also reported (Figure 1, eqs 1−7).[35−37]

Regen's seminal reports were soon followed by similar efforts describing the immobilization on cross-linked polystyrene not only of conventional phase-transfer catalysts such as phosphonium salts,[38−43] crown ethers,[38,44−47] and cryptands,[38,45,48] but also of micelle-related catalysts,[49] phosphoric triamides,[50] ureas,[51] and acyclic polyethers.[52−54]

Scheme 1. Structure of Polystyrene-Supported Ammonium and Phosphonium Salts and Crown Ethers[a]



1, Alk = Me, linear alkyls, $PhCH_2$
various m:n:p ratios

2a, X = N m:n:p = 25:73:2
2b, X = P m:n:p = 30:68:2

3, m:n:p = 5-62:94-37:1

[a] An outline of triphase catalysis is reported in the box.

Polymer-supported phase-transfer catalysis was extensively examined from a mechanistic point of view.[55] These studies proved to be very important for future developments of polymer-supported catalysis in general and will be discussed in some details here. On the basis of a number of investigations[34,41,42,56−60] that considered several factors (such as stirring rate, catalyst particle size, degree of polymer cross-linking, and solvent effect), it was concluded that reaction rates were faster (i) with polymer-bound crown ethers > phosphonium salts ≫ ammonium salts, (ii) when high stirring rates were applied, (iii) when the catalyst was supported on beads of smaller size, (iv) when the polymer had a relatively low cross-linking, and (v) when a solvent inducing good swelling of the polymer was employed.

It was also noted,[42,47,56−58,60,61] however, that the catalytic activity of the insoluble polystyrene-supported catalysts was strongly reduced in comparison with that of their nonsupported soluble counterparts, likely because the rates of reactions were limited by

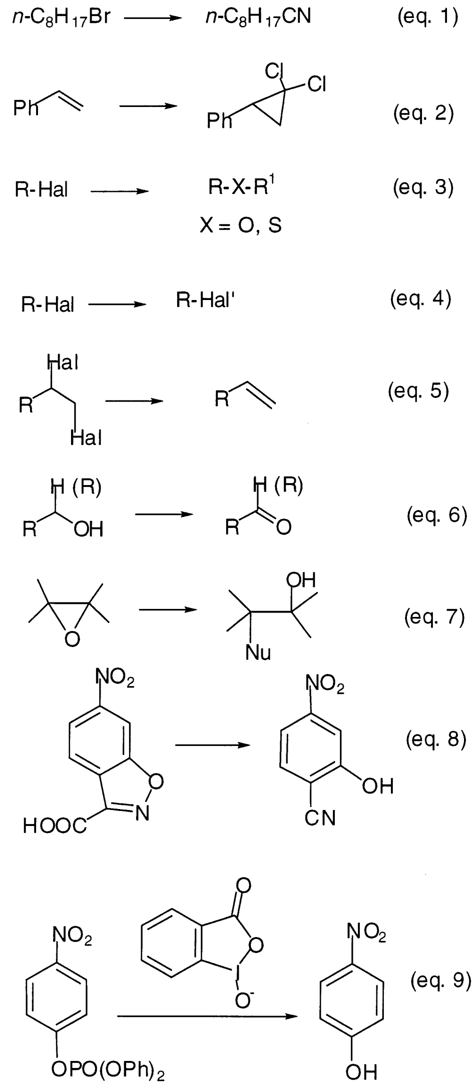


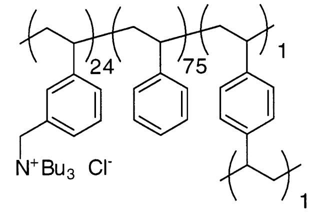
Figure 1. Reactions catalyzed by insoluble polymer-supported phase-transfer catalysts.

mass transfer of reactants from solution to the bead surface and by intraparticle diffusion of reactants from the surface to the active sites within the beads.[62]

In an attempt to circumvent this problem, Montanari and co-workers[41,45,58−60] discovered that the insertion of a long chain as a spacer separating the polymer backbone from the catalytic sites in ammonium (**2a**) and phosphonium (**2b**) salts and crown ethers (**3**) greatly enhanced the catalytic activity of the supported system (Scheme 1). The combination of this topological device, which also has the beneficial side effect of enhancing the lipophilicity of the catalyst, with the use of 1% instead of 2% DVB cross-linked polystyrene made the catalytic sites more readily available. Thus, catalytic activities 2−4 times higher than those of nonspaced catalysts and almost comparable with (even if still lower than) that of nonsupported, structurally related species were observed. From a more general point of view, it must be noted that the introduction of a spacer to improve the reactivity of immobilized reagents and catalysts has since then become a commonly used device in polymer-supported chemistry.[6−11]

In related studies, it was also discovered that high-speed magnetic stirring pulverized the polymer beads of the catalyst, preventing simple recovering of the catalyst by filtration.[53,63] Accordingly, the recycling of insoluble polymer-supported phase-transfer catalysts was sometimes reported[36] but not very thoroughly investigated. The use of microwaves was eventually proposed as a bead-respectful alternative to other stirring methods.[63]

Scheme 2. Structure of a Cationic Poloymer Colloid Catalysts



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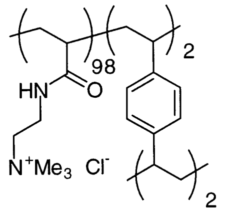
Insoluble polymer colloids,[64] having much smaller sizes and greater surface areas per unit mass with respect to polystyrene beads, were also employed to overcome the rate limitations due to diffusion phenomena.[65] Catalyst **4** (Scheme 2), prepared by emulsion polymerization,[66] was a submicroscopic anion-exchange resin with particle size 50 times larger than that of spherical micelles and 200−2000 times smaller than the diameter of typical Merrifield polystyrene beads. The resin **4** was recoverable either by ultrafiltration or by coagulation followed by conventional filtration. Compound **4** was shown to strongly accelerate the decarboxylation of 6-nitrobenzisoxazole-3-carboxylate (Figure 1, eq 8)[66] and the *o*-iodosobenzoate-catalyzed hydrolysis of *p*-nitrophenyl diphenyl phosphate (Figure 1, eq 9).[67]

A new solution to the problems associated with polymer loading and accessibility of reactive sites was recently proposed by Kirshning, Kunz, and co-workers.[68] They employed polystyrene-supported quaternary ammonium salts featuring different counteranions (BH_4^-, $Br(OAc)_2^-$, N_3^-, CN^-, F^-) in the development of flow-through microreactors. First, a 2% DVB cross-linked chloromethylated polystyrene was generated inside highly porous glass rods. Exhaustive amination with trimethylamine afforded a polymer-supported ammonium salt with a high surface area and wedged inside the microchannel pore system of the support. Its swelling and shrinking was therefore predetermined by the volume of the pores inside the rod, the size of which remained unchanged thus securing almost constant flow. The rods were then charged in a reactor through which the solution containing the reagents was forced to flow. Various noncatalytic reactions (acetophenone reduction, cyclohexanol oxidation, nucleophilic displacement of bromine atom in benzyl bromide) were thus performed in times shorter than those required with conventional polymer-bound reagents. Extension of this technique to catalytic reactions can represent a great improvement in polymer-supported catalysis.

2.1.2. Polyacrylamide-Supported Catalysts

After Tomoi and co-workers[50] discovered that polystyrene-supported phosphoric triamides efficiently catalyzed phase-transfer reactions (such as bromide/

Scheme 3. Structure of Polyacrylamide-Supported Ammonium Salt



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iodide and bromide/cyanide exchange), polyacrylamides, either as such[69] or properly substituted and quaternized,[70] were employed to promote ethers,[69] azidohydrins,[70] halohydrins,[71] and thiocyanohydrins[72] formation (Figure 1, eqs 3 and 7). While nonquaternized polyacrylamides showed catalytic activity inferior than that of polystyrene supported phosphonium salts,[69] the quaternized derivative **5** cross-linked with 2% DVB (Scheme 3) proved to be an efficient recoverable and recyclable catalyst for the nucleophilic ring opening of epoxides in water.[70−72]

2.2. Catalysts Anchored to Soluble Supports

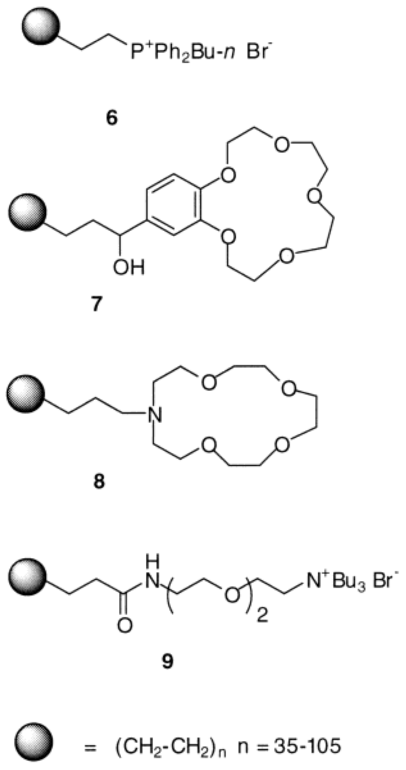
As pointed out in the previous section as well as in two recent excellent reviews,[73,74] the advantages inherent in the use of insoluble polymer-supported catalysts are accompanied by several shortcomings, mainly imputable to the fact that the diffusion of reagents and substrates in to and out of an insoluble polymer matrix can seriously affect the catalyst's reactivity. Since the 1960s soluble polymeric supports have been envisaged as possible alternatives to their insoluble counterparts for catalyst immobilization.[4] However, since the recovery and recycling of the catalyst was the major reason for anchoring a catalyst to a polymer, only those polymer featuring solubility properties suitable for catalyst recovery were practically developed.

Among soluble polymers, polyethylene and poly(ethylene glycol) have been by far the most widely used for the immobilization of phase-transfer catalysts.

2.2.1. Polyethylene-Supported Catalysts

In 1985 Bergbreiter and Blanton reported ethylene oligomers with M_W in the range 1000−3000 Da containing terminal groups such as phosphonium salts, crown ethers, and azacrown ethers.[75] These were prepared by anionic oligomerization of ethylene with *n*-butyllithium as an initiator, followed by quenching with different electrophiles to create a suitable functionality to generate or attach the catalyst. In Scheme 4 the structures of some of the systems synthesized (**6**−**8**) are reported. These catalysts showed temperature-dependent solubility properties similar to polyethylene, being insoluble at 25 °C and soluble in organic solvents at 90−110 °C (this property will later be called "thermoresponsiveness").[73] Therefore, after being used in a homogeneous reaction at high temperature, they can be readily separated from the reaction mixture by cooling-induced precipitation and filtration.

Scheme 4. Structure of Polyethylene-Supported Phase-Transfer Catalysts



Catalysts **6**−**8** were tested in some standard reactions carried out under phase-transfer catalysis conditions to compare them to the nonsupported and the previously examined insoluble polymer-supported catalysts. As an example of transformation occurring under liquid−liquid conditions, the *n*-octyl bromide/iodide exchange in xylene/aqueous NaI at 110 °C was considered (Figure 1, eq 4). The results showed that the polyethylene supported crown ether **7** was as active as its polystyrene-supported counterpart, and only slighly less active than the nonsupported catalyst benzo-15-crown-5. Remarkably, compound **7** was recovered and recycled through four reaction cycles without any appreciable loss in activity.

The phosphonium salt **6** behaved similarly to **7**, being almost as reactive as the nonsupported counterpart and more active than its polystyrene-supported analogue. In this case however, catalyst recycling, although possible, was less successful due to the intrinsic thermal instability of phosphonium salts when heated above 100°C. Obviously, neither **6** nor **7** showed the sensitivity toward the size of the substrate displayed by their polystyrene-supported analogues.

The temperature-dependent solubility of catalysts **6**−**8** allowed a practical use of solid−liquid phase-transfer conditions. In this case, the inorganic reagent (e.g. NaI, NaCN, $NaBH_4$) was suspended in the solution of the substrate (*n*-octylbromide, *n*-octanal) in the organic solvent (typically, xylene). The catalyst (0.5% molar) was then added and the temparature raised to 110 °C to ensure its solubility. At the end of the reaction, hot filtration allowed the removal of the excess inorganic reagent, and cooling the recovery of the catalyst and a very simple product isolation.

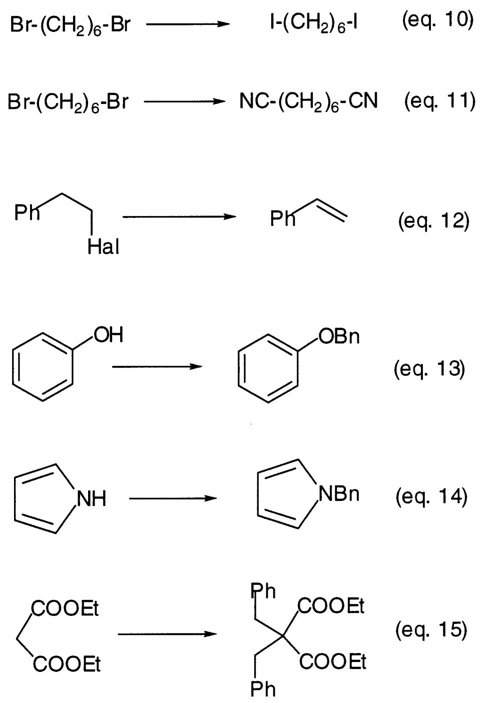


Figure 2. Reactions catalyzed by soluble polymer-supported phase transfer catalysts.

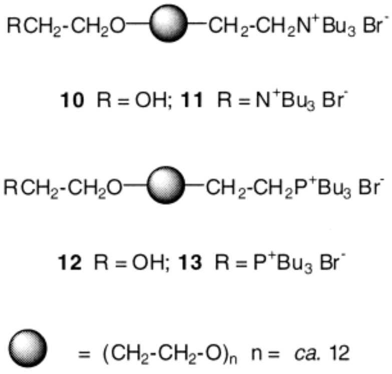
More recently, Grinberg and co-workers[76] used commercially available oxidized polyethylene as a bifunctional support for the immobilization of quaternary ammonium salts by amidation with diamino derivatives of poly(ethylene glycol)s followed by quaternization with excess butyl bromide. Among the nine catalysts obtained, compound **9** (Scheme 4) was found to be the more active in promoting the conversion of 1,6-dibromohexane into the corresponding di-iodide (Figure 2, eq 10) or dinitrile (Figure 2, eq 11), carried out under liquid−liquid conditions in toluene/aqueous NaI or NaCN at 100 °C. Its activity, however, was about two-thirds that of tetrabutylammonium bromide (TBAB). Remarkably, catalyst **9** was thermally stable up to 170 °C. Exploiting its thermoresponsiveness, it was possible to recover and recycle the catalyst for a second cycle without observing any decrease in activity.

2.2.2. Poly(Ethylene Glycol)-Supported Catalysts

Also poly(ethylene glycol)s (PEGs) have extensively been used as inexpensive and easily functionalized supports for the immobilization of reagents, and the recovery and recycling of catalysts.[74] Provided that their M_W's are greater than 2000 Da, PEGs are solid crystaline materials readily soluble in water and polar organic solvents (e.g., dichloromethane, acetonitrile, DMF, DMSO) and insoluble in less polar solvents (e.g., hexane, diethyl ether, *tert*-butylmethyl ether).

Therefore, exploiting this solubility property as a phase separation device, it is possible to use a PEG-supported catalyst under homogeneous catalysis conditions (where the catalyst is expected to perform at its best) and, simply by decreasing the solvent polarity, to precipitate, recover, and recycle the catalyst as if it were bound to a solid support.

Scheme 5. Structure of Mono- and Bifunctional Poly(ethylene glycol)-Supported Onium Salts



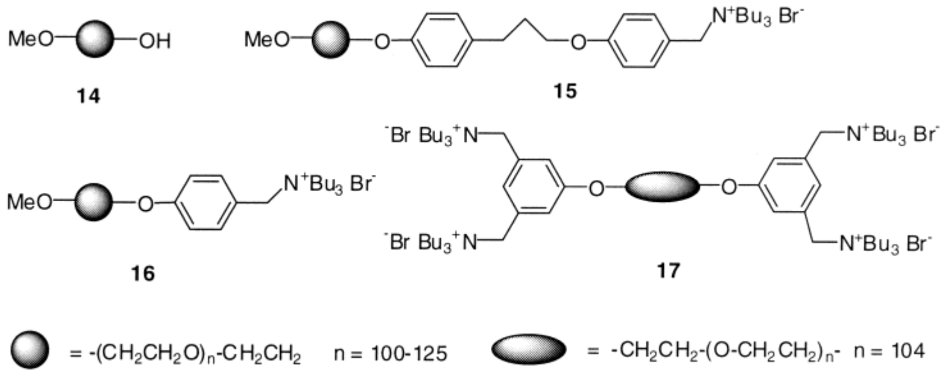
Even if the first attachment of a quaternary ammonium salt to poly(ethylene glycol)[77] dated back to 1970,[78] the study of the catalytic activity of these and related derivatives was reported only in 1991, when Grinberg and Shaubi[79] described the synthesis of the mono- and bifunctionalized onium salts **10**−**13** supported on PEG_{600} (Scheme 5).

The catalytic activity of these compounds was established by studying the dehydrohalogenation of (2-haloethyl)benzene to styrene (Figure 2, eq 12) under liquid−liquid conditions in toluene/60% aqueous KOH at 50−85 °C. Working at 85 °C, it was found that **10** was a much more active catalyst than both TBAB and PEG_{600}. This implicitly showed that the PEG portion of the catalyst contributed to a very limited extent to its ability to facilitate the reaction. By running the same reaction at 50 °C, the order of activity of **10**−**13** was established as **12** > **10** > **13** > **11**. Unfortunately, no examples of reaction carried out under solid−liquid conditions were reported, and the low M_W of the support prevented a straightforward catalyst recovery and recycling.

Catalyst recycling was the major goal of a later work.[80] To secure the desired solubility property of the support, the monomethyl ether of PEG_{5000} **14** ($MeOPEG_{5000}$) (Scheme 6) was selected for catalyst immobilization. This was transformed by standard functional group manipulation into adduct **15** (80% overall yield for the six steps from **14**), which can be considered a PEG-supported version of benzyl tributylammonium bromide.

Compound **15** (0.04 mol equiv) proved to be an excellent phase-transfer catalyst for a variety of reactions, such as bromide/iodide and bromide/cyanide exchange in *n*-octyl and benzyl derivatives (Figure 1, eq 4 and 1), dichlorocyclopropanation of styrene (Figure 1, eq 2), *O*-benzylation of phenol (Figure 2, eq 13), and *N*-benzylation of pyrrole (Figure 2, eq 14), carried out under liquid−liquid conditions in a mixture of dichloromethane and an aqueous solution of the appropriate inorganic salt at 25−40 °C.[80] The products were obtained in yields comparable or identical to those reported in the literature with related nonsupported catalysts and higher than those observed with polystyrene supported catalysts at higher temperatures and longer reaction times. It is interesting to note here that adduct **16**, featuring a shorter spacer separating the

Scheme 6. Structure of Poly(ethylene glycol)-Supported Ammonium Salts



polymer core from the catalytic site, was not as effective as **15** in these reactions.

As anticipated on the basis of Bergbreiter's work,[75] catalyst **15** outperformed all of the nonsupporterd and supported ammonium salts reported so far when employed under solid−liquid conditions in the presence of NaOH and of dichloromethane as the organic solvent. In this case, even the use of only 0.01 mol equiv of the catalyst at room temperature secured the benzylation of phenol in 95% yield in 22 h and the benzylation of pyrrole in 99% yield in less than 15 min.

The fast- and high-yielding benzylation of pyrrole was considered as a probing test for catalyst recycling. Thus, a sample of the catalyst, recovered by precipitation induced by addition of diethyl ether to the reaction mixture followed by filtration, catalyzed two additional reactions occurring in 95% and 93% yield, respectively, under the same conditions (0.01 mol equiv of **15**, 15 min, rt). Remarkably, the catalyst recovered for the third time was able to promote the benzylation of phenol in 92% yield (instead of the 95% yield observed for the first cycle, see above). The possibility of working at low temperature, which is due to the high activity of **15**, clearly was beneficial for its stability and, hence, recyclability. The role of the PEG part of the catalyst as an effective solubilizing agent of inorganic salts in organic solution could also be invoked to account for the efficiency of **15**.[80−82]

Even if catalyst **15** featured a number of interesting properties, it was clearly amenable to further improvement. For instance, the high M_W of the PEG residue, which is essential for efficient recovery and recycling, clearly brought along the undesirable drawback of requiring the handling of relatively large weight amount of material even if working with relatively small mole amount of catalyst. Indeed, catalyst **15** with its calculated M_W of ca. 5500 Da had a loading as low as 0.182 mmol/g. Practically, this means that if 0.01 mol equiv of the catalyst **15** is to be used to catalyze a reaction carried out on a 1 mol scale of substrate, 55 g of catalyst is required.

To solve this problem, the tetrakis ammonium catalyst **17**[83] (Scheme 6) was prepared starting from PEG_{4600} via the corresponding tetraol,[84] in 71% overall yield. The catalyst loading was 0.679 mmol/g, 3.73 times higher than that of **15**. Its catalytic efficiency was accordingly improved. For instance the solid−liquid benzylation of phenol (0.01 mol equiv of catalyst, dichloromethane, solid NaOH, rt) occurred in 95% yield after only 3 h reaction time (vs 22 h with **15**). Under the same conditions, the benzylation of pyrrole was over in 5 min (vs 15 min with **15**) and can be carried out in 85% yield with only 0.001 mol equiv of catalyst. Catalyst **17** very efficiently promoted also the dibenzylation of ethyl malonate (Figure 2, eq 15; 99% yield, 5 min, rt, 0.03 mol equiv of catalyst) and the dichlorocyclopropanation of styrene (Figure 1, eq 2; 98% yield, 30 min, rt, 0.01 mol equiv of catalyst). The latter reaction was used to test catalyst recycling, which was shown to be possible for 5 cycles with isolated yields of 97%, 98%, 97%, and 95% for the 2nd, 3rd, 4th, and 5th cycle, respectively.

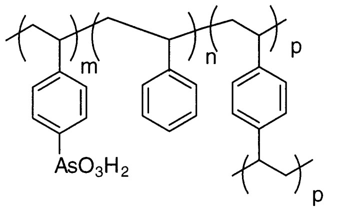
In commenting the catalytic efficiency of the PEG-supported catalyst **17**, a useful comparison can be made with the dendrimeric poly(pentaerythrol)-based polyammonium salt synthesized by Ford,[85] featuring a surface containing up to 36 trimethylammonium groups. In this case the presence of at least 12 catalytic sites was required for a strong catalytic activity, whereas the use of the corresponding tetrakis ammonium salt did not lead to any rate enhancement with respect to noncatalyzed reactions (the recycling of these dendritic catalysts was not reported). It is also worth mentioning that the mere increase of the number of catalytic sites had a negative effect on the rates of the phase-transfer reactions catalyzed by polystyrene-supported catalysts. [86]

2.3. Oxidation Catalysts Anchored to Polymer Supports

2.3.1. Arsonic Acids

In 1979 Jacobson, Mares, and Zambri reported the synthesis of the insoluble polystyrene-supported arsonic acids **18**−**20** (Scheme 7) possessing different degrees of functionalization (7%, 25%, and 50%, respectively).[87] These polymers were obtained by para-bromination of 1% DVB-cross-linked polystyrene, followed by lithiation, reaction with triethylarsenite, and oxidation with hydrogen peroxide. They were employed as readily separable and recoverable catalysts (0.03 mol equiv) in two industrially important reactions such as the Baeyer−Villiger oxidation of ketones[87] and the epoxidation of alkenes.[88]

Scheme 7. Structure of Supported Arsonic Acids



18 m:n:p = 7:92:1
19 m:n:p = 25:74:1
20 m:n:p = 50:49:1

By operating in a two-phase system consisting of a homogeneous dioxane solution of a cyclic ketone and 90% hydrogen peroxide at 80°C, excellent yields and high lactone selectivity were observed after 2−10 h reaction time at room temperature (Figure 3, eq 16).[87] Taking into account the loading of arsonic acid, the activity of the three catalysts was found to be practically identical. For all ketones studied, the rates of oxidation were about three times slower than those in the presence of equivalent quantities of either benzene- or *p*-toluenearsonic acid. Thus, also in this case, diffusion of the substrate into the polymer plays a relevant role in determining the rate of the reaction. Most important, the catalysts could be filtered off and recycled for a total of four cycles without any apparent loss of activity. By working under triphase catalysis conditions (achieved by replacing water-miscible dioxane with water-immiscible chloroform), it was possible to replace 90% aqueous hydrogen peroxide with the more easy-to-handle 30% solution. This, however, occurred at the expenses of the reaction rate, which was about one-fourth that observed in the two-phase reaction.

The use of **18**−**20** as catalysts in the epoxidation of di-, tri-, and tetrasubstituted alkenes followed very similar trends (Figure 3, eq 17).[88] Remarkably, allylic alcohols could also be epoxidized in good yields and selectivity under both the two-phase and three-phase conditions.

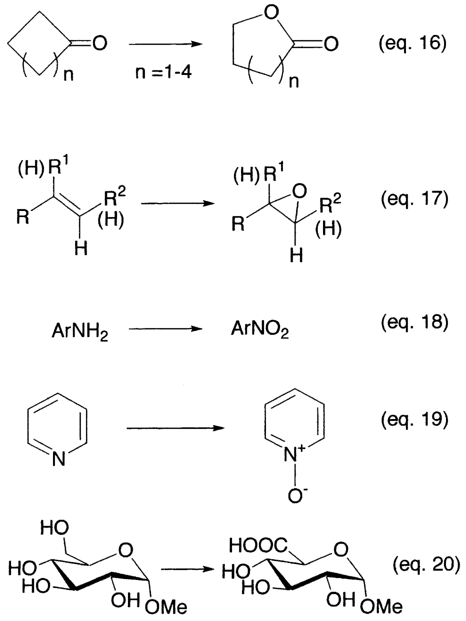


Figure 3. Oxidation reactions catalyzed by polymer-supported catalysts.

2.3.2. Ketones

In dioxirane mediated oxidations, the oxidizing agent is generated in situ from ketones and Oxone.[89] In principle, these processes require only a catalytic amount of ketone, and indeed, chiral ketones have been used as enantioselective catalysts for alkene epoxidation.[13] However, the turnover number of ketone catalysts is generally very low, since these compounds are unstable under the reaction conditions, being largely destroyed by Baeyer−Villiger oxidation.

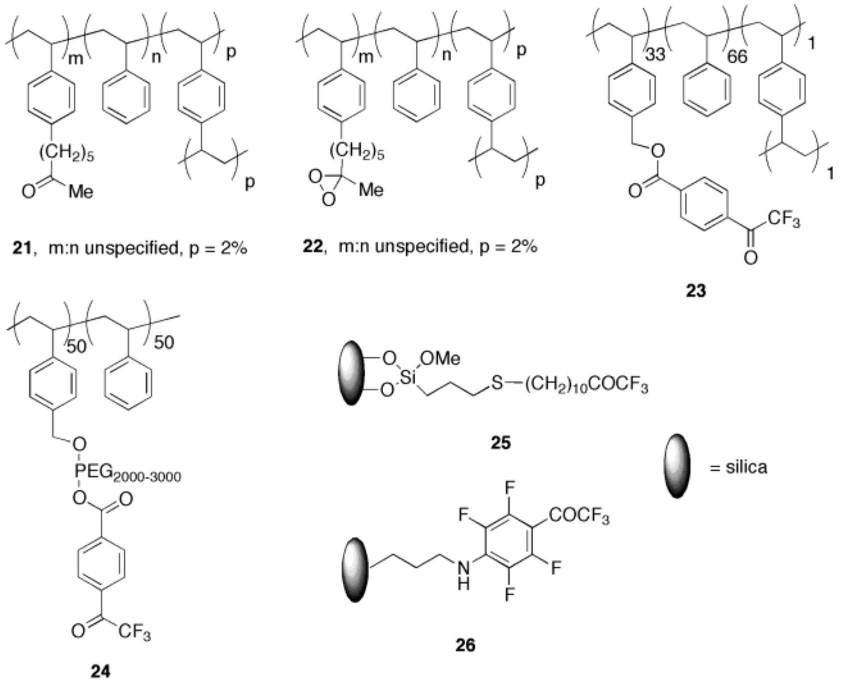
Ketone attachment to a support was first envisaged as a possible means to prevent catalyst decomposition in 1996,[90] when a 2% DVB cross-linked polystyrene was transformed in five steps into ketone **21** and, eventually, in dioxirane **22** (Scheme 8). This compound was isolated and employed in more than stoichiometric amounts (2 mol equiv/mol equiv of substrate) in chloroform at 30°C to obtain nitroarenes from anilines (Figure 3, eq 18; 78−88% yield), pyridine-*N*-oxides from pyridines (Figure 3, eq 19; 80−85% yield), and epoxides from alkenes (Figure 3, eq 17; 73−82% yield). The supported ketone, recovered at the end of the reaction, was regenerated and reused in at least four subsequent reactions without any loss of activity.

Two years later, trifluoroacetophenone was supported on hydroxymethyl polystyrene and on TentaGel S−Br to afford adducts **23** and **24** (Scheme 8).[91] They were converted in situ into the corresponding dioxiranes and used (again in a 2-fold excess) in the epoxidation of various electron rich alkenes (trans and cis stilbene, trans-chalcol, tri-*O*-acetylglucal) carried out in acetonitrile/aqueous EDTA at room temperature. The TentaGel-supported reagent **24** performed better than **23** and similarly to related, nonsupported trifluoromethyl acetophenones. An unspecified number of recyclings were also claimed.

The reaction was eventually made substoichiometric (that is, not really catalytic) in supported ketone by Song and co-workers, which covalently attached a trifluoromethyl ketone to a functionalized silica gel by means of a long aliphatic chain and a sulfur containing spacer.[92] When adduct **25** (Scheme 8, 0.5 mol equiv) was employed in the presence of 2.07 mol equiv of Oxone, 8.7 mol equiv of potassium carbonate, and 1 mol equiv of alkene in acetonitrile/aqueous EDTA at room temperature, epoxidation neatly occurred in high yield (9 examples). Remarkably, the catalyst was readily recovered by filtration and recycled nine times without any significant loss of activity. In securing this behavior, the presence of the support seemed particularly important, since the structurally related nonsupported catalyst 1,1,1-trifluoromethyldodecan-2-one was shown to be rapidly degraded under the reaction conditions after a single run.

Very recently,[93] perfluoroketone **26** (Scheme 8) was prepared as a supported synthetic equivalent of the toxic and volatile hexafluoroacetone, a known catalyst for different hydrogen peroxide mediated oxida-

Scheme 8. Structure of Supported Ketones Employed as Catalysts in Oxidation Reactions



tions of nucleophilic substrates. This compound (0.0625 mol equiv), immobilized on silica by the sol–gel method, was shown to catalyze the oxidation of pyridines (to the corresponding *N*-oxides), anilines (mostly to diazenes 1-oxide), and alkenes (to epoxides and diols) in the presence of 60% hydrogen peroxide in acetonitrile under rather drastic conditions (closed vials, 12 h, 80°C). Adduct **26** could be recovered by filtration and recycled for at least five reaction cycles occurring in unchanged high yields.

2.3.3. Nitroxyl Radicals

Nitroxyl (aminoxyl) radicals[94] are useful catalysts for the oxidation of alcohols carried out in the presence of a variety of inexpensive terminal oxidants. Among these radicals, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) played by far the leading role and has found extensive application in organic synthesis. Even if only 0.01 mol equiv of the catalyst are used, its recovery and recycling by immobilization on different supports has been actively investigated.[95]

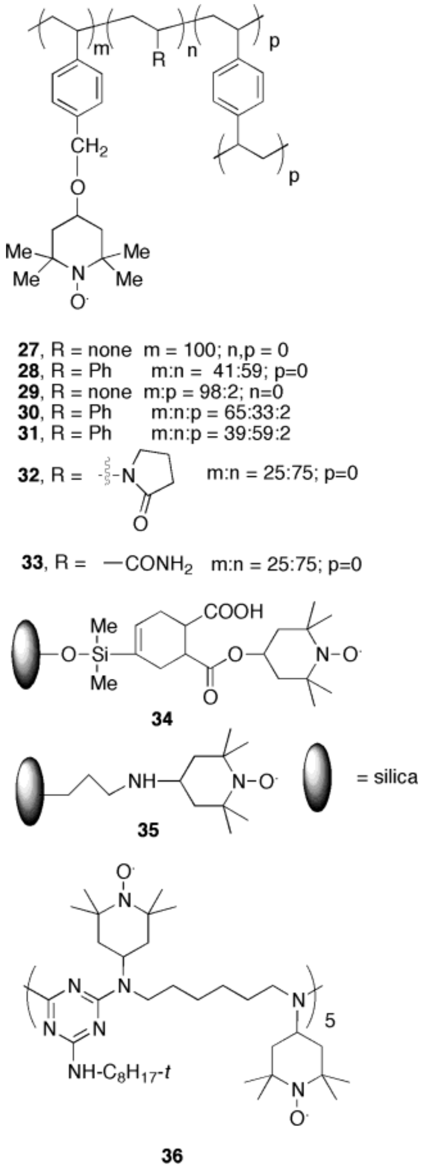
In 1983, Endo and co-workers reported the synthesis of soluble (**27** and **28**) and insoluble polystyrene-type polymers (**29**–**33**) featuring a TEMPO residue (Scheme 9).[96] A 0.04 mol equiv sample of the catalyst was employed in combination with potassium ferricyanide in alkaline water/acetonitrile as solvent for the oxidation of benzyl alcohol to benzaldehyde at room temperature. Hydrophilic, insoluble catalysts **32** and **33** (operating in a triphase mode) were shown to accelerate the reaction more than both soluble and insoluble hydrophobic catalysts **27**–**31**. The fact that low-loaded polymer perform better than high-loaded ones in this reaction was confirmed using **29**–**31** as catalysts and cupric chloride as the terminal oxidant.[97]

While no mention of recovery and recycling of catalysts **27**–**33** was provided in these works, it was later reported that the silica-supported TEMPO **34** (Scheme 9) could be recycled 45 times in the benzyl alcohol oxidation promoted by cupric chloride.[98] This catalyst was also shown to be effective in the oxidation of other primary and secondary alcohols and diols, and generally more efficient than its analogue supported on ferrite.

Other silica- and inorganic material-supported TEMPOs were subsequently reported by several groups. Among these, a thorough study by Bolm and co-workers[99] showed that catalyst **35** (Scheme 9) could be employed in combination with bleach, a particularly convenient terminal oxidant.[100] With this catalyst (0.006 mol equiv) yields up to 99% were observed after 60 min reaction time in the oxidation of primary and secondary alcohols. Although **35** suffered partial degradation, attributed to the high density of the catlytic sites on the silica surface, it was possible to recover and recycle the catalyst for at least 10 reaction cycles with less than 10% decrease in chemical yields at constant reaction times. Remarkably, it was also shown that catalyst recycling did not affect the high selectivity for the oxidation of primary versus secondary alcohols characteristic of this protocol.

The organic polymer Chimassorb 944 (M_W ca. 3000 Da) was selected by Sheldon and co-workers as a solubility device for the immobilization and recycling of the TEMPO catalyst **36** (or PIPO, after polyamine immobilized piperidinyl oxyl).[101,102] This soluble catalyst (0.01 mol equiv) performed very nicely in the bleach promoted oxidation of alcohols to aldehydes and ketones (70–99% yield, 94–99% selectivity) and of methyl α-D-glucopyranoside to the corresponding acid (Figure 3, eq 20; 70% yield). In addition **36** catalyzed the aerobic oxidation of benzyl alcohol in combination with cuprous chloride. These reactions could be carried out both in dichloromethane and in the absence of solvent and were shown to occur in shorter times than those employing the previously

Scheme 9. Structure of Supported TEMPOs Employed as Catalysts in Oxidation Reactions



described supported catalysts. Precipitation of **36** from the dichloromethane solution by addition of *tert*-butylmethyl ether allowed catalyst recovery and recycling (two cycles).

2.4. Acidic Catalysts Employed in Protection and Deprotection Reactions

2.4.1. Pyridinium Salts

After sulfonic acid-based ion exchange[27] and Nafion-H[29,30] resins have been shown to catalyze different protection and deprotection reactions of oxygen containing substrates (alcohols, phenols, acids, acetals), *N*-protonated derivatives of polyvinylpyridine emerged as more mild and versatile catalysts for these transformations.

In particular, Menger and Chu[103] discovered that the *p*-toluenesulfonate salts of the commercially available poly(4-vinylpyridine) **37** and poly(2-vinylpyridine) **38** (Scheme 10) were efficient catalysts for the tetrahydropyranylation of primary, secondary, and tertiary alcohols carried out in benzene at room temperature (Figure 4, eq 21; 72−97% yield). To secure reaction heterogeneity and simple recovery and recycling, the catalysts were absorbed on a large excess of Celite. Remarkably, the pyridinium salt of the cation-exchange resin Dowex 50 × 8−50, the *p*-toluenesulfonate salts of the anion-exchange resin Amberlite IRA-400, and the triflate salt of poly(4-vinylpyridine) were found to be useless in these reactions.

The use of the insoluble, highly cross-linked copolymer made of 4-vinylpyridine (75%) and DVB (25%) allowed to avoid the inert support.[104] Its hydrochloride **39** was shown to catalyze the acetalyzation of aldehydes and ketones with ethylen glycol (Figure 4, eq 22; 62−98% yield) and the acetylation of 1-butanol (Figure 4, eq 23; quantitative yield), both reactions having been carried out at room temperature for 1 h in the absence of solvent. The catalyst was readily recovered by filtration and recycled up to five times without any loss in catalytic activity. Later on,[105] a very similar catalyst was employed in the tetrahydropyranylation of primary, secondary, and tertiary alcohols and phenols (84−98% yield) carried out in refluxing dihydropyran as solvent (Figure 4, eq 21). More recently, it was shown that the *p*-toluenesulfonate salt of a polymer similar to **37** (2% DVB cross-linking) catalyzed the deprotection of pyranyl ethers in a 1:1 v/v ethanol:THF solution at 75°C (86−100% yield).[106]

2.4.2. Poly(N-isopropylacrylamide)-Based Catalysts

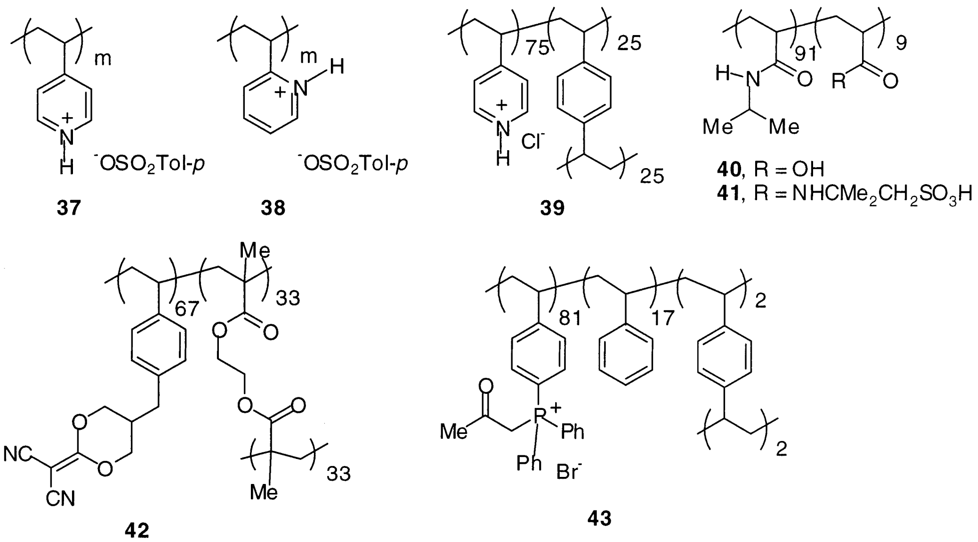
Poly(*N*-isopropylacrylamide) (PNIPAM) has been reported by Bergbreiter[107] as a "smart polymer"[108] possessing the interesting peculiarity of being soluble in cold water and insoluble in the same solvent when heated above its lower critical solution temperature (LCST). As a result, PNIPAM supported species can be separated and recovered by simple heating and then reused after adding fresh cold water. Among others, the two copolymers **40** and **41** (Scheme 10), having LCST of 35 and >100 °C, respectively, were synthesized and tested in the hydrolysis of acetophenone dimethylacetal and cyclohexanone ethylenglycol ketal in toluene/water (Figure 4, eq 24).

These studies showed that the activity of these acidic catalysts was dependent on, but not strictly regulated by, a temperature change. For instance, catalyst **40** was more active at 24 than at 1°C but, when heated above its LCST at 48 °C, still showed an activity between those observed at 1 and 24 °C, a clear indication that the precipitated, heterogeneous catalyst could still promote the reaction.

2.4.3. Dicyanoketene Acetals

In a series of papers[109−111] Masaki and co-workers developed adduct **42** (Scheme 10) as a conceptually different supported catalyst for the monothioacetalization of acetals (Figure 4, eq 25) and the cleavage of acetals and silyl ethers Figure 4, eq 24 and 26). This insoluble π-acid was prepared by copolymerization of a styrene carrying a dicyanoketene acetal in the para position and ethylene glycol dimethylacrylate as a cross-linking agent.

Scheme 10. Structure of Acidic Supported Catalysts



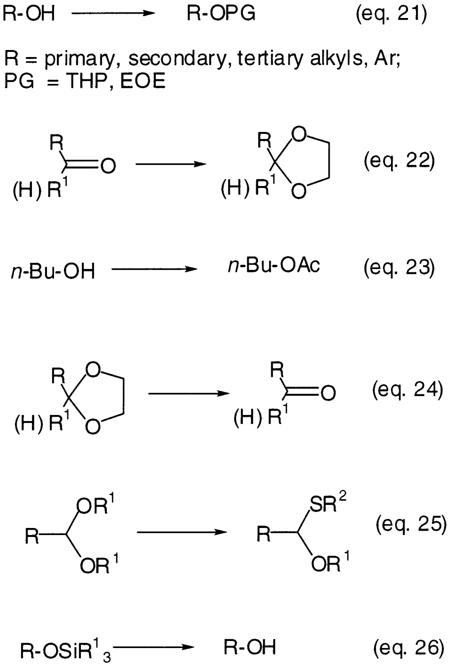


Figure 4. Protection and deprotection reactions catalyzed by polymer-supported catalysts.

Compound **42** (0.4 mol equiv, loading of 2.74 mmol/g) was used to promote (i) the conversions of different acetals into the corresponding mothioacetals by reaction with thiophenol or trimethylsilylthiophenol in acetonitrile at 60 °C,[109] (ii) the deprotection of acetals to the corresponding carbonyl compounds in acetonitrile:water 9:1 at room temperature,[110] and (iii) the cleavage of TMS and TBDMS ethers to the corresponding alcohols under the same conditions.[110] The catalyst showed a remarkable selectivity for acetal hydrolysis versus desilylation or detetrahydropyranylation reactions and, more interestingly, a much enhanced activity with respect to the monomeric dicyanoketene acetal species.[111] Successful catalyst recovery and recycling (two cycles) was also performed.[109]

2.4.4. Phosphonium Salts

The insoluble supported catalyst **43**[112] (Scheme 10) was prepared from the corresponding copolymeric phosphine by alkylation with bromoacetone and shown to be an excellent promoter for the tetrahydropyranylation and ethoxyethylation of primary, secondary, and tertiary alcohols, and phenols (Figure 4, eq 21) under mild conditions (0.01 mol equiv of catalyst, dichloromethane, rt; >90% yield). Compound **43** catalyzed also the corresponding deprotection reaction in methanol in similarly high yields. Catalyst recovery by filtration and recycling was possible for at least four cycles in both processes, even if a slow decrease in efficiency was observed.

2.5. Acidic Catalysts Employed in C–C Bond-Forming Reactions

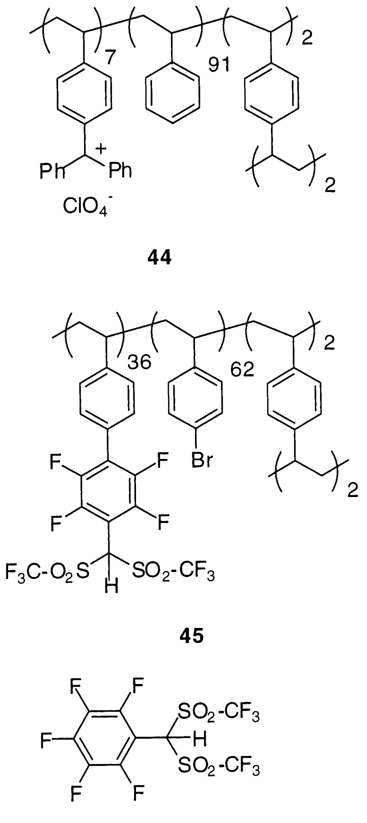
2.5.1. Trityl Perchlorate

Following the discovery that trityl perchlorate catalyzed the aldol-type reaction of acetals and aldehydes with silyl enolethers, Mukaiyama and Iwakiri[113] described the synthesis of adduct **44** (Scheme 11) in which the trityl moiety was anchored on a 2% DVB cross-linked polystyrene. The insoluble catalyst (0.02–0.03 mol equiv) was employed in dichloromethane at −78 °C to promote the condensation of several ketone-derived silyl enolethers with dimethylacetals, trimethyl orthoformate, and benzaldehyde in good to excellent yields (Figure 5, eq 27–29). The reactions were carried out both in batch and in a flow system with comparable results. In particular, the latter reaction mode allowed a very easy regeneration of the catalyst when it had lost some of its activity (generally after the third cycle) by washing it with an acetic anhydride solution of perchloric acid.

2.5.2. Dicyanoketene Acetals

The π-acidic catalyst **42** (Scheme 10) was shown to be an effective promoter (0.2 mol equiv) for the addition of silylated nucleophiles (trimethylsilyl cyanide, trimethylsilyl enolethers of acetophenone and

Scheme 11. Structure of Acidic Supported Catalysts Employed in C−C Bond Forming Reactions



44

45

46

2-acetylfuran; allyltrimethysilane gave no reaction) to a variety of dimethylacetals of aldehydes and ketones (Figure 5, eq 30 and 31).[114] The corresponding adducts were isolated in fair to excellent yield after 2−24 h reaction in refluxing acetonitrile. After washing with water and ethyl acetate and drying under vacuum, the recovered catalyst could be reused without any loss of activity.

Extension of the use of **42** to the condensation between *N*-arylaldimines derived from aromatic aldehydes with four silyl enolethers and two silyl keteneacetals allowed to isolate the corresponding Mannich-type adducts in fair to good yields (Figure 5, eq 32 and 33).[115] Acetophenone-derived imine and *N*-aliphatic aldimines were poorly or not at all reactive. Remarkably, the process was highly chemoselective in favor of aldimine vs aldehyde reaction, thus allowing a convenient three-components condensation.

2.5.3. Tetrafluorophenylbis(trifluoromethanesulfonyl)-methane

In an attempt to obtain a resin-bound Brønsted superacid showing swelling properties superior than Nafion-H as well as a broader range of application under milder conditions, Yamamoto and co-workers recently described the polystyrene-bound tetrafluorophenylbis-(trifluoromethanesulfonyl)methane **45** (Scheme 11).[116] This was prepared by reaction of the lithium salt of adduct **46** with lithiated poly(4-bromostyrene) cross-linked with 2% DVB, and it had a loading of 1.01 mmol of acidic unit per g of resin.

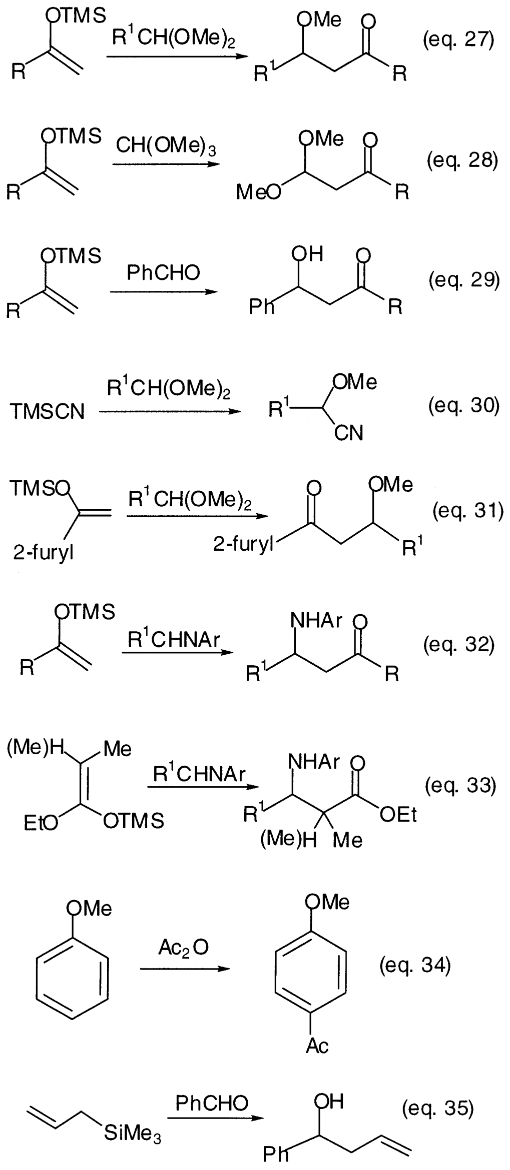
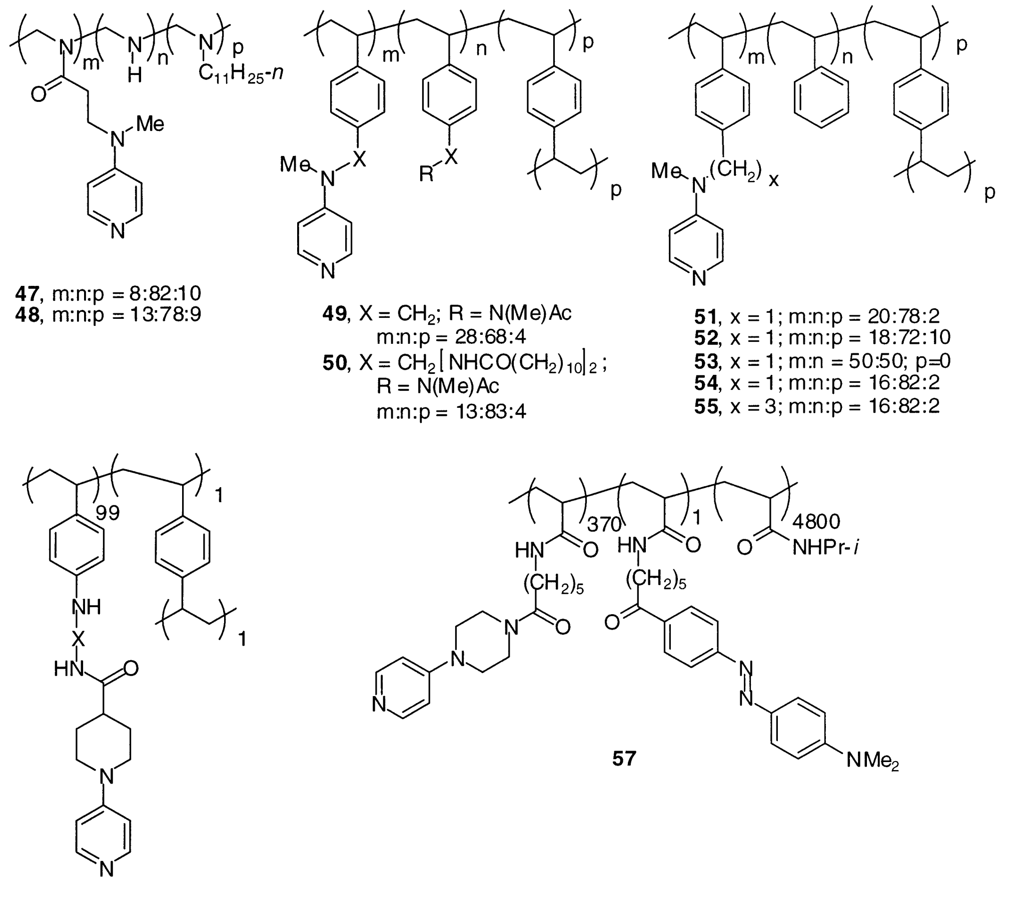


Figure 5. C−C bond forming reactions catalyzed by polymer-supported catalysts.

It was first shown that 0.001−0.01 mol equiv of this catalyst promoted the following: the acetylation of menthol with acetic anhydride (1 h, rt, 100% yield); the esterification of 3-phenyl-propanoic acid with methanol (29 h, rt, 94% yield); and the acetalization of 3-phenylpropanal with trimethylorthoformate (1 h, 0 °C, >99% yield). All of these results very favorably compared with those obtained in the same reactions and under similar conditions with a Nafion-H/silica nanocomposite catalyst.

Much more relevant were the applications of this polymer-supported superacid to C−C bond-forming reactions.[116] In this context, 0.03 mol equiv of compound **45** was enough to catalyze the following: the Friedel-Craft acylation of anisole with acetic anhydride (Figure 5, eq 34; nitromethane, 2 h, 50 °C, >99% yield); the aldol condensation between benzaldehyde and acetophenone trimethylsilyl enolether (Figure 5, eq 29; toluene, 7 h, −78 °C); and the allylation of benzaldehyde with allyl trimethylsilane (Figure 5, eq 35; dichloromethane, 1 h, −40 °C). Catalyst recovery was readily obtained by filtration.

Scheme 12. Structure of DMAP-Related Catalysts Employed in Protection/Deprotection Reactions



47, m:n:p = 8:82:10
48, m:n:p = 13:78:9

49, X = CH_2; R = N(Me)Ac
m:n:p = 28:68:4
50, X = $CH_2[NHCO(CH_2)_{10}]_2$;
R = N(Me)Ac
m:n:p = 13:83:4

51, x = 1; m:n:p = 20:78:2
52, x = 1; m:n:p = 18:72:10
53, x = 1; m:n = 50:50; p=0
54, x = 1; m:n:p = 16:82:2
55, x = 3; m:n:p = 16:82:2

56, X = C(O)-$(CH_2)_5$

57

Recycling was possible for at least 10 cycles without loss of activity.

As a further development of this approach, a single-pass reaction column system was devised to conveniently perform the above-mentioned and other reactions in high yields.[117]

2.6. Basic Catalysts

Basic catalysis in general and basic supported catalysis in particular are research areas less developed than acidic catalysis.[118] Most of the efforts in the field of supported basic catalysis involved the use of inorganic supports, such as mesoporous silicas and zeolites. Only a few examples of basic catalysts immobilized on polymeric matrixes have been reported.

2.6.1. 4-(Dimethylamino)pyridine Analogues

The widespread applications of 4-(dimethylamino)-pyridine (DMAP) in synthetic organic chemistry led several groups to develop polymer-supported version of this reagent. In some instances, the immobilized species was used in catalytic amount.

The first example of a DMAP-like molecule supported on a polymer matrix was described by Klotz and co-workers.[119,120] They prepared the poly(ethylene imine)-derived species **47** and **48** (Scheme 12), having different contents of active sites (8% and 13%, respectively), that were employed to efficiently catalyze the hydrolysis of some *p*-nitrophenyl esters in aqueous solution. Noticeably, the supported catalysts performed better than DMAP itself under the selected reaction conditions.

Subsequently, Shinkai et al.[121] reported two polystyrene-supported version of DMAP, namely, adducts **49** and **50** (Scheme 12). Compound **49** was obtained from 4%-DVB cross-linked chloromethylated polystyrene, by exhaustive amination with methylamine followed by reaction with 4-chloropyridine and acetylation of the unreacted methylamino groups. Compound **50** featured long spacer chains separating the polymer backbone from the same terminal groups of **49**. Virtually at the same rate, both polymers (0.1 mol equiv) catalyzed the methyl ester formation of various carboxylic acids in good yields (excess methanol, stoichiometric DCC, dichloromethane, rt). The reactions, however, were found to be clearly slower than those promoted by DMAP. The catalysts could be recycled in a second run occurring with unchanged yields.

Tomoi and co-workers[122] synthesized the insoluble polymers **51** and **52** (Scheme 12) by copolymerization of 4-(*N*-methyl-*N*-*p*-vinylbenzylamino)pyridine with styrene in the presence of 2% and 10% DVB, respectively. This synthetic approach was preferred to the amination of cross-linked chloromethylated polystyrene with the *N*-sodium salt of 4-methylaminopyridine, which left a number of unreacted chloromethyl groups that could possibly interact with the basic sites of the polymer.

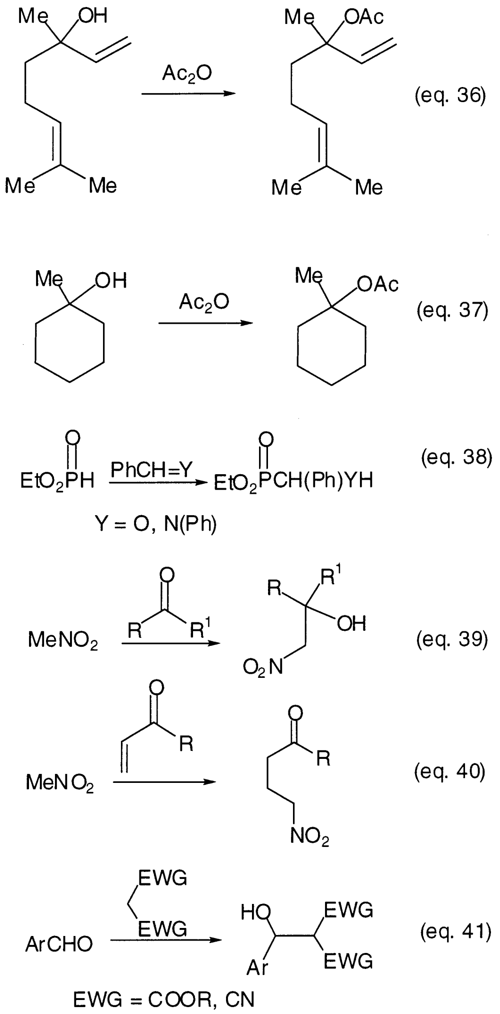


Figure 6. Miscellaneous reactions catalyzed by polymer-supported basic catalysts.

The acetylation of linalool with acetic anhydride carried out in the presence of stoichiometric triethylamine (Figure 6, eq 36; benzene, 60 °C) was chosen as a model reaction to study the catalytic activity of **51** and **52**. Compound **51** (0.2 mol equiv) displayed an activity that was slightly lower than that of DMAP. This was explained in terms of the stronger electron-withdrawing nature of the *N*-benzyl group of **51** with respect to the *N*-methyl group of DMAP, which resulted in a destabilization of the intermediate acetylpyridinum species. However, since **51** was more active than **52**, it was concluded that also diffusion phenomena played an important role.

Remarkably, catalyst **51**, recovered by filtration, treated with aqueous sodium hydroxide, and dried under vacuum, was recycled three times without a significant decrease in catalytic activity.

Menger and McCann[123] later on reported that the non-cross-linked polymer **53** (0.04 mol equiv) (Scheme 12), obtained by amination of commercially available poly(vinylbenzyl chloride), catalyzed several esterification reactions of secondary and tertiary alcohols in yields that were constantly slightly lower than those obtained with DMAP as the catalyst. Compound **53** was also effective in the *tert*-butyldimethylsilylation and tritylation of steroidal alcohols, and in the *N*-acetylation of indole.

Fréchet and co-workers[124] synthesized adducts **54** and **55** and compared their catalytic activities. As can be seen in Scheme 12, **54** was very similar to Tomoi's **51**, differing only in the monomer distribution. However, the synthetic approach toward these compounds was different, since, in Fréchet's hands, the amination reaction of chloromethylated polystyrene, found to provide an unsatisfactory access to **51** by Tomoi (see above), worked very nicely.

In this study, the model reaction was the acetylation of 1-methylcyclohexanol (Figure 6, eq 37) carried out in toluene at 60 °C in the presence of 0.05 mol equiv of catalyst and stoichiometric triethylamine. By comparing DMAP with **54** and **55**, it was found that the latter, featuring a spacer chain inserted between the polystyrene skeleton and the pyridine nucleus, was almost as reactive as DMAP and 1.5 times more reactive than **54**. Other copolymers obtained using 4-vinylpyridine instead of styrene in the copolymerization were found to be less catalytically active.[125]

Structurally different DMAP-type supported derivatives were the subject of the work of Verducci,[126] Bergbreiter,[127] and Mathias.[128] In particular, adduct **56** (Scheme 12), obtained from 1% DVB cross-linked aminomethyl polystyrene by attachment of a 4-carbonyl-*N*-(4′-pyridino) piperidine unit through an amide spacer, showed 90% of the DMAP efficiency in catalyzing the reaction of eq 37 (Figure 6) (0.2 mol equiv of catalyst, acetic anhydride, triethylamine, benzene, 70 °C). Other related catalysts featuring longer spacer chain gave similar results, whereas an increase in the catalyst loading was found to be detrimental by a "catalyst's self-inhibition" mechanism. Finally, the catalyst could be recovered and recycled 10 times showing an overall 30% loss of efficiency.[126]

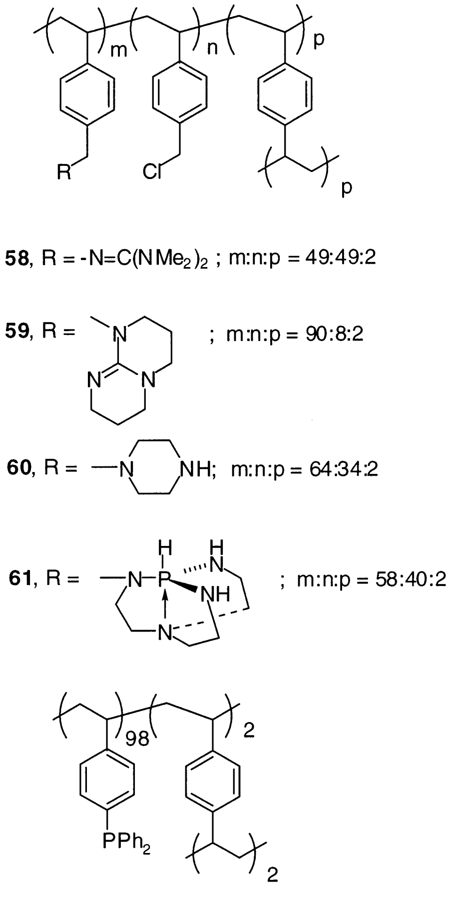
Adduct **57**,[127] featuring a DMAP-like residue and a diazo dye moiety both anchored on a PNIPAM backbone, was recently prepared by Bergbreiter and co-workers. It was employed to efficiently catalyze the acetylation of 1-methylcyclohexanol (0.05 mol equiv of catalyst, acetic anhydride, trietylamine) and the reaction between phenols and di-*tert*-butyloxycarbonate (0.0025 mol equiv of catalyst) in dichloromethane at room temperature. The catalyst, soluble in polar solvents and water, was recovered by precipitation with hexanes, a procedure that left less than 0.1% of **57** in solution (by UV−vis spectroscopy exploting the presence of the dye). Catalyst recycling was demostrated for at least three cycles in both reactions.

The only other soluble catalyst containing DMAP-like groups was obtained by polymerization of 4-(*N*,*N*-diallylamino)pyridine.[128] It showed an exceptionally high efficiency in promoting the hydrolysis of *p*-nitrophenyl esters of straight-chain carboxylic acids carried out in water, higher even than that of 4-(pyrrolidino)pyridine (that, in its turn is higher than DMAP's). Unfortunately, neither its application to other reactions nor its recovery and recycling was studied.

2.6.2. Alkylguanidine Analogues

The ability of guanidines and related compounds to act as basic catalysts in a number of transforma-

Scheme 13. Structure of Basic Supported Catalysts Employed in Miscellaneous Reactions



58, R = -N=C(NMe$_2$)$_2$; m:n:p = 49:49:2

59, R = ; m:n:p = 90:8:2

60, R = ; m:n:p = 64:34:2

61, R = ; m:n:p = 58:40:2

62

tions prompted their immobilization on different polymers. For instance, adducts **58** and **59** (Scheme 13) have been synthesized starting from cross-linked chloromethylated polystyrene by nucleophilic substitution with 1,1,3,3-tetramethylguanidine or 1,5,7-triazabicyclo[4.4.0]dec-5-ene, respectively.[129] These compounds have been showed to promote the transesterification of soybean oil with methanol (0.05 mol equiv of catalyst, 70 °C), an industrial process exploited for the preparation of the methyl esters of fatty acids. The catalytic efficiencies of the two adducts were similar and slightly inferior to those of the corresponding nonsupported bases. Insertion of a spacer chain made of five methylene units between the polymer backbone and the catalytic sites did not lead to faster reactions. Interestingly, the use of a starting polymer with a 4-fold higher loading led to a completely inactive catalyst, likely by intramolecular alkylation of the nitrogen atoms of the basic moieties by proximal chloromethyl units.[130] Unfortunately both **58** and **59** showed extensive leaching of their active sites upon recycling, which resulted in a comparable loss of catalytic efficiency.

Adduct **59** (Scheme 13) has been found to be a good catalyst for the addition of diethylphosphite to carbonyl compounds and imines (Figure 6, eq 38; 75−93% yield) and for the Henry and Michael addition of nitromethane to saturated (80−95% yield) and unsaturated ketones (70−90% yield), respectively (Figure 6, eq 39 and 40).[131]

2.6.3. Miscellaneous Basic Catalysts

The simple piperazine derivative **60** (Scheme 13) has been prepared from cross-linked chloromethylated polystyrene and used as an alternative to piperidine to promote the formation of a small library of differently substituted caffeic acids by Knoevenagel condensation.[132] In contrast to the soluble base, which led to the formation of difficult-to-remove, piperidine-containing byproducts, this insoluble catalyst promoted clean reactions of malonates, malononitrile, and cyanoacetates with a variety of aromatic and heteroaromatic aldehydes in good to excellent yields (Figure 6, eq 41; 0.075 mol equiv of catalyst, refluxing ethanol, 2 h). It is interesting to note that catalyst **60** performed as efficiently as the MCM-41-supported analogue of compound **59** that has been used in very similar reactions.[133,134]

The insoluble procatalyst **61** (Scheme 13) has been prepared[135] from 1% cross-linked chloromethylated polystyrene and employed in combination with excess NaH to promote alkene synthesis by the dehydrohalogenation (Figure 2, eq 12) or debromination (Figure 1, eq 5) of a number of haloalkanes in nearly quatitative yields (0.1 mol equiv of catalyst, acetonitrile, rt). Although not as active as its nonsupported counterpart, compound **61** allowed for ready isolation of high-purity products and was easily recovered and recycled.

Finally, the commercially available polystyrene-supported version of triphenylphosphine **62**[136] catalyzed the isomerization of (*Z*)- to (*E*)-nitroalkenes which were isolated in pure form after simple filtration of the polymeric species.[137]

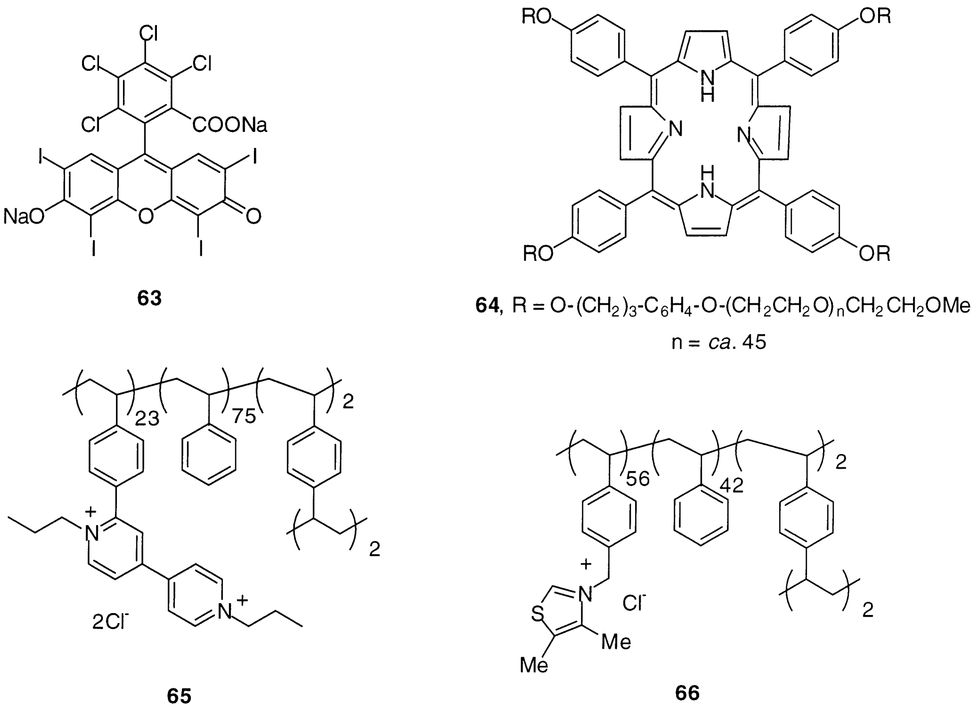
2.7. Miscellaneous Achiral Catalysts

In as early as 1973, the photosensitizer Rose Bengal **63** (Scheme 14) was supported on cross-linked chloromethylated polystyrene (likely through the phenoxy function), and the resulting species was employed in catalytic amount to promote some photooxidations reactions involving singlet oxygen. These transformations occurred with the same efficiency of those involving **63** itself.[138]

An efficient catalyst for some related reactions was reported much more recently, when a tetraaryl substituted porphyrin was supported on four residues of MeOPEG$_{2000}$ to afford adduct **64**.[139] This compound, readily soluble in dichloromethane, was employed to transform bisdialine, dimenthene (Figure 7, eq 42), phellandrene, and dicyclopentadiene (Figure 7, eq 43) into the corresponding oxidation products in yields similar to or even superior than those observed when working with identical concentration of tetraphenylporphyrin as catalyst. The supported reagent allowed very simple product isolation and was stable enough to be recovered and recycled for six reaction cycles in constant yields and stereoselectivity.

Some polymer containing the viologen structure have been described by Endo and co-workers to be employed in reduction reactions.[140] For instance, adduct **65** (Scheme 14), obtained by lithiation of brominated polystyrene, reaction with 4,4′-bipyridine

Scheme 14. Structure of Miscellaneous Supported Catalysts



63

64, $R = O\text{-}(CH_2)_3\text{-}C_6H_4\text{-}O\text{-}(CH_2CH_2O)_nCH_2CH_2OMe$

n = *ca.* 45

65

66

and quaternization, catalyzed the sodium dithionite reduction of azobenzene to idrazobenzene in good yield.

Synthetically more relevant was a study by Iranian workers that immobilized 4,5-dimethythiazole on highly functionalized, 2% DVB cross-linked chloromethylated polystyrene to obtain adduct **66** (Scheme 14).[141] A 0.1 mol equiv sample of this compound catalyzed the acyloin condensation of aliphatic, aromatic, and heteroaromatic aldehydes, carried out in the presence of trietylamine as the base in ethanol at room temperature, in good to excellent yields (Figure 7, eq 44). The catalyst displayed a remarkable stability, since the same sample of compound **66** was found to catalyze the condensation of benzaldehyde in 91% yield after as many as twenty reaction cycles.

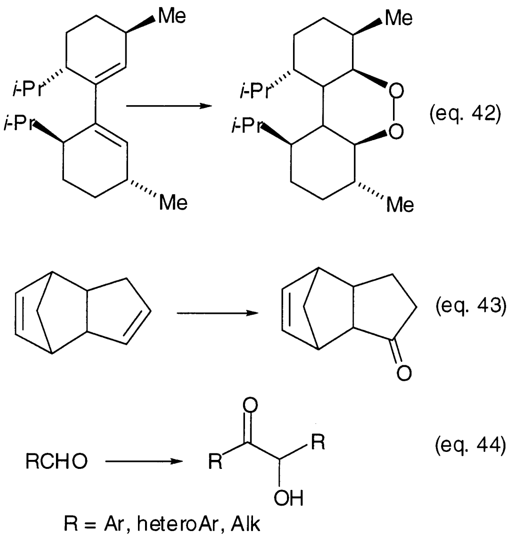


Figure 7. Miscellaneous reactions catalyzed by polymer-supported catalysts.

3. Chiral Polymer-Supported Catalysts

The tremendous interest in "asymmetric catalysis", which has revolutionized the chemists' approach toward the synthesis of enantiomerically enriched compounds, resulted in an extensive effort devoted to the immobilization of chiral catalysts on various types of supports.[142] Obviously, along with the above-mentioned practical advantages associated with catalyst immobilization, the cost of the catalyst itself was a factor that played in favor of the possibility of easy recovery and recycling.

Not different from metal based species, chiral organic catalysts[12] have also been subjected to polymer-supporting. As in the case of polymer-supported achiral catalysts, the immobilization of chiral phase-transfer catalysts[14] provided the first demonstrations of the feasibility of this approach.

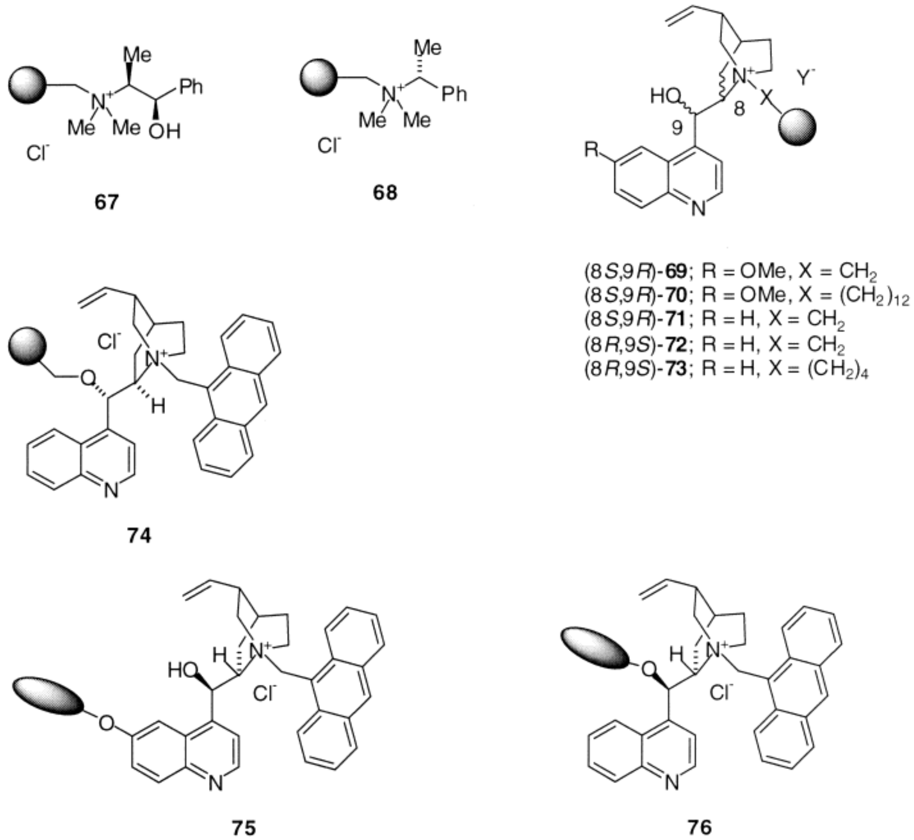
3.1.Chiral Phase-Transfer Catalysts

3.1.1. Polystyrene-Supported Phase-Transfer Catalysts

In 1977 Chiellini and Solaro reported the immobilization of (1*R*,2*S*)-*N*-methylephedrine and (*R*)-*N*,*N*-dimethyl α-methylbenzylamine on chloromethylated polystyrene by nitrogen quaternization.[143] Under phase-transfer catalysis conditions, the resulting adducts **67** and **68** (Scheme 15) were employed to catalyze the ethylation of α-cyanotoluene (Figure 8, eq 45), the dichlorocyclopropanation of styrene (Figure 1, eq 2), and the haloform reaction of benzaldehyde (Figure 8, eq 46) in good chemical yields and "low but definite steroeselectivity", which is enantiomeric excess (ee) $\leq 10\%$.

Soon thereafter, Colonna and co-workers[144] observed a maximum 23% ee for the epoxide product of the Darzens reaction between 4-methylphenyl chloromethyl sulfone and 2-butanone (Figure 8, eq

Scheme 15. Structure of Chiral Phase-Transfer Catalysts Supported on Polystyrene and Poly(ethylene glycol)[a]



[a] In **67**−**74**, (shaded circle) = polystyrene with different degree of divinylbenzene cross-linking; in **75**, (shaded oblong circle) = MeOPEG$_{5000}$O−C$_6$H$_4$−(CH$_2$)$_3$−; in **76**, (shaded oblong circle) = MeOPEG$_{5000}$O−C$_6$H$_4$−(CH$_2$)$_3$O−Ph−CH$_2$.

47), carried out in the presence of 0.05 mol equiv of compound **67** in acetonitrile/50% aqueous sodium hydroxide two phase system at room temperature.

Improvement in stereoselectivity was looked for in the more rigid structure of *Cinchona* alkaloids, whose ability to catalyze a variety of processes[19] had already been recognized at the time. Interestingly, the alkaloid skeleton offers different sites for polymer attachment. The more commonly exploited bridge-head nitrogen was selected by Kobayashi and Iwai[145] for the immobilization of quinine by quaternization with standard and modified DVB cross-linked polystyrene. Thus, adducts **69** (Y = Cl) and **70** (Y = Br) (Scheme 15) were prepared and employed as catalysts (0.2 mol equiv) in the Weitz-Scheffer epoxidation of chalcone (Figure 8, eq 48) in the presence of sodium hydroxide and in a 30% hydrogen peroxide/toluene two-phase mixture as solvent. Extremely low ee (up to 4%) were observed, with the spaced catalyst **70** performing less poorly than **69**.

A couple of years later, Hodge and co-workers[146] anchored cinchonidine and cinchonine to 20% DVB cross-linked chloromethylated polystyrene to afford adducts **71** (Y = F) and **72** (Y = HCO$_3$) (Scheme 15). Catalyst **71** (0.05 mol equiv) promoted the Michael addition of methyl (1-oxoindan-2-yl)-carboxylate to 3-buten-2-one (Figure 8, eq 49) to afford the (*S*)-configurated product in 27% ee and 61% yield after 10 days of reaction at room temperature in toluene. The pseudo-enantiomeric adduct **72** was a less stereoselective but more chemically efficient catalyst, leading to the (*R*)-enantiomer in 13% ee and 94% yield after a 5 days of reaction.

The advent in the early 90's of the O'Donnell-Corey-Lygo protocol for the highly enantioselective alkylation of amino acids imines under PTC conditions catalyzed by quaternized cinchona alkaloids[14,19] led to a series of investigations on the use of supported catalysts in these reactions.

In this context, Najera and co-workers[147] discovered that **71** (Y = Cl; polystyrene is 1% DVB cross-linked) promoted the benzylation of the benzophenone imine of glycine *i*-propylester (Figure 8, eq 50) carried out in 25% aqueous NaOH and toluene at 0 °C to afford the (*S*)-product in 90% yield and 90% ee. The use of different ester alkyl residues (ethyl, *tert*-butyl), higher reaction temperature (25 °C), and, much more surprisingly, very similar alkylating agents (4-bromo-, 4-nitro-, 4-methoxybenzylbromide, and 2-bromomethylnaphthalene) depressed the ee to 40−60%. Even more surprising was the observation that, under the best conditions, catalyst **72** (Y = Cl; polystyrene is 1% DVB cross-linked) afforded the (*R*)-alkylated product in only 40% ee. Catalyst recovery and recycling was also reported.

Subsequently, Cahard and co-workers examined the insertion of spacer chains of different length (4, 6, or 8 methylene units) between the polymer and the quaternized nitrogen.[148] It was found that the use of catalyst **73** (Y = Cl; polystyrene is 1% DVB cross-linked) (Scheme 15) improved the ee of the (*R*)-configurated benzylation product of benzophenone

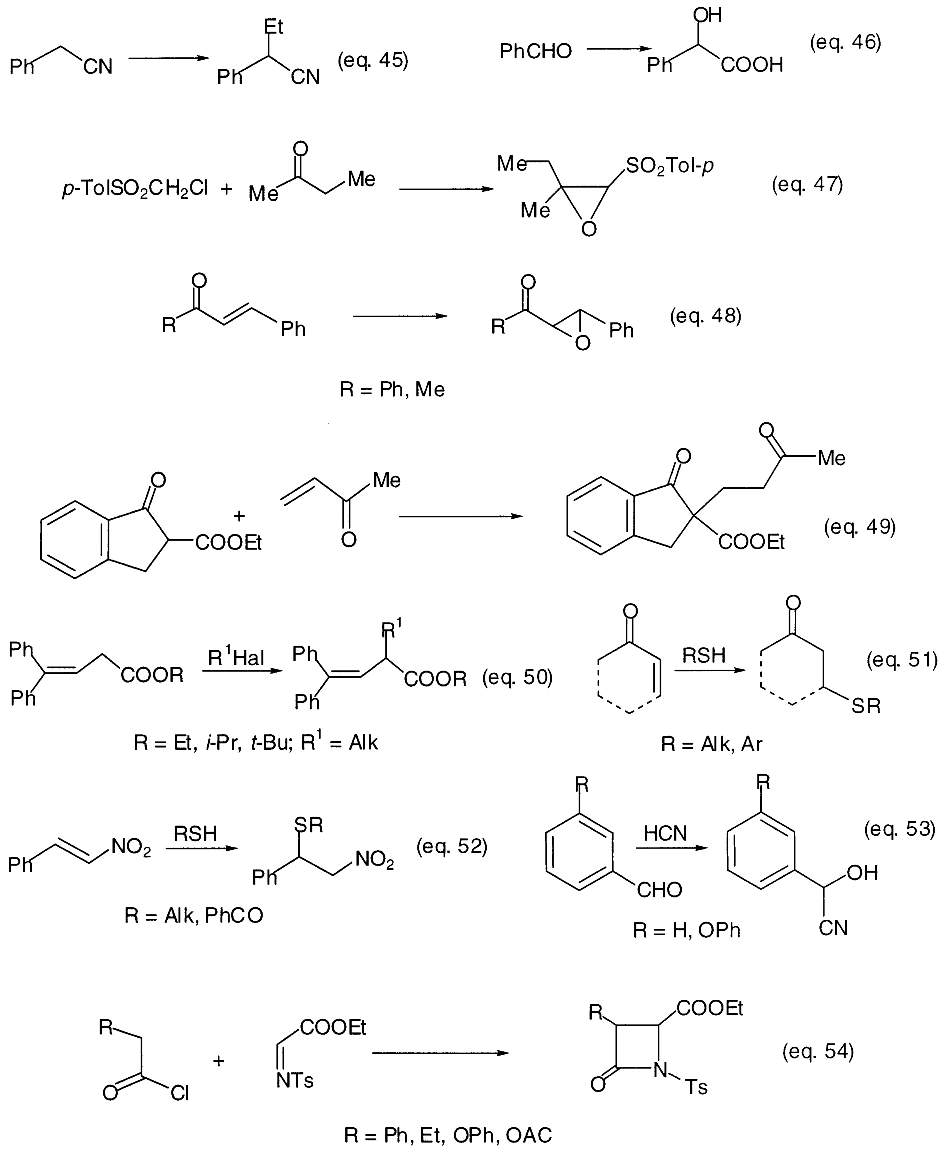


Figure 8. Stereoselective reactions catalyzed by *Cinchona* alkaloid-derived polymer-supported catalysts.

imine glycine *tert*-butylester up to 81% (0.1 mol equiv of catalyst, 50% aqueous NaOH/toluene, 0 °C, 15 h). The introduction of the spacer chains, however, had a dramatic effect on the stereochemical outcome of the reaction in that both the cinchonine and cinchonidine derived catalysts inexplicably afforded the (*R*)-configurated product notwithstanding their pseudo-enantiomeric structure (due to the opposite configuration at C-8 and C-9 of the alkaloid moiety).

The same authors then reported a second generation catalyst, namely **74** (Scheme 15). This adduct incorporated the 9-anthracenylmethyl residue at nitrogen (previously selected by Corey for maximum stereoselectivity) and featured the polystyrene residue attached to the alkaloid oxygen atom at C-9.[149] By working in toluene at −50 °C in the presence of excess solid cesium hydroxide and 0.1 mol equiv of catalyst **74**, the reaction of eq 50 ($R = t$-Bu, $R^1 =$ benzyl) occurred in 67% yield affording the expected (*S*)-product in 94% ee, a value very close to that observed with the nonsupported catalyst. Unfortunately (and, again, inexplicably), the pseudoenantiomer of **74** proved to be much less stereoselective affording the (*R*)-product in only 23% ee. No mention of catalyst recycling was reported.

The asymmetric synthesis of benzoin (Figure 7, eq 45, R = Ph; 14% ee) catalyzed by the cyanide salt of quaternized strychnine supported on 2% DVB cross-linked polystyrene has also been described.[150]

3.1.2 Poly(Ethylene Glycol)-Supported Phase-Transfer Catalysts

The soluble catalysts **75** and **76** (Scheme 15) were prepared by attaching two different $MeOPEG_{5000}$/spacer fragments to the *N*-anthracenylmethyl salts of *nor*-quinine and cinchonidine, respectively.[151] When tested in the standard benzylation reaction mentioned above (Figure 8, eq 50), catalyst **75** behaved unsatisfactorily both under liquid/liquid and solid/liquid conditions, affording the product in ≤12% ee. The use of compound **76** was less disappointing: under the best conditions (0.1 mol equiv of catalyst, solid CsOH, dichloromethane, −78 °C, 60 h) the (*S*)-product was obtained in 75% yield and 64% ee. The latter was clearly lower than that observed with the insoluble catalyst **74**.

To understand the reason of this result, control experiments were carried out to ascertain the role played by PEG on the reaction outcome.[151] Thus, it was demonstrated that the addition of the bismethyl ether of PEG_{2000} depressed to 65% the ee of a reaction carried out with the nonsupported catalyst under Corey's condition. Since the value was in line with that observed with **76**, it was proposed that PEG played a role in solubilizing the inorganic species in the organic solution promoting a poorly stereocontrolled reaction pathway that did not require the catalyst to occur. In the course of this study, it was also found that both the supported and the nonsupported catalysts were quite unstable, thus preventing any possibility of recovery and recycling.

3.2. Non-Ionic Catalysts Derived from the *Cinchona* Alkaloids

As mentioned above, different sites of attachment have been exploited to synthesize polymer-bound chiral catalysts derived from the alkaloids of the *Cinchona* family. In the case of nonionic catalyst, the two most commonly used connection sites were the double bond of the quinuclidine residue and the oxygen atom at C-9, the former being largely preferred.

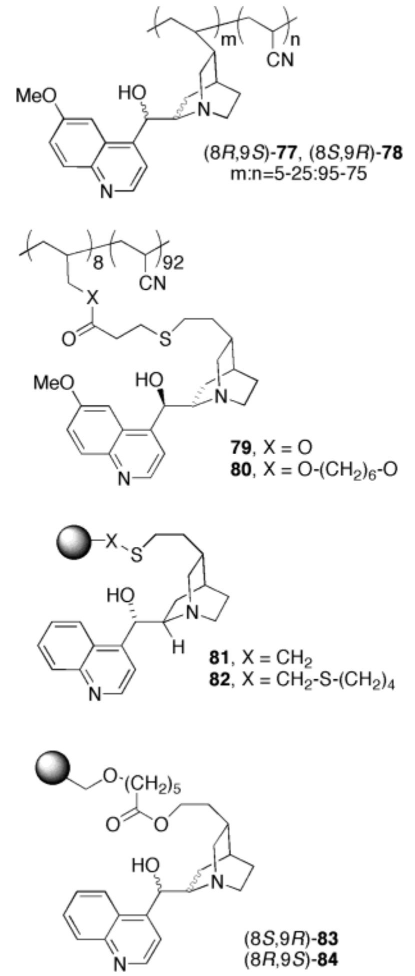
3.2.1. Catalysts Supported through the Double Bond

In 1978 Kobayashi and Iwai synthesized some copolymers constituted of acrylonitrile and *Cinchona* alkaloids in various ratios.[152] They reasoned that leaving the catalitically active functional groups of the alkaloid (namely, the bridge-head nitrogen and the hydroxy group) uninvolved in the connection to the polymer should generate a more stereoselective catalyst. Among others, they prepared adducts **77** and **78** (Scheme 16), derived from quinidine and quinine, respectively. These material were readily soluble in polar aprotic solvents such as DMF and DMSO and insoluble in less-polar solvents, thus allowing for their simple recovery by a precipitation induced by solvent polarity change.

Catalyst **77** (0.05 mol equiv) promoted the Michael addition of eq 49, Figure 8, to afford the dextrorotatory product in 92% yield and 42% ee (toluene, rt, 48 h). Catalyst recovery but not its recycling was reported. The use of **78** under the same conditions led to the enantiomeric compound in 98% yield and 30% ee.[152,153] Other reactions catalyzed by **77** were the additions of dodecanethiol to 3-methyl-3-buten-2-one (Figure 8, eq 51; 76% yield, 57% ee),[152] of benzylmercaptan to β-nitrostyrene (Figure 8, eq 52; 54% yield, 18% ee),[154] and of hydrogen cyanide to 3-phenoxybenzaldehyde (Figure 8, eq 53; 98% yield, 46% ee). [155]

The introduction of spacer groups between the polymer backbone and the alkaloid moiety was investigated with the aim of obtaining more stereoselective catalysts.[156] Toward this end Oda and coworkers added a 3-mercaptopropionic acid unit to the quinine double bond, and transformed the terminal carboxy group into esters having polymerizable double bond at the end of their alkyl residues. Co-polimerization of these derivatives with acrylonitrile gave adducts **79** and **80** (Scheme 16).

Scheme 16. Structure of Supported *Cinchona* Alkaloids Catalysts[a]



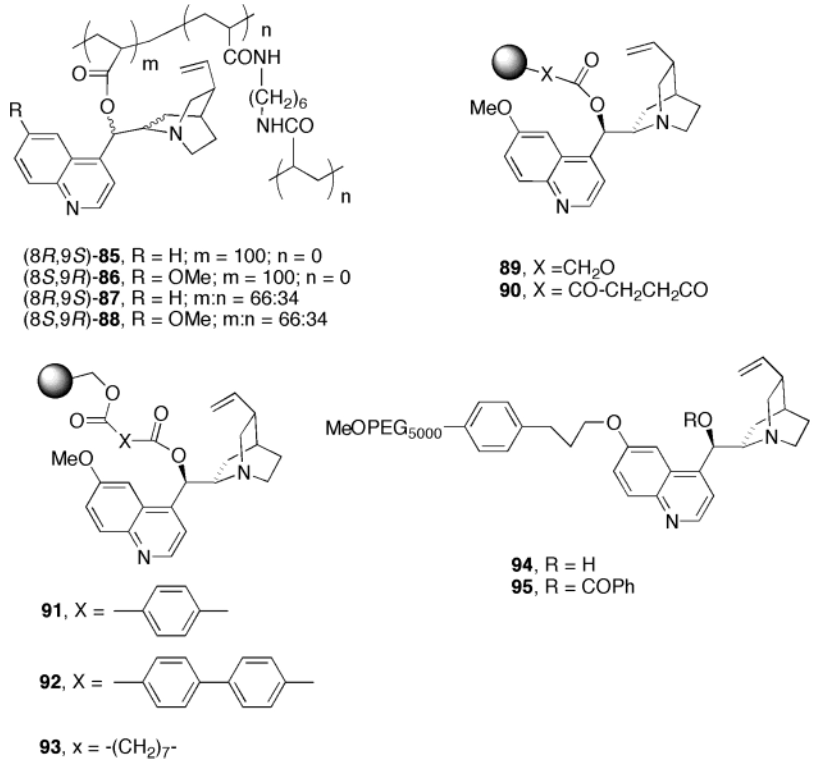
[a] In **81**−**84**, (shaded circle) = 1% cross-linked polystyrene.

Their use (0.05 mol equiv of catalyst, toluene, −48 °C, 28 h) improved the enantioselectivity of eq 49 (Figure 8) up to 62% and 65% ee, respectively, from the 49% ee observed with Kobayashi's catalysts **78** under identical conditions. The stereoselectivity, however, still remained lower than that observed with a structurally related nonsupported catalyst (ee 75%).[156]

The alkaloid double bond was also exploited to anchor *Cinchona* alkaloids to 1% DVB cross-linked chloromethylated polystyrene by means of different spacers. Thus, adducts **81** and **82** (Scheme 16) were obtained by Hodge and co-workers and tested in some conjugate addititons of thiols and thiolbenzoic acid to cyclohexenone and nitrostyrene (Figure 8, eq 51 and 52).[157] Catalyst **81** proved the most successful, being able to promote the reaction of 4-thiocresol and cyclohexenone in up to 45% ee (0.05 mol equiv of catalyst, toluene, rt, 24 h, 81% yield). Recovery and recycling of catalyst **81** was possible for three additional cycles in which both the chemical yield and the enantioselectivity were maintained (average values: 75% yield and 43% ee).

Introduction of a hydroxy group at the terminal atom of the double bond of quinine and quinidine was

Scheme 17. Structure of Supported Cinchona Alkaloids Catalysts[a]



(8*R*,9*S*)-**85**, R = H; m = 100; n = 0
(8*S*,9*R*)-**86**, R = OMe; m = 100; n = 0
(8*R*,9*S*)-**87**, R = H; m:n = 66:34
(8*S*,9*R*)-**88**, R = OMe; m:n = 66:34

89, X = CH_2O
90, X = $CO\text{-}CH_2CH_2CO$

94, R = H
95, R = COPh

91, X =
92, X =
93, x = $\text{-}(CH_2)_7\text{-}$

[a] In **89** and **90**, (shaded circle) = 1% cross-linked polystyrene; in **91**−**93**, (shaded circle) = Wang resin.

envisaged by d'Angelo and co-workers as a suitable means to provide a new mode of attachment of these alkaloids to 1% DVB cross-linked chloromethylated polystyrene.[158] A small collection of 10 supported catalysts was thus obtained featuring different spacers between the polymer and the pseudo-enantiomeric alkaloid.

These catalysts were tested in the paradigmatic Michael addition described above (Figure 8, eq 49; 0.1 mol equiv of catalyst, dichloromethane, 20 °C, rt). The quinine-derived catalyst **83** (Scheme 16) was the more stereoselective affording the (*R*)-configurated product in 85% yield and 87% ee. Surprisingly, the quinidine-based catalyst **84** was much less selective (39% ee) in the production of the same enantiomer. Even if this behavior has some precedent in the reactions promoted by other polymer-supported *Cinchona* alkaloids catalysts,[148] these results demonstrated how relatively small changes in the polymer/catalyst ensemble may produce dramatic and unexplicable effects in the stereochemical outcome of the reaction.

3.2.2. Catalysts Supported through the Oxygen Atom at C-9

Introduction of an acryloyl residue at the oxygen atom at C-9 of cinchoninine and quinine provided a suitable handle to generate homo-[159,160] and copolymers[161] of these alkaloids. Soluble adducts **85** and **86** and their cross-linked insoluble counterparts **87** and **88** (Scheme 17) were prepared[161] following this strategy. They were employed to catalyze the low-temperature addition of methanol to methylphenyl ketene to afford methyl 2-phenylpropionate (0.01 mol equiv of catalyst, toluene, −78 °C, 20 h). Cinchonine-derived catalysts **85** and **87** performed similarly affording the (*S*)-ester in 35 and 34% ee, respectively. The ee were higher than those obtained with their quinine-derived analogues **86** and **88**, which led to the (*R*)-product in 15% and 12% ee, respectively.

The C-9 oxygen atom of quinine was exploited by Hermann and Wynberg to connect this alkaloid to 2% DVB cross-linked polystyrene.[162,163] The resulting catalysts **89** and **90** (Scheme 17), however, displayed very modest stereoselectivity (ee ≤11%) in the Michael reaction of eq 49 (Figure 8), whereas their non supported counterparts were much more efficient (up to 53% ee).

Very recently, Lectka and co-workers[164] showed all the potentiality of polymer-supported *Cinchona* alkaloids to act as chiral catalysts in a spectacular application of one of these reagents to the stereoselective synthesis of β-lactams carried out on sequentially linked columns. The crucial stereoselctive step was based on previous work by the same group, which established how quinine derivatives can act as catalysts for the 2 + 2 Staudinger reaction between ketenes and imines.[165]

The supported compounds **91**−**93** (Scheme 17) were prepared by connecting the oxygen atom at C-9 of quinine to 1% DVB cross-linked, insoluble, and highly loaded Wang resin through difunctional spacers. These differed in length and conformational mobility. Among the catalysts, compound **92**, featuring a long and rigid spacer, performed better than both **91** and **93** in the synthesis of 1-*p*-tolylsulfonyl-3-phenyl-4-carbethoxy β-lactam by the cycloaddition of phenyl ketene with the *N*-tosylimine of ethyl glyoxalate (Figure 8, eq 54). The product was obtained in 62% yield as a 93:7 mixture of cis and trans azetidinones, the major diastereoisomer having a 90% ee. Quite interestingly, a few number of runs (five to ten) were necessary to obtained a catalyst aged enough to afford consistent results, since quinine “bleeding” from the freshly prepared catalyst was found to occur. A properly aged resin performed with no erosion in yield or selectivity for as many as sixty cycles.

Three different reaction setups were then assembled to carry out the reaction on sequentially linked columns. The first assembly featured three columns: the top one contained a polystyrene supported base[166] to generate the ketene from the acid chloride at low temperature. The THF ketene solution was then allowed to percolate into the second column containing catalyst **91** where a THF solution of the imine was slowly introduced through a port. Final passage of the mixture through a third column, containing aminomethylated polystyrene as scavenger, removed the unreacted imine and ketene allowing elution of the crude product having 93% ee. A single crystallization gave the enantiopure β-lactam in 65% yield. After washing with different solvents and drying under high vacuum, the whole system was reassembled for subsequent cycles. At the sixtieth cycle level, the chemical yield was still 62% for a product of 90% ee. The pseudoenantiomeric catalyst obtained from quinidine behaved similarly, affording the enantiomeric azetidinone in almost identical yield and ee.

A modification of this methodology was obtained in a second column assembly, which allowed in situ imine preparation from the corresponding α-chloroamine in a column parallel to the one where the ketene was generated. After extensive investigation, the best stationary phase for imine production was found to be a 1/6 w/w Celite/NaH mixture.

An alternative version of this protocol involved the use of a top colum loaded with a 5/1 w/w mixture of supported catalyst **91** and powdered potassium carbonate cooled at −43 °C. In this column a solution of the ketene precursor (phenylacetic acid chloride) and one of the imine were percolated; the catalyst promoted first the dehydrohalogenation reaction to the ketene and then the 2 + 2 cycloaddition, having been restored back to its basic form by the inorganic base. Final purification by the scavenger resin-containing column afforded the product in 58% yield and 88% ee. Enantiopure material was obtained by crystallization. Remarkably, an increase of the amount of potassium carbonate (up to a 10/1 carbonate/catalyst ratio) allowed to scale-up the reaction to obtain 1 g of product per run.

3.2.3. Catalysts Supported through Other Connections

The catalysts **94** and **95** (Scheme 17),[151] supported on a modified $MeOPEG_{5000}$, have been prepared by demethylation of quinine and subsequent etherification. Their solubility, however, was not a sufficient feature to achieve good level of stereoselectivity in the conjugate addition of thiophenol to cyclohexenone (Figure 8, eq 51), a reaction that, in the presence of 0.05 mol equiv of **94**, led to the product in 75% yield and only 22% ee (toluene, 24 h, rt). It must be remembered that the use of 0.01 mol equiv of nonsupported quinine as the catalyst afforded the product in 41% ee.[167] The possibility that the PEG portion of **94** depresses the stereoselectivity preventing formation of the hydrogen bond between the catalyst and the substrate (a mechanistic factor regarded as relevant in this reaction [167]) can tentatively rationalize this disappointing result.

3.3. Catalysts Derived from Amino Acids

Amino acids and their derivatives represent an obvious source of chiral organic catalysts, which has been fully exploited by synthetic organic chemists.[16,17,20] Their ready availability and different functionalizations in the side chains allowed for a number of applications in the field of supported catalysis.

3.3.1. Cyclic Dipeptides

After the discovery by Inoue and co-workers that cyclic dipeptides, such as *cyclo* [(*S*)-phenylalanyl-(*S*)-histidyl], could catalyze the enantioselective addition of hydrogen cyanide to aldehydes,[168] a few reports appeared in the literature describing the immobilization of related dipeptides on polymeric matrixes.

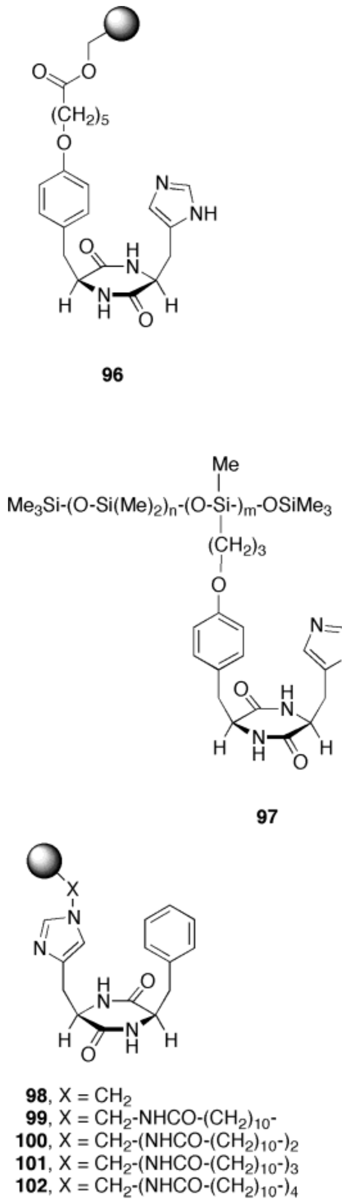
In 1992, Jackson and Kim[169] replaced the phenylalaninyl residue of the catalyst with tyrosine, to the end of exploiting the hydroxy group for the connection to the polymer. Thus, catalysts **96**, supported on 1% DVB cross-linked chloromethylated polystyrene, and **97**, anchored on a siloxane copolymer, were prepared (Scheme 18).

The behavior of these catalysts, however, was disappointing, since they promoted the transformation of aromatic aldehydes into the corresponding cyanohydrins (Figure 8, eq 53) in up to 30% ee, respectively (0.02 mol equiv of catalyst, toluene, −5 °C, 24−48 h). Control experiments showed that the introduction of the alkoxy group in the para position of the phenyl residue of phenylalanine in the nonsupported catalyst per se depressed the enantioselectivity of the reaction, even if not at the dramatic extent observed in the case of adducts **96** and **97**.

In an attempt to improve these results, Song and co-workers synthesized a series of related catalysts.[170] They used 2% DVB cross-linked polystyrene as the support. To this polymer a *cyclo* [(*R*)-phenylalanyl-(*R*)-histidyl] was anchored by means of the nonbasic nitrogen atom of the imidazole residue to afford adduct **98** (Scheme 18). The catalysts **99**−**102** containing four spacers of different length (12−48 atoms) were also prepared. When tested in the conversion of 3-phenoxybenzaldehyde to the corresponding cyanohydrin (Figure 8, eq 54), however, these catalysts afforded the product in ≤18% ee (toluene, −20 °C, 15−24 h), thus confirming that Inoue’s catalyst is extremely intolerable to polymer supporting.

Well aware of this fact, Shvo and co-workers[171] selected entrapment of the unmodified Inoue’s dipeptide, rather than its immobilization by covalent modification, with the hope of obtaining a recyclable catalyst. Thus, *cyclo*-[(*S*)-phenylalanyl-(*S*)-histidyl] was entrapped into a silicon-based sol−gel matrix

Scheme 18. Structure of Supported Dipeptide Catalysts[a]



[a] In **96**, (shaded circle) = 1% cross-linked polystyrene; in **98**–**102**, (shaded circle) = 2% cross-linked polystyrene.

made of tetramethoxy silane and methyl trimethoxysilane, and the resulting species was employed to promote the hydrocyanation of benzaldehyde (0.025 mol equiv of catalyst, toluene 5 °C, 27 h). The product was obtained in up to 80% yield and 98% ee, much in line with Inoue's results. Unfortunately, very disappointing results were obtained in a second hydrocyanation cycle, independently of the method used for catalyst recovery. Since very little leaching of the dipeptide from the matrix was observed (7–14%) these finding remained unexplained.

3.3.2. Amino Acids and Derivatives

In 1998, Jacobsen and Sigman[172] used a combinatorial approach en route to the identification of an enantioselective organocatalyst for the addition of hydrogen cyanide to *N*-allylbenzaldimine (Figure 9, eq 55). In this context, three libraries of 12, 48, and 132 elements, respectively, were synthesized inserting different spacer/amino acid/spacer sequences between 1% DVB cross-linked aminomethylated polystyrene on one side and various salicylimines on the other side, to afford catalysts having the general formula **103** (Scheme 19). Screening among the library components allowed to improve an initial 19% ee up to an 80% ee value. The identification of the optimized catalyst **104** led to the synthesis of its nonsupported counterpart **105**, which performed slightly better than **104** (91% ee; 0.02 mol equiv of catalyst, toluene, −78 °C, 24 h). Remarkably, highly enantioselective reactions of aliphatic imines were also possible with compound **105**.

Proline is one of the first amino acid that has been recognized as an organocatalyst.[16] Since the report by Eder, Sauer, and Wiechert on the asymmetric synthesis of the Wieland-Mischler ketone via Robinson annulation,[173] proline has been employed in a number of enantioselective syntheses, including aldol and iminoaldol condensations, and Michael addition. A soluble polymer-supported version of this versatile catalyst, **106** (Scheme 19) has been prepared by anchoring (2*S*,4*R*)-4-hydroxyproline to the monomethyl ether of PEG_{5000} by means of a succinate spacer.[174]

Adduct **106** can be considered a minimalist version of a type I aldolase enzyme, with the polymer chain replacing the peptide backbone of the enzyme and the proline residue acting as its active site. In the presence of 0.25–0.35 mol equiv of this catalyst, acetone reacted with enolizable and nonenolizable aldehydes (Figure 9, eq 56) in DMF at room temperature (40–60 h) to afford β-ketols in yield (up to 80%) and ee (up to >98%),[174a] comparable to those obtained using nonsupported proline derivatives as the catalysts (that however gave faster reactions).[175] The use of **106** was extended to the condensation of hydroxyacetone with cyclohexanecarboxyaldehyde that afforded the corresponding *anti*-α,β-dihydroxyketone in 48% yield and 96% ee (anti/syn ratio > 20/1). The double loaded catalyst **107** (Scheme 19) behaved similarly to **106** while allowing to use half the weight amount of catalyst.

Replacement of the aldehyde component of the aldol reactions with imines (either preformed or generated in situ) opened access to synthetically relevant β-amino- and syn-β-amino-α-hydroxyketones, which were obtained in moderate to good yields (up to 80%) and good to high diastereo- and enantioselectivity (Figure 9, eq 57; ee up to 97%).[174b] PEG-supported proline **106** was also employed [174b] to promote the Robinson annulation between 2-methyl-1,3-cyclohexanedione and 3-buten-2-one (Figure 9, eq 58; DMSO, rt, 90 h), which afforded the product in 55% yield and 75% ee, values nicely comparable to those observed with proline as the catalyst (49% yield; 76% ee).[173] It is worth mentioning that the use of hydroxyproline anchored via a spacer to 1% DVB cross-linked chloromethylated polystyrene as the insoluble catalyst for the aldol step of this annulation reaction led to the product in only 29% yield and 39% ee.[176]

As far catalyst recycling is concerned, it was shown that adduct **106** could easily be recovered exploiting

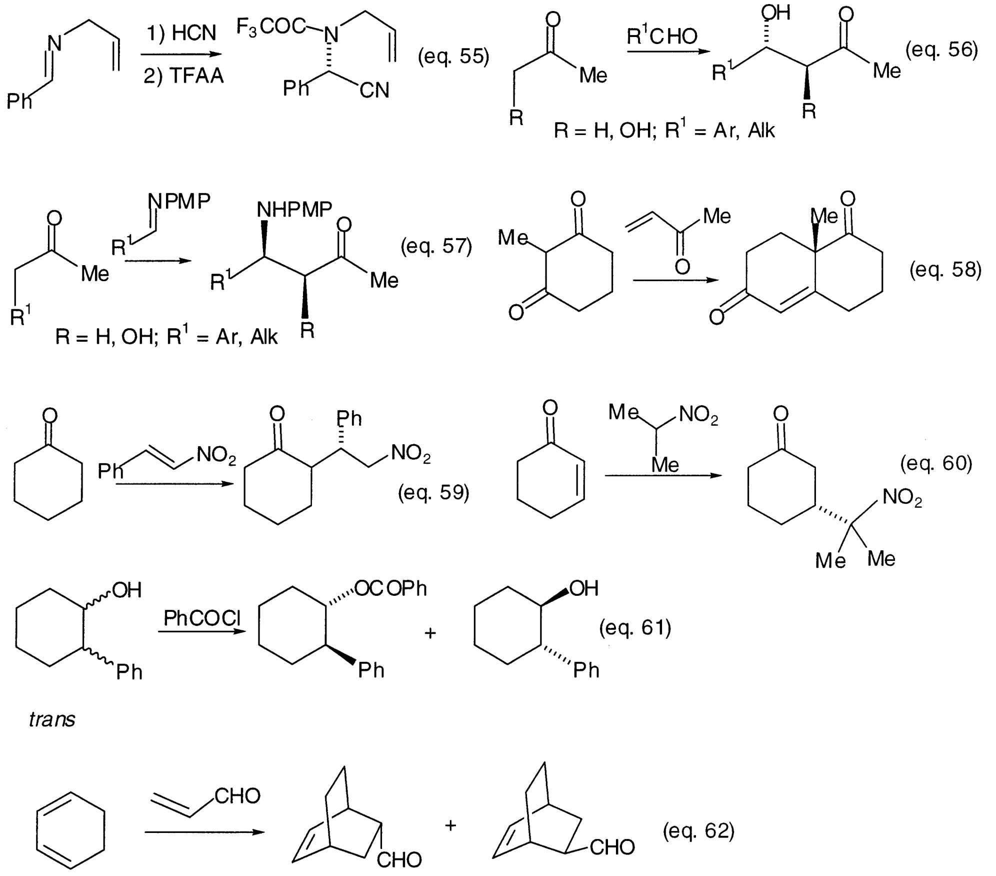


Figure 9. Stereoselective reactions catalyzed by amino acid-derived polymer-supported catalysts.

its solubility properties and recycled 3/4 times in all of the above-mentioned reactions. These, however, occurred in slowly diminishing yields and virtually unchanged ee's. The decrease in chemical efficiency was surprising, since NMR analysis did not show any sign of catalyst decomposition upon recycling.

Finally, catalyst **106** was tested in some Michael-type syntheses of γ-nitroketones.[177] However, both the addition of cyclic ketones to nitrostyrene (Figure 9, eq 59; up to 60% yield and 35% ee) and of 2-nitropropane to cyclohexenenone (Figure 9, eq 60; up to 65% yield and 42% ee) displayed enantioselectivities inferior than those observed with the nonsupported catalysts.[178,179]

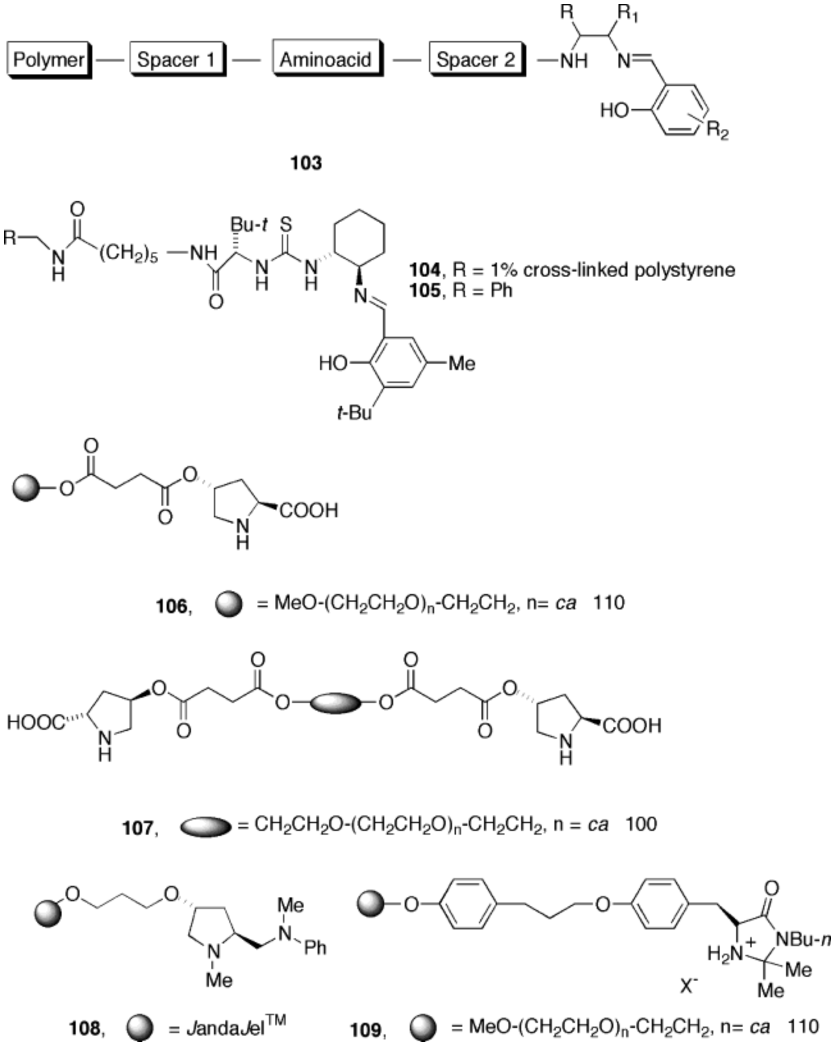
The (2*S*,4*R*)-4-hydroxy-*N*-methylproline derivative **108** supported on *J*anda*J*el (a more swellable version of cross-linked polystyrene)[180] (Scheme 19) was employed by Janda and co-workers to catalyze the kinetic resolution of some cyclic secondary alcohols (Figure 9, eq 61).[181] In the presence of 0.15 mol equiv of the catalyst, it was shown that the benzoylation of racemic *trans*-2-phenylcyclohexanol (benzoyl chloride, triethylamine, dichloromethane, −78 °C, 11 h) afforded a 44% yield of (1*S*,2*R*)−(2-phenyl)cyclohexyl benzoate in 96% ee and a 45% yield of the unreacted (1*R*,2*S*)-2-phenylcyclohexanol in 85% ee. Extension of the process to acyclic alcohols was less successful. Recovery and recycling of the insoluble catalyst was demonstrated for up to five reaction cycles occurring in unchanged yield and ee.

Recently, protonated phenylalanine-derived imidazolidinones emerged as versatile organic catalysts for a number of processes, including Diels−Alder and 1,3-dipolar cycloadditions.[182] Replacement of the amino acid with tyrosine offered a handle for supporting the catalyst on a modified MeOPEG$_{5000}$ through the hydroxy group. Thus, the soluble adduct **109** (Scheme 19) was prepared and tested in the Diels−Alder reaction between acrolein and 1,3-cyclohexadiene (Figure 9, eq 62).[183] Under the best conditions, which involved the use of the trifluoroacetate salt of **109** (0.1 mol equiv) in a 95/5 acetonitrile/water mixture at room temperature for 40 h, the product was obtained in 67% yield as a 94/6 mixture of endo/exo isomers having 92% and 86% ee, respectively.

This result was not so different from that obtained[182] with 0.05 mol equiv of the nonsupported catalyst (hydrochloride form), which led to the endo isomer in 82% yield and 94% ee. Unfortunately, catalyst **109** (as well as its nonsupported, commercially available counterpart) proved to be rather unstable under the reaction conditions. Accordingly, catalyst recycling over four cycles showed a marked decrease in the chemical yield of the reaction (from 67 to 38%), while the ee was eroded more slowly (from 92 to 85%).

The use of a *J*anda*J*el-supported imidazolidinone similar to **109** was subsequently described by Pihko and co-workers.[184] This catalyst (0.2 mol equiv) was found to promote the cycloaddition of eq 62 (Figure 9) in 30% yield affording the endo isomer having 98% ee. The reactions of other aldehydes and dienes were also descibed. Remarkably, a slightly modified cata-

Scheme 19. Structure of Supported Catalysts Containing Amino Acids and Their Derivatives



lyst sample supported on silica performed much better in terms of chemical yield. The increase in the polarity of the support on passing from *J*anda*J*el to silica was believed to increase the efficiency of the catalyst in this cycloaddition reaction involving highly polar transition states and an iminium ion.[184]

3.3.3. Poly(Amino Acids)

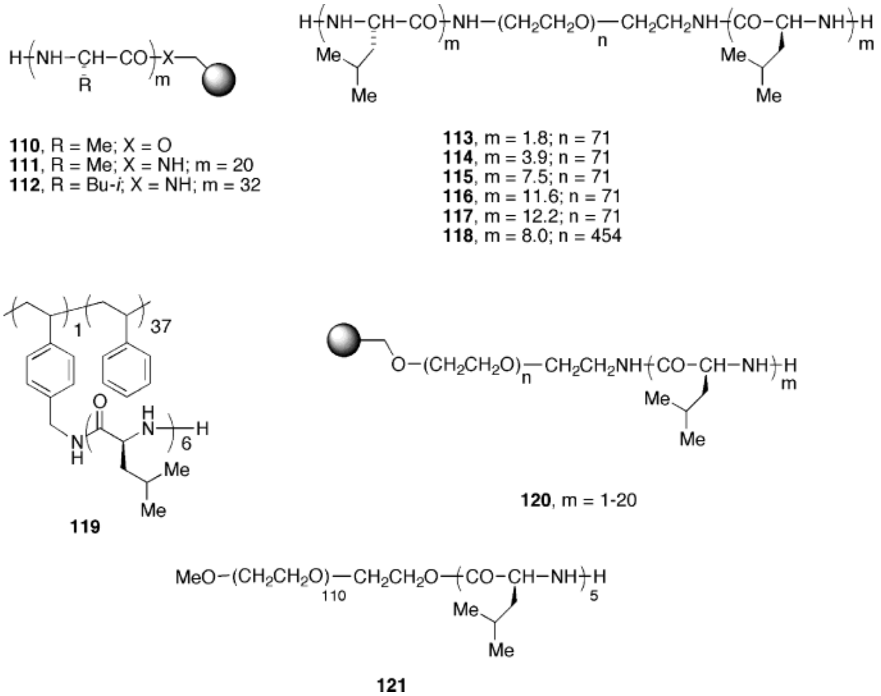
Since the early 1970s simple polymers of single amino acids have been extensively employed as catalysts for the (poorly) enantioselective addition of thiols to unsaturated ketones, as demonstrated by the work of Inoue and his group.[185] Decisive impulse to a wider application of these organocatalysts in synthetic organic chemistry was provided by the work of Julià and Colonna in the early 1980s.[186−189] They discovered that the use of poly(amino acids), having hydrophobic side chains, as catalyst in a triphase system made of the insoluble catalyst, a toluene solution of an α,β-unsaturated ketone (typically: chalcone), and basic 30% aqueous hydrogen peroxide, resulted in the formation of α,β-epoxyketones in almost perfect ee.

The applications of this reaction to synthetic chemistry and its mechanistic implications have recently been reviewed by Wills,[190] Pu,[191] and Skidmore,[192] and therefore will not be reexamined here (reference to reports not included in ref. 190-192 are provided).[193−195] On the contrary, the immobilization of poly(amino acids) on polymeric supports is still attracting a lot of interest and therefore will be discussed in detail.

Julià and Colonna reported the immobilization of polyalanine by connecting the C-terminus of the poly(amino acid) to DVB cross-linked hydroxymethylated polystyrene.[189] The resulting adduct **110** (Scheme 20) promoted the epoxidation of chalcone (Figure 8, eq 48, R = Ph; toluene, NaOH, hydrogen peroxide, rt, 48 h) to afford the product in 82% yield and 84% ee, both values being slightly inferior than those observed with the nonsupported catalyst. Recovery and recycling of **110** occurred at the expenses of the reaction stereoselectivity, the second and third cycle leading to a product of 75% and 52% ee, respectively.

A more efficient polymer-supported catalyst was prepared by Itsuno and co-workers in 1990, when they connected polyalanine and polyleucine molecules, having various monomer contents, to 2% DVB cross-linked aminomethylated polystyrene.[196] Among the catalysts obtained, compounds **111** and **112** (Scheme 20) were the most effective. Under the above-mentioned reaction conditions, the use of 0.2

Scheme 20. Structure of Supported Poly(Amino Acids) Catalysts for the Epoxidation of Unsaturated Ketones[a]



[a] In **110**−**112** and **120**, (shaded circle) = cross-linked polystyrene.

mol equiv of these catalysts led to the formation of epoxychalcone in 66% and 92% yield, and 93% and 99% ee with **111** and **112**, respectively. The reaction of other chalcones, modified in their aromatic portions, proceeded similarly well. The use of an insoluble macroporous polymer or a soluble linear polystyrene as supports was much less successful.

Itsuno's catalyst **112** was successively exploited by Roberts and co-workers[197] in an improved procedure for chalcone epoxidation, which involved the use of the urea/hydrogen peroxide complex as the oxidant and DBU as the base in anhydrous THF at room temperature. Under these conditions, fast (30 min), high yielding (85−100%), and highly stereoselective (>95% ee) reactions were observed.

Remarkably, also 4-phenyl-3-buten-2-one (Figure 8, eq 48, R = Me) was oxidized in 70% yield and 83% ee under the anhydrous conditions, thus suggesting that the new protocol could broaden the scope of the Julià-Colonna method by allowing its application to unsaturated ketones other than chalcone. The total syntheses of the pharmaceuticals diltiazem and taxol[198] and the epoxidation of trisubstituted ketones[199] demonstrated this point. As a further improvement, solid sodium percarbonate was employed to replace both the urea/hydrogen peroxide complex and DBU; the use of this oxidant allowed a 6-fold increase in the substrate/catalyst ratio.[200]

The insertion of a PEG spacer and a hydroxymethylphenoxyacetic acid linker between the polystyrene support and the polyleucine residue allowed for the first time the use of a peptide synthesizer for the preparation of active epoxidation catalysts,[201] which previously had been obtained only by the classic *N*-carboxyanhydride approach. The use of the synthesizer also opened access to catalysts containing poly(amino acid) residues of accurate length and featuring preestablished sequences of L- and D-amino acid.[202] The availability of these catalysts was crucial for establishing some mechanistic features of the enantioselective epoxidation reaction.[203]

Notwithstanding the above-mentioned improvements, recovery and recycling of these catalysts remained a problem. The best solution was found by Roberts and co-workers[204,205] in the adsorption of the poly(amino acid) on silica gel, which produced a very active catalyst recoverable by filtration and recyclable at least five times without any appreciable loss in activity and stereoselectivity. Other inorganic supports turned out to be less suitable for this purpose.

The first soluble version of the Julià-Colonna catalyst was reported in 2001, when Roberts and coworkers described the synthesis of the triblock PEG-polyleucine adducts **113-117** (Scheme 20).[206] They were prepared by using the commercially available *O*,*O*′-bis(2-aminoethyl)- poly(ethylene glycol) of average M_W 3350 Da as the initiator of the polymerization of (*L*)-leucine *N*-carboxyanhydride.

The obtained polymers contained polyleucine residues of different length connected to the termini of the PEG moiety. Of these catalysts, **114** and **115**, containing polypeptide residues of ca. four and eight amino acids, respectively, were more efficient than **113**, **116**, and **117** in promoting the epoxidation of chalcone (urea/hydrogen peroxide complex, DBU, THF). As far as the stereoselectivity of the epoxidation is concerned, **114**−**117** behaved similarly well (up to 98% ee), and much better than both **113** and the insoluble catalyst containing polyleucine residues of comparably short length immobilized on the PEG-modified polystyrene mentioned above.[201]

On the basis of these results, the high molecular weight soluble catalyst **118** (Scheme 20; average M_W of the PEG fragment 20 000 Da), featuring two terminal leucine octamers, was synthesized by Degussa researchers.[207] This catalyst was employed to promote the epoxidation of chalcone (99% yield, 94% ee) in a continuously operated membrane reactor, where catalyst retention was achieved by means of a nanofiltration membrane. This equipment allowed 25 reaction cycles to occur with almost unchanged conversions and stereoselectivity, after which some decrease in both values were observed. The soluble catalyst **119**, supported on linear polystyrene (Scheme 20), was also prepared [207] and found to be slightly more active than **118**. Its behavior on prolonged use was similar to that of its PEG-supported analogue.

Berkessel and co-workers prepared a series of catalysts having general structure **120** (Scheme 20) by attaching the C-terminus of leucine oligomers of different length to the PEG modified DVB cross-linked polystyrene TentaGel S NH_2.[208] These compounds were used to establish that a polymer-supported catalyst containing as few as five amino acid residues was able to catalyze the Julià-Colonna epoxidation of chalcone with up to 98% ee. By replacing the insoluble support of **120** with soluble MeOPEG, adduct **121** was obtained (Scheme 20). Also with this catalyst, a leucine pentamer was found to be the minimum structural requirement for achieving substantial stereocontrol ($>$50% ee). Since at least four amino acids residues are required to form one turn of the α-helical structure, it was concluded that one complete turn was required for efficient stereoselectivity. The fact that, in the case of nonsupported polyleucine catalyst, the onset of stereoselectivity was observed around the decamer level suggested that the poly(ethylene glycol) portions of **120** and **121** could act as a helix surrogate forcing oligopeptide to adopt the helical arrangement at shorter chain lengths.

The relevance of the helical motif was further demonstrated by attaching five glycine residues at the N-terminus of the polyleucine fragment. Interestingly, the resulting catalyst did not promote any stereoselectivity in the reaction. This effect was directly related to the poor propensity of glycines to propagate the α-helix of polyleucine in the N-terminus region of the catalyst, which was suggested to be crucial for catalytic activity.[208]

Finally, it must be noted that the use of poly(β-amino acids) instead of poly(α-amino acids) was met with different success. In the hands of Berkessel and co-workers,[208] TentaGel-supported pentameric catalysts derived from *trans*-2-aminocyclehexanecarboxylic acid and 3-amino-5-methylhexanoic acid were totally uneffective (1−2% conversion after 24 h in the epoxidation of chalcone). On the other hand, Roberts and co-workers[209] obtained low to high conversions and ee carrying out the same reaction in the presence of the icosimer of 3-amino-5-methylhexanoic acid bound to PEG-modified polystyrene as the catalyst.

4. Conclusions

It was the aim of this review to describe how, in less than 25 years, polymer-supported organic catalysts have turned from chemical curiosities into powerful synthetic tools readily available to the chemical community.

From a practical perspective, it is interesting to note that, in many instances, polymer-supported organic catalysts having an efficiency similar to (or even higher than) that of their nonsupported counterparts have been synthesized. However, in many more cases the supported catalysts' performances fell short of the expectations. In addition, way too often the reasons of a failure have neither been understood nor tentatively explained. This has been particularly true in the case of chiral catalysts.

Supported catalysts' success or failure seem to be independent of the soluble/insoluble nature of the support, or of the class of compounds to which the catalyst belongs. Rather, they seem to depend on whether the polymer support is an innocent bystander that does not interfere with the reaction course or exerts a negative influence on the process by some nonforeseeable effects. Moreover, any prediction on a catalyst recyclability is less reliable than the tossing of a coin.

On the basis of the results reported in this survey and our own experience in the field, we would like to suggest that the following points should be considered in designing a polymer-supported organic catalyst.

- The stability of the nonsupported catalyst under the reaction conditions is a prerequisite that has to be firmly established both in the presence and in the absence of the intended support.
- The steric and electronic effects exerted by the structural modification of the catalyst required for immobilization should be minimized.
- In addition to the obvious effects on solubility and accessibility of the active site, the polymer can influence the catalyst sterically and electronically and have a dramatic effect on the polarity of the microenvironment surrounding the catalytic site.
- The introduction of a spacer separating the catalyst from the polymer is a reasonable but fallible option to minimize the influence of the support. Again, the choice of the spacer must take into account steric, electronic, and polarity effects.
- Obviously, the choice of the polymer determines the recovery/recycling protocol. This is very important, since a simple effective recycling is the main reason that justifies catalyst immobilization. In designing the supported catalyst, recovery techniques that do not require actual isolation of the catalyst should be preferred, independently of how much "harmless" the isolation procedures might appear. Nanofiltration for soluble catalysts[207] and immobilization on columns or reactors for insoluble catalysts[164] have provided the best results, at least in terms of recycling numbers and efficiency. Remarkably, both these examples concern the use of chiral catalysts.

It is easily foreseeable how practical applications of polymer-supported catalysts will further expand in the future. This will be due to the continuing improvements brought about by the advancements in the technology of chemical processes, and to the obvious advantages that the use of a recyclable catalyst enjoy in terms of cost and impact on the environment. It is also evident, however, that a much deeper understanding of how a supported catalyst really works is necessary, and that only a multydisciplinary effort by chemists of different backgrounds will have a chance to achieve this goal.

5. Abbreviations

Glossary

DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DMAP	4-dimethylamino pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DVB	divinylbenzene
EDTA	ethylenediaminetetraacetic acid
EOE	ethoxyethyl
LCST	lower critical solution temperature
MCM	Mobil Corporation mesopore
MeOPEG	monomethyl ether of poly(ethylene glycol)
PEG	poly(ethylene glycol)
PIPO	polyamine immobilized piperidinyl oxyl
PNIPAM	poly(*N*-isopropylacrylamide)
PMP	4-MeOPh
rt	room temperature
TBAB	tetrabutyl ammonium bromide
TBDMS	*t*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
THF	tetrahydrofuran
THP	tetrahydropyranyl
TMS	trimethylsilyl

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