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Immobilization of Organic Catalysts: When, Why, and How

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This manuscript is dedicated to Professor Mauro Cinquini on the occasion of his retirement.

Abstract: This review article is divided in two parts. In the first part (Sections **2** and **3**) selected examples of the publications that appeared in the literature in the period 2003–2005 in the field of immobilized organic catalysis are presented. When appropriate, the results of these publications are compared to those reported earlier and already discussed in a previous review article (see ref.[4]). On the basis of this survey, in Section **4** some general considerations about when and why a supported version of an organic catalyst is worth developing are proposed. In Section **4** a list of suggestions about how the process of immobilization should be carried out is also included, taking into account several factors such as the properties of the catalyst, the nature of the support, and the mode of connection of the catalyst to the support.

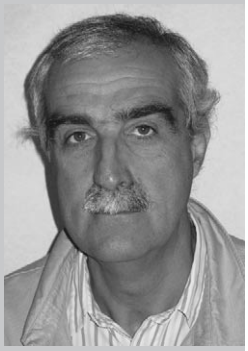
Keywords: catalysis; catalyst immobilization; catalyst recovery and recycling; organic catalysis; organic synthesis; stereoselective synthesis

1 Introduction

Although the concept of organic catalysis was first introduced by the German chemist Langenbeck back in 1928,[1] and the expression "organische Katalyse" first appeared in the literature in 1931,[2] there is not a generally accepted definition of organic catalyst. Indeed, chemists seem to have been more interested in establishing what an organic catalyst *is not* rather than in defining what an organic catalyst actually is. For instance, Langenbeck was mainly interested in recognizing an organic catalyst as a chemical entity analogous to, but distinct from, an enzyme.[1] In the 1990s and early 2000s, during the re-discovery of organocatalysis as a powerful synthetic methodology, it was the metal-free nature of the organic catalyst that appealed to, and, accordingly, was emphasized by practitioners in the field. However, the fact that an organic catalyst is neither an enzyme nor a metal-based catalyst seems the only matter everybody can agree upon.

Still, "in the golden age of organocatalysis",[3] when countless papers appear on the subject in every new issue of the chemistry journals, a more defined picture of what an organic catalyst is is clearly needed. Recently, it was proposed to define an organic catalyst as: "an organic compound of relatively low molecular weight and simple structure capable of promoting a given transformation in substoichiometric quantity".[4] This definition is broad enough to encompass the proteiform structural diversity of organic catalysts, but, for the very same reason, presents some pitfalls.

First of all, catalysts exist that embed transition metals as a structural feature not involved in the catalytic activity, as in the case for instance of Fu's chiral 4-dimethylaminopyridine (DMAP) analogues containing a ferrocenyl moiety.[5] Strictly speaking, these catalysts are organometallic compounds, and as such do



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 Princeton University, he moved to the University of Cagliari and then came back as an associate professor to the University of Milano, where has been professor of organic chemistry since 1994. The discovery of new stereoselective organic catalysts, the development of supported catalytic systems, and the study of the through-space interaction between aryls and perfluoroaryls are among his recent research topics.

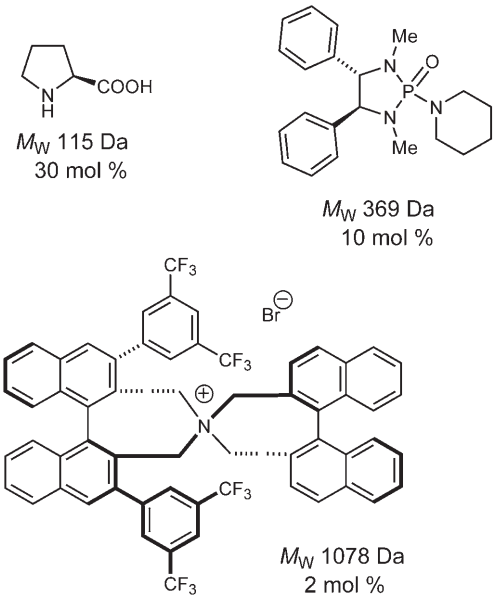


Figure 1. Organic catalysts employed in aldol reactions.

not seem to fit in the above-mentioned definition. The non-involvement of the metal in the catalytic activity, however, should be enough to warrant the classification also of these compounds as organic catalysts.

The necessity of setting a molecular weight (M_W) limit and some restraints on the structural complexity of an organic catalyst clearly derives from the fact that one of the *raison d'être* of organic catalysis as an alternative to enzymatic or organometallic catalysis is the structural simplicity of the catalyst. However, while everybody would agree that an organic catalyst should not be a huge, enzyme-like molecule, it would be extremely limiting to impose that all organic catalysts must share the beautifully self-contained structure of proline.

Nevertheless, a limit in the M_W of the catalyst seems necessary, in order to avoid running a reaction in which one hundred milligrams of a substrate are reacted in the presence of one gram of catalyst. It seems reasonable that the M_W limit should be related to the amount of organic catalyst required to perfom the reaction. A catalyst loading of 1–2 mol% well tolerates a catalyst's M_W of 1000 daltons; if the loading is 10 mol%, the M_W should not exceed 500 daltons; and only for organic catalysts sharing the size of proline can a loading as large as 30 mol% be regarded as practical.

Limitations in structural complexity are also quite difficult to establish. Common sense, however, suggests that these limitations should be related to the extent of synthetic modification required in order to obtain the catalyst from a cheap and largely available starting material. A long and tedious synthetic procedure obviously subtracts most of the appeal of an organic catalyst, and appears to be justified only if the catalyst displays unique catalytic activity and excellent chemical behavior. To illustrate this point, a comparison among three organic catalysts of different molecular weights, employed loading, and structural complexity is reported in Figure 1.

As can be seen from the reported data, these catalysts meet the criteria established above for classification as organic catalysts, because the increase in M_W and synthetic complexity observed on passing from proline to Denmark's phosphoramide[6] and Maruoka's spiro ammonium salt[7] is balanced by the decrease in the molar amount of catalyst employed. For example, the weight amounts of the catalysts of Figure 1 needed to perform a reaction on 10 mmol of substrate is 345 mg for proline, 369 mg for the phosphoramide, and 216 mg for the ammonium salt. Thus, even if a definition of an organic catalyst that is at the same time general and specific seems difficult to propose, the conceptual and practical boundaries within which an organic compound can be regarded as an organic catalyst appear to be clearly defined.

As mentioned above, from the very outset organic catalysts have been considered as convenient alternatives to enzymes, being more stable, less expensive, and broader in scope than their biological counterparts.[8] Since enzymes are well known for their chemical and stereochemical specificities, obtaining similar properties with a simpler, metal-free molecule has always been considered one of the goals of organocatalysis. It is very interesting to note that, as the result of the recent "gold rush" in this field,[3,9–11] organic catalysts have been discovered that are endowed with substrate selectivities typical of enzymes.

For instance, with a combination of catalytic amounts of the chiral phosphoric acid derived from a modified binaphthol depicted in Figure 2 and of a di-

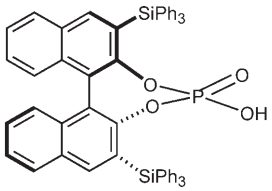


Figure 2. Structure of an organic catalyst for the reductive amination of ketones.

hydropyridine as the reducing species, MacMillan was able to perform a metal-free, highly enantioselective reductive amination of ketones. Remarkably, only aryl and alkyl *methyl* ketones can be employed succesfully in this reaction, whereas *ethyl* ketones are reduced much more sluggishly and with lower stereocontrol.[12]

Among the advantages that organic catalysts can present over enzymes and metal-based catalysts is the possibility of ready immobilization on a support with the aim of facilitating catalyst recovery and recycling.[13–16] Indeed, one can expect the connection to a support to have a stronger impact on the structure and the properties of an enzyme than on that of a simple organic compound. In addition, the immobilization of an organocatalyst can lead to a loading of active molecules per weight unit of polymer definitely higher than in the case of the enzyme, as simply inferred on the basis of molecular size consideration.

On the other hand, the immobilization of an organometallic catalyst, generally obtained by anchoring an organic ligand on the support followed by metal addition, suffers from the serious drawback of metal leaching, that in most cases allows the efficient recovery of the *ligand* but not that of the whole catalytic system, that must be restored by metal replenishment before recycling.[17]

As we have pointed out in a recent survey on the subject,[4] the development of immobilized versions of an organic catalyst shortly followed the discovery of the catalyst itself.[18] In many instances, the main goal of the immobilization was the simplification of the reaction work-up, the separation of the product being simpler in the case of a supported rather than of a non-supported catalyst. It can safely be anticipated, however, that with the continuing discovery of more and more sophisticated organic catalysts also recovery and recycling will surely become an important issue in justifying catalyst immobilization.

Using the published review as a starting point,[4] the present article will cover the relevant achievements reported in the field of immobilized organic catalysis from the beginning of the year 2003 up to the end of the year 2005. Then, on the basis of this and the previous survey, the pre-requisites (when), the reasons (why), and the methodologies (how), for organic catalyst immobilization will be briefly examined. The aim of this discussion will be to provide the reader with the practical tools necessary to decide whether an immobilized organic catalyst is worth developing.

2 Achiral Organic Catalysts

2.1 Catalysts for Oxidation Reactions

Since the goal of avoiding the use of environmentally unfriendly or toxic metals has always been considered extremely important, the development of efficient metal-free oxidation catalysts has been very actively pursued in the field of organocatalysis. Many of the organic catalysts identified in recent years have also been immobilized on different supports. Among these, oxoammonium ions for the selective oxidation of alcohols, and ketones for the epoxidation of alkenes occupy a preminent position.

2.1.1 Oxoammonium ions

Oxoammonium ions[19] such as those derived from 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) can be conveniently employed in combination with inexpensive, safe, and easy-to-handle terminal oxidants in the conversion of alcohols into aldehydes, ketones, and carboxylic acids. However, separation of the products from TEMPO can be problematic, especially when the reactions are run on a large scale. After immobilization on insoluble supports such as silica was proposed as a solution to these problems,[4,20] the development of TEMPO or TEMPO analogues anchored on the soluble support Chimassorb 944 (M_W *ca.* 3000 daltons) was actively investigated with the aim of replicating as much as possible the remarkable features of the non-supported catalytic system.[4,21] More recently, examples of poly(ethylene glycol)-supported TEMPO have been reported (Figure 3).

In the first of these reports,[22] the monomethyl ether of poly(ethylene glycol) of M_W 5000 daltons ($MeOPEG_{5000}$) was connected to 4-hydroxy-substituted TEMPO by means of a spacer containing inert ether bonds to afford compound **1**. This compound was used in combination with different terminal oxidants such as bis(acetoxy)iodobenzene, trichloroisocyanuric acid, and sodium hypochlorite in the oxidation of 1-octanol to octanal [Scheme 1, Eq. (1)]. High conversion (98%) and selectivity (95%) were observed with the convenient oxidant NaOCl under bromide-free conditions in the presence of only 1 mol% of the supported reagent and after a reaction time as short as 30 min in dichloromethane (DCM) at 0 °C. This reaction could be extended to acyclic and cyclic primary and secondary alcohols with excellent results.

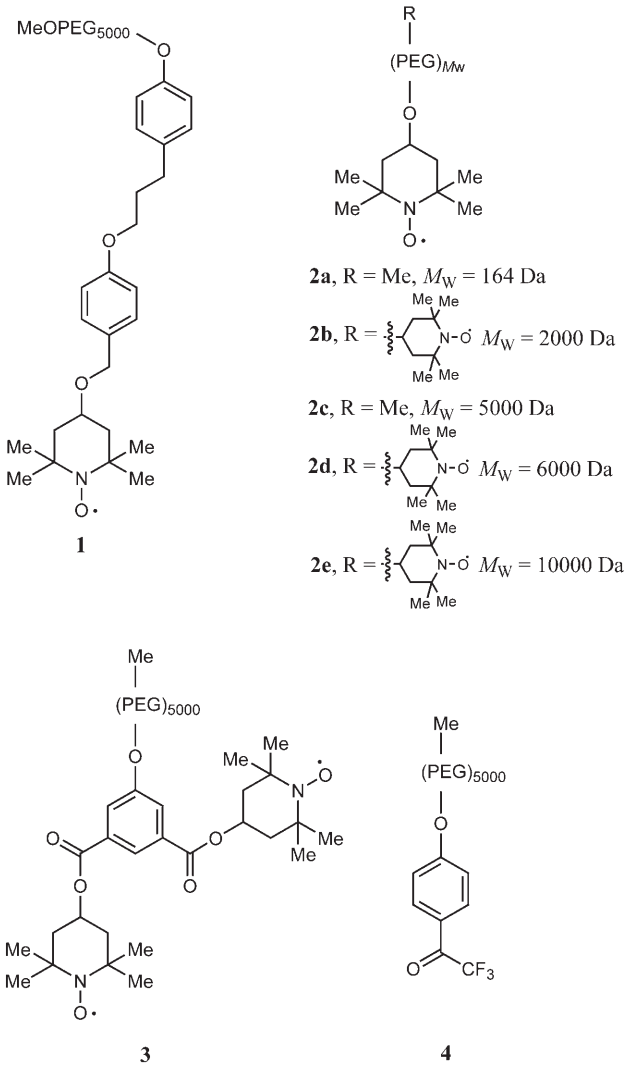
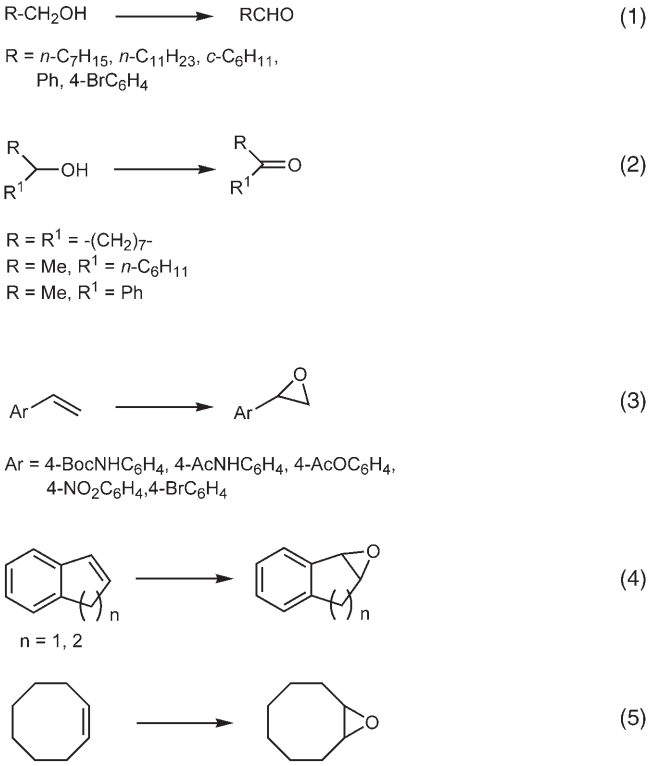


Figure 3. Structure of supported oxidation pre-catalysts.

Remarkable was also the fact that the PEG-supported TEMPO maintained the good selectivity for primary *vs.* secondary benzylic alcohol oxidation typical of non-supported TEMPO.

Catalyst recovery exploited the well known different solubility of PEG in solvents of different polarity.[4] In this case, where a PEG of relatively high M_W was employed, addition of diethyl ether to the reaction mixture induced the precipitation of compound **1**. Subsequent filtration allowed recovery of the supported reagent with less than 10% weight loss for each recovery. (Obviously the reaction scale can affect the efficiency of this procedure). Catalyst recycling was demonstrated to be possible for seven reaction cycles in the oxidation of 1-octanol, that occurred in undiminished conversion and selectivity under the same reaction conditions.[23]

In a subsequent work,[24] 4-hydroxy substituted TEMPO was anchored to mono- and non-methylated PEG of different M_W (164, 2000, 5000, 6000, and



Scheme 1. Reactions promoted by oxidation catalysts.

10000 daltons) without the insertion of any spacer between the polymer backbone and the nitroxyl radical (Figure 3). The resulting species **2a–e** (1 mol%), carrying either one or two TEMPO residues, were used in combination with NaOCl/NaBr in the oxidation of primary alcohols to the corresponding aldehydes [Scheme 1, Eq. (1)] carried out in DCM at 0°C. While the lower M_W catalysts (164 and 2000 daltons) exhibited nearly complete conversion independently of the substrate, the other catalysts performed much better with the unhindered alcohols undecan-1-ol and geraniol (>96% yield) than with benzyl alcohol (66%) and cyclohexylmethanol (57%). This behavior was found to be irrespective of the presence of one or two TEMPO units at the end of the PEG chain. Four catalyst recyclings were possible, the rate of oxidation decreasing sharply on passing from the first to the second reaction and then remaining roughly constant.

To circumvent these problems, the insertion of 5-hydroxyisophthalic acid as a branched spacer between TEMPO and the PEG backbone was investigated (Figure 3).[24,25] In combination with NaOCl, the resulting pre-catalyst **3** promoted very fast reactions (for instance, 1 min to reach complete conversions in the case of 1-undecanol) that were only marginally affected by the branching of the substrate. Also catalyst recycling occurred with minimal deactivation (about 1% decrerase in yield over three cycles), thus showing the importance of separating the catalyst active site from the support bulky structure.[4,26]

The benefecial effect of the spacer was also demonstrated in a subsequent work[27] where pre-catalysts **1** and **2c** (1–5 mol%) were employed for the oxidation of primary and secondary alcohols using oxygen as the terminal oxidant in the presence of 2 mol% of $Co(NO_3)_2$ hydrate and $Mn(NO_3)_2$ hydrate as co-catalyst.[28] For instance, under these conditions oxidation of 1-octanol and cyclooctanol [Scheme 1, Eqs. (1) and (2)] occurred in quantitative yield with **1** and in only about 65% yield with **2c**. Recycling of both pre-catalysts was demonstrated for the oxidation of 4-bromobenzyl alcohol for six reaction cycles occurring in slowly decreasing yields (>99% first cycle and 74% sixth cycle in the case of **1**; >99% first cycle and 80% sixth cycle in the case of **2c**).

Very recently, 4-hydroxy-TEMPO anchored onto the polymer FibreCat™ was employed to catalyze the aerobic oxidation of primary alcohols to aldehydes.[29] FibreCat™ is a carboxylic acid-functionalized, insoluble polymer featuring a high density of functional groups that in this case allowed one to obtained a loading of nitroxyl radical as high as 2.3 mmol g^{-1}. In the presence of 10 mol% of the pre-catalyst and of 2 mol% each of the above-mentioned cobalt and manganese cocatalysts, aldehydes were obtained from the corresponding alcohols in quantitative yield and complete selectivity in 1–3 h reaction time (AcOH, 40 °C).

It is interesting to note that when the reaction was extended to the secondary alcohol 2-octanol relatively long reaction times (24 h) were necessary to complete a quantitative transformation. These results, that represent the first example of the use of oxygen as the terminal oxidant in combination with a TEMPO supported on an insoluble polymer, clearly show the difference in reactivity between soluble and insoluble catalysts. Recycling of FibreCat™-TEMPO was demonstrated for five cycles in which the catalyst was readily isolated by filtration and re-used without any further activation process to afford virtually constant yields in the octanol to octanal conversion.

Finally, a reaction in which both the catalyst and the terminal oxidant were employed as supported materials has been reported.[30] In the presence of 1 mol% of 4-hydroxy-TEMPO immobilized on insoluble but readily swellable *J*anda*J*el[31] (loading 2.0 mmol g^{-1}), and of polystyrene bound (diacetoxy)-iodosobenzene (2 mol equivs.),[32] aldehydes and ketones were obtained from the corresponding alcohols in fair to quantitative yields after 5–48 h in dichloroethane at 70 °C. The very high yield observed in the oxidation of 2-phenylethanol (96%) was maintained for two subsequent reaction cycles in which the catalyst was recycled and the oxidant was replenished [Scheme 1, Eq. (2)].

2.1.2 Ketones

The dioxirane-mediated oxidation of various substrates carried out in the presence of ketones as dioxirane precursors and oxone as the terminal oxidant is a convenient metal-free procedure that has found a variety of synthetic applications.[33] Even if the reaction requires the use of catalytic amounts of ketone, degradation of the catalyst by a concomitant Baeyer–Villiger process calls for the employment of stoichiometric or even excess amounts of ketone. Immobilization on different supports was investigated as a possible means to circumvent this problem by increasing the pre-catalyst stability.

After several attempts in which immobilized ketones were used in stoichiometric amounts,[4] the first examples of reactions catalyzed by an insoluble, silica-supported perfluoroacetophenone were described.[34] These transformations included conversion of pyridines to pyridine *N*-oxides, anilines to diazene 1-oxides, and alkenes to epoxides and diols. However, the harsh reaction conditions under which these reaction were performed (60% hydrogen peroxide as the oxidant, 80 °C, 12 h) were a clear indication that wide margins of improvement were available.

This goal was obtained by replacing insoluble with soluble supports.[35] 4-Hydroxy-α,α,α-trifluoroacetophenone was anchored on $MeOPEG_{5000}$ to afford ketone **4**. In the presence of 10 mol% of this species and oxone (3 mol equivs.) in dioxane/water, several aryl- and alkyl-substituted olefins were converted into the corresponding epoxides in 70–90% yield after only 5 min reaction time at room temperature. Contrary to previous examples[34] no diol formation was observed [Scheme 1, Eqs. (3) and (4)].

Attempts at pre-catalyst recycling, after its recovery by precipitation with diethyl ether during the reaction work-up, were successful, since at least five reaction cycles were shown to be possible in constant yield. However, the reactions employing the recycled catalysts required longer reaction times (30 min) to afford the same yield as the first cycle. This behavior appears to be a common feature of many processes involving recycled PEG-supported catalysts, and will be discussed later in this article.

An alternative to ketone recovery after a dioxirane-promoted epoxidation in water has recently been proposed.[36] In this work, acetone has been attached to an amphiphilic linear chain made of a short PEG block (six ethylene glycol units) terminating in an *n*-decyl residue. The ketone, employed as pre-catalyst in the cyclooctene epoxidation carried out with oxone in aqueous micellar solution (1 h, 5 °C, 78% yield), was recovered in 93% yield by extraction from the aqueous phase followed by chromatographic separation. Catalyst recycling was not reported [Scheme 1, Eq. (5)].

2.2 Lewis Base Catalysts

The ubiquitous involvement of Lewis bases as organic catalysts in many relevant reactions prompted their immobilization on a variety of supports. Pioneering efforts in this context were mainly devoted to the use of insoluble supports.[4] Among these, polystyrenes with various degrees of cross-linking found widespread use. More recently, also soluble supports received considerable attention.

2.2.1 4-Dimethylaminopyridine Analogues

The widespread applications of 4-dimethylaminopyridine (DMAP) in organic synthesis greatly contributed to the establishment of organocatalysis as a useful synthetic tool.[37] Of the several examples of DMAP analogues anchored on insoluble supports,[4] Tomoi's polystyrene-supported catalyst **5** (Figure 4), originally reported in 1982 for the acetylation of hindered alcohols,[38] has been recently rediscovered and applied in different types of Baylis–Hillman reactions.[39] For instance at a loading of 20 mol% in DMF, compound **5** promoted the condensation between 4-nitrobenzaldehyde and 3-buten-2-one (MVK) in DMF at 20°C in 89% yield [Scheme 2, Eq. (6)]. Catalyst recycling required re-activation with NaOH for subsequent reactions to occur in yields comparable to those observed in the first cycle.[40]

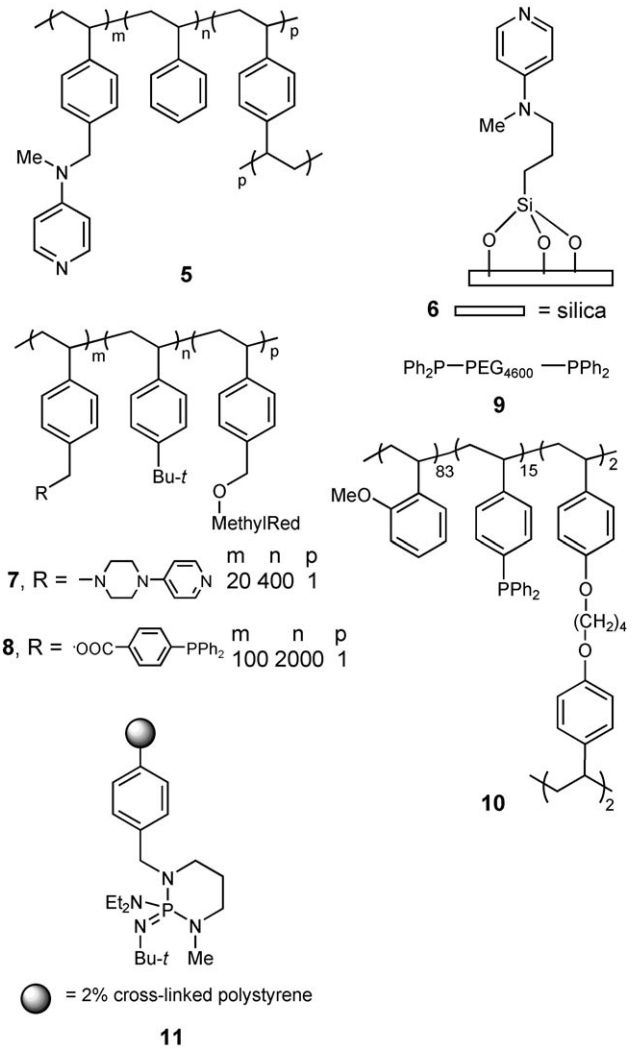
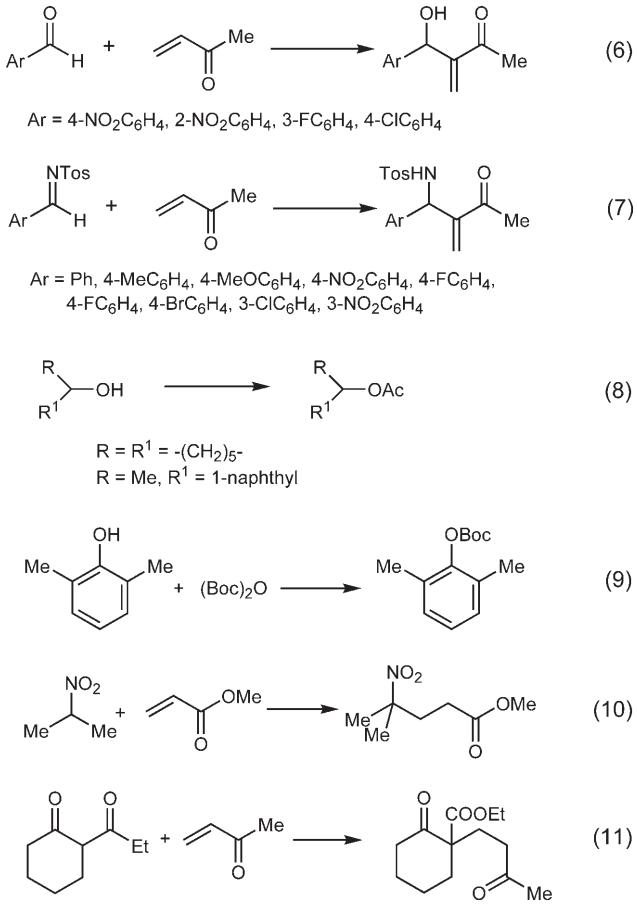


Figure 4. Structure of supported Lewis base catalysts.



Scheme 2. Reactions promoted by Lewis base catalysts.

The same catalyst **5** (20 mol%) was also employed in the so called aza-Baylis–Hillman addition of MVK to *N*-tosylimines derived from aromatic aldehydes. In DCM at room temperature the slow reaction (3 d) afforded 47–58% yield of the products. The recycled catalyst, recovered by filtration, performed slightly worse at each new cycle, the yield observed in the fourth cycle being about 2/3 of that of the first reaction [Scheme 2, Eq. (7)].[41] When imines were replaced by electron-poor aromatic aldehydes [Scheme 2, Eq. (6)], better yields were observed in shorter reaction times. To obtain these good results, however, the reactions had to be carried out in *t*-amyl alcohol as the solvent. Under optimized conditions

(20 mol% of catalyst **5**, room temperature, reaction time 1 d) catalyst recycling became possible in undiminished yields for at least 5 cycles.[41]

In a very recent study,[42] a DMAP analogue was readily supported on the mesoporous silicate MCM to afford DMAP-MSN nanospheres indicated with formula **6** in Figure 4. By a combination of techniques these were found to have an average diameter of 400 nm, a surface area of 835 $m^2 g^{-1}$, and average pore diameter of about 20 Å. The loading of functional groups was estimated at 1.6 mmol g^{-1}. This material, employed at the 30 mol% level, showed an excellent catalytic performance in the Baylis–Hillman reaction between aromatic aldehydes and MVK carried out in a 3:1 THF:water mixture at 50 °C for 24 h. As expected electron-poor aldehydes reacted better than their electron-rich counterparts, and linear enones were found to be more reactive than cyclic enones.

DMAP-MSN **6** (7.5 mol%) was also shown to catalyze the acetylation of secondary alcohols with acetic anhydride and TEA carried out in benzene at 60 °C for 2.5 h ($\geq$ 90% yield; tertiary alcohols reacted sluggishly). The acetylation of 1-(1-naphthyl)ethanol was selected for catalyst recyclability studies [Scheme 2, Eq. (8)]. It was shown that the same catalyst sample, isolated by decanting the liquid phase after centrifugation of the reaction mixture and drying the resulting solid in air, could be re-used for ten reaction cycles without any appreciable erosion of the chemical yield. Consistent with this observation, the TEM micrograph analysis of the catalyst particles showed that the mesopores of DMAP-MSN **6** were not destroyed by chemical or thermal decomposition induced by the repeated use as a catalyst.

Examples of DMAP analogues immobilized on soluble supports are less frequent.[4] They are all due to the excellent work that Bergbreiter and his group[43,44] devoted to the development of soluble polymeric supports for facile catalyst recovery by the use of thermomorphic systems or of latent biphasic separation. Recent research in this context led to the identification of poly(4-*tert*-butylstyrene) (PtBS) as a particularly convenient support for homogeneous catalysts and to the synthesis of the supported DMAP analogue **7** depicted in Figure 4.[45] The solubility of PtBS in heptane makes it useful in liquid/liquid biphasic separation, a technique that does not involve polymer precipitation by a change in solvent polarity nor the use of a large amount of apolar solvent to induce precipitation (as in the case of PEG) .

Catalyst **7** (M_W 48000 daltons) was assembled by radical initiated co-polymerization of three styrene momomers carrying in the *para* position a *tert*-butyl group, a Methyl Red dye residue, and a 4-(1-piperazinyl)pyridine moiety, respectively. The dye was introduced as a visual device to allow simple evaluation of the efficiency of the catalyst separation from the reaction mixture. In the presence of 1 mol% of catalyst, 2,6-dimethylphenol reacted with Boc anhydride in a homogeneous 1:1 heptane:ethanol mixture to afford the corresponding carbonate [Scheme 2, Eq. (9)]. Upon addition of a small amount of water (<10 vol%), phase separation occurred. As shown by its color (and as confirmed by UV spectroscopy) only the heptane phase contained the catalyst. On the contrary the product partitioned in both phases, and recovery from the aqueous phase allowed one to isolate only 34% of the carbonate. However, by recycling the heptane phase for four additional reaction cycles, yields of 61, 82, 95, and 99% were observed, as the result of product saturation of the heptane layer that increases the product concentration in the aqueous phase.

2.2.2 Phosphine-Type Catalysts

While a number of achiral and chiral phosphines have been anchored on various supports to act as ligands in organometallic catalysis,[14,46] the use of these compounds as Lewis basic organic catalysts is less frequent.

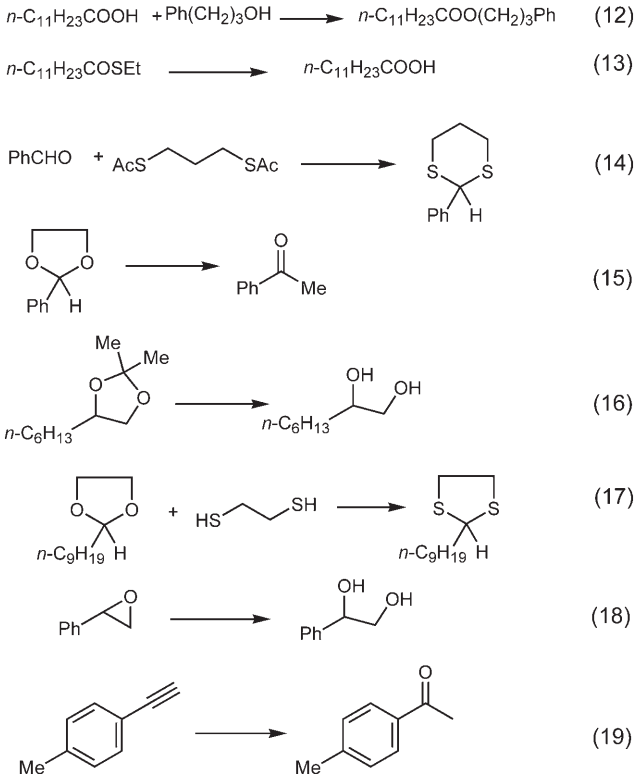
Among those recently reported, Bergbreiter's soluble co-polymer **8** (Figure 4), related to compound **7**, was employed to promote the Michael-type addition of 2-nitropropane to methyl acrylate [Scheme 2, Eq. (10)].[45] The reaction required 10 mol% of catalyst and occurred at room temperature in the usual homogeneous 1:1 heptane:ethanol mixture that was used to facilitate catalyst recovery and recycling by phase separation after addition of a small volume of water. As in the case of the reaction catalyzed by compound **7** (see above), the yield of the first reaction cycle was low (31%) but slowly increased to level off at 72% after the fifth cycle. Also in this case partial solubility of the product in the heptane phase was shown to be responsible for this behavior.

In the same article describing the use of catalyst **5**,[41] Shi also reported the preparation of the PEG supported bisphosphine **9** (Figure 4) that was obtained by simple addition of lithium diphenylphosphine to the bis-mesylate of PEG_{4600}. This compound (10 mol%) was used to promote the aza-Baylis–Hillman reaction between *N*-tosylimines and MVK [Scheme 2, Eq. (7)] to afford the products in moderate yield similar to those observed under DMAP **5** catalysis. More interesting was the finding that also phenyl acrylate can be used as Baylis–Hillman donor in this reaction, the α-methylene-β-amino esters being obtained in 50–87% yield. Catalyst recycling was hampered by phosphine to phosphine oxide oxidation that obviously inactivated the catalyst.

Very recently, Shi and Toy reported that the *J*anda-*J*el supported phosphine **10** (loading 1.0 mmol g^{-1})

containing a methoxy group on the polystyrene backbone was an excellent catalyst (10 mol%) for the aza-Baylis–Hilmann addition of MVK (up to 97% yield), acrolein (up to 75%), and phenyl acrylate (up to 81%) to aryl-*N*-tosylimines.[47] It is interesting to note that these reactions proceeded better in THF than in many other solvents. This fact was related to the excellent swelling of the polymer in THF.

Finally, the commercially available iminophosphorane **11** immobilized on 1% cross-linked polystyrene (5 mol%) was employed to catalyze the Michael addition of a variety of β-dicarbonyl compounds to acrolein, MVK [Scheme 2, Eq. (11)], and acrylonitrile in THF at room temperature (77–98% yield).[48] When recycling experiments were performed, it was discovered that only the use of prolonged reaction times secured similarly high yields. The catalyst's inactivation was ascribed to mechanical instability of the polymer beads when exposed to magnetic stirring, that crunched the beads into an inactive powder. The use of non-destructive rotatory stirring by-passed this problem, securing catalyst recyclability up to five reaction cycles in high yields.



Scheme 3. Reactions promoted by acid catalysts.

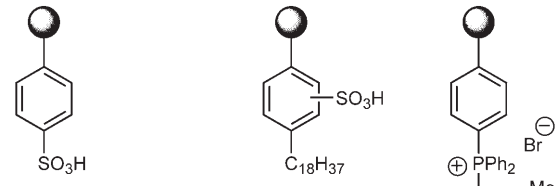
2.3 Acid Catalysts

2.3.1 Brønsted Acids

After extensive work describing the use of sulfonic acid-based ion exchange and Nafion resins,[4,49] recent interest in the application of supported Brønsted acids focused on the development of polystyrene-supported sulfonic acids to be used in water.[50–53]

In a study devoted to the identification of a supported catalyst for the esterification of dodecanoic acid with 3-phenylpropan-1-ol in water [Scheme 3, Eq. (12)], Kobayashi and co-workers discovered that sulfonic acid **12a** (Figure 5), having a loading of 0.879 mmol g^{-1}, performed much worse than its less loaded analogue **12b** (0.352 mmol g^{-1}) under the same reaction conditions (10 mol% of catalyst, 40 °C, 48 h). This observation was rationalized on the basis of the greater affinity of **12b**, less polar than **12a**, for the lipophilic reagents, and prompted the synthesis of the even more apolar catalyst **13a** (1.01 mmol g^{-1}). This proved to be superior to **12b** in a series of similar esterification reactions. For instance, dodecyl dodecanoate was obtained in 71% and 96% yield in the presence of **12b** and **13a**, respectively.[50]

The hydrophobic catalyst **12c** (10 mol%) was then employed to promote the high-yielding hydrolysis of thioesters in refluxing water (24 h), a reaction in which both the ion-exchange resin DOWEX 50W-X2 and Nafion-H were completely uneffective [Scheme 3, Eq. (13)]. Recycling of catalyst **12c** was demonstrated for three subsequent hydrolyses of dodecyl thioacetate, all occurring in quantitative yield. Catalyst **12c** was also shown to promote, under the same conditions, the reaction of thioesters with benzylic alcohols to afford the corresponding thioethers, and the thioketalization of benzaldehyde with 1,3-propanedithiol bisacetate [Scheme 3, Eq. (14)].[51]



12a, 0.879 mmol g^{-1} **13a**, 1.01 mmol g^{-1}
12b, 0.352 mmol g^{-1} **13b**, 0.17 mmol g^{-1}
12c, 0.462 mmol g^{-1} **13c**, 0.41 mmol g^{-1}

14

Figure 5. Structure of supported acid catalysts.

Based on the observation that less polar catalysts performed better than more polar ones in these reactions in water, poorly loaded supported sulfonic acids **13b** (0.17 mmol g^{-1}) and **13c** (0.41 mmol g^{-1}) were prepared and employed in a series of hydrolysis and transprotection reactions. Thus, compound **13b** (1 mol%) catalyzed: i) the conversion of 2-methyl-2-phenyl-1,3-dioxolane to acetophenone [30 min, 96% yield, Scheme 3, Eq. (15)]; ii) the hydrolysis of the

acetonide of 1,2-octanediol [2 h, 93% yield, Scheme 3, Eq. (16)]; iii) the conversion of 2-nonyl-1,3-dioxolane to 2-nonyl-1,3-dithiolane with 1,2-ethanedithiol [1 h, 95% yield, Scheme 3, Eq. (17)]; and iv) the hydrolysis of styrene oxide to 1-phenyl-1,2-ethanediol [30 min, 100% yield, Scheme 3, Eq. (18)]. Catalyst **13c** (10 mol%) in turn, promoted the hydration of 4-methylphenylacetylene to 4-methylacetophenone in 81% yield [refluxing water, 48 h, Scheme 3, Eq. (19)].[52,54]

Finally, polyphosphoric acid readily supported on silica gel was employed (unspecified amount) in the conversion of aldehydes and ketones into oxathio- and dithioacetals in good to high yield (dichloroethane, room temperature 30–60 min). After filtration and drying, the catalyst was re-used four times with marginal decreases in chemical yields.[54]

2.3.2 Lewis Acids

The acetonylphosphonium bromide **14** immobilized on 2% cross-linked polystyrene (Figure 5) was used as Lewis acid to catalyze (2–10 mol%) the reaction of 3-phenylpropanal and cyclohexanecarboxyaldehyde with alcohols, thiols, diols, and dithiols in DCM (room temperature, 48 h) to afford the corresponding acetals and thioacetals in generally high yields. The catalyst, recovered by filtration, rinsed with benzene, and dried under vacuum, could be recycled four times to promote the reaction in slowly decreasing chemical yields.[55]

2.4 Thiazolium Salts

After the pioneering work of Breslow on the involvement of thiazolium salts as "aldehyde activators" in the benzoin condensation,[56] this class of compounds has found widespread applications in organic catalysis. Among these applications, the Stetter reaction occupies a preminent position, because it opens access to otherwise difficult-to-obtain 1,4-dicarbonyl compounds.[57] After scattered reports on the immobilization of thiazolium salts on cross-linked polystyrene in the early 1980s,[4,58] a resurgence of interest in organic catalysis led to the development of a new example of these supported catalysts (Figure 6).[59]

Thiazolium salt **16** was obtained by ring-opening methatesis polymerization (ROMP) of norbornene **15** carried out in the presence of a cross-linking agent. The resulting insoluble polymer showed a high loading of active groups (2.52 mmol g^{-1}) and was employed as a catalyst (16 mol%) in the reaction of linear aliphatic aldehydes with unsaturated aliphatic and aromatic ketones to afford the corresponding 1,4-diketones [Scheme 4, Eq. (20)] in very high yields

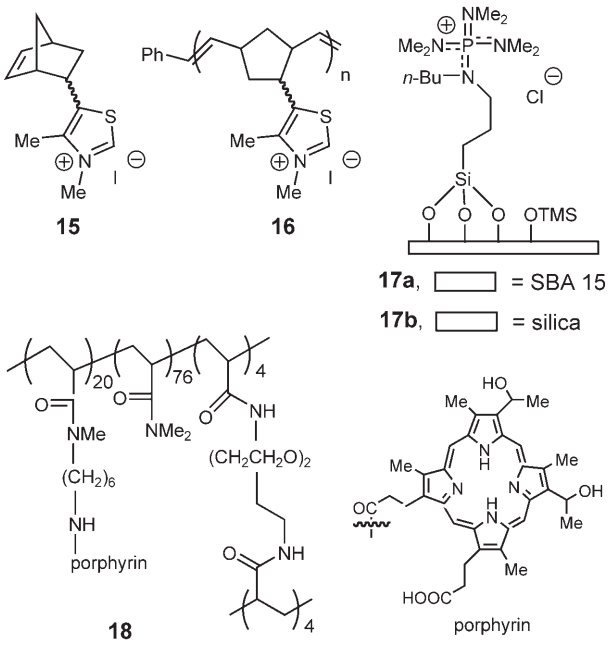
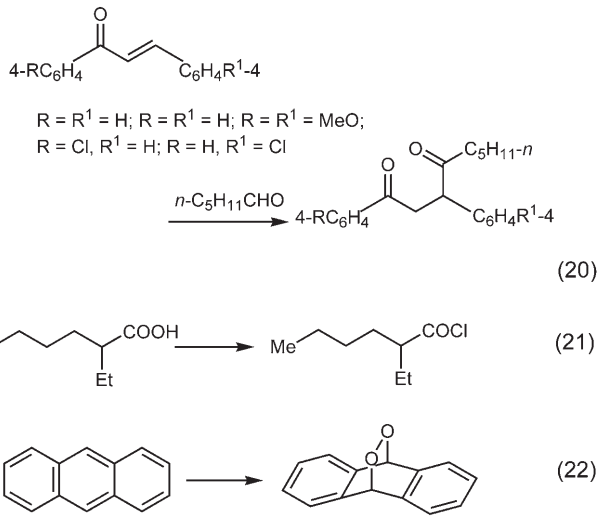


Figure 6. Structure of supported catalysts **16–18**.



Scheme 4. Reactions promoted by thiazolium and miscellaneous catalysts.

(TEA, DMF, 80 °C, 22–72 h). The catalyst was recovered by filtration, rinsed, and re-used four times without a significant loss in activity. Interestingly, a competing benzoin reaction was observed when benzaldehyde was used instead of alkyl aldehydes.

2.5 Miscellaneous Catalysts

The large flat nuclei of phosphazenes efficiently delocalize positive charges. Accordingly, hydrochlorides of these very strong bases (e.g., phosphazenium chlor-

ides) can behave as catalysts supplying chloride ions in the conversion of carboxylic acids to acid clorides. On this basis, phosphazenium chloride **17a**, immobilized on SBA-15 mesoporous material, and **17b**, immobilized on silica were prepared (Figure 6).[60] They had an average pore diameter of 100 and 150 Å, and a loading of 0.36 and 0.22 mmol g^{-1}, respectively. Both materials were found to be exceptionally active catalysts for the reaction of aromatic, and linear and branched aliphatic acids with thionyl chloride or phosgene to afford their acyl chlorides free of the corresponding anhydrides. For instance, 2-ethylhexanoic acid chloride [Scheme 4, Eq. (21)] was obtained in 100% conversion and 99% selectivity when reacted for 30 min with thionyl chloride in the presence of 10 mol% of **17a** or **17b** at 25°C in DCM. In the absence of catalyst, the same reaction (40°C, 18 h) proceeded with 95% conversion and only 60% selectivity. The catalyst, recovered by decanting the reacted materials, could be recycled five times after addition of new reactants without appreciable loss in catalytic activity. A continuous flow chlorination of 2-ethylhexanoic acid was also performed by passing the reactants through the catalyst bed.

After a PEG-supported soluble porphyrin had been synthesized and employed as catalyst for some photooxidation reactions involving singlet oxygen,[4,61] an related, insoluble catalyst was recently prepared by Wentworth and co-workers.[62] Compound **18** (Figure 6) was obtained by anchoring a porphyrin nucleus to a highly swellable poly(acrylamide) matrix. This compound (15 mol%) catalyzed the photooxidation of anthracene with singlet oxygen (DCM, 4°C, 4 h) to afford the corresponding hydroperoxide in 66% yield [Scheme 4, Eq. (22)]. Most importantly, isolation of the product required only filtration of the resin and removal of the solvent.

2.6 Bifunctional Catalysts

The ubiquitous presence of cooperative general acid and basic catalysts in the active sites of enzymes led Lin and co-worker to develop bifunctional organic catalysts immobilized on a solid support.[63] Mesoporous silica nanospheres **19a–c** (Figure 7) were obtained by a simple three-component condensation procedure. By varying the molar ratios among the reagents, spherical materials carrying the relative loadings of a general acid, the ureidopropyl group, and a general base, the 3-[2-(2-aminoethylamino)ethylamino]propyl group indicated in Figure 7, were synthesized. The overall loadings were 1.3, 1.0, and 1.5 mmol g^{-1} and the average pore diameters 27.8. 22.9, and 25.9 Å for **19a**, **19b**, and **19c**, respectively.

The catalytically active residues were chosen with the aim of promoting the nucleophilic addition of acetone, nitromethane, and trimethylsilyl cyanide to 4-nitrobenzaldehyde [Scheme 5, Eqs. (23–25)]. The role of the ureido group was that of activating the aldehyde carbonyl group by double hydrogen bonding. The secondary amine was responsible for activation

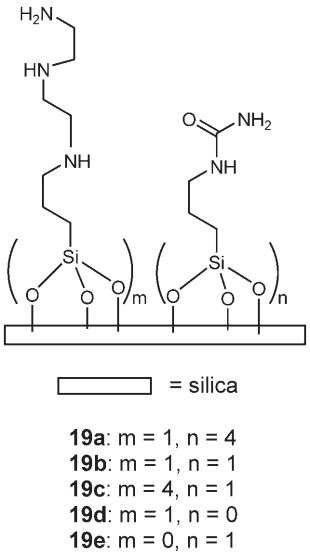
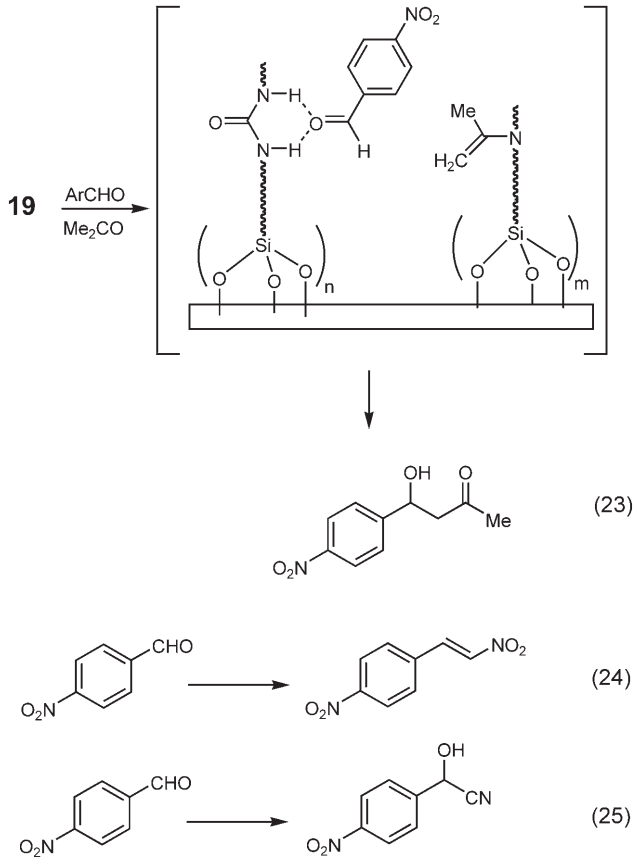


Figure 7. Structure of supported bifunctional catalysts.



Scheme 5. Reactions promoted by bifunctional catalysts.

of the nucleophile by enamine formation from acetone [see intermediate in Scheme 5, Eq. (23)], deprotonation of nitromethane, and generation of a more reactive hypervalent silicon species in the case of trimethylsilyl cyanide. Cooperation between the catalyst sites of **19a,c** was expected because of their proximity on the nanosphere surface. The observation of enhanced rates with respect to the reactions catalyzed by nanospheres **19d** and **19e**, decorated with only one of the two catalytic groups, was also anticipated.

Catalyst **19a** featuring a 1:4 ratio of secondary amine:ureido residues, proved to be the most effective in all three reactions. As expected, the aldol condensation carried out in acetone at 50 °C in the presence of 5 mol% of bifunctional catalyst **19a** occurred at a rate that was 2.0, 2.6, and 4.2 times faster than that observed with catalysts **19b**, **19c**, and **19d**, respectively; compound **19e** was not a catalyst for this process.[64] The Henry reaction required only 1 mol% of catalyst **19a** to proceed in high yield in nitromethane at 90 °C. In this case the differences in reaction rate with respect to catalysts **19b**, **19c**, **19d**, and **19e** were 1.3, 1.9, 2.3, and 22, respectively. A reason for this less marked difference can be found in the fact that, contrary to the aldol process, in the nitroaldol condensation also the mono-functionalized ureido catalyst **19e** shows some activity. The addition of trimethylsilyl cyanide gave results similar to the Henry reaction. Also in this case only 1 mol% of **19a** was enough for the reaction to proceed effectively in toluene at 50 °C. The reaction catalyzed by **19a** was found to be 1.6, 2.5, 2.5, and 6.0 times faster than those observed with catalysts **19b**, **19c**, **19d**, and **19e**, respectively.

The recovery and recycling of the bifunctional catalysts were then studied. The catalysts were recovered by centrifugation and recycled three times without further purification. A $<10\%$ decrease in reaction rates was observed after each cycle. This was ascribed to partial inactivation of the catalysts by deposition of amorphous substances deriving from reactants or products on the nanosphere surface, as demonstrated by TEM micrography.

3 Chiral Organic Catalysts

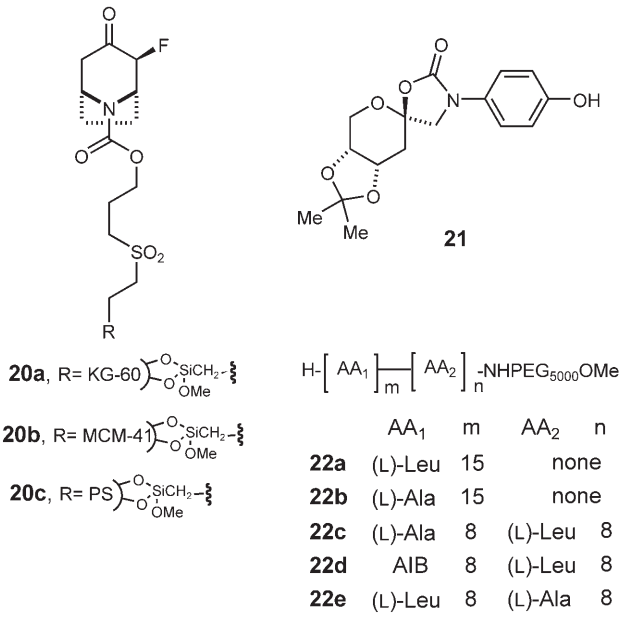
Most of the recent research activity in the field of organocatalysis has been devoted to chiral catalysts and exceptional results have been obtained for a variety of different fundamental organic transformations.[3,11] Because at the present stage the research efforts have focussed on catalyst discovery, the development of immobilized chiral catalysts has been less intensively pursued. Indeed, since the publication of the previous review,[4] only a limited number of new examples of supported chiral organocatalysts or of new applications of already reported catalysts have been described. These examples are presented below, roughly in the same order followed above for the discussion of achiral catalysts.

3.1 Catalysts for Oxidation Reactions

3.1.1 Ketones

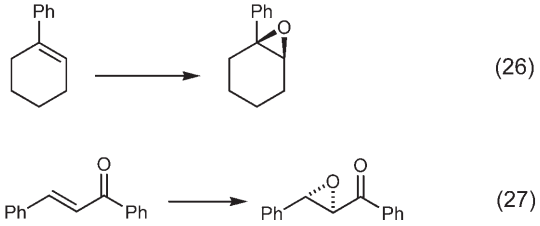
Dioxiranes derived from chiral ketones have extensively been used as organocatalysts to promote the enantioselective epoxidation of alkenes.[33b] The first examples of immobilized chiral ketones to be employed in this reaction were reported by Sartori, Armstrong, and co-workers.[65] They first anchored a modified racemic tropinone on amorphous silica KG-60, mesoporous silica MCM-41, and 2% cross-linked polystyrene to obtain the insoluble precatalysts **20a–c** reported in Figure 8.

By studying the epoxidation of 1-phenylcyclohexene [Scheme 6, Eq. (26)] as the model reaction (40 mol% of catalyst, oxone as the teminal oxidant, acetonitrile, aqueous $NaHCO_3$, room temperature, 1 h), it was discovered that the siliceous materials, having



	AA_1	m	AA_2	n
22a	(L)-Leu	15	none	
22b	(L)-Ala	15	none	
22c	(L)-Ala	8	(L)-Leu	8
22d	AIB	8	(L)-Leu	8
22e	(L)-Leu	8	(L)-Ala	8

Figure 8. Structures of chiral oxidation catalysts.



Scheme 6. Reactions promoted by chiral oxidation catalysts.

different porosity and loading (200 and 670 $m^2 g^{-1}$, and 0.58 and 0.78 $mmol g^{-1}$, for **20a** and **20b**, respectively), performed much better than the polystyrene-supported ketone.

Modified tropinone samples having 78% enantiomeric excess (*ee*) were then supported on KG-60 and MCM-41. These precatalysts were employed to promote the epoxidation of a series of trisubstituted alkenes (same conditions as above) in > 93% conversions, > 91% yields, and 58–80% *ee* (corrected for the *ee* of tropinone). It is important to note that the observed *ee* were only slightly lower than those obtained with the non-supported catalyst that, however, was employed in a lower loading (10 mol%). Finally, it was shown that the catalysts recovered by filtration, washed with acetonitrile and dried, could be recycled three times to promote the reaction with unchanged activity and stereoselectivity.

Since it is well known that sugar-derived dioxiranes are excellent organic catalysts for the enantioselective epoxidation of alkenes,[66] several experiments were carried out with the aim of anchoring precatalyst **21** (Figure 8) on $MeOPEG_{5000}$ by using the phenol oxygen as connecting element.[67] This support was considerd particularly convenient considering that the epoxidation reaction is carried out in a solvent mixture perfectly suitable for the use of PEG. However, ketone **21** proved to be very unstable under the reaction conditions necessary for the connection to the polymer, and supported precatalysts of reasonable purity could not be obtained.

3.1.2 Polyamino Acids

After extended work had been devoted to the study of insoluble polystyrene-supported polyamino acids[4] as catalysts for the enantioselective epoxidation of unsaturated carbonyl compounds,[68] later efforts, focussed on catalyst's immobilization on soluble PEGs, proved the superiority of the latter support. This work eventually led to the development of a chalcone epoxidation process [Scheme 6, Eq. (27)] carried out at the industrial level in 99% yield and 94% *ee* in a continuously operated membrane reactor where catalyst recycling was made possible by a nanofiltration membrane.[11,69]

In subsequent work, Kelly and Roberts prepared a new soluble catalysts **22a** by attaching a polyleucine chain to $MeOPEG_{5000}NH_2$ (Figure 8).[70] This catalyst, the peptide fragment of which was shown by CD measurements to exist mostly in the α-helical structure (86%), was found to promote the epoxidation of chalcone with the urea/hydrogen peroxide complex in 95% conversion and 97% *ee* (DBU, THF, room temperature, 3 h). The use of other solvents led to either lower yields or lower *ee*.

A catalyst's structure/activity relationship study was then carried out by synthesizing the PEG conjugates **22b–e**, featuring polyamino acid chains of different length and monomer content, and testing them in the same reaction. Replacement of polyleucine with a polyalanine chain of similar length resulted in the loss of almost all the catalytic activity (conversion 10%) and most of the stereoselectivity (28% *ee*). CD measurements on **22b** showed that the α-helical structure was also largely lost in this catalyst. The Ala_8-Leu_8 catalyst **22c**, which retained a high degree of α-helicity in its structure (63%), maintained excellent enantioselectivity (97% *ee*) but was less active than **22a** (58% conversion). Both yields and *ee* further decreased on passing to catalysts **22d** and **22e**, a trend which paralleled that of their content in α-helical structure. Thus, the existence of a direct relationship between content of α-helical structure and catalytic activity and, to a lesser extent, enantioselectivity was demonstrated. Further experiments showed that the minimum number of Leu residues necessary to achieve high stereoselectivity with these PEG-supported catalysts was 6, in agreement with the observation that at least four amino acids are required to form a whole turn of the α-helical structure.

3.2 Lewis Base Catalysts

3.2.1 4-Dimethylaminopyridine Analogues

While the use of a variety of chiral DMAP analogues as organic catalysts has been reported in the literature,[11] only a couple of examples of supported versions of these compounds have been described so far. Researchers at GSK recently described a family of chiral acylating catalysts based on the *N*-4′-pyridinyl-α-methylproline structure capable of promoting the kinetic resolution of alcohols with a high level of enantioselectivity.[71] The ready availability of these compounds suggested an exploitation of the presence of their easily functionalizable carboxy function to immobilize these catalysts on different polymer supports.[72]

Among others, derivatives **23a–c** collected in Figure 9 were prepared connecting *N*-4′-pyridinyl-α-methylproline to low- and high-loading polystyrene (LLPS and HLPS), and to Wang resin by standard condensation methods. These compounds were tested as insoluble catalysts (5 mol%) in the kinetic resolution of *cis*-1,2-cyclohexanediol mono-4-dimethylaminobenzoate [Scheme 7, Eq. (27)] carried out with a deficiency of isobutyric anhydride in DCM (room temperature, 16 h). By stopping the reaction at about 50% conversion, it was possible to recover the unreacted (−)-alcohol in about 75% *ee*. This was increased up to 93% by allowing the reaction to pro-

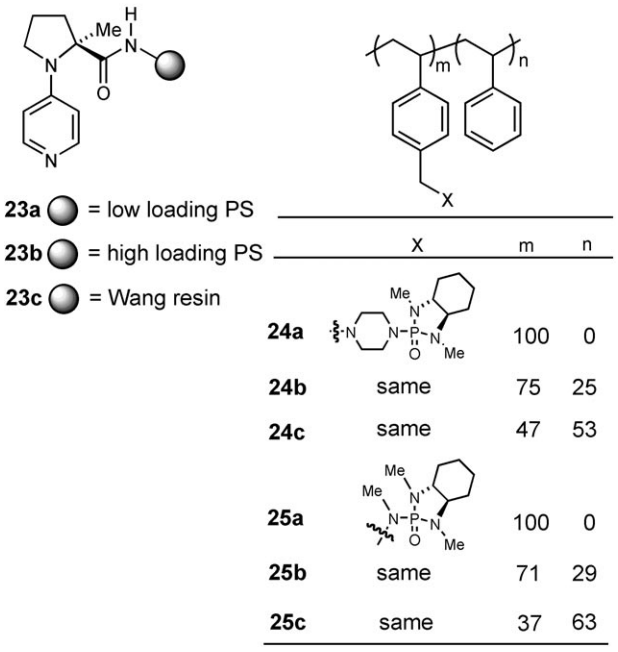
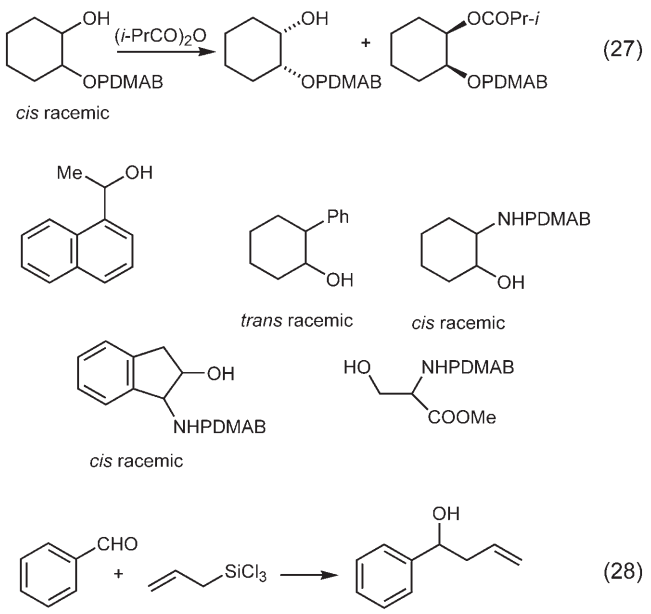


Figure 9. Structures of chiral Lewis base catalysts.



Scheme 7. Reactions promoted by chiral Lewis base catalysts.

ceed up to 67% conversion. No appreciable difference in chemical or stereochemical efficiency was observed as a function of the polymeric support.

Catalyst **23b**, recovered by filtration and thoroughly washed with DCM, was employed in three additional runs to afford the resolved product in slighltly higher *ee* at identical conversions. However, the activity of the recycled catalyst was somewhat lower than that of the fresh one, since longer reaction times were necessary to obtain the same conversions. Extension of the use of catalyst **23b** to the kinetic resolution of other secondary alcohols was possible, although the immobilized catalyst performed constantly less efficiently than its best non-supported analogue.[71,73]

3.2.2 Phosphoramides

Denmark's seminal work on the use of chiral Lewis bases in general and of chiral phosphoramides in particular as organic catalysts[6] greatly contributed to the establishment of organocatalysis as a valuable tool in stereoselective synthesis.[11] Notwithstanding the fact that these catalysts can promote very important processes such as the allylation of aldehydes with allyltrichlorosilane[74a] or the aldol addition of trichlorosilyl enol ethers to aldehydes,[74b] the first and only example of immobilization of chiral phosphoramides on a polymeric matrix has been reported only in 2005.[75,76]

Derivatives **24a–c** and **25a–c** (Figure 9) of different active site contents, were obtained either by homopolymerization of styrene monomers containing two different phosphoramide residues (**24a** and **25a**) or by copolymerization of these monomers with unfunctionalized styrene (**24b,c** and **25b,c** see Figure 9 for monomer contents). These compounds were used as catalysts (10 mol%) to promote the allylation of benzaldehyde with allyltrichlorosilane [Scheme 7, Eq. (28)] in the presence of excess Hunig's base (DCM, −78 °C, 6 h). It was found that catalysts **25a–c** performed equally well (82–84% yield, 62–63% *ee*) and better than **24a–c** (43–62% yield, 49–51% *ee*).

Remarkably, the whole set of the supported catalysts **24/25** proved to be more efficient than the corresponding non-supported derivatives featuring a benzyl group instead of the polymer residue both in terms of yield and of stereoselectivity. Since it has been shown that bis-phosphoramides are more efficient than mono-phosphoramides in promoting the allylation reaction,[74a] the better results obtained with **24/25** were regarded as suggestive that two phosphoramide groups of the supported catalysts could bind the hypervalent octahedrally coordinated silicon atom believed to be involved in the transition structure of the reaction. In other words, the polymer backbone apparently forces two catalyst sites into such a close proximity that they can behave as a bis-phosphoramide.[77] Neither the recycling of **24** and **25** nor the extension of their use to the allylation of aldehydes different from benzaldehyde has been described.

3.3 Catalysts Derived from *Cinchona* Alkaloids

The potentiality of the use of *Cinchona* alkaloids as organocatalysts was recognized a long time ago.[78]

Taking advantage of the possibility of exploiting different functionalities on the alkaloid as handles for attaching it on a support, a variety of immobilized versions of these catalysts have been reported.[4] After most of the earlier efforts were concentrated on the use of insoluble supports, with spectacular results being obtained in particular by Lectka and co-workers in the case of a β-lactam synthesis,[79] more recent research was devoted to the use of soluble supports. Among these, PEG played a major role.

For instance, Cahard and co-workers described the synthesis of two catalysts where cinchonidine (**26a**) and cinchonine (**26b**) were connected through their bridgehead nitrogen atoms to $MeOPEG_{5000}$ by an ester linker (Figure 10).[80] These catalysts (10 mol%)

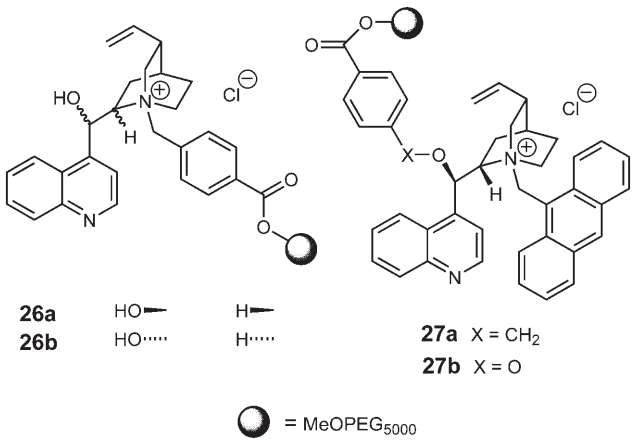
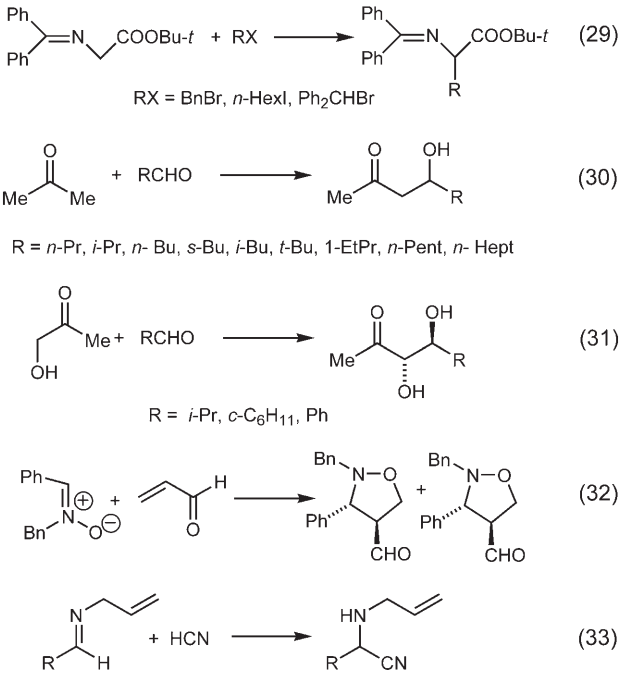


Figure 10. Structures of catalysts derived from *Cinchona* alkaloids.

were tested in the standard O'Donnell–Corey–Lygo[81] alkylation of *tert*-butyl glycinate benzophenone imine [benzyl bromide, toluene, 50% aqueous KOH, 0°C, 15 h, Scheme 8, Eq. (29)] to afford the (*S*)-product in 81% *ee* and the (*R*)-product in 53% *ee* using **26a** and **26b**, respectively (chemical yield was slightly >80% in both cases; the use of other alkylating agents resulted in much lower *ee*: 20% with *n*-hexyl iodide; 34% with benzhydryl bromide).

The relatively large difference in the observed *ee* is puzzling, since the *quasi*-enantiomeric structure of the alkaloid catalysts should secure virtually identical *ee* for both enantiomers.[81] It must be noted, however, that this anaomalous behavior has some precedents in the same reaction catalyzed by the same alkaloids immobilized on insoluble supports.[4,82] Also surprising was the strong variation of the stereoselectivity of the alkylation observed on changing the reaction solvent. For instance, on passing from toluene to the very similar benzene, xylene, or trifluoromethylbenzene a decrease in the *ee* from 81 to 64, 58, and 39%, respectively, was observed. Moreover, while the product was obtained in 65% *ee* in carbon tetrachloride, both



Scheme 8. Reactions promoted by *Cinchona* alkaloids and amino acids.

DCM and chloroform led to extremely low *ee* (3 and 1%, respectively), and THF to a reversal in the sense of enantioselectivity. Decreasing the M_W of the PEG chain from 5000 to 750 daltons was detrimental for the enantioselectivity of the reaction. Attempts at recycling catalyst **26a** were met with a dramatic drop in enantioselectivity, ascribed to the instability of the catalyst's ester linkage under the reaction conditions.

In attempting to improve these results, catalysts **27a,b** were prepared (Figure 10).[80,83] The rational for the choice of the hydroxy group of the alkaloid as the handle for polymer attachment rested on the Corey's and Lygo's observation that only in the presence of a very bulky 9-anthracenylmethyl residue at the bridgehead nitrogen of the non-supported catalyst could top levels of *ee* be observed. Thus, the commercially available quaternary ammonium salts derived from cinchonidine and cinchonine were anchored to $MeOPEG_{5000}$ using slightly different linkages. Under the best reaction conditions (10 mol% of catalyst, toluene, solid CsOH, −60°C, 72 h), the cinchonidine catalyst **27a** afforded the benzylated glycine derivative in 67% yield and 71% *ee*, a result that did not improve those obtained with **26a**.

3.4 Catalysts Derived from Amino Acids

Since its origins,[1,2] stereoselective organic catalysis had amino acid-derived catalysts at its very core. Undoubtedly, the possibility of finding the Holy Grail of

enzymatic reactivity all concentrated in the simple structure of an amino acid has been one of the main stimuli that spurred research in this field. The fact that in some fortunate instances (proline, to name one) the Holy Grail has actually been found justifies previous and future efforts in this sense.

The immobilization of these compounds on a support can be seen as an attempt to develop a minimalistic version of an enzyme, with the amino acid playing the role of the enzyme's active site and the polymer that of an oversimplified peptide backbone not directly involved in the catalytic activity.[84]

While the relatively low cost of many amino acids apparently does not seem to justify the procedure of immobilization, it must be remembered that a number of opportunities can be offered by a supported catalyst, in terms of different (not necessarily improved) solubility properties, easy separation of the products from the catalysts, catalyst recyclability, and so on.

The centrality of proline in stereoselective organic catalysis[3,11] has led to the development of several immobilized versions of this catalyst, both soluble[84] and insoluble.[85] Their behavior has already been discussed in the previous review.[4] More recent efforts involved the synthesis of prolinamide **28** (Figure 11) obtained by condensation of proline with 4-methylbenzhydrylamino polystyrene (MBHA).[86a] This catalyst (20 mol%) was employed in the aldol reaction of acetone (68 mol equivs.) with linear and branched aliphatic aldehydes [25°C, 48 h, Scheme 8, Eq. (30)] to afford the aldol products in moderate yields (40–75%). Satisfactory *ee*s were observed only in the case of sterically hindered aldehydes such as pivalaldehyde (86%) and 2-ethylbutanal (80%), whereas the products obtained from linear aldehydes showed *ee*s averaging around 50%. When the catalyst, recovered by filtration, was recycled for a subsequent run slightly lower yields and *ee*s were observed.

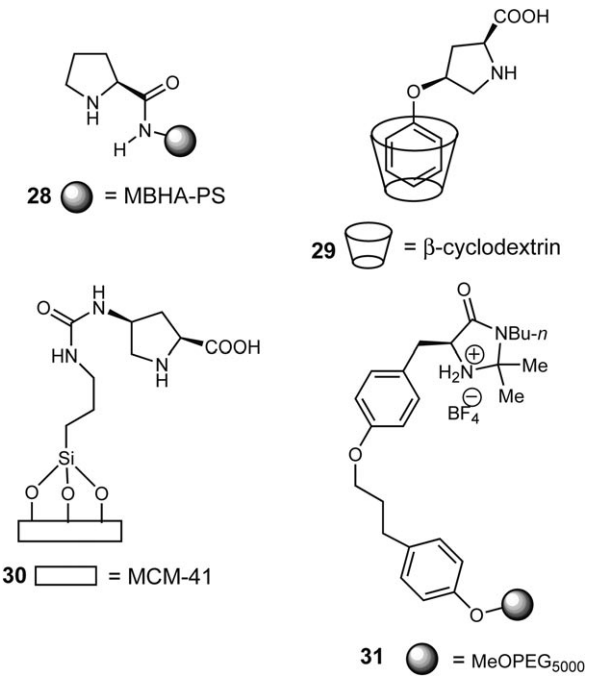


Figure 11. Structures of chiral catalysts derived from amino acids.

An interesting non-covalent immobilization technique was exploited by Zhang and co-workers in the synthesis of catalyst **29** (Figure 11). In this case the apolar phenyl ring of 4-phenoxyproline served as the handle for including the amino acid into the β-cyclodextrin cavity. Interestingly, the amount of catalyst actually included was found to be directly dependent on the temperature of the inclusion reaction, with higher temperatures leading to a higher extent of inclusion. Thus, catalyst samples with different loadings could be obtained.[87]

Using the aldol addition of acetone (68 mmol) to 2-nitrobenzaldehyde as the model reaction [Scheme 5, Eq. (23)], it was shown that in the presence of the highest loaded catalyst (10 mol%) the product could be obtained in 90% yield and 83% *ee* after 16 h at room temperature. The reaction time could be shortened to 8 h by tripling the amount of catalyst, a change that did not exert any effect on the yield or the stereoselectivity of the process. Extension of the reaction to other aryl aldehydes substituted with electron-withdrawing groups was possible with slightly inferior results. The catalyst was recovered by filtration and employed for three subsequent runs occurring in slowly decreasing yields (90%, 1st run; 79%, 4th run) and unchanged *ee*, a behavior that almost perfectly paralleled that observed for PEG-supported proline over the same number of recycling experiments.[84]

The modified proline **30** where the catalyst is immobilized on the mesoporous siliceous material MCM-41 (Figure 11)[88] has recently been prepared by the standard reaction sequence involving introduction on the catalyst of a side arm terminating in a triethoxysilane residue and refluxing the mixture of the modified proline and the support in toluene containing traces of water.[88a] Compound **30** had an active site loading of 0.52 mmol g^{-1}. Large amounts of this catalyst (47–52 mol%) were then employed to promote the reaction between 2-hydroxyacetone and isobutyraldehyde (room temperature, 24 h) and benzaldehyde (90°C, 24 h) in DMSO or toluene [Scheme 8, Eq. (31)] to afford the products in yields that were only marginally higher than the amount of catalyst used (55–60%). The reaction times were significantly shortened to 10–30 min by the use of microwave irradiation, a procedure that also led to some improvement of the yield. In agreement with the behavior of the non-supported catalyst, compound **30** promoted the exclusive formation of *anti* diols of >99% *ee* in

the process involving isobutyraldehyde, while *syn* diols of 80% *ee* were obtained with poor diastereoselection (*syn*/*anti* ratio 1.4/1) in the case of benzaldehyde. Two recyclings of the catalyst recovered by filtration were shown to occur in slowly decreasing yield and unchanged stereoselectivity.

Imidazolidin-4-ones, originally proposed as organic catalysts by MacMillan and co-workers,[89] have found widespread use in a number of relevant processes.[3,11] Their relevance led two groups to develop soluble[90] and insoluble[91] supported versions of these catalysts to promote the enantioselective Diels–Alder cycloaddition of dienes with unsaturated aldehydes. A comparison among these catalysts[92] showed that the *J*an-da*J*el-supported catalyst[91] performed better not only than its PEG-[90] and silica-supported[91] analogues (which behaved almost identically), but, quite surprisingly, also than the non-supported compound.[89]

More recent work[92] was devoted to the use of the PEG-supported imidazolidinone **31** (Figure 11) as catalyst for 1,3-dipolar cycloadditions.[93] By reacting *N*-benzyl-*C*-phenylnitrone with acrolein [Scheme 8, Eq. (32)], it was shown that the outcome of the reaction was strongly dependent on the nature of the acid employed to generate the catalyst, and that only the use of HBF_4 as in the case of **31** allowed one to obtain reproducible results. Under the best reaction conditions (20 mol% of catalyst, DCM, −20 °C, 120 h) the product was obtained in 71% yield as an 85:15 *trans/cis* mixture of isomers, the major one having 87% *ee*. Extension of the reaction to crotonaldehyde and other nitrones led to similar results.

A comparison of the results obtained with catalyst **31** with those obtained by MacMillan[93] indicates that the major difference between the PEG-supported and the non-supported catalyst resides in the chemical rather than in the stereochemical efficiency. Indeed, while the supported catalyst gave *trans*/*cis* ratios almost identical to and *ee* only 3–6% lower than those obtained with the non-supported catalyst, the difference in chemical yields was larger, ranging from 9 to 27%.

After recovery of the PEG-supported catalyst by precipitation with diethyl ether and filtration, the dried catalyst was recycled twice in the reaction of *N*-benzyl-*C*-phenylnitrone with acrolein (same conditions as above) to afford the product with a constant level of diastereo- and enantioselectivity but in clearly diminishing chemical yields. With the goal of explaining this behavior several experiments were carried out. First, the supported catalyst was examined by ^1H NMR after each recovery to show degradation, increasing after each cycle. The NMR analysis was suggestive of an imidazolidinone ring opening process. In order to check whether the instability of catalyst **31** was induced by the presence of the polymer, the triflate salt of the non-supported imidazolidinone was kept for 120 h at 24 °C in a 95/5 CD_3CN/D_2O mixture both in the presence and in the absence of the bismethyl ether of PEG_{2000}. In neither case was degradation observed by NMR, thus suggesting that the polymer is not playing a leading role in provoking the instability of the supported catalysts.

These findings seemed to point to catalyst degradation induced by the presence of the reagents, and indeed further NMR analysis showed extensive catalyst degradation with acrolein as the aldehyde, less degradation with crotonaldehyde, and essentially no degradation with cinnamaldehyde (nitrone did not exert any effect on the catalyst stability). In agreement with the results of these experiments, we could observe that also the non-supported catalyst showed a marked instability and decrease in chemical efficiency when recycled.[92]

4 A Short Discussion on the Practical Aspects of Catalyst Immobilization

In this section the practical aspects associated with the immobilization of an organic catalyst on a support, as they emerged from the examples of catalyst immobilization presented in the previous sections of this article and in the published review,[4] will be briefly examined. Even if the author will try to be as impartial as possible, it seems unavoidable that the following discussion will be biased by his experience in the field and his personal research interests.

4.1 When?

Every other consideration of opportunity and convenience being at the moment disregarded, the decision to immobilize an organic catalyst on a support should be taken only when some general prerequisite conditions have been satisfied. Of these, the most important is that only catalysts really versatile in scope (that is, catalysts capable of promoting more than one type of reaction, or tolerating a real variety of substrates in a given transformation) are worth considering as possible candidates for immobilization. High catalytic efficiency is another irrenunciable condition.

These statements seem so obvious to be redundant, but their importance cannot be overemphasized once it is considered how strong an effect the attachment of the support can exert on the catalyst. In general, the supported catalyst should be expected to be more sterically hindered and hence less accessible than its non-supported counterpart. As a result of the immobilization, a decrease in chemical activity should be expected and this is indeed what happens in the majority of cases (but exceptions had been report-

ed).[18,91,100] Thus, only very active catalysts have the best chances to preserve their reactivity or have it only acceptably depressed upon immobilization.

The catalyst's tolerance of structurally different substrates is another likely (and, indeed, frequent) victim of the immobilization, because it might happen that the reagents are not as free to interact with the supported catalyst's active site as with the non-supported one's. The same goes for stereoselectivity, a feature that often depends on the fact that the substrate must adopt a well-defined orientation relative to the catalyst for the transformation to occur in a stereoselective fashion. Clearly, the immediate surroundings of the active site can deeply affect the approach event, exerting undesirable stereochemical effects. In this respect, it must be said that while it is possible that a very active non-supported catalyst will maintain its chemical activity also when immobilized, a highly stereoselective catalyst is more prone to give up its stereodiscriminating ability upon immobilization

Another very important prerequisite condition is catalyst stability, since this can decisively affect recycling, which represents a major goal of catalyst immobilization (see below in the "Why?" section). In this respect it is worth mentioning that very seldom does the inventor of a new organic catalyst take the time for a thorough assessment of its stability under the reaction conditions or in the presence of the reagents to which the catalyst is exposed by its standard applications (see above the discussion about the recycling of PEG-imidazolidinone **31**). Needless to say, also the support can affect the stability of the catalyst, both positively and negatively. Thus, control experiments in which the non-supportred catalyst is employed in the presence of the support should be carried out before deciding whether a catalyst is really worth developing.

4.2 Why?

A number of reasons justify the immobilization of an organic catalyst. The simpler separation of the catalyst from the reaction mixture, the easier isolation of the reaction products, and catalyst recovery and recycling[14,94] are the most important.

In the context of separation, immobilization is often used to change the catalyst's solubility properties. In this case, the support acts as a "solubility device". Without entering for the time being in the dichotomy between soluble and insoluble catalysts (see below in the "How?" section), immobilization on an insoluble support such as a siliceous material or a cross-linked polystyrene can make the catalyst insoluble in the reaction medium and thus physically removable by filtration. In contrast, immobilization can allow the catalyst to be soluble in the reaction medium as long as the reaction proceeds, and then to become insoluble when the reaction is over. The switch in solubility can be induced by a change in the medium's polarity as in the case of PEG[94] or, even more simply, by changing the temperature of the reaction mixture, as in the case of thermomorphic polymers.[43] Another possibility is offered, for instance, by PtBS as a support that allows catalyst recycling by a technique called "latent biphasic separation".[45]

In the context of catalyst separation and recycling, immobilization seems to work at its best when it leads to a catalyst that need not be removed from the reaction vessel. This is the case, for instance, of continuous flow methods,[95] when the immobilized catalyst permanently resides in the reactor where it transforms the entering starting materials into the exiting products.[69,79,96] The retention of the catalyst inside the reaction vessel can be achieved by different techinques ranging from ultrafiltration through an M_W-selective membrane to immobilization on a silica gel column. It is important to note that, under continuous flow conditions, product separation from the catalyst, catalyst recovery, and catalyst recycling are achieved in a single operation. The convenience of this approach is demonstrated by the fact that one of the highest recycling numbers for an organic catalyst (60 cycles) has been reported for a spectacular enantioselective β-lactam synthesis carried out under the continuous flow mode.[79]

Catalyst instability can be another reason for immobilization. Organic catalysts do exist that slowly decompose under the conditions necessary for their reaction and release trace amounts of by-products that must be separated from the products. If decomposition is slow and the catalyst is very chemically active, this phenomenon does not markedly affect the efficiency of the catalyst and its recycling, but product purification remains a problem. This is the case, for instance, of the reactions involving TEMPO and porphyrin as catalysts, since these compounds release highly colored materials that are very difficult to dispose of. Immobilization of the catalyst can solve this problem because also the decomposed materials are supported and can be removed from the reaction medium in the process of catalyst recovery.

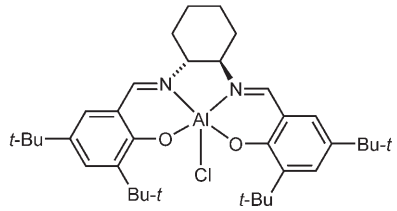
Immobilization is obviously convenient if the catalyst is expensive, or has been obtained after a complex synthesis, or is employed in a relatively large amount. It is important however that, in this case, the synthesis of the supported catalyst should exploit a starting material comparable in cost and synthetic complexity to that of the compound used for the synthesis of the non-supported catalyst (for the sake of simplicity, the cost of the polymer and of the linker is not considered in this discussion).

To explain this point, let us consider proline and its supported versions. Some of the latter have been de-

veloped using *trans*-4-hydroxyproline as the starting material in order to exploit the hydroxy group as an handle for support.[84a,88a] Considering that the cost of proline (€ 97.00 for 100 g)[97] is less than half that of *trans*-4-hydroxyproline (€ 225.00 for 100 g), it can be concluded that, even if the catalyst is generally used at quite high loadings (20–30 mol%), the immobilization of proline through the hydroxy group is not economically convenient unless the supported catalyst could be recycled for a number of times. On the contrary, the synthesis of the supported catalyst **28** (Figure 11)[86] starts from proline itself and therefore seems economically affordable. The same holds true for the PEG-immobilized imidazolidinone **31** (Figure 11) obtained from tyrosine[90] (€ 42.00 for 100 g)[97] a starting material more convenient than phenylalanine (€ 83.00 for 100 g) used for the synthesis of the non-supported catalyst.[89]

Last but definitely not least, immobilization of an organic catalyst can be used to facilitate the process of catalyst optimization. Surprisingly, there is a single example of the application of this methodology reported so far.[18] Even if this approach has already been discussed previously,[4] its conceptual relevance suggests that it deserves to be briefly examined also in this review.

The Strecker hydrocyanation of imines is a fundamental process in synthetic organic chemistry. Chiral Lewis acid catalysts are employed to activate the imine and provide the facial discrimination necessary to allow the stereoselective attack of the cyanide ion on the imine carbon. Among many metal-based activators, Jacobsen's salen/aluminum complex **32** reported in Figure 12 stands out as a relatively inexpensive



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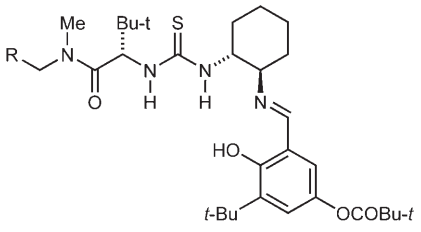

33a R = 1% cross-linked polystyrene
33b R = H

Figure 12. Structures of chiral catalysts for the Strecker reaction.

and efficient catalyst, capable of promoting the hydrocyanation of the *N*-allylimines of aromatic aldehydes in excellent yield (up to 91%) and *ee* (up to 95%) at a low catalyst loading (5 mol%) and low temperature [Scheme 8, Eq. (33)].[98]

The same group developed a fully organic catalyst for the Strecker reaction using a thiourea-based chiral Brønsted acid that turned out to be much more chemically active, stereoselective, and broad in application than the salen complex.[18] The optimization of the catalyst structure began with a modification of the salen ligand by replacement of one of its imino functions with L-leucine containing dipeptide-like residues. The modifications were carried out on an insoluble polystyrene support while using the principles of combinatorial chemistry for sorting out the best amino acid, diamine, and diamine-amino acid linker combination. The first obtained ligands were tested in the presence of different metals to discover that the best stereocontrol (a meagre 19% *ee*) was observed *in the absence* of any metal. The screening of a small library of polymer-bound organic catalysts (48 members) led to the selection of an ensemble of amino acid, chiral diamine, salicylaldehyde substituents, and amino acid protecting group that improved the *ee* of the Strecker reaction up to 55%. Based on this result, a third, larger library of 132 polymer-supported members was prepared, the further screening of which led to the identification of the supported thiourea catalyst **33a** and of its non-supported counterpart **33b** as the best ones. At a loading as low as 1 mol%, **33b** promoted the hydrocyanation of *N*-allyl- or *N*-benzylimines derived from aromatic and aliphatic aldehydes and of some ketones in very high yield and almost complete stereoselectivity. It is interesting to note that the soluble and the resin-bound catalyst performed equally well. Recovery and recycling of the supported catalyst was demonstrated to occur without any erosion of chemical and stereochemical efficiency over 10 reaction cycles.

Given these excellent results, it is surprising that this approach has not been used more extensively for organic catalyst discovery. The success of this methodology is made more complete by the fact that catalysts **33** are among the few chiral organic catalyst to be currently employed at the industrial level.[11]

4.3 How?

Several matters must be dealt with in establishing the best conditions for immobilizing an organic catalyst on a support. The choice of the support itself is likely the most relevant. The decision about where on the catalyst the handle for the connection to the support should be located ranks second in importance, followed by that on what kind of linker, if any, must be

inserted between the catalyst active site and the support.

Given the huge numbers of examples of immobilized organic catalysts reported in the literature, the viable options are way too many to allow the proposal of a comprehensive set of rules. Rather, it is my strong belief that the best immobilization procedure must be selected for each individual case, taking into account not only the structure of the catalyst but also the reactions the catalyst will promote, the physical and chemical properties of the products, the possible presence of by-products, the mode of catalyst recovery and recycling, *et cetera*. Still, some general considerations can be put forward as they are suggested by common sense and literature results.

The choice of the support is crucial, because the properties of the support influence the catalyst behavior at every level. Relevant features of the support are: solubility profile, cost, commercial availability, degree of functionalization, and a possible involvement of the support backbone in the reaction.

The solubility properties are the most important, the decision to develop a homogeneous or a heterogeneous catalytic system being the first to be made. As mentioned before, even such a fundamental matter cannot be decided upon once and for all, and there is not and cannot be a general consensus about whether working with a soluble catalyst is better or worse than working with an insoluble one. In principle, one can expect a heterogeneous catalyst to be less reactive than a homogeneous one, but a number of results indicate that definitely this is not always the case. On the other hand, insoluble catalysts seem to be more easily recovered and thus more easily recycled than soluble ones. Again, it must be remembered that catalyst recovery is not a mandatory condition for recycling, as demonstrated by the development of continuous flow methods in which the soluble catalyst resides permanently into the reaction vessel. Moreover, a number of catalysts have solubility properties that can be varied by changing the environmental conditions, such as medium polarity and reaction temperature, thus coupling the advantages of homogeneous and heterogeneous systems.

The cost of the support, that should be evaluated not in terms of how much must be paid for a gram of support, but rather in terms of how much must be paid for the loading of functional groups present in a gram of support, can range over a difference of several orders of magnitude. It seems reasonable that there should be some sort of relation between the cost of the catalyst and that of the support, in the sense that the immobilization of an inexpensive catalyst on a very expensive polymer should be regarded as a chemical oxymoron. Also in this context, however, the goal of catalyst immobilization should guide the choice of the support. Thus, if the immobilization is required for simplifying the catalyst identification and optimization, for instance, by a combinatorial approach, the cost of the support is not a very relevant issue, given the relatively small amount of support actually employed. On the other hand, catalysts anchored to cheap supports have a better chance to be developed and employed on a practical scale.

The importance of the commercial availability of the support goes well beyond practical reasons and often deeply influences the process of supported catalyst design and development. It is quite obvious that an organic chemist with limited or no experience in polymer or material chemistry will be very reluctant to tackle the problems connected with support synthesis. On the contrary, most of his or her efforts will be devoted to the identification of a good catalytic system to be anchored on one of the many supports commercially available. Moreover, it is generally believed that the commercial availability of the support is an irrenunciable pre-requisite for the supported catalyst to have a chance to be adopted outside the laboratory of its inventor.Thus, the catalyst will be designed having in mind an available support, and, accordingly, the choice of the support has a strong impact on the design process. This attitude is extremely limiting, because on one hand polymer and material chemists will tend to attach only known catalysts to custom-made and carefully crafted supports; on the other hand, organic chemists will anchor sophisticated catalysts to possibly not ideal supports.

While an interdisciplinary effort is the obvious solution to these problems, an extensive examination of the procedures reported in the experimental sections of the papers selected for this review clearly showed that a number of extremely interesting, non-commercially available materials can readily be synthesized by very simple procedures (their structural analysis can still be a problem). Therefore, the choice of the support should really be seen as a further opportunity in developing an immobilized catalyst rather than a limitation to imaginative catalyst design.

The degree of functionalization is a very important factor in determining the choice of a support for catalyst immobilization. In principle, a high number of functional groups per gram should allow the introduction of a high number of catalyst sites and, accordingly, to decrease the weight amount of supported catalyst employed. The weight amount of immobilized catalyst necessary to promote a reaction is a problem with important practical consequences and must always be kept in mind. To illustrate this point, let us consider a catalyst supported on a monofunctionalized PEG_{5000} sample. If the catalyst must be used at the 10 mol% loading to promote the transformation of 1 mmol of a substrate whose M_W is 100 daltons, then about 0.5 g of supported catalyst must be used to process 0.1 g of substrate, a clearly unpractical scenar-

io. However, it must be remembered that it is not always true that a high density of catalytic sites directly translates into high activity. Examples exist in which a too crowded active site distribution resulted in catalyst inactivation.[4,52,99]

To conclude the discussion on the choice of the support, the possible involvement of the support itself in the chemical reaction promoted by the supported catalyst must be considered. First of all it is important to recognize the fact that the support largely outweighs the catalyst in molecular mass and thus its structure influences the environment around the active sites. For instance, polystyrene- and silica-based supports are likely to create local environments of different polarity that can accelerate or slow down the catalyzed reaction, for instance, by facilitating or preventing the diffusion of the reactants into the support and their interaction with the catalyst.

The support can also play a more decisive role, directly interacting with the reaction partners in competition or cooperation with the catalyst. To explain this point let us consider the PEG-supported phase-transfer catalysts **34** and **35** depicted in Figure 13.

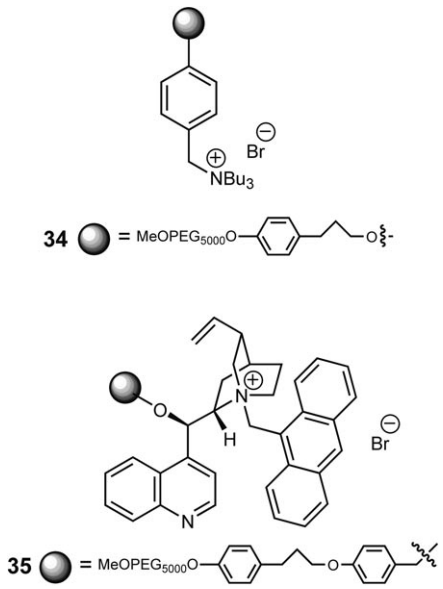

Figure 13. Structures of PEG-supported phase-transfer catalysts.

Catalyst **34** is an exceptionally active promoter for a variety of standard transformations occurring under phase-transfer catalysis conditions.[100] Its activity is superior to that of the structurally related non-supported catalyst tributylbenzylammonium bromide in the reactions involving the use of solid NaOH under solid-liquid conditions (for instance, *N*- and *O*-benzylation of pyrrole and phenol; dichlorocyclopropanation of styrene). It seems possible that the catalyst benefits from the involvement of the support, because the polyethylenoxy chain of PEG can complex the alkaline cation of the base helping the transfer of the HO^- counterion in the organic phase.[101]

Prompted by these results, the extension of the use of PEG as a support to a chiral phase-transfer catalyst was attempted.[83] Thus, the *Cinchona* alkaloid-derived ammonium salt employed by Corey and Lygo in the stereoselective alkylation of amino acid precursors was immobilized on a modifed PEG similar to that used in the case of **34**. The behavior of the obtained catalyst **35**, however, fell short of the expectations. Indeed, while this catalyst (10 mol%) showed good catalytic activity promoting the benzylation of the benzophenone imine derived from *tert*-butyl glycinate [Scheme 8, Eq. (29)] in 92% yield (solid CsOH, DCM,-78 to 23 °C, 22 h), the observed *ee* was only 30%. Even if this was increased to 64% by maintaining the reaction temperature at −78 °C and prolonging the reaction time to 60 h, the top level of stereoselectivity obtained with the non-supported catalyst could not be matched. PEG was considered to be responsible, at least in part, for these results because of the following effects. By increasing the polarity around the catalyst, PEG prevents the formation of a tight ion pair between the enolate and the chiral ammonium salt, the formation of which is regarded as crucial for high stereocontrol.[81] Moreover, PEG enhances the solubility of the inorganic cation in the organic phase leading to a competing non-stereoselective alkylation occurring on the achiral cesium enolate. To check the validity of this hypothesis, control experiments were carried out by performing the reaction with the non-supported catalyst in the presence of the bis-methyl ether of PEG_{2000}. The observed *ee* was 65%, a value that was in good agreement with that observed with catalyst **35** but largely inferior to the >90% *ee* easily achieved with the non-supported catalyst. While in retrospect one can say that the behavior of the chiral catalyst **35** could be at least in part anticipated on the basis of what was observed with achiral **34**, these results are another demonstration of how dangerous generalizations can be for the identification of a good catalyst/support pair.

As mentioned at the beginning of this section, the decision about where on the catalyst the handle for the connection to the support should be located is also quite relevant. On the basis of the idea that the support should exert the minimum effect on the catalyst, it seems obvious that the longer the distance between the catalyst and the support is, the higher are the chances for the supported catalyst to mimic the behavior of the non-supported one. This line of reasoning also suggests that bonds of relatively low conformational mobility should be preferred for the connection in order to avoid that the active part of the catalyst could fold back onto the support. The vast majority of supported catalysts, and especially chiral

ones, have been developed following this principles. However, a too strict observance of this approach can entail some drawbacks.

One can be that the immobilization requires very expensive starting materials. Another, that a relatively long sequence of synthetic modifications of the non-supported catalyst could be necessary to get a compound suitable for immobilization. Supported proline **30** (Figure 11) serves to illustrate this point.[88] The synthesis of the catalyst precursor selected for the immobilization, *cis*-4-amino-*N*-Cbz-proline, starts from very expensive *N*-Cbz-*trans*-hydroxyproline and requires five transformations. The considerations about the cost of the supported catalyst *vs.* that of the non-supported one made above suggest that catalyst **30** can hardly be considered of any practical use.

In addition, literature data suggest that the importance of the principle of maximum separation between the catalyst and the support is likely to be overestimated. Consider, for instance, the supported proline **28** (Figure 11).[86a] In this case the location selected for the connection between the catalyst and the polymer is in the immediate vicinity of the active site and involves the carboxy group of proline, that is believed to be deeply involved in the catalytic cycle. However, the amide group can effectively replace the carboxy residue in the catalytic cycle,[86b] and the supported catalyst maintains its catalytic activity. The fact that compound **28** is obtained in one step from proline itself, makes this supported proline probably the most convenient among those reported so far.

Another example in this line is provided by the chiral DMAP analogues **23a,c** reported in Figure 9 and employed in the kinetic resolution of secondary alcohols by enantioselective acylation [Scheme 7, Eq. (27)].[72] In this case the distance between the catalyst active site (the pyridine nitrogen) and the connection to the support is relatively short. This choice turned out to be functional to the success of the catalyst, since the amide proton is believed to play an active and decisive role in promoting the stereoselectivity of the reaction (by H-bonding the fast reacting alcohol) and the polymer backbone, residing in the proximity of the active site, can provide beneficial stereodiscriminating effects.

The problem of securing a suitable separation between the active site and the support to enhance catalyst accessibility can also be approached by the insertion of a linker or spacer. The use of this topological device, originally proposed by Montanari and coworkers as a tool to improve the reactivity of phase-transfer catalysts immobilized on cross-linked polystyrene,[4,26,102] has become a general feature of supported catalysts ever since. It is interesting to note that the insertion of a spacer can solve problems of catalyst reactivity not only related to accessibility.[103] For instance, a linker can help to create a microenvironment around the catalyst active site more suitable to the catalytic activity than that provided by the support. This was the case, for instance, of the polystyrene-supported ammonium and phosphonium salts mentioned above,[102] where the insertion of linear *n*-dodecyl linker chains between the catalyst and the support increased the lipophilicity of the catalyst, so enhancing its reactivity up to four times.

Remarkably, and quite surprisingly, the beneficial effects of a separation between catalyst and support have been shown also in the case of soluble supports. For instance, the catalytic activity of the PEG supported phase-transfer catalyst **34** (Figure 13) was shown to be more than twice that of the catalyst in which the benzylammonium group was directly connected to the PEG chain.[100] A similar effect has recently been observed also for the PEG-supported TEMPO **1** (Figure 3).[27]

In concluding the discussion on the use of the linker, some consideration on the chemical nature of the linker itself must be made. It is quite evident that the linker should contain atoms and bonds that are inert under the reaction conditions.[104] However, the commercial availability of suitable starting materials does not always allow the fulfillment of this rather obvious principle. To illustrate this point, consider the chiral supported ketones **20a,c** (Figure 8) employed as catalyst for the stereoselective epoxidation of alkenes [Scheme 6, Eq. (26)].[65] These were assembled using commercially available 3-trimethoxysilylpropanethiol to provide a convenient connection to the silica surface on one side and to the chiral ketone on the other. Under the reaction conditions selected for alkene epoxidation, however, it was discovered that the sulfur atom of the linker was oxidized to a mixture of sulfoxide and sulfone, a process that resulted in a decrerased oxidative ability of the catalyst. Preoxidation of the catalyst was necessary to solve this problem.

Finally, it must be mentioned that the accessibility of the catalyst's active sites can also be enhanced by bringing them as much as possible to the surface of the solid support without making recourse to a linker. This possibility was recently demonstrated in the case of some polystyrene-supported phase-transfer catalysts by changing the procedure for the synthesis of the backbone.[105] Indeed, the delayed addition of 4-chloromethylstyrene to the co-polymerization mixture containing styrene and divinylbenzene led to an increase of the surface-exposed chloromethyl groups that were eventually exploited for catalyst attachment. By doubling the number of the accessible catalyst sites, a doubled catalyst activity was observed. However, further attempts at increased accessibility did not result in further improvements in the catalytic activity.

5 Conclusions

It was the aim of this review to show advantages and drawbacks of the use of immobilized organic catalysts from both conceptual and practical standpoints. The survey of selected examples chosen among the recent acquisitions in the field, combined to a comparison of these with previously reviewed results,[4] allowed us to present some general considerations about when and why a supported version of an organic catalyst is worth developing. A list of suggestions about how the process of immobilization should be carried out was also presented, taking into account several factors such as the properties of the catalyst, the nature of the support, and the mode of connection of the catalyst to the support. From this discussion supported organic catalysis emerges as field of research still in its infancy and open to great expansion in the future provided that organic, polymer and material chemists will be able to combine their efforts in a multidsciplinary approach.[106]

Acknowledgements

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