Recoverable and recyclable chiral organic catalysts

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In the present perspective article a few selected, significant works reported in the field of supported chiral organic catalysts will be presented, with a special attention to the papers appeared that after 2002. A few considerations on the methodologies, the future and the problems related to the immobilization of chiral organic catalysts will also be briefly discussed.

1. Introduction

Stereoselective organic catalysis represents one of the more rapidly expanding fields of research in modern organic chemistry. A number of fundamental organic reactions that once required the use of metal-based enantiopure catalysts can now be performed, with equal levels of chemical and stereochemical efficiency, employing substoichiometric amounts of structurally simple organic molecules.[1]

To give an idea why the recent years were appropriately defined "the golden age of organocatalysis",[1] it is worth mentioning that in the years 2004 and 2005 the number of publications appearing in major journals dealing *exclusively* with stereoselective organic catalysis is close to 500.[2–4]

What does the term "organic catalyst" really mean? 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".[5] Even with its own limitations[6] the definition is broad enough to cover the great structural diversity of organic catalysts and accounts for the only two characteristics which everybody agrees upon: an organic catalyst is neither an enzyme nor a metal-based catalyst. In this context, the term "organic" is synonymous with "metal-free" with all the advantages of performing a reaction under metal-free conditions. These advantages might include, *inter alia*, the possibility of working in wet solvents and under an aerobic atmosphere, dealing with a stable and robust catalyst and avoiding the problem of a (possibly) expensive and toxic metal leaching into the organic product.

Maurizio Benaglia was born in Bergamo in 1966. After he completed his doctoral studies in 1994 on the stereoselective synthesis of β-lactams under the supervision of Prof. Mauro Cinquini, at the University of Milan, he joined the group of Prof. Jay. S. Siegel, at the University of California, San Diego, where he worked on the stereocontrolled synthesis of supramolecular structures. In 1997 he moved back to Milan, where he became assistant professor at Department of Organic and Industrial Chemistry, University of Milan.In 2001 he won the "Giacomo Ciamician" Medal of the Italian Chemical Society.He is the author of more than 80 publications on scientific international journals, including four review articles and a book chapter. His current research activity concerns the development of new asymmetric catalysts, the immobilization of organic and organometallic catalysts on solid supports and the study of supramolecular devices.

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2. Chiral organic catalysts

Chiral organic catalysts may be seen as a simplified version of enzymes, from which they are conceptually derived and to which are often compared.[7] Even if they rarely display the remarkable selectivity peculiar to enzymes, generally organic catalysts are more stable than bio-catalysts and show a larger field of application under a variety of conditions unsustainable by enzymes. Furthermore organic catalysts may be readily immobilized on a support with the aim of facilitating catalyst recovery and recycling;[8] it is reasonable to suppose that a simple organic compound will be less affected by the connection to a support than a more structurally complex (and somehow more "delicate") enzyme. In addition, simply considering the molecular size of the two systems, it is quite obvious that 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.

Organic catalysts are also more readily amenable than metal-based catalysts to anchoring on a support with the aim of facilitating the separation of the product from the catalyst and the recovery and recycling of the latter.[9–11] Indeed, it has repeatedly been shown that the use of a metal-based catalyst immobilized on a support is often problematic because of possible extensive metal leaching and requires catalyst regeneration by metal replenishment before recycling.

But why one should develop a solid supported version of a chiral organic catalyst? As we have pointed out in a recent survey covering the subject up to the end of the year 2002,[5] the development of immobilized versions of an organic catalyst shortly followed the discovery of the catalyst itself. In many instances, as already pointed out, the main goal of the

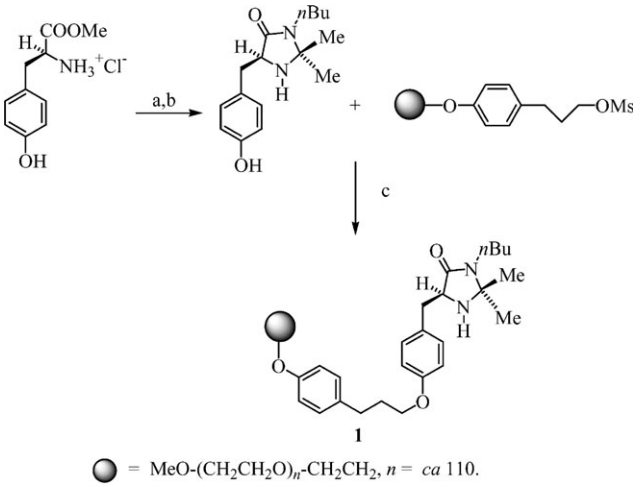


Fig. 1 *Reagents and conditions*: a: $nBuNH_2$, EtOH, 30 °C, 48 h; b: Me_2CO, MeOH, cat. PTSA, 60 °C, 20 h; c: Cs_2CO_3 , DMF, 60 °C, 24 h.

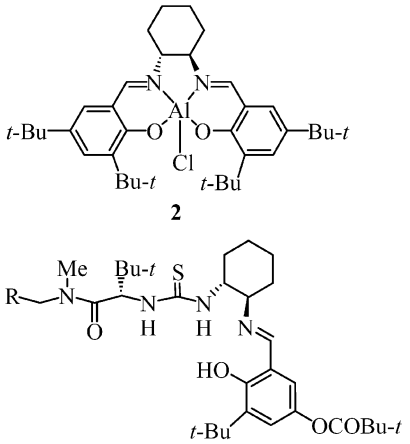


Fig. 2

immobilization was the simplification of the reaction work-up, the recovery and hopefully the recycling of the precious chiral catalyst. But besides the recovery and the recycling of the catalyst, other problems may be tackled by supporting a catalytic species.

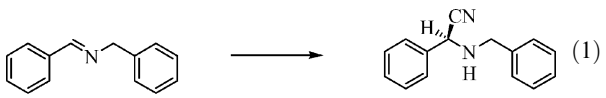
Catalyst instability can be another reason for immobilization. Organic catalysts do exist that slowly decompose under the conditions necessary for their reaction and release trace amounts of by-products that must be separated from the products. For instance in oxidations promoted by TEMPO[12] or photooxygenation reactions catalysed by porphyrin[13] the release of highly colored materials derived from the catalysts made the product purification a real problem. Immobilization of the catalyst can solve this problem because the decomposed material is also 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 relatively large amounts. It is worth mentioning however that 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. This is the case, for example, for the PEG-immobilized imidazolidinone **1** (Fig. 1); it was obtained from tyrosine[14] (€42 for 100 g) a starting material more convenient than phenylalanine (€83 for 100 g) used for the synthesis of the non-supported catalyst.[15]

The preparation of supported catalysts for use in environmentally friendly or green solvents, as part of the drive towards developing more Green Chemistry, is also becoming more widespread.

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 and this deserves a special mention.[16]

The Jacobsen's salen–aluminium complex **2** reported in Fig. 2 is a relatively inexpensive and efficient catalyst, capable of promoting the hydrocyanation of the *N*-allyl imines of aromatic aldehydes in excellent yield (up to 91%) and ee (up to 95%) at a low catalyst loading (5 mol%) and low temperature.[16] 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.[16] The optimization of the catalyst structure was realized through a series of modifications of the salen ligand carried out on an insoluble polystyrene support and using the principles of combinatorial chemistry for finding out the best amino acid, diamine, and diamine–amino acid linker combination. The screening of three successive libraries led to the identification of the supported thiourea catalyst **3a** as the best one form which the non-supported counterpart **3b** was derived. At a loading as low as 1 mol%, **3b** promoted the hydrocyanation of *N*-allyl or -benzyl imines derived from aromatic and aliphatic aldehydes and of some ketones in very high yield and almost complete stereoselectivity (eqn (1)). It is interesting to note that the soluble and the resin bound catalysts 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.



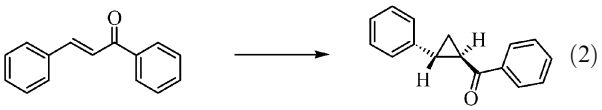
Given these excellent results, it is surprising that this approach has not been used more extensively for chiral organic catalyst discovery. The success of this methodology is even more significant if one considers that catalysts **3** are among the few chiral organic catalysts to be currently employed at the industrial level.[4]

So far, in the field of organocatalysis the research efforts have mainly focused on catalyst discovery; therefore the development of immobilized chiral catalysts has less intensively been pursued. Indeed, since the publication of our previous review covering the immobilization of *achiral and*

chiral organic catalysts up to 2002,[5] only a limited number of new examples of supported chiral organocatalysts or of new applications of already reported catalysts have been described. The present perspective article will specially discuss those recent papers that appeared after 2003; a few considerations on the methodologies, the future and the problems related to chiral organic catalyst immobilization will be also briefly presented.[17]

2.A Enantioselective C–O bond forming catalysts

One of the areas of most intense research activity over the past year has been the development of supported catalysts for asymmetric epoxidation. A well known method for the stereoselective epoxidation of α,β-unsaturated ketones, discovered and developed in the nineteen eighties by Julia and Colonna involves the use of catalytic amount of polymeric amino acids, able to catalyze the Weitz–Scheffer epoxidation of chalcone using basic hydrogen peroxide, with high enantioselectivity (eqn (2)). The original protocol describes a triphasic system, but advances in the field have been made through the introduction of biphasic protocols leading to an expansion in the range of enones as suitable substrates. Immobilization of the poly(amino acid) on silica had been already described by Roberts and provided the optimum heterogeneous catalyst in terms of efficiency, stability and ease of recycling.[18]

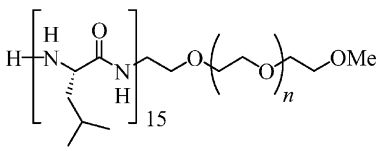

(2)

In 2001 the same author reported a study on the effect of the primary structure of the polypeptide catalyst and the preparation, conformational analysis and synthetic use of the first soluble version of the Julia–Colonna catalyst.[19] A polyethylene glycol (PEG)-bound poly-L-leucine promoted the conversion of chalcone in epoxychalcone up to 97% ee (Fig. 3). The system is efficient even if short chain length polyleucine is employed; by FT-IR investigation it has been shown that the catalytically active polyleucine components of these polymers have an α-helical structure. A series of L-Leu 1–20 oligomer peptides were attached to TentaGel S NH_2 and it was found that five to six L-Leu residues were sufficient to catalyze the epoxidation of chalcone with 96–98% ee.[20]

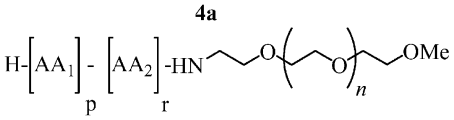
Recent studies about PEG-supported poly(amino acid)s led to the development of a chalcone epoxidation process (occurring in 99% yield and 94% ee) carried out at the industrial level in a continuously operated reactor where catalyst recycling was made possible by a nanofiltration membrane.[21]

In subsequent work, Kelly and Roberts prepared a new soluble catalyst **4a** by attaching a polyleucine chain to $MeOPEG_{5000}NH_2$ (Fig. 3).[22] 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 structure–activity relationship study was then carried out by synthesizing the PEG conjugates **4b–e**, featuring poly(amino 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 measurement on **4b** showed that also the α-helical structure was also largely lost in this catalyst. The Ala_8-Leu_8 catalyst **4c**, which retained a high degree of α-helicity in its structure (63%), maintained excellent enantioselectivity (97% ee) but was less active than **4a** (58% conversion). Both yields and ee further decreased on passing to catalysts **4d** and **4e**, as their α-helical structure content decreased. Thus, the existence of a direct relationship between α-helical structure content 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.



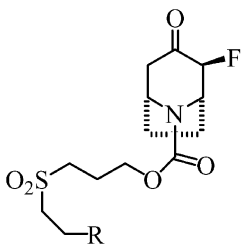
4a



$n = ca\ 110.$

	AA_1	p	AA_2	r
4b	(L)-Ala	15	none	
4c	(L)-Ala	8	(L)-Leu	8
4d	AIB	8	(L)-Leu	8
4e	(L)-Leu	8	(L)-Ala	8

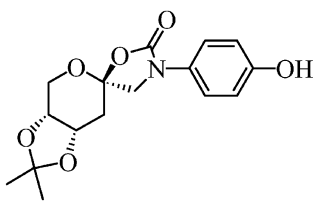
Fig. 3



5a R = KG-60

5b R = MCM-41

5c R = PS

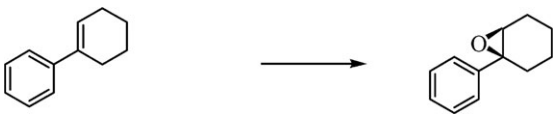


6

Fig. 4

Dioxiranes derived from chiral ketones have extensively been used to promote the enantioselective epoxidation of alkenes.[23] The first examples of immobilized chiral ketones to be employed in this reaction were reported by Sartori, Armstrong, and coworkers.[24] 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 **5a–c** reported in Fig. 4.

By studying the epoxidation of 1-phenylcyclohexene as the model reaction (40 mol% of catalyst, Oxone as the terminal oxidant, acetonitrile, aqueous $NaHCO_3$, room temperature, 1 h), it was discovered that the siliceous materials, having different porosity and loading (200 and 670 $m^2\ g^{-1}$, and 0.58 and 0.78 mmol g^{-1}, for **5a** and **5b**, respectively), performed much better than the polystyrene-supported ketone (eqn (3)).



(3)

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's 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,[25] several experiments were carried out with the aim of anchoring precatalyst **6** (Fig. 4) on $MeOPEG_{5000}$ by using the phenol oxygen as connecting element. This support was considered particularly convenient considering that the epoxidation reaction is carried out in a solvent mixture perfectly suitable for the use of PEG. However, ketone **6** 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.[26]

2.B Lewis base catalysts

The use of a variety of chiral DMAP analogs as organic catalysts is very well known,[3] but 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.[27] The ready availability of these compounds suggested the employment of the easily functionalizable carboxy function to immobilize these catalysts on different polymer supports.[28]

Among others, derivatives **7a–c** collected in Fig. 5 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

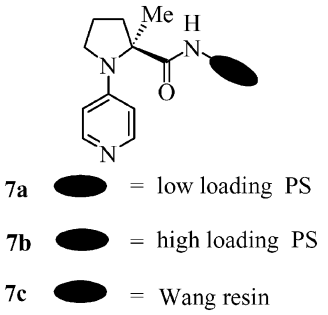
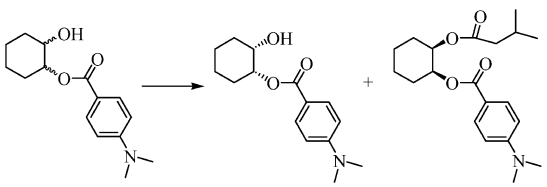


Fig. 5

were tested as insoluble catalysts (5 mol%) in the kinetic resolution of *cis*-1,2-cyclohexanediol mono-4-dimethylaminobenzoate carried out with a deficiency of isobutyric anhydride in DCM (room temperature, 16 h) (eqn (4)). 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 proceed up to 67% conversion. No appreciable difference in chemical or stereochemical efficiency was observed as a function of the polymeric support.

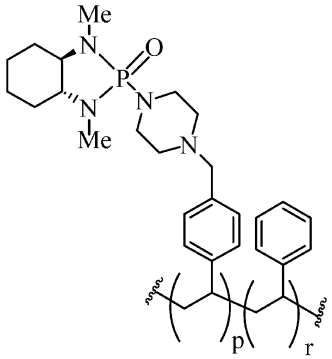


(4)

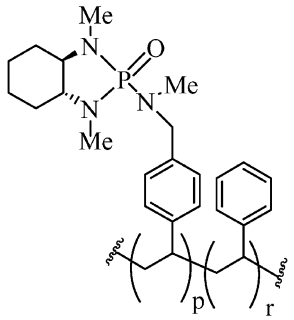
Catalyst **7b**, recovered by filtration and thoroughly washed with DCM, was employed in three additional runs to afford the resolved product in slightly higher ee at identical conversions. However, the activity of the recycled catalyst was somewhat lower than that of the fresh one, since longer reaction times were necessary to obtain the same conversions. Extension of the use of catalyst **7b** to the kinetic resolution of other secondary alcohols was possible, although the immobilized catalyst performed consistently less efficiently than its best non-supported analog.[27,29]

Chiral phosphoramides were developed as organic catalysts first by Denmark;[30] however, notwithstanding the fact that these catalysts can promote very important processes as the allylation of aldehydes with allyl trichlorosilane[31a] or the aldol condensation of trichlorosilyl enol ethers with aldehydes,[31b,c] the first example of immobilization of chiral phosphoramides on a polymeric matrix was reported only in 2005.[32]

Derivatives **8a–c** and **9a–c** (Fig. 6) of different active site contents, were obtained either by homopolymerization of styrene monomers containing two different phosphoramide residues (**8a** and **9a**) or by copolymerization of these monomers with unfunctionalized styrene (**8b,c** and **9b,c** see Fig. 6 for monomer contents). These compounds were used as catalysts (10 mol%) to promote the allylation of benzaldehyde with allyl trichlorosilane in the presence of excess diisopropylethylamine (DCM, −78 °C, 6 h) (eqn (5)). It was found that catalysts **9a–c** performed equally well (82–84% yield, 62–63% ee) and better than **8a–c** (43–62% yield, 49–51% ee).

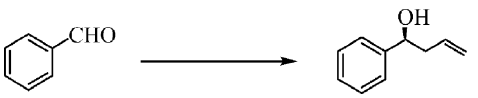


	p	r
8a	100	0
8b	75	25
8c	47	53



	p	r
9a	100	0
9b	71	29
9c	37	63

Fig. 6



(5)

Remarkably, the whole set of the supported catalysts **8/9** 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,[31a] the better results obtained with **8/9** 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 close proximity that they can behave as bis-phosphoramides.[33] Neither the recycling of **8** and **9** nor the extension of their use to the allylation of aldehydes different from benzaldehyde has been described.

Cinchona alkaloids represent another class of compounds widely employed as chiral organocatalysts.[34] 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.[5]

In this field Lectka and co-workers obtained spectacular results in a highly stereoselective synthesis of β-lactam.[35] It was realized a process which involves the use of solid-phase reagents and catalysts that constitute the packing of a "series of reaction columns". In Fig. 7 the chemical steps in the catalytic asymmetric synthesis of β-lactams are illustrated,

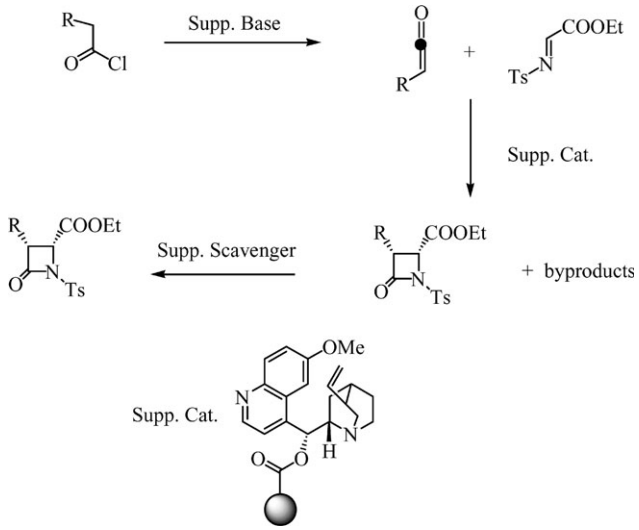


Fig. 7

including a ketene generation step (SP base), the β-lactam formation (SP catalyst) and a purification step (SP scavenger). The catalyst involved is also shown in the Figure; a quinine derivative, **10**, anchored to Wang resin through an appropriate spacer, is able to afford the products with very high stereoselectivity (>90% ee). Notably, the conduction of chemical reactions on sequential columns allowed easy recovery of catalyst and reagents, and simplified purification steps that avoid the need for chromatography.

It is important to note that, under continuous flow conditions, product separation from the catalyst, catalyst recovery, and catalyst recycling are obtained in a single operation. The convenience of this approach is demonstrated by the fact that for this system one of the highest recycling numbers for a chiral organic catalyst (60 cycles) has been obtained.[35]

A few years ago Cahard had presented the contributions of his group on the use of immobilized *Cinchona* alkaloid derivatives in asymmetric phase transfer catalyzed (PTC) reactions, focusing on Michael addition onto enones, construction of quaternary fluorinated carbon centers and alkylation of the benzophenone imine of glycine *tert*-butyl ester (Fig. 8).[36]

Two types of polymer supported ammonium salts of *Cinchona* alkaloids were prepared and their activity evaluated, the polymer being polystyrene; the enantioselectivity was found to be strongly dependent on the alkaloid immobilized; usually the type II catalysts gave better results than the type I catalysts, but no recovery or cycling was attempted.

In a more recent work, the same author described the synthesis of two catalysts where cinchonidine (**11a**) and cinchonine (**11b**) were connected through their bridgehead nitrogen atom to $MeOPEG_{5000}$ by an ester linker (Fig. 8).[37] These catalysts (10 mol%) were tested in the standard O'Donnell–Corey–Lygo alkylation of *tert*-butyl glycinate benzophenone imine (benzyl bromide, toluene, 50% aqueous KOH, 0 °C, 15 h) to afford the (*S*)-product in 81% ee and the (*R*)-product in 53% ee using **11a** and **11b**, respectively (eqn (6)). The chemical yield was about 80% in both cases; the use of other alkylating agents resulted in much lower ee (20% with *n*-hexyl iodide; 34% with benzhydryl bromide).

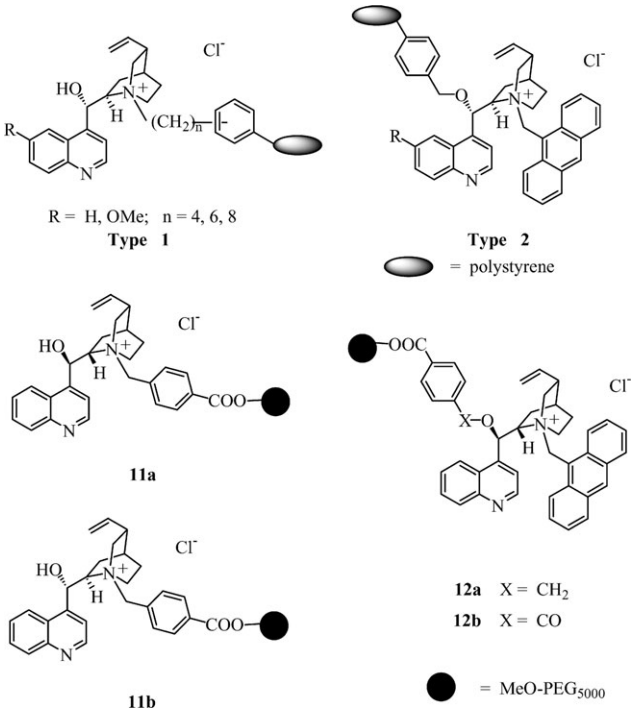
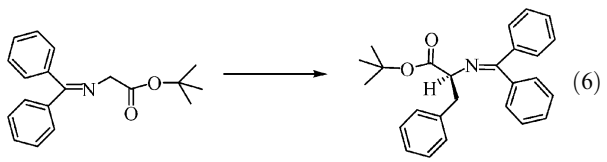


Fig. 8



The relatively large difference in the observed ee is quire surprising, since the quasi-enantiomeric structure of the alkaloid catalysts should secure virtually identical ee for both enantiomers; it must be noted that the phenomenon was observed already in previous works of the same group.[5,38]

Equally surprising and without reasonable explanation was the strong variation of the stereoselectivity of the alkylation observed on changing the reaction solvent: toluene (81% ee), benzene (64% ee), xylene (58% ee), carbon tetrachloride (65% ee), DCM 3% ee!). 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 **11a** led to 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 **12a,b** were prepared (Fig. 8).[37] In this approach the very bulky 9-anthracenylmethyl residue at the bridgehead nitrogen, considered necessary to obtain very high levels of enantioselectivity, was kept in the alkaloid that was connected to the polymer through its hydroxy group.[39] Thus, the commercially available quaternary ammonium salts derived from cinchonidine and cinchonine were anchored to $MeOPEG_{5000}$ using different linkages. Under the best reaction conditions (10 mol% of catalyst, toluene, solid CsOH, −60 °C, 72 h), the cinchonidine catalyst **12a** afforded the benzylated glycine derivative in 67% yield and 71% ee, a result that did not improve on those obtained with **11a**. It must be remembered that in a previous study it was found both supported and nonsupported phase-transfer catalysts were quite unstable, thus preventing any possibility of recycling.[39]

2.C Catalysts derived from amino acids

Enantioselective catalysis promoted by enantiomerically pure amines (aminocatalysis) is receiving considerable interest due to the ubiquitous presence and ready availability of these compounds in the chiral pool. In this context amino acids have always played a key role.[1,4]

While the relatively low cost of many amino acids apparently does not seem to justify the preparation of supported catalysts derived from amino acids, other reasons, as mentioned above, may drive the immobilization of chiral catalysts, like experimentation with different solubility properties, easy separation of the products from the catalysts and catalyst recyclability. It should be mentioned at this point that in principle amine-based catalysts offer also the possibility of recovery by exploiting their solubility profiles in acids.

The immobilization of these compounds on a support can also be seen as an attempt to develop a minimalistic version of an enzyme, with the amino acid playing the role of the enzyme active site and the polymer that of an oversimplified peptide backbone not directly involved in the catalytic activity.[40]

One of the most successful and versatile chiral organic catalysts, proline, was immobilized very soon after the first seminal works of List and Barbas, both on soluble[40] (Fig. 9, catalyst **13**) and insoluble[41] supports. Their behavior has already been discussed.[5] More recently the modified proline **14** immobilized on the mesoporous siliceous material MCM-41 (Fig. 9)[42] has been prepared, with an active site loading of 0.52 mmol g^{-1}. Large amounts of this catalyst (47–52 mol%) were then employed to promote the condensation between hydroxyacetone and isobutyraldehyde (room temperature, 24 h) and benzaldehyde (90 °C, 24 h) in DMSO or toluene to afford the products in yields that were only marginally higher than the amount of catalyst used (55–60%) (eqn (7)). The reaction times were significantly shortened to 10–30 min by the use of microwave irradiation. Two recyclings of the catalyst

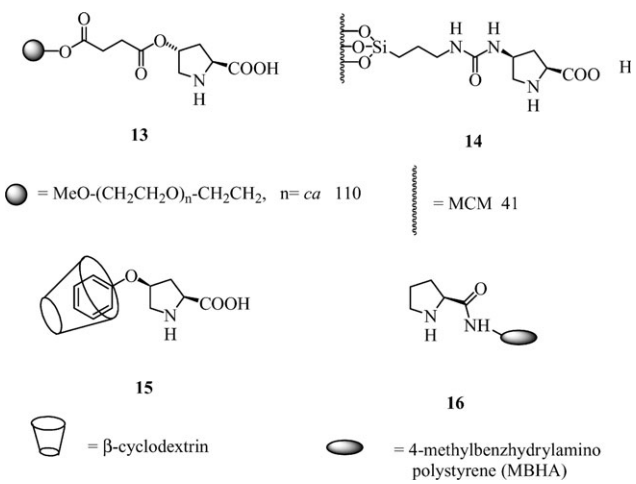
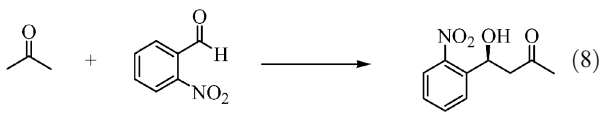


Fig. 9

recovered by filtration were shown to occur in slowly decreasing yield and unchanged stereoselectivity.

(7)

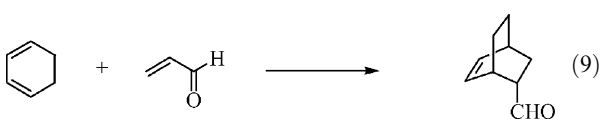
Later, an interesting non-covalent immobilization technique was exploited by Zhang and co-workers in the synthesis of catalyst **15** (Fig. 9). In this case the apolar phenyl ring of 4-phenoxyproline served as the handle for including the amino acid in the β-cyclodextrin cavity. Interestingly, the amount of catalyst actually included was found to be directly dependent on the temperature of the inclusion reaction, with higher temperatures leading to higher extent of inclusion. Thus, catalyst samples with different loadings could be obtained.[43] In the aldol addition of acetone to 2-nitrobenzaldehyde it was shown that in the presence of the highest loaded catalyst (10% mol/cat) the product could be obtained in 90% yield and 83% ee after 16 h at room temperature (eqn (8)). The catalyst was recovered by filtration and employed for three subsequent runs occurring in slowly decreasing yields (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.[40]



(8)

It must be noted that also the synthesis of supported prolinamides like **16** (Fig. 9), obtained by condensation of proline with 4-methylbenzhydrylamino polystyrene (MBHA), was reported.[44] This catalyst (20 mol%) was employed in the aldol condensation of acetone with linear and branched aliphatic aldehydes to afford the aldol products in moderate yields (40–75%) and satisfactory ee's only in the case of sterically hindered aldehydes such as pivalaldehyde (86% ee). In a second run with a sample of recovered catalyst slightly lower yields and ee's were observed.

Another chiral organic catalyst of major success is MacMillan's catalyst, **17**,[45] which has found widespread use in a number of relevant processes.[1,4] Immobilized versions of these catalysts for the enantioselective Diels–Alder cycloaddition of dienes with unsaturated aldehydes were developed on soluble (PEG-supported catalyst **1**, Fig. 10)[14] and insoluble[46] supports (catalysts **18** and **19**, Fig. 10). A comparison among these catalysts showed that the *Janda*Jel-supported catalyst **18**[46] performed better not only than its PEG[14] and silica-supported[46] analogs (which behaved almost identically to each other), but, quite surprisingly, also than the non-supported compound (eqn (9)).



(9)

The PEG-supported imidazolidinone **1** (Fig. 11) was later employed in 1,3-dipolar cycloadditions.[47] By reacting *N*-benzyl-*C*-phenylnitrone with acrolein, 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 **1** allowed reproducible results to be obtained. 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 *trans* one having 87% ee.

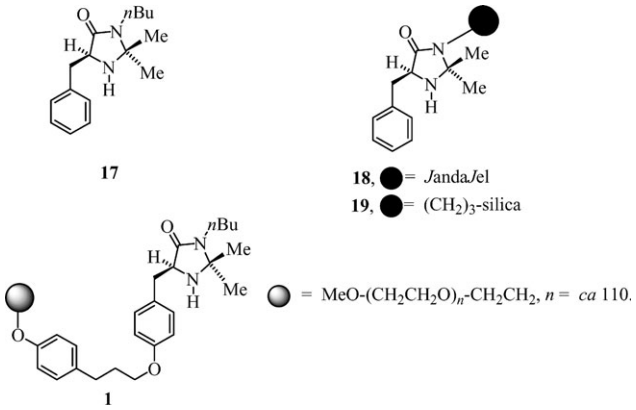


Fig. 10

A comparison of the results obtained with catalyst **1** with those obtained by MacMillan[48] 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%.

The PEG-supported catalyst was recycled twice to afford the product with constant level of diastereo- and enantioselectivity but in chemical yields diminishing from 71 to 38%. In order to explain this behavior several experiments were carried out. First, after each recovery the supported catalyst was examined by ^1H NMR and showed degradation, increasing after each cycle, probably due to an imidazolidinone ring opening process. 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

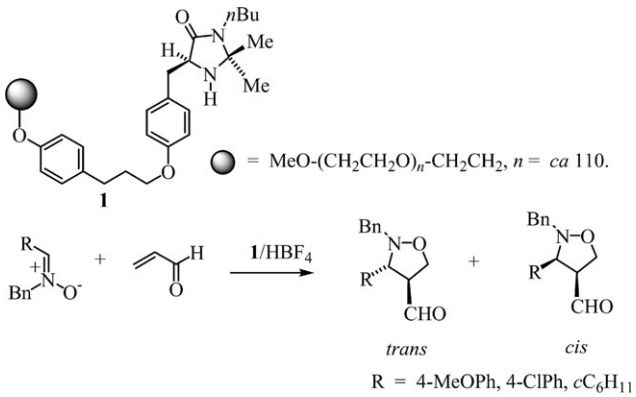


Fig. 11

bismethyl ether of PEG_{2000} and 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 reagents, and indeed further NMR analysis showed extensive catalyst degradation in the presence of acrolein, less degradation with crotonaldehyde, and essentially no degradation with cinnamaldehyde (the nitrone did not exert any effect on the catalyst stability). In agreement with the results of these experiments, we observed that also the non-supported catalyst showed a marked instability and decrease in chemical efficiency when recycled.[47]

3. Outlook and perspectives

On the basis of our experience in the field of supported organic catalysts a few general considerations may be attempted.

A judicious choice of the catalyst to be immobilized is the first point to think about. Possible candidates to be supported must be catalysts of great versatility and of wide tolerance of structurally different substrates, possibly with a high catalytic efficiency and with a well tested stability. Very seldom the stability of a new organic catalyst under the reaction conditions of its standard applications is studied; therefore it is a good policy to make preliminary investigation on the real stability of the catalyst before its immobilization (see above the discussion about the recycling of PEG–imidazolidinone **1**).

Another point of obvious interest is the choice of the support, which is crucial, since several features of the support may influence the catalyst behavior at every level. The solubility properties are the most important, the decision to develop a homogeneous or a heterogeneous catalytic system being the first to be made in designing immobilization. It is not possible to say whether is better to work with a soluble or insoluble catalyst, each one having positive and negative characteristics. While the homogenous catalytic system is expected to be more reactive, stereochemically more efficient (because it operates in solution exactly like the nonsupported system) and more reliable in reproducibility than a heterogeneously supported catalyst, the latter one is normally believed to be more stable, easier to handle and more simply recovered and recycled. An ideal support does not exist, but probably the best immobilization technique must be selected for each specific catalytic system to be supported. In this sense, significant progress could derive from the development of a interdisciplinary expertise with the contributions of organic, polymer and material chemists. This could allow also the solution of some problems related to the cost and the commercial availability of the support, which is another issue of great importance in determining (and somehow limiting) the choice of the support.

In the context of catalyst separation and recycling, it must be noted that a system where a catalyst must not be removed from the reaction vessel is very attractive. An example comes from continuous flow methods,[49] when the immobilized catalyst permanently resides in the reactor where it transforms the entering starting materials into the exiting products. The retention of the catalyst inside the reaction vessel can be achieved by different techniques ranging from ultrafiltration through a M_w-selective membrane to immobilization on a silica gel column.[50]

Another point of discussion is the presence of a linker. If it is true 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, the higher are the chances for the supported catalyst to mimic the behavior of its non-supported analog. Following this idea an appropriate spacer[51] was often introduced to separate the catalytically active site from the support;[52] the methodology has been applied also to soluble supports,[53] even if it is worth mentioning that it has been demonstrated how the principle of maximum separation between the catalyst and the support is likely to be overestimated (see for example the proline derivative of ref. 44).

In conclusion, it is clear now that asymmetric organocatalysis has achieved the same relevance to stereoselective synthesis as organometallic catalysis, and it can be safely anticipated that novel *fully organic* methods will soon be developed to perform a even wider variety of reactions. In this context, the development of immobilized chiral organic catalysts will play an important role, in contributing to further expand the applicability of organic catalysts and even in helping to discover new chiral organic catalytic species. The immobilization of chiral organic catalysts represents a relatively new field of research, in great expansion and open to the interdisciplinary contributions of organic and material chemists.

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