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ADVANTAGES IN SUPPORTING CHIRAL ORGANOCATALYSTS

An overview on the advances in supporting organocatalysts for their use and recycle in the asymmetric synthesis is presented, focusing on the main approaches for the immobilization and highlighting those examples in which supported and unsupported version of the catalyst behave similarly and high level of recyclability have been obtained.

Enantiomerically pure substances, important both in the fields of pharmaceuticals, agrochemicals and fine chemicals as well as key-intermediates in the organic synthesis, until recently have been obtained mainly by employing two classes of catalysts: transition metal complexes and enzymes. In the last decade, a third class is pushing up and growing in importance: organic catalysts, also called organocatalysts. These are small organic molecules which do not contain a metal element as catalytic centre in their structure and they are able, in substoichiometric amounts, to promote an acceleration in chemical reactions [1-2], see Fig. 1 for some example of organocatalysts. In addition, organocatalysts are generally robust and low-cost compounds, non-toxic with high resistance to air and moisture. All these advantages are in striking contrast with enzymes, which are very expensive, rather unstable and condition dependent, or with metal complexes which are often moisture and oxygen sensitive and requires demanding reaction conditions such as absolute solvents, low temperature, inert atmosphere etc. All the above points prompted the birth and exponential growth of a

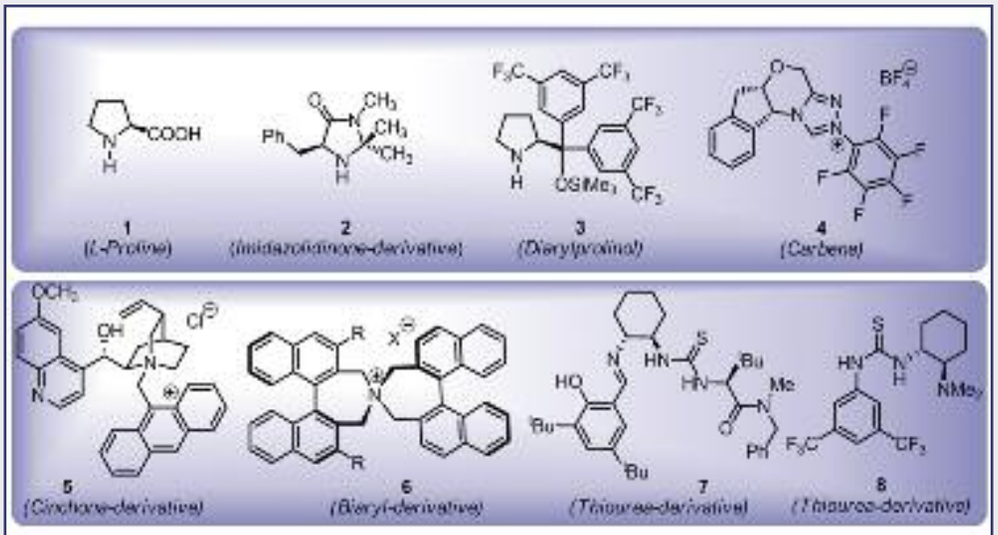

Fig. 1 - Chemical structures of some of the most representative and widely used organocatalysts

new branch of chemistry: *organocatalysis*.

Although during the end of the 19th and early and medium 20th centuries some organically catalyzed reaction have been described, it was only until 2000 when organocatalysis has been applied to enantioselective synthesis. In that year, List re-discovered the proline-catalyzed aldol reaction [3], and some months later MacMillan reported an enantioselective Diels-Alder reaction catalyzed by imidazolidinone derivatives and coined the term organocatalysis for first time [4]. Since then, several organometallic catalyzed organic reactions can now be carried out, with the same levels of chemical and stereochemical outcome, employing organocatalysts and the "gold rush" officially started [5].

Generally speaking, organocatalysts develop two main tasks: in one hand, they are responsible for the activation of the electrophile or nucleophile of the reaction (or both of them in the case of bifunctional catalysts) and, in the other hand, they are liable for the induction of the enantioselectivity of the reaction. The organocatalyst behaves as a shield by blocking preferentially one of the two prochiral faces of the substrate (which usually has a prochiral Csp^2 centre, at least in the transition state), making possible that the reaction with the corresponding electrophile or nucleofile takes place from the unshielded side (see Fig. 2). The substrate may be activated by the organocatalyst both by covalent linking or by non-covalent interactions. In the former case we may find two big classes of catalysts: secondary amines (**1-3**), and carbenes (**4**). On the other hand, activation of substrates by mean of non-covalent bonds may take place through ionic interactions, as in the case of Cinchona-based phase transfer catalysts (**5**) or binaphthyl-derivatives (**6**), or by mean of hydrogen bonds, in this case employing bifunctional thiourea-derivatives (**7-8**).

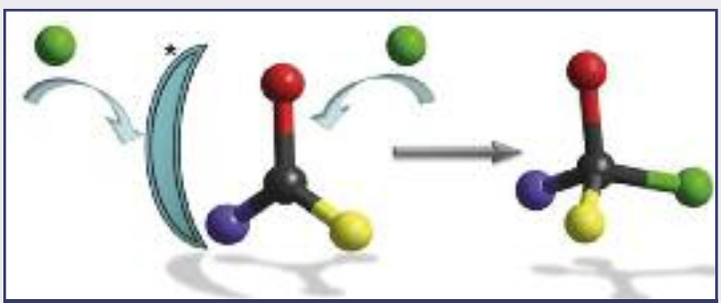

Fig. 2 - Schematic and simplistic representation of an organocatalytic reaction

Immobilization of organic catalysts

Shortly after the first studies in the field, due to the tremendous interest in asymmetric organocatalysis, some supported version of organocatalyst appeared in the literature [6-9]. The main reasons that prompted chemists to immobilize organic catalysts lied in the search for some cheap and recoverable material, able to be reused for several cycles. In addition, immobilization results to be convenient especially when sophisticated and synthetically time-consuming catalysts in up to 20-30 mol% are used. Moreover, since the catalyst recovery is usually carried out by mean of simple methods like solvent extraction or, more likely, by simple filtration, the immobilization results in a simpler work-up of the reactions with beneficial effects under the process sustainability point of view. Nevertheless, although, academically speaking, all the existing organocatalysts may be "heterogenized", it is obvious that just in the case of highly versatile and efficient catalysts, able to promote several organic processes with high levels of activity and

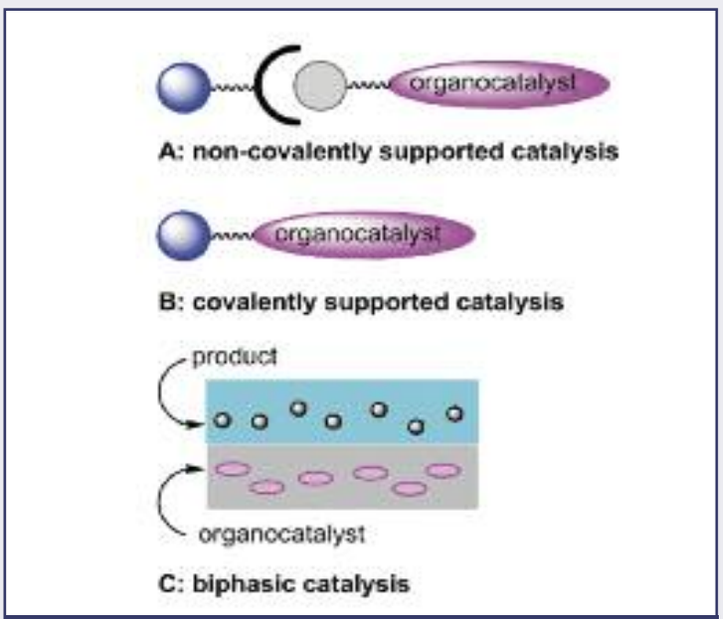

Fig. 3 - Different approaches for organocatalyst immobilization

stereoselectivity, should be taken into account for immobilization. When a material fulfill the above requirements, probably it become suitable for industrial purposes since it could be able to simplify several synthetic processes, especially for fine chemical and pharmaceuticals. As a matter of fact, immobilization may be of interest since the additional morphological properties of heterogeneous supports, such as polystyrene or silica, or the choice of the linker between support and catalyst may have a great influence on the outcome of the reactions, also due to electronic or steric effects as well as to the changes of polarity into the reaction environment.

As a consequence, these materials can be modulated in such a way that high stereoselectivities can be achieved.

The immobilization of the organocatalysts that need to be used under heterogeneous conditions can be achieved through different and generally applicable approaches (Fig. 3):

A) *Non-covalently supported catalysts*. The organic catalyst is adsorbed (*e.g.* onto ionic liquids-modified SiO_2), dissolved (*e.g.* polyelectrolytes), included (*e.g.* β-CD, zeolites, clays) or linked by electrostatic interactions (*e.g.* PS-SO_3H, Layered Double Hydroxides) in the support.

B) *Covalently supported catalysts*. The organocatalyst is covalently linked to a soluble (*e.g.* PEG, dendrimer) or insoluble (*e.g.* MCM-41, polystyrene, magnetite) support.

C) *Biphasic catalysts*. The organocatalyst is dissolved and remains into ionic liquids (ILs) and, after the reaction, the product is separated by distillation, extraction or any other physical mean. Ionic liquid-anchored organocatalysts can be considered as an advanced development of this approach since this simplify the workup and avoid extraction and phase separation.

In the following sections these three points will be discussed in a more detailed way, focusing our interest only in asymmetric processes, pointing out on the most important and recent literature, especially highlighting highly recyclable materials which displayed analogue or even better performances than their unsupported counterparts.

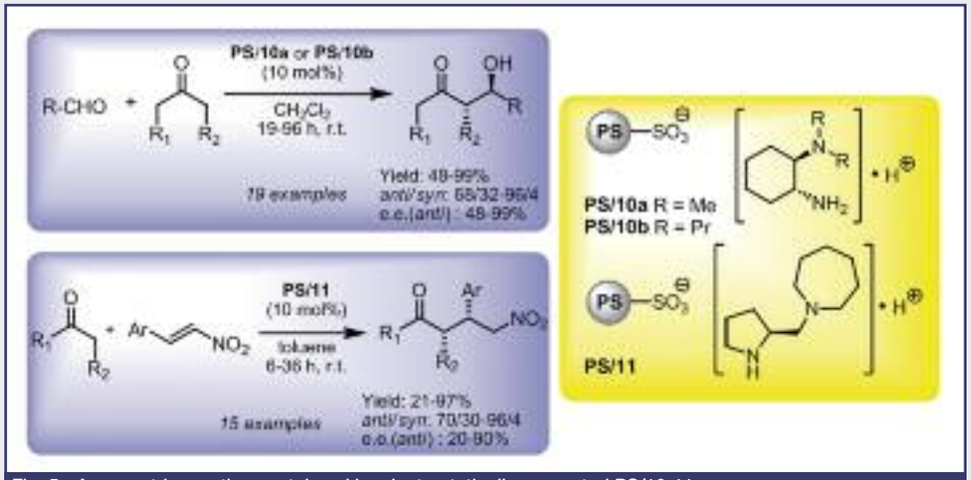

Fig. 5 - Asymmetric reactions catalyzed by electrostatically supported PS/10-11

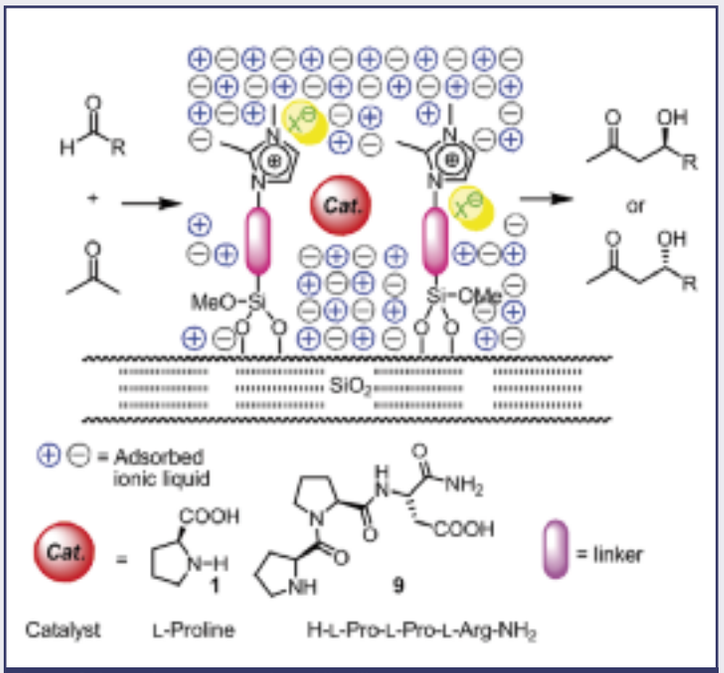

Fig. 4 - Schematic representation of IL-silica supported organocatalysts in the aldol reaction

Non-covalently supported catalysts

As stated before, soon after the birth of organocatalysis, the high catalyst loading required for the successful outcome of the reactions drove chemists toward the search of catalyst recovery and recycling. In this light, Barbas as soon as 2001 tempted to immobilize proline in a silica gel column leaving reactants for aldol reaction incubated during two days [10]. However, even if some result has been obtained, the lower activity and optical yield make them to give up to follow on with this approach. It should be noticed that, although proline is not expensive and its recovery does not represent an important issue, there are other reasons that justify its immobilization, covalently or not. In fact, the immobilization process may lead to an enhancement in the stereochemical efficiency of a given reaction due to the changed environment close to the catalyst. Moreover, new solubility profiles may be studied as well as the influence of the support on catalyst behavior.

Some years later, Gruttadauria succeded in supporting non-covalently proline on silica by modifying the above approach [11-12]. Here, proline, was immobilized by adsorption on the surface of silica gel modified with a monolayer of covalently attached ionic liquid (IL) (Fig. 4). To this system, an additional IL layer was also added by adsorption in order that both layers can serve as the reaction phase in which the chiral catalyst is dis-

solved. Interestingly, good values of yields and enantioselectivity were achieved with this easily recoverable material that worked efficiently for 13 cycles. Better results than those obtained under homogeneous conditions, were obtained when proline was immobilized onto different supported-ILs with no additional adsorbed IL layer [13]. The more expensive tripeptide H-L-Pro-L-Pro-L-Asp-NH_2 **9** gave similar results in comparison with the homogeneous system. Very recently, a series of noncovalently supported heterogeneous chiral amine catalysts for asymmetric aldol and Michael reaction has been reported [14]. The immobilization strategy employed chiral diamines and polystyrene/sulfonic acids. Using these conditions, several chiral amines were supported and investigated. Good results were obtained with amines **10a** and **10b** (Fig. 5). Interestingly, in the aldol reaction the enantioselectivity was reversed with respect to the other chiral amines or proline. Recycling experiments showed, after 5 cycles, no decrease in diastereo- and enantioselectivity. However, a drop in activity was observed. Studies carried out on Michael addition of cyclohexanone to β-nitrostyrenes indicated that the optimal catalyst was PS/11 (10 mol%) in toluene at r.t. Nevertheless, recycling experiments showed a great drop in activity after 6 cycles. Regeneration of catalyst by washing with HCl/dioxane and recharging with fresh amine, restored activity and stereoselectivity, although proved some catalyst leaching.

Amine **11** was also found to be an active and recyclable catalyst for aldol and Michael reaction when supported onto polyoxometalates (POMs) [15-16]. In addition, POMs revealed to be suitable supports for a wide range of primary amines able to promote *syn*-aldol reaction of hydroxy ketones with high yields and level of stereoselectivity [17]. Very recently, POMs have been also employed as recoverable support for several amines in the Diels-Alder reaction of α-substituted acroleins under aqueous conditions (Fig. 6) [18]. Catalyst POM-supported amine **12** was thus recycled and reused six times with only slightly reduced activity and selectivity. Similarly, a montomorillonite entrapped MacMillan's imidazolidinone **13** has been employed in the asymmetric Diels-Alder reaction (Fig. 6) [19]. This catalyst

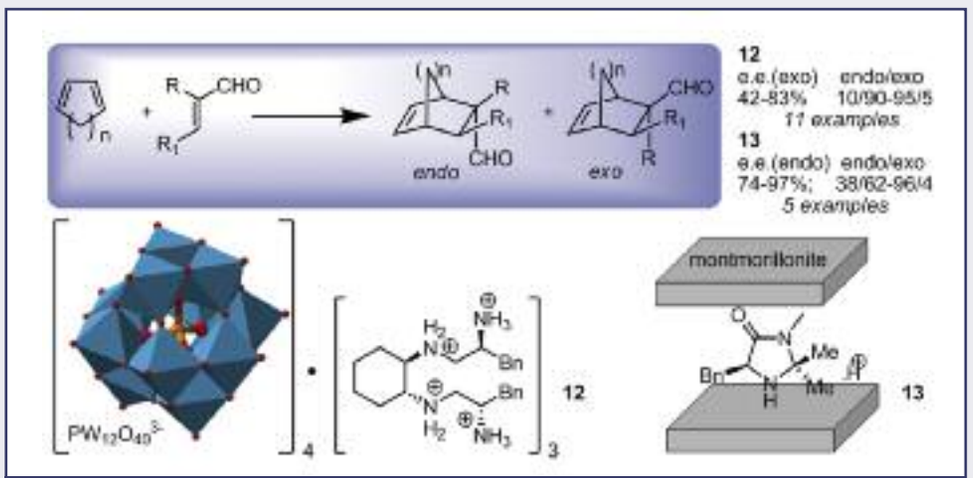

Fig. 6 - Diels-Alder reaction promoted by catalysts 12 and 13

Fig. 7 - Covalent and non covalent supports for organic catalysts

resulted to be highly recyclable, with no losses in yields and stereoselectivity. In addition, in some case, higher enantioselectivities have been obtained in comparison with the unsupported catalyst.

Covalently supported catalysts

Although the non covalent immobilization is a quick and useful approach, that does not require any chemical modification on the catalyst, often some leaching may take place, leading to diminished activities, contamination of reaction products and, especially in the case of expensive compounds, the lost of the organocatalyst. To remedy, several covalent anchoring strategies have been designed and a number of different supports have been successfully employed (Fig. 7) [6, 7, 20, 21].

In this regard, the choice of the support is crucially important as well as the spacer to be employed to link support and organocatalyst together. Two kind of spacer may be used: chemically inert, namely an aliphatic chain; or active linker, able to interact with substrates by mean of H-bonds or electrostatic interactions.

Often supported catalysts show a decreased activity in comparison with their homogeneous versions. This fact can be accounted for the limited mobility of the anchored catalyst, which has to wait that substrates went to him, limiting thus the frequency of productive collisions. Another important issue for covalently-supported catalysts is the catalyst loading. Albeit high loadings are often welcome by the researchers, these not always are directly correlated to higher activity. In fact, space crowded catalysts may result in less active or inactive materials since substrates have not access to catalytic sites or close in space catalyst molecules

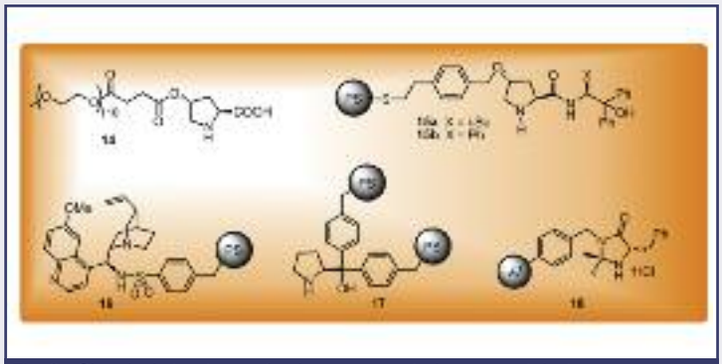

Fig. 8 - Chemical structures of polymer-supported organocatalysts

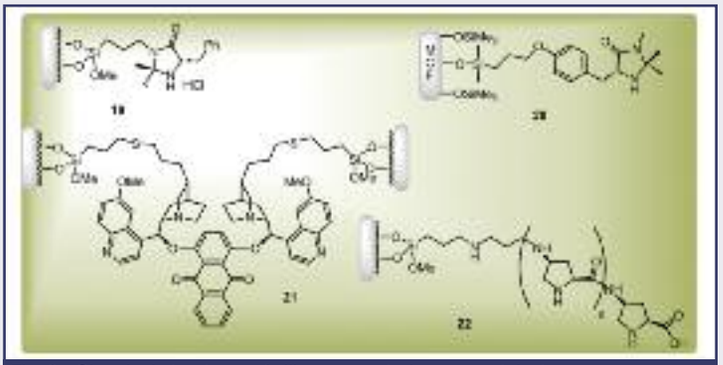

Fig. 9 - Chemical structures of silica-supported organocatalysts

may interact bothering each other. This aspect can clearly be noticed in the case of dendrimers bearing several proline moieties at the peripheral positions [22-23] as well as for polystyrene-supported proline-dendrimers. These latter displayed lower activity and selectivity for the aldol reaction than proline itself [24], thus not justifying the high cost for their immobilization.

On the other hand, immediately after the seminal work of List [3], Benaglia and co-workers prepared the soluble poly(ethylene glycol)-Proline hybrid **14** with the idea of recover the catalyst by adding a precipitating solvent [25-26].

This catalyst represent an example of monophase catalysis with biphase separation, the supported catalyst working in homogenous conditions and being separated by precipitation and filtration in heterogeneous conditions. In this manner, **14** resulted a versatile material able to catalyze aldol, Mannich as well as Michael reaction. Recycling studies revealed that after 3 cycles ee values are maintained with a low decrease in activity.

Several organic catalysts have been covalently supported onto insoluble cross-linked polystyrene [20], among them, very promising resulted to be prolinamides **15a-b**. These resins were able to catalyze aldol reaction with excellent levels of stereoselectivity even at rt, showing high ee for aldol products derived from acetone [27-28]. Furthermore, these catalysts displayed an outstanding recyclability, being reused **15a** and **15b** for 12 and 22 cycles, respectively. Very recently the high reusable polymer-supported Cinchona-catalyst **16** has been described [29]. Interestingly, such a material showed an impressive activity for the asymmetrization of cyclic *meso*-anhydrides by mean of enantioselective methanolysis, yielding quantitative products with excellent ee in all the cases studied in at least ten consecutive cycles. In 2008, Schore showed the versatility of cross-linked diphenylprolinol **17**, which was used in asymmetric epoxidation, Michael reaction and in a three-component Michael/Michael/aldol cascade process [30].

Finally, Pihko successfully designed a synthetic strategy allowing the covalent immobilization of MacMillan imidazolidinone **18** onto a JandaJel™ support, Fig. 8 [31]. This catalyst was employed for the asymmetric Diels-Alder reaction, giving rise, in some case, to better performances than the unsupported catalyst. Excellent results were obtained also when the same authors supported MacMillan's catalyst onto a functionalized silica gel (catalyst **19**, Fig. 9) [31].

Some year later, Ying and co-workers immobilized imidazolidinone onto a partially capped siliceous mesocellular foam (MCF) [32].

The so-obtained material **20** was employed with success for the enantioselective Diels-Alder and Friedel-Crafts reactions, resulting recyclable for 4 cycles. As already seen for polymer supported organocatalysts, Cinchona-derivatives are suitable catalysts for the asymmetrization of cyclic *meso*-anhydrides. In 2004 silica-supported catalyst **21** has been used in the enantioselective alcoholysis for 5 consecutive runs with no changes in activity nor in enantioselectivity [33].

More recently, a series of silica-supported proline-based peptides **22a-c** has been synthesized and applied as catalyst for the direct asymmetric intermolecular aldol reaction (Fig. 9) [34]. The supported peptide composed by two L-proline units (**22b**) was found to be the most active. Moreover, such a catalyst could be recovered and reused for at least 5 times without losses.

Analogously, in 2008 a series of oligopeptides have been anchored onto the surface of magnetic nanoparticles (MNP) through an ionic liquid spacer (**23a-c** in Fig. 10) [35]. These materials have been used in the aldol reaction with a broad ketone scope, and the authors noticed that when hydrophobic anions were used, the yield and enantioselectivity were greatly enhanced. In addition, the catalysts have been recovered and reused for 5 cycles by simply using an external magnet in order to separate the solid from the reaction solution, although with a decrease in conversion.

The same year, Luo and co-workers reported the MNP-supported asymmetric amine **24**, able to catalyze aldol reaction with good to excellent yields and selectivity, which was recycled up to 11 times [36]. Noticeably, until the eighth cycle with no changes with respect the first one, afterward with a slight decrease in conversion and a strong variation in diastereoselectivity. But the “Oscar” to the recyclability goes to MNP-supported DMAP analogue **25** (Fig. 10) [37]. Such catalyst was able to promote the kinetic resolution of *sec*-alcohols with synthetically useful selectivity under process-scale friendly conditions, allowing the isolation of resolved alcohols with good to excellent ee for up to 32 cycles!

Up to now, in this Critical Review, some practical examples of supported organic catalysts have been presented. In the next few lines we want to show some "exotic" example, in which non conventional supports have been employed. To the best of our knowledge in the literature is present only one report dealing with the use of expensive gold nanoparticles (GNPs) as support. In fact, GNPs functionalized with a valine-derived formamide have been developed as effective homogenous catalysts for the asymmetric reduction of ketimines with trichlorosilane [38]. In this case, recovery and recycle (4 cycles) of the catalyst was carried out by precipitation from the reaction mixture, even if a marked decrease in enantioselectivity was observed. On the other hand, DNA-templated synthesis has emerged as a powerful tool to steer reactivity by modulating nature's approach to increase the effective molarity of the reactants and thereby significantly accelerating chemical reactions. In 2007 Marx reported a proline tethered to one DNA strand acting as a catalyst for the cross-aldol reaction between an aldehyde tethered to a complementary DNA sequence and a non-tethered ketone (Fig. 11) [39]. Proline-modified DNA system **26** was used in stoichiometric amount leading to acceptable yields. On the contrary, a proline-dipeptide (not showed here) was used in substoichiometric amount, cycling the temperature between rt and 80 °C (duplex denaturation temperature) in order to have a more efficient catalytic system. The same authors one year later described a novel system for the aldol reaction based on the binding between a G quadruplex endowed with a proline moiety and a porphyrin-tethered aldehyde [40].

Biphasic catalysts

In this section we will focus our attention only on ionic liquids covalently linked to organic catalysts and on fluorinated organocatalysts confined into an alogenated liquid phase. In the first approach a chiral (or non-chiral) unit is covalently tethered to an ionic liquid moiety, the former can serve as a catalytic site and the latter as phase tags. The use of ionic liquids as phase tags for organocatalysts can play up to three roles: a) they can facilitate catalyst recycling; b) they can offer enhanced reactivity; c) they can offer enhanced enantioselectivity acting as chiral-induction groups. By choosing different cations and anions solubility of ionic liquids can be readily tuned allowing to get phase separation from organic as well as aqueous media. This approach can be also applied to ionic liquid-anchored organocatalysts in order to separate the catalytic molecule from the product and to allow its reuse.

Ionic liquid-anchored organic catalysts may be very active because of their intrinsic homogeneous nature, but their recovery may require a precipitation or an extraction process which only seldom is quantitative. Curiously, it was not only 2006 when the first example of an organocatalyst anchored to an ionic liquid was reported. Aldol reactions performed in neat ketone employing **27** (30 mol%) (Fig. 12) gave quite superior results to those obtained with native L-proline [41]. In addition, four cycles were carried out with almost unchanged yield and enantioselectivity.

Very recently, Trombini and co-workers discovered a very active catalyst [42]. In fact, compound **28** can be efficiently used as organocatalyst in the aldol reaction in the 0.5-2 mol% range, reaching as down as 0.1 mol% for the most active aldehydes. These low charges avoid the need for catalyst recovery. Also proline derivative **29**, resulted an efficient catalyst for the aldol reaction between acetone and several aldehydes [43].

Aldol products were obtained in good yields and good to high ee being the catalyst recovered and reused four times with unchanged results. In 2008, a new ionic liquid-anchored proline derivative bearing a long alkyl chain at the imidazolium nitrogen atoms **30** was prepared [44]. Good results were obtained with this water-unsoluble catalyst which afforded aldol products in low to high yield and high stereoselecivity but, although it was used in 30 mol%. In 2006 the first paper of ionic liquid-anchored organocatalysts for Michael addition reactions was reported [45].

Several pyrrolidine derivatives (**31-33**, **35-36**) were tested in the Michael reaction between cyclohexanone and *trans*-β-nitrostyrene. Organocatalysts were used in 15 mol% in the presence of trifluoroacetic acid as additive (5 mol%). Catalysts **31** and **32** performed better compared to the other catalysts. Recycling experiments, carried out using catalyst **32**, showed no loss in stereoselectivity after four cycles but a loss in activity.

Organocatalysts **31** and **32** were also employed in several Michael addition reactions affording the final products in excellent stereoselectivity in the case of cyclohexanone. Cyclopentanone, acetone,

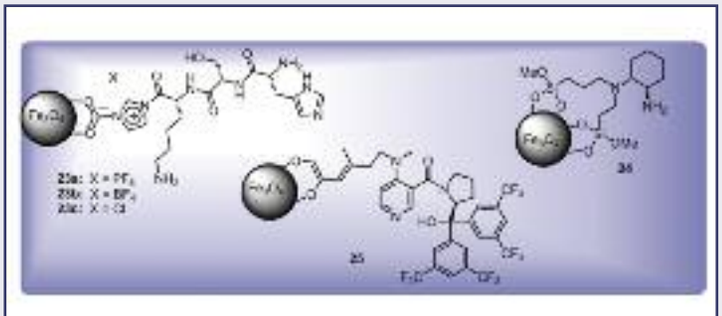

Fig. 10 - Chemical structures of magnetic nanoparticles-supported organocatalysts

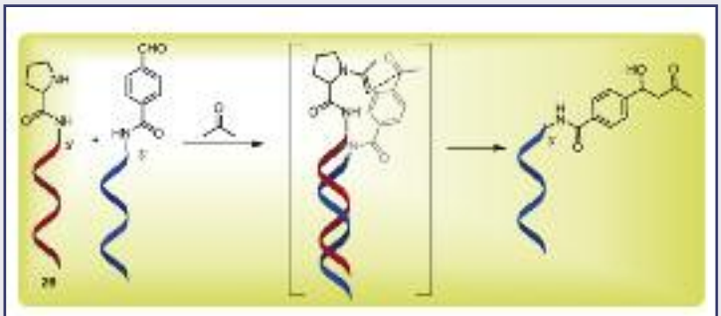

Fig. 11 - Aldol reaction catalyzed from DNA-tethered Proline

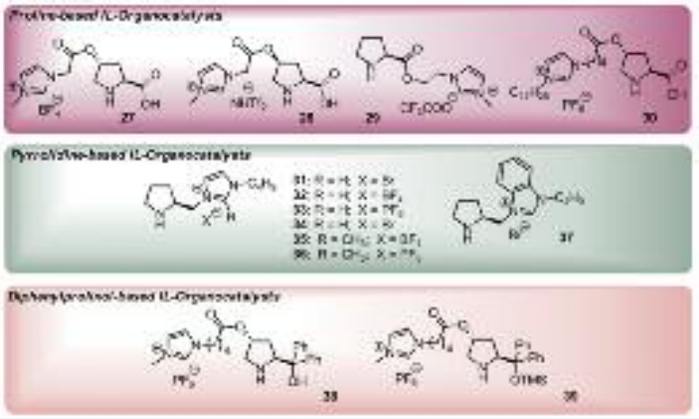

Fig. 12 - Chemical structures of IL-tagged organocatalysts

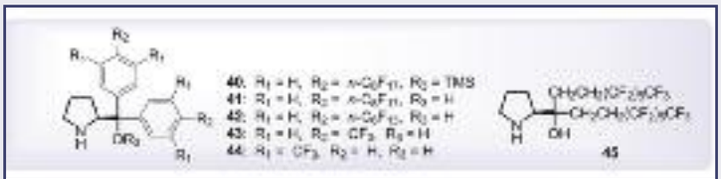

Fig. 13 - Chemical structures of fluorous prolinol organocatalysts

isobutyraldehyde and isovaleraldehyde gave adducts with lower stereoselectivity. Ionic liquid-anchored pyrrolidine organocatalysts were also employed for the enantioselective desymmetrization of prochiral ketones via asymmetric Michael addition reactions to nitrostyrenes. In addition to several known organocatalysts (**31-33**) two new organocatalysts (**34** and **37**) were also examined [46]. Change of anions Cl, Br with BF_4, PF_6 (**31-34**) led to comparable stereoselectivity but increased activity. Better performances were displayed by organocatalyst **37**. Moreover, screening of additives revealed that salicylic acid was the best one. Under these conditions (**37** 10 mol%, salicylic acid 5 mol%, no added solvent) several Michael addition reactions between prochiral ketones and nitrostyrenes were carried out with high yields and stereoselectivities. Moreover, organocatalyst **37** was recovered by precipitation and reused up to four cycles with unchanged stereoselectivity but diminished activity. On the other hand, two ionic liquid-anchored α,α-diphenyl-(*S*)-prolinols **38-39** were used as catalysts in the Michael reaction between α,β-enals and dialkyl malonates [47]. Derivative **39** resulted the best catalyst affording the final products in high yields and enantioselectivities, and it was recovered after solvent evaporation and phase separation and used for six consecutive cycles. In 2006 Wang reported a diarylprolinol derivative endowed with two long flourous alkyl chains **40** (Fig. 13) [48]. This organocatalyst promoted the asymmetric Michael reaction with excellent levels of enantio- and diastereoselectivities when used in alogenated solvents. Interestingly, the catalyst was efficiently recovered by means of flourous solid phase extraction and reused for 8 consecutive cycles with a decrease in activity but not in stereoselectivity. Analogously, Zhu employed catalysts **41-45** for the asymmetric epoxidation of α,β-enones in the presence of *tert*-butyl hydrogenperoxyde as the oxidant agent [49]. Good enantioselectivities were achieved in alogenated solvents, resulting **41** the best catalyst which was recycled by simply cooling followed by filtration and reused four times with no changes of activity.

Outlooks and perspectives

Immobilization of organic catalysts, covalently or not, has attracted much interest. It is fascinating how the immobilization of these simple molecules has stimulated the synthetic creativity of researchers [6, 7, 20]. Covalently-linked organocatalysts make the recovery procedure very easy, avoiding leaching of catalyst and simplifying the product isolation. This is true in the case of heterogeneous supports such as cross-linked polystyrene or silica. In these cases, the morphological properties of the support have a great influence on the outcome of the reactions. As a consequence, these materials may be less effective than their non-supported homogeneous counterparts but, in other cases they can be modulated in such a way that higher stereoselectivities can be achieved. In our opinion, studies for new highly active, stereoselective and highly recyclable organocatalysts are always desirable, since so far in the adolescent field of organocatalysis the research efforts have mainly be focused on catalyst discovery rather than on the immobilization of chiral catalysts. In fact, we think that other supports may be investigated in order to exploit their effect on enantioselective reactions. Some novel sup-

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port may be represented by single- and multi- walled carbon nanotubes, which can be used both as covalent or as a non-covalent supports [50]. In the latter case, pyrene-containing organocatalysts may represent good candidates for supramolecular supported catalysts. Also nanostructured inorganic supports may be useful as reactant-confining nanoreactors in order to lead to improved conversions and selectivities. A novel approach in this sense may be represented by the hybrid metal-organic frameworks (MOFs) [51], crystalline materials assembled by the bonding of metal ions with polyfunctional organic ligands. MOFs in some case may display catalytic activity by itself or may be modified in order to promote organic reactions. To date nothing has been reported on organocatalysts confined inside MOFs' structures nor as a part of the constituting organic-framework. This approach may leads to highly organized catalytic spaces or nanovessels, and may constitutes a real step-further in the field of organocatalysis. Noticeably, almost no investigations have been carried out about the use of continuous flow methods in organocatalysis, nor in the use of supercritical fluids as reaction media. To date, only two very recent examples deal with systems in which the catalyst must not be removed from the reaction vessel [52-53]. We strongly believe that further interesting developments in this appealing field will appear soon.

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RIASSUNTO

Vantaggi nell'immobilizzazione di organocatalizzatori chirali

L'organocatalisi rappresenta oggigiorno un'area indipendente, all'interno della catalisi asimmetrica, capace di complementare la catalisi organometallica e quella enzimatica nella sintesi di molecole organiche chirali. Subito dopo la nascita dell'organocatalisi i chimici hanno cercato, con alterne fortune, di immobilizzare i catalizzatori con lo scopo di poterli facilmente recuperare e quindi riciclare. In questo articolo verranno discussi i vantaggi dell'immobilizzazione, le tecniche impiegate e alcuni degli esempi più significativi presenti in letteratura.