Supported proline and proline-derivatives as recyclable organocatalysts

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In the last eight years, L-proline and L-proline derivatives, such as substituted prolinamides or pyrrolidines, have been successfully used as organocatalysts in several reactions. In this *critical review* we summarize the immobilization procedures of such organocatalysts highlighting their application, recoverability and reusability (86 references).

Introduction

Organocatalysts, metal-free organic compounds of relatively low molecular weight and simple structure capable of promoting a reaction in a substoichiometric amount, have received paramount interest in the last years.[1] Since 2000, when List *et al*. reported the direct asymmetric aldol reaction catalyzed by proline, which followed the seminal Hajos–Parrish–Eder–Sauer–Wiechert reaction,[2] this topic has attracted many researchers worldwide. L-Proline[3] can be regarded as the simplest "enzyme" and, in addition to the aldol reaction,[4] it has been successfully applied to many other reactions such as Robinson annulation,[2b,d,5] Mannich reactions,[6] Michael reactions,[7] direct electrophilic α-aminations,[8] Diels–Alder reactions,[9] Baylis–Hillman reactions,[10] aza-Morita-Baylis–Hillman reactions,[11] α-selenenylation,[12] oxidation,[13] chlorination[14] and others.[15]

At the same time, efforts were devoted to the immobilization and recycling of L-proline. Since the first full paper on the use of L-proline as an organocatalyst,[4a] this point has received attention. Actually, L-proline is inexpensive and available in both enantiomeric forms, so its immobilization could be considered useless. It should be noted that immobilization of proline is expensive, because a proline derivative is used as starting material, usually a hydroxy-*N*-substitued-L-proline, and several synthetic steps may be necessary for its immobilization. To counterbalance this point, the supported proline material should be easily recovered and reused many times with unchanged reactivity and selectivity. However, at least two "driving forces" for proline immobilization may be considered. The first one is that proline is used up to 30 mol%, which can be regarded as a large amount of catalyst, especially if the reaction is carried out on multigram scale, moreover immobilization of proline may enhance its activity and stereoselectivity. The second "driving force" is that, in our opinion, an improved proline immobilization strategy may be then applied to a more expensive organocatalyst and, hence, its recovery and re-use could be of still higher value, from an economical point of view, so increasing the greenness of the process. Moreover, immobilization allows the use of supported proline derivatives in different solvents and, in general, enables the exploration of new solubility profiles for the immobilized catalytic species. Finally, immobilization gives the possibility to explore modifications of the properties of the supported catalysts by employing specific characteristics of the support.

In recent years, supported chiral organic catalysts have been the subject of many reviews.[16] Here we would like to focus our attention only on proline, mainly for aldol reactions, but other applications will be also discussed, and proline derivatives with regards to stereoselective synthesis *via* enamine. The interest in these materials arises because they are active organocatalysts for many useful transformations and because they are good "probes" for the preparation of new catalytic materials.

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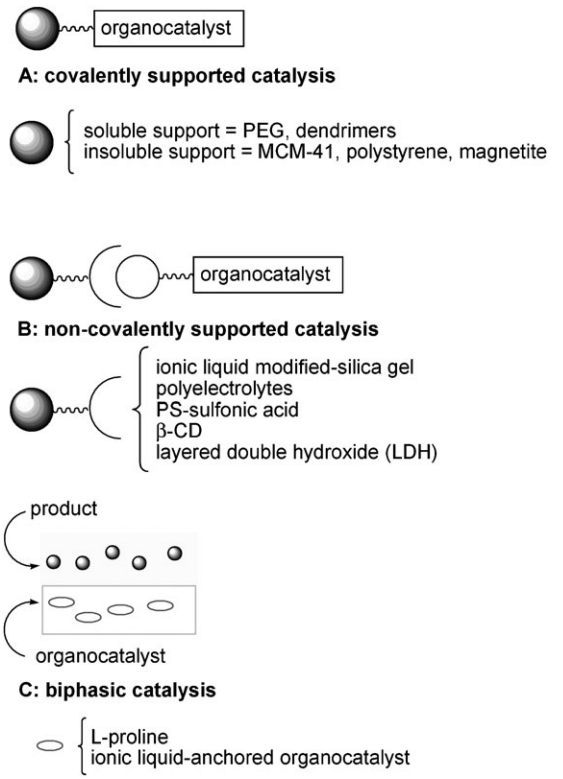
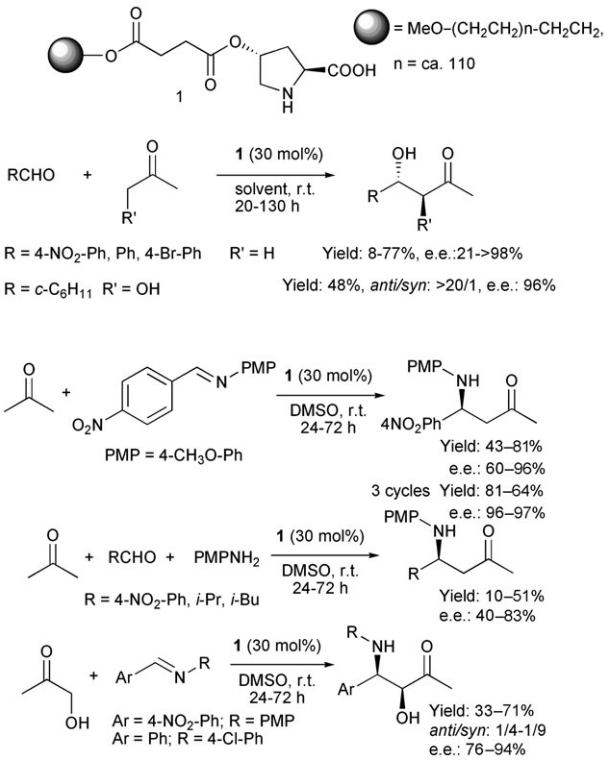


Fig. 1 General approaches for organocatalyst immobilization.



Scheme 1

Three different general approaches can be summarized for organocatalyst immobilization (Fig. 1). Covalently-supported catalysts **A**: in this case L-proline, or a proline derivative, has been covalently anchored to a soluble (*e.g.* PEG, dendrimer) or insoluble (*e.g.* MCM-41, polystyrene, magnetite) support. Non-covalently supported catalysts **B**: in this case the organocatalyst has been adsorbed (*e.g.* onto IL-modified SiO_2), dissolved (*e.g.* polyelectrolytes), included (*e.g.* β-CD) or linked by electrostatic interactions (*e.g.* PS/SO_3H, LDH) in several supports. Biphasic catalysts **C**: in this case L-proline has been dissolved into ionic liquids and the product extracted using an immiscible solvent. As an advanced development of this approach, ionic liquid-anchored L-proline or its derivatives have been also employed.

This review will consider the type of support (polymer, silica, ionic liquid, magnetite, dendrimer, cyclodextrin, DNA, layered double hydroxide) for proline and proline derivatives immobilization, highlighting their application, recoverability and reusability.

Polymer-supported proline

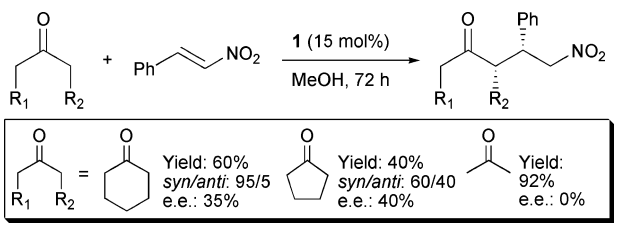
PEG-supported proline

Immobilization of (2*S*,4*R*)-4-hydroxyproline on PEG_{500} monomethyl ether by means of a succinate spacer gave the recyclable soluble catalyst **1** that promoted the enantioselective aldol condensation between acetone or hydroxyacetone with several aldehydes. The same catalyst was also used in the synthesis of the Wieland–Mischler ketone and in the Mannich reaction (Scheme 1).[17]

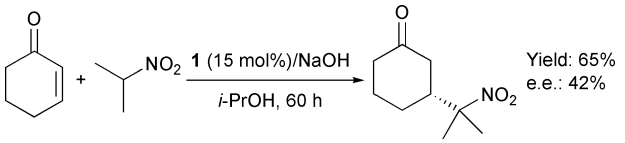
The PEG/Pro catalyst **1** gave a similar yield and enantioselectivity compared to non-supported proline. Recovery of catalyst was achieved by precipitation with diethyl ether and filtration (70–80% yield). It was re-used three times in the aldol reaction between acetone and 4-nitrobenzaldehyde giving the same ee value but decreasing yield (68–51%). Recycling studies (3 cycles) performed on the Mannich reaction with a preformed imine gave the same ee values and a decrease in yield (81–64%). Later, the PEG/Pro catalyst **1** was employed in the addition of ketones to β-nitrostyrene (Scheme 2) and in the addition of 2-nitropropane to cyclohexenone.[18]

The addition of ketones to β-nitrostyrene gave lower ee values (up to 40%) than those observed with proline, fair yields (up to 60%) and good diastereoselectivity (up to 95 : 5 *syn* : *anti* ratios). Recycling of the catalyst was carried out for four cycles giving decreasing yield (60–18%), diastereoselectivity [(95 : 5)–(90 : 10)] and enantioselectivity (35–20%).

Addition of 2-nitropropane to cyclohexenone (Scheme 3) was carried out using the sodium salt of PEG/Pro catalyst **1** in *i*-propanol as solvent. An interesting ee value of 50% was obtained which was comparable (59%) to that obtained using rubidium prolinate as catalyst. However, a longer reaction



Scheme 2



Scheme 3

time, needed to increase the yield from 36 to 65% led to a lower ee value (42%). Recycling investigations showed no decrease in isolated yield (65%) but a decreased enantioselectivity (42–32%).

More recently, similar PEG/Pro catalysts **2–4** (Fig. 2) were prepared starting from MeOPEG monosuccinate (M_W = 2000 or 5000).[19] A preliminary investigation, using as test reaction the addition of cyclohexanone to β-nitrostyrene, showed that catalyst **4** (5 mol%) gave better results both in terms of yield and stereoselectivity (yield: 92%, *syn* : *anti*: >98 : 2, ee: 46%) compared to **2** and **3**. However, using the non-supported catalyst **5** (10 mol%) ee value was higher (yield: 59%, *syn* : *anti*: >98 : 2, ee: 54%). Screening of solvents showed $CHCl_3$–MeOH (1 : 1 v/v) as the optimal reaction medium.

Catalyst **4** was used in 5 mol% in the Michael reaction between various ketones and β-nitrostyrene. The reaction gave products in good yields (39–94%) and high diastereoselectivity (>98 : 2). The enantiomeric excesses ranged from 5 to 86% and were higher than those obtained with non-supported proline or using the PEG/Pro catalyst **1**.[17] The authors proposed a model to explain the observed stereoselectivity (Scheme 4).

Also in this case, recycling of catalyst was performed by precipitation and filtration (average recovery yields: 80–90%). Recycling study, performed using cyclohexanone as ketone, showed after four cycles, a dramatic decrease both in yield (94–24%) and enantioselectivity (60-<10%).

A different approach consisted of the use of PEG-400 as reaction medium for reaction between acetone and aldehydes using native proline (10 mol%).[20] The reactions were faster than in DMSO, giving good isolated yields (58–94%). In several cases ee values were lower than those obtained using proline in DMSO (Scheme 5).

This methodology allowed the recovery of proline. At the end of each cycle the product was extracted with diethyl ether while PEG + proline was re-used for the subsequent cycle. After ten cycles a slowly decreasing yield was observed (94–84%) while enantioselectivity was maintained.

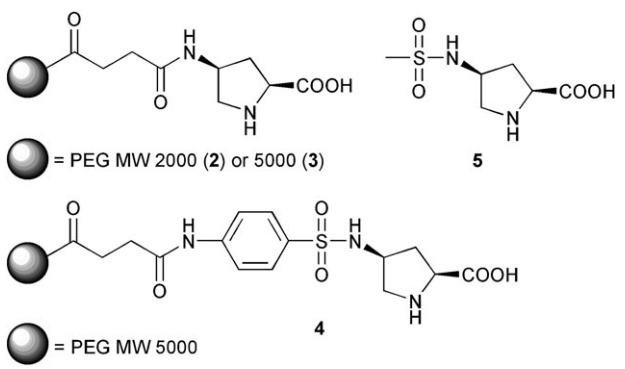
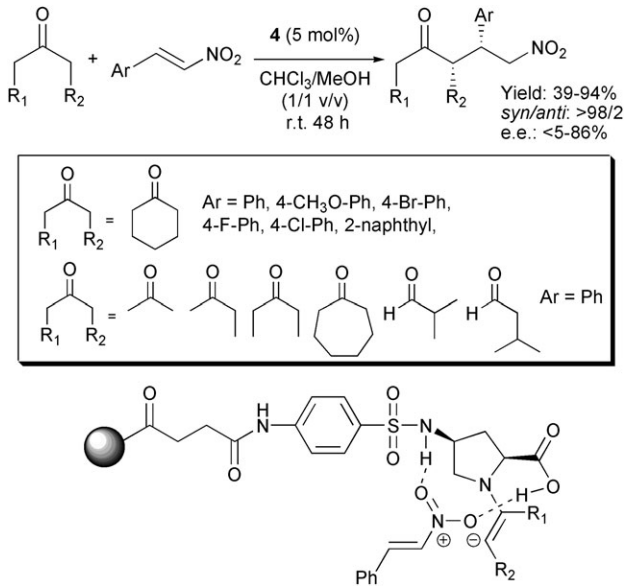


Fig. 2 Chemical structures for catalysts **2–5**.



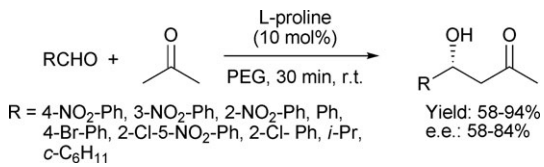
Scheme 4

Polystyrene-supported proline

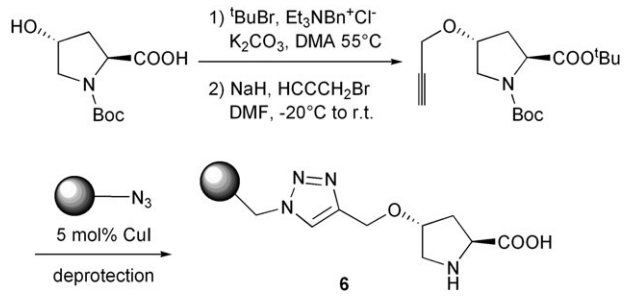
Proline, covalently attached to a heterogeneous insoluble support, can be recovered by simple filtration without the need of precipitation. Polystyrene-supported proline is an interesting approach in order to get an insoluble proline-based catalyst. The first example of polystyrene-supported proline dates back to 1985.[21] Proline polymer-bound resins, in which the degree of cross-linking, the content of proline and spacers were varied, were used as catalysts in the asymmetric Robinson cyclization.

New developments in this field were reported in 2006. Resin **6** was prepared by 1,3-dipolar cycloaddition of an azide-substituted Merrifield resin with an *O*-propargyl hydroxy proline (Scheme 6).[22] This resin was used in the aldol reaction between several ketones (cyclohexanone, cyclopentanone, acetone and hydroxy acetone) and arylaldehydes. Solvent screening showed that the reaction worked nicely in water. Both diastereo- and enantioselectivity were good, whereas DMF and DMSO gave lower stereoselectivity. However, by increasing the amount of water in these solvents, higher stereoselectivity was observed (Scheme 7).

On the other hand, the yield was lower in water. To improve the aldol yield, reaction time was increased and a catalytic amount of water-soluble DiMePEG (M_W *ca.* 2000, 10 mol%) was added with the hope of facilitating diffusion to the resin. Using optimal conditions, aldol products were obtained in 18–97% yield, (58 : 42)–(98 : 2) d.r. and 45–97% ee in 18–144 h. No decrease in performance was observed after three



Scheme 5



Scheme 6

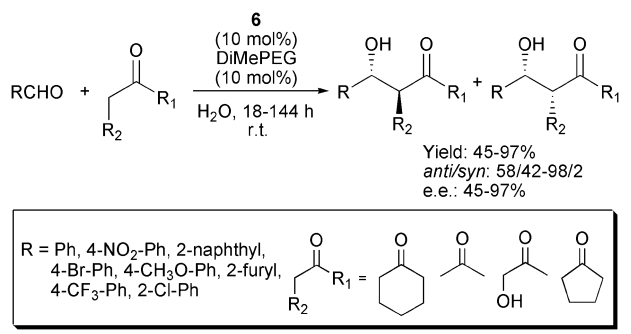
cycles, moreover the authors reported that the reactions were carried out using recycled samples of resin.

The same resin **6** was employed in the α-aminoxylation of aldehydes and ketones (Scheme 8).[23] Preliminary studies on the α-aminoxylation of cyclohexanone pointed out that good yield and high enantioselectivity may be reached carrying out the reaction in DMF with slow addition of nitrosobenzene (over 3 h). This methodology fits the experimental procedure developed by Hayashi[13e] using native proline, while low yields were obtained when the procedure developed by Córdova[13d] was used. Moreover, using **6**, reaction rates were improved compared to native proline.

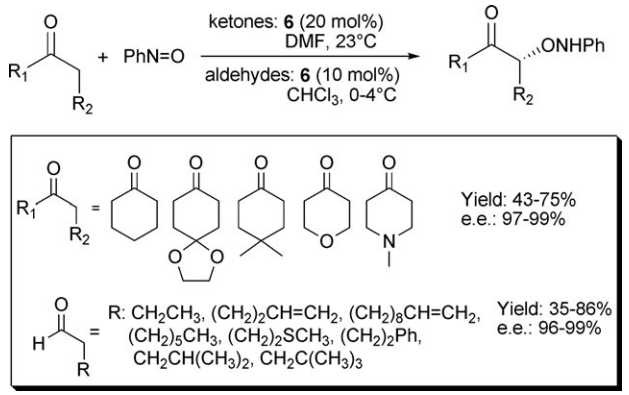
Using optimal conditions α-aminoxylation of ketones gave products in 97–99% ee and 49–75% yield (determined by NMR, isolated yields were lower because the chromatographic process induced partial O–N cleavage). Encouraged by the interesting results obtained, resin **6** was successfully used in the α-aminoxylation of aldehydes. Products were obtained in a short time in good yield (35–86%) and excellent ee (96–99%). Product isolation was easily achieved by filtration followed by removal of solvents and unreacted cyclohexanone under reduced pressure. Recycling investigations showed that resin could be re-used three times without loss enantioselectivity and slowly diminishing yield (81–75%).

Resins **7** and **8** were prepared and used as catalysts in the Michael addition reaction (Scheme 9).[24] The catalysts were prepared through Cu-catalyzed 1,3-dipolar cycloaddition between (*S*)-2-azidomethylpyrrolidine and alkynyl-functionalized Merrifield resins.

Optimization of the reaction conditions showed that good results were obtained using resin **8**, water as reaction medium and DiMePEG (10 mol%). Catalyst **8** was used in 10 mol% at r.t. for 24 h to give addition products in good yields (40–85%) and selectivity [d.r. (89 : 11)–(>99 : 1); ee 26–(>99%)]. No



Scheme 7



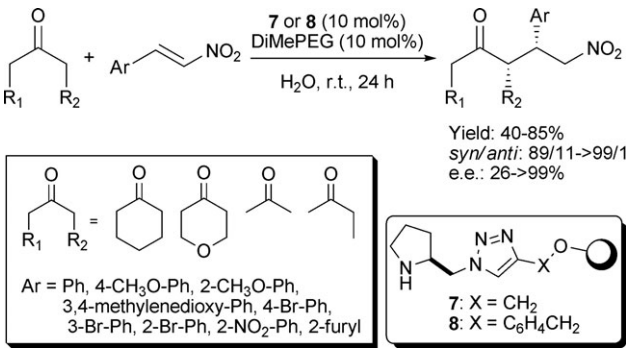
Scheme 8

decrease was observed in the isolated yield or in the stereoselectivity parameters after three consecutive uses. The resin was also tested in the Michael addition of aldehydes to nitrostyrene. High conversions and diastereoselectivities were obtained for linear aldehydes. Ee values were only moderate. A β-branched aldehyde (*i*-valeraldehyde) gave poor conversion and ee, while an α-branched aldehyde (cyclohexane–carboxaldehyde) did not react.

Very recently, five polystyrene-supported proline resins (Fig. 3) were investigated in the aldol reaction between cyclohexanone and benzaldehyde in water.[25] Using 10 mol% of catalyst, good results were obtained with resin **12** (yield: 74%; d.r.: 96 : 4; ee: 98%; 24 h). The reaction time was shortened (12 h) when the reaction was carried out at 40 °C without deterioration in stereocontrol. Interestingly, whereas the reaction mixtures with catalysts **6**, **9–11** were multiphase systems, with resin **12** a gel-like single phase, containing up to 24% in weight of water, was formed. This behaviour arised from the formation of a hydrogen-bond network connecting the proline and 1,2,3-triazole unit.

Catalyst **12** was used in the adol reactions between cyclohexanone or cyclopentanone and several arylaldehydes with high yields and stereoselectivities (Scheme 10). In absence of water lower stereoselectivity was observed. Finally, cross-aldol reaction of propanal gave the product in a 5 : 1 *anti* : *syn* ratio and 97% ee even using only 1 mol% of **12**. Such a resin was recycled and re-used five times without any appreciable loss in yield or in stereoselectivity.

Proline and prolinamide were supported on polystyrene using a different synthetic strategy.[26] The anchorage was



Scheme 9

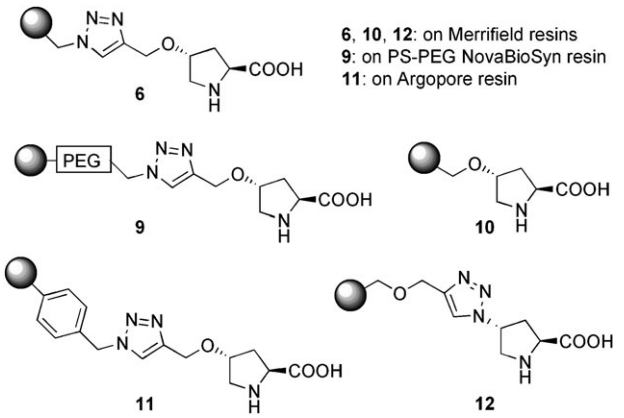


Fig. 3 Chemical structures for catalysts **6, 9–12**.

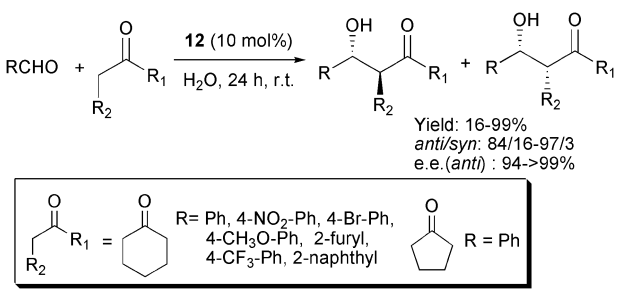
accomplished in two steps: (a) synthesis of styrene derivative of hydroxyproline or prolinamide; (b) radical reaction between a mercaptomethyl polymer-bound and styrene derivative followed by deprotection (Scheme 11).

The proline-based polymer **13** was employed as catalyst in the aldol reaction between cyclohexanone and several 4-substituted benzaldehydes in the presence of water. No additive was used. Conversions (71–98%), d.r. [(92 : 8)–(96 : 4) *anti* : *syn*] and ee (93–98%) were high. After four cycles no decrease in stereoselectivity was observed, however decreasing conversion was obtained.

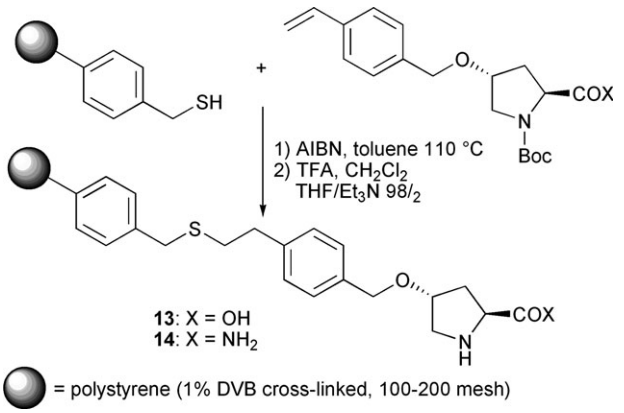
Both resins **13** and **14** were used in the α-selenenylation of aldehydes (Scheme 12). Resin **13** gave high isolated yields (85–97%) when used in 30 mol%. Resin **14** was more efficient than resin **13**, indeed it was used in a lower amount (5 mol%) to give, after the same time, comparable yields.

By contrast, recycling investigations showed that resin **13** was more recyclable than resin **14** in the α-selenenylation reaction. After 4 cycles no decrease in yield was observed with resin **13** while resin **14** gave lower yield after 4 cycles (96–40%).

Later, the same year, a full paper appeared reporting more examples about the use of resin **13** in the aldol reaction between several ketones and aldehydes.[27] Solvent screening showed that the reaction took place only in the presence of water. Other solvents, such as DMSO, DMF, $CHCl_3$ or dioxane, did not promote the reaction. However, when water was added to these solvents the reaction took place, although in lower yield. Use of methanol promoted the reaction, but again in lower yield while other alcoholic solvents showed no activity. Using optimal conditions high yields and stereoselectivities were obtained



Scheme 10

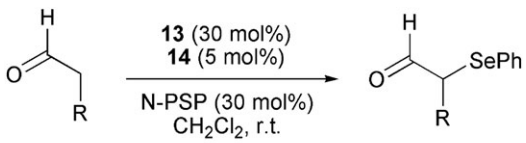


Scheme 11

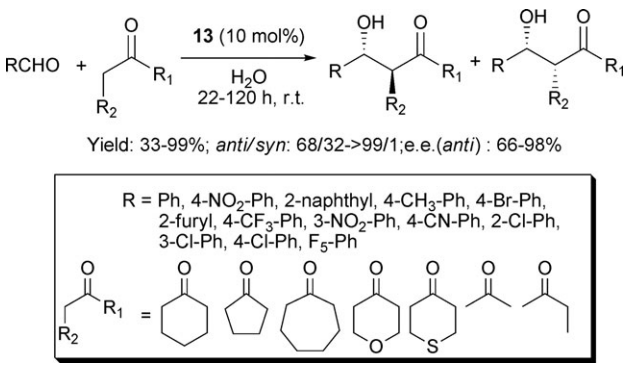
(Scheme 13). So the presence of water both promoted the reaction and improved the stereoselectivity.

A model to explain the observed higher stereoselectivity, compared to those obtained using non-supported proline, was given. The hydrophilic proline lies in the polymer/water interface. This creates an inner hydrophobic core in which the reaction takes place (Fig. 4). Recycling studies performed using the reaction between cyclohexanone and 4-nitrobenzaldehyde showed no decrease in yield and stereoselectivity after five cycles. This different behaviour compared to previous results was ascribed to the changed washing procedure.

Resin **13** was also used, employing imidazole as co-catalyst, in the Baylis–Hillman reaction between methyl or ethyl vinyl ketone and several arylaldehydes (Scheme 14).[28] Isolated yields ranged from low to high. No enantioselectivity was observed in the proline/imidazole catalyzed intermolecular Baylis–Hillman, both under heterogeneous and homogeneous conditions.[29] Once again, the catalyst was easily recovered and re-used for 5 cycles, in the reaction between MVK and 4-nitrobenzaldehyde, with small decrease in activity (91–85%).



Scheme 12



Scheme 13

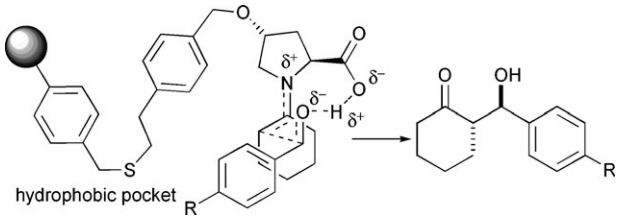
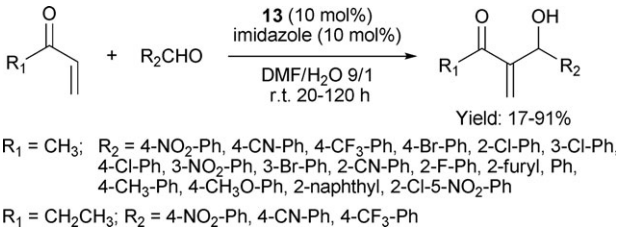


Fig. 4 Proposed transition state model for aldol reaction using **13**.



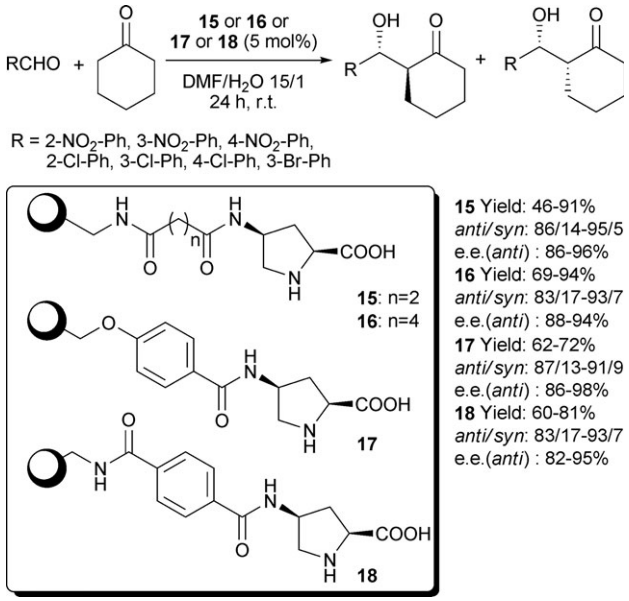
Scheme 14

The synthesis of two proline-based linear polystyrene-supported catalysts **15** and **16** was also reported.[30] These catalysts were prepared from (2*S*,4*S*)-*N*-Cbz-4-aminoproline methyl ester which was reacted with succinic anhydride or hexanoic acid. The compounds were immobilized onto the linear aminomethyl polystyrene (M_W = *ca.* 5000, f = 0.56 mmol g^{-1}). Preliminary investigations carried out using resin **15** (5 mol%) as catalyst in the reaction between cyclohexanone and 2-nitrobenzaldehyde, indicated that the best solvent mixture was DMF–H_2O 15 : 1. The catalyst, soluble in the reaction condition, was recovered by precipitation with diethyl ether and filtration and used in five subsequent cycles to give no decrease in diastereomeric ratio and in ee value. However, the reactivity decreased (73–59%). Catalysts **15** and **16** were used in the reaction of cyclohexanone and several EWG-substituted benzaldehydes. Good yields (46–94%), d.r. [(83 : 17)–(95 : 5)] and ee (84–96%) were obtained (Scheme 15).

Reactions were also carried out in a ketone–water mixture to give the product with similar stereoselectivity but, lower yields. 2-Nitrobenzaldehyde was also used in the reaction with cyclopentanone (yield: 42–86%; d.r.: (70 : 30)–(80 : 20); ee: 92–94%) and acetone (yield: 40–72%; ee: 76–78%). Disappointingly, in these reactions a very large excess of ketone was used (15–36 equiv.).

The same authors reported other two polystyrene-supported prolines (**17** and **18**) (Scheme 15).[31] These materials were prepared from (2*S*, 4*S*)-*N*-Cbz-4-aminoproline methyl ester and 4-hydroxy benzoic acid or terephthaloyl dichloride, which were, respectively, immobilized onto linear chloromethyl polystyrene and aminomethyl polystyrene. Such materials were used in the same reactions and conditions seen for the resins **15** and **16**. The aldol products were obtained in similar yields and selectivities. Again, a large excess of ketone was used. Resin **17** was recovered and re-used for further 4 cycles giving slowly diminishing yield (61–56%) and comparable ee value (93–88%).

Very recently, noncovalently supported heterogeneous chiral amine catalysts for asymmetric aldol and Michael reaction have been reported.[32] The immobilization strategy employed

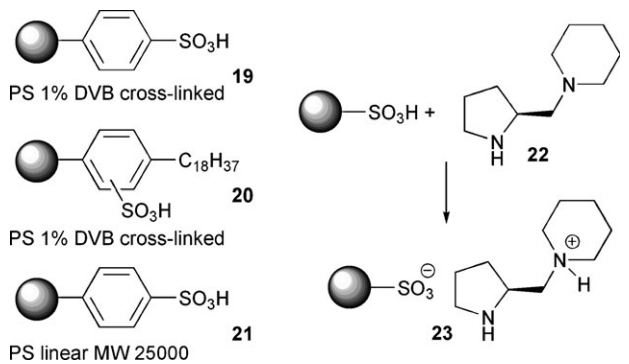


Scheme 15

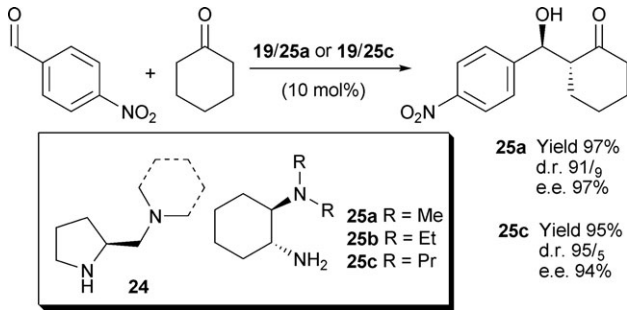
chiral diamines and polystyrene/sulfonic acids. Several PS/sulfonic acids **19–21** were prepared, with different SO_3H loading. The PS/sulfonic acids (PS 1% DVB, cross-linked, 200–400 mesh) were treated with 1.2 equiv. of chiral diamine **22** in CH_2Cl_2 (Scheme 16). The reaction mixture was then filtered and washed. The chiral diamine **22** was supported on these resins and these materials were tested in the reaction between cyclohexanone and 4-nitrobenzaldehyde.

Such preliminary investigations showed that resin **19** with a SO_3H loading of 1.09 mmol g^{-1} was the optimal support for further developments. After studies on solvent effects, CH_2Cl_2 was chosen as reaction medium. Using these conditions, several chiral amines of general formula **24** and **25** were supported and investigated. Good results were obtained with amines **25a** and **25c** (Scheme 17).

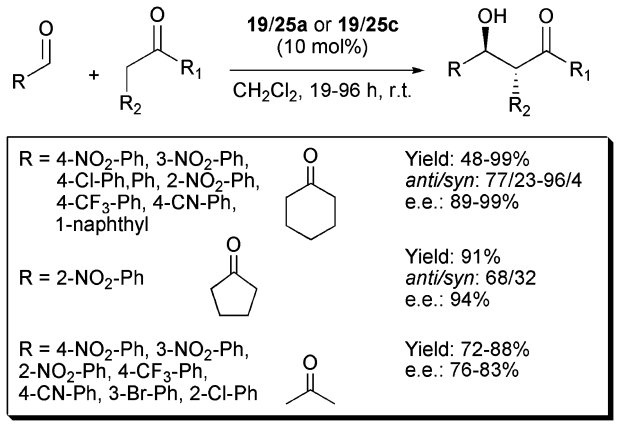
These results represent the first examples of supported chiral primary amine catalysts. Moreover the enantioselectivity was reversed with respect to the other chiral amines or proline. A set of aryldehydes was used obtaining good results (Scheme 18). Recycling experiments showed, after 5 cycles, no decrease in diastereo- and enantioselectivity. However, a drop in activity was observed. The catalyst was reactivated but, even if yield was high, a small decrease in



Scheme 16



Scheme 17



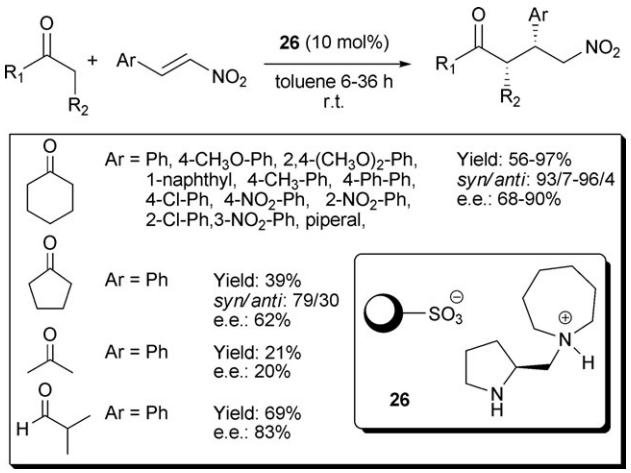
Scheme 18

enantioselectivity was obtained. Even if the catalyst was noncovalently supported, experiments revealed that the process was essentially heterogeneous.

Studies carried out on Michael addition of cyclohexanone to β-nitrostyrene indicated that the optimal catalyst was **26** (10 mol%) in toluene at r.t. (Scheme 19). Nevertheless, recycling experiments showed a great drop in activity after 6 cycles. Regeneration of catalyst restored activity and stereoselectivity.

Unsubstituted prolinamide is not effective as a catalyst in the aldol reaction because the CONH is insufficiently acidic. However, prolinamides of general form **27** showed good activity and enantioselectivity.[33] The hydroxy group forms a second hydrogen bond to the carbonyl oxygen in the aldol transition state, reinforcing the effect of the NH and restoring activity. Dipeptides Pro-Ser and Pro-Thr resemble **27**, so these molecules were immobilized onto polymer in order to test their catalytic activity (Fig. 5).[34]

Peptides were synthesized on Novasyn TG amino resin, an amine-terminated PEG polystyrene graft copolymer. Several di- and tripeptides were supported and these materials used in the aldol reaction between acetone and 4-nitrobenzaldehyde (Scheme 20). Reactions were carried out in acetone at 20 °C for 24 h. Yields ranged from 13 to >99% and ee values from 22 to 77%. Higher enantioselectivities were obtained with polymer-bound tripeptides but the corresponding yields were lower. H-Pro-Ser-NH/TG was used also in a number of solvents (acetone–water, DMSO–acetone, CH_2Cl_2–acetone at 20 °C) and at several temperatures (acetone at −15, −25 and −45 °C). The best result was obtained in acetone at −25 °C.



Scheme 19

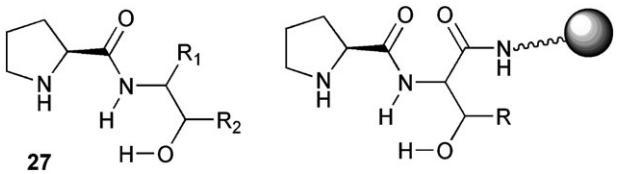


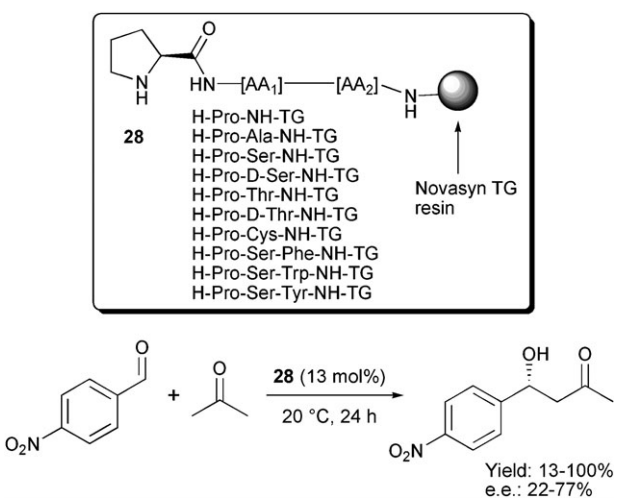
Fig. 5 General structures for substituted prolinamides and supported prolinamides.

After 41 h the product was obtained in >98% conversion and 82% ee

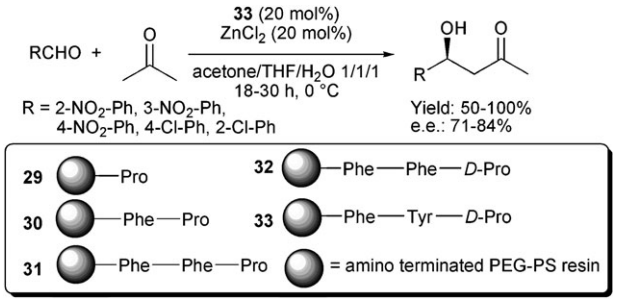
Pro-Ser dipeptide was also immobilized on aminomethyl polystyrene resin. The material H-Pro-Ser-NH/PS was tested giving similar ee value (60%) but only 26% yield (H-Pro-Ser-NH/TG: ee 63%, yield 94%). No recycling investigations were performed.

Proline and di- and tripeptides were immobilized onto polyethyleneglycol grafted on cross-linked polystyrene (PEG-PS) resin (Scheme 21).[35]

Immobilized peptide catalysts were prepared on a terminally aminated PEG/PS (loading = 0.20 mmol g^{-1}) resin by the standard Fmoc SPPS procedure. Preliminary investigations



Scheme 20



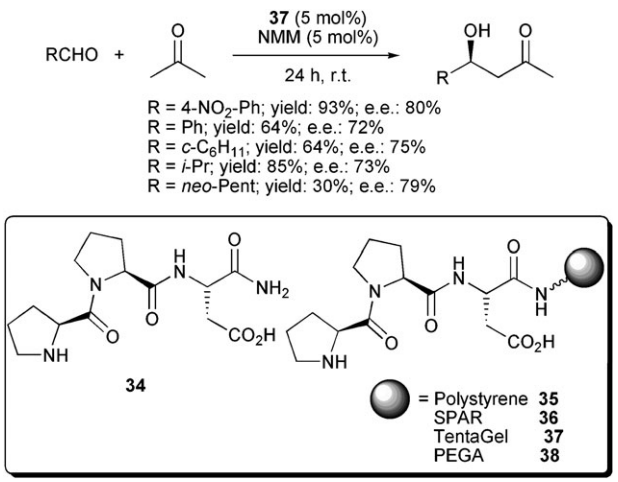
Scheme 21

were carried out using 4-nitrobenzaldehyde and acetone (10 vol%) in water at r.t. for 6 h giving the adduct product in high yield [(78–(>99%)] and low ee (12–34%). The best result was obtained when the reaction was performed in acetone–water–THF 1 : 1 : 1 (v/v/v) at 0 °C using 20% of catalyst **31** or **33** and $ZnCl_2$ (**31**: yield >99%, ee 64%; **33**: yield 66%, ee 73%). Catalysts **31** and **33** gave products with opposite configuration.

Catalyst **33** was used with the above conditions in the aldol reaction between acetone and five EWG-substituted benzaldehydes (Scheme 21). Products were obtained in 50–(>99)% yield and 71–84% ee. Recycling studies (5 cycles) showed no decrease both in yield and in enantioselectivity. However, $ZnCl_2$ was added to each cycle in order to maintain efficiency and selectivity.

Tripeptide H-L-Pro-L-Pro-L-Asp-NH_2 **34** was found a powerful catalyst for the aldol reaction between acetone and aldehydes.[36] It was used in 1 mol% giving, in several cases, better ee values than proline. The versatility of this catalyst was improved by immobilization on a solid support and also by functionalization with a short polyethylene glycol linker at the C-terminus. Tripeptide H-L-Pro-L-Pro-L-Asp-NH_2 **34** was therefore anchored on different resins: polystyrene **35** (ε-aminocaproic acid was used as a spacer between the polystyrene resin and the peptide), SPAR (polyacrylamide) **36**, TentaGel (polyethylene glycol–polystyrene) **37** and PEGA (polyethylene glycol–polyacrylamide) **38** (Scheme 22).[37]

These catalytic materials were evaluated in the reaction between acetone and 4-nitrobenzaldehyde. The reactions were performed at r.t. for 18 h with 1 mol% of the catalyst and *N*-methylmorpholine as base. TentaGel- and PEGA-based catalysts gave comparable results with the non-supported catalyst. Further studies using these supports at different loadings showed that TentaGel with a loading of 0.1–0.2 mmol g^{-1} was the optimal support. This catalyst was used in the reaction between acetone and five aldehydes (RCHO, R = Ph, *c*-Hex, *i*-Pr, *n*-Pr, *neo*-Pent) to give comparable results to those obtained with non-supported peptide. Recycling studies showed that enantioselectivity was maintained for at least 8 cycles while activity decreased after 3 cycles.



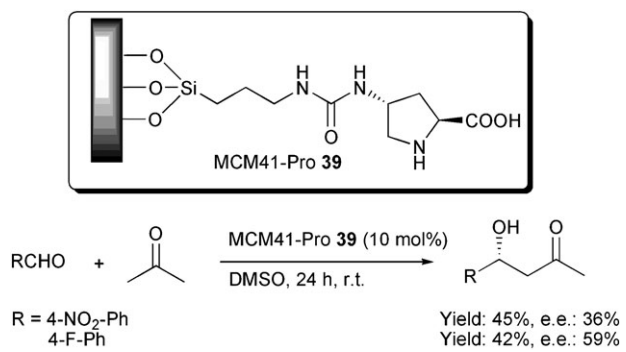
Scheme 22

Silica-supported proline

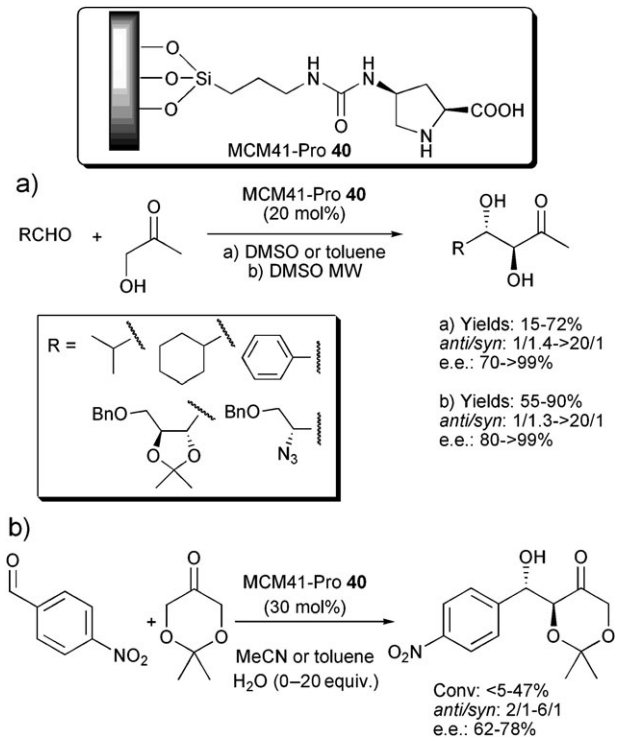
Immobilization of proline by simple adsorption on silica gel gave a reduced enantioselectivity.[4a] Recently an interesting observation has been made.[38] Immobilization of proline on γ-Al_2O_3 gave an inversion of enantioselectivity in the direct aldol reaction between arylaldehydes and acetone. However, the ee values were low. Moreover, the inversion phenomenon was quite general. Indeed, the reaction between acetone and 4-nitrobenzaldehyde catalyzed by 8 different aminoacids immobilized on γ-Al_2O_3 always gave the reversed *S* configuration. This effect was not observed when *i*-butyraldehyde was used. A model to explain this outcome was given.

To the best of our knowledge the first example of proline covalently attached to silica for the aldol reaction was reported in 2003.[39] Proline was immobilized on mesoporous support (MCM-41). MCM41-Pro **39** was prepared in several steps starting from (2*S*,4*R*)-4-hydroxyproline. Only two aldol reactions were investigated (Scheme 23). Both yield and enantioselectivity were not good. Poorer results were obtained with proline covalently attached on amourphous SiO_2 or with a benzylpenicillin derivative covalently attached both on MCM-41 and on SiO_2. Recycling investigations (3 cycles) using MCM-41 **39** showed a decrease both in activity and enantioselectivity.

Later, a similar material, having (*S*) configuration at proline C-4 atom, was prepared in several steps starting from (2*S*,4*R*)-*N*-Cbz-4-hydroxyproline.[40] Among several different supports, the catalyst MCM41/Pro **40** gave the best results. Such catalyst was used in DMSO or toluene for the aldol reaction between hydroxyacetone and five aldehydes (Scheme 24). In general, yields were higher using homogeneous conditions. Only *i*-butyraldehyde gave the same ee value both under homogeneous and heterogeneous conditions. With



Scheme 23



Scheme 24

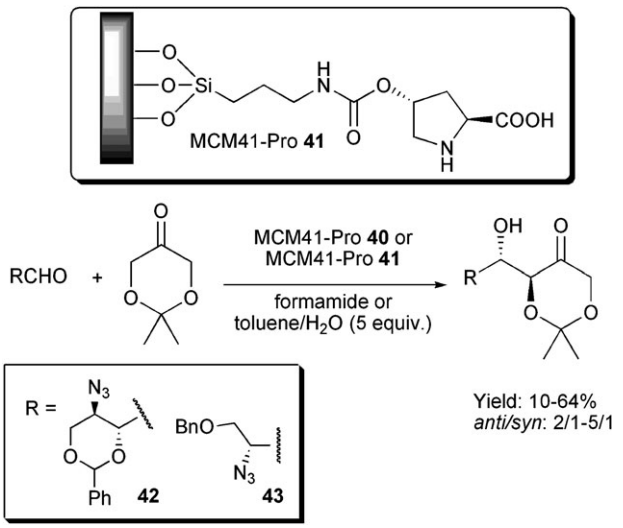
cyclohexane–carboxaldehyde and benzaldehyde, MCM41/Pro **40** gave lower ee value. Interestingly, the last two aldehydes provided diastereoselectivity complementary to the homogeneous catalyst. This result was ascribed to interactions of the reactants with the solid support. Because of the harsh conditions required for condensation (90 °C), MCM41/Pro **40** was also used in DMSO with the assistance of microwave heating. Reaction times were reduced and yields increased. The catalyst was recycled twice using *i*-butyraldehyde showing decreased yield (45–40%) and unchanged diastereomeric ratio. However, no data were reported about the ee values.

Later, the same authors reported further investigations on asymmetric aldol reaction catalyzed by MCM41/Pro **40**.[41] Solvent screening for the reaction between 4-nitrobenzaldehyde and dioxanone showed that the reaction proceeded more efficiently in hydrophilic polar solvent. However, addition of small amount of water (up to 5 equiv.) had a positive effect on the rate and the stereoselectivity of the reaction carried out in toluene. Excess of water (10 or 20 equiv.) gave a drastic drop of reactivity.

Dioxanone was used in the reaction with aldehydes **42** and **43** furnishing useful intermediates for the synthesis of azasugars. In addition to MCM41/Pro **40**, catalyst MCM41/Pro **41**, in which the urea group was replaced by a carbamate group with configuration change at C-4 of the proline ring, was used. The latter catalyst gave lower diastereoselectivities and ee values (Scheme 25).

Only one recycle was performed using 4-nitrobenzaldehyde in formamide as solvent. A small decrease both in yield and ee was observed.

A different application of proline onto silica was reported in 2001.[42] Silica-supported methylcellulose–proline–Pt complex



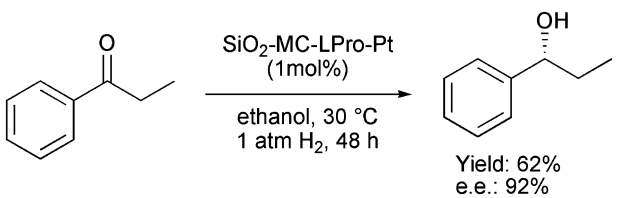
Scheme 25

(SiO_2/MC–LP–Pt) was easily prepared by impregnation of methylcellulose and proline from aqueous solution, then $H_2PtCl_6{\cdot}6H_2O$ in ethanol was added and the mixture refluxed to give a gray solid. This material was found to be an active catalyst for asymmetric hydrogenation of propiophenone to (*R*)-1-phenyl-1-propanol at 30 °C under atmospheric hydrogen pressure. The product was obtained in 62% yield and 92% ee (Scheme 26). The catalyst was recovered and recycling experiments (4 cycles) showed no decrease both in yield and enantioselectivity.

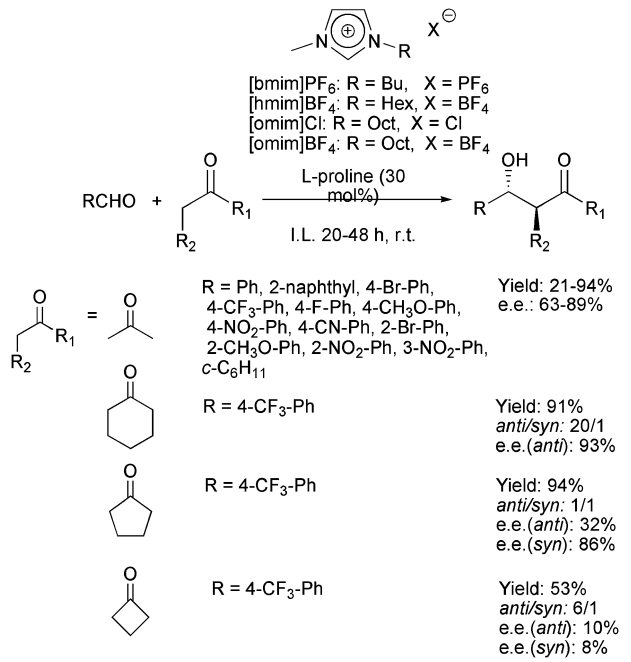
Ionic liquid-supported proline

Ionic liquids as solvents. Several authors used ionic liquids or modified-ionic liquids (task-specific ionic liquids) to immobilize organic catalysts. First reports dealt with the use of proline in methylimidazolium-type ionic liquids (Scheme 27).[43,44]

[Bmim]PF_6 was used to immobilize proline (30 mol%) as catalyst in the aldol reaction between acetone and several substituted benzaldehydes.[43] Yields and ee ranged from 55 to 94% and from 63 to 82%, respectively. Recycling experiments (up to 3 cycles) showed decreased yields and selectivities. Interestingly, proline was used also in 1–5 mol% with good results in the reaction between acetone and 4-trifluoromethylbenzaldehyde. High yield (91%), d.r. (20 : 1, *anti* : *syn*) and ee (93%) were obtained in the reaction between the above aldehyde and cyclohexanone. Ionic liquids (Scheme 27) were investigated as medium for the aldol reaction between acetone and benzaldehyde.[44] [Bmim]PF_6 was selected as reaction medium for other four reactions. Good yields (58–83%) and ee (67–89%) were obtained. Recycling experiments (4 cycles)



Scheme 26



Scheme 27

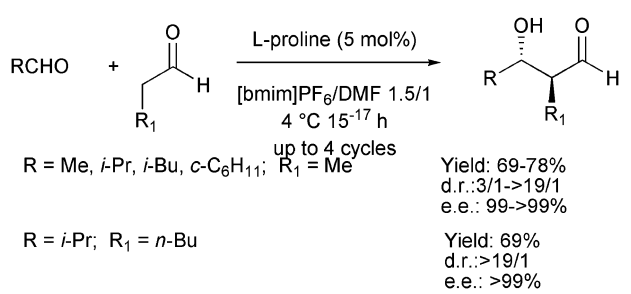
showed a slightly decrease in yield (58–52%) and selectivity (71–67%).

Better results were obtained in the cross-aldol reaction.[45] Using proline (5 mol%) in [bmim]PF_6–DMF 1.5 : 1 at 4 °C for 15–17 h, good yields (69–78%) and excellent stereoselectivities [d.r.: (3 : 1)–(>19 : 1); ee: 99–(>99%)] were obtained (Scheme 28).

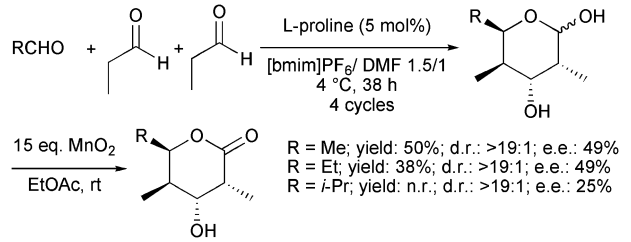
This methodology was also applied to the direct assembly of pyranoses with good results (Scheme 29). Several recycling experiments were carried out. In all the cases no decrease both in yields and stereoselectivities was observed.

The enantioselective aldol reaction between acetone and aromatic aldehydes using *N*-toluenesulfonylproline **44** in [bmim]PF_6 was also reported (Scheme 30). Results were comparable to those obtained by simple proline in ionic liquid. Recycling studies were also performed.[46]

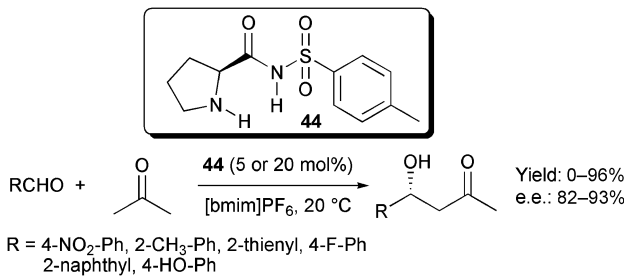
The direct aldol reaction between acetone or butanone and several aldehydes was carried out using prolinamide **45** (20 mol%) in [bmim]BF_4 at 0 °C.[47] Good yields and excellent enantioselectivities were obtained (Scheme 31). Noticeably, ee values were higher than those obtained by the same catalyst in acetone at −20 °C. Recycling experiments carried out using 4-trifluoromethylbenzaldehyde and acetone showed no



Scheme 28



Scheme 29



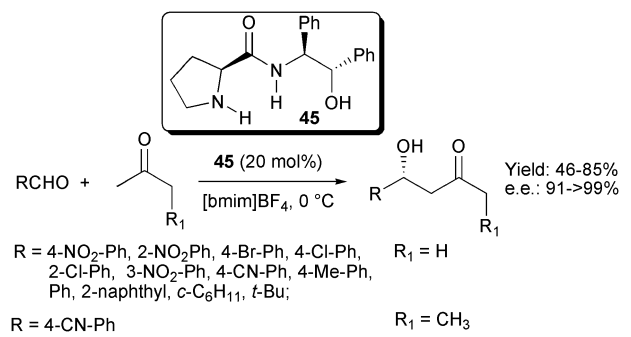
Scheme 30

decrease in enantioselectivity after 4 cycles but dropped in activity in the last cycle (79–41%).

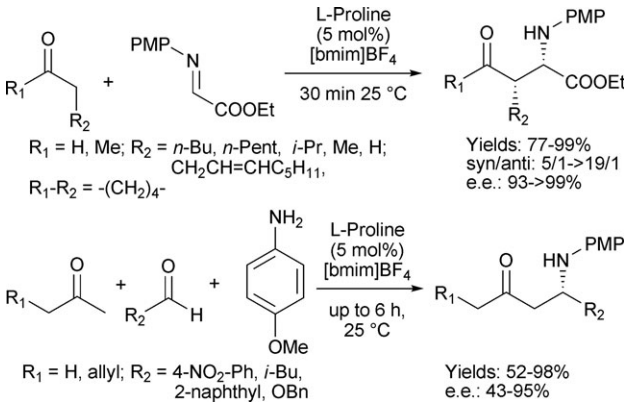
[Bmim]BF_4 was successfully employed in the Mannich reaction between aldehydes and ketones with pre-formed or *in situ* generated imines (Scheme 32). Proline was used in low amount (5 mol%). High stereoselectivities and faster (*ca.* 4–50 times) reaction rates were observed. Recycling studies (4 cycles) carried out using cyclohexanone and pre-formed imine showed no decrease in stereoselectivity but, a decrease in yield (83–99%).[48] Interestingly, the authors revealed limitations on the use of ionic liquids in these reactions, such as poor results obtained with hydroxyacetone.

Other authors claimed that using the amide-task-specific ionic liquid [demim]BF_4, better results were obtained compared to [bmim]BF_4 or DMF.[49] Reaction between *i*-valeraldehyde, acetone and several aromatic amines gave the products with good yield and enantioselectivity (Scheme 33). Recycling experiments (4 cycles) showed no decrease in enantioselectivity and a small decrease in yield (96–85%).

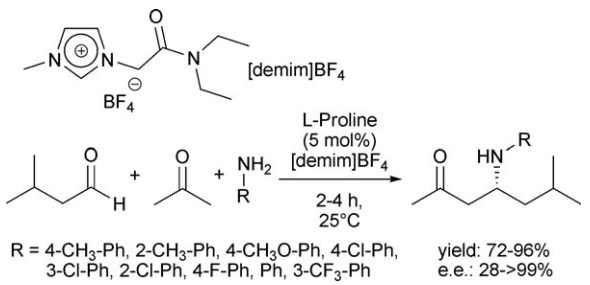
Proline immobilized in ionic liquids was also used in the α-aminoxylation of aldehydes and ketones.[50] A set of ionic liquids was firstly tested in the α-aminoxylation of propanal and cyclohexanone with very good results (Scheme 34).



Scheme 31



Scheme 32



Scheme 33

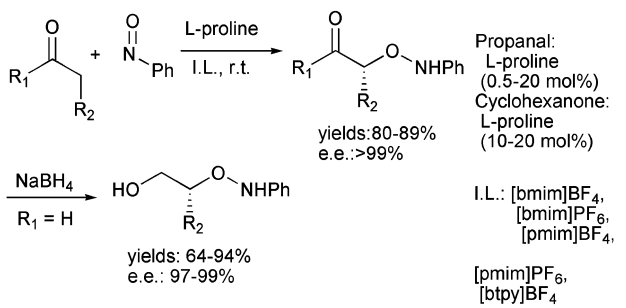
[Bmim]BF_4 was used for further studies obtaining excellent results with several aldehydes and ketones (Scheme 35).

Recycling experiments were carried out for 6 cycles using both propanal and cyclohexanone. In both case a small decrease in activity was observed (94–83%, propanal; 89–81% cyclohexanone).

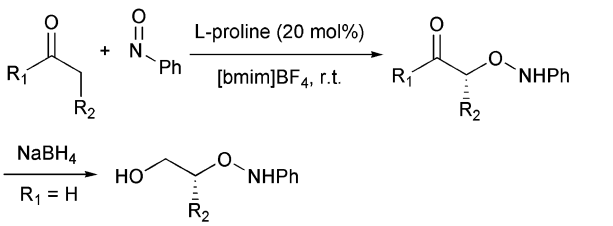
A similar research independently appeared (Scheme 36). The ionic liquid of choice was [bmim]BF_4 and proline was used from 1–5 to 20 mol%. Four subsequent cycles were performed.[51]

A set of organocatalysts was screened for the Michael addition of aldehydes and ketones to β-nitrostyrene in [bmim]PF_6. Proline (5 mol%) was found to be the most promising and was used in the above reaction with a large variety of substrates (Scheme 37) at r.t. or 80 °C. Yields ranged from 0 to 90%, d.r. from 1 : 1 to 12 : 1, ee from 0 to 60%. No recycling studies were reported.[52]

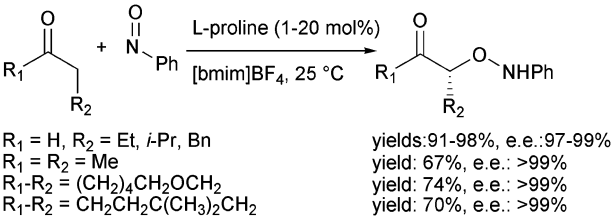
Proline-catalyzed Michael addition of cyclohexanone to β-nitrostyrene in several ionic liquids was later reported.[53]



Scheme 34



Scheme 35

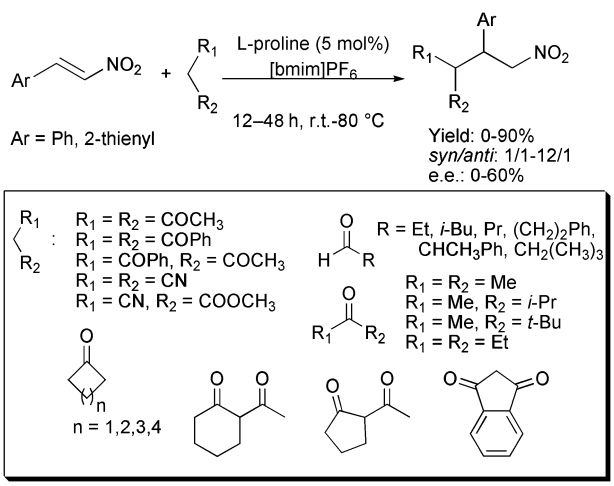


Scheme 36

The best result was obtained using 40 mol% of proline in [moemim]OMs (yield: 75%, d.e.: 90%, ee: 75%). The same reaction carried out in DMSO or MeOH gave much lower stereoselectivity (20 and 50%, respectively). The reusability of the catalytic system was also tested in three consecutive runs; yield was comparable to that obtained in the first run but a decrease in enantioselectivity was observed both in second and third run (73–47–26%).

Michael addition of *i*-valeraldehyde to β-nitrostyrene catalyzed by *N*-toluenesulfonylproline **44** was studied in several ionic liquids (Fig. 6).[54]

Reaction with [bmim]$CH_3CH_2OSO_3$ gave poor yield (40%) after 5 days (32% ee). Adding 10 equivalents of water the activity increased (83% after 1 day) but, the ee decreased (24%). A further cycle showed decreased activity (70%). Reaction in the other ionic liquids both in the presence of water and in the absence showed that activity depended on the acidity or basicity of the ionic liquid. Good yields (up to 98%)



Scheme 37

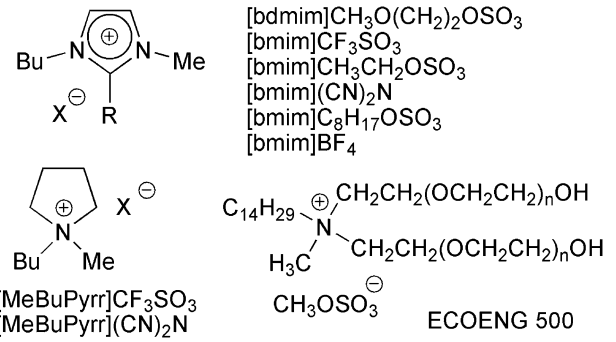


Fig. 6 Ionic liquids used in ref. 54.

were obtained with [bmim]$C_8H_{17}OSO_3$ and [bmim]BF_4. Using [bmim]BF_4 a good ee value was obtained (70%). Interestingly, [bmim]CF_3SO_3, [bmim]$CH_3CH_2OSO_3$ and [MeBuPyrr]CF_3SO_3 gave (2*S*, 3*R*)-2-isopropyl-4-nitro-3-phenylbutanal while the other ionic liquids showed a reversed enantioselectivity. Reaction between cyclohexanone and β-nitrostyrene using [bmim]BF_4 gave the addition product in 44 and 60% ee with (2*S*,1′*R*) configuration. Diastereoselectivity was high in every case [(90: 10)–(95 : 5)] (Fig. 7).

The Michael addition of different thiophenols and thiols to several acceptors catalyzed by proline (5 mol%) was investigated in [bmim]PF_6.[55] Reaction times ranged from 5 to 480 minutes while yields ranged from 18 to 99% (Scheme 38). No stereoselectivity was observed. No recycling experiments were carried out.

Fourteen organocatalysts were tested for the addition of thiophenol to chalcone in [bmim]PF_6.[56] High yields (76–99%) in a short time (10 min) were obtained. Reaction between several thiols and α-enones in different ionic liquids gave the addition products in high yields, however, the products were also obtained without the need for proline (Scheme 39). In every case no stereoselectivity was observed. No recycling experiments were carried out.

Proline immobilized in [bmim]BF_4, in the presence of CuBr and K_2CO_3, was found to be an effective catalyst for the cross-coupling of vinyl bromide with thiols.[57] Immobilization of proline in ionic liquid gave higher yields than reactions carried out in DMF or DMSO (Scheme 40).

Yields were high (75–96%) and stereoselectivity ranged from 86 : 14 to 98 : 2. Ionic liquid allowed recycling of both

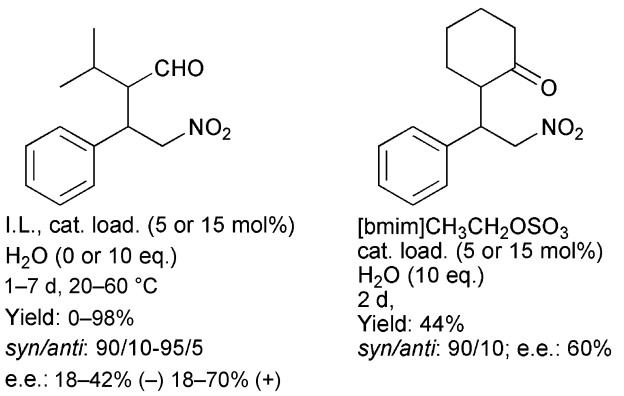
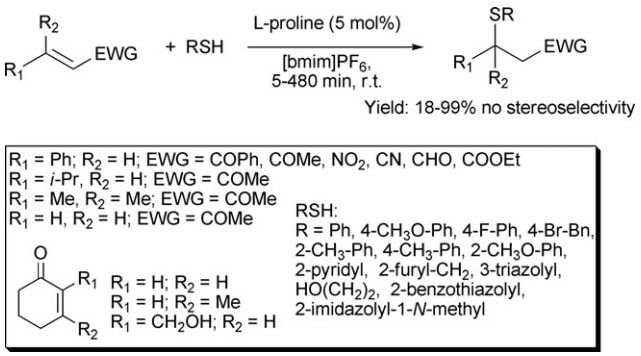
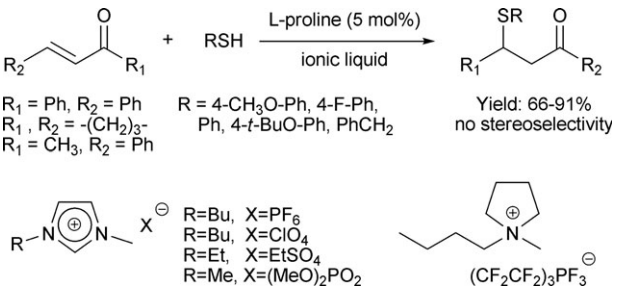


Fig. 7 Data from ref. 54.



Scheme 38



Scheme 39

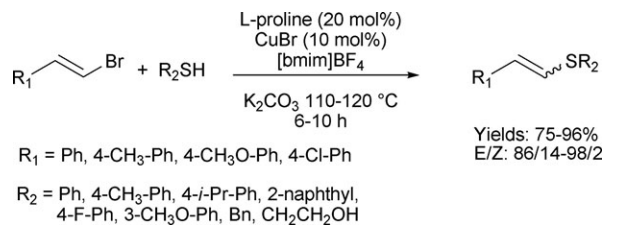
proline and CuBr. Recycling experiments (4 cycles) showed a small decrease in yield (96–87%).

The Knoevenagel condensation of diethylmalonate and various aldehydes was performed using proline immobilized in [bmim]BF_4 or [emim]BF_4 at 35–50 °C for 6–48 h.[58] Except for 4-nitrobenzaldehyde, conversions were high. Immobilization of proline in ionic liquid gave higher conversions compared to other solvents such as H_2O, DMSO, methanol, ethanol or heptane (Scheme 41). Immobilization allowed recycling of proline. After 4 cycles no decrease in conversion was observed.

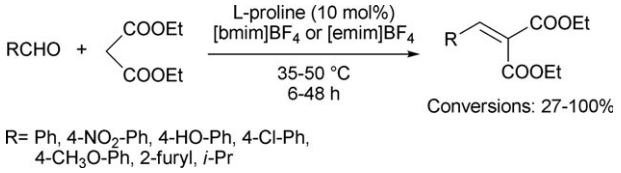
Proline was found to be an effective catalyst, among other organocatalysts, in the addition of aldehydes to diethyl azodicarboxylate in [bmim]BF_4.[59] Oxazolidinones were obtained from modest to good yields, while enantioselectivities were comparable to those observed under common solvents except for benzaldehyde (ee $<1\%$). The corresponding reaction with ketones did not produce useful results. No recycling experiments were performed (Scheme 42).

Ionic liquid-anchored proline and its derivatives

The ionic liquid moiety can be used as soluble support for organocatalysts. One advantage of using an ionic-liquid-



Scheme 40



Scheme 41

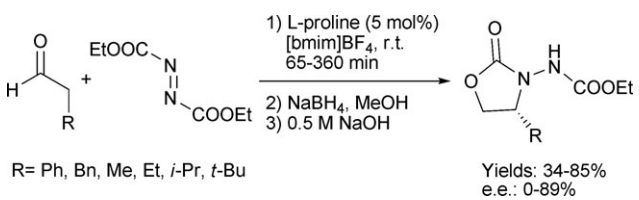
supported chiral catalyst is that the catalyst can be recovered easily from the reaction mixture simply by solubility difference. Proline was successfully anchored to ionic liquid by reaction of *N*-benzyloxycarbonyl-(2*S*,4*R*)-4-hydroxyproline benzyl ester with ionic liquid carboxylic acid **46** followed by deprotection (Scheme 43).[60]

Catalyst **47** was used in the direct aldol reaction between acetone or butanone and several aldehydes both in neat acetone and in DMSO. For the sake of comparison, reactions were also carried out with proline both in acetone and in DMSO. The aldol reactions performed in pure ketone with **47** gave quite comparable or superior results to those obtained in DMSO. Reaction results using proline in neat ketone are much lower than those obtained from DMSO. Then ionic liquid-supported catalyst **47** gave superior results when the reactions were performed in neat acetone. Recovery of the catalyst was performed after removing the volatile component under reduced pressure, treatment with dichloromethane and centrifugation. The dichloromethane solution contained the crude products while the dichloromethane insoluble catalyst **47** was dried under vacuum for 1 h. Recycling studies (4 cycles) of aldol reaction between acetone and 4-nitrobenzaldehyde showed that catalyst **47** was re-usable (yield: 68–64%; ee: 85–82%).

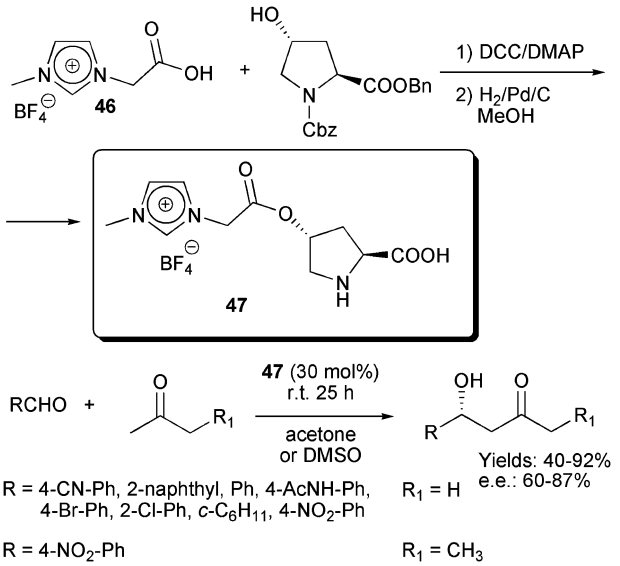
A similar approach was later reported.[61] Ionic liquid-supported proline **49** was prepared by nucleophilic substitution of the protected hydroxyproline and ionic liquid **48** followed by deprotection. This supported organocatalyst was used in the aldol reaction between acetone and several aldehydes at r.t. in [bmim]BF_4. The aldol products were generated in good yields (53–94%) and enantioselectivities (64–93%) (Scheme 44).

The recyclability was tested in six consecutive cycles that showed only minor decrease in yields and no decrease in ee values (data not reported).

Ionic liquid-supported proline **51** and **52** were also used in the direct aldol reaction (Scheme 45).[62] Compounds **51** and **52** were prepared from the same intermediate chloroacetate **50**. Reactions were carried out in [bmim]Tf_2N and [bmim]TfO. After preliminary studies reactions were performed using immobilized proline **52** (5 mol%) in [bmim]Tf_2N at r.t. for 24 h. Yields ranged from 36 to 78% with good stereoselectivities [d.r.: (67 : 33)–(85 : 15); ee: 75–94%]. Recycling experiments using acetone and 4-nitrobenzaldehyde showed a decreased yield after 3 cycles (75–30%) and a small decrease in enantioselectivity (85–80%).



Scheme 42

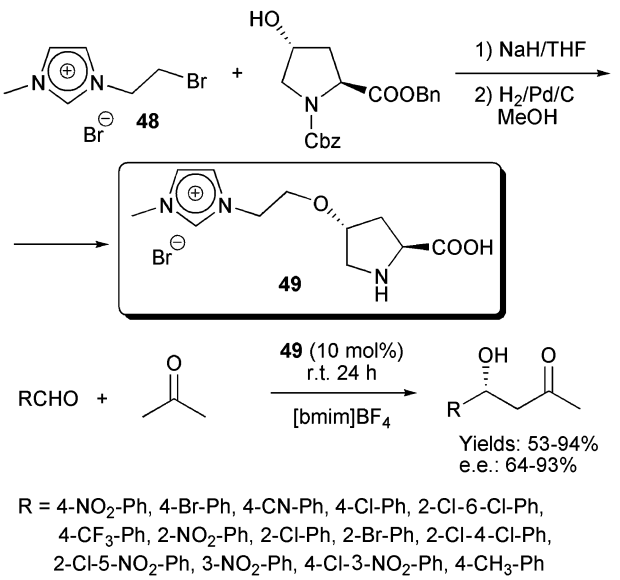


Scheme 43

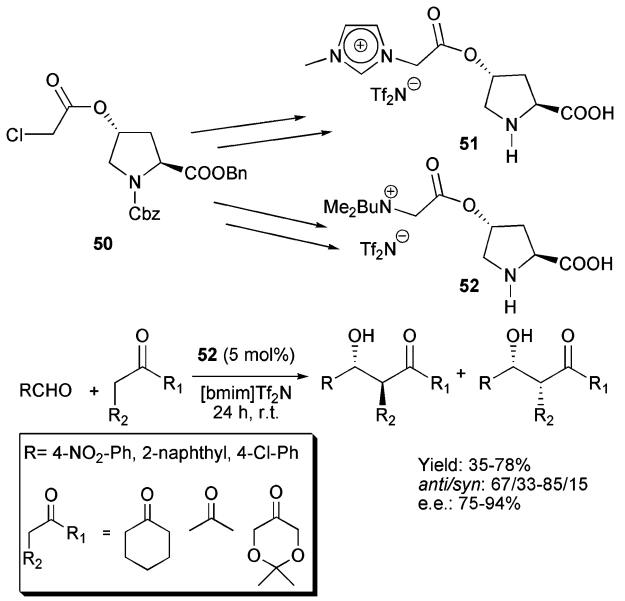
A novel proline-modified task-specific chiral ionic liquid **53** was synthesized and used as a recoverable catalyst for direct asymmetric aldol reactions in the presence of water (Scheme 46).[63] Because of its hydrophobicity, catalyst **53** was not soluble in water. This catalyst was used with four substituted benzaldehydes giving results comparable to or worse than those reported in literature.

The catalyst was recovered by extraction with diethyl ether and recycling experiments (5 cycles) using cyclohexanone and 4-CH_3O_2C-benzaldehyde showed no decrease both in conversion and stereoselectivity.

Pyrrolidine-immobilized ionic liquids **54–63** (Fig. 8) were prepared and tested as catalysts (20 mol%) in the aldol reaction between acetone and 4-nitrobenzaldehyde.[64] Yields



Scheme 44



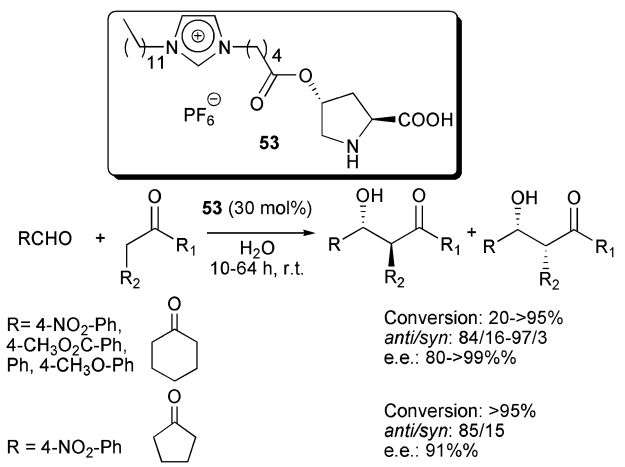
Scheme 45

ranged from 28 to 69%. Higher yields were obtained using catalyst **55** in presence of H_2O (20% v) and CH_3COOH (5 mol%). These conditions were used in the aldol reaction between different aromatic aldehydes and ketones to give product in good yield but low stereoselectivity (Scheme 47). Recycling of the catalytic system for 6 cycles gave reproducible ee values for the *anti* product but, decreased activity and diastereoselectivity.

Ionic liquid-supported pyrrolidine derivatives **54–60** were successfully employed in the Michael addition of ketones and aldehydes to nitroolefines (Scheme 48).[65] High yields and excellent stereoselectivities were obtained using catalyst **54** or **55** (15 mol%) in presence of TFA (5 mol%).

Catalyst **55** was recovered by precipitation with diethyl ether. However, authors did not report the recovered yield. Re-use (4 cycles) showed no decrease in stereoselectivity but loss in activity.

Other ionic liquid-supported pyrrolidine derivatives were used as catalysts in the Michael reaction. Catalyst **65** was



Scheme 46

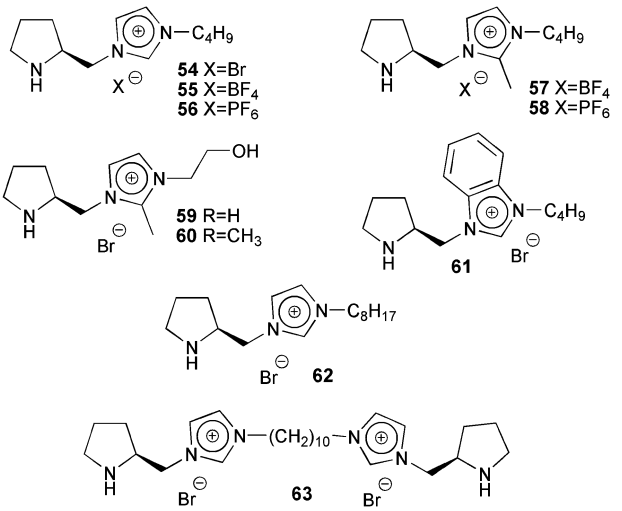


Fig. 8 Catalysts used in ref. 64.

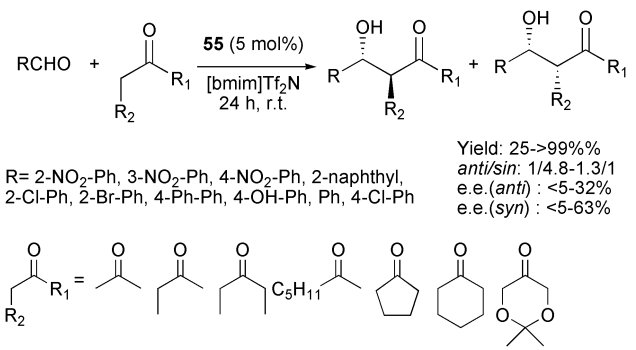
prepared from imidazolium derivative **64** and (*S*)-2-(azidomethyl)pyrrolidine.[66]

Yields and stereoselectivities were excellent when cyclohexanone was used, lower stereoselectivities were obtained with other carbonyl compounds (Scheme 49). Recycling studies (4 cycles) showed no decrease both in yield and stereoselectivity.

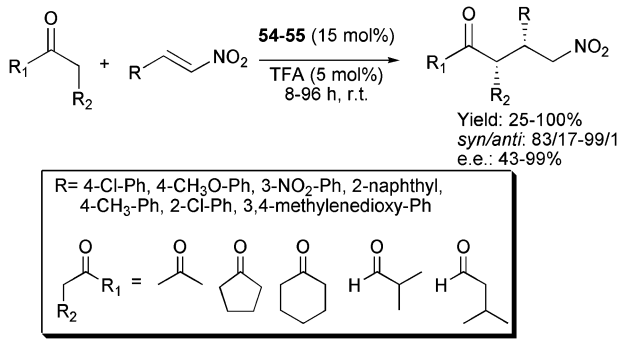
Ionic liquid-supported pyrrolidine **66** was prepared in few steps from (*S*)-2-aminomethyl-*N*-Boc-pyrrolidine and 3-chloropropanesulfonyl chloride. The catalyst was used for several Michael addition reactions of aldehydes with nitroolefins (Scheme 50).[67] Preliminary studies showed the optimal conditions (cat. 20 mol%, 4 °C, 6 d). Yields ranged from 29 to good 64%, stereoselectivities were good [*syn* : *anti* (89 : 11)–(97 : 3); ee 64–88%]. The catalyst was recovered by precipitation with diethyl ether but, no recovered yield was given. Recycling experiments (3 cycles) showed no decrease both in yield and enantioselectivity.

Proline in supported ionic liquid matrices

Since ionic liquids are expensive, it is desirable to minimize the amount of utilized ionic liquid in a process allowing at the same time an easy recovery of the catalyst. Following the new concept of supported ionic liquid catalysis, the first example of supported ionic liquid asymmetric catalysis was reported.[68] This concept was applied to a proline-catalyzed aldol reaction.



Scheme 47

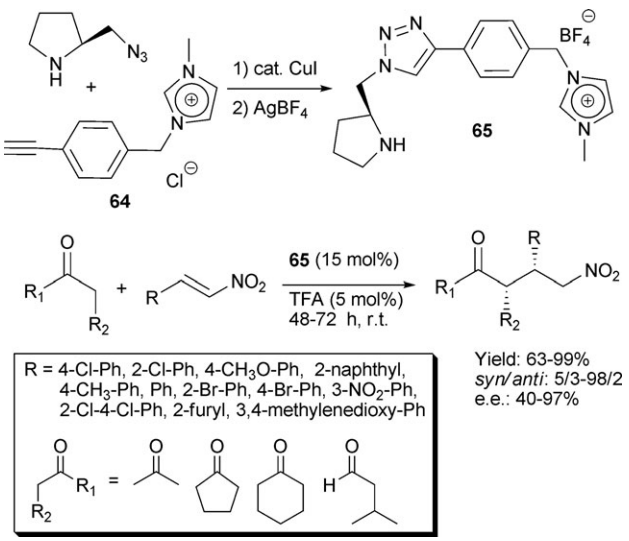


Scheme 48

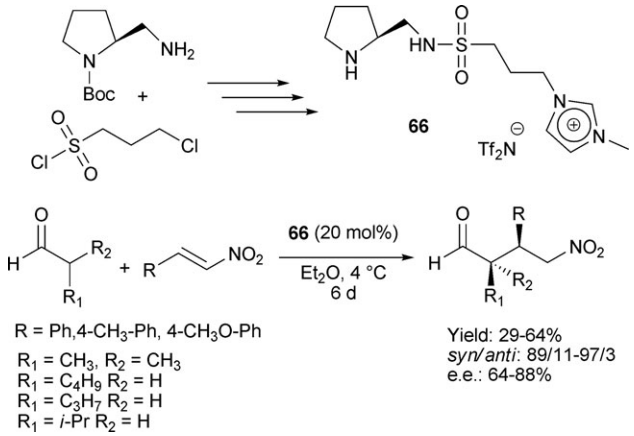
Ionic liquids were covalently attached to the surface of silica gel with or without additional adsorbed ionic liquid. These layers serve as the reaction phase in which the homogeneous catalyst is dissolved. Modified silica gel were prepared by grafting the proper (3-trimethoxysilylpropyl)-derivative.

Six modified silica gels were prepared (Scheme 51).[69] To silica gels **68** and **70** additional [bmim]BF_4 and [4mbp]BF_4 was respectively adsorbed. Finally, these two ionic liquids were adsorbed onto non-modified silica gel. Proline was supported by adsorption from a water–acetonitrile or from a methanolic solution after evaporation of the solvent. Aldol reaction between acetone and benzaldehyde was used to test these materials. Yields were modest (12–55%), however the ee strongly depended from the nature of the support. The highest yields and ee values were obtained with proline supported onto silica containing covalently attached ionic liquid (**68** and **70**) with or without additional adsorbed ionic liquid.

Silica gels **71** and **72** and silica gels containing only adsorbed ionic liquids gave poor results. These data showed that silica gel surface are better modified with a monolayer of covalently attached ionic liquid as support for proline. Based on these results catalytic materials **70**/Pro and **68**–[bmim]BF_4/Pro were tested with a range of EWG-substituted benzaldehydes. Several recycling studies were carried out. The best system was **68**/[bmim]BF_4/Pro with proline added from a methanolic solution. After 7 cycles the ee value was still good, however a decrease in conversion was observed.



Scheme 49

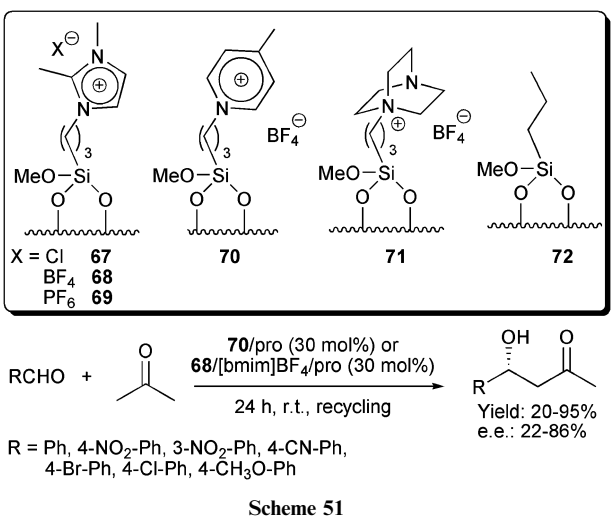


Scheme 50

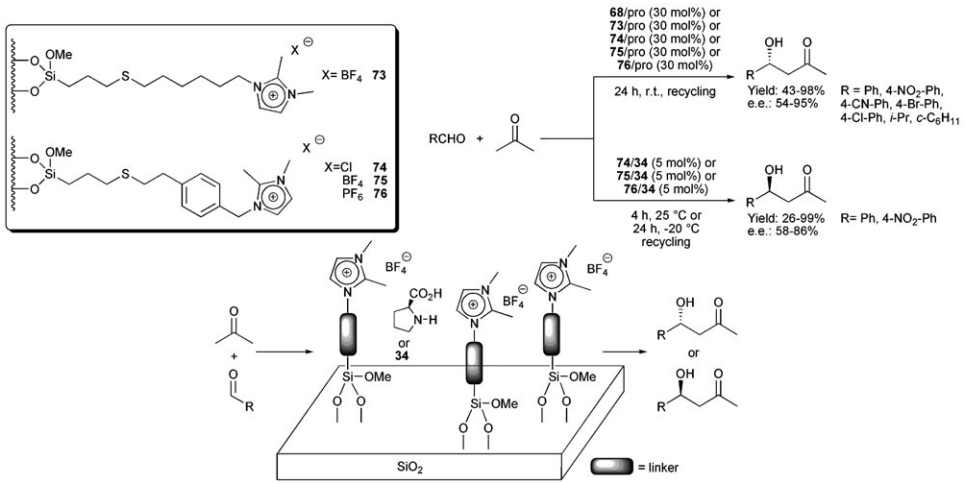
The support was then regenerated washing the modified silica with methanol to remove exhausted proline and adsorbed ionic liquid and recharged with fresh [bmim]BF_4/proline. The regenerated material was successfully used for further 6 cycles with high yield and enantioselectivity.

Further improvements of this methodology were later reported.[70] New modified silica gels **73–76** were prepared (Scheme 52). Proline was adsorbed from a methanolic solution without additional adsorbed ionic liquid and the catalytic materials were used in the aldol reaction between acetone and several aldehydes. The efficiency was checked in subsequent cycles and the best results were obtained with **75**/Pro material. It was used for up to 9 cycles without decrease in yield or enantioselectivity. In addition to proline, tripeptide **34** was also adsorbed on modified-silica gels **74–76**. The best results were obtained using support **75** at −20 °C. Recycling studies (4 cycles) showed decreased conversion (91–42%) while ee remained unchanged (83%).

Following previous studies about the use of poly(diallyldimethylammonium) chloride[71] for catalyst immobilization, proline was supported on polyelectrolytes **77–80** which were obtained from poly(diallyldimethylammonium) chloride by



Scheme 51



Scheme 52

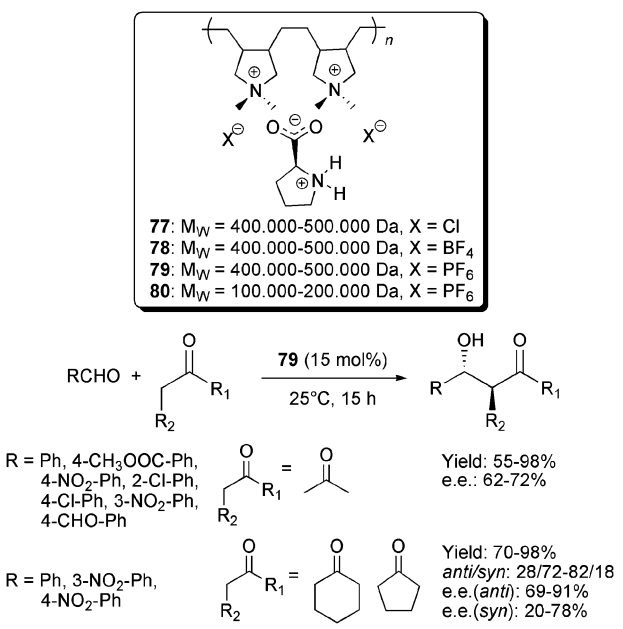
reaction with HBF_4 or HPF_6.[72] Polyelectrolytes **77–80**, which were poorly soluble in water, precipitated from the reaction mixture. Proline was supported by mixing each polymer solution (suspension) in CH_3OH with methanolic solution of the organocatalyst. Evaporation of the solvent afforded the supported catalyst. First the catalytic activity of catalysts **77–80** was studied using the aldol reaction between acetone and benzaldehyde as a model. Acetone was used in a 30-fold excess at 25 °C for 15 h. The proline amount was 15 mol%. Each catalyst was used twice. Only catalysts **79** and **80** showed no decrease in the yield after recycling (54%) while ee values were always the same whichever was the catalyst (67%). Based on these results, catalyst **79** was used for further studies. Six EWG-substituted benzaldehydes were allowed to react with acetone. Aldol products were obtained in 58–98% while ee values were comparable to those reported for the reaction catalyzed by modified silica-supported proline and by proline-solvent systems (DMSO, PEG, $[bmim]PF_6$). The catalyst was filtered and used for six cycles without decrease in yields and enantioselectivities. The same catalyst was also used in the reaction between X-benzaldehydes (X = H, 3-NO_2, 4-NO_2) and cyclopentanone or cyclohexanone. Both yields, d.r. and ee values were not good (Scheme 53).

Proline was supported as an anion in a polystyrene-supported imidazolium resin which was prepared in few steps (Scheme 54).[73] Four different loading levels of the proline unit were prepared. Materials **81–82** were investigated in the CuI-catalyzed *N*-arylation of nitrogen-containing heterocycles. A preliminary survey of reaction conditions was conducted using 4-bromoanisole and imidazole. The best results were obtained in DMSO at 120 °C for 60 h under N_2 using 2.4 equiv. of K_2CO_3 as base in the presence of a catalyst system generated *in situ* from 10 mol% of CuI and **81** (proline loading: 0.69 mmol g^{-1}) containing 20 mol% of proline unit.

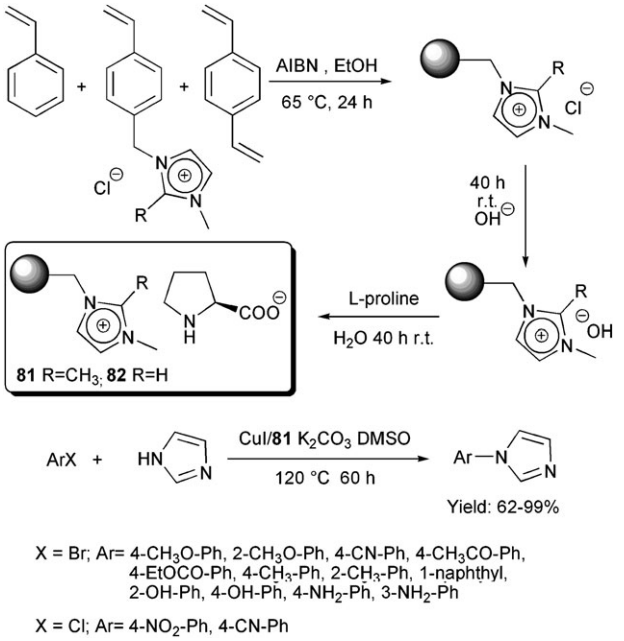
Using the above conditions, several bromo- and chlorobenzene derivatives were used in the reaction with imidazole. High yields were obtained. Recyclability was examined in nine consecutive cycles of the reaction between imidazole and 4-bromobenzonitrile at 90 °C. The yield decreased from 95 to 73%. Noticeably, the ICP-AES analysis of the supernatant indicated a negligible leaching of CuI from every cycle.

Proline was also immobilized as anion in ionic liquids.[74] (2-Hydroxyethyl)trimethylammonium (*S*)-2-pyrrolidinecarboxylic acid salt ([Choline][Pro]) **83** was synthesized by ion exchange and neutralization. This ionic liquid was used as catalyst for direct aldol reactions (Scheme 55).

Reactions carried out using 4-nitrobenzaldehyde and acetone took place in a very short time (1 min) using **83** in 30 mol%. In these conditions the aldol product **85** was obtained in comparable yield with respect to **84**. In order to minimize the amount of compound **85**, reactions were carried out in water. The aldol product **84** was obtained in high yield (90%; **85**: 8%). Using the new conditions several aldehydes and ketones were employed giving satisfactory yields. Recycling studies showed that recovery of catalyst was very easy when the reactions were carried out in water, because **83** was present in the aqueous phase while the product was in the oily phase. Up to four cycles were performed without decrease in activity.



Scheme 53



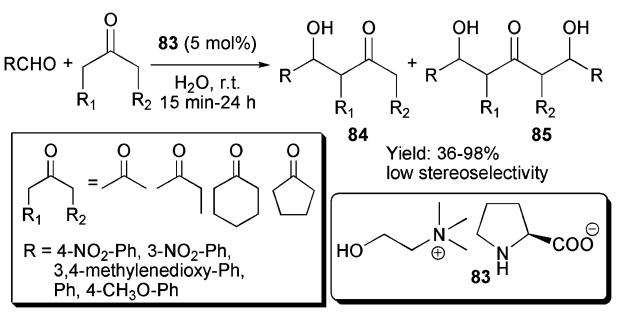
Scheme 54

Unfortunately, the ee values were less than 10% both in aqueous and non-aqueous cases.

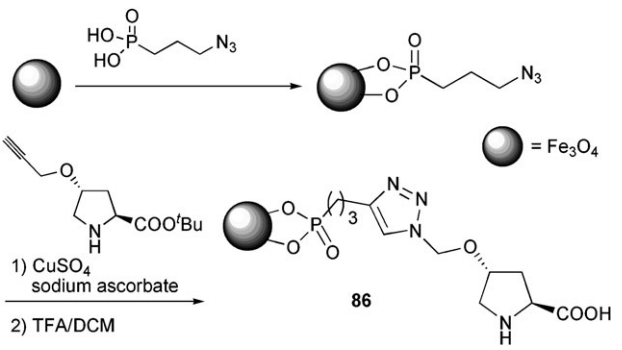
Magnetite-supported proline

The CuI catalyzed Ullmann-type coupling reactions of aryl/heteroaryl bromides with various nitrogen heterocycles was independently investigated using a magnetic nanoparticle-supported proline.[75] Magnetite (Fe_3O_4) nanoparticles were prepared by coprecipitation of iron(II) and iron(III) ions in basic solution at 85 °C. This material was prepared as outlined in Scheme 56. Azide-functionalized magnetite was prepared by treating magnetite nanoparticles with the 3-azidopropyl-phosphonic acid ligand. Immobilization of proline was achieved by the Cu(I)-catalyzed cycloaddition followed by deprotection. Loading of proline was approximately 2 mmol g^{-1} as determined by elemental analysis.

Several *N*-arylations of *N*-heterocycles with aryl and heteroaryl bromides were performed (Scheme 57). Except for 4-bromoanisole, yields were excellent. Recycling experiments were carried out for less cycles compared to the previous report (4 cycles) and showed a small decrease in activity (98–93%). The catalyst was recovered from the product by exposure to an external magnet.



Scheme 55



Scheme 56

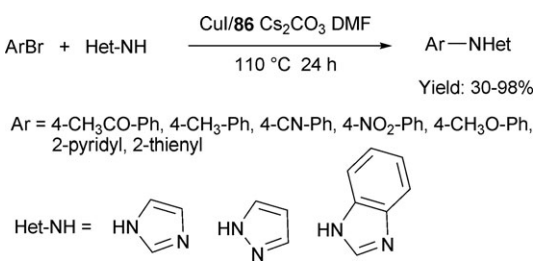
Dendrimer-supported proline

A series of surface-functionalized poly(propyleneimine) dendrimers (five generations) based on proline were synthesized and evaluated as catalysts for asymmetric aldol reactions.[76] Dendrimer catalysts **88–92** were prepared starting from commercially available diaminobutane poly(propyleneimine) dendrimers DAB(AM)$_n$ containing n = 4, 8, 16, 32 or 64 free amino groups, which were coupled with the carboxylic acid **87**. Deprotection afforded chiral dendrimers containing 4, 8, 16, 32 or 64 proline moieties at the periphery (Scheme 58).

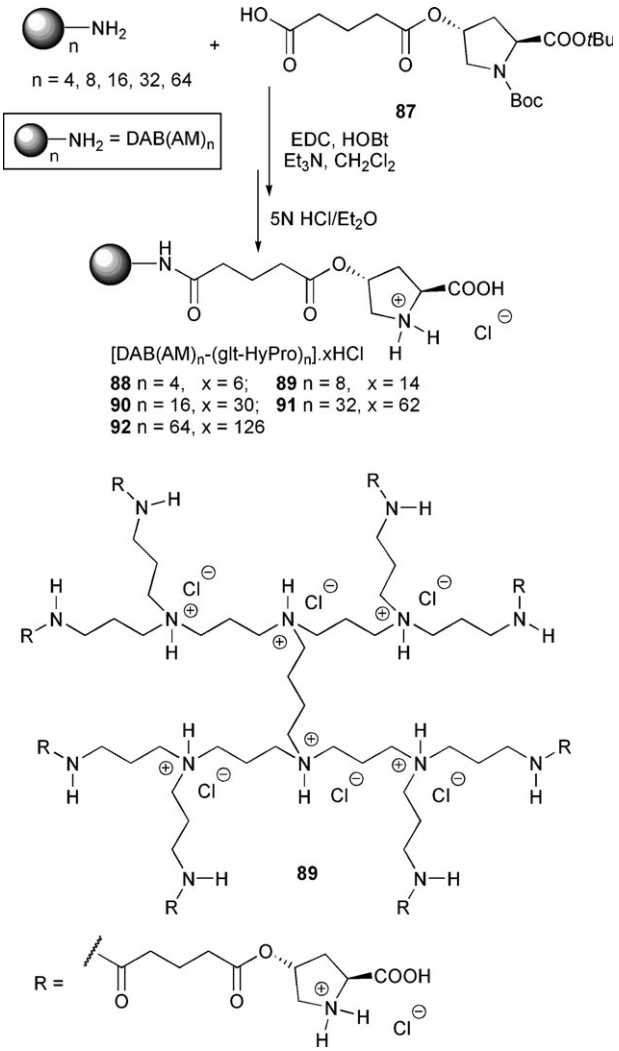
After preliminary screening using acetone and 4-nitrobenzaldehyde as a test reaction, the second generation dendrimer **89** was found the most promising catalyst. However, only three reactions were reported, using 4-nitro-, 4-bromo- and 2-chorobenzaldehyde with acetone. Catalyst **89** was found to be more active than proline. Indeed, using 6.5 mol% of **89**, the products of the aldol reactions were obtained in comparable yields and ee values to those obtained using proline and also in much less time (**89**: 2 h; proline: 16–18 h). No recycling procedures were reported.

Chiral dendritic catalysts **95a–c** derived from proline-*N*-sulfonamide were prepared (Scheme 59).[77] These catalytic materials were tested in the aldol reaction between cyclohexanone and 4-nitrobenzaldehyde in the presence of water as reaction medium. For the sake of comparison, prolinamide **44, 93–94** were also investigated. The best result was obtained with catalyst **95b**. Using this catalyst several aldol reactions were carried out.

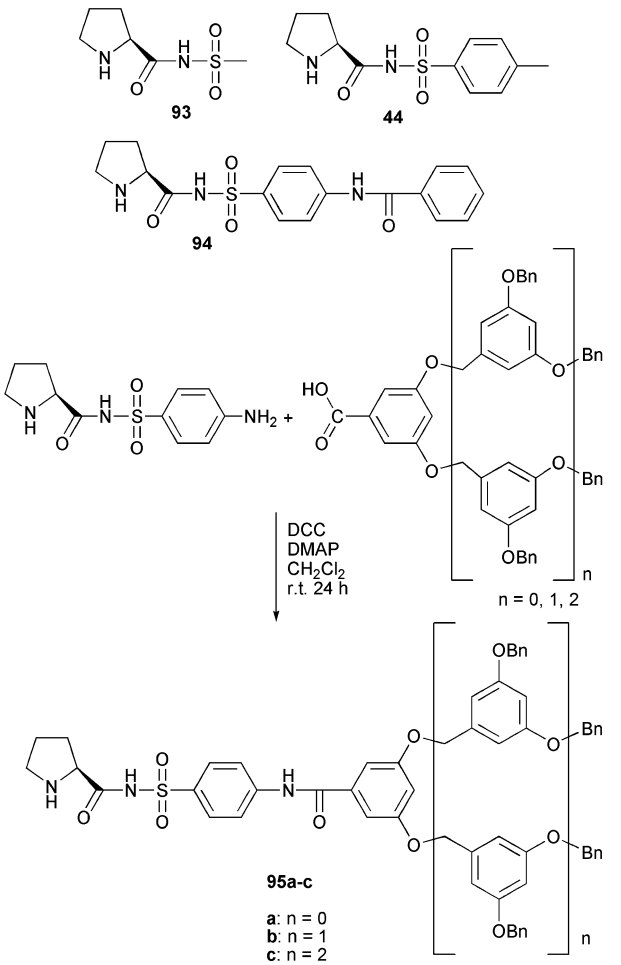
Good yields and excellent stereoselectivities were obtained (Scheme 60). Dendritic materials were recovered by precipitation and filtration. Different solvents were tested in order to find the optimal conditions for recovery. Recycling investigations were carried out for 4 cycles giving reproducible excellent



Scheme 57



Scheme 58



Scheme 59

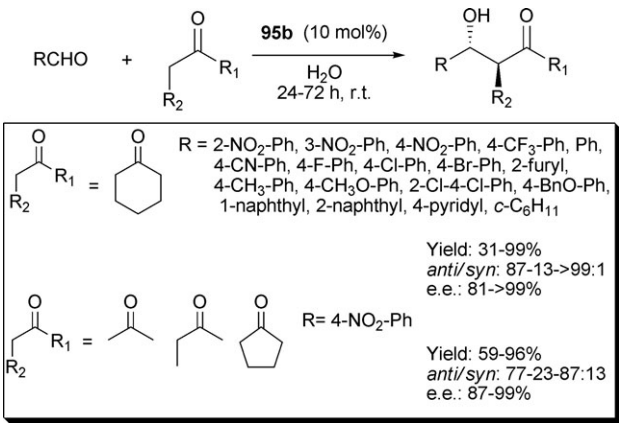
yields and stereoselectivities. Yield of recovered catalyst was about 95% in each cycle.

A dendritic effect in asymmetric aldol reaction was claimed when polymer-supported proline-decorated dendrons were used.[78] The polymer-bound chloromethyl-terminated first to third generation resins were converted to benzylazide resin and then transformed into the active catalysts **96–98** by cycloaddition reaction and subsequent deprotection. In addition, Wang bromo PS resin **99** was also used as support for non-dendritic material (Scheme 61).

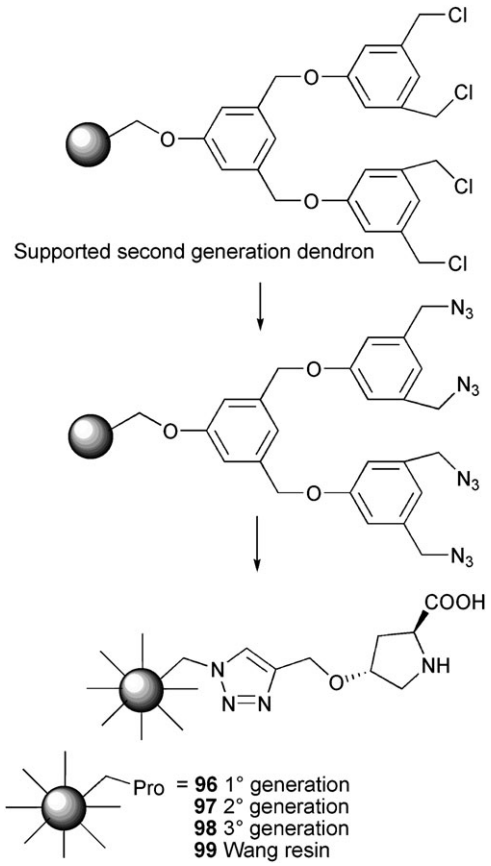
Studies were performed using aldol reaction between acetone and benzaldehyde or 4-nitrobenzaldehyde. Results showed that materials **96** and **97** gave better yields and ee values than non-dendritic material **99**. However, recycling studies, which included also catalyst **98**, showed that dendronization negatively affected the activity which dropped after 3 cycles. Only catalyst **99** was recyclable but yield and enantioselectivity were poor.

Several peptide dendrimers were prepared and investigated as synthetic models for aldolase enzymes.[79] Only one aldolase dendrimer (**100**) gave the aldol product in good ee value (61%) and in 69% conversion in 36 h. The reaction was much faster in water (>99% conversion in 3 h at 25 °C with 1 mol% catalyst) but not enantioselective (Fig. 9).

Four diphenylprolinol TMS ether/dendrite catalysts **101–104** were synthesized and used in the asymmetric Michael addition of aldehydes to β-nitrostyrene.[80] Optimal conditions were found using catalyst **102** (10 mol%) in CCl_4 at r.t. (Scheme 62).



Scheme 60



Scheme 61

Good yields and high stereoselectivities were observed. The catalyst was recovered by precipitation (recovered yield 86%) and reused four times. A small decrease both in yield and diastereoselectivity was observed [81–65%; (81 : 19)–(75 : 25)] while enantioselectivity remained unchanged.

Cyclodextrin-supported proline

Immobilization of proline derivatives into the β-cyclodextrin cavity as catalysts for direct asymmetric aldol reactions was also reported (Scheme 63). Inclusion of proline was easily achieved by refluxing a solution of (4*S*)-phenoxyproline and β-cyclodextrin. Removal of the solvent gave the immobilized (4*S*)-phenoxyproline **105**.[81] Evidence for the formation of the complex was obtained from ^{1}H NMR, ^{13}C NMR and UV-Vis spectra.

Catalyst **105** was employed in 10 mol% in the reaction between acetone and five substituted benzaldehydes. Good yields and good ee values were obtained. Moreover, this catalyst was easily recovered by filtration, and recycling experiments (4 cycles) were performed. No decrease in yield and enantioselectivity was observed.

More recently, a similar approach was followed by using the inclusion complex **106** of an adamantane proline derivative and β-cyclodextrin. This complex was used as a catalyst in the aldol reaction between several aromatic aldehydes and cyclohexanone (Scheme 64).[82] The catalyst was employed in water to yield hydroxy ketones in high stereoselectivity. Recycling

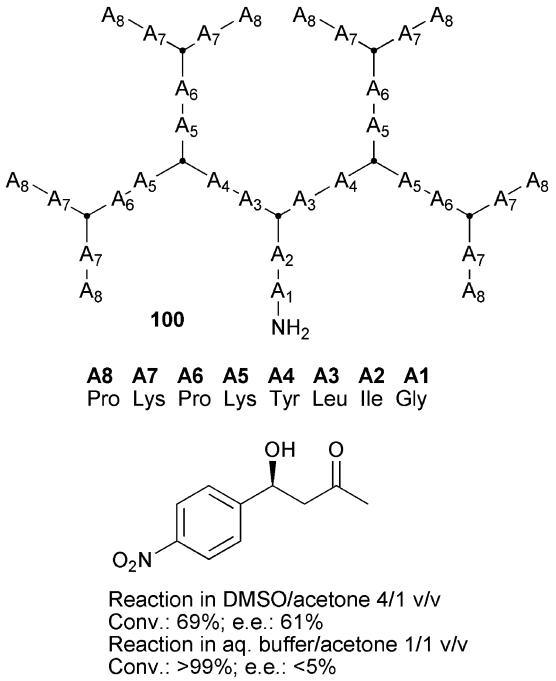
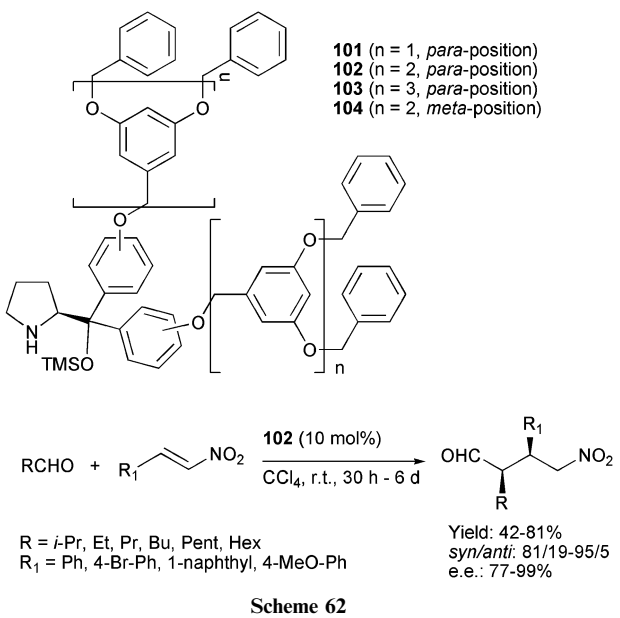


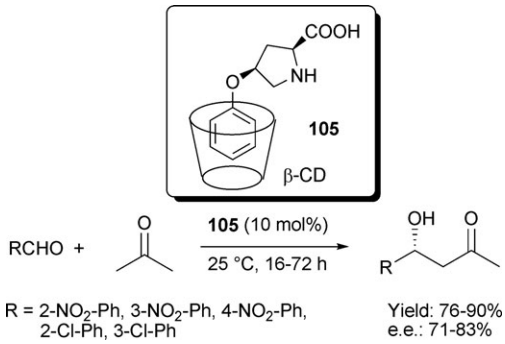
Fig. 9 Structure of aldolase dendrimer **100** and respective results from ref. 79.

investigations (4 cycles) showed no decrease in activity and stereoselectivity.

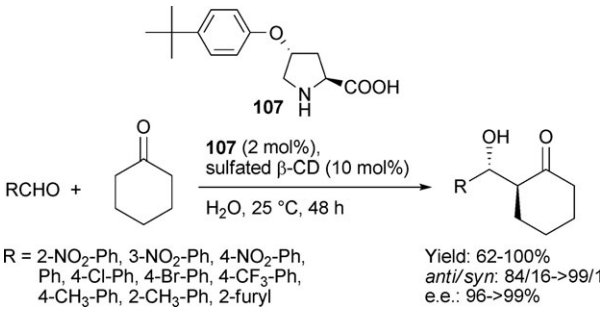
trans-4-(4-*tert*-Butylphenoxy)proline **107** was used as a catalyst (2 mol%) in the aldol reaction between cyclohexanone and several arylaldehydes in water in the presence of sulfated β-cyclodextrin (10 mol%) (Scheme 65).[83] When the reaction between cyclohexanone and benzaldehyde was performed without sulfated γ-cyclodextrin, the product was obtained in a 78% yield, 90 : 10 *anti* : *syn* ratio and 92% ee. When the reaction was performed in the presence of 10 mol% of sulfated β-cyclodextrin both yield and d.r. ratio did not change, but the ee value increased to 96%. Using



Scheme 62



Scheme 63



Scheme 65

these conditions high yields, d.r. ratios and excellent ee values were obtained. Authors concluded that the aldol reaction occurred in the water phase where organocatalyst **107** resided with sulfated β-CD. Noticeably, this approach allowed the use of stoichiometric amount of cyclohexanone. No recycling studies were carried out.

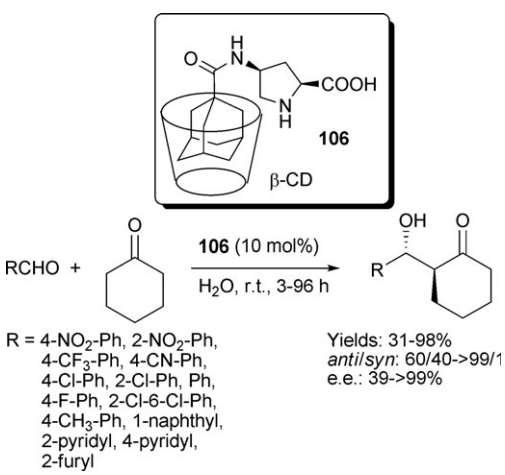
DNA-Supported proline

Recently, it has been reckoned that a proline tethered to one DNA strand might act as a catalyst for the cross-aldol reaction between an aldehyde tethered to a complementary DNA sequence and a non-tethered ketone.[84] Oligonucleotide **108**, which contains a proline moiety at its 5′-terminus and a complementary strand which bears an aldehyde at its 3′-terminus (**109**) were synthesized. The proline-modified DNA system **108** was found to be an excellent catalyst, tolerating DMSO as co-solvent in cases where water-insoluble ketones were employed (Scheme 66).

Catalyst **108** was used in a stoichiometric amount, whereas optimization of the proline catalyst design gave catalyst **110**, which was used in a substoichiometric amount employing a temperature cycling.

Layered double hydroxide-supported proline

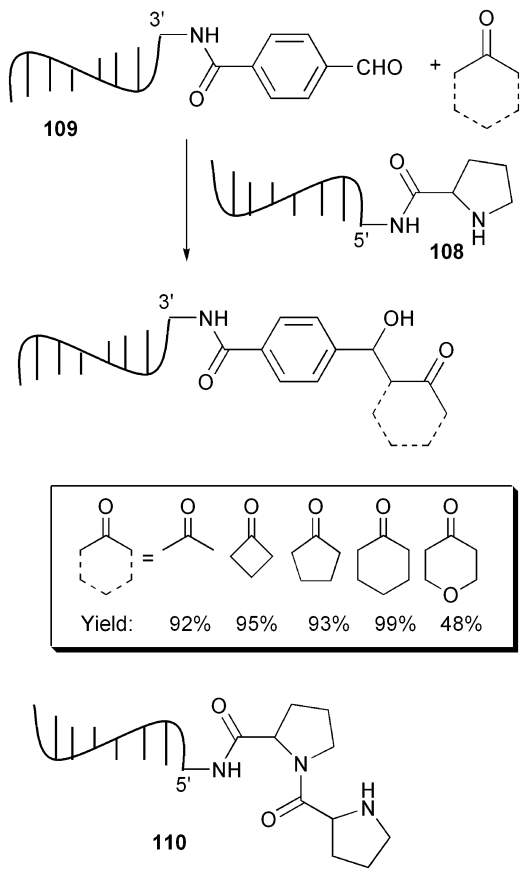
Proline was immobilized by intercalation in Mg–Al layered double hydroxide (LHD), also known as hydrotalcite-like compounds, a class of synthetic anionic layered clays represented by the general formula $[M^{II}_{1-x}M^{III}_{x}(OH)_2]^{x+}(A^{n-})_{x/n}\cdot yH_2O$.[85] Several Mg/Al L-Pro LDH materials were prepared with proline content ranging from 0.9 to 1.8 mmol g^{-1}. The materials were characterized and thermal and UV stability of the immobilized proline was tested showing that the restricted catalyst was very stable. One of these materials was used in the asymmetric aldol reaction between acetone and benzaldehyde. The product was obtained in high yield (90%) and enantioselectivity (94%). This selectivity is one of the highest obtained for the above reaction. Disappointingly, no other examples were reported and no recycling studies were performed.



Scheme 64

Conclusions

As can be seen from the data reported, immobilization of proline and proline derivatives has attracted much interest.



Scheme 66

It is fascinating how immobilization of these simple molecules has stimulated the synthetic creativity of researchers. On the basis of these reports, some consideration may be attempted. Covalently-linked organocatalysts make the recovery procedure very easy, avoiding leaching of catalyst. This is true in the case of heterogeneous supports such as 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 the case of covalently linked homogeneous organocatalysts these materials may be more active because of their homogeneous nature, but recovery of the catalyst requires precipitation which may not be quantitative. Using covalently linked organocatalysts it is possible to carry out reactions in highly polar solvents, such as water, which have been used in many applications. On the other hand, immobilization requires several synthetic steps. So, in this case it is desirable to employ only few high yielding steps using cheap starting material. The obtained material must be highly recyclable or easily regenerable. Immobilization of more expensive proline derivatives should be more interesting. Non-covalent linkage is very interesting since native proline or simple derivatives may be immobilized without the need for their modification. However, leaching should be considered a drawback. For instance, reactions in the presence of water cannot be performed. Use of biphasic catalysis is simple, especially if simple proline is used. In several cases reactions in ionic liquids were faster than the corresponding reactions in usual organic solvents. However ionic liquids are still expensive and recovery of products by extraction is tedious.

Immobilization of these organocatalysts is an interesting strategy since, in many cases, higher yields and stereoselectivities have been obtained compared to the native organocatalyst. As an example, the reaction between cyclohexanone and benzaldehyde in DMSO catalyzed by proline (30 mol%) gave the aldol product after 4 days in 85% yield with no diastereoselectivity and moderate enantioselectivity.[86] Using immobilized proline a lesser amount of catalyst was used (10 mol%) and higher stereoselectivity was obtained (d.r. 95 : 5; ee: 98%).[25]

Indeed, in many cases, use of immobilized proline or its derivative gave a more-active catalyst and higher stereoselectivity. Moreover, immobilization of proline and its derivatives allows their use in aqueous media, which is of special interest because it is directly relevant to the class I aldolase-catalyzed reactions under physiological conditions.

However, in our opinion, studies for new highly active, stereoselective and highly recyclable organocatalysts are always desirable. Organocatalysts more complex than proline or simple prolinamide or pyrrolidine derivatives may be used, and other supports may be investigated. Noticeably, no investigations have been reported about the use of continuous flow methods. Indeed, a system in which the catalyst must not be removed from the reaction vessel is very attractive. We strongly believe that further interesting developments in this field will appear soon.

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