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Supported ionic liquid asymmetric catalysis. A new method for chiral catalysts recycling. The case of proline-catalyzed aldol reaction

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Abstract—A new method for chiral catalysts recycling, based on the supported ionic liquid asymmetric catalysis concept, has been developed. This concept involves the treatment of a monolayer of covalently attached ionic liquid on the surface of silica gel with additional ionic liquid. These layers serve as the reaction phase in which the homogeneous chiral catalyst is dissolved. As first application of this concept the L-proline-catalyzed aldol reaction has been carried out. Good yields and ee values, comparable with those obtained under homogeneous conditions have been obtained. Moreover, this material shows high regenerability.

Homogeneous asymmetric catalysis is one of the most important developments in chemistry. The separation of the product from the reaction mixture, the recovery of the catalysts, and the need for organic solvents are the major disadvantages in the homogeneous catalytic process. For such economical and environmental reasons the recovery and reuse of such catalysts has became an important area of research.[1] Unfortunately, the immobilization of chiral catalysts often results in lower activities and enantioselectivities as compared to those observed for their homogeneous counterparts. More recently, room-temperature ionic liquids (RTIL) have became very useful solvents for synthesis and catalysis.[2] Since they are able to dissolve a great variety of catalysts, they have found several application in their immobilization and recycling.

The aldol reaction is one of the most important carbon–carbon bond-forming processes utilized in organic synthesis. The direct asymmetric aldol reaction between an aldehyde and an unmodified ketone is the most efficient approach from the point of view of atom-economy. Proline-catalyzed asymmetric reactions including aldol,[3] Mannich,[4] Michael,[5] and other analogous reactions[6] have been recently reported. Nonetheless proline has long been known to catalyze enantioselective Robinson annulation processes.[7]

The proline-catalyzed reactions are carried out under homogeneous conditions. Several methods have been studied in order to allow the catalyst recovery. In 2001 two routes were reported for this purpose.[3c] The first method was based on the fact that proline is not soluble in chloroform. The reaction carried out in this solvent allowed a facile recovery of the proline catalyst by filtration. The second approach was based on the immobilization of the proline on a silica gel column. Both methods gave a reduced enantiomeric excess. Good yields and ee values, compared to those obtained using nonsupported proline, were obtained by poly(ethyleneglycol)-supported proline.[8] Up to four cycles were reported with virtually unchanged ee values, but in slowly diminishing yields. Furthermore, three lots of research about the use of L-proline in ionic liquid as reusable catalyst for aldol reaction were reported.[9] In both cases bmimPF_6 was the ionic liquid of choice. Good yields and good to high selectivities were obtained. Recycling studies showed slightly diminished yields and ee values. In one case excellent enantioselectivities, even after four recycles, were found in the cross-aldol reactions.[9c] However, DMF was used as co-solvent. Ionic liquids

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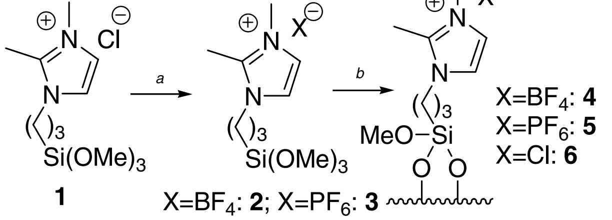
were also employed for asymmetric Mannich reactions involving ketone and aldehyde nucleophiles. In this case L-proline in bmimBF_4 was used.[10] However, we believe that a good recyclable form of L-proline for asymmetric aldol and related reactions is still desirable.

Here we report the first example of supported ionic liquid asymmetric catalysis. Recently it has been reported the new concept of supported ionic liquid catalysis, which involves the treatment of a monolayer of covalently attached ionic liquid on the surface of silica gel with additional ionic liquid.[11] These layers serve as the reaction phase in which the homogeneous catalyst is dissolved. Since ionic liquids are expensive it is desirable to minimize the amount of utilized ionic liquid in a process allowing at the same time a facile recovery of the catalyst. We applied the concept of supported ionic liquid asymmetric catalysis to L-proline asymmetric aldol reaction. The question is: can proline supported in such a manner give high yields and ee values? We started from two contrasting observations. Proline supported on silica gel gave low ee values[3c] whereas proline in RTIL gave comparable levels of ee values with respect to those obtained under homogeneous conditions.[9]

We investigated if the covalently attached and the adsorbed ionic liquid may offer a suitable phase in which the proline asymmetric aldol reaction can be carried out.

First we prepared the ionic liquids **2** and **3** by reaction of (3-chloropropyl)trimethoxysilane and 1,2-dimethylimidazole to give 1,3-dimethyl-3-(3-trimethoxysilylpropyl)-imidazolium chloride **1**. Chloride **1** was treated with either sodium tetrafluoroborate or sodium hexafluorophosphate in acetone to give the corresponding derivatives **2** and **3**. Then, pretreated silica gel was refluxed with a chloroform solution of compounds **1**–**3** to give, after a condensation reaction, the modified support materials **4**–**6** (Scheme 1).[12] At this stage no efforts have been made to fully characterize these materials.[13]

Next we prepared the supported proline material. To a solution containing L-proline in bmimBF_4 (or bmimPF_6)/water/acetonitrile the modified silica gel **4** or **5** was added. After the solvent was removed under reduced pressure a white powder was obtained (**4**/bmimBF_4 proline; **5**/bmimPF_6 proline)[14] (Scheme 1).



1

X=BF_4: **2**; X=PF_6: **3**

X=BF_4: **4**
X=PF_6: **5**
X=Cl: **6**

Scheme 1. Reagents and conditions: (a) $NaBF_4$ or $NaPF_6$, acetone, rt, 3 d, **2** (75%), **3** (60%); (b) SiO_2 (0.04–0.063 mm), $CHCl_3$, 65 °C, 26 h.

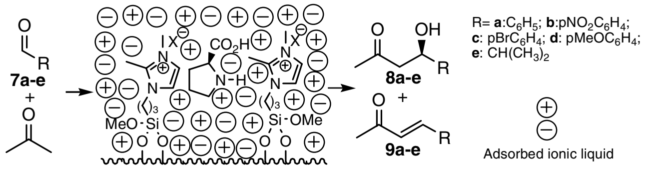


Figure 1. Supported ionic liquid asymmetric catalysis.

At first we investigated the aldol reaction between acetone and benzaldehyde. The reaction was carried out by simply mixing the supported proline (30% mol) with acetone and benzaldehyde (Fig. 1).[15] For the sake of comparison we also carried out the reaction with L-proline supported on modified silica gels **4** and **6** (**4**/proline; **6**/proline) and with L-proline supported on silica gel containing adsorbed bmimBF_4 (SiO_2/bmimBF_4 proline). The **4**/bmimBF_4 proline system gave the best result (entry 1). Indeed, we found a 51% of isolated yield with 64% ee. This ee is comparable with that obtained under the homogeneous condition (60% ee, entry 6) and with the PEG-proline/DMF system (59% ee, entry 9) and slightly lower than that observed in pure ionic liquid (entries 7–8) (Table 1).

Interestingly the **4**/proline system gave the same ee but at a lower yield (entry 2). A meaningful decrease in ee was observed with SiO_2/bmimBF_4 proline system (entry 3). Also **5**/bmimPF_6 proline gave a decreased ee with a very low yield (entry 4). Again good yield was obtained with the **6**/proline system, but with low ee (entry 5). Moreover, in the latter case a high amount of undesirable α,β-unsaturated compound **9a** was isolated. Results in entries 1–3 seem to indicate that, in order to achieve good yield and ee, the surface of silica gel must be functionalized with covalently attached ionic liquid. The additional adsorbed ionic liquid does not have any effect on the ee, but a better isolated yield may be obtained. However, adsorbed ionic liquid does not have any beneficial effect on the ee. Even the anion seems to play an important role. Indeed, both the **5**/bmimPF_6 proline (see entries 1 and 4) and **6**/proline (see entries 2 and 5) system gave poor ee.

Table 1. Aldol reaction between acetone and benzaldehyde (**7a**) with different L-proline catalyst forms

Entry	Catalyst	**7/8/9** ratio[a]	**8** (%)[b]	ee **8** (%)[c]
1[d]	**4**/bmimBF_4 Proline	21:67:12	51	64
2[d]	**4**/Proline	27:59:14	40	64
3[d]	SiO_2/bmimBF_4 Proline	50:43:7	38	12
4[d]	**5**/bmimPF_6 Proline	71:26:3	15	52
5[d]	**6**/Proline	1:61:38	59	40
6[e]	Proline/DMSO	—	62	60
7[f]	Proline/bmimPF_6	13:75:12	58	71
8[g]	Proline/bmimPF_6	—	55	76
9[h]	PEG-proline/DMF	—	45	59

[a] Determined by ^{1}H NMR.
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] Reaction time 18 h.
[e] Ref. 3c.
[f] Ref. 9b.
[g] Ref. 9a.
[h] Ref. 8.

Table 2. Aldol reaction of compounds **7a–e** in the presence of **4**/bmimBF$_4$ proline catalyst and recycling studies

Entry	Cycle	**7**	**7/8/9** ratio[a]	**8** (%)[b]	ee **8** (%)[c]
1	1	**a**	21:67:12	51	64
2	2	**a**	26:66:8	51	64
3	3	**a**	28:66:6	51	64
4	1	**b**	<1:98:<1	85	66
5	2	**b**	<1:98:<1	84	66
6	3	**b**	<1:98:<1	93	68
7	4	**b**	<1:98:<1	90	70
8	1	**c**	12:79:9	75	70[d]
9	2	**d**	92:7:1	5	Nd
10	3	**b**	<1:98:<1	92	70
11	1	**e**	Nd	75	96

[a] Determined by ^{1}H NMR.

[b] Isolated yield.

[c] Determined by chiral HPLC.

[d] Determined by ^{1}H NMR using Eu(hfc)$_3$.

After these preliminary results we started investigations about the regenerability of the system (Table 2). We chose the **4**/bmimBF$_4$ proline system since it gave a higher yield and ee. The **4**/bmimBF$_4$ proline system was used three times in the reaction with benzaldehyde (entries 1–3) giving highly reproducible results. Although the ee was slightly lower than that observed under homogeneous ionic liquid conditions,[9] in the latter case a decrease in ee and yield was observed even after one cycle.[9a] At the end of each cycle the modified silica gel was slightly concentrated, to remove acetone, and filtered with diethyl ether.[16] It was dried for a few minutes under reduced pressure then reused. Next we checked the reaction with *p*-nitrobenzaldehyde. This reaction was carried out four times (entries 4–7). Only aldol product was found with isolated yield ranging from 84% to 93% and good ee. The ee was lower than that in homogeneous conditions,[3c] but better than in ionic liquid.[9a] However, our results about recycling were much better than those obtained with poly(ethylene glycol)-supported proline.[8] Indeed, even if ee values were slightly higher, yields were lower and significantly decreased after four cycles. Moreover, it should be remembered that the reactions with the latter system were carried out in toxic solvents such as DMF. The reaction with *p*-bromobenzaldehyde gave the aldol product in good yield and ee (entry 8), very similar to that obtained both in DMSO[3c] and bmimPF$_6$.[9b] The catalyst was reused in the reaction with *p*-methoxybenzaldehyde that, however, gave a very low yield (entry 9). In order to test if the catalyst was still working the third use was carried out with *p*-nitrobenzaldehyde. Again high yield and ee were obtained (entry 10). The reaction with isobutyraldehyde gave good isolated yield and high ee (entry 11), comparable to that obtained in DMSO.[3c]

In summary these results support our idea that the supported ionic liquid asymmetric catalysis could be an interesting methodology for catalyst recycling. The useful level of isolated yields and ee values coupled with very easy recovery make this material very promising. In our laboratory further applications are currently under progress.[17]

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References and notes

1. (a) Song, C. E.; Lee, S. *Chem. Rev.* **2002**, *102*, 3495–3524; (b) Fan, Q.-H.; Chan, A. S. C. *Chem. Rev.* **2002**, *102*, 3385–3466; (c) *Chiral Catalyst Immobilization and Recycling*; De Vos, D. E., Vankelecom, I. F. J., Jacobs, P. A., Eds.; Weinheim: Wiley-VCH, 2000.
2. (a) Welton, T. *Chem. Rev.* **1999**, *99*, 2071–2083; (b) Zhao, D.; Wu, M.; Kou, Y.; Min, E. *Catal. Today* **2002**, *74*, 157–189.
3. Selected examples: (a) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396; (b) List, B.; Castello, C. *Org. Lett.* **2001**, *3*, 573–575; (c) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267; (d) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798–6799; (e) Chowdary, N. S.; Ramachary, D. B.; Córdova, A.; Barbas, C. F., III. *Tetrahedron Lett.* **2002**, *43*, 9591–9595; (f) Córdova, A.; Notz, W.; Barbas, C. F., III. *J. Org. Chem.* **2002**, *67*, 301–303; (g) Bøgevig, A.; Poulsen, T. B.; Zhuang, W.; Jørgensen, K. A. *Synlett* **2003**, 1915–1918; (h) Pan, Q.; Zou, B.; Wang, Y.; Ma, D. *Org. Lett.* **2004**, *6*, 1009–1012.
4. Selected examples: (a) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827–833; (b) Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1842–1843; (c) Córdova, A. *Chem. Eur. J.* **2004**, *10*, 1987–1997.
5. (a) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423–2425; (b) Enders, D.; Seki, A. *Synlett* **2002**, 26–28.
6. Selected examples: (a) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656–5657; (b) Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bøgevig, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254–6255; (c) Duthaler, R. O. *Angew. Chem., Int. Ed.* **2003**, *42*, 975–978; (d) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 1112–1115; (e) Bøgevig, A.; Sundén, H.; Córdova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1109–1112.
7. Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496.
8. Benaglia, M.; Cinquini, M.; Cozzi, F.; Puglisi, A.; Celentano, G. *Adv. Synth. Catal.* **2002**, *344*, 533–542.
9. (a) Kotrusz, P.; Kmentová, I.; Gotov, B.; Toma, Š.; Solčániová, E. *Chem. Commun.* **2002**, 2510–2511; (b) Loh, T.-P.; Feng, L.-C.; Yang, H.-Y.; Yang, J.-Y. *Tetrahedron Lett.* **2002**, *43*, 8741–8743; (c) Córdova, A. *Tetrahedron Lett.* **2004**, *45*, 3949–3952.
10. Chowdari, N. S.; Ramachary, D. B.; Barbas, C. F., III. *Synlett* **2003**, 1906–1909.
11. Mehnert, C. P.; Cook, R. A.; Dispenziere, N. C.; Afeworki, M. *J. Am. Chem. Soc.* **2002**, *124*, 12932–12933.
12. Compound **2** (3.46 g, 10 mmol) or **3** (4.04 g, 10 mmol) or **1** (2.95 g, 10 mmol) was dissolved in chloroform (50 mL) and treated with silica gel (Merck, 0.063–0.2 mm, BET surface area 453 m^2/g, dried under vacuum and heated to 180 °C overnight; 3.0 g). The mixture was heated under reflux (65 °C) for 26 h. After cooling at room temperature, the solid was isolated by filtration and washed with acetonitrile (50 mL) and diethyl ether (50 mL). The solid was dried under reduced pressure to give a white powder (**4**, 4.2 g; **5**, 4.3 g; **1**, 3.9 g).

13. BET surface area: **4** (185 m^2/g), **5** (123 m^2/g), **6** (283 m^2/g).
14. *Preparation of* **4**/*bmimBF$_4$ proline*. In a round bottom flask were added L-proline (17.5 mg, 0.15 mmol), bmimBF$_4$ (130 mg), water (0.4 mL) and acetonitrile (0.5 mL). To this solution the modified silica gel (**4**) was added. The mixture was shaken for a few minutes then evaporated under reduced pressure for 25 h to give a white powder. BET surface area of **4**/bmimBF$_4$ proline: 38 m^2/g. **5**/bmimPF$_6$ proline: 66 m^2/g.
15. *General procedure for aldol reaction*. A solution of aldehyde (0.5 mmol) in acetone (1 mL) was added to the **4**/bmimBF$_4$ proline system (650 mg, 30% L-proline). The mixture was stirred at room temperature for 18 h, then it was slightly concentrated under reduced pressure. The mixture was taken with diethyl ether and filtered under reduced pressure. The solution was evaporated, checked by NMR and finally purified by chromatography (light petroleum/ethyl acetate) to give the aldol product. The catalytic system was dried for a few minutes then reused.
16. No leaching of proline was observed (NMR determination).
17. Two proline-catalyzed Mannich reactions have been carried out: (a) acetone, *p*-nitrobenzaldehyde and *p*-anisidine with **4**/bmimBF$_4$ proline used four times and (b) acetone and the corresponding preformed imine with fresh **4**/bmimBF$_4$ proline. Both reactions gave the β-amino ketone in 60% yield.[4a]