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L-Proline in an ionic liquid as an efficient and reusable catalyst for direct asymmetric aldol reactions

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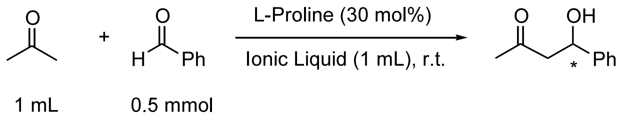
Abstract—L-proline in imidazolium-based ionic liquids has been successfully used as an efficient and reusable catalyst for direct asymmetric aldol reactions. © 2002 Published by Elsevier Science Ltd.

The asymmetric aldol reaction is one of the most efficient processes for the synthesis of optically active β-hydroxy carbonyl compounds which are important intermediates in organic synthesis. Among them, the direct asymmetric aldol reaction between an aldehyde and an unmodified ketone is the most efficient and attractive from the point of atom-economy.[1,2] Recently, the commercially available amino acid L-proline has been elegantly used to catalyze the direct asymmetric aldol reaction, affording β-hydroxy carbonyl compounds with moderate to excellent ee values.[3–5] However, this reaction was carried out in organic solvents (DMSO, DMF, chloroform, acetone, THF, or acetonitrile), whose toxic and/or hazardous properties limit the use of this reaction in industrial processes as solvents like DMSO or acetone can only be used without significant risks in academic laboratories. Furthermore, it is rather difficult to reuse the chiral catalyst.

In recent years, ionic liquids have attracted great interest among synthetic organic chemists because they have been shown to function as novel green reaction media.[6,7] This is mainly due to their nonvolatile nature, insolubility in some solvents as well as their ability to dissolve catalysts, allowing their easy recycling. In this study, we investigated the catalytic activity of L-proline in imidazolium-based ionic liquids for the direct asymmetric aldol reaction as well as its regenerability. To the best of our knowledge, this is the first demonstration of a direct asymmetric aldol reaction carried out in an ionic liquid.



(1)

We initiated our study by using benzaldehyde and acetone as substrates in various ionic liquids (a moderate ee value (60%) in DMSO has been reported in the literature[4a,c]) (Eq. (1)). To a dried round bottomed flask charged with L-proline (30 mol%, 17.3 mg) was added the ionic liquid (1 mL) followed by acetone (1 mL) and benzaldehyde (0.5 mmol, 51 μL) at room temperature. After some time, the reaction mixture was extracted with ether (4×15 mL) to leave the ionic liquid containing L-proline. According to the above procedure, a series of imidazolium-based ionic liquids were examined. The results are summarized in Table 1. It can be seen that all ionic liquids gave the desired aldol addition product with comparable or better ee (58–78%) than the literature.[4a,c] It was found that the reaction carried out in omimCl was faster than those in other ionic liquids. After 20 h, all the aldehyde had been consumed. However, the formation of an elimination product affected the yield of the desired aldol addition product (entry 2). An unexpected finding was achieved by using bmim PF_6, which produced no elimination product within 20 h (entry 4). *The effect of the amount of catalyst and ketone on the yield and the ee was briefly investigated using 5 mol% L-proline and 10 equiv. of acetone to benzaldehyde in bmim PF_6 (entry 6). The desired aldol product was isolated in 43% yield (65% ee) after 48 h, which suggested that the use of less catalyst and ketone can affect the reaction rate but not the ee value.*

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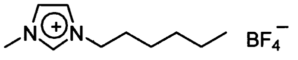
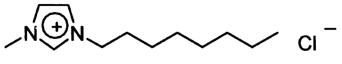
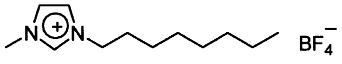
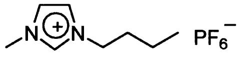
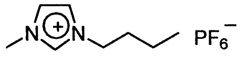
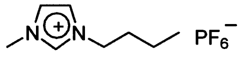
Table 1. L-Proline-catalyzed asymmetric direct aldol reaction of acetone and benzaldehyde in various ionic liquids

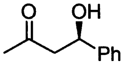
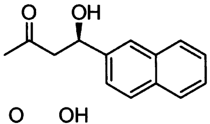
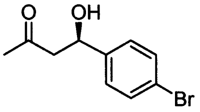
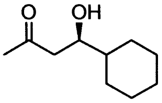
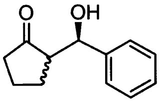
Entry	Ionic Liquids	Time	ST:EP:AP[b]	Isolated yield (%)	ee (%)[c]
1	 hmim BF_4	45 h	6:34:60	50	58
2	 omim Cl	20 h	0:55:45	30	78
3	 omim BF_4	20 h	11:16:73	59	71
4	 bmim PF_6	20 h	40:0:60	48	71[a]
5	 bmim PF_6	45 h	13:12:75	65	71
6	 bmim PF_6	48 h	34:7:59	43	65[d]

[a] No elimination product was detected by ^{1}H NMR.. [b] ST = starting material (benzaldehyde), EP = elimination product, AP = aldol product. Relative ratio was estimated based on crude NMR. [c] The ee was determined by chiral HPLC analysis using a Chiralcel OB column. [d] This reaction was carried out using 5 mol% L-proline and 10 equivalents of acetone.

Considering both the yield and ee value of the reaction, we decided to employ bmim PF_6 as the reaction media to investigate further the scope and limitation of this type of reaction. In our study, both aromatic and aliphatic aldehydes were examined by employing 30 mol% L-proline, 1 mL acetone in 1 mL bmim PF_6 (Table 2). In all cases, the expected aldol addition products were obtained in good yields with moderate to excellent ee values. Besides acetone, cyclopentanone was also studied and an excellent yield together with good diastereoselectivity was observed.

With the success of the above reactions, we continued our study by exploring the recyclability of the catalyst which is important from the industrial point of view, especially when expensive catalysts are used. We carried out our study by using the reaction of acetone and benzaldehyde in bmim PF_6 as a model study. After the

Table 2. L-Proline-catalyzed asymmetric direct aldol reactions in bmim PF_6

Entry	Products	Time	ST:EP:AP[a]	Isolated yield (%)	ee (%)[b]
1		25 h	13:12:75	58	71
2		25 h	15:14:71	60	69
3		25 h	6:8:86	72	67
4		25 h	8:11:81	65	89
5		25 h	5:0:95	83 *dr: 61: 39*[c]	n.d[d]

[a] ST = starting material (aldehyde), EP = elimination product, AP = aldol product. Relative ratio was estimated based on crude NMR. [b] The ee was determined by chiral HPLC analysis using a Chiralcel OB column or chirapak AD column. [c] Relative stereochemistry not determined. [d] n.d. = not determined, since the two diastereoisomers cannot be separated by flash column chromatography, we were unable to analyze the *ee*.

Table 3. Recycling study of the L-proline-catalyzed direct asymmetric aldol reaction

Times	ST:EP:AP[a]	Isolated yield (%)	ee (%)[b]
1	13:12:75	58	71
2	19:10:71	56	71
3	17:16:67	53	69
4	11:23:66	52	67

[a] ST = starting material (aldehyde), EP = elimination product, AP = aldol product. Relative ratio was estimated based on crude NMR.

[b] The ee was determined by chiral HPLC analysis using a Chiralcel OB column.

reaction was completed, the reaction mixture was extracted with ether (4×15 mL) to give the ionic liquid residue containing L-proline (from ^{1}H NMR, there was no aldol addition product). The ^{1}H NMR of the crude product showed the absence of L-proline. To the residue was added acetone and benzaldehyde and the reaction mixture was stirred at room temperature. This process was repeated four times and it was found that the desired aldol product could still be obtained with a comparable yield and ee value (Table 3).

In summary, the L-proline-catalyzed direct asymmetric aldol reaction has been successfully carried out in imidazolium-based ionic liquids with comparable or better ee values. In most cases, less elimination product or no elimination product was detected. Further study regarding the recycling of the catalyst has revealed that L-proline in an ionic liquid can be reused at least four times with comparable yields and ee values. The possibility of carrying out asymmetric reactions using a chiral catalyst in an ionic liquid greatly enhances the synthetic value of ionic liquids as green reaction media. Research along this direction is in progress.

Typical experimental procedure: To a dried 25 mL round-bottomed flask charged with L-proline (0.15 mmol, 17.3 mg) was added bmim PF_6 (1 mL) followed by acetone (1 mL) and benzaldehyde (0.5 mmol, 51 μL) at ambient temperature. The reaction mixture was stirred at that temperature for 25 h before extraction with ether (4×15 mL). The combined ether layers were concentrated in vacuo. The pure aldol addition product was obtained as a colorless oil after flash silica gel column chromatography, eluting with *n*-hexane: EtOAc = 6:1. Yield: 58%; $R_f = 0.35$ (*n*-hexane:ethyl acetate = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.20 (s, 3H, C*H*$_3$), 2.79–2.94 (m, 2H, C*H*$_2$), 3.28 (br, 1H, CHO*H*), 5.16 (dd, $J = 3.5$, 8.7 Hz, 1H, C*H*OH), 7.26–7.36 (m, 5H, *Ph*); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 30.7 (*C*H$_3$), 51.9 (*C*H$_2$), 69.8 (*C*HOH), 125.6, 127.7, 128.5, 142.7 (*Ph*), 209.0 (*C*=O); MS (EI) (*m*/*z*, relative intensity): 164 (28), 146 (22), 131 (32), 106 (100), 77 (97), 58 (25), 43 (52); HRMS (EI) [M$^+$]: calcd for $C_{10}H_{12}O_2$ 164.0833 found 164.0837; FTIR (neat, KBr plate) cm^{-1}: 2960, 2922, 2852, 1707, 1453, 1417, 1394; HPLC (Chiralcel OB, *n*-hexane/*i*-PrOH = 95:5, flow rate 0.5 mL/min, $\lambda = 254$ nm) t_R (major) = 37.78 min, t_R (minor) = 34.67 min; $[\alpha]_D^{28} = +55.4°$ (*c* 1.0, $CHCl_3$). The residual ionic liquid containing L-proline was further concentrated in vacuo to remove ether or acetone before reuse.

Acknowledgements

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