Chiral Ionic Liquid Containing L-Proline Unit as a Highly Efficient and Recyclable Asymmetric Organocatalyst for Aldol Reaction

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A functionalized chiral ionic liquid (CIL) containing L-proline unit exhibits as a highly efficient and recyclable asymmetric organocatalyst for aldol condensation of aldehydes and ketones in [Bmim][BF_4] at room temperature, which afford the corresponding products with satisfactory isolated yields and enantiomeric excesses.

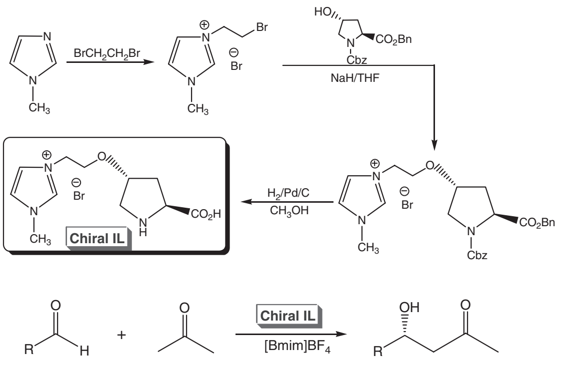
β-Hydroxy carbonyl and 1,3-diol units are frequently found in the skeleton of natural products. The aldol reaction is a powerful and concise method for preparing these units from two carbonyl compounds such as a ketone and an aldehyde, or an aldehyde and an aldehyde. Over the last three decade, the catalytic enantioselective aldol reaction has received a great deal of attention from synthetic organic chemists.[1] Mukaiyama et al. established the chiral Lewis acid-catalyzed aldol reactions,[2] Denmark et al. developed chiral Lewis base-catalyzed aldol reactions,[3] and Barbas et al. demonstrated antibodies[4] and aldolase enzymes[5] catalyzed aldol reactions, as the principal chemical reactions for the stereoselective construction of complex polyol architecture. In comparison with the above-mentioned processes using the pregeneration of enolates or enolate equivalents as the aldol donor, the direct aldol reaction is highly economic. In 1997, Shibasaki et al. reported the first example of a direct asymmetric aldol reaction catalyzed by heterobimetallic complexes.[6] Three years later, Trost and Ito designed a zinc complex for the direct catalytic asymmetric aldol reaction with high enantioselectivities.[7] Meanwhile, List, Barbas, and their co-workers found that L-proline could work as a catalyst in the direct asymmetric aldol reaction between a ketone and an aldehyde.[8] Since then, L-proline and its structural analogues have been widely used in asymmetric catalytic direct aldol reactions.[9] However, highly enantioselective for a comparably narrow range of substrates and requirement of 30 mol % catalyst loading are usually observed in some cases. So, it is desirable to develop highly enantioselective and efficient chiral organocatalysts with broad substrate applicability and low catalyst loading or their recyclability in this field.

In the last decade, room temperature ionic liquids (ILs) have attracted much attention as environmentally benign reaction media because of their many fascinating and intriguing properties such as high thermal and chemical stability, no measurable vapor pressure, no flammability, and high loading capacity.[10] They have been widely used in many areas of organic,[11] organometallic,[12] and enzymatic syntheses[13] as well as in analytical applications.[14] In most cases, ILs can be recycled easily. Chiral ILs are particularly attractive owing to their potential for chiral discrimination, as in asymmetric synthesis and optical resolution of racemates. Recent publications have documented the preparation of various chiral ILs and their potential utility as reaction media for inducing asymmetric synthesis.[15] However, there are few reports on chiral ILs for inducing asymmetric reaction, but efficient one with high enantiomeric excess (ee) is still rare.[16]

Here, we wish to explore a functionalized chiral ionic liquid (CIL) containing L-proline unit as a highly efficient and recyclable asymmetric organocatalyst for aldol reactions. In the presence of the CIL (approximately 10 mol % of L-proline unit), the aldol reactions between acetone and a variety of aldehydes occurred smoothly in 1-*n*-butyl-3-methylimidazolium tetrafluoroborate [Bmim][BF_4] to afford the corresponding products with satisfactory isolated yields (53–94%) and ee (64–93%). It is noteworthy that both of the CIL and [Bmim][BF_4] are recycled up to six times with only minor decreases in product yields, but always maintenances in ee.

The synthesis of the chiral ionic liquid containing L-proline unit was carried out following the route described in Scheme 1. It was readily prepared through a straightforward three-step procedure from commercially available starting materials and reagents in good yield and high purity.

For the evaluation of the catalytic properties of chiral ionic liquid catalyst and optimization of aldol reaction conditions, the reaction between *p*-nitrobenzaldehyde and acetone served as a model reaction. The aldol reaction took place smoothly at room temperature in the presence of chiral ionic liquid (10 mol %) in [Bmim][BF_4] to generate the product in 94% yield and 82% ee. It is better than the results from the use of acetone, DMSO or [Bmim][PF_6] as the solvent. The anion of the ionic liquids affects on the reaction. A slightly lower yield and ee were observed using [Bmim][PF_6] as solvent instead of [Bmim][BF_4]. The reaction temperature plays an important role in the reaction. At the room temperature (25 °C), the reaction took place smoothly with both good isolated yield and enantioselectivity. A slightly higher yield was obtained along with sacrificing ee when the reaction was performed at 40 °C. Meanwhile, a slightly higher ee was observed along with decreasing yield when the



Scheme 1.

Table 1. Chiral ionic liquid catalyzed asymmetric aldol reaction[a]

Entry	Aldehyde	Ketone	Yield[b]/%	ee[c]/%
1	p-$\mathrm{NO_2C_6H_4CHO}$	$\mathrm{CH_3COCH_3}$	94	82
2	p-$\mathrm{BrC_6H_4CHO}$	$\mathrm{CH_3COCH_3}$	72	83
3	p-$\mathrm{ClC_6H_4CHO}$	$\mathrm{CH_3COCH_3}$	76	84
4	p-$\mathrm{CNC_6H_4CHO}$	$\mathrm{CH_3COCH_3}$	84	83
5	p-$\mathrm{CF_3C_6H_4CHO}$	$\mathrm{CH_3COCH_3}$	82	86
6	o-$\mathrm{NO_2C_6H_4CHO}$	$\mathrm{CH_3COCH_3}$	90	92
7	o-$\mathrm{ClC_6H_4CHO}$	$\mathrm{CH_3COCH_3}$	70	93
8	o-$\mathrm{BrC_6H_4CHO}$	$\mathrm{CH_3COCH_3}$	75	82
9	2-Cl-6-$\mathrm{ClC_6H_3CHO}$	$\mathrm{CH_3COCH_3}$	93	84
10	2-Cl-4-$\mathrm{ClC_6H_3CHO}$	$\mathrm{CH_3COCH_3}$	82	64
11	2-Cl-5-$\mathrm{NO_2C_6H_3CHO}$	$\mathrm{CH_3COCH_3}$	92	76
12	m-$\mathrm{NO_2C_6H_4CHO}$	$\mathrm{CH_3COCH_3}$	94	84
13	4-Cl-3-$\mathrm{NO_2C_6H_3CHO}$	$\mathrm{CH_3COCH_3}$	84	65
14	p-$\mathrm{CH_3C_6H_4CHO}$	$\mathrm{CH_3COCH_3}$	53	77

[a] Aldehyde (0.5 mmol), acetone (1.0 mL), [Bmim][$\mathrm{BF_4}$] (1.0 mL), and chiral ionic liquid (contains 0.05 mmol of L-proline unit) was stirred at room temperature for 24 h. [b] Isolated yields. [c] Determined by chiral HPLC analysis.

reaction was performed at 0 to −10 °C. It is interesting to note that both of isolated yields and ee were maintained when more than 10 mol % of chiral ionic liquid loading was added to the reaction. A lower yield of aldol product was isolated when less than 10 mol % of chiral ionic liquid was used in the reaction. It was found that the reaction was accomplished as the reaction was carried out for more than 24 h.

To examine the versatility of this method, we extended our studies to a variety of aldehydes and acetone. As the results shown in Table 1, aromatic aldehydes bearing electron-withdrawing groups, such as chloro, bromo, cyano, trifluoromethyl, and nitro groups, were able to undergo smoothly aldol condensation with acetone in the presence of chiral ionic liquid (10 mol %) in [Bmim][$\mathrm{BF_4}$] at room temperature. The reactions generated the corresponding aldol products in good yields (53–94%) and good enantioselectivities (64–93% ee). However, aromatic aldehydes bearing electron-donating group, such as methyl, was also able to undergo aldol condensation with acetone under the standard reaction conditions in lower yields (53%) and good enantioselectivity (77% ee).

To screen the recyclability of chiral ionic liquid (CIL) and [Bmim][$\mathrm{BF_4}$], a more practical method was applied to the reaction between p-nitrobenzaldehyde and acetone under present reaction conditions. When p-nitrobenzaldehyde was treated with acetone with a catalyst loading of 10 mol % L-proline unit at room temperature for 24 h, the desired aldol condensation product was obtained in 94% yield with 82% ee. After carrying out a reaction, isolating the product from the reaction mixture, washing with solvents, drying, and recovering CIL and [Bmim][$\mathrm{BF_4}$], fresh starting materials were charged into the reaction system. The reactions still proceeded well. The CIL and [Bmim][$\mathrm{BF_4}$] are recycled six repetitive cycles with only minor decreases in product yields, but always maintenances ee.

In conclusion, we have developed a chiral ionic liquid containing L-proline unit for asymmetric inducing direct aldol reaction between aldehyde and ketone. The reaction was carried out in the presence of the CIL (10 mol % of L-proline unit) in [Bmim][$\mathrm{BF_4}$] at room temperature. The reactions generated the corresponding products with satisfactory isolated yields and ee. It is noteworthy that both of CIL and [Bmim][$\mathrm{BF_4}$] are recycled up to six times with only minor decreases in product yields, but always maintenances in ee.

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