Asymmetric direct aldol reaction catalyzed by an L-prolinamide derivative: considerable improvement of the catalytic efficiency in the ionic liquid†

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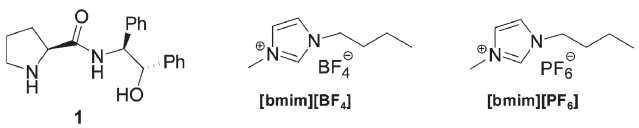
The asymmetric direct aldol reactions of a wide scope of aldehydes with unmodified ketones in the presence of 20 mol% (*S,S,S*)-pyrrolidine-2-carboxylic acid (2′-hydroxyl-1′,2′-diphenyl-ethyl)-amine (1) were performed in ionic liquids; aldol products with 91 to >99% ees for aromatic aldehydes and 99% ees for alphatic aldehydes were offered by the present procedure.

The aldol reaction is one of the most powerful methods of forming carbon–carbon bonds. Its great synthetic utility in organic synthesis has promoted a rapid development of numerous highly enantioselective chiral catalysts.[1] Direct aldol reaction is highly atomically economic, compared with the well established processes using enol or enolate derivatives as the aldol donor.[2] Recently, a highly enantioselective direct aldol reaction in the presence of a catalytic amount of Lewis acid has been reported.[3] Pioneered by List and Barbas III and their co-workers, L-proline has been a very popular organocatalyst for aldol and other reactions involving an enamine intermediate in their transition state.[4] However, only fair enantioselectivity is provided by L-proline for direct aldol reactions of aromatic aldehydes with unmodified ketones.[4a,b] We very recently found that an L-prolinamide **1** derived from (1*S*,2*S*)-1,2-diphenyl-2-aminoethanol, a more active catalyst than L-proline, efficiently catalyzes the direct aldol reaction with high enantioslectivity for both aromatic and aliphatic aldehydes. However, limitations such as excellent enantioselectivity (>90% ee) only observed for 4-substituted benzaldehydes and α-unbranched aliphatic aldehydes still need to be solved.[5] Ionic liquids have been widely used as environmentally benign solvents to replace common organic media.[6] Moreover, they are reusable, allow for simple isolation of products and enable the easy recovery of catalysts. More interesting is the enhancement of reaction efficiency by using ionic liquids as solvents.[7] Thus, the employment of an ionic liquid as the solvent for an atomically economic reaction such as the asymmetric direct aldol reaction will make the process more environmentally benign and more economical. Aldol reactions in the presence of L-proline in ionic liquids have been documented, but reduced enantioselectivity was observed in most of cases.[8] Herein we wish to present that the L-prolinamide **1** catalyzed direct aldol reaction of aldehydes with ketone in ionic liquids leads to a remarkable improvement of reaction performance in comparison with that in organic solvents.



In the presence of 20 mol% of the organocatalyst **1**, ionic liquid solvents such as [bmim][BF_4] and [bmim][PF_6] are first examined for direct aldol reaction of 4-nitrobenzaldehyde with acetone. The results are summarized in Table 1. At room temperature, the aldol reaction proceeded smoothly to give rise to the product in 83% yield and a much higher enantioselectivity (87% ee) than that resulting from the use of acetone as the solvent (69% ee) (entry 1). Significantly, high yield (82%) and excellent enanantioselectivity (94% ee) were obtained by performing the reaction at 0 °C for 14 h, which is also much greater than the reaction in the organic solvent (entry 2). Further lowering the reaction temperature to −25 °C resulted in an enhancement in the enantioselectivity (96% ee) without sacrificing the yield (entry 3). However, a similar reaction was performed in the organic solvent at low temperature with a moderate yield.[5] The anion of the ionic liquid has an influence on the reaction. Using [bmim][PF_6] as a solvent instead of [bmim][BF_4], a slightly lower enantioselectivity was observed (entry 4), and thus [bmim][BF_4] became the solvent of choice. Notably, high enatioselectivity was still maintained in the presence of reduced catalyst loading (entries 5 and 6). As little as 5 mol% of **1** is enough to catalyze the aldol reaction with 65% yield and 94% ee at 0 °C (entry 6), which is comparable with the result from a similar reaction catalyzed by 20 mol% of **1** at −25 °C in the organic solvent.[5] On the contrary, the same reaction catalyzed by 20 mol% of L-proline led to only 78% ee (entry 7).

Table 1 The direct aldol reaction of 4-nitrobenzaldehyde **2a** with acetone catalyzed by **1** in ionic liquids[a]

Entry	Solvent	Amount of **1**/mol%	*T*/°C	*t*/h	Yield[b] (%)	ee[c] (%)
1	[bmim][BF_4]	20	Rt	10	83	87 (69)
2	[bmim][BF_4]	20	0	14	82	94 (78)
3	[bmim][BF_4]	20	−25	24	82	96 (93)
4	[bmim][PF_6]	20	0	15	81	88
5	[bmim][BF_4]	10	0	24	81	94
6	[bmim][BF_4]	5	0	48	65	94
7	[bmim][BF_4]	[d]	0	14	88	78

[a] A reaction mixture of 4-nitrobenzaldehyde (0.5 mmol) and acetone (1 mL) catalyzed by 20 mol% **1** in ionic liquid (2.0 mL). [b] Isolated yield. [c] Determined by HPLC (see ESI), and the ee values in parentheses are those obtained with **1** in acetone (ref. 5). [d] In the presence of 20 mol% L-proline.

† Electronic supplementary information (ESI) available: Experimental details. See http://www.rsc.org/suppdata/cc/b4/b417267a/

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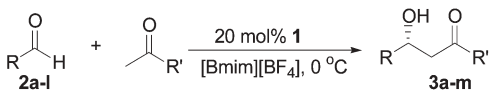
Asymmetric direct aldol reactions of a wide range of aromatic and aliphatic aldehydes with acetone and butanone were performed in [bmim][BF_4] at 0 °C. As the data shown in Table 2 indicate, in all cases examined, obvious improvements in enantioselectivities were observed when compared to the related **1** catalyzed aldol reactions in the organic solvent at low temperature (−25 °C).[5] More significant examples are the reactions of 2-chlorobenzaldehyde (**2e**) and β-naphthaldehyde (**2g**), which offer aldol products in much higher enantiomeric excesses at 0 °C than the related reactions in organic solvent at −25 °C (entries 5 and 7). Some aromatic aldehydes such as 2-nitrobenzaldehyde (**2b**), benzaldehyde (**2f**), 4-methylbenzaldehyde (**2i**), as well as 3-nitrobenzaldehyde (**2j**) previously reacted with acetone in the organic solvent to generate corresponding products with enantioselectivities ranging from 78% to 87% ee,[5] however their similar reactions lead to formation of aldol products with much higher enantioslectivities of up to 96% ee in ionic liquid at −25 °C (entries 2, 6, 9 and 10). The improved enantioselectivity was also observed with the reaction of aliphatic aldehydes by performing the reaction in the ionic liquid. For example, the reaction of cyclohexaldehyde (**2k**) with acetone also results in a higher enantioselectivity in the ionic liquid (99% ee, $R:S = 199:1$) at 0 °C than that in acetone at −25 °C (97% ee, $R:S = 66:1$). Remarkably, the enantioselectivity of the aldol reaction of 4-cyanobenzaldehyde with 2-butanone jumps to >99% ee upon employing [bmim][BF_4] as the solvent (entry 13). To our knowledge, these are the best results of asymmetric direct aldol reactions promoted by an organocatalyst (metal-free) so far.

The improved catalytic performance of organocatalyst **1** in ionic liquids might be due to the stabilization[6] of the iminium intermediate formed from the ketone and the secondary amine of **1** or because of the enhanced nucleophicility of the enamine. Studies to clarify these aspects are underway.

Table 2 Direct aldol reactions of acetone with aldehydes by chiral organic catalyst **1** in [bmim][BF_4]

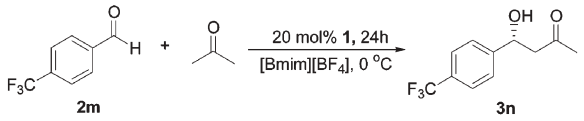


2a-l **3a-m**

Entry	Product	R	R′	Yield[b] (%)	ee[c] (%)
1	**3a**	4-$NO_2C_6H_4$	CH_3	82 (66)	94 (93)
2	**3b**	2-$NO_2C_6H_4$	CH_3	84 (52)	96[d] (78)
3	**3c**	4-BrC_6H_4	CH_3	75 (77)	91 (90)
4	**3d**	4-ClC_6H_4	CH_3	76 (75)	95[d] (93)
5	**3e**	2-ClC_6H_4	CH_3	84 (83)	91 (85)
6	**3f**	Ph	CH_3	50 (51)	92[d] (83)
7	**3g**	β-naphthyl	CH_3	85 (93)	91 (84)
8	**3h**	4-CNC_6H_4	CH_3	67 (63)	93 (88)
9	**3i**	4-Me C_6H_4	CH_3	50 (48)	92[d] (84)
10	**3j**	3-NO_2 C_6H_4	CH_3	82 (63)	96[d] (87)
11	**3k**	*c*-C_6H_{11}	CH_3	70 (85)	99 (97)
12	**3l**	*t*-Bu	CH_3	46 (51)	99 (>99)
13	**3m**	4-CNC_6H_4	C_2H_5	62 (32)	>99 (90)

[a] A reaction mixture of 4-nitrobenzaldehyde (0.5 mmol) and acetone (1 mL) catalyzed by 20 mol% **1** in ionic liquid (2.0 mL) at 0 °C for 24 h. [b] Isolated yield, and the yields in parentheses are those obtained with **1** in acetone at −25 °C (ref. 5). [c] Determined by HPLC, and the ee values in parentheses are those obtained with **1** in acetone at −25 °C (ref. 5). [d] The reaction was performed at −25 °C.

Table 3 Studies on catalyst recycling[a]



2m **3n**

Entry	Recycle	Yield[b] (%)	ee[c] (%)
1		80	94
2	1st	79	94
3	2nd	79	94
4	3rd	41	93

[a] A reaction mixture of 4-trifluoromethylbenzaldehyde (0.5 mmol) and acetone (1 mL) catalyzed by 20 mol% **1** in ionic liquid (2.0 mL) at 0 °C. [b] Isolated yield. [c] Determined by HPLC.

The possibility of reusing or recycling the organocatalyst **1** was finally examined by employing the direct aldol reaction of 4-trifluoromethylbenzaldehyde with acetone in [bmim][BF_4] as a model. The data shown in Table 3 illustrate that the catalyst **1** can be reused at least twice without sacrificing the yield and enantioselectivity (94% ee) (entries 2 and 3).

In summary, the asymmetric direct aldol reactions of a wide range of aldehydes with unmodified ketones in ionic liquids were investigated. Remarkably higher enantioselectivities were provided by the reactions in ionic liquids. Excellent enantioselectivities of 91 to >99% ees for aromatic aldehydes and of 99% ees for tested aliphatic aldehydes were afforded under the optimal conditions. The catalyst **1** can be reused at least twice without loss of its efficiency.

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