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L-Proline-Catalyzed Asymmetric Direct Aldol Reaction of Heteroaromatic Aldehydes and Acetone: Improvement of Catalytic Efficiency in Ionic Liquid bmim [BF_4]

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Abstract: L-proline in bmim [BF_4] ionic liquid has been successfully used as an efficient and reusable catalyst for the direct asymmetric aldol reaction of acetone with different heteroaromatic aldehydes to afford higher selectivity of the aldol products with good enantioselectivity.

Keywords: asymmetric aldol, enantiomeric excess, heteroaromatic aldehlydes β-hydroxy carbonyl compounds, ionic liquid, L-proline

INTRODUCTION

The aldol reaction constitutes a fundamental synthetic methodology for forming carbon–carbon bonds, and nature itself seems to prefer this reaction in its biosynthetic processes, for example, in the prebiotic formation of saccharides.[1] Its great synthetic utility in organic synthesis has promoted a rapid development of numerous highly enantioselective catalysts.[2] Synthetic methodologies involving both aldolase and catalytic antibodies have been extensively developed for accomplishing aldol reactions with high efficiency and selectivity.[3]

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Pioneered by List, Barbas, and their coworkers, L-proline has been a very popular organocatalyst for aldol and other reactions involving an enamine intermediate in their transition state.[4] However, the reactivity and selectivity of some of these proline-catalyzed aldol reactions have serious limitations because of the difficulty in modifying the structure of proline. Furthermore, a substoichiometric amount of proline is often necessary to achieve reasonable yields in the direct aldol reaction of aldehydes with acetone.

Most of the reported aldol reactions were carried out in polar organic solvents such as dimethyl sulfoxide (DMSO), dimethylformamide (DMF), chloroform ($CHCl_3$), tetrahydrofuran (THF), or acetonitrile (CH_3CN). Moreover, proline is known to undergo decarboxylation when it is reacted with electron-deficient aromatic aldehydes.[5] In the past few years, room-temperature ionic liquids (RTILs, usually organic onium salts) have been proposed as environmentally benign alternatives to conventional organic solvents.[6] These ionic liquids have been used largely as solvents in organic synthesis, biocatalysis, and electrochemistry separation processes.[7] 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.[8] Thus, the employment of an ionic liquid as the solvent for an atom-economical reaction such as the asymmetric direct aldol reaction will make the process more environmentally benign and economical. Aldol reactions in the presence of L-proline in ionic liquids have been documented earlier.[9]

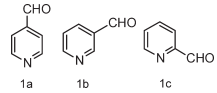
Regarding the aldol reactions with heteroaromatic aldehydes, Chimni et al. reported the pyrrolidine-catalyzed direct aldol reaction of heteroaromatic aldehydes with acetone, in which they documented the less catalytic efficiency of proline compared to pyrrolidine.[10a] Maruoka et al. designed an artificial amino acid catalyst for the direct asymmetric aldol reaction of heteroaromatic, olefinic, and aromatic aldehydes, in which decarboxylation was not observed.[10b]

Herein, we present the L-proline-catalyzed asymmetric direct aldol reaction of heteroaromatic aldehydes with acetone in ionic liquids, which leads to a remarkable improvement of the reaction in comparison to organic solvents. To the best of our knowledge, this is the first demonstration of asymmetric direct aldol reaction of heteroaromatic aldehydes and acetone in ionic liquids.

RESULTS AND DISCUSSION

We initially screened the reaction of acetone with substituted pyridine aldehydes in different solvents at room temperature (Table 1). In general, aldol adducts in very low yields with good enantioselectivity are obtained in polar solvents such as DMSO, NMP, and DMF. The ^1H NMR spectra revealed that part of the proline and the aldehyde under anhydrous conditions condensed to form a bicyclic oxazolidinone.[5] The aldol reaction is very clean

Table 1. Direct catalytic asymmetric aldol reaction of acetone with different heteroaromatic aldehydes in different solvents[a]



Entry	Aldehyde	Solvent	Time (h)	Yield[b] (%)	Ee[c] (%)
1	1a	DMSO	24	<10	70
2	1a	NMP	24	<10	70
3	1a	H_2O	12	84	18
4	1b	DMSO	24	<10	68
5	1b	NMP	24	<10	73
6	1b	H_2O	36	42	10
7	1c	DMSO	24	<5	55
8	1c	NMP	24	<10	46
9	1c	H_2O	12	59	0

[a]All reactions were carried out with 20 mol% catalyst, aldehyde (1 mmol), acetone (1 mL), and solvent (2 mL).
[b]Yields based on ^{1}H NMR.
[c]The ee is determined by chiral HPLC using Diacel Chiralpak AS-H, OJ-H.

in water as the solvent (Table 1, entries 3, 6, and 9) but has poor enantioselectivity. This could be because of the hydrolysis of oxazolidinone in water. To improve the rate as well as the enantioselectivity, a mixed-solvent system with different mol% of water in DMSO was screened for pyridine-2-carboxaldehyde reaction (Table 2). An acceleration in the rate of aldol reaction is observed as the percentage of water content is increased but at the expense of enantioselectivity.

Based on the enhancement of the rate of reaction in polar solvents such as water, we made an attempt to observe the reactivity in room-temperature ionic

Table 2. Effect of water on proline-catalyzed direct asymmetric aldol reaction of acetone with pyridine-2-carboxaldehyde at room temperature[a]

Entry	Solvent	H_2O (vol%)	Yield[b] (%)	Ee[c] (%)
1	DMSO	0	10	55
2	DMSO	5	29	50
3	DMSO	10	37	48
4	DMSO	50	41	5
5	—	100	60	0

[a]All reactions were carried out with 20 mol% catalyst, aldehyde (1 mmol), acetone (1 mL), and solvent (2 mL).
[b]Yields based on ^{1}H NMR.
[c]The ee is determined by chiral HPLC with Diacel Chiralpak AS-H, OJ-H.

liquids (RTILs, usually organic onium salts). In the presence of 20 mol% of L-proline, the direct aldol reaction of acetone with pyridine-4-carboxaldehyde was examined in ionic liquid ([bmim] [BF4]). Surprisingly, the reactions in ionic liquids are very clean and much faster than those in DMSO and NMP. The enantioselectivities are also retained. Moreover, oxazolidinone, which was the major adduct in the case of proline-catalyzed direct aldol reactions, is not observed. The improved catalytic performance in ionic liquid might be due to the stabilization of the imminium intermediate formed from the ketones and the secondary amine of the proline or because of the enhanced nucleophilicity of the enamine. Further, we have done the aldol reaction of other pyridine aldehydes in [bmim][BF4], which resulted in higher yields compared to the organic solvents (Table 3).

The possibility of recycling the catalyst was finally examined by employing the direct aldol reaction of pyridine-4-carboxaldehyde with acetone in [bmim] [BF4]. The data shown in Table 4 illustrate that the catalyst can be reused at least three times without sacrificing the yield and enantioselectivity.

EXPERIMENTAL

General

The heteroaromatic aldehydes and proline were purchased from Aldrich and used without further purification. Acetone and other solvents were purchased from S. D. Fine Chemicals, India. ACME silica gel (100–200 mesh) was used for column chromatography, and thin-layer chromatography (TLC) was performed on Merck precoated silica-gel 60-F254 plates. All the other solvents and chemicals were obtained from commercial sources and purified using standard methods.

Table 3. Direct asymmetric aldol reaction of acetone with heteroaromatic aldehydes in bmim [BF4][a]

Entry	R-CHO	Time (h)	Yield[b] (%)	Ee[c] (%)
1	2-pyridyl	12	50	56
2	3-pyridyl	6	95	74
3	4-pyridyl	6	98	70

[a]All reactions were carried out with 20 mol% catalyst, aldehyde (1 mmol), acetone (1 mL), bmim[BF4] (1 mL).

[b]Yields based on ^{1}H NMR.

[c]The ee is determined by chiral HPLC using Diacel Chiralpak AS-H, OJ-H.

Table 4. Studies on catalyst recycling[a]

Entry	Cycle	Yield[b] (%)	Ee[c] (%)
1		98	70
2	1	98	70
3	2	98	70
4	3	96	68

[a]A reaction mixture of pyridine-4-carboxaldehyde (1 mmol) and acetone (1 mL) catalyzed by 20 mol% L-proline in ionic liquid (1 mL) at room temperature.
[b]Yields based on ^{1}H NMR.
[c]Determined by HPLC using Diacel Chiralpak AS-H.

Preparation of bmim [BF_4] Ionic Liquid

The RTIL bmim [BF_4] was synthesized according to the general procedure reported in the literature.[9]

General Reaction Procedure and Reusability Protocol for Asymmetric Aldol Reaction

To a dry 25-mL, round-bottomed flask charged with L-proline (0.20 mmol, 23 mg), bmim-BF4 (1 mL) was added, followed by acetone (1 mL) and aldehyde (1 mmol, 0.1 mL) at room temperature. The reaction mixture was stirred for 6 h before extraction with ether (4 × 10 mL). The combined ether layers were concentrated in vacuum to give the pure aldol addition product. The residual ionic liquid containing L-proline was further concentrated in vacuum to remove ether or acetone before use.

CONCLUSION

In conclusion, the asymmetric direct aldol reactions of heteroaromatic aldehydes with acetone in imidazolium-based ionic liquid are investigated. Higher yields and good ees are obtained under the optimal conditions. Further study regarding the recycling of the catalyst has revealed that L-proline in an ionic liquid can be reused with comparable yields and enantioselectivities. 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.

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