An Efficient Ionic Liquid Additive for Proline-catalyzed Direct Asymmetric Aldol Reactions between Cyclic Ketones and Aromatic Aldehydes

Yunbo Qian, Xin Zheng, Xu Wang, Shiyong Xiao, and Yongmei Wang*
Department of Chemistry, The Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, P. R. China

(Received March 23, 2009; CL-090284; E-mail: ymw@nankai.edu.cn)

An ionic liquid [EMIm][CF_3COO] proved to be an efficient additive for proline-catalyzed direct asymmetric aldol reactions between cyclic ketones and aromatic aldehydes in [BMIm]BF_4 at room temperature. Corresponding aldol products in low to good yields (trace–93%) and excellent enantiomeric excesses (up to 98%) were afforded. Recycling of the catalyst and additive together with the solvent ([BMIm]BF_4) was possible up to 5 runs with only slight reduction in activity.

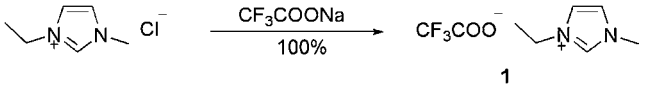
The asymmetric aldol reaction is one of the most important carbon–carbon bond-forming reactions in organic synthesis[1] for the production of enantiomerically enriched β-hydroxy ketones which are essential building blocks in the synthesis of polyfunctional compounds and natural products.[2] Since Barbas et al.[3] reported the direct aldol reaction catalyzed by (*S*)-proline under mild conditions, the use of small organic molecules as catalysts has received great attention. Over the past few years, (*S*)-proline and its structural analogues have been continuously developed for direct asymmetric aldol reactions.[4,5]

During the last decade, room temperature ionic liquids (ILs) have attracted much attention as environmentally benign reaction media because of their fascinating and characteristic properties.[6] Ionic liquids have also been introduced into direct aldol reactions mainly as green solvents to replace organic solvents such as DMF or DMSO.[7] Recently, chiral ionic liquids (CILs) have become a research focus of increasing importance owing to their potential for chiral discrimination in asymmetric synthesis and optical resolution of racemates.[8] However, there are few examples reported using ionic liquid as an additive in a catalytic amount. Furthermore, proline-catalyzed direct asymmetric aldol reactions between cyclic ketones and aromatic aldehydes in ionic liquid have not been systemically investigated. Herein, we would like to report the application of [EMIm][CF_3COO] (**1**) (Scheme 1) as an efficient additive for proline-catalyzed direct asymmetric aldol reactions in [BMIm]BF_4. Although the exact role of **1** is still under investigation, we assume that an interaction exists between proline and the anion CF_3COO^-, which could stabilize the enamine intermediate of the aldol reaction.

The ionic liquid [EMIm][CF_3COO] (**1**) could be easily obtained in 100% overall yield according to the reference[9] (Scheme 1).

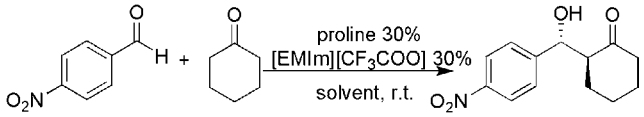
Originally, a model reaction of 4-nitrobenzaldehyde and 3.5 equiv of cyclohexanone was carried out at room temperature catalyzed by proline with the addition of [EMIm][CF_3COO]. Table 1 summarized the results. Compared to reactions using organic solvent DMSO or cyclohexanone, reactions performed in [BMIm]BF_4 gave the best result (Table 1, Entry 8). In the presence of 10 equiv of water, the aldol product could be obtained in 87% overall yield together with a 16:84 dr (diastereomer ratio) value and up to 97% ee for the anti isomer. Reaction without the addition of **1** in the presence of water was also carried out, the stereoselectivity was not satisfied (Table 1, Entry 10). When the ionic liquid **1** was used directly as a solvent (Table 1, Entry 11), there was also a slight decrease in the enantioselectivity. Entry 12 showed that an increased amount of cyclohexanone (5 equiv) improved the yield slightly but led to moderate dr value (32:68). Based on this result, it is also important to control the ratio of the substrates.

With the optimized conditions in hand, we then examined a variety of aromatic aldehydes and cyclic ketones to establish the general efficacy of the catalytic transformation. As illustrated in Table 2, the reaction was dramatically dependent on the electronic effects of the aldehyde. Aromatic aldehydes with electron-withdrawing groups in the para position reacted smoothly with cyclohexanone, giving the corresponding aldol products in good yield and excellent ee for anti isomers. (Table 2, Entries 1 and 4–6). As a result of the steric hindrance, the aldehyde bearing a nitro group in the ortho position showed lower reactivity, the product was isolated in 34% yield with a weak diasteroselectivity (Table 2, Entry 2). Unsubstituted aromatic aldehyde also gave



Scheme 1. Synthesis of ionic liquid: 1-Ethyl-3-methylimidazolium trifluoroacetate ([EMIm][CF_3COO]).

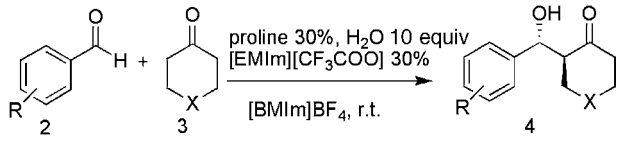
Table 1. The model reaction of 4-nitrobenzaldehyde and cyclohexanone in the presence of [EMIm][CF_3COO] (**1**)



Entry	Solvent	H_2O (equiv)	Yield[a] /%	dr[b] (syn/anti)	ee[b]/% (syn/anti)
1	DMSO	—[e]	89	44:56	68/75
2	DMSO	15	97	44:56	88/88
3	cyclohexanone	—[e]	98	43:57	86/89
4	cyclohexanone	5	94	37:63	87/93
5	cyclohexanone	15	90	32:68	86/91
6	[BMIm]BF_4	—[e]	87	33:67	65/95
7	[BMIm]BF_4	5	71	23:77	72/96
8	[BMIm]BF_4	10	87	16:84	58/97
9	[BMIm]BF_4	15	82	34:66	85/94
10[c]	[BMIm]BF_4	10	85	32:68	67/89
11	[EMIm][CF_3COO]	10	91	19:81	80/82
12[d]	[BMIm]BF_4	10	91	32:68	75/93

[a]Isolated yields after column chromatography. [b]Determined by HPLC analysis on a chiral AD-H column. [c]No [EMIm][CF_3COO] was added. [d]5 equiv of cyclohexanone was added. [e]Not added.

Table 2. Proline-catalyzed direct aldol reaction of cyclic ketones with aromatic aldehydes in the presence of [EMIm]-[CF_3COO] (**1**)



2 3 4

Entry	R	X	T /h	Yield[a] /%	dr[b] (syn/anti)	ee[c]/% (syn/anti)
1	*p*-NO_2	CH_2	12	87	16:84	/97
2	*o*-NO_2	CH_2	72	34	40:60	/97
3	*m*-NO_2	CH_2	72	62	19:81	/96
4	*p*-CF_3	CH_2	48	85	16:84	/92
5	*p*-Br	CH_2	72	77	19:81	/94
6	*p*-Cl	CH_2	72	74	12:88	/89
7	H	CH_2	72	59	15:85	/94
8	*p*-OMe	CH_2	72	<10	—[h]	—[h]
9	*p*-NO_2	—	12	93	64:36[b,c]	81/89
10	*p*-NO_2	S	72	67	50:50[b,c]	94/97
11	*p*-NO_2	$CHCH_3$	48	75	29:71[d]	98[e]
12	*p*-NO_2	$(CH_2)_2$	72	trace	—[h]	—[h]
13	*p*-NO_2	acetone	12	92	—[i]	74
14[f]	*p*-NO_2	CH_2	12	91	24:76	86/95
15[f]	*p*-NO_2	CH_2	12	92	28:72	72/94
16[f]	*p*-NO_2	CH_2	12	88	31:69	68/96
17[f]	*p*-NO_2	CH_2	12	90	38:62	82/94
18[f,g]	*p*-NO_2	CH_2	12	93	29:71	78/94

[a]Isolated yields after column chromatography. [b]Determined by ^{1}H NMR of the crude product. [c]Determined by HPLC analysis on a chiral AD-H column. [d]The ratio of the major isomer shown with all the other isomers. [e]The major isomer. [f]Reuse conditions. [g]9 μL water (5 equiv) was added. [h]No data. [i]No dr value.

good stereoselectivity in moderate yield (Table 2, Entry 7). There was almost no product obtained (yield < 10%) when *p*-methoxylbenzaldehyde reacted with cyclohexanone even for 72 h (Table 2, Entry 8).

Other cyclic ketones were also tested with *p*-nitrobenzaldehyde, each reaciton gave aldol product in good yield except cycloheptanone (Table 2, Entries 9–12). Although good to excellent ee values were attained in almost all cases, the diastereoselctivities were not satisfactory. Acetone was also tested, but the enantioselectivity of 74% ee did not show any improvement although with a high yield (Table 2, Entry 13).

Recycling of catalyst and solvent was investigated in terms of green chemsitry. (Table 2, Entries 14–18). We carried out our study by using a model reaction. After the reaction was completed, the product and the remained substrates were extracted by ether. The residue was dried and reused directly as catalyst and solvent for the next time. When recycling repeated four times, about equal amounts of the product was produced with a slight decrease in the enantioselectivity. Entry 18 in Table 2 proved that the decreased diastereoselectivity was partly attributed to loss of water.

To conclude, we have applied the ionic liquid [EMIm]-[CF_3COO] as an efficient additive for proline-catalyzed direct asymmetric aldol reactions between cyclic ketones and aromatic aldehydes in [BMIm]BF_4 at room temperature. The corresponding aldol products with low to good yields (trace–93%) and excellent enantiomeric excesses (up to 98%) were afforded. Recycling of the catalyst and additive together with the solvent ([BMIm]BF_4) was possible up to 5 runs with only slight reduction in activity.

References and Notes

1 a) C. H. Heathcock, in *Comprehensive Organic Synthesis*, ed. by B. M. Trost, I. Fleming, Pergamon, Oxford, **1991**, Vol. 2. b) *Modern Aldol Reactions*, ed. by R. Mahrwarld, Wiley-VCH, Weinheim, **2004**, Vol. 1.

2 a) P. Decker, H. Schweer, *Origins Life Evol. Biosphere* **1984**, *14*, 335. b) T. Mukaiyama, *Tetrahedron* **1999**, *55*, 8609. c) K. C. Nicolaou, D. Vourloumis, N. Winssinger, P. S. Baran, *Angew. Chem., Int. Ed.* **2000**, *39*, 44.

3 a) B. List, R. A. Lerner, C. F. Barbas, III, *J. Am. Chem. Soc.* **2000**, *122*, 2395. b) K. Sakthivel, W. Notz, T. Bui, C. F. Barbas, III, *J. Am. Chem. Soc.* **2001**, *123*, 5260.

4 Reviews: a) G. Guillena, C. Nájera, D. J. Ramón, *Tetrahedron: Asymmetry* **2007**, *18*, 2249. b) B. List, *Synlett* **2001**, 1675. c) B. List, *Tetrahedron* **2002**, *58*, 5573. d) W. Notz, F. Tanaka, C. F. Barbas, III, *Acc. Chem. Res.* **2004**, *37*, 580.

5 Examples: a) J. Huang, X. Zhang, D. W. Armstrong, *Angew. Chem., Int. Ed.* **2007**, *46*, 9073. b) F. Wang, Y. Xiong, X. Liu, X. Feng, *Adv. Synth. Catal.* **2007**, *349*, 2665. c) H. Inoue, M. Kikuchi, J. Ito, H. Nishiyama, *Tetrahedron* **2008**, *64*, 493. d) S. Luo, J. Li, H. Xu, L. Zhang, J.-P. Cheng, *Org. Lett.* **2007**, *9*, 3675. e) V. Maya, M. Raj, V. K. Singh, *Org. Lett.* **2007**, *9*, 2593. f) J. Shah, H. Blumenthal, Z. Yacob, J. Liebscher, *Adv. Synth. Catal.* **2008**, *350*, 1267. g) D. E. Siyutkin, A. S. Kucherenko, M. I. Struchkova, S. G. Zlotin, *Tetrahedron Lett.* **2008**, *49*, 1212. h) M. Lombardo, S. Easwar, F. Pasi, C. Trombini, *Adv. Synth. Catal.* **2009**, *351*, 276. i) S.-P. Zhang, X.-K. Fu, S.-D. Fu, J.-F. Pan, *Catal. Commun.* **2009**, *10*, 401. j) S. Aratake, T. Itoh, T. Okano, T. Usui, M. Shoji, Y. Hayashi, *Chem. Commun.* **2007**, 2524. k) Y. Hayashi, T. Sumiya, J. Takahashi, H. Gotoh, T. Urushima, M. Shoji, *Angew. Chem., Int. Ed.* **2006**, *45*, 958.

6 a) T. Welton, *Chem. Rev.* **1999**, *99*, 2071. b) P. Wasserscheid, T. Welton, *Ionic Liquids in Synthesis*, Wiley-VCH, Weinheim, Germany, **2003**. c) P. Wasserscheid, W. Keim, *Angew. Chem., Int. Ed.* **2000**, *39*, 3772.

7 a) A. Córdova, *Tetrahedron Lett.* **2004**, *45*, 3949. b) H.-M. Guo, L.-F. Cun, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang, *Chem. Commun.* **2005**, 1450. c) J. Shah, H. Blumenthal, Z. Yacob, J. Liebscher, *Adv. Synth. Catal.* **2008**, *350*, 1267. d) Y.-H. Liu, Y.-W. Zhang, Y.-P. Ding, Z.-X. Shen, X.-Q. Luo, *Chin. J. Chem.* **2005**, *23*, 634.

8 a) R. Gausepohl, P. Buskens, J. Kleinen, A. Bruckmann, C. W. Lehmann, J. Klankermayer, W. Leitner, *Angew. Chem., Int. Ed.* **2006**, *45*, 3689. b) P. S. Schulz, N. Müller, A. Bösmann, P. Wasserscheid, *Angew. Chem., Int. Ed.* **2007**, *46*, 1293. c) J. Ding, V. Desikan, X. Han, T. L. Xiao, R. Ding, W. S. Jenks, D. W. Armstrong, *Org. Lett.* **2005**, *7*, 335. d) J. Ding, D. W. Armstrong, *Chirality* **2005**, *17*, 281. e) C. Baudequin, D. Bregeon, J. Levillain, F. Guillen, J.-C. Plaquevent, A.-C. Gaumont, *Tetrahedron: Asymmetry* **2005**, *16*, 3921. f) J. Levillain, G. Dubant, I. Abrunhosa, M. Gulea, A.-C. Gaumont, *Chem. Commun.* **2003**, 2914.

9 K. K. Laali, V. J. Gettwert, *J. Org. Chem.* **2001**, *66*, 35.

Published on the web (Advance View) May 16, 2009; doi:10.1246/cl.2009.576