

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

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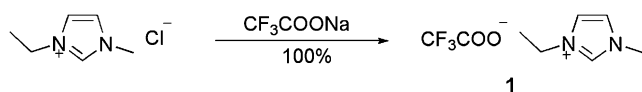
An ionic liquid [EMIm][CF₃COO] proved to be an efficient additive for proline-catalyzed direct asymmetric aldol reactions between cyclic ketones and aromatic aldehydes in [BMIm]BF₄ at room temperature. Corresponding aldol products in low to good yields (trace–93%) and excellent enantiomeric excesses (up to 98%) were afforded. Recycling of the catalyst and additive together with the solvent ([BMIm]BF₄) 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 synthesis¹ 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][CF₃COO] (**1**) (Scheme 1) as an efficient additive for proline-catalyzed direct asymmetric aldol reactions in [BMIm]BF₄. Although the exact role of **1** is still under investigation, we assume that an interaction exists between proline and the anion CF₃COO[−], which could stabilize the enamine intermediate of the aldol reaction.

The ionic liquid [EMIm][CF₃COO] (**1**) could be easily obtained in 100% overall yield according to the reference⁹ (Scheme 1).

Originally, a model reaction of 4-nitrobenzaldehyde and 3.5 equiv of cyclohexanone was carried out at room temperature



Scheme 1. Synthesis of ionic liquid: 1-Ethyl-3-methylimidazolium trifluoroacetate ([EMIm][CF₃COO]).

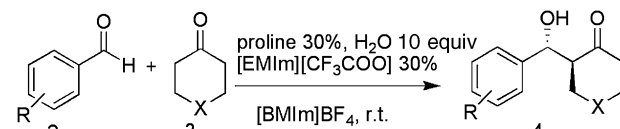
catalyzed by proline with the addition of [EMIm][CF₃COO]. Table 1 summarized the results. Compared to reactions using organic solvent DMSO or cyclohexanone, reactions performed in [BMIm]BF₄ gave the best result (Table 1, Entry 8). In the presence of 10 equiv of water, the aldol product could be obtained 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 diastereoselectivity (Table 2, Entry 2). Unsubstituted aromatic aldehyde also gave

Table 1. The model reaction of 4-nitrobenzaldehyde and cyclohexanone in the presence of [EMIm][CF₃COO] (**1**)

Entry	Solvent	H ₂ O (equiv)	Yield ^a /%	dr ^b (syn/anti)	ee ^b /% (syn/anti)
1	DMSO	— ^c	89	44:56	68/75
2	DMSO	15	97	44:56	88/88
3	cyclohexanone	— ^c	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	— ^c	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 ₃ COO]	10	91	19:81	80/82
12 ^d	[BMIm]BF ₄	10	91	32:68	75/93

^aIsolated yields after column chromatography. ^bDetermined by HPLC analysis on a chiral AD-H column. ^cNo [EMIm][CF₃COO] was added. ^d5 equiv of cyclohexanone was added. ^eNot added.

Table 2. Proline-catalyzed direct aldol reaction of cyclic ketones with aromatic aldehydes in the presence of [EMIm]-[CF₃COO] (**1**)


Entry	R	X	T /h	Yield ^a /%	dr ^b (syn/anti)	ee ^c /% (syn/anti)
1	<i>p</i> -NO ₂	CH ₂	12	87	16:84	/97
2	<i>o</i> -NO ₂	CH ₂	72	34	40:60	/97
3	<i>m</i> -NO ₂	CH ₂	72	62	19:81	/96
4	<i>p</i> -CF ₃	CH ₂	48	85	16:84	/92
5	<i>p</i> -Br	CH ₂	72	77	19:81	/94
6	<i>p</i> -Cl	CH ₂	72	74	12:88	/89
7	H	CH ₂	72	59	15:85	/94
8	<i>p</i> -OMe	CH ₂	72	<10	— ^h	— ^h
9	<i>p</i> -NO ₂	—	12	93	64:36 ^{b,c}	81/89
10	<i>p</i> -NO ₂	S	72	67	50:50 ^{b,c}	94/97
11	<i>p</i> -NO ₂	CHCH ₃	48	75	29:71 ^d	98 ^e
12	<i>p</i> -NO ₂	(CH ₂) ₂	72	trace	— ^h	— ^h
13	<i>p</i> -NO ₂	acetone	12	92	— ⁱ	74
14 ^f	<i>p</i> -NO ₂	CH ₂	12	91	24:76	86/95
15 ^f	<i>p</i> -NO ₂	CH ₂	12	92	28:72	72/94
16 ^f	<i>p</i> -NO ₂	CH ₂	12	88	31:69	68/96
17 ^f	<i>p</i> -NO ₂	CH ₂	12	90	38:62	82/94
18 ^{f,g}	<i>p</i> -NO ₂	CH ₂	12	93	29:71	78/94

^aIsolated yields after column chromatography. ^bDetermined by ¹H NMR of the crude product. ^cDetermined by HPLC analysis on a chiral AD-H column. ^dThe ratio of the major isomer shown with all the other isomers. ^eThe major isomer. ^fReuse conditions. ^g9 μL water (5 equiv) was added. ^hNo data. ⁱNo dr value.

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

Other cyclic ketones were also tested with *p*-nitrobenzaldehyde, each reaction 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 diastereoselectivities 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 chemistry. (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]-[CF₃COO] as an efficient additive for proline-catalyzed direct asymmetric aldol reactions between cyclic ketones and aromatic aldehydes in [BMIm]BF₄ at room temperature. The corresponding aldol products with low to good yields (trace–93%) and ex-

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