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Functionalized ionic liquids catalyzed direct aldol reactions

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Abstract—A series of functionalized ionic liquids (FILs) incorporated with chiral-pyrrolidine unit have been synthesized and tested as reusable organocatalysts for direct aldol reactions. FIL **1b** in combination with acetic acid and water as additives could effectively catalyze direct aldol reactions of various ketone donors in high yields and the FIL catalyst was easily recycled and reused for six times with slight reduction in activity. Based on experimental observations as well as previous reports, we proposed that the reactions occurred via *syn*-enamine intermediate and the ionic-liquid moiety in the FIL provides some space shielding for the participating aldehyde acceptors that accounts for the modest enantioselectivities observed in the reactions.

1. Introduction

Functionalized ionic liquids (FILs, or task-specific ionic liquids, TSILs) are receiving growing attention recently due to their tunable features for various targeted chemical tasks and the advantages as reusable homogenous supports, reagents, and catalysts with green credential.[1] Endowed with catalytically active groups, functional ionic liquids (FILs) have been developed and successfully applied to catalyze a number of chemical transformations.[1h,i] This kind of ionic liquids still maintains the unique properties of ionic liquids, therefore can be easily recycled and reused as homogenous small molecular catalysts. Up to now, FIL catalysis has been mainly focused on exploring acid[2] or base[3] mediated reactions. Considering the 'designer' properties of ionic liquids, there remains tremendous potential for FIL catalysis. Previously, we have reported that functionalized ionic liquids with chiral secondary amine groups could efficiently catalyze the asymmetric Michael addition reaction via enamine mechanism.[4] Our further exploration indicated that this series of FILs should be applicable in a range of enamine-based organocatalytic processes. Here, we wish to report the application of FILs as reusable organocatalysts for direct aldol reactions.

The aldol reaction is one of the most important carbon–carbon bond-forming reactions in organic synthesis.[5] Direct aldol reaction employs unmodified aldehyde or ketone as aldol donors instead of the preformed enolates and is therefore highly atomically economic. There have been tremendous efforts toward developing highly efficient catalysts for direct aldol reaction in recent years.[6] In this endeavor, the development of organocatalysts is among the most important advances.[7] Since the discovery of L-proline as asymmetric catalyst for direct aldol reaction,[8] a number of proline derivatives have been developed as highly stereoselective organocatalysts for direct aldol reactions.[9] However, large loading of these chiral-pyrrolidine catalysts is normally required to achieve good yields with the exception of limited number of examples.[10] The development of recyclable and reusable organocatalysts is therefore of great importance in terms of atomic economy. On the other hand, biphasic technology using ionic liquids as reaction media has become one of the effective ways for recycling homogenous catalysts and this strategy has also been applied in organocatalysis but with limited success due to the poor solubility of most organocatalysts in ionic liquids.[11] More recently, basic ionic liquids were shown to promote the direct aldol reaction of ketones.[12] However, these ionic liquids either demonstrated low catalytic activity requiring large amount of catalysts (30 mol % or more) or only promoted the aldol condensation reactions. As an extension to our previous work on FIL catalysis,[4] we envisaged that FIL with a 'privileged' pyrrolidine moiety would be able to promote the direct aldol reaction via an enamine intermediate (Fig. 1), and meanwhile maintains the biphasic properties of ionic liquid, thereby ensuring good recyclability and reusability. Herein, we presented a full account of this study.

Keywords: Functionalized ionic liquid; Organocatalyst; Direct aldol reaction.

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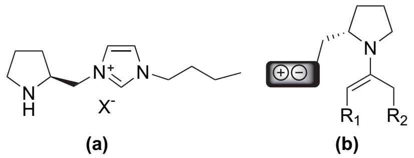


Figure 1. Pyrrolidine-type functional ionic liquids (**a**) and the enamine intermediate (**b**).

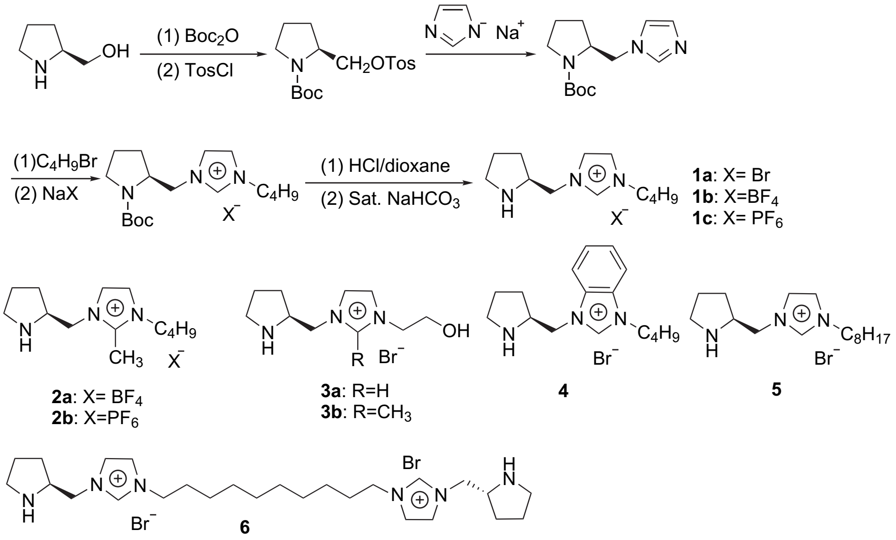
2. Result and discussion

2.1. Synthesis of the FILs

The pyrrolidine-type FILs were synthesized using the ‘chiral pool’ strategy with L-prolinol as the starting material (Scheme 1).[13] The synthesis was quite straight forward, affording the desired FIL in good total yields (70%, **1a**, for example). In this synthetic pathway, the ionic liquids were formed by quaternization of the pyrrolidine-imidazole precursor. By doing so, the synthetic procedure allows for facile variations on the cations, anions, and side chains of the FILs, a feature that is essential for diversity-oriented catalyst screening. All the FILs obtained are viscous liquids at room temperature and soluble in moderate polar solvents such as chloroform, dichloromethane, and methanol but insoluble in less polar solvents such as ethyl ether, ethyl acetate, and hexane.

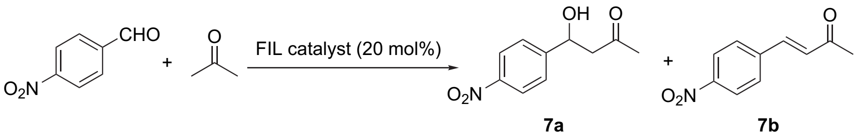
2.2. Catalysts screening

The synthetic FILs were next tested in the model reaction of *p*-nitrobenzaldehyde and acetone (Table 1). As shown in Table 1, all the FILs can catalyze the reaction, provided the desired direct aldol products along with some dehydration



Scheme 1. Synthetic procedure of the FILs.

Table 1. Functionalized ionic liquids catalyzed direct aldol reactions of *p*-nitrobenzaldehyde and acetone



Entry	Catalyst	T[a] (h)	Yield of product[c] (%)	
			7a	**7b**
1	**1a**	24	28	33
2	**1b**	12	47	22
3	**1c**	14	42	17
4	**2a**	17	43	21
5	**2b**	9	53	13
6	**3a**	14	53	6
7	**3b**	12	61	6
8	**4**	22	43	14
9	**5**	19	38	22
10[b]	**6**	17	69	9

[a] The reaction is completed at the time indicated.
[b] Catalyst of 10 mol % was used.
[c] Isolated yields.