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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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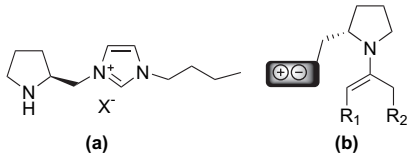


Figure 1. Pyrrolidine-type functional ionic liquids (**a**) and the enamine intermediate (**b**).

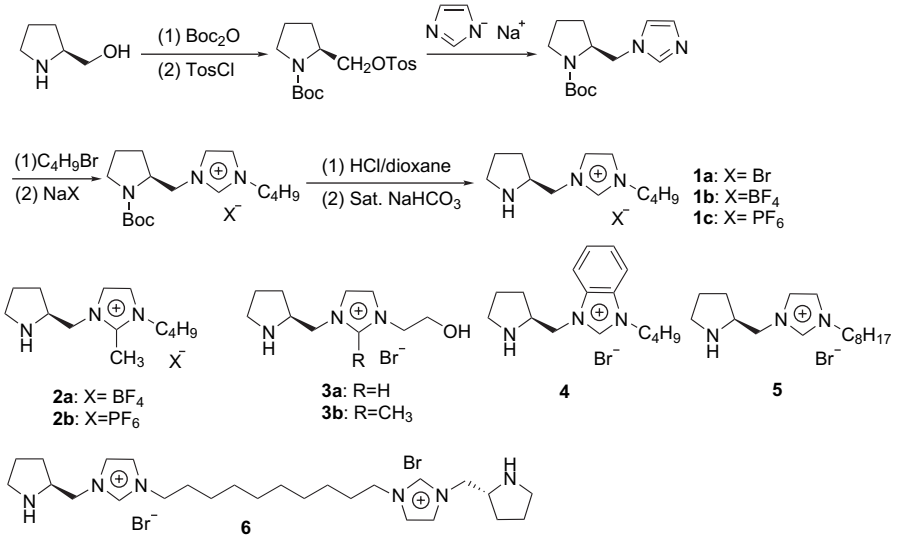
2. Result and discussion

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.

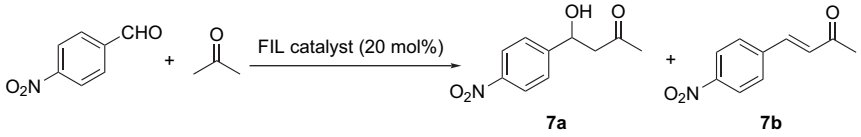
2.2. Catalysts screening

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.

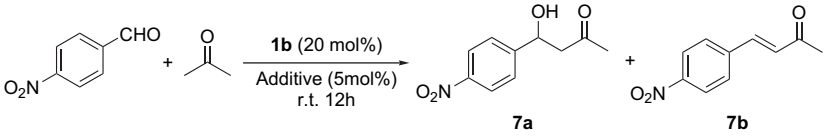
by-products. The catalytic activities and the distributions of products varied slightly with different ionic-liquid units in the FIL catalysts. For example, the swap of the anion from Br^- to BF_4^- led to slightly improved activity as well as higher yield of the aldol product over the dehydration product (Table 1, entry 2 vs entry 1, and entry 5 vs entry 4). Overall, FILs **3b** and **6** gave the best outcome in terms of the yield of aldol products. Unfortunately, all the FILs examined demonstrated low enantioselectivities in the reaction (ca. 10% ee).

2.3. Optimization of the reaction conditions

Previously, we have observed that acidic additive can enhance the catalytic ability of FILs in asymmetric Michael addition reactions.[4a] In the current study, we found that hydroxyl group containing FILs **3a** and **3b** afforded higher yields of the aldol product (Table 1, entries 6 and 7), suggesting a synergistic effect of the protic group on the desired aldol pathway. A range of acidic additives were next surveyed for their effect on the direct aldol reaction using a non-hydroxyl containing catalyst **1b** (Table 2). As indicated in Table 2, the addition of acidic additives had significant impact on the reactions. While weak acids such as acetic acid and water as additive favored the formation of aldol product **7a** (Table 2, entries 2 and 4), strong acids such as PTSA, CSA, and TFA were shown to severely retard the reaction (Table 2, entries 3, 5, and 6). The experiments with three chloroacetic acids gave mixed results (Table 2, entries 7–9), suggesting that acidity may not be the sole acting factor. Finally, optimal results were achieved by the combination of water and acetic acid (Table 2, entry 11). In aqueous acetone with 5 mol % HOAc as an additive, the reaction catalyzed by **1b** (20 mol %) afforded 88% yield of aldol product **7a** and only trace of dehydration product **7b**. In sharp contrast, the same reaction in neat acetone gave 47% yield of **7a** and 22% yield of **7b** (Table 2, entry 1 vs entry 11). As suggested by numerous previous studies,[9,14] acidic additives in the reaction may promote the enamine catalytic cycle, thereby accelerating the reaction rate and suppressing the general base-mediated condensation pathway.

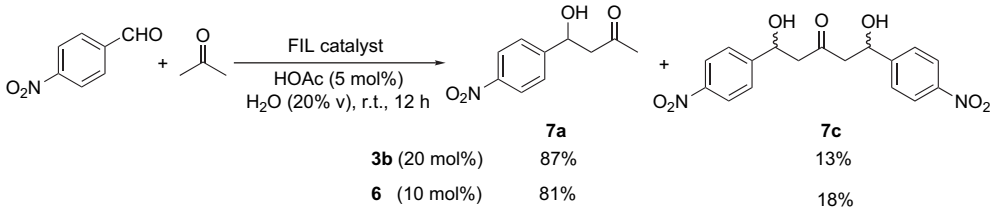
FILs **3b** and **6**, the identified better catalysts in the initial screening, were also examined under the optimized conditions. Interestingly, the reaction produced minor bis-aldol product **7c**, besides the major aldol product **7a** (Scheme 2), and no dehydration product **7b** was detected in these cases. Overall, FIL **1b** performed better than **3b** and **6** under the optimized conditions in terms of yield of the desired aldol product **7a**. FIL **1b** was therefore selected for further substrates' examination.

Table 2. Additive effect of **1b** catalyzed direct aldol reaction



Entry	Additive (5 mol %)	Yield[c,d] (%)	
		7a	**7b**
1	None	47	22
2	H_2O (acetone/H_2O=4:1)	55	4
3	TFA	4	6
4	AcOH	56	8
5	CSA	6	4
6	PTSA	5	2
7	$ClCH_2COOH$	42	19
8	$Cl_2CHCOOH$	14	32
9	Cl_3CCOOH	31	7
10	H_2O+$ClCH_2COOH$[a]	83	Trace
11	H_2O+AcOH[b]	88	Trace

[a] Reaction in H_2O/acetone (1:4, v/v) with 5 mol % $ClCH_2COOH$.
[b] Reaction in H_2O/acetone (1:4, v/v) with 5 mol % AcOH.
[c] Isolated yields. TFA: trifluoroacetic acid; CSA: camphor sulfonic acid; PTSA: *p*-toluenesulfonic acid.
[d] No effect on the enantioselectivities was observed, ee was around 10%.



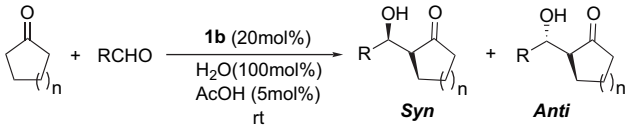
Scheme 2.

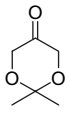
2.4. Substrates' scope

With **1b** as the identified FIL catalyst, we next explored the substrates' scope under the optimized conditions and the results are summarized in Tables 3 and 4. Table 3 lists the results of acyclic ketones. While the reactions between acetone and active aromatic aldehydes afforded the desired aldol products in high yields with no dehydration products isolated (Table 3, entries 1–4), the reactions with less reactive aromatic aldehydes produced significant amount of dehydration products besides the aldol products (Table 3, entries 5 and 6). In the reaction of *p*-hydroxybenzaldehyde, only aldol condensation product was isolated in 83% yield (Table 3, entry 7).

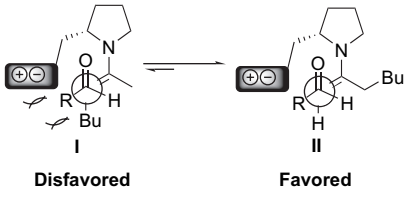
Other acyclic ketones also worked well in the reactions (Table 3, entries 8–13). Notably, methyl ethyl ketone underwent reaction with *p*-nitrobenzaldehyde with complete regioselectivity favoring the branched product in high yield (96%) and moderate diastereoselectivity (*syn*/*anti*=3.6:1) and enantioselectivity (56 and 51% ee for *syn* and *anti*-isomer, respectively) (Table 3, entry 8). In contrast, higher *n*-alkyl methyl ketone such as pentyl methyl ketone afforded aldol products with complete reversed regioselectivity favoring the linear product (Table 3, entries 11–13). In these cases, minor dehydrated products were also isolated (entries 11 and 12). The reversed regioselectivity can be rationalized by considering a *syn*-enamine intermediate (Scheme 3). Previously, we have shown that FILs such as **1b** preferentially formed *syn*-enamine intermediates with ketone donors. In the case of *n*-pentyl methyl ketone, the space-demanding pentyl group would disfavor the *syn*-enamine **I**, whereas favor the linear *syn*-enamine **II** in the direct aldol reactions. As a result, only linear aldol products were obtained in the reactions of *n*-pentyl methyl ketone.

Table 4. FIL **1b** catalyzed direct aldol reaction of cyclic ketones



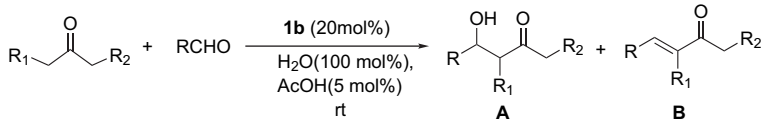
Entry	*n*	R	Time (h)	A			
				syn/*anti*[a]	Yield[b] (%)	ee_{syn}[c] (%)	ee_{anti}[c] (%)
1	1	*o*-NO_2Ph	2	4.8:1	92	11	26
2	1	*m*-NO_2Ph	6	2.5:1	92	11	5
3	1	*p*-NO_2Ph	6	2.8:1	87	7	5
4	2	*o*-NO_2Ph	12	1:1.1	>99	63	32
5	2	*m*-NO_2Ph	12	1:1.1	92	46	21
6	2	*p*-NO_2Ph	12	1:1	93	41	10
7	2	*p*-ClPh	84	1:1.1	68	32	20
8	2	Ph	80	1:1.3	66	46	30
9	3	*p*-NO_2Ph	105	1:1.2	50	43	<5
10	4	*p*-NO_2Ph	105	1.3:1	35	<5	<5
11		*p*-NO_2Ph	36	1:1.9	83	N.d.	11

[a] Determined by ^{1}H NMR.
[b] Isolated yield.
[c] Determined by HPLC.



Scheme 3. Transition state of the reaction of *n*-butyl methyl ketone.

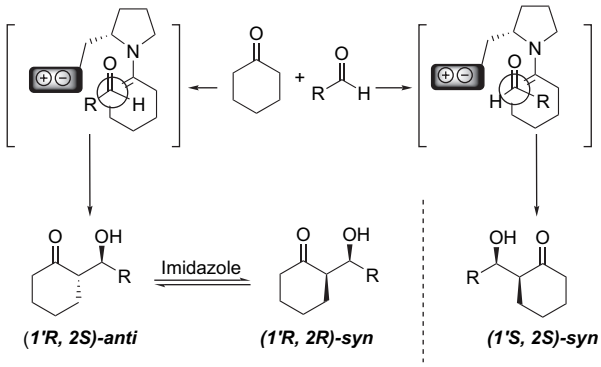
Table 3. FIL **1b** catalyzed direct aldol reaction of acyclic ketones[a]



Entry	R	R_1	R_2	Time (h)	A		B
					Yield[b] (%)	*syn*:*anti*[c]	Yield[b] (%)
1	*o*-NO_2Ph	H	H	11	89	—	—
2	*m*-NO_2Ph	H	H	11	91	—	—
3	*o*-ClPh	H	H	11	93	—	—
4	*o*-BrPh	H	H	13	86	—	—
5	1-Napth	H	H	82	60	—	29
6	*p*-PhPh	H	H	107	35	—	40
7	*p*-HOPh	H	H	109	—	—	83
8	*p*-NO_2Ph	CH_3	H	60	96	3.6:1[d]	—
9	*p*-NO_2Ph	OBn	H	48	78	1:1.2	—
10	*p*-NO_2Ph	CH_3	CH_3	60	25	1.1:1	—
11	*p*-NO_2Ph	H	*n*-Bu	48	59	9[e]	29
12	*m*-NO_2Ph	H	*n*-Bu	75	55	13[e]	39
13	*o*-NO_2Ph	H	*n*-Bu	75	87	25[e]	—

[a] The reactions of acetone were carried out in acetone/H_2O (4:1, v/v) with 5 mol % of AcOH.
[b] Isolated yields.
[c] Determined by ^{1}H NMR.
[d] ee determined by HPLC on a chiral column: 56% ee (*syn*), 51% ee (*anti*).
[e] ee value.

In the presence of FIL **1b**, cyclic ketones also worked well under the optimized conditions (Table 4), and the reactions generated the desired aldol products in high yields and moderate stereoselectivities. The modest enantioselectivities in these reactions can be explained by the transition state shown in Scheme 4, wherein the ionic-liquid moiety would block the *Si*-face of the *syn*-enamine. In this model, the absence of directing hydrogen bond and electrostatic interaction (like that in asymmetric Michael reaction) between participating aldehyde and the enamine intermediate would account for the poor diastereoselectivities observed. The absolute configuration of the *syn*-isomer was determined by correlation with its *anti*-isomer via imidazole-mediated *syn–anti* isomerization.[15]



Scheme 4. Proposed transition states for the direct aldol reaction of ketones.

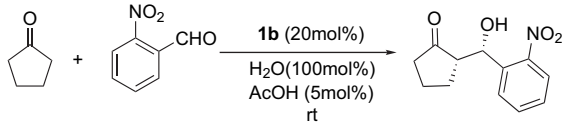
2.5. Mechanism of the reactions

Based on the experimental observations and previous studies, we proposed that FIL-catalyzed direct aldol reactions predominantly occur via the enamine pathway (Scheme 5), wherein the FIL catalysts formed *syn*-enamine with ketone donors (Schemes 3 and 4).[7] On the other hand, the dehydration side reaction might be explained by a aldimine-Mannich catalytic cycle. The aldimine intermediates formed from FIL catalyst and aldehyde, undergoes Mannich type reaction with ketone enamine to give the β-aminoketone, which upon elimination, leading to dehydration product.[16]

2.6. Reusability of the FIL catalysts

The recyclability and reusability of FIL catalysts were examined for the reactions of cyclopentanone and *o*-nitrobenzaldehyde with **1b** as the representative catalyst. It was found that FIL **1b** still maintained the biphasic property of ionic liquids and could be easily recycled by precipitation with diethyl ether. As revealed in Table 5, the catalyst could be recycled and reused for at least six times with a slightly decreased activity.

Table 5. Recycle of FIL **1b** in the reaction of cyclopentanone with *o*-nitrobenzaldehyde

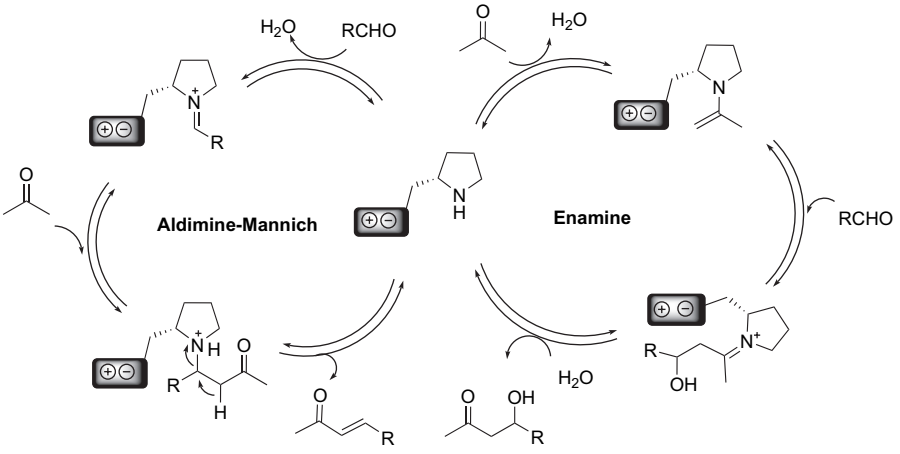


Run	Time (h)	*syn*/*anti*[a]	Yield[b] (%)	ee$_{syn}$[c] (%)	ee$_{anti}$[c] (%)
1	2	4.8:1	92	11	26
2	4	4.5:1	92	11	28
3	7	4.7:1	94	9	36
4	12	4.0:1	89	<5	33
5	11	2.4:1	96	<5	37
6	17	2.1:1	90	7	35

[a] Determined by ^{1}H NMR.
[b] Isolated yield.
[c] Determined by HPLC with a chiral column.

3. Conclusion

We have synthesized and screened a series of pyrrolidine-containing FILs for catalysis of direct aldol reactions. It was found that the FILs could effectively catalyze direct aldol reactions with only 20 mol % load of the catalyst. Acidic additives such as acetic acid and water could facilitate the desired aldol reaction and suppress the formation of aldol condensation products. FIL **1b** in combination with acetic and water was found to catalyze direct aldol reactions of a range of ketones and aldehydes in high yields. The reactions are believed to occur via a *syn*-enamine intermediate



Scheme 5. Proposed mechanisms for FIL-catalyzed direct aldol reactions.

and the ionic-liquid moiety would provide certain space shielding for the participating aldehyde acceptors. This space-shielding effect accounts for the modest enantioselectivities observed in the reactions. As testimony to the ionic-liquid properties, FIL **1b** could be easily recycled and reused for six times with slightly reduced activities. Overall, our current studies proved that FIL could be used as highly efficient and reusable organocatalyst for direct aldol reactions. The results and observations in this study could also provide useful knowledge for the design of new type of FILs with improved enantioselectivities.[17]

4. Experimental section

4.1. General procedure

In a 5 mL vial, **1b** (30 mg, 0.1 mmol), aldehyde (0.5 mmol), and ketone (5.0 mmol) were mixed in the presence of H_2O (0.5 mmol) and acetic acid (0.025 mmol). The resulting homogenous solution was stirred at ambient temperature and monitored by TLC. After the indicated reaction time, the solution was extracted with diethyl ether. The ether extract was rotary evaporated and the crude product was purified by flash chromatography on silica gel to afford the desired product. The remaining layer was further vacuumed to dryness and the resulting catalyst was reused directly for the next run. The reactions using the recycled catalyst were conducted in the same manner.

Most of the aldol products are known compounds.[9,10,16b]

4.1.1. 3-(Benzyloxy)-4-hydroxy-4-(4-nitrophenyl)butan-2-one (Table 3, entry 9). Only pure *anti*-isomer was isolated. IR (KBr, cm^{-1}): 3376, 1706, 1604, 1520, 1451, 1348; ^1H NMR (300 MHz, $CDCl_3$): δ 2.15 (3H, s), 3.35 (1H, br s), 3.90 (1H, d, J=6.6 Hz), 4.30 (1H, d, J=8.7 Hz), 4.51 (1H, d, J=8.7 Hz), 5.02 (1H, d, J=6.6 Hz), 7.12–7.14 (2H, m), 7.29–7.31 (3H, m), 7.52 (2H, d, J=9.0 Hz), 8.16 (2H, d, J=9.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 27.7, 73.5, 73.8, 87.0, 123.4, 127.8, 128.1, 128.4, 128.6, 136.3, 147.0, 147.6, 209.9. HRMS for $C_{17}H_{17}N_3O_5Na^+$ (M+Na^+) calcd 338.1004, found 338.1010.

4.1.2. 1-Hydroxy-1-(4-nitrophenyl)octan-3-one (Table 3, entry 11). IR (KBr, cm^{-1}): 3470, 1707, 1602, 1520, 1461, 1347; ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (3H, t, J=6.9 Hz), 1.24–1.32 (4H, m), 1.56–1.63 (2H, m), 2.45 (2H, t, J=7.5 Hz), 2.84 (2H, d, J=7.5 Hz), 3.80 (1H, br s), 5.26 (1H, t, J=6.0 Hz), 7.54 (2H, d, J=9.0 Hz), 8.18 (2H, d, J=9.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.8, 22.3, 23.2, 31.2, 43.6, 50.5, 69.0, 123.7, 126.4, 147.3, 150.3, 211.1. HRMS for $C_{14}H_{19}NO_4^+$ (M^+) calcd 265.1314, found 265.1317.

4.1.3. (*E*)-1-(4-Nitrophenyl)oct-1-en-3-one (Table 3, entry 11). IR (KBr, cm^{-1}): 3111, 2956, 2928, 1661, 1594, 1513, 1463, 1404, 1342; ^1H NMR (300 MHz, $CDCl_3$): δ 0.89–0.94 (3H, m), 1.32–1.37 (4H, m), 1.65–1.74 (2H, m), 2.68 (2H, t, J=7.5 Hz), 6.85 (2H, d, J=16.2 Hz), 7.56 (2H, d, J=16.2 Hz), 7.69 (2H, d, J=8.7 Hz), 8.24 (2H, d, J=8.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.9, 22.4, 23.8, 31.4, 41.5, 124.2, 128.8, 129.6, 139.1, 140.9, 148.5, 199.8. HRMS for $C_{14}H_{17}NO_3^+$ (M^+) calcd 247.1208, found 247.1211.

4.1.4. 1-Hydroxy-1-(3-nitrophenyl)octan-3-one (Table 3, entry 12). IR (KBr, cm^{-1}): 3464, 3091, 1710, 1617, 1583, 1530, 1406, 1349; ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (3H, t, J=6.6 Hz), 1.23–1.32 (4H, m), 1.56–1.64 (2H, m), 2.46 (2H, t, J=7.2 Hz), 2.85 (2H, d, J=6.0 Hz), 3.91 (1H, s), 5.26 (1H, t, J=5.7 Hz), 7.52 (1H, t, J=7.8, 8.1 Hz), 7.28 (1H, d, J=7.8 Hz), 8.09–8.12 (1H, m), 8.23 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.8, 22.4, 23.2, 31.2, 40.7, 43.6, 50.6, 68.9, 120.7, 122.4, 129.4, 131.9, 145.2, 148.3, 211.1. HRMS for $C_{14}H_{19}NO_4^+$ (M^+) calcd 265.1314, found 265.1318.

4.1.5. (*E*)-1-(3-Nitrophenyl)oct-1-en-3-one (Table 3, entry 12). IR (KBr, cm^{-1}): 3121, 2934, 2846, 1664, 1617, 1529, 1461, 1403, 1348; ^1H NMR (300 MHz, $CDCl_3$): δ 0.87–0.91 (3H, m), 1.30–1.37 (4H, m), 1.65–1.75 (2H, m), 2.69 (2H, t, J=7.2 Hz), 6.88 (1H, d, J=16.2 Hz), 7.56–7.62 (2H, m), 7.86 (1H, d, J=7.8 Hz), 8.24 (1H, d, J=8.4 Hz), 8.41 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.9, 22.5, 23.8, 31.4, 41.5, 122.4, 124.5, 128.5, 129.9, 133.8, 136.5, 139.1, 148.7, 199.8. HRMS for $C_{14}H_{17}NO_3^+$ (M^+) calcd 247.1208, found 247.1212.

4.1.6. 1-Hydroxy-1-(2-nitrophenyl)octan-3-one (Table 3, entry 13). IR (KBr, cm^{-1}): 3472, 2930, 1709, 1611, 1577, 1525, 1461, 1346; ^1H NMR (300 MHz, $CDCl_3$): δ 0.89 (3H, t, J=6.6 Hz), 1.26–1.31 (4H, m), 1.57–1.62 (2H, m), 2.43–2.50 (2H, m), 2.65–2.74 (1H, dd, J=9.3, 17.4, 9.3 Hz), 3.03–3.09 (1H, dd, J=2.4, 17.4, 2.4 Hz), 4.05 (1H, s), 5.65 (1H, d, J=9.0 Hz), 7.42–7.45 (1H, m), 7.63–7.66 (1H, m), 7.87–7.94 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.7, 22.6, 23.2, 31.2, 43.3, 50.1, 65.6, 124.4, 128.2, 133.7, 138.7, 147.1, 211.2. HRMS for $C_{14}H_{19}NO_4Na^+$ (M+Na^+) calcd 288.1212, found 288.1216.

4.2. Synthesis of FILs

The preparation of FILs followed our published procedure.[4]

4.2.1. Representative procedure for the synthesis of 1b. To a solution of (*S*)-Boc-prolinol (11.3 g, 56 mmol) in 100 mL of pyridine was added portionwise *p*-toluenesulfonyl chloride (13.1 g, 68.8 mmol) at 0 °C. The reaction mixture was stirred overnight. The mixture was then diluted with 350 mL of ethyl acetate and washed with cold 1 N HCl (200 mL×5), saturated $NaHCO_3$ (150 mL×2), and brine (100 mL×2). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford pale yellow syrup 18.0 g, which was directly used for next step without purification. To the solution of the tosylation product (6.6 g, 18.6 mmol) in 60 mL of anhydrous acetonitrile was added imidazole sodium salt (Na^+Im^-, 2.51 g, 27.9 mmol). The mixture was heated to reflux for 1.5 h and then cooled to room temperature. Solvent was removed under vacuo and the residue was diluted with 60 mL of water. The resulted mixture was extracted with chloroform (100 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatograph on silica gel to give the desired product as pale yellow solid (3.80 g, 83% yield). $[\alpha]_D^{25}$ −128.0 (*c* 1.0,

$CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.27–1.28 (1H, m), 1.48 (9H, s), 1.60–1.75 (2H, br), 1.89–1.94 (1H, m), 3.14–3.37 (2H, m), 3.99–4.08 (2H, m), 4.22–4.26 (1H, m), 6.87 (1H, s), 7.04 (1H, s), 7.44 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.3, 28.5, 29.1, 47.0, 48.6, 57.2, 79.8, 119.9, 129.4, 137.7, 162.3.

Under Ar, tosylation product of (*S*)-Boc-prolinol obtained from the former step (1.38 g, 5.50 mmol) and *n*-butylbromide (1.51 g, 11.0 mmol) were mixed in toluene (15 mL). The solution was kept at 70 °C and stirred for 24 h. The solvent was then removed under vacuo and the residue was purified by flash chromatograph on silica gel to afford a pale yellow viscous liquid (1.98 g, 93% yield). $[\alpha]_D^{25}$ −10.6 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.98 (3H, t *J*=7.38, 7.32 Hz), 1.42 (11H, m), 1.79–2.15 (6H, m), 3.23–3.52 (2H, m), 4.12–4.24 (1H, m), 4.25–4.41 (2H, m), 4.48–4.72 (2H, m), 7.38 (1H, s), 7.41 (1H, s), 10.53 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.4, 19.4, 23.6, 28.3, 28.5, 32.1, 47.0, 49.9, 51.9, 57.1, 80.1, 121.5, 122.7, 137.7, 155.1; LC–MS: 308.15 (M^+), 78.99, 81.02 (Br^-).

To a solution of Boc-protected pyrrolidinyl-imidazolium bromide (1.01 g, 2.70 mmol) in acetonitrile and acetone (50 mL, 9:1), was added well-sieved $NaBF_4$ (1.32 g, 12.02 mmol). The mixture was vigorously stirred at room temperature for three days. Filtered to remove the inorganic salts and the filtrate was triturated with $AgBF_4$ solution (in acetonitrile) till no precipitation was formed. Filtered again and concentrated. The residue was diluted with CH_2Cl_2 and the insoluble part was removed by filtration. The clear filtrate was concentrated under vacuo and the residue was treated in 4 M HCl dioxane solution. The solution was concentrated under vacuo to give the hydrogen chloride salts, which was subsequently neutralized in saturated $NaHCO_3$ solution (70 mL). The aqueous solution was evaporated to dryness under vacuo and the solid residue was extracted with chloroform (20 mL×6). The combined organic layer was concentrated in vacuo to afford a pale yellow and clear liquid **1b** (0.8 g, 100% yield). $[\alpha]_D^{25}$ +25.5 (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}): 3428, 2961, 1562, 1401, 1083; ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (3H, t, *J*=7.5 Hz), 1.26–1.33 (3H, m), 1.63–1.65 (2H, m), 1.77–1.82 (2H, m), 1.90–1.93 (1H, m), 2.78–2.86 (2H, m), 3.49–3.52 (1H, m), 3.89–3.97 (1H, m), 4.12–4.22 (3H, m), 7.27 (1H, s), 7.47 (1H, s), 8.97 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.3, 19.4, 25.9, 29.0, 31.9, 46.5, 49.7, 54.3, 57.4, 121.5, 123.3, 136.1. HRMS for $C_{12}H_{22}N_3^+$ (M^+) calcd 208.1808, found 208.1806.

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