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Synthesis of new chiral ionic liquids from natural acids and their applications in enantioselective Michael addition

Zhiming Wang,[a] Qiang Wang,[a,b] Yu Zhang[a] and Weiliang Bao[a,*]

[a]*Zhejiang University, Xi Xi Campus, Department of Chemistry, Hangzhou, Zhejiang 310028, China*
[b]*Ningbo University, Department of Chemistry, Ningbo, Zhejiang 315211, China*

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Abstract—Two kinds of novel chiral ionic liquids based on imidazolium have been synthesized from chiral pool by a simple and straightforward procedure in good overall yields (44–60%). The application of CILs as reaction media in the enantioselective Michael addition of diethyl malonate to 1,3-diphenyl-prop-2-en-1-one has also been studied (yield 90–96%, 10–25% ee).

Room temperature ionic liquids (RTILs) are novel and promising materials for a variety of chemical applications.[1] Because of their unique physical and chemical properties, RTILs have been widely applied in organic reactions as 'green solvents' for they can accelerate reaction rates, improve selectivities, and facilitate catalyst recovery, etc.[1,2] In view of the emerging importance of ILs as reaction media in organic synthesis, several groups have recently focused on the synthesis of chiral ionic liquids (CILs Fig. 1) for their particularly potential applications to chiral discrimination, including asymmetric synthesis and optical resolution of racemates.[3–9] For example, Seddon et al. prepared the chiral lactate salt of 1-butyl-3-methyl imidazolium (**I**) and investigated Diels–Alder reactions therein (however, <5% ee were obtained).[3] Wasserscheid and co-workers synthesized CIL as chiral shift reagent in ^{19}F NMR for *rac*-Mosher's acid sodium salt.[4] More recently, the use of CILs as reaction media in the asymmetric Baylis–Hillman reaction was reported and significant enantiomeric excesses were obtained (20–44% ee).[10] The study of the application of CILs in asymmetric synthesis is not only an opportunity but also a challenge for researchers.[1c] It is interesting, meaningful, and necessary to synthesize different kinds of CILs from different starting materials, especially from the chiral pool. Herein, we wish to report the synthesis of new CILs based on imidazolium salt in which the core of positive charge is attached on the carbon adjacent to the chiral center.

Good chemical stability, especially configurational stability, is one of the most important criteria for synthesis of CILs and a necessary property for their application to chiral discrimination. Noteworthy, the results of Mikami et al. indicated that the presence of a nitrogen cation adjacent to chiral center (a secondary carbon) makes the racemization of the CILs possible.[9] However, most of CILs, particularly CILs from the chiral pool, have the structural unit that the core of positive charge is directly resided at the chiral center. Therefore, we plan to synthesize the CILs with 'better' configurational stability from chiral pool to overcome this drawback.

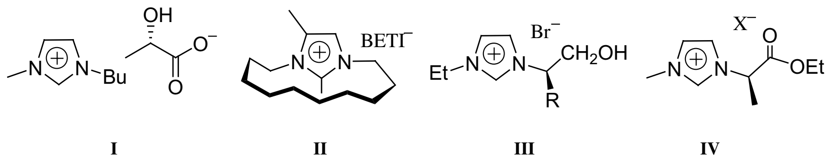

Figure 1. Examples of chiral ionic liquids.

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[*] Corresponding author. Tel./fax: +86 571 88911554; e-mail: wbao@hzcnc.com

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Firstly, we used the commercially available and inexpensive L-(+)-diethyl tartarate (**1a**) as the starting material. According to Johnson's work on *O*-benzylation of ethyl (S)-lactate,[11] *O*-benzylation of **1a** with sodium hydride and benzyl bromide in THF/DMF afforded the ester (**2a**) in 80% yield, and $[\alpha]_D^{20}$ +79.0 (neat 1 dm) was recorded. Compared with the methods of Seebach and Yamamoto et al., severe and high price reagents, such as thallium alkoxide and 18-crown-6, were avoided.[12,13] The diol **3a** was obtained by the reduction of **2a** with LiAlH$_4$ in >99% optical purity (yield 89%, $[\alpha]_D^{20}$ +13.1 (ethanol, *c* 4.9)) (lit.[12] +13.2). Ditosylate **4a** was prepared under standard conditions in a yield of 88%. When we followed Kündig's procedure[14] to transform **4a** to **5a**, the reaction rate was very slow (Table 1, entry 1). We also examined the reaction in acetone and even longer reaction time was needed (Table 1, entry 2). Since some recent reports have indicated that ILs not only can be used as the excellent reaction reagents[15,16] but also as the efficient promoting reaction solvents in nucleophilic substitution reactions,[17,18] we tried the reaction in ILs and excellent results were obtained. Especially, when conducted in [bmim]Br, the reaction finished after only 1 h with rather high yield (Table 1, entry 4). Herein, [bmim]Br was used both as excellent 'green' reagent and solvent. The IL can be successfully recycled and reused following Nguyen's process (Table 1, entry 5).[16] Finally, the target molecule **6a** was obtained by the quarternization reaction of **5a** and 1-methylimidazole in acetone. Thus, the imidazolium salt **6a** was prepared in five steps from chiral pool in 51% overall yield (Scheme 1).

Table 1. Synthesis of dibromide **5a** from ditosylate **4a** in different solvents

Entry[a]	Solvent	Temp (°C)	Time (h)	Yield (%)[c]
1	DMSO	60	20	89
2	Acetone	60	48	85
3	[bmim]BF$_4$	80	2	90
4[b]	[bmim]Br	80	1	93[d]
5[b]	[bmim]Br[e]	80	1	92[d]

[a] All the reactions were run with ditosylate **4a** (2 mmol) and LiBr (4 mmol) in solvent (5 mL), unless specified.

[b] The reaction was run with ditosylate **4a** (2 mmol) and [bmim]Br (5 mL).

[c] Isolated yield based on ditosylate **4a**.

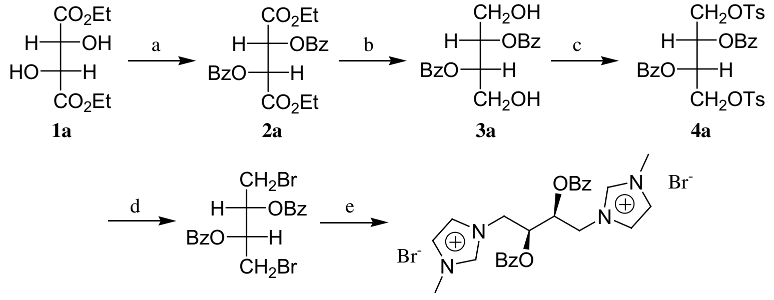
[d] $[\alpha]_D^{20}$ +11.4 (CHCl$_3$, *c* 5.8) (lit.[13] +11.72).

[e] The ionic liquid was recycled and reused following Nguyen's process.

Compared with common ILs (mp <100 °C), the melting point of the interesting imidazolium salt **6a** with C_2 symmetry axis is high (182–183 °C). For further investigation, we also chose the commercially available and inexpensive L-(−)-ethyl lactate as the starting material to synthesize the CIL and hoped to get a low melting point one. CIL **6b** was obtained in five steps from chiral pool in 60% overall yield, according to the route of Scheme 2. Encouragingly, the new CIL **6b** has a low melting point (57–58 °C) and no racemization was detected in a basic (1 M NaOH) or acidic (1 M HCl) condition, even when heated. It has a good solubility in water, acetone, DMSO, and even in CHCl$_3$.

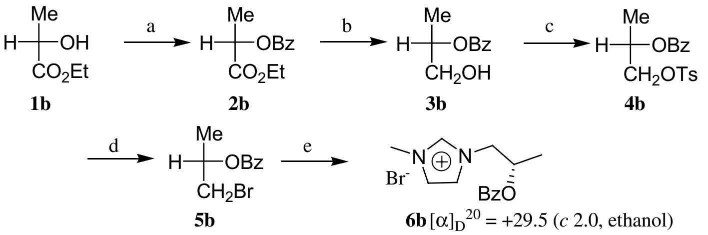
Anion exchange was performed to get salts **7**–**8a** and **7**–**8b** (Scheme 3). The melting point of the CIL **8b** (41–42 °C) is the lowest compared with the CILs **7a** (88–90 °C), **8a** (129–130 °C), and **7b** (92–93 °C). The CILs **7a** and **7b** are both hydrophobic and immiscible with ether, therefore, the traces of organic or inorganic impurities can be removed by extraction with water or ether. There is another merit in the synthetic pathway: both the anion exchange reactions were completed in less than 0.5 h and the reaction yields were rather high. It is beneficial to synthesize CILs in large scale for further investigations.

Activities on asymmetric induction of CIL **8b** as 'chiral induction solvent' were evaluated by Michael addition of diethyl malonate to 1,3-diphenylprop-2-en-1-one and the results were summarized in Table 2. Since low reaction temperature is needed to enhance the chiral induction and the melting points of the CILs are more than 40 °C, the co-solvent is necessary to let the reaction mixture stir smoothly. Compared with DMSO and DMF, better results were obtained (yield 95%, 24% ee) when toluene was used as the co-solvent (Table 2, entries 1–3), perhaps owing to different solubilities of the CIL in different co-solvents. When anion Br$^-$ was used instead of BF$_4^-$, a slight increase of ee was detected. On the other hand, when anion PF$_6^-$ was used, a slight decrease of ee was detected. At the same time, when the CIL with C$_2$ symmetry axis (**7a**) was used in the reaction system, only 10% ee was obtained. It seems that different anions

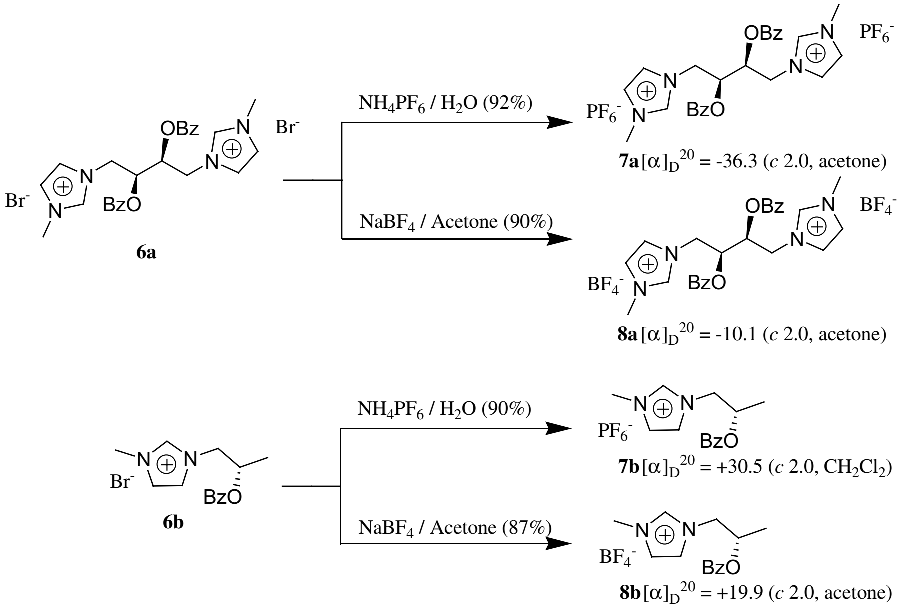


6a $[\alpha]_D^{20}$ = -31.0 (*c* 2.0, ethanol)

Scheme 1. Reagents and conditions: (a) BzBr, NaH, THF/DMF (1:1), 80%; (b) LiAlH$_4$, Et$_2$O, 89%; (c) TsCl, pyridine, 88%; (d) 1-butyl-3-methylimidazolium bromide, 80 °C, 96%; (e) 1-methylimidazole, acetone, reflux, 85%.

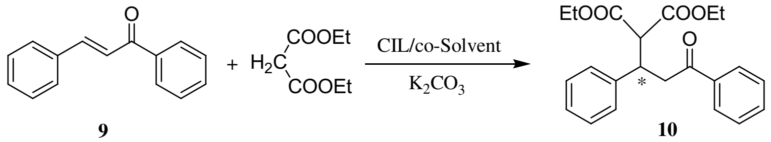


Scheme 2. Reagents and conditions: (a) BzBr, NaH, THF/DMF (2:1), 89%; (b) $LiAlH_4$, Et_2O, 90%; (c) TsCl, pyridine, 91%; (d) 1-butyl-3-methylimidazolium bromide, 80 °C, 96%; (e) 1-methylimidazole, acetone, reflux, 86%.



Scheme 3. Anion exchange.

Table 2. Enantioselective Michael addition of diethyl malonate to 1,3-diphenylprop-2-en-1-one in CIL



Entry[a]	CIL	Co-solvent	Time (h)	Yield (%)[b]	ee (%)[c]	$[\alpha]_D^{25}$
1	**8b**	Toluene	10	95	24	+1.50
2	**8b**	DMSO	6	90	17	+1.10
3	**8b**	DMF	7	91	16	+1.00
4	**6b**	Toluene	10	96	25	+1.60
5	**7b**	Toluene	10	93	23	+1.46
6	**7a**	Toluene	12	95	10	+0.64

[a] Reaction conditions: diethyl malonate (1.2 mmol), 1,3-diphenylprop-2-en-1-one (1.0 mmol), K_2CO_3 (3.0 mmol) in CILs (10 mmol) and co-solvent (1 mL) at rt.

[b] Isolated yields based on **9**.

[c] Enantiomeric excesses were determined from optical rotations.[19]

or cations in CILs have the different effects on the enantioselectivity of the reaction.

In summary, two kinds of new imidazolium CILs with ‘better’ configurational stability have been prepared from the chiral pool by a simple and straightforward procedure in good overall yields (44–60%, selected data are listed in Ref. 20). And the application of CILs as reaction media and chiral reagent for the enantioselective Michael addition of diethyl malonate to 1,3-diphenyl-prop-2-en-1-one has also been studied. Although the enantiomeric excesses are moderate at present, the results of this work have provided meaningful insights in the understanding of the use of CILs in asymmetric induction. Applications of chiral ILs as green media for other asymmetric syn-thesis and catalysis are actively investigated in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.04.134.

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20. All compounds reported here were duly characterized. Selected data: **7a**: mp 88–90 °C; $[\alpha]_D^{20}$ −36.3 (*c* 2.0, acetone); ^{1}H NMR (DMSO-d_6) δ 3.80 (s, 6H), 4.04 (d, $J = 9.20$ Hz, 2H), 4.28–4.34 (m, 4H), 4.46–4.61 (m, 4H), 7.12–7.15 (m, 4H), 7.31–7.32 (m, 6H), 7.60–7.63 (m, 4H), 9.02 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 36.23, 49.19, 72.98, 76.72, 123.30, 123.95, 128.45, 128.55, 128.82, 137.64, 137.67; IR 3474, 3184, 3131, 1596 cm^{-1}; Anal. Calcd for $C_{26}H_{32}F_{12}N_4O_2P_2$: C, 43.22; H, 4.46; N, 7.75. Found: C, 43.12; H, 4.73; N, 7.55. **8a**: mp 129–130 °C; $[\alpha]_D^{20}$ −10.1 (*c* 2.0, acetone); ^{1}H NMR (DMSO-d_6) δ 3.79 (s, 6H), 4.05 (d, $J = 8.80$ Hz, 2H), 4.29–4.35 (m, 4H), 4.46–4.61 (m, 4H), 7.13–7.15 (m, 4H), 7.29–7.32 (m, 6H), 7.60–7.63 (m, 4H), 9.03 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 36.26, 49.36, 73.04, 76.82, 123.34, 123.99, 128.46, 128.59, 128.86, 137.73; IR 3463, 3155, 3101, 1685, 1574 cm^{-1}; Anal. Calcd for $C_{26}H_{32}B_2F_8N_4O_2$: C, 51.52; H, 5.32; N, 9.24. Found: C, 51.46; H, 5.47; N, 9.14. **7b**: mp 92–93 °C; $[\alpha]_D^{20}$ +30.5 (*c* 2.0, CH_2Cl_2); ^{1}H NMR (DMSO-d_6) δ 1.15 (d, $J = 5.60$ Hz, 3H), 3.78– 3.85 (m, 4H, CH_3, CH), 4.14 (dd, $J = 14.20$ Hz, $J' = 7.40$ Hz, 1H), 4.33 (dd, $J = 14.00$ Hz, $J' = 3.20$ Hz, 1H), 4.37 (d, $J = 12.00$ Hz, 1H), 4.54 (d, $J = 12.40$ Hz, 1H), 7.16–7.19 (m, 2H), 7.28–7.31 (m, 3H), 7.63–7.64 (m, 2H), 9.01 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 16.96, 36.16, 53.72, 70.09, 72.88, 123.51, 123.68, 127.93, 127.95, 128.67, 137.42, 138.56; IR 3454, 3183, 1632 cm^{-1}; Anal. Calcd for $C_{14}H_{19}F_6N_2OP$: C, 44.69; H, 5.09; N, 7.44. Found: C, 44.50; H, 5.28; N, 7.33. **8b**: mp 41–42 °C; $[\alpha]_D^{20}$ +19.9 (*c* 2.0, acetone); ^{1}H NMR (DMSO-d_6) δ 1.16 (d, $J = 6.40$ Hz, 3H), 3.78–3.85 (m, 4H, CH_3, CH), 4.12–4.17 (m, 1H), 4.32–4.39 (m, 2H), 4.55 (d, $J = 12.40$ Hz, 1H), 7.17–7.19 (m, 2H), 7.29–7.32 (m, 3H), 7.62–7.63 (m, 2H), 8.99 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 17.05, 36.21, 53.79, 70.18, 72.98, 123.56, 123.73, 128.04, 128.75, 137.46, 138.64; IR 3443, 3155,1635 cm^{-1}; Anal. Calcd for $C_{14}H_{19}BF_4N_2O$: C, 52.86; H, 6.02; N, 8.81. Found: C, 52.74; H, 6.15; N, 8.78.