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Design and synthesis of bistereogenic chiral ionic liquids and their use as solvents for asymmetric Baylis–Hillman reactions†

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Three novel chiral ionic liquids (CILs) containing two chiral centers in the side chain bonded to the 2-position of the imidazolium cation and different anions have been synthesized, characterized and used as chiral solvents for asymmetric Baylis–Hillman (BH) reactions; good yields and fair enantioselectivities were obtained.

The toxic and volatile nature of many organic solvents that are widely used in organic synthesis has posed a serious threat to the environment. Efforts aimed at replacing these volatile organic solvents with environmentally friendly ones as reaction media have been pursued in recent years. Performing organic reactions in ionic liquids (ILs) has received considerable attention owing to the intriguing properties of ILs, which include lack of measurable vapor pressure, high chemical and thermal stability, noncombustibility, and high ionic conductivity, compared to typical organic solvents.[1] Moreover, the solubility of ILs can be tuned readily by modifying their cations and anions so that they can be separated easily from organic solvents as well as aqueous media. As a result, numerous important organic reactions have been successfully conducted in ILs. Recently, chiral ionic liquids (CILs) have been the focus of attention, especially their effect on asymmetric reactions.[2,3] To date, there are only a few CILs that have been designed, synthesized, and used effectively as solvents and catalysts for asymmetric reactions; examples of reactions include the Baylis–Hillman (BH) reaction,[4] Michael addition,[5] aldol reactions,[6] and many other reactions.[7] A review of the literature reveals that most CILs that have been successfully used to influence asymmetric reactions contain one chiral center, and only a limited number contain two chiral centers. Such bistereogenic CILs have been successfully used for chiral discrimination and other applications in asymmetric synthesis;[4,5a,8] examples of bistereogenic chiral ionic liquids are shown in Fig. 1. This 'designer' feature of ionic liquids opens up new areas of research for their design and use as solvents for asymmetric reactions. Herein, we wish to report the synthesis of bistereogenic CILs and their use as solvents for asymmetric BH reactions.

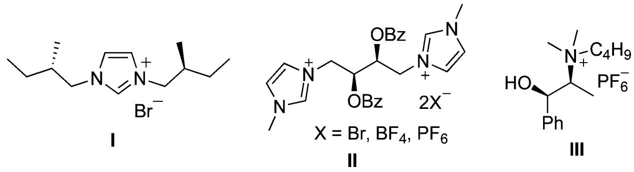

Fig. 1 Examples of known bistereogenic CILs.

The BH reaction has attracted much attention as a useful C–C bond formation reaction in organic synthesis, mainly because it efficiently converts simple starting materials into highly functionalized products. Recently, a highly enantioselective asymmetric BH reaction of acrylates and aldehydes has been achieved by the use of chiral Brønsted acids,[9] chiral lanthanide Lewis acids,[10] and quinidine-derived chiral nucleophilic amine catalysts.[11] In all these cases, a volatile organic solvent, such as THF, DMF, or CH_3CN was necessary. Recent research on the BH reaction, in which nonvolatile achiral ILs were used as solvents, has demonstrated that such IL media can accelerate the reaction rate.[12] However, low yields were obtained when the reaction was conducted in the presence of imidazolium-based ILs under basic conditions, due to the deprotonation that occurs in the C-2 position of the imidazolium cation, which results in undesired side products.[13] Owing to the versatility in the design of chiral ionic liquids to accomplish various tasks and to explore the use of imidazolium type CILs in the BH reaction, we have chosen to design a new type of CIL that contains the imidazolium cation as well as a side chain that contains two chiral centers, which is bonded to the 2-position of the imidazolium cation.[14] An important feature in the design is that there is not an acidic hydrogen at the C-2 position of the imidazolium ring. In addition, the hydroxyl and NH groups are present, which are propitious for the transfer of chirality *via* hydrogen bonding.

The synthesis is similar to that reported earlier;[14] the imidazole precursor was synthesized from commercially available 1-methyl-2-imidazole carboxaldehyde and (1*S*,2*R*)-norephedrine by a condensation reaction, and the intermediate imine was reduced by sodium borohydride, quenched with hydrochloric acid, followed by neutralization to form product **1**. The alkylation reaction is carried out under reflux using toluene for 12 hours to form the imidazolium bromide salt **2** in good yields and high purity. The syntheses of the corresponding bistereogenic CILs with different anions were carried out using anion exchange of the bromide anion with BF_4 and NTf_2 anions to form CILs **3**, and **4** respectively, which were purified with flash chromatography with a suitable solvent system (Scheme 1). The CIL **4** with NTf_2 as anion was a good liquid at room temperature and was found to be very soluble in common solvents, such as alcohols, CH_2Cl_2, ethyl acetate, DMF, and DMSO, but was immiscible with ether, hexane, and H_2O. The CILs **2** and **3** were highly viscous liquids at room temperature and were found to be only soluble in high polarity solvents, such as alcohols, DMF, H_2O and DMSO.

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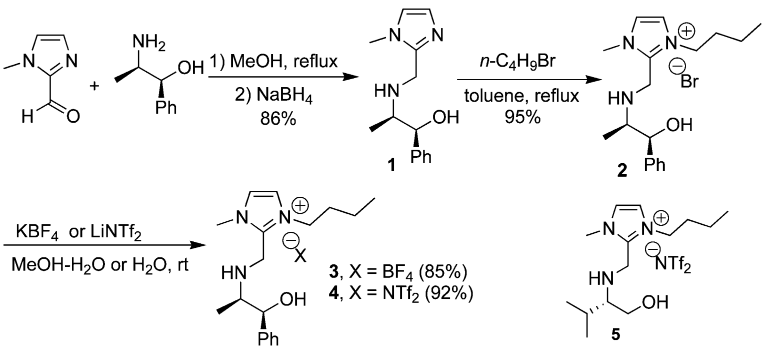
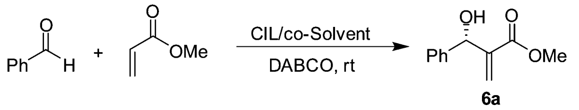


Scheme 1 The synthesis of bistereogenic CILs.

Optimization of asymmetric induction reaction conditions of CILs as chiral solvents was examined by using the BH reaction of benzaldehyde and methyl acrylate and DABCO was used as a Lewis base; the results are summarized in Table 1. Using CIL **4** with THF or toluene as co-solvents, the reaction gave the desired product **6a** in moderate yields and fair enantioselectivities with 80–85% CIL recovery (Table 1, entries 1–2). While using CH_2Cl_2 as co-solvent with CIL **4**, no enantioselectivity was observed (Table 1, entry 3). When protic solvents MeOH and H_2O were used as co-solvents with CILs **2**, **3**, and **4**, only minimal to no enantioselectivity was observed, although CILs **2** and **3** have good solubility in water (Table 1, entries 4–7). One possible explanation for the low or no enantiomeric excess in the presence of H_2O and MeOH is that there is a competition for hydrogen bonding with the substrate and such interactions are stronger with the substrate molecules, compared to those with the chiral ionic liquid, which in turn affect the stereoselectivity. However, when the CIL **4** was used as the solvent without a co-solvent, the desired adduct was obtained in 80% yield and 19% ee (Table 1, entry 8). The enantioselectivity was further increased to 25% ee when the reaction temperature was lowered to 4 °C without reduction in the reaction rate (Table 1, entry 9). Interestingly, using one chiral center ionic liquid **5** only resulted in 5% ee (Table 1, entry 10). The absolute configuration of **6a** was determined to be *S*, by comparing the specific rotation of **6a** with that reported elsewhere.[15] Although the research on chiral ionic liquids as solvents for asymmetric reactions is still at a preliminary stage and the enatioselectivities are often poor and even zero,[2] the results obtained for these bistereogenic chiral ionic liquids are promising.

Table 1 Optimization of asymmetric BH reaction of benzaldehyde and methyl acrylate[a]



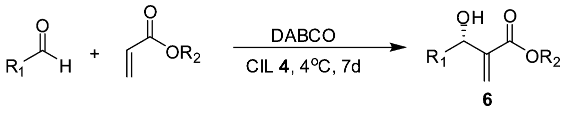
Entry	CIL	Co-solvent	T/d	Yield (%)[b]	Ee (%)[c]	CIL-recovery
1	**4**	THF	7	50	14	80%
2	**4**	Toluene	7	50	14	85%
3	**4**	CH_2Cl_2	7	45	Racemic	97%
4	**4**	MeOH	7	78	Racemic	91%
5	**2**	H_2O	2	80	5	96%
6	**3**	H_2O	2	20	3	55%
7	**4**	H_2O	7	< 5	Racemic	95%
8	**4**	None	7	80	19	96%
9[d]	**4**	None	7	82	25	97%
10	**5**	None	6	80	5	98%

[a] Reaction conditions: benzaldehyde (0.5 mmol), methyl acrylate (1.5 mmol), DABCO (1.0 mmol), CIL (4.0 mmol), co-solvent (0.5 mL). [b] Isolated yield. [c] Determined by HPLC (chiralpak AS-H). [d] The reaction temperature at 4 °C.

Next, investigations on asymmetric induction of CIL **4** as chiral solvent were carried out by using the BH reaction with a series of aldehydes and acrylates under the optimized reaction conditions of entry 9 (Table 1) and the results are summarized in Table 2. As shown in Table 2, all reactions occurred smoothly in the presence of CIL **4** under these standard conditions, giving the corresponding products **6a–g** in moderate to high yields. Typically, substituents on the aromatic aldehydes and acrylates influenced the enantioselectivities as well as the yields. For example, the reaction of the more steric *t*-butyl acrylate with benzaldehyde afforded adduct **6b** with a decreased yield and enantioselectivity compared to the methyl acrylate (Table 2, entries 1–2). Low enantioselectivities were observed in the cases of 4-chlorobenzaldehde and 4-nitrobenzaldehyde (Table 2, entries 3–4). While the reaction of 4-methoxybenzaldehyde with methyl acrylate gave adduct **6e** with a slightly increased ee, the reaction rate was slow (Table 2, entry 5). When the aliphatic aldehydes were used as substrates, very low enantioselectivities were observed, although the yields were high (Table 2, entries 6–7).

The enantioselectivities observed in the BH reactions could be explained by the presence of the hydroxyl and NH groups, which play an important role in the transfer of chirality *via* hydrogen

Table 2 BH reactions of aldehydes and acrylates using CIL **4** as solvent[16]



Entry	R$_1$	R$_2$	Product	Yield (%)[a]	Ee (%)[b]	CIL-recovery
1[c]	Ph	Me	**6a**	80	24	95%
2	Ph	*t*-Bu	**6b**	60	7	98%
3	4-Cl-C_6H_4	Me	**6c**	97	12	98%
4	4-NO_2-C_6H_4	Me	**6d**	80	18	95%
5	4-MeO-C_6H_4	Me	**6e**	38	23	95%
6	*i*-Pr	Me	**6f**	91	3	97%
7	$PhCH_2CH_2$	[d]	**6g**	90	2	95%

[a] Isolated yield. [b] Determined by HPLC (chiralpak AS-H). [c] The recycled CIL **4** was used as solvent. [d] Cyclohexenone was used.

bonding with the aldehyde substrate in a manner such that C–C bond formation would take place by the zwitterionic intermediate addition to the less hindered *Re* face of the aldehyde. A depiction of the bifurcated hydrogen bonding that is expected to stabilize the transition state and make the selectivity possible is shown in Fig. 2.

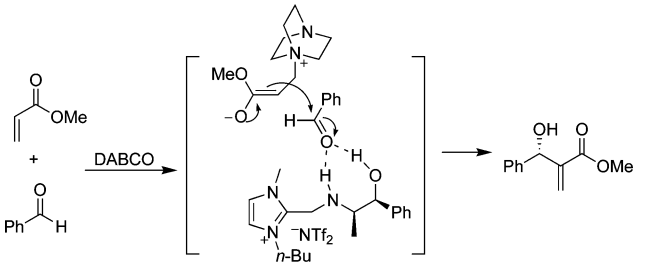


Fig. 2 Proposed mechanism for BH reaction using bistereogenic CIL as solvent.

In conclusion, three novel chiral ionic liquids have been designed and synthesized. These CILs were assembled by incorporating chiral side chains on the C-2 position of the imidazolium cation rings; this avoids the shortcomings of their traditional counterparts that can participate in deprotonation side reactions on their C-2 positions. Application of these new CILs as green media for asymmetric Baylis–Hillman reaction has been studied and afforded moderate to high yields (up to 97%) with fair enantioselectivities (up to 25% ee). Based on these preliminary results, the design of novel CILs, which is expected to afford higher levels of enantioselectivities for asymmetric reactions, is currently being investigated in our laboratory.

Acknowledgements

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16 *Typical procedure for BH reaction:* A mixture of aldehyde (1 mmol), acrylate (3 mmol), DABCO (1.5 mmol) and CIL **4** (4 mmol) was stirred for a period of time at the required temperature. The mixture was extracted with ether (2 mL × 3), concentrated and purified by flash chromatography and analyzed with ^{1}H-NMR. The ether insoluble CIL **4** was diluted in dichloromethane (15 mL) and washed with water (5 mL × 2). The organic layer was dried with anhydrous $CaCl_2$, filtered and evaporated in vacuum to afford the recycled CIL **4**. The CIL **4** was tested for its purity with spectral data and was found to be identical with the initial one. The recycled CIL was reused without significant loss of efficiency (Table 2, entry 1).