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First application of chiral ionic liquids in asymmetric Baylis–Hillman reaction

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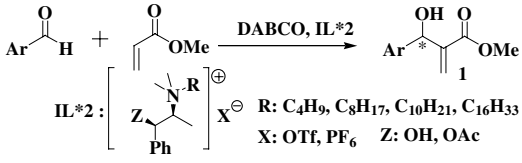
Abstract—The first example of the use of chiral ionic liquids as reaction media in the asymmetric Baylis–Hillman reaction was described using *N*-alkyl-*N*-methylephedrinium salts. Good yields and significant enantiomeric excesses were obtained.

Ionic liquids (ILs), or room temperature molten salts, have attracted much attention as new clean media for green chemistry, especially in synthetic and catalytic transformations.[1] Among them, chiral ILs are particularly attractive for their potential applications to chiral discrimination, including asymmetric synthesis and optical resolution of racemates. However, very few chiral ILs have been reported[2] and their use as reaction media in asymmetric transformations has been very limited. To the best of our knowledge, no significant enantioselectivity was observed so far.[3]

In connection with our studies on chiral ILs and our ongoing project on the asymmetric synthesis, we have recently reported the synthesis of chiral ILs possessing a chiral ephedrinium cation[4] using solvent-free reaction and microwave activation under green chemistry conditions.[5] In this communication, we describe the use of chiral ILs as reaction media for the first time in the asymmetric Baylis–Hillman reaction between benzaldehyde (Ar = Ph) and methyl acrylate (Scheme 1).

The Baylis–Hillman reaction has attracted considerable interest due to the fascinating tandem Michael-aldol sequence catalyzed by a Lewis base (such as a tertiary amine) or a Lewis acid and the promising utility of the multifunctional products. Recent literature continues to record impressive progress in rate acceleration as well as asymmetric induction based on imaginative ideas.[6]



Scheme 1. Asymmetric Baylis–Hillman reaction in the presence of chiral ILs as reaction media.

For our studies (Scheme 1, Ar = Ph), an asymmetric version of the Baylis–Hillman can be in principle carried out with a chiral source in any one of the two essential components either catalyst or solvent. In fact, several efforts have been made in using various asymmetric catalysts.[6] However, the enantioselectivities were found to be poor to moderate. Noticeable enhancements in both reaction rate and enantiomeric excess (ee) were observed under high-pressure conditions.[7] A highly enantioselective asymmetric Baylis–Hillman of aromatic aldehydes and imines has been achieved by Hatakeyama and co-workers.[8] using β-isocupreidine (β-ICD, cinchona alkaloid derivatives) as a chiral amine catalyst. Recently, Chen and co-workers.[9] described for the first time the use of novel camphor-derived dimerized ligands for chiral Lewis acid catalyzed asymmetric Baylis–Hillman reaction. Good enantioselectivities were obtained. In all cases, the use of aprotic polar solvent (DMF, CH_3CN) was necessary. On the other hand, no chiral solvent was reported in the literature for this transformation. Our aim was therefore to study the use of chiral ILs as reaction media in asymmetric Baylis–Hillman reaction, especially the transfer of chirality of these solvents due to their high degree of organization.

Keywords: Ionic liquids; Chirality; Baylis–Hillman reaction; Asymmetric synthesis.
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It should be pointed out that the use of chiral solvents in asymmetric syntheses was already reported in the literature.[10] However, low enantioselectivities were obtained and the difficult preparation of chiral solvents as well as their high cost often precluded their use. With regard to chiral ILs, due to their ease of synthesis, recyclability and their peculiar properties, these new chiral solvents should be highly more attractive than classical chiral solvents for asymmetric induction.

The use of achiral ILs as reaction media for the Baylis–Hillman reaction was described in the literature. However, low yields were obtained when the reaction was conducted in the presence of an imidazolium-based ionic liquid due to direct addition of the deprotonated imidazolium salt to aldehyde.[11] On the other hand, this reaction has been found to be accelerated in the presence of a catalytic amount of an imidazolium-based ionic liquid.[12] A moderate acceleration was observed when the above-mentioned ionic liquid was used in combination with Lewis acid. Kumar and Pawar[13] have shown that the DABCO-catalyzed Baylis–Hillman reaction has been shown to be improved in the chloroaluminate room temperature ionic liquids. The authors noted that these solvents could be recovered and reused without loss of efficiency. Recently, Chu and co-workers[14] described the use of butyldimethylimidazolium hexafluorophosphate ([bdmim][PF_6]) as solvent for this reaction. Unlike the commonly used [bmim][PF_6] that evidently reacts with electrophilic aldehyde under basic conditions, ionic liquid [bdmim][PF_6] is inert and the Baylis–Hillman reaction in this solvent proceeds smoothly with better yield.

In our initial studies, we attempt to optimize the reaction conditions for the Baylis–Hillman reaction between benzaldehyde and methyl acrylate using DABCO as Lewis base and in the presence of chiral ILs **2**, easily obtained in 'two-step sequence' reaction from (−)-*N*-methylephedrine.[5] Good yields and moderate enantiomeric excesses[15] were obtained. The main results are given in Table 1.

As illustrated in Table 1, the excess of chiral ILs leads to a noticeable enhancement in enantioselectivity (entries 1 and 4). However, low yields and considerable loss of benzaldehyde were observed when 3 equiv of chiral ILs were used, possibly owing to the instability of the benzaldehyde under these conditions. In fact, the low yields obtained in the presence of a large excess of ionic liquid are presumably due to the reaction between benzaldehyde and the alkoxy group resulting from the deprotonation of the hydroxy function on chiral ILs under basic conditions as already reported by Aggarwal et al.[11] A large excess of methyl acrylate (3 equiv for entry 6 and 1 equiv for entry 4) in the presence of a catalytic amount of DABCO (0.3 equiv) gave the same ee. On the other hand, the best enantioselectivity was obtained (44%) when the reaction was performed for 7 days (entry 8).

One of the major points of our work that has received considerable attention is the study of the transfer of chirality of these new chiral solvents in asymmetric transformations. Thus, a series of different alkyl chain lengths (R = C_4H_9, C_8H_{17}, $C_{10}H_{21}$, $C_{16}H_{33}$) was tested on this reaction model. However, no effect on the enantioselectivity was observed. On the other hand, a slight decrease of ee was detected when anion PF_6^- was used instead of OTf^- (Table 2, entries 1 and 2), perhaps owing to more decomposition of the chiral IL **2** (R = C_8H_{17}, X = PF_6) as already mentioned in the literature.[17]

It is important to note that the presence of the hydroxyl function on chiral ILs is propitious for the transfer of chirality. Thus, when the hydroxyl group was replaced by an acetyl group, only 6% ee was obtained (Table 2, entry 3). This was in fact already observed by Colonna and co-workers[18] in asymmetric induction in the borohydride reduction of carbonyl compounds by means of a chiral phase transfer catalyst. The noticeable influence of OH group is presumably connected to the intervention of a hydrogen bond with a carbonyl function (from either benzaldehyde or methyl acrylate) which implies a fixing point for chiral IL on reactants. It results in an

Table 1. Asymmetric Baylis–Hillman reaction in the presence of chiral ILs **2** (R = C_8H_{17}, X = OTf, Z = OH)

Entry	ILs **2** (equiv)	Conversion (%)[a]	Yield (%)[a]	(*R*)-**1** ee (%)[b]
1	0.5	86	76	20
2	1	85	78 (74)	23
3	1.5	85	73	28
4	3	65	45	32
5	1	83	67	24[c]
6	3	75	52 (50)	32[c]
7	3	60	30	24[c,d]
8	3	88	60	**44**[e]

Conditions = benzaldehyde–methyl acrylate–DABCO = 1:1:1. Temperature = 30 °C. Time = 4 days.

[a] Conversion and yield estimated by GC using an internal standard, isolated yields are given in brackets.

[b] ee determined by chiral HPLC[15] and configuration (*R*)-**1** determined by comparison of optical rotation with the literature value.[16]

[c] Benzaldehyde–methyl acrylate–DABCO = 1:3:0.3.

[d] Temperature = 50 °C.

[e] Time = 7 days.

Table 2. Asymmetric Baylis–Hillman reaction in the presence of chiral ILs **2** (R = C_8H_{17})

Entry	Chiral source **2**	Conversion (%)[a]	Yield (%)[a]	(*R*)-**1** ee (%)[b]
1	**2**, OTf, OH	85	78 (75)[c]	23 (24)[c]
2	**2**, PF_6, OH	87	74	20
3	**2**, OTf, OAc	89	77	6
4	(−)-NME	78	75	9[d]

Conditions = benzaldehyde–methyl acrylate–DABCO–**2** = 1:1:1:1. Temperature = 30 °C. Time = 4 days.

[a] Conversion and yield estimated by GC using an internal standard.

[b] ee determined by chiral HPLC[15] with a margin of error about 1%. Configuration (*R*)-**1** was determined by comparison of optical rotation with the literature value.[16]

[c] Yield and ee obtained by reaction with recycled chiral IL is given in brackets.

[d] (−)-*N*-Methylephedrine was used as a chiral source.

inflexible system and the origin for possible stereoselectivity.[18,19]

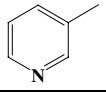
In order to show the efficacy of chiral ILs, especially their particular properties due to their high degree of organization, (−)-*N*-methylephedrine was used as a chiral catalyst for this study. A poor ee (only 9%) was detected in the similar reaction conditions (Table 2, entries 1 and 4). The use of recycled chiral ILs led to the same ee proving thus the possibility of reuse without loss of efficiency (Table 2, entry 1). As expected, when the (+)-ephedrinium salt **2** was used instead of the (−)-**2**, the direction of stereoselectivity was reversed to give (*S*)-**1** as a major product with comparable yield and ee. The main results were summarized in Table 2.

Next, attempts were carried out to extend the use of chiral ILs in the transfer of chirality. Thus, some others aldehydes were tested under similar conditions. All reactions were performed in the presence of 1 equiv of chiral ILs **2** (R = C_8H_{17}, X = OTf, Z = OH). A very low enantioselectivity was observed in the case of *p*-nitrobenzaldehyde and pyridine-3-carboxaldehyde (Table 3, entries 4 and 5) probably due to the formation of a hydrogen bond between the OH group of **2** with the NO_2 function or with the lone pair on N atom, respectively. A slight increase of ee (not optimized value) was detected when *p*-methoxybenzaldehyde, which is less reactive than benzaldehyde, was used (Table 3, entries 1 and 2). On the other hand, with the Cl group in *para*-position, lower ee was observed (Table 3, entries 1 and 3). The results obtained are given in Table 3.

In conclusion, we have taken advantage for the first time of the use of chiral ILs as reaction media in the enantioselective version of Baylis–Hillman reaction. Although the enantiomeric excesses are moderate at present, several important parameters have been studied and the results of this work have provided useful insights into the understanding of the use of chiral ILs in asymmetric induction. Based on these observations, the construction of novel chiral ILs, which should afford higher levels of enantioselectivities, is currently being investigated in our laboratory. The results of these studies will be communicated in due course.

Typical procedure: a mixture of benzaldehyde (1 mmol), methyl acrylate (1 mmol), DABCO (1 mmol) and chiral IL **2** (1 mmol) was stirred for a period of time and temperature (see Tables 1 and 2). The mixture was extracted with Et_2O (1 mL×3). After evaporation of solvent, the crude product was purified by flash chromatography or analyzed by GC. The ionic liquid was diluted in dichloromethane (20 mL) and then recycled by washing with water (10 mL×2). The organic phase was dried over anhydrous $MgSO_4$, filtered and evaporated in vacuo to afford the recycled ionic liquid. Spectra data (IR, ^1H and ^{13}C) were identical to the initial ionic liquid sample. This chiral IL was reused without loss of efficiency (Table 2, entry 1).

Table 3. Asymmetric Baylis–Hillman reaction in the presence of chiral ILs **2** (R = C_8H_{17}, Z = OH, X = OTf)

Entry	Ar	Conversion (%)[a]	Yield (%)[a]	**1** ee (%)[b]
1	Ph	85	78	23
2	*p*-MeOPh	50	36	30
3	*p*-ClPh	93	82	16
4	*p*-NO_2 Ph	95	87	1
5		95	83	6

Conditions = aldehyde–methyl acrylate–DABCO–**2** = 1:1:1:1. Temperature = 30 °C. Time = 4 days.

[a] Conversions and yields determined after flash chromatography.

[b] ee determined by chiral HPLC with a margin of error about 1%.

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