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Application of chiral ionic liquids in the copper catalyzed enantioselective 1,4-addition of diethylzinc to enones

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Abstract—Copper catalyzed enantioselective addition of diethylzinc to various enones has been achieved in the presence of a new class of chiral ionic liquid (ChirILs) derived from α-pinene. This first study on the application of ChirILs for the title reaction shows that the chiral reaction medium has a significant influence on chiral induction.

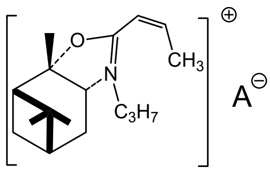
1. Introduction

The enantioselective conjugate additions to α,β-unsaturated carbonyl compounds are among the most useful transformations for stereoselective C–C bond formation in organic synthesis.[1] Numerous chiral auxiliaries and reagents have been developed toward this end.[2] The conjugate 1,4-addition of dialkylzinc to enones is one such reaction, which has gained lot of attention.[3–5] Catalytic systems with different metals have been studied for this reaction, however, application of copper in the presence of chiral ligands has gained most attention.[6] Also, chiral ligands such as chiral phosphites,[7] phosphoramides,[8] bisoxazoline,[9] diamines,[10] and bidentate P,N ligands,[11] Schiff-base ligands,[12] have been studied extensively. Though solvents are known to influence chiral properties,[13] the application of chiral solvents to achieve asymmetric induction has not been reported for 1,4-conjugate addition.

Recently, the study of ionic liquids has been increasing greatly.[14] These liquids have attracted the attention of synthetic chemists for some time owing to their remarkable properties. Being composed entirely of ions, they possess negligible vapor pressures, and the possibility of the wide range of cations and anions means that other solvent properties can be easily controlled. Currently, there is a great deal of interest in the use of these materials as solvents for a wide range of applications in organic, organometallic and bio-catalytic reactions.[15] Surprisingly, even with promising results seen for such reactions, attention toward chiral ionic liquids has been very limited. The only reported applications of ChirILs have been in the study of a Diels–Alder reaction,[16,17] Baylis–Hillman reaction[18] or as a reagent for chiral discrimination.[19,20] With earlier success in the preparation of enantiopure compounds in ionic liquids,[21,22] and our on going investigation of organic reactions in these new systems, herein, we report the first synthetic application of α-pinene based chiral ionic liquids in the copper-catalyzed enantioselective conjugate addition of diethylzinc to α,β-unsaturated enones.

2. Results and discussion

A large number of α-pinene-based effective reagents have been developed for various asymmetric organic transformations.[22] Terpene-based catalysts have also been used for asymmetric addition reactions.[23–25] This suggests the potential of solvents derived from a terpene in achieving similar results in the absence of any other chiral inducer. To this end, chiral ionic liquids **1** and **2** (Fig. 1) were



A = BF4, **1**
PF6, **2**

Figure 1. Chiral ionic liquids.

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prepared by alkylation of the corresponding oxazoline with an alkyl bromide, followed by anion exchange.[26] The oxazoline was prepared following a simple procedure, that is, by reaction of 3-aminohydroxypinane with an aliphatic acid,[27] while the aminohydroxypinane was prepared from α-pinene following the literature method.[28] Both ChirILs were obtained as pale brown liquids.

Having achieved the synthesis of these ChirILs containing the pinane moiety, as well as an oxazolium ring, we were interested in testing their potential for asymmetric induction. It has been reported earlier that the oxazolium ring of a chiral auxiliary plays an important role in coordination to copper catalysts.[29,30] Therefore, as a model reaction we studied the copper-catalyzed addition of diethylzinc to enones in the presence of ChirILs **1** and **2**.[31] Preliminary studies aimed at determining the influence of chiral ionic liquids revealed that the molar concentration of ChirILs had an effect on the enantioselectivity to a significant extent. Table 1 shows the results of the reaction between cyclohex-2-enone with diethylzinc in the presence of a chiral ionic liquid.[32] With only 3 mol % of ChirIL **1** employed (equal to copper trifluoromethanesulfonate), enantiomeric excess (ee) of the product was only 17%. When we increased the molar ratio of ChirIL, but kept the amount of $Cu(OTf)_2$ constant, the enantioselectivity improved gradually. However, only a small change in % ee was seen on increasing ChirIL **1** from 25 to 35 mol %. Therefore, the rest of the investigation was carried out with 35 mol % of ChirIL. With lower than a stoichiometric amount used here, ChirIL could be considered as an 'additive' or an 'adjuvant'.

Table 1. Effect of ChirIL mol % on enatiomeric excess

Entry	ChirIL **1** (%)	% ee[a]
1	3	17
2	5	23
3	10	38
4	15	51
5	25	74
6	35	76

[a] ee measurements were confirmed by HPLC analysis with a Chiralpak WH column.

Eqs. 1–3 in Figure 2 show the 1,4 addition of diethylzinc in the presence of **1** and **2** to cyclohexenone, cyclopentenone and chalcone, respectively. These substrates were chosen because a wide range of ligands have been tested for their effect with these enones, enabling a comparison of the efficiency of chiral ionic liquids. For our reaction, ChirIL was first mixed with $Cu(OTf)_2$ at room temperature. The addition of diethyl zinc (1 M in hexane) and enone was then performed at −20 °C. The reaction was stirred for 15 h and quenched with NH_4Cl at the same temperature. Conversion was measured by gas chromatography using *n*-undecane as an internal standard. The enantioselectivities were obtained through specific rotation measurement of the pure isolated product. The % ees were also confirmed by HPLC using Chiralpak WH column. Results are shown in Table 2.

In the cases of 2-cyclohexenone and 2-cyclopentenone, high conversions and fairly good enantioselectivities were obtained with ChirIL **1**. At this point, the active species inducing chirality is not understood. However, we believe that the induced chirality is due to the coordination of the Cu metal with the chiral ionic liquid, creating a chiral pocket which influences the selectivity of ethyl group transfer from diethylzinc to enone.

In the case of chalcone, the enantioselectivity of the product using ChirIL **1** is moderate. However, it is important to point out that this selectivity is still better than earlier reports of conjugate addition to chalcone in an ionic liquid using a chiral phase transfer catalyst.[34] Therefore, even with moderate % ee, our results are very important because for the first time we have shown that chiral ionic liquid

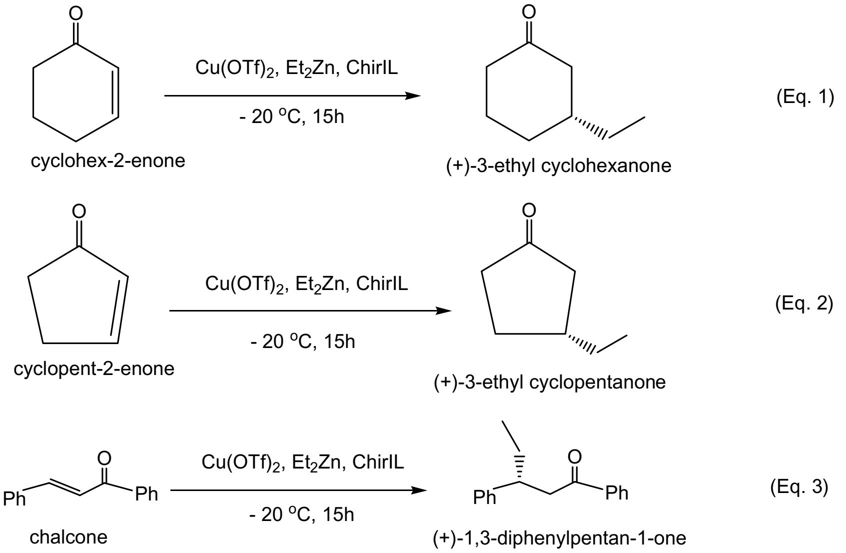

Figure 2. Copper-catalyzed 1,4-addition of diethylzinc to enones in chiral ionic liquids.

Table 2. Results of the 1,4-addition of diethylzinc to enones in the presence of chiral ionic liquids

Entry	Enone	ChirIL[a]	Temperature (°C)	Product	
				Yield[b] (%)	ee[c] (%)
1	Cyclohexenone	**1**	−20	90	76
2	Cyclohexenone	**1**	0 (23)	93 (94)	68 (52)
3	Cyclohexenone	**2**	−20	87	35
4	Cyclohexenone	**2**	0 (23)	90 (91)	26 (24)
5	Cyclopentenone	**1**	−20	40	73
6	Cyclopentenone	**1**	0 (23)	39 (46)	55 (50)
7	Cyclopentenone	**2**	−20	48	20
8	Cyclopentenone	**2**	0 (23)	48 (52)	15 (12)
9	Chalcone	**1**	−20	52	61
10	Chalcone	**1**	0 (23)	55 (57)	48 (37)
11	Chalcone	**2**	−20	55	37
12	Chalcone	**2**	0 (23)	57 (58)	28 (23)

[a] 35 mol % ChirIL mixed with 3 mol % $Cu(OTf)_2$.

[b] Isolated yield.

[c] Based on the specific rotation measured using ATUOPOL IV polarimeter. The ee measurements were also confirmed by HPLC using Chiralpak WH column.

can provide the same effect in inducing chirality in a conjugate addition, as seen through the combination of an ionic liquid and a chiral catalyst. Product enantioselectivities were lower for all three substrates using ChirIL **2**. Noticeable difference between results from **1** and **2** suggests that the chirality induced by the 'active species' is to some extent, also influenced by the achiral anion. Overall, this investigation has given us an important insight into the application of chiral ionic liquids as a source of chiral induction.

3. Conclusion

We have demonstrated that chiral ionic liquids could be 'designed' from a known chiral auxiliary such as α-pinene. It has been shown that these chiral ionic liquids can be used as an additive or a co-solvent to achieve asymmetric induction. Although, currently the enantioselectivity obtained is moderate to good, several important parameters have been studied. The useful insight into the understanding of the application of chiral ionic liquids has led to 'design' of other ChirILs derived from terpenes, which should afford higher enenioselectivities. The results of these studies will be reported in due course.

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27. (a) Synthesis of isopinocamphelyl oxazolium tetrafluroborate **1** ($[IpcOxa]^+[BF_4]^-$): Reacting isopinocamphelyl oxazolium bromide[31] with an aqueous solution of sodium tetrafluroborate gave product **1** as a viscous liquid. This was washed with water and acetone. The organic mass was dissolved in ether and dried on anhydrous $MgSO_4$. Evaporation of the solvent gave product **1**, yield: 83.7%; ^1H NMR δ: 0.86 (m, 3H, CH_3), 0.90 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 2.12 (1H, CH_2), 3.36 (1H, CH), 3.91 (1H, CH), 5.31 (1H, H), 5.43 (1H, H), 5.82 (1H, H). (b) Synthesis of isopinocamphelyl oxazolium hexafluoro-phosphate **2** ($[IpcOxa]^+[PF_6]^-$): Reaction of isopinocamphelyl oxazolium bromide,[31] with an aqueous solution of sodium hexafluorophosphate gave product **2** as a viscous liquid. This was washed first with water and then acetone. The organic mass was dissolved in ether, dried on anhydrous $MgSO_4$. Evaporation of the solvent gave product **2**, yield: 88%; ^1H NMR δ: 0.88 (m, 3H, CH_3), 0.90 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 2.14 (1H, CH_2), 3.38 (1H, CH), 3.91 (1H, CH), 5.36/5.37 (1H, H), 5.48/5.46 (1H, H), 5.84 (1H, H).
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32. *Representative reaction procedure (Table 1, entry 1)*: Copper trifluoromethanesulfonate (55.4 mg, 0.15 mmol, 3.0 mol %) was weighed in a glove box. This was then mixed with [IpcOxa][BF_4] (ChirIL **1**, 0.15 mmol, 3.0 mol %) under helium atmosphere and stirred for 1 h at room temperature. The mixture was cooled to −20 °C and 2-cyclohexenone (480.65 mg, 5 mmol) added, followed by the addition of Et_2Zn (6.5 mL, 1.3 equiv, 1 M in hexane), dropwise within 2 min. After stirring for 15 h at −20 °C, the reaction mixture was treated with saturated NH_4Cl and NH_3 (32%) solutions (10 mL each). *n*-Undecane (194 mg, 1.2 mmol) was mixed as an internal standard. The mixture was allowed to warm up to room temperature. After dilution with water and Et_2O (2 mL each) and stirring for 10 min, an aliquot of the organic phase was taken, filtered through a pad of cotton and analyzed by GC (95% yield). The aqueous phase was separated and extracted with Et_2O (3 × 3 mL). The combined organic phase was dried over $MgSO_4$. The solvent was removed at reduced pressure and the crude product purified by gradient flash column chromatography (silica gel, 2 × 15 cm, going from pentane to pentane/diethyl ether 4:1) to afford 0.57 g (90%) of 3-ethylcyclohexanone as a colorless liquid. $[\alpha] = +119.7$ (*c* 1%, chloroform); ee = 76% (compared with $[\alpha] = 156.0$ in chloroform).[33]
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