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Asymmetric reduction of aromatic ketones in pyridinium-based ionic liquids

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Abstract—The asymmetric reduction of aromatic ketones has been studied in pyridinium-based room temperature ionic liquids, namely, 1-ethyl-pyridinium tetrafluoroborate, $[EtPy]^+[BF_4]^-$ and 1-ethyl-pyridinium trifluoroacetate, $[EtPy]^+[CF_3COO]^-$. Ionic liquids were employed as solvents, while (*R*)-BINOL and (*R*)-BINOL-Br were used as chiral promoters. The effects of solvent, reaction time, temperature, catalyst loading and substituents were investigated. The reduction could be easily carried out in both ionic liquids with lower catalyst loading. 1-Ethyl-pyridinium tetrafluoroborate was recycled and reused efficiently.

1. Introduction

Enantioselective reduction of prochiral carbonyl compounds is an important method the for preparation of optically active alcohols.[1] Generally, aldehydes and ketones can be reduced to the corresponding alcohols by reductants, such as alkali metal aluminum hydrides, alkali metal borohydrides, and metal cyanoborohydride, while the asymmetric reduction of prochiral ketones to chiral alcohols with these metal hydrides can be achieved by the modification of the reagent with chiral ligands, such as alcohols or amines—R^*OH or RR^*NH.

Among commonly used reagents, lithium aluminum hydride (LAH) is a powerful reducing agent with high solubility in ether solvents. As a hydrogen donor, it is widely employed for reductions of aldehydes, ketones, esters, amides, and nitriles. In 1951, Bothner-By modified lithium aluminum hydride with (+)-camphor,[2] to achieve asymmetric reduction. Since then, a wide variety of chiral ligands derived from alkaloids,[3] sugars,[4] alcohols,[5] amines,[6] amino alcohols,[7] etc. have been employed with LAH ($LiAlH_4$) in order to induce asymmetric reduction in various organic solvents.

Recently, much attention has been focused on ionic liquids for their advantageous applications in organic reactions.[8] The increased interest in these solvents is mainly due to their highly polar, non-coordinating and good solvating properties.[9] Encouraged by earlier successful investigations with pyridinium based ionic liquids,[10] we embarked on the study of two ionic liquids, that is, $[EtPy]^+[CF_3COO]^-$ and $[EtPy]^+[BF_4]^-$ for the asymmetric reduction of aromatic ketones. Herein, we report the results of our study on the enantioselective reduction using $LiAlH_4$ and chiral ligands BINOL and Br-BINOL.

2. Results and discussion

The aromatic ketones treated with the complex of (*R*)-1,1′-bi-2-naphthol [(*R*)-BINOL] or its derivative (*R*)-6,6′-dibromo-1,1′-bi-2-naphthol [(*R*)-BINOL-Br] and lithium aluminum hydride were investigated in *N*-ethyl-pyridinium tetrafluoroborate $[EtPy]^+[BF_4]^-$ or *N*-ethyl-pyridinium trifluoroacetate $[EtPy]^+[CF_3COO]^-$, as shown in Figure 1.

It has been reported earlier[11] that in organic solvents the reduction with $LiAlH_4$ is more effective in the presence of ethanol. In order to study the influence of ethanol in ionic liquids and also the catalyst loading required, acetophenone was initially used as the representative ketone. The molar ratio of chiral ligand–$LiAlH_4$–ethanol, 1:1:1 was kept constant and the reaction studied at room temperature for 24 h. A parallel study was also performed under the same conditions, but in the absence of ethanol. Results are summarized in Table 1.

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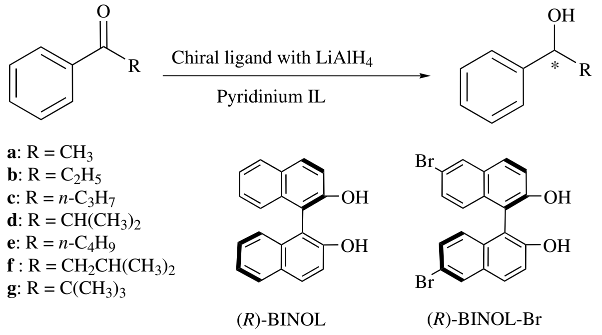

Figure 1. Asymmetric reduction of aromatic ketones.

Table 1. Asymmetric reduction of acetophenone with various amount of catalyst

Solvents	Dosage of catalyst[a] (equiv)	Yield/ee (%)	
		With ethanol	Without ethanol
THF[b]	2.0	95–100/64	—
$[EtPy]^+[CF_3COO]^-$	0.5	78/58	91/63
	1.0	96/66	99/68
	1.5	99/66	99/68
	2.0	99/68	99/68
	2.5	99/68	99/68
	3.0	99/69	99/68
$[EtPy]^+[BF_4]^-$	0.5	76/54	86/59
	1.0	97/63	99/66
	1.5	99/64	99/66
	2.0	99/65	99/66
	2.5	99/66	99/66
	3.0	99/66	99/66

[a] 1 equiv is counted on the basis of acetophenone (2 mmol).
[b] Reported by Noyori et al., 1979.

As the data show, 2 or more equivalents of the catalyst complex were needed when ethanol was used in the reaction, where as only 1 equiv of the catalyst complex was sufficient in the absence of ethanol. This indicates that ethanol does not have the same effect on the reagent efficiency in ionic liquids, as it does in organic solvents. This is because in organic solvents, ethanol forms an alkoxy complex with LiAlH$_4$–BINOL mixture, leaving one hydrogen for reduction.[11] On the other hand, anion of the ionic liquid could induce a similar effect on the reagent, thereby eliminating the need for ethanol. In both ionic liquids, optimal results were obtained in 4 h. Continuation of the reaction beyond this time did not improve the enantioselectivity (Table 2). The results were marginally better in $[EtPy]^+[CF_3COO]^-$.

Table 2. Reaction time effect of asymmetric reduction of acetophenone

Reaction time (h)	Yield/ee (%)	
	$[EtPy]^+[CF_3COO]^-$	$[EtPy]^+[BF_4]^-$
1	73/71	76/68
2	96/70	97/67
4	99/69	99/67
8	99/68	99/66
12	99/68	99/66
24	99/68	99/66

The reaction procedure developed with acetophenone was employed further for the reduction of other aromatic ketones. Since better results were seen in the reduction of acetophenone under different conditions in $[EtPy]^+[CF_3COO]^-$, compared to that in $[EtPy]^+[BF_4]^-$, rest of the studies was carried out in $[EtPy]^+[CF_3COO]^-$ only. These reactions were also studied at lower temperature with the hope of improving enantioselectivity. It should be noted that in the case of $[EtPy]^+[BF_4]^-$ as solvent, decreasing the temperature to 0 °C solidified the reaction mixture and it could not be used as solvent. Similarly, in the case of $[EtPy]^+[CF_3COO]^-$, decreasing the reaction temperature below −30 °C, solidified the reaction mixture. Therefore, reduction at 0 °C and −30 °C were studied in $[EtPy]^+[CF_3COO]^-$ only. The results are summarized in Table 3.

Table 3. Asymmetric reduction of ketones catalyzed by BINOL–LAH in $[EtPy]^+[CF_3COO]^-$

Entry	Ketone	Yield/ee (%)		
		rt (4 h)	0 °C (24 h)	−30 °C (24 h)
1	$C_6H_5COCH_3$	99/69	91/75	85/84
2	$C_6H_5COCH_2CH_3$	99/69	93/80	86/85
3	$C_6H_5CO(CH_2)_2CH_3$	98/70	91/79	83/84
4	$C_6H_5COCH(CH_3)_2$	97/69	85/78	79/82
5	$C_6H_5CO(CH_2)_3CH_3$	96/69	87/79	80/84
6	$C_6H_5COCH_2CH(CH_3)_2$	97/68	82/74	76/78
7	$C_6H_5COC(CH_3)_3$	95/59	79/64	71/70

As expected, a decrease in the reaction temperature to −30 °C, resulted in a significant increase in the product enantioselectivities for all ketones (Table 3). However, the overall yields decreased even with prolonged reaction period. Also due to steric hindrance, lower selectivity and yields are obtained in the reduction of phenyl-*t*-butyl ketone, as compared with other ketones.

We noticed that in the case of acetophenone, a homogeneous reaction mixture was formed, while solubility decreased with increase in the size of the alkyl substituent on ketone, and two phases were obtained in the case of phenyl-*t*-butyl ketone. This was overcome by stirring the reaction mixture at 250 rpm. As the data in Table 3 show, higher yields and enantioselectivity were seen in the case of ketones **a**–**f** (entries 1–6). Both yield and selectivity decreased with bulky *t*-Bu substituent (entry 7).

Further investigations were carried out with (*R*)-6,6′-dibromo-1,1′-bi-2-naphthol [(*R*)-BINOL-Br], to see if an electron withdrawing substituent on the chiral ligand, for example, bromine has any influence on product selectivity. Therefore, reductions were carried out under identical conditions as before, except using Br-BINOL in place of BINOL as chiral ligand. Results are summarized in Table 4. We saw an improved enantioselectivity in the reduction of all ketones, clearly indicating better influence of an electron withdrawing group at the 6,6′-position of BINOL, and an enhanced effect on selectivity.

Table 4. Asymmetric reduction of ketones catalyzed by BINOL-Br–LAH in $[EtPy]^+[CF_3COO]^-$

Entry	Ketones	Yield/ee (%)		
		rt (4 h)	0 °C (24 h)	−30 °C (24 h)
1	$C_6H_5COCH_3$	99/70	91/79	86/88
2	$C_6H_5COCH_2CH_3$	99/73	91/83	90/82
3	$C_6H_5CO(CH_2)_2CH_3$	99/74	83/90	82/90
4	$C_6H_5COCH(CH_3)_2$	97/70	85/80	80/87
5	$C_6H_5CO(CH_2)_3CH_3$	96/73	86/82	78/89
6	$C_6H_5COCH_2CH(CH_3)_2$	96/71	80/79	75/81
7	$C_6H_5COC(CH_3)_3$	93/62	75/68	68/74

The reusability of ionic liquids was also tested in the asymmetric reduction of acetophenone catalyzed by using (*R*)-BINOL–LAH complex. Therefore, after completion of the reaction, the organics were extracted into diethyl ether, and the ionic liquid was decanted and residual products distilled off. The ionic liquid was passed through a chromatographic column, washed with distilled water and dried under vacuum at 65 °C overnight before reuse. Table 5 shows the results with recycled and reused ionic liquids in the reduction of acetophenone.

Table 5. Recycling and reuse of ionic liquids

Recycling #	$[EtPy]^+[BF_4]^-$		$[EtPy]^+[CF_3COO]^-$	
	Recovered (wt %)	Yield/ee (%)	Recovered (wt %)	Yield/ee (%)
0	—	99/67	—	99/68
1	93	97/64	87	98/51
2	92	98/65	76	99/43
3	90	98/63	68	99/37

Ionic liquid $[EtPy]^+[BF_4]^-$ could be recovered efficiently and reused up to three times with negligible loss of activity and selectivity. However, $[EtPy]^+[CF_3COO]^-$ could not be easily recovered on subsequent reuse. This could be because a stronger complex was formed with $LiAlH_4$ and CF_3COO^-, which is also evident from the dark color of the ionic liquid after each subsequent recycling. Therefore, selectivity of the reduced products also dropped significantly.

3. Experimental

All analyses were carried out by HP 1050 HPLC equipped with a chiralcel OD-H column (hexanes/2-propanol = 75:25). Product formation was also conformed by ^1H NMR (500 MHz, in $CDCl_3$). Aromatic ketones were purchased from Sigma Aldrich Co. and used as received. Ionic liquids were prepared following the procedure reported earlier.[12]

3.1. General procedure for reduction

Reactions were carried out under a moisture free N_2 atmosphere. Ionic liquids were dried overnight in an oven at 70 °C before each use. Chiral ligand (*R*)-1,1′-bi-2-naphthol or (*R*)-6,6′-dibromo-1,1′-bi-2-naphthol (2 mmol, 1 equiv) was added to 2 ml of ionic liquid. The mixture was heated to 45 °C and stirred until the solid dissolved. Lithium aluminum hydride (2 mmol, 1 equiv) was slowly added to the mixture, which produced a very small amount of suspension. Furthermore, in this step, we noticed that some bubbles were generated. The mixture was stirred (250 rpm) for 30 min at the specified reaction temperature, and the aromatic ketone (2 mmol, 1 equiv) was added dropwise. The reaction mixture was stirred (250 rpm) at this temperature for the desired time period. Finally, 2 M HCl (5 ml), was added to quench the reaction mixture, which was then brought to room temperature. The organic compound was extracted by diethyl ether (5 ml), washed first with saturated sodium bicarbonate (5 ml) followed by brine (5 ml). Evaporation under reduced pressure yielded the concentrated organic mixture, which was further purified by flash chromatography (acetone/hexanes 1:7) to give purified products.

4. Conclusion

This is the first study demonstrating that the pyridinium based ionic liquids $[EtPy]^+[CF_3COO]^-$ and $[EtPy]^+[BF_4]^-$ can be used efficiently in the asymmetric reduction of aromatic ketones. High yield and ee have been achieved with low dosages of catalysis complex. Higher selectivity was obtained with Br-BINOL in $[EtPy]^+[CF_3COO]^-$ when compared to BINOL and/or $[EtPy]^+[BF_4]^-$. We have also shown that $[EtPy]^+[BF_4]^-$ could be recycled and reused efficiently.

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