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Highly Enantioselective α-Aminoxylation of Aldehydes and Ketones in Ionic Liquids

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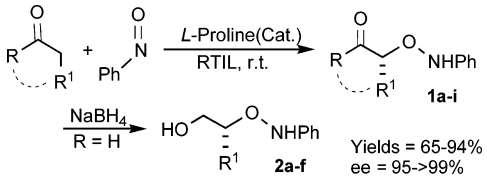

As the first example for the synthesis of optically active α-hydroxyaldehydes and α-hydroxyketones in ionic liquids, we applied RTILs into L-proline catalyzed direct enantioselective α-aminoxylation of both aldehydes and ketones successfully. This protocol features a number of advantages, such as recycling of green solvents and chiral organocatalyst, high yields, excellent enantioselectivities, short reaction times, and broad substrate scope.

Optically active α-hydroxyaldehydes and α-hydroxyketones are important building blocks in organic synthesis. These structure units are commonly found in biologically active natural products.[1] Recently, extensive researches have been carried out to find diastereoselective and enantioselective routes for their synthesis.[2] Several methods using catalytic asymmetric reactions are particularly useful, which include the Sharpless asymmetric dihydroxylation of enol ethers,[3] the asymmetric epoxidation of silyl enol ethers with a chiral dioxirane,[4] and the asymmetric epoxidation of enol ethers with a chiral Mn−Salen catalyst.[5] Most of these synthetic methods require multiple procedures. On the other hand, proline has drawn much attention because of its excellent behavior as chiral organocatalyst in many asymmetric reactions.[6] Very recently, there have been great interests on proline catalyzed direct asymmetric α-aminoxylation of aldehydes or ketones for the synthesis of optically active α-hydroxyaldehydes and α-hydroxyketones. In 2003, Zhong,[7] MacMillan,[8] and Hayashi et al.[9a] independently found that L-proline was able to catalyze the direct asymmetric α-aminoxylation of aldehydes with excellent enantioselectivities. Then Hayashi[9b] and Cordova et al.[1] simultaneously reported that ketones underwent proline catalyzed α-aminoxylation to give 2-aminoxy ketones with excellent enantioselectivities, which further reacted with copper sulfate to generate enantiopure α-hydroxyketones.

In recent years, ionic liquids played increasingly important roles in organic synthesis, because they displayed many advantages over common organic solvents, such as nonvolatilities, easy recycling, immiscibilities with many organic solvents, and good solvating properties for both inorganic and organic compounds.[10,11] A lot of organic,[10] organometallic,[10,11] and biocatalyzed reactions[11b,12] have been investigated in ionic liquids. The application of ionic liquids in asymmetric synthesis is receiving more and more attention. Several uses of ionic liquids in catalytic asymmetric reactions with good yields, high enantioselectivities, or other advantages are particularly attractive. In 2002, Toma et al. reported that proline-catalyzed asymmetric aldol reaction can be performed smoothly in 1-butyl-3-methyl imidazolium hexafluorophosphate [bmim][PF_6] in 46−94% yields with 47−82% ee.[13] In 2004, Li et al. disclosed the asymmetric aminohalogenation of functionalized alkenes in imidazolium tetrafluoroborate [bmim][BF_4] with good yields and diastereoselectivities.[14] In 2005, Jiang et al. found that in the presence of *L*-prolinamide, the asymmetric aldol reaction of aldehydes with unmodified ketones can be conducted in imidazolium ionic liquids with excellent enantioselectivities.[15] However, to the best our knowledge, there is no report on the application of ionic liquids in the asymmetric synthesis of optically active α-hydroxyaldehydes and α-hydroxyketones, including the L-proline catalyzed direct asymmetric aminoxylations of aldehydes and ketones. Considering that the L-proline catalyzed aminoxylations are performed in harmful solvents (such as CH_3CN, $CHCl_3$, DMSO, C_6H_6, etc.) and that L-proline, a metal-free catalyst, contains strong polar bonds, we planned to investigate whether room temperature ionic liquids (RTILs) could be used as user- and eco-friendly solvents, and simultaneously, as immobilizing media for the recycling of chiral catalyst in the aminoxylation reaction to produce optically active

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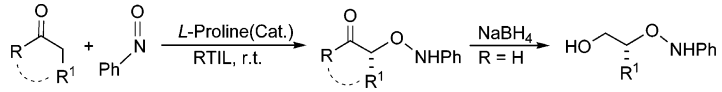
TABLE 1. L-Proline-Catalyzed Direct Asymmetric α-Aminoxylation of Propanal or Cyclohexanone in Various RTILs



a : R = H, R^1= Me;
g : R-R^1= $(CH_2)_4$

1a or **1g** **2a**

entry	R	R^1	RTIL[a]	catalyst (mol %)	time (min)	yield of **1g** (%)[b]	yield of **2a** (%)[b]	ee of **1g** (%)[c]	ee of **2a** (%)[c]
1	H	Me	[bmim][BF_4]	20	8		94		99
2	H	Me	[bmim][PF_6]	20	8		91		98
3	H	Me	[pmim][BF_4]	20	8		92		98
4	H	Me	[pmim][PF_6]	20	8		85		97
5	H	Me	[btpy][BF_4]	20	8		79		98
6	H	Me	[bmim][BF_4]	10	10		92		98
7	H	Me	[bmim][BF_4]	5	15		88		98
8	H	Me	[bmim][BF_4]	1	120		79		98
9	H	Me	[bmim][BF_4]	0.5	300		64		98
10	$(CH_2)_4$		[bmim][BF_4]	20	15	89		>99	
11	$(CH_2)_4$		[bmim][BF_4]	10	40	81		>99	
12	$(CH_2)_4$		[bmim][PF_6]	20	15	88		>99	
13	$(CH_2)_4$		[bmim][PF_6]	10	45	80		>99	
14	$(CH_2)_4$		[pmim][BF_4]	20	15	88		>99	
15	$(CH_2)_4$		[btpy][BF_4]	20	15	82		>99	

[a] pmim = propylmethylimidazolium, btpy = butylpyridinium. [b] Isolated yield. [c] Determined by chiral HPLC with a Chiralpak AD-H column.

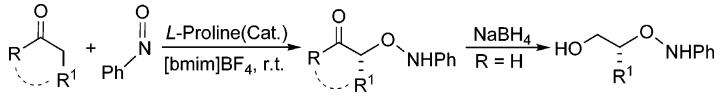
hydroxyaldehydes and hydroxyketones with high yields and excellent enantioselectivities.

Initially, 1-butyl-3-methyl imidazolium tetrafluoroborate [bmim]-[BF_4], which is one of the most common RTILs, was chosen as a solvent in the L-proline catalyzed direct asymmetric α-aminoxylation of aldehyde. We were pleased to find that using L-proline as a chiral organocatalyst, propanal could undergo α-aminoxylation with nitrosobenzene quickly (8 min) and completely in ionic liquid [bmim][BF_4] at room temperature (Table 1). Because the O-regioselective addition product **1a** is labile on silica gel for column chromatography, it had to be converted into the more stable 2-aminoxy alcohol **2a** by the successive treatment with sodium borohydride. Our experiment showed that after the one pot reaction, (2*R*)-2-aminoxy alcohol **2a** was isolated in excellent yield (94%) with excellent enantioselectivity (99% ee) (entry 1, Table 1). Further investigation demonstrated that the L-proline catalyzed direct asymmetric α-aminoxylation of propanal proceeded smoothly in various RTILs at room temperature, affording desired (2*R*)-2-aminoxy alcohol **2a** in good to excellent yields (79%−94%) with excellent enantioselectvities (97−99% ee). As shown in Table 1, the best RTILs for this reaction are ionic liquid [bmim][BF_4] and [bmim][PF_6]. The effects of the catalyst amount on yield and enantioselectivity were also studied. Experimental results showed that the catalyst loading had no significant effect on enantioselectivity even when the reaction was performed in 0.5 mol % proline (Table 1). However, a too small amount of catalyst would lead to a decrease of yields (entries 8 and 9, Table 1). On the basis of the above results, the best catalyst loading for yield and enantioselectivity of the aminoxylation reaction of propanal was 20 mol %. Moreover, we studied L-proline catalyzed direct α-aminoxylation of ketones in ionic liquids. In this experiment, cyclohexanone was selected as a model ketone. It was found that in the presence of 20 mol % of L-proline, cyclohexanone could also undergo the asymmetric aminoxylation reaction smoothly with nitrosobenzene in various ionic liquids at room temperature, giving the desired (2*R*)-2-aminoxy ketone **1g** in good yields with excellent enantioselectivities (>99% ee) (entries 10−15, Table 1).

Then, various aldehydes and ketones were examined in the asymmetric α-aminoxylation reaction with nitrosobenzene in ionic liquid [bmim][BF_4]. The experimental results showed that all of the aldehydes or ketones could undergo the L-proline direct aminoxylation smoothly and quickly (10−30 min) in ionic liquid [bmim][BF_4] at room temperature, affording the desired (2*R*)-2-aminoxy alcohols **2a**−**f** or (2*R*)-2-aminoxy ketones **1g**−**i** in moderate to excellent yields with excellent enantioselectivities (Table 2). This suggests that the α-aminoxylation reaction in ionic liquid [bmim][BF_4] has broad substrate scope. As shown in Table 1 and Table 2, the reaction of cyclohexanone in ionic liquids is faster than that in common organic solvents, where 5−12 h are reported to be required.[9b] Moreover, the yields of (2*R*)-2-aminoxy alcohols **2a**−**f** or (2*R*)-2-aminoxy ketones **1g**−**i** were significantly improved in ionic liquid [bmim][BF_4], as compared to that in common organic solvents.[1,7−9]

With the success of the α-aminoxylation reaction in ionic liquid, we continued our investigation in exploring the recyclability of ionic liquid and chiral catalyst owing to its importance from an industrial perspective. The L-proline catalyzed α-aminoxylation of propanal with nitrosobenzene in ionic liquid [bmim][BF_4] was chosen as a model. After the aminoxylation reaction was completed at room temperature, the reaction mixture was extracted with ethyl ether several times to collect α-aminoxylation product and to keep the [bmim][BF_4] containing L-proline. ^{1}HNMR indicated that there was no α-aminoxylation product in the ionic liquid layer after the extraction with ethyl ether. The ether layer was treated with sodium borohydride to form (2*R*)-2-aminoxy alcohol **2a**, and the ^{1}H NMR of crude product **2a** indicated the absence of L-proline. The recovered ionic liquid immobilizing L-proline was used in the α-aminoxylation again, and we found that the desired (2*R*)-2-aminoxy alcohol **2a** was still obtained in excellent yield (92%) with excellent enantioselectivity (98% ee) (entry 2, Table 3). Then, the recycling of ionic liquid and chiral catalyst in the

TABLE 2. L-Proline Catalyzed Direct α-Aminoxylation of Various Aldehydes and Ketones in [Bmim][BF_4][a]



1a-i **2a-f**

entry	R	R^1	time (min)	product	yield of **1** (%)[b]	yield of **2** (%)[b]	ee of **1** (%)[c]	ee of **2** (%)[c]
1	H	Me	10	**2a**		94		99
2	H	Et	10	**2b**		89		98
3	H	*n*-Pr	10	**2c**		84		97
4	H	*i*-Pr	10	**2d**		93		>99
5	H	*n*-Bu	10	**2e**		79		95
6	H	Bn	10	**2f**		85		>99
7	$(CH_2)_4$		15	**1g**	89		>99	
8	$CH_2CH_2OCH_2$		15	**1h**	85		99	
9	$CH_2CH_2NBnCH_2$		30	**1i**	68		>99	

[a] Using 20 mol % L-proline. [b] Isolated yield. [c] Determined by chiral HPLC with a Chiralpak AD-H column.

TABLE 3. Recycling Use of [Bmim][BF_4] and L-Proline in the Direct Asymmetric α-Aminoxylation of Propanal or Cyclohexanone[a]

entry	R	R^1	recycling time	time (min)	yield of **1g**[b] (%)	yield of **2a**[b] (%)	ee of **1g**[c] (%)	ee of **2a**[c] (%)
1	H	Me	1	10		94		99
2	H	Me	2	10		92		98
3	H	Me	3	10		88		98
4	H	Me	4	10		86		97
5	H	Me	5	12		85		97
6	H	Me	6	12		83		96
7	$(CH_2)_4$		1	15	89		>99	
8	$(CH_2)_4$		2	15	89		>99	
9	$(CH_2)_4$		3	15	87		>99	
10	$(CH_2)_4$		4	15	86		>99	
11	$(CH_2)_4$		5	15	82		99	
12	$(CH_2)_4$		6	15	81		99	

[a] Using 20 mol % L-Proline. [b] Isolated yield. [c] Determined by chiral HPLC with a Chiralpak AD-H column.

direct α-aminoxylation of cyclohexanone was also studied. After the aminoxylation reaction was finished, the reaction mixture was extracted with ethyl ether and the ionic liquid [bmim][BF_4] containing L-proline could also be recovered quantitatively. We employed the recovered ionic liquid immobilizing L-proline in the α-aminoxylation reaction and discovered that the desired (2*R*)-2-aminoxy ketone **1g** was also obtained in equally good yield (89%) with excellent enantioselectivity (>99% ee) (entry 8, Table 3). These recycling processes of α-aminoxylation of both propanal and cyclohexanone could be repeated for six times without significant decrease in enantioselectivities, and the reaction yields were slightly decreased with the increase of recycling times (Table 3).

In conclusion, we found that both aldehydes and ketones could undergo direct asymmetric α-aminoxylation reaction smoothly in RTILs, giving the desired (2*R*)-2-aminoxy alcohols **2a**−**f** or ketones **1g**−**i** in moderate to excellent yields. Compared with that in common solvents, the yields of the direct α-aminoxylation of both aldehydes and ketones are improved significantly in RTILs. At the same time, the direct α-aminoxylation of aldehydes and ketones keeps excellent enantioselectivities (95 → 99%) in various RTILs. It was also found that the direct aminoxylation of ketones was accelerated greatly in RTILs. Moreover, the ionic liquid containing L-proline could be recovered easily and quantitatively after the direct α-aminoxylation of aldehydes and ketones. The recovered ionic liquid immobilizing L-proline could be reused for six cycles, keeping the good yields and excellent enantioselectivities. The multitudinous advantages of α-aminoxylation in RTILs, such as easy recycling of solvents and chiral organocatalyst, high yields, excellent enantioselectivities, short reaction times, and broad substrate scope, make this synthetic method practical for organic synthesis and suitable for potential industrial applications in the future. On the basis of the present investigation, we are now carrying out the research on the applications of ionic liquids into other polar organocatalyst-mediated asymmetric reactions with high enantioselectivities.

Experimental Section

General Procedure of L-Proline Catalyzed Direct Asymmetric α-Aminoxylation of Aldehydes in Ionic Liquids. The mixture of aldehyde (1.8 mmol), nitrosobenzene (96.5 mg, 0.9 mmol), and L-proline (catalytic amount) in ionic liquid (1 mL) was stirred at room temperature for the time indicated in Tables 1−3. After the aminoxylation reaction was completed, the reaction mixture was extracted with ethyl ether (10 mL × 4). To the combined ether layer was added the solution of sodium borohydride (171 mg, 4.5 mmol) in ethanol (10 mL). The reaction mixture was stirred for 10 min at room temperature. Then, the reaction was quenched with water (10 mL), and the resulting mixture was extracted with ethyl acetate (5 mL × 3). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo after filtration. Purification by column chromatography (silica gel, ethyl acetate−petroleum ether as eluant) gave (2*R*)-2-aminoxy alcohol **2a**−**f** in good to excellent yield.

General Procedure of Asymmetric α-Aminoxylation of Ketones in Ionic Liquids. The mixture of ketone (2.7 mmol), nitrosobenzene (96.5 mg, 0.9 mmol), and L-proline (catalytic amount) in ionic liquid (1 mL) was stirred at room temperature for the time indicated in (Tables 1−3). After the aminoxylation reaction was completed, the reaction mixture was extracted with ethyl ether (10 mL × 4). Then, the combined organic extracts were concentrated in vacuo to give crude product, which was purified by column chromatography (silica gel, ethyl acetate-petrolium ether as eluant) to afford (2*R*)-2-aminoxy ketone **1g**−**i** in moderate to good yield.

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Supporting Information Available: Experimental data, ^{1}H NMR, MS, and chiral HPLC spectra of **2a**−**f** and **1g**−**i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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