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Biomimetic Catalysis in Ionic Liquids: Markedly Enhanced Enantioselectivity in Amino Acid-Catalyzed Directed Asymmetric Aldol Reactions

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Abstract

Amino acid-catalyzed directed asymmetric aldol reactions showed enhanced enantioselectivity when conducted in ionic liquids. Optically active products were afforded in better yields (up to 23% higher) and enantiomeric excess (up to 21% higher) in ionic liquids than in conventional organic solvents.

Keywords: Ionid Liquid, Aldol Reaction, Amino Acid, Catalysis

1. Introduction

Room-temperature ionic liquids are attracting growing interest as alternative reaction media for chemical transformations[1-2]. One major advantage of ionic liquids is that they have no detectable vapor pressure, making them environmentally benign. Hence, they are emerging as novel replacements for volatile organic solvents in industrial organic synthesis. Room-temperature ionic liquids are particularly promising as solvents for catalysis, allowing enhanced catalyst activity, selectivity, stability, and reusability. Research in this area has so far focused on transition metal-catalyzed transformations. Recently, research groups, including ours, have reported on the potential of ionic liquids as alternative reaction media for biocatalysis and biotransformation[3-4]. Ionic liquids demonstrated enhanced enzyme selectivity, thus proving to be useful media for enzymatic reactions of polar substrates such as carbohydrates and amino acids, which show poor solubility in conventional organic solvents.

Recently, List and Barbas have reported amino acid-catalyzed directed asymmetric aldol reactions of simple ketones with a variety of aldehydes[5,6]. Amino acids such as (*L*)-proline and 5,5-dimethyl thiazolinium-4-carboxylate (DMTC) probably function as micro-aldolases because their mechanisms are found in type-1 aldolases[7] and catalytic antibodies that type-I aldolases mimic (38C2 and 33F12)[8]. Although small-molecule catalysis has advantages, the yields and enantioselectivities are often low in comparison with organometallic catalysis for the same reactions. As part of our research on "biocatalysis in ionic liquids," we became interested in a biomimetic system. We herein report preliminary results showing that the use of ionic liquids significantly enhances enantioselectivity in a biomimetic system.

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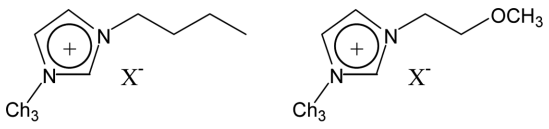
2. Experimental Section

2.1. General Procedure of Catalytic Aldol Reaction

(*L*)-proline (0.66 mmol) was stirred in 10 ml of ionic liquid/acetone (4:1) for 30 min. The aldehyde substrates (6.6 mmol) were added and the mixture was stirred for 12 h. The mixture was extracted with ethyl ether and the organic layer was concentrated to give after column chromatography (hexanes/ethyl acetate) pure aldol product. The optical purity was determined by HPLC using a chiral column (chiralcel OB).

3. Results and Discussion

An amino acid-catalyzed directed aldol reaction was chosen as the representative biomimetic system as it had been the prominent aldolase mimic reaction. Four ionic liquids, [BMIM]-[X] **1a-b** ($[BMIM]^+$=1-butyl-3-methylimidazolium; **1a**: X=PF_6; **1b**: X=BF_4), and [MOEMIM]-[X] **2a-b** ($[MOEMIM]^+$=1-methoxyethyl-3-methylimi-



1 X: **a** = PF_6, **b** = BF_4 **2** X: **a** = PF_6, **b** = BF_4

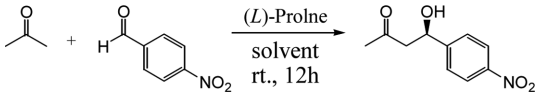
Fig. 1. Structure of room-temperature ionic liquids used in this study.

dazolium; **2a**: X=PF_6; **2b**: X=BF_4), acted as powerful media in (*L*)-proline-catalyzed directed aldol reactions, facilitating catalyst recovery and improving yields and enantiomeric excess.

3.1. Optimization of Reaction Conditions

In a preliminary study, (*L*)-proline (10 mol%) in ionic liquid/acetone (4:1) was reacted with 4-nitrobenzaldehyde at room temperature for 12 h. The solution mixture was then extracted with ethyl ether, and the organic phase concentrated. The organic residues were subjected to silica gel chromatography to obtain aldol products (*R*)-**3**. Optical purity was determined by HPLC using a chiral column (Table 1). The (*L*)-proline-catalyzed directed aldol reaction of acetone and 4-nitrobenzaldehyde proceeded with greater yield and enantiomeric excess in ionic liquids than in DMSO (Table 1, entries 1–5).

Table 1. (*L*)-Proline-Catalyzed Directed Asymmetric Aldol Reaction of Acetone with 4-Nitrobenzaldehyde.[a,b]



entry	solvent	yield (%)	ee (%)
1	DMSO	68	76
2	1a	78	85
3	1b	80	82
4	2a	76	84
5	2b	74	85

[a]Experimental procedure: (*L*)-proline (2.3 mg, 0.02 mmol) was stirred in 1 ml of 1a/acetone (4:1) for 15 min. 4-Nitrobenzaldehyde (30 mg, 0.2 mmol) was added and the mixture was stirred for 12 h. The mixture was extracted with ethyl ether and the organic layer was concentrated to give after column chromatography (hexanes/ethyl acetate (3:1)) pure aldol product. [b]The optical purity was determined by HPLC using a chiral column. Analytical condition: chiralcel OB, hexane/2-propanol=80/20, flow rate=1.0 mL/min, UV 217 nm

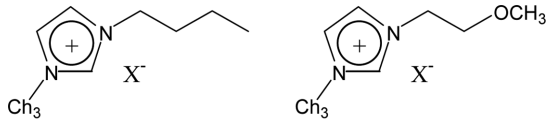
We observed that the properties of the ionic liquids (**1a** and **2a** are hydrophobic, while **1b** and **2b** are hydrophilic) did not affect the preliminary results, and aldol condensation products were observed in all reactions. However, when (*L*)-proline and ionic liquids were reused, the reaction proceeded to completion in the hydrophobic liquids (**1a**/**2a**) but not in the hydrophilic ionic liquids (**1b** and **2b**). The failure with the use of hydrophilic ionic liquids (**1b**/**2b**) could be due to catalyst deactivation by water produced in the first reaction.

3.2. Catalytic Asymmetric Aldol Reaction on Various Substrates

Consequently, (*L*)-proline- and DMTC-catalyzed directed aldol reactions of subsequent aldehydes were performed in the representative hydrophobic ionic liquid, **1a** (Figure 2).

In most cases, the reactions proceeded with higher yield and enantiomeric excess in the ionic liquid than in DMSO (Table 2). (*L*)-Proline catalysis in the ionic liquid increased the yields by 2–10% and ee by 5–15% relative to those in DMSO (Table 2, entries 1, 2, 6, 7, 11, 12, 16, and 17).

DMTC catalysis in the ionic liquid increased the yields by 10–26% and ee by 6–21% compared with those in DMSO (Table 2, entries 4, 5, 9, 10, 14, 15, 19, and 20). The ionic liquid containing (*L*)-proline was reused (Table 2, entries 3, 8, 13, and 18), but that containing DMTC was not due to loss of the iminium intermediate during ether extraction. When reused, the yields were around 10% higher than those in the initial reaction (Table 2, entries 2, 3, 7, 8, 12, 13, 17, 18, 22, and 23). These results indicated that intermediates from the first reaction were added to the product of the second reaction. It was observed that in most cases, the rate of the directed aldol addition reaction in ionic liquid



1 X: **a** = PF_6, **b** = BF_4 **2** X: **a** = PF_6, **b** = BF_4

Fig. 2. Amino Acid Catalyzed Directed Asymmetric Aldol Reaction of Acetone with Various Aldehydes.

Table 2. Directed Asymmetric Aldol Reaction Catalyzed by (*L*)-Proline and DMTC in DMSO and **1a**.[a]

entry	aldehyde	catalyst	solvent	yield (%)[b]	ee (%)[c]
1	3a	(*L*)-proline	DMSO	62	60
2			**1a**	64	67
3[d]			**1a**	77	74
4		DMTC	DMSO	60	89
5			**1a**	70	83
6	3b	(*L*)-proline	DMSO	94	69
7			**1a**	87	74
8[d]			**1a**	95	73
9		DMTC	DMSO	71	74
10			**1a**	85	83
11	3c	(*L*)-proline	DMSO	74	65
12			**1a**	74	80
13[d]			**1a**	79	79
14		DMTC	DMSO	65	67
15			**1a**	55	88
16	3d	(*L*)-proline	DMSO	68	76
17			**1a**	78	85
18[d]			**1a**	93	84
19		DMTC	DMSO	60	86
20			**1a**	86	92

[a]Typical experimental procedure: Catalyst (0.02 mmol) was stirred in 1ml of solvent/acetone (4:1) for 15 min. Aldehyde (0.2 mmol) was added and the mixture was stirred for 0.5-6d. The mixture was extracted with ethyl ether and the organic layer was concentrated to give after column chromatography (hexanes/ethyl acetate) pure aldol product. [b]Isolated yields after column chromatography. [c]The optical purity was determined by HPLC using a chiral column. Analytical condition: chiralcel OB, hexane/2-propanol=80/20 (4d), 95/5 (4b), 98/2 (4a, 4c), flow rate = 1.0 mL/min (4a-d), UV 217nm (4a-d). [d]The second run with reusing of catalyst and 1a.

was similar or slightly lower than that in DMSO. A major advantage of ionic liquids as solvents is that they can be readily reused together with catalysts. For the (*L*)-proline-catalyzed reaction of acetone and 4-nitrobenzaldehyde in ionic liquid **2a**, scale up was achieved without major difficulty, and the ionic liquid and catalyst could be reused twice without loss of yield or enantioselectivity.

These results demonstrate that amino acid-catalyzed directed aldol reactions are effective in ionic liquids, with impressive enantioselectivities. We have reported that the use of ionic liquids in biocatalysis can result in enhanced enzyme enantioselectivity. We now observe that the same is true for biomimetic synthesis. However, we cannot give a satisfactory explanation for these observations at present.

4. Conclusions

This work has demonstrated that ionic liquids are potentially better media for amino acid-catalyzed directed asymmetric aldol reactions than are conventional organic solvents. Accordingly, they may also be good alternative media for other biomimetic systems, as well as biocatalysis and biotransformations. Further studies to broaden the scope of amino acid catalysis in ionic liquids to directed aldol addition reactions, Mannich reactions, and Michael-type addition reactions are in progress in our laboratory.

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