ISSN 1070-4280, Russian Journal of Organic Chemistry, 2008, Vol. 44, No. 12, pp. 1807–1810. © Pleiades Publishing, Ltd., 2008.
Published in Russian in Zhurnal Organicheskoi Khimii, 2008, Vol. 44, No. 12, pp. 1834–1837.

Ionic Liquid-Supported Proline as Catalyst in Direct Asymmetric Aldol Reaction*

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Received April 9, 2007

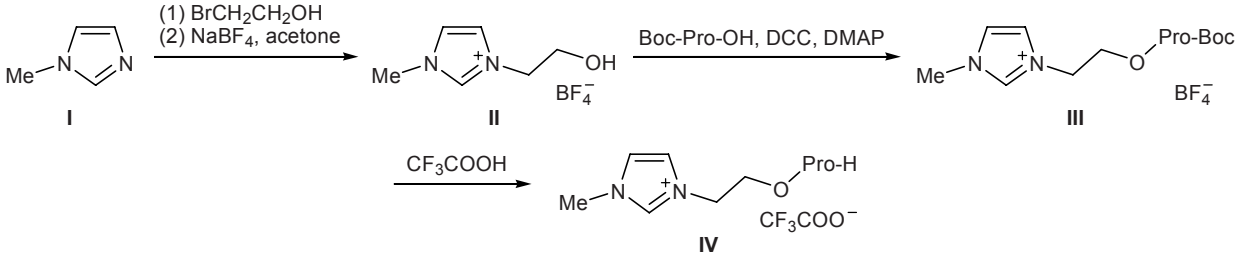
Abstract—Ionic-liquid-supported proline derivative was synthesized starting from L-proline and was used to catalyze direct asymmetric aldol reaction of acetone with aldehydes. The yield and optical purity of the condensation products, the corresponding β-hydroxy carbonyl compounds were comparable with those obtained under homogeneous conditions. Moreover, the catalyst can be reused for at least four times.

DOI: 10.1134/S1070428008120154

Asymmetric aldol reaction is one of the most important carbon–carbon bond-forming processes in organic synthesis [1]. Among these, the most efficient and attractive from the viewpoint of atom economy is direct asymmetric aldol reaction between an aldehyde and unmodified ketone [2]. L-Proline was recently used to catalyze direct asymmetric aldol reaction with formation of the corresponding β-hydroxy carbonyl compounds with moderate to excellent *ee* (enantiomeric excess) values [3–5]. The use of proline as catalyst is advantageous, for the procedure requires no metal derivatives and the catalyst is cheap and accessible in both enantiomerically pure forms. However, the reaction was carried out in an organic solvent (dimethyl sulfoxide, dimethylformamide, chloroform, tetrahydrofuran, or acetonitrile) whose toxic and/or hazardous properties restrict large-scale application of this procedure. Furthermore, it is rather difficult to reuse chiral catalyst.

In the recent years, ionic liquids have attracted considerable interest as environmentally benign reaction media due to their fascinating and intriguing properties, such as high thermal and chemical stabilities, negligible vapor pressure, nonflammability, friction reduction, antiwear performance, and high loading capacity [6]. Ionic liquids are also widely used as media for electrochemical technologies [7], chemical extraction [8], and other industrial processes [9]. In most cases, ionic liquids are readily regenerated and can be recycled. An attractive feature of ionic liquids is that their solubility can be tuned easily, so that they can be separated from both organic and aqueous phases, depending on the choice of cation and anion. The substrate solubility can also be controlled [10]. Therefore, such low molecular weight ionic liquids may serve as soluble supports for organic synthesis. Phase separation between ionic liquid phase, organic phase, and aqueous phase ensures isolation and purification of

Scheme 1.



* The text was submitted by the authors in English.

products [11]. Ionic liquids were recently used to carry out aldol condensations [12, 13].

In the present study we examined the catalytic activity of new ionic liquid-supported proline derivative in direct asymmetric aldol reaction of acetone with some aldehydes, as well as the possibility for recycling. To the best of our knowledge, this is the first example of direct asymmetric aldol condensation catalyzed by ionic liquid-supported proline.

Initially we prepared ionic liquid-supported proline **IV** according to the procedure described in [14], by reaction of 1-(2-hydroxyethyl)-1-methylimidazolium tetrafluoroborate (**II**) with Boc-L-proline and subsequent deprotection of proline derivative **III** by the action of trifluoroacetic acid (Scheme 1). Compound **IV** was then used to catalyze aldol condensation of acetone with some aromatic and aliphatic aldehydes (Scheme 2). The reactions were carried out with 10 mol % of the catalyst and 10 ml of acetone. In all cases, we isolated the expected aldol condensation products in good yields and with moderate to excellent *ee* values (Table 1).

Table 1. Asymmetric aldol condensation of acetone with aldehydes in the presence of L-proline derivative **IV**

Compound no.	Yield,[a] %	Enantiomeric excess *ee*,[b] %
Va	54	70
Vb	75	73
Vc	89	85
Vd	74	67
Ve	69	68
Vf	71	92

[a] Here and in Tables 2 and 3, yield of the product isolated by chromatography is given.

[b] Here and in Tables 2 and 3, *ee* was determined by chiral HPLC.

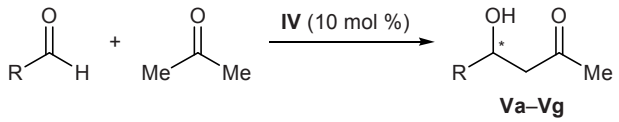
Table 2. Effect of the amount of catalyst **IV** on the yield and optical purity of hydroxy ketone **Vc** in the aldolization of acetone with *o*-nitrobenzaldehyde

Catalyst, mol %	Reaction time, h	Yield, %	Enantiomeric excess *ee*, %
0	24	0	–
1	48	41	82
5	36	76	85
10	24	89	85
10	36	90	85
30	24	92	84

Table 3. Recycling of ionic liquid-supported proline **IV** in the asymmetric aldol condensation of acetone with *o*-nitrobenzaldehyde

Cycle no.	Yield, %	Enantiomeric excess *ee*, %
1	89	85
2	92	86
3	88	85
4	86	84

Scheme 2.



R = Ph (**a**), 4-$O_2NC_6H_4$ (**b**), 2-$O_2NC_6H_4$ (**c**), 4-BrC_6H_4 (**d**), 4-MeC_6H_4 (**e**), *i*-Pr (**f**), 3-$O_2NC_6H_4$ (**g**).

Next we examined the effect of the amount of the catalyst in the reaction with *o*-nitrobenzaldehyde. No reaction occurred in the absence of ionic liquid-supported proline **IV**. Comparable results were obtained in the presence of 10 and 30 mol % of the catalyst (reaction time 36 and 24 h, respectively). At 5 mol % of the catalyst, the product yield decreased insignificantly, whereas in the presence of 1 mol % of **IV** (48 h) the yield was almost twice as low. In all cases, the enantioselectivity remained fairly high (82–85%; Table 2).

We then continued our study by exploring the recyclability of the catalyst, which is important from the viewpoint of large-scale processes, especially with expensive catalyst. As model reaction we used the condensation of acetone with *o*-nitrobenzaldehyde in the presence of ionic-liquid-supported proline **IV**. When the reaction was complete, the mixture was concentrated by removal of acetone and extracted with diethyl ether (3×20 ml). The residue was proline derivative **IV**; according to the ^{1}H NMR data, it contained no aldol condensation product. The catalyst was dried for 30 min under reduced pressure and reused. This procedure was repeated four times (Table 3). We observed only a slight decrease of the chemical yield and enantioselectivity, in keeping with the results obtained in the reaction in DMSO [4] and with bmimPF_6 [12]; however, *ee* values were lower than under homogeneous conditions [4].

We have no reasonable explanation for the observed drop in stereoselectivity. Even if *ee* values were slightly higher, the yields were lower, and they con-

siderably decreased after four cycles. Moreover, it should be remembered that the reaction with *o*-nitrobenzaldehyde was performed in toxic solvents such as dimethylformamide.

Our results demonstrate that ionic liquid-supported proline as catalyst provides a convenient approach to phase separation and isolation of the products, which may be used in other fields of organic synthesis. Ionic liquid-supported proline turned out to be a convenient catalyst for direct asymmetric aldol reaction. In most cases, no elimination products were detected, or they were formed in insignificant amounts. The ionic liquid catalyst may be reused at least four times without appreciable loss in efficiency and enantioselectivity. The results of our study indicate that further research in this line is fairly promising.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on Inova-400 (400 MHz; compounds **Va**–**Vg**, $CDCl_3$) and Jeol ECX Delta 2 spectrometers (500 MHz, salt **IV**) using tetramethylsilane as internal reference. The optical purities (*ee* values) were determined by high-performance liquid chromatography (HPLC) according to the procedure described in [15] on an Agilent Technologies 1100 instrument equipped with a UV detector (λ 254 nm); Daicel Chiralpak AS-H column; eluent hexane–propan-2-ol, 70:30, flow rate 1.0 ml/min. Products of the reaction of acetone with *o*-nitrobenzaldehyde were analyzed using Daicel Chiralcel OD column; eluent hexane–propan-2-ol, 85:15.

All commercially available reagents were used without additional purification. 1-(2-Hydroxyethyl)-1-methylimidazolium tetrafluoroborate (**II**) was synthesized from 1-methyl-1*H*-imidazole (**I**) and 2-bromoethanol in the presence of $NaBF_4$, following the procedure reported in [16] (Scheme 1); yield 92%, colorless liquid.

1-{2-[(2*S*)-1-(*tert*-Butoxycarbonyl)pyrrolidine-2-carbonyloxy]ethyl}-3-methyl-1*H*-imidazol-3-ium tetrafluoroborate (III). A 1 M solution of *N*,*N*′-dicyclohexylcarbodiimide (DCC) in methylene chloride, 10 ml, was added to a mixture of 1.07 g (5 mmol) of 1-(2-hydroxyethyl)-1-methylimidazolium tetrafluoroborate (**II**), 2.15 g (10 mmol) of Boc-L-proline, and 0.25 g (2 mmol) of 4-dimethylaminopyridine (DMAP) in 25 ml of anhydrous acetonitrile. The mixture was vigorously stirred for 18 h at room temperature under nitrogen and passed through a layer of Celite. The Celite layer was washed with acetonitrile, the washings were combined with the organic phase and concentrated under reduced pressure. The residue was washed with diethyl ether (3×20 ml) and dissolved in methylene chloride, and the solution was washed with 2 N hydrochloric acid (3×10 ml). The organic phase was dried over Na_2SO_4 and evaporated. Yield 1.85 g (90%), pale yellow oil.

1-Methyl-3-{2-[(2*S*)-pyrrolidine-2-carbonyloxy]-ethyl}-1*H*-imidazol-3-ium trifluoroacetate (IV). Compound **III**, 1.0 g (2.4 mmol), was dissolved in 10 ml of methylene chloride, 10 ml of trifluoroacetic acid was added, and the mixture was stirred for 30 min at room temperature under nitrogen. The mixture was evaporated under reduced pressure, and the residue was washed with two portions of diethyl ether and dried under reduced pressure. Yield 0.7 g (93%), pale yellow oil. ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 9.20 s (0.55H), 9.12 s (0.45H), 7.83 s (1H), 7.68 d (1H), 5.46–5.34 m (0.45H), 4.75–4.58 m (4H), 4.25–4.15 m (0.55H), 4.05 s (3H), 3.58–3.29 m (2H), 2.50–2.45 m (2H), 1.09–1.06 m (2H). ^{13}C NMR spectrum (acetone-d_6), δ_C, ppm: 168.4, 161.2 (0.45C), 161.1 (0.55C), 137.8, 124.0 (0.45C), 123.7 (0.55C), 117.8 (0.45C), 116.1 (0.55C), 64.9, 59.8, 48.5 (0.45C), 47.8 (0.55C), 35.8, 27.8, 23.8 (0.45C), 23.5 (0.55C).

General procedure for direct aldol condensation of acetone with aldehydes. A mixture of 10 mol % of compound **IV**, 10 ml of acetone, and 1 mmol of the corresponding aldehyde was stirred for 25 h at room temperature. The mixture was then extracted with diethyl ether (5×20 ml), and the catalyst was recovered. The extracts were combined and evaporated, and the aldol condensation product was isolated from the residue by flash chromatography on silica gel using hexane–ethyl acetate (6:1) as eluent. The catalyst was kept under reduced pressure to remove residual diethyl ether or acetone before reuse.

4-Hydroxy-4-phenylbutan-2-one (Va). ^{1}H NMR spectrum, δ, ppm: 2.19 s (3H, $COCH_3$), 2.80–2.82 m (2H, CH_2), 3.32 br.s (1H, OH), 5.12 d.d (1H, CH, J = 9.2, 3.1 Hz), 7.16–8.25 m (5H, H_{arom}).

4-Hydroxy-4-(4-nitrophenyl)butan-2-one (Vb). ^{1}H NMR spectrum, δ, ppm: 2.23 s (3H, $COCH_3$), 2.84–2.87 m (2H, CH_2), 3.57 br.s (1H, OH), 5.26–5.28 m (1H, CH), 7.55 d (2H, H_{arom}, J = 8.1 Hz), 8.22 d (2H, H_{arom}, J = 8.1 Hz).

4-Hydroxy-4-(2-nitrophenyl)butan-2-one (Vc). ^{1}H NMR spectrum, δ, ppm: 2.23 s (3H, $COCH_3$), 2.75 d.d (1H, CH_2, J = 17.2, 9.6 Hz), 3.09 d (1H, CH_2,

J = 17.2 Hz), 3.91 br.s (1H, OH), 5.67 d (1H, CH, J = 9.6 Hz), 7.42–7.93 m (4H, H_{arom}).

4-(4-Bromophenyl)-4-hydroxybutan-2-one (Vd). ^{1}H NMR spectrum, δ, ppm: 2.21 s (3H, $COCH_3$), 2.82–2.84 m (2H, CH_2), 3.37 d (1H, OH, J = 2.8 Hz), 5.10–5.14 m (1H, CH), 7.25 d (2H, H_{arom}, J = 8.4 Hz), 7.48 d (2H, H_{arom}, J = 8.4 Hz).

4-Hydroxy-4-(4-methylphenyl)butan-2-one (Ve). ^{1}H NMR spectrum, δ, ppm: 2.19 s (3H, $COCH_3$), 2.34 s (3H, $C_6H_4C\mathbf{H}_3$), 2.77–2.92 m (2H, CH_2), 3.26 br.s (1H, OH), 5.12 d.d (1H, CH, J = 9.2, 3.1 Hz), 7.16 d (2H, H_{arom}, J = 8.0 Hz), 8.22 d (2H, H_{arom}, J = 8.0 Hz).

4-Hydroxy-5-methylhexan-2-one (Vf). ^{1}H NMR spectrum, δ, ppm: 2.19 s (3H, $COCH_3$), 2.29 s (1H, CH), 2.37 s (6H, CH_3), 2.75–2.88 m (2H, CH_2), 3.46 br.s (1H, OH), 5.12 d.d (1H, CH, J = 9.2, 3.1 Hz).

4-Hydroxy-4-(3-nitrophenyl)butan-2-on (Vg). ^{1}H NMR spectrum, δ, ppm: 2.23 s (3H, $COCH_3$), 2.88–2.93 m (2H, CH_2), 3.60 d (1H, OH, J = 2.8 Hz), 5.26–5.28 m (1H, CH), 7.52–9.25 m (4H, H_{arom}).

This work was supported by the Natural Science Foundation of China (grant no. 20862004), by the Key Project of Science and Technology of Guizhou province (grant no. 2007-2022), and by the Special Scientific Research Foundation of Guizhou (grant no. TZJF-2006.25).

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