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ARTICLE

Effect of Additives on L-Proline Catalyzed Direct Asymmetric Aldol Reactions

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Abstract: The direct asymmetric aldol reaction of aromatic aldehydes with acetone catalyzed by L-proline was accelerated by the addition of diols or diphenols. The use of additives decrease the amount of L-proline needed and allowed the use of solvent free conditions. Catechol with two adjacent hydroxy groups on aromatic ring was the most efficient additive. Under the optimized conditions, 5 mol% L-proline with 1 mol% catechol gave excellent chiral selectivity (80% ee value) with > 90% yield, which was higher than that obtained using 30 mol% L-proline without an additive. Computations indicated that the additive promoted the reaction by an intermolecular hydrogen bond between the hydrogen of the hydroxyl group and the oxygen of the carbonyl group, which activated the carbonyl group of the aldehyde. Catechol with two adjacent hydroxyl groups on the aromatic ring can form two hydrogen bonds with the oxygen of the carbonyl group on the corresponding aldehyde. Therefore, the combination of L-proline and catechol was very efficient in catalyzing the direct asymmetric aldol reaction and gave a high yield in a short time.

Key words: L-proline; catechol; aromatic aldehyde; acetone; direct asymmetric aldol reaction; hydrogen bond interaction

The direct asymmetric aldol reaction is one of the most important carbon-carbon bond forming reaction to form either one or two vicinal stereo-centers in synthetic chemistry [1]. Yamada et al. [2] first reported the direct catalytic asymmetric aldol reactions of aldehydes with unmodified ketones, which brought about the revival of direct aldol reaction. More recently, new metal-free organocatalysts derived from L-proline were reported to be active in some cases [3–6]. Nevertheless, numerous drawbacks remain with using L-proline as the catalyst, including the use of a lot of the catalyst (30 mol%) and moderate activities [7–9]. Furthermore, high polarity solvents, e.g. *N*,*N*-dimethylformamide (DMF) or dimethyl sulfoxide (DMSO), are often necessary for the reaction. To solve these problems, attention was directed to the design of various proline derivatives [10–16] and novel potential catalysts based on the structure of proline [17,18]. Nevertheless, the use of such proline derivatives or *quasi*-proline as catalyst has been limited because their synthesis involves laborious routes.

The use of additives, such as bases, Lewis acids, and water, in the direct asymmetric aldol reaction provides an alternative approach to improve enantioselectivity and to accelerate the reaction [19–24]. Zhou et al. [25] recently employed (*R*)- and (*S*)-1,1′-bi-2-naphthol as promoter for the L-proline catalyzed aldol reaction. High catalyst loading (30 mol%) and long reaction time (48 h) were still required, although an enhanced enantioselectivity was obtained. The ability to use a lower catalyst loading and have higher reactivity is still needed for L-proline catalyzed asymmetric aldol reactions. Ji et al. [26] explored the influence of a multiple OH group phenol on the direct aldol reactions catalyzed by pyrrolidine and found that the multi-phenol (40 mol%) promoted the aldol reaction to proceed smoothly with 20 mol% loading of pyrrolidine. The positive effect of the multi-phenol encouraged us to employ cheap diols and diphenols as additives. We envisaged that the hydroxyl groups of diols and diphenols can interact with the carboxyl group of L-proline to activate the substrate, which

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would enhance catalytic efficiency. Here, a series of diols and diphenols were employed as additives in L-proline catalyzed asymmetric aldol reactions. The use of diols and diphenols, esp. diphenols with two adjacent hydroxyl groups on the aromatic ring, led to the expected higher conversion of 4-nitrobenzaldehyde under solvent-free conditions even when the L-proline loading was only 5 mol%. Quantum computation was used to study the role of the additive in the reaction. The result showed that hydrogen bond interactions between the aromatic aldehyde and the additive activated the carbonyl group of the aromatic aldehyde and enhanced its reactivity. The addition of a diphenol to the reaction medium provides a simple and efficient method to enhance the catalytic efficiency of direct asymmetric aldol reactions catalyzed by L-proline.

1 Experimental

1.1 General procedure for the direct aldol reaction

2,3-dihydroxynaphthalene and 2,2′-diphenol were purchased from TCI. The other commercially available chemicals were laboratory grade reagents from local suppliers. All solvents were purified by standard procedures before use.

L-proline (0.006 g, 0.025 mmol) and the additive (0.005 mmol) were stirred in 2 ml acetone at 25 °C for 15 min. Then 4-nitrobenzaldehyde (0.0756 g, 0.5 mmol) was added into the mixture under stirring for 4 h. The mixture was treated with saturated aqueous ammonium chloride. The aqueous layer was extracted several times with ethyl acetate. The combined organic layers were dried with anhydrous Na_2SO_4 and evaporated, worked up and purified by flash column chromatography on silica gel (200–300 mesh; eluent: hexane/ethyl acetate = 5:1) to give the desired products. Enantioselectivity was expressed as ee (%) = 100 × (R – S)/(R + S). The resolution and separation factors for the separation of the products and further structure identification by ^{1}H NMR and ^{13}C NMR were listed as follows.

(4*R*)-Hydroxy-4-(4′-nitrophenyl)-butan-2-one (**1a**). Isolated as oil by silica gel column chromatography (hexane/EtOAc = 5:1). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.216–7.280 (m, 4H), 5.27 (s, 1H), 3.67 (s, 1H), 2.87 (d, J = 6.7 Hz, 2H), 2.231 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 208.6, 150.0, 147.3, 126.4, 123.8, 68.9, 51.5, 30.7. The enantioselectivity was determined by a Shimadzu LC-10A_{vp} HPLC using a Daicel CHIRALPAK OB-H column (hexane/*i*-propanol = 85:15; flow rate: 0.8 ml/min; λ = 254 nm). Major enantiomer: t_R = 14.0 min; minor enantiomer: t_R = 16.1 min. Resolution: 1.29. Separation factor: 1.15.

(4*R*)-Hydroxy-4-(2-nitrophenyl)-butan-2-one (**1b**). Isolated as oil by silica gel column chromatography (hexane/EtOAc = 5:1). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.95–7.42 (m, 4H), 5.68 (d, J = 10.7Hz, 1H), 3.73 (s, 1H), 3.15–2.72 (m, 2H), 2.24 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 208.8, 147.2, 138.4, 133.8, 128.3, 128.2, 124.4, 65.7, 51.0, 30.4. The enantioselectivity was determined by a Shimadzu LC-10A_{vp} HPLC using a Daicel CHIRALPAK OB-H column (hexane/*i*-propanol = 85:15; flow rate: 0.8 ml/min; λ = 254 nm). Major enantiomer: t_R = 8.4 min; minor enantiomer: t_R = 7.3 min. Resolution: 2.83. Separation factor: 1.15.

(4*R*)-(2-Chlorophenyl)-4-hydroxy-2-butanone (**1c**). Isolated as oil by silica gel column chromatography (hexane/EtOAc = 5:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61–7.18 (m, 4H), 5.52–5.49 (m, 1H), 3.63 (s, 1H), 3.00–2.65 (m, 2H), 2.21 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 209.3, 140.1, 131.1, 129.3, 128.6, 127.3, 127.1, 66.6, 50.0, 30.6. The enantioselectivity was determined by Shimadzu LC-10A_{vp} HPLC using Daicel CHIRALPAK AD column (hexane/*i*-propanol = 92.5:7.5; flow rate: 0.8 ml/min; λ = 254 nm). Major enantiomer: t_R = 10.9 min; minor enantiomer: t_R = 12.3 min. Resolution: 3.28. Separation factor: 1.13.

(4*R*)-(4-Bromophenyl)-4-hydroxy-2-butanone (**1d**). Isolated as oil by silica gel column chromatography (hexane/EtOAc = 5:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47–7.21 (m, 4H), 5.10 (q, J = 8.7 Hz, 1H), 3.43 (s, 1H), 2.86–2.76 (m, 2H), 2.19(s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 208.8, 141.7, 131.6, 127.3, 121.4, 69.2, 51.7, 30.7. The enantioselectivity was determined by a Shimadzu LC-10A_{vp} HPLC using a Daicel CHIRALPAK AD column (hexane/*i*-propanol = 92.5:7.5; flow rate: 0.8 ml/min; λ = 254 nm). Major enantiomer: t_R = 15.2 min; minor enantiomer: t_R = 16.1 min. Resolution: 2.71. Separation factor: 1.06.

(4*R*)-(4-Acetamidophenyl)-4-hydroxy-2-butanone (**1e**). Isolated as oil by silica gel column chromatography (hexane/EtOAc = 5:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47–7.26 (m, 4H,), 5.12–5.11 (m, 1H), 3.34 (s, 1H), 2.89–2.77 (m, 2H), 2.20 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 209.2, 168.4, 138.7, 137.3, 126.3, 120.0, 69.5, 51.8, 20.8, 24.6. The enantioselectivity was determined by a Shimadzu LC-10A_{vp} HPLC using a Daicel CHIRALPAK AD column (hexane/*i*-propanol = 90:10; flow rate: 0.8 ml/min, λ = 254 nm). Major enantiomer: t_R = 50.0 min; minor enantiomer: t_R = 55.7 min. Resolution: 3.11. Separation factor: 1.11.

(4*R*)-Hydroxy-4-(2-naphthyl)-2-butanone (**1f**). Isolated as oil by silica gel column chromatography (hexane/EtOAc = 5:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80–7.43 (m, 7H), 5.31–5.29 (m, 1H), 3.50 (s, 1H), 2.96–2.84 (m, 2H), 2.18 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 209.1, 140.2, 133.3, 130.0, 128.4, 128.0, 127.7, 126.3, 126.0, 124.4, 123.8, 70.0, 51.9, 30.8. The enantioselectivity was determined by a Shimadzu LC-10A_{vp} HPLC using a Daicel CHIRALPAK AD column (hexane/*i*-propanol = 92.5:7.5; flow rate: 0.8 ml/min; λ = 254 nm). Major enantiomer: t_R = 22.6 min; minor enantiomer: t_R = 27.0 min. Resolution: 4.42. Separation factor: 1.19.

1.2 Quantum calculation