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Asymmetric Direct Aldol Reactions Catalyzed by a Simple Chiral Primary Diamine–Brønsted Acid Catalyst in/on Water

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Abstract: The direct asymmetric aldol reaction catalyzed by the simple and commercially available chiral primary diamines, (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine and (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine, is presented. The catalyst system is a primary amine with Brønsted acid–catalyzed direct aldol reaction of *p*-nitrobenzaldehyde and cyclohexanone with high chemo- and stereoselectivity on water, which furnishes the corresponding *β*-hydroxyketone with up to 94% ee.

Keywords: Aldol, asymmetric catalysis, organocatalysis, primary amine, water

INTRODUCTION

The asymmetric aldol reaction is plausibly an ancient transformation and one of the most powerful methods for the constructing carbon–carbon bonds in organic synthesis.[1] Organometallic complexes and Lewis base–based catalysts have been highly successful for the asymmetric aldol

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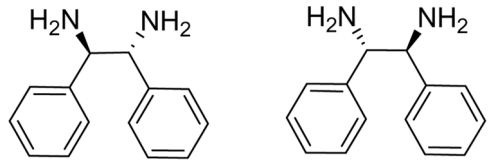
reaction of unmodified ketone and Mukaiyama-type silyl enol ethers in the past decades.[2] Recently, the development of organocatalytic stereoselective methods for asymmetric direct aldol reactions has been a subject of intense research. Since the pioneering work of List and coworkers in 2000,[3] the proline and its derivatives are arguably that the most efficient and versatile small organic "enzymes" that catalyze a wide range of organic transformations. There have been numerous reports on direct aldol reactions catalyzed by proline and its structural analogs that utilize the enamine mechanism,[4] which showes organocatalysis has experienced a renaissance in homogeneous catalysis and green chemistry.[5]

Currently, the use of water as solvent for asymmetric reactions is of great interest because of the low cost, safety, and environmentally benign nature of water.[6] However, the proline-catalyzed aldol reactions can only afford moderate to high enantioselectivity in organic solvents, and the presence of a large amount of water resulted in the formation of products with low or no enantioselectivity.[3] Recently, Hayashi et al. showed that direct asymmetric aldol reaction could be carried out with excellent enantioselectivity in water by employing proline-derivated organocatalysts.[7] Then the groups of Córdova and Lu demonstrated that primary amino acids such as alkaline and tryptophan could catalyze the aldol reaction with good enantioselectivity in the presence of water.[8] The recent progress with aqueous primary amino acid[8h] and diamine–Brønsted acid–catalyzed asymmetric aldol reactions[9], created great demand to study and develop novel, cheap, and simple amine catalysts in organic reactions. In our continuing interest in the development of organocatalytic protocols for carbon–carbon bond-forming transformation,[10] we report herein a simple chiral primary diamine–catalyzed direct aldol reaction with excellent stereoselectivity in/on water.

RESULTS AND DISCUSSION

Although the simple and commercially available chiral primary diamine (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine (**2**)–catalyzed aldol reaction in the absence of any Brønsted acids has been explored by Córdova et al., only low conversion (23% yield) with poor enantioselectivity (12% ee) was achieved after 3 days in the aldol reaction of *p*-nitrobenzaldehyde with cyclohexanone in wet dimethyl sulfoxide (DMSO). We reasoned that the by-product Shiff base was produced, which resulted in very low catalytic activity. It is hypothesized that primary diamine (Scheme 1, **1** or **2**) might be an efficient aldol catalyst in the presence of Brønsted acid in water.

In our initial study, we investigated the catalytic effects of chiral primary diamine (**1**) with various Brønsted acids in the direct aldol



1: (*R,R*)-diamine **2**: (*S,S*)-diamine

Scheme 1. The structure of (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine and (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine.

reactions between cyclohexanone and *p*-nitrobenzaldehyde in water. As shown in Table 1, among the Brønsted acids tested, D-camphorsulfonic acid, p-toluenesulfonic acid (TsOH), and trifluoromethanesulfonic acid (TfOH) were suitable Brønsted acids in this reaction (entries 1–4), and TfOH was best additive for the aldol reaction. 20 mol% of TfOH enabling

Table 1. Screening results of aldol reaction with diamine–Brønsted acid catalyst

Entry[a]	Solvent	Brønsted acid	Time (h)	Yield (%)[b]	*Anti*/*syn*[c]	Ee (%)[d]
1	H_2O	D-CSA	48	90	3:1	91
2	H_2O	TsOH	24	95	6:1	80
3	H_2O	TsOH[e]	24	37	6:1	81
4	H_2O	TfOH	12	92	9:1	94
5	H_2O	TfOH[e]	12	45	9:1	93
6	CH_2Cl_2	D-CSA	48	Trace	—	—
7	Solvent free	D-CSA	48	30	0.6:1	37
8	PEG-600	D-CSA	48	55	0.6:1	78
9	PEG-600/H_2O[f]	D-CSA	48	68	5:1	92
10	H_2O	TfOH	12	92	9:1	−94[g]
11	H_2O	TfOH	12	40	1:1	90[h]
12	H_2O	TfOH	12	85	3:1	93[i]

[a]The reactions were performed with 1.0 mmol of *p*-nitrobenzaldehyde, 10 equiv. of cyclohexanone, 10 mol% of (*R,R*)-diamine catalyst (**1**), 20 mol% Brønsted acid, 2 mL of H_2O, at room temperature.

[b]Isolated yield.

[c]Determined by H NMR analysis of the products.

[d]The ee % of *anti*-products.

[e]10 mol% of TsOH was used.

[f]PEG-600/H_2O = 1:1 (1mL/1mL).

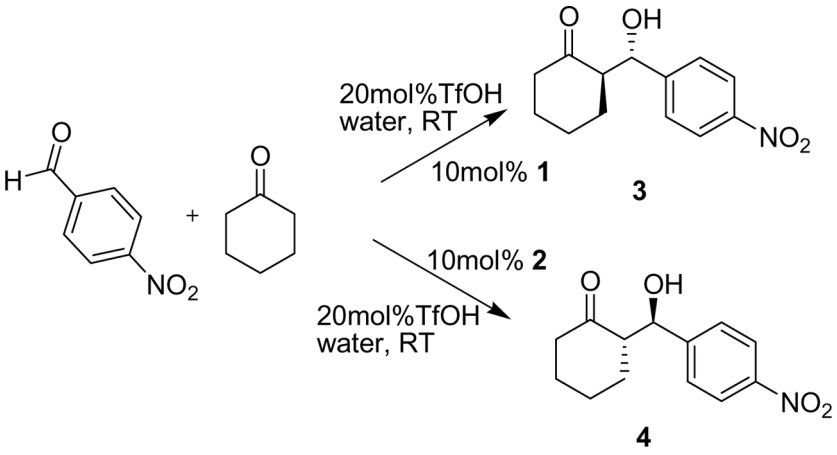
[g]Using 10 mol% of (*S,S*)-diamine catalyst (**2**).

[h]Using 1 mol% of catalyst.

[i]Using 5 mol% of catalyst.

the completion of reaction in 12 h (entry 4, 92% yield, 94% ee). With 10 mol% of Brønsted acid, the desired product was obtained in lower yield (entries 3 and 5), which confirmed the importance of Brønsted acid for primary amine-catalyzed aldol reaction. The role of Brønsted acid is probably related to its possible function in facilitating the enamine catalytic cycle.[11] The enantioselectivity of primary diamine (**1**) catalyzed aldol reaction was dramatically affected by solvent, low conversions with poor enantioselectivities were exhibited under solvent free conditions and in CH_2Cl_2 (entries 6 and 7), and notably, the aldol reaction performed under solvent-free conditions favored the *syn* -isomer. More interestingly, PEG-600 mediated the priamine-catalyzed aldol reaction with moderate yield (55%), and *syn*-isomer is the major aldol product with good enantioselectivity (entry 8, *anti*-/*syn* = 0.6:1, 67% ee for *syn*- and 78% ee for *anti*-product respectively). The addition of water (PEG/H2O = 1/1) increased the conversion and stereoselectivity of aldol reaction obviously (entry 9), which clearly showed the importance of water in primary diamine (**1**)–TfOH catalyzed aldol reaction. Under the best-screened conditions, the loading of catalyst could be reduced to 5 mol% while still maintaining excellent enantioselectivity and quite significant activity (entry 12).

We also investigated the relationship between the enantiomeric excess of the aldol product, derived from the aldol reaction shown in Scheme 2, and the optical purity of the chiral diamine (**1**). Plotting the enantiomeric excess of diamine versus that of β-hydroxy ketone **3** showed a linear correction (Figure 1). Our results supported the supposition that only one molecular primary diamine and two TfOH molecules catalyzed



Scheme 2. Primary amine-catalyzed direct aldol reaction of cyclohexanone and p-nitrobenzaldehyde.

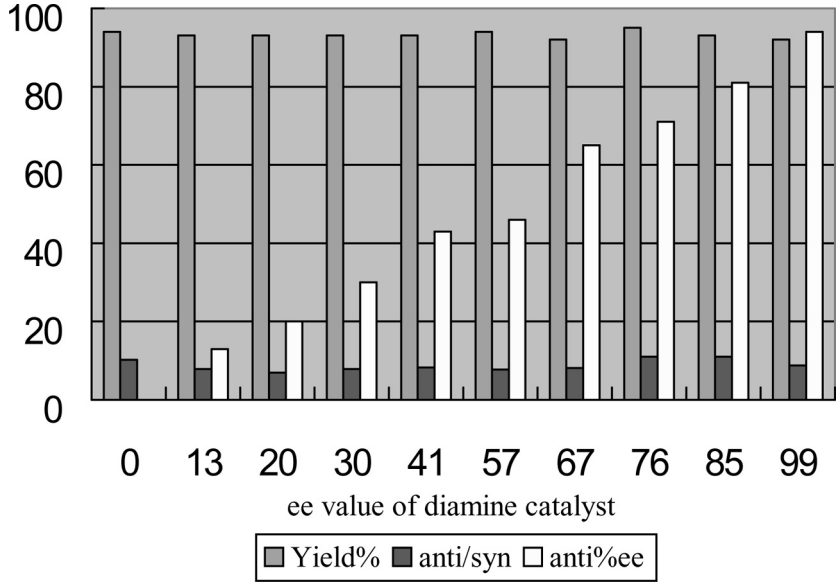


Figure 1. Relation between the enantiomeric excess of (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine and that of the aldol product **3** in the catalytic direct aldol reaction.

asymmetric aldol reaction. This correlation together with previous theoretical findings by Allemann et al.[12] for amino acid–catalyzed aldol reactions suggested that enamine mechanism is more favorable (Figure 2).

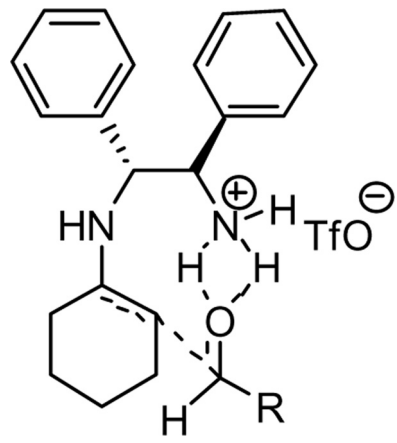
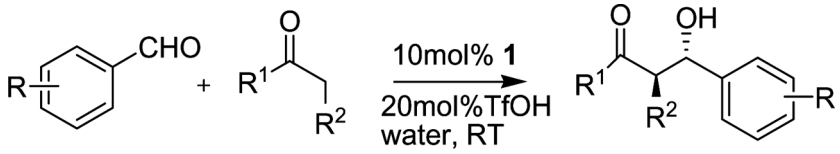


Figure 2. Proposed transition state for the aldol reaction of cyclohexanone.



Scheme 3. Primary amine-catalyzed direct aldol reactions.

Encouraged by these results, we also investigated the primary diamine–TfOH–catalyzed aqueous asymmetric aldol reaction for a set of different aldehydes and cyclic ketones on water (Scheme 3 and Table 2). We found that the primary diamine–TfOH mediated the enantioselective aldol reactions of cyclohexanone and various aromatic aldehydes with excellent enantioselectivities, giving the corresponding aldol products with 89–93% ee (entries 2–5). Unfortunately, the yields of aldol reactions of cyclohexanone and aromatic aldehydes without electron-deficient substituents is low; moreover, acyclic ketones, such as acetone and acetophenone, were bad donors and the aldol reaction did not occur. Hence, the primary diamine–TfOH exhibited substrate specificity in the aldol reaction.

In summary, we have shown that simple primary diamines, (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine and (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine, can catalyze the asymmetric aldol reaction in the presence of Brønsted acid on water. Excellent enantioselectivities were achieved in

Table 2. (*R,R*)-Diamine (1)-catalyzed direct aldol reactions of several substrates on water[a]

Entry	R	R^1, R^2	Yield (%)[b]	*Anti*/*syn*[c]	Ee(%)[d]	Ref.
1	*p*-NO_2	CH_3,H	NR[e]	—	—	
2	*o*-Cl	-$(CH_2)_4$-	22	20:1	93	13b
3	*p*-Br	-$(CH_2)_4$-	28	3:1	90	13c
4	*P*-Me	-$(CH_2)_4$-	20	3:1	89	13d
5	*p*-MeO	-$(CH_2)_4$-	15	19:1	90	13e
6	*p*-NO_2	-$(CH_2)_3$-	58	1/1.3	64	13f
7	*o*-NO_2	-$(CH_2)_4$-	39	3:1	72	13g
8	*o*-NO_2	-$(CH_2)_3$-	48	1.4/1	45	13h

[a]The reactions were performed with 1.0 mmol of aldehyde, 10 equiv. of ketone, 10 mol% of (*R,R*)-diamine catalyst (**1**), 20 mol% TfOH, 2 mL of H_2O, at room temperature, for 4 days (entries 1–5) or 1 day (entries 6–8).

[b]Isolated yield.

[c]Determined by H-NMR analysis of the products.

[d]The ee% of *anti*-products.

[e]NR: no reaction.

the aldol reaction of cyclohexanone and *p*-nitrobenzaldehyde with up to 94% ee and 92% yield. Notably, the presence of water both accelerated the reaction and improved the enantioselectivity, which suggests hydrogen bonding is of significant importance in the transition state. The mechanism and the transition-state model have been discussed on the basis of stereochemistry of the aldol products and enantiomeric excess relationships.

EXPERIMENTAL

All reagents and solvents were used directly without purification. Flash-column chromatography was performed over silica (200–300 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, and were referenced to the internal solvent signals. Infrared (IR) spectra were recorded using a Fourier transform infrared (FTIR) apparatus. Thin-layer chromatography (TLC) was performed using silica-gel F_{254} TLC plates and visualized with ultraviolet light. High pressure liquid chromatography (HPLC) was carried out with a Waters 2695 Millennium with photodiode array detector. All the aldol products were known[13] and confirmed by gas chromatography-mass spectrometry (GC-MS) and usual spectral methods (NMR and IR).

General Procedure for Aldol Reactions

A catalytic amount of (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (10 mol%) was added to a vial containing 4-benzaldehyde (0.5 mmol), cyclohexanone (2.5 mmol), TfOH (20 mol%), and 2 mL of water. After vigorous stirring at room temperature for the times shown in the tables, the reaction mixtures was poured into an extraction funnel containing brine and then diluted with distilled water and EtOAc. The aqueous phase was extracted with EtOAc. The combined organic phases were dried with Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by silica-gel column chromatography to furnish the desired aldol products. The ees of the aldol products were determined by chiral-phase HPLC analysis.

Data

(2 R,1′S)-2-[1′-Hydroxy-1′-(4-nitrophenyl)methyl]cyclohexan-1-one (Table 1)[8,13a]

^{1}H NMR (400 MHz, $CDCl_3$) (ppm): d = 1.32–1.72 (m, 4H), 1.80–1.88 (m, 1H), 2.08–2.15 (m, 1H), 2.32–2.41 (m, 1H), 2.47–2.51 (m, 1H), 2.56–2.61

(m, 1H), 4.08 (br s, 1H), 4.89–4.91 (d, J = 8.4 Hz,1H), 7.49–7.52 (m, 2H), 8.19–8.23 (m, 2H). ee was determined by HPLC analysis (Chiralpak OJ-H, hexane–2-PrOH = 70:30, 0.8 mL/min, 254 nm, 25 °C. *Anti*-diastereomer: t_r (minor) = 12.91 min, t_r (major) = 14.94 min.

(2 R,1′S)-2-[1′-Hydroxy-1′-(4-nitrophenyl)methyl]cyclopentan-1-one (Table 2, Entry 6)[13f]

^{1}H NMR (400 MHz, $CDCl_3$) (ppm): 1.46–1.59 (m, 1H), 1.70–1.77 (m, 2H), 2.01–2.04 (m, 1H), 2.24–2.30 (m, 1H), 2.38–2.40 (m, 1H), 2.44–2.49 (m, 1H), 4.72 (brs, 1H), 4.84–4.86 (d, $J = 9.2$ Hz, 1H), 7.51–7.55 (d, $J = 8.6$ Hz, 2H) 8.21–8.22 (d, $J = 8.8$ Hz, 2H). Ee was determined by HPLC analysis (Chiralpak AS-H, hexane–2-PrOH = 85:15, 1 mL/min, 254 nm, 25 °C *Anti*-diastereomer: t_r (major) = 23.86 min, t_r (minor) = 30.98 min).

(2 R,1′S)-2-[1′-Hydroxy-1′-(2-nitrophenyl)methyl]cyclohexan-1-one (Table 2, Entry 7)[13g]

^{1}H NMR (400 MHz, $CDCl_3$) (ppm): 1.53–1.73 (m, 4H) 1.73–1.78 (m, 1H) 1.82–1.86 (m, 1H), 2.33–2.34 (m, 1H), 2.42–2.43 (m, 1H), 2.76–2.77 (m, 1H), 4.17 (brs, 1H), 5.43–5.45 (d, $J = 7.2$ Hz,1H), 7.40–7.44 t,$J = 8.0$ Hz, 1H), 7.61–7.65 (t, $J = 7.6$ Hz, 1H), 7.75–7.77 (d, $J = 7.6$ Hz, 1H) 7.84–7.85 (d, $J = 8.4$ Hz,1H). Ee was determined by HPLC analysis (Chiralpak AD-H, hexane–2-PrOH = 95:5, 1–mL/min, 254 nm, 25 °C. *Anti*-diastereomer: t_r (minor) = 36.28 min, t_r (major) = 38.06 min).

(2 R,1′S)-2-[1′-Hydroxy-1′-(2-nitrophenyl)methyl] cyclopentan-1-one (Table 2, Entry 8)[13h]

^{1} H NMR (400 MHz, $CDCl_3$) (ppm): 1.72–1.78 (m, 3H), 2.01–2.05 (m, 1H), 2.34–2.79 (m, 3H), 5.42–5.44 (d, $J = 8.4$ Hz, 1H), 7.44–7.53 (m, 1H), 7.66 (m, 1H), 7.79–7.85 (m, 2H). Ee was determined by HPLC analysis (Chiralpak OD-H, hexane–2-PrOH = 95:5, 1 mL/min, 254 nm, 25 °C *Anti*-diastereomer: t_r (minor) = 26.90 min, t_r (major) = 30.38 min, 82% ee. 25 °C.

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