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A new chiral primary–tertiary diamine-Brønsted acid salt organocatalyst for the highly enantioselective direct anti-aldol and syn-Mannich reactions

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Abstract A new primary–tertiary diamine catalyst is easily prepared in a few steps from inexpensive, commercially available, enantiopure materials. This organocatalyst can be effective catalyzed the direct asymmetric aldol and Mannich reactions. The anti-aldol products can be obtained with up to a 99:1 anti/syn ratio and >98 % ee, while the syn-Mannich products could be obtained with up to a 99:1 syn/anti ratio and >99 % ee. Catalyst **1c** can be used efficiently on a large scale with the enantioselectivities of the anti-aldol and syn-Mannich reactions being maintained at the same level, which offers a great possibility for application in industry.

Keywords Cyclohexyldiamine · Aldol reactions · Mannich reactions · Large scale · Stoichiometric

Introduction

The development of stereoselective and enantioselective aldol and Mannich reactions have become interesting and challenging topics in modern organic and medicinal chemistry [1–3], because the resulting chiral β-hydroxy ketones and 1,2-amino alcohols belong to an extremely important class of biological compounds.

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In fact, β-hydroxy ketones and 1,2-amino alcohols can serve as versatile building blocks for the asymmetric synthesis of carbohydrates, amino acids, and many other biomolecules [4–6]. They also provide privileged structural functionalities that exist in many important natural products [7–12].

During the past few years, the field of asymmetric catalysis has been dominated by biocatalysts and metal catalysts. The advent of organocatalysis brought the prospect of a complementary mode of catalysis, with the potential for savings in cost, time, and energy, an easier experimental procedure, and reductions in chemical waste. For decades, one of the most difficult challenges has been the design of sustainable experimental processes, which are not only more economical but also more benign toward the environment and more practicable both in industry and in practice. Stimulated by this challenge, a great deal of effort is currently being made in the search for elegant and practical means for preparing highly stereoselective β-hydroxy ketones and 1,2-amino alcohols.

Since the pioneering findings by List, Barbas, and their co-workers that L-proline could work as an active organocatalyst in intermolecular direct aldol reactions, numerous organocatalysts have been developed for direct asymmetric aldol reactions [13–23]. Usually, enantioselective organocatalytic processes have typically been carried out in organic solvents, such as DMSO, DMF, or $CHCl_3$. The necessity to further reduce sources of pollution, such as the sometimes employed chlorinated solvents, has prompted scientists to search for organic reactions performed in the presence of water [24–32] or under solvent-free conditions [33, 34]. At the same time, the reactions using water as the solvent have attracted a great deal of attention, because water is an environmentally friendly, safe medium, which avoids the problems of pollution that are inherent with organic solvents [32–34]. On the other hand, organocatalyzed reactions under solvent-free conditions usually need shorter reaction times and result in simple and efficient work-up procedures [35–41]. For these reasons, organocatalyzed aldol reactions under solvent-free conditions or employing water as solvent have become a highly pursued goal in green chemistry.

Primary–tertiary diamines [42–48] are a type of important organic catalysts, which have achieved satisfactory results in the aspect of catalyzing Aldol [45, 49] and Michael [50, 51] reactions. But until now, they were seldom used in catalytic asymmetric two-component Mannich reactions. Here, we describe the first asymmetric syn-selective Mannich reactions of α-hydroxyketones catalyzed by a simple chiral amine catalyst. Hydroxyacetone is a very useful donor, and its Mannich reaction can yield synthetically versatile 1,2-amino alcohols. Even so, α-hydroxyacetone has seldom been used as a donor in asymmetric catalyzed direct two-component Mannich reactions [52–62]. Lu et al. reported direct anti-selective Mannich reactions between *O*-TBS-hydroxyacetone and various *N*-tosylimines derived from aromatic aldehydes in the presence of L-threonine-derived catalyst [63]. However, the result of catalyzing a direct Mannich reaction between hydroxylacetone with *N*-tosylimine is unsatisfactory, and the experimental process of removing the TBS group is troublesome. Therefore, direct Mannich reaction of catalyzing hydroxyacetone with *N*-tosylimine is more meaningful and useful.

Recently, primary–tertiary diamines have been frequently explored in organocatalysis [20, 23]. It has been found that, among the reported asymmetric organocatalysts,

most were prepared with complex procedures and/or required expensive reagents, which added hurdles for industrial production, so these organocatalysts were often only used in research laboratories. Therefore, the development of a new and effective primary–tertiary diamine catalyst, easily prepared in a few steps from inexpensive, commercially available, enantiopure materials, is urgently needed. This efficient catalyst can catalyze the direct aldol reactions by using stoichiometric amounts of ketones and various aryl aldehydes in the presence of water or under solvent-free conditions from a green chemistry and atom-economical perspective. It can also be used to catalyze the reaction of Mannich with high diastereoselectivity up to a 99:1 and enantioselective up to 99 % ee. In addition, this catalyst can be used in large-scale aldol and Mannich reactions with the enantioselectivity being maintained at the same level, which offers a great possibility for applications in industry.

Experimental

Materials and instruments

All chemicals were used as received unless otherwise noted. Reagent grade solvents were distilled prior to use. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25-mm silica gel plates visualized with UV light and/or by staining with ethanolic phosphomolybdic acid (PMA) and/or ninhydrin, both in ethanol stain. THF was freshly distilled from sodium-benzophenone ketyl radical under an argon atmosphere immediately prior to use. Flash column chromatography was performed on silica gel (200–300 mesh). NMR spectra were recorded on a 300-MHz instrument. Chemical shifts (δ) are given in ppm relative to TMS as the internal reference, and coupling constants (J) in Hz. IR spectra were recorded on a spectrometer. Melting points were measured on a digital melting-point apparatus. Mass spectra (MS) were measured with a spectrometer. Analytical high performance liquid chromatography (HPLC) was carried out on an Agilent 1200 instrument using Chiralpak AD-H (4.6 mm × 250 mm), Chiralcel OD-H (4.6 mm × 250 mm) columns. Optical rotations were measured on a JASCO P-1010 Polarimeter at $\lambda = 589$ nm.

The synthesis of the catalysts (Scheme 1)

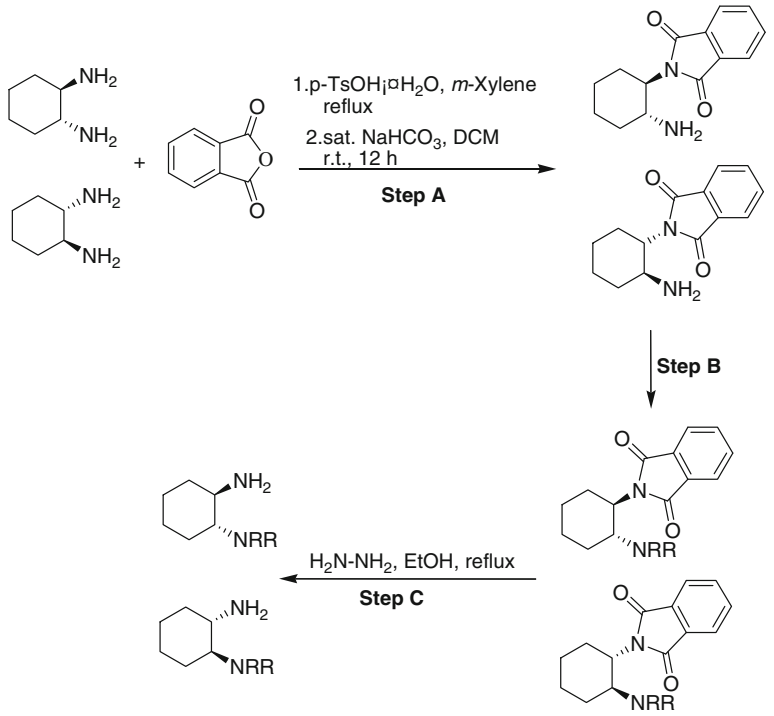
See Scheme 1.

Monoprotection of 1,2-diaminocyclohexane

Monoprotection of (1R, 2R)-1,2-diaminocyclohexane or (1S, 2S)-1,2-diaminocyclohexane was carried out following the literature procedure [64].

*Preparation of catalyst **1b** [65]*

A mixture of monoprotection of (1R, 2R)-1,2-diaminocyclohexane (3.55 mg, 14.5 mmol), 80 % formic acid (1.2 mL), and 36 % formaldehyde solution (0.5 mL,



Scheme 1 The synthesis of the catalysts

6.4 mmol) were stirred under reflux (oil bath 120 °C) for 6 h. The solvents were removed in vacuo and the product was extracted with dichloromethane and saturated $NaHCO_3$ solution. The organic solution was dried over $MgSO_4$ and evaporated to give the crude product. This product was directly purified through flash column chromatography on a silica gel to afford (1R, 2R)-*N*,*N*-Dimethyl-*N'*-phthaloyl-1,2-diaminocyclohexane as a white solid, yield 80 %.

A sample of (1R, 2R)-*N*,*N*-Dimethyl-*N'*-phthaloyl-1,2-diaminocyclohexane (7 mmol) was refluxed with hydrazine hydrate (0.84 mL) in ethanol (14 mL) for 2 h. After cooling, the solution was diluted with diethyl ether to precipitate phthaloyl hydrazide. The mixture was filtered and the filtrate evaporated to dryness. The products were purified by extraction into the dilute HCl, followed by neutralization with saturated $NaHCO_3$ solution, and back extraction with dichloromethane. Product **1b** was obtained as a yellow oil, yield 85 %; $[\alpha]_D^{20} = -38.7$ ($c = 1$, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.59$ (*dt*, $J = 3$, 9 Hz; 1H), 2.24 (*s*, 8H), 2.08–1.94 (*m*, 2H), 1.79–1.65 (*m*, 3H), 1.25–1.06 (*m*, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 69.5$, 51.3, 40.1, 34.8, 25.5, 25.0, 20.6; FT-IR (KBr): [cm^{-1}] = 2,929, 2,858, 2,825, 2,778, 1,668, 1,593, 1,512, 1,452, 1,358, 1,333, 1,270, 1,203, 1,153, 1,116, 1,089, 1,046, 943, 901, 872, 848, 820, 774, 566, 543. MS (ESI) m/z calcd. for ($C_8H_{18}N_2$) 142.24, found 143.63.

Preparation of catalyst ***1c*** *[65]*

To a solution of (1R, 2R)-*N*-phthaloyl-1,2-diamino-cyclohexane (2.44 g, 10 mmol) in acetonitrile (50 mL), K_2CO_3 (3.20 g, 23 mmol) and benzyl bromide (3 mL, 25 mmol) were added at room temperature. The mixture was refluxed with stirring for 4 h. The solvent was removed in vacuo and the mixture extracted with dichloromethane and saturated $NaHCO_3$ solution. The organic solution was dried over $MgSO_4$ and evaporated. The product was directly purified through flash column chromatography on a silica gel to afford (1R, 2R)-*N,N*-dibenzyl-*N'*-phthaloyl-1,2-diaminocyclohexane as a white solid, yield 92 %.

A sample of (1R, 2R)-*N,N*-dibenzyl-*N'*-phthaloyl-1,2-diaminocyclohexane (8 mmol) was refluxed with hydrazine hydrate (0.96 mL) in ethanol (16 mL) for 2 h. After cooling, the solution was diluted with diethyl ether to precipitate phthaloyl hydrazide. The mixture was filtered and the filtrate evaporated to dryness. The products were purified by extraction into the dilute HCl, followed by neutralization with saturated $NaHCO_3$ solution, and back extraction with dichloromethane. Product **1c** was obtained as a yellow oil, yield 85 %; $[\alpha]_D^{20} = -79.0$ ($c = 1$, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.30$–7.20 (*m*, 10H), 3.81 (*d*, $J = 13.5$ Hz, 2H), 3.37 (*d*, $J = 13.5$ Hz, 2H), 2.67 (*dt*, $J = 3.9$, 10.2 Hz; 1H), 2.12 (*m*, 1H), 1.98–1.94 (*m*, 2H), 1.79–1.58 (*m*, 4H), 1.27–0.84 (*m*, 4H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$): $\delta = 140.2$, 128.9, 128.3, 126.9, 64.6, 53.7, 51.1, 34.8, 25.7, 25.1, 22.5; FT-IR (KBr): [cm^{-1}] = 3,061, 3,027, 2,922, 2,855, 1,493, 1,451, 748, 699. MS (ESI) m/z calcd. for ($C_{20}H_{26}N_2$) 294.43, found 294.68.

Preparation of catalyst ***1d***

The general procedure described above was followed on a 4-mmol scale of (1S, 2S)-*N,N*-dibenzyl-*N'*-phthaloyl-1,2-diaminocyclohexane. Product **1d** was obtained as a yellow oil, yield 75 %; $[\alpha]_D^{20} = +62.1$ ($c = 1$, $CHCl_3$). ^{1} H NMR (300 MHz, $CDCl_3$): $\delta = 7.30$–7.21 (*m*, 10H), 3.81 (*d*, $J = 13.2$ Hz, 2H), 3.37 (*d*, $J = 13.5$ Hz, 2H), 2.68 (*dt*, $J = 3.6$, 10.2 Hz, 1H), 2.29–2.11 (*m*, 3H), 2.00–1.96 (*m*, 2H), 1.80–1.77 (*m*, 1H), 1.64–1.60 (*m*, 1H), 1.29–0.99 (*m*, 3H), 0.96–0.87 (*m*, 1H) ppm; ^{13} C NMR (75 MHz, $CDCl_3$): $\delta = 140.1$, 128.8, 128.3, 126.9, 64.4, 53.7, 53.7, 51.0, 34.5, 25.6, 25.1, 22.5; FT-IR (KBr): [cm^{-1}] = 3,060, 3,027, 2,928, 2,855, 1,493, 1,451, 747, 699. MS (ESI) m/z calcd. for ($C_{20}H_{26}N_2$) 294.43, found 294.69.

Preparation of catalyst ***1e***

The general procedure described above was followed on a 10-mmol scale of (1R, 2R)-*N,N*-Di(4-nitrobenzyl)-*N'*-phthaloyl-1,2-diaminocyclohexane. Product **1e** was obtained as a yellow oil, yield 65 %; $[\alpha]_D^{20} = +28.9$ ($c = 1$, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.17$ (*d*, $J = 9.0$ Hz, 2H), 7.50 (*d*, $J = 9.0$ Hz, 2H), 3.87 (*d*, $J = 15.0$ Hz, 2H), 2.60 (*d*, $J = 15.0$ Hz, 2H), 2.79 (*dt*, $J = 3.0$, 9.0 Hz, 1H), 2.15 (*m*, 1H), 2.03–2.00 (*m*, 2H), 1.86–1.65 (*m*, 4H), 1.30–0.96 (*m*, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 147.3$, 147.2, 129.3, 123.7, 65.5, 35.0, 25.5, 24.8, 22.9; FT-IR (KBr): [cm^{-1}] = 3,367, 3,109, 3,078, 2,930, 2,856, 2,450, 1,734,

1,647, 1,603, 1,518, 1,492, 1,449, 1,340, 1,244, 1,175, 1,108, 1,014, 988, 959, 851, 809, 741, 699. MS (ESI) m/z calcd. for ($C_{20}H_{24}N_4O_4$) 384.43, found 384.66.

*Preparation of catalyst **1f** [66]*

The general procedure described above was followed on a 10-mmol scale of (1R, 2R)-*N,N*-Di(4-nitrobenzyl)-*N'*-phthaloyl-1,2-diaminocyclohexane. Product **1f** was obtained as a yellow oil, yield 60 %; $[\alpha]_D^{20} = -58.0$ ($c = 1$, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.65$–2.52 (*m*, 4H), 2.31–2.25 (*m*, 1H), 2.71–1.84 (*m*, 4H), 1.77–1.68 (*m*, 6H), 1.25–1.04 (*m*, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 64.1$, 52.4, 46.9, 33.8, 25.1, 24.7, 23.5, 21.4; FT-IR (KBr): [cm^{-1}] = 2,928, 2,857, 2,805, 1,665, 1,582, 1,448, 1,357, 1,292, 1,244, 1,204, 1,120, 1,088, 941, 904, 751, 660. MS (ESI) m/z calcd. for ($C_{10}H_{20}N_2$) 168.16, found 168.54.

General procedure for aldol reaction of ketones with aldehydes

A mixture of organocatalyst **1c**/TfOH (10 mol %) and ketone (0.5 mmol) were stirred in water (0.5 mL) at room temperature. Subsequently, an aldehyde (0.5 mmol) was added and the reaction mixture was stirred at room temperature. Until the reaction was judged to be complete based on TLC analysis, the mixture was partitioned between a saturated solution of ammonium chloride and dichloromethane. The organic layer was separated and dried over anhydrous Na_2SO_4. It was purified over silica gel by column chromatography to give the pure product, then examined by HPLC to determine ee value (Fig. 1).

*(2S, 10R)-2-(Hydroxy-(4-nitrophenyl)-methyl)cy-clohexan-1-one (**5a**) [67]*

Isolated yield: 81 %; dr (anti/syn) = 99:1, ee = 98 %. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 80/20), 20 °C, 254 nm, 0.5 mL/min; major enantiomer $t_R = 36.1$ min and minor enantiomer $t_R = 47.2$ min. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.21$ (*d*, $J = 8.4$ Hz, 2H), 7.51 (*d*, $J = 8.5$ Hz, 2H), 4.91 (*dd*, $J = 8.3$ Hz and $J = 3.0$ Hz, 1H), 4.09 (*d*, 1H, $J = 3.0$ Hz), 2.40–2.64 (*m*, 2 H), 2.36 (*td*, $J = 13.2$ Hz and $J = 5.7$ Hz, 1H), 2.09–2.15 (*m*, 3 H), 1.78–1.85 (*m*, 1 H), 1.54–1.65 (*m*, 4H), 1.35–1.44 (*m*, 1H).

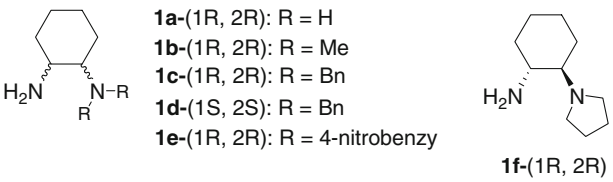


Fig. 1 The structure of the organocatalysts

*(2S, 10R)-2-(Hydroxy-(2-nitrophenyl)-methyl)cy-clohexan-1-one (**5b**) [67]*

Isolated yield: 73 %; dr (anti/syn) = 94:6, ee = 98 %. Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (hexane/2-propanol = 95/5), 20 °C, 254 nm, 0.5 mL/min; major enantiomer t_R = 47.2 min and minor enantiomer t_R = 40.8 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (*d*, *J* = 8.1 Hz, 1H), 7.77 (*d*, *J* = 7.8 Hz, 1H), 7.63 (*t*, *J* = 7.5 Hz, 1H), 7.43 (*t*, *J* = 7.8 Hz, 1H), 5.45 (*d*, *J* = 6.6 Hz, 1H), 3.90 (br, 1H), 2.82–2.70 (*m*, 1H), 2.50–2.40 (*m*, 1H), 2.34 (*td*, *J* = 12.3 Hz and *J* = 5.7 Hz, 1H), 2.15–2.06 (*m*, 1H), 1.90–1.55 (*m*, 4H).

*(2S, 10R)-2-(Hydroxy-(3-nitrophenyl)-methyl)cyc-cyclohexan-1-one (**5c**) [67]*

Isolated yield: 85 %; dr (anti/syn) = 98:2, ee = 97 %. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 80/20), 20 °C, 254 nm, 0.5 mL/min; major enantiomer t_R = 30.6 min and minor enantiomer t_R = 25.1 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.21 (*d*, *J* = 8.7 Hz, 2H), 7.51 (*d*, *J* = 8.7 Hz, 2H), 4.90 (*dd*, *J* = 8.4 Hz and *J* = 3.0 Hz, 1H), 4.09 (*d*, *J* = 3.0 Hz, 1H), 2.65–2.45 (*m*, 2H), 2.36 (*td*, *J* = 13.2 Hz and *J* = 5.7 Hz, 1H), 2.17–2.06 (*m*, 1H), 1.87–1.78 (*m,* 1H), 1.67–1.51 (*m*, 3H), 1.45–1.31 (*m*, 1H).

*(2S, 10R)-2-(Hydroxy-(2,4-dinitro-phenyl)-methyl- yl)-cyclohexan-1-one (**5d**) [67]*

Isolated yield: 75 %; dr (anti/syn) = 95:5, ee = 97 %. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 85/15), 25 °C, 254 nm, 1.0 mL/min; major enantiomer t_R = 26.3 min and minor enantiomer t_R = 29.8 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.75 (*d*, *J* = 2.4 Hz, 1H), 8.48 (*dd*, *J* = 8.4, 2.0 Hz, 1H), 8.09 (*d*, *J* = 8.8 Hz, 1H), 7.25 (*d*, *J* = 6.0 Hz, 2H), 5.06–4.90 (*d*, *J* = 8.4 Hz, 1H), 2.82–2.31 (*m*, 3H), 2.16–2.11 (*m*, 1H), 1.94–1.63 (*m*, 5H).

*(2S, 10R)-2-(Hydroxy-(4-(trifluoromethyl)phenyl) methyl)cyclohexan-1-one (**5e**) [67]*

Isolated yield: 63 %; dr (anti/syn) = 98:2, ee = 97 %. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 90/10), 21 °C, 254 nm, 0.5 mL/min; major enantiomer t_R = 27.3 min and minor enantiomer t_R = 35.1 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74–7.55 (*m*, 3H), 7.40 (*t*, *J* = 7.2 Hz, 1H), 5.30 (*d*, *J* = 9.3 Hz, 1H), 4.03 (*t*, *J* = 3.0 Hz, 1H), 2.81–2.69 (*m*, 1H), 2.55–2.45 (*m*, 1H), 2.37 (*td*, *J* = 12.9 Hz and *J* = 4.8 Hz, 1H), 2.15–2.03 (*m*, 1H), 1.81–149 (*m*, 3H), 1.48–1.23 (*m*, 1H).

*(2S, 10R)-2-(Hydroxyl(2-chlorophenyl)-methyl)cy- clohexan-1-one (**5f**) [67]*

Isolated yield: 70 %; dr (anti/syn) = 98:2, ee = 94 %. Enantiomeric excess was determined by HPLC with Chiralcel OD-H (hexane/i-PrOH = 95/5), 20 °C, 220 nm, flow rate 1.0 mL/min, major anti enantiomer t_R = 12.9 min and minor anti enantiomer t_R = 10.9 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 8.4 Hz,

1H), 7.20–7.34 (m, 3H), 5.35 (*d, J* = 8.0 Hz, 1H), 3.88 (*s*, 1H), 2.65–2.71 (*m*, 1H), 2.46–2.49 (*m*, 1H), 2.31–2.39 (*m*, 1H), 2.05– 2.13 (*m*, 1H), 1.53–1.84 (*m*, 5H).

*(2S, 10R)-2-(Hydroxy-(4-chlorophenyl)-methyl)cy-clohexan-1-one (**5g**) [67]*

Isolated yield: 55 %; dr (anti/syn) = 95:5, ee = 95 %. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 90/10), 21 °C, 220 nm, 0.5 mL/min; major enantiomer t_R = 34.2 min and minor enantiomer t_R = 40.7 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29 (*dd*, *J* = 20.4 Hz and *J* = 8.4 Hz, 4H), 4.76 (*dd*, *J* = 8.7 Hz and *J* = 2.7 Hz, 1H), 3.99 (*d*, *J* = 3.0 Hz, 1H), 2.61–2.44 (*m*, 2H), 2.35 (*td*, *J* = 12.9 Hz and *J* = 5.4 Hz, 1H), 2.15–2.05 (*m*, 1H), 1.85–1.75 (*m*, 1H), 1.70–1.50 (*m*, 3H), 1.37–1.20 (*m*, 1H).

*(2S, 10R)-2-(Hydroxy-(4-cyanophenyl)-methyl)cy-clohexan-1-one (**5h**) [67]*

Isolated yield: 75 %; dr (anti/syn) = 99:1, ee = 97 %. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 80/20), 20 °C, 254 nm, 0.5 mL/min; major enantiomer t_R = 36.7 min and minor enantiomer t_R = 46.5 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65 (*d*, *J* = 8.1 Hz, 2H), 7.45 (*d*, *J* = 8.1 Hz, 2H), 4.85 (*dd*, *J* = 8.1 Hz and *J* = 3.0 Hz, 1H), 4.11 (*d*, *J* = 3.0 Hz, 1H), 2.65–2.44 (*m*, 2H), 2.37 (*td*, *J* = 12.9 Hz and *J* = 6.0 Hz, 1H), 2.17–2.06 (*m*, 1H), 1.88–1.77 (*m*, 1H), 1.72–1.47 (*m*, 3H), 1.44–1.31 (*m*, 1H).

*(2S, 10R)-2-(Hydroxy-(4-bromophenyl)-methyl)c-yclohexan-1-one (**5i**) [67]*

Isolated yield: 62 %; dr (anti/syn) = 94:6, ee = 94 %. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 90/10), 20 °C, 220 nm, 0.8 mL/min; major anti enantiomer t_R = 21.1 min and minor anti enantiomer t_R = 25.4 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 (*d*, *J* = 8.1 Hz, 2H), 7.20 (*d*, *J* = 8.7 Hz, 2H), 4.75 (*dd*, *J* = 8.7 Hz and *J* = 2.7 Hz, 1H), 3.99 (*d*, *J* = 3.0 Hz, 1H), 2.61–2.44 (*m*, 2H), 2.35 (*td*, *J* = 12.9 Hz and *J* = 6.3 Hz, 1H), 2.15–2.04 (*m*, 1H), 1.85–1.75 (*m*, 1H), 1.70–1.50 (*m*, 3H), 1.37–1.20 (*m*, 1H).

*(2S, 10R)-2-(Hydroxy-(4-fluor-phenyl)-methyl)-cy-clohexan-1-one (**5j**) [67]*

Isolated yield: 50 %; dr (anti/syn) = 95:5, ee = 97 %. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 95/5), 20 °C, 220 nm, 1.0 mL/min; major enantiomer t_R = 25.3 min and minor enantiomer t_R = 29.2 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55–7.45 (*d*, *J* = 8.4 Hz, 2H), 7.20–7.15 (*d*, *J* = 8.4 Hz, 2H), 4.85–4.75 (*d*, *J* = 8.7 Hz, 1H), 2.60–2.30 (*m*, 3H), 2.20–2.00 (*m*, 1H), 1.85–1.50 (*m*, 5H), 1.40–1.20 (*m*, 1H).

*(2S, 10R)-2-(Hydroxy-(3-methoxy-phenyl)-methy-l)-cyclohexan-1-one (**5k**) [67]*

Isolated yield: 55 %; dr (anti/syn) = 95:5, ee = 98 %. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 90/10),

25 °C, 220 nm, 0.5 mL/min; major enantiomer t_R = 58.1 min and minor enantiomer t_R = 52.5 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28–7.33 (*m*, 1H), 6.80–7.00 (*m*, 3H), 4.75–4.85 (*d*, *J* = 8.7 Hz, 1H), 3.85 (*s*, 3H), 2.30–2.75 (*m*, 3H), 2.00–2.15 (*m*, 1H), 1.55–1.90 (*m*, 4H), 1.20–1.40 (*m*, 1H).

*(2S, 10R)-2-(Hydroxy-(1-naphthyl)-methyl)cycloh-exan-1-one (**5l**) [67]*

Isolated yield: 42 %; dr (anti/syn) = 97:3, ee = 96 %. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 95/5), 20 °C, 254 nm, 1.0 mL/min; major enantiomer t_R = 45.0 min and minor enantiomer t_R = 36.7 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70–7.90 (*m*, 4H), 7.40–7.55 (*m*, 2H), 4.90–5.05 (*d*, *J* = 8.7 Hz, 1H), 2.65–2.75 (*m*, 1H), 2.30–2.60 (*m*, 2H), 2.00–2.20 (*m*, 1H), 1.20–1.80 (*m*, 5H).

*(2S, 10R)-2-(Hydroxy-(phenyl)-methyl)cyclohexa-n-1-one (**5m**) [67]*

Isolated yield: 65 %; dr (anti/syn) = 92:8, ee = 97 %. Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (hexane/2-propanol = 90/10), 20 °C, 220 nm, 0.5 mL/min; major enantiomer t_R = 29.3 min and minor enantiomer t_R = 21.1 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.24 (*m*, 5H), 4.80 (*d*, *J* = 9.0 Hz, 1H), 4.00 (*m*, 1H), 2.70–2.56 (*m*, 1H), 2.55–2.44 (*m*, 1H), 2.34 (*td*, *J* = 12.3, 5.4 Hz, 1H), 2.16–2.03 (*m*, 1H), 1.87–1.73 (*m*, 1H), 1.72–1.50 (*m*, 3H), 1.40–1.22 (*m*, 1H).

*(2S, 10R)-2-(Hydroxy-(4-nitrophenyl)-methyl)-cyc-lopentan-1-one (**5n**) [67]*

Isolated yield: 50 %; dr (anti/syn) = 89:11, ee = 88 %. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 95/5), 20 °C, 254 nm, 1.0 mL/min; major enantiomer t_R = 63.2 min, minor enantiomer t_R = 67.2 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.21 (*d*, *J* = 8.7 Hz, 2H), 7.54 (*d*, *J* = 9.0 Hz, 2H), 4.85 (*d*, *J* = 9.0 Hz, 1H), 4.74 (*s*, 1H), 2.54–2.18 (*m*, 3H), 2.08–1.95 (*m*, 1H), 1.81–1.48 (*m*, 3H).

*(2S, 10R)-2-(Hydroxy(4-nitrophenyl)methyl)-4-methylcyclohexan-1-one (**5o**) [67]*

Isolated yield: 60 %; dr (anti/syn) = 99:1, ee (anti) = 94 %, Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 90/10), 20 °C, 254 nm, 1.0 mL/min; major enantiomer t_R = 24.1 min, minor enantiomer t_R = 23.2 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18–8.23 (*m*, 2H), 7.47–7.52 (*m*, 2H), 4.92 (*d*, *J* = 8.6 Hz, 1H), 3.82 (*br*, 1H), 2.72–2.78 (*m*, 1H), 2.48–2.50 (*m*, 1H), 2.36–2.43 (*m*, 1H), 2.07–2.09 (*m*, 1H), 1.89–1.93 (*m*, 1H), 1.78–1.81 (*m*, 1H), 1.54–1.60 (*m*, 1H), 1.33 (*m*, 1H), 1.05 (*d*, *J* = 6.9 Hz, 3H).

The characterizations of Mannich product [68]

Compound: a white solid; t_r (major) = 10 min, t_r (minor) = 11 min (Chiralcel AD-H, λ = 254 nm, *i*-PrOH/Hexanes = 20:80, flow rate = 1 mL/min); ^{1}H NMR

(300 MHz, $CDCl_3$) $\delta = 2.17$ (*s*, 3H), 2.36 (*s*, 3H), 4.57 (*s*, 1H), 4.90–4.93 (*d*, 1H), 5.73–5.76 (*d*, 1H), 7.08–7.15 (*m*, 4H), 7.38–7.41 (*d*, 2H), 7.46–7.49 (*d*, 2H), ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.25$, 26.10, 58.97, 79.87, 126.85, 127.79, 129.41, 130.37, 132.16, 138.55, 142.64, 209.63. MS (ESI) m/z: calcd. for: $C_{17}H_{18}N_2O_6S$ 378.09, found 378.40.

General procedure for large-scale aldol reactions

Method A: A mixture of organocatalyst **1c**/TfOH (10 mol %) and ketone (20 mmol) was stirred in the presence of water (20 mL) at room temperature. *Method B*: A mixture of organocatalyst **1c** (10 mol %), ketone (40 mL), and TfOH (10 mol %) was stirred without solvent at room temperature. To this, an aldehyde (20 mmol) was added after 30 min and the reaction mixture was stirred and the progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was partitioned between a saturated solution of ammonium chloride and dichloromethane. The organic layer was separated and dried over anhydrous Na_2SO_4. It was purified over silica gel by column chromatography to obtain the pure product. The chromatography purified aldol products were then examined by HPLC to determine ee value.

General procedure for Mannich reaction of hydroxyacetone with *N*-tosylimine

A mixture of organocatalyst **1c**/TfOH (10 mol%) and *N*-tosylimine (0.25 mmol) was stirred in MeOH (1 mL) at room temperature. To this, a hydroxyacetone (1 mmol) was added after 30 min and the reaction mixture was stirred and the progress of the reaction was monitored by TLC. After completion of the reaction, an amount of ethyl acetate and a few drops of dilute hydrochloric acid were added. It was purified over silica gel by column chromatography to obtain the pure product. The chromatography purified Mannich products were then examined by HPLC to determine ee value.

General procedure for large-scale Mannich reactions

A mixture of organocatalyst **1c**/TfOH (10 mol%) and *N*-tosylimine (20 mmol) was stirred in CH_3OH (80 mL) at room temperature. To this, a hydroxyacetone (80 mmol) was added after 30 min and the reaction mixture was stirred and the progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was partitioned between a saturated solution of ammonium chloride and dichloromethane. The organic layer was separated and dried over anhydrous Na_2SO_4. It was purified over silica gel by column chromatography to obtain the pure product. The chromatography purified aldol products were then examined by HPLC to determine ee value.

Results and discussion

In this work, a series of novel diamines (**1c–f**) and a known diamine (**1b**) were synthesized by coupling of bromides and phthalic anhydride monoprotected (1S,

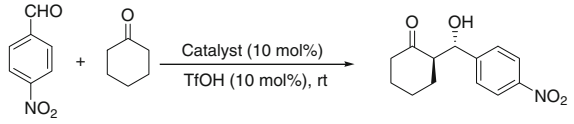
2S)- and (1R, 2R)-cyclohexyldiamine followed by deprotection with NH_2NH_2/EtOH, easily prepared in a few steps from inexpensive, commercially available, enantiopure materials.

The catalytic activities for the asymmetric direct aldol reaction were investigated by performing a model reaction using 4-nitrobenzaldehyde with cyclohexanone in the presence of water (Method A) and under solvent-free conditions with conventional magnetic stirring (Method B) at room temperature (Table 1). As depicted in Table 1 (entries 5, 6), catalyst **1c** exhibited high catalytic efficiency, whereas the different steric configuration **1a–b** and **1d–f** showed lower diastereoselectivities, which suggested that the steric property is essential to maximize the diastereoselectivities. The catalyst **1e**, having an electron-withdrawing group in the aromatic ring, afforded **5a** with good enantioselectivity on the one hand, but low yield and moderate diastereoselectivity on the other hand (Table 1, entries 9 and 10). Therefore, we chose **1c** as a catalyst for the aldol reaction. Using **1c** as catalyst, the effects of catalyst loading on the reaction of 4-nitrobenzaldehyde and cyclohexanone were investigated (Table 1, entries 13 and 16). When 5 mol% **1c** was used in the presence of water (Methods A and B), the aldol product could be obtained in low yield and moderate diastereoselectivities. When 1 equiv of cyclohexanone was used, the diastereoselectivity and enantioselectivity were not changed in the presence of water (Method A) or under solvent-free conditions (Method B) (Table 1, entries 15 and 17). The amount of solvent was also investigated: when 1 mL of water was used, the poor dr and ee value were obtained (entry 14). When 1 mL of cyclohexanone was used, the aldol product could be obtained in high yield with good stereoselectivity under solvent-free conditions (entry 18).

Considerations of stereoselectivity and reaction time led us to focus our next study under the optimal reaction conditions for Methods A and B, as follows: Method A: ketone (0.5 mmol), aldehyde (0.5 mmol), **1c**/TfOH (10 mol %) and H_2O (0.5 mL) at room temperature; Method B: ketone (1 mL), aldehyde (0.5 mmol), **1c**/TfOH (10 mol %) at room temperature. Under these conditions, the direct cross-aldol reaction of other several acceptor aromatic aldehydes with cyclohexanone was examined in order to study the reaction scope using water as solvent and under solvent-free conditions (Table 2). It can be seen that a wide range of aromatic aldehydes can effectively participate in the aldol reactions. From Table 2, we were able to access aldol adducts **5a–l** derived from their corresponding aromatic aldehydes and cyclohexanone. In general, the reactions between cyclohexanone and aromatic aldehydes bearing electron-withdrawing substituents furnished β-hydroxy carbonyl aldol products in good yields (63–98 %) and enantioselectivities (96–98 % ee for anti-isomer) within 15–80 h (Table 2, entries 1–10, 15, 16). In contrast, longer reaction times were required for aromatic aldehydes containing an electron-donating group to give comparatively lower yields (42–87 %), but without decrease of enantioselectivities. This can be explained in that electron-withdrawing groups enhance the electrophilicity of carbonyl carbons in aldehydes which facilitates the reaction, while electron-donating groups lessen the electrophilicity.

We also checked the aldol reactions of other ketones (4-methylcyclohexanone, cycloheptanone) with aromatic aldehydes using catalyst **1c** (10 mol%) (Table 3). The 4-methylcyclohexanone gave high diastereoselective and good enantioselective

Table 1 Aldol reaction of cyclohexanone with 4-nitrobenzaldehyde catalyzed by **1** in the presence of water (Method A) and under solvent-free conditions (Method B)



Entry	Catalyst	Method	Yield (%)[a]	Anti/syn[b]	ee[c]
1	**1a**	A	84	75:25	91
2	**1a**	B	55	77:23	85
3	**1b**	A	60	88:12	94
4	**1b**	B	87	83:17	95
5	**1c**	A	83	99:1	98
6	**1c**	B	75	94:6	95
7	**1d**	A	81	78:22	−96
8	**1d**	B	85	83:17	−95
9	**1e**	A	17	83:17	94
10	**1e**	B	34	81:19	92
11	**1f**	A	60	97:3	94
12	**1f**	B	65	82:18	96
13[d]	**1c**	A	50	93:7	98
14[f]	**1c**	A	72	98:2	97
15[e]	**1c**	A	81	99:1	98
16[d]	**1c**	B	55	93:7	92
17[e]	**1c**	B	70	95:5	95
18[g]	**1c**	B	93	99:1	98

Method A: cyclohexanone (1 mmol), aldehyde (0.5 mmol), catalyst/TfOH (0.05 mmol), solvent (0.5 mL) at room temperature. *Method B*: cyclohexanone (1 mmol), aldehyde (0.5 mmol), catalyst/TfOH (0.05 mmol) at room temperature

[a] The combined isolated yield of the diastereomers

[b] Determined by chiral HPLC analysis, major product is anti

[c] Determined by HPLC analysis of the anti product

[d] 5 mmol% **1c**/TfOH was used

[e] Cyclohexanone(0.5 mmol) was used

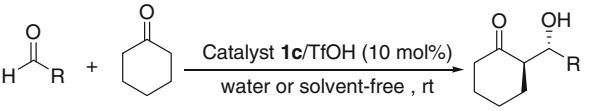
[f] 1 mL H_2O was used

[g] Cyclohexanone(1 mL) was used

(Table 3, entries 3 and 4). When cyclopentanone was used as an aldol donor, a good yield of (58–97 %) with moderate ee (84–90 %) for the anti-isomer was received; however, the diastereomeric ratio obtained was only (85/15–89/11) anti/syn (Table 3, entries 1 and 2).

We also investigated the asymmetric direct two-component Mannich reactions of hydroxyacetone to *N*-tosylimine in toluene (Table 4). A solvent screening (entries 1–7) was then performed to identify the best reaction conditions. Among the various

Table 2 Results of reaction of various aldehydes with cyclohexanone catalyzed by **1c** in the presence of water (Method A) and under solvent-free conditions (Method B)



3 **4a** **5**

Entry	*R*	Product	Method	Time (h)	Yield (%)[a]	Anti/syn[b]	ee (%)[c]
1	**4-NO_2-C_6H_4**	**5a**	A	50	81	99/1	98
2	**4-NO_2-C_6H_4**	**5a**	B	35	93	99/1	98
3	**2- NO_2-C_6H_4**	**5b**	A	50	73	94/6	98
4	**2- NO_2-C_6H_4**	**5b**	B	46	89	98/2	98
5	**3- NO_2-C_6H_4**	**5c**	A	55	85	98/2	97
6	**3- NO_2-C_6H_4**	**5c**	B	46	93	98/2	97
7	**2,4-$(NO_2)_2$-C_6H_4**	**5d**	A	55	75	95/5	97
8	**2,4-$(NO_2)_2$-C_6H_4**	**5d**	B	15	98	98/2	96
9	**4-CF_3-C_6H_4**	**5e**	A	80	63	98/2	97
10	**4-CF_3-C_6H_4**	**5e**	B	64	83	98/2	98
11	**2-Cl-C_6H_4**	**5f**	A	90	70	98/2	94
12	**2-Cl-C_6H_4**	**5f**	B	84	78	99/1	97
13	**4-Cl-C_6H_4**	**5g**	A	96	55	95/5	95
14	**4-Cl-C_6H_4**	**5g**	B	84	71	80/20	94
15	**4-CN-C_6H_4**	**5h**	A	72	75	99/1	97
16	**4-CN-C_6H_4**	**5h**	B	72	87	93/7	98
17	**4-Br-C_6H_4**	**5i**	A	96	62	94/6	94
18	**4-Br-C_6H_4**	**5i**	B	96	87	93/7	94
19	**4-F-C_6H_4**	**5j**	A	96	50	95/5	97
20	**4-F-C_6H_4**	**5j**	B	96	68	96/4	95
21	**3-MeO-C_6H_4**	**5k**	A	96	55	95:5	98
22	**3-MeO-C_6H_4**	**5k**	B	96	70	89:11	90
23	**1-naphthyl**	**5l**	A	96	42	97/3	96
24	**1-naphthyl**	**5l**	B	72	78	95/5	90

Method A: cyclohexanone (0.5 mmol), aldehyde (0.5 mmol), catalyst/TfOH (0.05 mmol), water (0.5 mL) at room temperature. *Method B*: cyclohexanone (1 mL), aldehyde (0.5 mmol), catalyst/TfOH (0.05 mmol) at room temperature

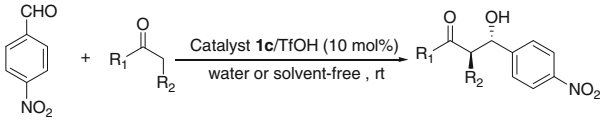
[a] The combined isolated yield of the diastereomers

[b] Determined by ^{1}H NMR of the crude product and by HPLC

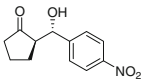
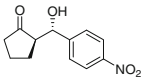
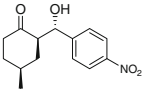
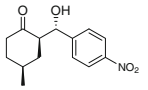
[c] Determined by chiral HPLC

organic solvents tested, the aprotic solvent obtained satisfactory results, CH_3OH was found to be the best solvent with good yield (up to 95 %), diastereoselectivities (up to 93:7), and enantioselectivity (up to 97 %) (entry 3). Then, we investigated the effects of catalyst loading on the reactions of hydroxyacetone with *N*-tosylimine. While the use of a relatively large amount (20 mol%) of inexpensive catalyst **1c** in

Table 3 Reactions of cyclopentanone and 4-methylcyclohexanone with *p*-nitrobenzaldehyde by **1c**



3a **4** **5**

Entry	Product	No.	Method	Yield (%)[a]	dr[b]	ee (%)[c]
1		**5m**	A	58	89:11	88
2		**5m**	B	97	85:15	90
3		**5n**	A	60	99:1	94
4		**5n**	B	89	98:2	96

Method A: ketones (0.5 mmol), aldehyde (0.5 mmol), catalyst/TfOH (0.05 mmol), solvent (0.5 mL) at room temperature. *Method B*: ketones (1 mL), aldehyde (0.5 mmol), catalyst/TfOH (0.05 mmol) at room temperature

[a] The combined isolated yield of the diastereomers

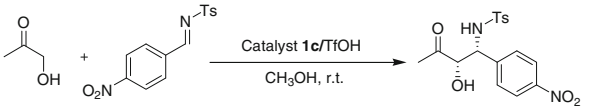
[b] Determined by chiral HPLC analysis, major product is anti

[c] Determined by HPLC analysis of the anti product

our original study may be justified, reducing catalyst loading would certainly constitute an improvement. Noticeably, when using 10–20 mol% of catalyst **1c**, the reaction was faster but the diastereoselectivity was lower than in the other cases (entries 3, 8). When the loading of catalyst **1c** was reduced to 2 mol% and the amount of CH_3OH was reduced to 1 mL, a good yield (85 %) and a high diastereoselective (up to 99:1) and enantioselective (up to 99 %) were obtained.

Asymmetric synthesis is dedicated to the preparation of chiral compounds with defined three-dimensional molecular structures. Its importance is probably best appreciated in the context of drug–receptor interactions, because most biological targets are chiral entities. Because of the synthetic versatility of amino carbonyl compounds, it is of great interest to generate Mannich products with either syn- or anti-selectivity. In the process of screening solvents, we found an interesting phenomenon: when using CH_3OH as a solvent, the absolute configuration of the syn-Mannich product was determined to be (*3S, 4R*), then the use of CH_3CN or *n*-butanol instead of CH_3OH, the absolute configuration of the anti-Mannich product was determined to be (*3R,4R*) (Table 5) (See Supplementary Material).

Table 4 Screening of the asymmetric Mannich reactions between hydroxyacetone and *N*-tosylimine



Entry	Catalyst	Solvent	Yield (%)[a]	dr (syn/anti)[b]	ee (syn)[c]
1	10	*m*-xylene	75	52:48	66
2	10	Dioxane	95	52:48	53
3	10	CH_3OH	95	93:7	97
4	10	$CHCl_3$	70	63:37	61
6	10	DMF	94	92:8	97
7	10	EtOH	90	97:3	96
8	20	CH_3OH	98	91:9	95
9	5	CH_3OH	90	95:5	97
10	2	CH_3OH	80	98:2	99
11[d]	2	CH_3OH	85	99:1	99

The reactions were performed with hydroxyacetone (1 mmol), *N*-tosylimine (0.25 mmol) and catalyst **1c** (0.025 mmol) in solvent (2 ml) at room temperature

[a] Isolated yield

[b] The syn to anti ratio was determined by ^{1}H NMR analysis of the crude products and by HPLC

[c] The ee value of the syn-isomer was determined by chiral HPLC analysis

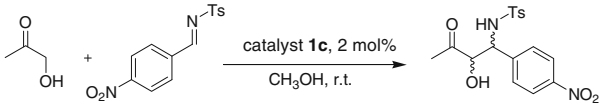
[d] 1 mL CH_3OH was used

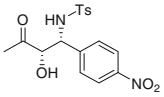
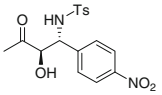
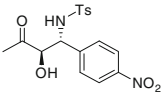
Such a switch of the diastereoselectivities of a given catalyst by changes in the solvent is unusual. It suggests that the conformation of the chiral amine catalyst is significantly different in the solvents leading to the formation of different chiral products, which offers a great possibility for obtaining different chiral amino alcohols.

We first performed a large-scale asymmetric direct two-component syn-Mannich reaction with 25 mmol of *N*-tosylimine, and 4 equiv of hydroxyacetone (Fig. 2) using a 250-mL round-bottomed flask. Although the diastereoselectivity and enantioselectivity (83 % yield, 99 % ee, 99:1 dr) were maintained at the same level for the large-scale reaction, the main limitation associated with syn-Mannich reaction is the requirement of a low catalyst loading of **1c**/TfOH (0.44 g, 2 mol%). This will raise a cost concern when large amounts of chiral materials are used for a large-scale synthesis in practical applications.

We further performed large-scale asymmetric aldol reactions, as follows: Method A: ketone (20 mmol), aldehyde (20 mmol), **1c**/TfOH (10 mol%) and H_2O (20 mL) at room temperature; Method B: ketone (40 mL), aldehyde (20 mmol), **1c**/TfOH (10 mol%) at room temperature. The large-scale experiments can be readily carried out using the same procedure as for the experimental scale reactions. As can be seen from the results summarized in Table 6, delightfully, the enantioselectivity was maintained at the same level for the large-scale reactions.

Table 5 Direct asymmetric Mannich reactions hydroxyacetone and *N*-tosylimine in various solvents, catalyzed by **1c**



Entry	Product	Solvent	Yield (%)[a]	dr (anti/syn)[b]	ee (%)[c]
1		CH_3OH	85	1:99	99
2		CH_3CN	70	68:32	72
3		*n*-Butanol	80	65:35	70

The reactions were performed with hydroxyacetone (1 mmol), *N*-tosylimine (0.25 mmol) and catalyst **1c** (0.005 mmol) in the solvent (1 ml) at room temperature

[a] Isolated yield

[b] The anti to syn ratio was determined by ^{1}H NMR analysis of the crude products and by HPLC

[c] The ee value was determined by chiral HPLC analysis

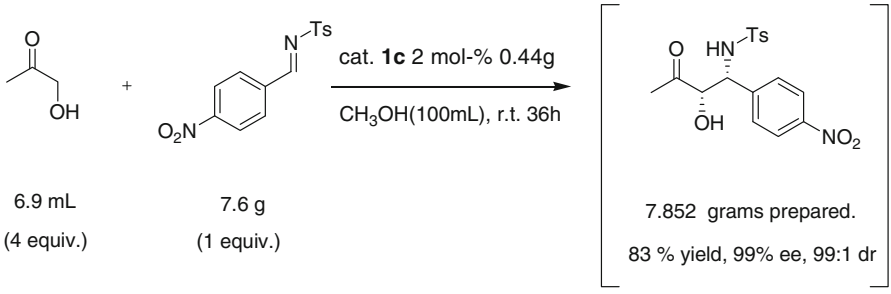
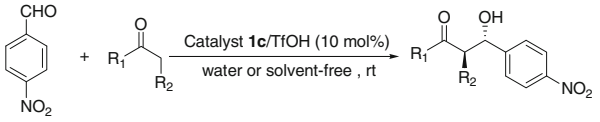


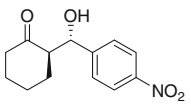
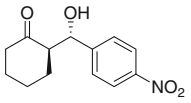
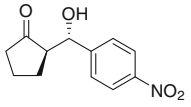
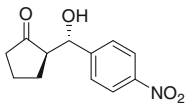
Fig. 2 Large-scale example of enantioselective syn-Mannich reaction

Conclusion

In summary, the catalysts can be easily prepared in a few steps from inexpensive, commercially available, enantiopure materials. The diamine **1c** is a robust and effective catalyst for direct aldol reactions with high diastereo- and enantioselectivities in the presence of water and under solvent-free conditions, which meet the demand of atom-economical and green chemistry. It was also used to catalytic

Table 6 Large-scale asymmetric aldol reactions



Entry	Product	Method	Time (h)	Yield (%)[a]	Anti/syn[b]	ee (%)[c]
1		A	50	78	>99:1	>98
2		B	50	83	92:8	98
3		A	50	51	93:7	88
4		B	50	85	80:20	89

Method A: ketones (20 mmol), aldehyde (20 mmol),catalyst **1c**/TfOH (2 mmol), solvent (20 mL) at room temperature. *Method B*: ketones (40 mL), aldehyde (20 mmol), catalyst **1c**/TfOH (2 mmol) at room temperature

[a] The combined isolated yield of the diastereomers

[b] Determined by chiral HPLC analysis, major product is anti

[c] Determined by HPLC analysis of the anti product

asymmetric two-component syn-Mannich reaction with good results. Notably, these organocatalyzed direct asymmetric anti-aldol and syn-Mannich reactions can be performed on a large scale with the enantioselectivity being maintained at the same level, which offers a great possibility for application in industry.

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