A Novel Chiral Aliphatic–Aromatic Diamine Promoted Direct, Highly Enantio- and Diastereoselective Michael Addition of Cyclohexanone to Nitroolefins Under Solvent-Free Conditions

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ABSTRACT A series of new highly efficient chiral aliphatic–aromatic diamine catalysts have been designed and successfully applied to the asymmetric Michael addition of cyclohexanone with nitroolefins under solvent-free conditions without any acidic additives. The desired adducts were obtained in high yields with excellent enantio- and diastereoselectivities of *syn* products (up to >99% ee, >99:1 dr). *Chirality 22:855–862, 2010.* © 2010 Wiley-Liss, Inc.

KEY WORDS: aliphatic–aromatic diamine; asymmetric; Michael addition; nitroolefin; solvent free

INTRODUCTION

Very recently, much attention has been paid to asymmetric reactions using small organic molecules as catalysts, which is mainly due to environmental concern where use of metals in the reactions would be avoided.[1–9] The Michael addition reaction represents one of the most general and versatile methods for carbon–carbon bonds formation in modern synthetic organic chemistry.[10–12] Among the variants of asymmetric conjugate additions,[13] nitroolefin-dependent Michael reactions are of special interest as these processes are the vital steps in the formations of amine, nitrile oxide, ketone, carboxylic acid, etc., which are recognized as synthetically interesting compounds.[14,15] In recent years, a great deal of effort has gone into the optimization of the structure of the chiral catalyst so as to achieve excellent selectivity and catalytic activity.[16–26] Of the developed organocatalysts in asymmetric catalysis, chiral diamines[27–35] derived from natural amino acids and cinchona alkaloids, which contain primary–secondary, primary–tertiary, secondary–secondary, and secondary–tertiary diamine catalysts, have proven to be powerful and been applied successfully to asymmetric catalytic Michael additions.

To the best of our knowledge, the recent inspiring successful applications of diamines in the enamine catalytic[36,37] conjugate addition of ketones or aldehydes with nitroolefins were almost aliphatic–aliphatic diamines. Only few examples[38] were described for the use of aliphatic–aromatic diamine catalysts in the conjugate addition of ketones or aldehydes to nitroolefins to date. As List[39] and Barbas'[40] pioneering works of the organcatalytic asymmetric Michael addition of ketone with nitroolefins, the cyclic five-membered secondary amine structure is now regarded as one of the "privileged" backbones in the design of organocatalysts.[17] Therefore, in this article, we disclose such a set of new diamine catalysts (Fig. 1), which comprise of the chiral pyrrolidine unit covalently adhered to aromatic amine moiety, so that the former could activate the donor ketone through forming enamine intermediate and the latter chiral-induce the acceptor β-nitroolefin via N—H hydrogen bonding and steric hindrance.

EXPERIMENTAL SECTION

General

Analytical thin layer chromatography was performed using glass plates precoated with 200–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Silica gel (200–400 mesh) and HG silica gel from Yantai Silica Gel Factory were used for chromatography. IR spectra were recorded on a Varian FT-1000 spectrophotometer using KBr optics. NMR spectra were recorded on Varian Inova-400 or Varian System-300 NMR spectrometer. High resolution mass spectra (HRMS) were obtained using MicroMass TOF-MS spectrometer (EI). Optical rotations were measured at 589 nm (Na D line) on a Autopol V Automatic polarimeter. The enantiomeric excesses of the products were determined by HPLC analysis on a Chiralpak AS-H or AD-H column using 2-propanol/hexane as the eluent.

Material

Commercial reagents were used as received, unless otherwise stated. All reactions unless otherwise noted were

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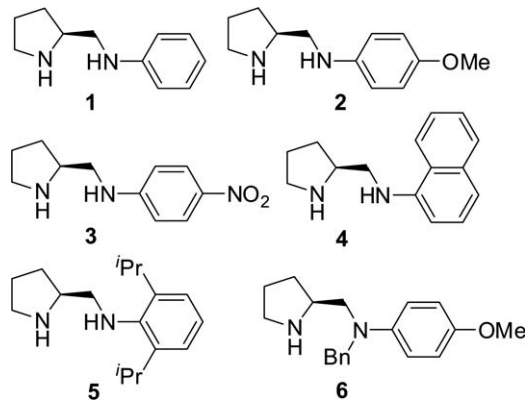


Fig. 1. Evaluated aliphatic–aromatic diamine catalysts.

carried out directly under air. THF was dried and distilled from sodium benzophenone under nitrogen just before use. Catalyst **1** is commercially available, catalysts **2**,[41] **3**,[38] and **4**[42] are known, which were prepared according to the literature methods or modification of the known procedures. The trans-substituted nitroolefins were synthesized according to the known procedure.[42–45]

Preparation of Pyrrolidine–Aromatic Diamine Bifunctional Organocatalysts 3, 5, and 6

(*S*)-4-Nitro-*N*-(pyrrolidin-2-ylmethyl)aniline (3). (*S*)-*N*-(4-nitrophenyl)pyrrolidine-2-carboxamide (**10**) was prepared from L-proline, according to the literature procedures,[46] which was directly subjected to the next step without further purification.

To a suspension of **10** (0.48 g, 2 mmol) and $NaBH_4$ (1.14 g, 30 mmol) in THF (40 mL) in an ice-water bath was added acetic acid (1.72 mL, 30 mmol) in THF (8 mL). The reaction mixture was then refluxed for 6 h. The solvent was removed and the residue was dissolved in chloroform (50 mL), washed with water, dried over anhydrous K_2CO_3, and concentrated.[47] The residue was dissolved in THF (80 mL) and 6 *N* HCl (8 mL) was added dropwise at 0°C. After refluxing for 8 h, the reaction mixture was cooled to 0°C, and water (10 mL) was added under stirring. The mixture was basified with 4 *N* NaOH solution and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried with anhydrous K_2CO_3, filtered and concentrated. The crude product was purified by column chromatography on silica gel (EtOAc/MeOH = 15/1) to give a yellow solid diamine **3** (0.15 g, 33%).[32] ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.11 (d, J = 9.2 Hz, 2H), 6.65 (d, J = 9.2 Hz, 2H), 5.02 (brs,1H), 3.88 (brs, 1H), 3.73–3.61 (m, 1H), 3.50–3.21 (m, 3H), 2.99 (dq, J = 8.1, 16.3 Hz, 1H), 2.32–2.18 (m, 1H), 2.15–1.98 (m, 1H), 1.98–1.80 (m, 1H), 1.77–1.62 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d^6) δ: 154.25, 136.08, 126.31, 110.90, 63.82, 54.27, 43.74, 29.25, 22.45 ppm.

(*S*)-2,6-Diisopropyl-*N*-(pyrrolidin-2-ylmethyl)aniline (5). (*S*)-*N*-(2,6-diisopropyl-phenyl) pyrrolidine-2-carboxamide (**14**) was synthesized from L-proline, according to the known methods,[46,48] which was directly subjected to the next step without further purification.

Compound **14** (4.80 g, 17.5 mmol) in THF (20 mL) was slowly added to a THF (40 mL) suspension of $LiAlH_4$ (2.0 g, 52.5 mmol) at 0°C under an argon atmosphere and the mixture was refluxed for 18 h. Then saturated Na_2SO_4 solution was added to the mixture at 0°C. After removal of the inorganic material by filtration, the filtrate was dried with anhydrous K_2CO_3. Removal of the solvent in vacuo and purification from column chromatography to afford **5** as a rufous oil (3.28 g, 72%).[49,50] ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.13–7.00 (m, 3H), 3.43–3.24 (m, 3H), 2.96 (t, J = 6.7 Hz, 2H), 2.85 (dd, J = 4.6, 11.5 Hz, 1H), 2.73 (dd, J = 8.3, 11.5 Hz, 1H), 2.39–1.49 (m, 5H), 1.43 (dt, J = 6.1, 12.2 Hz, 1H), 1.24 (d, J = 6.8 Hz, 12H) ^{13}C NMR (75 MHz, $CDCl_3$) δ: 143.62, 142.57, 123.67, 123.63, 58.96, 56.65, 46.69, 29.65, 27.70, 26.07, 24.45 ppm; IR (film) v_{max}: 3343, 3061, 2961, 2868, 1685, 1590, 1458, 1362, 1256, 1112 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{28}N_2$ 260.2252, found: 260.2257; $[\alpha]_D^{25}$ = +26.2 (c = 1.02, CH_2Cl_2).

(*S*)-*N*-benzyl-4-methoxy-*N*-(pyrrolidine-2-ylmethyl)aniline (**6**) was prepared according to the procedure described above (46% yield, colorless oil). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.34–7.14 (m, 5H), 6.83–6.68 (m, 4H), 4.63–4.46 (m, 2H), 3.73 (s, 3H), 3.50–3.23 (m, 3H), 3.01–2.79 (m, 2H), 2.36 (brs, 1H), 1.96–1.62 (m, 3H), 1.46–1.30 (m, 1H) ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.56, 143.29, 138.93, 128.25, 126.71, 126.48, 114.90, 114.45, 57.19, 57.09, 56.17, 55.37, 45.97, 29.30, 24.70. ppm; IR (film) v_{max}: 2954, 2870, 1513, 1452, 1242, 1042 cm^{-1}; HRMS calcd for $C_{19}H_{24}N_2O$ 296.1889, found: 296.1889; $[\alpha]_D^{25}$ = +14.7 (c = 1.02, CH_2Cl_2).

General Procedure for the Michael Addition of Cyclohexanone to Nitroolefins Catalyzed by Chiral Diamine 5

To a solution of cyclohexanone (0.62 mL, 6.0 mmol, 20 eq) and nitroolefin (0.3 mmol) was added catalyst **5** (7.8 mg, 10 mol%). The resulting mixture was stirred at room temperature. After the reaction was completed (monitored by TLC), the mixture was purified by column chromatography (eluent: petroleum ether/AcOEt = 10/1 to 5/1) to give the desired product.

Relative and absolute configurations of the products were determined by comparison with the known ^{1}H NMR, chiral HPLC analysis, and optical rotation values. Compounds reported in Table 2 are all known in the literatures.[14,16,17,32,51]

(*S*)-2-((*R*)-2-Nitro-1-phenylethyl)cyclohexanone (18a).[14] White solid, 99% yield; *syn/anti* = 98/2, ee (major) = 97%, determined by HPLC analysis (Chiralpak AS-H, *i*-PrOH/hexane = 10/90, flow rate 10 mL/min, λ = 210.5 nm, t_r (minor) = 8.92 min, t_r (major) = 12.17 min; $[\alpha]_D^{25}$ = –18.1 (c = 0.23, CH_2Cl_2) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.36–7.27 (m, 3H), 7.20–7.15 (m, 2H), 4.95 (dd, J = 4.5, 12.5 Hz, 1H), 4.63 (dd, J = 10.0, 12.5 Hz, 1H), 3.81–3.72 (m, 1H), 2.75–2.64 (m, 1H), 2.53–2.34 (m, 2H), 2.15–2.03 (m, 1H), 1.83–1.50 (m, 4H), 1.24 (qd, J = 3.5, 12.1 Hz, 1H).

(*S*)-2-((*R*)-1-(4-Chlorophenyl)-2-nitroethyl)cyclohexanone (18b).[32] White solid, 92% yield; *syn/anti* > 99:1, ee (major) = 99%, determined by HPLC analysis (Chiralpak AS-H, *i*-PrOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 210.5 nm, t_r (minor) = 19.37 min, t_r (major) = 22.11 min; $[\alpha]_D^{25}$ = –14.3 (*c* = 0.64, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.30 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 4.93 (dd, *J* = 4.5, 12.6 Hz, 1H), 4.61 (dd, *J* = 10.2, 12.3 Hz, 1H), 3.82–3.70 (m, 1H), 2.72–2.58 (m, 1H), 2.53–2.30 (m, 2H), 2.16–2.01 (m, 1H), 1.86–1.58 (m, 4H), 1.31–1.14 (m, 1H).

(*S*)-2-((*R*)-1-(2-Chlorophenyl)-2-nitroethyl)cyclohexanone (18c).[14] White solid, 99% yield; *syn/anti* > 99:1, ee (major) = 90%, determined by HPLC analysis (Chiralpak AS-H, *i*-PrOH/hexane = 20/80, flow rate 10 mL/min, λ = 210.5 nm, t_r (minor) = 8.66 min, t_r (major) = 11.14 min; $[\alpha]_D^{25}$ = –36.7 (*c* = 1.04, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.43–7.14 (m, 4H), 4.89 (d, *J* = 6.5 Hz, 2H), 4.36–4.21 (m, 1H), 2.99–2.83 (m, 1H), 2.53–2.30 (m, 2H), 2.16–2.02 (m, 1H), 1.86–1.49 (m, 4H), 1.41–1.23 (m, 1H).

(*S*)-2-((*R*)-1-(2,4-Dichlorophenyl)-2-nitroethyl)cyclohexanone (18d).[51] White solid, 93% yield; *syn/anti* > 99:1, ee (major) > 99%, determined by HPLC analysis (Chiralpak AD-H, *i*-PrOH/hexane = 10/90, flow rate 10 mL/min, λ = 210.5 nm, t_r (minor) = 8.78 min, t_r (major) = 11.47 min; $[\alpha]_D^{25}$ = −41.1 (*c* = 0.35, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.41 (d, *J* = 1.9 Hz, 1H), 7.26–7.14 (m, 2H), 4.88 (d, *J* = 6.9 Hz, 2H), 4.25 (dt, *J* = 7.0, 9.4 Hz, 1H), 2.94–2.80 (m, 1H), 2.53–2.31 (m, 2H), 2.18–2.06 (m, 1H), 1.88–1.52 (m, 4H), 1.42–1.23 (m, 1H).

(*S*)-2-((*R*)-1-(4-Bromophenyl)-2-nitroethyl)cyclohexanone (18e).[32] White solid, 90% yield; *syn/anti* = 98:2, ee (major) = 92%, determined by HPLC analysis (Chiralpak AS-H, *i*-PrOH/hexane = 20/80, flow rate 05 mL/min, λ = 210.5 nm, t_r (minor) = 19.96 min, t_r (major) = 30.32 min; $[\alpha]_D^{25}$ = –12.7 (*c* = 1.05, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.46 (d, *J* = 8.3 Hz, 2H), 7.06 (d, *J* = 8.3 Hz, 2H), 4.93 (dd, *J* = 4.5, 12.6 Hz, 1H), 4.60 (dd, *J* = 10.0, 12.5 Hz, 1H), 3.75 (td, *J* = 4.5, 9.9 Hz, 1H), 2.71–2.59 (m, 1H), 2.53–2.31 (m, 2H), 2.15–2.04 (m, 1H), 1.87–1.58 (m, 4H), 1.31–1.14 (m, 1H).

(*S*)-2-((*R*)-1-(2-Bromophenyl)-2-nitroethyl)cyclohexanone (18f).[16] White solid, 90% yield; *syn/anti* > 99:1, ee (major) = 92%, determined by HPLC analysis (Chiralpak AS-H, *i*-PrOH/hexane = 10/90, flow rate 08 mL/min, λ = 212.0 nm, t_r (minor) = 17.49 min, t_r (major) = 22.80 min;. $[\alpha]_D^{25}$ = –37.4 (*c* = 1.01, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.58 (d, *J* = 8.0 Hz, 1H), 7.35–7.09 (m, 3H), 5.01–4.82 (m, 2H), 4.38–4.24 (m, 1H), 3.01–2.81 (m, 1H), 2.54–2.32 (m, 2H), 2.16–2.04 (m, 1H), 1.88–1.61 (m, 4H), 1.45–1.31 (m, 1H).

(*S*)-2-((*R*)-1-(4-Fluorophenyl)-2-nitroethyl)cyclohexanone (18g).[32] White solid, 92% yield; *syn/anti* = 98:2, ee (major) = 90%, determined by HPLC analysis (Chiralpak AS-H, *i*-PrOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 210.5 nm, t_r (minor) = 15.93 min, t_r (major) = 23.40 min, $[\alpha]_D^{25}$ = –15.0 (*c* = 0.21, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.22–6.92 (m, 4H), 4.93 (dd, *J* = 4.5, 12.5 Hz, 1H), 4.60 (dd, *J* = 10.1, 12.4 Hz, 1H), 3.77 (td, *J* = 4.5, 9.9 Hz, 1H), 2.73–2.58 (m, 1H), 2.53–2.30 (m, 2H), 2.15–2.03 (m, 1H), 1.83–1.52 (m, 4H), 1.31–1.14 (m, 1H).

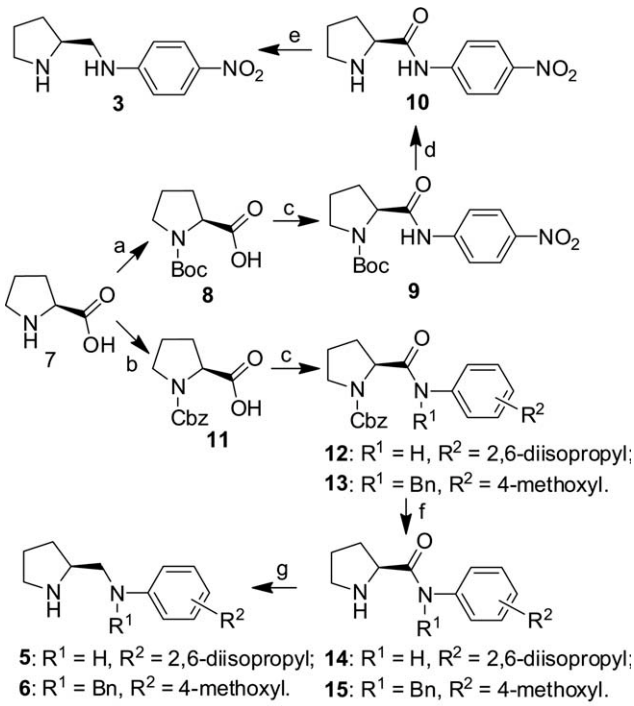
(*S*)-2-((*R*)-2-Nitro-1-*p*-tolylethyl)cyclohexanone (18h).[14] White solid, 99% yield; *syn/anti* = 99:1, ee (major) = 91%, determined by HPLC analysis (Chiralpak AS-H, *i*-PrOH/hexane = 20/80, flow rate 10 mL/min, λ = 211.7 nm, t_r (minor) = 7.26 min, t_r (major) = 10.76 min, $[\alpha]_D^{25}$ = –15.0 (*c* = 0.21, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.12 (d, *J* = 7.9 Hz, 2H), 7.04 (d, *J* = 8.0 Hz, 2H), 4.92 (dd, *J* = 4.5, 12.3 Hz, 1H), 4.61 (dd, *J* = 9.9, 12.3 Hz, 1H), 3.78–3.65 (m, 1H), 2.74–2.59 (m, 1H), 2.53–2.35 (m, 2H), 2.31 (s, 3H), 2.14–2.02 (m, 1H), 1.83–1.61 (m, 4H), 1.31–1.15 (m, 1H).

(*S*)-2-((*R*)-1-(4-Methoxyphenyl)-2-nitroethyl)cyclohexanone (18i).[32] White solid, 93% yield; *syn/anti* = 97:3, ee (major) = 92%, determined by HPLC analysis (Chiralpak AD-H, *i*-PrOH/hexane = 20/80, flow rate 05 mL/min, λ = 223.4 nm, t_r (minor) = 17.04 min, t_r (major) = 20.11 min, $[\alpha]_D^{25}$ = –11.2 (*c* = 0.61, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.08 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 4.91 (dd, *J* = 4.6, 12.3 Hz, 1H), 4.59 (dd, *J* = 10.0, 12.2 Hz, 1H), 3.78 (s, 3H), 3.76–3.65 (m, 1H), 2.71–2.58 (m, 1H), 2.53–2.31 (m, 2H), 2.15–2.02 (m, 1H), 1.85–1.58 (m, 4H), 1.31–1.14 (m, 2H).

(*S*)-2-((*R*)-1-(2-Methoxyphenyl)-2-nitroethyl)cyclohexanone (18j).[17] White solid, 99% yield; *syn/anti* = 97:3, ee (major) > 99%, determined by HPLC analysis (Chiralpak AS–H, *i*-PrOH/hexane = 15/85, flow rate 10 mL/min, λ = 211.7 nm, t_r (minor) = 9.99 min, t_r (major) = 11.14 min, $[\alpha]_D^{25}$ = –25.4 (*c* = 0.45, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.23 (d, *J* = 6.4 Hz, 1H), 7.09 (d, *J* = 6.5 Hz, 1H), 6.89 (t, *J* = 7.7 Hz, 2H), 4.91–4.76 (m, 2H), 4.02–3.90 (m, 1H), 3.84 (s, 3H), 3.06–2.90 (m, 1H), 2.54–2.30 (m, 2H), 2.15–2.00 (m, 1H), 1.81–1.54 (m, 4H), 1.30–1.11 (m, 1H).

(*S*)-2-((*R*)-2-Nitro-1-(4-nitrophenyl)-ethyl)cyclohexanone (18k).[14] Brown oil, 96% yield; *syn/anti* = 88:12, ee (major) = 84%, determined by HPLC analysis (Chiralpak AD-H, *i*-PrOH/hexane = 10/90, flow rate 10 mL/min, λ = 210.5 nm, t_r (minor) = 14.34 min, t_r (major) = 29.67 min, $[\alpha]_D^{25}$ = –22.1 (*c* = 0.46, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.20 (d, *J* = 8.6 Hz, 2H), 7.40 (d, *J* = 8.6 Hz, 2H), 5.00 (dd, *J* = 4.4, 13.0 Hz, 1H), 4.70 (dd, *J* = 10.1, 12.9 Hz, 1H), 4.00–3.88 (m, 1H), 2.81–2.64 (m, 1H), 2.55–2.31 (m, 2H), 2.19–2.06 (m, 1H), 1.76–1.55 (m, 3H), 1.38–1.15 (m, 2H).

(*S*)-2-((*R*)-1-(Naphthalen-2-yl)-2-nitroethyl)cyclohexanone (18l).[32] White solid, 88% yield; *syn/anti* = 99:1, ee (major) = 90%, determined by HPLC analysis (Chiralpak AS-H, *i*-PrOH/hexane = 50/50, flow rate 07 mL/min, λ = 223.4 nm, t_r (minor) = 9.11 min, t_r (major) = 14.94 min, $[\alpha]_D^{25}$ = −21.1 (*c* = 0.43, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.86 – 7.74 (m, 3H), 7.63 (s, 1H), 7.53–



Scheme 1. Synthesis of catalysts **3**, **5,** and **6.**

7.42 (m, 2H), 7.33–7.27 (m, 1H), 5.03 (dd, J = 4.5, 12.5 Hz, 1H), 4.74 (dd, J = 10.1, 12.4 Hz, 1H), 4.01–3.89 (m, 1H), 2.84–2.73 (m, 1H), 2.57–2.33 (m, 2H), 2.14–2.02 (m, 1H), 1.82–1.58 (m, 4H), 1.34–1.19 (m, 1H).

(*S*)-2-((*S*)-1-(Furan-2-yl)-2-nitroethyl)cyclohexanone (18m).[32] Clear and clorless oil, 97% yield; *syn/anti* = 98:2, ee (major) = 97%, determined by HPLC analysis (Chiralpak AD-H, *i*-PrOH/hexane = 5/95, flow rate 10 mL/min, λ = 210.5 nm, t_r (major) = 13.84 min, t_r (minor) = 17.06 min, $[\alpha]_D^{25} = -8.0$ (c = 0.28, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.35 (d, J = 1.0 Hz, 1H), 6.29 (dd, J = 1.9, 3.0 Hz, 1H), 6.18 (d, J = 3.0 Hz, 1H), 4.79 (dd, J = 4.8, 12.5 Hz, 1H), 4.67 (dd, J = 9.3, 12.4 Hz, 1H), 3.97 (td, J = 4.9, 9.1 Hz, 1H), 2.86–2.65 (m, 1H), 2.56–2.25 (m, 2H), 2.20–1.98 (m, 1H), 1.90–1.58 (m, 4H), 1.29 (qd, J = 3.8, 12.4 Hz, 1H).

(*S*)-2-((*S*)-2-Nitro-1-(thiophen-2-yl)-ethyl)cyclohexanone (18n).[32] White solid, >99% yield; *syn/anti* = 92:8, ee (major) = 89%; determined by HPLC analysis (Chiralpak AD-H, *i*-PrOH/hexane = 5/95, flow rate 10 mL/min, λ = 231.6 nm): t_r (minor) = 14.10 min, t_r (major) = 18.78 min, $[\alpha]_D^{25}$ –15.1 (c = 0.98, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.22 (d, J = 4.9 Hz, 1H), 6.94 (dd, J = 3.6, 4.9 Hz, 1H), 6.87 (d, J = 2.9 Hz, 1H), 4.89 (dd, J = 4.8, 12.6 Hz, 1H), 4.66 (dd, J = 9.3, 12.5 Hz, 1H), 4.13 (td, J = 4.8, 9.1 Hz, 1H), 2.75–2.61 (m, 1H), 2.53–2.29 (m, 2H), 2.17–2.03 (m, 1H), 1.98–1.79 (m, 2H), 1.75–1.58 (m, 2H), 1.32 (td, J = 3.6, 15.9 Hz, 1H).

(*S*)-2-((*S,E*)-1-Nitro-4-phenylbut-3-en-2-yl)cyclohexanone (18o).[25] Yellow solid, 94% yield; *syn/anti* = >99, 1, ee (major) = 88%, determined by HPLC analysis (Chiralpak AS-H, *i*-PrOH/hexane = 15/85, flow rate 10 mL/min, λ = 250.0 nm): t_r (minor) = 14.10 min, t_r (major) = 18.78 min, $[\alpha]_D^{25}$ –21.4 (c = 0.67, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.35–7.22 (m, 5H), 6.49 (d, J = 15.8 Hz, 1H), 6.02 (dd, J = 9.6, 15.8 Hz, 1H), 4.68(dd, J = 4.6, 11.9 Hz, 1H), 4.57 (dd, J = 8.5, 11.9 Hz, 1H), 3.39–3.31 (m, 1H), 2.58–2.51 (m, 1H), 2.47–2.32 (m, 2H), 2.19–2.05 (m, 2H), 1.92–1.90 (m, 1H), 1.74–1.65 (m, 2H), 1.45 (qd, J = 3.3, 12.5 Hz, 1H).

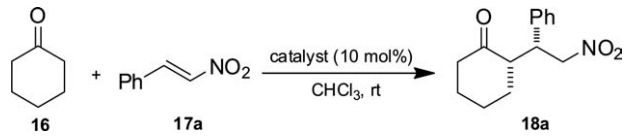
(*S*)-5-Nitro-4-phenylpentan-2-one (18q).[51] White solid, 77% yield; ee = 34%, determined by HPLC analysis (Chiralpak AS-H, *i*-PrOH/hexane = 25/75, flow rate 10 mL/min, λ = 210.5 nm): t_r (minor) = 39.76 min, t_r (major) = 44.67 min, $[\alpha]_D^{25}$ –4.7 (c = 0.13, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.35–7.28 (m, 3H), 7.16–7.12 (m, 2H), 4.60–4.44 (m, 2H), 3.95 (p, J = 7.1 Hz, 1H), 2.92–2.72 (m, 2H), 1.57 (s, 3H).

RESULTS AND DISCUSSION

The newly designed chiral aliphatic–aromatic diamines were synthesized from L-proline through simple conversions (Scheme 1) and evaluated as catalysts for the model reaction between cyclohexanone (**16**) and (*E*)-(2-nitrovinyl)benzene (**17a**). The reaction was conducted using chiral diamines **1–6,** respectively, in an excess of cyclohexanone at room temperature, and only the *syn*-product was obtained despite the various catalysts used.

Initially, a comparison was made among catalysts **1–3** bearing different kinds of subsistent groups in the aryl ring. The results showed that modulating N—H acidity of aromatic amine through altering substituent groups plays a key role in achieving good conversions and high level of steroselectivities. As shown in Table 1, catalyst **2** containing powerful electron-donating group is a tolerable catalyst for this reaction (Table 1, entry 2). To test the steric effects of aryl ring moiety, catalyst **4** were prepared and applied in the model reaction. To our delight, excellent diasteroselectivty (up to 99:1) and enantioselectivity (up to 97% ee) were obtained. However, the only dissatisfied aspect was the low yield (Table 1, entry 4). Based on the experimental results described above, we hypothesized that an appropriate combination of electron-donating and steric bulky elements in a chiral scaffold could result in a potential bifunctional organocatalyst. Therefore, we synthesized the chiral catalyst **5**, in which the isopropyl groups at positions 2 and 6 not only function as effective bulky group but also as electron-donating group, and the catalytic activity of which in the asymmetric direct Michael addition reaction was investigated. As expected, the model reaction took place smoothly to give the desired adduct in 96% yield with an 93% ee and 98:2 *syn/anti* ratio (Table 1, entry 5). Increasing the catalyst loading to 20 mol % could dra-

TABLE 1. Catalysts screening in the direct asymmetric nitro-Michael addition reaction of cyclohexanone[a]



16 17a 18a

Entry	Catalysts	Catalyst loading (mol %)	Additives	Time (h)	Yield (%)[b]	Dr[c] (*syn:anti*)	*Ee* (%)[d] *syn*
1	**1**	10	–	48	57	98:2	92
2	**2**	10	–	24	90	98:2	92
3	**3**	10	–	48	68	94:6	73
4	**4**	10	–	24	78	>99:1	97
5	**5**	10	–	24	96	98:2	93
6	**5**	20	–	12	98	97:3	84
7	**5**	5	–	54	87	98:2	90
8	**6**	10	–	72	69	94:6	21
9	**5**	10	TFA	48	<5	nd[e]	nd[e]
10	**5**	10	*p*TsOH	48	<5	nd[e]	nd[e]
11	**5**	10	HOAc	24	96	97:3	92
12	**5**	10	PhCOOH	20	92	98:2	92

[a]The reactions were performed with **16** (3 mmol), **17a** (0.3 mmol), and catalyst in $CHCl_3$ (0.5 mL) at room temperature, unless otherwise specified.
[b]Isolated yields after column chromatography.
[c]Diastereoselectivities were determined by ^1H NMR of the crude mixture or HPLC analysis.
[d]Ee's value were determined by HPLC using a Chiralpak AS-H or AD-H column. Absolute configuration was determined by comparison of the measured optical rotation with the reported data.
[e]Not determined.

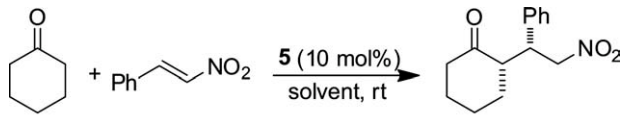
matically accelerate the reaction rate, but the enatioselectivity dropped. While decreased catalyst loading (5 mol %), resulted in slow reaction and low enantioselectivity (Table 1, entries 6–7). Removal of the hydrogen-bond donor group by *N*-benzylation leads to a sharp reduction of the enatioselectivity (Table 1, entry 8, only 21% ee was observed). This provides a valid proof for demonstrating that the N—H bond of the new catalyst has a profound influence on the steroselectivities.

It is worth mentioning here that, thus far, for all reported nitro-Michael addition mediated by chiral diamine catalysts, a suitable Brønsted acid must be used as a cocatalyst.[52,53] However, to our surprise, the reaction between cyclohexanone and *trans*-β-nitroolefin **17a** catalyzed by our alphatic–aromatic diamine catalysts proceeded smoothly, giving the conjugate adducts γ-nitro ketone in good yields and high steroselectivities without any additives.

Meanwhile, we also investigated the effects of some acid additives on the reaction yield and the stereoselectivites. As shown in Table 1 (entries 9–10), strong Brønsted acid TFA and *p*TsOH could not promote the Michael addition. And, no improvement in catalytic activity or selectivity was observed when relatively weak acid, such as HOAc and PhCOOH was employed as an additive (Table 1, entries 11∼12).

Screening of solvents with the best organocatalyst **5** has shown that solvent-free conditions (Table 2, entry 10) gave the highest yield and enantioselectivity. All solvents tested were dramatically disappointing. As shown in Table 2, in strong polar solvents such as DMF and *i*-PrOH, only a trace amount of the desired adduct was observed (Table 2, entries 1 and 2). Whereas, in less polar and nonpolar solvents, such as CH_3CN, THF, chlorinated solvents, toluene, and hexane, the Michael addition reaction ran smoothly to give product **18a** in moderate to excellent conversions with good to high enantioselectivities (Table 2, entries 3–

TABLE 2. Screening solvents[a]

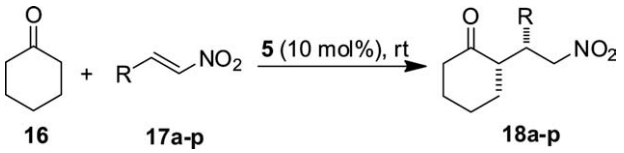


16 17a 18a

Entry	Solvent	Time (h)	Yield[b] (%)	Dr (*syn:anti*)[c]	*Ee* (%)[d] *syn*
1	DMF	108	<5	nd	nd
2	*i*PrOH	96	<5	nd	nd
3	CH_3CN	96	57	98:2	93
4	THF	96	71	96:4	86
5	$CHCl_3$	24	96	98:2	93
6	DCM	24	93	98:2	93
7	DCE	24	91	96:4	90
8	toluene	15	90	97:3	90
9	hexane	72	95	95:5	91
10[e]	solvent-free	12	99	98:2	97
11	water	72	79	98:2	90

[a]The reactions were performed with **16** (10 equiv), **17a** (0.3 mmol), **5** (10 mol %), and solvent (0.5 mL) at room temperature, unless stated otherwise.
[b]Isolated yields after column chromatography.
[c]Diastereoselectivities were determined by ^1H NMR of the crude mixture or HPLC analysis.
[d]Ee values were determined by HPLC analysis using a Chiralpak AS-H or AD-H column. Absolute configuration was determined by comparison of the measured optical rotation with the reported data.
[e]20 equiv cyclohexanone was used under solvent-free conditions.

TABLE 3. Scope of the reaction[a]



Entry	R	Adduct	Time (h)	Yield[b] (%)	Dr[c] (*syn/anti*)	*Ee*[d] (%) *syn*
1	Ph	**18a**	12	99	98:2	97
2	4-ClC_6H_4	**18b**	12	92	>99:1	99
3	2-ClC_6H_4	**18c**	12	>99	>99:1	90
4	2,4-$Cl_2C_6H_3$	**18d**	10	93	>99:1	>99
5	4-BrC_6H_4	**18e**	12	90	98:2	92
6	2-BrC_6H_4	**18f**	12	90	>99:1	92
7	4-FC_6H_4	**18g**	12	92	98:2	90
8	4-$CH_3C_6H_4$	**18h**	10	>99	99:1	91
9	4-$CH_3OC_6H_4$	**18i**	10	93	97:3	92
10	2-$CH_3OC_6H_4$	**18j**	10	>99	97:3	>99
11[e]	4-$NO_2C_6H_4$	**18k**	12	96	88:12	84
12	2-naphthyl	**18l**	12	88	99:1	90
13	2-furyl	**18m**	12	97	98:2	91
14	2-thienyl	**18n**	12	>99	92:8	89
15	CH=CHPh	**18o**	16	94	>99:1	88
16	$(CH_3)_2CH$	**18p**	48	<5	nd[f]	nd[f]

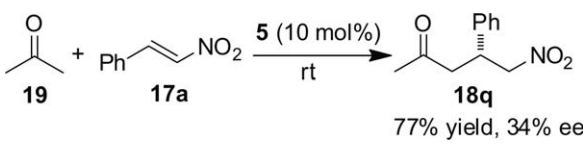
[a]Reaction conditions: **16** (20 equiv), **17** (0.3 mmol), **5** (10 mol %), rt.
[b]Isolated yields after column chromatography.
[c]Diastereoselectivities were determined by ^1H NMR of the crude mixture or HPLC analysis.
[d]Ee's value were determined by HPLC using a Chiralpak AS-H or AD-H column. Absolute configuration was determined by comparison of the measured optical rotation with the reported data.
[e]0.5 mL $CHCl_3$ was added as solvent.
[f]Not determined.

9). Interestingly, the reaction could also conducted in water.[19,34,51,54–56] But, to our regret, giving a lower yield and enantioselectivity (Table 2, entry 11). Under solvent-free conditions, the reaction occurred fastest, giving the desired adduct quantitively with the highest ee (97%) and excellent diastereoselectivity (98: 2 dr) (Table 2, entry 10).

Under the optimized conditions, a variety of nitroolefins with different structures were investigated, and the results are summarized in Table 3. Various styrene-type nitroolefins reacted efficently with cyclohexanone and excellent yields, diasteroselectivities and enantioselectivities were achieved. Generally, aryl groups containing electron-donating and halogenated substituents (Table 3, entries 1–10) marginally influenced the results, especially in diastereomeric ratio (97:3 to >99:1 *syn/anti*) and enantiomeric excess (90% to >99% ee). Strong electron withdrawing group nitro attached to benzene ring slightly lowered diasteroselectivetity and enantioselectivity (Table 3, entry 11). Naphthyl and heterocyclic nitroolefins also gave the corresponding products with good to excellent steroselectivities in high yields (Table 3, entries 12–14). Moreover, alkenyl substituted nitroolefin can also be employed successfully; the same good diastereo- and enantioselectivity were observed as those found in the aryl substituted ones (Table 3, entry 15). However, aliphatic aldehyde derived nitroolefin appeared to be an inappropriate candidate.

The asymmetric addition of acetone to nitrostyrene **17a** using **5** as a catalyst was also investigated. As shown in Scheme 2, which gave the desired product in 77% yield with 34% ee.

On the basis of the experimental results described above, a possible stereochemical model was depicted to account for the sterochemical outcome of the present reaction. As shown in Figure 2, the pyrrolidine ring firstly



Scheme 2. Reaction of acetone and nitroolefin **17a**.

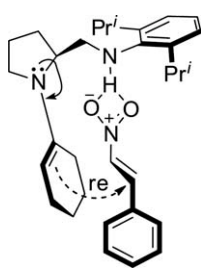


Fig. 2. Proposed transition state.

reacted with cyclohexanone to form an enamine intermediate. Subsequently, the N—H group on aryl amine moiety orientated the nitro group via a hydrogen bond so that the enamine could attack the nitroolefin from *re*-face to give the highly enantio- and diasteroselective adduct. The explanation is consistent with the experimental results.

CONCLUSIONS

In summary, we have developed a new highly efficient aliphatic–aromatic diamine organocatalyst, which has been successully applied to the asymmetric Michael reaction of cyclohexanone with nitroolefins of various substituents under solvent-free conditions. The main advantages of the catalyst are the ease of synthesis and very good enantioselection at room temperature without any acidic additives. The presence of N—H bond attached to aryl group, proved to be critical for the excellent performance of the catalyst system. Further investigation on the application of this bifunctional organocatalyst in asymmetric catalysis is still in progress.

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