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Article

Synthesis of *N*,*O*-Type Inherently Chiral Calix[4]arenes Substituted on the Lower Rim and their Organocatalysis Properties

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This work presented the first study of organocatalytic behaviors of inherently chiral calix[4] arenes substituted at the lower rim. A pair of *N*,*O*-type enantiomers based on inherently chiral calix[4]arenes substituted at the lower rim were readily synthesized and applied to catalyze Henry reaction between aromatic aldehydes and nitromethane. Their organocatalytic reaction can afford the desired products in excellent yields (up to 99%) but poor enantioselectivities (up to 7.5% ee).

Keywords: inherently chiral, calix[4]arene, asymmetric catalysis, Henry reaction

Introduction

Inherently chiral calixarenes as a novel type of chiral macrocyclic compounds have been intensively studied in the past three decades. To mimic enzymatic catalysis process and develop efficient chiral catalysts, a variety of inherently chiral calix[4]arenes substituted at the *meta* position and the upper rim have been applied as chiral organocatalysts in aldol reaction,[1] addition of diethylzinc to benzaldehyde,[2] Michael addition[3-7] and alkylation of a glycine derivative.[7] And the highest ee in these catalytic reactions is up to 31%.[6] However, until now inherently chiral calix[4]arenes substituted at the lower rim have not been applied in asymmetric organocatalysis although they have been frequently prepared and applied in chiral recognition.[8] To systematically study the application of inherently chiral calixarenes, it is necessary to explore the organocatalytic behaviors of inherently chiral calix[4] arenes substituted at the lower rim.

Henry reactions are one of the most useful and widely employed methods for carbon-carbon bond formation in organic chemistry. The resulting nitro alcohol (nitroaldol) products can be transformed into a number of nitrogen and oxygen-containing derivatives such as 1,2-amino alcohols, amino sugars, nitro ketones, nitro alkenes, ketones, and other important compounds.[9-14] It was reported that chiral *N*,*O*-type cupreidine derivatives can perform outstanding catalytical activities for Henry reaction. Mechanistic studies on their catalytic behaviors indicated they serve as acid-base bifunctional organocatalysts through H-bond interactions with the acceptor and donor components of the reactions through the quinuclidine nitrogen and the aromatic hydroxyl, respectively.[10,15,16] Therefore, we attempted to synthesize chiral *N*,*O*-type organocatalysts based on inherently chiral calix[4]arenes substituted at the lower rim, and selected Henry reaction between aromatic aldehydes and nitromethane as a model reaction to explore their organocatalytic abilities.

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Experimental

General experimental procedures

All reactions were conducted under atmosphere without special drying. All chemicals were purchased from commercial sources and used without further purification. Melting points were measured on RY-1G melting point apparatus. Nuclear magnetic resonance (NMR) spectra were performed on Bruker Avance 400 (^{1}H: 400 MHz, ^{13}C: 101 MHz). $CDCl_3$ (δ 7.26 ppm), DMSO-d_6 (δ 2.50, 3.33 ppm) or TMS (δ 0.00 ppm) was used as an internal standard for ^{1}H NMR spectra, $CDCl_3$ (δ 77.00 ppm), DMSO-d_6 (δ 39.58 ppm) or TMS (δ 0.00 ppm) was used as an internal standard for ^{13}C NMR spectra. The following abbreviations are used to indicate the multiplicity in NMR spectra: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, *J* indicates the NMR coupling constant measured in Hertz. The courses of the reactions were monitored by thin layer chromatography (TLC) using TLC aluminium sheets with silica gel 60 GF254. The

column chromatography was performed using silica gel 60. Optical rotations were measured on a Jasco P-2000 digital polarimeter. High-resolution mass spectra (HRMS) were recorded on a 7.0-T (Ionspec, Irvine, CA, USA) Fourier transform ion cyclotron resonance mass spectrometer.

Synthesis

To a stirred solution of **1a** (or **1b**)[17] (2.00 g, 1.98 mmol) in tetrahydrofuran (30 mL) was added sodium hydride (0.38 g, 7.9 mmol) at room temperature. The reaction mixture was heated at reflux for 4 h. Then the 2-methoxyethyl tosylate was added, and the stir was continued for 2 h and quenched with hydrocholoric acid (2.00 mol L^{-1}). The aqueous layer was extracted with dichloromethane, and the combined organic layers were washed with saturated brine, dried with anhydrous sodium sulfate. The solvent was removed under reduced pressure to yield product which was further purified by silica gel column chromatography (eluent = petroleum ether:ethyl acetate, 2:1, v/v). Compound **2a** (or **2b**) was obtained as white power.

2a

Yield: 1.6 g (80%); m.p. 108-111 °C; $[\alpha]_D^{25}$ = +0.1 (c = 1.8 g/100 mL, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, 1H, *J* 8.4 Hz, NH), 7.28 (m, 9H, Ar-H), 7.13 (dd, 2H, *J* 2.4, 2.4 Hz, Ar-H), 7.09 (dd, 2H, *J* 2.4, 2.4 Hz, Ar-H), 6.09 (dd, 2H, *J* 2.4, 2.4 Hz, Ar-H), 6.50 (dd, 2H, *J* 2.4, 2.4 Hz, Ar-H), 5.23-5.20 (m, 1H, Ph-CH), 4.55 (d, 1H, *J* 15.2 Hz, O-CH_2-CO), 4.11 (d, 1H, *J* 15.2 Hz, O-CH_2-CO), 4.00-3.07 (m, 14H, Ar-CH_2-Ar, O-$\underline{CH_2}$-CH_2-CH_3, O-$\underline{CH_2}$-$\underline{CH_2}$-O-CH_3), 3.04 (s, 3H, O-CH_3), 2.46 (s, 3H, Ar-CH_3), 1.84 (m, 2H, O-CH_2-$\underline{CH_2}$-CH_3), 1.53 (d, 3H, *J* 6.8 Hz, CH-$\underline{CH_3}$), 1.36 (s, 9H, *t*-Bu), 1.32 (s, 9H, *t*-Bu), 1.07 (s, 9H, *t*-Bu), 1.04 (s, 9H, *t*-Bu), 0.98 (t, 3H, *J* 14.8 Hz, O-CH_2-CH_2-$\underline{CH_3}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.8, 153.6, 147.2, 145.5, 145.2, 145.0, 144.6, 144.2, 140.8, 135.5, 135.4, 134.0, 131.9, 130.5, 129.6, 129.3, 128.7, 128.5, 126.1, 125.7, 125.7, 125.4, 125.1, 125.0, 124.9, 72.8, 71.8, 71.0, 70.4, 58.7, 58.6, 58.3, 37.0, 36.2, 34.4, 34.1, 33.8, 31.7, 31.6, 31.5, 31.4, 31.3, 31.2, 23.8, 21.8, 10.6. HRMS (ESI) *m/z*, calcd. for $C_{67}H_{87}NO_8SNa^+$ 1088.6152 $[M + Na]^+$, found 1088.5781 $[M + Na]^+$.

2b

Yield: 1.51 g (76%); m.p. 96-98 °C; $[\alpha]_D^{25}$ = −2.4 (c = 2.0 g/100 mL, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, 1H, *J* 8 Hz, NH), 7.28 (m, 9H, Ar-H), 7.18 (dd, 2H, *J* 2.4, 2.4 Hz, Ar-H), 7.08 (dd, 2H, *J* 2.4, 2.4 Hz, Ar-H), 6.89 (dd, 2H, *J* 2.4, 2.4 Hz, Ar-H), 6.48 (dd, 2H, *J* 2.4, 2.4 Hz, Ar-H), 5.35-5.25 (m, 1H, Ph-CH), 4.46 (d, 1H, *J* 14.8 Hz, O-CH_2-CO), 4.11 (d, 1H, *J* 14.8 Hz, O-CH_2-CO), 3.00-4.05 (m, 14H, Ar-CH_2-Ar, O-$\underline{CH_2}$-CH_2-CH_3, O-$\underline{CH_2}$-$\underline{CH_2}$-O-CH_3), 2.92 (s, 3H, O-CH_3), 2.46 (s, 3H, Ar-CH_3), 1.92-1.78 (m, 2H, O-CH_2-$\underline{CH_2}$-CH_3), 1.54 (d, 3H, *J* 7.2 Hz, CH-$\underline{CH_3}$), 1.39 (s, 9H, *t*-Bu), 1.35 (s, 9H, *t*-Bu), 1.05 (d, 18H, 2*t*-Bu), 0.97 (t, 3H, *J* 14.8 Hz, O-CH_2-CH_2-$\underline{CH_3}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 153.5, 153.0, 152.5, 147.4, 145.6, 145.5, 145.3, 145.2, 144.5, 144.4, 135.8, 135.4, 134.9, 134.1, 134.0, 131.6, 131.4, 130.2, 129.8, 129.7, 129.5, 128.9, 128.7, 128.4, 128.0, 127.4, 127.0, 126.8, 126.4, 126.2, 125.8, 125.6, 70.0, 69.5, 69.1, 67.7, 67.4, 57.6, 36.9, 36.5, 34.3, 34.2, 33.8, 31.7, 31.6, 31.4, 31.3, 23.8, 21.8, 21.0, 10.7. HRMS (ESI) *m/z*, calcd. for $C_{67}H_{87}NO_8SNa^+$ 1088.6152 $[M + Na]^+$, found 1088.5779 $[M + Na]^+$.

To a stirred solution of **2a** (or **2b**) (1.50 g, 1.42 mmol) in butyl alcohol (10 mL) was added potassium *tert*-butylate (2 g, 17.8 mmol) at room temperature. When the solid dissolved, dimethyl sulfoxide (1.50 mL) was added and the mixture was heated and stirred at 100 °C for 1 h. Then water (0.05 g, 2 equiv.) was added and heated at reflux for 24 h. The reaction mixture was evaporated to yield black oily liquid and redissolved in hydrochloric acid (30 mL) and dichloromethane (30 mL). The aqueous layer was extracted with dichloromethane (2 × 30 mL), and the combined organic layers were washed with brine, dried with anhydrous sodium sulfate, and evaporated to yield brown oily liquid. The product **3a** (or **3b**) was further purified by silica gel column chromatography (eluent = petroleum ether:ethyl acetate, 3:1, v/v).

3a

Yield: 0.81 g (54%); m.p. 110-113 °C; $[\alpha]_D^{25}$ = +7.4 (c = 6 g/100 mL, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H, COOH), 7.25 (s, 1H, OH), 7.09 (d, 1H, *J* 2 Hz, Ar-H), 6.99 (s, 2H, Ar-H), 6.97-6.90 (m, 3H, Ar-H), 6.86 (dd, 2H, *J* 2.4, 2.4 Hz, Ar-H), 4.85 (d, 1H, O-CH_2-CO, *J* 16.0 Hz), 4.50-3.60 (m, 11H, Ar-CH_2-Ar, O-CH_2-CH_2-O, O-CH_2-CO), 3.46 (s, 3H, O-CH_3), 3.38-3.21 (m, 4H, O-$\underline{CH_2}$-CH_2-CH_3, O-CH_2-CH_2-O), 2.10 (m, 2H, O-CH_2-CH_2-CH_3), 1.18 (d, 18H, 2*t*-Bu), 1.14 (s, 9H, *t*-Bu), 1.08 (t, 3H, *J* 14.8 Hz, O-CH_2-CH_2-$\underline{CH_3}$), 1.04 (s, 9H, *t*-Bu); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 151.3, 149.2, 147.1, 146.8, 146.0, 142.5, 134.0, 132.8, 129.2, 126.4, 125.9, 125.8, 125.7, 125.6, 125.5, 125.0, 78.9, 74.3, 71.6, 71.5, 58.8, 34.1, 32.3, 31.5, 31.4, 31.3, 31.2, 30.5, 22.8, 10.3. HRMS (ESI) *m/z*, calcd. for $C_{52}H_{70}O_7Na^+$ 806.5122 $[M + Na]^+$, found 829.5014 $[M + Na]^+$.

3b

Yield: 0.90 g (60%); m.p. 110-113 °C; $[\alpha]_D^{25}$ = −7.5 (c = 4.5 g/100 mL, CH_2Cl_2). The relative spectroscopic data were identical to those of **3a**.

To a stirring solution of **3a** (or **3b**) (0.50 g, 0.63 mmol) in dichloromethane was added *O*-benzotriazole-*N*,*N*,*N'*,*N'*-tetramethyl-uronium-hexafluorophosphate (0.36 g, 0.95 mmol) followed by the addition of 4-dimethyl aminopyridine (0.05 g, 0.41 mmol). The reaction mixture was stirred at room temperature for half an hour. *N*,*N*-Diethylamine was added and stirring was continued for 6 h at room temperature. The reaction mixture was quenched with dilute hydrochloric acid and the aqueous layer was extracted with dichloromethane (2 × 30 mL), and the combined organic layers were washed with brine, dried with anhydrous sodium sulfate, and evaporated to dryness. The product **4a** (or **4b**) was further purified by silica gel column chromatography (eluent = petroleum ether:ethyl acetate, 3:1, v/v).

4a

Yield: 0.32 g (65%); m.p. 96-98 °C; $[\alpha]_D^{25}$ = +5.8 (c = 2.2 g/100 mL, CH_2Cl_2); ^{1}H NMR (400 MHz, DMSO) δ 7.26 (s, 1H, OH), 7.04 (dd, 2H, *J* 2.4, 2.4 Hz, Ar-H), 6.98 (dd, 2H, *J* 2.4, 2.4 Hz, Ar-H), 6.66 (dd, 2H, *J* 2.4, 2.4 Hz, Ar-H), 6.53 (dd, 2H, *J* 2.4, 2.4 Hz, Ar-H), 4.72 (d, 1H, *J* 15.6 Hz, O-CH_2-CO), 4.52-4.40 (m, 3H, O-CH_2-CO, Ar-CH_2-Ar), 4.37 (d, 1H, Ar-CH_2-Ar, *J* 12.0 Hz), 4.29 (d, 1H, Ar-CH_2-Ar, *J* 12.0 Hz), 3.12 (m, 4H, Ar-CH_2-Ar), 3.90-3.70 (m, 2H, O-CH_2-CH_2-O), 3.50 (m, 4H, O-CH_2-CH_2-O, O-$\underline{CH_2}$-CH_2-CH_3), 3.45 (s, 3H, O-CH_3), 3.25-3.18 (m, 4H, N-$\underline{CH_2}$-CH_3), 2.05-1.93 (m, 2H, O-CH_2-$\underline{CH_2}$-CH_3), 1.32-1.15 (m, 24H, *t*-Bu, N-CH_2-$\underline{CH_3}$), 1.07 (t, 3H, *J* 14.8 Hz, O-CH_2-CH_2-$\underline{CH_3}$), 0.93 (s, 9H, *t*-Bu), 0.83 (s, 9H, *t*-Bu); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 152.8, 152.7, 151.9, 145.0, 144.7, 144.6, 144.4, 139.8, 134.2, 134.0, 133.0, 132.6, 132.5, 132.4, 127.7, 127.4, 125.3, 125.2, 125.1, 124.6, 124.5, 77.0, 73.1, 72.1, 70.7, 58.0, 33.6, 33.4, 33.3, 31.4, 31.2, 30.9, 30.8, 22.7, 14.1, 12.8, 10.5. HRMS (ESI) *m/z*, calcd. for $C_{56}H_{79}NO_6Na^+$ 861.5907 $[M + Na]^+$, found 884.5804 $[M + Na]^+$.

4b

Yield: 0.35 g (71%); m.p. 96-98 °C; $[\alpha]_D^{25}$ = −5.8 (c = 7.5 g/100 mL, CH_2Cl_2). The relative spectroscopic data were identical to those of **4a**.

To a solution of **4a** (or **4b**) (0.20 g, 0.24 mmol) in tetrahydrofuran (10 mL) was slowly added lithium aluminum hydride (0.18 g, 4.72 mmol) at 0 °C. After the mixture was stirred for 5 h at room temperature, the resulting mixture was filtered and the filtrate was concentrated. The reaction mixture was redissolved in hydrochloric acid (10 mL) and dichloromethane (10 mL). The aqueous layer was extracted with dichloromethane (2 × 10 mL), and the combined organic layers were washed with brine, dried with anhydrous sodium sulfate, and evaporated to yield white liquid. The product **5a** (or **5b**) was further purified by silica gel column chromatography (eluent = petroleum ether:ethyl acetate, 2:1, v/v).

5a

Yield: 0.07 g (33%); m.p. 78-81 °C; $[\alpha]_D^{25}$ = +2.8 (c = 7.5 g/100 mL, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (s, 2H, Ar-H), 7.05 (dd, 2H, *J* 2.4, 2.4 Hz, Ar-H), 6.52-6.50 (m, 4H, Ar-H), 5.75 (s, 1H, OH), 4.40-4.24 (m, 4H, Ar-CH_2-Ar), 4.22-4.05 (m, 4H, Ar-CH_2-Ar), 3.92 (m, 2H, O-CH_2-CH_2-O), 3.87-3.78 (m, 1H, O-$\underline{CH_2}$-CH_2-N), 3.77-3.67 (m, 1H, O-$\underline{CH_2}$-CH_2-N), 3.48 (s, 1H, O-CH_3), 3.29-3.13 (m, 4H, O-CH_2-CH_2-O, O-$\underline{CH_2}$-CH_2-CH_3), 3.04 (m, 2H, O-CH_2-$\underline{CH_2}$-N), 2.62 (m, 4H, N-$\underline{CH_2}$-CH_3), 2.08-1.84 (m, 2H, O-CH_2-$\underline{CH_2}$-CH_3), 1.33 (s, 9H, *t*-Bu), 1.32(s, 9H, *t*-Bu), 1.11 (t, 3H, *J* 14.2 Hz, O-CH_2-CH_2-$\underline{CH_3}$), 1.06 (t, 6H, *J* 14.4 Hz, N-CH_2-$\underline{CH_3}$), 0.83 (s, 9H, *t*-Bu), 0.81 (s, 9H, *t*-Bu); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.7, 150.7, 145.8, 145.2, 135.9, 135.8, 132.2, 131.9, 131.8, 129.2, 129.0, 125.7, 125.1, 125.0, 124.9, 124.8, 124.7, 78.1, 74.1, 71.4, 71.1, 58.9, 52.5, 47.8, 34.2, 33.8, 33.7, 33.6, 31.8, 31.7, 31.4, 31.3, 31.1, 31.0, 23.4, 11.8, 10.9. HRMS (ESI) *m/z*, calcd. for $C_{56}H_{81}NO_5H^+$ 848.6115 $[M + H]^+$, found 848.6186 $[M + H]^+$.

5b

Yield: 0.08 g (38%); m.p. 78-81 °C; $[\alpha]_D^{25}$ = −2.8 (c = 7.5 g/100 mL, CH_2Cl_2). The relative spectroscopic data were identical to those of **5a**.

General Henry reaction procedure

6 mmol nitromethane and 0.5 mmol% inherently chiral calix[4]arene catalyst were mixed and stirred in 4 mL solvent under nitrogen at an experimental temperature. After 15 minutes, 0.6 mmol aldehyde was added, and the mixture was continuously stirred. After completion, the reaction mixture was removed under reduced pressure. The crude residue was loaded directly onto a silica gel column and purified by flash chromatography as described below.

2-Nitro-1-(4-nitrophenyl)ethanol

The title compound was prepared according to the General experimental procedures section and purified by column chromatographic purification (CH_2Cl_2), giving a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.20 (s, 1H, -OH), 4.53-4.69 (m, 2H, -CH_2NO_2), 5.62 (ddd, *J* 4.0, 4.1, 8.1 Hz, 1H, -C$\underline{H}$OH), 7.65 (d, *J* 8.7 Hz, 2H, ArH), 8.27 (d, *J* 8.7 Hz, 2H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 69.9, 80.6, 124.2, 126.9, 144.9, 148.2.

2-Nitro-1-(4-cyanophenyl)ethanol

The title compound was prepared according to the General experimental procedures section and purified by column chromatographic purification (CH_2Cl_2), giving a white powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.31 (s, 1H, -OH), 4.52-4.62 (m, 2H, -CH_2NO_2), 5.55 (ddd, *J* 4.1, 4.2, 8.5 Hz, 1H, -C<u>H</u>OH), 7.57 (d, *J* 8.3 Hz, 2H, ArH), 7.70 (d, *J* 8.3 Hz, 2H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 70.1, 80.6, 112.9, 118.1, 126.7, 132.8, 143.0.

2-Nitro-1-(4-fluorophenyl)ethanol

The title compound was prepared according to the General experimental procedures section and purified by column chromatographic purification (CH_2Cl_2), giving a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.88 (s, 1H, -OH), 4.50 (dd, *J* 3.1, 13.4 Hz, 1H, -CH_2NO_2), 4.59 (dd, *J* 9.4, 13.4 Hz, 1H, -CH_2NO_2), 5.45 (dd, *J* 3.1, 9.4 Hz, 1H, -C<u>H</u>OH), 7.06-7.12 (m, 2H, ArH), 7.37-7.42 (m, 2H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 70.3, 81.1, 116.0, 127.8, 133.8, 162.9.

2-Nitro-1-(2-nitrophenyl)ethanol

The title compound was prepared according to the General experimental procedures section and purified by column chromatographic purification (petroleum ether:ethyl acetate, 5:1 v/v), giving a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.52 (s, 1H, -OH), 4.56 (dd, *J* 13.9, 8.8 Hz, 1H, -CH_2NO_2), 4.84 (dd, *J* 13.9, 2.2 Hz, 1H, -CH_2NO_2), 6.01 (ddd, *J* 2.2, 4.2, 8.8 Hz, 1H, -C<u>H</u>OH), 7.51-7.59 (m, 1H, ArH), 7.71-7.79 (m, 1H, ArH), 7.90-7.96 (m, 1H, ArH), 8.02-8.07 (m, 1H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 69.9, 80.6, 124.2, 126.9, 144.9, 148.2.

2-Nitro-1-(3-nitrophenyl)ethanol

The title compound was prepared according to the General experimental procedures section and purified by column chromatographic purification (petroleum ether:ethyl acetate, 5:1 v/v), giving a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.39 (s, 1H, -OH), 4.58-4.67 (m, 2H, -CH_2NO_2), 5.60 (dd, *J* 3.3, 9.3 Hz, 1H, -C<u>H</u>OH), 7.56-7.66 (m, 1H, ArH), 7.75-7.79 (m, 1H, ArH), 8.18-8.24 (m, 1H, ArH), 8.28-8.36 (m, 1H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 71.8, 83.2, 123.4, 127.0, 130.3, 137.6, 140.4, 147.6.

2-Nitro-1-(3-chlorophenyl)ethanol

The title compound was prepared according to the General experimental procedures section and purified by column chromatographic purification (petroleum ether:ethyl acetate, 5:1 v/v), giving a dark yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.01 (s, 1H, -OH), 4.48-4.60 (m, 2H, -CH_2NO_2), 5.44 (dd, *J* 3.9, 13.2 Hz, 1H, -C<u>H</u>OH), 7.24-7.29 (m, 2H, ArH), 7.31-7.36 (m, 1H, ArH), 7.42 (s, 1H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 71.8, 84.2, 128.3, 129.3, 130.5, 131.2, 134.2, 146.3.

2-Nitro-1-(4-methoxyphenyl)ethanol

The title compound was prepared according to the General experimental procedures section and purified by column chromatographic purification (petroleum ether:ethyl acetate, 3:1 v/v) gave a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.76 (s, 1H, -OH), 3.81 (s, 3H, -CH_3O), 4.48 (dd, *J* 2.9, 13.2 Hz, 1H, -CH_2NO_2), 4.60 (dd, *J* 9.6, 13.2 Hz, 1H, -CH_2NO_2), 5.40 (ddd, *J* 2.9, 4.2, 9.6 Hz, 1H, -C<u>H</u>OH), 6.92 (d, *J* 8.7 Hz, 2H, ArH), 7.32 (d, *J* 8.7 Hz, 2H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 69.9, 80.6, 124.2, 126.9, 144.9, 148.2.

2-Nitro-1-(2-methylphenyl)ethanol

The title compound was prepared according to the General experimental procedures section and purified by column chromatographic purification (petroleum ether:ethyl acetate, 10:1 v/v), giving a dark yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H, -CH_3), 2.69 (s, 1H, -OH), 4.41-4.45 (dd, *J* 2.8, 13.2 Hz, 1H, -C<u>H</u>OH), 4.51-4.57 (dd, *J* 9.6, 13.2 Hz, 1H, -C<u>H</u>OH), 5.44 (m, 1H, -C<u>H</u>OH), 7.20-7.29 (m, 3H, ArH), 7.50-7.53 (m, 1H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 10.1, 68.1, 80.4, 125.8, 127.0, 128.9, 131.1, 134.7, 136.5.

Results and Discussion

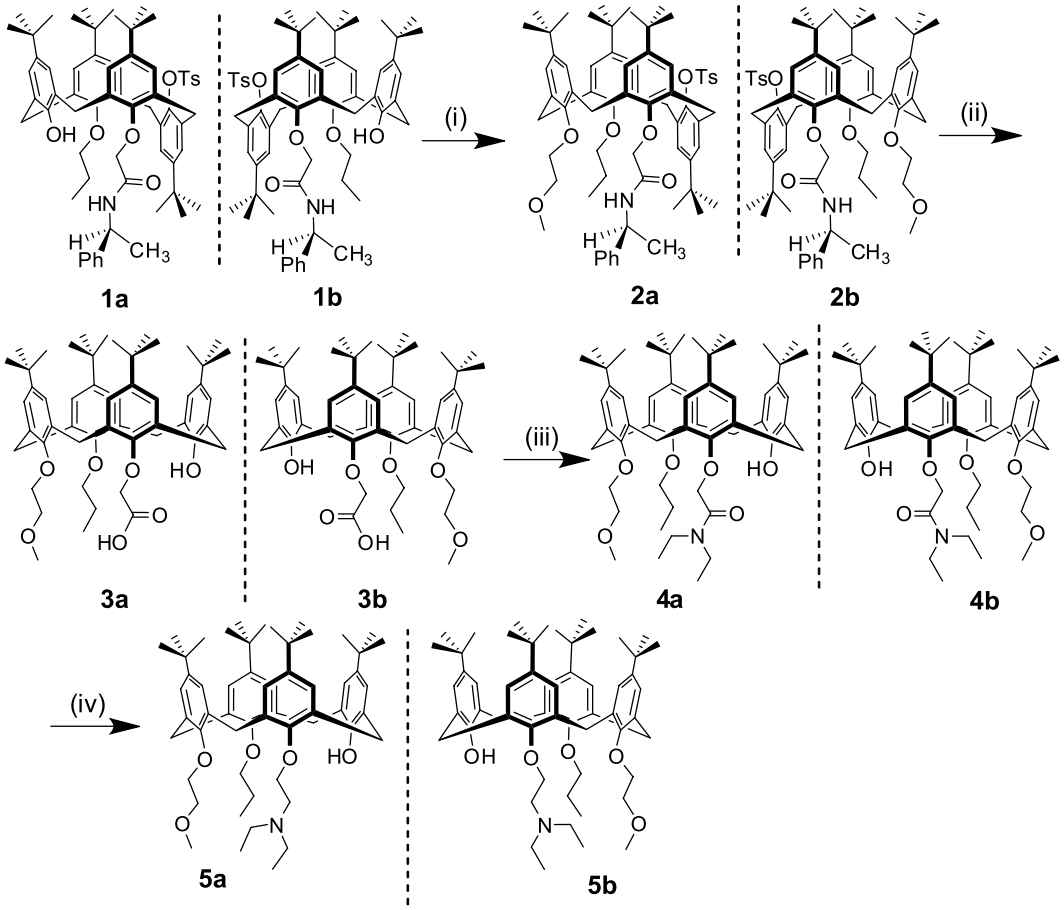
Synthesis

As shown in Scheme 1, starting from a pair of optically pure inherently chiral calix[4]arene diastereomers **1a** and **1b** reported by Kalchenko and co-workers,[17] the alkylation of their last hydroxy groups with 2-methoxyethyl tosylate readily afforded **2a** and **2b** in high yields, respectively. Acids **3a** and **3b** were obtained in moderate yields after the removal of *p*-toluenesulfonyl and phenylethylamide of **2a** and **2b** with *t*-BuOK in a mixed solvent, respectively. Diethylamine was coupled with **3a** and **3b**, respectively, in dicholomethane using 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) and 4-dimethylaminopyridine (DMAP) to produce amides **4a** and **4b**. The reduction of **4a** and **4b** with $LiAlH_4$ in THF gave novel *N*,*O*-type compounds **5a** and **5b**, respectively. The structures of **2a** and **2b**, **3a** and **3b**, **4a** and **4b**, and **5a** and **5b** were confirmed by their ^{1}H NMR, ^{13}C NMR and MS spectra. Their cone or partial cone conformation is clearly shown in the bridging methylene signals of their ^{13}C NMR, respectively.[18] Since **1a** and **1b** have been confirmed as a pair of diastereomers

by Kalchenko,[17] it is undoubtedly deduced that **2a** and **2b** are a pair of diastereomers, and **3a** ($[\alpha]_D^{25}$ = +7.4) and **3b** ($[\alpha]_D^{25}$ = −7.5), **4a** ($[\alpha]_D^{25}$ = +5.8) and **4b** ($[\alpha]_D^{25}$ = −5.8), and **5a** ($[\alpha]_D^{25}$ = +2.8) and **5b** ($[\alpha]_D^{25}$ = −2.8) are three pairs of enantiomers, respectively.

Asymmetric catalysis

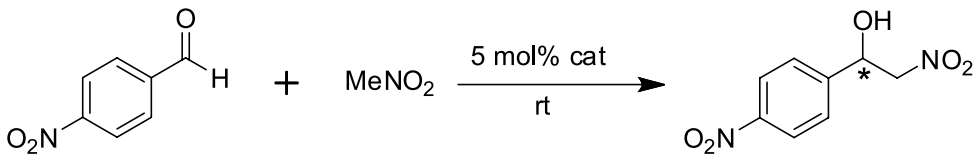
The catalytic abilities of **5a** and **5b** were explored as chiral organocatalysts for Henry (nitroaldol) reaction between 4-nitrobenzaldehyde and nitromethane. The effect of solvent on the reaction was firstly examined at room temperature. The results from the common different solvents were summarized in Table 1. It can be seen that the novel *N*,*O*-type organocatalysts **5a** and **5b** showed an ability to induce enantioselectivity more or less in different solvents. We were delighted to find that an amount of 5 mol% catalysts showed sufficient to achieve the reaction. The reaction in CH_3CN can not afford the desired product in 48 h (Table 1, entry 5). The yield (30%) and enantioselectivity (1.6% ee) using **5b** were comparably low in THF in 48 h (Table 1, entry 6). However, the excellent yields and notable enantioselectivities were obtained in 6 h when H_2O was added into CH_3CN and THF, respectively (Table 1, entries 1-4). The yields were not remarkably improved but the enantioselectivities were slightly enhanced in 6 h when H_2O was added into EtOH (Table 1, entries 7 and 8 *versus* entries 9 and 10). The highest enantioselectivity with 7.5% ee was achieved in a mixed protic solvent (EtOH/H_2O, 3:1, v/v) although the yield was not very high (54%) (Table 1, entry 7). These catalytic results showed that protic solvents (H_2O and EtOH) are more beneficial to Henry reaction with higher yield, better enantioselectivity and shorter time than aprotic solvents (CH_3CN and THF). It should be noted that the absolute configuration of major isomers can be puzzlingly inverted along solvent change. The absolute configuration of major isomers using **5a** is always *S*. However, that of major isomers using **5b** is *R* in THF/H_2O, THF and EtOH (Table 1, entries 4, 6 and 10), and *S* in CH_3CN/H_2O and EtOH/H_2O (Table 1, entries 2, 8 and 12). The absolute configuration inversion of major isomers along solvent change ever took place in the catalytic asymmetric addition of diethylzinc to benzaldehyde with inherently



(i) $TsOCH_2CH_2OCH_3$/NaH, THF; (ii) *t*-BuOK, H_2O/BuOH/DMSO; (iii) $HNEt_2$, HBTU, CH_2Cl_2; (iv) $LiAlH_4$/THF.

Scheme 1. Synthesis of inherently chiral calix[4]arenes substituted at the lower rim.

Table 1. Optimization of the reaction conditions

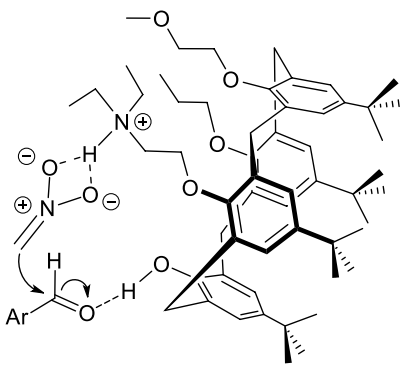


entry[a]	Catalyst	Solvent	Temperature / °C	time / h	Configuration	Yield[d] / %	ee[e] / %
1	**5a**	CH_3CN/H_2O[b]	rt	6	*S*	94	7.3
2	**5b**	CH_3CN/H_2O[b]	rt	6	*S*	93	5.4
3	**5a**	THF/H_2O[b]	rt	6	*S*	99	1.2
4	**5b**	THF/H_2O[b]	rt	6	*R*	99	4.0
5	**5b**	CH_3CN[c]	rt	48	–	–	–
6	**5b**	THF	rt	48	*R*	30	1.6
7	**5a**	$EtOH/H_2O$[b]	rt	6	*S*	54	7.5
8	**5b**	$EtOH/H_2O$[b]	rt	6	*R*	63	1.1
9	**5a**	EtOH	rt	6	*S*	60	2.3
10	**5b**	EtOH	rt	6	–	65	0
11	**5a**	$EtOH/H_2O$[b]	–10	24	*S*	84	0.1
12	**5b**	$EtOH/H_2O$[b]	–10	24	*S*	89	1.2
13	**5a**	$EtOH/H_2O$[b]	–25	72	–	60	0
14	**5b**	$EtOH/H_2O$[b]	–25	72	–	61	0

[a]The reaction was performed with 0.6 mmol 4-nitrobenzaldehyde and 6 mmol nitromethane in 4 mL solvent; [b]the volume ratio of the former to the latter is 3:1; [c]no desired product; [d]isolated yield; [e]enantiomeric excess was determined by HPLC using a Chiracel OD-H column. The absolute configurations of all products were determined by comparing the retention time from HPLC data on the products with those in the literature data.[19-21]

chiral calix[4]arenes containing quinolin-2-yl-methanol moiety.[2] According to the proposed mechanistic mode by Deng and co-workers,[15] we believe that the aldehyde is activated by the hydroxyl group through hydrogen bonding, while the nitromethane is activated by the tertiary amino group in **5a** or **5b** catalytic process (Scheme 2). The more beneficial effect of the protic solvent, especially the mixed solvent $EtOH/H_2O$, may be plausibly explained that they can effectively stabilize nitromethide anion and nitro aldol product through hydrogen bonding interaction.

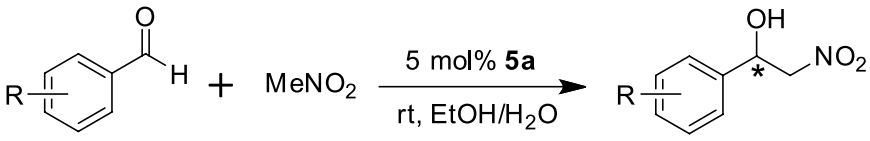
Lowering reaction temperature has frequently been reported to enhance the enantioselectivity of Henry reaction.[9-11] With the optimized solvents in hand, the effect of temperature on enantioselectivity in the Henry reaction is also studied in a mixed protic solvent ($EtOH/H_2O$, 3:1, v/v). The results from the different temperatures (Table 1) showed the enantioselectivity can not be further improved by lowering the temperature at the accompanying expense of increasing the reaction time. At –10 °C, the enantioselectivities became poorer (1.7% ee using **5a** and 1.2% ee using **5b**) and the reaction times were increased to 24 h although the yields were remarkably improved (Table 1, entries 7 and 8 *versus* entries 11 and 12). At –25 °C, the enantioselectivities can not be observed and the reaction times were further increased to 72 h although the yield changes were not obvious (Table 1, entries 7 and 8 *versus* entries 13 and 14).



Scheme 2. Proposed mode of action of catalyst **5a**.

Under the optimal reaction conditions (5 mol% catalyst, room temperature and a mixed protic solvent $EtOH/H_2O$), we then explored a variety of aromatic aldehydes using the catalyst **5a**. Compared to 4-nitrobenzaldehyde, the aromatic aldehydes bearing electron-withdrawing groups (4-CN, 4-F, 2-NO_2, 3-NO_2 and 3-Cl) produced comparable yields and lower enantiomeric excesses (Table 2, entries 1-5). However, the catalytic results from the aromatic aldehydes bearing electron-donating groups (4-MeO,

Table 2. 5a-promoted Henry reaction of nitromethane with different aromatic aldehydes



entry[a]	R	time / h	Configuration	Yield[c] / %	ee[d] / %
1	4-CN	36	*S*	98	2.1
2	4-F	36	*S*	85	0.2
3	2-NO_2	12	*S*	87	1.3
4	3-NO_2	16	*S*	83	1.2
5	3-Cl	24	*S*	80	2.7
6	4-MeO	48	*S*	25	1.0
7	4-$N(CH_3)_2$[b]	48	–	–	–
8	2-CH_3	48	*S*	68	0.5

[a]The reaction was performed with 0.6 mmol aromatic aldehyde and 6 mmol nitromethane in 4 mL solvent (EtOH:H_2O, 3:1, v/v); [b]no reaction; [c]isolated yield; [d]enantiomeric excess was determined by HPLC using a Chiracel OD-H column. The absolute configurations of all products were determined by comparing the retention time from HPLC data on the products with those in the literature data.[19-21]

4-$N(CH_3)_2$ and 2-CH_3) showed comparatively poorer. 4-Methoxybenzaldehyde and 2-methylbenzaldehyde only afforded 25% yield and 1.2% ee, and 68% yield and 0.5% ee in 48 h (Table 2, entries 6 and 8). Although a large quantity of the two substrates remained unreacted, their reactions were clean, and we did not observe dehydration to the corresponding nitroalkenes. The reaction with 4-dimethylaminobenzaldehyde can not take place in the tested condition. These catalytic results clearly showed that catalyst **5a** and the optimized reaction conditions can be applied in a wide scope of aromatic aldehydes, and electron-withdrawing groups on aromatic ring are more beneficial to Henry reaction than electron-donating ones.

In **5a** and **5b**, the ethylene links and methyl groups of their catalytic amino groups are free to rotate and the anchoring phenoxyl group can flap into and away from the calix cavity. Therefore, it can be conceived that their catalytic amino groups are also free to rotate. The nonsatisfactory solvent-dependent enantioselectivity may mainly be attributed to the high flexibility of their catalytic amino groups. Reducing the multiple factors of the high flexibility of the catalytic amino groups will be a huge challenge in the structural modification of inherently chiral calix[4]arenes substituted at the lower rim. So many heavy efforts have been made to structurally modify inherently chiral calix[4]arenes substituted at the *meta* position and the upper rim in Chen and Huang group[1,2] and Shimizu group.[3-7] However, the enantioselectivities in their asymmetric catalysis processes are always poor. Therefore, the asymmetric catalysis prospects of inherently chiral calix[4]arenes seem somewhat gloomy.

Conclusions

In conclusion, starting from a pair of reported inherently chiral calix[4]arene diastereomers, a pair of *N*,*O*-type enantiomers based on inherently chiral calix[4] arenes substituted at the lower rim were synthesized. Their organocatalytical behaviors on Henry reaction between aromatic aldehydes and nitromethane were studied in different solvent under different temperature. The aromatic aldehydes bearing electron-withdrawing groups, a mixed protic solvent and room temperature are beneficial for the organocatalytic reaction. The high flexibility of their catalytic amino groups may mainly result in the nonsatisfactory solvent-dependent enantioselectivity.

Supplementary Information

Supplementary information (NMR spectra of new compounds and HPLC spectra) is available free of charge at http://jbcs.sbq.org.br as PDF file.

Acknowledgments

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