J Incl Phenom Macrocycl Chem
DOI 10.1007/s10847-017-0761-1

ORIGINAL ARTICLE

Novel and highly efficient bifunctional calixarene thiourea derivatives as organocatalysts for enantioselective Michael reaction of nitroolefins with diketones

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Received: 14 April 2017 / Accepted: 31 October 2017

Abstract New bifunctional calixarene thiourea organocatalysts were synthesized and applied in catalytic asymmetric Michael addition of acetylacetone to various nitroolefins at room temperature. The corresponding adducts were obtained in good to excellent yields with excellent enantioselectivities (up to 92% *ee*). The present research demonstrates the advantages of incorporating two stereocontrolling structures into a single catalyst. Notably, it offers a simple and convenient doubly stereocontrolled approach for the catalytic asymmetric synthesis of a chiral organic molecule.

Keywords Calixarenes · Asymmetric Michael addition reactions · Thiourea · Organocatalysis · Enantioselectivity

Introduction

Recently, the design and application of organocatalysts have sustained much attention due to asymmetric organocatalysis emerging as an effective and environmentally friendly methodology for the catalytic production of the valuable synthetic building blocks. The chiral information in the catalyst has been placed at both the nitrogen terminus in the urea or thiourea or in the central chiral core [1]. In this respect [2], a few structures are used in the preparation of the catalysts, namely chiral diamines [3], both enantiomers of trans cyclohexane-1,2-diamine [4], binaphthyl amines [5], diamines derived from cinchona alkaloids [6], amino alcohols [7] and very recently, sugars [8].

Michael addition to electron deficient nitroolefins is one of the important reactions in organic synthesis that access to synthetically useful functionalized nitroalkanes [9]. Also the direct asymmetric Michael addition of carbon nucleophiles, such as aldehydes, ketones, and methylene-active substrates, to nitroolefins is one of the most attractive and atom-economical processes to access functionalized enantiomerically enriched nitroalkanes, and impressive progress was recently made in this area [10]. In contrast, the use of chiral bifunctional thioureas as powerful hydrogen-bond-donating organocatalysts for the synthesis of optically active compounds has become a new and exciting area of contemporary synthetic organic chemistry [11] since Jacobsen successfully develop an effective chiral Schiff base–thiourea catalyzed asymmetric Strecker reaction [12].

Calixarenes compose an important category of macrocyclic compound on account of their potential for forming host–guest complexes with varied classes of compounds in supramolecular chemistry [13]. The sites accesible on these macrocyclic compounds can be simply modified to tailor them for a great deal applications, such as phase-transfer catalysts, ionophores in catalysis, carriers in liquid membrane technology, heavy metal adsorption agents, alkali metal complexation agents, extractants for anions and cations, and chemical sensors [14]. The most popular chiral building blocks used, amino acids [15], peptides [16], amino alcohols [17], sugars [18], tartaric acid esters [19], binaphthyl [20], menthone [21], and guanidinium [22] groups offer a wide range of possibilities for providing calix [4] arenes with asymmetric features.

Thus, chiral calix [4] arene derivatives obtained in this way not only provide a controlled means for studying the fundamentals of non-covalent interactions in nature, but also open up new routes for developing novel enantioselective sensors, asymmetric catalysts, selectors and other molecular

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Published online: 08 November 2017

devices [23]. In the past few years, a series of thiourea-based catalysts were designed and synthesized because of their strong hydrogen-bonding activity and effectively catalyzed various types of asymmetric reactions. Impressive progress has been made in the development of new, readily available chiral organocatalysts. We had previously reported the synthesis of novel chiral calix [4] arenes containing various functionalities as organocatalysts and their catalytic activities in asymmetric Michael addition of aldehydes to nitroalkenes and maleimides [24–26]. Herein, we report the synthesis of calixarene-based chiral bifunctional organocatalysts bearing tertiary amine–thiourea moiety in both enantiomeric forms and their application in the catalytic conjugate addition of acetylacetone to nitroolefins.

Experimental

General

IR spectra were obtained on a Termo Scientific Nicolet iS5 FTIR spectrometer equipped with an ATR unit and are reported in wavenumbers (cm^{-1}). Melting points were determined on an Electrothermal 9100 apparatus in a sealed capillary. Optical rotations were obtained on an Atago AP-100 digital polarimeter. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were obtained at room temperature using $CDCl_3$ as solvent and chemical shifts are reported in sppm. Data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad), and coupling constants (Hz). Chiral HPLC analysis was carried out on Agilent 1100 equipment connected with Chiralpak Daicel AD-H and AS-H columns. Elemental analyses were performed using a Leco CHNS-932 analyzer. Crude products were purified by column chromatography on silica gel of 230–400 mesh. All solvents and reagents were purified by standard techniques.

Synthesis of catalysts

Chiral catalysts **1a**–**1b** and chiral *p*-tert-butylphenol derivatives **8, 9** and **10** were obtained following the literature procedure [25].

General procedure for the synthesis of 2a–2b and 3a–3b

The solution of **1a** or **1b** (1.484 g 1.38 mmol) in 20 mL dry acetonitrile was stirred for 30 min at room temperature. Propionaldehyde (0.936 g, 16.13 mmol) was then added and the resulting mixture was stirred for 15 min. $NaBH_3CN$ (0.596 g, 9.49 mmol) was then added, followed 15 min later by AcOH (0.025 mL, 0.44 mmol). After stirring 1 day at room temperature, the reaction mixture was diluted with 2% CH_3OH-CH_3Cl (150 mL), washed with 1N NaOH (4 × 45 mL). The aqueous layer was re-extracted with $CHCl_3$ (3 × 30 mL), the combined organic layer was dried over anhydrous $MgSO_4$. The crude product was directly loaded onto a silica gel column. Flash column chromatography using the indicated eluent ($CHCl_3$–MeOH) afforded the **2a**–**2b**.

25,27-Bis(3-((1*R*,2*R*)-2-dipropylaminocyclohexyl) thiourea)-26,28-dihydroxy-5,11,17,23-tetra(tert-butyl) -calix [4] arene (2a) and 25,27-Bis(3-((1*S*,2*S*)-2-dipropylaminocyclohexyl)thiourea)-26,28-dihydroxy-5,11,17, 23-tetra(tert-butyl)-calix [4] arene (2b)

(2a) Crystalline solid; 1.287 g, 75% yield; $\alpha_D^{25} + 3.32$ (*c* 1, $CHCl_3$); mp 175–177 °C; **(2b)** Crystalline solid; 1.236 g, 72% yield; $\alpha_D^{25} - 3.54$ (*c* 1, $CHCl_3$); mp 174-176 °C; IR (cm^{-1}): 595, 664, 752, 818, 870, 944, 1045, 1094, 1123, 1360, 1539, 1634, 2863, 2929, 2952, 3273; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.78–1.01 (m, 12H), 1.01 (s, 18H), 1.02–1.23 (m, 8H), 1.24 (s, 18H), 1.36–1.84 (m, 8H), 1.87–2.15 (m, 4H), 2.18–2.42 (m, 8H), 2.43–2.64 (m, 8H), 2.65–3.21 (m, 4H), 3.34 (d, 4H, *J* = 13.0 Hz), 3.74–4.01 (m, 8H), 4.03 (d, 4H, *J* = 13.2 Hz), 6.67 (s, 4H), 7.03 (s, 4H), 7.99 (bs, 2H), NH-signals could not be detected; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.5, 11.6, 16.5, 23.7, 24.4, 24.6, 31.0, 31.1, 31.4, 31.6, 33.8, 33.9, 125.1, 125.2, 125.4, 125.6, 132.5, 132.6, 136.1, 141.2, 141.5, 142.04, 146.92, 149.52, 150.4; Anal. Calcd. For $C_{76}H_{118}N_6O_4S_2$ (1243.94): C, 73.38; H, 9.56; N, 6.76%. Found: C, 73.54; H, 9.32; N, 6.51%.

General procedure for the synthesis of 3a–3b

To a solution of **1a** and **1b** (0.5 g, 0.46 mmol) in 10 mL dry CH_3CN and K_2CO_3 (0.29 g, 2.1 mmol) was added 3-phenylpropanal (0.25 g, 1.86 mmol) and the resulting mixture was heated to reflux for 32 h. The reaction mixture was allowed to warm slowly to room temperature and the solvent was removed in vacuo. The residue was dissolved in dichloromethane (10 mL) and water (10 mL); the aqueous phase was separated and extracted with dichloromethane (3 × 10 mL). The combined organic layer was dried over anhydrous $MgSO_4$. The crude product was directly loaded onto a silica gel column. Flash column chromatography using the indicated eluent ($CHCl_3$–MeOH) afforded the **3a**–**3b**.

25,27-Bis(3-((1*R*,2*R*)-2-(bis(3-phenylpropyl)) amino cyclohexyl)thiourea)-26,28-dihydroxy-5,11,17,23-tetra(tert-butyl)-calix [4] arene(3a) and 25,27-Bis(3-((1*S*,2*S*)-2-(bis(3-phenylpropyl)amino-cyclohexyl)thiourea))-26,28-dihydroxy-5,11,17,23-tetra(tert-butyl)-calix [4] arene(3b)

(**3a**) Crystalline solid; 0.541 g, 76% yield; α_D^{25} − 3.94 (c 1, $CHCl_3$); mp 116–118 °C; (**3b**) Crystalline solid; 0.534 g, 75% yield; α_D^{25} + 4.00 (c 1, $CHCl_3$); mp 119–121 °C; IR (cm^{-1}): 562, 590, 660, 745, 780, 818, 871, 943, 1045, 1123, 1195, 1298, 1360, 1452, 1483, 1544, 1601, 1667, 2860, 2948, 3266; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.02 (s, 18H), 1.09–1.26 (m, 8H), 1.29 (s, 18H), 1.45–2.01 (m, 12H), 2.11–2.38 (m, 8H), 2.40–2.64 (m, 8H), 2.65–2.84 (m, 8H), 2.90–3.15 (m, 4H), 3.33 (d, 4H, *J* = 13.2 Hz), 3.66–4.38 (m, 8H), 4.41 (d, 4H, *J* = 13.6 Hz), 6.74–7.10 (m, 8H), 7.14–7.40 (m, 20H), 7.88 (bs, 2H), NH-signals could not be detected; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6, 29.7, 31.0, 31.9, 32.0, 32.4, 33.5, 33.8, 34.4, 36.5, 50.3, 64.5, 65.6, 125.1, 125.6, 125.7, 128.4, 128.8, 129.0, 132.1, 132.6, 136.8, 139.4, 141.6, 142.1, 142.5, 142.7, 147.1, 147.5, 148.8, 149.5, 150.4, 159.9, 161.9; Anal. Calcd. for $C_{100}H_{134}N_6O_4S_2$ (1548.33): C, 77.57; H, 8.72; N, 5.43%. Found: C, 77.32; H, 8.51; N, 5.65%

Procedure for the synthesis of chiral *p*-tert-butylphenol analogue 11

The solution of **10** (0.04 g, 0.11 mmol) in 10 mL dry acetonitrile was stirred for 30 min at room temperature. Propionaldehyde (0.226 g, 3.9 mmol) was then added and the resulting mixture was stirred for 15 min. $NaBH_3CN$ (0.049 g, 0.78 mmol) was then added, followed 15 min later by AcOH (0.144 mL, 2.52 mmol). After stirring 4 h at room temperature, the reaction mixture was diluted with 2% CH_3OH–CH_3Cl (30 mL), washed with 1N NaOH (4 × 25 mL). The aqueous layer was re-extracted with $CHCl_3$ (3 × 20 mL), the combined organic layer was dried over anhydrous $MgSO_4$. The crude product was directly loaded onto a silica gel column. Flash column chromatography using the indicated eluent ($CHCl_3$–MeOH) afforded the **11**.

1-(3-(4-tert-butylphenoxy)propyl)-3-((1*S*,2*S*)-2(diethyla mino)cyclohexyl) thiourea (11)

Yellow oil; 0.037 g, 75% yield; α_D^{25} − 7.00 (*c* 1, $CHCl_3$); IR (cm^{-1}): 731, 1036, 1241, 1383, 1512, 1644, 2865, 2948, 3138; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.36–0.60 (m, 12H), 0.74–0.94 (m, 11H), 1.00–1.29 (m, 2H), 1.31–1.53 (m, 3H), 1.51–1.75 (m, 3H), 3.10–3.48 (m, 4H), 3.52–3.70 (m, 4H), 6.39–6.60 (m, 2H), 6.61–7.05 (m, 2H), NH-signals could not be detected; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.6, 11.3, 24.2, 24.3, 28.6, 31.5, 32.4, 34.1, 38.5, 113.9, 120.3, 143.7, 156.2; Anal. Calcd. For $C_{26}H_{45}N_3OS$ (447.72): C, 69.91; H, 10.13; N, 9.41%. Found: C, 69.62; H, 10.05; N, 9.62%.

General procedure for direct Aldol reaction

Acetylacetone **5** (0.1 mmol) was added to a mixture of catalyst (10 mol%) and the corresponding nitroolefin **4** (0.05 mmol) in CH_3CN (125 µL). The reaction mixture was stirred at room temperature for the required time. After the nitroolefin was consumed by TLC analysis, the residue was separated by flash chromatography over silica gel (petroleum ether/ethyl acetate) to give Michael adduct. The enantiomeric excess was determined by chiral HPLC with Daicel Chiralpak AD-H or AS-H columns. The absolute configuration of the products **6a–j** was determined by comparison with literature data: **6a** [1, 9], **6b, c, d, e** [1], **6f** [27], **6 g** [28], **6 h** [29], **6i** [30], **6j** [31].

(*S*)-3-(2-Nitro-1-phenylethyl)pentane-2,4-dione (6a)

This compound was obtained from *β*-nitrostyrene and acetylacetone to provide the title compound (97% yield) and purified by flash chromatography (petroleum ether/ethyl acetate = 5:1). α_D^{25}: + 196.2 (*c* = 1.0, $CHCl_3$); IR (cm^{-1}): 702, 1142, 1269, 1365, 1433, 1496, 1555, 1703, 1732; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.87 (s, 3H, COC*H*$_3$), 2.23 (s, 3H, COC*H*$_3$), 4.21–4.17 (m, 1H, ArC*H*CH_2), 4.30 (d, 1H, *J* = 10.5 Hz, COC*H*CO), 4.58–4.55 (m, 2H, CHC*H*$_2NO_2$), 7.12–7.10 (m, 2H, Ar*H*), 7.26–7.19 (m, 3H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.6, 30.5, 42.7, 70.7, 78.2, 127.9, 128.6, 129.3, 135.9, 201.0, 201.8; The enantiomeric excess was determined by HPLC (Chiralcel AS-H), Hexane: *i*-PrOH 85:15, UV 210 nm, flow rate 1 mL/min, *R*-isomer, t_R 22.39 min and *S*-isomer, t_R 14.43 min. 81% *ee*.

(*S*)-3-[1-(2-Bromophenyl)-2-nitroethyl]pentane-2,4-dione (6b)

This compound was obtained from 2-Br-*β*-nitrostyrene and acetylacetone to provide the title compound (65% yield) and purified by flash chromatography (petroleum ether/ethyl acetate = 6:1). α_D^{25}: +209.3 (*c* = 1.0, $CHCl_3$); IR (cm^{-1}): 765, 1152, 1260, 1359, 1433, 1469, 1553, 1705, 1727; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.04 (s, 3H, COC*H*$_3$), 2.29 (s, 3H, COC*H*$_3$), 4.59 (d, *J* = 9.4 Hz, 1H, COC*H*CO), 4.68–4.64 (m, 1H, ArC*H*CH_2), 4.85–4.71 (m, 2H, CHC*H*$_2NO_2$), 7.19–7.12 (m, 2H, Ar*H*), 7.30–7.26 (m, 1H, Ar*H*), 7.63 (d, *J* = 7.9 Hz, 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.3, 30.9, 41.0, 69.1, 76.2, 128.3, 129.9, 134.0, 135.0, 200.8, 201.9; The enantiomeric excess was determined by HPLC (Chiralcel AD-H), Hexane: *i*-PrOH 97:3, UV 210 nm, flow

rate 0.5 mL/min, *R*-isomer, t_R 27.30 min and *S*-isomer, t_R 22.44 min. 90% *ee*.

(*S*)-3-[1-(3-Bromophenyl)-2-nitroethyl]pentane-2,4-dione (6c)

This compound was obtained from 3-Br-β-nitrostyrene and acetylacetone to provide the title compound (72% yield) and purified by flash chromatography (petroleum ether/ethyl acetate = 6:1). α_D^{25}: +132.6 ($c = 1.0$, $CHCl_3$); IR (cm^{-1}): 699, 790, 1141, 1252, 1367, 1383, 1433, 1477, 1550, 1703, 1727; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.00 (s, 3H, $COCH_3$), 2.29 (s, 3H, $COCH_3$), 4.23–4.18 (m, 1H, $ArCHCH_2$), 4.33 (d, $J = 10.6$ Hz, 1H, $COCHCO$), 4.63–4.61 (m, 2H, $CHCH_2NO_2$), 7.26–7.11 (m, 2H, Ar*H*), 7.35 (s, 1H, Ar*H*), 7.43 (d, $J = 8.9$ Hz, 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.8, 30.5, 42.3, 70.3, 77.7, 123.3, 126.6, 130.8, 131.0, 131.8, 138.5, 200.4, 201.3; The enantiomeric excess was determined by HPLC (Chiralcel AD-H), Hexane: *i*-PrOH 85:15, UV 210 nm, flow rate 1 mL/min, *R*-isomer, t_R 34.26 min and *S*-isomer, t_R 17.67 min. 83% *ee*.

(*S*)-3-[1-(4-Bromophenyl)-2-nitroethyl]pentane-2,4-dione (6d)

This compound was obtained from 4-Br-β-nitrostyrene and acetylacetone to provide the title compound (81% yield) and purified by flash chromatography (petroleum ether/ethyl acetate = 5:1). α_D^{25}: +137.1 ($c = 1.0$, $CHCl_3$); IR (cm^{-1}): 818, 1140, 1264, 1362, 1431, 1490, 1547, 1699, 1729; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.98 (s, 3H, $COCH_3$), 2.30 (s, 3H, $COCH_3$), 4.24–4.18 (m, 1H, $ArCHCH_2$), 4.33 (d, $J = 10.8$ Hz, 1H, $COCHCO$), 4.61–4.59 (m, 2H, $CHCH_2NO_2$), 7.07 (d, $J = 8.4$ Hz, 2H, Ar*H*), 7.46 (d, $J = 8.5$ Hz, 2H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.7, 30.5, 42.2, 70.4, 77.8, 122.7, 129.6, 132.5, 135.0, 200.6, 201.4; The enantiomeric excess was determined by HPLC (Chiralcel AS-H), Hexane: *i*-PrOH 85:15, UV 210 nm, flow rate 1 mL/min, *R*-isomer, t_R 30.29 min and *S*-isomer, t_R 16.79 min. 83% *ee*.

(*R*)-3-[1-(2-Methoxyphenyl)-2-nitroethyl]pentane-2,4-dione (6e)

This compound was obtained from 2-MeO-β-nitrostyrene and acetylacetone to provide the title compound (93% yield) and purified by flash chromatography (petroleum ether/ethyl acetate = 4:1). α_D^{25}: −186.1 ($c = 1.0$, $CHCl_3$); IR (cm^{-1}): 758, 1024, 1159, 1247, 1359, 1494, 1552, 1596, 1702, 1727; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.93 (s, 3H, $COCH_3$), 2.28 (s, 3H, $COCH_3$), 3.88 (s, 3H, $ArOCH_3$), 4.51–4.45 (m, 1H, $COCHCO$), 4.61–4.56 (m, 2H, $CHCH_2NO_2$), 4.86–4.75 (m, 1H, $ArCHCH_2$), 6.91–6.87 (m, 2H, Ar*H*), 7.09–7.07 (m, 1H, Ar*H*), 7.29–7.24 (m, 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.7, 29.7, 30.4, 38.9, 55.4, 69.1, 111.2, 121.2, 123.5, 129.7, 130.2, 201.5, 202.3, The enantiomeric excess was determined by HPLC (Chiralcel AS-H), Hexane: *i*-PrOH 97:3, UV 210 nm, flow rate 0.5 mL/min, *R*-isomer, t_R 42.17 min and *S*-isomer, t_R 40.59 min. 92% *ee*.

(*S*)-3-[1-(4-Methoxyphenyl)-2-nitroethyl]pentane-2,4-dione (6f)

This compound was obtained from 4-MeO-β-nitrostyrene and acetylacetone to provide the title compound (95% yield) and purified by flash chromatography (petroleum ether/ethyl acetate = 5:1). α_D^{25}: +119.7 ($c = 2.5$, $CHCl_3$); IR (cm^{-1}): 812, 1141, 1171, 1261, 1363, 1438, 1515, 1549, 1614, 1705, 1733; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.93 (s, 3H, $COCH_3$), 2.28 (s, 3H, $COCH_3$), 3.76 (s, 3H, $ArOCH_3$), 4.21–4.15 (m,1H, $ArCHCH_2$), 4.32 (d, $J = 10.9$ Hz, 1H, $COCHCO$), 4.58–4.55 (m, 2H, $CHCH_2NO_2$), 6.83 (d, $J = 8.8$ Hz, 2H, Ar*H*), 7.09 (d, $J = 8.7$ Hz, 2H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.5, 30.4, 42.1, 55.2, 70.8, 78.4, 114.6, 127.6, 129.0, 159.4, 201.2, 201.9; The enantiomeric excess was determined by HPLC (Chiralcel AD-H), Hexane: *i*-PrOH 90:10, UV 210 nm, flow rate 1 mL/min, *R*-isomer, t_R 23.70 min and *S*-isomer, t_R 15.53 min. 82% *ee*.

(*R*)-3-[1-(4-Fluorophenyl)-2-nitroethyl]pentane-2,4-dione (6g)

This compound was obtained from 4-F-β-nitrostyrene and acetylacetone to provide the title compound (85% yield) and purified by flash chromatography (petroleum ether/ethyl acetate = 5:1). α_D^{25}: +12.9 ($c = 1$, $CHCl_3$); IR (cm^{-1}): 827, 1141, 1267, 1363, 1437, 1513, 1550, 1704, 1733; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.96 (s, 3H, $COCH_3$), 2.29 (s, 3H, $COCH_3$), 4.26–4.21 (m, 1H, $ArCHCH_2$), 4.33 (d, $J = 10.8$ Hz, 1H, $COCHCO$), 4.61–4.59 (m, 2H, $CHCH_2NO_2$), 7.04–6.99 (m, 2H, Ar*H*), 7.19–7.15 (m, 2H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.6, 30.5, 42.0, 70.6, 78.1, 116.3, 116.5, 129.6, 129.7, 131.7, 161.2, 163.7, 200.8, 201.5; The enantiomeric excess was determined by HPLC (Chiralcel AD-H), Hexane: *i*-PrOH 90:10, UV 210 nm, flow rate 1 mL/min, *R*-isomer, t_R 26.08 min and *S*-isomer, t_R 13.28 min. 79% *ee*.

(*R*)-3-[1-(4-Methylphenyl)-2-nitroethyl]pentane-2,4-dione (6h)

This compound was obtained from 4-Me-β-nitrostyrene and acetylacetone to provide the title compound (89% yield) and purified by flash chromatography (petroleum ether/ethyl acetate = 6:1). α_D^{25}: −78.2 ($c = 2.8$, $CHCl_3$); IR (cm^{-1}): 813, 1140, 1267, 1362, 1430, 1548, 1702, 1731; ^1H

NMR (400 MHz, $CDCl_3$): δ = 1.94 (s, 3H, COCH_3), 2.29 (s, 6H, COCH_3 + ArCH_3), 4.23–4.17 (m, 1H, ArCHCH$_2$), 4.33 (d, J = 10.8 Hz, 1H, COCHCO), 4.61–4.58 (m, 2H, CHCH_2NO$_2$), 7.13–7.07 (m, 4H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0, 29.4, 30.4, 42.4, 70.8, 78.3, 127.8, 130.0, 132.8, 138.3, 201.1, 201.9; The enantiomeric excess was determined by HPLC (Chiralcel AD-H), Hexane: *i*-PrOH 90:10, UV 210 nm, flow rate 0.8 mL/min, *R*-isomer, t_R 16.98 min and *S*-isomer, t_R 10.64 min. 77% *ee*.

(*S*)-3-[1-(4-Chlorophenyl)-2-nitroethyl]pentane-2,4-dione (6i)

This compound was obtained from 4-Cl-*β*-nitrostyrene and acetylacetone to provide the title compound (91% yield) and purified by flash chromatography (petroleum ether/ethyl acetate = 5:1). α_D^{25}: +19.2 (c = 0.5, $CHCl_3$); IR (cm^{-1}): 821, 1141, 1270, 1361, 1332, 1732, 1482, 1549, 1701; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.91 (s, 3H, COCH_3), 2.23 (s, 3H, COCH_3), 4.19–4.13 (m, 1H, ArCHCH$_2$), 4.27 (d, J = 10.5 Hz, 1H, COCHCO), 4.55–4.53 (m, 2H, CHCH_2NO$_2$), 7.08–7.06 (m, 2H, ArH), 7.26–7.23 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.7, 30.5, 42.1, 70.5, 77.9, 129.3, 129.6, 134.5, 200.6, 201.4; The enantiomeric excess was determined by HPLC (Chiralcel AS-H), Hexane: *i*-PrOH 85:15, UV 210 nm, flow rate 1 mL/min, *R*-isomer, t_R 31.46 min and *S*-isomer, t_R 15.24 min. 88% *ee*.

(*R*)-3-[1-(2,4-Dichlorophenyl)-2-nitroethyl]pentane-2,4-dione (6j)

This compound was obtained from 2,4-Cl-*β*-nitrostyrene and acetylacetone to provide the title compound (93% yield) and purified by flash chromatography (petroleum ether/ethyl acetate = 5:1). α_D^{25}: +59.1 (c = 2.25, $CHCl_3$); IR (cm^{-1}): 1360, 1378, 1475, 1550, 1704, 1730; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.06 (s, 3H, COCH_3), 2.29 (s, 3H, COCH_3), 4.54 (d, J = 9.7 Hz, 1H, COCHCO), 4.71–4.61 (m, 2H, CHCH_2NO$_2$), 4.84–4.80 (m, 1H, ArCHCH$_2$), 7.10 (d, J = 8.4 Hz, 1H, ArH), 7.24–7.21 (m, 1H, ArH), 7.45 (d, J = 2.1 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.6, 30.9, 38.4, 68.8, 76.0, 128.0, 130.5, 132.1, 134.5, 135.1, 200.5, 201.6; The enantiomeric excess was determined by HPLC (Chiralcel AD-H), Hexane: *i*-PrOH 90:10, UV 210 nm, flow rate 1 mL/min, *R*-isomer, t_R 12.21 min and *S*-isomer, t_R 9.68 min. 86% *ee*.

Results and discussion

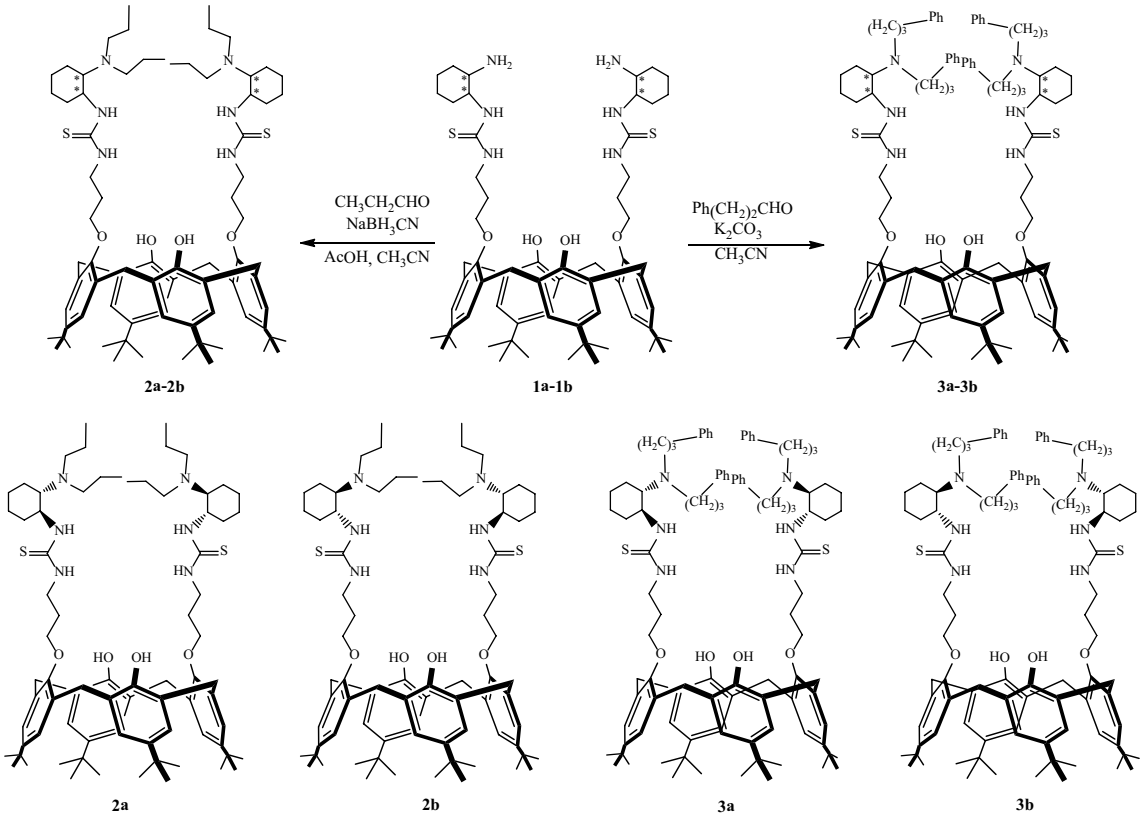
Bifunctional calixarene thiourea organocatalysts (1*R*, 2*R*)-**2a**, (1*S*, 2*S*)-**2b**, (1*R*, 2*R*)-**3a** and (1*S*, 2*S*)-**3b** were synthesized from the reaction of primary amine-thioureas **1a** and **1b** with propionaldehyde and 3-phenyl propanal according to the method reported by us [25] in 72–76% yields as shown in Scheme 1.

The ^{1}H NMR spectra of chiral calix [4] arene derivatives exhibit two sets of doublets 3.34 ppm (J = 13.0 Hz) and 4.03 ppm (J = 13.2 Hz) for **2a–b** and 3.33 ppm (J = 13.2 Hz) and 4.41 ppm (J = 13.6 Hz) for **3a**–**b** due to the bridging methylene protons. This indicates that chiral calix [4] arene derivatives adopt a cone conformation in $CHCl_3$.

The catalytic activity of these calixarene thiourea organocatalysts was initially evaluated in the conjugate addition reaction of acetylacetone (**5**) to *trans*-*β*-nitrostyrene **4a** in the presence of 10 mol% of catalyst **2a** at room temperature. To check the effect of various solvents for better yield and selectivities, the same reaction was tested in different solvents and the results were summarized in Table 1. Ten different solvents with organocatalyst **2a** were examined to find optimum reaction media and the conjugate addition reaction with organocatalyst **2a** in CH_3CN afforded the best enantioselectivity (81% *ee*; Table 1, Entry 7).

Solvent evaluation revealed that both the yield and the enantioselectivity were highly dependent on the solvent. Polar solvents such as 1,1-dichloroethane, EtOAc and CH_3CN gave higher yields and enantioselectivities (Table 1, entries 4, 5 and 7). When a nonpolar solvent such as toluene and CCl_4 were used, both the yield and enantioselectivity decreased remarkably (Table 1, entries 2 and 6). After selecting CH_3CN as the most efficient solvent, we proceeded to investigate the influence of different experimental parameters including temperature and catalyst loading in the asymmetric Michael addition reaction. The results were also summarized in Table 1, entries 11 and 12. In order to evaluate the efficiency of chiral bifunctional organocatalyst **2a** in the Michael addition of acetylacetone to *trans*- *β* -nitrostyrene, different catalyst loading (15 mol%) was also tested. Increasing of catalyst loading from 10 to 15% led to some loss in enantioselectivity and yield (Table 1, entry 11). In addition 0 °C showed less desired yields and enantioselectivities than the reaction at room temperature (Table 1, entry 12).

The influence of additives was also studied in an attempt to improve the turnover frequency of the catalyst by accelerating the rate of formation of the intermediate enamine. A survey of several acids including benzoic acid, acetic acid and trifluoroacetic acid did not improve catalyst efficiency and in some cases both the yield and selectivity decreased. (Table 2, entries 2, 5 and 9). Also when using (*R*-) or (*S*-) -1,1′-bi-2- naphthol, pyridine and quinine as additives, both yields and *ee* values were inferior. (Table 2, entries 3, 4, 6 and 7). The catalytic reactivity of **2a** was examined for the Michael addition of acetylacetone to *trans*-*β*-nitrostyrene, in CH_3CN without an additive could be the optimal reaction conditions.



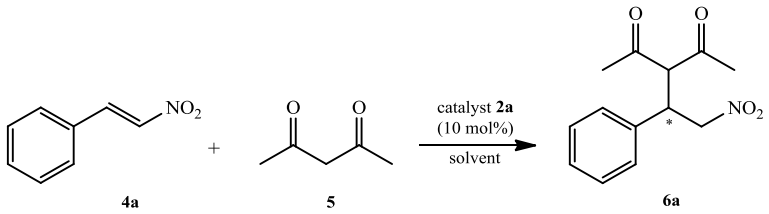
Scheme 1 Chiral calix [4] arene thiourea catalysts **2a/2b** and **3a/3b**

Chiral *p*-tert-butylphenol analogue **11** was synthesized to confirm the role of the achiral calixarene backbone from the chiral primary amine–thiourea **10**. Primary amine **10** was synthesized starting from *p*-tert-butyl phenol in four steps and 68% overall yield according to the known procedure [25] as described in Scheme 2. Then it was reacted with propionaldehyde and sodium cyanoborohydride in CH_3CN to obtain the chiral *p*-tert-butylphenol analogue **11**.

Both aliphatic and aromatic calix [4] arene-based thioureas **2a**–**2b** and **3a–3b** catalyze the Michael addition reaction of acetylacetone to *trans*-*β*-nitrostyrene in CH_3CN high enantioselectivities of up to 81% *ee* (Table 3). Different catalysts also led to different enantioexcess value. Catalyst (1*R*, 2*R*)-**2a**, was also superior to other tested catalysts, such as **2b, 3a, 3b** and **9** (Table 3, entry 1), resulting in both excellent yield and enantioselectivity. (1*S*, 2*S*)-**2b** (10 mol%) was screened as catalyst at room temperature the product was obtained in 86% yield and 79% *ee* (Table 3, entry 3). When using aromatic calix [4] arene-based thioureas **3a** and **3b** as catalyst, the enantioselectivity decreased dramatically and down to 73 and 72% (Table 3, entries 2 and 4). Chiral *p*-tert-butylphenol analogue **11** was tested as catalyst in Table 3, entry 5. When using **11** as catalyst, both yield and *ee* value were inferior (yield 85%, *ee* %51). It is interesting to note that the presence of bulky calixarene moiety of thiourea and the phenolic hydroxy groups on the calixarene scaffold as acidic additives plays a crucial role in helping to increase the electrophilicity of nitrostyrene and preorganising the reaction substrates. It was realized that the aliphatic calix [4] arene-based thiourea **2a** was found to be the best choice for this doubly stereocontrolled organocatalytic process.

Through extensive screening, the optimized reaction conditions of the Michael addition of acetylacetone to nitroolefins were set up (catalyst **2a**, acetonitrile as solvent, room temperature). The doubly stereocontrolled asymmetric addition of 2,4-pentanedione to a variety of nitroalkenes was examined considering the usefulness and versatility of adducts in organic synthesis. A variety of aryl nitroolefins (**4a–j**) reacted smoothly with acetylacetone (**5**) to afford the corresponding products (**6a–j**) in high yields (up to 97%) and excellent enantioselectivities (up to 92% *ee*) in the presence of 10 mol% of catalyst **2a** at room temperature within 8–24 h. It was seen that all reactions of aromatic nitroalkenes proceed smoothly affording the desired products of the (*S*) or (*R*) configuration with high to excellent enantioselectivities (Table 4, (*R*)-adducts, 77–92%, entries 5, 7, 8, 10 and (*S*)-adducts, 81–90%, entries 1–4, 6, 9) and yields. It appears that

Table 1 Optimization of reaction conditions for asymmetric Michael addition reactions between acetylacetone (**5**) and trans-*β*-nitrostyrene (**4a**)



4a **5** **6a**

Entry[a]	Catalyst	Solvent	Time (h)	Yield (%)[b]	*ee* (%)[c,d]
1	**2a**	CH_2Cl_2	8	92	72 (*S*)
2	**2a**	Toluene	8	94	73 (*S*)
3	**2a**	$CHCl_3$	4	89	70 (*S*)
4	**2a**	$ClCH_2CH_2Cl$	24	95	76 (*S*)
5	**2a**	EtOAc	24	93	78 (*S*)
6	**2a**	CCl_4	24	94	69 (*S*)
7	**2a**	CH_3CN	24	97	81 (*S*)
8	**2a**	THF	24	90	72 (*S*)
9	**2a**	MeOH	6	78	52 (*S*)
10	**2a**	DMF	6	65	63 (*S*)
11[e]	**2a**	CH_3CN	24	92	80 (*S*)
12[f]	**2a**	CH_3CN	24	83	76 (*S*)

[a]All reactions were carried out with *trans-β-nitrostyrene* (0.05 mmol), acetylacetone (0.1 mmol) and the catalyst indicated (10 mol%) in solvents (0.125 mL)

[b]Yield of the isolated product after column chromatography

[c]Analyzed in HPLC with chiral AS-H column

[d]The configuration was assigned by comparison of the retention time and specific rotation with literature data

[e]We employed 15 mol% of catalyst

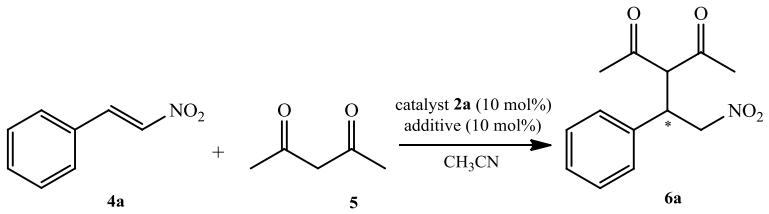
[f]Reaction was carried in an ice bath

the position and the electronic property of the substituents for aromatic rings of nitroalkenes **4a–j** are well tolerated by the enantioselective conjugate addition reactions. Whether electron-withdrawing (Table 4, entries 4, 7 and 9), electrondonating (Table 4, entries 6 and 8), or electron-neutral (Table 4, entry 1) groups on aromatic rings were used, the reactions proceeded smoothly to give the desired adducts in good yields (81–97%) with good enantioselectivity (77–88% *ee*). While substitution of the 2-Br-*β*-nitrostyrene at the ortho position was well tolerated, meta and para substitutions resulted in a loss of enantioselectivity (Table 4, entries 2–4). More significant example was the reaction of 2-MeO-*β*-nitrostyrene (**4e**) which offer Michael product in much higher enantiomeric excesses up to 92% *ee*.

Although the precise reaction mechanism needs further study, a possible transition state has been proposed based onthe observed stereoselectivities of the asymmetric Michael addition of acetylacetone to nitroolefins. A plausible catalytic mode representing the Michael addition of acetylacetone **5** to nitroolefins **4a–j** in the presence of **2a** as a catalyst proposed [32]. First, thiourea moieties of the catalyst **2a** was assumed to interact through hydrogen bonding with a nitro group of the nitroolefins while the tertiary amine deprotonates an acidic proton of acetylacetone, generating a ternary complex, meanwhile the hydroxyl group of the calix [4] arene and the nitro group may form another hydrogen bond, which enhances the electrophilicity of the nitroolefins. Steric hindrance from both moieties (calixarene moiety and the thiourea moiety) of the chiral bifunctional catalyst **2a** and the nuclephilic attack on the re-face of nitrostyrene might be helpful for the increased stereocontrol of the Michael addition reaction.

Surprisingly, the Michael addition of acetylacetone to nitroolefins in the presence of **2a** also led to the opposite asymmetric induction with high yields and enantioselectivities (Table 4, entries 5, 7, 8, 10) under the same conditions because of the nuclephilic attack on the opposite-face of nitrostyrene. This selectivity is the reverse of that normally found for this example in literatüre [33–35].

Table 2 Screening of additives for **2a** catalyzed addition of acetylacetone (**5**) to *trans-β*-nitrostyrene (**4a**)



Entry[a]	Additive (10 mol%)	Time (h)	Yield (%)[b]	*ee* (%)[c,d]
1	Et_3N	6	92	78 (*S*)
2	Benzoic acid	48	85	75 (*S*)
3	(*S*-)-1,1′-Bi-2-Naphthol	24	88	74(S)
4	(*R*-)-1,1′-Bi-2- Naphthol	24	83	76 (*S*)
5	AcOH	64	78	63 (*S*)
6	Pyridine	36	81	79 (*S*)
7	Quinine	36	79	78 (*S*)
8	*p*-TsOH	48	80	75 (*S*)
9	TFA	48	76	73 (*S*)
10	DMAP	96	< 1	n.d.[e]

[a]All reactions were carried out with *trans-β -nitrostyrene* (0.05 mmol), acetylacetone (0.1 mmol) and the catalyst indicated (10 mol%) in CH_3CN (0.125 mL)

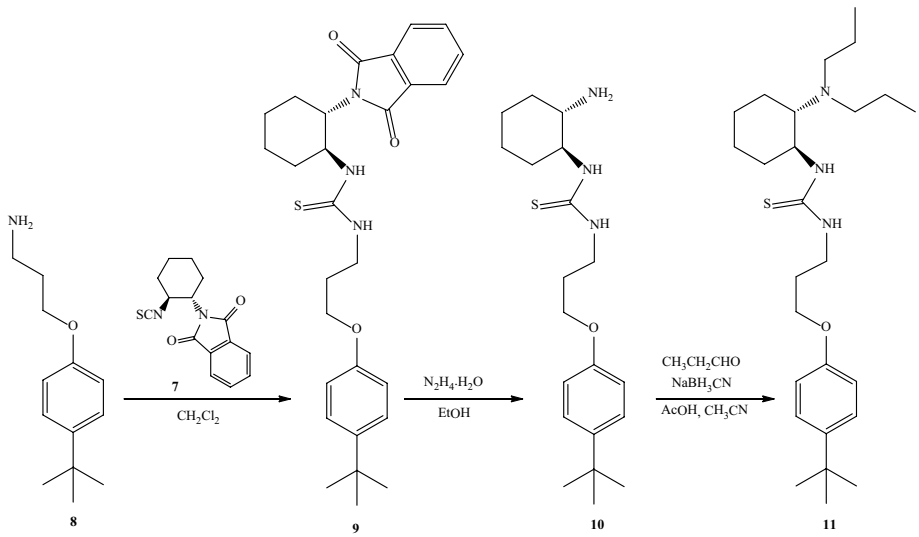
[b]Yield of the isolated product after column chromatography

[c]Analyzed in HPLC with chiral AS-H column

[d]The configuration was assigned by comparison of the retention time and specific rotation with literature data

[e]Not determined

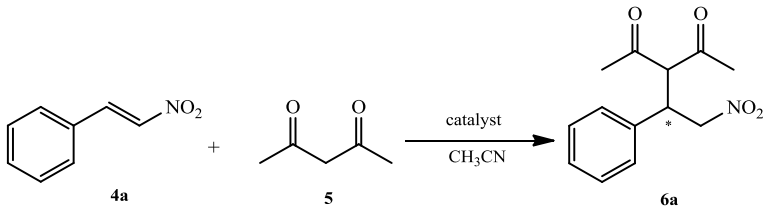
Scheme 2 Synthesis of chiral *p*-tert-butylphenol analogue **11**



Conclusion

In conclusion, a new class of bifunctional calixarene thiourea organocatalysts bearing multiple hydrogen bonding donors was synthesized and taking the Michael addition of dicarbonyl compounds to nitroolefins as a model we have tested the ability of these structures as enantioselective organocatalysts, proving the generality of their use. Among the tested catalysts, **2a**, was the most promising in yield and enantioselectivity. In optimal conditions,

Table 3 Screening of different catalyst in the asymmetric Michael addition reactions between acetylacetone (**5**) and *trans-β*-nitrostyrene (**4a**)



Entry[a]	Catalyst	Time (h)	Yield (%)[b]	*ee* (%)[c,d]
1	**2a**	24	97	81 (*S*)
2	**3a**	36	80	73 (*S*)
3	**2b**	24	86	79 (*S*)
4	**3b**	36	82	72 (*S*)
5	**11**	24	85	51 (*S*)

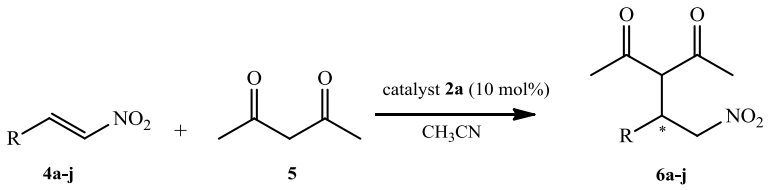
[a]All reactions were carried out with *trans-β -nitrostyrene* (0.05 mmol), acetylacetone (0.1 mmol) and the catalyst indicated (10 mol%) in CH_3CN (0.125 mL)

[b]Yield of the isolated product after column chromatography

[c]Analyzed in HPLC with chiral AS-H column

[d]The configuration was assigned by comparison of the retention time and specific rotation with literature data

Table 4 Asymmetric Michael addition reactions between acetylacetone and different nitroolefins



Entry[a]	R	Time (h)	Product	Yield (%)[b]	*ee* (%)[c,d]
1	C_6H_5	24	**6a**	97	81 (*S*)
2	2-Br-C_6H_4	24	**6b**	65	90 *(S)*
3	3-Br-C_6H_4	12	**6c**	72	83 (*S*)
4	4-Br-C_6H_4	12	**6d**	81	83(*S*)
5	2-MeO-C_6H_4	24	**6e**	93	92 (*R*)
6	4-MeO-C_6H_4	24	**6f**	95	82 (*S*)
7	4-F-C_6H_4	8	**6g**	85	79 (*R*)
8	4-Me-C_6H_4	24	**6h**	89	77 (*R*)
9	4-Cl-C_6H_4	8	**6i**	91	88 (*S*)
10	2,4-Cl-C_6H_3	8	**6j**	93	86 (*R*)

[a]All reactions were carried out with *trans-β -nitrostyrene* (0.05 mmol), acetylacetone (0.1 mmol) and the catalyst **2a** (10 mol%) in CH_3CN (0.125 mL)

[b]Yield of the isolated product after column chromatography

[c]Analyzed in HPLC with chiral AS-H and AD-H columns

[d]The configuration was assigned by comparison of the retention time and specific rotation with literature data

organocatalyst **2a** promoted the asymmetric conjugate addition of acetylacetone to various nitroolefins at room temperature in good yields (up to 97%) and with good enantioselectivity (up to 92% *ee*). Further investigation of these organocatalysts in other asymmetric reactions as well as a more detailed mechanism is currently on going in our laboratory.

Acknowledgements The authors gratefully acknowledge the financial support of this work given by the Scientific and Technological Research Council of Turkey (TUBITAK-113Z696) and Research Foundation of Necmettin Erbakan University (BAP-141110003).

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