Highly enantio- and diastereoselective Michael addition of cyclohexanone to nitroolefins catalyzed by a chiral glucose-based bifunctional secondary amine-thiourea catalyst†

Aidang Lu, Peng Gao, Yang Wu, Youming Wang, Zhenghong Zhou* and Chuchi Tang

Received 19th March 2009, Accepted 7th May 2009
First published as an Advance Article on the web 11th June 2009
DOI: 10.1039/b905306a

A novel bifunctional thiourea bearing a saccharide-scaffold and a secondary amino group was synthesized, and was proven to be an effective organocatalyst for the asymmetric Michael reaction of cyclohexanone to both aryl and alkyl nitroolefins. The corresponding adducts were obtained with excellent diastereo- (up to >99/1 *dr*) and enantioselectivities (up to 97% *ee*).

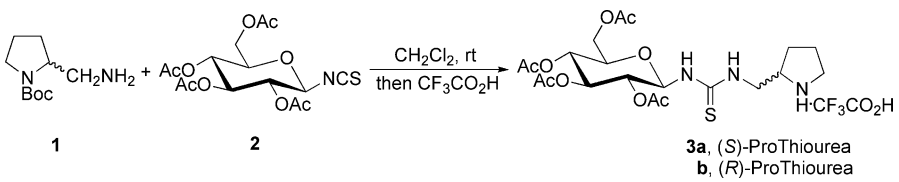
Introduction

The Michael addition of different nucleophiles to electron deficient nitroolefins is one of the most important reactions in organic synthesis that provides access to synthetically useful functionalized nitroalkanes.[1] Because of the versatile reactivity of the nitro functionality, the resulting nitroalkanes can be readily transformed into a wide range of synthetically valuable compounds, such as nitrile oxides,[2] amines,[3] ketones,[4] carboxylic acids[5] and other functional compounds.[6] Among them, the Michael addition of ketone to nitroolefins represents a convenient access to γ-nitroketones, which are valuable building blocks in organic synthesis. Since the first reports of an amine-catalyzed asymmetric addition of ketones to nitroalkenes in 2001,[7a–7c] extraordinary progress has been made with respect to both stereoselectivity and substrate scope using both secondary[8] and primary[9] chiral amine catalysts. Recently, chiral thiourea-based catalysts have emerged as powerful catalytic systems since Jacobsen successfully developed an efficient chiral Schiff base-thiourea catalyzed asymmetric Strecker reaction due to their strong activation of carbonyl and nitro groups through efficient double-hydrogen-bonding interactions.[10] Accordingly, some bifunctional chiral thiourea catalysts bearing a Schiff base moiety,[11] primary,[9b,9c,9g,9h] or secondary amino group[8k,12] were developed and functioned as efficient catalysts for the asymmetric Michael addition of ketone to nitroolefins. The great advantage of these types of organocatalysts is that one catalyst has two reaction–activation sites, which can activate both Michael donors (ketones) and acceptors (nitroolefins) simultaneously. Moreover, the selectivity and activity of can be obviously tuned by a simple change of the thiourea motif. Carbohydrates are in general very attractive scaffolds because of their availability and well defined stereocenters. The introduction of a saccharide scaffold into a bifunctional thiourea organocatalyst has proven to be a successful strategy to design new and efficient organocatalysts.[9g,13,14] With an interest in designing new organocatalysts for asymmetric organic transformations, novel bifunctional thiourea based catalysts **3** bearing a saccharide-scaffold and a secondary amino group were synthesized and their catalytic activity was evaluated in the asymmetric direct Michael addition of cyclohexanone to nitroolefins.

Results and discussion

The newly designed pyrrolidine-thioureas **3**, were easily prepared *via* the coupling of (*S*)- or (*R*)-*tert*-butyl 2-(aminomethyl)pyrrolidine-1-carboxylate **1**[15] and glucosyl isothiocyanate **2**[13] as shown in Scheme 1. Since the free bases of **3** were decomposed slowly on storage, we keep them in their trifluoroacetate form and employ the *in situ* generated free base as the catalyst with the addition of an organic base. In the control reactions, it was found that the obtained result of the *in situ* generated catalyst is consistent with that of directly using the free base as the catalyst. In addition, directly using the trifluo acetic salt **3a** as the catalyst failed; no reaction occurred, even after stirring the reaction mixture for 5 days.

With the catalyst in hand, the factors, such as catalyst loading, co-catalyst, and reaction temperature, influencing the reaction were thoroughly investigated employing the reaction between β-nitrostyrene and cyclohexanone as the model. The results were listed in Table 1.

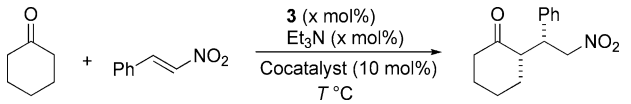


Scheme 1 Synthesis of thiourea **3**.

State Key Laboratory of Elemento-Organic Chemistry, Institute of Elemento-Organic Chemistry, Nankai University, Tianjin, 300071, P. R. China. E-mail: z.h.zhou@nankai.edu.cn; Fax: +86-22-23508939

† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra, HRMS and IR spectra of the thiourea catalysts **3** and the new Michael addition adducts, and HPLC data. See DOI: 10.1039/b905306a

Table 1 Optimization of reaction conditions[a]



4a 5a

Entry	**3** (x mol%)	Co-catalyst (10 mol%)	Temp. (°C)	Time (h)	Yield (%)[b]	Dr (*syn*/*anti*)[c]	Ee (%)[d]
1	**3a** (20)	—	20	36	85	95.5/4.5	89
2	**3a** (20)	$PrCO_2H$	20	12	>99	97/3	90
3	**3a** (20)	CH_3CO_2H	20	12	>99	86/14	70
4	**3a** (20)	$PhCO_2H$	20	12	88	95/5	80
5	**3a** (20)	$^tBuCO_2H$	20	16	>99	98/2	86
6	**3a** (20)	(*S*)-Mandelic acid	20	4	95	98/2	89
7	**3a** (20)	(*R*)-Mandelic acid	20	10	>99	98/2	87
8	**3a** (10)	$PrCO_2H$	20	55	>99	90/10	87
9	**3a** (30)	$PrCO_2H$	20	2	>99	95/5	87
10	**3a** (20)	$PrCO_2H$	0	48	>99	94/6	92
11	**3a** (20)	$PrCO_2H$	−15	60	98	99/1	95
12	**3a** (20)	$PrCO_2H$	−30	72	35[e]	91/9	91
13	**3b** (20)	$PrCO_2H$	−15	72	75[e]	99/1	−92

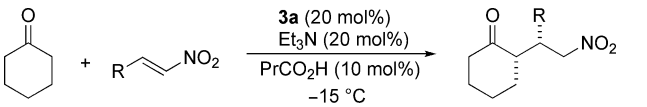
[a] All reactions were carried out using cyclohexanone (226 mg, 2.3 mol) and **4a** (0.23 mmol) in the presence of catalyst **3**. [b] Yield of the isolated product after chromatography on silica gel. [c] Determined by ^1H NMR. [d] Determined by chiral HPLC analysis. [e] This refers to the conversion of β-nitrostyrene.

As shown in Table 1, the acidic co-catalyst has an important influence on the reaction. The addition of 10 mol% of carboxylic acid as co-catalyst significantly accelerated the reaction rate relative to that of the catalyst in the absence of acidic co-catalyst. Among the employed carboxylic acids (Table 1, entries 2–7), butyric acid afforded the best result in terms of selectivity (Table 1, entry 2, 97/3 dr and 90% *ee*). Moreover, the reaction temperature was found to be an essential factor to the enantioselectivity of this reaction. The stereoselectivity was gradually increased by decreasing the reaction temperature from 20 to −15 °C (Table 1, entries 2, 10 and 11, 90–95% *ee*). However, further lowering the temperature to −30 °C resulted in a slight decrease of the enantiomeric excess of the adduct as well as the reaction rate (Table 1, entry 12, 91% *ee*). In addition, catalyst loading proved to be particularly important. For example, the use of both more or less thiourea organocatalyst led to a small loss of stereo-control (Table 1, entry 9, 87% *ee* and entry 8, 87% *ee*). Under the optimal reaction conditions (20 mol% of catalyst, 10 mol% of butyric acid as the co-catalyst, at −15 °C), bifunctional amine-thiourea **3b** derived from D-proline demonstrated much lower catalytic activity. Although the desired adduct was obtained with almost the same selectivity, the reaction became quite sluggish; only a conversion of 75% of the β-nitrostyrene was observed at a prolonged reaction time (Table 1, entry 11 *versus* entry 13). This indicates that the (*S*)-configuration of 1,2-diaminocyclohexane matched the α-D-glucopyranose to enhance the catalytic activity of the catalyst.

Encouraged by these results, we next probed the scope of the reaction with a variety of nitroolefins under the optimal reaction conditions. The results were summarized in Table 2.

As shown in Table 2, the reaction has broad applicability with respect to the niroolefins. The corresponding adducts were obtained in high enantioselectivity and with excellent *syn* diastereoselectivity in all the cases examined. Not only phenyl, but also electron-rich and electron-deficient aryl groups and heteroaromatic substituents can be present on the nitroolefin. Sterically demanding substrates are tolerated well in this reaction.

Table 2 Substrate scope of **3a** catalyzed asymmetric Michael addition of cyclohexanone to nitroolefins



4a–r 5a–r

Entry	R	Time (h)	Yield (%)[a]	Dr (*syn*/*anti*)[b]	Ee (%)[c]
1	Ph (**a**)	60	98	99/1	95
2	2-$CF_3C_6H_4$ (**b**)	49	76	97/3	97
3	3-$CF_3C_6H_4$ (**c**)	80	95	98.5/1.5	93
4	4-$CF_3C_6H_4$ (**d**)	80	71	97/3	95
5	4-ClC_6H_4 (**e**)	49	86	98/2	94
6	4-FC_6H_4 (**f**)	49	78	>99/1	95
7	2,4-$Cl_2C_6H_3$ (**g**)	96	87	>99/1	94
8	2-NO_2-5-ClC_6H_3 (**h**)	120	98	98/2	97
9	2-$MeOC_6H_4$ (**i**)	47	82	98/2	94
10	4-$MeOC_6H_4$ (**j**)	72	96	98/2	92
11	4-MeC_6H_4 (**k**)	49	81	98/2	93
12	2,4-$(MeO)_2C_6H_3$ (**l**)	120	90	97/3	93
13	4-Benzyloxy (**m**)	61	>99	97/3	92
14	Benzo[d][1,3]dioxol-5-yl (**n**)	52	>99	>99/1	96
15	1-Naphthyl (**o**)	49	88	99/1	94
16	2-Furyl (**p**)	52	81	92/8	92
17	(*E*)-Cinnamyl (**q**)	48	87	95/5	94
18	Phenylethyl (**r**)	35[d]	73	76/24	93

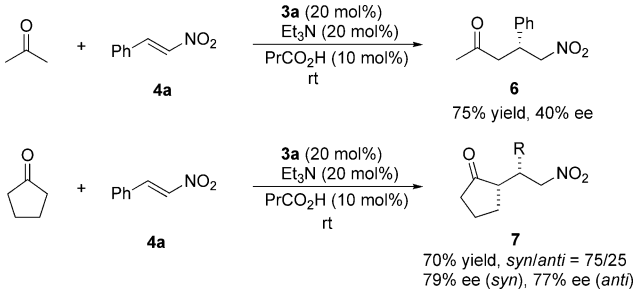
[a] Yield of the isolated product after chromatography on silica gel. [b] Determined by ^1H NMR. [c] Determined by chiral HPLC analysis. [d] The reaction was carried out at room temperature (25 °C).

For example, ortho substituted nitroolefins **4b**, **4g**, **4h**, **4i** and **4l** still go smoothly to afford the corresponding adducts in good yields as well as excellent enantioselectivities. Moreover, alkenyl substituted nitroolefin can also be employed successfully; the same high levels of diastereo- and enantioselectivity were observed as those found in the aryl substituted ones. Notably, aliphatic aldehyde derived nitroolefin also appeared to be a good candidate at an elevated temperature (Table 2, entry 18, *syn*/*anti* = 76/24, 93% *ee* for *syn*

isomer), which clearly demonstrated the broad generality of this asymmetric Michael addition reaction.

The relative and absolute configurations of the Michael addition products are shown in Table 2. The relative configurations were assigned by comparison of ^{1}H and ^{13}C NMR of the products with the known compounds. The absolute configuration of the major isomer was established by comparison to the literature value of optical rotation.

The asymmetric addition of other ketones to nitrostyrene **4a** using **3a** as a catalyst was also preliminarily investigated at room temperature. As shown in Scheme 2, acetone worked well to provide the desired product **6** in 75% yield with 40% *ee*. By performing the reaction of cyclopentanone and cycloheptanone, it was found that there is a dramatic dependence on ring size. Cyclopentanone resulted in a decrease in both diastereoselectivity and enantioselectivity, which gave the desired products **7** in fair yield with moderate selectivity (*syn*/*anti* = 75/25, 79% *ee* for *syn*-**7** and 77% *ee* for *anti*-**7**, respectively). The reaction of cycloheptanone is very sluggish under identical conditions, and failed to provide the corresponding adduct. This effect may be attributed to the difference of the barriers for the attack of pyrrolidine on the carbonyl group of the respective ketones to form the enamine transition state.[16]



Scheme 2 Reaction of other ketones.

Based on the experimental results, a possible transition state for this reaction was proposed to account for the observed high diastereo- and enantioselectivity. As shown in Fig. 1, the free base of **3a** functioned as a bifunctional catalyst. The pyrrolidine part of the catalyst reacted with carbonyl compounds to form an enamine with the aid of acidic co-catalyst, and at the same time, nitroolefin was activated *via* hydrogen-bonding interaction with the thiourea moiety as well as the Brønsted acid additive. Then, nucleophilic attack of the enamine to the nitroolefin from the *re*-face resulted in the formation of the desired product, which was consistent with the experimental results.

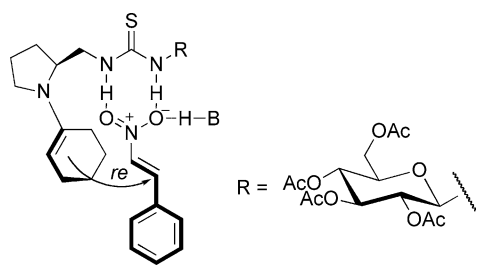


Fig. 1 Possible transition state of the present reaction.

Conclusions

We have developed a novel pyrrolidine-based thiourea catalyst bearing a saccharide-scaffold and a secondary amino group, which worked well as a bifunctional organocatalyst to promote the asymmetric Michael reaction of cyclohexanone to both aryl and alkyl nitroolefins. In these transformations, the prepared catalyst exhibits a high catalytic activity, and the reaction takes place with excellent diastereo- (up to >99/1 *dr*) and enantioselectivity (up to 97% *ee*), which may be potentially useful for preparing enantiomerically enriched γ-nitroketones. Further investigations on the application of this catalyst in asymmetric catalysis are in progress.

Experimental

General methods

All reagents and solvents were commercial grade and purified prior to use when necessary. NMR spectra were acquired on either a Bruker AMX-300 or Varian 400 MHz instrument. Chemical shifts are measured relative to residual solvent peaks as an internal standard set to δ 7.26 and δ 77.0 ($CDCl_3$). Specific rotations were measured on a Perkin-Elmer 341MC polarimeter. Enantiomeric excesses were determined on a HP-1100 instrument (chiral column; mobile phase: hexane/*i*-PrOH). Elemental analyses were conducted on a Yanaco CHN Corder MT-3 automatic analyzer. HRMS was performed on a Varian QFT-ESI instrument. Melting points were determined on a T-4 melting point apparatus. IR spectra were measured on Bruker FT-IR Equinox 55 and Bruker TENSOR 27 instruments. All temperatures were uncorrected.

Preparation of (*S*)- and (*R*)-1-glucosyl-3-(*N*-tert-butoxy-carbonyl-pyrrolidin-2-ylmethyl)thiourea

To a stirred solution of (*S*)- or (*R*)-tert-butyl 2-(aminomethyl)-pyrrolidine-1-carboxylate **1** (501 mg, 2.5 mmol) in dry CH_2Cl_2 (5 mL) was added a solution of glucosyl isothiocyanate **2** (941 mg, 2.5 mmol) in dry CH_2Cl_2 (5 mL) at room temperature. The reaction mixture was allowed to stir for complete consumption of **2** (monitored by TLC, about 6 h). After removal of solvent, the crude product was purified by column chromatography on silica gel (200–300 mesh, petroleum ether/ethyl acetate = 2/1) to afford the title compound as a white solid.

(*S*)-1-Glucosyl-3-(*N*-tert-butoxy-carbonyl-pyrrolidin-2-ylmethyl)-thiourea. 1.41 g, 96% yield, m.p. 79–81 °C, $[\alpha]_D^{20}$ −5.2 (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.45 (s, 9 H), 1.70–1.87 (m, 4 H), 1.99 (s, 3 H), 2.00 (s, 3 H), 2.01 (s, 3 H), 2.05 (s, 3 H), 3.27–3.36 (m, 3 H), 3.74–3.87 (m, 2 H), 4.00–4.12 (m, 2 H), 4.29 (dd, J = 4.2 and 12.3 Hz, 1 H), 4.96 (t, J = 9.6 Hz, 1 H), 5.07 (t, J = 9.6 Hz, 1 H), 5.32 (t, J = 9.6 Hz, 1 H), 5.53–5.56 (m, 1 H), 6.32 (br. s, 1 H), 8.61 (br. s, 1 H). ^{13}C NMR ($CDCl_3$, 75.0 MHz): 20.5, 20.6, 20.7, 23.9, 28.4, 47.4, 52.7, 56.5, 61.7, 68.3, 70.6, 73.0, 80.6, 82.3, 157.2, 169.5, 169.9, 170.6, 183.0. IR (KBr): ν 3315, 1748, 1668, 1551, 1413, 1369, 1223, 1070 cm^{-1}. HRMS (ESI) *m*/*z* calc'd for $C_{25}H_{39}N_3O_{11}S$ $[M + H]^+$: 532.2323, found 532.2333.

(*R*)-1-Glucosyl-3-(*N*-tert-butoxy-carbonyl-pyrrolidin-2-yl-methyl)-thiourea. 1.45g, 99% yield, m.p. 70–71 °C, $[\alpha]_{406}^{14}$ −18.4 (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.40 (s, 9 H),

1.61–1.81 (m, 4 H), 1.92 (s, 3 H), 1.94 (s, 3 H), 1.97 (s, 3 H), 1.98 (s, 3 H), 3.25–3.33 (m, 3 H), 3.60 (d, $J = 7.2$ Hz, 1 H), 3.94–4.20 (m, 4 H), 4.89 (t, $J = 9.0$ Hz, 1 H), 5.00 (t, $J = 9.0$ Hz, 1 H), 5.15 (t, $J = 9.0$ Hz, 1 H), 6.65 (br. s, 1 H), 8.47 (br. s, 1 H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 20.3, 20.4, 20.5, 23.7, 28.3, 29.4, 47.2, 52.7, 55.7, 61.2, 67.7, 70.2, 72.4, 72.7, 77.2, 80.2, 80.9, 156.9, 169.2, 169.7, 170.4, 170.5, 181.8. IR (KBr): ν 3322, 3265, 1751, 1666, 1549, 1367, 1226, 1038 cm^{-1}. Anal. calc'd for $C_{25}H_{39}N_3O_{11}S$: C, 50.92; H, 6.67; N, 7.13; Found: C, 50.74; H, 6.40; N, 7.08.

Preparation of (*S*)- and (*R*)-1-glucosyl-3-(pyrrolidin-2-ylmethyl)-thiourea trifluoroacetate (3a,b). The *N*-Boc-derivative (590 mg, 1.0 mmol) was dissolved in a mixture of trifluoroacetic acid and dichloromethane (4 mL, V/V = 1:1) and the resulting solution was stirred for 2 h at room temperature. After removal of solvent, the crude product was purified through column chromatography on silica gel (200–300 mesh, ethyl acetate) to afford the target compound as a white solid.

(*S*)-1-Glucosyl-3-(pyrrolidin-2-ylmethyl)-thiourea trifluoroacetate (3a). 543 mg, 90% yield, m.p. 86–89 °C, $[\alpha]_D^{20}$ –4.1 (c 1.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.78–1.82 (m, 1 H), 1.99 (s, 6 H), 2.00 (s, 3 H), 2.04 (s, 3 H), 2.10–2.13 (m, 3 H), 3.33 (s, 2 H), 3.82–3.85 (m, 2 H), 3.99 (s, 2 H), 4.10–4.14 (m, 1 H), 4.21 (dd, $J = 3.9$ and 12.0 Hz, 1 H), 4.96 (t, $J = 9.3$ Hz, 1 H), 5.05 (t, $J = 9.6$ Hz, 1 H), 5.28 (t, $J = 9.3$ Hz, 1 H), 5.60–5.62 (m, 1 H), 7.53 (br. s, 1 H), 8.49 (br. s, 1 H), 9.09 (br. s, 1 H), 9.96 (br. s, 1 H). ^{13}C NMR ($CDCl_3$, 75.0 MHz): 20.5, 20.5, 20.6, 20.7, 24.0, 27. 8, 45.3, 45.4, 61.0, 61.6, 68.2, 70.7, 73.1, 73.2, 82.4, 114.6, 169.5, 169.9, 170.7, 170.8, 185.3. IR (KBr): ν 3279, 1748, 1675, 1537, 1369, 1231, 1063 cm^{-1}. HRMS (ESI) *m/z* calc'd for $C_{22}H_{32}F_3N_3O_{11}S$ $[M - CF_3CO_2H + H]^+$: 490.1854, found 490.1845.

(*R*)-1-Glucosyl-3-(pyrrolidin-2-ylmethyl)-thiourea trifluoroacetate (3b). 597 mg, 99% yield, m.p. 90–92 °C, $[\alpha]_{406}^{14}$ –25.0 (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.69–1.73 (m, 1 H), 1.92 (s, 3 H), 1.95 (s, 3 H), 1.96 (s, 3 H), 1.98 (s, 3 H), 2.10–2.13 (m, 3 H), 3.28 (s, 2 H), 3.80–4.12 (m, 5 H), 4.90–5.01 (m, 4 H), 5.24 (t, $J = 9.3$ Hz, 1 H), 7.60 (br. s, 1 H), 8.30 (br. s, 1 H), 8.88 (br. s, 1 H), 9.23 (br. s, 1 H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 20.3, 20.4, 20.4, 23.7, 27.6, 45.3, 60.8, 61.5, 67.8, 70.5, 72.8, 73.0, 82.3, 114.8, 169.5, 169.9, 170.1, 170.2, 185.4. IR (KBr): ν 3686, 3063, 1749, 1681, 1553, 1371, 1207, 1038 cm^{-1}. Anal. calc'd for $C_{22}H_{32}F_3N_3O_{11}S$: C, 43.78; H, 5.34; N, 6.96; Found: C, 43.52; H, 5.12; N, 7.03.

General procedure for thiourea 3 catalyzed asymmetric Michael addition to nitroolefins

A mixture of the catalyst **3** (0.046 mmol) and triethylamine (0.046 mmol) in cyclohexanone (226 mg, 2.3 mmol) was stirred at room temperature for 30 min. Then, *n*-butyric acid (2 mg, 0.023 mmol) was added, and the reaction mixture was stirred for 15 min. To the resulting mixture was added nitroolefin (0.23 mmol) at the required temperature. After the reaction was complete (monitored by TLC), the mixture was purified by column chromatography on silica gel (200–300 mesh, PE/EtOAc = 15 : 1–10 : 1) to afford the product.

(*S*)-2-((*R*)-2-Nitro-1-phenylethyl)cyclohexanone (5a).[12b] White solid, 98% yield, m.p. 124–126 °C, $[\alpha]_D^{20}$ –31.5 (c 1.3, $CHCl_3$), *syn/anti* = 99/1, 95% *ee*. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.10–1.22 (m, 1 H), 1.47–1,73 (m, 4 H), 1.98–2.04 (m, 1 H), 2.26–2.44 (m, 2 H), 2.61 (m, 1 H), 3.69 (dt, $J = 4.5$ and 9.9 Hz, 1 H), 4.56 (dd, $J = 9.9$ and 12.6 Hz, 1 H), 4.87 (dd, $J = 4.5$ and 12.6 Hz, 1 H), 7.08–7.11 (m, 2 Harom), 7.19–7.27 (m, 3 Harom). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 25.1, 28.5, 33.2, 42.8, 44.0, 52.6, 78.9, 127.8, 128.2, 128.9, 137.8, 211.9. HPLC analysis (Chiralpak AD-H column, hexane:2-propanol = 85:15, flow rate = 1.0 mL/min, wavelength = 254 nm): *R*t = 8.25 (minor) and 9.94 min (major).

(*S*)-2-((*R*)-2-Nitro-1-(2-trifluoromethylphenyl)ethyl)-cyclohexanone (5b).[17] Brown oil, 76% yield, $[\alpha]_D^{20}$ –26.2 (c 1.3, $CHCl_3$), *syn/anti* = 97/3, 97% *ee*. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.29–1.36 (m, 1H), 1.57–1.80 (m, 4 H), 2.11–2.14 (m, 1 H), 2.39–2.50 (m, 2 H), 2.96–3.02 (m, 1 H), 4.09 (s, 1H), 4.76 (dd, $J = 3.2$ and 12.0 Hz, 1 H), 5.00 (dd, $J = 7.6$ and 11.6 Hz, 1 H), 7.36 (d, $J = 7.6$ Hz, 1 Harom), 7.39 (t, $J = 7.6$ Hz, 1 Harom), 7.55 (t, $J = 7.6$ Hz, 1 Harom), 7.68 (d, $J = 8.0$ Hz, 1 Harom). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 25.5, 28.8, 33. 6, 39.2, 43.0, 52.6, 78.5, 122.8, 125.5, 126.7 (q, $J = 5.8$ Hz), 127.8, 128.1, 132.5, 137.2, 133.7, 211.6. HPLC analysis (Chiralpak AS-H column, hexane:2-propanol = 90:10, flow rate = 0.7 mL/min, wavelength = 254 nm): *R*t = 10.71 (minor) and 12.16 min (major).

(*S*)-2-((*R*)-2-Nitro-1-(3-trifluoromethylphenyl)ethyl)-cyclohexanone (5c). Pale yellow oil, 95% yield, $[\alpha]_D^{20}$ –15.6 (c 0.9, $CHCl_3$), *syn/anti* = 98.5/1.5, 93% *ee*. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.56–1.83 (m, 5 H), 2.04–2.13 (m, 1 H), 2.33–2.51 (m, 2 H), 2.70 (m, 1 H), 3.86 (dt, $J = 4.8$ and 9.6 Hz, 1 H), 4.67 (dd, $J = 9.6$ and 12.9 Hz, 1 H), 4.96 (dd, $J = 4.5$ and 12.9 Hz, 1 H), 7.38–7.55 (m, 4 Harom). ^{13}C NMR ($CDCl_3$, 75.0 MHz): 25.1, 28.3, 33.2, 42.7, 43.8, 52.4, 78.3, 124.7, 124.7, 124.8, 124.8, 124.9, 124.9, 124.9, 125.0, 129.5, 131.7, 139.1, 211.1. HRMS (ESI) *m/z* calc'd for $C_{15}H_{16}F_3NO_3$ $[M + Na]^+$: 338.0974, found 338.0979. $C_{15}H_{16}F_3NO_3$ (315.28): calcd. C 57.14, H 5.12, N 4.44; found C 57.01, H 4.97, N 4.33. HPLC analysis (Chiralpak AS-H column, Hexane:2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm): *R*t = 11.71 (minor) and 21.06 min (major).

(*S*)-2-((*R*)-2-Nitro-1-(4-trifluoromethylphenyl)ethyl)-cyclohexanone (5d). [17] Yellow solid, 71% yield, m.p. 79–81 °C, $[\alpha]_D^{20}$ –21.4 (c 1.4, $CHCl_3$), *syn/anti* = 97/3, 95% *ee*. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.22–1.30 (m, 1H), 1.59–1.82 (m, 4 H), 2.06–2.10 (m, 1 H), 2.32–2.50 (m, 2 H), 2.65–2.74 (m, 1 H), 3.86 (dt, $J = 4.5$ and 9.6 Hz, 1H), 4.66 (dd, $J = 9.9$ and 12.6 Hz, 1 H), 4.96 (dd, $J = 4.5$ and 12.6 Hz, 1 H), 7.31 (d, $J = 8.1$ Hz, 2 Harom), 7.58 (d, $J = 8.1$ Hz, 2 Harom). ^{13}C NMR ($CDCl_3$, 75.0 MHz): 25.1, 28.3, 33.2, 42.7, 43.8, 52.4, 78.3, 125.9 (q, $J = 3.8$ Hz), 128.7, 129.9, 130.3, 142.1, 211.1. HPLC analysis (Chiralpak AS-H column, Hexane:2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm): *R*t = 11.03 (minor) and 16.63 min (major).

(*S*)-2-((*R*)-1-(4-Chlorophenyl)-2-nitroethyl)-cyclohexanone (5e). [18] Pale yellow solid, 86% yield, m.p. 93–96 °C, $[\alpha]_D^{20}$ –28.1 (c 1.6, $CHCl_3$), *syn/anti* = 98/2, 94% *ee*. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.17–1.23 (m, 1H), 1.55–1.81 (m, 4 H), 2.06–2.11 (m, 1 H), 2.33–2.48 (m, 2 H), 2.61–2.68 (m, 1 H), 3.75 (dt, $J = 4.4$ and 10.0 Hz, 1 H), 4.60 (dd, $J = 10.4$ and 12.4 Hz, 1 H), 4.93 (dd, $J = 4.4$ and 12.4 Hz, 1 H), 7.11 (d, $J = 8.0$ Hz, 2 Harom), 7.29 (d, $J = 8.0$ Hz, 2 Harom). ^{13}C NMR ($CDCl_3$, 75.0 MHz): 25.0, 28.4, 33.1, 42.7, 43.4, 52.4, 78.6, 129.1, 129.6, 133.6, 136.4, 211.4. HPLC analysis (Chiralpak AS-H column, hexane:2-propanol = 90:10,

flow rate = 1.0 mL/min, wavelength = 254 nm): *R*t = 16.25 (minor) and 26.15 min (major).

(*S*)-2-((*R*)-1–4-Fluorophenyl-2-nitroethyl)cyclohexanone (5f). [8a] Pale yellow solid, 78% yield, m.p. 64–66 °C, $[\alpha]_D^{20}$ −18.9 (c 1.8, $CHCl_3$), *syn*/*anti* = >99/1, 95% *ee*. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.10–1.25 (m, 1 H), 1.56–1.82 (m, 4 H), 2.01–2.10 (m, 1 H), 2.34–2.49 (m, 2 H), 2.65 (m, 1 H), 3.77 (dt, *J* = 4.0 and 9.6 Hz, 1 H), 4.60 (t, *J* = 11.2 Hz, 1 H), 4.93 (dd, *J* = 4.0 and 12.4 Hz, 1 H), 7.01 (dd, *J* = 8.0 and 8.4 Hz, 2 Harom), 7.15 (dd, *J* = 5.6 and 6.8 Hz, 2 Harom). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 24.0, 27.4, 32.1, 41.7, 42.3, 51.5, 77.8, 114.9 (d, *J* = 21.4 Hz), 128.8 (d, *J* = 8.0 Hz), 132.5 (d, *J* = 3.2 Hz), 161.1 (d, *J* = 246.7 Hz), 210.7. HPLC analysis (Chiralpak AS-H column, hexane:2-propanol = 90:10, flow rate = 0.7 mL/min, wavelength = 238 nm): *R*t = 26.01 (minor) and 37.87 min (major).

(*S*)-2-((*R*)-1-(2,4-Dichlorophenyl)-2-nitroethyl)-cyclohexanone (5g). [12b] Colorless crystal, 87% yield, m.p. 98–99 °C, $[\alpha]_D^{20}$ −27.0 (c 1.0, $CHCl_3$), *syn*/*anti* = >99/1, 94% *ee*. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.25–1.34 (m, 1H), 1.65–1.83 (m, 4 H), 2.11 (s, 1 H), 2.38–2.46 (m, 2 H), 2.87 (s, 1 H), 4.25 (s, 1 H), 4.88 (s, 2 H), 7.18–7.24 (m, 2 Harom), 7.40 (s, 1 Harom). ^{13}C NMR ($CDCl_3$, 75.0 MHz): 25.2, 28.4, 33.0, 40.6, 42.8, 51.6, 76.9, 127.7, 130.1, 130.3, 134.1, 134.2, 135.2, 211.2. HPLC analysis (Chiralpak AS-H column, hexane:2-propanol = 90:10, flow rate = 0.8 mL/min, wavelength = 238 nm): *R*t = 13.69 (minor) and 22.87 min (major).

(*S*)-2-((*R*)-1-(5-Chloro-2-nitrophenyl)-2-nitroethyl)-cyclohexanone (5h). Brown oil, 98% yield, $[\alpha]_D^{20}$ −137.9 (c 0.95, $CHCl_3$), *syn*/*anti* = 98/2, 97% *ee*. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.50–1.55 (m, 1H), 1.67 (broad s, 2 H), 1.6 (broad s, 2 H), 2.12 (broad s, 1 H), 2.36–2.49 (m, 2 H), 2.89 (broad s, 1 H), 4.37 (broad s, 1 H), 4.90 (broad s, 1 H), 7.39 (d, *J* = 8.4 Hz, 1 Harom), 7.47 (s, 1 Harom), 7.82 (d *J* = 8.4 Hz, 1 Harom). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 25.3, 28.2, 29.6, 33.2, 42.8, 52.2, 77.1, 126.5, 128.8, 129.5, 135.3, 139.5, 149.0, 210.7. HRMS (ESI) *m*/*z* calc'd for $C_{14}H_{15}ClN_2O_5$ $[M + Na]^+$: 349.0562, found 349.0567. $C_{14}H_{15}ClN_2O_5$ (326.73): calcd. C 51.46, H 4.63, N 8.57; found C 51.28, H 4.57, N 8.37. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 95:5, flow rate = 0.7 mL/min, wavelength = 220 nm): *R*t = 59.75 (major) and 87.55 min (minor).

(*S*)-2-((*R*)-1-(2-Methoxyphenyl)-2-nitroethyl)-cyclohexanone (5i). [19] White solid, 82% yield, m.p. 97–100 °C, $[\alpha]_D^{20}$ −28.5 (c 1.3, $CHCl_3$), *syn*/*anti* = 98/2, 94% *ee*. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.19–1.22 (m, 1H), 1.56–1.79 (m, 4 H), 2.05–2.08 (m, 1 H), 2.34–2.49 (m, 2 H), 2.97 (dt, *J* = 4.8 and 11.2 Hz, 1 H), 3.84 (s, 3 H), 3.93–3.99 (m, 1H), 4.78–4.87 (m, 2 H), 6.87 (d, *J* = 8.4 Hz, 1 Harom), 6.88 (t, *J* = 8.4 Hz, 1 Harom), 7.08 (d, *J* = 7.2 Hz, 1 Harom), 7.24 (t, *J* = 8.0 Hz, 1 Harom). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 25.2, 28.6, 33.3, 41.3, 42.7, 50.7, 55.4, 77.5, 111.0, 120.9, 125.4, 128.9, 131.0, 157.6, 212.5. HPLC analysis (Chiralpak AS-H column, Hexane:2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm): *R*t = 13.52 (minor) and 15.32 min (major).

(*S*)-2-((*R*)-1-(4-Methoxyphenyl)-2-nitroethyl)-cyclohexanone (5j). [12b] White solid, 96% yield, m.p. 115–117 °C, $[\alpha]_D^{20}$ −224.4 (c 1.2, $CHCl_3$), *syn*/*anti* = 98/2, 92% *ee*. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.19–1.25 (m, 1H), 1.53–1.74 (m, 4 H), 2.04–2.08 (m, 1 H), 2.34–2.46 (m, 2 H), 2.57–2.67 (m, 1 H), 3.66–3.72 (m, 1H), 3.75 (s, 3 H), 4.56 (dd, *J* = 9.9 and 12.3 Hz, 1 H), 4.89 (dd, *J* = 4.5 and 12.3 Hz, 1 H), 6.82 (d, *J* = 8.7 Hz, 2 Harom), 7.06 (d, *J* = 8.7 Hz, 2 Harom). ^{13}C NMR ($CDCl_3$, 75.0 MHz): 25.0, 28.5, 33.1, 42.7, 43.2, 52.7, 55.2, 79.1, 114.3, 129.2, 129.6, 159.0, 212.0. HPLC analysis (Chiralpak AS-H column, Hexane:2-propanol = 90:10, flow rate = 0.7 mL/min, wavelength = 254 nm): *R*t = 27.43 (minor) and 35.48 min (major).

(*S*)-2-((*R*)-1-(4-Methylphenyl)-2-nitroethyl)-cyclohexanone (5k). [18] White solid, 81% yield, m.p. 123–126 °C, $[\alpha]_D^{20}$ −23.8 (c 1.3, $CHCl_3$), *syn*/*anti* = 98/2, 93% *ee*. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.19–1.26 (m, 1H), 1.54–1.80 (m, 4 H), 2.05–2.09 (m, 1 H), 2.31 (s, 3 H), 2.34–2.49 (m, 2 H), 2.63–2.70 (m, 1 H), 3.71 (dt, *J* = 4.4 and 10.0 Hz, 1 H), 4.60 (dd, *J* = 10.4 and 12.0 Hz, 1 H), 4.91 (dd, *J* = 4.4 and 12.4 Hz, 1 H), 7.04 (d, *J* = 7.6 Hz, 2 Harom), 7.12 (d, *J* = 7.6 Hz, 2 Harom). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 20.0, 24.0, 27.5, 32.2, 41.7, 42.6, 51.6, 78.0, 127.0, 128.6, 133.6, 136.4, 211.1. HPLC analysis (Chiralpak AS-H column, hexane:2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm): *R*t = 10.78 (minor) and 17.96 min (major).

(*S*)-2-((*R*)-1-(2,4-Dimethoxyphenyl)-2-nitroethyl)-cyclohexanone (5l). [18] Yellow oil, 90% yield, $[\alpha]_D^{20}$ −30.0 (c 1.2, $CHCl_3$), *syn*/*anti* = 97/3, 93% *ee*. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.12–1.21 (m, 1H), 1.54–1.79 (m, 4 H), 2.03–2.07 (m, 1 H), 2.31–2.48 (m, 2 H), 2.92 (dt, *J* = 5.1 and 11.4 Hz, 1 H), 3.76 (s, 3 H), 3.80 (s, 3 H), 3.85–3.91 (m, 1H), 4.77–4.79 (m, 2 H), 6.37–6.43 (m, 2 Harom), 6.96 (d, *J* = 8.1 Hz, 1 Harom). ^{13}C NMR ($CDCl_3$, 75.0 MHz): 25.1, 28.5, 29.6, 33.2, 40.8, 42.6, 50.8, 55.2, 55.4, 77.7, 99.1, 104.4, 117.7, 131.4, 158.6, 160.4, 212.6. HPLC analysis (Chiralpak AS-H column, hexane:2-propanol = 2:98, flow rate = 1.0 mL/min, wavelength = 254 nm): *R*t = 38.05 (minor) and 55.05 min (major).

(*S*)-2-((*R*)-1-(4-Benzyloxyphenyl)-2-nitroethyl)-cyclohexanone (5m). White solid, >99% yield, m.p. 167–168 °C, $[\alpha]_D^{20}$ −18.4 (c 1.1, $CHCl_3$), *syn*/*anti* = 97/3, 92% *ee*. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.42–1.81 (m, 5 H), 2.06–2.09 (m, 1 H), 2.34–2.49 (m, 2 H), 2.62–2.68 (m, 1 H), 3.72 (dt, *J* = 4.4 and 9.6 Hz, 1 H), 4.59 (dd, *J* = 10.4 and 11.6 Hz, 1 H), 4.91 (dd, *J* = 4.4 and 12.4 Hz, 1 H), 6.93 (d, 2 Harom), 7.09 (d, 2 Harom), 7.33–7.43 (m, 5 Harom). ^{13}C NMR ($CDCl_3$, 75.0 MHz): 25.0, 28.5, 33.1, 42.7, 43.3, 52.7, 70.1, 79.1, 115.2, 127.5, 128.0, 128.6, 129.2, 130.0, 136.9, 158.4, 211.9. HRMS (ESI) *m*/*z* calc'd for $C_{21}H_{23}NO_4$ $[M + Na]^+$: 376.1519, found 376.1522. $C_{21}H_{23}NO_4$ (353.40): calcd. C 71.37, H 6.56, N 3.96; found C 71.09, H 6.43, N 3.76. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 98:2, flow rate = 1.0 mL/min, wavelength = 254 nm): *R*t = 45.67 (minor) and 56.00 min (major).

(*S*)-2-((*R*)-1-(Benzo[d][1,3]dioxol-5-yl)-2-nitroethyl)-cyclohexanone (5n). [12b] Pale brown solid, >99% yield, m.p. 144–145 °C, $[\alpha]_D^{20}$ −19.2 (c 1.3, $CHCl_3$), *syn*/*anti* = >99/1, 96% *ee*. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.19–1.22 (m, 1H), 1.56–1.69 (m, 2 H), 1.78 (br. s, 2 H), 2.06 (br. s, 1 H), 2.33–2.48 (m, 2 H), 2.58–2.62 (m, 1 H), 3.65–3.68 (m, 1H), 4.54 (t, *J* = 11.2 Hz, 1 H), 4.89 (dd, *J* = 2.8 and 12.0 Hz, 1 H), 5.94 (s, 2 H), 6.61 (d, *J* = 7.6 Hz, 1 Harom), 6.64 (s, 1 Harom), 6.73 (d, *J* = 7.6 Hz, 1 Harom). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 25.0, 28.5, 33.1, 42.7, 43.7, 52.7, 79.0, 101.2, 108.0, 108.6, 121.7, 131.3, 147.1, 148.1, 211.9. HPLC analysis (Chiralpak AD-H column, hexane:2-propanol = 85:15,

flow rate = 0.5 mL/min, wavelength = 254 nm): *R*t = 27.71 (minor) and 29.02 min (major).

(*S*)-2-((*R*)-1-(Naphthalen-1-yl)-2-nitroethyl)-cyclohexanone (5o). [12b] Pale brown solid, 88% yield, m.p. 116–119 °C, $[\alpha]_D^{20}$ −101.4 (c 1.1, $CHCl_3$), *syn*/*anti* = 99/1, 94% *ee*. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.20–1.30 (m, 1H), 1.50–1.69 (m, 4 H), 2.06–2.09 (m, 1 H), 2.37–2.52 (m, 2 H), 2.87 (s, 1 H), 4.77 (s, 1H), 4.91 (dd, *J* = 9.2 and 12.4 Hz, 1 H), 5.07 (dd, *J* = 4.0 and 12.4 Hz, 1 H), 7.38 (d, *J* = 7.6 Hz, 1 Harom), 7.44–7.58 (m, 3 Harom), 7.78 (d, *J* = 8.0 Hz, 1 Harom), 7.86 (d, *J* = 8.0 Hz, 1 Harom), 8.17 (s, 1 Harom). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 24.3, 27.7, 32.3, 35.8, 41.9, 52.8, 77.7, 121.8, 122.6, 124.4, 124.9, 125.6, 127.2, 128.0, 131.4, 133.0, 133.7, 211.3. HPLC analysis (Chiralpak AS-H column, hexane:2-propanol = 75:25, flow rate = 1.0 mL/min, wavelength = 238 nm): *R*t = 11.48 (minor) and 16.16 min (major).

(*S*)-2-((*S*)-1-(Furan-2-yl)-2-nitroethyl)cyclohexanone (5p). [12b] Brown oil, 81% yield, $[\alpha]_D^{20}$ −8.23 (c 0.85, $CHCl_3$), *syn*/*anti* = 92/8, 92% *ee*. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.29–1.32 (m, 1H), 1.61–1.84 (m, 4 H), 2.08–2.09 (m, 1 H), 2.32–2.47 (m, 2 H), 2.71–2.77 (m, 1 H), 3.93–3.99 (m, 1 H), 4.63–4.69 (m, 1 H), 4.78 (dd, *J* = 4.0 and 12.4 Hz, 1 H), 6.17 (s, 1 Harom), 6.27 (s, 1 Harom), 7.37 (s, 1 Harom). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 25.1, 27.2, 32.5, 37.6, 42.6, 51.1, 76.7, 109.0, 110.3, 142.3, 151.0, 211.0. HPLC analysis (Chiralpak AD-H column, hexane:2-propanol = 98:2, flow rate = 0.7 mL/min, wavelength = 254 nm): *R*t = 31.34 (major) and 40.84 min (minor).

(*S*)-2-((*S*,*E*)-1-Nitro-4-phenylbut-3-en-2-yl)-cyclohexanone (5q). Pale yellow solid, 92% yield, m.p. 78–81 °C, $[\alpha]_D^{20}$ −40.0 (c 1.1, $CHCl_3$), *syn*/*anti* = 95/5, 94% *ee*. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.42–1.51 (m, 1H), 1.66–1.71 (m, 3 H), 2.16–2.20 (m, 2 H), 2.33–2.48 (m, 2 H), 3.35–3.38 (m, 1H), 4.56–4.76 (m, 2 H), 6.03 (dd, *J* = 9.6, 15.6 Hz, 1 H), 6.50 (d, *J* = 15.6 Hz, 1 H), 7.25–7.34 (m, 5 Harom). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 25.0, 28.1, 32.5, 41.9, 42.6, 51.7, 78.0, 125.7, 126.4, 127.9, 128.6, 134.4, 136.3, 211.2. HRMS (ESI) *m*/*z* calc'd for $C_{16}H_{19}NO_3$ $[M + Na]^+$: 296.1257, found 296.1263. $C_{16}H_{19}NO_3$ (273.32): calcd. C 70.31, H 7.01, N 5.12; found C 70.27, H 6.95, N 5.02. HPLC analysis (Chiralpak AD-H column, hexane:2-propanol = 99:1, flow rate = 0.5 mL/min, wavelength = 254 nm): *R*t = 84.23 (minor) and 87.01 min (major).

(*S*)-2-((*S*)-1-Nitro-4-phenylbutan-2-yl)cyclohexanone (5r). Colorless oil, 92% yield, $[\alpha]_D^{20}$ −15.1 (c 1.7, $CHCl_3$), *syn*/*anti* = 76/24, 93% *ee* (*syn*), 88% *ee* (*anti*). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.43–1.53 (m, 1H), 1.64–1.70 (m, 3 H), 1.81–1.86 (m, 1 H), 1.93–1.95 (m, 1 H), 2.09–2.14 (m, 2 H), 2.28–2.39 (m, 2 H), 2.51–2.55 (m, 1 H), 2.63–2.72 (m, 3 H), 4.36 (dd, *J* = 6.0 and 12.4 Hz, 0.21 H, *anti*), 4.46 (dd, *J* = 6.0 and 12.4 Hz, 0.71 H, *syn*), 4.62 (dd, *J* = 6.0 and 12.4 Hz, 1 H), 7.17–7.22 (m, 3 Harom), 7.28–7.31 (m, 2 Harom). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 25.1 (*anti*), 25.2 (*syn*), 27.3 (*anti*), 27.6 (*syn*), 29.8 (*anti*), 30.2 (*syn*), 30.8 (*anti*), 31.3 (*syn*), 33.5 (*syn*), 33.7 (*anti*), 36.9 (*anti*), 37.0 (*syn*), 42.4 (*anti*), 42.5 (*syn*), 51.1 (*anti*), 51.4 (*syn*), 76.9, 126.1, 128.2, 128.5, 141.1, 211.1. HRMS (ESI) *m*/*z* calc'd for $C_{16}H_{21}NO_3$ $[M + Na]^+$: 298.1414, found 298.1411. $C_{16}H_{21}NO_3$ (275.34): calcd. C 69.79, H 7.69, N 5.09; found C 69.54, H 7.45, N 4.88. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 99:1, flow rate = 0.5 mL/min, wavelength = 254 nm): *R*t = 38.39 (major, *syn*), 43.17 (minor, *syn*), 40.05 (major, *anti*) and 46.92 min (minor, *anti*).

(*R*)-5-Nitro-4-phenylpentan-2-one (6). [12b] White solid, 75% yield, m.p. 90–92 °C, $[\alpha]_D^{20}$ −3.4 (c 1.7, $CHCl_3$), 40% *ee*. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.10 s, 3H), 2.91 (d, *J* = 6.8 Hz, 2 H), 4.00 (t, *J* = 6.8 Hz, 1 H), 4.56–4.71 (m, 2 H), 7.20–7.22 (m, 2 Harom), 7.26–7.32 (m, 3 Harom). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 30.3, 39.0, 46.1, 79.4, 109.0, 127.3, 127.8, 129.0, 138.8, 205.4. HPLC analysis (Chiralpak AD-H column, hexane:2-propanol = 99:1, flow rate = 0.5 mL/min, wavelength = 254 nm): *R*t = 19.70 (minor) and 29.55 min (major).

(*S*)-2-((*R*)-2-Nitro-1-phenylethyl)cyclopentanone (7). [12b] Brown oil, 70% yield, $[\alpha]_D^{20}$ −26.0 (c 1.0, $CHCl_3$), *syn*/*anti* = 72.5/27.5, 79% *ee* (*syn*), 77% *ee* (*anti*). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.43–1.53 (m, 1H), 1.68–1.73 (m, 1 H), 1.86–1.90 (m, 2 H), 2.08–2.17 (m, 1 H), 2.25–2.26 (m, 0.27 H, *anti*), 2.36–2.42 (m, 1 H), 2.51–2.53 (m, 0.31 H, *anti*), 3.68–3.70 (m, 0.70 H, *syn*), 3.82–3.83 (m, 0.30 H, *anti*), 4.08–4.09 (m, 0.26 H, *anti*), 4.71 (t, *J* = 11.2 Hz, 0.71 H, *syn*), 5.01 (d, *J* = 7.2 Hz, 0.71 H, *syn*), 5.33 (d, *J* = 12.8 Hz, 1 H, *syn*), 7.15–7.19 (m, 2 Harom), 7.26–7.31 (m, 3 Harom). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 20.3 (*syn*), 20.6 (*anti*), 28.3 (*syn*), 29.7 (*anti*), 38.7 (*syn*), 39.3 (*anti*), 44.0 (*anti*), 44.2 (*syn*), 50.5 (*syn*), 51.4 (*anti*), 77.2 (*anti*), 78.3 (*syn*), 127.9 (*anti*), 128.0 (*anti*), 128.0 (*syn*), 128.5 (*syn*), 128.8 (*syn*), 128.9 (*syn*), 129.0 (*anti*), 130.9 (*anti*), 137.4 (*anti*), 137.5 (*syn*), 218.5 (*syn*), 219.1 (*anti*). HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 95:5, flow rate = 1.0 mL/min, wavelength = 220 nm): *R*t = 12.29 (major, *anti*), 14.20 (minor, *anti*), 15.87 (minor, *syn*) and 21.09 min (major, *syn*).

Acknowledgements

We are grateful to the National Natural Science Foundation of China (No. 20772058) for generous financial support for our programs.

References

1 (*a*) For reviews, see: A. M. Berner, L. Tedeschi and D. Enders, *Eur. J. Org. Chem.*, 2002, 1877; (*b*) S. B. Tsogoeva, *Eur. J. Org. Chem.*, 2007, 1701.
2 (*a*) T. Mukaiyama and T. Hoshino, *J. Am. Chem. Soc.*, 1960, **82**, 5339; (*b*) G. Kumaran and G. H. Kulkarni, *Tetrahedron Lett.*, 1994, **35**, 5517.
3 (*a*) D. H. Lloyd and D. E. Nichols, *J. Org. Chem.*, 1986, **51**, 4294; (*b*) A. G. M. Barrett and C. D. Spilling, *Tetrahedron Lett.*, 1988, **29**, 5733; (*c*) R. E. Maeri, J. Heinzer and D. Seebach, *Liebigs Ann.*, 1995, 1193; (*d*) M.-A. Poupart, G. Fazal, S. Goulet and L. T. Mar, *J. Org. Chem.*, 1999, **64**, 1356.
4 (*a*) H. W. Pinnik, *Org. Reactions*, 1990, **38**, 655; (*b*) J. U. Nef, *Justus Liebigs Ann. Chem.*, 1894, **280**, 263; (*c*) R. Ballini and M. Petrini, *Tetrahedron*, 2004, **60**, 1017.
5 (*a*) V. Meyer and C. Wurster, *Ber.: Dtsch. Chem. Ges.*, 1873, **6**, 1167; (*b*) M. J. Kamlet, L. A. Kaplan and J. C. Dacons, *J. Org. Chem.*, 1961, **26**, 4371.
6 R. Tamura, A. Kamimura and N. Ono, *Synthesis*, 1991, 423.
7 (*a*) B. List, P. Pojarliev and H. J. Martin, *Org. Lett.*, 2001, **3**, 2423; (*b*) J. M. Betancourt, K. Saktivel, R. Thayumanavan and C. F. Barbas, III, *J. Am. Chem. Soc.*, 2001, **123**, 5260; (*c*) J. M. Betancourt and C. F. Barbas, III, *Org. Lett.*, 2001, **3**, 3737.
8 (*a*) Most resent examples, see: V. K. Vishnumaya Singh, *Org. Lett.*, 2007, **9**, 1117; (*b*) E. Alza, X. C. Cambeiro, C. Jimeno and M. A. Pericàs, *Org. Lett.*, 2007, **9**, 3717; (*c*) M. L. Clarke and J. A. Fuentes, *Angew. Chem. Int. Ed.*, 2007, **46**, 930; (*d*) D. Almaşi, D. A. Alonso, E. Gómez-Bengoa, Y. Nagel and C. Nájera, *Eur. J. Org. Chem.*, 2007, 2328; (*e*) L. Q. Gu, Y. Y. Wu, Y. Z. Zhang and G. Zhao, *J. Mol. Catal. A.*, 2007, **263**, 186; (*f*) F. Y. Liu, S. W. Wang and Y. G. Peng, *Synlett*, 2007, 2415;

(*g*) D. Diez, M. J. Gil, R. F. Moro, I. S. Marcos, P. García, P. Basabe, N. M. Garrido, H. B. Broughton and J. G. Urones, *Tetrahedron*, 2007, **63**, 740; (*h*) H. B. Chen, Y. Wang, S. Y. Wei and J. Sun, *Tetrahedron: Asymmetry*, 2007, **18**, 1308; (*i*) B. K. Ni, Q. Y. Zhang and A. D. Headley, *Tetrahedron: Asymmetry*, 2007, **18**, 1443; (*j*) D.-Q. Xu, B.-T. Wang, S.-P. Luo, H.-D. Yue, L.-P. Wang and Z.-Y. Xu, *Tetrahedron: Asymmetry*, 2007, **18**, 1788; (*k*) Y.-J. Cao, Y.-Y. Lai, X. Wang, Y.-J. Li and W.-J. Xiao, *Tetrahedron Lett.*, 2007, **48**, 21; (*l*) T. Mandal and C.-G. Zhao, *Tetrahedron Lett.*, 2007, **48**, 5803; (*m*) Q. Tao, G. Tang, K. Lin and Y.-F. Zhao, *Chirality*, 2008, **20**, 833; (*n*) S. Chandrasekhar, B. Tiwari, B. Parida and C. R. Reddy, *Tetrahedron: Asymmetry*, 2008, **19**, 495; (*o*) B. K. Ni, Q. Y. Zhang and A. D. Headley, *Tetrahedron Lett.*, 2008, **49**, 1249; (*p*) Y.-B. Zhao, L.-W. Zhang, L.-Y. Wu, X. Zhong, R. Li and J.-T. Ma, *Tetrahedron: Asymmetry*, 2008, **19**, 1352; (*q*) D.-Q. Xu, L.-P. Wang, S.-P. Luo, Y.-F. Wang, S. Zhang and Z.-Y. Xu, *Eur. J. Org. Chem.*, 2008, 1047; (*r*) P. H. Li, L. Wang, M. Wang and Y. C. Zhang, *Eur. J. Org. Chem.*, 2008, 1157; (*s*) T. Miao and L. Wang, *Tetrahedron Lett.*, 2008, **49**, 2173; (*t*) D.-Q. Xu, H.-D. Yue, S. P. Luo, A. B. Xia, S. Zhang and Z.-Y. Xu, *Org. Biomol. Chem.*, 2008, **6**, 2054; (*u*) G. H. Lv, R. Z. Jin, W. P. Mai and L. X. Gao, *Tetrahedron: Asymmetry*, 2008, **19**, 2568; (*v*) Q. Y. Zhang, B. K. Ni and A. D. Headley, *Tetrahedron*, 2008, **64**, 5091; (*w*) P. H. Li, L. Wang, Y. C. Zhang and G. W. Wang, *Tetrahedron*, 2008, **64**, 7633; (*x*) A. Quintard, C. Bournaud and A. Alexakis, *Chem. Eur. J.*, 2008, **14**, 7504.

9 (*a*) Y. M. Xu and A. Córdova, *Chem Commun.*, 2006, 460; (*b*) S. B. Tsogoeva and S. Wei, *Chem. Commun.*, 2006, 1451; (*c*) H. Huang and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2006, **128**, 7170; (*d*) M. P. Yalonde, Y. Chen and E. N. Jacobsen, *Angew. Chem. Int. Ed.*, 2006, **45**, 6366; (*e*) Y. M. Xu, W. B. Zou, H. Sundén, I. Ibrahem and A. Córdova, *Adv. Synth. Catal.*, 2006, **348**, 418; (*f*) S. H. McCooey and S. J. Connon, *Org. Lett.*, 2007, **9**, 599; (*g*) K. Liu, H.-F. Cui, J. Nie, K.-Y. Dong, X.-J. Li and J.-A. Ma, *Org. Lett.*, 2007, **9**, 923; (*h*) S. W. Wei, D. A. Yalalov, S. B. Tsogoeva and S. Schmatz, *Catal. Today*, 2007, **121**, 151; (*i*) Y. Xiong, Y. H. Wen, F. Wang, B. Gao, X. H. Liu, X. Huang and X. M. Feng, *Adv. Synth. Catal.*, 2007, **349**, 2156; (*j*) F. Xue, S. L. Zhang, W. H. Duan and W. Wang, *Adv. Synth. Catal.*, 2008, **350**, 2194.

10 (*a*) For reviews, see: P. R. Schreiner, *Chem. Soc. Rev.*, 2003, **32**, 289; (*b*) M. S. Taylor and E. N. Jacobsen, *Angew. Chem. Int. Ed.*, 2006, **45**, 1520; (*c*) S. J. Connon, *Chem. Eur. J.*, 2006, **12**, 5418; (*d*) Y. Takemoto, *Org. Biomol. Chem.*, 2005, **3**, 4299.

11 S. B. Tsogoeva, D. A. Yalalov, M. J. Hateley, C. Weckbecker and K. Huthmacher, *Eur. J. Org. Chem.*, 2005, 4995.

12 (*a*) Y.-J. Cao, H.-H. Lu, Y.-Y. Lai, L.-Q. Lu and W.-J. Xiao, *Synthesis*, 2006, 3795; (*b*) C.-L. Cao, M.-C. Ye, X.-L. Sun and Y. Tang, *Org. Lett.*, 2006, **8**, 2901.

13 C. G. Wang, Z. H. Zhou and C. C. Tang, *Org. Lett.*, 2008, **10**, 1707.

14 P. Gao, C. G. Wang, Y. Wu, Z. H. Zhou and C. C. Tang, *Eur. J. Org. Chem.*, 2008, 4563.

15 (*a*) E. A. A. Wallén, J. A. M. Christiaans, S. M. Saario, M. M. Forsberg, J. I. Venäläinen, H. M. Paso, P. T. Männistö and J. Gynther, *Bioorg. Med. Chem.*, 2002, **10**, 2199; (*b*) A. Slaitas and E. Yeheskiely, *Eur. J. Org. Chem.*, 2002, 2391; (*c*) W. Chu, J. Zhang, C. Zeng, J. Rothfuss, Z. Tu, Y. Chu, D. E. Reichert, M. J. Welch and R. H. Mach, *J. Med. Chem.*, 2005, **48**, 7637; (*d*) J. J. Li, J. C. Sutton, A. Nirschl, Y. Zou, H. Wang, C. Sun, Z. Pi, R. Johnson, S. R. Krystek, Jr., R. Seethala, R. Golla, P. G. Sleph, B. C. Beehler, G. J. Grover, A. Fura, V. P. Vyas, C. Y. Li, J. Z. Gougoutas, M. A. Galella, R. Zahler, J. Ostrowski and L. G. Hamann, *J. Med. Chem.*, 2007, **50**, 3015.

16 E. D. Butova, A. A. Fokin and P. R. Schreiner, *J. Org. Chem.*, 2007, **72**, 5689.

17 S. V. Pansare and K. Pandya, *J. Am. Chem. Soc.*, 2006, **128**, 9624–9625.

18 S. Z. Luo, H. Xu, X. L. Mi, J. Y. Li, X. X. Zheng and J. P. Cheng, *J. Org. Chem.*, 2006, **71**, 9244.

19 T. Ishii, S. Fujioka, Y. Sekiguchi and H. Kotsuki, *J. Am. Chem. Soc.*, 2004, **126**, 9558.