# An Effective Bifunctional Thiourea Catalyst for Highly Enantio- and Diastereoselective Michael Addition of Cyclohexanone to Nitroolefins

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**Abstract:** A series of new tunable and bifunctional thiourea catalysts have been synthesized and their catalytic activities are evaluated in the direct Michael addition of cyclohexanone to nitroolefins. High isolated yields (up to 97%), enantioselectivities (up to 98%) and diastereoselectivities (up to 99:1) were obtained under the optimal conditions.

**Key words:** Asymmetric catalysis, Michael addition, bifunctional thiourea catalyst, organocatalysis, nitroolefins

Michael addition is one of the most important C–C bond-forming reactions. In particular, the addition of nucleophiles to nitroolefins is very valuable for the generation of nitrogen-containing building blocks for organic synthesis.[1] Considerable efforts have been made in this area. Elegant examples include reactions catalyzed by metal–ligand complexes,[2] L-proline[3] and proline derivatives.[4] Since the late 1960s, advances in the development of metal-based chiral catalysts have provided a wealth of asymmetric Michael addition; however, relatively few reports have appeared that employed organic molecules as reaction catalysts despite the attendant potential for savings in cost, time, energy, operational complexity and chemical waste in comparison to chiral metal catalysts. Therefore, the design of new effective organocatalysts for asymmetric synthesis is of great interest.

Chiral thiourea catalysts have emerged as versatile catalytic systems. This is due to their strong double hydrogen-bonding effects and many notable results which have been recently achieved by Jacobsen and Takemoto and coworkers.[5] However, nearly all of these catalysts were just suitable for 1,3-dicarbonyl compounds and few reports were about direct Michael additions of cyclohexanone to nitroolefins.[6] Until recently Tsogoeva[6f] and Jacobsen[6h] have developed amine-thiourea catalysts for addition reactions of ketones and nitroolefins with moderate to excellent stereoselectivities. With the interest in designing new organocatalysts for organic transformations,[7] we synthesized a series of readily tunable and bifunctional (thio)urea catalysts **1**–**3** (Figure 1) and their catalytic activities were evaluated in the direct Michael addition of cyclohexanone to nitroolefins.

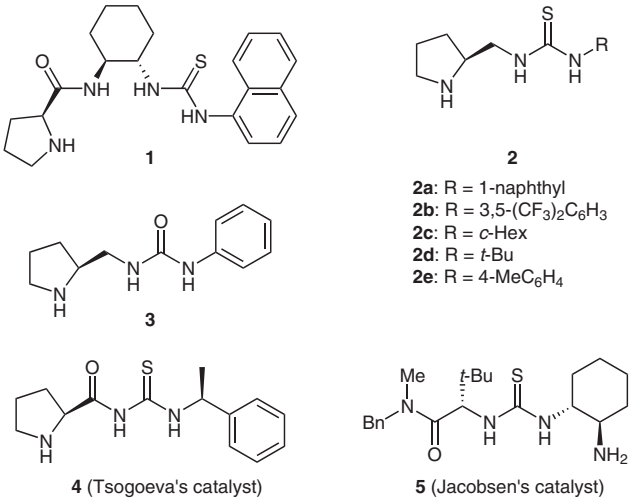


**Figure 1** Novel tunable and bifunctional amine-thiourea catalysts

In our system, one catalyst has two reaction–activation sites, which can activate both Michael donors and acceptors simultaneously. The selectivity and activity can be obviously tuned by a simple change of the thiourea motif. The catalytic potential of these catalysts was initially evaluated in the reaction of cyclohexanone (**6**) with β-nitrostyrene (**7a**) (Table 1).

As can be seen from Table 1, the L-prolinamide based catalyst **1** was initially tested, which was prepared according to our previous procedures.[7] It was found that the reaction proceeded slowly with an excellent diastereoselectivity but a poor enantioselectivity (entry 1 in Table 1). We then examined the bifunctional pyrrolidine-thiourea catalysts **2a**–**e**, which were synthesized from *N*-Boc-2-aminomethylpyrrolidine and isothiocyanate by a two-step procedure. All of these catalysts could effectively promote the reaction at ambient temperature in the presence of catalytic amount of acetic or benzoic acids.[8] As predicted, the catalytic activity and the selectivity of the reaction were apparently influenced by the thiourea unit of the catalyst (entries 2–6 in Table 1). If the thiourea moiety was replaced by a urea group (catalyst **3**), the enantioselectivity declined remarkably (entry 7 in Table 1) by maintaining almost the same level of diasteroselectivity. In these catalysts, the $CH_2$ group between the pyrrolidine and thiourea moiety was very important in order to maximize the reaction efficiency, because the reaction gave the product nearly in racemic form and a low yield with the use of cat-

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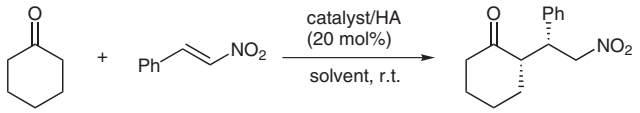
**Table 1** Optimization of Reaction Conditions for the Direct Michael Addition of Cyclohexanone (**6**) to β-Nitrostyrene (**7a**)[a]




**6** **7a** **8a**

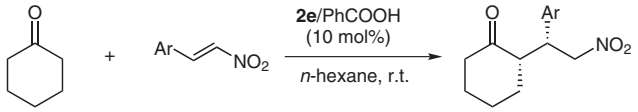
| Entry | Catalyst[b] | Solvent | Time (h) | Yield (%)[c] | dr (*syn*/*anti*)[d] | ee (%)[e] |
|---|---|---|---|---|---|---|
| 1 | **1** | $CHCl_3$ | 125 | 81 | 94:6 | 5 |
| 2 | **2a** | $CHCl_3$ | 18 | 69 | 92:8 | 89 |
| 3 | **2b** | $CHCl_3$ | 51 | 61 | 91:9 | 84 |
| 4 | **2c** | $CHCl_3$ | 41 | 60 | 89:11 | 87 |
| 5 | **2d** | $CHCl_3$ | 48 | 63 | 95:5 | 89 |
| 6 | **2e** | $CHCl_3$ | 29 | 66 | 96:4 | 91 |
| 7 | **3** | $CHCl_3$ | 60 | 51 | 92:8 | 70 |
| 8 | **2e** | $CHCl_3$ | 23 | 99 | 94:6 | 89 |
| 9 | **2e** | $CHCl_3$ | 15 | 91 | 95:5 | 91 |
| 10 | **2e** | $Et_2O$ | 15 | 79 | 93:7 | 88 |
| 11 | **2e** | 1,4-dioxane | 23 | 74 | 92:8 | 88 |
| 12 | **2e** | *n*-hexane | 15 | 93 | 97:3 | 93 |
| 13 | **2e** | MeOH | 120 | 0 | n.d. | n.d. |
| 14[f] | **2e** | *n*-hexane | 72 | 94 | 97:3 | 95 |
| 15[g] | **2e** | *n*-hexane | 17 | 94 | 96:4 | 92 |

[a] Unless otherwise specified, the reaction was carried out with 0.5 mmol of **7a** and 10 equiv of **6** in the presence of 20 mol% of catalyst/HA at room temperature in 2 mL of the solvent.
[b] The co-catalyst HA for entries 1–7 was AcOH, and benzoic acid was used in the cases of entries 8–15.
[c] Isolated yields.
[d] Determined by chiral HPLC analysis of the mixture of *syn*/*anti* products.
[e] Determined by chiral HPLC.
[f] 10 mol% of the catalyst was used.
[g] 10 mol% of the catalyst and 1 mL of *n*-hexane were used.

alyst **4**.[6f] Among the catalysts screened, **2e** exhibits the best catalytic performances (entry 6 in Table 1). Furthermore, when benzoic acid was employed as a co-catalyst instead of acetic acid, the yield of the product could be further improved to 99% with comparable stereoselectivity (entries 8 vs. 6 in Table 1). The solvent effects were also examined for this reaction. The polar solvents resulted in lower yields (entries 10 and 11 in Table 1), and even no reaction occurred when MeOH was used (entry 13 in Table 1). In contrast, the reaction proceeded smoothly in nonpolar solvents, with the best results being obtained when *n*-hexane was chosen as the solvent (entry 12 in Table 1). Significantly, when the catalyst loading was reduced to 10 mol%, the reaction still took place in high yield with excellent stereoselectivity (entry 14 in Table 1), though a longer reaction time was needed. However, this drawback could be overcome by running the reaction in high concentration (entry 15 in Table 1).

With the optimal reaction conditions in hand, a variety of aromatic nitroolefins were evaluated in the direct Michael addition and results are summarized in Table 2. Not only substituted nitrostyrenes (entries 1–12 in Table 2) but also other aromatic nitroolefins (entries 13–15 in Table 2) can be employed efficiently in Michael addition reactions, affording the corresponding nitro compounds with high to excellent enantioselectivities (up to 98%) and diastereoselectivities (up to 98:2) at an ambient temperature. In the case of 4-hydroxy-β-nitrostyrene, the reaction was slow, but the selectivity was still very good (entry 12 in Table 2). The scope of the Michael donors could be extended to heterocyclic ketones. For instance, the reaction of tetrahydro-4*H*-pyran-4-one with β-nitrostyrene gave the desired product in 92% yield with excellent stereoselectivities (dr: 98:2; ee: 90%) (entry 16 in Table 2). Both diastereo- and enantioselectivities of these Michael addition reactions could be further improved when these reactions were conducted at 0 °C (entries 2, 4, 11 and 14 in Table 2).

**Table 2** Michael Reactions of Cyclohexanone (**6**) to Nitroolefins **7** Catalyzed by **2e**[a]




**6** **7a–k** **8a–l**

| Entry | Ar | Product | Time (h) | Yield (%)[b] | dr (*syn*/*anti*)[c] | ee (%)[d] |
|---|---|---|---|---|---|---|
| 1 | Ph | **8a** | 11 | 93 | 96:4 | 92 |
| 2[e] | Ph | **8a** | 48 | 87 | 99:1 | 96 |
| 3 | 4-$ClC_6H_4$ | **8b** | 12 | 84 | 95:5 | 91 |
| 4[e] | 4-$ClC_6H_4$ | **8b** | 48 | 80 | 98:2 | 95 |
| 5 | 2-$ClC_6H_4$ | **8c** | 12 | 90 | 98:2 | 93 |
| 6 | 4-$MeC_6H_4$ | **8d** | 24 | 80 | 95:5 | 91 |
| 7 | 2,4-$Cl_2C_6H_3$ | **8e** | 10 | 93 | 98:2 | 98 |
| 8 | 4-$BrC_6H_4$ | **8f** | 10.5 | 92 | 97:3 | 98 |
| 9 | 3-$BrC_6H_4$ | **8g** | 31 | 78 | 96:4 | 93 |
| 10 | 4-$FC_6H_4$ | **8h** | 11 | 85 | 97:3 | 90 |
| 11[e] | 4-$FC_6H_4$ | **8h** | 53 | 78 | 99:1 | 94 |
| 12 | 4-$HOC_6H_4$ | **8i** | 7.5 d | 69 | 90:10 | 89 |
| 13 | 2-thienyl | **8j** | 18 | 88 | 90:10 | 83 |
| 14[e] | 2-thienyl | **8j** | 41 | 87 | 93:7 | 89 |
| 15 | 1-naphthyl | **8k** | 47 | 97 | 97:3 | 94 |
| 16[f] | Ph | **8l** | 12 | 92 | 98:2 | 90 |

[a] The reaction was conducted with catalyst **2e** (10 mol%), benzoic acid (10 mol%), **7** (0.5 mmol) and **6** (10 equiv) in *n*-hexane (1 mL).
[b] Isolated yields.
[c] Determined by chiral HPLC analysis of the mixture of *syn*/*anti* products.
[d] Determined by chiral HPLC.
[e] The reaction was conducted at 0 °C.
[f] Tetrahydro-4*H*-pyran-4-one was used as the Michael donor.

The absolute configuration of the major Michael adduct **8a** was determined to be (2*S*,1′*R*) by NMR analysis and the comparison of HPLC retention times with those in the literature.[6] This can be explained according to the suggested transition state **A** (Figure 2). During the course of the Michael addition, the secondary amine part of the catalyst reacted with cyclohexanone to form the enamine intermediate while the thiourea part of the catalyst activated the nitroolefins by the double hydrogen-bonding. Accordingly, we propose that the *re*-face of the enamine would attack at the *re*-face of the nitrostyrene.

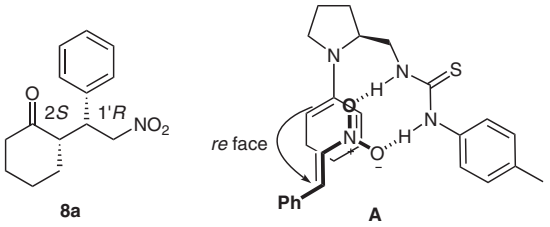
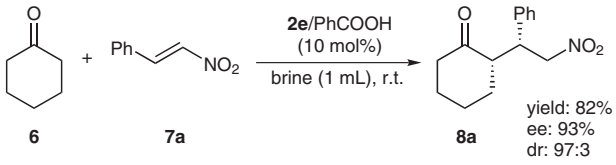



**Figure 2** Proposed transition state for asymmetric Michael addition

The model reaction could also be conducted in aqueous media. We have run the reaction in brine,[9] and to our great delight, the results are comparable with those in organic solvents (Equation 1).




**Equation 1**

In conclusion, we have developed a series of readily tunable and bifunctional secondary amine-thiourea catalysts for the direct Michael additions of cyclohexanone to nitroolefins.[10] Excellent enantio- and diastereoselectivities

have been obtained at an ambient temperature. Further investigation of the scope of these catalysts as well as the mechanistic aspects is underway in our laboratory.

$^1$H NMR spectra were recorded on Varian Mercury 400 (400 MHz) spectrophotometers. Chemical shifts are reported in ppm from the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm). $^{13}$C NMR spectra were recorded on Varian Mercury 400 (100 MHz) spectrophotometers with complete proton decoupling ($CDCl_3$: 77.0 ppm). Chiral HPLC was performed on an Agilent 1100 series instrument with chiral columns [Chirapak AS, AD, OD and OJ columns, (Daicel Chemical Ind., Ltd.)]. Elementary analyses were taken on a Vario EL III elementary analysis instrument.

Unless otherwise noted, materials were purchased from commercial suppliers and used without further purification. Dichloromethane and trichloromethane were freshly distilled from calcium hydride. Petroleum ether and ethyl acetate for flash column chromatography were distilled before use. Flash column chromatography was performed using 200–300 mesh silica gel.

**Catalysts 2; General Procedure**

*N*-Boc-(*S*)-2-aminomethylpyrrolidine (1 g, 5 mmol) was dissolved in $CH_2Cl_2$ (10 mL). The mixture was cooled to 0 °C and the appropriate isothiocyanate (5 mmol) was added dropwise to this solution. After the addition was complete, the mixture was allowed to warm to r.t. and stirred for 30 min. The solvent was then removed under reduced pressure. The residue was dissolved in a mixture of TFA–$CH_2Cl_2$ (1:4, 20 mL) and stirred for 2 h at r.t. The mixture was basified with concd aq ammonia and extracted with $CH_2Cl_2$ (3 × 30 mL). After the removal of the solvent under vacuum, the residue was purified by flash column chromatography on silica gel (eluent, EtOAc–MeOH, 1:1) to afford catalyst **2** as a white solid in 62–75% isolated yields.

**Catalyst 2a**

This catalyst was prepared according to the general procedure as described above in 70% isolated yield.

$^1$H NMR (400 MHz, $CDCl_3$/TMS): δ = 8.0 (s, 2 H), 7.99–7.78 (m, 2 H), 7.53–7.28 (m, 5 H), 6.85 (br, 1 H), 3.74–3.71 (m, 1 H), 3.36–3.27 (m, 2 H), 2.62–2.47 (m, 2 H), 1.87–1.71 (m, 1 H), 1.51–1.43 (m, 2 H), 1.25–1.21 (m, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$/TMS): δ = 181.3, 134.4, 132.3, 129.8, 128.3, 126.9, 126.7, 125.6, 125.1, 122.5, 57.0, 49.1, 46.0, 28.7, 25.5.

**Catalyst 2b**

The title compound was prepared according to the general procedure as described above in 62% yield.

$^1$H NMR (400 MHz, $CDCl_3$/TMS): δ = 4.05 (s, 1 H), 3.49–3.31 (m, 3 H), 2.97 (s, 2 H), 2.86 (s, 1 H), 1.98–1.65 (m, 14 H).

$^{13}$C NMR (100 MHz, $CDCl_3$/TMS): δ = 181.9, 53.2, 47.6, 45.7, 32.7, 28.6, 25.5, 24.7 (2 ×).

**Catalyst 2c**

The title compound was prepared according to the typical procedure, as described above in 72% yield.

$^1$H NMR (400 MHz, $CDCl_3$/TMS): δ = 8.04 (s, 2 H,), 7.78 (br, 1 H), 7.63–7.57 (s, 1 H), 6.85 (br, 1 H), 3.55 (s, 1 H), 3.49–3.31 (m, 2 H), 3.12 (s, 1 H), 2.86 (s, 1 H), 1.97–1.93 (m, 2 H), 1.76–1.72 (m, 1 H), 1.58–1.51 (m, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$/TMS): δ = 183.3, 134.4, 142.1, 131.7, 131.3, 124.5, 122.5, 121.8, 117.2, 59.4, 50.7, 46.1, 28.3, 27.1.

**Catalyst 2d**

The title compound was prepared according to the general procedure as described above in 62% yield.

$^1$H NMR (400 MHz, $CDCl_3$/TMS): δ = 5.03 (s, 2 H), 3.71–3.53 (m, 3 H), 3.00 (s, 2 H), 1.97–1.81 (m, 4 H), 1.63–1.45 (m, 11 H).

$^{13}$C NMR (100 MHz, $CDCl_3$/TMS): δ = 181.6, 58.7, 52.9, 456, 29.0, 28.5, 25.5.

**Catalyst 2e**

The title compound was prepared according to the general procedure as described above in 75% yield.

$^1$H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.17–6.97 (s, 4 H), 3.73 (s, 1 H), 3.45 (m, 2 H), 2.86–2.34 (m, 3 H), 2.17 (s, 3 H), 1.93–1.24 (m, 4 H).

$^{13}$C NMR (100 MHz, $CDCl_3$/TMS): δ = 180.6, 136.4, 134.2, 129.8, 124.8, 57.6, 48.9, 46.2, 28.8, 25.7, 20.9.

**Catalyst 3**

The title compound was prepared according to the general procedure as described above by using isocyanate instead of isothiocyanate in 75% yield.

$^1$H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.39–7.37 (s, 2 H), 7.14–7.13 (s, 2 H), 5.28 (s, 1 H), 3.44–3.31 (m, 3 H), 2.85 (m, 2 H), 2.62–2.56 (s, 1 H), 1.84–1.63 (m, 3 H), 1.47–1.41 (m, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$/TMS): δ = 157.5, 139.5, 128.7, 122.2, 118.8, 60.3, 45.8, 41.2, 31.0, 24.0.

**Michael Addition of Cyclohexanone (6) to Nitroolefins 7; General Procedure**

Catalyst **2e** (13 mg, 0.05 mmol), benzoic acid (6 mg, 0.05 mmol) and cyclohexanone (**6**; 490 mg, 5 mmol, 10 equiv) were dissolved in *n*-hexane (1 mL). After stirring the mixture for 15 min at r.t., the corresponding nitroolefin **7** (0.5 mmol, 1 equiv) was added and the mixture was stirred for the time given in Table 2 (monitored by TLC, petroleum ether–EtOAc, 4:1). The mixture was then concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography on silica gel (petroleum ether–EtOAc, 20:1 to 5:1) to obtain the desired product as a white solid. Relative and absolute configurations of the products were determined by comparison with the known $^1$H NMR, $^{13}$C NMR spectra, and chiral HPLC analysis.

**2-[2′-Nitro-1′-phenylethyl]cyclohexanone (8a)**

The title compound was prepared according to the general procedure as described above in 93% yield.

HPLC: Chiralpak AS-H, *i*-PrOH–hexane (25:75), flow rate 1.0 mL/min, λ = 254 nm; $t_R$ (minor isomer) = 10.1 min, $t_R$ (major isomer) = 14.6 min; ee = 93%.

$^1$H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.34–7.16 (m, 5 H), 4.94 (dd, *J* = 4.8, 12.8 Hz, 1 H), 4.63 (dd, *J* = 10.0, 11.2 Hz, 1 H), 3.79–3.74 (m, 1 H), 2.69–2.68 (m, 1 H), 2.49–2.37 (m, 2 H), 2.09–2.05 (m, 1 H), 1.79–1.54 (m, 3 H), 1.26–1.21 (m, 2 H).

$^{13}$C NMR (100 MHz, $CDCl_3$/TMS): δ = 211.9, 137.7, 128.9, 128.1, 127.7, 78.8, 52.5, 43.9, 42.7, 33.2, 28.5, 25.0.

Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.2; H, 6.62; N, 5.63.

**2-[1-(4-Chlorophenyl)-2-nitroethyl]cyclohexanone (8b)**

The title compound was prepared according to the general procedure as described above in 84% yield.

HPLC: Chiralpak AD-H, *i*-PrOH–hexane (10:90), flow rate 1.0 mL/min, λ = 254 nm; $t_R$ (minor isomer) = 13.4 min, $t_R$ (major isomer) = 20.0 min; ee = 91%.

$^1$H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.30 (d, *J* = 8.4 Hz, 1 H), 7.28 (d, *J* = 8.4 Hz, 1 H), 7.13 (d, *J* = 8.0 Hz, 1 H), 7.11 (d, *J* = 8.0 Hz, 1 H), 4.94 (dd, *J* = 4.4, 12.4 Hz, 1 H), 4.60 (dd, *J* = 10.2, 11.2 Hz, 1 H), 3.79–3.73 (m, 1 H), 2.67–2.61 (m, 1 H), 2.48–2.36 (m, 2 H), 2.09–2.07 (m, 1 H), 1.80–1.54 (m, 3 H), 1.26–1.18 (m, 2 H).

$^{13}$C NMR (100 MHz, $CDCl_3$/TMS): δ = 211.5, 136.2, 133.5, 129.5, 129.1, 78.5, 52.3, 43.3, 42.7, 33.1, 29.6, 28.4, 25.0.

Anal. Calcd for $C_{14}H_{16}ClNO_3$: C, 59.68; H, 5.72; N, 4.97. Found: C, 60.21; H, 5.94; N, 4.79.

**2-[1-(2-Chlorophenyl)-2-nitroethyl]cyclohexanone (8c)**
The title compound was prepared according to the general procedure as described above in 90% yield.

HPLC: Chiralpak AD-H, *i*-PrOH–hexane (5:95), flow rate 1.0 mL/min, λ = 254 nm; $t_R$ (minor isomer) = 27.6 min, $t_R$ (major isomer) = 49.3 min; ee = 93%.

$^1$H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.38–7.18 (m, 4 H), 4.90 (dd, *J* = 5.6, 10.8 Hz, 2 H), 4.30 (dd, *J* = 8.4, 14.0 Hz, 1 H), 2.93–2.87 (m, 1 H), 2.48–2.34 (m, 2 H), 2.12–2.06 (m, 1 H), 1.82–1.54 (m, 3 H), 1.38–1.26 (m, 2 H).

$^{13}$C NMR (100 MHz, $CDCl_3$/TMS): δ = 211.6, 135.4, 134.5, 130.2, 128.8, 127.3, 77.3, 51.6, 42.7, 40.8, 32.9, 28.4, 25.2.

Anal. Calcd for $C_{14}H_{16}ClNO_3$: C, 59.68; H, 5.72; N, 4.97. Found: C, 59.65; H, 5.78; N, 4.81.

**2-[1-(4-Methylphenyl)-2-nitroethyl]cyclohexanone (8d)**
The title compound was prepared according to the general procedure as described above in 80% yield.

HPLC: Chiralpak AD-H, *i*-PrOH–hexane (2:98), flow rate 0.5 mL/min, λ = 254 nm; $t_R$ (minor isomer) = 18.0 min, $t_R$ (major isomer) = 23.0 min; ee = 91%.

$^1$H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.13 (d, *J* = 8.0 Hz 1 H), 7.11 (d, *J* = 8.0 Hz, 1 H), 7.06 (d, *J* = 8.0 Hz, 1 H), 7.04 (d, *J* = 8.0 Hz, 1 H), 4.92 (dd, *J* = 4.0, 12.4 Hz, 1 H), 4.59 (dd, *J* = 10.0, 12.4 Hz, 1 H), 3.75–3.69 (m, 1 H), 2.69–2.63 (m, 1 H), 2.48–2.30 (m, 2 H), 2.09–2.04 (m, 1 H), 1.78–1.53 (m, 3 H), 1.26–1.19 (m, 2 H).

$^{13}$C NMR (100 MHz, $CDCl_3$/TMS): δ = 212.0, 137.3, 134.5, 129.5, 127.9, 78.9, 52.4, 43.5, 42.6, 33.1, 28.4, 24.9, 20.9.

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.14; H, 7.32; N, 5.30.

**2-[1-(2,4-Dichlorophenyl)-2-nitroethyl]cyclohexanone (8e)**
The title compound was prepared according to the general procedure as described above in 93% yield.

HPLC: Chiralpak AD-H, *i*-PrOH–hexane (10:90), flow rate 1.0 mL/min, λ = 254 nm; $t_R$ (minor) = 14.2 min, $t_R$ (major) = 22.7 min; ee = 98%.

$^1$H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.41 (s, 1 H), 7.40–7.17 (m, 2 H), 4.89 (dd, *J* = 7.6, 12.8 Hz, 2 H), 4.28–4.22 (m, 1 H), 2.90–2.83 (m, 1 H), 2.49–2.34 (m, 2 H), 2.12–2.09 (m, 1 H), 1.84–1.55 (m, 3 H), 1.38–1.26 (m, 2 H).

$^{13}$C NMR (100 MHz, $CDCl_3$/TMS): δ = 211.3, 135.2, 134.1, 134.0, 130.1, 127.7, 77.3, 51.6, 42.7, 40.6, 33.0, 28.4, 25.2.

Anal. Calcd for $C_{14}H_{15}Cl_2NO_3$: C, 53.18; H, 4.78; N, 4.43. Found: C, 52.49; H, 4.81; N, 4.24.

**2-[1-(4-Bromophenyl)-2-nitroethyl]cyclohexanone (8f)**
The title compound was prepared according to the general procedure as described above in 92% yield.

HPLC: Chiralpak AD-H, *i*-PrOH–hexane (10:90), flow rate 1.0 mL/min, λ = 254 nm; $t_R$ (minor) = 14.15 min, $t_R$ (major) = 22.7 min; ee = 98%.

$^1$H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.47 (d, *J* = 8.0 Hz, 1 H), 7.45 (d, *J* = 8.0 Hz, 1 H), 7.06 (d, *J* = 8.0 Hz, 2 H), 4.94 (dd, *J* = 4.4, 12.8 Hz, 1 H), 4.60 (dd, *J* = 10.4, 12.8 Hz, 1 H), 3.78–3.63 (m, 1 H), 2.66–2.64 (m, 1 H), 2.48–2.36 (m, 2 H), 2.10–2.06 (m, 1 H), 1.81–1.55 (m, 3 H), 1.24–1.20 (m, 2 H).

$^{13}$C NMR (100 MHz, $CDCl_3$/TMS): δ = 211.4, 136.8, 132.0, 129.9, 121.6, 78.4, 52.2, 43.4, 42.7, 33.1, 28.4, 25.0.

Anal. Calcd for $C_{14}H_{16}BrNO_3$: C, 51.55; H, 4.94; N, 4.29. Found: C, 51.35; H, 4.98; N, 4.20.

**2-[1-(3-Bromophenyl)-2-nitroethyl]cyclohexanone (8g)**
The title compound was prepared according to the general procedure as described above in 93% yield.

HPLC: Chiralpak AS-H, *i*-PrOH–hexane (10:90), flow rate 1.0 mL/min, λ = 254 nm; $t_R$ (minor) = 13.6 min, $t_R$ (major) = 27.1 min; ee = 93%.

$^1$H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.41–7.11 (m, 4 H), 4.94 (dd, *J* = 4.4, 12.8 Hz, 1 H), 4.61 (dd, *J* = 10, 12.8 Hz, 1 H), 3.78–3.65 (m, 1 H), 2.66–2.65 (m, 1 H), 2.48–2.36 (m, 2 H), 2.10–2.06 (m, 1 H), 1.81–1.55 (m, 3 H), 1.29–1.21 (m, 2 H).

$^{13}$C NMR (100 MHz, $CDCl_3$/TMS): δ = 211.4, 140.2, 131.1, 130.9, 130.4, 126.9, 122.9, 78.3, 52.2, 43.5, 42.7, 33.1, 28.4, 25.0.

Anal. Calcd for $C_{14}H_{16}BrNO_3$: C, 51.55; H, 4.94; N, 4.29. Found: C, 51.44; H, 4.95; N, 4.20.

**2-[1-(4-Fluorophenyl)-2-nitroethyl]cyclohexanone (8h)**
The title compound was prepared according to the general procedure as described above in 85% yield.

HPLC: Chiralpak OD-H, *i*-PrOH–hexane (5:95), flow rate 1.0 mL/min, λ = 254 nm; $t_R$ (minor) = 20.2 min, $t_R$ (major) = 23.0 min; ee = 94%.

$^1$H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.27–7.02 (m, 4 H), 4.95 (dd, *J* = 4.0, 12.8 Hz, 1 H), 4.74 (dd, *J* = 10.4, 12.8 Hz, 1 H), 3.75–3.69 (m, 1 H), 2.69–2.63 (m, 1 H), 2.46–2.38 (m, 2 H), 2.10–2.08 (m, 1 H), 1.82–1.59 (m, 3 H), 1.27–1.23 (m, 2 H).

$^{13}$C NMR (100 MHz, $CDCl_3$/TMS): δ = 211.6, 162.4, 159.9, 131.0, 130.9, 129.6, 129.5, 124.6, 124.4, 116.0, 115.8, 77.4, 50.9, 42.7, 39.9, 33.2, 28.4, 25.1.

Anal. Calcd for $C_{14}H_{16}FNO_3$: C, 63.39; H, 6.08; N, 5.28. Found: C, 63.62; H, 6.34; N, 5.07.

**2-[1-(4-Hydroxyphenyl)-2-nitroethyl]cyclohexanone (8i)**
The title compound was prepared according to the general procedure as described above in 69% yield.

HPLC: Chiralpak AD-H, *i*-PrOH–hexane (10:90), flow rate 1.0 mL/min, λ = 254 nm; $t_R$ (minor) = 12.2 min, $t_R$ (major) = 11.0 min; ee = 89%.

$^1$H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.02 (d, *J* = 8.6 Hz, 1 H), 6.99 (d, *J* = 8.6 Hz, 1 H), 6.77 (d, *J* = 8.8 Hz, 1 H), 6.75 (d, *J* = 8.8 Hz, 1 H), 4.90 (dd, *J* = 7.2 Hz, 1 H), 4.56 (t, *J* = 10.4 Hz, 1 H), 3.70 (s, 1 H), 3.56–3.50 (m, 1 H), 2.64–2.61 (m, 1 H), 2.47–2.37 (m, 2 H), 2.09–2.07 (m, 1 H), 1.76–1.56 (m, 3 H), 1.31–1.22 (m, 2 H).

$^{13}$C NMR (100 MHz, $CDCl_3$/TMS): δ = 213.3, 155.4, 129.4, 115.9, 79.2, 52.7, 43.2, 42.7, 33.2, 29.7, 28.6, 24.9.

Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.24; H, 6.45; N, 5.30.

**2-(2-Nitro-1-thiophen-2-ylethyl)cyclohexanone (8j)**
The title compound was prepared according to the general procedure as described above in 88% yield.

HPLC: Chiralpak AS-H, *i*-PrOH–hexane (10:90), flow rate 1.0 mL/min, λ = 254 nm; $t_R$ (minor) = 16.7 min, $t_R$ (major) = 22.7 min; ee = 83%.

$^1$H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.22 (d, 1 H, *J* = 4.8 Hz), 6.94–6.87 (m, 2 H), 4.89 (dd, *J* = 4.4, 12.4 Hz, 1 H), 4.64 (dd, *J* = 9.6, 12.8 Hz, 1 H), 4.16–4.11 (m, 1 H), 2.71–2.65 (m, 1 H), 2.48–2.33 (m, 2 H), 2.12–2.7 (m, 1 H), 1.94–1.59 (m, 3 H), 1.37–1.27 (m, 2 H).

$^{13}$C NMR (100 MHz, $CDCl_3$/TMS): δ = 211.1, 140.4, 126.8, 126.5, 124.9, 79.1, 53.2, 42.5, 39.3, 32.6, 28.2, 25.0.

Anal. Calcd for $C_{12}H_{15}NO_3S$: C, 56.90; H, 5.97; N, 5.53. Found: C, 57.0; H, 6.06; N, 5.40.

**2-[1-Naphthalen-1-yl-2-nitroethyl]cyclohexanone (8k)**

The title compound was prepared according to the general procedure as described above in 97% yield.

HPLC: Chiralpak AS-H, *i*-PrOH–hexane (50:50), flow rate 0.7 mL/min, λ = 254 nm; $t_R$ (minor) = 12.5 min, $t_R$ (major) = 17.8 min; ee = 94%.

$^1$H NMR (400 MHz, $CDCl_3$/TMS): δ = 8.16 (m, 1 H), 7.85 (d, *J* = 7.6 Hz, 1 H), 7.77 (d, *J* = 8.4 Hz, 1 H), 7.55–7.24 (m, 4 H), 5.06 (dd, *J* = 4.0, 12.4 Hz, 1 H), 4.88 (dd, *J* = 9.2, 22.0 Hz, 1 H), 4.76 (s, 1 H), 2.50 (m, 1 H), 2.42–2.38 (m, 2 H), 2.06–2.03 (m, 1 H), 1.69–1.46 (m, 3 H), 1.27–1.21 (m, 2 H).

$^{13}$C NMR (100 MHz, $CDCl_3$/TMS): δ = 212.3, 134.6, 133.9, 129.0, 128.1, 126.5, 125.8, 125.3, 123.6, 122.7, 78.7, 53.8, 42.8, 36.7, 33.2, 28.6, 25.2.

Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.52; H, 6.78; N, 4.43.

**2-[1-Phenyl-2-nitroethyl]tetrahydro-4*H*-pyran-4-one (8l)**

The title compound was prepared according to the general procedure as described above in 93% yield.

HPLC: Chiralpak AD-H, *i*-PrOH–hexane (10:90), flow rate 1.0 mL/min, λ = 254 nm; $t_R$ (minor) = 14.2 min, $t_R$ (major) = 22.7 min; ee = 98%.

$^1$H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.37–7.29 (m, 3 H), 7.25–7.19 (m, 2 H), 4.76–4.60 (m, 2 H), 4.01–3.95 (m, 1 H), 3.08–2.93 (m, 3 H), 2.88–2.75 (m, 3 H), 2.63–2.59 (m, 1 H), 2.48–2.42 (m, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$/TMS): δ = 209.4, 136.4, 129.2, 128.2, 128.1, 78.5, 54.9, 44.5, 43.4, 35.0, 31.5.

Anal. Calcd for $C_{13}H_{15}NO_4$: C, 58.55; H, 5.70; N, 5.28. Found: C, 58.73; H, 5.81; N, 5.24.

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