Prolinol Sulfinyl Ester Derivatives: Organocatalytic Michael Addition of Ketones to Nitroolefins under Neat Conditions

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Abstract: Highly enantioselective and diastereoselective Michael addition of ketones to nitroolefins catalyzed by prolinol sulfinyl ester was achieved in excellent yields under solvent-free conditions at room temperature.

Key words: catalysis, asymmetric synthesis, ketones, sulfinates, Michael additions, nitro compounds

The organocatalytic asymmetric Michael reaction of ketones and nitroolefins is one of the fundamental C–C bond-formation reactions in organic chemistry.[1] The nitro functionality can easily be transferred into, for example, a nitrile oxide, ketone, amine, or carboxylic acid, providing a wide range of synthetically interesting compounds. The synthesis of some important natural products and their building blocks relies on asymmetric Michael reactions.[2] Thus, this reaction has been attracting the interest of many organic chemists, and some good results have been achieved in the past years. Recently increasing attention has been paid to the design and application of organocatalysts in many asymmetric organic reactions.[3] Among the various organocatalysts, proline and its derivatives have been demonstrated to make up a successful class of organocatalysts in enamine chemistry.[1o,4,5] Some of them have been proven to be good catalysts for the catalytic asymmetric Michael reaction of ketones with nitroolefins.[5a,1f] Furthermore, green solvents such as water,[1f] brine,[1b] and ionic liquids[1c,j] can be good media for some of the reactions. Chen and co-workers developed functionalized chiral ionic liquids as efficient organocatalysts for Michael addition reactions.[1c,j] Although these catalytic processes provide a unique methodology in asymmetric Michael addition reactions, there is still a need for the development of new, effective catalysts.

In our work towards designing highly enantioselective organocatalysts for the Michael addition reaction of ketones with nitroolefins, we have devised a new type of chiral pyrrolidine catalyst with a sulfinate group adjacent to a stereogenic carbon center. The formation of the enamine from the ketone precursors in the presence of this catalyst causes the resulting sulfinate group to be effectively shielded from one side of an enamine double bond, forcing the nitroolefin acceptors to approach from the nonshielded side to give the desired Michael adducts in high enantio- and diastereoselectivity (Figure 1). We describe herein the application of our new simple organocatalyst in asymmetric Michael addition reactions.

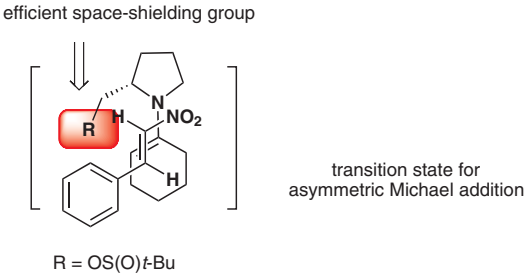
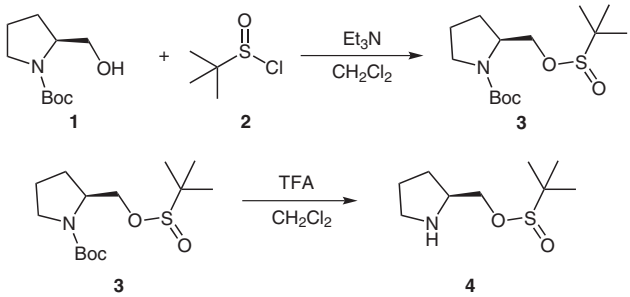


Figure 1 Transition state for asymmetric Michael addition

The catalyst (*S*)-pyrrolidin-2-ylmethyl 2-methylpropane-2-sulfinate (**4**) was synthesized by the reaction of *N*-Boc-prolinol (**1**) with 2-methylpropane-2-sulfinyl chloride (**2**) under basic conditions,[6] followed by deprotection of the *N*-Boc-substituted precursor **3** (Scheme 1). The new catalyst was then tested in the asymmetric Michael addition reaction of cyclohexanone (**6**) to β-nitrostyrene (**5a**) (Table 1).



Scheme 1 The synthesis of (*S*)-pyrrolidin-2-ylmethyl 2-methylpropane-2-sulfinate

We initially screened a series of organocatalysts for the Michael reaction between cyclohexanone (**6**) and nitroolefin **5a** under neat conditions at room temperature (23 °C). As shown by the results summarized in Table 1, the Michael addition reactions did not proceed in the presence of catalyst **4b**, **4d**, or **4e** (entries 3, 5, and 6); this was surprising. Although the adduct product can be obtained

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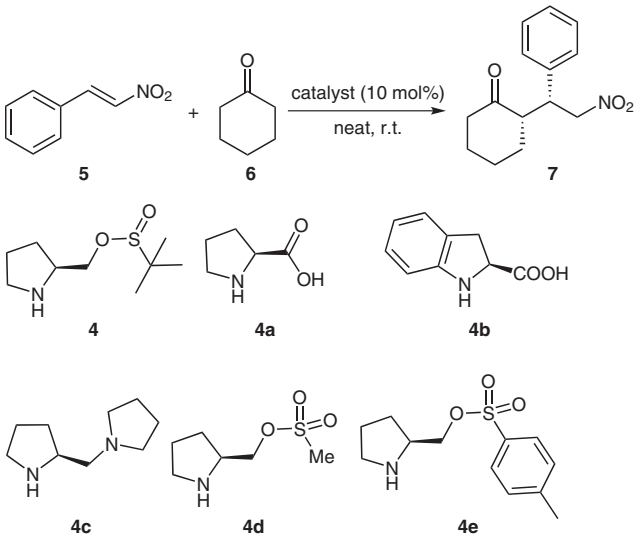
Table 1 Effect of Catalyst on the Michael Addition Reaction of Cyclohexanone (**6**) and Nitroolefin **5a**[a]



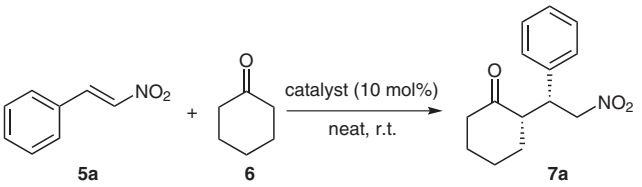
Entry	Catalyst	Time (h)	Yield[b,c] (%)	dr[d]	ee[e] (%)
1	**4**	24	97	98:2	97
2	**4a**	24	80	90:10	24
3	**4b**	48	NR	–	–
4	**4c**	48	48	95:5	86
5	**4d**	48	NR	–	–
6	**4e**	48	NR	–	–

[a] Reagents and conditions: **5a** (0.5 mmol, 1.0 equiv), **6** (1.5 mmol, 3.0 equiv), catalyst (10 mol%), neat, r.t.
[b] Isolated yield.
[c] NR = no reaction.
[d] The dr was determined by ^{1}H NMR spectroscopy of the crude mixture.
[e] The ee was determined by chiral HPLC analysis (Chiralpak AD-H, hexane–*i*-PrOH, 90:10).

in 80% yield and 90:10 diastereoselectivity with L-proline (**4a**) as catalyst (entry 2), the enantiomeric excess is very poor (24%). When 1,2′-methylenedipyrrolidine (**4c**) was used as the catalyst (entry 4), the adducts were obtained in relatively high diastereo- and enantioselectivity (95:5 dr and 86% ee), but the yield was poor even when the reaction time was extended from 24 to 48 hours. The best result was obtained with catalyst **4**, giving the product in up to 97% yield and excellent diastereo- and enantioselectivity (98:2 dr and 95% ee) after the reaction was run for 24 hours.

Encouraged by the results shown in Table 1, we tested the effect of the amount of cyclohexanone in this reaction. We found that nearly the same results were obtained when five equivalents and three equivalents of cyclohexanone were used (Table 2, entries 1 and 2). However, the reaction rate, yield, and enantiomeric excess were decreased when the amount of cyclohexanone was reduced to two equivalents and 1.2 equivalents (Table 2, entries 3 and 4). Hence, we chose three equivalents of cyclohexanone for future reactions. The reaction also did not proceed when triethylamine and trifluoroacetic acid were used as additives (Table 2, entries 5 and 6). The effect of a few solvents and different conditions on the conjugate addition reaction in the presence of **4** as the catalyst was then examined. Good results were achieved in dimethyl sulfoxide and chloroform, giving yields above 80% and enantiomeric excesses above 94% (Table 2, entries 7 and 8). When the reaction was carried out in tetrahydrofuran, the reaction was slow and the conjugate addition product **7a** was obtained in low yield after 48 hours at room temperature (entry 9). There was no reaction when the solvent was changed to a tetrahydrofuran–water mixture (1:1) (entry 10). Thus, the optimized conditions of the addition reaction consisted of the use of three equivalents of cyclohexanone and 10 mol% of **4** as catalyst under neat conditions at room temperature.

Table 2 The Michael Addition Reaction of Cyclohexanone with Nitroolefin **5a** Catalyzed by **4** under Different Conditions[a]



Entry	**6** (equiv)	Solvent	Additive	Time (h)	Yield[b,c] (%)	ee[d] (%)
1	5	–	–	24	97	95
2	3	–	–	24	97	97
3	2	–	–	36	76	90
4	1.2	–	–	48	48	91
5	3	–	Et_3N	48	NR	–
6	3	–	TFA	48	NR	–
7	3	DMSO	–	48	90	95
8	3	$CHCl_3$	–	48	81	94
9	3	THF	–	48	46	90
10	3	THF–H_2O (1:1)	–	48	NR	–

[a] Reagents and conditions: **5a** (0.5 mmol, 1.0 equiv), **6**, catalyst **4** (10 mol%), r.t.
[b] Isolated yield.
[c] NR = no reaction.
[d] The ee was determined by chiral HPLC analysis (Chiralpak AD-H, hexane–*i*-PrOH, 90:10).

With **4** as the selected catalyst, the scope of the Michael reaction was briefly explored under the optimized reaction conditions (Table 3). In general, the reaction worked quite well with cyclohexanone to give the desired Michael adducts in high yields and excellent diastereoselectivities and enantioselectivities. Both electron-rich and electron-deficient β-nitrostyrenes were excellent Michael acceptors for cyclohexanone. Just 10 mol% of the catalyst was

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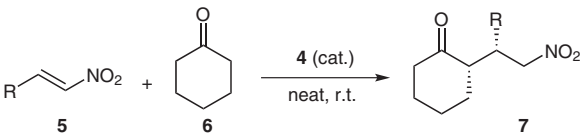
Table 3 Michael Addition of Cyclohexanone with Various Nitroolefins Catalyzed by **4** under Neat Conditions at Room Temperature[a]



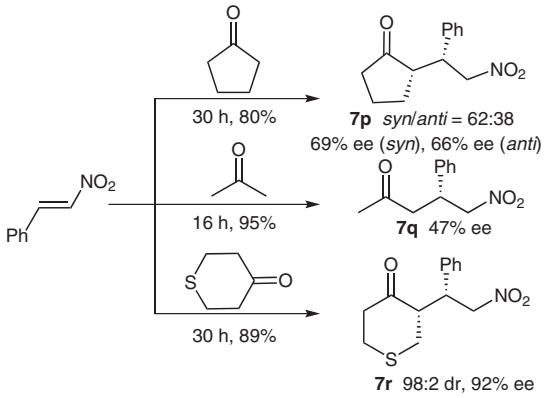
5 **6** **7**

Entry	R	7	Yield[b] (%)	*syn*/*anti*[c]	ee[d] (%)
1	Ph	**7a**	97	98:2	97
2	Tol	**7b**	99	95:5	94
3	PMP	**7c**	99	>99:1	94
4	4-ClC_6H_4	**7d**	97	96:4	94
5	CH=CHPh	**7e**	98	98:2	91
6	2-MeC_6H_4	**7f**	93	98:2	95
7	2-ClC_6H_4	**7g**	99	98:2	99
8	1,3-benzodioxol-5-yl	**7h**	93	98:2	95
9	3-MeC_6H_4	**7i**	97	99:1	93
10	2-furyl	**7j**	98	98:2	94
11	3-furyl	**7k**	99	99:1	96
12	3-$MeOC_6H_4$	**7l**	95	97:3	94
13	2-$MeOC_6H_4$	**7m**	96	98:2	94
14	2-thienyl	**7n**	93	95:5	93
15	2-naphthyl	**7o**	96	98:2	92

[a] Reagents and conditions: **5** (0.5 mmol, 1.0 equiv), **6** (1.5 mmol, 3.0 equiv), catalyst **4** (10 mol%), neat, r.t.
[b] Isolated yields.
[c] The *syn*/*anti* ratio was determined by ^{1}H NMR spectroscopy of the crude mixture or by HPLC analysis.
[d] The ee was determined by chiral HPLC analysis.

sufficient to promote the reactions, giving the desired Michael adducts in nearly quantitative yields in reasonable time.

The reactions of other Michael donors such as cyclopentanone, acetone, and tetrahydrothiopyran-4-one were also carried out in the presence of catalyst **4** (Scheme 2). Similar to the results reported by other research groups, the desired Michael addition product was obtained in high yields but relatively lower enantioselectivities. The absolute configurations of the Michael addition products were determined by ^{1}H NMR spectroscopy and comparison with the known products. Therefore, the transition state of this reaction shown in Figure 1 should be applicable to all the cases.



Scheme 2 The Michael addition of different Michael donors to β-nitrostyrene catalyzed by **4** under neat conditions at room temperature

Commercial-grade solvents and reagents were used without further purification, with the following exception: CH_2Cl_2 was distilled from CaH_2. Flash chromatography was performed over Merck silica gel 60, with freshly distilled solvents as eluents. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance DPX 300 and Bruker AMX 400 spectrophotometers ($CDCl_3$ as solvent). Chemical shifts were recorded relative to TMS (^{1}H NMR: δ = 0.0; ^{13}C NMR: δ = 0.0) and $CDCl_3$ (^{1}H NMR: δ = 7.2600, s; ^{13}C NMR: δ = 77.03, t). The proportions of diastereomers and geometric isomers were determined from the integration data of the ^{1}H NMR spectra. Enantioselectivities were determined by HPLC analysis (Daicel Chiracel AD-H or AS-H column, 25 °C) in comparison with racemic products. Optical rotations of samples in $CHCl_3$ were measured on a Schmidt & Haensdch polarimeter (Polartronic MH8) with a 10-cm cell. The absolute configurations of the products were determined by comparison with compounds previously published. Nitroolefins were prepared according to literature procedures.[1,2]

Nitro Ketones 7 by Michael Reactions of Nitroolefins with Ketones under Solvent-Free Conditions; General Procedure

Catalyst **4** (10.5 mg, 0.05 mmol) was added to a mixture of the nitroolefin (0.5 mmol) and the ketone or cyclohexanone (148 mg, 1.5 mmol). The reaction mixture was stirred for the indicated time under neat conditions at r.t. After completion of the reaction (monitored by TLC), H_2O (10 mL) was added, the mixture was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were dried (Na_2SO_4). The diastereoselectivity was determined by ^{1}H NMR analysis of the crude Michael product after short column chromatographic purification, and the ee was determined by chiral HPLC analysis. Relative and absolute configurations of the products were determined by comparison with the known ^{1}H NMR spectroscopy data, chiral HPLC analysis, and optical rotation values.

(*S*)-2-[(*R*)-2-Nitro-1-phenylethyl]cyclohexanone (7a)[1f]

Reaction time: 24 h; yield: 97%; ee determined by HPLC analysis [Chiralcel AD-H, *i*-PrOH–hexane, 10:90, 1.0 mL/min, 300 nm; t_R (minor) = 9.85 min, t_R (major) = 12.39 min]: 97% ee; $[\alpha]_D^{20}$ –18.0 (*c* 1.0, $CHCl_3$); *syn*/*anti* = 98:2.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.26 (m, 3 H), 7.16 (d, *J* = 7.2 Hz, 2 H), 4.94 (dd, *J* = 4.4, 12.4 Hz, 1 H), 4.63 (dd, *J* = 9.6, 12.4 Hz, 1 H), 3.76 (dt, *J* = 4.4, 10.0 Hz, 1 H), 2.68 (ddd, *J* = 4.8, 8.1, 11.7 Hz, 1 H), 2.49–2.38 (m, 2 H), 2.10–2.06 (m, 1 H), 1.79–1.55 (m, 4 H), 1.32–1.21 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.0, 137.8, 129.0, 128.2, 127.8, 78.9, 52.5, 44.0, 42.8, 33.2, 28.6, 25.1.

(*S*)-2-[(*R*)-2-Nitro-1-(4-tolyl)ethyl]cyclohexanone (7b)[1k]

Reaction time: 16 h; yield: 99%; ee determined by HPLC analysis [Chiralcel AS-H, *i*-PrOH–hexane, 15:85, 1.0 mL/min, 220 nm; t_R (minor) = 8.20 min, t_R (major) = 12.59 min]: 94% ee; $[\alpha]_D^{20}$ –15.3 (*c* 1.0, $CHCl_3$); *syn*/*anti* = 95:5.

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^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.12 (d, *J* = 8.1 Hz, 2 H), 7.04 (d, *J* = 8.1 Hz, 2 H), 4.92 (dd, *J* = 4.5, 12.3 Hz, 1 H), 4.61 (dd, *J* = 9.6, 12.4 Hz, 1 H), 3.72 (dt, *J* = 4.5, 9.9 Hz, 1 H), 2.66 (ddd, *J* = 4.4, 8.0, 12.3 Hz, 1 H), 2.50–2.36 (m, 2 H), 2.31 (s, 3 H), 2.10–2.04 (m, 1 H), 1.77–1.56 (m, 4 H), 1.28–1.21 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 212.0, 137.5, 134.6, 129.6, 128.0, 79.0, 52.6, 43.6, 42.7, 33.2, 28.5, 25.0, 21.1.

(*S*)-2-[(*R*)-1-(4-Methoxyphenyl)-2-nitroethyl]cyclohexanone (7c)[1k]

Reaction time: 22 h; yield: 99%; ee determined by HPLC analysis [Chiralcel AS-H, *i*-PrOH–hexane, 15:85, 1.0 mL/min, 220 nm; t_R (minor) = 18.61 min, t_R (major) = 23.79 min]: 94% ee; $[\alpha]_D^{20}$ –12.9 (*c* 1.0, $CHCl_3$); *syn*/*anti* = 95:5.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10 (d, *J* = 8.4 Hz, 2 H), 6.84 (d, *J* = 8.4 Hz, 2 H), 4.92 (dd, *J* = 6.4, 16.4 Hz, 1 H), 4.60 (dd, *J* = 13.2, 16.4 Hz, 1 H), 3.80 (s, 3 H), 3.73 (dt, *J* = 6.0, 13.2 Hz, 1 H), 2.66 (ddd, *J* = 5.2, 8.4, 14.6 Hz, 1 H), 2.51–2.35 (m, 2 H), 2.10–2.06 (m, 1 H), 1.78–1.56 (m, 4 H), 1.23–1.19 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 212.1, 159.0, 129.5, 129.2, 114.3, 79.1, 55.2, 52.7, 43.2, 42.7, 33.1, 28.5, 25.0.

(*S*)-2-[(*R*)-1-(4-Chlorophenyl)-2-nitroethyl]cyclohexanone (7d)[1f]

Reaction time: 30 h; yield: 99%; ee determined by HPLC analysis [Chiralcel AS-H, *i*-PrOH–hexane, 15:85, 1.0 mL/min, 230 nm; t_R (minor) = 10.93 min, t_R (major) = 16.88 min]: 91% ee; $[\alpha]_D^{20}$ –17.6 (*c* 1.0, $CHCl_3$); *syn*/*anti* = 94:6.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 11.2 Hz, 2 H), 7.12 (d, *J* = 11.2 Hz, 2 H), 4.93 (dd, *J* = 6.0, 16.4 Hz, 1 H), 4.60 (dd, *J* = 13.2, 16.8 Hz, 1 H), 3.80 (s, 3 H), 3.76 (dt, *J* = 6.4, 13.0 Hz, 1 H), 2.66 (ddd, *J* = 2.4, 6.0, 16.0 Hz, 1 H), 2.54–2.32 (m, 2 H), 2.12–2.05 (m, 1 H), 1.83–1.54 (m, 4 H), 1.30–1.20 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.5, 136.3, 133.7, 129.6, 129.2, 78.6, 52.4, 43.4, 42.8, 33.2, 28.4, 25.1.

(*S*)-2-[(*R*,*E*)-1-(Nitromethyl)-3-phenylprop-2-enyl]cyclohexanone (7e)[1g]

Reaction time: 24 h; yield: 99%; ee determined by HPLC analysis [Chiralcel AS-H, *i*-PrOH–hexane, 15:85, 1.0 mL/min, 220 nm; t_R (minor) = 9.99 min, t_R (major) = 15.48 min]: 91% ee; $[\alpha]_D^{20}$ –30.1 (*c* 1.0, $CHCl_3$); *syn*/*anti* = 98:2.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.23 (m, 5 H), 6.49 (d, *J* = 16.5 Hz, 1 H), 6.02 (dd, *J* = 9.6, 15.6 Hz, 1 H), 4.67 (dd, *J* = 5.1, 11.7 Hz, 1 H), 4.57 (dd, *J* = 8.4, 12.0 Hz, 1 H), 3.40–3.30 (m, 1 H), 2.59–2.35 (m, 3 H), 2.19–2.04 (m, 2 H), 1.93–1.89 (m, 1 H), 1.71–1.59 (m, 2 H), 1.48–1.26 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 211.3, 136.3, 134.4, 128.6, 127.9, 126.4, 125.7, 78.1, 51.7, 42.6, 41.9, 32.6, 28.1, 25.1.

(*S*)-2-[(*R*)-2-Nitro-1-(2-tolyl)ethyl]cyclohexanone (7f)[1f]

Reaction time: 33 h; yield: 99%; ee determined by HPLC analysis [Chiralcel AS-H, *i*-PrOH–hexane, 15:85, 1.0 mL/min, 220 nm; t_R (minor) = 8.41 min, t_R (major) = 11.72 min]: 95% ee; $[\alpha]_D^{20}$ –26.9 (*c* 1, $CHCl_3$); *syn*/*anti* = 97:3.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–6.96 (m, 4 H), 4.99 (dd, *J* = 6.0, 12.4 Hz, 1 H), 4.58 (dd, *J* = 12.4, 13.6 Hz, 1 H), 3.93 (dt, *J* = 4.0, 10.4 Hz, 1 H), 2.65 (ddd, *J* = 2.8, 8.4, 12.4 Hz, 1 H), 2.47–2.33 (m, 5 H), 2.17–2.03 (m, 1 H), 1.75–1.48 (m, 4 H), 1.27–1.17 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.3, 137.4, 136.5, 131.0, 127.3, 126.7, 125.7, 78.8, 53.4, 42.9, 38.3, 32.9, 28.8, 25.3, 19.9.

(*S*)-2-[(*R*)-(2-Chlorophenyl)-2-nitroethyl]cyclohexanone (7g)[1f]

Reaction time: 36 h; yield: 99%; ee determined by HPLC analysis [Chiralcel AS-H, *i*-PrOH–hexane, 15:85, 1.0 mL/min, 220 nm; t_R (minor) = 8.62 min, t_R (major) = 12.37 min]: 99% ee; $[\alpha]_D^{20}$ –47.4 (*c* 1.0, $CHCl_3$); *syn*/*anti* = 95:5.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.16 (m, 4 H), 4.92–4.82 (m, 2 H), 4.29 (dt, *J* = 4.8, 13.3 Hz, 1 H), 2.65 (ddd, *J* = 3.2, 8.4, 13.6 Hz, 1 H), 2.46–2.32 (m, 2 H), 2.10–2.05 (m, 1 H), 1.80–1.55 (m, 4 H), 1.36–1.27 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.7, 135.5, 134.6, 130.3, 129.4, 128.9, 127.4, 78.8, 51.5, 42.7, 38.3, 32.8, 28.3, 25.1.

(*S*)-2-[(*S*)-1-(1,3-Benzodioxol-5-yl)-2-nitroethyl]cyclohexanone (7h)[1f]

Reaction time: 24 h; yield: 93%; ee determined by HPLC analysis [Chiralcel AS-H, *i*-PrOH–hexane, 15:85, 1.0 mL/min, 220 nm; t_R (minor) = 31.11 min, t_R (major) = 37.68 min]: 95% ee; $[\alpha]_D^{20}$ –20.6 (*c* 1.0, $CHCl_3$); *syn*/*anti* = 98:2.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.76 (d, *J* = 8.0 Hz, 1 H), 6.67–6.63 (m, 2 H), 5.97 (s, 1 H), 4.92 (dd, *J* = 4.4, 12.4 Hz, 1 H), 4.55 (dd, *J* = 6.0, 9.6 Hz, 1 H), 3.69 (dt, *J* = 3.2, 8.4 Hz, 1 H), 2.64 (ddd, *J* = 2.8, 8.4, 13.2 Hz, 1 H), 2.48–2.39 (m, 2 H), 2.12–2.08 (m, 1 H), 1.84–1.58 (m, 4 H), 1.28–1.25 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.9, 148.1, 147.1.4, 131.3, 121.7, 108.6, 108.1, 101.2, 79.1, 52.7, 43.8, 42.8, 29.4, 28.6, 22.7.

(*S*)-2-[(*R*)-2-Nitro-1-(3-tolyl)ethyl]cyclohexanone (7i)[1f]

Reaction time: 25 h; yield: 99%; ee determined by HPLC analysis [Chiralcel AS-H, *i*-PrOH–hexane, 15:85, 1.0 mL/min, 220 nm; t_R (minor) = 9.27 min, t_R (major) = 12.10 min]: 93% ee; $[\alpha]_D^{20}$ –30.5 (*c* 1.0, $CHCl_3$); *syn*/*anti* = 99:1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–6.97 (m, 4 H), 4.94 (dd, *J* = 4.4, 12.4 Hz, 1 H), 4.64 (dd, *J* = 9.6, 12.4 Hz, 1 H), 3.73 (dt, *J* = 4.4, 9.8 Hz, 1 H), 2.69 (ddd, *J* = 4.0, 8.4, 13.2 Hz, 1 H), 2.53–2.35 (m, 5 H), 2.12–2.08 (m, 1 H), 1.83–1.55 (m, 4 H), 1.35–1.22 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.0, 144.6, 143.2, 129.0, 128.8, 128.6, 125.0, 78.9, 52.6, 43.9, 42.8, 33.3, 28.6, 25.0, 21.5.

(*S*)-2-[(*S*)-1-(2-Furyl)-2-nitroethyl]cyclohexanone (7j)[1d]

Reaction time: 16 h; yield: 99%; ee determined by HPLC analysis [Chiralcel AS-H, *i*-PrOH–hexane, 15:85, 1.0 mL/min, 230 nm; t_R (minor) = 12.05 min, t_R (major) = 13.10 min]: 94% ee; $[\alpha]_D^{20}$ –8.1 (*c* 1.0, $CHCl_3$); *syn*/*anti* = 95:5.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.30 (m, 1 H), 6.28 (dd, *J* = 2.0, 3.2 Hz, 1 H), 6.17 (d, *J* = 3.2 Hz, 1 H), 4. 78 (dd, *J* = 4.8, 12.4 Hz, 1 H), 4.66 (dd, *J* = 9.2, 12.4 Hz, 1 H), 3.96 (dt, *J* = 4.4, 9.0 Hz, 1 H), 2.74 (ddd, *J* = 2.8, 8.0, 13.2 Hz, 1 H), 2.47–2.31 (m, 2 H), 2.12–2.06 (m, 1 H), 1.85–1.58 (m, 4 H), 1.33–1.24 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.9, 150.9, 142.3, 110.3, 109.0, 77.9, 51.1, 42.6, 37.6, 32.5, 28.2, 25.1.

(*S*)-2-[(*S*)-1-(3-Furyl)-2-nitroethyl]cyclohexanone (7k)[1d]

Reaction time: 16 h; yield: 99%; ee determined by HPLC analysis [Chiralcel AS-H, *i*-PrOH–hexane, 15:85, 1.0 mL/min, 220 nm; t_R (minor) = 15.32 min, t_R (major) = 16.66 min]: 96% ee; $[\alpha]_D^{20}$ –15.6 (*c* 1.0, $CHCl_3$); *syn*/*anti* = 99:1.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 2.1 Hz, 1 H), 7.29 (d, *J* = 2.1 Hz, 1 H), 6.26 (s, 1 H), 4.76 (dd, *J* = 5.1, 16.4 Hz, 1 H), 4.58 (dd, *J* = 9.0, 12.0 Hz, 1 H), 3.80 (dt, *J* = 5.1, 10.2 Hz, 1 H), 2.60 (ddd, *J* = 4.8, 8.1, 13.2 Hz, 1 H), 2.44–2.35 (m, 2 H), 2.11–1.94 (m, 3 H), 1.88–1.60 (m, 2 H), 1.34–1.26 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 211.3, 143.6, 140.8, 121.4, 109.1, 78.3, 51.9, 42.6, 34.6, 32.4, 28.1, 25.0.

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(*S*)-2-[(*S*)-1-(3-Methoxyphenyl)-2-nitroethyl]cyclohexanone (7l)[1d]

Reaction time: 20 h; yield: 95%; ee determined by HPLC analysis [Chiralcel AS-H, *i*-PrOH–hexane, 15:85, 1.0 mL/min, 220 nm; t_R (minor) = 10.53 min, t_R (major) = 11.92 min]: 94% ee; $[\alpha]_D^{20}$ –27.9 (*c* 1.0, $CHCl_3$); *syn*/*anti* = 97:3.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.83–6.73 (m, 3 H), 4.95 (dd, *J* = 3.2, 8.0 Hz, 1 H), 4.63 (dd, *J* = 3.6, 8.8 Hz, 1 H), 3.81–3.74 (m, 4 H), 2.68 (ddd, *J* = 2.4, 7.8, 12.2 Hz, 1 H), 2.50–2.39 (m, 2 H), 2.11–2.08 (m, 1 H), 1.78–1.57 (m, 4 H), 1.28–1.24 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.0, 159.9, 139.4, 130.0, 120.3, 114.5, 112.6, 78.8, 55.2, 52.5, 43.9, 42.8, 33.2, 28.6, 25.1.

(*S*)-2-[(*S*)-1-(2-Methoxyphenyl)-2-nitroethyl]cyclohexanone (7m)[1f]

Reaction time: 20 h; yield: 96%; ee determined by HPLC analysis [Chiralcel AS-H, *i*-PrOH–hexane, 15:85, 1.0 mL/min, 220 nm; t_R (minor) = 10.53 min, t_R (major) = 11.92 min]: 94% ee; $[\alpha]_D^{20}$ –36.9 (*c* 1.0, $CHCl_3$); *syn*/*anti* = 98:2.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.22 (m, 1 H), 7.08 (d, *J* = 7.2 Hz, 1 H), 6.86–6.90 (m, 2 H), 4.84–4.81 (m, 2 H), 3.96, (dt, *J* = 2.8, 8.4 Hz, 1 H), 3.84 (s, 3 H), 2.67 (ddd, *J* = 2.8, 8.0, 12.0 Hz, 1 H), 2.48–2.37 (m, 2 H), 2.08–2.05 (m, 1 H), 1.78–1.55 (m, 4 H), 1.25–1.18 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.6, 157.6, 131.0, 129.0, 125.4, 120.9, 111.0, 77.6, 55.4, 50.2, 42.8, 41.3, 33.3, 28.6, 25.2.

(*S*)-2-[(*R*)-2-Nitro-1-(2-thienyl)ethyl]cyclohexanone (7n)[1f]

Reaction time: 24 h; yield: 93%; ee determined by HPLC analysis [Chiralcel AS-H, *i*-PrOH–hexane, 15:85, 1.0 mL/min, 220 nm; t_R (minor) = 13.74 min, t_R (major) = 17.88 min]: 93% ee; $[\alpha]_D^{20}$ –26.1 (*c* 1.0, $CHCl_3$); *syn*/*anti* = 95:5.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 4.8 Hz, 1 H), 6.96–6.89 (m, 2 H), 4.91 (dd, *J* = 4.8, 12.0 Hz, 1 H), 4.66 (dd, *J* = 7.2, 13.2 Hz, 1 H), 4.15 (dt, *J* = 4.4, 11.2 Hz, 1 H), 2.69 (ddd, *J* = 3.2, 8.0, 13.2 Hz, 1 H), 2.49–2.38 (m, 2 H), 2.13–2.09 (m, 1 H), 1.94–1.84 (m, 2 H), 1.71–1.62 (m, 2 H), 1.38–1.27 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 211.3, 140.5, 127.0, 126.7, 125.0, 79.2, 53.4, 42.6, 39.4, 32.8, 28.3, 25.1.

(*S*)-2-[(*S*)-1-(2-Naphthyl)-2-nitroethyl]cyclohexanone (7o)[1f]

Reaction time: 24 h; yield: 96%; ee determined by HPLC analysis [Chiralcel AS-H, *i*-PrOH–hexane, 15:85, 1.0 mL/min, 220 nm; t_R (minor) = 13.72 min, t_R (major) = 19.22 min]: 92% ee; $[\alpha]_D^{20}$ –79.5 (*c* 1.0, $CHCl_3$); *syn*/*anti* = 98:2.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (s, 1 H), 8.04–8.02 (m, 2 H), 7.62–7.31 (m, 4 H), 5.26 (dd, *J* = 4.8, 12.0 Hz, 1 H), 5.00 (dd, *J* = 5.6, 10.0 Hz, 1 H), 4.98 (s, 1 H), 2.88 (s, 1 H), 2.46–2.33 (m, 2 H), 2.12–2.05 (m, 1 H), 1.86–1.41 (m, 4 H), 1.31–1.22 (m, 1 H).

2-[(*S*)-2-Nitro-1-phenylethyl]cyclopentanone (7p)[1f]

Reaction time: 30 h; yield: 80%; ee determined by HPLC analysis [Chiralcel AD-H, *i*-PrOH–hexane, 10:90, 1.0 mL/min, 220 nm; t_R (major, *anti*) = 8.37 min, t_R (minor, *anti*) = 9.35 min; t_R (minor, *syn*) = 10.00 min, t_R (major, *syn*) = 12.86 min]: 66% ee (*anti*), 69% ee (*syn*); $[\alpha]_D^{20}$ –19.4 (*c* 1.0, $CHCl_3$); *syn*/*anti* = 1:0.6.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.26 (m, 5.2 H), 7.20–7.16 (m, 3.1 H), 5.33 (dd, *J* = 5.6, 12.8 Hz, 1 H), 5.02 (d, *J* = 8.0 Hz, 1.2 H), 4.72 (dd, *J* = 2.4, 12.0 Hz, 1 H), 3.83 (dt, *J* = 4.4, 10.0 Hz, 0.6 H), 3.70 (dt, *J* = 4.4, 10.0 Hz, 1 H), 2.41–2.08 (m, 4.2 H), 1.95–1.66 (m, 4.8 H), 1.56–1.48 (m, 1.6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 218.5, 218.4, 137.7, 137.6, 129.0, 128.9, 128.5, 128.4, 128.0, 127.9, 78.3, 78.2, 51.4, 50.5, 44.2, 44.1, 39.3, 38.7, 28.3, 27.0, 20.6, 20.3.

(*S*)-5-Nitro-4-phenylpentan-2-one (7q)[1f]

Reaction time: 16 h; yield: 95%; ee determined by HPLC analysis [Chiralcel AD-H, *i*-PrOH–hexane, 5:95, 1.0 mL/min, 254 nm; t_R (minor) = 21.22 min, t_R (major) = 29.00 min]: 45% ee; $[\alpha]_D^{20}$ 2.6 (*c* 1.1, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.22 (m, 5 H), 4.75–4.59 (m, 2 H), 4.07–3.98 (m, 1 H), 2.94 (d, *J* = 11.2 Hz, 2 H), 2.14 (s, 3 H).

(*S*)-3-[(*S*)-2-Nitro-1-phenylethyl]tetrahydrothiopyran-4-one (7r)[1f]

Reaction time: 30 h; yield: 89%; ee determined by HPLC analysis [Chiralcel AS-H, *i*-PrOH–hexane, 15:85, 1.0 mL/min, 220 nm; t_R (minor) = 17.61 min, t_R (major) = 22.44 min]: 92% ee; $[\alpha]_D^{20}$ –49.1 (*c* 1.0, $CHCl_3$); *syn*/*anti* = 98:2.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.19 (m, 5 H), 4.74 (dd, *J* = 4.8, 13.2 Hz, 1 H), 4.63 (dd, *J* = 2.1, 11.6 Hz, 1 H), 3.98 (dt, *J* = 4.8, 10.4 Hz, 1 H), 3.09–2.77 (m, 4 H), 2.65–2.60 (m, 1 H), 2.49–2.43 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.6, 136.58, 129.4, 128.3, 128.2, 78.6, 55.0, 44.6, 43.5, 35.2, 31.6.

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