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Tropos Biphenol Derived Chiral Thiophosphoramide Catalysed Highly Diastereo- and Enantioselective Michael Addition of Cyclic Ketones to Nitro Olefins

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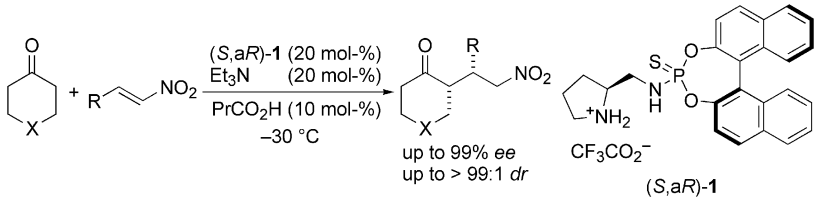
Chirality transfer from (*S*)-2-(aminomethyl)pyrrolidine to the tropos biphenyl skeleton has been observed in the preparation of a chirally flexible biphenol-derived novel chiral thiophosphoramide to afford exclusively the thermodynamically favoured diastereomer. This novel secondary amine–thiophosphoramide has proven to be an effective bifunctional organocatalyst for the asymmetric Michael addition of cyclohexanone to both aryl- and alkyl-substituted nitro olefins. The corresponding adducts were obtained with excellent diastereo- (up to >99:1 *dr*) and enantioselectivities (up to >99 % *ee*).

Introduction

Chirally flexible (tropos) ligands with a low rotation barrier that are highly modular, versatile, and easy to synthesize without resolution have been a focus of interest in recent transition-metal-catalysed reactions.[1] For example, although the tropos Biphep ligand [2,2′-bis(diphenylphosphanyl)-1,1′-biphenyl] is not resolvable at room temperature due to fast racemization, the chirality of the racemic Biphep–metal complex can be controlled by induction of the chiral diamine[2] or chiral diene[3] leading to the single Biphep–metal enantiomer, and this resulting enantiopure metal complex can behave as an efficient catalyst in asymmetric reactions. However, to the best of our knowledge, this strategy has never been documented in organocatalysis. We have recently developed (*S*,a*R*)-pyrrolidine–thiophosphoramide (*S*,a*R*)-**1** as an efficient organocatalyst for promoting the asymmetric Michael addition of cyclic ketones to nitro olefins (Scheme 1).[4] It is believed that thiophosphoramide (*S*,a*R*)-**1** functions as a bifunctional organocatalyst; the "privileged" pyrrolidine backbone may serve as the catalytic site and the thiophosphoramide moiety as hydrogen-bonding donor for the activation of nitro olefin substrates and the formation of a well-controlled transition state. Although excellent results have been achieved for catalyst (*S*,a*R*)-**1**, the need for a combination of (*R*)-binaphthol and (*S*)-2-(aminomethyl)pyrrolidine to afford satisfactory results makes this catalyst less competitive, and the development of a more economic chiral thiophosphoramide organocatalyst remains an important challenge. We envisioned that, like transition-metal catalysis, the chirality of the axially flexible biphenyl moiety may be controlled by chirality transfer from (*S*)-2-(aminomethyl)pyrrolidine to the tropos biphenyl group to form a thermodynamically favourable diastereomer that can also be employed as a chiral organocatalyst to promote the asymmetric Michael addition of ketones to nitro oelefins. Herein we describe a new chiral catalyst bearing a tropos biphenyl skeleton for the asymmetric conjugate addition of ketones to nitroalkenes.



Scheme 1. Thiophosphoramide (*S*,a*R*)-**1** catalysed asymmetric Michael addition of cyclic ketones to nitro olefins.

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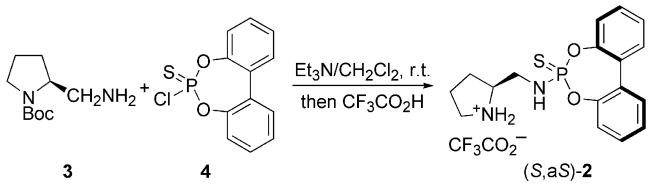
Results and Discussion

As shown in Scheme 2, the trifluoroacetic acid salts of newly designed pyrrolidine–thiophosphoramide **2** were readily prepared by the coupling of *tert*-butyl (*S*)-2-(aminomethyl)pyrrolidine-1-carboxylate (**3**)[5] and *O*,*O*-(2,2′-biphenylyl) phosphorochloridothioate (**4**)[6] and successive removal of the protecting group with trifluoroacetic acid.



Scheme 2. Synthesis of chiral thiophosphoramide (*S*,a*S*)-**2**.

As we anticipated, when the chirally rigid binaphthalene skeleton was replaced by a flexible biphenyl moiety, chirality transfer from (*S*)-2-(aminomethyl)pyrrolidine to tropos biphenol was observed to afford exclusively a thermodynamically favoured diastereomer **2**, which corresponds to the single peak at δ = 83.38 ppm in the ^{31}P NMR spectrum. The relative configuration of the thermodynamically favourable diastereomer was determined to be (*S*,a*S*) by X-ray analysis of a single crystal obtained from a solution of **2** in MeOH/*i*PrOH (2:1, v/v; Figure 1).[7]

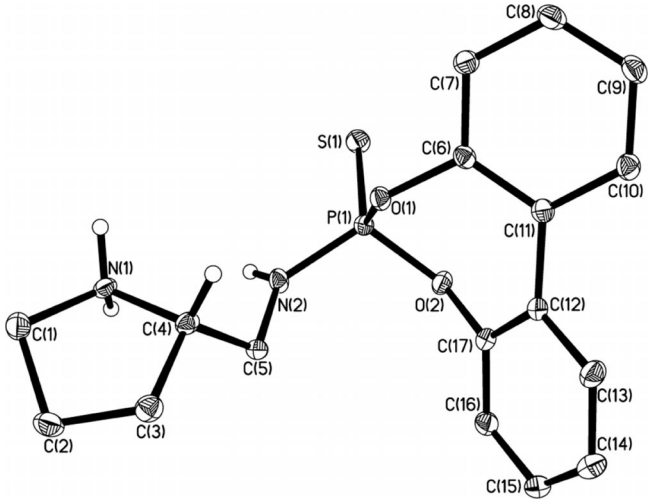
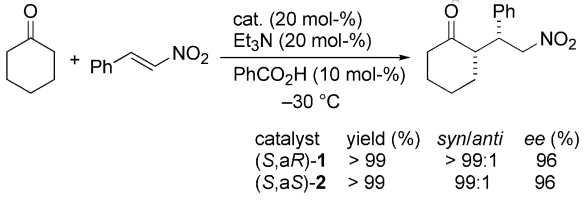


Figure 1. X-ray structure of the thermodynamically favoured diastereomer **2**. Most of the hydrogen atoms and the trifluoroacetate anion have been omitted for clarity.

With the thermodynamically favoured diastereomer (*S*,a*S*)-**2** in hand, the catalytic performance of (*S*,a*S*)-**2** was initially evaluated in the Michael addition of cyclohexanone to (*E*)-β-nitrostyrene as the model reaction under the optimal reaction conditions for the thiophosphoramide catalyst (*S*,a*R*)-**1** (benzoic acid as the acidic co-catalyst, –30 °C in neat cyclohexanone). Almost the same level of stereoselectivity was observed for the newly developed catalyst (*S*,a*S*)-**2** as with (*S*,a*R*)-**1**. The corresponding Michael adduct was obtained in excellent yield (>99%) with high diastereo- (*syn*/*anti* 99:1) and enantioselectivity (96% *ee*; Scheme 3).



catalyst	yield (%)	*syn*/*anti*	*ee* (%)
(*S*,a*R*)-**1**	> 99	> 99:1	96
(*S*,a*S*)-**2**	> 99	99:1	96

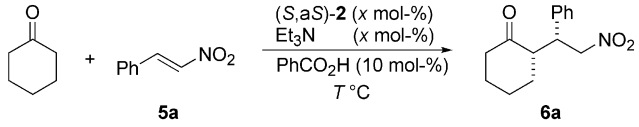
Scheme 3. Preliminary comparison of the catalytic activities of (*S*,a*R*)-**1** and (*S*,a*S*)-**2**.

Encouraged by this result, other parameters influencing the reaction, such as reaction temperature and catalyst loading, were also examined by employing benzoic acid as the acidic additive, but the results obtained were not better (Table 1). Similarly to the (*S*,a*R*)-**1**-catalysed Michael addition to β-nitrostyrene, the reaction temperature was found to have a noticeable effect on the reaction. The enantioselectivity gradually increased by decreasing the reaction temperature from 25 to –30 °C (Table 1, Entries 1 and 3–5, 90–96% *ee*). The reaction became quite sluggish on further lowering of the temperature to –40 °C, and the product was obtained in a rather low yield with a slight loss of stereocontrol even after a prolonged reaction time (Table 1, Entry 6). In addition, reduction of the amount of (*S*,a*S*)-**2** from 20 to 10 mol-% led to a clear decrease in both the turnover frequency and the stereoselectivity (Table 1, Entry 1 vs. Entry 2).

By using the optimized reaction conditions, we next probed the scope of the reaction with a variety of nitro olefins. The results are summarized in Table 2.

As shown in Table 2, the reaction has a broad applicability with respect to the nitro olefins. Excellent yields (up to >99%) and stereoselectivities (up to >99:1 *dr*, >99% *ee*) were achieved with various styrene-type nitro olefins bearing either electron-donating or -withdrawing substituents regardless of the nature and the position of the substituted group on the benzene ring (Table 2, Entries 2–10). 1-Naphthyl- and 2-furyl-substituted aromatic nitroalkenes also worked well giving satisfactory stereoselectivities (Table 2, Entries 11 and 12). Notably, the aliphatic aldehyde derived nitro olefin **5n** also appeared to be a good candidate at an elevated temperature, affording the desired product with the same high levels of enantioselectivity as those found in the aryl-substituted ones, albeit with a moderate diastereoselectivity (Table 2, Entry 14, *syn*/*anti* = 79:21, 93% *ee* for the *syn* isomer). Moreover, although a little loss of stereocontrol was observed, alkenyl-substituted nitro olefin **5m** can also be employed successfully (Table 2, Entry 13). Compared with the results obtained for the previously reported (*R*)-binaphthol-derived chiral thiophosphoramide catalyst (*S*,a*R*)-**1**, it is worth noting that comparable or even better stereoselective results were obtained in some cases (Table 2, Entries 3, 4, 6, 12 and 14) for the newly developed chiral catalyst (*S*,a*S*)-**2** bearing a tropos biphenyl skeleton. Because chirally flexible (tropos) biphenols are easy to synthesize without resolution, catalyst (*S*,a*S*)-**2** has a great advantage over the catalyst (*S*,a*R*)-**1** derived from optically active

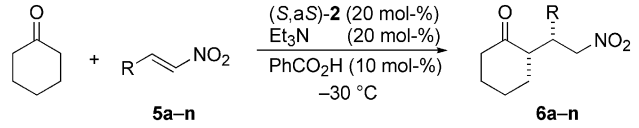
Table 1. Optimization of the reaction conditions for the Michael addition with (*S*,a*S*)-**2** as catalyst.[a]



Entry	**2** [mol-%]	Temp. [°C]	Time [h]	Yield [%][b]	*dr* [*syn*/*anti*][c]	*ee* [%][d]
1	20	25	1	>99	99:1	90
2	10	25	2	96	98:2	87
3	20	0	4	99	>99:1	92
4	20	–15	7	95	>99:1	94
5	20	–30	22	96	>99:1	96
6	20	–40	63	52	>99:1	94

[a] All reactions were performed with cyclohexanone (226 mg, 2.3 mmol) and nitro olefin **5a** (0.23 mmol) in the presence of catalyst (*S*,a*S*)-**2**. [b] Yield of the isolated product after chromatography on silica gel. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by chiral HPLC analysis.

Table 2. Substrate scope of the (*S*,a*S*)-**2**-catalysed asymmetric Michael addition of cyclohexanone to nitro olefins.[a]

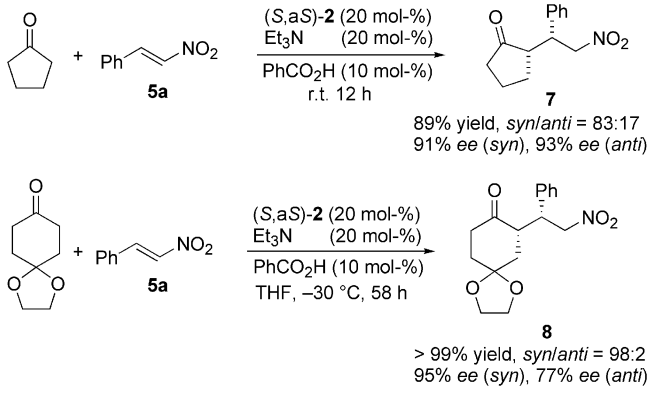


Entry	R	Time [h]	Yield [%][b]	*dr* [*syn*/*anti*][c]	*ee* [%][d]
1	Ph (**a**)	22	>99	99:1 (>99:1)	96 (96)
2	3-$CF_3C_6H_4$ (**b**)	24	87	98:2 (98:2)	95 (96)
3	4-$CF_3C_6H_4$ (**c**)	30	83	>99:1 (>99:1)	>99 (99)
4	4-FC_6H_4 (**d**)	19	90	>99:1 (99:1)	99 (97)
5	4-ClC_6H_4 (**e**)	21	>99	99:1 (98:2)	95 (98)
6	2-BrC_6H_4 (**f**)	21	95	>99:1 (>99:1)	98 (97)
7	4-BrC_6H_4 (**g**)	21	97	99:1 (>99:1)	97 (98)
8	2-$MeOC_6H_4$ (**h**)	19	>99	99:1 (99:1)	96 (96)
9	4-MeC_6H_4 (**i**)	19	>99	99:1 (99:1)	96 (97)
10	benzo[*d*][1,3]dioxol-5-yl (**j**)	40	95	>99:1 (>99:1)	97 (98)
11	1-naphthyl (**k**)	19	>99	98:2 (>99:1)	96 (97)
12	2-furyl (**l**)	16	>99	>99:1 (98:2)	96 (95)
13	(*E*)-styryl (**m**)[e]	17	90	92:8 (93:7)	87 (89)
14	2-phenylethyl (**n**)[e]	4	89	79:21 (73:27)	93 (91)

[a] All reactions were performed with cyclohexanone (226 mg, 2.3 mmol) and nitro olefin **5** (0.23 mmol) in the presence of catalyst (*S*,a*S*)-**2**. [b] Yield of the isolated product after chromatography on silica gel. [c] Determined by ^{1}H NMR spectroscopy. Values in parentheses were obtained with catalyst (*S*,a*R*)-**1**. The relative configurations were assigned by comparison of the ^{1}H and ^{13}C NMR spectra of the products with those of the known compounds. [d] Determined by chiral HPLC analysis. Values in parentheses were obtained with catalyst (*S*,a*R*)-**1**. The absolute configuration of the major isomer was established by comparison with the literature value of the optical rotation. [e] The reaction was carried out at room temperature (25 °C).

binaphthol and may be potentially useful for the preparation of enantiomerically enriched γ-nitro ketones.

We also carried out preliminary investigations on the asymmetric addition of other ketones to nitrostyrene **5a** using (*S*,a*S*)-**2** as catalyst. For example, the challenging cyclopentanone worked well to provide the desired product **7** in 89% yield with excellent enantioselectivity (91% *ee* for *syn*-**7** and 93% *ee* for *anti*-**7**, respectively) and good diastereoselectivity (*syn*/*anti* = 83:17; Scheme 4) at room temperature. Cyclohexane-1,4-dione monoethylene acetal also reacted smoothly with **4a** in THF at –30 °C to give the corresponding adduct **8** in quantitative yield with excellent stereoselectivities (*syn*/*anti* = 98:2, 95% *ee* for the major stereoisomer). These results are also comparable to those observed for catalyst (*S*,a*R*)-**1**.



Scheme 4. Reactions of other ketones in the Michael addition reaction.

Conclusions

We have reported that a thiophosphoramide bearing a biphenyl skeleton can acquire axial chirality by the reaction of the corresponding achiral thiophosphoryl chloride with the chiral inducer *tert*-butyl (*S*)-2-(aminomethyl)pyrrolidine-1-carboxylate. The single thermodynamically favoured diastereomer formed has proven to be an efficient bifunctional organocatalyst for promoting the highly diastereo- and enantioselective Michael addition of cyclic ketones to both aryl and alkyl nitro olefins. Further investigations into the application of this catalyst in asymmetric catalysis are in progress.

Experimental Section

General Methods: All reagents and solvents were of commercial grade and purified prior to use when necessary. NMR spectra were acquired with either a Bruker AMX-300 or Varian 400 MHz instrument. Chemical shifts were measured relative to residual solvent peaks as internal standard [δ = 7.26 and 77.0 ppm ($CDCl_3$)]. Specific rotations were measured with a Perkin–Elmer 341MC polarimeter. Enantiomeric excesses were determined by using an HP-1100 instrument (chiral column; mobile phase: hexane/*i*PrOH). HRMS was performed with a Varian QFT-ESI instrument. Melting points were determined with a Taike X-4 melting-point apparatus. IR spectra were recorded with Bruker FT-IR Equinox 55 and TENSOR 27 instruments.

Preparation of Chiral Thiophosphoramide (*S*,a*S*)-2: A solution of thiophosphoryl chloride **4** (707 mg, 2.5 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise to a stirred solution of *tert*-butyl (*S*)-2-(aminomethyl)pyrrolidine-1-carboxylate (**3**; 501 mg, 2.5 mmol) and triethylamine (5.0 mmol) in dry CH_2Cl_2 (5 mL) at room temperature. The reaction mixture was heated at reflux until complete consumption of **4** (monitored by TLC). The resulting mixture was allowed to cool to room temperature, and washed successively with 2 M HCl and saturated $NaHCO_3$. After removal of the solvent, the crude product was used directly in the next step without purification. The crude product was dissolved in a mixture of trifluoroacetic acid and dichloromethane (4 mL, v/v = 1:1), and the resulting solution was stirred at room temperature for 2 h. After removal of the solvent, the crude product was purified by column chromatography on silica gel (200–300 mesh; ethyl acetate) to afford the target compound **2**. White solid, 1.00 g, 87% yield (two steps), m.p. 124–126 °C, $[\alpha]_D^{20}$ = –5.2 (*c* = 1.0, MeOH). ^{1}H NMR (CD_3OD, 400 MHz): δ = 1.71–1.80 (m, 1 H, C*H*H), 1.92–2.03 (m, 2 H, CH_2), 2.06–2.14 (m, 1 H, CH*H*), 3.18–3.31 (m, 2 H, NCH_2), 3.38 (dd, *J* = 6.4 and 10.4 Hz, 2 H, NCH_2), 3.58–3.66 (m, 1 H, NCH), 7.21 (d, *J* = 8.0 Hz, 2 H_{ar}), 7.35 (t, *J* = 7.6 Hz, 2 H_{ar}), 7.43 (t, *J* = 7.6 Hz, 2 H_{ar}), 7.57 (dd, *J* = 7.6 and 1.2 Hz, 2 H_{ar}) ppm. ^{13}C NMR (CD_3OD, 100.6 MHz): δ = 24.1, 28.4, 43.9, 46.7, 62.5, 123.1, 127.7, 130.5, 131.0, 131.1, 149.5, 149.6, 149.7, 163.0, 163.3 ppm. ^{31}P NMR (CD_3OD, 161.7 MHz): δ = 83.38 ppm. IR (KBr): $\tilde{\nu}$ = 3647, 3246, 2950, 1680, 1434, 1202, 1134, 1094, 925, 897, 772, 751 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{20}F_3N_2O_4PS$ [M – CF_3CO_2H + H]$^+$ 347.0978; found 347.0976.

General Procedure for Thiophosphoramide (*S*,a*S*)-2 Catalysed Asymmetric Michael Addition to Nitro Olefins: A mixture of the catalyst (*S*,a*S*)-**2** (0.046 mmol) and triethylamine (0.046 mmol) in cyclohexanone (226 mg, 2.3 mmol) was stirred at room temperature for 30 min. Then benzoic acid (2.8 mg, 0.023 mmol) was added, and the reaction mixture was stirred for 15 min. The nitro olefin (0.23 mmol) was added to the resulting mixture 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) to afford the product.

(*S*)-2-[(*R*)-2-Nitro-1-phenylethyl]cyclohexanone (6a):[8] White solid, 57 mg, >99% yield, m.p. 124–126 °C, $[\alpha]_D^{20}$ = –30.5 (*c* = 1.0, $CHCl_3$), *syn*/*anti* = 99:1, 96% *ee*. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.10–1.22 (m, 1 H, one proton of CH_2), 1.47–1.73 (m, 4 H, 2 CH_2), 1.98–2.04 (m, 1 H, one proton of CH_2), 2.26–2.44 (m, 2 H, CH_2), 2.61 (m, 1 H, CH), 3.69 (dt, *J* = 4.5 and 9.9 Hz, 1 H, CH), 4.56 (dd, *J* = 9.9 and 12.6 Hz, 1 H, one proton of NCH_2), 4.87 (dd, *J* = 4.5 and 12.6 Hz, 1 H, one proton of NCH_2), 7.08–7.11 (m, 2 H_{ar}), 7.19–7.27 (m, 3 H_{ar}) ppm. ^{13}C NMR ($CDCl_3$, 75.0 MHz): δ = 25.1, 28.5, 33.2, 42.8, 44.0, 52.6, 78.9, 127.8, 128.2, 128.9, 137.8, 211.9 ppm. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 85:15, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 8.06 (minor), 9.74 (major) min.

(*S*)-2-[(*R*)-2-Nitro-1-(3-trifluoromethylphenyl)ethyl]cyclohexanone (6b):[5] Pale-yellow oil, 63 mg, 87% yield, $[\alpha]_D^{20}$ = –19.4 (*c* = 1.6, $CHCl_3$), *syn*/*anti* = 98:2, 95% *ee*. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.56–1.83 (m, 5 H, 2 CH_2 and one proton of CH_2), 2.04–2.13 (m, 1 H, one proton of CH_2), 2.33–2.51 (m, 2 H, CH_2), 2.70 (m, 1 H, CH), 3.86 (dt, *J* = 4.8 and 9.6 Hz, 1 H, CH), 4.67 (dd, *J* = 9.6 and 12.9 Hz, 1 H, one proton of NCH_2), 4.96 (dd, *J* = 4.5 and 12.9 Hz, 1 H, one proton of NCH_2), 7.38–7.55 (m, 4 H_{ar}) ppm. ^{13}C NMR ($CDCl_3$, 75.0 MHz): δ = 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 ppm. HPLC analysis (Chiralpak AS-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 13.63 (minor) and 26.94 (major) min.

(*S*)-2-[(*R*)-2-Nitro-1-(4-trifluoromethylphenyl)ethyl]cyclohexanone (6c):[9] White solid, 60 mg, 83% yield, m.p. 79–81 °C, $[\alpha]_D^{20}$ = –27.5 (*c* = 2.5, $CHCl_3$), *syn*/*anti* = >99:1, >99% *ee*. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.22–1.30 (m, 1 H, one proton of CH_2), 1.59–1.82 (m, 4 H, 2 CH_2), 2.06–2.10 (m, 1 H, one proton of CH_2), 2.32–2.50 (m, 2 H, CH_2), 2.65–2.74 (m, 1 H, CH), 3.86 (dt, *J* = 4.5 and 9.6 Hz, 1 H, CH), 4.66 (dd, *J* = 9.9 and 12.6 Hz, 1 H, one proton of NCH_2), 4.96 (dd, *J* = 4.5 and 12.6 Hz, 1 H, one proton of NCH_2), 7.31 (d, *J* = 8.1 Hz, 2 H_{ar}), 7.58 (d, *J* = 8.1 Hz, 2 H_{ar}) ppm. ^{13}C NMR ($CDCl_3$, 75.0 MHz): δ = 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 ppm. HPLC analysis (Chiralpak AS-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 12.15 (minor) and 20.25 (major) min.

(*S*)-2-[(*R*)-1-(4-Fluorophenyl)-2-nitroethyl]cyclohexanone (6d):[10] Pale-yellow solid, 55 mg, 90% yield, m.p. 64–66 °C, $[\alpha]_D^{20}$ = –29.2 (*c* = 0.8, $CHCl_3$), *syn*/*anti* = >99:1, 99% *ee*. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.10–1.25 (m, 1 H, one proton of CH_2), 1.56–1.82 (m, 4 H, 2 CH_2), 2.01–2.10 (m, 1 H, one proton of CH_2), 2.34–2.49 (m, 2 H, CH_2), 2.65 (m, 1 H, CH), 3.77 (dt, *J* = 4.0 and 9.6 Hz, 1 H, CH), 4.60 (t, *J* = 11.2 Hz, 1 H, one proton of NCH_2), 4.93 (dd, *J* = 4.0 and 12.4 Hz, 1 H, one proton of NCH_2), 7.01 (dd, *J* = 8.0 and 8.4 Hz, 2 H_{ar}), 7.15 (dd, *J* = 5.6 and 6.8 Hz, 2 H_{ar}) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 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 ppm. HPLC analysis (Chiralpak AS-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 22.85 (minor) and 34.24 (major) min.

(*S*)-2-[(*R*)-1-(4-Chlorophenyl)-2-nitroethyl]cyclohexanone (6e):[11] Pale-yellow solid, 64.7 mg, >99% yield, m.p. 93–96 °C, $[\alpha]_D^{20}$ =

–27.7 (c = 1.9, $CHCl_3$), *syn*/*anti* = 99:1, 95% *ee*. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.17–1.23 (m, 1 H, one proton of CH_2), 1.55–1.81 (m, 4 H, 2 CH_2), 2.06–2.11 (m, 1 H, CH), 2.33–2.48 (m, 2 H, CH_2), 2.61–2.68 (m, 1 H, CH), 3.75 (dt, J = 4.4 and 10.0 Hz, 1 H, CH), 4.60 (dd, J = 10.4 and 12.4 Hz, 1 H, one proton of NCH_2), 4.93 (dd, J = 4.4 and 12.4 Hz, 1 H, one proton of NCH_2), 7.11 (d, J = 8.0 Hz, 2 H_{ar}), 7.29 (d, J = 8.0 Hz, 2 H_{ar}) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 25.0, 28.4, 33.1, 42.7, 43.4, 52.4, 78.6, 129.1, 129.6, 133.6, 136.4, 211.4 ppm. HPLC analysis (Chiralpak AS-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 17.91 (minor) and 28.63 (major) min.

(*S*)-2-[(*R*)-1-(2-Bromophenyl)-2-nitroethyl]cyclohexanone (6f):[8] Pale-yellow solid, 71 mg, 95% yield, m.p. 80–82 °C, $[\alpha]_D^{20}$ = –50.8 (c = 1.0, $CHCl_3$), *syn*/*anti* = >99:1, 98% *ee*. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.26–1.35 (m, 1 H, one proton of CH_2), 1.51–1.76 (m, 4 H, 2 CH_2), 2.01–2.04 (m, 1 H, one proton of CH_2), 2.27–2.47 (m, 2 H, CH_2), 2.83 (br. s, 1 H, CH), 4.24 (br. s, 1 H, CH), 4.82 (s, 2 H, NCH_2), 7.05 (t, J = 7.6 Hz, 1 H_{ar}), 7.14 (d, J = 7.6 Hz, 1 H_{ar}), 7.22–7.24 (m, 1 H_{ar}), 7.50 (d, J = 8.0 Hz, 1 H_{ar}) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 25.3, 28.5, 33.0, 42.8, 52.1, 77.2, 128.0, 129.1, 133.7, 137.2, 211.5 ppm. HPLC analysis (Chiralpak AS-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 238 nm): R_t = 16.85 (minor) and 22.87 min (major).

(*S*)-2-[(*R*)-1-(4-Bromophenyl)-2-nitroethyl]cyclohexanone (6g):[8] White solid, 73 mg, 97% yield, m.p. 120–122 °C, $[\alpha]_D^{20}$ = –24.2 (c = 1.0, $CHCl_3$), *syn*/*anti* = 99:1, 97% *ee*. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.17–1.27 (m, 1 H, one proton of CH_2), 1.52–1.81 (m, 4 H, 2 CH_2), 2.07–2.10 (m, 1 H, one proton of CH_2), 2.33–2.41 (m, 1 H, C*H*H), 2.45–2.49 (m, 1 H, CH*H*), 2.61–2.68 (m, 1 H, CH), 3.74 (dt, J = 4.4 and 9.6 Hz, 1 H, CH), 4.60 (t, J = 11.2 Hz, 1 H, one proton of NCH_2), 4.93 (dd, J = 4.4 and 12.4 Hz, 1 H, one proton of NCH_2), 7.06 (d, J = 8.0 Hz, 2 H_{ar}), 7.57 (d, J = 8.0 Hz, 2 H_{ar}) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 25.1, 28.4, 33.1, 42.7, 43.4, 52.3, 78.5, 121.7, 129.9, 132.1, 136.8, 211.4 ppm. HPLC analysis (Chiralpak AS-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 238 nm): R_t = 18.90 (major) and 32.01 min (minor).

(*S*)-2-[(*R*)-1-(2-Methoxyphenyl)-2-nitroethyl]cyclohexanone (6h):[12] White solid, 64 mg, 60 mg, >99% yield, m.p. 97–100 °C, $[\alpha]_D^{20}$ = –28.8 (c = 1.0, $CHCl_3$), *syn*/*anti* = 99:1, 96% *ee*. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.19–1.22 (m, 1 H, one proton of CH_2), 1.56–1.79 (m, 4 H, 2 CH_2), 2.05–2.08 (m, 1 H, one proton of CH_2), 2.34–2.49 (m, 2 H, CH_2), 2.97 (dt, J = 4.8 and 11.2 Hz, 1 H, CH), 3.84 (s, 3 H, OCH_3), 3.93–3.99 (m, 1 H, CH), 4.78–4.87 (m, 2 H, NCH_2), 6.87 (d, J = 8.4 Hz, 1 H_{ar}), 6.88 (t, J = 8.4 Hz, 1 H_{ar}), 7.08 (d, J = 7.2 Hz, 1 H_{ar}), 7.24 (t, J = 8.0 Hz, 1 H_{ar}) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 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 ppm. HPLC analysis (Chiralpak AS-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 15.78 (minor) and 18.02 (major) min.

(*S*)-2-[(*R*)-1-(4-Methylphenyl)-2-nitroethyl]cyclohexanone (6i):[11] White solid, 60 mg, >99% yield, m.p. 123–126 °C, $[\alpha]_D^{20}$ = –28.3 (c = 1.0, $CHCl_3$), *syn*/*anti* = 99:1, 96% *ee*. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.19–1.26 (m, 1 H, one proton of CH_2), 1.54–1.80 (m, 4 H, 2 CH_2), 2.05–2.09 (m, 1 H, one proton of CH_2), 2.31 (s, 3 H, CH_3), 2.34–2.49 (m, 2 H, CH_2), 2.63–2.70 (m, 1 H, CH), 3.71 (dt, J = 4.4 and 10.0 Hz, 1 H, CH), 4.60 (dd, J = 10.4 and 12.0 Hz, 1 H, one proton of NCH_2), 4.91 (dd, J = 4.4 and 12.4 Hz, 1 H, one proton of NCH_2), 7.04 (d, J = 7.6 Hz, 2 H_{ar}), 7.12 (d, J = 7.6 Hz, 2 H_{ar}) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 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 ppm. HPLC analysis (Chiralpak AS-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 12.73 (minor) and 21.92 (major) min.

(*S*)-2-[(*R*)-1-(Benzo[*d*][1,3]dioxol-5-yl)-2-nitroethyl]cyclohexanone (6j):[8] Pale-brown solid, 64 mg, 95% yield, m.p. 144–145 °C, $[\alpha]_D^{20}$ = –20.0 (c = 1.0, $CHCl_3$), *syn*/*anti* = >99:1, 97% *ee*. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.19–1.22 (m, 1 H, one proton of CH_2), 1.56–1.69 (m, 2 H, CH_2), 1.78 (br. s, 2 H, CH_2), 2.06 (br. s, 1 H, one proton of CH_2), 2.33–2.48 (m, 2 H, CH_2), 2.58–2.62 (m, 1 H, CH), 3.65–3.68 (m, 1 H, CH), 4.54 (t, J = 11.2 Hz, 1 H, one proton of NCH_2), 4.89 (dd, J = 2.8 and 12.0 Hz, 1 H, one proton of NCH_2), 5.94 (s, 2 H, OCH_2O), 6.61 (d, J = 7.6 Hz, 1 H_{ar}), 6.64 (s, 1 H_{ar}), 6.73 (d, J = 7.6 Hz, 1 H_{ar}) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 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 ppm. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 90:10, flow rate = 0.5 mL/min, wavelength = 254 nm): t_R = 36.91 (minor) and 38.90 (major) min.

(*S*)-2-[(*R*)-1-Naphthyl-2-nitroethyl]cyclohexanone (6k):[8] Pale-brown solid, 68 mg, >99% yield, m.p. 116–119 °C, $[\alpha]_D^{20}$ = –115.5 (c = 1.0, $CHCl_3$), *syn*/*anti* = 98:2, 96% *ee*. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.20–1.30 (m, 1 H, one proton of CH_2), 1.50–1.69 (m, 4 H, 2 CH_2), 2.06–2.09 (m, 1 H, one proton of CH_2), 2.37–2.52 (m, 2 H, CH_2), 2.87 (s, 1 H, CH), 4.77 (s, 1 H, CH), 4.91 (dd, J = 9.2 and 12.4 Hz, 1 H, one proton of NCH_2), 5.07 (dd, J = 4.0 and 12.4 Hz, 1 H, one proton of NCH_2), 7.38 (d, J = 7.6 Hz, 1 H_{ar}), 7.44–7.58 (m, 3 H_{ar}), 7.78 (d, J = 8.0 Hz, 1 H_{ar}), 7.86 (d, J = 8.0 Hz, 1 H_{ar}), 8.17 (s, 1 H_{ar}) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 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 ppm. HPLC analysis (Chiralpak AS-H column, hexane/2-propanol = 75:25, flow rate = 1.0 mL/min, wavelength = 238 nm): t_R = 12.85 (minor) and 18.58 (major) min.

(*S*)-2-[(*S*)-1-(2-Furyl)-2-nitroethyl]cyclohexanone (6l):[8] Brown oil, 54 mg, >99% yield, $[\alpha]_D^{20}$ = –9.3 (c = 1.0, $CHCl_3$), *syn*/*anti* = >99:1, 96% *ee*. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.29–1.32 (m, 1 H, one proton of CH_2), 1.61–1.84 (m, 4 H, 2 CH_2), 2.08–2.09 (m, 1 H, one proton of CH_2), 2.32–2.47 (m, 2 H, CH_2), 2.71–2.77 (m, 1 H, CH), 3.93–3.99 (m, 1 H, CH), 4.63–4.69 (m, 1 H, one proton of NCH_2), 4.78 (dd, J = 4.0 and 12.4 Hz, 1 H, one proton of NCH_2), 6.17 (s, 1 H_{ar}), 6.27 (s, 1 H_{ar}), 7.37 (s, 1 H_{ar}) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 25.1, 27.2, 32.5, 37.6, 42.6, 51.1, 76.7, 109.0, 110.3, 142.3, 151.0, 211.0 ppm. HPLC analysis (Chiralpak AS-H column, hexane/2-propanol = 85:15, flow rate = 0.7 mL/min, wavelength = 230 nm): t_R = 15.20 (major) and 17.41 (minor) min.

(*S*)-2-[(*S*,*E*)-1-Nitro-4-phenylbut-3-en-2-yl]cyclohexanone (6m):[5] Pale-yellow solid, 57 mg, 90% yield, m.p. 78–81 °C, $[\alpha]_D^{20}$ = –42.1 (c = 1.2, $CHCl_3$), *syn*/*anti* = 92:8, 87% *ee*. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.42–1.51 (m, 1 H, one proton of CH_2), 1.66–1.71 (m, 3 H, CH_2 and one proton of CH_2), 2.16–2.20 (m, 2 H, CH_2), 2.33–2.48 (m, 2 H, CH_2), 3.35–3.38 (m, 1 H, CH), 4.56–4.76 (m, 2 H, NCH_2), 6.03 (dd, J = 9.6 and 15.6 Hz, 1 H, =CH), 6.50 (d, J = 15.6 Hz, 1 H, =CH), 7.25–7.34 (m, 5 H_{ar}) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 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 ppm. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 98:2, flow rate = 0.5 mL/min, wavelength = 254 nm): t_R = 50.27 (minor) and 52.28 (major) min.

(*S*)-2-[(*S*)-1-Nitro-4-phenylbutan-2-yl]cyclohexanone (6n):[5] Colourless oil, 56 mg, 89% yield, $[\alpha]_D^{20}$ = –9.4 (c = 1.5, $CHCl_3$), *syn*/*anti* = 79:21, 93% *ee*. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.43–1.53 (m, 1 H, one proton of CH_2), 1.64–1.70 (m, 3 H, CH_2 and one proton of CH_2), 1.81–1.86 (m, 1 H, one proton of CH_2), 1.93–1.95 (m, 1

H, one proton of CH_2), 2.09–2.14 (m, 2 H, CH_2), 2.28–2.39 (m, 2 H, CH_2), 2.51–2.55 (m, 1 H, CH), 2.63–2.72 (m, 3 H, CH_2 and CH), 4.36 (dd, J = 6.0 and 12.4 Hz, 0.21 H, *anti*), 4.46 (dd, J = 6.0 and 12.4 Hz, 0.79 H, *syn*), 4.62 (dd, J = 6.0 and 12.4 Hz, 1 H, one proton of NCH_2), 7.17–7.22 (m, 3 H_{ar}), 7.28–7.31 (m, 2 H_{ar}) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 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 ppm. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 98:2, flow rate = 0.5 mL/min, wavelength = 254 nm): t_R = 34.61 (major), 39.40 (minor) min.

(*S*)-2-[(*R*)-2-Nitro-1-phenylethyl]cyclopentanone (7):[8] White solid, 56 mg, 89% yield, m.p. 116–119 °C, $[\alpha]_D^{20}$ = –18.5 (c = 1.0, $CHCl_3$), *syn*/*anti* = 83:17, 91% *ee* (*syn*), 93% *ee* (*anti*): ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.43–1.52 (m, 1 H, one proton of CH_2), 1.68–1.75 (m, 1 H, one proton of CH_2), 1.85–1.96 (m, 2 H, CH_2), 2.08–2.18 (m, 1 H, one proton of CH_2), 2.32–2.43 (m, 1.83 H, *syn*), 2.49–2.55 (m, 0.17 H, *anti*), 3.66–3.72 (m, 0.83 H, *syn*), 3.82–3.85 (m, 0.17 H, *anti*), 4.71 (dd, J = 10.0 and 12.8 Hz, 1 H, one proton of NCH_2), 5.34 (dd, J = 5.6 and 12.8 Hz, 1 H, one proton of NCH_2), 7.15–7.19 (m, 2 H_{ar}), 7.28–7.34 (m, 3 H_{ar}) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 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*) ppm. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, wavelength = 220 nm): t_R = 12.34 (major, *anti*), 14.06 (minor, *anti*), 15.46 (minor, *syn*) and 21.01 (major, *syn*) min.

(*S*)-7-[(*R*)-2-Nitro-1-phenylethyl]-1,4-dioxaspiro[4.5]decan-8-one (8):[13] White solid, 70 mg, >99% yield, m.p. 125–127 °C, $[\alpha]_D^{20}$ = –9.5 (c = 1.0, $CHCl_3$), *syn*/*anti* = 98:2, 95% *ee*. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.57 (t, J = 12.8 Hz, 1 H, one proton of CH_2), 1.62–1.72 (m, 1 H, one proton of CH_2), 1.97 (dt, J = 5.2 and 13.2 Hz, 1 H, one proton of CH_2), 2.03–2.09 (m, 1 H, one proton of CH_2), 2.48 (dt, J = 4.4 and 13.6 Hz, 1 H, one proton of CH_2), 2.72 (dt, J = 6.4 and 13.6 Hz, 1 H, one proton of CH_2), 3.05–3.12 (m, 1 H, CH), 3.81–4.00 (m, 5 H, 2 OCH_2 and CH), 4.63 (dd, J = 10.0 and 12.4 Hz, 1 H, one proton of NCH_2), 4.96 (dd, J = 4.8 and 12.4 Hz, 1 H, one proton of NCH_2), 7.17–7.19 (m, 2 H_{ar}), 7.28–7.36 (m, 3 H_{ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.0, 38.6, 39.3, 43.4, 48.1, 64.5, 64.7, 78.9, 106.9, 127.8, 128.2, 129.0, 137.2, 210.3 ppm. HPLC analysis (Chiralpak AS-H, hexane/*i*PrOH = 80:20, flow rate 1.0 mL/min, wavelength = 210 nm): t_R = 17.20 (minor) and 27.08 (major) min.

Supporting Information (see footnote on the first page of this article): NMR, IR and HR mass spectra of the catalyst as well as the chiral HPLC data of the Michael addition products.

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