A chiral amino-naphthalene-derived prolinamide catalyst for the enantioselective Michael addition of ketones to nitroolefins

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An enantioselective Michael addition of ketones to nitroolefins has been accomplished using a novel chiral amino-naphthalene-derived prolinamides catalyst **1**. The desired Michael adducts were obtained in high yields (up to 93%) as well as good diastereoselectivities (>99:1) and enantioselectivities (48%-99% *ee*).

Keywords: amino-naphthalene-derived prolinamide, Michael addition, ketone, nitroolefins

The conjugate Michael addition[1] plays an important role in numerous asymmetric carbon–carbon bond-forming reactions since it represents one of the most elegant and attractive ways to introduce chirality into a Michael acceptor.[2–6] In particular, the asymmetric Michael reaction of carbonyl compounds to nitroolefins represents an easy approach to the formation of synthetically useful γ-nitro carbonyl compounds, which serve as versatile intermediates for the preparation of complex organic targets.[7–9] List[10] and Barbas[11] firstly reported the addition of ketones to *trans*-β-nitrostyrene with *L*-proline as the catalyst with good diastereoselectivity but very poor enantioselectivities (0-23% *ee*). Thus, the development of enantioselective catalytic protocols for this key reaction has received considerable attention. In the past, a number of efficient and highly selective catalytic systems have been designed for this addition reaction, such as pyrrolidine sulfonamides,[12] dehydrobietylamine,[13] diamines,[14] thiourea-secondary amines,[15] primary amine-thioureas,[16] thiourea-tertiary amine,[17] bis–secondary–tertiary triamine,[18] pyrrolidinyl-camphor derivatives,[19] and bifunctional guanidines,[20] *etc*. Among these, chiral amines based on intermolecular H-bonding cores dominate the field.

Recently the development of bifunctional asymmetric catalysts has been a fruitful area of investigation. The basis of these catalysis, was the synergistic activation of the nucleophile and electrophile by two or more reactive centers involving a combination of a Lewis acid or Lewis base working in concert. This gave high reaction rates and excellent stereoselectivities.[21] Alonso and coworkers[22] reported an example of this bifunctional asymmetric catalysts, in which a series of amino-alcohol-derived prolinamides were applied to the asymmetric Michael addition of ketones to *trans*-β-nitrostyrene with high levels of *syn*-diastereoselectivity (up to 94%) and enantioselectivity (41-81% *ee*). Consequently, we have developed novel amino-naphthalene-derived prolinamides as catalysts for the asymmetric Michael addition reaction.

Results and discussion

We synthesised the novel derived prolinamide catalysts **1**–**7** which were similar to amino-alcohol-derived prolinamide. These catalysts contained a pyrrolidine ring as a Brønsted base to generate the nucleophile, and also included another Brønsted base and acidic phenolic hydroxyl group. When these two groups combined with the electrophile by double H-bonding, classical electrostatic effects served to decrease the electron density of these species, activating it towards nucleophilic attack,[21] furthermore, it plays an active part in enantioselectivity inducement.

Chiral amino-naphthalene-derived prolinamides catalysts **1**–**6** were easily prepared from (*S*)-proline **12** as shown in Scheme 1. (*S*)-Proline **12** was firstly protected with the benzyloxycarbonyl (Cbz) group as (*S*)-*N*-(benzyloxycarbonyl) proline **13**.[23] Then the protected proline **13** was transformed into prolinamide derivatives **14** by reaction with the corresponding chiral amine and β-amino alcohol in the presence of Et_3N and isobutyl chloroformate[22]. The catalysts **1**-**6** were obtained by the hydrogenolysis of **14** in the presence of a Pd/C catalyst under hydrogen at ordinary pressure. The catalyst **1** reacted with MeI to give catalyst **7** in the presence of K_2CO_3 as shown in Scheme 2.

We investigated the catalytic activity of **1**-**7** for the asymmetric Michael additon of cyclohexanone **8a** to *trans*-β-nitrostyrene **9a** as a model reaction (Scheme 3), and the results were summarized in Table 1.

The reaction was first carried out at room temperature in the presence of catalyst **1** with benzoic acid as the additive and ethanol as the solvent. However, it afforded the adduct with poor enantioselectivity (40% *ee*), albeit with good diastereoselectivity (94:6 dr) and high yield (91%). Fortunately, excellent enantioselectivitie (>99% *ee*) was obtained (Table 1, entry 2), when the reaction temperature was decreased to 0 °C. The other catalysts **2**–**7** were examined in this Michael reaction, but the enantioselectivities decreased, only 38–89% *ee* (Table 1, entries 3–8). When phenolic hydroxyl of catalyst **7** was protected by a methyl group, the enantioselectivity was only 38%. Obviously, the presence of the phenolic hydroxyl was important for the selectivity of the process (Table 1, entries 4 and 8). Catalysts **2** and **3** derived from (*R*)-1-(amino(phenyl) methyl)naphthalen-2-ol and *race*-1-(amino(phenyl)methyl)na phthalen-2-ol were not effective compared with catalyst **1**. Double H-bonding did not combine the catalyst with *trans*-β-nitrostyrene, when electron-donating groups increased the electronic density of chiral amide. A series of solvents and additives were also investigated. In general, the catalyst exhibited higher activity in protic solvent such as EtOH compared with aprotic solvent and both a higher yield (91%) and higher enantioselectivity (>99%) were obtained (Table 1, entry 2). The reactions proceeded more rapidly in the presence of strong acids as additives, but the enantioselectivities were poor (Table 1, entries 16 and 17).

With the optimal conditions to hand, the reactions of a variety of nitroolefins with ketones were investigated, and the results were shown in Table 2. Firstly, different nitroolefins were probed and the reactions reached completion, affording good yields (up to 93%). However, the reaction involving 2-nitrovinylcyclohexane or butan-2-one produced a trace of products (Table 2, entries 12 and 14). To our surprise, results show moderate enantioselectivities (48–67% *ee*), when the nitroolefins possessed different substituents. The possible reason is that both the amide *NH* and the phenolic hydroxyl in the catalyst activate the nitro alkene by the combination of upto three hydrogen bonds, favouring the approach of the nitroalkene from the *Re* face of the *anti* enamine. But another

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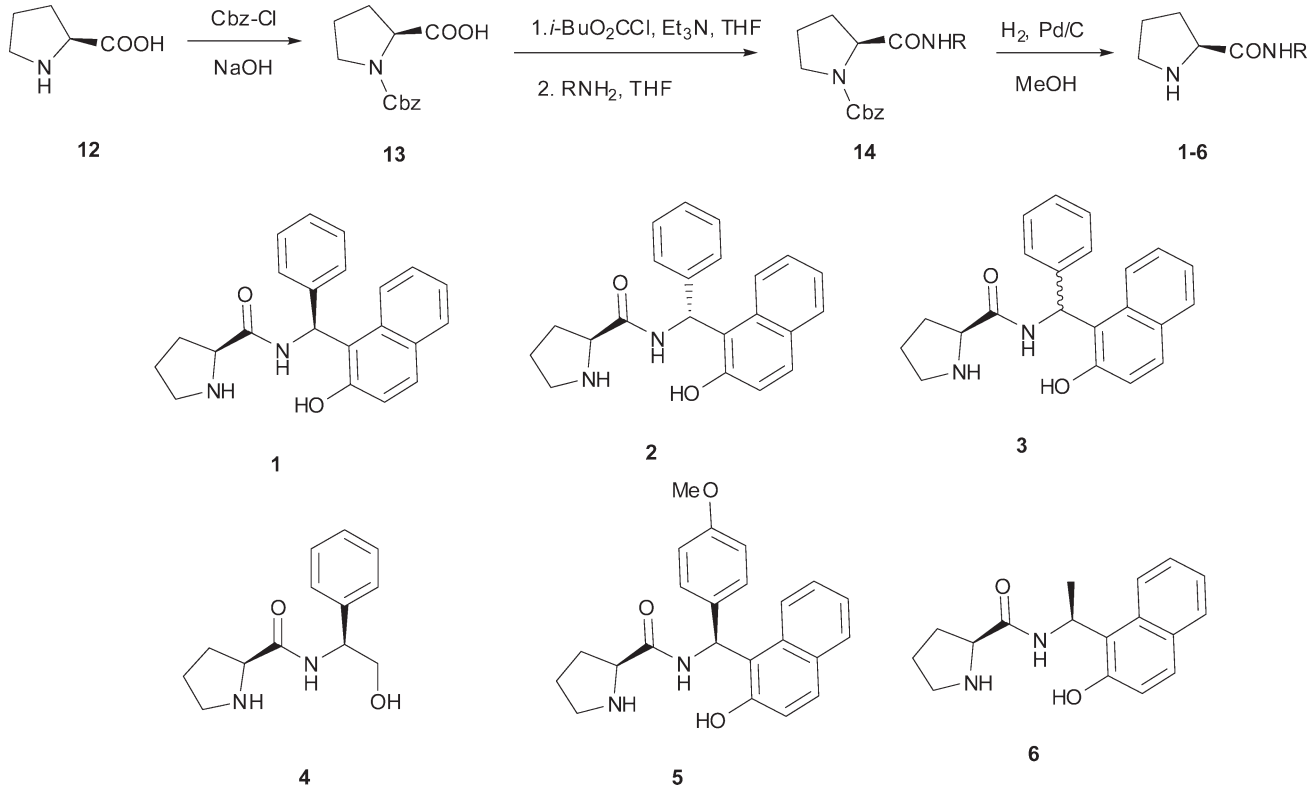
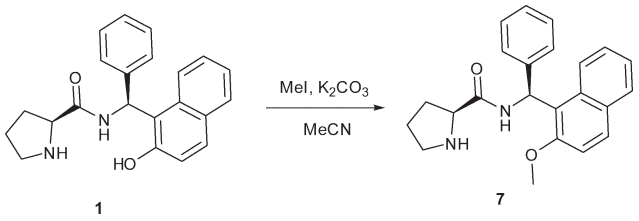
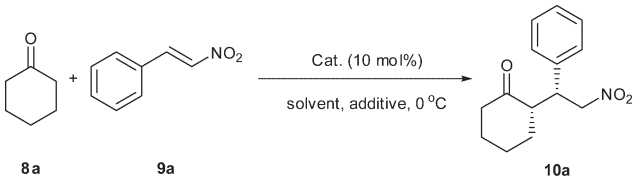


Scheme 1



Scheme 2



Scheme 3

enantiomer is also formed through a *Si* approach of the nitroalkene to the *anti* enamine.[22] However, catalyst **1** had a high catalytic activity for the reaction of cyclohexanone with nitrostyrene with excellent enantioselectivity (>99% *ee*). The results show that electronic effect are not important for asymmetric Michael addition reactions in the presence of catalyst **1** (Scheme 4).

The possible mechanism of asymmetric Michael addition reactions of cyclohexanone to nitrostyrene catalysed by **1** is considered as follows (Scheme 5).

In summary, a series of chiral amino-naphthalene-derived prolinamides were examined as the catalysts in the asymmetric Michael addition reactions of ketones to nitroolefins. Among these catalysts, the organocatalyst **1** showed the highest catalytic activity toward this reaction to furnish the corresponding adducts in excellent yields (up to 93%) and useful stereoselectivities (48–99% *ee*).

Experimental

The chiral amino-napthalenes were synthesised according to the published procedures.[24] All other reagents are commercially available. Melting points were measured on a Büchi B-540 capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet Aviatar-370 instrument; as KBr discs. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 400 MHz instrument using $CDCl_3$ or DMSO-d_6 as the solvent, and chemical shifts were expressed in parts per million (ppm) using TMS as an internal standard. Mass spectra were obtained on a Thermo Finnigan LCQ-Advantage spectrometer. Flash column chromatography was carried out on 200–300 mesh silica gel.

Synthesis of catalysts **1**–**7***; general procedure*

Cbz-protected proline **13** (5.00 g, 20 mmol) and Et_3N (2.02 g, 20 mmol) were dissolved in THF (60 mL) and cooled to 0 °C. Isobutyl chloroformate (2.17 g, 20 mmol) dissolved in THF (40 mL), was added slowly, the solution was stirred for 0.5 h. Then (*S*)-1-[amino(phenyl)methyl] naphthalen-2-ol (5.00 g, 20 mmol) dissolved in THF (40 mL) was added slowly and the reaction temperature was maintained at 0 °C. After being stirred for 3 h, the solution was filtered and the solvent was removed *in vacuo* to give a thick yellow oil that was purified by flash chromatography on silica gel (pentane/ethyl acetate, 1:1) to yield the desired white solid **14** (7.7 g, 80%). Compound **14** (4.8 g, 10 mmol) was dissolved in anhydrous MeOH (30 mL), and Pd/C (10%, w/w) (0.48 g) was added to the solution. The mixture was stirred under a hydrogen atmosphere for 6 h. The solution was filtered and the filtrate was concentrated under reduced pressure. The residue which was obtained was then subjected to flash chromatography on silica gel (pentane/ethyl acetate = 1:2, v/v) to afford yellow solid **1** (3.11g, 90%).

The catalyst **1** (1.7 g, 5 mmol), MeI (1.42 g, 10 mmol) and K_2CO_3 (2.76 g, 20 mmol) were dissolved in MeCN (20 mL) and the solvent was stirred for 5 h. Then the reaction solution was filtered and the filtrate was concentrated under reduced pressure. The obtained residue was then subjected to flash chromatography on silica gel (pentane/ethyl acetate = 1:1, v/v) to afford yellow solid **7** (1.44 g, 80%).

(S)-N-((S)-(2-Hydroxynaphthalen-1-yl)(phenyl)methyl)pyrrolidine-2-carboxamide (**1**): Yellow solid; m.p. 204.4–205.9 °C; IR (KBr): ν_{max} = 3321, 1631, 1526, 1271 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.46 (s, 1H), 7.80 (s, 1H), 7.82–7.75 (m, 2H), 7.46 (t, *J* = 6.4 Hz,

Table 1 Catalytic asymmetric Michael reaction of cyclohexanone to nitrostyrene under various conditions[a]

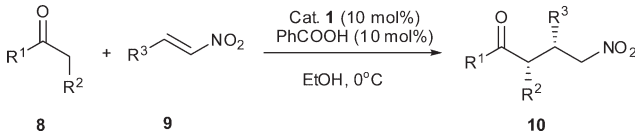
Entry	Catalyst	Solvents	Additives	Time/h	Yield[b]/%	dr[c](syn/anti)	*ee*[d]/%
1[e]	**1**	EtOH	PhCOOH	48	91	94:6	40
2	**1**	EtOH	PhCOOH	48	93	99:1	>99
3	**2**	EtOH	PhCOOH	48	89	96:4	57
4	**3**	EtOH	PhCOOH	48	90	>99:1	89
5	**4**	EtOH	PhCOOH	48	80	95:5	38
6	**5**	EtOH	PhCOOH	48	89	98:2	56
7	**6**	EtOH	PhCOOH	48	91	>99:1	53
8	**7**	EtOH	PhCOOH	48	88	98:2	51
9	**1**	free	PhCOOH	60	90	97:3	50
10	**1**	DMSO	PhCOOH	48	95	99:1	53
11	**1**	CH_2Cl_2	PhCOOH	48	87	94:6	34
12	**1**	THF	PhCOOH	48	91	99:1	77
13	**1**	AcOEt	PhCOOH	48	89	98:2	47
14	**1**	*n*-hexane	PhCOOH	72	85	99:1	40
15	**1**	EtOH	free	48	86	98:2	50
16	**1**	EtOH	HCl	18	90	96:4	41
17	**1**	EtOH	*p*-TSA	18	92	95:5	48

[a] Reaction conditions: **8a** (5 mmol), **9a** (0.5 mmol), catalyst (10 mol%), additive (10 mol%) and solvent (1 mL) at 0 °C.
[b] Isolated yield.
[c] Determined by ^{1}H NMR spectroscopy or HPLC.
[d] Determined by chiral HPLC analysis.
[e] The reaction was carried out at room temperature.

Table 2 Asymmetric Michael addition reactions of ketones to nitroolefins[a]

Entry	R^1, R^2	R^3	Time /h	Products	Yield/%[b]	dr[c](syn/anti)	*ee*[d]/%
1	-$(CH_2)_4$-	C_6H_5	48	**10a**	93%	>99:1	>99
2	-$(CH_2)_4$-	4-$OMeC_6H_4$	72	**10b**	83%	>99:1	53
3	-$(CH_2)_4$-	3,4-$Me_2C_6H_3$	72	**10c**	86%	97:3	52
4	-$(CH_2)_4$-	4-ClC_6H_4	48	**10d**	87%	96:4	56
5	-$(CH_2)_4$-	4-BrC_6H_4	48	**10e**	88%	98:2	55
6	-$(CH_2)_4$-	3-$O_2NC_6H_4$	48	**10f**	88%	92:8	51
7	-$(CH_2)_4$-	3-OHC_6H_4	72	**10g**	90%	>99:1	55
8	-$(CH_2)_4$-	2-FC_6H_4	48	**10h**	87%	>99:1	67
9	-$(CH_2)_4$-	2-$OMeC_6H_4$	72	**10i**	91%	98:2	59
10	-$(CH_2)_4$-	1-Naphthyl	48	**10j**	86%	97:3	50
11	-$(CH_2)_4$-	2-Furanyl	48	**10k**	81%	98:2	52
12	-$(CH_2)_4$-	Cyclohexyl	72	**10l**	Trace	–	–
13	Me, H	C_6H_5	72	**10m**	73%	95:5	48
14	Et, H	C_6H_5	72	**10n**	Trace	–	–

[a] Reaction conditions: **8** (5 mmol), **9** (0.5 mmol), **1** (0.05 mmol), benzoic acid (0.05 mmol) and EtOH (1 mL) at 0 °C.
[b] Isolated yield.
[c] Determined by ^{1}H NMR spectroscopy or HPLC.
[d] Determined by chiral HPLC analysis.



Scheme 4

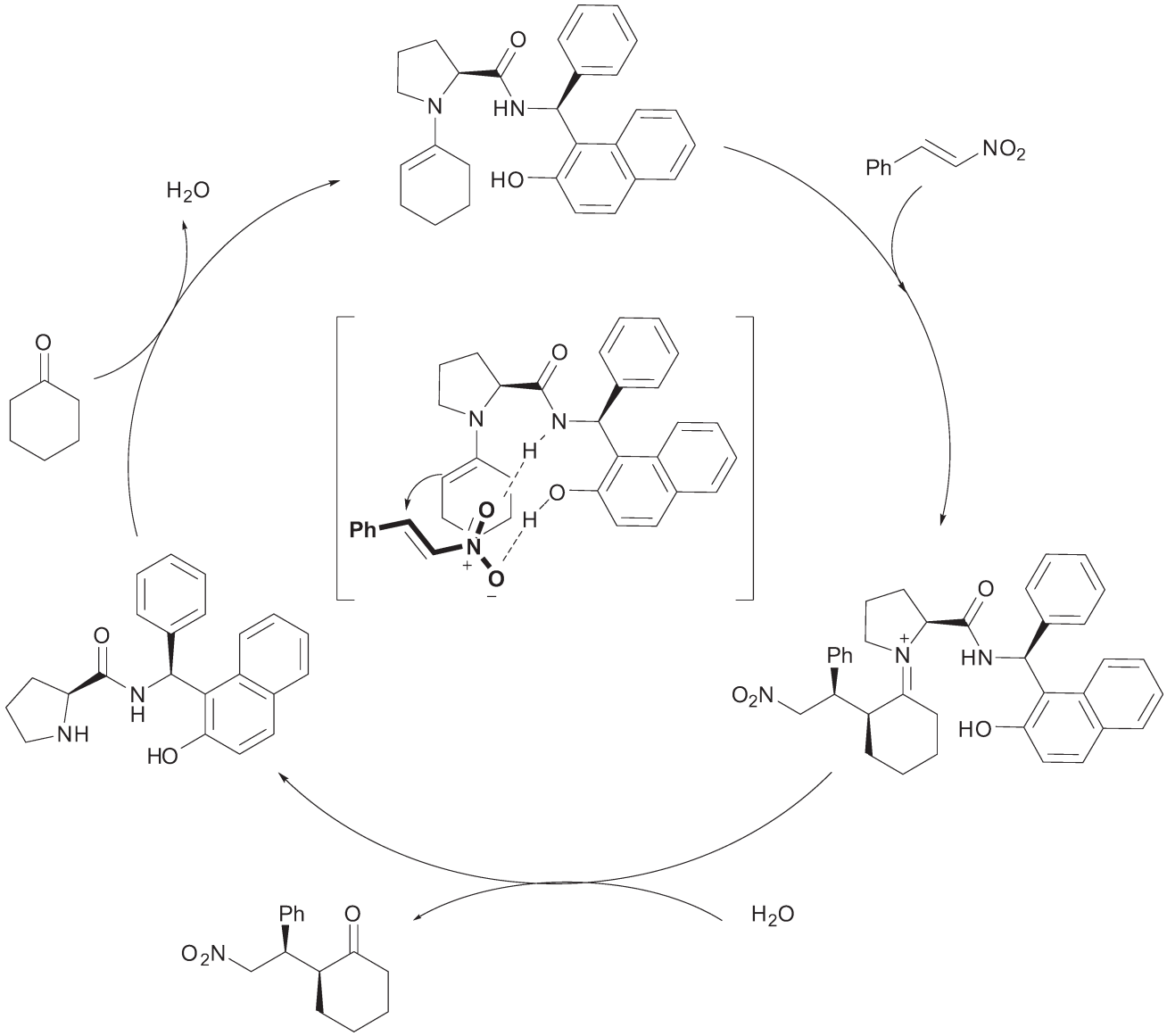
1H), 7.28 (t, *J* = 7.2 Hz, 1H), 7.24-7.11 (m, 7H), 7.05 (s, 1H), 3.63–3.60 (m, 1H), 2.98–2.92 (m, 1H), 2.85–2.79 (m, 1H), 2.07–1.99 (m, 1H), 1.89–1.82 (m, 1H), 1.60–1.59 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.6, 153.0, 142.6, 132.0, 129.0, 128.5, 127.9, 126.7, 126.0, 125.5, 122.4, 121.8, 118.4, 60.3, 47.1, 46.8, 30.7, 26.1; MS (ESI): *m/z* (%) = 347 (100) [M+1]$^+$. HRMS-ESI: *m/z* (M$^+$+1) Calcd for $C_{22}H_{23}N_2O_2$: 347.1762; found: 347.1764.

(S)-N-((R)-(2-Hydroxynaphthalen-1-yl)(phenyl)methyl)pyrrolidine-2-carboxamide (**2**): Yellow solid; m.p. 205.4–206.8 °C; IR (KBr): ν_{max} = 3321, 1615, 1515, 1463 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.48 (s,1H), 7.98 (s,1H), 7.82–7.74 (m, 2H), 7.45(t, *J* = 6.8 Hz, 1H), 7.30–7.19 (m, 5H), 7.16–7.11 (m, 2H), 7.04 (s, 1H), 3.75–3.60 (m, 1H), 2.98–2.80 (m, 1H), 2.65–2.50 (m, 1H), 2.08–1.82 (m, 1H), 1.75–1.38 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.5, 153.2, 142.1, 132.7, 129.1, 128.6, 128.1, 126.5, 126.1, 125.5, 122.4, 121.6, 117.2, 60.7, 48.1, 46.4, 30.8, 25.1; MS (ESI): *m/z* (%) = 347 (100) [M+1]$^+$. HRMS-ESI: *m/z* (M$^+$+1) Calcd for $C_{22}H_{23}N_2O_2$: 347.1762; found: 347.1764.

(2S)-N-((2-Hydroxynaphthalen-1-yl)(phenyl)methyl)pyrrolidine-2-carboxamide (**3**): Yellow solid; m.p. 205.2–207.0 °C; IR (KBr): ν_{max} = 3321, 1615, 1526, 1271 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.41 (s, 1H), 7.84 (s, 1H), 7.82–7.79 (m, 2H), 7.50–7.49 (m, 1H), 7.30–7.14 (m, 6H), 7.05 (s, 1H), 3.83–3.71 (m, 1H), 2.92–2.79 (m, 1H), 2.52–2.48 (m, 1H), 2.08–2.01 (m, 1H), 1.71–1.57 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.3, 153.4, 141.3, 133.5, 129.2, 128.8, 128.3, 126.3, 126.2, 125.5, 122.3, 121.4, 115.6, 63.4, 49.1, 45.6, 30.9, 24.4; MS (ESI): *m/z* (%) = 347 (100) [M+1]$^+$. HRMS-ESI: *m/z* (M$^+$+1) Calcd for $C_{22}H_{23}N_2O_2$: 347.1762; found: 347.1764.

(S)-N-((S)-2-Hydroxy-1-phenylethyl)pyrrolidine-2-carboxamide (**4**): Yellow solid; m.p. 121.3–123.7 °C; IR (KBr): ν_{max} = 3306, 1648, 1551, 1256 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.35 (d, *J* = 8 Hz, 1H), 7.30–7.18 (m, 5H), 4.80–4.75 (m, 1H), 3.59–3.52 (m, 3H), 2.84–2.80 (m, 2H), 2.00–1.91 (m, 1H), 1.69–1.56 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.6, 141.0, 127.9, 126.6, 64.5, 60.22, 54.3, 46.7, 30.5, 25.8; MS (ESI): *m/z* (%) = 235 (100) [M+1]$^+$. HRMS-ESI: *m/z* (M$^+$+1) Calcd for $C_{13}H_{19}N_2O_2$: 235.1441; found: 235.1442.

(S)-N-((S)-(2-Hydroxynaphthalen-1-yl)(4-methoxyphenyl)methyl) pyrrolidine-2-carboxamide (**5**): Yellow solid; m.p. 213.2–215.1 °C; IR (KBr): ν_{max} = 1651, 1511, 1248, 1274 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.81–7.71 (m, 2H), 7.37–6.96 (m, 6H), 6.84–6.80 (m, 2H), 3.70 (s, 3H), 3.42–3.38 (m, 1H), 2.88–2.72 (m, 1H), 2.30–1.50 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.7, 157.5, 153.8, 131.9, 131.4, 199.8, 128.9, 128.5, 127.1, 126.7, 122.3, 118.4, 115.2, 67.9, 64.4, 54.9, 47.6, 29.9, 23.4; MS (ESI): *m/z* (%) = 377 (100)



Scheme 5

[M+1]$^+$. HRMS-ESI: *m/z* (M$^+$+1) Calcd for $C_{22}H_{23}N_2O_2$: 377.1863; found: 377.1860.

(S)-N-((S)-1-(2-Hydroxynaphthalen-1-yl)ethyl)pyrrolidine-2-carboxamide (**6**): White solid; m.p. 113.8–115.5 °C; IR (KBr): ν_{max} = 2969, 1631, 1517, 1272 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.03 (m, 1H), 7.72–7.70 (m, 2H),7.39–7.24 (m, 4H), 6.00 (s, 1H), 4.13–4.08 (m, 1H), 2.90–2.89 (m, 2H), 2.08–2.01 (m, 2H), 1.26–1.22 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.0, 153.4, 133.5, 128.8, 128.3, 126.3, 123.8, 123.2, 118.9, 115.4 , 63.4, 45.6, 45.3 , 30.9, 24.9, 22.2; MS (ESI): *m/z* (%) = 285 (100) [M+1]$^+$. HRMS-ESI: *m/z* (M$^+$+1) Calcd for $C_{17}H_{21}N_2O_2$: 285.1596; found: 285.1598.

(S)-N-((S)-(2-methoxynaphthalen-1-yl)(phenyl)methyl)pyrrolidine-2-carboxamide (**7**): White solid; m.p. 113.8–115.5 °C; IR (KBr): ν_{max} = 2969, 1631, 1517, 1272 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.85 (d, *J* = 9.6 Hz, 1H), 8.21 (d, *J* = 9.2 Hz, 1H), 7.82–7.87 (m, 2H), 7.17–7.53 (m, 9H), 3.80 (m, 1H), 3.63 (m, 1H), 2.83–2.79 (m, 1H), 2.47–2.35 (m, 1H), 2.09–1.98 (m, 1H), 1.75–1.59 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.3, 155.8, 142.6, 132.8, 130.3, 129.9, 129.0, 128.5, 127.6, 126.9, 126.4, 124.3, 123.7, 114.7, 62.9, 57.8, 49.1, 45.6, 30.9, 24.4; MS (ESI): *m/z* (%) = 361 (100) [M+1]$^+$. HRMS-ESI: *m/z* (M$^+$+1) Calcd for $C_{23}H_{25}N_2O_2$: 361.1917; found: 361.1919.

Synthesis of **10a–n***; general procedure*

The catalyst **1** (10 mol %), PhCOOH (10 mol %) and ketones (5 mmol) were mixed in EtOH (1 mL), and the nitro olefin (0.5 mmol) was added. The mixture was stirred at 0 °C and the reaction was monitored by TLC. The product was purified by silica gel column chromatography (petroleum ether:EtOAc = 6:1, v/v).

(S)-2-((R)-2-Nitro-1-phenylethyl)cyclohexanone (**10a**): White solid; m.p. 128.2–130.1 °C (lit.[25] 124–126 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34–7.18 (m, 5H), 4.94 (dd, *J* = 12.4, 4.4 Hz, 1H), 4.63 (dd, *J* = 12.4, 10.0 Hz, 1H), 3.76 (td, *J* = 10.0, 4.4Hz, 1H), 2.72–2.63 (m, 1H), 2.50–2.35 (m, 2H), 2.09–2.06 (m, 1H), 1.77–1.56 (m, 4H), 1.28–1.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 211.9, 137.8, 129.0, 128.3, 127.9, 79.1, 52.8, 44.2, 43.1, 33.6, 28.9, 25.4; MS (ESI): *m/z* (%) = 253 (100) [M+1]$^+$; HPLC (Chiralcel AS-H, *i*-PrOH/*n*-hexane = 15/85, flow rate = 1.0 mL min^{-1}, λ = 206 nm): t_{minor} =10.5 min, t_{major} = 15.3 min, >99% *ee*. $[\alpha]_D^{20}$ = –16.4° (c = 0.28, CH_2Cl_2).

(S)-2-((R)-1-(4-Methoxyphenyl)-2-nitroethyl)cyclohexanone (**10b**): White solid; m.p. 153.5–154.8 °C (lit.[26] 153-154 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.08 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 4.91 (dd, *J* = 12.4, 4.4 Hz, 1H), 4.58 (dd, *J* = 12.4, 10.0 Hz, 1H), 3.78 (s, 3H), 3.71 (td, *J* = 10.0, 4.8Hz, 1H), 2.68–2.61 (m, 1H), 2.49–2.34 (m, 2H), 2.15–2.10 (m, 1H), 1.81–1.58 (m, 4H), 1.28–1.18(m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 212.0, 159.0, 129.5, 129.1, 114.26, 79.1, 55.2, 52.6, 43.2, 42.7, 33.1, 28.5, 25.0; MS (ESI): *m/z* (%) = 278 (100) [M+1]$^+$; HPLC (Chiralcel AS-H, *i*-PrOH/*n*-hexane = 15/85, flow rate = 1.0 mL min^{-1}, λ = 206 nm): t_{minor} =14.4 min, t_{major} = 16.9 min, 53% *ee*. $[\alpha]_D^{20}$ = –7.5° (c = 0.50, CH_2Cl_2).

(S)-2-((R)-1-(3,4-Dimethylphenyl)-2-nitroethyl)cyclohexanone (**10c**): White solid; m.p. 137.6–138.3 °C (lit.[18] not reported); ^{1}H NMR (400 MHz,

$CDCl_3$) δ = 7.07 (d, *J* = 7.6 Hz, 1H), 6.90-6.87 (m, 2H), 4.91 (dd, *J* = 12.4, 4.4 Hz, 1H), 4.60 (dd, *J* = 12.4, 10.0 Hz, 1H), 3.68 (td, *J* = 10.0, 4.4 Hz, 1H), 2.69–2.62 (m, 1H), 2.50–2.36 (m, 2H), 2.22 (d, *J* = 4.8 Hz, 6H), 2.10–2.04 (m, 1H), 1.80–1.60 (m, 4H), 1.29–1.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 212.2, 137.1, 136.0, 135.0, 130.0, 129.4, 125.3, 79.0, 52.6, 43.6, 42.7, 33.2, 28.6, 25.0, 19.9, 19.4.; MS (ESI): *m/z* (%) = 276 (100) $[M+1]^+$; HPLC (Chiralcel AS-H, *i*-PrOH/*n*-hexane = 15/85, flow rate = 1.0 mL min^{-1}, λ = 206 nm): t_{minor} = 8.4 min, t_{major} = 13.1 min, 52% *ee*. $[\alpha]_D^{20}$ = –7.6° (c = 0.50, CH_2Cl_2).

(S)-2-((R)-1-(4-Chlorophenyl)-2-nitroethyl)cyclohexanone (**10d**): White solid; m.p. 93.7–96.4 °C (lit.[25] 93–96 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.30 (d, *J* = 8.5 Hz, 2H), 7.12 (d, *J* = 8.5 Hz, 2H), 4.94 (dd, *J* = 12.6, 4.5 Hz, 1H), 4.60 (dd, *J* = 12.6, 10.1 Hz, 1H), 3.76 (td, *J* = 9.9, 4.5 Hz, 1H), 2.68–2.61 (m, 1H), 2.50–2.34 (m, 2H), 2.12–2.05 (m, 1H), 1.82–1.58 (m, 4H), 1.28–1.17 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 211.1, 136.1, 133.4, 129.4, 129.0, 78.5, 52.4, 43.4, 42.8, 33.2, 28.5, 25.1; MS (ESI): *m/z* (%) = 281 (100) $[M+1]^+$; HPLC (Chiralcel AS-H, *i*-PrOH/*n*-hexane = 15/85, flow rate = 1.0 mL min^{-1}, λ = 206 nm): t_{minor} =10.4 min, t_{major} = 16.3 min, 56% *ee*. $[\alpha]_D^{20}$ = –13.4° (c = 0.50, CH_2Cl_2).

(S)-2-((R)-1-(4-Bromophenyl)-2-nitroethyl)cyclohexanone (**10e**): White solid; m.p. 117.4–119.1 °C (lit.[25] 120–122 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.43 (d, *J* = 8.4 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 4.92 (dd, *J* = 12.4, 4.4 Hz, 1H), 4.59 (dd, *J* = 12.4, 10.0 Hz, 1H), 3.74 (td, *J* = 10.0, 4.4 Hz, 1H), 2.67–2.61 (m, 1H), 2.49–2.33 (m, 2H), 2.09–2.04 (m, 1H), 1.81–1.56 (m, 4H), 1.27–1.17 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 211.1, 136.6, 131.9, 129.7, 121.6, 78.5, 52.4, 43.5, 42.8, 33.2, 28.5, 25.2. MS (ESI): *m/z* (%) = 326 (100) $[M+1]^+$; HPLC (Chiralcel AS-H, *i*-PrOH/*n*-hexane = 15/85, flow rate = 1.0 mL min^{-1}, λ = 206 nm): t_{minor} =11.4 min, t_{major} = 18.5 min, 55% *ee*. $[\alpha]_D^{20}$ = –13.4° (c = 0.50, CH_2Cl_2).

(S)-2-((R)-2-Nitro-1-(3-Nitrophenyl)ethyl)cyclohexanone (**10f**): White solid; m.p. 78.6–79.9 °C (lit.[27] 76–79 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.13–8.06 (m, 2H), 7.56–7.48 (m, 2H), 4.99 (dd, *J* = 12.8, 4.4 Hz, 1H), 4.67 (dd, *J* = 12.4, 10.0 Hz, 1H), 3.95–3.87 (m, 1H), 2.75–2.68 (m, 1H), 2.49–2.33 (m, 2H), 2.11–2.08 (m, 1H), 1.82–1.70 (m, 1H), 1.69–1.56 (m, 3H), 1.30–1.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 211.7, 136.5, 133.8, 129.7, 129.3, 78.8, 52.6, 43.5, 42.9, 33.4, 28.7, 25.3; MS (ESI): *m/z* (%) = 293 (100) $[M+1]^+$; HPLC (Chiralcel AS-H, *i*-PrOH/*n*-hexane = 15/85, flow rate = 1.0 mL min^{-1}, λ = 206 nm): t_{minor} = 30.3 min, t_{major} = 55.1 min, 51% *ee*. $[\alpha]_D^{20}$ = –13.3° (c = 0.50, CH_2Cl_2).

(S)-2-((R)-1-(3-Hydroxyphenyl)-2-nitroethyl)cyclohexanone (**10g**): White solid; m.p. 123.1–125.3 °C (lit.[29] not reported); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.24–7.13 (m, 2H), 6.73–6.64 (m, 2H), 4.89 (dd, J = 12.8, 3.6 Hz, 1H), 4.57 (dd, *J* = 12.8, 10.0 Hz, 1H), 3.71–3.65 (m, 1H), 2.64–2.60 (m, 1H), 2.47–2.31 (m, 2H), 2.05–2.04 (m, 1H),1.85–1.55 (m, 4H), 1.23–1.21 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 212.7, 156.4,139.7, 130.4, 120.4, 115.4, 115.1, 79.0,52.7, 44.0, 43.0, 42.2, 33.4, 28.8, 27.2, 25.2, 25.1; MS (ESI*): m/z* (%) = 264 (100) $[M+1]^+$; HPLC (Chiralcel AS-H, *i*-PrOH/*n*-hexane = 15/85, flow rate = 1.0 mL min^{-1}, λ = 206 nm): t_{minor} = 13.3 min, t_{major} = 22.8 min, 55% *ee*. $[\alpha]_D^{20}$ = –13.4° (c = 0.50, CH_2Cl_2).

(S)-2-((R)-1-(2-Fluorophenyl)-2-nitroethyl)cyclohexanone (**10h**): White solid; m.p. 93.7–95.4 °C (lit.[28] 95–96 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36 (d, *J* = 8.0 Hz,1H), 7.22–7.17(m, 2H), 4.92–4.86 (m, 2H), 4.31–4.25 (m, 1H), 2.94–2.87 (m, 1H), 2.49–2.34 (m, 1H), 2.11–2.04 (m, 1H), 1.83–1.61 (m, 2H), 1.38–1.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 211.5, 135.5, 134.6, 130.4, 129.5, 129.0, 127.5, 76.9, 52.0, 43.1, 41.3, 33.4, 28.9, 25.6; MS (ESI): *m/z* (%) = 278 (100) $[M+1]^+$; HPLC (Chiralcel AS-H, *i*-PrOH/*n*-hexane = 15/85, flow rate = 1.0 mL min^{-1}, λ = 206 nm): t_{minor} = 9.9 min, t_{major} = 12.0 min, 67% *ee*. $[\alpha]_D^{20}$ = –13.2° (c = 0.50, CH_2Cl_2).

(S)-2-((R)-1-(2-Methoxyphenyl)-2-nitroethyl)cyclohexanone (**10i**)*:* White solid; m.p. 107.3–108.8 °C (lit.[25] 97–100 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.27–7.22 (m, 1H), 7.08 (dd, *J* = 7.4, 1.6 Hz, 1H), 6.91–6.86 (m, 2H), 4.85–4.79 (m, 2H), 3.99–3.93 (m, 1H), 3.84 (s, 3H), 3.01–2.94 (m, 1H), 2.49–2.35 (m, 2H), 2.10–2.05 (m, 1H), 1.80–1.60 (m, 4H), 1.25–1.16 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 212.4, 157.4, 130.8, 128.8, 125.2, 120.7, 110.8, 77.3, 55.2, 50.4, 42.5, 41.1, 33.1, 28.4, 25.0; MS (ESI): *m/z* (%) = 278 (100) $[M+1]^+$; HPLC (Chiralcel AS-H, *i*-PrOH/*n*-hexane = 15/85, flow rate = 1.0 mL min^{-1}, λ = 206 nm): t_{minor} =15.7 min, t_{major} = 17.4 min, 59% *ee*. $[\alpha]_D^{20}$ = –22.9° (c = 0.50, CH_2Cl_2).

(S)-2-((R)-1-(Naphthalen-1-yl)-2-nitroethyl)cyclohexanone (**10j**): White solid; m.p. 136.5–137.9 °C (lit.[26] 133–134 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.15–8.14 (m, 1H), 7.84 (d, *J* = 8 Hz, 1H), 7.76 (d, *J* = 8.4 Hz), 7.56–7.42 (m, 3H), 7.36 (d, *J* = 7.2 Hz, 1H), 5.06 (dd, *J* = 12.8, 4.4 Hz), 4.93–4.88 (m, 1H), 4.76–4.73 (m, 1H), 2.87–2.85 (m, 1H), 2.53–2.38 (m, 2H), 2.11–2.05 (m, 1H), 1.72–1.47 (m, 4H), 1.3–1.2 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 212.3, 136.2, 134.5, 132.6, 128.4, 128.3, 128.1, 127.1, 126.9, 126.5, 124.7, 78.2, 55.4, 43.3, 40.7, 28.5, 25.6, 23.6; MS (ESI): *m/z* (%) = 298 (100) $[M+1]^+$; HPLC (Chiralcel AS-H, *i*-PrOH/*n*-hexane = 15/85, flow rate = 1.0 mL min^{-1}, λ = 206 nm): t_{minor} =13.6 min, t_{major} = 19.3 min, 50% *ee*. $[\alpha]_D^{20}$ = –13.9° (c = 0.50, CH_2Cl_2).

(S)-2-((R)-1-(Furan-2-yl)-2-nitroethyl)cyclohexanone (**10k**)*:* Brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35–7.34 (m, 1H), 6.29 (dd, *J* = 3.2, 2.0 Hz, 1H), 6.18 (d, *J* = 3.2, 1H), 4.79 (dd, *J* = 12.4, 4.8 Hz, 1H), 4.67 (dd, *J* = 12.4, 9.6 Hz, 1H), 3.97 (td, *J* = 9.2, 4.8 Hz, 1H), 2.79–2.72 (m, 1H), 2.49–2.33 (m, 2H), 2.13–2.08 (m, 1H), 1.86–1.62 (m, 4H), 1.34–1.24(m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 211.2, 211.1, 151.3, 142.6, 110.6, 109.3, 77.6, 51.4, 42.8, 37.9, 32.7, 28.5, 25.4; MS (ESI): *m/z* (%) = 237 (100) $[M+1]^+$; HPLC (Chiralcel AS-H, *i*-PrOH/*n*-hexane = 15/85, flow rate = 1.0 mL min^{-1}, λ = 206 nm): t_{minor} = 11.8 min, t_{major} = 13.2 min, 52% *ee*. $[\alpha]_D^{20}$ = –8.3° (c = 0.24, CH_2Cl_2).

(S)-5-Nitro-4-phenylpentan-2-one (**10m**): Colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35–7.21 (m, 5H), 4.70 (dd, *J* = 12.4, 6.8 Hz, 1H), 4.60 (dd, *J* = 12.4, 7.6 Hz, 1H), 4.05-3.95 (m, 1H), 2.92 (d, *J* = 7.2 Hz, 2H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 205.0, 138.4, 128.7, 127.5, 127.0, 79.1, 45.8, 38.7, 30.0; MS (ESI): *m/z* (%) = 237 (100) $[M+1]^+$; HPLC (Chiralcel AS-H, *i*-PrOH/*n*-hexane = 15/85, flow rate = 1.0 mL min^{-1}, λ = 206 nm): t_{minor} =14.2 min, t_{major} = 20.3 min, 48% *ee*. $[\alpha]_D^{20}$ = –4.8° (c = 0.50, CH_2Cl_2).

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