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Pyrrolidine–pyridine base catalysts for the enantioselective Michael addition of ketones to chalcones

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ABSTRACT

A series of pyrrolidine–pyridine base organocatalysts have been developed and **3a** found to be a highly effective catalyst for the asymmetric Michael addition reactions of ketones to chalcones. The reaction generated the corresponding products 1, 5-diketones in excellent diastereoselectivities (up to >99:1 dr) and enantioselectivities (up to 100% ee).

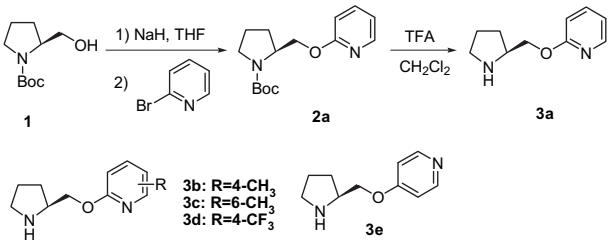
1. Introduction

The Michael reaction is one of the most popular carbon–carbon bond-forming reactions in organic synthesis.[1] Over the past few years, there has been a tremendous increase in research activities on the development of organocatalysts for asymmetric carbon–carbon bond-forming reactions,[2] especially for the Michael addition reactions.[3] However, most of the reactions employ highly activated Michael acceptors, such as nitroalkenes.[4] Enantioselective catalytic conjugate addition of ketones with enones remains a challenging reaction. Jørgensen and co-workers have reported Michael additions of aldehydes to enones catalyzed by a chiral organocatalyst pyrrolidine.[5] List and Gellman have independently used MacMillan's imidazolidinones as organocatalysts for intramolecular and intermolecular Michael reactions of aldehydes with enones.[6] Only two papers have been published on the asymmetric Michael addition of ketones to chalcones. Wang et al. studied this reaction using a chiral pyrrolidinylmethylsulfonamide,[7] and we reported an amino acid ionic liquid serving as a catalyst for this type Michael addition reaction.[8] Unfortunately, these organocatalysts have some drawbacks, such as long reaction time (more than 4 days) or high catalyst loading (200 mol %), and the later will put up the cost and limit its application in the pharmaceutical industry. In addition, a large excess of ketones (normally 10 equiv) is also generally required to achieve good enatioselectivity. Therefore, the design and development of highly active chiral organocatalysts aimed at overcoming these limitations to achieve high activities with ketones and chalcones in Michael conjugate additions remains a major challenge in synthetic organic chemistry.

Herein, we designed and synthesized a series of pyrrolidine–pyridine organocatalysts, which were tested in the asymmetric Michael addition of ketones to chalcones providing high enantioselectivities and diastereoselectivities.

2. Results and discussion

A series of the pyrrolidine–pyridine type catalysts **3** were prepared from the 'chiral pool' using Boc-L-prolinol as the starting material.[9] The synthetic procedures were quite straightforward. First, Boc-L-prolinol was coupled with an equivalent of bromopyridines followed by the treatment of TFA in CH_2Cl_2. The product, such as **3a**,[10] was obtained in 65% overall yield (Scheme 1).[11]



Scheme 1. Synthesis of the catalysts.

The preliminary experiments were conducted by taking cyclohexanone **4a** as a donor and chalcone **5a** as an acceptor using 20 mol % of the synthesized pyrrolidine–pyridine type catalysts **3** in THF (Table 1).

The catalyst **3a** promoted the addition with a high diastereoselectivity (97:3 dr) and enantioselectivity (86% ee) (Table 1, entry 1). Chiral catalysts **3b** and **3d** also gave good diastereoselectivities (99:1 and 98:2 dr, respectively), but they gave lower

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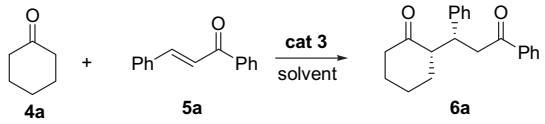
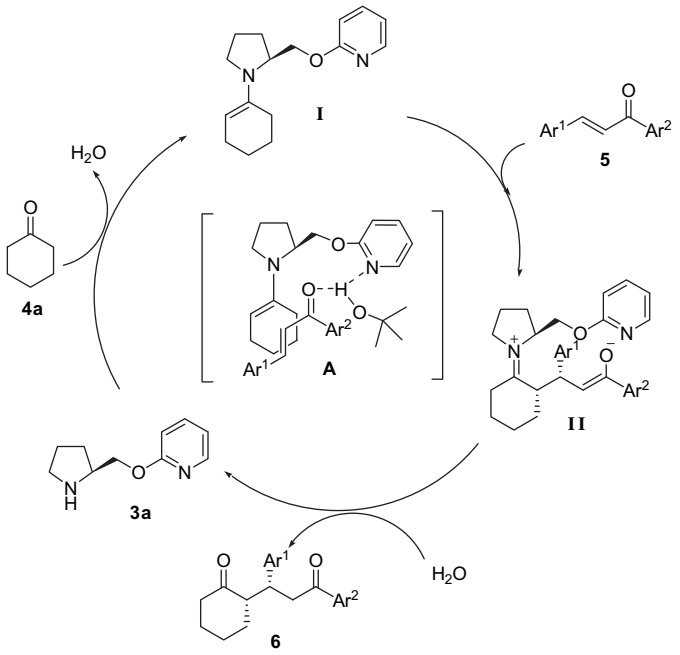
Table 1
The effect of catalysts **3** in asymmetric Michael additions of cyclohexanone **4a** and chalcone **5a**[a]



Entry	Cat.	Solvent (1 mL)	Time (h)	Yield[b] (%)	dr[c]	ee[d] (%)
1	**3a**	THF	120	61	97:3	86
2	**3b**	THF	120	45	99:1	85
3	**3c**	THF	120	21	92:8	63
4	**3d**	THF	120	38	98:2	83
5	**3e**	THF	120	0	—	—
6	**3a**	Cyclohexanone	115	<5	nd	nd
7	**3a**	Et_2O	115	30	99:1	78
8	**3a**	CH_3OH	115	21	98:2	83
9	**3a**	*i*-PrOH	115	45	99:1	85
10	**3a**	*n*-PrOH	96	40	98:2	97
11	**3a**	*t*-BuOH	118	44	>99:1	99
12	**3a**	*t*-BuOH[e]	112	57	>99:1	99.4
13	**3a**	*t*-BuOH[f]	58	73	99:1	100

[a] All reactions were conducted in solvent (1.0 mL) using **4a** (0.1 mL, 1.0 mmol) and **5a** (41 mg, 0.2 mmol) in the presence of 20 mol % of the catalyst **3**.
[b] Isolated yield.
[c] Determined by ^1H NMR spectroscopy.
[d] Determined by HPLC analysis (Chiralcel AD-H column).
[e] Solvent *t*-BuOH (0.5 mL) was used.
[f] Solvent *t*-BuOH (0.2 mL) was used.

yields and enantioselectivities than **3a** (Table 1, entries 2 and 4). The catalyst **3c**, with 6-methylpyridine, proceeded slowly in very low yield (21% yield) with only a moderate enantioselectivity (63% ee) (Table 1, entry 3). The catalyst **3e** was not an effective catalyst for this process (Table 1, entry 5). The possible reason is that the catalyst **3e** could not form the transition state A with ketones to chalcones (Scheme 2).

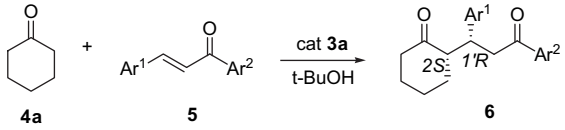


Scheme 2. Proposed mechanism for the **3a**-catalyzed Michael addition.

Compound **3a** was then taken as the catalyst of choice and evaluated for the reaction in different solvents (Table 1, entries 6–13). The yields and enantioselectivities of **3a** differed significantly. When cyclohexanone was used as the solvent, less than 5% of the product was obtained (Table 1, entry 6). When the reaction was performed in Et_2O, CH_3OH or *i*-PrOH, the product **6a** was formed in low yields and moderate to high enantioselectivities (Table 1, entries 7–9). Good results were observed when *n*-PrOH or *t*-BuOH were used (97% and 99% ee, respectively) (Table 1, entries 10–11). If reduced the volume of *t*-BuOH, the reaction of cyclohexanone **4a** with chalcone **5a** took place to form adduct **6a** more rapidly (in 58 h) with a remarkably high level of stereocontrol (100% ee and 99:1 dr, Table 1, entry 13).

Having established the optimal reaction conditions for Michael addition of cyclohexanone **4a** with chalcone **5a**, we then examined cyclohexanone **4a** with other chalcones in *t*-BuOH catalyzed by **3a** (20 mol %) at room temperature to establish the general utility of this asymmetric transformation. As shown in Table 2, the Michael adducts obtained with good to excellent levels of enantioselectivities (80–100% ee) and exceptionally high diastereoselectivities

Table 2
Catalytic asymmetric Michael addition reactions of cyclohexanone **4a** with chalcones **5**[a]



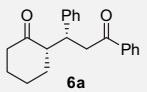
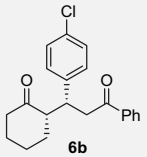
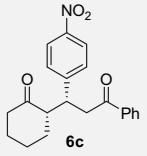
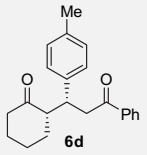
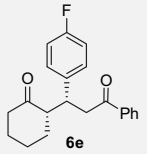
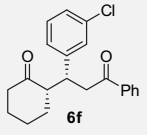
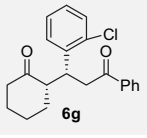
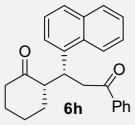
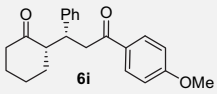
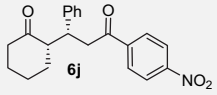
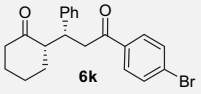
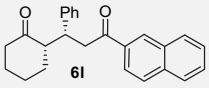
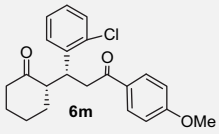
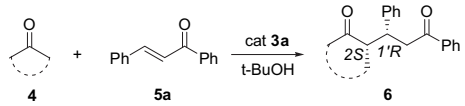
Entry	Product	Time (h)	Yield[b] (%)	dr[c]	ee[d] (%)
1	 **6a**	58	73	99:1	100
2	 **6b**	90	59	99:1	91
3	 **6c**	48	93	>99:1	88
4	 **6d**	57	58	>99:1	86
5[e]	 **6e**	48	70	>99:1	84
6	 **6f**	72	65	>99:1	86
7	 **6g**	72	54	>99:1	89

Table 2 (*continued*)

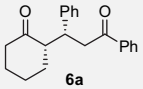
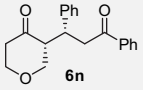
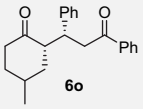
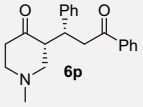
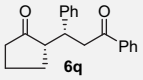
Entry	Product	Time (h)	Yield[b] (%)	dr[c]	ee[d] (%)
8	 **6h**	72	48	>99:1	88
9	 **6i**	96	45	>99:1	85
10	 **6j**	48	90	99:1	80
11	 **6k**	48	63	>99:1	86
12	 **6l**	48	56	>99:1	86
13	 **6m**	96	62	>99:1	89

[a] All reactions were conducted in solvent (0.2 mL) using **4a** (0.1 mL, 1.0 mmol) and **5** (0.2 mmol) in the presence of 20 mol % of the catalyst **3a** (7 mg, 0.04 mmol).
[b] Isolated yield.
[c] Determined by ^{1}H NMR spectroscopy.
[d] Determined by HPLC analysis (Chiralcel AD-H column).
[e] Determined by HPLC analysis (Chiralcel OD-H column).

Table 3
Catalytic asymmetric Michael addition reactions of cyclic ketones **4** with chalcone **5a**[a]



4 **5a** **6**

Entry	Product	Time (h)	Yield[b] (%)	dr[c]	ee[d] (%)
1	 **6a**	58	73	99:1	100
2	 **6n**	48	57	93:7	84
3	 **6o**	72	69	>99:1	86
4	 **6p**	48	65	84:16	84
5	 **6q**	48	55	82:18	71

[a] All reactions were conducted in solvent (0.2 mL) using **4** (0.1 mL, 1.0 mmol) and **5a** (41 mg, 0.2 mmol) in the presence of 20 mol % of the catalyst **3a**(7 mg, 0.04 mmol).
[b] Isolated yield.
[c] Determined by ^{1}H NMR spectroscopy.
[d] Determined by HPLC analysis (Chiralcel AD-H column).

(≥99:1 dr) regardless of the electronic nature of the aromatic substituents.

Other cyclic ketones were also found to be compatible with **3a** under the optimized conditions (Table 3). Reactions with six-membered ring ketone gave the Michael adducts with high to excellent enantioselectivities (84–100% ee) (Table 3, entries 1–4). However, when cyclopentanone was used as substrate, only moderate enantioselectivity was obtained (Table 3, entry 5).

The absolute stereochemical results can be explained by the concept of an acyclic synclinal transition state, as proposed by Seebach and Golinski.[12] It is accepted that when primary or secondary chiral amines are used as organocatalysts, the reaction clearly involves an enamine pathway. As shown in Scheme 2, first, the catalyst **3a** forms a chiral enamine I with cyclohexenone **4a**, then the Michael reaction of the enamine-activated **I** and the chalcone **5** leads to formation of the corresponding product **6** via the transition state A. The catalyst **3a** continues the subsequent catalytic cycle. The transition state A is very important in this asymmetric Michael addition of ketones to chalcones, in which the pyridine ring plays an important role in shielding the *si*-face of enamine double bond and activating chalcones, if the catalyst could not form transition state A, such as **3e**, the catalyst would be not effective for this reaction.

3. Conclusions

In summary, we have designed and synthesized a series of novel pyrrolidine–pyridine organocatalysts, developed a procedure for catalytic asymmetric Michael addition reaction of ketones with chalcones. The main advantages of this catalyst are the ease of synthesis and the use of small excess of ketones (5 equiv). In the presence of the (*S*)-pyrrolidine–pyridine catalyst **3a**, the process is carried out under mild reaction conditions, and ketones could react with various chalcones to afford synthetically useful 1,5-dicarbonyl compounds in moderate to good yields with high to excellent levels of enantioselectivities and diastereoselectivities. Further investigations of this novel transformation and the application of these organocatalysts in asymmetric catalysis are still in progress.

4. Experimental

4.1. General information

All the solvents were purified according to standard procedures. The ^{1}H NMR spectra were recorded at 300 MHz or 400 MHz, ^{13}C NMR spectra were recorded at 75 MHz or 100 MHz. ^{1}H and ^{13}C NMR chemical shifts were calibrated to tetramethylsilane as an external reference. Coupling constants are given in hertz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; m, multiplet. HRMS were recorded on an IonSpec FT-ICR mass spectrometer with ESI resource. Melting points were measured on an RY-I apparatus and were reported uncorrected. Optical rotations were measured on a Perkin–Elmer 341 Polarimeter at 20 °C. HPLC analysis was performed on Shimadzu CTO-10AS by using a Chiralpak AD-H or OD-H column purchased from Daicel Chemical Industries.

The chemicals were purchased from commercial suppliers (Aldrich, USA and Shanghai Chemical Company, China), and were

used without purification prior to use. All reactions unless otherwise noted were carried out directly under air.

4.2. General procedure for the synthesis of catalysts

*4.2.1. 2-(((S)-Pyrrolidin-2-yl)methoxy)pyridine (**3a**).* A solution of **1** (3.02 g, 15 mmol) in dry THF (30 mL) under N_2 was cooled to 0 °C and stirred for 10 min. NaH (2.16 g, 90 mmol) was added and the mixture was stirred for 20 min. The mixture was warmed to room temperature and stirred overnight, then a solution of 2-bromopyridine (1.7 g, 15 mmol) in THF (5 mL) was added. The mixture was heated to reflux for 24 h. After evaporation of the THF, ethyl acetate (80 mL) was added, and the solution was washed with water (30 mL), brine (30 mL), and dried over Na_2SO_4, then filtered. The ethyl acetate was concentrated under reduced pressure. The crude product was purified by column chromatography with petroleum ether/ethyl acetate (8:1) to afford 2.9 g (71%) of **2a** as a colorless oil.

To a solution of **2a** (1.0 g, 3.6 mmol) in CH_2Cl_2 (10 mL) was added dropwise TFA (8 mL) at 0 °C. The mixture was warmed to room temperature and stirred overnight. After removal of the organic solvents under vacuum, the residue was dissolved in CH_2Cl_2 (10 mL) and treated with saturated Na_2CO_3 solution (30 mL) for 1 h at room temperature. The aqueous layer was extracted with CH_2Cl_2 three times (15 mL×3) and the combined extracts were washed with brine (15 mL), then dried over anhydrous Na_2SO_4. Concentration in vacuo after filtration gave **3a** as colorless oil (587 mg, 92%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.72–1.81 (m, 1H), 1.90–1.97 (m, 2H), 2.04–2.13 (m, 1H), 3.09–3.23 (m, 2H), 3.81–3.87 (m, 1H), 4.31 (dd, 1H, J_1=6.8 Hz, J_2=11.6 Hz), 4.51 (dd, 1H, J_1=3.6 Hz, J_2=11.6 Hz), 6.79 (d, 1H, J=8.4 Hz), 6.89–6.92 (m, 1H), 7.57–7.62 (m, 1H), 8.10–8.12 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 24.29, 27.02, 45.48, 58.25, 65.84, 111.23, 117.49, 139.08, 146.51, 162.98; HRMS calcd for $C_{10}H_{14}N_2ONa^+$ $(M+Na)^+$ 201.0998, found 201.0992; $[\alpha]_D^{20}$=+33.6° (c=0.5, CH_2Cl_2).

*4.2.2. 2-(((S)-Pyrrolidin-2-yl)methoxy)-4-methylpyridine (**3b**).* This was prepared as per our general procedure to afford the product **3b** as a light yellow solid; yield 92%; mp 58–59 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.52–1.63 (m, 1H), 1.71–2.01 (m, 3H), 2.28 (s, 3H), 2.95–3.08 (m, 2H), 3.54–3.66 (m, 1H), 3.88 (s, 1H), 4.16 (dd, 1H, J_1=10 Hz, J_2=14.4 Hz), 4.33 (dd, 1H, J_1=5.2 Hz, J_2=14 Hz), 6.58 (s, 1H), 6.70 (d, 1H, J=6.8 Hz), 7.98 (d, 1H, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.90, 25.19, 27.77, 46.34, 57.41, 68.46, 111.17, 118.45, 146.24, 150.00, 164.04; HRMS calcd for $C_{11}H_{16}N_2O_5Na^+$ $(M+Na)^+$ 215.1155, found 215.1162; $[\alpha]_D^{20}$=+14.1° (c=0.5, CH_2Cl_2).

*4.2.3. 2-(((S)-Pyrrolidin-2-yl)methoxy)-6-methylpyridine (**3c**).* This was prepared as per our general procedure to afford the product **3c** as a brown oil; yield 95%; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.65–1.74 (m, 1H), 1.85–1.92 (m, 2H), 1.97–2.07 (m, 1H), 2.43 (s, 3H), 3.03–3.15 (m, 2H), 3.66–3.77 (m, 1H), 4.24 (dd, 1H, J_1=6.8 Hz, J_2=11.6 Hz), 4.41 (dd, 1H, J_1=3.6 Hz, J_2=11.6 Hz), 6.57 (d, 1H, J=8 Hz), 6.74 (d, 1H, J=7.2 Hz), 7.47 (t, 1H, 8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 22.99, 24.05, 26.38, 44.88, 56.86, 66.86, 106.59, 115.37, 138.31, 155.06, 162.02; HRMS calcd for $C_{11}H_{16}N_2OH^+$ $(M+H)^+$ 193.1335, found 193.1339; $[\alpha]_D^{20}$=−20.0° (c=0.5, CH_2Cl_2).

*4.2.4. 2-(((S)-Pyrrolidin-2-yl)methoxy)-4-(trifluoromethyl)-pyridine (**3d**).* This was prepared as per our general procedure to afford the product **3c** as a colorless oil; yield 98%; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.48–1.56 (m, 1H), 1.70–1.97 (m, 3H), 2.23 (s, 1H), 2.91–3.04 (m, 2H), 3.49–3.56 (m, 1H), 4.19 (dd, 1H, J_1=7.6 Hz, J_2=10.4 Hz), 4.33 (dd, 1H, J_1=4.4 Hz, J_2=10.8 Hz), 6.98 (s, 1H), 7.04 (d, 1H, J=5.2 Hz), 8.27 (d, 1H, J=5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 25.36, 27.91, 46.59, 56.95, 69.80, 107.82, 112.18, 123.97, 140.95, 148.18, 164.21; HRMS calcd for $C_{11}H_{13}F_3N_2OH^+$ $(M+H)^+$ 247.1053, found 247.1056; $[\alpha]_D^{20}$=+9.6° (c=0.5, CH_2Cl_2).

*4.2.5. 4-(((S)-Pyrrolidin-2-yl)methoxy)pyridine(**3e**).* This was prepared as per our general procedure to afford the product **3a** as a yellow liquid; yield 91%; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.48–1.60 (m, 1H), 1.73–1.87 (m, 2H), 1.92–2.01 (m, 1H), 2.34 (s, 1H), 2.92–3.02 (m, 2H), 3.49–3.58 (m, 1H), 3.85–3.97 (m, 2H), 6.79–6.81 (m, 2H), 8.40–8.42 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 25.28, 27.97, 46.60, 56.78, 71.28, 110.23, 151.01, 164.89; HRMS calcd for $C_{10}H_{14}N_2ONa^+$ $(M+Na)^+$ 201.0998, found 201.0999; $[\alpha]_D^{20}$=+9.6° (c=0.5, CH_2Cl_2).

4.3. Typical procedure for Michael addition reaction

Catalyst **3a** (7.0 mg, 0.04 mmol) was added to a vial containing cyclohexanone (0.1 mL, 1.0 mmol) and chalcone **5a** (41 mg, 0.2 mmol) in *t*-BuOH (0.2 mL) at room temperature. The mixture was stirred vigorously and monitored by TLC. When the reaction was finished, the mixture was concentrated under vacuum. The residue was purified by flash silica gel chromatography (ethyl acetate/hexane=1:6) to afford the adduct as a white solid; yield: 55 mg (73%; 99:1 dr (determined by ^{1}H NMR) and 100% ee); Chiralpak AD-H column (*i*-PrOH/hexane=10:90, flow rate 1.0 mL/min, λ=254 nm): t_R=19.37 min (major) and 22.74 min (minor).

*4.3.1. (S)-2-((R)-3-Oxo-1,3-diphenylpropyl)cyclohexanone (**6a**)[13].* The ee was determined by HPLC analysis (Chiralpak AD-H, *i*-PrOH/hexane=10:90, 1.0 mL/min, 254 nm, t_R (major)=19.37 min, t_R (minor)=22.74 min), 100% ee; $[\alpha]_D^{20}$=−56.8 (c 0.79, CH_2Cl_2).

*4.3.2. (S)-2-((R)-1-(4-Chlorophenyl)-3-oxo-3-phenylprop-yl)cyclohexanone (**6b**)[7].* The ee was determined by HPLC analysis (Chiralpak AD-H, *i*-PrOH/hexane=10:90, 1.0 mL/min, 254 nm, t_R (minor)=17.15 min, t_R (major)=20.60 min), 91% ee; $[\alpha]_D^{20}$=−64.0 (c 0.81, CH_2Cl_2).

*4.3.3. (S)-2-((R)-1-(4-Nitrophenyl)-3-oxo-3-phenylprop-yl)cyclohexanone (**6c**)[7].* The ee was determined by HPLC analysis (Chiralpak AD-H, *i*-PrOH/hexane=10:90, 1.0 mL/min, 254 nm, t_R (minor)=44.96 min, t_R (major)=54.436 min), 88% ee; $[\alpha]_D^{20}$=−15.3 (c 0.79, CH_2Cl_2).

*4.3.4. (S)-2-((R)-3-Oxo-3-phenyl-1-p-tolylpropyl)cyclohexanone (**6d**)[14].* The ee was determined by HPLC analysis (Chiralpak AD-H, *i*-PrOH/hexane=10:90, 1.0 mL/min, 254 nm, t_R (minor)=13.37 min, t_R (major)=18.76 min), 86% ee; $[\alpha]_D^{20}$=−18.2 (c 0.81, CH_2Cl_2).

*4.3.5. (S)-2-((R)-1-(4-Fluorophenyl)-3-oxo-3-phenylpropyl)-cyclohexanone (**6e**). syn/anti*=>99:1 (by ^{1}H NMR); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21–1.27 (m, 1H), 1.53–1.81 (m, 4H), 1.97–2.05 (m, 1H), 2.32–2.43 (m, 1H), 2.48–2.56 (m, 1H), 2.72 (dt, 1H, J_1=10.0 Hz, J_2=4.8 Hz), 3.15 (dd, 1H, J_1=10.0 Hz, J_2=16.0 Hz), 3.49 (dd, 1H, J_1=4.0 Hz, J_2=16.0 Hz), 3.67 (dt, 1H, J_1=10.0 Hz, J_2=4.0 Hz), 7.07 (t, 2H, J=8.8 Hz), 7.13–7.18 (m, 3H), 7.23–7.27 (m, 2H), 7.93–7.97 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 24.22, 28.56, 32.59, 41.42, 42.40, 44.29, 55.81, 115.35, 115.64, 126.69, 128.28, 128.51, 130.76, 130.89, 141.82, 197.25, 213.60; HRMS calcd for $C_{21}H_{21}FO_2Na^+$ $(M+Na)^+$ 347.1419, found 347.1422. The ee was determined by HPLC analysis (Chiralpak OD-H, *i*-PrOH/hexane=10:90, 1.0 mL/min, 254 nm, t_R (minor)=7.10 min, t_R (major)=9.22 min), 84% ee; $[\alpha]_D^{20}$=−74.2 (c 0.81, CH_2Cl_2).

*4.3.6. (S)-2-((R)-1-(3-Chlorophenyl)-3-oxo-3-phenylprop-yl)cyclohexanone (**6f**). syn/anti*=>99:1 (by ^{1}H NMR); ^{1}H NMR (400 MHz,

$CDCl_3$): δ 1.21–1.29 (m, 1H), 1.53–1.81 (m, 4H), 1.99–2.04 (m, 1H), 2.34–2.42 (m, 1H), 2.46–2.52 (m, 1H), 2.70 (dt, 1H, J_1=10.0 Hz, J_2=4.8 Hz), 3.22 (dd, 1H, J_1=9.6 Hz, J_2=16.4 Hz), 3.49 (dd, 1H, J_1=3.6 Hz, J_2=16.4 Hz), 3.71 (dt, 1H, J_1=9.6 Hz, J_2=3.6 Hz), 7.08–7.20 (m, 4H), 7.42 (t, 2H, J=7.6 Hz), 7.52 (t, 1H, J=7.2 Hz), 7.90 (d, 2H, J=7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 24.36, 28.51, 31.60, 40.74, 42.47, 43.85, 55.49, 126.85, 128.13, 128.35, 128.53, 129.71, 133.00, 134.25, 136.84, 144.36, 198.31, 213.04; HRMS calcd for $C_{21}H_{22}ClO_2^+$ $(M+H)^+$ 341.1303, found 341.1299. The ee was determined by HPLC analysis (Chiralpak AD-H, *i*-PrOH/hexane=10:90, 1.0 mL/min, 254 nm, t_R (minor)=11.62 min, t_R (major)=21.16 min), 86% ee; $[\alpha]_D^{20}$=−72.9 (*c* 0.79, CH_2Cl_2).

*4.3.7. (S)-2-((R)-1-(2-Chlorophenyl)-3-oxo-3-phenylprop-yl)-cyclohexanone (**6g**)*[7]. The ee was determined by HPLC analysis (Chiralpak AD-H, *i*-PrOH/hexane=10:90, 1.0 mL/min, 254 nm, t_R (minor)=12.81 min, t_R (major)=21.37 min), 89% ee; $[\alpha]_D^{20}$=−126.8 (*c* 0.81, CH_2Cl_2).

*4.3.8. (S)-2-((R)-1-(Naphthalen-1-yl)-3-oxo-3-phenylprop-yl)cyclohexanone (**6h**). syn/anti*=>99:1 (by ^{1}H NMR); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25–1.30 (m, 1H), 1.46–1.78 (m, 4H), 1.95–2.04 (m, 1H), 2.37–2.46 (m, 1H), 2.50–2.58 (m, 1H), 2.87 (dt, 1H, J_1=10.0 Hz, J_2=4.8 Hz), 3.45 (dd, 1H, J_1=10.0 Hz, J_2=16.0 Hz), 3.69 (dd, 1H, J_1=3.6 Hz, J_2=16.4 Hz), 3.68 (dt, 1H, J_1=9.6 Hz, J_2=3.6 Hz), 7.34–7.47 (m, 7H), 7.67–7.72 (m, 1H), 7.80–7.86 (m, 3H), 8.11–8.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 19.17, 24.62, 28.70, 29.71, 32.77, 42.63, 44.71, 123.57, 125.45, 125.98, 127.03, 128.12, 128.39, 128.76, 132.73, 137.04, 198.83, 213.89; HRMS calcd for $C_{25}H_{24}O_2Na^+$ $(M+Na)^+$ 379.1669, found 379.1672. The ee was determined by HPLC analysis (Chiralpak AD-H, *i*-PrOH/hexane=10:90, 1.0 mL/min, 254 nm, t_R (minor)=13.26 min, t_R (major)=26.39 min), 88% ee; $[\alpha]_D^{20}$=−179.5 (*c* 0.81, CH_2Cl_2).

*4.3.9. (S)-2-((R)-3-(4-Methoxyphenyl)-3-oxo-1-phenylprop-yl)cyclohexanone (**6i**)*[7]. The ee was determined by HPLC analysis (Chiralpak AD-H, *i*-PrOH/hexane=10:90, 1.0 mL/min, 254 nm, t_R (minor)=66.36 min, t_R (major)=71.18 min), 85% ee; $[\alpha]_D^{20}$=−8.9 (*c* 0.81, CH_2Cl_2).

*4.3.10. (S)-2-((R)-3-(4-Nitrophenyl)-3-oxo-1-phenylpropyl)-cyclohexanone (**6j**)*[15]. The ee was determined by HPLC analysis (Chiralpak OD-H, *i*-PrOH/hexane=10:90, 1.0 mL/min, 254 nm, t_R (minor)=20.88 min, t_R (major)=31.39 min), 80% ee; $[\alpha]_D^{20}$=−37.2 (*c* 0.80, CH_2Cl_2).

*4.3.11. (S)-2-((R)-3-(4-Bromophenyl)-3-oxo-1-phenylprop-yl)cyclohexanone (**6k**). syn/anti*=>99:1 (by ^{1}H NMR); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18–1.27 (m, 1H), 1.53–1.80 (m, 4H), 1.96–2.01 (m, 1H), 2.35–2.43 (m, 1H), 2.47–2.53 (m, 1H), 2.71 (dt, 1H, J_1=10.0 Hz, J_2=4.8 Hz), 3.13 (dd, 1H, J_1=9.6 Hz, J_2=15.6 Hz), 3.48 (dd, 1H, J_1=4.0 Hz, J_2=16.0 Hz), 3.65 (dt, 1H, J_1=10.0 Hz, J_2=4.0 Hz), 7.12–7.18 (m, 3H), 7.23–7.27 (m, 2H), 7.55 (d, 2H, J=8.4 Hz), 7.78 (d, 2H, J=8.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 22.63, 25.34, 28.57, 31.57, 41.43, 44.36, 55.78, 126.72, 128.26, 128.53, 129.76, 131.75, 135.76, 141.71, 197.87, 214.22; HRMS calcd for $C_{21}H_{22}BrO_2^+$ $(M+H)^+$ 385.0798, found 385.0800. The ee was determined by HPLC analysis (Chiralpak AD-H, *i*-PrOH/hexane=10:90, 1.0 mL/min, 254 nm, t_R (major)=28.83 min, t_R (minor)=31.29 min), 86% ee; $[\alpha]_D^{20}$=−25.9 (*c* 0.81, CH_2Cl_2).

*4.3.12. (S)-2-((R)-3-(Naphthalen-3-yl)-3-oxo-1-phenylprop-yl)cyclohexanone (**6l**). syn/anti*=>99:1 (by ^{1}H NMR); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23–1.33 (m, 1H), 1.51–1.83 (m, 4H), 1.97–2.04 (m, 1H), 2.29–2.46 (m, 1H), 2.51–2.61 (m, 1H), 2.77 (dt, 1H, J_1=10.2 Hz, J_2=5.1 Hz), 3.34 (dd, 1H, J_1=9.6 Hz, J_2=15.9 Hz), 3.63 (dd, 1H, J_1=3.9 Hz, J_2=15.9 Hz), 3.78 (dt, 1H, J_1=9.9 Hz, J_2=3.9 Hz), 7.16–7.32 (m, 5H), 7.50–7.59 (m, 2H), 7.81–7.84 (m, 2H), 7.92–7.97 (m, 2H), 8.49 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 24.13, 28.60, 32.53, 41.42, 42.38, 44.36, 55.91, 124.02, 126.59, 126.65, 127.70, 128.25, 128.29, 128.50, 129.65, 129.95, 132.52, 136.30, 135.48, 141.97, 198.76, 213.80; HRMS calcd for $C_{25}H_{24}O_2Na^+$ $(M+Na)^+$379.1669, found 379.1663. The ee was determined by HPLC analysis (Chiralpak AD-H, *i*-PrOH/hexane=10:90, 1.0 mL/min, 254 nm, t_R (major)=25.86 min, t_R (minor)=34.87 min), 86% ee; $[\alpha]_D^{20}$=−41.0 (*c* 0.80, CH_2Cl_2).

*4.3.13. (S)-2-((R)-1-(2-Chlorophenyl)-3-(4-methoxyphenyl)-3-oxo-propyl)cyclohexanone (**6m**)*[8]. The ee was determined by HPLC analysis (Chiralpak AD-H, *i*-PrOH/hexane=30:70, 1.0 mL/min, 254 nm, t_R (minor)=15.14 min, t_R (major)=28.04 min), 89% ee; $[\alpha]_D^{20}$=−76.0 (*c* 0.80, CH_2Cl_2).

*4.3.14. (R)-Tetrahydro-3-((R)-3-oxo-1,3-diphenylpropyl)-pyran-4-one (**6n**). syn/anti*=93:7 (by ^{1}H NMR); ^{1}H NMR (400 MHz, $CDCl_3$): δ2.39–2.43 (m, 1H), 2.64–2.74 (m, 2H), 2.86–3.02 (m, 4H), 7.19–7.24 (m, 3H), 7.38–7.42 (m, 3H), 7.47–7.51 (m, 2H), 7.87 (d, 2H, J=6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 38.79, 42.37, 43.78, 57.14, 68.85, 71.14, 125.54, 127.02, 128.03, 128.20, 128.48, 128.75, 132.93, 136.97, 141.15, 198.02, 208.96; HRMS calcd for $C_{20}H_{20}O_3Na^+$ $(M+Na)^+$ 330.6464, found 330.6468. The ee was determined by HPLC analysis (Chiralpak AD-H, *i*-PrOH/hexane=15:85, 0.7 mL/min, 254 nm, t_R (minor)=25.92 min, t_R (major)=27.39 min), 84% ee; $[\alpha]_D^{20}$=−25.7 (*c* 0.80, CH_2Cl_2).

*4.3.15. (2S)-4-Methyl-2-((R)-3-oxo-1,3-diphenylpropyl)-cyclohexanone (**6o**). syn/anti*=>99:1 (by ^{1}H NMR); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (d, 3H, J=6.6 Hz), 1.25–1.35 (m, 1H), 1.40–1.54 (m, 2H), 2.00–2.09 (m, 1H), 2.11–2.21 (m, 1H), 2.63–2.74 (m, 2H), 3.19 (dd, 1H, J_1=4.5 Hz, J_2=17.4 Hz), 3.35 (dd, 1H, J_1=8.4 Hz, J_2=17.4 Hz), 3.82–3.90 (m, 1H), 7.16–7.31 (m, 5H), 7.35–7.40 (m, 2H), 7.47–7.52 (m, 1H), 7.83 (d, 2H, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 20.65, 26.23, 35.25, 37.82, 38.82, 40.84, 43.93, 54.89, 126.78, 127.99, 128.10, 128.44, 128.67, 132.91, 137.00, 142.14, 198.26, 215.07. The ee was determined by HPLC analysis (Chiralpak AD-H, *i*-PrOH/hexane=10:90, 1.0 mL/min, 254 nm, t_R (minor)=12.86 min, t_R (major)=13.38 min), 86% ee; $[\alpha]_D^{20}$=−45.2 (*c* 0.81, CH_2Cl_2).

*4.3.16. (R)-1-Methyl-3-((R)-3-oxo-1,3-diphenylpropyl)piperidin-4-one (**6p**)*[16]. The ee was determined by HPLC analysis (Chiralpak AD-H, *i*-PrOH/hexane=20:80, 0.6 mL/min, 254 nm, t_R (minor)=17.46 min, t_R (major)=22.31 min), 84% ee; $[\alpha]_D^{20}$=−63.4 (*c* 0.81, CH_2Cl_2).

*4.3.17. (S)-2-((R)-3-Oxo-1,3-diphenylpropyl)cyclopentanone (**6q**)*[17]. The ee was determined by HPLC analysis (Chiralpak OD-H, *i*-PrOH/hexane=10:90, 1.0 mL/min, 254 nm, t_R (major)=8.10 min, t_R (minor)=10.62 min), 71% ee; $[\alpha]_D^{20}$=−33.5 (*c* 0.79, CH_2Cl_2).

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Supplementary data

Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2009.09.001.

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