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Thiophosphoramide catalyzed asymmetric Michael addition of cyclopentanone to chalcones

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ABSTRACT

Thiophosphoramide **1b** was found to be an effective bifunctional organocatalyst in the asymmetric Michael reaction of cyclopentanone to various chalcones, affording the corresponding adducts in satisfactory yields with moderate to excellent diastereo- (up to 90/10 dr) and enantioselectivities (up to 92% ee).

1. Introduction

The asymmetric Michael addition reaction, which enables access to a variety of optically active adducts, is widely recognized as one of the most powerful carbon–carbon bond-forming reactions in organic synthesis.[1] Over the past decade, significant progress has been made in the field of organocatalyzed asymmetric Michael addition to highly active Michael acceptors, such as nitroolefins.[2] In contrast, the organocatalyzed asymmetric Michael additions of less reactive α,β-unsaturated ketones have received little attention. Jørgensen developed the highly enantioselective chiral imidazolidine catalyzed addition of nitroalkanes[3] and malonates[4] to α,β-unsaturated enones. Asymmetric intramolecular and intermolecular Michael reactions of aldehydes with enones have been achieved in the presence of chiral imidazolidinones[5] or chiral pyrrolidines.[6] Most recently, the asymmetric vinylogous Michael reactions of α,β-unsaturated ketones with γ-butenolide were also documented.[7] We noticed that organocatalytic asymmetric Michael addition reactions of simple ketones, especially cyclopentanones, with chalcones still remain a challenge, probably due to the low reactivity and high steric hindrance of the substrates. Employing (*S*)-pyrrolidinesulfonamide[8] and (*S*)-prolinol ether[9] as the catalysts, highly enantioselective Michael additions of cyclohexanone to chalcones were realized. However, the reaction of cyclopentanone and chalcone gave only 73% and 71% ee, respectively. Therefore, the development of a novel organocatalytic system to achieve highly enantioselective Michael additions of the problematic cyclopentanone to chalcones remains a major challenge in synthetic organic chemistry. Herein, we report the asymmetric Michael addition of cyclopentanone to chalcones catalyzed by a chiral bifunctional thiophosphoramide catalyst, affording the corresponding adducts with good to excellent enantioselectivities.[10]

2. Results and discussion

Recently, we have demonstrated that functionalized thiophosphoramides can function as efficient hydrogen-bond donor catalysts in asymmetric nitro-Michael addition reactions.[11] Hence, a series of chiral pyrrolidine-based thiophoramide catalysts **1a–d** were chosen as catalyst candidates (Fig. 1); the conjugate addition of cyclopentanone to chalcone **2a** was selected as a model reaction.

At first, the conjugate addition to chalcone **2a** was performed in neat cyclopentanone in the presence of 20 mol % of each of these catalysts as well as 10 mol % of benzoic acid as cocatalyst (Table 1). The results listed in Table 1 indicate that all the thiophosphoramide catalysts tested are active for this transformation. However, both the diastereo- and enantioselectivity are highly dependent on the substituents at the phosphorus atom. For example, the use of acyclic thiophosphoramidate catalysts **1a** and **1b** resulted in the formation of an *anti*-diastereomer as the major product, whereas *syn*-selectivity was observed for the cyclic thiophosphoramidate catalysts **1c**, **1d** (Table 1, entries 1 and 2 vs entries 3–5). Moreover, thiophosphoramidate (*S*,a*R*)-**1d** and (*R*,a*R*)-**1d** both bearing an (*R*)-binaphthol skeleton derived from L- and D-proline, respectively, afforded product **3a** with opposite stereochemistry, indicating that the stereochemistry of the newly formed stereogenic center is determined by the chirality of the pyrrolidine part rather than that of the binaphthol. In terms of enantioselectivity of the major diastereomer, catalyst **1b** gave the best results. Hence we chose thiophosphoramide **1b** as the catalyst for further optimization.[12]

To further improve the diastereo- and enantioselectivity of this reaction, the effect of different solvents on the reaction was investigated in the presence of 20 mol % catalyst **1b** and 10 mol % benzoic acid. In general, a marked decrease in reaction rate was observed when performing the reaction in a different solvent (Table 1, entries 6–10). However, the employment of toluene as a solvent resulted in a dramatical improvement both in terms of the diastereo- and enantioselectivity of the reaction, providing the

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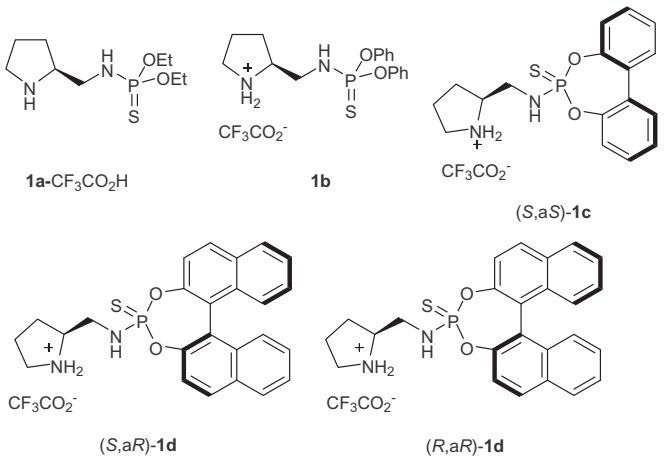
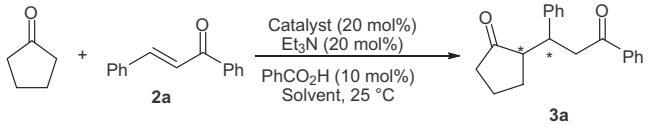


Figure 1. Different pyrrolidine-based organocatalysts.

anti-diastereomer with an ee value of 92% as the major product. No improvement in results was obtained by either adjusting the catalyst loading (Table 1, entry 11 vs entry 10) or changing the co-catalyst.[13]

Table 1
Catalyst evaluation and optimization of reaction conditions[a]



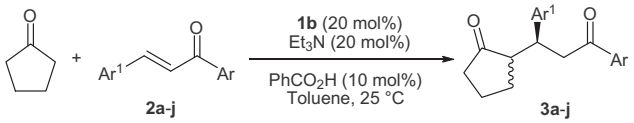
Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)	*anti*/*syn*[c]	Ee[d] (%)
1	**1a**	Neat	11	55	69/31	66/100
2	**1b**/Et_3N	Neat	36	68	67/33	71/98
3	**1c**/Et_3N	Neat	26	79	28/72	70/66
4	(*S*,a*R*)-**1d**/Et_3N	Neat	26	80	38/62	74/49
5	(*R*,a*R*)-**1d**/Et_3N	Neat	11	82	26/74	−61/−66
6	**1b**/Et_3N	EtOH	6 d	75	68/32	74/74
7	**1b**/Et_3N	CH_2Cl_2	10 d	62	85/15	71/62
8	**1b**/Et_3N	CH_3CN	7 d	85	82/18	77/69
9	**1b**/Et_3N	THF	10 d	50	87/13	68/65
10	**1b**/Et_3N	$PhCH_3$	7 d	98	90/10	92/77
11[e]	**1b**/Et_3N	$PhCH_3$	10 d	50	84/16	80/62

[a] Reaction conditions: cyclopentanone (2 mmol, 10 equiv), chalcone **2a** (0.2 mmol) in solvent (0.5 mL), 25 °C.
[b] Yield of the isolated product after chromatography on silica gel.
[c] Determined by ^1H NMR.
[d] Determined by Chiral HPLC analysis.
[e] With 15 mol % of catalyst **1b**.

With the optimized reaction conditions in hand, we next studied the generality of the reaction with a variety of chalcones. The results were summarized in Table 2.

As shown in Table 2, the reaction has a broad applicability with respect to chalcones. However, the enantioselectivity of the reaction is greatly dependent on the nature of the chalcone substrates. Unsubstituted chalcone **2a** was the optimal substrate, giving the conjugate addition product **3a** with a high level of enantioselectivity (Table 2, entry 1, 92% ee). The introduction of a substituent on either Ar or Ar^1 led to a decrease in enantioselectivity, affording the desired product with only moderate ee values (ranging from 58% to 71% ee for the major diastereomer, Table 2, entries 2–10). Moreover, when Ar was a phenyl group (Table 2, entries 1–6), although the electronic nature of the substituents on Ar^1 in the chalcones

Table 2
Substrate scope of **1b** catalyzed asymmetric Michael addition of cyclopentanone to chalcones[a]



Entry	Ar, Ar^1	Time (d)	Yield[b] (%)	*anti*/*syn*[c]	Ee[d] (%)
1	Ph, Ph **a**	7	98	90/10	92/77
2	Ph, 2-$NO_2C_6H_4$ **b**	10	42	60/40	71/71
3	Ph, 4-$CF_3C_6H_4$ **c**	3	90	65/35	66/61
4	Ph, 4-BrC_6H_4 **d**	6	93	71/29	61/58
5	Ph, 4-MeC_6H_4 **e**	6	77	90/10	62/46
6	Ph, 4-$MeOC_6H_4$ **f**	7	54	85/15	65/63
7	4-BrC_6H_4, Ph **g**	2	89	80/20	59/55
8	4-$NO_2C_6H_4$, 2-$MeOC_6H_4$ **h**	2	83	60/40	64/27
9	4-$NO_2C_6H_4$, 4-$MeOC_6H_4$ **i**	6	59	64/36	60/51
10	4-MeC_6H_4, Ph **j**	10	64	72/28	58/53

[a] Reaction conditions: cyclopentanone (2 mmol, 10 equiv), chalcones **2** (0.2 mmol) in toluene (0.5 mL), 25 °C.
[b] Yield of the isolated product after chromatography on silica gel.
[c] Determined by ^1H NMR.
[d] Determined by chiral HPLC analysis.

did not influence the enantioselectivity, the diastereoselectivity of the reaction was significantly influenced by the nature of the substituents on Ar^1. Generally, an electron-donating group on Ar^1 is obviously favorable for the *anti*-selectivity of the reaction, while the introduction of an electron-withdrawing group on Ar^1 resulted in marked decrease in diastereoselectivity (Table 2, entries 5 and 6 vs entries 2–4).

The relative and absolute configuration of the compounds **3a** and **3j** were determined by comparison of specific rotation values and the retention times of each stereomer in the chiral HPLC spectra with the reported results in the literature.[10] The stereochemistry of the other products was assigned by analogy.

Based on the experimental results, a possible transition state for this reaction was proposed to account for the observed diastereo- and enantioselectivity. As shown in Fig. 2, the free base of **1b** functioned as a bifunctional catalyst. The pyrrolidine ring will first react with cyclopentanone to form an enamine with the aid of benzoic acid. Subsequently, the acidic hydrogen will activate and orientate the carbonyl group of chalcone through a hydrogen-bonding interaction so that the enamine will undertake preferentially nucleophilic attack from its *Re*-face onto the *Re*-face of the chalcone to give the (*S*,*S*)-product as the major stereoisomer.

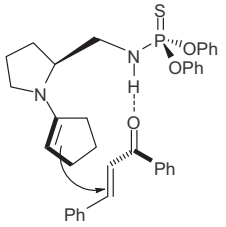


Figure 2. Possible transition state for the present reaction.

3. Conclusions

We have demonstrated that chiral pyrrolidine-based thiophosphoramides are efficient catalysts for the asymmetric Michael addition of cyclopentanone to chalcone. In the presence of 20 mol % of **1b**, the reaction of different chalcones proceeded smoothly to afford the corresponding adducts with moderate to excellent levels of diastereo- and enantioselectivities.

4. Experimental

4.1. General procedure for thiophosphoramide 1b catalyzed asymmetric Michael addition of cyclopentanone to chalcones

A mixture of thiophosphoramide **1b** (0.04 mmol), triethylamine (0.04 mmol) and cyclopentanone (2 mmol, 10 equiv) in toluene (0.5 mL) was stirred at 25 °C for 15 min. Then, benzoic acid (2.4 mg, 0.02 mmol) was added, and the reaction mixture was stirred for 15 min. To the resulting mixture was added chalcone **2** (0.2 mmol) at the same temperature. After the reaction was complete (monitored by TLC), the mixture was purified by column chromatography on silica gel (100–200 mesh, PE/EtOAc) to afford the desired conjugate addition product **3**.

4.1.1. 2-((*S*)-3-Oxo-1,3-diphenylpropyl)cyclopentanone 3a

Pale yellow solid, 98% yield, mp 74 °C. $[\alpha]_D^{20} = -25.4$ (*c* 1.0, $CHCl_3$), *syn*/*anti*: 10/90, 77% ee for *syn*-isomer and 92% ee for *anti*-isomer. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.48–1.94 (m, 4H), 2.02–2.12 (m, 1H), 2.21–2.28 (m, 1H), 2.42–2.54 (m, 1H), 3.36 (dd, *J* = 7.6 and 16.8 Hz, 0.90H), 3.47 (dd, *J* = 10.0 and 20.0 Hz, 0.10H), 3.68–3.90 (m, 2H), 7.15–7.28 (m, 5Harom), 7.39–7.53 (m, 3Harom), 7.90–7.98 (m, 2Harom). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 20.2 (*anti*), 20.5 (*syn*), 27.1 (*syn*), 27.9 (*anti*), 38.8 (*anti*), 39.6 (*syn*), 40.8 (*anti*), 41.0 (*syn*), 42.9, 52.9 (*anti*), 53.0 (*syn*), 126.6 (*anti*), 126.7 (*syn*), 128.0 (*anti*), 128.1 (*syn*), 128.2, 128.3, 128.4, 128.5, 132.8, (*anti*), 133.0 (*syn*), 137.0, 142.3 (*syn*), 142.5 (*anti*), 198.6 (*anti*), 199.0 (*syn*), 219.8 (*anti*), 220.5 (*syn*). HRMS (ESI) *m*/*z* calcd for $C_{20}H_{20}O_2$ $[M+Na]^+$: 315.1355, found 315.1355. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, wavelength = 220 nm): R_t = 16.96 (major, *syn*-isomer), 20.38 (minor, *syn*-isomer), 31.53 (major, *anti*-isomer) and 50.52 min (minor, *anti*-isomer).

4.1.2. 2-((*S*)-3-Oxo-3-phenyl-1-(4-trifluoromethylphenyl)-propyl)cyclopentanone 3b

Yellowish-green oil, 42% yield, $[\alpha]_D^{20} = -93.4$ (*c* 1.0, $CHCl_3$), *syn*/*anti*: 40/60, 71% ee for *syn*-isomer and 71% ee for *anti*-isomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.68–1.74 (m, 2H), 1.79–1.88 (m, 1H), 2.00–2.10 (m, 1H), 2.22–2.37 (m, 2H), 2.55–2.73 (m, 1H), 3.40 (dd, *J* = 10.0 and 18.0 Hz, 0.60H), 3.59 (d, *J* = 6.8 Hz, 0.40H), 4.10–4.39 (m, 2H), 7.29–7.32 (m, 1Harom), 7.38–7.44 (m, 2Harom), 7.46–7.53 (m, 3Harom), 7.74 (t, *J* = 8.0 Hz, 1Harom), 7.87–7.90 (m, 2Harom). ^{13}C NMR (100.6 MHz, $CDCl_3$): 20.2 (*anti*), 20.4 (*syn*), 27.2 (*syn*), 29.0 (*anti*), 34.2 (*anti*), 35.0 (*syn*), 38.8 (*anti*), 39.0 (*syn*), 40.8 (*syn*), 43.0 (*anti*), 51.9 (*anti*), 53.0 (*syn*), 124.1 (*anti*), 124.3 (*syn*), 127.1 (*anti*), 127.2 (*syn*), 128.0, 128.4 (*anti*), 128.5 (*anti*), 128.7 (*syn*), 128.9 (*syn*), 132.3 (*syn*), 132.5 (*anti*), 133.0 (*anti*), 133.2 (*syn*), 136.4 (*anti*), 137.0 (*syn*), 150.7 (*syn*), 150.8 (*anti*), 197.5 (*syn*), 197.7 (*anti*), 218.9 (*syn*), 219.6 (*anti*). HRMS (ESI) *m*/*z* calcd for $C_{20}H_{19}NO_4$ $[M+Na]^+$: 320.1206, found 320.1208. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 60:40, flow rate = 1.0 mL/min, wavelength = 220 nm): R_t = 8.89 (major, *syn*-isomer), 10.60 (minor, *syn*-isomer), 15.01 (major, *anti*-isomer) and 33.45 min (major, *anti*-isomer).

4.1.3. 2-((*S*)-3-Oxo-3-phenyl-1-(4-trifluoromethylphenyl)-propyl)cyclopentanone 3c

Yellow oil, 90% yield, $[\alpha]_D^{20} = -23.2$ (*c* 1.1, $CHCl_3$), *syn*/*anti*: 35/65, 61% ee for *syn*-isomer and 66% ee for *anti*-isomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44–1.76 (m, 2H), 1.84–1.94 (m, 2H), 1.99–2.16 (m, 1H), 2.25–2.33 (m, 1H), 2.45–2.57 (m, 1H), 3.39 (dd, *J* = 8.0 and 17.2 Hz, 0.65H), 3.54 (dd, *J* = 8.0 and 17.2 Hz, 0.35H), 3.70–3.80 (m, 1H), 3.84–3.96 (m, 1H), 7.36 (d, *J* = 8.0 Hz, 2Harom), 7.44 (d, *J* = 8.0 Hz, 2Harom), 7.52–7.57 (m, 3Harom), 7.90–7.96 (m, 2Harom). ^{13}C NMR (100.6 MHz, $CDCl_3$): 20.2 (*anti*), 20.4 (*syn*), 27.0 (*syn*), 28.0 (*anti*), 38.7 (*anti*), 39.4 (*syn*), 40.5 (*anti*), 40.6 (*syn*), 42.5, 52.6 (*anti*), 53.2 (*syn*), 125.4, 128.0, 128.1, 128.6, 128.7, 128.8, 133.1, 133.2, 136.8, 146.5, 146.7, 198.0 (*anti*), 198.3 (*syn*), 219.2 (*anti*), 219.7 (*syn*). HRMS (ESI) *m*/*z* calcd for $C_{21}H_{19}F_3O_2$ $[M+Na]^+$: 383.1229, found 383.1236. HPLC analysis (Chiralpak OD-H column, hexane/2-propanol = 99:1, flow rate = 1.0 mL/min, wavelength = 220 nm): R_t = 24.35 (minor, *syn*-isomer), 26.60 (major, *syn*-isomer), 30.56 (minor, *anti*-isomer) and 33.92 min (major, *anti*-isomer).

4.1.4. 2-((*S*)-1-(4-Bromophenyl)-3-oxo-3-phenylpropyl)-cyclopentanone 3d

Yellow oil, 93% yield, $[\alpha]_D^{20} = -27.4$ (*c* 1.0, $CHCl_3$), *syn*/*anti*: 29/71, 58% ee for *syn*-isomer and 60% ee for *anti*-isomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45–1.73 (m, 2H), 1.83–1.94 (m, 2H), 2.02–2.11 (m, 1H), 2.23–2.30 (m, 1H), 2.40–2.52 (m, 1H), 3.31 (dd, *J* = 8.0 and 16.8 Hz, 0.71H), 3.48 (dd, *J* = 9.6 and 18.8 Hz, 0.29H), 3.65–3.74 (m, 1.29H), 3.85 (dd, *J* = 5.6 and 17.2 Hz, 0.71H), 7.10 (d, *J* = 8.4 Hz, 2Harom), 7.38 (d, *J* = 8.4 Hz, 2Harom), 7.40–7.54 (m, 3Harom), 7.89–7.96 (m, 2Harom). ^{13}C NMR (100.6 MHz, $CDCl_3$): 20.2 (*anti*), 20.4 (*syn*), 27.1 (*syn*), 27.8 (*anti*), 38.7 (*anti*), 39.6 (*syn*), 40.2 (*syn*), 40.3 (*anti*), 40.7 (*syn*), 42.6 (*anti*), 52.7 (*anti*), 53.0 (*syn*), 120.4 (*anti*), 120.5 (*syn*), 128.0 (*anti*), 128.1 (*syn*), 128.5, 130.0 (*anti*), 130.2 (*syn*), 131.4 (*anti*), 131.5 (*syn*), 133.0 (*anti*), 133.1 (*syn*), 136.9, 141.3 (*syn*), 141.4 (*anti*), 198.2 (*anti*), 198.5 (*syn*), 219.3 (*anti*), 220.1 (*syn*). HRMS (ESI) *m*/*z* calcd for $C_{20}H_{19}{}^{79}BrO_2$ $[M+Na]^+$: 398.0461, found 398.0468. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 220 nm): R_t = 13.99 (major, *syn*-isomer), 21.95 (minor, *syn*-isomer), 24.39 (major, *anti*-isomer) and 31.10 min (minor, *anti*-isomer).

4.1.5. 2-((*S*)-1-(4-Methylphenyl)-3-oxo-3-phenylpropyl)-cyclopentanone 3e

Yellow oil, 77% yield, $[\alpha]_D^{20} = -39.2$ (*c* 1.0, $CHCl_3$), *syn*/*anti*: 10/90, 46% ee for *syn*-isomer and 62% ee for *anti*-isomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.51–1.58 (m, 1H), 1.65–1.75 (m, 1H), 1.86–1.90 (m, 2H), 2.03–2.12 (m, 1H), 2.21–2.24 (m, 1H), 2.29 (s, 3H), 2.45 (q, *J* = 8.4 Hz, 1H), 3.34 (dd, *J* = 7.2 and 16.8 Hz, 0.90H), 3.45 (dd, *J* = 6.0 and 16.0 Hz, 0.10H), 3.67 (dd, *J* = 7.2 and 14.0 Hz, 1H), 3.84 (dd, *J* = 6.0 and 16.8 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 2Harom), 7.11 (d, *J* = 8.4 Hz, 2Harom), 7.42 (t, *J* = 7.6 Hz, 2Harom), 7.52 (t, *J* = 7.2 Hz, 1Harom), 7.91–7.99 (m, 2Harom). ^{13}C NMR (100.6 MHz, $CDCl_3$): 20.1 (*anti*), 20.4 (*syn*), 20.9, 27.0 (*syn*), 27.7 (*anti*), 38.7 (*anti*), 39.6 (*syn*), 40.3 (*anti*), 40.5 (*syn*), 40.8 (*syn*), 42.9 (*anti*), 52.9 (*anti*), 53.0 (*syn*), 127.9, 128.0, 128.4, 129.0, 132.7 (*anti*), 132.9 (*syn*), 135.9 (*anti*), 136.1 (*syn*), 137.0, 139.1 (*syn*), 139.3 (*anti*), 198.6 (*anti*), 199.0 (*syn*), 219.8 (*anti*), 220.5 (*syn*). HRMS (ESI) *m*/*z* calcd for $C_{21}H_{22}O_2$ $[M+Na]^+$: 329.1512, found 329.1508. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, wavelength = 220 nm): R_t = 17.90 (major, *syn*-isomer), 23.96 (minor, *syn*-isomer), 30.49 (major, *anti*-isomer) and 35.19 min (minor, *anti*-isomer).

4.1.6. 2-((*S*)-1-(4-Methoxyphenyl)-3-oxo-3-phenylpropyl)-cyclopentanone 3f

Yellow oil, 54% yield, $[\alpha]_D^{20} = -30.2$ (*c* 1.0, $CHCl_3$), *syn*/*anti*: 15/85, 63% ee for *syn*-isomer and 65% ee for *anti*-isomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.50–1.60 (m, 1H), 1.67–1.79 (m, 1H), 1.90–1.92 (m, 2H), 2.02–2.11 (m, 1H), 2.23–2.29 (m, 1H), 2.41–2.51 (m, 1H), 3.35 (dd, *J* = 7.6 and 16.4 Hz, 0.85H), 3.47 (dd, *J* = 6.4 and 16.4 Hz, 0.15H), 3.69 (dd, *J* = 7.2 and 14.0 Hz, 1H), 3.77 (s, 3H), 3.83 (dd, *J* = 6.0 and 16.8 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 2Harom), 7.15 (d, *J* = 8.4 Hz, 2Harom), 7.42–7.54 (m, 3Harom), 7.92–8.00 (m, 2Harom). ^{13}C NMR (100.6 MHz, $CDCl_3$): 20.2 (*anti*), 20.5 (*syn*), 27.1 (*syn*), 27.6 (*anti*), 38.8 (*anti*), 39.7 (*syn*), 40.0 (*syn*), 41.1 (*anti*),

43.0, 53.0, 55.1, 113.7, 128.0 (*anti*), 128.1 (*syn*), 128.4, 129.2 (*anti*), 129.4 (*syn*), 132.8 (*anti*), 132.9 (*syn*), 134.1 (*syn*), 134.3 (*anti*), 137.0, 158.1 (*anti*), 158.2 (*syn*), 198.7 (*anti*), 199.1 (*syn*), 219.9 (*anti*), 220.8 (*syn*). HRMS (ESI) *m*/*z* calcd for $C_{21}H_{22}O_3$ $[M+Na]^+$: 345.1461, found 345.1458. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 75:25, flow rate = 1.0 mL/min, wavelength = 220 nm): R_t = 10.56 (major, *syn*-isomer), 15.35 (minor, *syn*-isomer), 16.61 (major, *anti*-isomer) and 21.10 min (minor, *anti*-isomer).

4.1.7. 2-((*S*)-3-(4-Bromophenyl)-3-oxo-1-phenylpropyl)-cyclopentanone 3g

White solid, 89% yield, mp 110–112 °C, $[\alpha]_D^{20} = -21.6$ (*c* 1.0, $CHCl_3$), *syn*/*anti*: 20/80, 55% ee for *syn*-isomer and 59% ee for *anti*-isomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.52–1.97 (m, 4H), 2.09–2.18 (m, 1H), 2.24–2.33 (m, 1H), 2.43–2.57 (m, 1H), 3.32 (dd, *J* = 7.6 and 16.8 Hz, 0.80H), 3.45 (dd, *J* = 10.6 and 17.2 Hz, 0.20H), 3.63–3.82 (m, 1.20H), 3.90 (dd, *J* = 6.0 and 16.8 Hz, 0.80H), 7.19–7.32 (m, 5Harom), 7.58 (d, *J* = 8.8 Hz, 2Harom), 7.80 (d, *J* = 8.4 Hz, 1.60Harom), 7.86 (d, *J* = 8.8 Hz, 0.40Harom). ^{13}C NMR (100.6 MHz, $CDCl_3$): 20.2 (*anti*), 20.5 (*syn*), 27.0 (*syn*), 28.2 (*anti*), 38.8 (*anti*), 39.6 (*syn*), 40.8 (*syn*), 41.0 (*anti*), 43.4, 52.8 (*anti*), 53.0 (*syn*), 126.7 (*anti*), 126.8 (*syn*), 128.0 (*syn*), 128.1 (*anti*), 128.3 (*syn*), 128.4 (*anti*), 128.5, 131.8 (*anti*), 131.9 (*syn*), 135.7 (*syn*), 135.8 (*anti*), 142.0 (*syn*), 142.4 (*anti*), 197.6 (*anti*), 198.1 (*syn*), 219.9 (*anti*), 220.6 (*syn*). HRMS (ESI) *m*/*z* calcd for $C_{20}H_{19}{}^{79}BrO_2$ $[M+Na]^+$: 393.0461, found 393.0470. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 60:40, flow rate = 1.0 mL/min, wavelength = 220 nm): R_t = 9.36 (major, *syn*-isomer), 12.71 (minor, *syn*-isomer), 14.80 (major, *anti*-isomer) and 26.01 min (minor, *anti*-isomer).

4.1.8. 2-((*S*)-1-(2-Methoxyphenyl)-3-(4-nitrophenyl)-3-oxopropyl)cyclopentanone 3h

Yellow oil, 59% yield, $[\alpha]_D^{20} = -16.8$ (*c* 0.70, $CHCl_3$), *syn*/*anti*: 40/60, 27% ee for *syn*-isomer and 64% ee for *anti*-isomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.58–1.89 (m, 3H), 1.92–2.11 (m, 1.5H), 2.21–2.33 (m, 1.5H), 2.55–2.71 (m, 1H), 3.37 (dd, *J* = 8.4 and 16.8 Hz, 0.60H), 3.41 (dd, *J* = 7.6 and 16.4 Hz, 0.40H), 3.66–3.74 (m, 1H), 3.77 (s, 3H), 4.12 (dd, *J* = 4.8 and 16.4 Hz, 0.60H), 4.28–4.32 (m, 0.40H), 6.84–6.90 (m, 2Harom), 7.12–7.21 (m, 2Harom), 8.05 (d, *J* = 8.8 Hz, 1.20Harom), 8.10 (d, *J* = 9.2 Hz, 0.80Harom), 8.25 (d, *J* = 8.8 Hz, 2Harom). ^{13}C NMR (100.6 MHz, $CDCl_3$): 20.2 (*anti*), 20.5 (*syn*), 26.7 (*syn*), 29.5 (*anti*), 33.5 (*anti*), 37.8 (*syn*), 38.8 (*syn*), 39.2 (*anti*), 40.5 (*syn*), 42.8 (*anti*), 51.3 (*anti*), 52.0 (*syn*), 55.2, 110.6 (*syn*), 110.9 (*anti*), 120.7, 123.6 (*anti*), 123.7 (*syn*), 127.9 (*syn*), 128.0 (*anti*), 128.4 (*syn*), 129.1 (*anti*), 129.2 (*anti*), 129.8 (*syn*), 130.0 (*syn*), 130.2 (*anti*), 141.6 (*syn*), 142.0 (*anti*), 150.0 (*anti*), 150.2 (*syn*), 157.0 (*syn*), 157.3 (*anti*), 198.0 (*anti*), 198.1 (*syn*), 220.4 (*syn*), 221.2 (*anti*). HRMS (ESI) *m*/*z* calcd for $C_{21}H_{21}NO_5$ $[M+Na]^+$: 390.1312, found 390.1310. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 65:35, flow rate = 1.0 mL/min, wavelength = 220 nm): R_t = 14.46 (major, *syn*-isomer), 15.30 (minor, *anti*-isomer), 16.65 (minor, *syn*-isomer) and 18.36 min (major, *anti*-isomer).

4.1.9. 2-((*S*)-1-(4-Methoxyphenyl)-3-(4-nitrophenyl)-3-oxopropyl)cyclopentanone 3i

Yellow oil, 83% yield, $[\alpha]_D^{20} = -10.0$ (*c* 1.0, $CHCl_3$), *syn*/*anti*: 36/64, 51% ee for *syn*-isomer and 60% ee for *anti*-isomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.48–1.56 (m, 1H), 1.67–1.96 (m, 3H), 2.09–2.18 (m, 1H), 2.22–2.33 (m, 1H), 2.42–2.52 (m, 1H), 3.29 (dd, *J* = 8.0 and 16.8 Hz, 0.64H), 3.45–3.58 (m, 1H), 3.66–3.71 (m, 0.36H), 3.76 (s, 3H), 3.82 (dd, *J* = 3.2 and 16.8 Hz, 0.36H), 3.97 (dd, *J* = 5.6 and 16.8 Hz, 0.64H), 6.81 (d, *J* = 8.8 Hz, 2Harom), 7.10 (d, *J* = 8.8 Hz, 2Harom), 8.04 (d, *J* = 8.8 Hz, 1.28Harom), 8.11 (d, *J* = 8.8 Hz, 0.72Harom), 8.27 (d, *J* = 8.0 Hz, 2Harom). ^{13}C NMR (100.6 MHz, $CDCl_3$): 20.2 (*anti*), 20.5 (*syn*), 27.0 (*anti*), 28.5 (*syn*), 29.7 (*syn*), 38.9 (*anti*), 39.8 (*syn*), 40.5 (*anti*), 41.7 (*syn*), 44.0 (*anti*), 52.9 (*syn*), 55.2 (*anti*), 113.9, 123.8, 129.0 (*anti*), 129.1 (*anti*), 129.2 (*syn*), 129.3 (*syn*), 133.5 (*syn*), 134.2 (*anti*), 141.4 (*syn*), 141.6 (*anti*), 150.1 (*anti*), 150.2 (*syn*), 158.3 (*anti*), 158.5 (*syn*), 197.4 (*anti*), 197.9 (*syn*), 220.2 (*anti*), 221.0 (*syn*). HRMS (ESI) *m*/*z* calcd for $C_{21}H_{21}NO_5$ $[M+Na]^+$: 390.1312, found 390.1312. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 65:35, flow rate = 1.0 mL/min, wavelength = 220 nm): R_t = 18.50 (major, *syn*-isomer), 29.74 (minor, *syn*-isomer), 31.90 (major, *anti*-isomer) and 33.69 min (minor, *anti*-isomer).

4.1.10. 2-((*S*)-1-(4-Methoxyphenyl)-3-(4-nitrophenyl)-3-oxopropyl)cyclopentanone 3j

White solid, 64% yield, mp 126–128 °C. $[\alpha]_D^{20} = -15.3$ (*c* 0.30, $CHCl_3$), *syn*/*anti*: 28/72, 53% ee for *syn*-isomer and 57% ee for *anti*-isomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.60–1.79 (m, 3H), 1.85–1.92 (m, 1H), 2.07–2.13 (m, 1H), 2.18–2.24 (m, 1H), 2.37 (s, 3H), 2.42–2.52 (m, 1H), 3.31 (dd, *J* = 7.6 and 16.8 Hz, 0.28H), 3.41 (dd, *J* = 10.6 and 16.8 Hz, 0.72H), 3.65–3.82 (m, 2H), 7.15–7.23 (m, 7Harom), 7.78–7.86 (m, 2Harom). ^{13}C NMR (100.6 MHz, $CDCl_3$): 20.5 (*anti*), 21.5 (*syn*), 27.1 (*anti*), 29.6 (*syn*), 39.7 (*syn*), 39.6 (*anti*), 40.7 (*anti*), 40.8 (*syn*), 41.0 (*anti*), 42.7 (*syn*), 52.9 (*syn*), 53.0 (*anti*), 26.5, 126.6, 128.1, 128.2, 128.4, 129.1, 134.6, 142.4 (*syn*), 142.5 (*anti*), 143.6 (*syn*), 143.7 (*anti*), 198.2 (*syn*), 198.6 (*anti*), 219.7 (*syn*), 220.4 (*anti*). HRMS (ESI) *m*/*z* calcd for $C_{21}H_{22}O_2$ $[M+Na]^+$: 329.1512, found 329.1511. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 60:40, flow rate = 1.0 mL/min, wavelength = 220 nm): R_t = 9.41 (major, *syn*-isomer), 12.57 (minor, *syn*-isomer), 14.07 (major, *anti*-isomer) and 27.94 min (minor, *anti*-isomer).

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