Organocatalyzed highly stereoselective Michael addition of ketones to alkylidene malonates and nitroolefins using chiral primary-secondary diamine catalysts based on bispidine†

Jie Liu,‡ Zhigang Yang,‡ Xiaohua Liu, Zhen Wang, Yanling Liu, Sha Bai, Lili Lin and Xiaoming Feng*

Received 4th June 2009, Accepted 10th July 2009
First published as an Advance Article on the web 10th August 2009
DOI: 10.1039/b910939k

Organocatalysts containing primary-secondary diamines based on bispidine have been developed to catalyze the asymmetric Michael addition of ketones to alkylidene malonates and nitroalkenes. The corresponding products were obtained in high yields (up to 99%) with high diastereoselectivities (up to 99:1) and high enantioselectivities (up to 97% ee) under mild conditions using either environmentally benign water as the solvent or no solvent.

Introduction

The conjugate addition of carbon nucleophiles to electron poor alkenes is one of the most important carbon–carbon bond forming reactions in organic synthesis.[1] The asymmetric version offers a powerful tool for constructing enantioenriched, highly functionalized carbon skeletons for the total synthesis of natural and biologically active compounds. And thus considerable attention has been given to developing efficient catalytic systems with green reaction conditions during the past decades.[2] Well-designed catalytic enantioselective conjugate additions of ketones or aldehydes to Michael acceptors, such as α,β-unsaturated aldehydes,[3] ketones,[4] sulfones[5] and phosphonates,[6] have recently been reported. In contrast, little progress has been made in the development of alkylidene malonates as Michael acceptors.[7] So far, only the Barbas' and Tang's groups have independently reported pyrrolidine-based diamine and trifluoromethanesulfonamide as organocatalysts for the Michael addition between alkylidene malonates and ketones.[7a,7b] Moreover, nitroalkenes are also the most prominent examples of Michael acceptors.[2h,8] Although the asymmetric Michael reactions of simple aliphatic acyclo- and cycloketones to nitroalkenes have been investigated intensely, the reaction of aromatic ketones has rarely been reported to date.[9] Therefore, the development of efficient organocatalysts for the Michael addition of alkylidene malonates and nitroalkenes is still challenging. Very recently, we have reported bispidine-based primary-secondary diamine catalysts, which were successfully applied to the asymmetric direct aldol reaction of functionalized ketones and conjugate addition of aliphatic ketones to nitroalkenes.[10] In view of the great potential of the bispidine-based primary-secondary diamine catalysts, we would like to further extend the use of these catalysts. Herein, we describe bispidine-based organocatalysts for the asymmetric Michael addition of alkylidene malonates in high yields (up to 99%) with high diastereoselectivities (up to 99:1) and high enantioselectivities (up to 97% ee), as well as the asymmetric Michael reaction of aromatic ketones to nitroolefins in high yields (up to 88%) with high enantioselectivities (up to 96% ee) under operationally simple conditions using environmentally benign water as solvent.

Results and discussion

From the mechanistic perspective, the enamine-catalytic Michael addition and the hydrogen-bond-activated carbonyl group have emerged in a number of enantioselective reactions. In combination with our experiences in previous work,[10] we envisaged that ketone and alkylidene malonates might be synergistically activated by chiral bispidine-based primary-secondary diamine organocatalysts, and hence facilitate the asymmetric Michael addition reaction (Fig. 1).

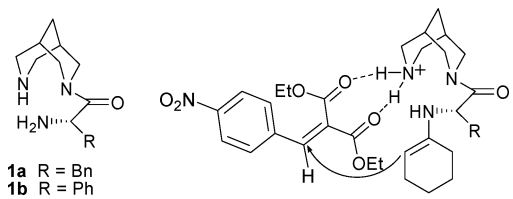


Fig. 1 Catalysts used in this study and proposed strategy for activating the substrates.

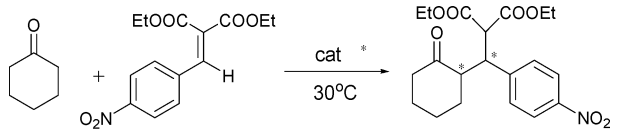
In light of the above consideration, diethyl 2-(4-nitrobenzylidene) malonate and cyclohexanone were selected as the model compounds for catalyst screening. The results are listed in Table 1. Initial studies showed that 20 mol% catalyst **1a** could catalyze the Michael addition to afford the desired product in 38% yield with 78:22 diastereoselectivity and 30% ee (major) (Table 1, entry 1). Further improvement of the yield and ee were achieved by using catalyst **1b** derived from L-phenylglycine (Table 1, entry 2). This result encouraged us to optimize the reaction conditions to further improve the diastereoselectivity and enantioselectivity. To our delight, the addition of acid additives not only accelerated this reaction but also improved ee values (Table 1, entries 3–8).

Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, P. R. China. E-mail: xmfeng@scu.edu.cn; Fax: + 86 28 85418249; Tel: + 86 28 85418249

† Electronic supplementary information (ESI) available: General information; general procedure for the asymmetric Michael reaction; optimization of conditions; spectral characterization data and HPLC conditions for Michael addition products; copies of NMR spectra for Michael addition products; references. See DOI: 10.1039/b910939k

‡ These individuals contributed equally to this work

Table 1 Identification of the most efficient catalyst system and optimization of the reactions[a]



2a **3a** **4a**

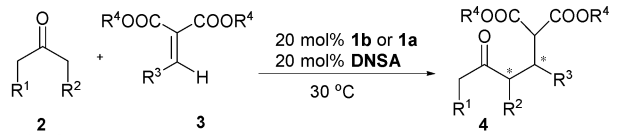
Entry	Catalyst	Solvent	Yield (%)[b]	syn/anti[c]	Ee (%)[c,h]
1	**1a**	–	38	78:22	30(70)
2	**1b**	–	55	84:16	64(79)
3	**1b**/PhCOOH[g]	–	58	73:27	67(86)
4	**1b**/HCOOH[g]	–	26	71:29	63(86)
5	**1b**/TsOH[g]	–	52	84:16	91(89)
6	**1b**/TFA[g]	–	trace	–	–
7	**1b**/TBBP[d,g]	–	99	82:18	95(61)
8	**1b**/DNSA[e,g]	–	99	73:27	93(96)
9[f]	**1b**/DNSA[e,g]	toluene	99	69:31	93(96)
10[f]	**1b**/DNSA[e,g]	THF	99	78:22	94(96)
11[f]	**1b**/DNSA[e,g]	$CHCl_3$	99	76:24	94(96)
12[f]	**1b**/DNSA[e,g]	DMSO	59	90:10	94(97)
13[f]	**1b**/DNSA[e,g]	MeOH	99	77:23	95(98)
14[f]	**1b**/DNSA[e,g]	H_2O	99	98:2	95

[a] Unless noted, reactions were carried out with 0.1 mmol 2-(4-nitrobenzylidene) malonate, 0.5 mL cyclohexanone and 20 mol% catalyst at 30 °C for 72 h. [b] Isolated yield. [c] Determined by HPLC analysis or ^{1}H NMR. [d] TBBP = 3,3′,5,5′-tetrabromobiphenol. [e] DNSA = 3,5-dinitrosalicyclic acid. [f] $V_{cyclohexanone}$:$V_{solvent}$ = 2:1. [g] **1b**/acid = 1/1. [h] Data in parentheses is the ee value of minor product.

Thus, the reaction was best performed using a combination of **1b/DNSA** in 99% yield with 73:27 diastereoselectivity and 93% ee (major) (Table 1, entry 8). Although toluene, MeOH, THF, DMSO and $CHCl_3$ could be employed as the solvents of the reaction to give high enantioselectivities (Table 1, entries 8–13), the optimal procedure was to perform the reaction in water[11] (Table 1, entry 14), which gave a 99% yield with 98:2 diastereoselectivity and 95% ee (major). In this typical Michael reaction, the reaction mixture was a two phase system. Other conditions such as the ratio of the catalyst and acid additives, amount of water and reaction temperature were also investigated, but no superior result was obtained. Through the extensive screening, the optimized catalytic system was found to be **1b/DNSA** = 1/1, 0.1 mmol diethyl 2-(4-nitrobenzylidene) malonate, 0.5 mL cyclohexanone and 0.25 mL H_2O as solvent at 30 °C.

Under the optimized conditions, a variety of alkylidene malonate substrates were investigated, and the corresponding products were obtained in moderate to high yields with high diastereoselectivities (up to 99:1) and excellent ee values (up to 97% ee) (Table 2, entries 1–15). The electronic properties and steric hindrance of the substituents at the aromatic ring had no obvious effect on the diastereoselectivity and enantioselectivity, but affected the yields strongly (Table 2, entries 1–14). Alkylidene malonates with electron-withdrawing groups gave higher yields than those with electron-donating groups (Table 2, entries 1–5, 9, 13, 14 *vs* 6–8, 11). Dimethyl 2-(3-methylbutylidene) malonate proceeded smoothly but gave poor enantioselectivity (Table 2, entry 15). In addition, the reactivity and selectivity were quite sensitive to the size of the malonates (Table 2, entries 1, 13, 16). Excellent enantioselectivity was obtained for less sterically

Table 2 Asymmetric Michael addition reaction of ketones to alkylidene malonates[a]



2 **3** **4**

2a: R^1, R^2 = -$(CH_2)_3$-
2b: R^1 = H, R^2 = H
2c: R^1, R^2 = -$(CH_2)_2$-
2d: R^1 = Me, R^2 = Me

Entry	2	R^3	R^4	4	Yield (%)[b]	syn/anti[c]	Ee (%)[c]
1	**2a**	4-NO_2Ph	Et	**4a**	99	98:2	95
2	**2a**	4-ClPh	Et	**4b**	90	98:2	92
3	**2a**	4-BrPh	Et	**4c**	78	98:2	96
4	**2a**	4-CNPh	Et	**4d**	99	96:4	95
5	**2a**	4-CF_3Ph	Et	**4e**	94	97:3	95
6	**2a**	Ph	Et	**4f**	72	98:2	96
7	**2a**	4-MePh	Et	**4g**	80	98:2	90
8	**2a**	4-MeOPh	Et	**4h**	44	99:1	95
9	**2a**	3-NO_2Ph	Et	**4i**	99	97:3	95
10	**2a**	3,4-Cl_2Ph	Et	**4j**	96	97:3	95
11	**2a**	2-MePh	Et	**4k**	58	95:5	94
12	**2a**	2-naphthyl	Et	**4l**	70	98:2	95
13	**2a**	4-NO_2Ph	Me	**4m**	98	96:4	97[e]
14	**2a**	3-NO_2Ph	Me	**4n**	99	99:1	95
15	**2a**	*i*-Bu	Et	**4o**	82	95:5	30
16	**2a**	4-NO_2Ph	*i*-Pr	**4p**	–	–	–
17[d]	**2b**	4-NO_2Ph	Et	**4q**	85	–	86
18[d]	**2b**	3-NO_2Ph	Et	**4r**	81	–	86
19[d]	**2b**	4-NO_2Ph	Me	**4s**	90	–	87
20[d]	**2b**	3-NO_2Ph	Me	**4t**	92	–	84
21[d]	**2b**	4-NO_2Ph	*i*-Pr	**4u**	33	–	87
22[d]	**2b**	4-NO_2Ph	Bn	**4v**	78	–	85[f]
23[d]	**2c**	4-NO_2Ph	Me	**4w**	51	2:1	75
24[g]	**2d**	4-NO_2Ph	Et	**4x**	14	9:1	81

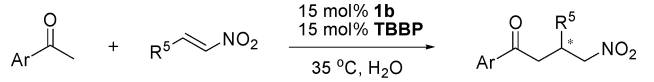
[a] Unless noted, reactions were carried out with 0.1 mmol alkylidene malonate, 0.5 mL cyclohexanone, 0.25 mL H_2O and 20 mol% catalyst (**1b/DNSA** = 1/1) at 30 °C for 3–9 d. [b] Isolated yield. [c] Determined by HPLC analysis or ^{1}H NMR. [d] The reaction was carried out with 0.1 mmol alkylidene malonate, 0.5 mL acetone (cyclopentanone) and 20 mol% catalyst (**1a/DNSA** = 1/1) at 30 °C for 4–5 d. [e] The absolute configuration of the product was (*S*, *S*) and determined by comparison with literature.[7b] [f] The absolute configuration of the product was *R* and determined by comparison with literature.[12c] [g] The procedure is the same as given in footnote *a* but without H_2O.

demanding malonates, while the desired product was not detected for the alkylidene diisopropyl malonates (Table 2, entry 16).

The reaction of other ketones, such as acetone, cyclopentanone and 3-pentanone, with several representative alkylidene malonates was also examined (Table 2, entries 17–24). Interestingly, ketones with different structures worked well in the presence of different catalysts (**1a/DNSA** or **1b/DNAS)**. Generally, these reactions were performed under solvent-free conditions with 20 mol% **1a** (or **1b**) catalyst and 20 mol% **DNSA** as an additive, and gave the corresponding products in good yields and high enantioselectivities. Notably, for alkylidene dimethyl or dibenzyl malonates, the method provides another protocol for producing useful intermediates which can be easily converted to synthetically useful δ-ketoesters and tetrahydroquinoline.[12]

To extend the application of our catalyst, further examination of the substrates focused on the Michael addition of aromatic ketones to nitroolefins (Table 3). First, the conjugate addition of acetophenone to a variety of nitroolefins was investigated

Table 3 Enantioselective Michael addition of aromatic ketones to nitroolefins[a]



5 6 7

Entry	Ar	R^5	7	Yield (%)[b]	Ee (%)[c]
1	Ph	Ph	**7a**	85	93(*R*)[e]
2	Ph	4-MePh	**7b**	83	91(*R*)[e]
3	Ph	4-MeOPh	**7c**	81	90(*R*)[e]
4	Ph	4-NO_2Ph	**7d**	81	87
5	Ph	3-MeOPh	**7e**	70	91(*R*)[e]
6	Ph	3-NO_2Ph	**7f**	80	87(*R*)[e]
7	Ph	2-ClPh	**7g**	52	88(*R*)[e]
8	Ph	2-NO_2Ph	**7h**	43	92
9	Ph	2,4-Cl_2Ph	**7i**	78	94
10	Ph		**7j**	77	92(*R*)[e]
11	Ph	1-naphthyl	**7k**	85	96
12	Ph	2-naphthyl	**7l**	80	90(*R*)[e]
13	Ph	2-furyl	**7m**	58	93
14	4-FPh	Ph	**7n**	70	90(*R*)[e]
15	3-MeOPh	Ph	**7o**	85	91(*R*)[e]
16	2-MePh	Ph	**7p**	42	92
17	2-FPh	Ph	**7q**	62	94
18[d]	2-naphthyl	Ph	**7r**	88	90(*R*)[e]
19	2-furyl	Ph	**7s**	40	79(*R*)[e]

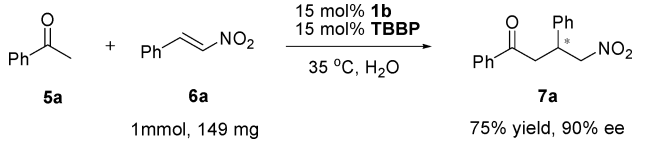
[a] Unless noted, reactions were carried out with 0.1 mmol nitroolefin, aromatic ketone (10 equiv.), 1.0 mL H_2O and 15 mol% catalyst (**1b/TBBP** = 1/1) at 35 °C for 3–4 d. [b] Isolated yield. [c] Determined by HPLC analysis. [d] 0.2 mL CH_2Cl_2 was added. [e] The absolute configurations were determined by comparison with literature.[9b,9c,13]

under similar optimized conditions (**1b/TBBP** = 1/1, 0.1 mmol nitroolefin, 10.0 equiv. acetophenone and 1.0 mL H_2O as solvent at 35 °C) (Table 3, entries 1–13). Excellent enantioselectivities (up to 96% ee) were gained for aromatic- and heteroaromatic-substituted nitroolefins. However, the yields of the reaction were affected by the position of the substituted group on the aromatic nitroolefins (Table 3, entries 2–8). For ortho-substituted nitroolefins, low yields were observed (Table 3, entries 7–8). Next, a series of aromatic ketone substrates were probed and gave the desired products in moderate to good yields (40–88%) and high enantioselectivities (up to 94% ee) (Table 3, entries 14–19). Similarly, the position and electronic property of the substituted group of the aromatic ketones influenced slightly the enantioselectivities of this reaction (Table 3, entries 14–17). No matter whether electron-withdrawing (Table 3, entries 14, 17) or electron-donating (Table 3, entries 15, 16) substituted aromatic ketones were used, the reactions proceeded smoothly to give high enantioselectivities. However, hetero-aromatic ketone afforded only 40% yield and 79% ee (Table 3, entry 19).

In addition, when the reaction with **6a** was scaled up tenfold with 15 mol% catalyst (**1b/TBBP** = 1/1) at 35 °C, good results (75% yield and 90% ee) were still obtained (Scheme 1).

Conclusions

In summary, we have developed a highly stereoselective Michael addition of ketones to alkylidene malonates and aromatic ketones to nitroalkenes by using a chiral primary-secondary diamine



5a **6a** **7a**

1mmol, 149 mg 75% yield, 90% ee

Scheme 1 Asymmetric Michael addition of acetophenone **5a** to nitroalkene **6a** on a tenfold scale.

catalyst based on bispidine. All reactions performed well under mild conditions using environmentally benign water as the solvent or were solvent free. High yields (up to 99%) with high diastereoselectivities (up to 99:1) and excellent enantioselectivities (up to 97% ee) were achieved for a range of alkylidene malonates and nitroalkenes. These Michael adducts are versatile chiral intermediates by virtue of the range of subsequent transformations to functional groups that are possible. Further application of the catalyst system to other reactions is underway.

Experimental

General methods and materials

General methods. ^{1}H NMR spectra were recorded at 400 MHz or 600 MHz. The chemical shifts were recorded in ppm relative to tetramethylsilane and with the solvent resonance as the internal standard. Data were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), integration. ^{13}C NMR data were collected at 100 MHz or 150 MHz with complete proton decoupling. Chemical shifts were reported in ppm from the tetramethylsilane with the solvent resonance as internal standard. Enantiomeric excesses were determined by chiral HPLC analysis on Daicel Chiralcel AD-H/IA/AS-H in comparison with the authentic racemates. Optical rotations were reported as follows: $[\alpha]_D^T$ (c: g/100 mL, in solvent). ESI-HRMS spectra were recorded on a commercial apparatus and methanol was used to dissolve the sample.

Materials. Alkylidene malonates and nitroalkenes were prepared according to the literature procedures.[14] Acetone, cyclohexanone, aromatic ketones and simple aliphatic acycloketones were commercially available and directly used without further purification. All kinds of acids and solvents also were commercially available and directly used without further purification. Catalysts **1a–1b** were synthesized according to the previous literature.[10] The spectra and other data were consistent with the reported values.

General procedure for the Michael reactions

To anhydrous cyclohexanone (0.5 mL) was added the corresponding alkylidene malonate (0.1 mmol), catalyst **1b** (5.2 mg, 0.02 mmol, 20 mol%), 3,5-dinitrosalicyclic acid (4.6 mg, 0.02 mmol, 20 mol%) and water (0.25 mL). The resulting mixture was stirred at 30 °C for the indicated time. The mixture was directly purified through flash column chromatography on a silica gel (eluent: pet/ethyl acetate = 4/1 or 10/1) to give the desired product.

To the mixture of catalyst **1b** (3.9 mg, 15 mol%), 3,3′,5,5′-tetrabromobiphenol (7.5 mg, 15 mol%), nitroolefin (14.9 mg, 0.1 mmol) and acetophenone (10 equiv.) was added water (1.0 mL).

The reaction mixture was stirred at 35 °C for the indicated time. Then the reaction was quenched by the addition of 1.0 *N* KOH solution (0.3 mL). After 2 min, the crude product was purified by silica gel column chromatography (eluent: pet/ethyl acetate=10/1–4/1) to afford the desired product. The Michael products were characterized by HRMS, ^{1}H NMR, and ^{13}C NMR spectroscopy.

Diethyl 2-((4-nitrophenyl) (2-oxocyclohexyl) methyl) malonate (4a). ($C_{20}H_{25}NO_7$) Reaction time 3 d, 99% yield, 95% *ee*. HPLC DAICEL CHIRALCEL IA, 2-propanol/*n*-hexane = 30/70, flow rate = 0.8 mL/min, λ = 210 nm, retention time: 12.5 min (minor) and 20.0 min (major); syn/anti = 98/2; ^{1}H NMR (400 MHz, $CDCl_3$) 1.01 (t, J = 7.2 Hz, 3H), 1.08–1.14 (m, 1H), 1.20 (t, J = 7.2 Hz, 3H), 1.54–1.59 (m, 2H), 1.74–1.81 (m, 2H), 1.97–2.01 (m, 1H), 2.29–2.44 (m, 2H), 2.89–2.95 (m, 1H), 3.94 (q, J = 7.2 Hz, 2H), 4.00 (d, J = 5.2 Hz, 1H), 4.09–4.19 (m, 3H), 7.47 (d, J = 8.4 Hz, 2H), 8.10 (d, J = 8.4 Hz, 2H) ppm, ^{13}C NMR (150 MHz, $CDCl_3$) 13.8, 13.9, 24.9, 27.6, 31.4, 42.2, 43.1, 52.5, 54.9, 61.4, 61.8, 123.1, 130.7, 146.7, 146.9, 167.6, 168.1, 210.7 ppm; HRMS (ESI-TOF) calcd for $C_{20}H_{26}NO_7$ ([M + H$^+$]) = 392.1704, Found 392.1700.

Diethyl 2-((4-chlorophenyl) (2-oxocyclohexyl) methyl) malonate (4b). ($C_{20}H_{25}ClO_5$) Reaction time 8 d, 90% yield, 92% *ee*. HPLC DAICEL CHIRALCEL ADH, 2-propanol/*n*-hexane = 10/90, flow rate = 0.8 mL/min, λ = 238 nm, retention time: 17.2 min (minor) and 23.4 min (major); syn/anti = 98/2; ^{1}H NMR (600 MHz, $CDCl_3$) 1.03 (t, J = 7.2 Hz, 3H), 1.12–1.16 (m, 1H), 1.22 (t, J = 7.2 Hz, 3H), 1.55–1.61 (m, 2H), 1.77–1.79 (m, 2H), 1.97–1.99 (m, 1H), 2.31–2.36 (m, 1H), 2.43–2.46 (m, 1H), 2.86–2.88 (m, 1H), 3.93–4.03 (m, 4H), 4.12 (q, J = 7.2 Hz, 2H), 7.21–7.24 (m, 4H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) 13.8, 14.0, 24.7, 27.8, 31.5, 42.1, 42.9, 53.0, 55.5, 61.2, 61.6, 128.2, 131.0, 132.8, 137.3, 167.9, 168.4, 211.5 ppm; HRMS (ESI-TOF) calcd for $C_{20}H_{25}ClO_5Na$ ([M + Na$^+$]) = 403.1283, Found 403.1281.

Diethyl 2-((4-bromophenyl) (2-oxocyclohexyl) methyl) malonate (4c). ($C_{20}H_{25}BrO_5$) Reaction time 8 d, 78% yield, 96% *ee*. HPLC DAICEL CHIRALCEL ADH, 2-propanol/*n*-hexane = 10/90, flow rate = 1.0 mL/min, λ = 238 nm, retention time: 15.0 min (minor) and 20.6 min (major); syn/anti = 98/2; ^{1}H NMR (400 MHz, $CDCl_3$) 1.01 (t, J = 7.2 Hz, 3H), 1.12–1.14 (m, 1H), 1.22 (t, J = 7.2 Hz, 3H), 1.53–1.61 (m, 2H), 1.69–1.71 (m, 2H), 1.95–1.96 (m, 1H), 2.31–2.34 (m, 1H), 2.40–2.44 (m, 1H), 2.84–2.87 (m, 1H), 3.90–4.01 (m, 4H), 4.10 (q, J = 7.2 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H) ppm.

Diethyl 2-((4-cyanophenyl) (2-oxocyclohexyl) methyl) malonate (4d). ($C_{21}H_{25}NO_5$) Reaction time 9 d, 99% yield, 95% *ee*. HPLC DAICEL CHIRALCEL ADH, 2-propanol/*n*-hexane = 30/70, flow rate = 0.8 mL/min, λ = 210 nm, retention time: 13.7 min (minor) and 21.4 min (major); syn/anti = 96/4; ^{1}H NMR (400 MHz, $CDCl_3$) 1.01 (t, J = 7.2 Hz, 3H), 1.07–1.13 (m, 1H), 1.20 (t, J = 7.2 Hz, 3H), 1.53–1.58 (m, 2H), 1.77–1.79 (m, 2H), 2.00–2.02 (m, 1H), 2.28–2.36 (m, 1H), 2.39–2.43 (m, 1H), 2.87–2.93 (m, 1H), 3.90–3.98 (m, 3H), 4.08–4.14 (m, 3H), 7.41 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 13.8, 14.0, 24.9, 27.7, 31.4, 42.2, 43.4, 52.6, 55.0, 61.4, 61.8, 110.9, 118.7, 130.6, 131.8, 144.5, 167.7, 168.1, 210.9 ppm; HRMS (ESI-TOF) calcd for $C_{21}H_{25}NO_5Na$ ([M + Na$^+$]) = 394.1625, Found 394.1625.

Diethyl 2-((2-oxocyclohexyl) (4-(trifluoromethyl) phenyl) methyl) malonate (4e). ($C_{21}H_{25}F_3O_5$) Reaction time 9 d, 94% yield, 95% *ee*. HPLC DAICEL CHIRALCEL ADH, 2-propanol/*n*-hexane = 10/90, flow rate = 0.8 mL/min, λ = 210 nm, retention time: 13.7 min (minor) and 21.4 min (major); syn/anti = 97/3; ^{1}H NMR (600 MHz, $CDCl_3$) 0.98 (t, J = 7.2 Hz, 3H), 1.12–1.17 (m, 1H), 1.22 (t, J = 7.2 Hz, 3H), 1.57–1.60 (m, 2H), 1.79–1.80 (m, 2H), 2.00 (s, 1H), 2.33–2.38 (m, 1H), 2.44–2.45 (m, 1H), 2.92–2.96 (m, 1H), 3.93–4.00 (m, 3H), 4.11–4.15 (m, 3H), 7.42 (d, J = 7.8 Hz, 2H), 7.52 (d, J = 7.8 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 13.6, 13.9, 24.8, 27.7, 31.5, 42.1, 43.3, 52.8, 55.3, 61.3, 61.6, 124.1 (q, J = 270.5 Hz), 124.9 (q, J = 3.0 Hz), 129.2 (q, J = 31.5 Hz), 130.1, 143.0, 167.8, 168.3, 211.2 ppm; HRMS (ESI-TOF) calcd for $C_{21}H_{26}F_3O_5$ ([M + H$^+$]) = 415.1727, Found 415.1729.

Diethyl 2-((2-oxocyclohexyl) (phenyl) methyl) malonate (4f). ($C_{20}H_{26}O_5$) Reaction time 8 d, 72% yield, 96% *ee*. $[\alpha]_D^{20}$ = −38.6 (*c* 0.40 in $CHCl_3$) HPLC DAICEL CHIRALCEL ADH, 2-propanol/*n*-hexane = 10/90, flow rate = 0.8 mL/min, λ = 210 nm, retention time: 14.0 min (minor) and 17.3 min (major); syn/anti = 98/2; ^{1}H NMR (400 MHz, $CDCl_3$) 1.00 (t, J = 7.2 Hz, 3H), 1.15–1.19 (m, 1H), 1.24 (t, J = 7.2 Hz, 3H), 1.54–1.60 (m, 2H), 1.64–1.66 (m, 2H), 1.74–1.78 (m, 1H), 2.36–2.40 (m, 1H), 2.46–2.51 (m, 1H), 2.91 (m, 1H), 3.90–3.96 (m, 3H), 4.03 (m, 1H), 4.13 (q, J = 7.2 Hz, 2H), 7.20–7.36 (m, 5H) ppm.

Diethyl 2-((2-oxocyclohexyl) (*p*-tolyl) methyl) malonate (4g). ($C_{21}H_{28}O_5$) Reaction time 8 d, 80% yield, 90% *ee*. HPLC DAICEL CHIRALCEL IA, 2-propanol/*n*-hexane = 10/90, flow rate = 0.8 mL/min, λ = 210 nm, retention time: 12.1 min (minor) and 16.1 min (major); syn/anti = 98/2; ^{1}H NMR (400 MHz, $CDCl_3$) 1.01 (t, J = 7.2 Hz, 3H), 1.23 (t, J = 7.2 Hz, 3H), 1.26 (m, 1H), 1.62–1.67 (m, 2H), 1.73–1.77 (m, 2H), 1.93 (m, 1H), 2.29 (s, 3H), 2.34–2.38 (m, 1H), 2.44–2.49 (m, 1H), 2.87 (m, 1H), 3.90–4.00 (m, 4H), 4.12 (q, J = 7.2 Hz, 2H), 7.06 (d, J = 7.6 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 13.7, 14.0, 21.0, 24.4, 27.9, 31.7, 42.0, 43.3, 53.5, 56.1, 61.1, 61.5, 128.8, 129.4, 135.7, 136.5, 168.1, 168.7, 212.2 ppm; HRMS (ESI-TOF) calcd for $C_{21}H_{29}O_5$ ([M + H$^+$]) = 361.2010, Found 361.2014.

Diethyl 2-((4-methoxyphenyl) (2-oxocyclohexyl) methyl) malonate (4h). ($C_{21}H_{28}O_6$) Reaction time 9 d, 44% yield, 95% *ee*. HPLC DAICEL CHIRALCEL ADH, 2-propanol/*n*-hexane = 10/90, flow rate = 0.8 mL/min, λ = 210 nm, retention time: 23.9 min (minor) and 31.4 min (major); syn/anti = 99/1; ^{1}H NMR (400 MHz, $CDCl_3$) 1.01 (t, J = 7.2 Hz, 3H), 1.18 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H), 1.53–1.64 (m, 2H), 1.75–1.79 (m, 2H), 1.93–1.95 (m, 1H), 2.33–2.37 (m, 1H), 2.44–2.48 (m, 1H), 2.84–2.85 (m, 1H), 3.77 (s, 3H), 3.89–3.97 (m, 4H), 4.12 (q, J = 7.2 Hz, 2H), 6.79 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 8.8 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 13.8, 14.0, 24.5, 27.8, 31.6, 42.0, 42.9, 53.5, 55.1, 56.1, 61.1, 61.5, 113.4, 130.6, 130.7, 158.4, 168.1, 168.7, 212.2 ppm; HRMS (ESI-TOF) calcd for $C_{21}H_{28}O_6Na$ ([M + Na$^+$]) = 399.1778, Found 399.1794.

Diethyl 2-((3-nitrophenyl) (2-oxocyclohexyl) methyl) malonate (4i). ($C_{20}H_{25}NO_7$) Reaction time 3 d, 99% yield, 95% *ee*. HPLC DAICEL CHIRALCEL ADH, 2-propanol/*n*-hexane = 30/70,

flow rate = 0.8 mL/min, λ = 254 nm, retention time: 11.2 min (minor) and 14.7 min (major); syn/anti = 97/3; ^{1}H NMR (400 MHz, $CDCl_3$) 1.02 (t, J = 7.2 Hz, 3H), 1.11–1.16 (m, 1H), 1.21 (t, J = 7.2 Hz, 3H), 1.54–1.61 (m, 2H), 1.80–1.84 (m, 2H), 2.00–2.02 (m, 1H), 2.32–2.44 (m, 2H), 2.93–2.99 (m, 1H), 3.96 (q, J = 7.2 Hz, 2H), 4.03 (d, J = 9.2 Hz, 1H), 4.13 (m, 3H), 7.44 (t, J = 8.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H), 8.13 (s, 1H) ppm.

Diethyl 2-((3,4-dichlorophenyl) (2-oxocyclohexyl) methyl) malonate (4j). ($C_{20}H_{24}Cl_2O_5$) Reaction time 9 d, 96% yield, 95% *ee*. HPLC DAICEL CHIRALCEL IA, 2-propanol/*n*-hexane = 10/90, flow rate = 0.8 mL/min, λ = 210 nm, retention time: 13.8 min (minor) and 18.9 min (major); syn/anti = 97/3; ^{1}H NMR (400 MHz, $CDCl_3$) 1.05 (t, J = 7.2 Hz, 3H), 1.12–1.14 (m, 1H), 1.21 (t, J = 7.2 Hz, 3H), 1.55–1.59 (m, 2H), 1.78–1.80 (m, 2H), 1.99–2.03 (m, 1H), 2.32–2.37 (m, 1H), 2.40–2.44 (m, 1H), 2.84–2.89 (m, 1H), 3.91–4.00 (m, 4H), 4.12 (q, J = 7.2 Hz, 2H), 7.14–7.16 (m, 1H), 7.31–7.38 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 13.8, 14.0, 24.8, 27.8, 31.6, 42.2, 42.7, 52.6, 55.1, 61.4, 61.7, 129.3, 130.0, 131.0, 131.6, 132.0, 139.2, 167.8, 168.2, 211.1 ppm; HRMS (ESI-TOF) calcd for $C_{20}H_{25}Cl_2O_5$ ([M + H^+]) = 415.1074, Found 415.1068.

Diethyl 2-((2-oxocyclohexyl) (*o*-tolyl) methyl) malonate (4k). ($C_{21}H_{28}O_5$) Reaction time 8 d, 58% yield, 94% *ee*. HPLC DAICEL CHIRALCEL IA, 2-propanol/*n*-hexane = 10/90, flow rate = 0.8 mL/min, λ = 210 nm, retention time: 8.2 min (minor) and 12.4 min (major); syn/anti = 95/5; ^{1}H NMR (400 MHz, $CDCl_3$) 0.98 (t, J = 7.2 Hz, 3H), 1.22 (t, J = 7.2 Hz, 3H), 1.25 (m, 1H), 1.55–1.60 (m, 2H), 1.68–1.73 (m, 2H), 1.94–1.95 (m,1H), 2.35–2.43 (m, 2H), 2.46 (s, 3H), 2.92–2.98 (m, 1H), 3.84–3.91 (m, 3H), 4.09 (q, J = 7.2 Hz, 2H), 4.24 (t, J = 9.6 Hz, 1H), 7.08–7.14 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 13.7, 13.9, 20.3, 24.8, 28.4, 32.4, 38.3, 42.1, 54.9, 57.2, 61.0, 61.5, 126.1, 126.6, 127.0, 130.5, 137.8, 138.5, 168.2, 168.9, 212.8 ppm; HRMS (ESI-TOF) calcd for $C_{21}H_{29}O_5$ ([M + H^+]) = 361.2010, Found 361.2014.

Diethyl 2-(naphthalen-2-yl (2-oxocyclohexyl) methyl) malonate (4l). ($C_{24}H_{28}O_5$) Reaction time 9 d, 70% yield, 95% *ee*. HPLC DAICEL CHIRALCEL ADH, 2-propanol/*n*-hexane = 10/90, flow rate = 1.0 mL/min, λ = 254 nm, retention time: 16.8 min (minor) and 25.8 min (major); syn/anti = 98/2; ^{1}H NMR (400 MHz, $CDCl_3$) 0.91 (t, J = 7.2 Hz, 3H), 1.18 (m, 1H), 1.22 (t, J = 7.2 Hz, 3H), 1.56–1.60 (m, 2H), 1.73–1.77 (m, 2H), 1.93–1.97 (m, 1H), 2.37–2.39 (m, 1H), 2.46–2.51 (m, 1H), 2.97–3.03 (m, 1H), 3.87 (q, J = 7.2 Hz, 2H), 4.04 (d, J = 9.2 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 4.21 (t, J = 8.8 Hz, 1H), 7.41–7.46 (m, 3H), 7.71–7.79 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 13.7, 14.0, 24.5, 27.9, 31.9, 42.1, 43.8, 53.4, 56.1, 61.1, 61.6, 125.8, 126.0, 127.5, 127.5, 127.7, 127.8, 128.5, 132.5, 133.1, 136.5, 168.1, 168.7, 212.1 ppm; HRMS (ESI-TOF) calcd for $C_{24}H_{28}NO_5Na$ ([M + Na^+]) = 419.1829, Found 419.1831.

Dimethyl 2-((4-nitrophenyl) (2-oxocyclohexyl) methyl) malonate (4m). ($C_{18}H_{21}NO_7$) Reaction time 3 d, 98% yield, 97% *ee*. HPLC DAICEL CHIRALCEL ADH, 2-propanol/*n*-hexane = 10/90, flow rate = 0.7 mL/min, λ = 254 nm, retention time: 43.2 min (minor) and 57.0 min (major); syn/anti = 96/4; ^{1}H NMR (600 MHz, $CDCl_3$) 1.10–1.13 (m,1H), 1.54–1.62 (m, 2H), 1.75–1.77 (m, 2H), 2.01–2.03 (m, 1H), 2.34–2.39 (m, 1H), 2.42–2.44 (m, 1H), 2.95–2.99 (m, 1H), 3.51 (s, 3H), 3.67 (s, 3H), 4.05–4.06 (m, 1H), 4.12–4.15 (m, 1H), 7.46 (d, J = 8.4 Hz, 2H), 8.12 (d, J = 8.4 Hz, 2H) ppm.

Dimethyl 2-((3-nitrophenyl) (2-oxocyclohexyl) methyl) malonate (4n). ($C_{18}H_{21}NO_7$) Reaction time 3 d, 99% yield, 95% *ee*. $[\alpha]_D^{20}$ = –49.6 (*c* 1.28 in $CHCl_3$) HPLC DAICEL CHIRALCEL ADH, 2-propanol/*n*-hexane = 30/70, flow rate = 0.8 mL/min, λ = 254 nm, retention time: 10.9 min (minor) and 13.5 min (major); syn/anti = 99/1; ^{1}H NMR (400 MHz, $CDCl_3$) 1.10–1.13 (m,1H), 1.55–1.59 (m, 2H), 1.76–1.80 (m, 2H), 2.01–2.04 (m, 1H), 2.42–2.45 (m, 2H), 2.97–3.03 (m, 1H), 3.52 (s, 3H), 3.67 (s, 3H), 4.06–4.12 (m, 2H), 7.45 (t, J = 8.0 Hz, 1H), 7.67 (d, J = 7.6 Hz, 1H), 8.06–8.11 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 25.0, 28.0, 32.0, 42.4, 43.4, 52.4, 52.5, 52.7, 54.7, 122.3, 124.0, 129.1, 136.5, 140.9, 148.0, 168.2, 168.6, 211.2 ppm; HRMS (ESI-TOF) calcd for $C_{18}H_{22}NO_7$ ([M + H^+]) = 364.1391, Found 364.1393.

Diethyl 2-(3-methyl-1-(2-oxocyclohexyl) butyl) malonate (4o). ($C_{18}H_{30}O_5$) Reaction time 4 d, 82% yield, 30% *ee*. HPLC DAICEL CHIRALCEL ADH, 2-propanol/*n*-hexane = 10/90, flow rate = 0.8 mL/min, λ = 210 nm, retention time: 5.7 min (major) and 6.4 min (minor); syn/anti = 95/5; ^{1}H NMR (600 MHz, $CDCl_3$) 0.91 (d, J = 12.6 Hz, 3H), 0.92 (d, J = 13.2 Hz, 3H), 1.21–1.28 (m, 9H), 1.41–1.46 (m, 2H), 1.61–1.65 (m, 2H), 1.89 (m, 1H), 2.03–2.06 (m, 2H), 2.30 (m, 1H), 2.39–2.41 (m, 1H), 2.62–2.64 (m, 1H), 2.96–2.98 (m, 1H), 3.50 (d, J = 6.0 Hz, 1H), 4.41–4.20 (m, 4H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) 14.0, 14.1, 22.3, 23.0, 25.5, 26.1, 27.6, 29.7, 33.2, 38.6, 42.3, 52.4, 54.1, 61.1, 61.2, 169.2, 169.2, 211.2 ppm;

Diethyl 2-(1-(4-nitrophenyl)-3-oxobutyl) malonate (4q). ($C_{17}H_{21}NO_7$) Reaction time 4 d, 85% yield, 86% *ee*. $[\alpha]_D^{20}$ = 12.2 (*c* 0.640 in $CHCl_3$). HPLC DAICEL CHIRALCEL ADH, 2-propanol/*n*-hexane = 30/70, flow rate = 0.8 mL/min, λ = 210 nm, retention time: 12.7 min (minor) and 29.7 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) 1.06 (t, J = 7.2 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H), 2.056 (s, 3H), 2.92–3.07 (m, 2H), 3.72 (d, J = 9.6 Hz, 1H), 3.96–4.01 (m, 2H), 4.06–4.11 (m, 1H), 4.17–4.23 (m, 2H), 7.45 (d, J = 8.8 Hz, 2H), 8.14 (d, J = 8.4 Hz, 2H) ppm.

Diethyl 2-(1-(3-nitrophenyl)-3-oxobutyl) malonate (4r). ($C_{17}H_{21}NO_7$) Reaction time 4 d, 81% yield, 86% *ee*. $[\alpha]_D^{20}$ = 26.9 (*c* 0.234 in $CHCl_3$). HPLC DAICEL CHIRALCEL IA, 2-propanol/*n*-hexane = 30/70, flow rate = 0.8 mL/min, λ = 254 nm, retention time: 8.9 min (minor) and 12.8 min (major); ^{1}H NMR (600 MHz, $CDCl_3$) 1.06 (t, J = 7.2 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H), 2.08 (s, 3H), 2.97–3.02 (m, 1H), 3.06–3.09 (m, 1H), 3.73 (d, J = 9.6 Hz, 1H), 3.98–4.02 (m, 2H), 4.08–4.12 (m, 1H), 4.19–4.22 (m, 2H), 7.46 (t, J = 7.8 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 8.13 (s, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) 13.8, 14.0, 30.3, 39.6, 46.7, 56.6, 61.7, 61.9, 122.3, 122.8, 129.3, 135.2, 143.0, 148.2, 167.3, 167.7, 205.1 ppm; HRMS (ESI-TOF) calcd for $C_{17}H_{22}NO_7$ ([M + H^+]) = 352.1391, Found 352.1391.

Dimethyl 2-(1-(4-nitrophenyl)-3-oxobutyl) malonate (4s). ($C_{15}H_{17}NO_7$) Reaction time 4 d, 90% yield, 87% *ee*. $[\alpha]_D^{20}$ = 11.1 (*c* 0.484 in $CHCl_3$). HPLC DAICEL CHIRALCEL ADH, 2-propanol/*n*-hexane = 30/70, flow rate = 0.8 mL/min, λ = 210 nm, retention time: 13.3 min (minor) and 20.2 min (major);

^{1}H NMR (400 MHz, $CDCl_3$) 2.07 (s, 3H), 2.93–3.08 (m, 2H), 3.54 (s, 3H), 3.75 (s, 3H), 4.09 (m, 1H), 7.44 (d, J = 8.4 Hz, 2H), 8.14 (d, J = 8.0 Hz, 2H) ppm.

Dimethyl 2-(1-(3-nitrophenyl)-3-oxobutyl) malonate (4t). ($C_{15}H_{17}NO_7$) Reaction time 4 d, 92% yield, 84% *ee*. $[\alpha]_D^{20}$ = 12.1 (*c* 0.594 in $CHCl_3$). HPLC DAICEL CHIRALCEL IA, 2-propanol/*n*-hexane = 30/70, flow rate = 0.8 mL/min, λ = 210 nm, retention time: 10.0 min (minor) and 10.7 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) 2.09 (s, 3H), 2.97–3.11 (m, 2H), 3.56 (s, 3H), 3.75 (s, 3H), 3.76–3.78 (m, 1H), 4.11 (m, 1H), 7.47 (t, J = 8.0 Hz, 1H), 7.65 (d, J = 7.6 Hz, 1H), 8.08–8.12 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 30.3, 39.6, 46.5, 52.6, 52.9, 56.3, 122.4, 122.6, 129.4, 135.2, 142.9, 148.3, 167.7, 168.1, 205.1 ppm; HRMS (ESI-TOF) calcd for $C_{15}H_{17}NO_7K$ ([M + K^+]) = 362.0637, Found 362.0627.

Diisopropyl 2-(1-(4-nitrophenyl)-3-oxobutyl) malonate (4u). ($C_{19}H_{25}NO_7$) Reaction time 4 d, 33% yield, 87% *ee*. $[\alpha]_D^{20}$ =9.8 (*c* 0.410 in $CHCl_3$). HPLC DAICEL CHIRALCEL ADH, 2-propanol/*n*-hexane = 30/70, flow rate = 0.8 mL/min, λ = 254 nm, retention time: 11.7 min (minor) and 31.2 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) 1.02 (d, J = 6.4 Hz, 3H), 1.07 (d, J = 6.4 Hz, 3H), 1.23 (d, J = 6.4 Hz, 3H), 1.24 (d, J = 6.4 Hz, 3H), 2.06 (s, 3H), 2.91–3.07 (m, 2H), 3.67 (d, J = 9.6 Hz, 1H), 4.06 (m, 1H), 4.81 (m, 1H), 5.06 (m, 1H), 7.46 (d, J = 8.8 Hz, 2H), 8.14 (d, J = 8.8 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 21.4, 21.4, 21.5, 21.6, 30.3, 39.7, 47.1, 56.8, 69.3, 69.7, 123.6, 129.4, 147.0, 148.6, 166.7, 167.3, 205.1 ppm; HRMS (ESI-TOF) calcd for $C_{19}H_{25}O_7K$ ([M + K^+]) = 418.1263, Found 418.1269.

Dibenzyl 2-(1-(4-nitrophenyl)-3-oxobutyl) malonate (4v). ($C_{27}H_{25}NO_7$) Reaction time 4 d, 78% yield, 85% *ee*. $[\alpha]_D^{20}$ = 22.0 (*c* 0.240 in $CHCl_3$) HPLC DAICEL CHIRALCEL ADH, 2-propanol/*n*-hexane = 30/70, flow rate = 0.8 mL/min, λ = 210 nm, retention time: 31.7 min (minor) and 62.1 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) 1.96 (s, 3H), 2.89–2.91 (m, 2H), 3.83 (d, J = 9.6 Hz, 1H), 4.04–4.10 (m, 1H), 4.92 (s, 2H), 5.15 (s, 2H), 7.06–7.08 (m, 2H), 7.21–7.34 (m, 10H), 7.95 (d, J = 8.8 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 30.2, 39.9, 46.6, 56.4, 67.4, 67.6, 123.6, 128.5, 128.6, 128.7, 129.2, 134.7, 134.9, 146.9, 147.9, 166.9, 167.4, 205.0 ppm; HRMS (ESI-TOF) calcd for $C_{27}H_{26}O_7$ ([M + H^+]) = 476.1704, Found 476.1712.

Dimethyl 2-((4-nitrophenyl) (2-oxocyclopentyl) methyl) malonate (4w). ($C_{17}H_{19}NO_7$) Reaction time 5 d, 51% yield, 75% *ee*. HPLC DAICEL CHIRALCEL IA, 2-propanol/*n*-hexane = 10/90, flow rate = 1.0 mL/min, λ = 254 nm, retention time: 31.7 min (minor) and 34.4 min (major); syn/anti = 2/1; ^{1}H NMR (600 MHz, $CDCl_3$) 1.46–1.49 (m, 1H), 1.64–1.71 (m, 1H), 1.81–1.91 (m, 2H), 2.05–2.07 (m, 1H), 2.23–2.27 (m, 1H), 2.56–2.58 (m, 1H), 3.48 (s, 3H), 3.75 (s, 3H), 4.07–4.10 (m, 1H), 4.19–4.20 (m, 1H), 7.37–7.40 (m, 2H), 8.12 (d, J = 8.4 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 20.3, 20.5, 26.4, 38.4, 43.9, 51.5, 52.6, 53.0, 53.1, 54.4, 123.4, 130.0, 146.0, 147.1, 167.7, 168.2, 217.5 ppm.

Diethyl 2-(2-methyl-1-(4-nitrophenyl)-3-oxopentyl) malonate (4x). ($C_{19}H_{25}NO_7$) Reaction time 4 d, 14% yield, 81% *ee*. HPLC DAICEL CHIRALCEL ADH, 2-propanol/*n*-hexane = 10/90, flow rate = 0.8 mL/min, λ = 210 nm, retention time: 17.8 min (minor) and 21.3 min (major); syn/anti = 9/1; ^{1}H NMR (600 MHz, $CDCl_3$) 0.87 (d, J = 7.2 Hz, 3H), 1.05–1.08 (m, 6H), 1.22–1.26 (m, 3H), 2.56–2.60 (m, 2H), 3.15–3.20 (m, 1H), 3.84 (d, J = 8.4 Hz, 1H), 3.95–4.01 (m, 3H), 4.12–4.15 (m, 2H), 7.42 (d, J = 9.0 Hz, 2H), 8.15 (d, J = 8.4 Hz, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) 7.6, 13.8, 13.9, 15.0, 34.8, 46.0, 47.8, 55.1, 61.6, 61.8, 123.3, 130.3, 146.3, 147.1, 167.5, 167.8, 212.8 ppm.

4-Nitro-1,3-diphenylbutan-1-one (7a). ($C_{16}H_{15}NO_3$) Reaction time 3 d, 85% yield, 93% ee. $[\alpha]_D^{20}$ = 21.1 (*c* 0.360 in $CHCl_3$). HPLC DAICEL CHIRALCEL ADH, 2-propanol/*n*-hexane = 10/90, flow rate = 1.0 mL/min, λ = 254 nm, retention time: 14.4 min (minor) and 19.7 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) 3.42–3.54 (m, 2H), 4.26 (m, 1H), 4.72 (dd, J = 8.0 Hz, 12.4 Hz, 1H), 4.86 (dd, J = 6.8 Hz, 12.8 Hz, 1H), 7.16–7.38 (m, 5H), 7.44–7.48 (m, 2H), 7.58–7.62 (t, J = 7.2 Hz, 1H), 7.93–7.95 (d, J = 8.0 Hz, 2H) ppm.

4-Nitro-1-phenyl-3-*p*-tolylbutan-1-one (7b). ($C_{17}H_{17}NO_3$) Reaction time 3 d, 83% yield, 91% *ee*. $[\alpha]_D^{20}$ = 26.2 (*c* 0.344 in $CHCl_3$). HPLC DAICEL CHIRALCEL ADH, 2-propanol/*n*-hexane = 10/90, flow rate = 1.0 mL/min, λ = 254 nm, retention time: 12.8 min (minor) and 17.6 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) 2.31 (s, 3H), 3.38–3.50 (m, 2H), 4.19 (m, 1H), 4.67 (dd, J = 8.0 Hz, 12.4 Hz, 1H), 4.82 (dd, J = 6.4 Hz, 12.4 Hz, 1H), 7.13–7.19 (m, 4H), 7.44–7.48 (m, 2H), 7.56–7.60 (m,1H), 7.91–7.93 (m, 2H) ppm.

3-(4-Methoxyphenyl)-4-nitro-1-phenylbutan-1-one (7c). ($C_{17}H_{17}NO_4$) Reaction time 4 d, 81% yield, 90% *ee*. $[\alpha]_D^{20}$ = 20.5 (*c* 0.278 in $CHCl_3$). HPLC DAICEL CHIRALCEL ADH, 2-propanol/*n*-hexane = 20/80, flow rate = 1.0 mL/min, λ = 254 nm, retention time: 14.0 min (minor) and 19.2 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) 3.43 (m, 2H), 3.78 (s, 3H), 4.18 (m, 1H), 4.65 (dd, J = 8.0 Hz, 12.4 Hz, 1H), 4.80 (dd, J = 6.8 Hz, 12.4 Hz, 1H), 6.84–6.88 (m, 2H), 7.18–7.22 (m, 2H), 7.44–7.71 (m, 3H), 7.92 (d, J = 6.0 Hz, 2H) ppm.

4-Nitro-3-(4-nitrophenyl)-1-phenylbutan-1-one (7d). ($C_{16}H_{14}N_2O_5$) Reaction time 3 d, 81% yield, 87% *ee*. $[\alpha]_D^{20}$ = 39.9 (*c* 0.464 in $CHCl_3$). HPLC DAICEL CHIRALCEL IA, 2-propanol/*n*-hexane = 20/80, flow rate = 1.0 mL/min, λ = 254 nm, retention time: 22.8 min (minor) and 33.4 min (major); ^{1}H NMR (600 MHz, $CDCl_3$) 3.47–3.54 (m, 2H), 4.37 (m, 1H), 4.74 (dd, J = 8.4 Hz, 13.2 Hz, 1H), 4.87 (dd, J = 6.0 Hz, 13.2 Hz, 1H), 7.46–7.51 (m, 4H), 7.59–7.61 (m, 1H), 7.90–7.92 (m, 2H), 8.20–8.22 (m, 2H) ppm.

3-(3-methoxyphenyl)-4-nitro-1-phenylbutan-1-one (7e). ($C_{17}H_{17}NO_4$) Reaction time 3 d, 70% yield, 91% *ee*. $[\alpha]_D^{20}$ = 24.3 (*c* 0.408 in $CHCl_3$). HPLC DAICEL CHIRALCEL IA, 2-propanol/*n*-hexane = 10/90, flow rate = 1.0 mL/min, λ = 254 nm, retention time: 15.1 min (minor) and 17.7 min (major); ^{1}H NMR (600 MHz, $CDCl_3$) 3.41–3.52 (m, 2H), 3.81 (s, 3H), 4.22 (m, 1H), 4.70 (dd, J = 7.8 Hz, 12.6 Hz, 1H), 4.84 (dd, J = 7.2 Hz, 12.6 Hz, 1H), 6.82–6.89 (m, 3H), 7.27–7.29 (m, 1H), 7.47–7.49 (m, 2H), 7.59–7.61 (m,1H), 7.95 (d, J = 7.2 Hz, 2H) ppm; ^{13}C NMR (100 MHz, CDCl3) 39.3, 41.5, 55.3, 79.5, 112.9, 113.7, 119.6, 128.0, 128.8, 130.1, 133.6, 136.4, 140.7, 160.0, 196.8 ppm.

4-Nitro-3-(3-nitrophenyl)-1-phenylbutan-1-one (7f). ($C_{16}H_{14}N_2O_5$) Reaction time 60 h, 80% yield, 87% *ee*. $[\alpha]_D^{20}$ = 18.4

(c 0.396 in $CHCl_3$). HPLC DAICEL CHIRALCEL ADH, 2-propanol/n-hexane = 20/80, flow rate = 1.0 mL/min, λ = 254 nm, retention time: 15.2 min (minor) and 17.9 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) 3.51–3.53 (m, 2H), 4.38 (m, 1H), 4.74–4.77 (dd, J = 8.0 Hz, 12.8 Hz, 1H), 4.87–4.92 (dd, J = 6.0 Hz, 12.8 Hz, 1H), 7.46–7.63 (m, 4H), 7.68–7.71 (m, 1H), 7.92–7.94 (m, 2H), 8.14–8.20 (m, 2H) ppm.

3-(2-Chlorophenyl)-4-nitro-1-phenylbutan-1-one (7g). **($C_{16}H_{14}NClO_3$)** Reaction time 3 d, 52% yield, 88% *ee*. $[\alpha]_D^{20}$ = 19.0 (c 0.294 in $CHCl_3$). HPLC DAICEL CHIRALCEL IA, 2-propanol/n-hexane = 10/90, flow rate = 1.0 mL/min, λ = 254 nm, retention time: 12.2 min (minor) and 13.3 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) 3.57–3.60 (m, 2H), 4.72 (m, 1H), 4.89–4.91 (m, 2H), 7.23–7.33 (m, 2H), 7.43–7.51 (m, 3H), 7.59–7.63 (m, 2H), 7.96–7.98 (m, 2H) ppm.

4-Nitro-3-(2-nitrophenyl)-1-phenylbutan-1-one (7h). **($C_{16}H_{14}N_2O_5$)** Reaction time 4 d, 43% yield, 92% *ee*. $[\alpha]_D^{20}$ = 85.4 (c 0.240 in $CHCl_3$). HPLC DAICEL CHIRALCEL IA, 2-propanol/n-hexane = 20/80, flow rate = 1.0 mL/min, λ = 254 nm, retention time: 14.4 min (minor) and 16.8 min (major); ^{1}H NMR (600 MHz, $CDCl_3$) 3.60 (m, 2H), 4.74 (m, 1H), 4.72–4.76 (m, 1H), 4.90–4.98 (m, 2H), 7.43–7.48 (m, 4H), 7.57–7.60 (m, 2H), 7.90–7.93 (m, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) 34.3, 40.7, 78.2, 125.3, 128.0, 128.6, 128.7, 128.8, 133.3, 133.7, 133.8, 136.0, 150.0, 196.2 ppm.; HRMS (ESI-TOF) calcd for $C_{16}H_{14}N_2NaO_5$ ([M + Na^+]) = 337.0795, Found: 337.0807.

3-(2,4-Dichlorophenyl)-4-nitro-1-phenylbutan-1-one (7i). **($C_{16}H_{12}NCl_2O_3$)** Reaction time 3 d, 78% yield, 94% *ee*. $[\alpha]_D^{20}$ = 22.0 (c 0.496 in $CHCl_3$). HPLC DAICEL CHIRALCEL ADH, 2-propanol/n-hexane = 10/90, flow rate = 1.0 mL/min, λ = 254 nm, retention time: 13.4 min (minor) and 15.2 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) 3.48–3.61 (m, 2H), 4.64 (m, 1H), 4.84–4.86 (m, 2H), 7.23–7.26 (m, 2H), 7.44–7.50 (m, 3H), 7.58–7.62 (m, 1H), 7.93 (m, 2H) ppm.

3-(Benzo[*d*][1,3]dioxol-5-yl)-4-nitro-1-phenylbutan-1-one (7j). **($C_{17}H_{15}NO_5$)** Reaction time 4 d, 77% yield, 92% *ee*. $[\alpha]_D^{20}$ = 20.7 (c 0.484 in $CHCl_3$). HPLC DAICEL CHIRALCEL ADH, 2-propanol/n-hexane = 20/80, flow rate = 1.0 mL/min, λ = 254 nm, retention time: 15.6 min (minor) and 19.6 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) 2.88 (s, 1H), 2.96 (s, 1H), 3.34–3.47 (m, 2H), 4.15 (m, 1H), 4.62 (dd, J = 8.0 Hz, 12.4 Hz, 1H), 4.78 (dd, J = 6.4 Hz, 12.4 Hz, 1H), 6.74–6.76 (m, 3H), 7.45–7.48 (m, 2H), 7.56–7.60 (m, 1H), 7.91–7.93 (d, J = 8.0 Hz, 2H) ppm.

3-(Naphthalen-1-yl)-4-nitro-1-phenylbutan-1-one (7k). **($C_{20}H_{17}NO_3$)** Reaction time 3 d, 85% yield, 96% *ee*. $[\alpha]_D^{20}$ = 52.8 (c 0.572 in $CHCl_3$). HPLC DAICEL CHIRALCEL ASH, 2-propanol/n-hexane = 10/90, flow rate = 1.0 mL/min, λ = 254 nm, retention time: 26.0 min (minor) and 34.8 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) 3.62–3.64 (m, 2H), 4.92 (m, 1H), 5.18 (t, J = 6.8 Hz, 1H), 7.39–7.52 (m, 4H), 7.52–7.63 (m, 3H), 7.78–7.80 (m, 1H), 7.88–7.95 (m 3H), 8.23 (d, J = 8.4 Hz, 1H) ppm.

3-(Naphthalen-2-yl)-4-nitro-1-phenylbutan-1-one (7l). **($C_{20}H_{17}NO_3$)** Reaction time 3 d, 80% yield, 90% *ee*. $[\alpha]_D^{20}$ = 21.1 (c 0.418 in $CHCl_3$). HPLC DAICEL CHIRALCEL ADH, 2-propanol/n-hexane = 20/80, flow rate = 1.0 mL/min, λ = 254 nm, retention time: 12.4 min (minor) and 14.9 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) 3.50–3.60 (m, 2H), 4.41 (m, 1H), 4.80 (dd, J = 8.0 Hz, 12.8 Hz, 1H), 4.92 (dd, J = 6.8 Hz, 12.8 Hz, 1H), 7.40–7.50 (m, 5H), 7.56–7.60 (m, 1H), 7.74 (m, 1H), 7.79–7.85 (m, 3H), 7.92–7.95 (m, 2H) ppm.

3-(Furan-2-yl)-4-nitro-1-phenylbutan-1-one (7m). **($C_{14}H_{13}NO_4$)** Reaction time 4 d, 58% yield, 93% *ee*. $[\alpha]_D^{20}$ = 11.8 (c 0.272 in $CHCl_3$). HPLC DAICEL CHIRALCEL ADH, 2-propanol/n-hexane = 10/90, flow rate = 1.0 mL/min, λ = 254 nm, retention time: 12.1 min (minor) and 14.7 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) 3.40–3.56 (m, 2H), 4.34 (m, 1H), 4.72–4.84 (m, 2H), 6.19 (d, J = 3.2 Hz, 1H), 6.29 (dd, J = 2.0 Hz, 3.2 Hz, 1H), 7.34 (m, 1H), 7.46–7.50 (m, 2H), 7.51–7.61 (m, 1H), 7.94–7.96 (m, 2H) ppm.

1-(4-Fluorophenyl)-4-nitro-3-phenylbutan-1-one (7n). **($C_{16}H_{14}NFO_3$)** Reaction time 3 d, 70% yield, 90% *ee*. $[\alpha]_D^{20}$ = 18.5 (c 0.368 in $CHCl_3$). HPLC DAICEL CHIRALCEL IA, 2-propanol/n-hexane = 20/80, flow rate = 1.0 mL/min, λ = 254 nm, retention time: 9.8 min (minor) and 11.7 min (major); ^{1}H NMR (600 MHz, $CDCl_3$) 3.39–3.47 (m, 2H), 4.22 (m, 1H), 4.69 (dd, J = 7.8 Hz, 12.6 Hz, 1H), 4.82 (dd, J = 6.6 Hz, 12.6 Hz, 1H), 7.11–7.14 (m, 2H), 7.27–7.28 (m, 3H), 7.33–7.35 (m, 2H), 7.94–7.96 (m, 2H) ppm.

1-(3-Methoxyphenyl)-4-nitro-3-phenylbutan-1-one (7o). **($C_{17}H_{17}NO_4$)** Reaction time 3 d, 85% yield, 91% *ee*. $[\alpha]_D^{20}$ = 12.7 (c 0.386 in $CHCl_3$). HPLC DAICEL CHIRALCEL ADH, 2-propanol/n-hexane = 10/90, flow rate = 1.0 mL/min, λ = 254 nm, retention time: 18.9 min (minor) and 24.0 min (major); ^{1}H NMR (600 MHz, $CDCl_3$) 3.44 (m, 2H), 3.84 (s, 3H), 4.22 (m, 1H), 4.69 (dd, J = 7.8 Hz, 12.6 Hz, 1H), 4.82 (dd, J = 6.6 Hz, 12.6 Hz, 1H), 7.11–7.13 (m, 1H), 7.27–7.38 (m, 5H), 7.43 (s, 1H), 7.49–7.50 (m, 1H) ppm.

4-Nitro-3-phenyl-1-*o*-tolylbutan-1-one (7p). **($C_{17}H_{17}NO_3$)** Reaction time 4 d, 42% yield, 92% *ee*. $[\alpha]_D^{20}$ = 8.7 (c 0.150 in $CHCl_3$). HPLC DAICEL CHIRALCEL ADH, 2-propanol/n-hexane = 10/90, flow rate = 1.0 mL/min, λ = 254 nm, retention time: 10.6 min (minor) and 13.8 min (major); ^{1}H NMR (600 MHz, $CDCl_3$) 2.34 (s, 3H), 3.36 (d, J = 6.6 Hz, 2H), 4.18 (m, 1H), 4.67 (dd, J = 7.2 Hz, 12.0 Hz, 1H), 4.78 (dd, J = 7.2 Hz, 12.6 Hz, 1H), 7.21–7.27 (m, 5H), 7.31–7.33 (m, 2H), 7.35–7.37 (m, 1H), 7.55 (d, J = 7.8 Hz, 1H) ppm;^{13}C NMR (150 MHz,$CDCl_3$) 21.1, 36.7, 44.3, 79.7, 125.77, 127.5, 127.9, 128.3, 129.1, 131.7, 132.1, 137.2, 138.5, 138.9, 200.7 ppm; HRMS (ESI-TOF) calcd for $C_{17}H_{17}NNaO_3$ ([M + Na^+]) = 306.1101, Found: 306.1097.

1-(2-Fluorophenyl)-4-nitro-3-phenylbutan-1-one (7q). **($C_{16}H_{14}FNO_3$)** Reaction time 4 d, 62% yield, 94% *ee*. $[\alpha]_D^{20}$ = 33.2 (c 0.202 in $CHCl_3$) HPLC DAICEL CHIRALCEL IA, 2-propanol/n-hexane = 10/90, flow rate = 1.0 mL/min, λ = 254 nm, retention time: 10.0 min (minor) and 11.8 min (major); ^{1}H NMR (600 MHz, $CDCl_3$) 3.40–3.51 (m, 2H), 4.22 (m, 1H), 4.66 (dd, J = 8.4 Hz, 12.6 Hz, 1H), 4.78 (dd, J = 6.6 Hz, 12.6 Hz, 1H), 7.11–7.14 (m, 1H), 7.19–7.22 (m, 1H), 7.24–7.27 (m, 3H), 7.32–7.33 (m, 2H), 7.50–7.54 (m, 1H), 7.79 (d, J = 7.2 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) 39.2 (d, J = 1.5 Hz), 46.4 (d, J = 9.0 Hz), 79.7, 116.7 (d, J = 24.0 Hz), 124.7 (d, J = 3.0 Hz), 125.0 (d, J = 12.0 Hz), 127.7 (d, J = 46.5 Hz), 129.0, 130.7 (d,

J = 1.5 Hz), 135.1 (d, J = 9.0 Hz), 139.1, 161.2, 162.8, 195.1 (d, J = 4.5 Hz) ppm; HRMS (ESI-TOF) calcd for $C_{16}H_{14}FNNaO_3$ ([M + Na^+]) = 310.0850, Found: 310.0856.

1-(Naphthalen-2-yl)-4-nitro-3-phenylbutan-1-one (7r). ($C_{20}H_{17}NO_3$) Reaction time 3 d, 88% yield, 90% *ee*. $[\alpha]_D^{20}$ = 63.8 (*c* 0.282 in $CHCl_3$). HPLC DAICEL CHIRALCEL IA, 2-propanol/*n*-hexane = 20/80, flow rate = 1.0 mL/min, λ = 254 nm, retention time: 11.9 min (minor) and 17.4 min (major); ^{1}H NMR (600 MHz, $CDCl_3$) 3.55–3.63 (m, 2H), 4.29 (m, 1H), 4.73 (dd, J = 7.8 Hz, 12.6 Hz, 1H), 4.88 (dd, J = 6.6 Hz, 12.6 Hz, 1H), 7.27–7.36 (m, 5H), 7.55–7.63 (m, 2H), 7.86–7.99 (m, 4H), 8.42 (s, 1H) ppm.

1-(Furan-2-yl)-4-nitro-3-phenylbutan-1-one (7s). ($C_{14}H_{13}NO_4$) Reaction time 4 d, 40% yield, 79% *ee*. $[\alpha]_D^{20}$ = 31.6 (*c* 0.228 in $CHCl_3$). HPLC DAICEL CHIRALCEL ADH, 2-propanol/*n*-hexane = 20/80, flow rate = 1.0 mL/min, λ = 254 nm, retention time: 10.1 min (minor) and 12.7 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) 3.24–3.39 (m, 2H), 4.19 (m, 1H), 4.68 (dd, J = 8.0 Hz, 12.4 Hz, 1H), 4.80 (dd, J = 8.0 Hz, 12.4 Hz, 1H), 6.53–6.54 (m, 1H), 7.18–7.19 (m, 1H), 7.27–7.35 (m, 5H), 7.57 (m, 1H) ppm.

Acknowledgements

We appreciate the National Natural Science Foundation of China (Nos. 20732003 and 20602025) and the Ministry of Education (2007061009) for financial support. We also thank Sichuan University Analytical & Testing Center for NMR analysis and the State Key Laboratory of Biotherapy for HRMS analysis.

References

1 For general reviews on conjugate additions see: (*a*) P. Perlmutter, *Conjugate Addition Reactions in Organic Synthesis*, (Eds., J. E. Baldwin, P. D. Magnus), Pergamon Press, Oxford, 1992; (*b*) M. E. Jung, *Comprehensive Organic Synthesis*, (Ed., B. M. Trost), Pergamon Press, Oxford, 1991, vol. 4, pp. 1.

2 For reviews on catalytic asymmetric Michael additions, see: (*a*) K. Tomioka, Y. Nagaoka and M. Yamaguchi, in *Comprehensive Asymmetric Catalysis*, (Eds., E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, 1999, Vol. 3, pp. 1105; (*b*) M. P. Sibi and S. Manyem, *Tetrahedron*, 2000, **56**, 8033; (*c*) N. Krause and A. Hoffmann-Röder, *Synthesis*, 2001, 171; (*d*) M. Kanai and M. Shibasaki, in *Catalytic Asymmetric Synthesis*, (Ed., I. Ojima), 2nd ed., Wiley, New York, 2000, pp. 569; (*e*) S. B. Tsogoeva, *Eur. J. Org. Chem.*, 2007, 1701; (*f*) J. L. Vicario, D. Badía and L. Carrillo, *Synthesis*, 2007, 2065; (*g*) D. Almasi, D. A. Alonso and C. Nájera, *Tetrahedron: Asymmetry*, 2007, **18**, 299; (*h*) O. M. Berner, L. Tedeschi and D. Enders, *Eur. J. Org. Chem.*, 2002, 1877; (*i*) K. Fagnou and M. Lautens, *Chem. Rev.*, 2003, **103**, 169; (*j*) R. Ballini, G. Bosica, D. Fiorini, A. Palmieri and M. Petrini, *Chem. Rev.*, 2005, **105**, 933; (*k*) S. Mukherjee, J. W. Yang, S. Hoffmann and B. List, *Chem. Rev.*, 2007, **107**, 5471; (*l*) S. Sulzer-Mossé and A. Alexakis, *Chem. Commun.*, 2007, 3123; (*m*) L. W. Xu and Y. X. Lu, *Org. Biomol. Chem.*, 2008, **6**, 2047; (*n*) L. W. Xu, J. Luo and Y. X. Lu, *Chem. Commun.*, 2009, 1807.

3 (*a*) B. C. Hong, M. F. Wu, H. C. Tseng and J. H. Liao, *Org. Lett.*, 2006, **8**, 2217; (*b*) M. Marigo, S. Bertelsen, A. Landa and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2006, **128**, 5475.

4 (*a*) P. Melchiorre and K. A. Jørgensen, *J. Org. Chem.*, 2003, **68**, 4151; (*b*) M. T. Hechavarria Fonseca and B. List, *Angew. Chem., Int. Ed.*, 2004, **43**, 3958; (*c*) T. J. Peelen, Y. G. Chi and S. H. Gellman, *J. Am. Chem. Soc.*, 2005, **127**, 11598; (*d*) J. Wang, H. Li, L. S. Zu and W. Wang, *Adv. Synth. Catal.*, 2006, **348**, 425.

5 S. Sulzer-Mossé and A. Alexakis, *Org. Lett.*, 2005, **7**, 4361.

6 S. Sulzer-Mossé, M. Tissot and A. Alexakis, *Org. Lett.*, 2007, **9**, 3749.

7 (*a*) J. M. Betancort, K. Sakthivel, R. Thayumannavan and C. F. Barbas III, *Tetrahedron Lett*, 2001, **42**, 4441; (*b*) C. L. Cao, X. L. Sun, J. L. Zhou and Y. Tang, *J. Org. Chem.*, 2007, **72**, 4073; (*c*) J. M. Betancort, K. Sak, R. Thayumanavan, F. Tanaka and C. F. Barbas III, *Synthesis*, 2004, 1509; (*d*) G. L. Zhao, J. Vesely, J. L. Sun, K. E. Christensen, C. Bonneau and A. Córdova, *Adv. Synth. Catal.*, 2008, **350**, 657.

8 (*a*) T. Ishii, S. Fujioka, Y. Sekiguchi and H. Kotsuki, *J. Am. Chem. Soc.*, 2004, **126**, 9558; (*b*) B. List, P. Pojarlier and H. J. Martin, *Org. Lett.*, 2001, **3**, 2423; (*c*) W. Wang, J. Wang and H. Li, *Angew. Chem., Int. Ed.*, 2005, **44**, 1369; (*d*) Y. Hayashi, H. Gotoh, T. Hayashi and M. Shoji, *Angew. Chem., Int. Ed.*, 2005, **44**, 4212; (*e*) S. Z. Luo, X. L. Mi, L. Zhang, S. Liu, H. Xu and J. P. Cheng, *Angew. Chem., Int. Ed.*, 2006, **45**, 3093; (*f*) S. V. Pansare and K. Pandya, *J. Am. Chem. Soc.*, 2006, **128**, 9624; (*g*) S. B. Tsogoeva and S. W. Wei, *Chem. Commun.*, 2006, 1451; (*h*) C. L. Cao, M. C. Ye, X. L. Sun and Y. Tang, *Org. Lett.*, 2006, **8**, 2901; (*i*) L. S. Zu, J. Wang, H. Li and W. Wang, *Org. Lett.*, 2006, **8**, 3077; (*j*) J. Wang, H. Li, B. Lou, L. S. Zu, H. Guo and W. Wang, *Chem.–Eur. J.*, 2006, **12**, 4321; (*k*) N. Mase, K. Wattanbe, H. Yoda, K. Takabe, F. Tanaka and C. F. Barbas III, *J. Am. Chem. Soc.*, 2006, **128**, 4966; (*l*) D. Enders, S. Chow and Eur, *J. Org. Chem.*, 2006, 4578; (*m*) Y. M. Xu and A. Córdova, *Chem. Commun.*, 2006, 460; (*n*) Y. M. Xu, W. B. Zou, H. Sundén, I. Ibrahem and A. Cordóva, *Adv. Synth. Catal.*, 2006, **348**, 418; (*o*) P. Kotrusz, S. Toma, H. G. Schmalz and A. Adler, *Eur. J. Org. Chem.*, 2004, 1577; (*p*) O. Andrey, A. Alexakis and G. Bernardinelli, *Org. Lett.*, 2003, **5**, 2559; (*q*) A. Alexakis and O. Andrey, *Org. Lett.*, 2002, **4**, 3611; (*r*) K. Sakthivel, W. Notz, T. Bui and C. F. Barbas III, *J. Am. Chem. Soc.*, 2001, **123**, 5260; (*s*) C. Palomo, S. Vera, A. Mielgo and E. Gómez-Bengona, *Angew. Chem., Int. Ed.*, 2006, **45**, 5984; (*t*) D. Enders, M. R. M. Hüttl, C. Grondal and G. Raabe, *Nature*, 2006, **441**, 861; (*u*) H. M. Li, Y. Wang, L. Tang, F. H. Wu, X. F. Liu, C. Y. Guo, B. M. Foxman and L. Deng, *Angew. Chem., Int. Ed.*, 2005, **44**, 105; (*v*) M. Terada, H. Ube and Y. Yaguchi, *J. Am. Chem. Soc.*, 2006, **128**, 1454.

9 (*a*) H. B. Huang and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2006, **128**, 7170; (*b*) K. Liu, H. F. Cui, J. Nie, K. Y. Dong, X. J. Li and J. A. Ma, *Org. Lett.*, 2007, **9**, 923; (*c*) X. X. Jiang, Y. F. Zhang, A. S. C. Chan and R. Wang, *Org. Lett.*, 2009, **11**, 153; (*d*) D. Enders and A. Seki, *Synlett*, 2002, **1**, 26; (*e*) R. Rasappan and O. Reiser, *Eur. J. Org. Chem.*, 2009, 1305; (*f*) F. Xue, S. L. Zhang, W. H. Duan and W. Wang, *Adv. Synth. Catal.*, 2008, **350**, 2194.

10 (*a*) J. Liu, Z. G. Yang, Z. Wang, F. Wang, X. H. Chen, X. H. Liu, X. M. Feng, Z. S. Su and C. W. Hu, *J. Am. Chem. Soc.*, 2008, **130**, 5654; (*b*) Z. G. Yang, J. Liu, X. H. Liu, Z. Wang, X. M. Feng, Z. S. Su and C.W. Hu, *Adv. Synth. Catal.*, 2008, **350**, 2001.

11 (*a*) N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka and C. F. Barbas, III, *J. Am. Chem. Soc.*, 2006, **128**, 734; (*b*) Y. Hayashi, T. Sumiya, J. Takahashi, H. Gotoh, T. Urushima and M. Shoji, *Angew. Chem., Int. Ed.*, 2006, **45**, 958; (*c*) N. Mase, K. Watanabe, H. Yoda, K. Takabe, F. Tanaka and C. F. Barbas, III, *J. Am. Chem. Soc.*, 2006, **128**, 4966; (*d*) J. M. Huang, X. T. Zhang and D. W. Armsttrong, *Angew. Chem., Int. Ed.*, 2007, **46**, 9073; (*e*) Z. Q. Jiang, Z. A. Liang, X. Y. Wu and Y. X. Lu, *Chem. Commun.*, 2006, 2801; (*f*) X. Y. Wu, Z. Q. Jiang, H. M. Shen and Y. X. Lu, *Adv. Synth. Catal.*, 2007, **349**, 812.

12 (*a*) N. Halland, P. S. Abured and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2003, **42**, 661; (*b*) V. Wascholowski, K. R. Knudsen, C. E. T. Mitchell and S. V. Ley, *Chem.–Eur. J.*, 2008, **14**, 6155; (*c*) Y. Q. Yang and G. Zhao, *Chem.–Eur. J.*, 2008, **14**, 10888.

13 (*a*) D. A. Evans, S. Mito and D. Seidel, *J. Am. Chem. Soc.*, 2007, **129**, 11583; (*b*) P. Suresh and K. Pitchumani, *Tetrahedron: Asymmetry*, 2008, **19**, 2037.

14 (*a*) C. F. H. Allen and F. W. Spangler, *Org. Syn. Coll.*, 1955, **Vol. 3**, 377; (*b*) M. S. Newman and D. K. Phillips, *J. Am. Chem. Soc.*, 1959, **81**, 3667; (*c*) M. S. Newman and H. R. Flanagan, *J. Org. Chem.*, 1958, **23**, 796; (*d*) G. Kumaran and G. H. Kulkarni, *Synthesis.*, 1995, 1545; (*e*) J. T. Liu and C. F. Yao, *Tetrahedron Lett.*, 2001, **42**, 6147; (*f*) R. K. Bowman and J. S. Johnson, *J. Org. Chem.*, 2004, **69**, 8537.