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Chloramphenicol base chemistry. Part 11:[1] chloramphenicol base-derived thiourea-catalyzed enantioselective Michael addition of malononitrile to α,β-unsaturated ketones

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ABSTRACT

The first chloramphenicol base-derived thiourea-catalyzed enantioselective Michael addition of malononitrile to α,β-unsaturated ketones is reported. The Michael adducts were obtained in good to excellent yields (up to 98% yield) and enantioselectivities (up to 94% *ee*). This reaction has a broad substrate scope to various α,β-unsaturated ketones. With this in mind, this methodology was successfully applied to the synthesis of a chiral piperidone, an advanced building block for dihydropyridinone $P2X_7$ receptor antagonists.

1. Introduction

It is well known that there has been a growing interest in the catalytic asymmetric Michael addition of malononitriles to α,β-unsaturated ketones,[2] versatile building blocks for the preparation of pharmaceuticals, agrochemicals and natural products.[3] To date, a variety of organocatalysts have been discovered and proven to be highly effective and selective for this transformation.[4] In particular, chiral bifunctional amine-thiourea organocatalysts provide an important subset (see Fig. 1),[5] such as the cinchona alkaloids **1**, cyclohexane diamine **2**, diphenyl ethylene diamine **3**, natural amino acid **4** and Brønsted acid/base BINOL **5**, because of their simultaneous activation of both nucleophile and electrophile through efficient double-hydrogen-bonding interactions. However, cinchona alkaloid-type organocatalysts are the most common, while organocatalysts bearing unnatural scaffolds are rare. Therefore, the search for alternative cost-effective and easily prepared organocatalysts for the asymmetric Michael additions is warranted in asymmetric catalysis.

Over the past few decades, we have developed an array of efficient organocatalysts, which are readily available from the very inexpensive chiral chloramphenicol base scaffold, including ureas, thioureas **6**, sulfonamides and squaramides, and reported their application in various asymmetric transformations with high stereocontrol.[6]

Motivated by the promising catalytic results and our continuing interest in the chloramphenicol base organocatalysis, we decided to investigate the possibility of enantioselective Michael additions of malononitrile to α,β-unsaturated ketones using our previously

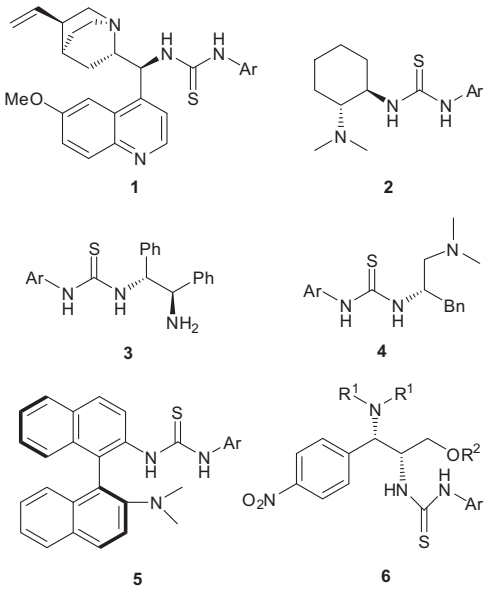

Figure 1. Structures of bifunctional thiourea organocatalysts.

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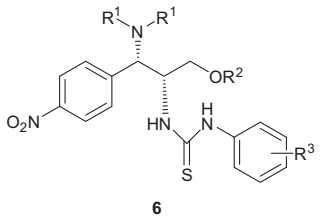
developed bifunctional organocatalysts with a chloramphenicol base motif.[6d] Herein, we report an account of the results on this subject and their application in the asymmetric synthesis of a key chiral piperidone intermediate for the preparation of dihydropyridinone $P2X_7$ receptor antagonists.[6b,7]

2. Results and discussion

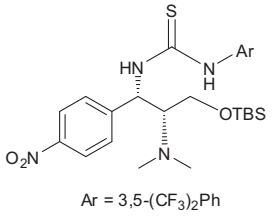
We initially selected the asymmetric Michael addition of malononitrile to α,β-unsaturated ketone **11a** as a model reaction. A variety of different bifunctional chloramphenicol base-derived organocatalysts were screened against this reaction in toluene at room temperature using a catalyst loading of 10 mol% (Table 1). The results revealed that the outcome of the Michael addition reaction varied greatly depending on the nature of the organocatalyst. Thiourea catalysts **6a–c** bearing modifications totheir tertiary amine moiety were used in a similar manner to provide the desired adduct **13a** in moderate to good yields (67–81%) and with good enantioselectivities (80–86% *ee*) (Table 1, entries 1–3). Catalyst **6a** gave the most promising results in terms of the enantioselectivity (86% *ee*) and chemical yield (81%) of the product (Table 1, entry 1). Catalyst **6e** bearing a *p*-methyl substituent on the aromatic ring of its thiourea-moiety gave much lower enantioselectivity than catalyst **6d** bearing a *p*-trifluoromethyl group at the same position (Table 1, entries 4 and 5). Furthermore, catalyst **6f** without a *tert*-butyldimethylsilyl (TBS) group showed lower enantioselectivity (45% *ee*, Table 1, entry 6). Catalyst **7** gave lower enantioselectivity than its regioisomeric counterpart **6a** (56% *ee*, Table 1, entry 7). In addition to thiourea organocatalysts, we also examined other types of bifunctional organocatalysts derived from chloramphenicol base. Moderate enantioselectivities were obtained with the urea catalyst **8** (65% *ee*) and the squaramide catalyst **9** (68% *ee*) (Table 1, entries 8–9). In contrast, the use of sulfonamide **10** featuring a single N–H group led to a considerable decrease in the yield and enantioselectivity (20% yield, 4% *ee*, Table 1, entry 10).

Table 1
The screening of different bifunctional organocatalysts derived from chloramphenicol base[a]

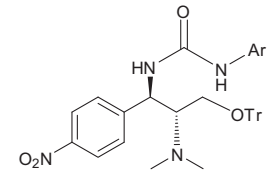


6

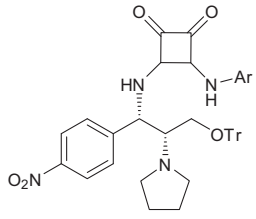
6a: R^1 = Me, R^2 = TBS, R^3 = 3,5-$(CF_3)_2$;
6b: R^1 = $(CH_2)_4$, R^2 = TBS, R^3 = 3,5-$(CF_3)_2$;
6c: R^1 = $(CH_2)_5$, R^2 = TBS, R^3 = 3,5-$(CF_3)_2$;
6d: R^1 = Me, R^2 = TBS, R^3 = 4-CF_3;
6e: R^1 = Me, R^2 = TBS, R^3 = 4-CH_3;
6f: R^1 = Me, R^2 = OH, R^3 = 3,5-$(CF_3)_2$.



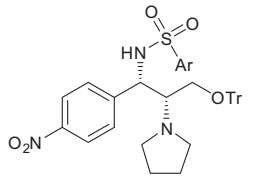
Ar = 3,5-$(CF_3)_2$Ph
7



Ar = 3,5-$(CF_3)_2$Ph, Tr = Ph_3C
8



Ar = 3,5-$(CF_3)_2$Ph, Tr = Ph_3C
9



Ar = 3,5-$(CF_3)_2$Ph, Tr = Ph_3C
10

Entry	Catalyst	Yield (%)[b]	*ee* (%)[c,d]
1	**6a**	81	86
2	**6b**	67	82
3	**6c**	71	80
4	**6d**	63	76
5	**6e**	68	34
6	**6f**	88	45
7	**7**	69	56
8	**8**	80	65
9	**9**	66	68
10	**10**	20	4

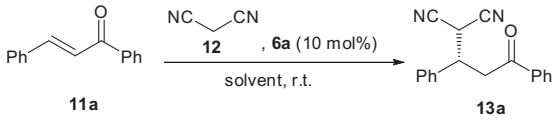
[a] Unless otherwise noted, all reactions were carried out with α, β-unsaturated ketone **11a** (0.2 mmol), malononitrile **12** (0.3 mmol) and catalyst (10 mol%) in 0.4 mL toluene at r.t. for 7 days.
[b] Yield of isolated product.
[c] Determined by HPLC.
[d] Absolute configuration was determined by comparing the sign of the specific rotation of the major enantiomer with known data.

Having identified thiourea **6a** as the optimal catalyst for this transformation, we proceeded to investigate the effect of the solvent on the reactivity and enantioselectivity of the asymmetric Michael addition of malononitrile to α,β-ketone **11a** at room temperature. The results revealed that toluene gave the best enantioselectivity (86% *ee*) (Table 2, entry 1), whereas MeCN and EtOH gave low yields of the desired addition product with no enantioselectivity (Table 2, entries 9–10). A slight decrease in the enantioselectivity was observed in xylene (83% *ee*) (Table 2, entry 2). Hexane, CH_2Cl_2 and $CHCl_3$ gave moderate yields of the desired addition product (55–74%) with reasonable enantioselectivities (67–76% *ee*), while methyl *tert*-butyl ether gave a low yield (22%) (Table 2, entries 3–6). The use of 1,4-dioxane or tetrahydrofuran (THF) led to a decrease in the enantioselectivity (38–50% *ee*) and a poor yield (12–18%) (Table 2, entries 7 and 8). Some of the other reaction parameters were also investigated, including the catalyst loading, concentration and temperature, but offered very little improvement in the reaction rate with equivalent and lower levels of enantioselectivities (55–86% *ee*) (Table 2, entries 11–13).

With the optimal reaction conditions in hand, we proceeded to investigate the scope of this asymmetric Michael addition by reacting malononitrile with a variety of α,β-unsaturated ketones **11**, and the results are shown in Table 3. Substrates bearing a variety of different electronic and sterically demanding substituents on the aromatic ring (R^1) were well tolerated, including naphthyl and heteroaromatic groups, which reacted smoothly to afford the corresponding addition products in moderate to high yields (65–98%) and with good enantioselectivities (78–86% *ee*) (Table 3, entries 1–18). 2,4-Dien-1-one **11s** afforded the 1,4-adduct with 84% *ee* (Table 3, entry 19). When R^1 were alkyl groups, good enantioselectivities (81–88% *ee*) were also obtained, albeit with low yields (25–50%) (Table 3, entries 20–21). A variety of different substituents were also tolerated on the aromatic ring of the R^2 group, with the corresponding adducts being obtained in high yields (85–95%) with good to high enantioselectivities (77–94% *ee*) after a long reaction period (Table 3, entries 22–26).

To explain the stereoselectivity observed in this reaction, we have proposed a plausible reaction pathway for the Michael addition of malononitrile **12** to α,β-unsaturated ketone **11a** in the presence of the bifunctional chloramphenicol base-derived thiourea organocatalyst **6a**, which is shown in Scheme 1. The chloramphenicol base-derived thiourea organocatalyst **6a** plays a bifunctional role in the catalytic process. Malononitrile **12** would be deprotonated by the tertiary amine moiety of **6a**, and the resulting pronucleophile would be activated by hydrogen bonding with the protonated tertiary amine nitrogen, whereas the thiourea moiety of **6a** would activate the carbonyl group of the α,β-unsaturated ketone **11a** through double hydrogen bonding, to give a ternary complex. The pronucleophile would subsequently attack the acti-

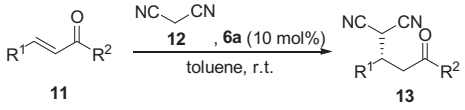
Table 2
Optimization of the reaction conditions with catalyst **6a**[a]



Entry	Solvent	*t* (d)	Yield (%)[b]	*ee* (%)[c,d]
1	Toluene	7	81	86
2	Xylene	7	89	83
3	Hexane	7	71	67
4	$CHCl_3$	7	74	76
5	CH_2Cl_2	7	55	68
6	MTBE	7	22	74
7	1,4-Dioxane	7	18	50
8	THF	7	12	38
9	EtOH	7	21	6
10	MeCN	7	15	rac
11[e]	Toluene	6.5	82	86
12[f]	Toluene	4	93	63
13[g]	Toluene	5	73	55

[a] Unless otherwise noted, all reactions were carried out with α, β-unsaturated ketone **11a** (0.2 mmol), malononitrile **12** (0.3 mmol) and catalyst **6a** (10 mol%) in 0.4 mL solvent at r.t.
[b] Yield of isolated product.
[c] Determined by HPLC.
[d] Absolute configuration was determined by comparing the sign of the specific rotation of the major enantiomer with known data.
[e] 20 mol% catalyst was used.
[f] 0.2 mL toluene was used.
[g] Reaction was performed at 50 °C.

Table 3
Asymmetric Michael addition of malononitrile **12** to a series of α,β-unsaturated ketones **11** in the presence of catalyst **6a**[a]



Entry	R^1	R^2	*t* (d)	Yield (%)[b]	*ee* (%)[c,d]
1	Ph	Ph	7	81 **13a**	86
2	4-MePh	Ph	7	81 **13b**	82
3	4-MeOPh	Ph	7	78 **13c**	80
4	3-MeOPh	Ph	7	83 **13d**	80
5	4-FPh	Ph	7	98 **13e**	79
6	2-FPh	Ph	7	89 **13f**	78
7	4-ClPh	Ph	7	96 **13g**	82
8	3-ClPh	Ph	7	91 **13h**	80
9	4-BrPh	Ph	7	95 **13i**	84
10	3-BrPh	Ph	7	88 **13j**	80
11	2-BrPh	Ph	7	85 **13k**	82
12	4-CF_3Ph	Ph	7	96 **13l**	82
13	3-CF_3Ph	Ph	7	93 **13m**	80
14	4-^{t}BuPh	Ph	8	65 **13n**	80
15	3,4-Cl_2Ph	Ph	8	88 **13o**	84
16	2-Naphthyl	Ph	7	85 **13p**	82
17	2-Thienyl	Ph	8	88 **13q**	75
18	5-Cl-2-Thienyl	Ph	8	83 **13r**	79
19	$Ph(CH)_2$	Ph	10	30 **13s**	84
20	Cyclohexyl	Ph	10	50 **13t**	86
21	*t*-Bu	Ph	10	25 **13u**	88
22	Ph	4-MeOPh	8	90 **13v**	94
23	Ph	4-NO_2Ph	3.5	95 **13w**	85
24	Ph	4-ClPh	8	93 **13x**	77
25	Ph	2-Naphthyl	8	85 **13y**	87
26	Ph	2-Thienyl	8	95 **13z**	91

[a] Unless otherwise noted, all reactions were carried out with α, β-unsaturated ketones **11** (0.2 mmol), malononitrile **12** (0.3 mmol) and catalyst **6a** (10 mol%) in 0.4 mL toluene at r.t.
[b] Yield of isolated product.
[c] Determined by HPLC.
[d] Absolute configuration was determined by comparing the sign of the specific rotation of the major enantiomer with known data.

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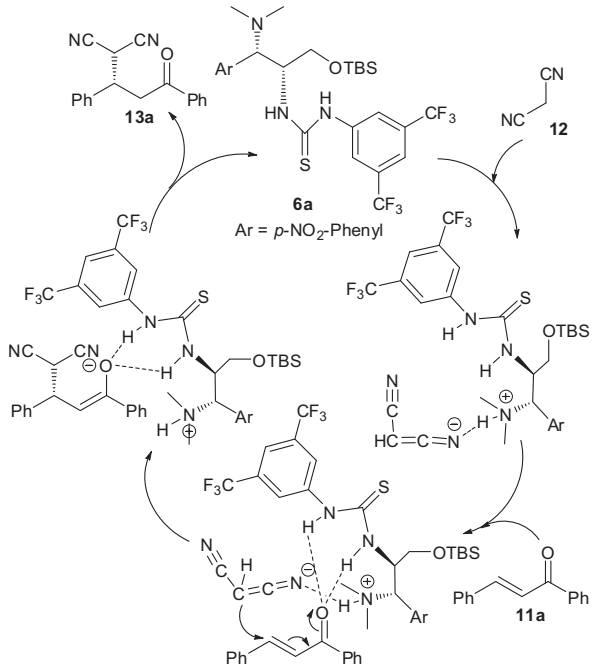
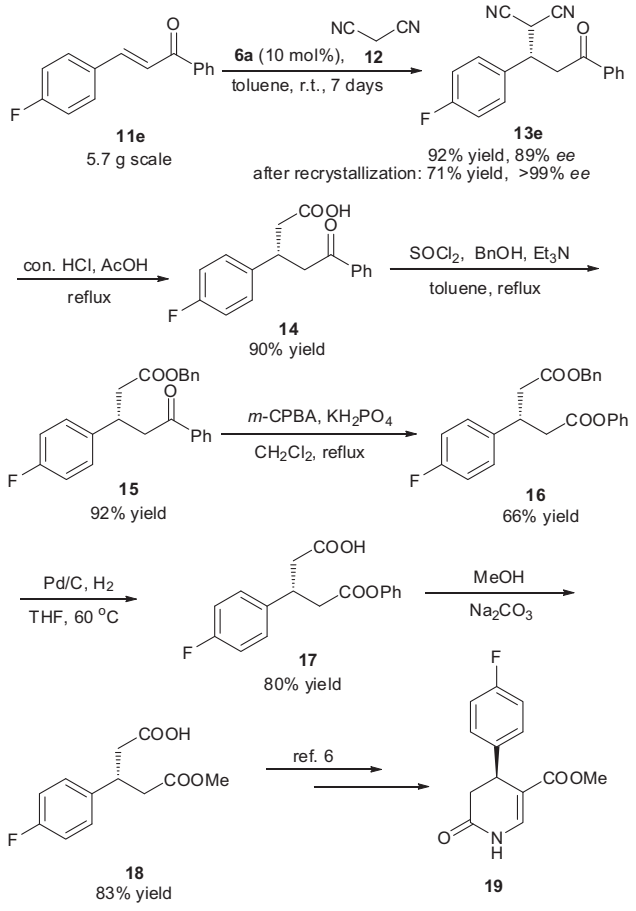


Scheme 1. Plausible mechanism for the Michael addition of malononitrile **12** to α,β-unsaturated ketone **11a** in the presence of the bifunctional chloramphenicol base-derived thiourea organocatalyst **6a**.



Scheme 2. Application of **6a** in the asymmetric synthesis of (*S*)-piperidone **19**.

vated **11a** from the *Si* face leading to the formation of the (*S*)-configured product as the major stereoisomer, which is consistent with the observed results.

To illustrate the synthetic utility of this methodology, we conducted a novel enantioselective synthesis of the chiral piperidone (*S*)-**19**, which is a key intermediate in the synthesis of dihydropyridinone $P2X_7$ receptor antagonists (Scheme 2).[6b,7] Our synthetic strategy started from the known α,β-unsaturated ketone **11e**, which was obtained *via* the aldol condensation of 4-fluorobenzaldehyde and acetophenone under standard conditions.[8] The asymmetric Michael addition of malononitrile to **11e** in the presence of 10 mol% catalyst **6a** was carried out in toluene at room temperature to give the addition product (*S*)-**13e** in 92% yield and with 89% *ee*. The enantiomeric purity of **13e** was upgraded to >99% *ee* following a single recrystallization from *n*-hexane/EtOAc (8:1, v/v). The hydrolysis and decarboxylation of (*S*)-**13e** with acetic acid and concentrated HCl were conducted as a one-pot procedure to give acid **14** in 90% yield. Acid **14** was treated with thionyl chloride in toluene at reflux, and the resulting acid chloride was reacted with benzyl alcohol and triethylamine to give ester **15** in 92% yield. Ester **15** was converted into diester **16** in 66% yield *via* a Baeyer–Villiger oxidation using *m*-chloroperoxy benzoic acid (*m*CPBA) as an oxidant in the presence of KH_2PO_4 in boiling CH_2Cl_2.[9] Diester **16** was then debenzylated by hydrogenation with Pd/C in THF at 60 °C to provide acid **17**, which was transesterified in MeOH with Na_2CO_3 to furnish **18** in 83% yield. The chiral acid methyl ester **18** was converted into chiral piperidone (*S*)-**19** through sequential α-formylation and cyclization reactions using Huang's procedure.[7]

3. Conclusion

In conclusion, bifunctional chloramphenicol base-derived thiourea organocatalysts were successfully applied for the first time to the asymmetric Michael addition of malononitrile to α,β-unsaturated ketones. The optimal catalyst **6a** allowed for the addition of malononitrile to a broad range of α,β-unsaturated ketones to afford the corresponding adducts with good yields and enantioselectivities. Moreover, the utility of this methodology was demonstrated by the synthesis of the chiral piperidone, an advanced building block in the construction of $P2X_7$ receptor antagonists. Further investigation into the application of these catalysts in other asymmetric transformations is currently underway in our laboratory.

4. Experimental

4.1. General

Unless otherwise specified, all reagents and solvent were purchased from commercial sources and used as received. ^1H (400 MHz) and ^{13}C (100 MHz) NMR were recorded on a Bruker Avance 400 spectrometer in $CDCl_3$ or d_6-DMSO using tetramethyl silane (TMS) as internal standards. Coupling constant (*J*) values are given in Hz. Melting points were measured on WRS-1B digital melting-point apparatus. Products were purified by flash column chromatography on silica gel purchased from Qingdao Haiyang Chemical Co., Ltd. Optical rotations were measured by a Rudolph AUTOPOL I Automatic Polarimeter. HRMS were recorded on a Bruker micrOTOF spectrometer. HPLC analysis were performed with Daicel Chiralpak AD-H column (25 cm × 4.6 mm × 5 μm), Chiralpak OD-H column (25 cm × 4.6 mm × 5 μm) and Chiralpak AS-H column (25 cm × 4.6 mm × 5 μm). All catalysts were prepared according to reported procedure.[6d] α,β-Unsaturated ketones were prepared *via* aldol condensation using standard conditions.[8]

4.2. Typical procedure for asymmetric Michael addition of malononitrile 12 to α,β-unsaturated ketones 11

To a stirred solution of the α,β-unsaturated ketones **11** (0.2 mmol) and catalyst **6a** (12.5 mg, 0.02 mmol) in toluene (0.4 mL) was added the malononitrile **12** (0.3 mmol) at room temperature. The reaction was monitored by TLC; after complete consumption of the α,β-unsaturated ketones **11**, the solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography with petroleum ether (PE)/EtOAc = 8/1.

4.2.1. (*S*)-2-(3-Oxo-1,3-diphenylpropyl)malononitrile 13a

White solid, yield 81%, 86% *ee*; m.p. 123.2–128.1 °C; $[\alpha]_D^{20} = -4.0$ (*c* 1.0, CH_2Cl_2) (lit.[2h] $[\alpha]_D^{20} = -12.6$ (*c* 0.27, CH_2Cl_2)); chiral HPLC (Chiralcel AD-H column), hexane/*i*-PrOH = 80/20, flow rate: 1.0 mL/min, UV detection at 254 nm, t(minor) = 8.965 min, t(major) = 11.695 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97 (d, *J* = 7.6 Hz, 2H), 7.63 (t, *J* = 7.3 Hz, 1H), 7.54–7.37 (m, 7H), 4.64 (d, *J* = 5.1 Hz, 1H), 3.97 (dt, *J* = 7.9, 5.4 Hz, 1H), 3.78–3.59 ppm (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.69, 136.60, 135.85, 134.19, 129.37, 129.20, 128.96, 128.15, 128.05, 111.94, 111.78, 41.24, 40.15, 28.84 ppm.

4.2.2. (*S*)-2-(1-(4-Methylphenyl)-3-oxo-3-phenylpropyl)malononitrile 13b

Yellow oil, yield 81%, 82% *ee*; $[\alpha]_D^{20} = -1.3$ (*c* 1.0, CH_2Cl_2) (lit.[2h] $[\alpha]_D^{20} = -2.4$ (*c* 0.166, CH_2Cl_2)); chiral HPLC (Chiralcel AD-H column), hexane/*i*-PrOH = 80/20, flow rate: 1.0 mL/min, UV detection at 254 nm, t(minor) = 8.767 min, t(major) = 12.262 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.01–7.93 (m, 2H), 7.68–7.58 (m, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 4.62 (d, *J* = 5.1 Hz, 1H), 3.93 (dt, *J* = 8.3, 5.3 Hz, 2H), 3.66 ppm (qd, *J* = 18.4, 6.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.78, 139.08, 135.91, 134.14, 133.61, 130.01, 128.95, 128.15, 127.90, 112.08, 111.89, 40.93, 40.20, 29.00, 21.19 ppm.

4.2.3. (*S*)-2-(1-(4-Methoxyphenyl)-3-oxo-3-phenylpropyl)malononitrile 13c

Yellow solid, yield 78%, 80% *ee*, m.p. 110.8–114.3 °C; $[\alpha]_D^{20} = -2.0$ (*c* 0.48, CH_2Cl_2) (lit.[2h] $[\alpha]_D^{20} = -0.5$ (*c* 0.208, CH_2Cl_2)); chiral HPLC (Chiralcel AD-H column), hexane/*i*-PrOH = 80/20, flow rate: 1.0 mL/min, UV detection at 254 nm, t(minor) = 11.481 min, t(major) = 17.773 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.05–7.88 (m, 1H), 7.73–7.57 (m, 2H), 7.49 (dd, *J* = 10.6, 4.8 Hz, 1H), 7.44–7.30 (m, 2H), 7.01–6.88 (m, 2H), 4.60 (d, *J* = 5.1 Hz, 1H), 3.92 (dt, *J* = 8.3, 5.3 Hz, 1H), 3.82 (s, 3H), 3.64 ppm (qd, *J* = 18.3, 6.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.82, 160.09, 135.89, 134.15, 129.22, 128.95, 128.52, 128.14, 114.68, 112.12, 111.89, 55.36, 40.62, 40.28, 29.16 ppm.

4.2.4. (*S*)-2-(1-(3-Methoxyphenyl)-3-oxo-3-phenylpropyl)malononitrile 13d

Yellow oil, yield 83%, 80% *ee*, $[\alpha]_D^{20} = -3.13$ (*c* = 0.37 in CH_2Cl_2) (lit.[2h] $[\alpha]_D^{20} = -8.33$ (*c* = 0.144 in CH_2Cl_2)); chiral HPLC (Chiralcel AD-H column), hexane/*i*-PrOH = 80/20, flow rate: 1.0 mL/min, UV detection at 254 nm, t(minor) = 10.298 min, t(major) = 11.945 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98–7.92 (m, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.01 (d, *J* = 7.7 Hz, 1H), 6.97 (t, *J* = 2.0 Hz, 1H), 6.91 (dd, *J* = 8.3, 2.4 Hz, 1H), 4.61 (d, *J* = 5.2 Hz, 1H), 3.96–3.87 (m, 1H), 3.81 (s, 3H), 3.72–3.58 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.67, 160.12, 138.15, 135.87, 134.16, 130.43, 128.95, 128.16, 120.14, 114.36, 114.06, 112.03, 111.90, 55.38, 41.21, 40.19, 28.79 ppm.

4.2.5. (*S*)-2-(1-(4-Fluorophenyl)-3-oxo-3-phenylpropyl)malononitrile 13e

White solid, yield 98%, 79% *ee*; m.p. 103.8–106.2 °C; $[\alpha]_D^{20} = -0.4$ (*c* 1.0, CH_2Cl_2) (lit.[2h] $[\alpha]_D^{20} = -5.6$ (*c* 0.288 in CH_2Cl_2)); chiral HPLC (Chiralcel AD-H column), hexane/*i*-PrOH = 80/20, flow rate: 1.0 mL/min, UV detection at 254 nm, t(minor) = 9.023 min, t(major) = 12.8 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.00–7.93 (m, 2H), 7.67–7.60 (m, 1H), 7.55–7.41 (m, 4H), 7.18–7.09 (m, 2H), 4.62 (d, *J* = 5.1 Hz, 1H), 3.97 (dt, *J* = 8.4, 5.3 Hz, 1H), 3.65 ppm (qd, *J* = 18.4, 6.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.47, 164.27, 161.80, 135.74, 134.29, 132.40, 129.93, 129.84, 129.00, 128.14, 116.50, 116.28, 111.85, 111.63, 40.58, 40.18, 28.93 ppm.

4.2.6. (*S*)-2-(1-(2-Fluorophenyl)-3-oxo-3-phenylpropyl)malononitrile 13f

Yellow solid, yield 89%, 78% *ee*; m.p. 82.8–84.2 °C; $[\alpha]_D^{20} = +20$ (*c* 0.24, CH_2Cl_2); chiral HPLC (Chiralcel AD-H column), hexane/*i*-PrOH = 80/20, flow rate: 1.0 mL/min, UV detection at 254 nm, t(minor) = 9.745 min, t(major) = 11.047 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.01–7.92 (m, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 3H), 7.38 (td, *J* = 7.4, 1.5 Hz, 1H), 7.28–7.10 (m, 2H), 4.63 (d, *J* = 6.3 Hz, 1H), 4.39 (q, *J* = 6.8 Hz, 1H), 3.71 ppm (d, *J* = 6.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.07, 161.78, 159.32, 135.76, 134.17, 130.88, 130.79, 129.11, 129.08, 128.95, 128.13, 125.09, 125.05, 123.80, 123.67, 116.49, 116.27, 111.63, 111.59, 39.52, 35.11, 27.66 ppm. HRMS (ESI$^+$) calcd for $C_{18}H_{13}FN_2O$ $[M+H]^+$ = 293.1085, found: 293.1092.

4.2.7. (*S*)-2-(1-(4-Chlorophenyl)-3-oxo-3-phenylpropyl)malononitrile 13g

Yellow solid, yield 96%, 82% *ee*, m.p. 124.4–126.8 °C; $[\alpha]_D^{20} = -3.4$ (*c* 0.5, CH_2Cl_2) (lit.[2h] $[\alpha]_D^{20} = -5.15$ (*c* 0.194, CH_2Cl_2)); chiral HPLC (Chiralcel AD-H column), hexane/*i*-PrOH = 80/20, flow rate: 1.0 mL/min, UV detection at 254 nm, t(minor) = 9.459 min, t(major) = 14.071 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.99–7.93 (m, 2H), 7.64 (ddd, *J* = 8.7, 2.5, 1.2 Hz, 1H), 7.54–7.47 (m, 2H), 7.45–7.38 (m, 4H), 4.62 (d, *J* = 5.1 Hz, 1H), 3.95 (dt, *J* = 8.3, 5.3 Hz, 1H), 3.65 ppm (qd, *J* = 18.4, 6.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.35, 135.69, 135.27, 134.99, 134.33, 129.59, 129.45, 129.01, 128.14, 111.75, 111.55, 40.71, 40.01, 28.74 ppm.

4.2.8. (*S*)-2-(1-(3-Chlorophenyl)-3-oxo-3-phenylpropyl)malononitrile 13h

Yellow oil, yield 91%, 80% *ee*, $[\alpha]_D^{20} = -0.5$ (*c* 0.3, CH_2Cl_2) (lit.[2h] $[\alpha]_D^{20} = -13.48$ (*c* = 0.178 in CH_2Cl_2)); chiral HPLC (Chiralcel AD-H column), hexane/*i*-PrOH = 80/20, flow rate: 1.0 mL/min, UV detection at 254 nm, t(minor) = 8.205 min, t(major) = 10.137 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.03–7.93 (m, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 2H), 7.45 (d, *J* = 1.2 Hz, 1H), 7.44–7.33 (m, 3H), 4.64 (d, *J* = 5.2 Hz, 1H), 3.95 (dt, *J* = 8.3, 5.3 Hz, 1H), 3.66 ppm (qd, *J* = 18.4, 6.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.26, 138.54, 135.68, 135.23, 134.32, 130.65, 129.49, 129.00, 128.24, 128.16, 126.34, 111.66, 111.49, 40.90, 40.03, 28.60 ppm.

4.2.9. (*S*)-2-(1-(4-Bromophenyl)-3-oxo-3-phenylpropyl)malononitrile 13i

Yellow oil, yield 95%, 84% *ee*, $[\alpha]_D^{20} = -4.28$ (*c* = 1.15 in CH_2Cl_2) (lit.[2t] $[\alpha]_D^{20} = -2.3$ (*c* 0.35, CH_2Cl_2)); chiral HPLC (Chiralcel AD-H column), hexane/*i*-PrOH = 80/20, flow rate: 1.0 mL/min, UV detection at 254 nm, t(minor) = 9.858 min, t(major) = 14.919 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.00–7.93 (m, 1H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.60–7.54 (m, 1H), 7.51 (t, *J* = 7.7 Hz, 1H), 7.34 (d, *J* = 8.5 Hz, 1H), 4.62 (d, *J* = 5.1 Hz, 1H), 3.94 (dt, *J* = 8.4, 5.3 Hz, 1H), 3.65 ppm (qd, *J* = 18.4, 6.9 Hz, 1H). ^{13}C NMR (100 MHz,

$CDCl_3$) δ = 196.32, 135.68, 135.50, 134.33, 132.56, 129.73, 129.01, 128.14, 123.44, 111.72, 111.53, 40.78, 39.95, 28.65 ppm.

4.2.10. (*S*)-2-(1-(3-Bromophenyl)-3-oxo-3-phenylpropyl)malononitrile 13j

Yellow oil, yield 88%, 80% *ee*, $[\alpha]_D^{20}$ = −0.25 (*c* 1.2, CH_2Cl_2) (lit.[2t] $[\alpha]_D^{20}$ = −6.0 (*c* 1.47, CH_2Cl_2)); chiral HPLC (Chiralcel AD-H column), hexane/*i*-PrOH = 80/20, flow rate: 1.0 mL/min, UV detection at 254 nm, t(minor) = 8.464 min, t(major) = 10.569 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.05–7.95 (m, 2H), 7.70–7.61 (m, 2H), 7.54 (dt, *J* = 15.5, 7.9 Hz, 3H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.33 (t, *J* = 7.9 Hz, 1H), 4.66 (d, *J* = 5.2 Hz, 1H), 3.96 (dt, *J* = 8.2, 5.4 Hz, 1H), 3.68 ppm (qd, *J* = 18.4, 6.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.24, 138.75, 135.64, 134.34, 132.46, 131.12, 130.90, 129.00, 128.16, 126.79, 123.36, 111.61, 111.44, 40.84, 40.02, 28.59 ppm.

4.2.11. (*S*)-2-(1-(2-Bromophenyl)-3-oxo-3-phenylpropyl)malononitrile 13k

Yellow oil, yield 85%, 82% *ee*, $[\alpha]_D^{20}$ = +16 (*c* 1.0, CH_2Cl_2); chiral HPLC (Chiralcel AS-H column), hexane/*i*-PrOH = 90/10, flow rate: 1.0 mL/min, UV detection at 254 nm, t(minor) = 23.756 min, t(major) = 27.856 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97 (d, *J* = 7.4 Hz, 2H), 7.72–7.58 (m, 2H), 7.50 (t, *J* = 7.8 Hz, 3H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.29–7.20 (m, 1H), 4.64 (dt, *J* = 12.6, 3.8 Hz, 1H), 3.85–3.74 (m, 1H), 3.74–3.62 ppm (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 195.84, 135.76, 134.17, 134.01, 130.42, 128.96, 128.48, 128.17, 127.91, 124.95, 111.86, 111.31, 77.42, 77.10, 76.79, 39.74, 39.48, 27.34 ppm. HRMS (ESI$^+$) calcd for $C_{18}H_{13}BrN_2O$ $[M+H]^+$ = 353.0284, found: 353.0293.

4.2.12. (*S*)-2-(1-(4-Trifluoromethylphenyl)-3-oxo-3-phenylpropyl) malononitrile 13l

Yellow solid, yield 96%, 82% *ee*; m.p. 88.7–91.1 °C; $[\alpha]_D^{20}$ = −2.5 (*c* 0.8, $CHCl_3$) (lit.[2i] $[\alpha]_D^{20}$ = −7.0 (*c* 0.3, $CHCl_3$)); chiral HPLC (Chiralcel AD-H column), hexane/*i*-PrOH = 80/20, flow rate: 1.0 mL/min, UV detection at 254 nm, t(minor) = 7.251 min, t(major) = 10.627 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.01–7.94 (m, 2H), 7.75–7.68 (m, 2H), 7.63 (dt, *J* = 11.7, 7.8 Hz, 3H), 7.51 (t, *J* = 7.8 Hz, 2H), 4.67 (d, *J* = 5.1 Hz, 1H), 4.05 (dt, *J* = 8.2, 5.3 Hz, 1H), 3.70 ppm (qd, *J* = 18.4, 6.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.13, 140.41, 135.59, 134.41, 129.03, 128.63, 128.14, 126.39, 126.36, 111.56, 111.40, 41.03, 39.89, 28.49 ppm.

4.2.13. (*S*)-2-(1-(3-Trifluoromethylphenyl)-3-oxo-3-phenylpropyl) malononitrile 13m

Yellow oil, yield 93%, 80% *ee*; $[\alpha]_D^{20}$ = −0.4 (*c* = 0.32, CH_2Cl_2); chiral HPLC (Chiralcel AD-H column), hexane/*i*-PrOH = 80/20, flow rate: 1.0 mL/min, UV detection at 254 nm, t(minor) = 6.196 min, t(major) = 8.099 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.02–7.94 (m, 2H), 7.75–7.46 (m, 7H), 4.66 (d, *J* = 5.2 Hz, 1H), 4.06 (dt, *J* = 8.5, 5.2 Hz, 1H), 3.70 ppm (qd, *J* = 18.4, 6.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.18, 137.57, 135.61, 134.39, 131.56, 129.98, 129.02, 128.16, 126.17, 125.01, 124.97, 111.58, 111.40, 77.41, 77.09, 76.77, 41.09, 39.93, 28.60 ppm. HRMS (ESI$^+$) calcd for $C_{19}H_{13}F_3N_2O$ $[M+Na]^+$ = 365.0872, found: 365.0872.

4.2.14. (*S*)-2-(1-(4-*tert*-Butylphenyl)-3-oxo-3-phenylpropyl)-malononitrile 13n

Yellow oil, yield 65%, 80% *ee*; $[\alpha]_D^{20}$ = +37.5 (*c* 0.8, CH_2Cl_2); chiral HPLC (Chiralcel AD-H column), hexane/*i*-PrOH = 80/20, flow rate: 1.0 mL/min, UV detection at 254 nm, t(minor) = 6.66 min, t(major) = 9.393 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97 (d, *J* = 7.5 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.55–7.35 (m, 6H), 4.64 (d, *J* = 5.0 Hz, 1H), 3.95 (dt, *J* = 8.2, 5.3 Hz, 1H), 3.76–3.59 (m, 2H), 1.33 ppm (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.84, 152.17, 135.89, 134.14, 133.49, 128.94, 128.14, 127.70, 126.26, 112.03, 111.86, 40.80, 40.20, 34.68, 31.26, 28.86 ppm. HRMS (ESI$^+$) calcd for $C_{22}H_{22}N_2O$ $[M+H]^+$ = 331.1805, found: 331.1801.

4.2.15. (*S*)-2-(1-(3,4-Dichlorophenyl)-3-oxo-3-phenylpropyl) malononitrile 13o

Yellow oil, yield 88%, 84% *ee*; $[\alpha]_D^{20}$ = +6.6 (*c* 0.44, CH_2Cl_2); chiral HPLC (Chiralcel AD-H column), hexane/*i*-PrOH = 80/20, flow rate: 1.0 mL/min, UV detection at 254 nm, t(minor) = 8.534 min, t(major) = 11.674 min; ^{1}H NMR (400 MHz, d_6-DMSO) δ = 8.00 (d, *J* = 7.4 Hz, 2H), 7.84 (d, *J* = 2.0 Hz, 1H), 7.71–7.62 (m, 2H), 7.53 (t, *J* = 7.6 Hz, 3H), 5.29 (d, *J* = 6.5 Hz, 1H), 4.18 (dt, *J* = 8.1, 6.0 Hz, 1H), 3.93 (dd, *J* = 18.3, 8.5 Hz, 1H), 3.70 ppm (dd, *J* = 18.3, 5.5 Hz, 1H). ^{13}C NMR (100 MHz, d_6-DMSO) δ = 196.66, 139.53, 136.39, 134.16, 131.75, 131.50, 131.22, 131.01, 129.23, 128.61, 113.65, 113.41, 29.39 ppm. HRMS (ESI$^+$) calcd for C18H12Cl2N2O $[M+Na]^+$ = 365.0226, found: 365.0226.

4.2.16. (*S*)-2-(1-(Naphthalen-2-yl)-3-oxo-3-phenylpropyl)malononitrile 13p

Yellow solid, yield 85%, 82% *ee*; m.p. 122.2–125.5 °C; $[\alpha]_D^{20}$ = −9.0 (*c* 0.8, CH_2Cl_2) (lit.[2h] $[\alpha]_D^{20}$ = −4.55 (*c* 0.198, CH_2Cl_2)); chiral HPLC (Chiralcel AD-H column), hexane/*i*-PrOH = 80/20, flow rate: 1.0 mL/min, UV detection at 254 nm, t(minor) = 12.185 min, t (major) = 16.772 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.03–7.96 (m, 2H), 7.96–7.91 (m, 2H), 7.88 (td, *J* = 7.2, 3.4 Hz, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.59–7.47 (m, 5H), 4.73 (d, *J* = 5.2 Hz, 1H), 4.15 (dt, *J* = 8.4, 5.3 Hz, 1H), 3.79 ppm (qd, *J* = 18.4, 6.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.62, 135.85, 134.20, 134.00, 133.43, 133.31, 129.37, 128.97, 128.22, 128.17, 127.81, 127.52, 126.88, 126.84, 125.23, 111.93, 111.83, 41.41, 40.34, 28.85 ppm.

4.2.17. (*S*)-2-(1-(Thiophen-2-yl)-3-oxo-3-phenylpropyl)malononitrile 13q

Yellow oil, yield 88%, 75% *ee*; $[\alpha]_D^{20}$ = +10 (*c* 0.5, CH_2Cl_2) (lit.[2h] $[\alpha]_D^{20}$ = −1.5 (*c* 0.068, CH_2Cl_2)); chiral HPLC (Chiralcel AD-H column), hexane/*i*-PrOH = 97/3, flow rate: 1.0 mL/min, UV detection at 254 nm, t(minor) = 44.382 min, t(major) = 60.619 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.01–7.94 (m, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 7.33 (dd, *J* = 5.1, 0.7 Hz, 1H), 7.23 (d, *J* = 3.5 Hz, 1H), 7.05 (dd, *J* = 5.1, 3.6 Hz, 1H), 4.67 (d, *J* = 5.0 Hz, 1H), 4.30 (dt, *J* = 11.2, 5.6 Hz, 1H), 3.77–3.63 ppm (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.24, 138.63, 135.66, 134.31, 129.00, 128.20, 127.51, 127.21, 126.11, 111.81, 111.53, 41.49, 37.26, 29.59 ppm.

4.2.18. (*S*)-2-(1-(5-Chlorothiophen-2-yl)-3-oxo-3-phenylpropyl)malono nitrile 13r

Yellow solid, yield 83%, 79% *ee*; m.p. 75.3–78.9 °C; $[\alpha]_D^{20}$ = +17.6 (*c* 0.37, CH_2Cl_2); chiral HPLC (Chiralcel AD-H column), hexane/*i*-PrOH = 80/20, flow rate: 1.0 mL/min, UV detection at 254 nm, t (minor) = 8.87 min, t(major) = 12.169 min;^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97 (d, *J* = 7.5 Hz, 2H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 2H), 7.00 (d, *J* = 3.8 Hz, 1H), 6.86 (d, *J* = 3.8 Hz, 1H), 4.65 (d, *J* = 5.1 Hz, 1H), 4.16 (dt, *J* = 7.7, 5.4 Hz, 1H), 3.75–3.55 ppm (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 195.92, 137.09, 135.48, 134.46, 130.93, 129.04, 128.19, 126.93, 126.44, 111.56, 111.28, 41.07, 37.78, 29.26 ppm. HRMS (ESI$^+$) calcd for $C_{16}H_{11}ClN_2OS$ $[M+Na]^+$ = 337.0184, found: 337.0184.

4.2.19. (*R*,*E*)-2-(5-Oxo-1,5-diphenylpent-1-en-3-yl)malononitrile 13s

Yellow oil, yield 30%, 82% *ee*; $[\alpha]_D^{20}$ = −5.65 (*c* 0.23, CH_2Cl_2) (lit.[2h] $[\alpha]_D^{20}$ = −0.65 (*c* 0.154, CH_2Cl_2)); chiral HPLC (Chiralcel AD-H column), hexane/*i*-PrOH = 80/20, flow rate: 1.0 mL/min, UV detection at 254 nm, t(minor) = 9.58 min, t(major) = 12.647 min;

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.02–7.93 (m, 2H), 7.64 (t, J = 7.4 Hz, 1H), 7.55–7.47 (m, 2H), 7.46–7.39 (m, 2H), 7.39–7.28 (m, 3H), 6.80 (d, J = 15.7 Hz, 1H), 6.24 (dd, J = 15.7, 8.9 Hz, 1H), 4.56 (d, J = 4.8 Hz, 1H), 3.61–3.52 (m, 1H), 3.52–3.38 ppm (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.76, 136.35, 135.90, 135.45, 134.21, 128.99, 128.79, 128.71, 128.15, 126.88, 123.41, 112.10, 111.66, 40.02, 39.73, 27.63 ppm.

4.2.20. (*S*)-2-(1-Cyclohexyl-3-oxo-3-phenylpropyl)malononitrile 13t

Yellow oil, yield 50%, 86% *ee*; $[\alpha]_D^{20}$ = +40.65 (*c* 0.46, CH_2Cl_2) (lit.[2h] $[\alpha]_D^{20}$ = +37.2 (*c* 0.086, CH_2Cl_2)); chiral HPLC (Chiralcel AD-H column), hexane/*i*-PrOH = 95/5, flow rate: 1.0 mL/min, UV detection at 254 nm, t(minor) = 12.674 min, t(major) = 14.18 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.02–7.93 (m, 2H), 7.62 (t, J = 7.4 Hz, 1H), 7.50 (t, J = 7.7 Hz, 2H), 4.36 (d, J = 4.8 Hz, 1H), 3.36 (dd, J = 18.5, 4.6 Hz, 1H), 3.16 (dd, J = 18.5, 7.9 Hz, 1H), 2.74 (dq, J = 9.9, 4.9 Hz, 1H), 1.93–1.67 (m, 6H), 1.42–1.03 ppm (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 197.26, 136.06, 133.98, 128.90, 128.12, 112.57, 112.49, 40.21, 40.06, 37.01, 31.20, 29.31, 26.22, 26.10, 25.95, 25.34 ppm.

4.2.21. (*S*)-3-(2, 2-Methyl-5-oxo-5-phenylpentyl)malononitrile 13u

Yellow oil, yield 25%, 88% *ee*; $[\alpha]_D^{20}$ = +26.3 (*c* 0.19, CH_2Cl_2) (lit.[2h] $[\alpha]_D^{20}$ = +38.1 (*c* 0.042, CH_2Cl_2)); chiral HPLC (Chiralcel AD-H column), hexane/*i*-PrOH = 95/5, flow rate: 1.0 mL/min, UV detection at 254 nm, t(major) = 13.667 min, t(minor) = 15.556 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.06–7.97 (m, 2H), 7.62 (t, J = 7.4 Hz, 1H), 7.51 (t, J = 7.7 Hz, 2H), 4.10 (d, J = 2.9 Hz, 1H), 3.40 (dd, J = 18.5, 4.4 Hz, 1H), 3.19 (dd, J = 18.5, 7.1 Hz, 1H), 2.93 (ddd, J = 7.2, 4.4, 2.9 Hz, 1H), 1.09 ppm (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.76, 136.11, 133.87, 128.89, 128.19, 113.16, 113.09, 44.46, 37.22, 34.28, 27.72, 24.00 ppm.

4.2.22. (*S*)-2-(3-(4-Methoxyphenyl)-3-oxo-1-phenylpropyl)malononitrile 13v

Yellow oil, yield 90%, 94% *ee*; $[\alpha]_D^{20}$ = +13.8 (*c* 0.3, CH_2Cl_2) (lit.[2t] $[\alpha]_D^{20}$ = +12.2 (*c* 1.21, CH_2Cl_2)); chiral HPLC (Chiralcel AD-H column), hexane/*i*-PrOH = 80/20, flow rate: 1.0 mL/min, UV detection at 254 nm, t(minor) = 15.705 min, t(major) = 23.465 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.95 (d, J = 8.8 Hz, 2H), 7.51–7.35 (m, 5H), 6.95 (d, J = 8.8 Hz, 2H), 4.68 (d, J = 5.1 Hz, 1H), 4.00–3.90 (m, 1H), 3.88 (s, 3H), 3.61 ppm (qd, J = 18.2, 6.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 195.07, 164.34, 136.75, 130.52, 129.32, 129.13, 128.92, 128.07, 114.11, 112.03, 111.85, 55.63, 41.32, 39.68, 28.80 ppm.

4.2.23. (*S*)-2-(3-(4-Nitrophenyl)-3-oxo-1-phenylpropyl)malononitrile 13w

Yellow oil, yield 95%, 85% *ee*; $[\alpha]_D^{20}$ = +16.8 (*c* 0.31, CH_2Cl_2) (lit.[2w] $[\alpha]_D^{20}$ = −6.67 (*c* = 0.854 in CH_2Cl_2) for (*R*)-isomer); chiral HPLC (Chiralcel AD-H column), hexane/*i*-PrOH = 80/20, flow rate: 1.0 mL/min, UV detection at 254 nm, t(major) = 22.313 min, t(minor) = 25.990 min; ^{1}H NMR (400 MHz, d_6-DMSO) δ = 7.46 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 8.9 Hz, 2H), 6.64 (d, J = 7.2 Hz, 2H), 6.49 (ddd, J = 10.9, 9.6, 5.8 Hz, 3H), 4.37 (d, J = 6.1 Hz, 1H), 3.22 (dd, J = 13.9, 6.0 Hz, 1H), 3.09 (dd, J = 18.2, 8.1 Hz, 1H), 2.90 ppm (dd, J = 18.2, 5.8 Hz, 1H). ^{13}C NMR (100 MHz, d_6-DMSO) δ = 201.01, 155.35, 145.81, 142.80, 134.78, 133.89, 133.54, 133.48, 129.05, 118.62, 118.33, 117.29, 46.03, 45.45, 34.50, 13.65 ppm.

4.2.24. (*S*)-2-(3-(4-Chlorophenyl)-3-oxo-1-phenylpropyl)malononitrile 13x

White solid, yield 93%, 77% *ee*; m.p. 148.9–151.3 °C; $[\alpha]_D^{20}$ = +21.8 (*c* 0.22, CH_2Cl_2) (lit.[2h] $[\alpha]_D^{20}$ = +7.9 (*c* 0.254, CH_2Cl_2)); chiral HPLC (Chiralcel AD-H column), hexane/*i*-PrOH = 80/20, flow rate: 1.0 mL/min, UV detection at 254 nm, t(minor) = 10.994 min, t(major) = 13.159 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.90 (d, J = 8.6 Hz, 2H), 7.51–7.37 (m, 7H), 4.60 (d, J = 5.2 Hz, 1H), 3.96 (dt, J = 7.8, 5.6 Hz, 1H), 3.74–3.54 ppm (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 195.46, 140.77, 136.44, 134.14, 129.54, 129.41, 129.30, 129.28, 127.98, 111.84, 111.73, 41.19, 40.15, 28.84 ppm.

4.2.25. (*S*)-2-(3-(2-Naphthyl)-3-oxo-1-phenylpropyl)malononitrile 13y

Yellow solid, yield 85%, 87% *ee*; m.p. 49.5–53.2 °C; $[\alpha]_D^{20}$ = +41.67 (*c* = 0.22 in CH_2Cl_2) (lit.[2h] $[\alpha]_D^{20}$ = +26.7 (*c* = 0.206 in CH_2Cl_2)); chiral HPLC (Chiralcel AD-H column), hexane/*i*-PrOH = 80/20, flow rate: 1.0 mL/min, UV detection at 254 nm, t(minor) = 12.848 min, t(major) = 27.705 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.48 (s, 1H), 8.05–7.94 (m, 2H), 7.94–7.84 (m, 2H), 7.68–7.55 (m, 2H), 7.55–7.36 (m, 5H), 4.69 (d, J = 5.1 Hz, 1H), 4.03 (dt, J = 7.9, 5.5 Hz, 1H), 3.90–3.73 ppm (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.57, 136.68, 136.01, 133.18, 132.41, 130.22, 129.73, 129.39, 129.22, 129.15, 128.91, 128.10, 127.91, 127.23, 123.39, 112.02, 111.88, 41.37, 40.19, 28.93 ppm.

4.2.26. (*S*)-2-(3-(2-Thienyl)-3-oxo-1-phenylpropyl)malononitrile 13z

Yellow solid, yield 95%, 91% *ee*; m.p. 83.8–87.2 °C; $[\alpha]_D^{20}$ = +5.8 (*c* 0.38, CH_2Cl_2) (lit.[2h] $[\alpha]_D^{20}$ = −1.8 (*c* 0.278, CH_2Cl_2)); chiral HPLC (Chiralcel AD-H column), hexane/*i*-PrOH = 80/20, flow rate: 1.0 mL/min, UV detection at 254 nm, t(minor) = 10.688 min, t(major) = 13.131 min; ^{1}H NMR (400 MHz, d_6-DMSO) δ = 8.04 (dd, J = 32.5, 3.6 Hz, 2H), 7.55–7.19 (m, 6H), 5.27 (d, J = 6.2 Hz, 1H), 4.17–3.97 (m, 1H), 3.81 (dd, J = 17.2, 8.5 Hz, 1H), 3.56 ppm (dd, J = 17.2, 5.4 Hz, 1H). ^{13}C NMR (100 MHz, d_6-DMSO) δ = 189.84, 143.61, 137.95, 136.01, 134.52, 129.34, 129.16, 128.81, 128.67, 113.87, 113.61, 40.95, 29.67 ppm.

4.3. Catalytic asymmetric synthesis of (*S*)-piperidone 19

4.3.1. (*S*)-2-(1-(4-Fluorophenyl)-3-oxo-3-phenylpropyl)malononitrile 13e

To the stirred solution of the α,β-unsaturated ketones **11e** (5.7 g, 25.3 mmol) and catalyst **6a** (1.58 g, 2.53 mmol) in toluene (50.6 mL) was added malononitrile **12** (2.5 g, 38 mmol) at room temperature. The reaction was monitored by TLC; after complete consumption of the α,β-unsaturated ketones **11e**, the solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography with PE/EtOAc = 8/1 to give the product as a white solid, yield 92%, 89% *ee*; $[\alpha]_D^{20}$ = −0.4 (*c* 1.0, CH_2Cl_2) (lit.[2h] $[\alpha]_D^{20}$ = −5.6 (*c* 0.288, CH_2Cl_2)); chiral HPLC (Chiralcel AD-H column), hexane/*i*-PrOH = 80/20, flow rate: 1.0 mL/min, UV detection at 254 nm, t(minor) = 8.909 min, t(major) = 12.617 min. After a single recrystallization from hexane/AcOEt 8:1, white thin piece crystals were obtained in 71% yield, 99% *ee*, $[\alpha]_D^{20}$ = −6.9 (*c* 1.0, CH_2Cl_2).

4.3.2. (*S*)-3-(4-Fluorophenyl)-5-oxo-5-phenylpentanoic acid 14

To the solution of **13e** (5.2 g, 18 mmol) in AcOH (45 mL) was added con. HCl (36 ml), the mixture was refluxed overnight. The reaction mixture was cooled room temperature, the solid were filtered, washed with water and dried at 80 °C to give **14** as white solid, yield 90%, m.p. 136.6–139.8 °C; $[\alpha]_D^{20}$ = 16 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, d_6-DMSO) δ = 12.11 (s, 1H), 7.92 (d, J = 7.5 Hz, 2H), 7.60 (t, J = 7.2 Hz, 1H), 7.49 (t, J = 7.6 Hz, 2H), 7.34 (dd, J = 8.2, 5.7 Hz, 2H), 7.06 (t, J = 8.8 Hz, 2H), 3.68 (dt, J = 14.2, 7.0 Hz, 1H), 3.47 (d, J = 7.8 Hz, 1H), 2.72 (dd, J = 15.8, 6.1 Hz, 1H), 2.56 ppm (dd, J = 15.8, 8.7 Hz, 1H). ^{13}C NMR (100 MHz, d_6-DMSO)

δ = 198.89, 173.35, 162.44, 160.04, 140.47, 140.44, 137.15, 133.65, 129.93, 129.85, 129.15, 128.37, 115.37, 115.16, 44.49, 40.92, 37.06 ppm. HRMS (ESI^+) calcd for $C_{17}H_{15}FO_4$ $[M+H]^+$ = 287.1078, found: 287.1088.

4.3.3. Benzyl (*S*)-3-(4-fluorophenyl)-5-oxo-5-phenylpentanoate 15

Thionyl chloride (24.3 mmol, 1.76 mL) was added to a suspension of **14** (4.6 g, 16.2 mmol) in dry toluene (32 mL) at 0 °C. After the addition, the mixture was heated at reflux for 12 h, and then the reaction mixture was cooled to room temperature and concentrated under reduced pressure to give a yellow oil. The obtained oil was added to the solution of triethylamine (1.0 mmol, 0.14 mL) and benzyl alcohol (0.32 mmol, 42 μL) at 0 °C. The mixture was refluxed for 12 h after the addition, then cooled to room temperature and quenched with saturated aq. $NaHCO_3$ (30 mL). The mixture was diluted with ethyl acetate (30 mL), the organic solution was washed with saturated aq. $NaHCO_3$ (30 mL), water (30 mL) and brine (10 mL). The organic layer was then dried over Na_2SO_4 and concentrated *in vacuo* to give a brown oil. The crude product was purified by flash chromatography with PE/EtOAc = 12/1 to give the product as a white solid, yield 92%, 99% *ee*, m.p. 60.1–63.3 °C; $[\alpha]_D^{20}$ = +8.5 (*c* 1.0, CH_2Cl_2); chiral HPLC (Chiralcel AD-H column), hexane/*i*-PrOH = 80/20, flow rate: 1.0 mL/min, UV detection at 254 nm, t(minor) = 10.486 min, t(major) = 13.747 min. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.89 (d, *J* = 7.6 Hz, 2H), 7.55 (t, *J* = 7.0 Hz, 1H), 7.43 (t, *J* = 7.1 Hz, 2H), 7.37–7.14 (m, 7H), 6.94 (t, *J* = 8.0 Hz, 2H), 5.03 (s, 2H), 3.99–3.83 (m, 1H), 3.45–3.24 (m, 2H), 2.86 (dd, *J* = 15.4, 6.6 Hz, 1H), 2.72 ppm (dd, *J* = 15.2, 8.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 197.91, 171.50, 162.87, 160.44, 138.82, 136.83, 135.75, 133.23, 128.99, 128.91, 128.65, 128.53, 128.27, 128.06, 115.53, 115.32, 66.34, 44.60, 40.89, 36.94 ppm. HRMS (ESI^+) calcd for $C_{24}H_{21}FO_3$ $[M+H]^+$ = 377.1547, found: 377.1538.

4.3.4. 1-Benzyl 5-phenyl (*R*)-3-(4-fluorophenyl)pentanedioate 16

To a stirred solution of **15** (5.6 mg, 15 mmol) in dichloroethane (150 mL) at room temperature were added KH_2PO_4 (20 g, 150 mmol) and *m*-chloroperbenzoic acid (25.8 g, 150 mmol). After being stirred for 4 days at 60 °C, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$. The resulting mixture was extracted with diethyl ether. The combined organic extracts were washed with ice-cooled saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash silica gel column chromatography with PE/EtOAc = 8/1 to give **16** as a white solid yield 66%, 99% *ee*, m.p. 89.7–92.5 °C; $[\alpha]_D^{20}$ = +20.5 (*c* 1.0, CH_2Cl_2); chiral HPLC (Chiralcel AD-H column), hexane/*i*-PrOH = 80/20, flow rate: 1.0 mL/min, UV detection at 254 nm, t(major) = 9.44 min, t(minor) = 10.491 min. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.33 (t, *J* = 7.4 Hz, 5H), 7.29–7.17 (m, 5H), 7.01 (t, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.1 Hz, 2H), 5.07 (s, 2H), 3.87–3.74 (m, 1H), 3.00 (dd, *J* = 15.5, 6.4 Hz, 1H), 2.92–2.81 (m, 2H), 2.77 ppm (dd, *J* = 15.5, 8.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.17, 169.94, 163.14, 160.70, 150.46, 137.66, 135.68, 129.43, 129.09, 129.01, 128.58, 128.33, 128.28, 125.92, 121.43, 115.69, 115.48, 66.48, 40.78, 37.96 ppm. HRMS (ESI^+) calcd for C24H21FO4 $[M+H]^+$ = 393.1497, found: 393.1490.

4.3.5. (*R*)-3-(4-Fluorophenyl)-5-oxo-5-phenoxypentanoic acid 17

Compound **16** (3.85 g, 9.8 mmol) and 5% Pd/C (1.0 g) were suspended in THF (50 mL) and stirred under an H_2 atmosphere at 30 °C for 12 h. The reaction mixture was filtered and evaporated to give a light yellow oil. The residue was purified by flash silica gel column chromatography with PE/EtOAc = 5/1 to give **17** as a white solid yield 80%, 99% *ee*, m.p. 109.1–111.9 °C; $[\alpha]_D^{20}$ = −11.3 (*c* 1.0, $CHCl_3$); chiral HPLC (Chiralcel AS-H) column, hexane/*i*-PrOH = 90/10, flow rate: 0.5 mL/min, UV detection at 225 nm, t(major) = 27.048 min, t(minor) = 31.807 min. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.38–7.24 (m, 4H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.04 (t, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 7.9 Hz, 2H), 3.82–3.69 (m, 1H), 3.01 (dd, *J* = 15.5, 6.4 Hz, 1H), 2.93–2.79 (m, 2H), 2.74 ppm (dd, *J* = 16.1, 7.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.52, 169.99, 163.18, 160.74, 150.40, 137.57, 137.54, 129.44, 129.05, 128.97, 125.97, 121.40, 115.77, 115.56, 40.70, 40.40, 37.50 ppm. HRMS (ESI^+) calcd for $C_{17}H15FO_4$ $[M+Na]^+$ = 325.0847, found: 325.0848.

4.3.6. (*R*)-3-(4-Fluorophenyl)-5-methoxy-5-oxopentanoic acid 18

To a solution of **17** (0.604 g, 2.0 mmol) in MeOH (10 mL) was added Na_2CO_3 (0.636 g, 6.0 mmol). The mixture was stirred at room temperature for 24 and then concentrated under reduced pressure. The residue was dissolved in H_2O (30 mL), the solution was washed with CH_2Cl_2 (2 × 20 mL) and the aqueous layers were acidified with excess 2 M HCl, followed by extraction with EtOAc (3 × 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to afford **18** as a white solid without further purification by flash chromatography. Yield 83%, 92% *ee*, m.p. 95.7–99.1 °C; $[\alpha]_D^{20}$ = +8.0 (*c* 1.0, $CHCl_3$) (lit.[6d] $[\alpha]_D^{20}$ = +5.7 (*c* 1.0, $CHCl_3$)); chiral HPLC (Chiralcel AD-H) column, hexane/*i*-PrOH = 90/10, flow rate: 0.5 mL/min, UV detection at 254 nm, t(major) = 21.708 min, t(minor) = 19.202 min. After a single recrystallization from toluene/hexane 3:2, white solids were obtained from mother liquid in 66% yield, 97% *ee*, $[\alpha]_D^{20}$ = +8.5 (*c* = 1.0 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 9.39 (s, 1H), 7.23–7.13 (m, 2H), 6.97 (t, *J* = 8.5 Hz, 2H), 3.74–3.51 (m, 4H), 2.92–2.47 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.68, 172.28, 163.28, 160.84, 138.27, 138.24, 129.09, 129.01, 115.89, 115.68, 51.99, 40.78, 40.64, 37.58 ppm.

4.3.7. (*S*)-4-(4-Fluorophenyl)-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylic acid methyl ester 19

To a solution of diisopropylamine (0.352 mL, 2.5 mmol) in THF (1 mL) was added *n*-BuLi (1 mL, 2.5 mmol, 2.5 M in hexane) at −10 °C. After the addition, the mixture was stirred at 0 °C for 15 min. The mixture was then cooled to −55 °C, after which the solution of **18** (0.24 g, 1.0 mmol) in THF (1 mL) was added to the reaction mixture. After the addition, the reaction mixture was stirred at −55 °C for 40 min. Then methyl formate (0.16 mL, 2.79 mmol) was added to the reaction mixture, after which the reaction mixture was slowly warmed to −20 °C, and then stirred at −20 °C for 1 h. Next, 3 M HCl (2.1 mL) was slowly added to the reaction mixture and extracted with EtOAc (15 mL). The organic phase was washed with brine and concentrated to give a yellow oil. To this oil, AcOH (0.86 mL, 15 mmol) and NH_4OAc (0.23 g, 3 mmol) were added and the mixture was warmed to 80 °C and stirred overnight. The reaction mixture was cooled to room temperature and H_2O (2.1 mL) was added slowly to the reaction mixture. After the addition, the mixture was stirred at room temperature for 2 h. Next, EtOAc (20 mL) was added to the reaction mixture, and the mixture was washed with H_2O (3 × 15 mL) and brine, dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash silica gel column chromatography with PE/EtOAc = 4/1 to give **19** as a white solid yield 41%, 97% *ee*, m.p. 191.8–194.2 °C; $[\alpha]_D^{20}$ = +52.4 (*c* 1.2, $CHCl_3$); chiral HPLC (Chiralcel AD-H column), hexane/*i*-PrOH = 90/10, flow rate: 0.5 mL/min, UV detection at 254 nm, t(major) = 31.373 min, t(minor) = 23.192 min. ^1H NMR (400 MHz, d_6-DMSO) δ 9.97 (d, *J* = 4.7 Hz, 1H), 7.44 (d, *J* = 5.5 Hz, 1H), 7.25–7.16 (m, 2H), 7.11 (t, *J* = 8.8 Hz, 2H), 4.07 (d, *J* = 7.9 Hz, 1H), 3.60

(s, 3H), 3.02 (dd, J = 16.4, 8.3 Hz, 1H), 2.42 (d, J = 16.4 Hz, 1H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 169.75, 166.49, 162.77, 160.36, 138.79, 138.76, 137.75, 128.85, 128.77, 116.00, 115.79, 108.84, 51.74, 38.78, 35.79.

A. Supplementary data

Supplementary data (NMR spectra for all of the new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetasy.2017.05.015.

References

1. For Part 10 see: Wang, H.; Yan, L.; Wu, Y.; Chen, F. *Tetrahedron* **2017**, *19*, 2793.
2. For selected examples of asymmetric conjugate additions of malononitriles, see: (a) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 11204; (b) Itoh, K.; Oderaotoshi, Y. *Tetrahedron: Asymmetry* **2003**, *14*, 635; (c) Taylor, M. S.; Zalatan, D. N.; Lerchner, A. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 1313; (d) Hoash, Y.; Okino, T.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 4032; (e) Inokuma, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2006**, *128*, 9413; (f) Wang, J.; Li, H.; Zu, L.; Jiang, W.; Xie, H.; Duan, W.; Wang, W. *J. Am. Chem. Soc.* **2006**, *128*, 12652; (g) Li, X. F.; Cun, L. F.; Lian, C. X.; Zhong, L.; Chen, Y. C.; Liao, J.; Zhu, J.; Deng, J. G. *Org. Biomol. Chem.* **2008**, *6*, 349; (h) Shi, J.; Wang, M.; He, L.; Zheng, K.; Liu, X. H.; Lin, L. L.; Feng, X. M. *Chem. Commun.* **2009**, 4711; (i) Russo, A.; Perfetto, A.; Lattanzi, A. *Adv. Synth. Catal.* **2009**, *351*, 3067; (j) Xie, J. W.; Huang, X.; Fan, L. P.; Xu, D. C.; Li, X. S.; Su, H.; Wen, Y. H. *Adv. Synth. Catal.* **2009**, *351*, 3077; (k) Zhao, S. L.; Zheng, C. W. *Tetrahedron: Asymmetry* **2009**, *1046*, 20; (l) Huang, X.; Li, P.; Li, X. S.; Xu, D. C.; Xie, J. W. *Org. Biomol. Chem.* **2010**, *8*, 4527; (m) Ren, Q.; Gao, Y. J.; Wang, J. *Chem. Eur. J* **2010**, *16*, 13594; (n) Jing, L. H.; Wei, J. T.; Zhou, L.; Huang, Z. Y.; Li, Z. K.; Wu, D.; Xiang, H. F.; Zhou, X. G. *Chem. Eur. J.* **2010**, *16*, 10955; (o) Oliva, C. G.; Silva, A. M. S.; Resende, D. I. S. P.; Paz, F. A. A.; Cavaleiro, J. A. S. *Eur. J. Org. Chem.* **2010**, 3449; (p) Hu, Z. P.; Lou, C. L.; Wang, J. J.; Chen, C. X.; Yan, M. *J. Org. Chem.* **2011**, *76*, 3797; (q) Li, X. M.; Wang, B.; Zhang, J. M.; Yan, M. *Org. Lett.* **2011**, *13*, 374; (r) Russo, A.; Capobianco, A.; Perfetto, A.; Lattanzi, A.; Peluso, A. *Eur. J. Org. Chem.* **1922**, *2011*; (s) Molleti, N.; Rana, N. K.; Singh, V. C. *Org. Lett.* **2012**, *14*, 4322; (t) Yang, W.; Jia, Y.; Du, D. M. *Org. Biomol. Chem.* **2012**, *10*, 332; (u) Gao, Y.; Yang, W.; Du, D. *Tetrahedron: Asymmetry* **2012**, *23*, 339; (v) Arai, T.; Oka, I.; Morihata, T.; Awata, A.; Masu, H. *Chem. Eur. J.* **2013**, *19*, 1554; (w) Li, X.; Ma, Y.; Xing, Z.; Tang, N.; Zhu, J.; Deng, J. *Tetrahedron Lett.* **2014**, *55*, 3868.
3. (a) Freeman, F. *Chem. Rev.* **1969**, *69*, 591; (b) van Es, T.; Staskun, B. *Org. Synth.* **1971**, *51*, 20; (c) Weiberth, F. J.; Hall, S. S. *J. Org. Chem.* **1987**, *52*, 3901; (d) Roy, A.; Paul, T.; Drew, M. G. B.; Mukherjee, D. *Tetrahedron Lett.* **2003**, *44*, 4835; (e) Chen, Y. C.; Xue, D.; Deng, J. G.; Cui, X.; Zhu, J.; Jiang, Y. Z. *Tetrahedron Lett.* **2004**, *7*, 1555; (f) Mueller, J.; Wuertele, C.; Walter, O.; Schindler, S. *Angew. Chem. Int. Ed.* **2007**, *46*, 7775; (g) Zhu, D. M.; Ankati, H.; Mukherjee, C.; Yang, Y.; Biehl, E. R.; Hua, L. *Org. Lett.* **2007**, *9*, 2561; (h) Föster, S.; Tverskoy, O.; Helmchen, G. *Synlett* **2008**, 2803; (i) Yang, K. S.; Nibbs, A. E.; Türkmen, Y. E.; Rawal, V. H. *J. Am. Chem. Soc.* **2013**, *135*, 16050; (j) Khan, A.; Yang, L.; Xu, J.; Jin, L. Y.; Zhang, Y. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 11257.
4. For selected reviews of asymmetric Michael addition, see: (a) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033; (b) Krause, N.; Hoffmann-Roder, A. *Synthesis* **2001**, 171; (c) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **1877**, *2002*; (d) Kanemasa, S.; Ito, K. *Eur. J. Org. Chem.* **2004**, 4741; (e) Sarah, M.; Olivier, A.; Alexandre, A. *Chimia* **2006**, *60*, 216; (f) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701; (g) Sulzer-Mossé, S.; Alexakis, A. *Chem. Commun.* **2007**, 3123; (h) Vicario, J. L.; Badía, D.; Carrillo, L. *Synthesis* **2007**, 2065; (i) Almasi, D.; Alonso, D. A. *Tetrahedron: Asymmetry* **2007**, *18*, 299; (j) Christoffers, J.; Koripelly, G.; Rosiak, A.; Rösle, M. *Synthesis* **2007**, 1279; (k) Alexakis, A.; Bäkvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796; (l) Jautze, S.; Peters, R. *Synthesis* **2010**, 365; Somanathan, R.; Chavez, D.; Servin, F. A.; Romero, J. A.; Navarrete, A.; Parra-Hake, M.; Aguirre, G.; Anaya de Parrodi, C.; Gonzalez, J. *Curr. Org. Chem.* **2012**, *16*, 2440.
5. For selected reviews of bifunctional amine-thiourea organocatalysts, see: (a) Groger, H. *Chem. Eur. J.* **2001**, *7*, 5246; (b) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187; (c) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138; (d) Ma, J. A.; Cahard, D. *Angew. Chem. Int. Ed.* **2004**, *43*, 4566; (e) Pihko, P. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2062; (f) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299; (g) Kanai, M.; Kato, N.; Ichikawa, E.; Shibasaki, M. *Synlett* **2005**, 1491; (h) Connon, S. J. *Chem. Eur. J.* **2006**, *12*, 5418; (i) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520; (j) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999; (k) Connon, S. J. *Chem. Commun.* **2008**, 2499; (l) Fang, X.; Wang, C. J.; Fang, X. *Chem. Commun.* **2015**, *51*, 1185.
6. (a) Wang, S. X.; Chen, F. E. *Adv. Synth. Catal.* **2009**, *351*, 547; (b) Yang, H. J.; Xiong, F. J.; Li, J.; Chen, F. E. *Chin. Chem. Lett.* **2013**, *24*, 553; (c) Yang, H. J.; Xiong, F. J.; Chen, X. F.; Chen, F. E. *Eur. J. Org. Chem.* **2013**, 4495; (d) Yan, L. J.; Wang, H. F.; Chen, W. X.; Tao, Y.; Jin, K. J.; Chen, F. E. *ChemCatChem* **2016**, *8*, 2249; (e) Wang, H.; Yan, L.; Xiong, F.; Wu, Y.; Chen, F. *RSC Adv.* **2016**, *6*, 75470; (f) Wang, X. L.; Xu, L. J.; Yan, L. J.; Wang, H. F.; Han, S.; Wu, Y.; Chen, F. E. *Tetrahedron* **2016**, *72*, 1787; (g) Wang, X. L.; Xu, L. J.; Xiong, F. J.; Wu, Y.; Chen, F. E. *RSC Adv.* **2016**, *6*, 37701.
7. (a) Huang, X.; Zhu, J.; Broadbent, S. *Tetrahedron Lett.* **2010**, *51*, 1554; (b) Huang, X.; Broadbent, S.; Dvorak, C.; Zhao, S. H. *Org. Process Res. Dev.* **2010**, *14*, 612.
8. (a) Kohler, E. P.; Chadwell, H. M. *Org. Synth. Col.* **1932**, *I*, 78; (b) Riahi, A.; Thorey, C.; Hénin, F.; Muzart, J. *Synth. Commun.* **1998**, *28*, 4339.
9. Yang, D.; Wang, L.; Zhao, D.; Han, F.; Zhang, B.; Wang, R. *Chem. Eur. J.* **2013**, *19*, 4691.