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Highly enantioselective Michael additions of α-cyanoacetate with chalcones catalyzed by bifunctional cinchona-derived thiourea organocatalyst

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Abstract—The conjugate addition of ethyl α-cyanoacetate with chalcones has been developed. In the presence of cinchona alkaloid-derived thiourea organocatalyst **1i** (10 mol %), ethyl α-cyanoacetate could react with various chalcones to afford Michael adducts with high yields (80–92%) and enantioselectivities (83–95% ee).

1. Introduction

The Michael addition of carbon nucleophiles to electron-deficient alkenes is one of the most powerful tools for carbon–carbon bond formation. Considerable efforts have been directed toward the development of catalytic asymmetric versions of this process.[1] 1,3-Dicarbonyl compounds and their equivalents have been widely used as C-nucleophiles in the Michael addition.[2] Among them, α-cyanoacetates, which contain the two useful functional groups of nitrile and ester, have received considerable attention. The enantioselective addition of α-cyanoacetates to enones could be catalyzed by chiral ligand–metal complexes, such as Rh,[3] Pd[4] or salen-Al,[5] and applied in the synthesis of β-amino acids, as well as in the further total syntheses of paroxetine[5b] and quinine.[5a] Recently highly enantioselective Michael addition of various C-nucleophiles were achieved by using organocatalysts.[6–8] Suitable organocatalysts included proline-derived reagents, pyrrolidine-derived compounds, cinchona alkaloids, thiourea–amine, and cinchona-derived thiourea compounds.[9] Cinchona alkaloids demonstrated prominent bifunctional catalytic abilities, most of the time, for both nucleophiles and electrophiles as hydrogen-bond acceptors and donors, respectively.[10] More recently, Takemoto reported the highly enantioselective Michael addition of α-cyanoacetate with a bidentate substrate, α,β-unsaturated imines catalyzed by thiourea-type organocatalyst.[11] Herein, we report a catalytic and highly enantioselective addition reaction of α-cyanoacetate with monodentate Michael acceptors, chalcone derivatives, in the presence of a bifunctional thiourea organocatalyst derived from hydroquinine. (Fig. 1).

2. Results and discussion

Initially, four natural cinchona alkaloids **1a–d** were used in the asymmetric Michael addition of ethyl α-cyanoacetates **2** with chalcone **3a**. As shown in Table 1, for catalysts **1a–c** very low yields and ee values were obtained (entries 1–3). In the case of quinine **1d**, a relatively high enantioselectivity (72% ee) was reached, but the yield of **4a** was still low (28%, entry 4). Subsequently, modified cinchona alkaloids **1e–h** based on quinine **1d** were used in the reaction of **2** with **3a**. When 9-OH was capped by Bn, the catalytic ability of the resulting Q-Obn **1f** dropped noticeably (entry 6). Although 6′-OH quinine alkaloids proved to be efficient catalysts in the conjugate addition of α-cyanoacetates with other type of Michael acceptors such as vinyl sulfone or acrylonitrile,[8b–e] 6′-OH catalysts **1e** and **1g** for the reaction of **2** with **3a** provided low yields and poor ee, or in some cases did not work at all (entries 5 and 7). Catalyst **1h**, the reduction product of **1d**, provided a good yield (78%) with 72% ee of *syn*- and *anti*-**4a** (entry 8).

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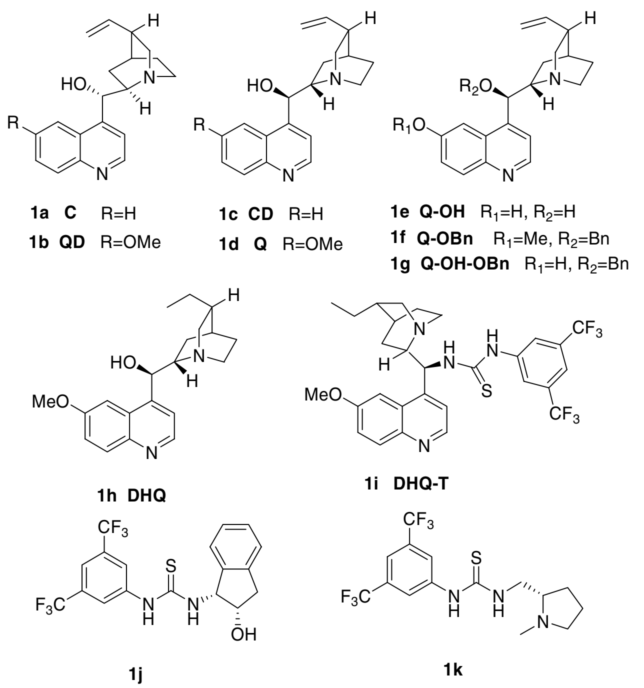
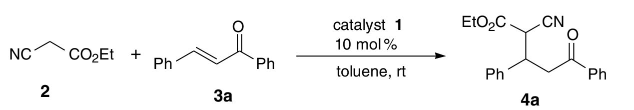


Figure 1. Three types of organocatalysts.

Table 1. Catalytic asymmetric reactions of **2** with **3a**[a]



Entry	Catalyst[a]	Time (h)	Yield[b] (%) (*syn*/*anti*)[c]	ee of *syn*/*anti*-**4a**[d] (%)
1	**1a**	36	<5 (n.d.)[e]	0
2	**1b**	36	<10 (65/35)	46/46
3	**1c**	36	<5 (61/39)	39/39
4	**1d**	36	28 (62/38)	72/72
5	**1e**	36	<5 (n.d.)[e]	33/33
6	**1f**	36	<5 (n.d.)[e]	12/12
7	**1g**	36	—[f]	—
8	**1h**	72	78 (63/37)	72/72
9	**1i**	72	82 (61/39)	87/87
10	**1j**[g]	36	60 (60/40)	0
11	**1k**	72	36 (63/37)	5/5

[a] Catalyst loading: 10 mol %.
[b] Yield of isolated product.
[c] Determined by ^{1}H NMR.
[d] Determined by chiral HPLC.
[e] Not determined.
[f] No reaction occurred.
[g] With 0.5 equiv Et_3N.

It was noted that a combination of a thiourea moiety and *tert*-amino group could offer an efficient catalytic ability for the Michael addition. Unfortunately, the use of thiourea organocatalysts **1j** and **1k** in the reaction of **2** with **3a** only afforded very poor enantioselectivities of **4a** (entries 10 and 11). To obtain higher yield and enantioselectivity, further modification for the cinchona catalyst was performed. We were pleased to find that a bifunctional thiourea organocatalyst derived from hydroquinine **1i**[12] resulted in a good yield of **4a** (82%) with high enantioselectivity (entry 9). Although the diastereomeric ratio (*syn*/*anti*) of the product mixture **4a** was moderate (61:39), the enantioselectivities of each diastereomer were the same (87%). Cinchona alkaloids **1a–i**, except for **1b**, afforded **4a** in the same antipodes.

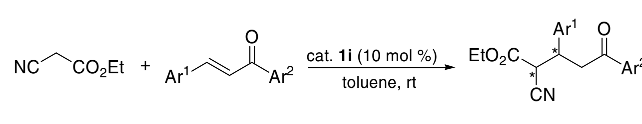
The reaction conditions were optimized under catalysis with **1i**. It was found that toluene was a better solvent than THF, and that the reaction in CH_2Cl_2 and CH_3CN afforded low yield and ees (Table 2, entries 1–4). The reaction temperature has an impact on the reaction speed, but a limited effect on the enantioselectivity (entries 4–7). Considering the reaction time and selectivity, toluene as a solvent, at room temperature, and 10 mol % catalyst loading were chosen as the general reaction conditions.

Table 2. Reaction conditions for the Michael addition of **2** with **3a**[a]

Entry	Solvent	Temperature (°C)	Time (h)	Yield[b] (%) (*syn*/*anti*)[c]	ee of *syn*/*anti*-**4a**[d] (%)
1	THF	rt	72	80 (63/37)	81/82
2	CH_2Cl_2	rt	72	40 (62/38)	79/80
3	CH_3CN	rt	72	30 (64/36)	60/60
4	Toluene	rt	72	82 (61/39)	87/87
5	Toluene	−45	144	30 (62/38)	84/85
6	Toluene	0	144	84 (63/37)	88/89
7	Toluene	60	60	90 (60/40)	85/84
8[e]	Toluene	rt	144	86 (63/37)	89/89
9	Xylene	rt	72	83 (62/38)	86/86

[a] Catalyst: **1i** (10 mol %).
[b] Isolated yield.
[c] Determined by ^{1}H NMR.
[d] Determined by chiral HPLC analysis.
[e] 5% Catalyst was used.

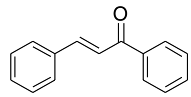
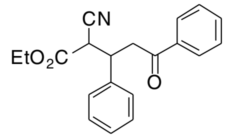
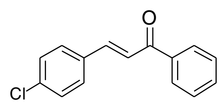
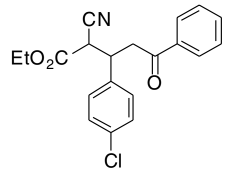
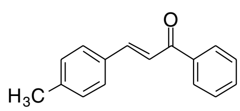
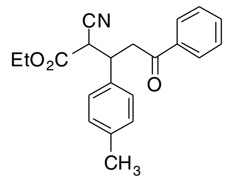
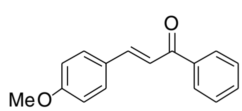
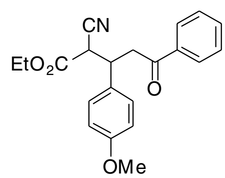
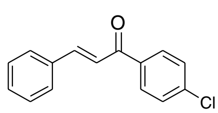
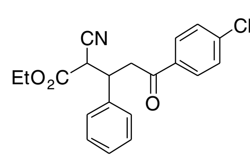
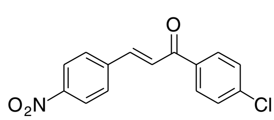
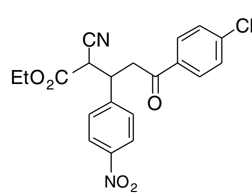
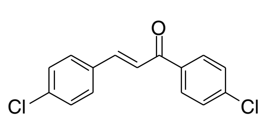
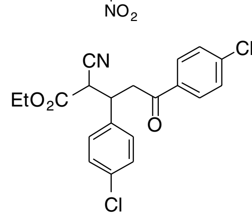
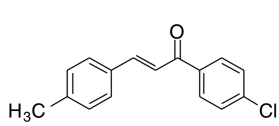
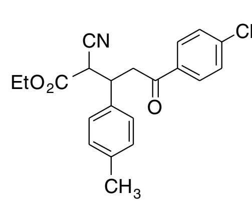
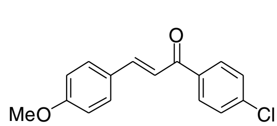
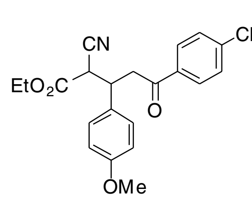
The addition of ethyl α-cyanoacetate **2** to various chalcones **3a–p** catalyzed by **1i** was proved to be remarkably general (Scheme 1, Table 3). Although electron-donating or electron-withdrawing substituents at the 4′-position of the Ar^1 group decrease or promote the reaction rate (entries 8, 9 vs 5 and entries 6, 7 vs 5), both had very limited effect on the enantioselectivity. Conversely, 4′-Cl of the Ar^2 group not only increased the activities of chalcones, but also benefited for the enantioselectivities (entries 1–4 vs 5–9). When Ar^2 was a heteroaromatic substituent, the reaction of chalcones **3j–p** gave high yields and ees with shorter reaction time, probably due to an additional coordination of 2′-hetero atom of Ar^2 causing **3j–p** to be bidentate substrates.



Scheme 1.

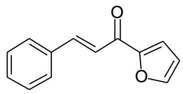
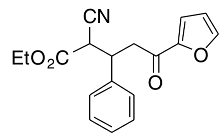
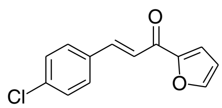
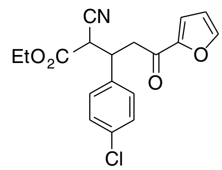
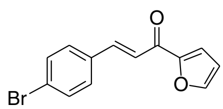
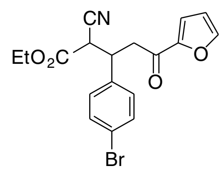
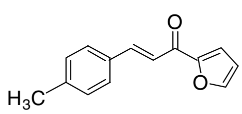
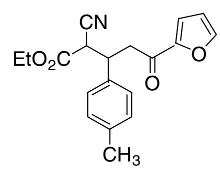
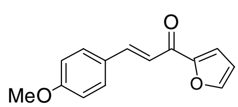
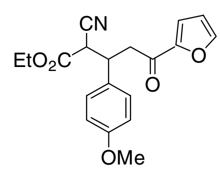
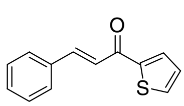
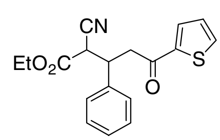
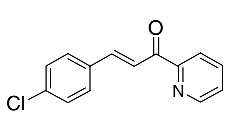
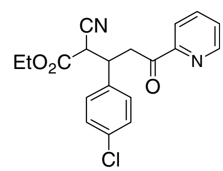
The absolute configuration of *syn*-**4k** was deduced to be (2*S*,3*S*) by X-ray crystallography analysis (Fig. 2). In order to determine the absolute configuration of the major isomer of *anti*-**4k**, decarboxylation[5c] of the mixture of *syn*- and *anti*-**4k** (1.2:1) proceeded smoothly to provide

Table 3. Asymmetric Michael reactions of **2** with **3a**–**p**[a]

Entry	Chalcone	Time (h)	Product	Yield[b] (%) (*syn*/*anti*)[c]	ee[d] of *syn*/*anti* (%)
1	**3a** 	144	**4a** 	84 (63/37)	88/89
2	**3b** 	72	**4b** 	88 (64/36)	88/88
3	**3c** 	144	**4c** 	82 (60/40)	88/89
4	**3d** 	144	**4d** 	82 (59/41)	83/83
5	**3e** 	72	**4e** 	88 (62/38)	92/94
6	**3f** 	24	**4f** 	92 (60/40)	89/86
7	**3g** 	24	**4g** 	89 (63/37)	88/88
8	**3h** 	120	**4h** 	93 (60/40)	91/91
9	**3i** 	96	**4i** 	84 (59/41)	88/88

(*continued on next page*)

Table 3 (*continued*)

Entry	Chalcone	Time (h)	Product	Yield[b] (%) (*syn*/*anti*)[c]	ee[d] of *syn*/*anti* (%)
10	**3j** 	24	**4j** 	95 (67/33)	93/92
11	**3k** 	36	**4k** 	91 (62/38)	93/93 (>99/—[e])[f]
12	**3l** 	24	**4l** 	90 (63/37)	94/93
13	**3m** 	48	**4m** 	89 (60/40)	93/93
14	**3n** 	24	**4n** 	94 (61/39)	93/93 (99/99)[f]
15	**3o** 	30	**4o** 	92 (61/39)	87/87 (93/93)[f]
16	**3p** 	20	**4p** 	80 (60/40)	94/95

[a] Catalyst: **1i** (10 mol %); reaction temperature: room temperature.
[b] Isolated yield.
[c] Determined by ^{1}H NMR.
[d] Determined by chiral HPLC.
[e] Not determined.
[f] After recrystallization.

3-(4-chlorophenyl)-5-(furan-2-yl)-5-oxopentanenitrile **5** in 85% yield with 93% ee (Scheme 2). Similarly starting from *syn*-**4k**, product **5** was obtained with the same enantioselectivity (93% ee) and configuration. No racemization was observed during the course of decarboxylation. The C3 configuration of *anti*-**4k** can be deduced as (*S*) by the C3 (*S*)-configuration of *syn*-**4k**, while the absolute configuration of *anti*-**4k** should be assigned as (2*R*,3*S*).

The proposed transition state of the reaction is shown in Figure 3. The enolization of α-cyanoacetate is catalyzed by the tertiary amine group in the quinoline moiety of **1i**. As a bifunctional catalyst **1i** could also coordinate with the carbonyl group of chalcones through hydrogen-bonding interaction of thiourea moiety.[13] The attack of α-cyanoacetate enolate to the chalcone from the *Si* face of the double bond of the chalcone molecule is controlled

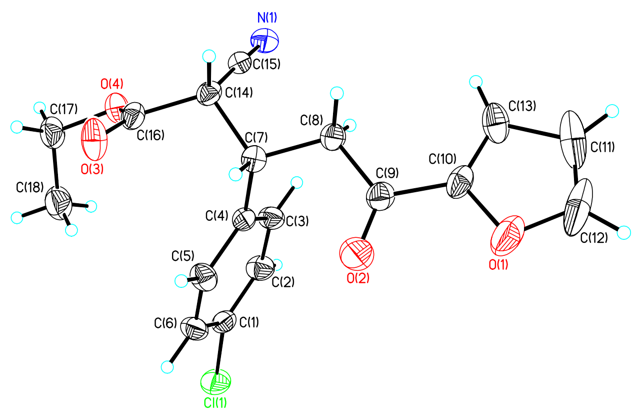
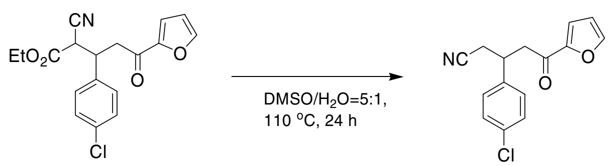


Figure 2. ORTEP presentation of (2*S*,3*S*)-**4k**.

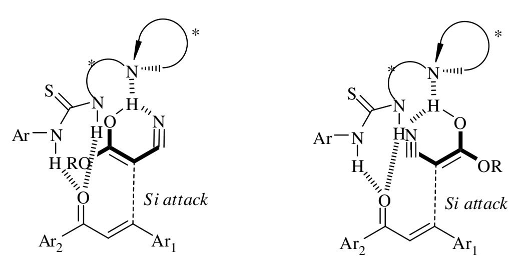


4k, *syn*/*anti* = 1.2:1 *syn*/*anti* = 18:1

5, 85% 93% ee 93% ee

Scheme 2.

by multi-point hydrogen-bond interaction, leading to excellent C3-(*S*)-stereoselectivities. The coordination of α-cyanoacetate enolate with the basic quinuclidine nitrogen atom of catalyst **1i** could adopt two possible modes **I** or **II** (Fig. 3). The difference between **I** and **II** is probably not large enough to reach high C-2 stereoselectivity, resulting in poor diastereoselectivities of the Michael addition products. However, poorly selective protonation of the transient enol intermediate after Michael addition may also lead to low diastereoselectivities. Chelation of the carbonyl group of the chalcone molecule with the thiourea moiety provides excellent stereocontrol in the reaction involving a monodentate carbonyl compound.



I **II**

Figure 3.

3. Conclusions

In the presence of a cinchona-derived bifunctional thiourea catalyst, the Michael addition of α-cyanoacetates to chalcones had been developed. The reaction proceeds in high enantioselectivity (83–95% ee) and good to excellent yields (80–95%). The Michael adducts provide versatile β-amino acid precursors and building blocks in organic synthesis. Further investigation in improving the diastereoselectivity and deriving the Michael products into useful compounds is currently in process.

4. Experimental

4.1. General

IR spectra were recorded on a BrukerTensor 27 infra-red spectrometer. ^{1}H and ^{13}C NMR spectra were measured on a Bruker AV-300 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. Mass spectra were recorded on a GCT-MS Micromass spectrometer. Elemental analyses were performed on a Carlo Flash 1112 Element Analysis instrument. Melting points were measured by a Beijing-Tike X-4 apparatus and are uncorrected. Optical rotations were measured on a Perkin Elmer 3411C instrument (589 nm). The X-ray crystal structures were measured on Rigaku R-axis RAPID IP. Common reagents and materials were purchased from commercial sources and purified before used. According to the reported procedure,[12e] **1i** was synthesized, $[\alpha]_D^{20} = -120.0$ (*c* 0.5, $CHCl_3$) lit. $[\alpha]_D^{25} = -124.6$ (*c* 0.5, $CHCl_3$).

4.2. Typical procedure for conjugate addition reaction of ethyl α-cyanoacetate with chalcones

To a solution of ethyl α-cyanoacetate **2** (15 μL, 0.15 mmol) and *trans*-chalcone **3a** (20.8 mg, 0.1 mmol) in toluene (0.2 mL), catalyst **1i** (6 mg, 0.01 mmol) was added at room temperature. The reaction was monitored by TLC. After **3a** disappeared, the reaction mixture was concentrated in vacuum. The residue was purified by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 6:1) to give **4a**[14] as a colorless oil (26.7 mg, 82%).

4.2.1. Ethyl 2-cyano-5-oxo-3,5-diphenylpentanoate 4a. A colorless oil in 82% yield. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.98$–7.95 (m, 2H), 7.59–7.55 (m, 1H), 7.50–7.25 (m, 7H), 4.37 (d, $J = 5.5$ Hz, 1H), 4.22–4.06 (m, 3H), 3.91 (d, $J = 5.1$ Hz, 1H), 3.77–3.45 (m, 2H), 1.22, 1.11 (2t, $J = 7.1$ Hz, 3H). The ratio of the *syn*- to *anti*-isomer (62:38) was determined by the proton absorptions at 4.37 and 3.91; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 197.1(196.6)^*$, 165.1(164.9), 139.3(138.4), 136.5(136.3), 133.7(133.5), 129.0(128.9), 128.8(128.7), 128.2(127.7), 128.1, 115.7(115.6), 77.1, 63.0(62.7), 44.2(43.3), 41.6(40.6), 40.8(40.1), 13.8. (* The data in parentheses are diastereomeric peak.) IR (film): $\nu = 2250$, 1743, 1685, 1596, 1580, 1496, 1449, 1252, 1210 cm^{-1}. Ees were determined by HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 70:30, flow rate = 0.3 mL/min, 5 °C): for *anti*-isomer: $t_{minor} = 39.9$ min and $t_{major} = 45.7$ min, 87% ee; for *syn*-isomer: $t_{minor} = 36.8$ min and $t_{major} = 63.4$ min, 87% ee.

4.2.2. Ethyl 3-(4-chlorophenyl)-2-cyano-5-oxo-5-phenylpentanoate 4b. A colorless oil in 88% yield was obtained by flash chromatography on silica gel (elution gradient: ethyl acetate/petroleum ether = 1:10–1:8). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.97$–7.94 (m, 2H), 7.60–7.57 (m, 1H), 7.50–

7.46 (m, 2H), 7.38–7.26 (m, 4H), 4.32 (d, $J = 5.4$ Hz, 1H), 4.22–4.08 (m, 3H), 3.88 (d, $J = 5.2$ Hz, 1H), 3.72–3.46 (m, 2H), 1.22, 1.15 (2t, $J = 7.1$ Hz, 3H). The ratio of the *syn*- to *anti*-isomer (64:36) was determined by the proton absorptions at $\delta = 4.32$ and 3.88. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 196.8(196.3)$, 164.9(164.7), 137.7(136.9), 136.3(136.1), 134.2, 133.9(133.6), 129.5, 129.2, 129.0, 128.8, 128.8, 128.0, 115.4, 63.1(62.8), 43.9(43.2), 41.5(40.2), 40.4(39.5), 13.9; IR (film): $\nu = 2250$, 1743, 1685, 1597, 1580, 1494, 1448, 1254, 1211, 1015 cm^{-1}. Ees were determined by HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 70:30, flow rate = 0.3 mL/min, 5 °C): for *syn*-isomer: $t_{minor} = 43.0$ min and $t_{major} = 65.6$ min, 88% ee; for *anti*-isomer: $t_{minor} = 40.4$ min and $t_{major} = 73.6$ min, 88% ee.

4.2.3. Ethyl 2-cyano-5-oxo-5-phenyl-3-*p*-tolylpentanoate 4c. A colorless oil in 82% yield was obtained by flash chromatography on silica gel (elution gradient: ethyl acetate/petroleum ether = 1:10–1:8). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.98$–7.93 (m, 2H), 7.59–7.56 (m, 1H), 7.50–7.45 (m, 2H), 7.31–7.24 (m, 2H), 7.16–7.13 (m, 2H), 4.33 (d, $J = 5.5$ Hz, 1H), 4.19–4.08 (m, 3H), 3.89 (d, $J = 5.1$ Hz, 1H), 3.70–3.42 (m, 2H), 2.31 (s, 3H), 1.23, 1.14 (2t, $J = 7.1$ Hz, 3H). The ratio of the *syn*- to *anti*-isomer (60:40) was determined by the proton absorptions at $\delta = 4.33$ and 3.89. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 197.2(196.7)$, 165.2(165.0), 138.0(137.8), 136.5(136.3), 135.3, 133.7(133.5), 129.6, 129.5, 128.8, 128.7, 128.0, 127.9, 127.5, 115.7, 77.1, 62.9(62.6), 44.3(43.4), 41.7(40.4), 40.5(39.8), 21.1, 13.8. IR (film): $\nu = 2249$, 1743, 1684, 1597, 1580, 1515, 1448, 1252, 1209 cm^{-1}. Ees were determined by HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 70:30, flow rate = 0.3 mL/min, 5 °C): *syn*-isomer: $t_{minor} = 43.0$ min and $t_{major} = 55.7$ min, 88% ee; for *anti*-isomer: $t_{minor} = 38.9$ min and $t_{major} = 66.9$ min, 89% ee.

4.2.4. Ethyl 2-cyano-3-(4-methoxyphenyl)-5-oxo-5-phenylpentanoate 4d. A yellowish oil in 82% yield was obtained by flash chromatography on silica gel (elution gradient: ethyl acetate/petroleum ether = 1:10–1:8). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.98$–7.95 (m, 2H), 7.59–7.55 (m, 1H), 7.50–7.45 (m, 2H), 7.35–7.26 (m, 2H), 6.88–6.85 (m, 2H), 4.31 (d, $J = 5.4$ Hz, 1H), 4.19–4.09 (m, 3H), 3.88 (d, $J = 5.2$ Hz, 1H), 3.78 (s, 3H), 3.730–3.45 (m, 2H), 1.21, 1.14 (2t, $J = 7.1$ Hz, 3H). The ratio of the *syn*- to *anti*-isomer (59:41) was determined by the proton absorptions at $\delta = 4.31$ and 3.88. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 197.2(196.7)$, 165.2(165.0), 159.4(159.3), 133.7(133.4), 130.4, 129.2, 128.8, 128.7, 128.0, 115.8(115.7), 114.3(114.2), 62.9(62.6), 55.2, 44.3(43.6), 41.8(40.2), 40.7(39.4), 13.9. IR (film): $\nu = 2250$, 1742, 1684, 1596, 1581, 1515, 1448, 1252, 1210 cm^{-1}. Ees were determined by HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 70:30, flow rate = 0.3 mL/min, 5 °C): for *syn*-isomer: $t_{minor} = 38.6$ min and $t_{major} = 65.1$ min, 83% ee; for *anti*-isomer: $t_{minor} = 35.7$ min and $t_{major} = 82.1$ min, 83% ee.

4.2.5. Ethyl 5-(4-chlorophenyl)-2-cyano-5-oxo-3-phenylpentanoate 4e. A colorless oil in 88% yield was obtained by flash chromatography on silica gel (elution gradient: ethyl acetate/petroleum ether = 1:10–1:8). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.92$–7.87 (m, 2H), 7.45–7.26 (m, 7H), 4.33 (d, $J = 5.6$ Hz, 1H), 4.21–4.04 (m, 3H), 3.90 (d, $J = 5.1$ Hz, 1H), 3.72–3.46 (m, 2H), 1.22, 1.10 (2t, $J = 7.1$ Hz, 3H). The ratio of the *syn*- to *anti*-isomer (62:38) was determined by the proton absorptions at $\delta = 4.33$ and 3.90. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 195.9(195.4)$, 165.1(164.9), 140.2(140.0), 139.1(138.2), 134.7(134.6), 129.5, 129.1(129.0), 129.0(128.9), 128.3(128.2), 128.0(127.6), 115.7(115.6), 77.1, 63.0(62.7), 44.1(43.2), 41.6(40.6), 40.79(40.1), 13.8. IR (film): $\nu = 2250$, 1743, 1685, 1590, 1571, 1496, 1455, 1252, 1209 cm^{-1}. Ees were determined by HPLC (Daicel Chiralpak AS-H, hexane/*i*-PrOH = 70:30, flow rate = 0.4 mL/min, 5 °C): for *syn*-isomer: $t_{minor} = 37.0$ min and $t_{major} = 58.9$ min, 92% ee; for *anti*-isomer: $t_{minor} = 39.9$ min and $t_{major} = 46.1$ min, 94% ee.

4.2.6. Ethyl 5-(4-chlorophenyl)-2-cyano-3-(4-nitrophenyl)-5-oxo-pentanoate 4f. A colorless oil in 92% yield was obtained by flash chromatography on silica gel (elution gradient: ethyl acetate/petroleum ether = 1:10–1:8). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.23$–8.19 (m, 2H), 7.92–7.86 (m, 2H), 7.64–7.56 (m, 2H), 7.8–7.44 (m, 2H), 4.36 (d, $J = 5.4$ Hz, 1H), 4.32–4.10 (m, 3H), 3.94 (d, $J = 5.2$ Hz, 1H), 3.74–3.51 (m, 2H), 1.25, 1.17 (2t, $J = 7.1$ Hz, 3H). The ratio of the *syn*- to *anti*-isomer (60:40) was determined by the proton absorptions at $\delta = 4.36$ and 3.94. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 195.0(194.7)$, 164.5(164.3), 147.7(147.6), 146.4(145.5), 140.6(140.5), 134.2(134.2), 129.5, 129.3(129.3), 129.2(128.9), 124.2(124.0), 115.1, 77.1, 63.5(63.2), 43.3(42.7), 41.2(40.2), 40.2(39.6), 13.9. IR (film): $\nu = 2250$, 1743, 1686, 1590, 1571, 1522, 1490, 1348, 1251, 1211 cm^{-1}. HRMS (FAB) m/z calcd for $C_{20}H_{17}ClN_2O_5$ (M+H): 401.0904, found 401.0895. Ees were determined by HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 70:30, flow rate = 0.3 mL/min, 5 °C): for *syn*-isomer: $t_{minor} = 134.1$ min and $t_{major} = 205.8$ min, 89% ee; for *anti*-isomer: $t_{minor} = 128.9$ min and $t_{major} = 243.2$ min, 86% ee.

4.2.7. Ethyl 3,5-bis(4-chlorophenyl)-2-cyano-5-oxo-pentanoate 4g. A colorless oil in 89% yield was obtained by flash chromatography on silica gel (elution gradient: ethyl acetate/petroleum ether = 1:8–1:6). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.93$–7.88 (m, 2H), 7.49–7.44 (m, 2H), 7.40–7.33 (m, 4H), 4.32 (d, $J = 5.5$ Hz, 1H), 4.25–4.10 (m, 3H), 3.89 (d, $J = 5.2$ Hz, 1H), 3.70–3.45 (m, 2H), 1.25, 1.17 (2t, $J = 7.1$ Hz, 3H). The ratio of the *syn*- to *anti*-isomer (63:37) was determined by the proton absorptions at $\delta = 4.32$ and 3.89. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 195.5(195.1)$, 164.8(164.6), 140.4, 137.6(136.7), 134.6/134.5, 134.3(134.1), 129.4, 129.2, 129.2, 129.1, 129.1, 115.3, 63.1(62.8), 43.8(43.0), 41.5(40.1), 40.5(39.4), 13.8. IR (film): $\nu = 2250$, 1742, 1685, 1590, 1572, 1492, 1445, 1251, 1209, 1092, 828 cm^{-1}. HRMS (FAB): m/z calcd for $C_{20}H_{18}Cl_2NO_3$ (M+H): 390.0664, found 390.0659. Ees were determined by HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 70:30, flow rate = 0.3 mL/min, 5 °C): for *syn*-isomer: $t_{minor} = 52.5$ min and $t_{major} = 77.8$ min, 88% ee; for *anti*-isomer: $t_{minor} = 56.7$ min, $t_{major} = 115.4$ min, 88% ee.

4.2.8. Ethyl 5-(4-chlorophenyl)-2-cyano-5-oxo-3-*p*-tolylpentanoate 4h. A colorless oil in 93% yield was obtained by flash chromatography on silica gel (elution gradient: ethyl acetate/petroleum ether = 1:8–1:6). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.91–7.86$ (m, 2H), 7.45–7.41 (m, 2H), 7.29–7.22 (m, 2H), 7.15–7.12 (m, 2H), 4.30 (d, $J = 5.9$ Hz, 1H), 4.20–4.06 (m, 3H), 3.88 (d, $J = 5.2$ Hz, 1H), 3.69–3.44 (m, 2H), 2.31 (s, 3H), 1.13, 1.05 (2t, $J = 7.1$ Hz, 3H). The ratio of the *syn*- to *anti*-isomer (62:38) was determined by the proton absorptions at $\delta = 4.30$ and 3.88. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 196.0(195.5)$, 165.1(165.0), 140.2(139.9), 138.0(137.8), 136.1(135.2), 134.8(134.7), 129.7, 129.5, 129.5, 129.1(129.0), 127.9(127.5), 115.7(115.6), 77.1, 63.0(62.6), 44.2(43.4), 41.7/40.6, 40.4(39.8), 21.0, 13.8. IR (film): $v = 2250$, 1743, 1686, 1590, 1572, 1489, 1446, 1252, 1207, 818 cm^{-1}. HRMS (FAB): m/z calcd for $C_{21}H_{21}ClNO_3$ (M+H): 370.1210, found 370.1207. Ees were determined by HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 70:30, flow rate = 0.3 mL/min, 5 °C): for *syn*-isomer: $t_{minor} = 54.5$ min and $t_{major} = 68.4$ min, 91% ee; for *anti*-isomer: $t_{minor} = 48.3$ min and $t_{major} = 100.0$ min, 91% ee.

4.2.9. Ethyl 5-(4-chlorophenyl)-2-cyano-3-(4-methoxyphenyl)-5-oxo-pentanoate 4i. A colorless oil in 84% yield was obtained by flash chromatography on silica gel (elution gradient: ethyl acetate/petroleum ether = 1:8–1:6). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.92–7.86$ (m, 2H), 7.46–7.42 (m, 2H), 7.34–7.26 (m, 2H), 6.89–6.84 (m, 2H), 4.29 (d, $J = 5.2$ Hz, 1H), 4.22–4.06 (m, 3H), 3.87 (d, $J = 5.2$ Hz, 1H), 3.78 (s, 3H), 3.68–3.44 (m, 2H), 1.22, 1.14 (2t, $J = 7.1$ Hz, 3H). The ratio of *syn*- to *anti*-isomer (59:41) was determined by the proton absorptions at $\delta = 4.29$ and 3.87. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 196.0(195.5)$, 165.1(164.9), 159.5(159.3), 140.2(140.0), 134.6, 131.0(130.1), 129.5, 129.1(129.1), 129.0(128.7), 115.6, 114.4(114.2), 63.0(62.7), 44.2(43.5), 41.8(40.7), 40.2(39.4), 13.8. IR (film): $v = 2250$, 1742, 1685, 1590, 1572, 1492, 1445, 1251, 1209, 829 cm^{-1}. HRMS (FAB): m/z calcd for $C_{21}H_{21}ClNO_4$ (M+H): 386.1159, found 386.1152. Ees were determined by HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 70:30, flow rate = 0.3 mL/min, 5 °C): for *syn*-isomer: $t_{minor} = 74.0$ min and $t_{major} = 100.0$ min, 88% ee; for *anti*-isomer: $t_{minor} = 68.5$ min and $t_{major} = 176.1$ min, 88% ee.

4.2.10. Ethyl 2-cyano-5-(furan-2-yl)-5-oxo-3-phenylpentanoate 4j. A white solid in 95% yield was obtained by flash chromatography on silica gel (elution gradient: ethyl acetate/petroleum ether = 1:6–1:4). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.60–7.59$ (m, 1H), 7.41–7.23 (m, 6H), 6.56–6.54 (m, 1H), 4.28 (d, $J = 5.6$ Hz, 1H), 4.21–4.02 (m, 3H), 3.88 (d, $J = 5.4$ Hz, 1H), 3.60–3.38 (m, 2H), 1.12, 1.02 (2t, $J = 7.1$ Hz, 3H). The ratio of the *syn*- to *anti*-isomer (67:33) was determined by the proton absorptions at $\delta = 4.28$ and 3.88. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 186.0(185.6)$, 165.0(164.8), 152.3, 146.9(146.6), 138.9(138.1), 128.9(128.8), 128.2(128.1), 128.0(127.7), 117.8(117.4), 115.6(115.5), 112.5(112.4), 63.0(62.6), 44.1(43.4), 41.3(40.6), 40.4(40.0), 13.8. IR (film): $v = 2248$, 1741, 1664, 1276, 1037 cm^{-1}. HRMS (FAB): m/z calcd for $C_{18}H_{18}NO_4$ (M+H): 312.1236, found 312.1233. Ees were determined by HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 70:30, flow rate = 0.3 mL/min, 5 °C): for *syn*-isomer: $t_{minor} = 39.2$ min and $t_{major} = 47.9$ min, 93% ee; for *anti*-isomer: $t_{minor} = 35.9$ min and $t_{major} = 58.6$ min, 92% ee.

4.2.11. Ethyl 3-(4-chlorophenyl)-2-cyano-5-(furan-2-yl)-5-oxo-pentanoate 4k. A white solid in 91% yield was obtained by flash chromatography on silica gel (elution gradient: ethyl acetate/petroleum ether = 1:6–1:4). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.51–7.48$ (m, 1H), 7.27–7.13 (m, 5H), 6.46–6.44 (m, 1H), 4.15 (d, $J = 5.5$ Hz, 1H), 4.12–3.97 (m, 3H), 3.78 (d, $J = 5.5$ Hz, 1H), 3.45–3.28 (m, 2H), 1.12, 1.05 (2t, $J = 7.1$ Hz, 3H). The ratio of the *syn*- to *anti*-isomer (67:33) was determined by the proton absorptions at $\delta = 4.15$ and 3.78. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 185.6(185.3)$, 164.7(164.6), 152.2(152.2), 147.0(146.7), 137.7(136.5), 134.2(134.0), 129.5(129.2), 129.1(129.0), 117.9(117.6), 115.6(115.5), 112.6(112.5), 63.1(62.8), 43.8(43.2), 41.2(40.2), 40.0(39.3), 13.8. IR (film): $v = 2252$, 1743, 1673, 1569, 1493, 1468, 1255, 1015 cm^{-1}. HRMS (FAB): m/z calcd for $C_{18}H_{17}ClNO_4$ (M+H): 346.0846, found 346.0843. Ees were determined by HPLC (Daicel Chiralpak AS-H, hexane/*i*-PrOH = 70:30, flow rate = 0.5 mL/min, 10 °C): for *syn*-isomer: $t_{minor} = 39.6$ min and $t_{major} = 58.7$ min, 93% ee; for *anti*-isomer: $t_{minor} = 45.9$ min and $t_{major} = 50.5$ min, 93% ee. The crystal (*syn*-**4k**, mp: 94–96 °C) used for the X-ray study had the dimensions $0.75 \times 0.26 \times 0.15$ mm^3. Crystal data: $C_{18}H_{16}ClNO_4$, Mr = 345.77; monoclinic; space group, $P2(1)$, $a = 7.0340(14)$ Å, $b = 10.199(2)$ Å, $c = 11.881(2)$ Å, $V = 850.2(3)$ Å^3, $Z = 2$, $D_{calcd} = 1.351$ g/cm^3, $F0 = 3449$, $\lambda = 0.71073$ Å. Final R indices $[I > 2\sigma(I)]$ $R_1 = 0.0489$, $wR_2 = 0.1222$, absolute structure parameter 0.06(9). CCDC No. 638112.

4.2.12. Ethyl 3-(4-bromophenyl)-2-cyano-5-(furan-2-yl)-5-oxo-pentanoate 4l. A white solid in 90% yield was obtained by flash chromatography on silica gel (elution gradient: ethyl acetate/petroleum ether = 1:6–1:4). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.60–7.58$ (m, 1H), 7.42–7.47 (m, 2H), 7.30–7.19 (m, 3H), 6.56–6.52 (m, 1H), 4.26 (d, $J = 5.5$ Hz, 1H), 4.19–4.07 (m, 3H), 3.89 (d, $J = 5.5$ Hz, 1H), 3.53–3.42 (m, 2H), 1.22, 1.14 (2t, $J = 7.1$ Hz, 3H). The ratio of *syn*- to *anti*-isomer (67:33) was determined by the proton absorptions at $\delta = 4.15$ and 3.78. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 185.6(185.2)$, 164.7(164.6), 152.2(152.1), 147.0(146.8), 137.9(137.1), 132(131.9), 129.8(129.5), 122.3(122.1), 117.9(117.9), 115.4(115.3), 112.6(112.6), 63.1(62.9), 43.8(43.2), 41.2(40.1), 40.0(39.3), 13.8. IR (KBr): $v = 2907$, 2252, 1738, 1760 cm^{-1}. HRMS (EI): m/z calcd for $C_{18}H_{17}BrNO_4$: 389.0263, found 389.0267. Ees were determined by HPLC (Daicel Chiralpak OD-H, hexane/*i*-PrOH = 70:30, flow rate = 0.5 mL/min, 7 °C): for *syn*-isomer: $t_{minor} = 30.0$ min and $t_{major} = 31.3$ min, 94% ee; for *anti*-isomer: $t_{minor} = 36.0$ min and $t_{major} = 39.8$ min, 93% ee.

4.2.13. Ethyl 2-cyano-5-(furan-2-yl)-5-oxo-3-*p*-tolylpentanoate 4m. A white solid in 89% yield was obtained by flash chromatography on silica gel (elution gradient: ethyl acetate/petroleum ether = 1:6–1:4). ^{1}H NMR (300 MHz,

$CDCl_3$): $\delta = 7.51–7.48$ (m, 1H), 7.20–7.03 (m, 5H), 6.47–6.45 (m, 1H), 4.17 (d, $J = 5.6$ Hz, 1H), 4.13–3.95 (m, 3H), 3.78 (d, $J = 5.4$ Hz, 1H), 3.48–3.27 (m, 2H), 2.22 (s, 3H), 1.13, 1.05 (2t, $J = 7.1$ Hz, 3H). The ratio of the *syn*- to *anti*-isomer (60:40) was determined by the proton absorptions at $\delta = 4.17$ and 3.78. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 186.1(185.6)$, 165.0(164.9), 152.4(152.3), 146.8(146.6), 138.0(137.8), 135.9(135.0), 129.6(129.5), 127.9(127.5), 117.7(117.4), 115.6(115.5), 112.5(112.4), 62.9(62.6), 44.3(43.5), 41.4(40.4), 40.3(39.6), 21.0, 13.8. IR (film): $\nu = 2250$, 1739, 1669, 1564, 1415, 1467, 1249, 1037 cm^{-1}. HRMS (FAB): *m*/*z* calcd for $C_{19}H_{20}NO_4$ (M+H): 326.1392, found 326.1386. Ees were determined by HPLC (Daicel Chiralpak OD-H, hexane/*i*-PrOH = 70:30, flow rate = 0.5 mL/min, 5 °C): for *syn*-isomer: $t_{minor} = 36.3$ min and $t_{major} = 48.3$ min, 93% ee; for *anti*-isomer: $t_{minor} = 39.2$ min and $t_{major} = 44.4$ min, 93% ee.

4.2.14. Ethyl 2-cyano-5-(furan-2-yl)-3-(4-methoxyphenyl)-5-oxo-pentanoate 4n. A white solid in 94% yield was obtained by flash chromatography on silica gel (elution gradient: ethyl acetate/petroleum ether = 1:6–1:4). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.50–7.47$(m, 1H), 7.23–7.13 (m, 3H), 6.78–6.73 (m, 3H) 6.46–6.44 (m, 1H), 4.13 (d, $J = 5.4$ Hz, 1H), 4.09–3.95 (m, 3H), 3.77 (d, $J = 5.4$ Hz, 1H), 3.43–3.19 (m, 2H), 1.12, 1.05 (2t, $J = 7.1$ Hz, 3H). The ratio of the *syn*- to *anti*-isomer (61:39) was determined by the proton absorptions at $\delta = 4.17$ and 3.78. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 186.1(185.7)$, 165.0(164.9), 159.4.4(159.3), 152.4(152.3), 146.9(146.6), 130.8(130.0), 129.2(128.8), 117.8(117.5), 115.6, 114.3(114.2), 12.5(112.4), 62.9(62.6), 44.3(43.5), 41.4(40.4), 40.3(39.6), 21.0, 13.8. IR (film): $\nu = 2250$, 1742, 1673, 1612, 1569, 1514, 1467, 1254, 1031 cm^{-1}. Elemental Anal. Calcd for $C_{19}H_{19}NO_5$: C, 60.60; H, 5.65; N, 4.11. Found: C, 60.49; H, 5.64; N, 4.14. Ees were determined by HPLC (Daicel Chiralpak AS-H, hexane/*i*-PrOH = 70:30, flow rate = 0.5 mL/min, 25 °C): for *syn*-isomer: $t_{minor} = 40.1$ min and $t_{major} = 53.8$ min, 93% ee; for *anti*-isomer: $t_{minor} = 44.2$ min and $t_{major} = 112.4$ min, 93% ee.

4.2.15. Ethyl 2-cyano-5-oxo-3-phenyl-5-(thiophen-2-yl)pentanoate 4o. A white solid in 92% yield was obtained by flash chromatography on silica gel (elution gradient: ethyl acetate/petroleum ether = 1:6–1:4). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.79–7.77$ (m, 1H), 7.69–7.67 (m, 1H), 7.40–7.26 (m, 5H), 7.15–7.14 (m, 1H), 4.32 (d, $J = 5.5$ Hz, 1H), 4.21–4.03 (m, 3H), 3.90 (d, $J = 5.2$ Hz, 1H), 3.69–3.42 (m, 2H), 1.20, 1.08 (2t, $J = 7.1$ Hz, 3H). The ratio of the *syn*- to *anti*-isomer (61:39) was determined by the proton absorptions at $\delta = 4.32$ and 3.90. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 189.9(189.3)$, 165.0(164.8), 143.6(143.4), 139.0(138.1), 134.5(134.2), 132.5(132.3), 129.0(128.9), 128.3, 128.2(128.1), 128.0(127.7), 115.6(115.5), 63.0(62.7), 44.0(43.3), 42.2(41.0), 41.2(40.3), 13.8. IR (film): $\nu = 2251$, 1744, 1661, 1519, 1496, 1455, 1416, 1256, 1214, 1027 cm^{-1}. HRMS (FAB): *m*/*z* calcd for $C_{18}H_{18}NO_3S$ (M+H): 328.1007, found 328.1004. Ees were determined by HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 70:30, flow rate = 0.3 mL/min, 5 °C): for *syn*-isomer: $t_{minor} = 43.0$ min and $t_{major} = 52.4$ min, 87% ee; for *anti*-isomer: $t_{minor} = 38.6$ min and $t_{major} = 58.0$ min, 87% ee.

4.2.16. Ethyl 3-(4-chlorophenyl)-2-cyano-5-oxo-5-(pyridin-2-yl)pentanoate 4p. A white solid in 80% yield was obtained by flash chromatography on silica gel (elution gradient: ethyl acetate/petroleum ether = 1:6–1:4). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.71–8.69$ (m, 1H), 8.03–7.95 (m, 1H), 7.88–7.79 (m, 1H), 7.54–7.48 (m, 1H), 7.41–7.28 (m, 4H), 4.28 (d, $J = 5.5$ Hz, 1H), 4.23–4.08 (m, 3H), 4.00–3.75 (m, 2H), 1.25, 1.18 (2t, $J = 7.1$ Hz, 3H). The ratio of the *syn*- to *anti*-isomer (60:40) was determined by the proton absorptions at $\delta = 4.28$ and 3.87. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 198.7/198.2$, 164.9, 152.6(152.5), 149.1(149.1), 137.7, 137.0(136.9), 134.0(133.8), 129.6(129.3), 129.0(128.9), 127.7(127.6), 121.8, 115.6, 63.0(62.8), 44.1(43.4), 40.8(39.8), 40.4(39.7), 13.9. IR (film): $\nu = 2250$, 1744, 1700, 1584, 1493, 1464, 1266, 1093, 739 cm^{-1}. HRMS (FAB) *m*/*z* calcd for $C_{19}H_{18}ClN_2O_3$ (M+H): 357.1006, found 357.1000. Ees were determined by HPLC (Daicel Chiralpak AS-H, hexane/*i*-PrOH = 70:30, flow rate = 0.3 mL/min, 10 °C): for *syn*-isomer: $t_{minor} = 33.8$ min and $t_{major} = 42.3$ min, 94% ee; for *anti*-isomer: $t_{minor} = 45.8$ min and $t_{major} = 55.4$ min, 95% ee.

4.3. (*S*)-3-(4-Chlorophenyl)-5-(furan-2-yl)-5-oxopentanenitrile 5

A mixture of *syn*- and *anti*-**4k** (34.5 mg, 0.1 mol) was dissolved in dimethylsulfoxide/water (5:1, 2 mL), followed by stirring at 110 °C for 24 h. After cooling to room temperature, 20% aqueous lithium bromide solution (5 mL) was added, and the reaction mixture was extracted with dichloromethane (5 × 10 mL). The combined organic extracts were washed twice with 20% lithium bromide solution (2 × 10 mL), dried over sodium sulfate, and concentrated. The residue was purified by flash chromatography on silica gel (eluent: ethyl acetate/petroleum ether = 1:4–1:3), yielding a viscous colorless oil **5** (23 mg, 85% yield with 93% ee). $[\alpha]_D^{20} = +28.0$ (*c* 0.85, $CHCl_3$).^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.59$ (d, $J = 1.0$ Hz, 1H), 8.34–7.21 (m, 5H), 6.56, 6.54 (dd, $J = 1.7$, 3.6 Hz, 1H), 3.76–3.67 (m, 1H), 3.41–3.26 (m, 2H), 2.79–2.73 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 186.0$, 152.3, 146.8, 139.3, 133.6, 129.2, 128.6, 117.8, 117.7, 42.3, 36.1, 24.3. IR (film): $\nu = 2247$, 1673 cm^{-1}. HRMS (EI): *m*/*z* calcd for $C_{15}H_{12}ClNO_2$: 273.0557, found 273.0559. Ee was determined by HPLC analysis (Daicel chiralcel AD-H, hexane/*i*-propanol = 70:30, 0.6 mL/min, 25 °C): $t_{minor} = 12.0$ min and $t_{major} = 17.1$ min.

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References

1. For reviews, see: (a) Tomioka, K.; Nagaoka, Y.; Yamaguchi, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 3, Chapters 31.1 and 31.2; (b) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171–196; (c) Sibi, M. P.; Manyem, S.

Tetrahedron **2000**, *56*, 8033–8061; (d) Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1688–1690.

2. (a) Perlmutter, P. *Conjugate Addition Reaction in Organic Synthesis*; Pergamon: Oxford, 1992; (b) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933.
3. (a) Motoyama, Y.; Koga, Y.; Kobayashi, K.; Aoki, K.; Nishiyama, H. *Chem. Eur. J.* **2002**, *8*, 2968–2975; (b) Inagaki, K.; Nozaki, K.; Takaya, M. *Synlett* **1997**, 119–120; (c) Sawamura, M.; Hamashima, H.; Ito, Y. *Tetrahedron* **1994**, *50*, 4439–4454; (d) Sawamura, M.; Hamashima, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 8295–8296.
4. Takenaka, K.; Uozumi, Y. *Org. Lett.* **2004**, *6*, 1833–1835.
5. (a) Raheem, I. T.; Goodman, S. N.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 706–707; (b) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 11204–11205; (c) Taylor, M. S.; Zalatan, D. N.; Lerchner, A. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 1313–1317.
6. For selected examples, 1,3-diketones: (a) Wang, J.; Li, H.; Duan, W.-H.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4713–4716; Malonate esters: (b) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673; (c) Brandau, S.; Landa, A.; Franzen, J.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4305–4309; (d) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119–125; (e) Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906–9907; (f) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 661–665; β-Ketoesters: (g) Berkessel, A.; Cleemann, F.; Mukherjee, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 947–950; (h) Li, H.-M.; Tang, L.; Wu, F.-H.; Liu, X.-F.; Guo, C.-Y.; Foxman, B. M.; Deng, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 105–108.
7. For selected examples, Nitroesters: (a) Prieto, A.; Halland, N.; Jørgensen, K. A. *Org. Lett.* **2005**, *7*, 3897–3900; 1,3-Dinitriles: (b) Hoashi, Y.; Okino, T.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 4032–4035; Nitroalkanes: (c) Hanessian, S.; Pham, V. *Org. Lett.* **2000**, *2*, 2975–2978; (d) Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **2000**, *2*, 4257–4259; (e) Wang, J.; Li, H.; Zu, L.-S.; Jiang, W.; Wang, W. *Adv. Synth. Catal.* **2006**, *348*, 2047–2050.
8. For selected examples, cyanoacetates: (a) Wu, F.; Hong, R.; Khan, J.; Liu, X.; Deng, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 4301–4305; (b) Liu, T.-Y.; Long, J.; Li, B.-J.; Jiang, L.; Li, R.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Org. Biomol. Chem.* **2006**, *4*, 2097–2099; (c) Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 3928–3930; (d) Li, H.; Song, J.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2005**, *127*, 8948–8949; (e) Wang, B.-M.; Wu, F.-H.; Wang, Y.; Liu, X.-F.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 768–769.
9. Reviews: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138–5175; (b) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520–1543; (c) Special issue on organocatalysis: Houk, K. N., List, B., Eds.; *Acc. Chem. Res.* **2004**, *37*, 487–631.
10. Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621–631.
11. Inokuma, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2006**, *128*, 9413–9419.
12. For Michael addition: (a) Vakulya, B.; Varga, S.; Csampai, A.; Soos, T. *Org. Lett.* **2005**, *7*, 1967–1969; (b) Wang, J.; Li, H.; Zu, L.; Jiang, W.; Xie, H.; Duan, W.; Wang, W. *J. Am. Chem. Soc.* **2006**, *128*, 12652–12653; (c) Tillman, A. L.; Ye, J.; Dixon, D. J. *Chem. Commun.* **2006**, 1191–1193; (d) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481–4483; (e) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367–6370; (f) Li, B.-J.; Jiang, L.; Liu, M.; Chen, Y.-C.; Ding, L. S.; Wu, Y. *Synlett* **2005**, 603–606; For Mannich reaction: (g) Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048–6049; (h) Marcelli, T.; van der Haas, R. N. S.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 929–931; (i) Bernardi, L.; Fini, F.; Herrera, R. P.; Ricci, A.; Sgarzani, V. *Tetrahedron* **2006**, *62*, 375–380; For Friedel–Craft reaction: (j) Yang, Y.-Q.; Song, J.; Hong, R.; Li, H.-M.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 8156–8157.
13. Two distinct reaction pathways were discussed: Hamza, A.; Schubert, G.; Soo's, T.; Papai, I. *J. Am. Chem. Soc.* **2006**, *128*, 13151–13160.
14. El-Sadany, S. K.; Sharaf, S. M.; Darwish, A. I.; Youssef, A. A. *Indian J. Chem., Sect. B* **1991**, *30*, 567–573.