

Enantioselective Michael Addition of α -Substituted Cyanoacetates to Vinyl Ketones Catalyzed by Bifunctional Organocatalysts

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Abstract: A highly enantioselective Michael addition of α -substituted cyanoacetates to vinyl ketones was accomplished in the presence of simple bifunctional thiourea/tertiary amine organocatalysts. A number of α -aryl or alkyl cyanoacetates have been successfully applied to give multifunctional compounds with an all-carbon-substituted

tuted quaternary stereocenter in excellent enantioselectivities (82–97% *ee*) and yields (61–99%). The optical pure adducts could be smoothly converted

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to variously structured $\beta^{2,2}$ -amino acid esters. Moreover, an interesting reaction model involving multiple hydrogen-bonding interactions amongst the thiourea/tertiary amine catalyst and the reactants has been proposed based on the absolute configuration of the adduct and computational studies.

Introduction

There is a high demand for enantiopure β -amino acids in both academia and industry owing to their unique pharmacological properties, their occurrence in natural products, and as potential precursors for β -lactams.^[1] Furthermore, the corresponding β -peptides can form much more stable secondary structures (turns, sheets, and helices) in solution than their α -peptidic natural counterparts.^[2] Therefore the development of efficient protocols for the enantioselective synthesis of β -amino acids has been the subject of ever-growing interest over the past years. Different from their α -amino acid correlates, β -amino acids have a more complicated structural designation because the amino group is shifted away from the carboxyl group by one carbon in the skeleton (Figure 1). Although a number of methods have been suc-

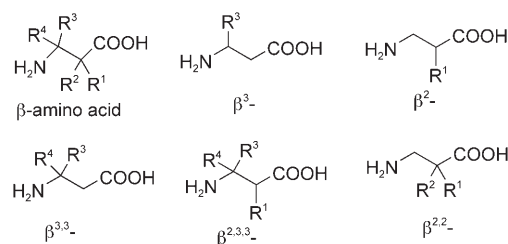


Figure 1. Designation of β -amino acids.

cessfully developed for the synthesis of β^3 -amino acids^[3] or β^2 -amino acids,^[4] the stereoselective preparation of $\beta^{3,3}$ -amino acids, $\beta^{2,3,3}$ -amino acids, or $\beta^{2,2}$ -amino acids still remains a major challenge for synthetic chemists,^[1c,d] especially in catalytic strategies, as an all-carbon-substituted quaternary stereocenter has to be generated.^[5] It could be envisioned that $\beta^{2,2}$ -amino acids might be easily accessible from the corresponding chiral α,α -disubstituted cyanoacetates,^[6] which could be prepared through the direct asymmetric Michael addition of α -substituted cyanoacetates to activated vinyl compounds (Scheme 1).



Scheme 1. Retrosynthesis of $\beta^{2,2}$ -amino acids. EWG = electron withdrawing group.

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Supporting information for this article is available on the WWW under <http://www.chemurj.org/> or from the author and contains computational studies, NMR, HRMS, and HPLC spectra for all products.

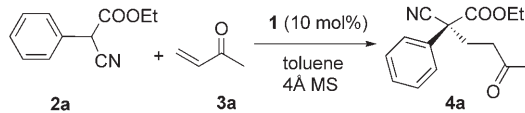
The α -cyano ester stereocenter is readily epimerizable, and therefore the use of α -substituted cyanoacetate derivatives offers the possibility of generating a configurationally stable quaternary stereocenter under kinetic control. The formation of such nucleophilic species is easy by in situ deprotonation of α -acidic hydrocarbons, and direct carbon-carbon bond-forming reactions, such as Michael additions, to construct a quaternary carbon center, may be conducted in an operationally simple and atom economical way. However, in comparison with their β -dicarbonyl analogues,^[7] the application of α -substituted cyanoacetates in catalytic asymmetric Michael additions is far from satisfying, probably owing to their incapability of two-point binding with catalysts. In 1992, Ito and co-workers reported the conjugate reaction of α -methyl cyanoacetate and vinyl ketones catalyzed by rhodium-TRAP (TRAP = 2,2''-bis[1-(diphenylphosphino)ethyl]-1,1''-biferrocene) complex in less than 90% *ee*, while other substituted cyanoacetates have not been tested.^[8] Various palladium or platinum complexes have also been tested in the asymmetric Michael addition of α -methyl cyanoacetates and vinyl ketones, but low to moderate *ee* was achieved.^[9] Recently, Jacobsen presented the highly enantioselective Michael addition of α -substituted cyanoacetates to α,β -unsaturated imides or ketones in the presence of a Salen-Al complex.^[10] On the other hand, the natural cinchona alkaloids have been applied in the asymmetric catalysis of ethyl α -phenyl cyanoacetate and methyl vinyl ketone (MVK) three decades ago,^[11] but good *ee* has only been achieved very recently in the addition reactions of α -substituted cyanoacetates catalyzed by some modified cinchona alkaloids.^[12] Therefore, the development of efficient enantioselective catalytic systems for α -substituted cyanoacetates is highly desirable. Recently, we have shown that bifunctional thiourea/tertiary amine compounds^[13,14] derived from simple chiral diamines are highly enantioselective organocatalysts for the Michael addition of α -substituted cyanoacetates to vinyl sulfones, and chiral $\beta^{2,2}$ -amino acid esters could be smoothly prepared from the addition products.^[15] Nevertheless, in an effort to develop more applicable asymmetric transformations of cyanoacetates, we found that the Michael acceptors were not limited to vinyl sulfones. Here we would like to report the highly enantioselective Michael addition of α -substituted cyanoacetates to vinyl ketones promoted by simple bifunctional thiourea/tertiary amine organocatalysts,^[16] giving a more efficient protocol for structurally variable acyclic and cyclic $\beta^{2,2}$ -amino acid esters.

Results and Discussion

Catalysts screening: Bifunctional thiourea/tertiary amine catalysts **1a–e** (10 mol%) with various chiral scaffolds, which have

been successfully applied in a range of asymmetric 1,2- or 1,4-addition reactions,^[13] were screened in the Michael addition of ethyl α -phenyl cyanoacetate **2a** and methyl vinyl ketone **3a** (MVK) in toluene at room temperature. Some 4 Å molecular sieves were used to remove a trace amount of water in the reaction. As summarized in Table 1, all cata-

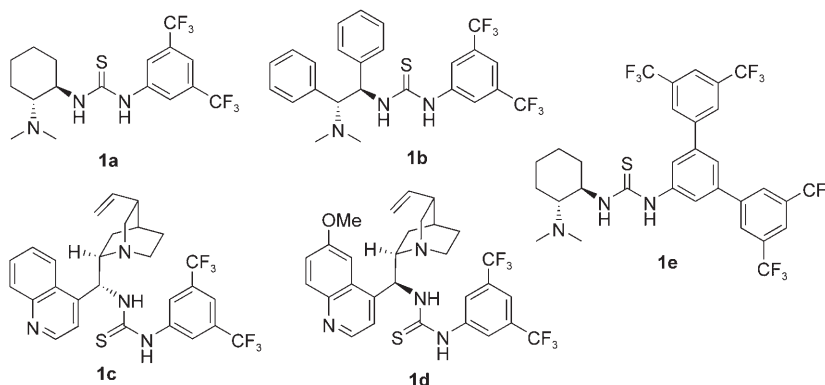
Table 1. Catalysts screening studies of the Michael addition of α -phenyl cyanoacetate **2a** to methyl vinyl ketone **3a**.^[a]



Entry	Cat. 1	<i>T</i> [°C]	<i>t</i> [h]	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	1a	20	4	96	73
2	1b	20	4	54	56
3	1c	20	4	95	60
4	1d	20	4	97	62
5	1e	20	4	80	60
6 ^[d]	1a	20	4	75	40
7	1a	-40	48	95	86
8	1d	-40	48	93	75
9	1a	-60	96	95	91

[a] Reaction conditions: **2a** (0.1 mmol), **3a** (0.2 mmol), and catalyst **1** (0.01 mmol) were stirred in toluene (1 mL). After the stated time, the product was purified by FC. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Dichloromethane as the solvent.

lysts exhibited high catalytic activity and the Michael addition product **4a** was cleanly isolated (Table 1, entries 1–5). The highest enantioselectivity (73% *ee*) was observed in the reaction catalyzed by **1a**, derived from (*R,R*)-1,2-diaminocyclohexane (entry 1). As previously reported,^[15] the enantioselectivity was also dramatically decreased in dichloromethane (entry 6). Subsequently, we conducted the Michael reaction at lower temperature to improve the enantioselectivity. We were pleased to find that a high *ee* (86% *ee*) was obtained when using **1a** as the catalyst at -40°C (entry 7). Lower *ee* was observed in the presence of quinine derivative **1d** under the same conditions (entry 8). Moreover, the reaction could be smoothly conducted at -60°C catalyzed by **1a** (10 mol%), and an excellent *ee* (91% *ee*) was achieved in 95% yield after 96 h (entry 9).



Michael addition of α -aryl cyanoacetates to vinyl ketones:

With the optimized reaction conditions in hand, the scope and limitation of the bifunctional organocatalyst **1a** promoted asymmetric Michael reactions were explored. A series of α -aryl substituted ethyl cyanoacetates **2** were reacted with vinyl ketones **3** in the presence of 10 mol % of **1a** at -60°C . As summarized in Table 2, excellent enantioselectivities

Table 2. Asymmetric Michael addition of α -aryl cyanoacetates **2** to vinyl ketones **3**.^[a]

Entry	Ar	3	Product 4	Yield [%] ^[b]	ee [%] ^[c]
1	Ph (2a)	3a	4a	95	91
2	<i>p</i> -Cl-Ph (2b)	3a	4b	87	87
3	<i>p</i> -Br-Ph (2c)	3a	4c	86	86
4	<i>p</i> -F-Ph (2d)	3a	4d	94	92
5	<i>o</i> -F-Ph (2e)	3a	4e	95	95
6	<i>m</i> -CF ₃ -Ph (2f)	3a	4f	95	85
7	<i>p</i> -CH ₃ O-Ph (2g)	3a	4g	95	90
8	3,4-(CH ₃ O) ₂ -Ph (2h)	3a	4h	88	95
9	2-thienyl (2i)	3a	4i	93	82
10	Ph (2a)	3b	4j	94	86
11	<i>p</i> -Br-Ph (2c)	3b	4k	93	85
12 ^[e]	<i>o</i> -F-Ph (2e)	3b	4l ^[d]	90	97
13	<i>p</i> -CH ₃ O-Ph (2g)	3b	4m	95	89
14 ^[e]	1-naphthyl (2j)	3b	4n	97	91
15	<i>o</i> -F-Ph (2e)	3c	4o	99	92
16	<i>o</i> -F-Ph (2e)	3d	4p	97	91
17	<i>o</i> -F-Ph (2e)	3e	4q	97	97
18	Ph (2a)	3e	4r	99	93

[a] Reaction conditions: **2** (0.1 mmol), **3** (0.2 mmol), and catalyst **1a** (0.01 mmol) were stirred in toluene (1 mL) at -60°C for 96 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The absolute configuration was determined to be *S*, and other Michael addition products were assigned accordingly. [e] After 120 h.

(85–95% *ee*) with high yields (86–95%) were obtained in the reactions of MVK **3a** and α -aryl cyanoacetates **2b–f** with various electron-withdrawing substituents at *para*, *meta*, or *ortho* positions (Table 2, entries 2–6). Notably, aryl substrates **2g** and **2h** with electron-donating substituents also exhibited high reactivity and excellent *ee* was achieved (entries 7 and 8). For thienyl derivative **2i**, a lower *ee* (82% *ee*) was given under the same conditions (entry 9). On the other hand, a variety of aryl vinyl ketones **3b–d** and 2-thienyl vinyl ketone **3e** could be also successfully applied in the Michael reactions with variously substituted α -aryl cyanoacetates (entries 10–18), and generally excellent *ee* and yields were achieved under the optimized conditions, even for the bulky 1-naphthyl substrate **2j** (entry 14).

Michael addition of α -alkyl cyanoacetates to aryl vinyl ketones: Subsequently we investigated the Michael reactions of α -alkyl cyanoacetates and vinyl ketones. Although very poor reactivity was observed in the reaction of α -methyl cyanoacetate **2k** and MVK **3a** at ambient temperature in the

presence of **1a** (10 mol%), we delightfully found that the Michael reaction could be considerably accelerated by employing the more reactive phenyl vinyl ketone **3b** as the Michael acceptor. As summarized in Table 3, the addition

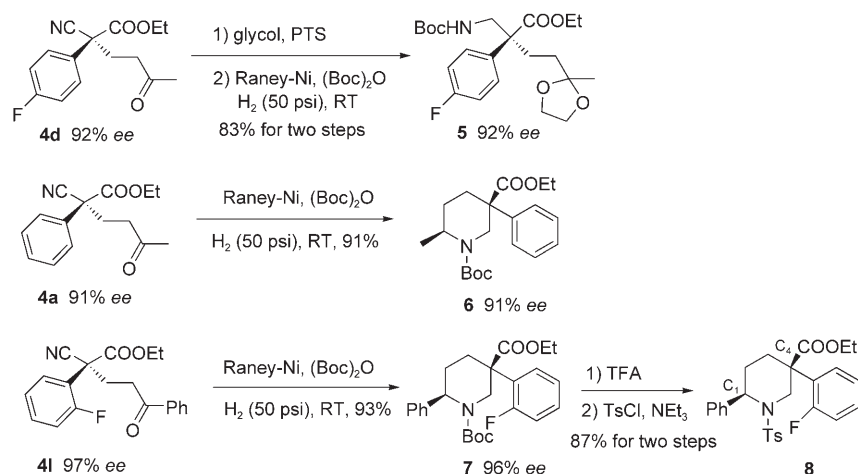
Table 3. Asymmetric Michael addition of α -alkyl cyanoacetates **2** to aryl vinyl ketone **3**.^[a]

Entry	R	3	T [°C]	t [h]	Product 4	Yield [%] ^[b]	ee [%] ^[c]
1	methyl (2k)	3b	20	5	4s	81	73
2	methyl (2k)	3b	-60	96	4s ^[d]	76	91
3	<i>n</i> -butyl (2l)	3b	-60	96	4t	72	92
4	benzyl (2m)	3b	-60	96	4u	90	92
5	isopropyl (2n)	3b	-20	120	4v	66	93
6	methyl (2k)	3c	-60	96	4w	67	85
7	methyl (2k)	3d	-60	96	4x	61	85
8	methyl (2k)	3e	-60	96	4y	91	96
9	benzyl (2m)	3e	-60	96	4z	98	97

[a] Reaction conditions: **2** (0.1 mmol), **3** (0.2 mmol), and catalyst **1a** (0.01 mmol) were stirred in toluene (1 mL). [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Absolute configuration was determined by comparison with reported optical rotation, see reference [8]. Other adducts were assigned accordingly.

product **4s** was obtained in 81% yield with 73% *ee* at room temperature after 5 h (Table 3, entry 1). Gratifyingly, the Michael reaction of α -methyl cyanoacetate **2k** and phenyl vinyl ketone **3b** could smoothly proceed at lower temperature. An excellent *ee* (91% *ee*) was achieved with good yield (76%) at -60°C for 96 h (entry 2). α -*n*-Butyl and benzyl substrates **2l** and **2m** were also successfully applied under the same conditions and excellent results were obtained (entries 3 and 4). Substrate **2n** with a branched alkyl group showed slightly lower reactivity, but a high *ee* (91% *ee*) was still obtained at -20°C (entry 5). In addition, aryl vinyl ketones with electron-withdrawing or -donating substituents gave good results in the reactions with α -methyl cyanoacetate **2k** (entries 6 and 7). Notably, 2-thienyl vinyl ketone **3e** exhibited higher reactivity, and excellent *ee* and yields were gained (entries 8 and 9).

Synthesis of $\beta^{2,2}$ -amino acids from the adducts: Scheme 2 illustrates the synthetic versatility of the multifunctional Michael addition products in this methodology. The ketone group of compound **4d** was protected as a glycol ketal, and then the cyano group was easily converted to the protected amino group in the presence of (Boc)₂O through Raney-Ni-catalyzed hydrogenation,^[15] to give functionalized $\beta^{2,2}$ -amino ester **5**. The ketone group might allow further transformations, and thus variously structured $\beta^{2,2}$ -amino acids might be accessible. On the other hand, 3-piperidinecarboxylate derivatives **6** and **7** could be easily prepared in a pot from the addition products **4a** and **4l**, respectively. Only one dia-



Scheme 2. Synthesis of various β^2 -amino acid esters.

stereomer was detected for both cyclic products. The chiral 3-benzyl 3-piperidinecarboxylate is an important intermediate in the synthesis of potent growth hormone secretagogues,^[17] thus the current methodology supplies a facile synthetic route to variously structured 3-piperidinecarboxylic analogues. Moreover, to determine the absolute configuration of the piperidine derivative, the Boc group of compound **7** was converted to a tosyl functionality. Fortunately, single crystals suitable for X-ray crystallographic analysis were obtained from enantiopure **8**. The absolute configuration of **8** was determined to be (C_1R , C_4S), so the absolute configuration of the α -quaternary carbon center of Michael addition product **4i** was *S* (Figure 2).

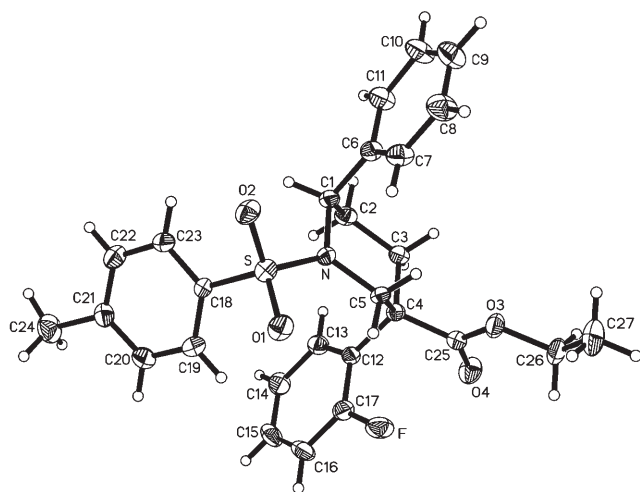


Figure 2. X-ray structure of compound **8**.

Stereochemical course of the asymmetric induction: Based on the absolute configuration of **4i**, the possible reaction intermediates in the Michael addition of **2e** to **3b** were investigated. With the help of PM3 (semi-empirical method) calculations,^[18] it is found that, apart from the H-bonding be-

tween the OH group of the enolate and the $(CH_3)_2N$ group, there is a weak hydrogen-bonding interaction between the OEt group of the enolate and a NH of the thiourea moiety, which is thought to be essential to keep the enolate in a more rigid conformation and afford better enantiocontrol in this reaction. Therefore, the nucleophile **2e** and the electrophile **3b** are simultaneously activated by bifunctional organocatalyst **1a** through multiple hydrogen-bonding interactions, and the desired *S* enantiomer is produced through *Re*-face attack

of the *Z*-enolate of **2e** (Figure 3a). In contrast, the *Si*-face attack of the *E* enolate of **2e** would be highly disfavored because of the steric interaction between the bulky aryl group and phenyl vinyl ketone **3b**. In addition, the relative space from the α -carbon of the enolate and the β -vinyl carbon of **3b** in calculated mode (Figure 3b) is also remoter than that

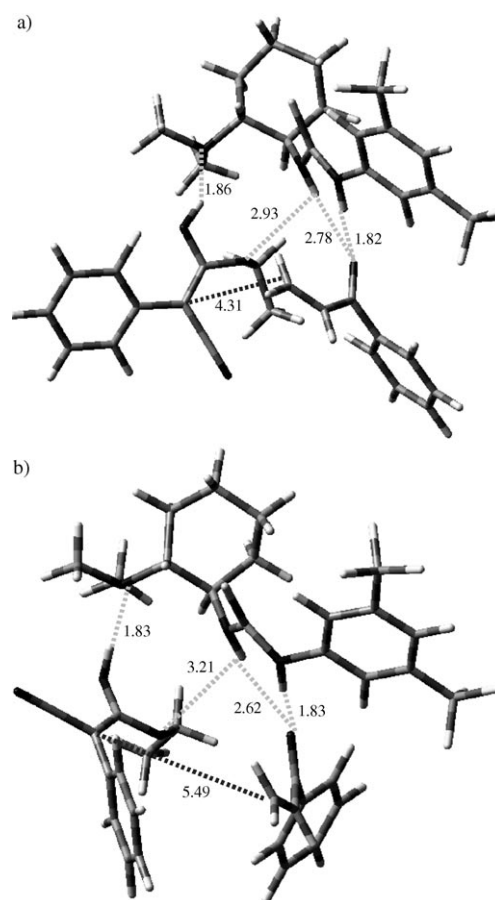


Figure 3. Possible active intermediates in the Michael reaction catalyzed by **1a**.

in mode (Figure 3a) (5.49 Å versus 4.31 Å), probably because of steric reasons.

Conclusion

We have presented a highly enantioselective Michael addition of α -substituted cyanoacetates to vinyl ketones synergistically promoted by simple bifunctional thiourea/tertiary amine organocatalysts. The reaction scope is substantial and a number of α -aryl or alkyl cyanoacetates could be successfully applied to give multifunctional compounds with an all-carbon-substituted quaternary stereocenter with excellent enantioselectivities (82–97% *ee*). Moreover, the biologically important $\beta^{2,2}$ -amino acid esters with various structures could be efficiently prepared from the optical pure adducts. In addition, based on the absolute configuration of the conjugate adduct and computational studies, an interesting reaction model involving multiple hydrogen-bonding interactions amongst the thiourea/tertiary amine catalyst and the reactants has been proposed. Currently work is actively under way to expand this organocatalytic system to other valuable transformations.

Experimental Section

General: TLC was performed on glass-backed silica plates. Column chromatography was performed by using silica gel (200–300 mesh) with ethyl acetate/petroleum ether as eluent. ^1H and ^{13}C NMR spectra were recorded on Bruker 300 or 400 MHz spectrometers. Chemical shifts were reported in ppm downfield from TMS with the solvent resonance as the internal standard. ESI-HRMS spectra were recorded on BioTOF instrument of Bruker Daltonics. Enantiomeric excess was determined by HPLC analysis on Chiralpak AS, AD, OD or OJ columns. Bifunctional thiourea/tertiary amine catalysts **1a–f** were prepared as previously reported.^[13] α -Substituted cyanoacetates **2¹⁹** and aryl vinyl ketones **3b–e²⁰** were prepared according to literature procedures.

General procedures for asymmetric Michael addition: Catalyst **1a** (4.2 mg, 0.01 mmol, 10 mol%), α -substituted cyanoacetate **2** (0.1 mmol), and 4 Å MS (20 mg) were stirred in dry toluene (0.5 mL) and cooled to the desired temperature under argon. Then vinyl ketone **3** (0.2 mmol) in dry toluene (0.5 mL) was added. After the stated reaction time, the product was purified by flash chromatography (FC) on silica gel (Previously saturated with cold petroleum ether; in general slightly lower enantioselectivity was obtained when FC was conducted at room temperature, probably due to the rapid reaction of the unchanged starting materials in column) to give the addition product **4**.

(S)-Ethyl 2-cyano-5-oxo-2-phenylhexanoate (4a): Colorless oil; Yield: 95%; $R_f=0.1$ (petroleum ether/EtOAc 20:1); $[\alpha]_D^{20}=+4.9$ ($c=0.25$ in CHCl_3); 91% *ee* (determined by HPLC analysis: Daicel chiralcel AS, hexane/*i*PrOH 90:10, 1.0 mL min⁻¹, $\lambda=254$ nm, $t(\text{minor})=11.95$ min, $t(\text{major})=12.91$ min); ^1H NMR (400 MHz, CDCl_3): $\delta=7.55$ – 7.51 (m, 2H), 7.45–7.37 (m, 3H), 4.31–4.18 (m, 2H), 2.71–2.60 (m, 2H), 2.54–2.43 (m, 2H), 2.14 (s, 3H), 1.25 ppm (t, $J=6.8$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3): $\delta=205.9$, 167.1, 133.8, 129.2, 129.0, 126.0, 118.0, 63.4, 53.0, 39.3, 31.6, 30.0, 13.8 ppm; IR (film): $\tilde{\nu}=2246$, 1742, 1717 cm⁻¹; ESI-HRMS: m/z : calcd for $\text{C}_{15}\text{H}_{17}\text{NO}_3+\text{Na}$: 282.1101; found: 282.1103.

(S)-Ethyl 2-(4'-chlorophenyl)-2-cyano-5-oxohexanoate (4b): Colorless oil; Yield: 87%; $R_f=0.1$ (petroleum ether/EtOAc 20:1); $[\alpha]_D^{20}=+4.5$ ($c=0.44$ in CHCl_3); 87% *ee* (determined by HPLC analysis: Daicel chiralcel AS, hexane/*i*PrOH 90:10, 1.0 mL min⁻¹, $\lambda=254$ nm, $t(\text{minor})=10.51$ min,

$t(\text{major})=12.63$ min); ^1H NMR (300 MHz, CDCl_3): $\delta=7.47$ (d, $J=8.9$ Hz, 2H), 7.38 (d, $J=8.9$ Hz, 2H), 4.28–4.20 (m, 2H), 2.66–2.57 (m, 2H), 2.53–2.34 (m, 2H), 2.14 (s, 3H), 1.24 ppm (t, $J=7.2$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3): $\delta=205.6$, 166.8, 135.3, 132.4, 129.4, 127.5, 117.7, 63.6, 52.6, 39.2, 31.6, 30.0, 13.8 ppm; IR (film): $\tilde{\nu}=2247$, 1745, 1718 cm⁻¹; ESI-HRMS: m/z : calcd for $\text{C}_{15}\text{H}_{16}\text{ClNO}_3+\text{Na}$: 316.0711; found: 316.0713.

(S)-Ethyl 2-(4'-bromophenyl)-2-cyano-5-oxohexanoate (4c): Colorless oil; Yield: 86%; $R_f=0.1$ (petroleum ether/EtOAc 20:1); $[\alpha]_D^{20}=+5.4$ ($c=0.21$ in CHCl_3); 86% *ee* (determined by HPLC analysis: Daicel chiralcel AS, hexane/*i*PrOH 90:10, 1.0 mL min⁻¹, $\lambda=254$ nm, $t(\text{minor})=11.36$ min, $t(\text{major})=13.56$ min); ^1H NMR (300 MHz, CDCl_3): $\delta=7.54$ (d, $J=8.8$ Hz, 2H), 7.41 (d, $J=8.8$ Hz, 2H), 4.28–4.19 (m, 2H), 2.66–2.57 (m, 2H), 2.53–2.36 (m, 2H), 2.14 (s, 3H), 1.24 ppm (t, $J=7.1$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3): $\delta=205.6$, 166.7, 132.9, 132.4, 127.8, 123.4, 117.6, 63.6, 52.7, 39.2, 31.5, 30.0, 13.8 ppm; IR (film): $\tilde{\nu}=2246$, 1745, 1718 cm⁻¹; ESI-HRMS: m/z : calcd for $\text{C}_{15}\text{H}_{16}\text{BrNO}_3+\text{Na}$: 360.0206; found: 360.0209.

(S)-Ethyl 2-(4'-fluorophenyl)-2-cyano-5-oxohexanoate (4d): Colorless oil; Yield: 94%; $R_f=0.1$ (petroleum ether/EtOAc 20:1); $[\alpha]_D^{20}=+9.0$ ($c=0.42$ in CHCl_3); 92% *ee* (determined by HPLC analysis: Daicel chiralcel AS, hexane/*i*PrOH 90:10, 1.0 mL min⁻¹, $\lambda=220$ nm, $t(\text{minor})=11.40$ min, $t(\text{major})=13.53$ min); ^1H NMR (300 MHz, CDCl_3): $\delta=7.55$ – 7.50 (m, 2H), 7.19–7.08 (m, 2H), 4.29–4.20 (m, 2H), 2.67–2.58 (m, 2H), 2.54–2.35 (m, 2H), 2.15 (s, 3H), 1.25 ppm (t, $J=7.1$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3): $\delta=205.7$, 167.0, 162.8 (d, $^1J(\text{C},\text{F})=247.9$ Hz), 129.6, 128.0 (d, $^3J(\text{C},\text{F})=8.4$ Hz), 117.8, 116.2 (d, $^2J(\text{C},\text{F})=21.8$ Hz), 63.5, 52.4, 39.2, 31.6, 29.9, 13.7 ppm; IR (film): $\tilde{\nu}=1742$, 1717 cm⁻¹; ESI-HRMS: m/z : calcd for $\text{C}_{15}\text{H}_{16}\text{FNO}_3+\text{Na}$: 300.1006; found 300.0999.

(S)-Ethyl 2-(2'-fluorophenyl)-2-cyano-5-oxohexanoate (4e): Colorless oil; Yield: 95%; $R_f=0.1$ (petroleum ether/EtOAc 20:1); $[\alpha]_D^{20}=+0.9$ ($c=0.33$ in CHCl_3); 95% *ee* (determined by HPLC analysis: Daicel chiralcel AD, hexane/*i*PrOH 90:10, 1.0 mL min⁻¹, $\lambda=220$ nm, $t(\text{major})=8.58$ min, $t(\text{minor})=9.35$ min); ^1H NMR (300 MHz, CDCl_3): $\delta=7.54$ (t, $J=7.8$ Hz, 1H), 7.44–7.37 (m, 1H), 7.22 (d, $J=7.5$ Hz, 1H), 7.15–7.08 (m, 1H), 4.33–4.25 (m, 2H), 2.74–2.59 (m, 2H), 2.57–2.49 (m, 2H), 2.15 (s, 3H), 1.27 ppm (t, $J=7.1$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3): $\delta=205.7$, 166.3, 160.0 (d, $^1J(\text{C},\text{F})=248.0$ Hz), 131.0 (d, $^3J(\text{C},\text{F})=8.0$ Hz), 128.4, 124.7 (d, $^3J(\text{C},\text{F})=3.0$ Hz), 122.4 (d, $^2J(\text{C},\text{F})=12.1$ Hz), 117.2, 116.5 (d, $^1J(\text{C},\text{F})=21.3$ Hz), 63.5, 49.5, 39.1, 30.0, 29.4, 13.7 ppm; IR (film): $\tilde{\nu}=2245$, 1749, 1717 cm⁻¹; ESI-HRMS: m/z : calcd for $\text{C}_{15}\text{H}_{16}\text{FNO}_3+\text{Na}$: 300.1006; found: 300.0997.

(S)-Ethyl 2-cyano-5-oxo-2-(3'-(trifluoromethyl)phenyl)hexanoate (4f): Colorless oil; Yield: 95%; $R_f=0.1$ (petroleum ether/EtOAc 20:1); $[\alpha]_D^{20}=+6.6$ ($c=0.38$ in CHCl_3); 85% *ee* (determined by HPLC analysis: Daicel chiralcel OD, hexane/*i*PrOH 90:10, 1.0 mL min⁻¹, $\lambda=220$ nm, $t(\text{minor})=7.12$ min, $t(\text{major})=8.29$ min); ^1H NMR (300 MHz, CDCl_3): $\delta=7.79$ (s, 1H), 7.76 (d, $J=7.8$, 1H), 7.67 (d, $J=7.8$ Hz, 1H), 7.57 (t, $J=7.8$ Hz, 1H), 4.31–4.24 (m, 2H), 2.72–2.64 (m, 2H), 2.57–2.35 (m, 2H), 2.16 (s, 3H), 1.26 ppm (t, $J=7.1$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3): $\delta=205.5$, 166.5, 135.1, 131.7 (q, $^2J(\text{C},\text{F})=32.8$ Hz), 129.9, 129.5, 128.2, 126.1 (d, $^3J(\text{C},\text{F})=3.3$ Hz), 123.5 (q, $^1J(\text{C},\text{F})=270.8$ Hz), 123.0 (d, $^3J(\text{C},\text{F})=3.5$ Hz), 117.4, 63.8, 53.0, 39.2, 31.8, 29.9, 13.7 ppm; IR (film): $\tilde{\nu}=2248$, 1746, 1718 cm⁻¹; ESI-HRMS: m/z : calcd for $\text{C}_{16}\text{H}_{16}\text{F}_3\text{NO}_3+\text{Na}$: 350.0974; found: 350.0980.

(S)-Ethyl 2-cyano-2-(4'-methoxyphenyl)-5-oxohexanoate (4g): Colorless oil; Yield: 95%; $R_f=0.15$ (petroleum ether/EtOAc 10:1); $[\alpha]_D^{20}=+7.2$ ($c=0.44$ in CHCl_3); 90% *ee* (determined by HPLC analysis: Daicel chiralcel AD, hexane/*i*PrOH 90:10, 1.0 mL min⁻¹, $\lambda=220$ nm, $t(\text{major})=12.45$ min, $t(\text{minor})=13.14$ min); ^1H NMR (300 MHz, CDCl_3): $\delta=7.44$ (d, $J=8.9$ Hz, 2H), 6.92 (d, $J=8.9$ Hz, 2H), 4.27–4.18 (m, 2H), 3.81 (s, 3H), 2.65–2.44 (m, 4H), 2.14 (s, 3H), 1.24 ppm (t, $J=7.1$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3): $\delta=205.9$, 167.3, 159.9, 127.2, 125.6, 118.2, 114.4, 63.2, 55.3, 52.3, 39.2, 31.5, 29.9, 13.7 ppm; IR (film): $\tilde{\nu}=2246$, 1741, 1717 cm⁻¹; ESI-HRMS: m/z : calcd for $\text{C}_{16}\text{H}_{19}\text{NO}_4+\text{Na}$: 312.1206; found: 312.1209.

(S)-Ethyl 2-cyano-2-(3',4'-dimethoxyphenyl)-5-oxohexanoate (4h): Colorless oil; Yield: 88%; $R_f=0.15$ (petroleum ether/EtOAc 7:1); $[\alpha]_D^{20}=+5.8$

(*c* = 0.36 in CHCl₃); 95% *ee* (determined by HPLC analysis: Daicel chiralcel AD, hexane/*i*PrOH 90:10, 1.0 mL min⁻¹, λ = 220 nm, *t*(minor) = 14.82 min, *t*(major) = 15.66 min); ¹H NMR (300 MHz, CDCl₃): δ = 7.09 (dd, *J* = 2.3, 8.4 Hz, 1H), 6.98 (d, *J* = 2.2 Hz, 1H), 6.86 (d, *J* = 8.5 Hz, 1H), 4.29–4.19 (m, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 2.70–2.35 (m, 4H), 2.14 (s, 3H), 1.25 ppm (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 205.9, 167.2, 149.4, 149.2, 125.8, 118.5, 118.1, 111.1, 108.7, 63.2, 55.9, 55.8, 52.5, 39.2, 31.4, 29.9, 13.7 ppm; IR (film): ν̄ = 2246, 1743, 1720 cm⁻¹; ESI-HRMS: *m/z*: calcd for C₁₇H₂₁NO₅ + Na: 342.1312; found: 342.1322.

(S)-Ethyl 2-cyano-5-oxo-2-(thien-2-yl)hexanoate (4i): Colorless oil; Yield: 93%; *R*_f = 0.1 (petroleum ether/EtOAc 20:1); [α]_D²⁰ = -13.1 (*c* = 0.21 in CHCl₃); 82% *ee* (determined by HPLC analysis: Daicel chiralcel OJ, hexane/*i*PrOH 90:10, 1.0 mL min⁻¹, λ = 220 nm, *t*(major) = 29.57 min, *t*(minor) = 35.41 min); ¹H NMR (300 MHz, CDCl₃): δ = 7.34 (dd, *J* = 1.3, 5.2 Hz, 1H), 7.25 (dd, *J* = 1.3, 3.7 Hz, 1H), 7.0 (dd, *J* = 3.7, 18.6 Hz, 1H), 4.32–4.24 (m, 2H), 2.67–2.48 (m, 4H), 2.16 (s, 3H), 1.30 ppm (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 205.5, 166.5, 136.5, 127.1, 126.9, 117.4, 63.7, 50.1, 39.2, 33.1, 30.0, 13.8 ppm; IR (film): ν̄ = 2247, 1742, 1717 cm⁻¹; ESI-HRMS: *m/z*: calcd for C₁₃H₁₅NO₅S + Na: 288.0665; found: 288.0658.

(S)-Ethyl 2-cyano-5-oxo-2,5-diphenylpentanoate (4j): Colorless oil; Yield: 94%; *R*_f = 0.1 (petroleum ether/EtOAc 35:1); [α]_D²⁰ = +21.4 (*c* = 0.58 in CHCl₃); 86% *ee* (determined by HPLC analysis: Daicel chiralcel OD, hexane/*i*PrOH 90:10, 1.0 mL min⁻¹, λ = 220 nm, *t*(minor) = 7.45 min, *t*(major) = 8.95 min); ¹H NMR (300 MHz, CDCl₃): δ = 7.93–7.90 (m, 2H), 7.60–7.54 (m, 3H), 7.47–7.39 (m, 5H), 4.32–4.20 (m, 2H), 3.29–3.17 (m, 1H), 3.09–2.98 (m, 1H), 2.87–2.77 (m, 1H), 2.70–2.60 (m, 1H), 1.26 ppm (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 197.5, 167.2, 136.2, 133.9, 133.4, 129.3, 129.1, 128.6, 128.0, 126.0, 118.2, 63.4, 53.3, 34.5, 32.2, 13.8 ppm; IR (film): ν̄ = 2245, 1743, 1683 cm⁻¹; ESI-HRMS: *m/z*: calcd for C₂₀H₁₉NO₅ + Na: 344.1257; found: 344.1255.

(S)-Ethyl 2-(4'-bromophenyl)-2-cyano-5-oxo-5-phenylpentanoate (4k): Colorless oil; Yield: 93%; *R*_f = 0.1 (petroleum ether/EtOAc 45:1); [α]_D²⁰ = +21.1 (*c* = 0.44 in CHCl₃); 85% *ee* (determined by HPLC analysis: Daicel chiralcel OD, hexane/*i*PrOH 90:10, 1.0 mL min⁻¹, λ = 254 nm, *t*(minor) = 9.56 min, *t*(major) = 11.87 min); ¹H NMR (300 MHz, CDCl₃): δ = 7.93–7.90 (m, 2H), 7.60–7.52 (m, 3H), 7.50–7.43 (m, 4H), 4.29–4.22 (m, 2H), 3.27–3.16 (m, 1H), 3.08–2.97 (m, 1H), 2.86–2.76 (m, 1H), 2.67–2.57 (m, 1H), 1.26 ppm (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 197.3, 166.8, 136.1, 133.4, 133.0, 132.4, 128.6, 128.0, 127.8, 123.5, 117.7, 63.6, 52.9, 34.4, 32.1, 13.8 ppm; IR (film): ν̄ = 1742, 1685 cm⁻¹; ESI-HRMS: *m/z*: calcd for C₂₀H₁₈BrNO₅ + Na: 422.0362; found: 422.0364.

(S)-Ethyl 2-cyano-2-(2'-fluorophenyl)-5-oxo-5-phenylpentanoate (4l): Colorless oil; Yield: 90%; *R*_f = 0.1 (petroleum ether/EtOAc 45:1); [α]_D²⁰ = +16.0 (*c* = 0.30 in CHCl₃); 97% *ee* (determined by HPLC analysis: Daicel chiralcel AD, hexane/*i*PrOH 90:10, 1.0 mL min⁻¹, λ = 254 nm, *t*(major) = 13.23 min, *t*(minor) = 15.13 min); ¹H NMR (300 MHz, CDCl₃): δ = 7.94–7.91 (m, 2H), 7.63–7.54 (m, 2H), 7.48–7.38 (m, 3H), 7.27–7.22 (m, 1H), 7.16–7.10 (m, 1H), 4.35–4.28 (m, 2H), 3.36–3.25 (m, 1H), 3.15–3.04 (m, 1H), 2.90–2.70 (m, 2H), 1.28 ppm (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 197.4, 166.4, 160.0 (d, ¹*J*(C,F) = 248.0 Hz), 136.2, 133.4, 131.1 (d, ³*J*(C,F) = 8.6 Hz), 128.6, 128.4, 128.0, 124.8 (d, ³*J*(C,F) = 3.2 Hz), 122.5 (d, ²*J*(C,F) = 12.3 Hz), 117.3, 116.6 (d, ²*J*(C,F) = 21.4 Hz), 63.5, 49.7, 34.4, 30.1, 13.8 ppm; IR (film): ν̄ = 1744, 1684 cm⁻¹; ESI-HRMS: *m/z*: calcd for C₂₀H₁₈FNO₅ + Na: 362.1163; found: 362.1180.

(S)-Ethyl 2-cyano-2-(4'-methoxyphenyl)-5-oxo-5-phenylpentanoate (4m): Colorless oil; Yield: 95%; *R*_f = 0.1 (petroleum ether/EtOAc 20:1); [α]_D²⁰ = +17.9 (*c* = 0.38 in CHCl₃); 89% *ee* (determined by HPLC analysis: Daicel chiralcel OD, hexane/*i*PrOH 90:10, 1.0 mL min⁻¹, λ = 254 nm, *t*(minor) = 10.71 min, *t*(major) = 11.75 min); ¹H NMR (300 MHz, CDCl₃): δ = 7.93–7.90 (m, 2H), 7.59–7.42 (m, 5H), 6.96–6.91 (m, 2H), 4.28–4.22 (m, 2H), 3.82 (s, 3H), 3.26–3.15 (m, 1H), 3.08–2.97 (m, 1H), 2.84–2.74 (m, 1H), 2.69–2.59 (m, 1H), 1.26 ppm (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 197.6, 167.4, 160.0, 136.3, 133.4, 129.1, 128.6, 128.0, 127.4, 125.7, 118.4, 114.6, 63.3, 55.3, 52.6, 34.5, 32.1, 13.8 ppm; IR (film): ν̄ = 2246, 1742, 1686 cm⁻¹; ESI-HRMS: *m/z*: calcd for C₂₁H₂₁NO₄ + Na: 374.1363; found: 374.1360.

(S)-Ethyl 2-cyano-2-(naphthalen-1-yl)-5-oxo-5-phenylpentanoate (4n): Colorless oil; Yield: 97%; *R*_f = 0.1 (petroleum ether/EtOAc 55:1); [α]_D²⁰ = -25.8 (*c* = 0.52 in CHCl₃); 91% *ee* (determined by HPLC analysis: Daicel chiralcel AS, hexane/*i*PrOH 90:10, 1.0 mL min⁻¹, λ = 220 nm, *t*(major) = 12.37 min, *t*(minor) = 14.83 min); ¹H NMR (300 MHz, CDCl₃): δ = 8.13 (d, *J* = 8.4 Hz, 1H), 7.96–7.91 (m, 4H), 7.82 (d, *J* = 7.4 Hz, 1H), 7.58–7.46 (m, 6H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.35–3.25 (m, 2H), 3.09–3.03 (m, 2H), 1.15 ppm (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 197.5, 168.4, 136.2, 134.4, 133.4, 130.4, 130.0, 129.8, 129.5, 128.7, 128.0, 127.2, 126.2, 125.5, 125.1, 122.9, 118.6, 63.5, 52.5, 34.6, 30.3, 13.8 ppm; IR (film): ν̄ = 1738, 1676 cm⁻¹; ESI-HRMS: *m/z*: calcd for C₂₄H₂₁NO₅ + Na: 394.1414; found: 394.1422.

(S)-Ethyl 5-(4'-bromophenyl)-2-cyano-2-(2'-fluorophenyl)-5-oxopentanoate (4o): Colorless oil; Yield: 99%; *R*_f = 0.1 (petroleum ether/EtOAc 45:1); [α]_D²⁰ = +19.4 (*c* = 0.83 in CHCl₃); 92% *ee* (determined by HPLC analysis: Daicel chiralcel AD, hexane/*i*PrOH 90:10, 1.0 mL min⁻¹, λ = 254 nm, *t*(minor) = 14.69 min, *t*(major) = 15.90 min); ¹H NMR (300 MHz, CDCl₃): δ = 7.81 (d, *J* = 8.7 Hz, 2H), 7.65–7.59 (m, 3H), 7.48–7.40 (m, 1H), 7.27 (d, *J* = 1.3, 7.6 Hz, 1H), 7.19–7.12 (m, 1H), 4.38–4.31 (m, 2H), 3.35–3.24 (m, 1H), 3.14–3.03 (m, 1H), 2.92–2.82 (m, 1H), 2.79–2.69 (m, 1H), 1.30 ppm (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 196.4, 166.3, 159.7 (d, ¹*J*(C,F) = 248.0 Hz), 135.0, 132.0, 131.1 (d, ³*J*(C,F) = 8.5 Hz), 129.5, 128.6, 128.4, 124.8 (d, ³*J*(C,F) = 3.2 Hz), 122.5 (d, ²*J*(C,F) = 12.2 Hz), 117.2, 116.6 (d, ²*J*(C,F) = 21.3 Hz), 63.6, 49.7, 34.4, 30.0, 13.7 ppm; IR (film): ν̄ = 2240, 1738, 1680 cm⁻¹; ESI-HRMS: *m/z*: calcd for C₂₀H₁₇BrFNO₅ + Na: 440.0268; found: 440.0272.

(S)-Ethyl 2-cyano-2-(2'-fluorophenyl)-5-(4'-methoxyphenyl)-5-oxopentanoate (4p): Colorless oil; Yield: 97%; *R*_f = 0.1 (petroleum ether/EtOAc 20:1); [α]_D²⁰ = +17.1 (*c* = 0.67 in CHCl₃); 91% *ee* (determined by HPLC analysis: Daicel chiralcel AD, hexane/*i*PrOH 90:10, 1.0 mL min⁻¹, λ = 254 nm, *t*(minor) = 22.43 min, *t*(major) = 24.65 min); ¹H NMR (300 MHz, CDCl₃): δ = 7.94 (d, *J* = 8.9 Hz, 2H), 7.62 (td, *J* = 1.6, 7.8 Hz, 1H), 7.45–7.40 (m, 1H), 7.30–7.24 (m, 1H), 7.19–7.12 (m, 1H), 6.95 (d, *J* = 8.9 Hz, 2H), 4.38–4.30 (m, 2H), 3.89 (s, 3H), 3.33–3.22 (m, 1H), 3.13–3.02 (m, 1H), 2.92–2.70 (m, 2H), 1.31 ppm (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 195.9, 166.5, 163.7, 159.8 (d, ¹*J*(C,F) = 248.0 Hz), 131.1 (d, ³*J*(C,F) = 8.5 Hz), 130.3, 129.4, 128.4, 124.8 (d, ³*J*(C,F) = 3.1 Hz), 122.6 (d, ²*J*(C,F) = 12.2 Hz), 117.4, 116.5 (d, ²*J*(C,F) = 21.4 Hz), 113.8, 63.5, 55.4, 49.7, 34.0, 30.2, 13.8 ppm; IR (film): ν̄ = 2287, 1739, 1672 cm⁻¹; ESI-HRMS: *m/z*: calcd for C₂₁H₂₀FNO₅ + Na: 392.1269; found: 392.1275.

(S)-Ethyl 2-cyano-2-(2'-fluorophenyl)-5-oxo-5-(thiophen-2-yl)pentanoate (4q): Colorless oil; Yield: 97%; *R*_f = 0.1 (petroleum ether/EtOAc 20:1); [α]_D²⁰ = +10.3 (*c* = 0.55 in CHCl₃); 97% *ee* (determined by HPLC analysis: Daicel chiralcel AD, hexane/*i*PrOH 90:10, 1.0 mL min⁻¹, λ = 254 nm, *t*(major) = 13.28 min, *t*(minor) = 23.68 min); ¹H NMR (300 MHz, CDCl₃): δ = 7.74 (dd, *J* = 1.1, 3.8 Hz, 1H), 7.68 (dd, *J* = 1.1, 5.0 Hz, 1H), 7.62 (td, *J* = 1.7, 7.8 Hz, 1H), 7.48–7.40 (m, 1H), 7.26 (td, *J* = 1.3, 7.7 Hz, 1H), 7.19–7.12 (m, 1H), 4.38–4.31 (m, 2H), 3.32–3.21 (m, 1H), 3.11–3.01 (m, 1H), 2.92–2.70 (m, 2H), 1.31 ppm (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 190.2, 166.3, 159.8 (d, ¹*J*(C,F) = 248.0 Hz), 143.4, 134.0, 132.2, 131.1 (d, ³*J*(C,F) = 8.6 Hz), 128.5, 128.2, 124.8 (d, ³*J*(C,F) = 3.2 Hz), 122.4 (d, ²*J*(C,F) = 12.2 Hz), 117.2, 116.6 (d, ²*J*(C,F) = 21.4 Hz), 63.6, 49.8, 35.0, 30.2, 13.8 ppm; IR (film): ν̄ = 2246, 1748, 1667 cm⁻¹; ESI-HRMS: *m/z*: calcd for C₁₈H₁₆FNO₅S + Na: 368.0727; found: 368.0736.

(S)-Ethyl 2-cyano-2-cyano-2-phenyl-5-(thiophen-2-yl)pentanoate (4r): Colorless oil; Yield: 99%; *R*_f = 0.1 (petroleum ether/EtOAc = 20:1); [α]_D²⁰ = +20.6 (*c* = 0.57 in CHCl₃); 93% *ee* (determined by HPLC analysis: Daicel chiralcel OD, hexane/*i*PrOH 90:10, 1.0 mL min⁻¹, λ = 254 nm, *t*(minor) = 8.91 min, *t*(major) = 10.37 min); ¹H NMR (300 MHz, CDCl₃): δ = 7.72 (dd, *J* = 1.1, 3.8 Hz, 1H), 7.67 (dd, *J* = 1.1, 5.0 Hz, 1H), 7.63–7.59 (m, 2H), 7.49–7.41 (m, 3H), 7.16–7.13 (m, 1H), 4.32–4.26 (m, 2H), 3.24–3.13 (m, 1H), 3.05–2.94 (m, 1H), 2.89–2.79 (m, 1H), 2.73–2.63 (m, 1H), 1.28 ppm (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 190.4, 167.1, 143.5, 134.0, 133.8, 132.2, 129.3, 129.1, 128.1, 126.0, 118.1, 63.4, 53.3, 35.1, 32.4, 13.8 ppm; IR (film): ν̄ = 2249, 1738, 1651 cm⁻¹; ESI-HRMS: *m/z*: calcd for C₁₈H₁₇NO₅S + Na: 350.0821; found: 350.0807.

(R)-Ethyl 2-cyano-2-methyl-5-oxo-5-phenylpentanoate (4s): Colorless oil; Yield: 76%; *R*_f = 0.1 (petroleum ether/EtOAc 30:1); [α]_D²⁰ = +10.7

(*c* = 0.34 in CHCl₃); 91% *ee* (determined by HPLC analysis: Daicel chiralcel OJ, hexane/*i*PrOH 90:10, 1.0 mL min⁻¹, λ = 220 nm, *t*(major) = 20.25 min, *t*(minor) = 23.26 min); ¹H NMR (400 MHz, CDCl₃): δ = 7.98–7.96 (m, 2H), 7.59 (t, *J* = 7.2 Hz, 1H), 7.48 (t, *J* = 7.2 Hz, 2H), 4.32–4.24 (m, 2H), 3.29–3.11 (m, 2H), 2.49–2.41 (m, 1H), 2.28–2.21 (m, 1H), 1.68 (s, 3H), 1.33 ppm (t, *J* = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 197.4, 168.9, 136.2, 133.5, 128.7, 128.0, 119.7, 63.0, 43.3, 34.4, 32.1, 23.7, 14.0 ppm; IR (film): $\tilde{\nu}$ = 2244, 1738, 1684 cm⁻¹; ESI-HRMS: *m/z*: calcd for C₁₅H₁₇NO₃ + Na: 282.1101; found: 282.1103.

(R)-Ethyl 2-cyano-2-(3-oxo-3-phenylpropyl)hexanoate (4t): Colorless oil; Yield 72%; *R*_f = 0.1 (petroleum ether/EtOAc 55:1); [*α*]_D²⁰ = +3.1 (*c* = 0.26 in CHCl₃); 92% *ee* (determined by HPLC analysis: Daicel chiralcel AS, hexane/*i*PrOH 90:10, 1.0 mL min⁻¹, λ = 220 nm, *t*(major) = 6.78 min, *t*(minor) = 7.47 min); ¹H NMR (300 MHz, CDCl₃): δ = 7.96 (d, *J* = 7.2 Hz, 2H), 7.59 (t, *J* = 7.1 Hz, 1H), 7.48 (t, *J* = 7.2 Hz, 2H), 4.29 (q, *J* = 7.1 Hz, 2H), 3.33–3.22 (m, 1H), 3.11–3.00 (m, 1H), 2.46–2.36 (m, 1H), 2.30–2.20 (m, 1H), 2.05–1.95 (m, 1H), 1.90–1.80 (m, 1H), 1.41–1.25 (m, 7H), 0.93 ppm (t, *J* = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 197.5, 168.7, 136.2, 133.4, 128.7, 128.0, 119.1, 62.8, 49.1, 37.3, 34.4, 31.3, 27.5, 22.4, 14.1, 13.7 ppm; IR (film): $\tilde{\nu}$ = 2244, 1740, 1688 cm⁻¹; ESI-HRMS: *m/z*: calcd for C₁₈H₂₃NO₃ + Na: 324.1570; found: 324.1564.

(S)-Ethyl 2-benzyl-2-cyano-5-oxo-5-phenylpentanoate (4u): Colorless oil; Yield: 90%; *R*_f = 0.1 (petroleum ether/EtOAc 35:1); [*α*]_D²⁰ = +18.0 (*c* = 0.50 in CHCl₃); 92% *ee* (determined by HPLC analysis: Daicel chiralcel AS, hexane/*i*PrOH 90:10, 1.0 mL min⁻¹, λ = 220 nm, *t*(major) = 10.54 min, *t*(minor) = 13.90 min); ¹H NMR (300 MHz, CDCl₃): δ = 7.98–7.94 (m, 2H), 7.61–7.56 (m, 1H), 7.50–7.45 (m, 1H), 7.36–7.30 (m, 5H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.35–3.24 (m, 2H), 3.17–3.01 (m, 2H), 2.58–2.48 (m, 1H), 2.36–2.26 (m, 1H), 1.17 ppm (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 197.3, 168.1, 136.2, 133.8, 133.5, 129.9, 128.7, 128.6, 128.0, 118.7, 62.9, 50.7, 43.3, 34.4, 31.3, 13.9 ppm; IR (film): $\tilde{\nu}$ = 2245, 1740, 1687 cm⁻¹; ESI-HRMS: *m/z*: calcd for C₂₁H₂₁NO₃ + Na: 358.1414; found: 358.1401.

(S)-Ethyl 2-cyano-2-isopropyl-5-oxo-5-phenylpentanoate (4v): Colorless oil; Yield: 66%; *R*_f = 0.1 (petroleum ether/EtOAc 45:1); [*α*]_D²⁰ = +15.8 (*c* = 0.32 in CHCl₃); 93% *ee* (determined by HPLC analysis: Daicel chiralcel AS, hexane/*i*PrOH 90:10, 1.0 mL min⁻¹, λ = 254 nm, *t*(major) = 6.90 min, *t*(minor) = 10.74 min); ¹H NMR (300 MHz, CDCl₃): δ = 7.97–7.93 (m, 2H), 7.61–7.56 (m, 1H), 7.50–7.45 (m, 2H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.27–3.22 (m, 1H), 2.99–2.92 (m, 1H), 2.35–2.24 (m, 3H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.17 (d, *J* = 6.8 Hz, 3H), 1.08 ppm (d, *J* = 6.7 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 197.6, 168.8, 136.2, 133.4, 128.7, 128.0, 118.0, 62.7, 54.9, 35.2, 34.7, 29.1, 19.0, 17.7, 14.1 ppm; IR (film): $\tilde{\nu}$ = 2242, 1739, 1688 cm⁻¹; ESI-HRMS: *m/z*: calcd for C₁₇H₂₁NO₃ + Na: 310.1414; found: 310.1411.

(R)-Ethyl 5-(4'-bromophenyl)-2-cyano-2-methyl-5-oxopentanoate (4w): Colorless oil; Yield: 67%; *R*_f = 0.1 (petroleum ether/EtOAc 50:1); [*α*]_D²⁰ = +2.8 (*c* = 0.35 in CHCl₃); 85% *ee* (determined by HPLC analysis: Daicel chiralcel AD, hexane/*i*PrOH 90:10, 1.0 mL min⁻¹, λ = 254 nm, *t*(minor) = 9.29 min, *t*(major) = 9.91 min); ¹H NMR (300 MHz, CDCl₃): δ = 7.87–7.83 (m, 2H), 7.67–7.62 (m, 2H), 4.34–4.27 (m, 2H), 3.28–3.07 (m, 2H), 2.51–2.41 (m, 1H), 2.30–2.20 (m, 1H), 1.70 (s, 3H), 1.35 ppm (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 196.4, 168.8, 135.0, 132.0, 129.5, 128.7, 119.6, 63.0, 43.2, 34.4, 31.9, 23.7, 14.0 ppm; IR (film): $\tilde{\nu}$ = 2251, 1726, 1690 cm⁻¹; ESI-HRMS: *m/z*: calcd for C₁₅H₁₆BrNO₃ + Na: 360.0206; found: 360.0196.

(R)-Ethyl 2-cyano-5-(4'-methoxyphenyl)-2-methyl-5-oxopentanoate (4x): Colorless oil; Yield 61%; *R*_f = 0.1 (petroleum ether/EtOAc 25:1); [*α*]_D²⁰ = +3.3 (*c* = 0.29 in CHCl₃); 85% *ee* (determined by HPLC analysis: Daicel chiralcel AD, hexane/*i*PrOH 90:10, 1.0 mL min⁻¹, λ = 254 nm, *t*(minor) = 13.52 min, *t*(major) = 14.34 min); ¹H NMR (300 MHz, CDCl₃): δ = 7.97 (d, *J* = 6.9 Hz, 2H), 6.97 (d, *J* = 7.0 Hz, 2H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.90 (s, 3H), 3.27–3.05 (m, 2H), 2.50–2.40 (m, 1H), 2.30–2.20 (m, 1H), 1.70 (s, 3H), 1.35 ppm (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 195.9, 168.9, 163.7, 130.3, 129.3, 119.7, 113.8, 62.9, 55.5, 43.3, 34.0, 32.3, 23.6, 13.9 ppm; IR (film): $\tilde{\nu}$ = 2245, 1732, 1683 cm⁻¹; ESI-HRMS: *m/z*: calcd for C₁₆H₁₉NO₄ + Na: 312.1206; found: 312.1197.

(R)-Ethyl 2-cyano-2-methyl-5-oxo-5-(thiophen-2-yl)pentanoate (4y): Colorless oil; Yield: 91%; *R*_f = 0.1 (petroleum ether/EtOAc 25:1); [*α*]_D²⁰ = +5.0 (*c* = 0.48 in CHCl₃); 96% *ee* (determined by HPLC analysis: Daicel chiralcel OJ, hexane/*i*PrOH 90:10, 1.0 mL min⁻¹, λ = 254 nm, *t*(major) = 25.01 min, *t*(minor) = 27.52 min); ¹H NMR (300 MHz, CDCl₃): δ = 7.79 (dd, *J* = 1.1, 3.8 Hz, 1H), 7.70 (dd, *J* = 1.1, 4.9 Hz, 1H), 7.19–7.16 (m, 1H), 4.34–4.27 (m, 2H), 3.26–3.06 (m, 2H), 2.52–2.42 (m, 1H), 2.31–2.21 (m, 1H), 1.70 (s, 3H), 1.35 ppm (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 190.3, 168.8, 143.4, 134.1, 132.2, 128.2, 119.6, 63.0, 43.3, 35.0, 32.2, 23.6, 13.9 ppm; IR (film): $\tilde{\nu}$ = 2244, 1737, 1672 cm⁻¹; ESI-HRMS: *m/z*: calcd for C₁₃H₁₅NO₃S + Na: 288.0665; found: 288.0663.

(S)-Ethyl 2-benzyl-2-cyano-5-oxo-5-(thiophen-2-yl)pentanoate (4z): Colorless oil; Yield 98%; *R*_f = 0.1 (petroleum ether/EtOAc 25:1); [*α*]_D²⁰ = +16.3 (*c* = 0.63 in CHCl₃); 97% *ee* (determined by HPLC analysis: Daicel chiralcel OD, hexane/*i*PrOH 90:10, 1.0 mL min⁻¹, λ = 254 nm, *t*(minor) = 14.54 min, *t*(major) = 17.09 min); ¹H NMR (300 MHz, CDCl₃): δ = 7.77 (dd, *J* = 1.1, 3.8 Hz, 1H), 7.69 (dd, *J* = 1.1, 5.0 Hz, 1H), 7.40–7.32 (m, 5H), 7.18–7.15 (m, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.33–3.14 (m, 3H), 3.10–2.99 (m, 1H), 2.61–2.51 (m, 1H), 2.37–2.27 (m, 1H), 1.21 ppm (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 190.1, 168.0, 143.4, 134.1, 133.8, 132.2, 129.9, 128.6, 128.2, 127.9, 118.5, 62.9, 50.7, 43.2, 35.0, 31.3, 13.8 ppm; IR (film): $\tilde{\nu}$ = 2248, 1735, 1671 cm⁻¹; ESI-HRMS: *m/z*: calcd for C₁₉H₁₉NO₃S + Na: 364.0978; found: 364.0974.

Synthesis of optically active β²²-amino acid esters 5, 6, and 7

Compound 5: Ethylene glycol (59.8 mg, 0.96 mmol) was added to a solution of **4d** (134.0 mg, 0.48 mmol, 92% *ee*) and *p*TsOH (18.3 mg, 0.096 mmol) in benzene (10 mL). The mixture was heated to reflux for 6 h. After concentration, the residue was subjected to flash chromatography (elution gradient: petroleum ether/EtOAc 25:1) to give the ketal intermediate. (Boc)₂O (116.0 mg, 0.53 mmol) and Raney-Ni (28.5 mg) were added to a solution of above compound in ethanol (3.0 mL). The mixture was stirred under H₂ (50 psi) at room temperature for 12 h. Then the mixture was filtered through celite, washed with EtOAc (20 mL) and the resulting filtrate was concentrated in vacuum. The residue was subjected to flash chromatography to give the Boc-protected β²²-amino ester **5** (168.8 mg, 83% yield for two steps). *R*_f = 0.15 (petroleum ether/EtOAc 10:1); [*α*]_D²⁰ = +21.7 (*c* = 0.78 in CHCl₃); 92% *ee* (determined by HPLC analysis: Daicel chiralcel AD, hexane/*i*PrOH 90:10, 1.0 mL min⁻¹, λ = 254 nm, *t*(major) = 12.33 min, *t*(minor) = 13.89 min); ¹H NMR (300 MHz, CDCl₃): δ = 7.25–7.22 (m, 2H), 7.06–7.00 (m, 2H), 4.78 (t, *J* = 5.6 Hz, 1H), 4.25–4.17 (m, 2H), 3.97–3.89 (m, 4H), 3.78–3.73 (m, 1H), 3.61–3.56 (m, 1H), 2.13–2.07 (m, 2H), 1.71–1.65 (m, 1H), 1.57–1.51 (m, 1H), 1.37 (s, 9H), 1.32 (s, 3H), 1.25 ppm (t, *J* = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 174.5, 161.7 (d, ¹*J*(C,F) = 244.7 Hz), 155.6, 135.7, 128.4 (d, ³*J*(C,F) = 7.7 Hz), 115.2 (d, ²*J*(C,F) = 21.2 Hz), 109.6, 79.1, 64.5, 61.1, 54.3, 45.4, 33.4, 25.7, 28.2, 23.7, 14.0 ppm; IR (KBr): $\tilde{\nu}$ = 3460, 3388, 1722 cm⁻¹; ESI-HRMS: *m/z*: calcd for C₂₂H₃₂FNO₆ + Na: 448.2106; found: 448.2105.

Compound 6: Compound **6** was prepared by a similar hydrogenation procedure to the above (31.6 mg, 91% yield); *R*_f = 0.10 (petroleum ether/EtOAc 50:1); [*α*]_D²⁰ = +78.4 (*c* = 0.56 in CHCl₃); 91% *ee* (determined by HPLC analysis: Daicel chiralcel AD, hexane/*i*PrOH 95:5, 1.0 mL min⁻¹, λ = 254 nm, *t*(major) = 8.23 min, *t*(minor) = 8.97 min); ¹H NMR (400 MHz, CDCl₃): δ = 7.48 (d, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.22 (t, *J* = 7.2 Hz, 1H), 4.89 (d, *J* = 14.0 Hz, 1H), 4.30–4.20 (m, 1H), 4.09–3.97 (m, 2H), 3.17 (d, *J* = 14.4 Hz, 1H), 2.49–2.43 (m, 1H), 2.14 (td, *J* = 5.6, 14.2 Hz, 1H), 1.59–1.46 (m, 10H), 1.34–1.30 (m, 1H), 1.18–1.11 ppm (m, 6H); ¹³C NMR (75 MHz, CDCl₃): δ = 174.1, 154.6, 138.2, 128.3, 127.4, 126.8, 79.7, 60.9, 49.5, 45.2, 42.2, 28.4, 27.1, 25.2, 15.6, 13.9 ppm; IR (KBr): $\tilde{\nu}$ = 1729, 1691 cm⁻¹; ESI-HRMS: *m/z*: calcd for C₂₀H₂₉NO₄ + Na: 370.1989; found: 370.2004.

Compound 7: Compound **7** was prepared by a similar hydrogenation procedure to above (103.0 mg, 93% yield); *R*_f = 0.15 (petroleum ether/EtOAc 50:1); [*α*]_D²⁰ = +87.7 (*c* = 0.31 in CHCl₃); 96% *ee* (determined by HPLC analysis: Daicel chiralcel AS, hexane/*i*PrOH 90:10, 1.0 mL min⁻¹, λ = 254 nm, *t*(major) = 4.30 min, *t*(minor) = 4.72 min); ¹H NMR (300 MHz, CDCl₃): δ = 7.59 (t, *J* = 8.0 Hz, 1H), 7.38–7.31 (m, 2H), 7.30–7.21 (m, 4H), 7.17–7.12 (m, 1H), 7.06–6.99 (m, 1H), 5.31 (brs, 1H), 4.80 (d, *J* = 13.7 Hz, 1H), 4.06 (q, *J* = 7.1 Hz, 2H), 3.30 (d, *J* = 14.2 Hz, 1H),

2.24–2.17 (m, 3H), 1.96 (brs, 1H), 1.38 (s, 9H), 1.09 ppm (t, $J=7.1$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3): $\delta=173.9, 161.1$ (d, $^1J(\text{C},\text{F})=245.3$ Hz), 155.3, 139.9, 129.5 (d, $^3J(\text{C},\text{F})=3.9$ Hz), 128.9, 128.7, 128.4, 126.8, 126.1, 123.9, 115.8 (d, $^2J(\text{C},\text{F})=22.7$ Hz), 80.3, 61.1, 53.0, 48.4, 44.8, 28.2, 26.9, 24.3, 13.9 ppm; IR (KBr): $\tilde{\nu}=1733, 1691\text{ cm}^{-1}$; ESI-HRMS: m/z : calcd for $\text{C}_{25}\text{H}_{30}\text{FNO}_4+\text{Na}$: 450.2051; found: 450.2039.

X-ray crystallographic determination of 8: Trifluoroacetic acid (2.0 mL) was added to a solution of **7** (75.0 mg, 0.18 mmol, 96% ee) in CH_2Cl_2 (5.0 mL). The mixture was stirred at room temperature for 30 min, and then the mixture was concentrated in vacuum. The residue was purified by flash chromatography (elution gradient: petroleum ether/EtOAc 10:1) to give the $\beta^{2,2}$ -amino ester intermediate. *p*-Toluenesulfonyl chloride (35.1 mg, 0.18 mmol) in CH_2Cl_2 (5.0 mL) was dropped into a solution of the above compound and NEt_3 (48.7 μL , 0.35 mmol) in CH_2Cl_2 (5.0 mL) at 0°C. After 12 h, the solution was concentrated in vacuum. The residue was purified by flash chromatography to give compound **8** (74.0 mg, 87% yield for two steps). $R_f=0.10$ (petroleum ether/EtOAc 15:1); $[\alpha]_D^{20}=+22.4$ ($c=0.37$ in CHCl_3); ^1H NMR (300 MHz, CDCl_3): $\delta=7.57$ (t, $J=8.0$ Hz, 1H), 7.30–7.15 (m, 8H), 7.11 (t, $J=7.6$ Hz, 1H), 7.01–6.92 (m, 3H), 5.09 (t, $J=4.5$ Hz, 1H), 4.51 (d, $J=13.9$ Hz, 1H), 4.13–4.04 (m, 2H), 3.83 (d, $J=13.9$ Hz, 1H), 2.34 (s, 3H), 2.23–2.09 (m, 4H), 1.11 ppm (t, $J=7.1$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3): $\delta=173.6, 161.0$ (d, $^1J(\text{C},\text{F})=245.6$ Hz), 142.6, 139.0, 136.7, 129.4 (d, $^3J(\text{C},\text{F})=3.6$ Hz), 129.2, 129.0, 128.9, 128.4, 127.7, 127.5, 127.2, 127.0, 124.1, 115.9 (d, $^2J(\text{C},\text{F})=22.7$ Hz), 61.3, 56.1, 47.4, 47.1, 26.7, 25.9, 21.4, 13.8 ppm; IR (KBr): $\tilde{\nu}=1729\text{ cm}^{-1}$; ESI-HRMS: m/z : calcd for $\text{C}_{27}\text{H}_{28}\text{FNO}_4\text{S}+\text{Na}$: 504.1615; found: 504.1609. Single crystals of enantiopure **8** suitable for X-ray analysis were obtained by recrystallization from acetone/hexane at room temperature. Crystal data for **8**: $\text{C}_{27}\text{H}_{28}\text{FNO}_4\text{S}$ (481.56), orthorhombic, space group $P2_12_12_1$, $a=9.667(4)$, $b=12.493(5)$, $c=20.354(8)$ Å, $U=2458.1(17)$ Å³, $Z=4$, specimen $0.52\times 0.40\times 0.38\text{ mm}^3$, $T=299(2)$ K, SIEMENS P4 diffractometer, absorption coefficient 0.173 mm^{-1} , reflections collected: 5437, independent reflections: 4570 [$R_{\text{int}}=0.0267$], refinement by full-matrix least-squares on F^2 , data/restraints/parameters 4570/0/309, goodness-of-fit on $F^2=0.852$, final R indices [$I>2\sigma(I)$] $R1=0.0446$, $wR2=0.0630$, R indices (all data) $R1=0.0869$, $wR2=0.0691$, largest diff. peak and hole 0.187 and $-0.168\text{ e}\text{\AA}^{-3}$. CCDC-617621 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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- [1] For recent reviews see: a) M. Liu, M. P. Sibi, *Tetrahedron* **2002**, *58*, 7991–8035; b) J. -A. Ma, *Angew. Chem.* **2003**, *115*, 4426–4435; *Angew. Chem. Int. Ed.* **2003**, *42*, 4290–4299; c) N. Sewald, *Angew. Chem.* **2003**, *115*, 5972–5973; *Angew. Chem. Int. Ed.* **2003**, *42*, 5794–5795; d) S. Abele, D. Seebach, *Eur. J. Org. Chem.* **2000**, 1–15; e) A. G. Wenzel, E. N. Jacobsen, *Asymmetric Catalysis in Enantioselective Synthesis of β -Amino Acids*, Harvard Univ., Cambridge, MA 02138, USA; f) E. Juaristi, *Enantioselective Synthesis of β -Amino Acids*, Wiley, New York, **2005**.
- [2] For recent reviews see: a) F. Fülöp, T. A. Martinek, G. K. Tóth, *Chem. Soc. Rev.* **2006**, *35*, 323–334; b) R. P. Cheng, S. H. Gellman, W. F. DeGrado, *Chem. Rev.* **2001**, *101*, 3219–3232.
- [3] For recent examples see: a) D. J. Guerin, S. J. Miller, *J. Am. Chem. Soc.* **2002**, *124*, 2134–2136 and references therein; b) A. G. Wenzel, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 12964–12965; c) H.-P. Wu, G. Hoge, *Org. Lett.* **2004**, *6*, 3645–3647; d) Y. Hsiao, N. R. Rivera, T. Rosner, S. W. Krska, E. Njolito, F. Wang, Y. Sun, J. D. III Armstrong, E. J. J. Grabowski, R. D. Tillyer, F. Spindler, C. Malan, *J. Am. Chem. Soc.* **2004**, *126*, 9918–9919; e) L. Qiu, F. Y. Kwong, J. Wu, W. H. Lam, S. Chan, W.-Y. Yu, Y.-M. Li, R. Guo, Z. Zhou, A. S. C. Chan, *J. Am. Chem. Soc.* **2006**, *128*, 5955–5965 and references therein.
- [4] a) N. Sewald, V. Wendisch, *Tetrahedron: Asymmetry* **1998**, *9*, 1341–1344; b) A. Duursma, A. J. Minnaard, B. L. Feringa, *J. Am. Chem. Soc.* **2003**, *125*, 3700–3701; c) A. Rimkus, N. Sewald, *Org. Lett.* **2003**, *5*, 79–90; d) U. Eilita, F. LeBmann, O. Seidelmann, V. Wendisch, *Tetrahedron: Asymmetry* **2003**, *14*, 189–191; e) M. P. Sibi, K. Patil, *Angew. Chem.* **2004**, *116*, 1255–1258; *Angew. Chem. Int. Ed.* **2004**, *43*, 1235–1238; f) M. P. Sibi, H. Tatamidani, K. Patil, *Org. Lett.* **2005**, *7*, 2571–2573.
- [5] For recent reviews on catalytic enantioselective construction of all-carbon quaternary chiral centers see: a) J. Christoffers, A. Baro, *Adv. Synth. Catal.* **2005**, *347*, 1473–1482; b) E. A. Peterson, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 11943–11948; c) C. J. Douglas, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5363–5367; d) D. J. Ramon, M. Yus, *Curr. Org. Chem.* **2004**, *8*, 149–183.
- [6] For examples by using chiral auxiliary strategies see: a) C. Catiavela, M. D. Díaz-de-Villegas, J. A. Gálvez, *J. Org. Chem.* **1994**, *59*, 2497–2505; b) R. Badorrey, C. Catiavela, M. D. Díaz-de-Villegas, J. A. Gálvez, Y. Lapeña, *Tetrahedron: Asymmetry* **1997**, *8*, 311–317; c) A. Avenoza, C. Catiavela, M. Paris, J. M. Peregrina, *Tetrahedron: Asymmetry* **1995**, *6*, 1409–1418.
- [7] For recent examples see: a) M. Watanabe, A. Ikagawa, H. Wang, K. Murata, T. Ikariya, *J. Am. Chem. Soc.* **2004**, *126*, 11148–11149; b) D. A. Evans, R. J. Thomson, F. Franco, *J. Am. Chem. Soc.* **2005**, *127*, 10816–10817; c) H. Li, Y. Wang, L. Tang, L. Deng, *J. Am. Chem. Soc.* **2004**, *126*, 9906–9907; d) H. Li, Y. Wang, L. Tang, F. Wu, X. Liu, C. Guo, B. M. Foxman, L. Deng, *Angew. Chem.* **2005**, *117*, 107–110; *Angew. Chem. Int. Ed.* **2005**, *44*, 105–108; e) M. Terada, H. Ube, Y. Yaguchi, *J. Am. Chem. Soc.* **2006**, *128*, 1454–1455; f) S. Brandau, A. Landa, J. Franzén, M. Marigo, K. A. Jørgensen, *Angew. Chem.* **2006**, *118*, 4411–4415; *Angew. Chem. Int. Ed.* **2006**, *45*, 4305–4309.
- [8] a) M. Sawamura, H. Hamashima, Y. Ito, *J. Am. Chem. Soc.* **1992**, *114*, 8295–8296; b) M. Sawamura, H. Hamashima, Y. Ito, *Tetrahedron* **1994**, *50*, 4439–4454; c) K. Inagaki, K. Nozaki, H. Takaya, *Synlett* **1997**, 119–120; d) For the Michael reaction of an α -cyano Weinreb amide: M. Sawamura, H. Hamashima, H. Shinoto, Y. Ito, *Tetrahedron Lett.* **1995**, *36*, 6479–6482.
- [9] a) M. A. Stark, G. Jones, C. J. Richards, *Organometallics* **2000**, *19*, 1282–1291; b) C. Mazet, L. H. Gade, *Chem. Eur. J.* **2003**, *9*, 1759–1767; c) K. Takenaka, Y. Uozumi, *Org. Lett.* **2004**, *6*, 1833–1835; d) K. Takenaka, M. Minakawa, Y. Uozumi, *J. Am. Chem. Soc.* **2005**, *127*, 12273–12281; e) A. J. Blacker, M. L. Clarke, M. S. Ito, M. F. Mahon, J. M. J. Williams, *Organometallics* **1999**, *18*, 2867–2873.
- [10] a) M. S. Taylor, E. N. Jacobsen, *J. Am. Chem. Soc.* **2003**, *125*, 11204–11205; b) M. S. Taylor, D. N. Zalatan, A. M. Lerchner, E. N. Jacobsen, *J. Am. Chem. Soc.* **2005**, *127*, 1313–1317.
- [11] H. Wynberg, R. Helder, *Tetrahedron Lett.* **1975**, *16*, 4057–4060.
- [12] a) H. Li, Y. Wang, L. Tang, F. Wu, X. Liu, C. Guo, B. M. Foxman, L. Deng, *Angew. Chem.* **2005**, *117*, 107–110; *Angew. Chem. Int. Ed.* **2005**, *44*, 105–108; b) H. Li, J. Song, X. Liu, L. Deng, *J. Am. Chem. Soc.* **2005**, *127*, 8948–8949; c) Y. Wang, X. Liu, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 3928–3930; d) F. Wu, R. Hong, J. Khan, X. Liu, L. Deng, *Angew. Chem.* **2006**, *118*, 4407–4411; *Angew. Chem. Int. Ed.* **2006**, *45*, 4301–4305; For other work by Jørgensen et al see: e) T. B. Poulsen, C. Alemparte, S. Saaby, M. Bella, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 2956–2959; *Angew. Chem. Int. Ed.* **2005**, *44*, 2896–2899; f) S. Saaby, M. Bella, K. A. Jørgensen, *J. Am. Chem. Soc.* **2004**, *126*, 8120–8121; g) M. Bell, K. Frisch, K. A. Jørgensen, *J. Org. Chem.* **2006**, *71*, 5407–5410.
- [13] a) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673; b) T. Okino, S. Nakamura, T. Furukawa, Y. Takemoto, *Org. Lett.* **2004**, *6*, 625–627; c) T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119–125; d) Y. Hoashi, T. Okino, Y. Takemoto, *Angew. Chem.* **2005**, *117*, 4100–

- 4103; *Angew. Chem. Int. Ed.* **2005**, *44*, 4032–4035; e) B.-J. Li, L. Jiang, M. Liu, Y.-C. Chen, L.-S. Ding, Y. Wu, *Synlett* **2005**, 603–606; f) B. Vakulya, S. Varga, A. Csampai, T. Sóos, *Org. Lett.* **2005**, *7*, 1967–1969; g) A. Berkessel, F. Cleemann, S. Mukherjee, T. N. Müller, J. Lex, *Angew. Chem.* **2005**, *117*, 817–821; *Angew. Chem. Int. Ed.* **2005**, *44*, 807–811; h) A. Berkessel, S. Mukherjee, F. Cleemann, T. N. Müller, J. Lex, *Chem. Commun.* **2005**, 1898–1900; i) A. Berkessel, F. Cleemann, S. Mukherjee, *Angew. Chem.* **2005**, *117*, 7632–7635; *Angew. Chem. Int. Ed.* **2005**, *44*, 7466–7469; j) J. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.* **2005**, 4481–4483; k) S. H. McCooey, S. J. Connon, *Angew. Chem.* **2005**, *117*, 6525–6528; *Angew. Chem. Int. Ed.* **2005**, *44*, 6367–6370; l) J. Wang, H. Li, X. Yu, L. Zu, W. Wang, *Org. Lett.* **2005**, *7*, 4293–4296; m) J. Wang, H. Li, W. Duan, L. Zu, W. Wang, *Org. Lett.* **2005**, *7*, 4713–4716; n) A. L. Tillman, J. Ye, D. J. Dixon, *Chem. Commun.* **2006**, 1191–1193; o) J. Song, Y. Wang, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 6048–6049; p) Y.-Q. Wang, J. Song, R. Hong, H. Li, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 8156–8157.
- [14] For reviews on thiourea-based organocatalysts see: a) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289–296; b) P. M. Pihko, *Angew. Chem.* **2004**, *116*, 2110–2113; *Angew. Chem. Int. Ed.* **2004**, *43*, 2062–2064; c) Y. Takemoto, *Org. Biomol. Chem.* **2005**, *3*, 4299; d) M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550–1573; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520–1543; e) S. T. Connon, *Chem. Eur. J.* **2006**, *12*, 5418–5427.
- [15] T.-Y. Liu, J. Long, B.-J. Li, L. Jiang, R. Li, Y. Wu, L.-S. Ding, Y.-C. Chen, *Org. Biomol. Chem.* **2006**, *4*, 2097–2099.
- [16] For recent reviews on organocatalysis see: a) P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248–5286; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175; b) Special issue (Eds.: K. N. Houk, B. List), *Acc. Chem. Res.*, Vol. 37, 8th ed., **2004**; c) J. Seayad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719–724; d) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis*, Wiley-VCH, **2005**.
- [17] a) L. Yang, G. Morriello, A. A. Patchett, K. Leung, T. Jacks, K. Cheng, K. D. Schleim, W. Feeney, W. W.-S. Chan, S.-H. L. Chiu, R. G. Smith, *J. Med. Chem.* **1998**, *41*, 2439–2441; b) P. E. Malignes, M. M. Chartrain, V. Upadhyay, D. Cohen, R. A. Reamer, D. Askin, R. P. Volante, P. J. Reider, *J. Org. Chem.* **1998**, *63*, 9548–9551; c) B. J. Paul, B. J. Littler, F. Jos, P. F. Vogt, S. H. Pines, *Org. Process Res. Dev.* **2006**, *10*, 339–345.
- [18] For details see the Supporting Information.
- [19] J. Andraos, Y. Chiang, A. J. Kresge, I. G. Pojarlieff, N. P. Schepp, J. Wirz, *J. Am. Chem. Soc.* **1994**, *116*, 73–81.
- [20] F. F. Blicke, J. H. Burckhalter, *J. Am. Chem. Soc.* **1942**, *64*, 451–454.

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