Chiral Guanidine-Catalyzed Asymmetric Direct Vinylogous Michael Reaction of α,β-Unsaturated γ-Butyrolactam with Alkylidene Malonates

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1. General Remarks

The $^1$H NMR spectra were recorded at 300 MHz or 400 MHz. The chemical shifts are reported in ppm downfield to CDCl$_3$ ($\delta = 7.26$) or $d_6$-DMSO ($\delta = 2.50$) for $^1$H NMR. Coupling constants in $^1$H NMR were in Hz. $^{13}$C NMR spectra were collected on commercial instruments (75 MHz or 100 MHz) with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as internal standard (CDCl$_3$, $\delta = 77.0$ or $d_6$-DMSO, $\delta = 39.4$). The enantiomeric excess (ee) of the products were determined by HPLC using Chiralpak AD-H or IA columns with hexane/isopropanol as eluent, and the retention times were compared to corresponding racemic samples. Optical rotations were measured on a commercial polarimeter and reported as follows: $[\alpha]_D^T$ (c = g/100 mL, in solvent). Melting points (m.p.) were measured on electrothermal digital melting point apparatus and were uncorrected.

$\alpha,\beta$-Unsaturated $\gamma$-butyrolactam 4 was prepared according to the reported procedure.$^1$ The guanidines were prepared according to the methods mentioned in catalyst preparation section.$^2$
2. Procedure and Characterization of the catalysts\textsuperscript{[2]}

To a solution of A (2.4 g, 9.4 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (40 mL) was added Et\textsubscript{3}N (1.31 mL, 9.4 mmol), isobutyl carbonochloridate (1.23 mL, 9.4 mmol) at 0 °C under stirring. After 10 min, (1S, 2S)-1,2-diphenylethane-1,2-diamine (0.951 g, 4.48 mmol) was added. The reaction was allowed to warm to room temperature and detected by TLC. Overnight, the mixture was washed with 1 N KHSO\textsubscript{4} solution, saturated NaHCO\textsubscript{3} solution, brine, dried over anhydrous Na\textsubscript{2}SO\textsubscript{4} and concentrated and purified through flash chromatograph (EtOAc : petroleum ether = 1 : 3) as white solid. TFA (6 mL) was added to the CH\textsubscript{2}Cl\textsubscript{2} (6 mL) solution of the amide, and stirred until reaction was finished (1 h). Then, the solvent was evaporated, and H\textsubscript{2}O (10 mL) was added. The pH value of the mixture was brought into the range of 10–12 by the addition of 2 N NaOH solution. The aqueous phase was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 \times 30 mL). The combined organic phase was washed with brine, dried over anhydrous Na\textsubscript{2}SO\textsubscript{4}, and evaporated in vacuo to get a kind of white foam 3.

\[(2S,3aS,6aS)-N-((1S,2S)-2-((2R,3aS,6aS)-octahydrocyclopenta[b]pyrrole-2-carboxamido)-1,2-diphenylethyl)-octahydrocyclopenta[b]pyrrole-2-carboxamide \ (3): \ [\alpha]_{D}^{15} = -7.4 \ (c = 0.20, \text{in MeOH}). \text{m.p.} 90 – 94 ^\circ \text{C}. \] \[\text{^1H NMR (400 MHz, d}_6-\text{DMSO}) \delta 8.53 \ (2 \ H, d, J = 8.3 \text{ Hz}), \ 7.25 – 7.10 \ (10 \ H, m), 5.24\]
2.4 M n-BuLi in n-hexane (4.2 eq, 2.63 mL) was injected into a solution of 3 (730 mg, 1.5 mmol) in THF (40 mL) dropwise over 10 mins under nitrogen atmosphere at −20 °C with well stirring. For additional 10 mins, a solution of N,N’-dicyclohexylcarbodiimide (1.3 eq., 402 mg, 1.95 mmol) in 10 mL THF was added dropwise in 10 mins. The reaction was allowed to warm to room temperature, and detected by TLC. After 48 h, the mixture was evaporated under reduced pressure to get rid of THF, and the pH value of the mixture was brought into the range of 0–1 by the addition of 2 N HCl. The aqueous phase was extracted with CH₂Cl₂ (3 × 30 mL). The combined organic phase was washed with brine, dried over anhydrous MgSO₄, and evaporated in vacuum, and purified through flash chromatograph on silica gel (EtOAc : MeOH = 3:1) to produce E. The white foam E in CH₂Cl₂ (10 mL) was added 5 N NaOH (10 mL) and stirred until the basification was finished (10 mins). The pH value of the mixture was kept in the range of 11–12. The aqueous phase was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic phase was washed with 3 N NaOH in brine, dried over anhydrous NaSO₄ and evaporated in vacuum. Finally, a white solid 2 was obtained. Then it was dissolved in CH₂Cl₂ and filtration through Celite to remove the silicone gel, concentrated to get a kind of white solid (540 mg, 52% yield).

(2S,3aS,6aS)-N-((1S,2S)-2-((2R,3aS,6aS)-1-(carbamimidoyl)-octahydrocyclopenta[b]pyrrole-2-carboxamido)-1,2-diphenylethyl)-octahydrocyclopenta[b]pyrrole-2-carboxamide (2): [α]D¹⁶ = −53.0 (c = 0.23, in CH₂Cl₂). m.p. 78 – 82 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.24 – 6.97 (10 H, m), 5.15 (2 H, s), 4.68 (1 H, s), 4.03 (1 H, d, J = 4.8 Hz), 3.71 (1 H, t, J = 6.4 Hz), 3.58 (1 H, t, J = 8.4 Hz), 3.01 (2 H, s), 2.65 – 2.44 (2 H, m), 2.31 – 2.19 (1 H, m), 2.15-1.95 (2 H, m), 1.94 – 1.41 (20 H, m), 1.40 – 0.91 (15 H, m). ¹³C NMR δ (75 MHz, CDCl₃): 174.60, 174.06, 171.75, 139.61, 138.89, 128.06, 127.98, 127.86, 127.83, 127.71, 127.28, 127.19, 127.05, 126.82, 126.23, 77.20, 66.65, 65.92, 64.94, 63.56, 62.56, 58.44, 58.03, 57.21, 43.35, 42.79,
42.62, 38.17, 35.06, 34.92, 33.38, 33.07, 32.50, 30.74, 29.58, 25.49, 25.31, 24.93, 24.63, 23.72. HRMS (ESI): calcd for C_{43}H_{60}N_{6}O_{2} [M+H^+] 693.4851, found 693.4852.

To a solution of A (1.28 g, 5 mmol) in CH_{2}Cl_{2} (40 mL) was added Et_{3}N (0.84 mL, 6 mmol), isobutyl carbonochloridate (0.84 mL, 6 mmol) at 0 °C under stirring. After 10 min, F (1.54 g, 4.5 mmol) was added. The reaction was allowed to warm to room temperature, and detected by TLC. After 3 hours, the mixture was washed with 1 N KHSO_{4} solution, saturated NaHCO_{3} solution, brine, dried over anhydrous Na_{2}SO_{4} and concentrated and purified through flash chromatograph (EtOAc : petroleum ether = 1 : 2) as white solid. TFA (4 mL) was added to the CH_{2}Cl_{2} (4 mL) solution of the amide and stirred until reaction was finished (1 h). Then, the solvent was evaporated, and H_{2}O (10 mL) was added. The pH value of the mixture was brought into the range of 10–12 by the addition of 2 N NaOH solution. The aqueous phase was extracted with CH_{2}Cl_{2} (3 × 30 mL). The combined organic phase was washed with brine, dried over anhydrous Na_{2}SO_{4} and evaporated in vacuo to get a kind of white foam H.

To a solution of H (1.811 g, 3.78 mmol) in CH_{3}CN (15 mL) was added paraformaldehyde (CH_{2}O)_{n}
(0.341 g, 11.34 mmol, 3 eq) at r.t. under stirring. After 10 min, NaBH₄CN (0.275 g, 4.16 mmol, 1.1 eq) was added stirring for 15 min, then glacial acetic acid (0.65 mL, 11.34 mmol, 3.0 eq) was added. The reaction was detected by TLC. After 2 hours, the residue was filtered, the organic phase was concentrated and dissolved in CH₂Cl₂. The pH value of the mixture was brought into the range of 7–8 by the addition of sat. NaHCO₃ solution. The aqueous phase was extracted with CH₂Cl₂ (3 × 30 mL). The combined organic phase was washed with brine, dried over anhydrous Na₂SO₄, concentrated and purified through flash chromatograph (EtOAc : petroleum ether = 1 : 3) to get a white solid I. Then I and NH₂-NH₂ • H₂O was dissolved in EtOH, and the reaction was allowed to reflux, and detected by TLC. After 3 hours, the residue was filtered, the organic phase was concentrated and dissolved in CH₂Cl₂. This step was repeated third times, then the mixture was concentrated and purified through flash chromatograph (EtOAc : petroleum ether = 1 : 1) to get a kind of white foam J.

Synthesis of L from J was according to the procedure for H from F. The mixture was isolated by column chromatography on silica gel (EtOAc : petroleum ether = 4 : 1) to afford L as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.28 (1 H, d, J = 8.0 Hz), 7.87 (1 H, d, J = 7.6 Hz), 7.26 – 6.92 (10 H, m), 5.30 – 5.15 (2 H, m), 3.74 (1 H, t, J = 6.0 Hz), 3.62 (1 H, t, J = 8.0 Hz), 2.92 (2 H, t, J = 8.8 Hz), 2.74 (2 H, s), 2.55 – 2.42 (2 H, m), 2.37 – 2.20 (5 H, m), 1.75 – 1.65 (1 H, m), 1.65 – 1.55 (1 H, m), 1.55 – 1.35 (7 H, m), 1.35 – 1.17 (3 H, m), 1.17 – 1.05 (1 H, m). ¹³C NMR δ (100 MHz, CDCl₃): 174.24, 174.04, 138.66, 128.36, 128.34 127.58, 127.54, 127.28, 127.27, 72.43, 71.38, 63.67, 62.47, 57.66, 57.64, 42.67, 41.20, 40.53, 38.36, 37.93, 35.13, 33.33, 32.82, 32.39, 24.00, 23.72.

2.4 M n-BuLi in n-hexane (3.5 eq, 1.45 mL) was injected into a solution of L (497 mg, 0.993 mmol) in THF (40 mL) dropwise over 10 mins under nitrogen atmosphere at −20 °C with well stirring. For additional 10 mins, a solution of N,N'-dicyclohexylcarbodiimide (1.5 eq., 307 mg, 1.49 mmol) in 10 mL THF was added dropwise in 10 mins. The reaction was allowed to warm to room temperature, and detected by TLC. After 48 h, the mixture was evaporated under reduced pressure to get rid of THF, and the pH value of the mixture was brought into the range of 0–1 by the addition of 2 N HCl. The aqueous phase was extracted with CH₂Cl₂ (3 × 30 mL). The combined organic phase was washed with brine, dried over anhydrous MgSO₄, evaporated in vacuum, and purified through flash chromatograph on silica gel (EtOAc : MeOH = 5:1) to produce O. The white foam O in CH₂Cl₂ (10 mL) was added 5
N NaOH (10 mL) and stirred until the basification was finished (10 mins). The pH value of the mixture was kept in the range of 11–12. The aqueous phase was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic phase was washed with 3 N NaOH in birne, dried over anhydrous NaSO₄ and evaporated in vacuum. Finally, a white solid 9 was obtained. Then it was dissolved in CH₂Cl₂, and filtration through Celite to remove the silicone gel, concentrated to get a kind of white solid (442 mg, 63% yield).

\[(2S,3aS,6aS)-N-(1S,2S)-2-((2R,3aS,6aS)-1-(carbamimidoyl)-octahydrocyclcopenta[b]pyrrole-2-carboxamido)-1,2-diphenylethyl)-1-methyl-octahydrocyclopenta[b]pyrrole-2-carboxamide (9): \ [\alpha]_{D}^{15} = -119.5 \ (c = 0.23, \ \text{in} \ \text{CHCl}_3). \ \text{m.p.} \ 58 – 62 ^\circ\text{C}. \ ¹H \ \text{NMR (300 MHz, CDCl}_3) \ \delta \ 7.18 – 6.95 \ (10 \ H, \ m), 5.25 – 5.05 \ (2 \ H, \ m), 4.72 \ (1 \ H, \ s), 4.01 \ (1 \ H, \ d, \ J = 4.5 \ Hz), 3.05 – 2.93 \ (2 \ H, \ m), 2.93 – 2.80 \ (2 \ H, \ m), 2.60 – 2.40 \ (2 \ H, \ m), 2.31 – 2.21 \ (4 \ H, \ m), 2.10 – 1.87 \ (2 \ H, \ m), 1.62 \ (19 \ H, \ m), 1.41 – 1.07 \ (15 \ H, \ m). \ ¹³C \ \text{NMR} (75 \ MHz, \ \text{CDCl}_3): \ 174.35, 173.34, 140.15, 138.77, 127.94, 127.83, 127.29, 127.19, 126.93, 77.20, 72.32, 71.44, 65.49, 62.07, 58.11, 57.90, 42.47, 41.14, 40.59, 38.21, 34.09, 33.45, 32.71, 31.87, 30.98, 30.24, 29.64, 25.54, 25.42, 25.32, 24.74, 24.13. \ \text{HRMS (ESI): calcd for C}_{44}H_{64}N_{6}O_{2} \ [\text{M+H}^+] \ 707.5007, \ \text{found} \ 707.5001. \]

C₂-symmetric bisguanidine catalysts, perviously used in the catalytic asymmetric reactions of azlactone, afforded complex mixtures.
When α,β-unsaturated ketones, such as chalcone and cinnamone, were tested under the optimized conditions for this reaction, unsatisfied results were obtained. For chalcone, the corresponding product was obtained in 43% yield, 8% ee, 2:1 dr (47% ee for the minor isomer), although γ-butyrolactam was greatly consumed. For cinnamone, only trace amount of the desired product was obtained in 24 hours.

3. General procedure for the catalytic asymmetric vinylogous Michael reaction

α,β-Unsaturated γ-butyrolactam 4 (9.2 mg, 0.05 mmol) and the catalyst 2 (1.7 mg, 0.0025 mmol) were added into PhCF₃ (0.25 mL), then stirred for 15–30 mins at ambient temperature. Then the diethyl benzylidemalonates 5a (24.8 mg, 0.1 mmol) was added. The mixture was stirred at 30 °C for 18 hours. After that, the reaction mixture was purified directly by flash chromatography to give desired product 6a in 82% yield. The syn/anti ratio of the product was determined by ¹H NMR analysis or HPLC.

**tert-butyl 2-(3-ethoxy-2-(ethoxycarbonyl)-3-oxo-1-phenylpropyl)-5-oxo-2H-pyrrole-1(5H)-carboxylate (6a):** The reaction time is 18 hours. The mixture was isolated by column chromatography on silica gel (3:1 P.E./EtOAc) to afford 6a (82% yield, 95:5 dr and 94% ee). ¹H NMR (300 MHz, CDCl₃) δ 7.36 – 7.27 (3H, m), 7.21 – 7.19 (2H, m), 7.08 – 7.06 (1H, m), 6.13 (1H, dd, J = 7.6, 1.4 Hz), 4.84 (1H, t, J = 1.7 Hz), 4.50 (1H, dd, J = 13.2, 3.6 Hz), 4.22 (2H, dd, J = 7.2, 1.5 Hz), 3.93 – 3.81 (3H, m), 1.65 (9H, s), 1.27 (3H, t, J = 7.1Hz), 0.88 (3H, t, J = 7.1 Hz) ppm. ¹³C NMR δ (75 MHz, CDCl₃): 168.70, 167.81, 167.07, 149.29, 146.46, 137.11, 128.80, 128.43, 128.24, 127.78, 83.54, 65.52, 62.58, 61.48, 51.89, 45.69, 28.17, 13.82, 13.52. HRMS (ESI): calcd for C₂₃H₂₉NO₇ [M+Na⁺] 454.1836, found 454.1837. The ee was determined by HPLC analysis using a Chiral ADH column (n-hexane/2-propanol 80: 20, 1.0 mL/min, λ = 210 nm; t₁ = 5.1 min, t₂ = 12.2 min).
**tert-butyl 2-(3-methoxy-2-(methoxycarbonyl)-3-oxo-1-phenylpropyl)-5-oxo-2H-pyrrole-1(5H)-carboxylate** (6b): The reaction time is 18 hours. The mixture was isolated by column chromatography on silica gel (3:1 P.E./EtOAc) to afford 6b (85% yield, 95:5 dr and 93% ee). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.36 – 7.27 (3H, m), 7.20 – 7.18 (2H, m), 7.04 (1H, dd, $J = 6.2$, 1.6 Hz), 6.15 (1H, dd, $J = 6.2$, 1.6 Hz), 4.81 (1H, dt, $J = 3.6$, 1.8 Hz), 4.53 (1 H, dd, $J = 12.3$, 3.5 Hz), 3.85 (1H, d, $J = 12.3$ Hz), 3.76 (3H, s), 3.43 (3H, s), 1.65 (9H, s) ppm. $^{13}$C NMR $\delta$ (75 MHz, CDCl$_3$): 168.71, 168.04, 167.41, 149.13, 146.05, 137.03, 128.90, 128.54, 127.89, 127.81, 83.60, 65.56, 53.51, 52.61, 51.25, 45.50, 28.11. HRMS (ESI): calcd for C$_{21}$H$_{25}$NO$_7$ [M+Na$^+$] 426.1523, found 426.1537. The ee was determined by HPLC analysis using a Chiral ADH column ($n$-hexane/2-propanol 85: 15, 1.0 mL/min, $\lambda = 210$ nm; $t_1 = 6.9$ min, $t_2 = 14.4$ min).
**tert-butyl 2-(3-(benzyl)-2-(benzyloxycarbonyl)-3-oxo-1-phenylpropyl)-5-oxo-2H-pyrrole-1(5H)-carboxylate (6c):** The reaction time is 18 hours. The mixture was isolated by column chromatography on silica gel (3:1 P.E./EtOAc) to afford 6c (83% yield, 95: 5 dr and 91% ee). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.33 – 7.26 (7H, m), 7.25 – 7.11 (6H, m), 7.03 (1H, dd, $J$ = 6.2, 2.0 Hz), 7.01 – 6.93 (2H, m), 6.11 (1H, dd, $J$ = 6.2, 1.6 Hz), 5.29 (1H, d, $J$ = 12.2 Hz), 5.11 (1H, d, $J$ = 12.2 Hz), 4.91 – 4.86 (1H, m), 4.84 (2H, s), 4.55 (1H, dt, $J$ = 8.8, 4.4 Hz), 3.98 (1H, d, $J$ = 12.3 Hz), 1.65 (9H, s) ppm. $^{13}$C NMR $\delta$ (75 MHz, CDCl$_3$): 168.79, 167.46, 166.75, 149.30, 146.48, 136.68, 135.11, 134.81, 128.88, 128.49, 128.43, 128.36, 128.26, 128.17, 128.07, 128.05, 127.92, 127.83, 83.64, 68.12, 67.24, 65.40, 51.75, 45.66, 28.14. HRMS (ESI): calcd for C$_{33}$H$_{33}$NO$_7$ [M+Na$^+$] 578.2149, found 578.2146. The ee was determined by HPLC analysis using a Chiral IA column ($n$-hexane/2-propanol 80: 20, 1.0 mL/min, $\lambda$ = 210 nm; $t_1$ = 8.7 min, $t_2$ = 18.5 min).
**tert-butyl 2-(3-ethoxy-2-(ethoxycarbonyl)-1-(4-fluorophenyl)-3-oxopropyl)-5-oxo-2H-pyrrole-1(5H)-carboxylate (6d):** The reaction time is 12 hours. The mixture was isolated by column chromatography on silica gel (3:1 P.E./EtOAc) to afford 6d (78% yield, 95: 5 dr and 94% ee). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.20 – 7.12 (2 H, m), 7.07 – 6.95 (3 H, m), 6.10 (1 H, d, $J = 6.1$ Hz), 4.84 (1 H, s), 4.43 (1 H, dd, $J = 12.2, 3.2$ Hz), 4.19 (2 H, tt, $J = 10.8, 5.3$ Hz), 3.91 (2 H, dq, $J = 11.0, 3.7$ Hz), 3.82 (1 H, d, $J = 12.2$ Hz), 1.62 (9 H, s), 1.26 (3H, t, $J = 7.0$ Hz), 0.90 (3 H, t, $J = 7.1$ Hz). $^{13}$C NMR δ (75 MHz, CDCl$_3$): 168.48, 167.64, 166.98, 163.67, 149.42, 146.44, 132.60, 129.88 (d, $J = 8.0$ Hz), 128.43, 115.83, 83.57, 65.09, 62.53, 61.52, 52.13, 45.07, 28.09, 13.77, 13.55. HRMS (ESI): calcd for C$_{23}$H$_{28}$FNO$_7$ [M+Na$^+$] 472.1742, found 472.1749. The ee was determined by HPLC analysis using a Chiral ADH column (n-hexane/2-propanol 90: 10, 1.0 mL/min, $\lambda = 210$ nm; $t_1 = 7.8$ min, $t_2 = 25.4$ min).
**tert-butyl 2-(1-(2-chlorophenyl)-3-ethoxy-2-(ethoxycarbonyl)-3-oxopropyl)-5-oxo-2H-pyrrole-1(5H)-carboxylate (6e):** The reaction time is 12 hours. The mixture was isolated by column chromatography on silica gel (3:1 P.E./EtOAc) to afford 6e (75% yield, 95: 5 dr and 93% ee). ¹H NMR (300 MHz, CDCl₃) δ 7.43 – 7.34 (1 H, m), 7.24 – 7.16 (2 H, m), 7.13 – 7.03 (2 H, m), 6.02 (1 H, dd, J = 6.1, 1.5 Hz), 5.16 – 5.08 (1 H, m), 4.92 (1 H, dd, J = 12.2, 3.6 Hz), 4.33 – 4.21 (2 H, m), 4.01 – 3.93 (1 H, m), 3.93 – 3.80 (2 H, m), 1.62 (9 H, s), 1.29 (3 H, t, J = 7.2 Hz), 0.88 (3 H, t, J = 7.2 Hz) ppm. ¹³C NMR δ (75 MHz, CDCl₃): 168.94, 167.75, 166.94, 149.96, 147.59, 134.91, 133.90, 130.19, 128.99, 128.92, 127.85, 126.79, 83.77, 62.74, 62.41, 61.55, 52.72, 42.34, 28.19, 13.87, 13.47. HRMS (ESI): calcd for C₂₃H₂₈O₇ClNO₇ [M+Na⁺] 488.1447, found 488.1449. The ee was determined by HPLC analysis using a Chiral ADH column (n-hexane/2-propanol 95: 5, 1.0 mL/min, λ = 210 nm; t₁ = 13.4 min, t₂ = 15.0 min).
** tert-butyl 2-(1-(3-chlorophenyl)-3-ethoxy-2-(ethoxycarbonyl)-3-oxopropyl)-5-oxo-2H-pyrrole-1(5H)-carboxylate (6f):** The reaction time is 12 hours. The mixture was isolated by column chromatography on silica gel (3:1 P.E./EtOAc) to afford 6f (80% yield, 94:6 dr and 90% ee). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.28 – 7.23 (2 H, m), 7.22 – 7.17 (1 H, m), 7.11 – 7.03 (2 H, m), 6.14 (1 H, dd, $J$ = 6.2, 1.6 Hz), 4.86 – 4.79 (1 H, m), 4.45 (1 H, dd, $J$ = 12.2, 3.3 Hz), 4.26 – 4.16 (2 H, m), 3.93 (2 H, qd, $J$ = 7.1, 2.5 Hz), 3.83 (1 H, d, $J$ = 12.2 Hz), 1.63 (9 H, s), 1.25 (3H, t, $J$ = 7.1 Hz), 0.94 (3 H, t, $J$ = 7.1 Hz) ppm. $^{13}$C NMR $\delta$ (75 MHz, CDCl$_3$): 168.35, 167.54, 166.85, 149.34, 146.09, 139.07, 134.63, 130.03, 128.64, 128.46, 128.02, 126.31, 83.68, 65.04, 62.64, 61.63, 51.69, 45.36, 28.11, 13.77, 13.57. HRMS (ESI): calcd for C$_{23}$H$_{28}$O$_4$N$_2$Cl [M+Na$^+$] 488.1447, found 488.1453. The ee was determined by HPLC analysis using a Chiral ADH column ($n$-hexane/2-propanol 90: 10, 1.0 mL/min, $\lambda$ = 210 nm; $t_1$ = 6.8 min, $t_2$ = 15.9 min).
tert-butyl 2-(1-(4-chlorophenyl)-3-ethoxy-2-(ethoxycarbonyl)-3-oxopropyl)-5-oxo-2H-pyrrole-1(5H)-carboxylate (6g): The reaction time is 12 hours. The mixture was isolated by column chromatography on silica gel (3:1 P.E./EtOAc) to afford 6g (85% yield, 95:5 dr and 92% ee). \( ^1 \)H NMR (300 MHz, CDCl3) \( \delta \) 7.31 – 7.26 (2 H, m), 7.17 – 7.11 (2 H, m), 7.02 (1 H, dd, \( J = 6.1, 1.9 \) Hz), 6.11 (1 H, dd, \( J = 6.3, 1.5 \) Hz), 4.83 (1 H, d, \( J = 1.5 \) Hz), 4.42 (1 H, dd, \( J = 12.1, 3.3 \) Hz), 4.28 – 4.15 (2 H, m), 3.91 (2 H, qd, \( J = 7.2, 3.6 \) Hz), 3.82 (1 H, d, \( J = 12.3 \) Hz), 1.62 (9 H, s), 1.26 (3 H, t, \( J = 6.4 \) Hz), 0.93 (3 H, t, \( J = 7.1 \) Hz) ppm. 
\( ^{13} \)C NMR \( \delta \) (75 MHz, CDCl3): 168.40, 167.58, 166.91, 149.41, 146.28, 135.41, 133.66, 129.56, 128.93, 128.52, 83.62, 64.97, 62.57, 61.59, 51.91, 45.16, 28.10, 13.77, 13.58. HRMS (ESI): calcd for C\(_{23}\)H\(_{28}\)ClNO\(_7\) [M+Na\(^+\)] 488.1447, found 488.1449. The ee was determined by HPLC analysis using a Chiral ADH column (\( n \)-hexane/\( 2 \)-propanol 90:10, 1.0 mL/min, \( \lambda = 210 \) nm; \( t_1 = 8.7 \) min, \( t_2 = 26.4 \) min)
** tert-butyl 2-(1-(3-bromophenyl)-3-ethoxy-2-(ethoxycarbonyl)-3-oxopropyl)-5-oxo-2H-pyrrole-1(5H)-carboxylate (6h)**: The reaction time is 12 hours.

The mixture was isolated by column chromatography on silica gel (3:1 P.E./EtOAc) to afford 6h (85% yield, 94:6 dr and 93% ee). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.45 – 7.30 (2 H, m), 7.22 – 7.17 (1 H, m), 7.15 – 7.10 (1 H, m), 7.04 (1 H, dd, $J = 6.2$, 1.8 Hz), 6.13 (1 H, dd, $J = 6.1$, 1.3 Hz), 4.85 – 4.78 (1 H, m), 4.43 (1 H, dd, $J = 12.2$, 3.3 Hz), 4.19 (2 H, q, $J = 7.1$ Hz), 3.92 (2 H, ddd, $J = 14.1$, 7.1, 2.0 Hz), 3.82 (1 H, d, $J = 12.2$ Hz), 1.62 (9 H, s), 1.25 (3 H, t, $J = 7.1$ Hz), 0.93 (3 H, t, $J = 7.1$ Hz). $^{13}$C NMR δ (75 MHz, CDCl$_3$): 168.29, 167.48, 166.80, 149.29, 146.02, 139.32, 131.33, 130.90, 130.27, 128.62, 126.72, 122.75, 83.64, 65.02, 62.60, 61.60, 51.61, 45.29, 28.08, 13.73, 13.56. HRMS (ESI): calcd for C$_{23}$H$_{28}$BrNO$_7$ [M+Na$^+$] 532.0941, found 532.0941. The ee was determined by HPLC analysis using a Chiral ADH column (n-hexane/2-propanol 90: 10, 1.0 mL/min, $\lambda = 210$ nm; $t_1 = 6.9$ min, $t_2 = 15.4$ min)
** tert-butyl 2-(1-(4-bromophenyl)-3-ethoxy-2-(ethoxycarbonyl)-3-oxopropyl)-5-oxo-2H-pyrrole-1(5H)-carboxylate (6i):** The reaction time is 12 hours. The mixture was isolated by column chromatography on silica gel (3:1 P.E./EtOAc) to afford 6i (86% yield, 95: 5 dr and 93% ee). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.48 – 7.40 (2 H, m), 7.10 – 7.04 (2 H, m), 7.01 (1 H, dd, $J = 6.2$, 2.0 Hz), 6.10 (1 H, dd, $J = 6.1$, 1.5 Hz), 4.86 – 4.79 (1 H, m), 4.41 (1 H, dd, $J = 12.2$, 3.3 Hz), 4.25 – 4.15 (2 H, m), 3.91 (2 H, qd, $J = 7.1$, 3.5 Hz), 3.81 (1 H, d, $J = 12.2$ Hz), 1.61 (9 H, s), 1.25 (3 H, t, $J = 6.3$ Hz), 0.93 (3 H, t, $J = 7.1$ Hz). $^{13}$C NMR δ (75 MHz, CDCl$_3$): 168.35, 167.54, 166.87, 149.38, 146.22, 135.95, 131.87, 129.86, 128.52, 121.72, 83.60, 64.88, 62.55, 61.58, 51.81, 45.20, 28.08, 13.75, 13.57. HRMS (ESI): calcd for C$_{23}$H$_{28}$BrNO$_7$ [M+Na$^+$] 532.0941, found 532.0948. The ee was determined by HPLC analysis using a Chiral ADH column ($n$-hexane/2-propanol 90: 10, 1.0 mL/min, $\lambda = 210$ nm; $t_1 = 9.2$ min, $t_2 = 26.9$ min)
**tert-butyl 2-(3-ethoxy-2-(ethoxycarbonyl)-3-oxo-1-m-tolylpropyl)-5-oxo-2H-pyrrole-1(5H)-carboxylate (6j):** The reaction time is 18 hours. The mixture was isolated by column chromatography on silica gel (3:1 P.E./EtOAc) to afford 6j (76% yield, 95: 5 dr and 93% ee). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.21 (1 H, t, $J$ = 7.6 Hz), 7.11 – 7.01 (3 H, m), 6.98 (1 H, d, $J$ = 7.7 Hz), 6.15 (1 H, dd, $J$ = 6.2, 1.7 Hz), 4.81 (1 H, dt, $J$ = 3.7, 1.9 Hz), 4.48 (1 H, dd, $J$ = 12.2, 3.5 Hz), 4.25 – 4.15 (2 H, m), 3.98 – 3.84 (2 H, m), 3.80 (1 H, d, $J$ = 12.2 Hz), 2.33 (3 H, s), 1.65 (9 H, s), 1.27 (3H, t, $J$ = 6.4 Hz), 0.90 (3 H, t, $J$ = 7.1 Hz). $^{13}$C NMR $\delta$ (75 MHz, CDCl$_3$): 168.64, 167.83, 167.09, 149.31, 146.47, 138.45, 137.17, 129.20, 128.62, 128.48, 128.40, 125.01, 83.47, 65.68, 62.54, 61.41, 51.83, 45.54, 28.19, 21.41, 13.81, 13.55. HRMS (ESI): calcd for C$_{24}$H$_{31}$NO$_7$ [M+Na$^+$] 468.1993, found 468.2010. The ee was determined by HPLC analysis using a Chiral ADH column (n-hexane/2-propanol 90: 10, 1.0 mL/min, $\lambda$ = 210 nm; $t_1$ = 6.2 min, $t_2$ = 14.2 min)
**tert-butyl 2-(3-ethoxy-2-(ethoxycarbonyl)-3-oxo-1-p-tolylpropyl)-5-oxo-2H-pyrrole-1(5H)-carboxylate (6k):** The reaction time is 18 hours. The mixture was isolated by column chromatography on silica gel (3:1 P.E./EtOAc) to afford 6k (82% yield, 95: 5 dr and 93% ee). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.14 – 7.05 (5 H, m), 6.12 (1 H, dd, $J = 6.2, 1.6$ Hz), 4.85 – 4.78 (1 H, m), 4.46 (1 H, dd, $J = 12.2, 3.5$ Hz), 4.21 (2 H, tt, $J = 7.1, 3.6$ Hz), 3.97 – 3.83 (2 H, m), 3.81 (1 H, d, $J = 12.2$ Hz), 2.31 (3 H, s), 1.65 (9 H, s), 1.28 (3 H, t, $J = 7.2$ Hz), 0.92 (3 H, t, $J = 7.1$ Hz). $^{13}$C NMR $\delta$ (75 MHz, CDCl$_3$): 168.80, 167.87, 167.12, 149.27, 146.60, 137.45, 133.98, 129.46, 128.35, 128.07, 83.49, 65.67, 62.55, 61.44, 51.90, 45.28, 28.17, 21.02, 13.81, 13.58. HRMS (ESI): calcd for C$_{24}$H$_{31}$NO$_7$ [M+Na$^+$] 468.1993, found 468.2004. The ee was determined by HPLC analysis using a Chiral IA column (n-hexane/2-propanol 90: 10, 1.0 mL/min, $\lambda = 210$ nm; $t_1 = 7.8$ min, $t_2 = 15.4$ min)
**tert-butyl 2-(3-ethoxy-2-(ethoxycarbonyl)-1-(3-methoxyphenyl)-3-oxopropyl)-5-oxo-2H-pyrrole-1(5H)-carboxylate (6l)**: The reaction time is 18 hours. The mixture was isolated by column chromatography on silica gel (3:1 P.E./EtOAc) to afford 6l (93% yield, 95: 5 dr and 93% ee). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.23 (1 H, d, $J = 7.8$ Hz), 7.07 (1 H, dd, $J = 6.2$, 2.0 Hz), 6.82 – 6.75 (3 H, m), 6.14 (1 H, dd, $J = 6.1$, 1.6), 4.87 – 4.79 (1 H, m), 4.48 (1 H, dd, $J = 12.5$, 3.8 Hz), 4.25 – 4.15 (2 H, m), 3.99 – 3.85 (2 H, m), 3.78 (3 H, s), 1.65 (9 H, s), 1.27 (3 H, t, $J = 7.2$ Hz), 0.93 (3 H, t, $J = 7.2$ Hz). $^{13}$C NMR $\delta$ (75 MHz, CDCl$_3$): 168.71, 167.75, 167.02, 159.80, 146.44, 138.78, 129.80, 128.80, 128.42, 120.23, 114.31, 112.98, 83.51, 65.55, 62.62, 61.49, 55.18, 51.77, 45.57, 29.66, 13.79, 13.56. HRMS (ESI): calcd for C$_{24}$H$_{31}$NO$_8$ [M+Na$^+$] 484.1942, found 484.1951. The ee was determined by HPLC analysis using a Chiral IA column ($n$-hexane/2-propanol 90: 10, 1.0 mL/min, $\lambda = 210$ nm; $t_1 = 8.5$ min, $t_2 = 15.9$ min)
**Retention Time** | **Area** | **% Area** | **Height** | **% Height**
---|---|---|---|---
1 | 8.530 | 5291488 | 92.73 | 297640 | 95.57
2 | 13.766 | 37434 | 0.66 | 1622 | 0.52
3 | 15.950 | 183525 | 3.22 | 6874 | 2.21
4 | 18.473 | 194124 | 3.40 | 5301 | 1.70

**tert-butyl 2-(3-ethoxy-2-(ethoxycarbonyl)-1-(4-methoxyphenyl)-3-oxopropyl)-5-oxo-2H-pyrrole-1(5H)-carboxylate (6m):** The reaction time is 24 hours. The mixture was isolated by column chromatography on silica gel (3:1 P.E./EtOAc) to afford 6m (72% yield, 95: 5 dr and 93% ee). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.15 – 7.03 (3 H, m), 6.85 (2 H, d, $J = 8.7$ Hz), 6.12 (1 H, dd, $J = 6.1$, 1.6 Hz), 4.82 (1 H, dd, $J = 3.5$, 1.8 Hz), 4.42 (1 H, dd, $J = 12.2$, 3.4 Hz), 4.21 (2 H, qd, $J = 7.1$, 2.3 Hz), 3.97 – 3.84 (2 H, m), 3.78 (3 H, s), 1.64 (9 H, s), 1.26 (3 H, t, $J = 7.2$ Hz), 0.92 (3 H, t, $J = 7.1$ Hz). $^{13}$C NMR δ (75 MHz, CDCl$_3$): 168.81, 167.86, 167.16, 158.96, 146.77, 132.06, 130.77, 129.35, 128.32, 114.12, 81.98, 65.61, 62.52, 61.46, 55.22, 52.16, 45.01, 28.16, 13.83, 13.63. HRMS (ESI): calcd for C$_{24}$H$_{31}$NO$_8$ [M+Na$^+$] 484.1942, found 484.1954. The ee was determined by HPLC analysis using a Chiral IA column ($n$-hexane/2-propanol 90: 10, 1.0 mL/min, $\lambda = 210$ nm; $t_1 = 10.4$ min, $t_2 = 25.2$ min)
**tert-butyl 2-(1-(benzo[d][1,3]dioxol-5-yl)-3-ethoxy-2-(ethoxycarbonyl)-3-oxopropyl)-5-oxo-2H-pyrrole-1(5H)-carboxylate (6n):** The reaction time is 36 hours. The mixture was isolated by column chromatography on silica gel (3:1 P.E./EtOAc) to afford 6n (64% yield, 90:10 dr and 91% ee). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.08 (1 H, dd, $J = 6.1$, 1.8 Hz), 6.74 (1 H, d, $J = 8.0$ Hz), 6.69 – 6.58 (2 H, m), 6.13 (1 H, d, $J = 6.1$ Hz), 5.94 (2 H, s), 4.81 (1 H, s), 4.38 (1 H, dd, $J = 12.3$, 3.3 Hz), 4.20 (2 H, q, $J = 7.1$ Hz), 4.01 – 3.87 (2 H, m), 3.77 (1 H, d, $J = 12.2$ Hz), 1.63 (9 H, s), 1.25 (3 H, t, $J = 7.1$ Hz), 0.97 (3 H, t, $J = 7.1$ Hz). $^{13}$C NMR $\delta$ (75 MHz, CDCl$_3$): 168.66, 167.72, 167.04, 149.31, 147.87, 147.01, 146.64, 130.58, 128.35, 121.32, 108.72, 108.40, 101.18, 83.52, 65.48, 62.54, 61.48, 52.11, 45.35, 28.12, 13.79, 13.66. HRMS (ESI): calcd for C$_{24}$H$_{29}$NO$_9$ [M+Na$^+$] 498.1735, found 498.1734. The ee was determined by HPLC analysis using a Chiral ADH column (n-hexane/2-propanol 90: 10, 1.0 mL/min, $\lambda = 210$ nm; $t_1 = 11.0$ min, $t_2 = 28.1$ min)
** tert-butyl 2-(3-ethoxy-2-(ethoxycarbonyl)-1-(biphenyl-4-yl)-3-oxopropyl)-5-oxo-2H-pyrrole-1(5H)-carboxylate (60):** The reaction time is 18 hours.

The mixture was isolated by column chromatography on silica gel (3:1 P.E./EtOAc) to afford 60 (83% yield, 95: 5 dr and 90% ee). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.61 – 7.52 (4 H, m), 7.46 – 7.40 (2 H, m), 7.37 – 7.40 (1 H, m), 7.28 (2 H, d, J = 8.2 Hz), 7.11 (1 H, dd, J = 6.2, 1.9 Hz), 6.16 (1 H, dd, J = 6.1, 1.4 Hz), 4.87 (1 H, d, J = 1.5 Hz), 4.56 (1 H, dd, J = 12.2, 3.4 Hz), 4.28 – 4.16 (2 H, m), 4.00 – 3.88 (2 H, m), 3.88 – 3.81 (1 H, m), 1.66 (9 H, s), 1.28 (3 H, t, J = 7.2 Hz), 0.91 (3 H, t, J = 7.1 Hz). $^{13}$C NMR δ (75 MHz, CDCl$_3$): 168.64, 167.71, 167.02, 149.21, 146.40, 140.53, 140.15, 136.06, 128.75, 128.57, 128.44, 127.44, 127.37, 126.89, 83.51, 65.47, 62.56, 61.48, 51.78, 45.29, 28.11, 13.76, 13.51. HRMS (ESI): calcd for C$_{29}$H$_{33}$NO$_7$ [M+Na$^+$] 530.2149, found 530.2155. The ee was determined by HPLC analysis using a Chiral ADH column (n-hexane/2-propanol 80: 20, 1.0 mL/min, λ = 210 nm; $t_1$ = 6.6 min, $t_2$ = 12.2 min)
**tert-butyl 2-(3-ethoxy-2-(ethoxycarbonyl)-3-oxo-1-(3-phenoxyphenyl) propyl)-5-oxo-2H-pyrrole-1(5H)-carboxylate (6p):** The reaction time is 18 hours. The mixture was isolated by column chromatography on silica gel (3:1 P.E./EtOAc) to afford 6p (89% yield, 95:5 dr and 89% ee). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.38 – 7.24 (3 H, m), 7.14 – 7.08 (1 H, m), 7.04 (1 H, dd, $J = 6.2$, 2.0 Hz), 6.98 – 6.88 (4 H, m), 6.83 (1 H, d, $J = 1.8$ Hz), 6.12 (1 H, dd, $J = 6.2$, 1.7 Hz), 4.82 (1 H, dt, $J = 3.5$, 1.9 Hz), 4.44 (1 H, dd, $J = 12.2$, 3.3 Hz), 4.24 – 4.14 (2 H, m), 4.00 – 3.87 (2 H, m), 3.79 (1 H, d, $J = 12.2$ Hz), 1.57 (9 H, s), 1.24 (3 H, t, $J = 7.1$ Hz), 0.96 (3 H, t, $J = 7.1$ Hz). $^{13}$C NMR $\delta$ (75 MHz, CDCl$_3$): 168.59, 167.63, 166.88, 157.61, 156.59, 149.08, 146.28, 139.02, 130.05, 129.80, 128.44, 123.58, 122.71, 118.98, 118.40, 117.87, 83.48, 65.29, 62.57, 61.48, 51.68, 45.46, 28.03, 13.73, 13.59. HRMS (ESI): calcd for C$_{29}$H$_{33}$NO$_8$ [M+Na$^+$] 546.2098, found 546.2109. The ee was determined by HPLC analysis using a Chiral ADH column ($n$-hexane/2-propanol 80: 20, 1.0 mL/min, $\lambda = 210$ nm; $t_1 = 4.5$ min, $t_2 = 7.6$ min)
**tert-butyl 2-(3-ethoxy-2-(ethoxycarbonyl)-3-oxo-1-(thiophen-2-yl)propyl)-5-oxo-2H-pyrrole-1(5H)-carboxylate (6q):** The reaction time is 18 hours. The mixture was isolated by column chromatography on silica gel (3:1 P.E./EtOAc) to afford 6q (72% yield, 95:5 dr and 90% ee). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.23 – 7.13 (2 H, m), 6.95 – 6.91 (1 H, m), 6.86 (1 H, d, $J = 3.4$ Hz), 6.12 (1 H, dd, $J = 6.1$, 1.7 Hz), 4.92 (1 H, dt, $J = 3.6$, 1.9 Hz), 4.72 (1 H, dd, $J = 11.9$, 3.2 Hz), 4.28 – 4.11 (2 H, m), 4.00 – 3.86 (2 H, m), 3.73 (1 H, d, $J = 11.9$ Hz), 1.61 (9 H, s), 1.24 (3 H, t, $J = 7.1$ Hz), 0.96 (3 H, t, $J = 7.1$ Hz). $^{13}$C NMR δ (75 MHz, CDCl$_3$): 168.64, 167.17, 166.77, 149.15, 146.79, 138.97, 128.43, 126.83, 126.18, 124.87, 83.57, 65.05, 62.51, 61.56, 53.60, 41.03, 28.06, 13.75, 13.54. HRMS (ESI): calcd for C$_{21}$H$_{27}$NO$_7$S [M+Na$^+$] 460.1400, found 460.1404. The ee was determined by HPLC analysis using a Chiral ADH column (n-hexane/2-propanol 80: 20, 1.0 mL/min, $\lambda = 210$ nm; $t_1 = 5.2$ min, $t_2 = 11.4$ min)
*tert*-butyl 2-(3-ethoxy-2-(ethoxycarbonyl)-3-oxo-1-(thiophen-3-yl)propyl)-5-oxo-2*H*-pyrrole-1(5*H*)-carboxylate (6r): The reaction time is 18 hours. The mixture was isolated by column chromatography on silica gel (3:1 P.E./EtOAc) to afford 6r (70% yield, 93:7 dr and 91% ee). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.32 – 7.24 (1 H, m), 7.08 – 7.04 (2 H, m), 6.98 – 6.92 (1 H, m), 6.11 (1 H, dd, \(J = 6.1, 1.5\) Hz), 4.89 – 4.82 (1 H, m), 4.58 (1 H, dd, \(J = 12.0, 3.3\) Hz), 4.25 – 4.13 (2 H, m), 4.00 – 3.84 (2 H, m), 3.74 (1 H, d, \(J = 12.0\) Hz), 1.61 (9 H, s), 1.24 (3 H, t, \(J = 7.1\) Hz), 0.93 (3 H, t, \(J = 7.1\) Hz). \(^13\)C NMR \(\delta\) (75 MHz, CDCl\(_3\)): 168.61, 167.53, 167.08, 149.29, 146.94, 137.28, 128.26, 127.41, 126.24, 122.60, 83.43, 64.79, 62.43, 61.48, 52.70, 41.30, 28.07, 13.76, 13.51. HRMS (ESI): calcd for C\(_{21}\)H\(_{27}\)NO\(_7\)S [M+Na\(^+\)] 460.1400, found 460.1402. The ee was determined by HPLC analysis using a Chiral ADH column (\(n\)-hexane/2-propanol 80: 20, 1.0 mL/min, \(\lambda = 210\) nm; \(t_1 = 5.2\) min, \(t_2 = 13.2\) min)
**tert-buty** 2-(3-ethoxy-2-(ethoxycarbonyl)-1-(naphthalen-2-yl)-3-oxopropyl)-5-oxo-2H-pyrrole-1(5H)-carboxylate (6s): The reaction time is 18 hours. The mixture was isolated by column chromatography on silica gel (3:1 P.E./EtOAc) to afford 6s (82% yield, 93:7 dr and 91% ee). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.88 – 7.73 (3 H, m), 7.64 (1 H, s), 7.53 – 7.43 (2 H, m), 7.36 (1 H, dd, $J = 8.5$, 1.6 Hz), 7.10 (1 H, dd, $J = 6.2$, 2.0 Hz), 6.15 (1 H, dd, $J = 6.1$, 1.6 Hz), 4.96 – 4.88 (1 H, m), 4.69 (1 H, dd, $J = 12.2$, 3.5 Hz), 4.30 – 4.18 (2 H, m), 3.97 (1 H, d, $J = 12.2$ Hz), 3.85 (2 H, dtt, $J = 10.8$, 7.1, 3.7 Hz), 1.68 (9 H, s), 1.28 (3 H, t, $J = 7.1$ Hz), 0.83 (3 H, t, $J = 7.1$ Hz). $^{13}$C NMR δ (75 MHz, CDCl$_3$): 168.58, 167.75, 167.03, 149.28, 146.33, 134.71, 133.12, 132.61, 128.65, 128.48, 127.68, 127.62, 126.84, 126.46, 126.22, 126.20, 83.55, 65.50, 62.60, 61.46, 51.83, 45.61, 28.15, 13.78, 13.53. HRMS (ESI): calcd for C$_{27}$H$_{31}$NO$_7$ [M+Na$^+$] 504.1993, found 504.2006. The ee was determined by HPLC analysis using a Chiral ADH column (n-hexane/2-propanol 80: 20, 1.0 mL/min; $\lambda = 210$ nm; $t_1 = 6.7$ min, $t_2 = 13.7$ min)
(E)-tert-butyl 2-(1-ethoxy-2-(ethoxycarbonyl)-1-oxo-5-phenylpent-4-en-3-yl)-5-oxo-2H-pyrrole-1(5H)-carboxylate (6t): The reaction time is 12 hours. The mixture was isolated by column chromatography on silica gel (3:1 P.E./EtOAc) to afford 6t (75% yield, 81:19 dr and 78% ee). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.34 – 7.30 (4 H, m), 7.27 – 7.18 (2 H, m), 6.60 (1 H, d, $J = 15.7$ Hz), 6.23 – 6.08 (2 H, m), 4.89 – 4.81 (1 H, m), 4.24 – 4.13 (2 H, m), 4.05 (2 H, dt, $J = 7.1$, 3.8 Hz), 3.95 (1 H, td, $J = 9.5$, 3.7 Hz), 3.46 (1 H, d, $J = 9.2$ Hz), 1.61 (9 H, s), 1.23 (3 H, t, $J = 7.1$ Hz), 1.13 (3 H, t, $J = 7.1$ Hz). $^{13}$C NMR $\delta$ (75 MHz, CDCl$_3$): 168.78, 167.74, 167.68, 149.36, 147.59, 136.00, 135.45, 128.57, 123.39, 123.39, 83.55, 64.94, 62.06, 61.51, 51.69, 44.11, 28.02, 13.96, 13.88. HRMS (ESI): calcd for C$_{25}$H$_{31}$NO$_7$ [M+Na$^+$] 480.1993, found 480.1997. The ee was determined by HPLC analysis using a Chiral ADH column (n-hexane/2-propanol 80: 20, 1.0 mL/min, $\lambda = 210$ nm; $t_1 = 5.7$ min, $t_2 = 12.1$ min).
tert-buty1 2-(1-cyclohexyl-3-ethoxy-2-(ethoxycarbonyl)-3-oxopropyl)-5-oxo-2H-pyrrole-1(5H)-carboxylate (6u): The reaction time is 18 hours. The mixture was isolated by column chromatography on silica gel (3:1 P.E./EtOAc) to afford 6u (70% yield, 95: 5 dr and 90% ee). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.15 (1 H, d, $J = 6.2$ Hz), 6.06 (1 H, d, $J = 6.1$ Hz), 4.96 (1 H, s), 4.11 (4 H, dt, $J = 12.2, 6.1$ Hz), 3.21 (1 H, d, $J = 5.1$ Hz), 3.17-3.12 (1 H, m), 1.99 – 1.62 (7 H, m), 1.56 (9 H, s), 1.29 – 1.14 (10 H, m). $^{13}$C NMR $\delta$ (75 MHz, CDCl$_3$): 169.15, 169.09, 168.47, 147.88, 127.65, 83.44, 62.40, 61.90, 61.16, 48.90, 44.68, 37.72, 31.89, 31.15, 28.06, 26.42, 26.21, 13.90, 13.84. HRMS (ESI): calcd for C$_{23}$H$_{35}$NO$_7$ [M+Na$^+$] 460.2306, found 460.2314. The ee was determined by HPLC analysis using a Chiral ADH column (n-hexane/2-propanol 95: 5, 1.0 mL/min, $\lambda = 210$ nm; $t_1 = 12.7$ min, $t_2 = 14.3$ min)
4. Transformation of the products 6 to 5-substituted pyrrolidin-2-one 8

\[
\text{diethyl } 2-((5\text{-oxo-2,5-dihydro-1H-pyrrol-2-yl})(\text{phenyl)methyl})\text{malonate (7a):}
\]

To a solution of \textit{syn}-6a (363 mg, 0.84 mmol, 1.0 equiv) in CH\(_2\)Cl\(_2\) (10.0 mL), TFA (2 mL) was added at room temperature, then stirred for 20 mins. After checking the complete consumption of the starting material by TLC, a solution of 2 \textit{N} NaOH was added to reaction solution until pH = 10 and extracted with CH\(_2\)Cl\(_2\) (30 x 3 mL). The combined organic phase was washed with brine, and dried over anhydrous Na\(_2\)SO\(_4\). After evaporation of solvent, the residue was isolated by column chromatography on silica gel (1:2 P.E./EtOAc) to afford 7a (99% yield and 92% ee). The desired product was recrystallized in petroleum/CH\(_2\)Cl\(_2\) to get the optical pure product as single isomer (73% yield, 99% ee). \([\alpha]_{D}^{15} = +126.7 \text{ (c = 0.18, in CH}_2\text{Cl}_2).\) m.p. 118 – 120 °C. 

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.32-7.15 (5 H, m), 6.94 (1 H, \text{d, } J 5.0), 6.91 – 6.74 (1 H, m), 5.93 (1 H, d, \text{J 5.2}), 4.60 (1 H, s), 4.28 (2 H, q, \text{ J 6.7}), 4.00-3.80 (4 H, m), 1.31 (3 H, t, \text{J 7.0}), 0.96 (3 H, t, \text{J 6.6}).

\(^{13}\)C NMR \(\delta\) (100 MHz, CDCl\(_3\)): 174.01, 168.43, 167.09, 148.09, 135.95, 128.46, 128.45, 128.09, 127.89, 62.36, 61.67, 61.14, 54.56, 47.42, 14.05, 13.66. HRMS (ESI): calcd for C\(_{18}\)H\(_{21}\)NO\(_5\) [M+H\(^+\)] 332.1492, found 332.1504. The ee was determined by HPLC analysis using a Chiral IA column (\textit{n}-hexane/2-propanol 70: 30, 1.0 mL/min, \(\lambda = 210 \text{ nm; } t_1 = 5.8 \text{ min, } t_2 = 13.9 \text{ min).}
Data obtained after recrystallization

diethyl 2-((4-bromophenyl)(5-oxo-2,5-dihydro-1H-pyrrol-2-yl)methyl) malonate (7i): Prepared according to the procedure for 7a, from 6i (423 mg, 0.83 mmol) and TFA for 20 mins to provide the crude product. The mixture was isolated by column chromatography on silica gel (1:2 P.E./EtOAc) to afford 7i (99% yield and 93% ee). [α]D<sup>15</sup> = +140.5 (c = 0.22, in CH<sub>2</sub>Cl<sub>2</sub>). m.p. 144 – 146 °C. ¹H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.42-7.25 (3 H, m), 7.07 (2 H, d, J 7.8), 6.92 (1 H, d, J 3.8), 5.92 (1 H, d, J 4.3), 4.60 (1 H, s), 4.28 (2 H, q, J 6.8), 4.05 – 3.88 (3 H, m), 3.86-3.75 (1 H, m), 1.30 (3 H, t, J 6.9), 1.01 (3 H, t, J 6.8). ¹³C NMR δ (100 MHz, CDCl<sub>3</sub>): 174.34, 168.16, 166.96, 148.12, 134.67, 131.47, 130.21, 128.27, 121.90, 62.44, 61.80, 60.63, 54.46, 46.74, 14.04, 13.74. HRMS (ESI): calcd for C<sub>18</sub>H<sub>20</sub>BrNO<sub>5</sub> [M+H<sup>+</sup>] 410.0598, found 410.0631. The ee was determined by HPLC analysis using a Chiral ADH column (n-hexane/2-propanol 70: 30, 1.0 mL/min, λ = 210 nm; t<sub>1</sub> = 5.7 min, t<sub>2</sub> = 14.4 min).
diethyl 2-((5-oxopyrrolidin-2-yl)(phenyl)methyl)malonate (8a): A suspension of 7a (718mg, 2.17 mmol) and Pd/C (140 mg, 20 wt%) in 20 mL EtOAc is placed under hydrogen atmosphere at room temperature and stirred overnight. The solution is filtered and the solvent is removed under reduced pressure to give the mixture, which was isolated by column chromatography on silica gel (1:2 P.E./EtOAc) to afford 8a (99% yield and 98% ee). \([\alpha]_{D}^{22} = +18.7 \text{ (} c = 0.60, \text{ in } \text{CH}_2\text{Cl}_2\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.38-7.18 (5 H, m), 6.81 (1 H, s), 4.26 (2 H, q, \(J = 6.8\)), 4.06 (1 H, d, \(J = 5.7\)), 3.99 – 3.83 (3 H, m), 3.51 (1 H, dd, \(J = 10.9, 3.0\)), 2.29 – 2.13 (1 H, m), 2.04 – 1.92 (1 H, m), 1.83 (1 H, t, \(J = 11.0\)), 1.48 (1 H, dt, \(J = 17.7, 8.8\)), 1.29 (3 H, t, \(J = 6.9\)), 0.94 (3 H, t, \(J = 6.6\)). \(^{13}\)C NMR \(\delta\) (100 MHz, CDCl\(_3\)): 178.79, 168.39, 167.26, 136.22, 129.49, 128.48, 127.73, 62.02, 61.42, 55.62, 54.63, 50.02, 29.49, 25.04, 14.03, 13.63. HRMS (ESI): calcd for C\(_{18}\)H\(_{23}\)NO\(_5\) [M+H\(^{+}\)] 334.1649, found 334.1649. The ee was determined by HPLC analysis using a Chiral ADH column (\(n\)-hexane/2-propanol 70: 30, 1.0 mL/min, \(\lambda = 210 \text{ nm; } t_1 = 5.7 \text{ min, } t_2 = 8.9 \text{ min).
5. References


6. Copy of 1H NMR and 13C NMR spectra
7. X-ray Structure of 7i

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$\rho_{\text{calc}}\, \text{mg/mm}^3$ 1.241

$m/\text{mm}^{-1}$ 1.900

$F(000)$ 836.0

Crystal size/mm$^3$ $0.42 \times 0.32 \times 0.28$

$2\Theta$ range for data collection 5.94 to 50.04°

Index ranges $-9 \leq h \leq 9$, $-11 \leq k \leq 14$, $-25 \leq l \leq 15$

Reflections collected 8232

Independent reflections 3798 ($R(\text{int}) = 0.0542$)

Data/restraints/parameters 3798/5/241

Goodness-of-fit on $F^2$ 0.992

Final $R$ indexes [$I \geq 2\sigma(I)$] $R_1 = 0.0958$, $wR_2 = 0.2459$

Final $R$ indexes [all data] $R_1 = 0.1340$, $wR_2 = 0.2810$

Largest diff. peak/hole / e Å$^{-3}$ 0.56 / -0.43

Flack parameter 0.10(3)