Highly Efficient Enantioselective Three-Component Synthesis of 2-Amino-4\(H\)-Chromenes Catalysed by Chiral Tertiary Amine-Thioureas

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General information. All the enantioselective three-component reactions of salicylaldehyde, malononitrile/cyanoacetate with nitromethane were carried out with flame-dried Schlenk-type glassware. The chiral tertiary amino-thiourea catalysts derived from (1R, 2R)-cyclohexane-1,2-diamine were synthesized according to reference.\textsuperscript{[1]} The catalyst derived from cinchona alkaloids was synthesized according to reference.\textsuperscript{[2]} All the other reagents were purchased from commercial suppliers and purified by standard techniques. Flash column chromatography was performed using silica gel (200–400 mesh). For thin-layer chromatography (TLC), silica gel plates (HSGF 254) were used and compounds were visualized by irradiation with UV light. \textsuperscript{1}H NMR (300 MHz) and \textsuperscript{13}C NMR (75 MHz) spectra were recorded at 300 MHz NMR spectrometer in CDCl\textsubscript{3} or DMSO-d\textsubscript{6}. All chemical shifts (\(\delta\)) are given in ppm relative to TMS (\(\delta = 0\) ppm) as internal standard. Data are reported as follows: chemical shift, multiplicity, coupling constants and integration. Melting points were uncorrected. IR spectra were reported in frequency of absorption (cm\textsuperscript{-1}). High resolution mass spectral (HRMS) data were obtained with an ionization mode of ESI.

References


X-ray crystallographic analysis

The single crystals of the products \textbf{4b}, \textbf{5b} and the intermediate \textbf{1a} suitable for X-ray crystallographic analysis were obtained by recrystallization from dichloromethane/isopropanol, dichloromethane/n-hexane, and dichloromethane respectively. The single crystal X-ray diffraction data for the three compounds were collected on a diffractometer with graphite
monochromated Mo Kα radiation ($\lambda = 0.71073$ Å) at room temperature. Saint program and SADABS program carried out the data integration. The structure was solved by a direct method and refined on $F^2$ using SHELXTL suite of program. All non-hydrogen atoms were anisotropically refined by full-matrix least squares methods. All hydrogen atoms were geometrically generated and isotropically refined using a riding model. The details of the X-ray data collection, structure solution and structure refinements are given in Table S1.

**Table S1** Crystallographic data and structural refinement details for compound 4b, 5b and 1a.

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<th>Compound</th>
<th>4b</th>
<th>5b</th>
<th>1a</th>
</tr>
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<tr>
<td>Formula</td>
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<td>293(2)</td>
<td>293(2)</td>
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<td>P2₁/c</td>
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<td>5.413(2)</td>
<td>11.833(4)</td>
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<td>b/Å</td>
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<td>17.675(7)</td>
<td>9.268(3)</td>
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<td>c/Å</td>
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<td>7.539(3)</td>
<td>7.280(2)</td>
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<td>$\beta$°</td>
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<td>V/Å³</td>
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<td>717.2(5)</td>
<td>794.2(4)</td>
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<td>4</td>
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<td>$\mu$(Mo Ka), mm⁻¹</td>
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<td>2.3 to 27.5</td>
<td>1.7 to 27.6</td>
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<tr>
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<td>6600</td>
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<tr>
<td>Unique reflections/R(int)</td>
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<td>2951 / R(int) = 0.056</td>
<td>1835 / R(int) = 0.021</td>
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<td>Goodness-of-fit on F²</td>
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<td>0.98</td>
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<tr>
<td>R, $R_w$ [I &gt; 2σ(I)]</td>
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<td>0.0530, 0.1773</td>
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<td>CCDC No.</td>
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<td>860044</td>
<td>860046</td>
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**Figure S1**  X-ray structure (50% probability ellipsoids) of 4b, 5b and 1a.
**Scheme S1** Control experiments for mechanistic study.

\[
\text{1a} \quad \text{CHO} \quad + \quad \text{CH}_3\text{NO}_2 \quad 3 \quad \text{(1.5 eq.)} \quad \xrightarrow{(+)-C1 (10 mol\%)} \quad \text{No reaction}
\]

\[
\text{1a} \quad \text{CHO} \quad + \quad \text{CN} \quad \xrightarrow{ (+)-C1 (10 mol\%)} \quad \text{6a} \quad \text{NH}_2 \quad + \quad \text{la} \quad \text{NH}
\]

**General procedure for the enantioselective three-component reaction:** To a solution of salicylaldehyde 1 (0.3 mmol, 1.0 equiv), malononitrile/ethyl cyanoacetate 2 (0.36 mmol, 1.2 equiv), nitromethane 3 (0.45 mmol, 1.5 equiv) and 50 mg of 4Å MS in CH$_2$Cl$_2$ (1.5 mL) at room temperature, was added catalyst C3 (0.03 mmol) in one portion. The resulting reaction mixture was stirred at room temperature and monitored by TLC. Upon completion, the solvent was removed under vacuum and the residue was purified by flash chromatography to afford the desired product.
(R)-2-Amino-4-(nitromethyl)-4H-chromene-3-carbonitrile (4a): Purified by column chromatography (petroleum ether/ethyl acetate = 3/1) to afford a yellow solid in 88% yield and 84% ee. The ee was determined by HPLC analysis using a Chiralcel OJ-H column (3/2 hexane/i-PrOH; flow rate 1.0 mL/min; λ = 254 nm; t_major = 25.8 min, t_minor = 19.9 min). [α]_D^{20} = −66.3 (c = 0.51, EtOAc). Mp: 139–140 °C. IR (KBr): ν = 3451, 3337, 2191, 1655, 1612, 1584, 1491, 1460, 1379, 1275, 1227 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 7.35–7.28 (m, 1H), 7.21–7.13 (m, 2H), 7.04 (d, J = 8.2 Hz, 1H), 4.85 (s, 2H), 4.62 (dd, J = 12.1, 4.7 Hz, 1H), 4.50 (dd, J = 12.1, 7.1 Hz, 1H), 4.37 (dd, J = 7.1, 4.7 Hz, 1H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 161.7, 149.3, 129.6, 127.9, 125.7, 118.6, 116.9, 80.2, 54.2, 34.8 ppm. HRMS (ESI): calcd for C₁₁H₁₀N₃O₃ [M+H]^+ 232.0722; found 232.0711.

(R)-2-Amino-6-bromo-4-(nitromethyl)-4H-chromene-3-carbonitrile (4b): Purified by column chromatography (petroleum ether/ethyl acetate = 3/1) to afford a white solid in 92% yield and 87% ee. The ee was determined by HPLC analysis using a Chiralcel OJ-H column (3/2 hexane/i-PrOH; flow rate 1.0 mL/min; λ = 254 nm; t_R = 34.9 (major), 21.7 (minor) min). [α]_D^{20} = −15.7 (c = 0.61, EtOAc). Mp: 177–178 °C. IR (KBr): ν = 3456, 3308, 2205, 1653, 1637, 1601, 1574, 1530, 1481, 1423, 1375, 1271, 1225 cm⁻¹. ¹H NMR (300 MHz, DMSO-d₆): δ = 7.63 (s, 1H ), 7.49 (d, J = 8.7 Hz, 1H), 7.23 (s, 2H), 6.99 (d, J = 8.7 Hz, 1H), 4.87 (dd, J = 12.8, 4.8 Hz, 1H), 4.69 (dd, J = 12.8, 4.8 Hz, 1H), 4.33 (t, J = 4.8 Hz, 1H) ppm. ¹³C NMR (75 MHz, DMSO-d₆): δ = 162.3, 149.2, 132.2, 131.3, 122.4, 119.9, 118.9, 118.8, 80.8, 50.2, 34.7 ppm. HRMS (ESI): calcd for C₁₁H₉BrN₃O₃ [M+H]^+ 309.9827; found 309.9816.

(R)-2-Amino-6-chloro-4-(nitromethyl)-4H-chromene-3-carbonitrile (4c): Purified by column chromatography (petroleum ether/ethyl acetate = 3/1) to afford a white solid in 85% yield and 82% ee. The ee was determined by HPLC analysis using a Chiralcel OJ-H column (3/2 hexane/i-PrOH; flow rate 1.0 mL/min; λ = 254 nm; t_R = 33.5 (major), 18.1 (minor) min). [α]_D^{20} = −24.7 (c = 0.59, EtOAc). Mp: 165–166 °C. IR
(KBr): $\nu = 3460, 3308, 2205, 1655, 1530, 1483, 1427, 1377, 1271, 1227 \text{ cm}^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta = 7.51$ (d, $J = 2.5$ Hz, 1H), 7.37 (dd, $J = 8.7, 2.5$ Hz, 1H), 7.21 (s, 2H), 7.06 (d, $J = 8.7$ Hz, 1H), 4.87 (dd, $J = 12.6, 5.0$ Hz, 1H), 4.70 (dd, $J = 12.6, 4.8$ Hz, 1H), 4.33 (t, $J = 4.8$ Hz, 1H) ppm. $^{13}C$ NMR (75 MHz, DMSO-$d_6$): $\delta = 162.3, 148.8, 129.4, 128.7, 128.4, 122.0, 119.9, 118.5, 80.8, 50.2, 34.8$ ppm.

HRMS (ESI): calcd for C$_{11}$H$_9$ClN$_3$O$_3$ [M+H]$^+$ 266.0332; found 266.0320.

(R)-2-Amino-6-nitro-4-(nitromethyl)-4$H$-chromene-3-carbonitrile (4d): Purified by column chromatography (petroleum ether/ethyl acetate = 2/1) to afford a yellow solid in 80% yield and 81% ee. The ee was determined by HPLC analysis using a Chiralcel OJ-H column (1/3 hexane/i-PrOH; flow rate 1.0 mL/min; $\lambda = 254$ nm; $t_R$ = 30.0 (major), 19.3 (minor) min). $[\alpha]_D^{20} = +26.5$ ($c = 0.46$, EtOAc). Mp: 171–172°C.

IR (KBr): $\nu = 3449, 3362, 2191, 1651, 1582, 1416, 1348, 1306, 1264 \text{ cm}^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta = 8.41$ (d, $J = 2.7$ Hz, 1H), 8.19 (dd, $J = 9.0, 2.7$ Hz, 1H), 7.38 (s, 2H), 4.90 (dd, $J = 12.8, 4.7$ Hz, 1H), 4.72 (dd, $J = 12.8, 4.7$ Hz, 1H), 4.38 (t, $J = 4.7$ Hz, 1H) ppm. $^{13}C$ NMR (75 MHz, DMSO-$d_6$): $\delta = 161.8, 154.4, 144.2, 125.2, 125.1, 121.6, 119.5, 118.0, 80.7, 50.3, 34.5$ ppm. HRMS (ESI): calcd for C$_{11}$H$_8$N$_4$O$_5$Na [M+Na]$^+$ 299.0392; found 299.0387.

(R)-2-Amino-6,8-dibromo-4-(nitromethyl)-4$H$-chromene-3-carbonitrile (4e): Purified by column chromatography (petroleum ether/ethyl acetate = 3/1) to afford a white solid in 78% yield and 96% ee. The ee was determined by HPLC analysis using a Chiralcel OJ-H column (1/1 hexane/i-PrOH; flow rate 1.0 mL/min; $\lambda = 254$ nm; $t_R$ = 28.9 (major), 20.0 (minor) min). $[\alpha]_D^{20} = 33.8$ ($c = 0.55$, EtOAc). Mp: 211–212°C. IR (KBr): $\nu = 3431, 3316, 2207, 1659, 1614, 1541, 1458, 1418, 1377, 1246, 1196 \text{ cm}^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta = 7.88$ (s, 1H), 7.66 (s, 1H), 7.38 (s, 2H), 4.90 (dd, $J = 12.8, 4.7$ Hz, 1H), 4.72 (dd, $J = 12.8, 4.7$ Hz, 1H), 4.38 (t, $J = 4.7$ Hz, 1H) ppm. $^{13}C$ NMR (75 MHz, DMSO-$d_6$): $\delta = 161.4, 145.9, 134.3, 130.4, 123.5, 118.9, 116.2, 110.5, 80.1, 50.1, 34.6$ ppm. HRMS (ESI): calcd for C$_{11}$H$_7$Br$_2$N$_3$O$_3$Na [M+Na]$^+$ 409.8752; found

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(R)-2-Amino-6,8-dichloro-4-(nitromethyl)-4H-chromene-3-carbonitrile (4f): Purified by column chromatography (petroleum ether/ethyl acetate = 3/1) to afford a yellow solid in 75% yield and 80% ee. The ee was determined by HPLC analysis using a Chiralcel OJ-H column (1/1 hexane/i-PrOH; flow rate 1.0 mL/min; λ = 254 nm; t_R = 30.6 (major), 17.0 (minor) min). Mp: 208–209°C. IR (KBr): ν = 3428, 3318, 2210, 1661, 1616, 1572, 1464, 1423, 1381, 1248, 1200 cm⁻¹. ¹H NMR (300 MHz, DMSO-d₆): δ = 7.67 (d, J = 2.4 Hz, 1H), 7.52 (d, J = 2.4 Hz, 1H), 7.39 (s, 2H), 4.91 (dd, J = 12.9, 4.8 Hz, 1H), 4.72 (dd, J = 12.9, 4.8 Hz, 1H), 4.38 (t, J = 4.8 Hz, 1H) ppm. ¹³C NMR (75 MHz, DMSO-d₆): δ = 161.3, 144.5, 128.9, 128.2, 127.0, 123.2, 121.2, 119.0, 80.1, 49.9, 34.5 ppm. HRMS (ESI): calcd for C₁₁H₈Cl₂N₃O₃ [M+H]+ 299.9942; found 299.9936.

(R)-2-Amino-5-methoxy-4-(nitromethyl)-4H-chromene-3-carbonitrile (4g): Purified by column chromatography (petroleum ether/ethyl acetate = 3/1) to afford a yellow solid in 64% yield and 83% ee. The ee was determined by HPLC analysis using a Chiralcel OJ-H column (1/1 hexane/i-PrOH; flow rate 1.0 mL/min; λ = 254 nm; t_R = 20.7 (major), 16.1 (minor) min). [α]_D²⁰ = −29.2 (c = 0.52, EtOAc). Mp: 139–140°C. IR (KBr): ν = 3445, 3331, 2191, 1651, 1635, 1618, 1599, 1487, 1472, 1423, 1253, 1090 cm⁻¹. ¹H NMR (300 MHz, DMSO-d₆): δ = 7.30 (t, J = 8.3 Hz, 1H), 7.16 (s, 2H), 6.85 (d, J = 8.3 Hz, 1H), 6.64 (d, J = 8.3 Hz, 1H), 4.67–4.56 (m, 2H), 4.24 (t, J = 4.7 Hz, 1H), 3.83 (s, 3H) ppm. ¹³C NMR (75 MHz, DMSO-d₆): δ = 162.5, 156.7, 150.7, 130.0, 120.2, 108.9, 108.2, 107.3, 79.6, 56.6, 50.7, 31.7 ppm. HRMS (ESI): calcd for C₁₂H₁₀N₃O₄ [M+H]+ 262.0828; found 262.0820.

2-Amino-4-(1-nitroethyl)-4H-chromene-3-carbonitrile (4h): Purified by column chromatography (petroleum ether/ethyl acetate = 3/1) to afford a white solid in 88% yield, 43/57 dr and 58% ee₁, 75% ee₂. The ee was determined by HPLC analysis using a Chiralcel OJ-H column (9/1 hexane/i-PrOH; flow rate 1.0 mL/min; λ = 254 nm; t_R = 20.1 (major), 13.9 (minor) min). [α]_D²⁰ = −27.5 (c = 0.52, EtOAc). Mp: 223°C. IR (KBr): ν = 3428, 3322, 2210, 1660, 1616, 1572, 1464, 1423, 1318, 1248, 1200 cm⁻¹. ¹H NMR (300 MHz, DMSO-d₆): δ = 7.64 (d, J = 2.4 Hz, 1H), 7.51 (d, J = 2.4 Hz, 1H), 7.38 (s, 2H), 4.91 (dd, J = 12.9, 4.8 Hz, 1H), 4.73 (dd, J = 12.9, 4.8 Hz, 1H), 4.38 (t, J = 4.8 Hz, 1H) ppm. ¹³C NMR (75 MHz, DMSO-d₆): δ = 161.3, 144.5, 128.9, 128.2, 127.0, 123.2, 121.2, 119.0, 80.1, 49.9, 34.5 ppm. HRMS (ESI): calcd for C₁₃H₁₁N₃O₄ [M+Na]+ 285.0643; found 285.0642.
mL/min; λ = 254 nm; tR = 65.4 (major), 74.8 (minor), 100.0 (major), 84.2 (minor) min). \([\alpha]_D^{20} = -35.9 \ (c = 1.03, \text{EtOAc})\). Mp: 138–139°C. IR (KBr): v = 3319, 3269, 2197, 1638, 1605, 1578, 1541, 1487, 1456, 1420, 1389, 1362 cm\(^{-1}\). \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta = 7.39–7.13 \ (m, 5H), 7.10–7.01 \ (m, 1H), 4.87–4.71 \ (m, 1H), 4.29–4.18 \ (m, 1H), 1.38–1.26 \ (m, 3H) \ ppm. \(^13\)C NMR (75.5 MHz, DMSO-\(d_6\)): \(\delta = 163.2, 163.0, 149.9, 149.8, 129.1, 128.5, 128.3, 124.8, 120.2, 119.81, 119.79, 119.4, 116.1, 115.9, 87.3, 86.9, 49.2, 48.4, 14.1, 13.5 \ ppm. HRMS (ESI): calcd for C\(_{12}\)H\(_{12}\)N\(_3\)O\(_3\) [M + H]\(^+\) 246.0878; found 246.0870.

\((S)\)-Ethyl 2-amino-4-(nitromethyl)-4\(H\)-chromene-3-carboxylate (5a): Purified by column chromatography (petroleum ether/ethyl acetate = 10/1) to afford a white solid in 76% yield and 87% ee. The ee was determined by HPLC analysis using a Chiralcel OJ-H column (3/2 hexane/\(i\)-PrOH; flow rate 1.0 mL/min; λ = 254 nm; tR = 20.7 (major), 13.8 (minor) min). \([\alpha]_D^{20} = 87.7 \ (c = 0.9, \text{EtOAc})\). Mp: 109–110°C. IR (KBr): v = 3451, 3316, 1672, 1630, 1537, 1512, 1485, 1456, 1410, 1300 cm\(^{-1}\). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 7.31–7.24 \ (m, 1H), 7.21–7.09 \ (m, 2H), 7.05–6.99 \ (m, 1H), 6.82–5.88 \ (br s, 2H), 4.65 \ (dd, \(J = 8.0, 4.4 \ Hz, 1H), 4.54 \ (dd, J = 11.2, 4.4 \ Hz, 1H), 4.39 \ (dd, J = 11.2, 8.0 \ Hz, 1H), 4.30–4.19 \ (m, 2H), 1.34 \ (t, J = 7.1 \ Hz, 3H) \ ppm. \(^13\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 168.3, 162.0, 149.8, 128.9, 128.2, 125.0, 121.8, 116.3, 81.2, 73.0, 59.9, 34.3, 14.5 \ ppm. HRMS (ESI): calcd for C\(_{13}\)H\(_{15}\)N\(_2\)O\(_5\) [M+H]\(^+\) 279.0981; found 279.0969.

\((S)\)-Ethyl 2-amino-6-bromo-4-(nitromethyl)-4\(H\)-chromene-3-carboxylate (5b): Purified by column chromatography (petroleum ether/ethyl acetate = 10/1) to afford a white solid in 83% yield and 91% ee. The ee was determined by HPLC analysis using a Chiralcel OJ-H column/OJ-H column (8/1 hexane/\(i\)-PrOH; flow rate 1.0 mL/min; λ = 254 nm; tR = 111.2 (major), 127.1 (minor) min). \([\alpha]_D^{20} = 35.9 \ (c = 1.38, \text{EtOAc})\). Mp: 128–129°C. IR (KBr): v = 3462, 3306, 1676, 1616, 1541, 1477, 1410, 1379, 1315, 1290, 1221 cm\(^{-1}\). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 7.38 \ (dd, J = 8.7, 2.4 \ Hz, 1H), 7.34 \ (d, J = 2.4 \ Hz, 1H), 6.91 \ (d, J = 8.7 \ Hz, 1H), 6.80–5.88 \ (br s, 2H), 4.59 \ (dd, J = 7.5, 4.2 \ Hz, 1H), 4.50 \ (dd, J = 11.7, 4.2 \ Hz, 1H), 4.43 \ (dd, J = 11.7, 7.5 \ Hz,
(S)-Ethyl 2-amino-6-chloro-4-(nitromethyl)-4H-chromene-3-carboxylate (5c): Purified by column chromatography (petroleum ether/ethyl acetate = 10/1) to afford a white solid in 76% yield and 84% ee. The ee was determined by HPLC analysis using a Chiralcel AS-H column (11/1 hexane/i-PrOH; flow rate 1.0 mL/min; λ = 254 nm; tR = 23.7 (major), 27.1 (minor) min). [α]D20 = 29.1 (c = 1.05, EtOAc). Mp: 141–142°C. IR (KBr): ν = 3474, 3312, 2982, 1678, 1620, 1541, 1483, 1418, 1377, 1317, 1292, 1221 cm–1. 1H NMR (300 MHz, CDCl3): δ = 7.24 (dd, J = 8.7, 2.4 Hz, 1H), 7.19 (d, J = 2.4 Hz, 1H), 6.96 (d, J = 8.7 Hz, 1H), 6.82–5.95 (br s, 2H), 4.59 (dd, J = 7.5, 4.2 Hz, 1H), 4.52 (dd, J = 11.6, 4.2 Hz, 1H), 4.43 (dd, J = 11.6, 7.5 Hz, 1H), 4.30–4.18 (m, 2H), 1.34 (t, J = 7.2 Hz, 3H) ppm. 13C NMR (75 MHz, CDCl3): δ = 167.9, 161.5, 148.3, 129.8, 128.8, 127.8, 123.3, 117.5, 80.6, 72.3, 59.9, 33.9, 14.3 ppm. HRMS (ESI): calcd for C13H14BrN2O5 [M+H]+ 313.0591; Found 313.0578.

(S)-Ethyl 2-amino-6,8-dibromo-4-(nitromethyl)-4H-chromene-3-carboxylate (5d): Purified by column chromatography (petroleum ether/ethyl acetate = 10/1) to afford a white solid in 78% yield and 89% ee. The ee was determined by HPLC analysis using a Chiralpak AS-H column (16/1 hexane/i-PrOH; flow rate 1.0 mL/min; λ = 254 nm; tR = 69.6 (major), 80.2 (minor) min). [α]D20 = 14.3 (c = 0.88, EtOAc). Mp: 187–188°C. IR (KBr): ν = 3458, 3318, 1678, 1614, 1572, 1541, 1520, 1454, 1400, 1385, 1344, 1315, 1279, 1248 cm–1. 1H NMR (300 MHz, CDCl3): δ = 7.65 (d, J = 2.1 Hz, 1H), 7.29 (d, J = 2.1 Hz, 1H), 6.97–5.79 (br s, 2H), 4.62 (dd, J = 7.8, 4.2 Hz, 1H), 4.51 (dd, J = 11.8, 4.3 Hz, 1H), 4.41 (dd, J = 11.8, 7.9 Hz, 1H), 4.25 (q, J = 7.2 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H) ppm. 13C NMR (75 MHz, CDCl3): δ = 167.7, 161.3, 146.2, 135.0, 130.1, 125.2, 117.4, 111.2, 80.5, 72.7, 60.2, 34.4, 14.4 ppm. HRMS (ESI): calcd for C13H13Br2N2O5 [M+H]+ 357.0074; Found 357.0086.
434.9191; found 434.9182.

(S)-Ethyl 2-amino-6,8-dichloro-4-(nitromethyl)-4H-chromene-3-carboxylate (5e): Purified by column chromatography (petroleum ether/ethyl acetate = 10/1) to afford a white solid in 81% yield and 77% ee. The ee was determined by HPLC analysis using a Chiralpak AS-H column/AS-H column (30/1 hexane/i-PrOH; flow rate 1.0 mL/min; λ = 254 nm; tR = 115.5 (major), 132.3 (minor) min). [α]D20 = 30.7 (c = 1.08, EtOAc). Mp: 148–149°C. IR (KBr): v = 3468, 3316, 1678, 1616, 1582, 1541, 1460, 1387, 1317, 1279, 1252 cm⁻¹. 1H NMR (300 MHz, CDCl3): δ = 7.35 (d, J = 2.4 Hz, 1H), 7.10 (d, J = 2.4 Hz, 1H), 6.96–5.72 (br s, 2H), 4.62 (dd, J = 7.8, 4.2 Hz, 1H), 4.52 (dd, J = 11.8, 4.2 Hz, 1H), 4.41 (dd, J = 11.8, 7.9 Hz, 1H), 4.31–4.20 (m, 2H), 1.34 (t, J = 7.2 Hz, 3H) ppm. 13C NMR (75 MHz, CDCl3): δ = 167.7, 161.3, 144.7, 129.4, 126.5, 124.9, 122.5, 80.5, 72.5, 60.2, 34.4, 14.4 ppm. HRMS (ESI): calcd for C13H13Cl2N2O5 [M+H]⁺ 347.0201; found 347.0190.

(S)-Ethyl 2-amino-6-methoxy-4-(nitromethyl)-4H-chromene-3-carboxylate (5f): Purified by column chromatography (petroleum ether/ethyl acetate = 10/1) to afford a white solid in 86% yield and 77% ee. The ee was determined by HPLC analysis using a Chiralcel OJ-H column/OJ-H column (2/1 hexane/i-PrOH; flow rate 1.0 mL/min; λ = 254 nm; tR = 45.4 (major), 55.7 (minor) min). [α]D20 = 63.9 (c = 0.97, EtOAc). Mp: 109–110°C. IR (KBr): v = 3422, 3292, 2982, 1674, 1620, 1597, 1547, 1491, 1414, 1379, 1344, 1292, 1271, 1221 cm⁻¹. 1H NMR (300 MHz, CDCl3): δ = 6.94 (d, J = 9.0 Hz, 1H), 6.80 (dd, J = 9.0, 3.0 Hz, 1H), 6.68 (d, J = 3.0 Hz, 1H), 6.62–5.99 (br s, 2H), 4.62 (dd, J = 8.0, 4.4 Hz, 1H), 4.53 (dd, J = 11.4, 4.4 Hz, 1H), 4.39 (dd, J = 11.3, 8.0 Hz, 1H), 4.29–4.18 (m, 2H), 3.76 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H) ppm. 13C NMR (75 MHz, CDCl3): δ = 168.2, 162.1, 156.3, 143.6, 122.3, 116.9, 114.7, 112.0, 80.9, 72.3, 59.7, 55.5, 34.5, 14.3 ppm. HRMS (ESI): calcd for C14H17N2O6 [M+H]⁺ 309.1086; found 309.1080.

(S)-Ethyl 2-amino-5,7-dichloro-4-(nitromethyl)-4H-chromene-3-carboxylate (5g): Purified by column chromatography (petroleum ether/ethyl acetate = 10/1) to afford a white solid in 77% yield and 77% ee. The ee was determined by HPLC analysis using a Chiralpak AS-H column/AS-H column (30/1 hexane/i-PrOH; flow rate 1.0 mL/min; λ = 254 nm; tR = 115.5 (major), 132.3 (minor) min). [α]D20 = 30.7 (c = 1.08, EtOAc). Mp: 148–149°C. IR (KBr): v = 3468, 3316, 1678, 1616, 1582, 1541, 1460, 1387, 1317, 1279, 1252 cm⁻¹. 1H NMR (300 MHz, CDCl3): δ = 7.35 (d, J = 2.4 Hz, 1H), 7.10 (d, J = 2.4 Hz, 1H), 6.96–5.72 (br s, 2H), 4.62 (dd, J = 7.8, 4.2 Hz, 1H), 4.52 (dd, J = 11.8, 4.2 Hz, 1H), 4.41 (dd, J = 11.8, 7.9 Hz, 1H), 4.31–4.20 (m, 2H), 1.34 (t, J = 7.2 Hz, 3H) ppm. 13C NMR (75 MHz, CDCl3): δ = 167.7, 161.3, 144.7, 129.4, 126.5, 124.9, 122.5, 80.5, 72.5, 60.2, 34.4, 14.4 ppm. HRMS (ESI): calcd for C13H13Cl2N2O5 [M+H]⁺ 347.0201; found 347.0190.
chromatography (petroleum ether/ethyl acetate = 4/1) to afford a white solid in 76% yield and 87% ee. The ee was determined by HPLC analysis using a Chiralcel AS-H column (40/1 hexane/i-PrOH; flow rate 1.0 mL/min; λ = 254 nm; t_R = 24.9 (major), 21.1 (minor) min). [α]_D^{20} = 73.5 (c = 0.49, EtOAc). Mp: 105–106°C. IR (KBr): ν = 3443, 3312, 2982, 1682, 1633, 1603, 1550, 1520, 1462, 1408, 1379, 1301, 1261, 1219 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 7.25 (d, J = 2.0 Hz, 1H), 6.99 (d, J = 2.0 Hz, 1H), 6.80–5.90 (br s, 2H), 4.73–4.63 (m, 2H), 4.42–4.18 (m, 2H), 1.34 (t, J = 7.1 Hz, 3H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 167.8, 161.2, 151.6, 134.4, 133.4, 125.6, 118.9, 115.8, 78.3, 72.6, 60.2, 32.8, 14.5 ppm. HRMS (ESI): calcd for C₁₃H₁₃N₂O₅Cl₂ [M+H]⁺ 347.0201; found 347.0196.

(5)-Ethyl 2-amino-5-methoxy-4-(nitromethyl)-4H-chromene-3-carboxylate (5h): Purified by column chromatography (petroleum ether/ethyl acetate = 6/1) to afford a yellow solid in 41% yield and 61% ee. The ee was determined by HPLC analysis using a Chiralcel AS-H column (16/1 hexane/i-PrOH; flow rate 1.0 mL/min; λ = 254 nm; t_R = 54.8 (major), 43.2 (minor) min). [α]D^{20} = 35.9 (c = 0.58, EtOAc). Mp: 104–105°C. IR (KBr): ν = 3441, 3308, 2982, 1682, 1643, 1545, 1524, 1470, 1439, 1283, 1223, 1202, 1097, 1070 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 7.22 (t, J = 8.3 Hz, 1H), 6.67 (d, J = 8.3 Hz, 1H), 6.63 (d, J = 8.3 Hz, 1H), 4.68–4.58 (m, 3H), 4.32–4.15 (m, 2H), 3.88 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 168.6, 161.8, 156.6, 151.0, 128.9, 110.3, 108.7, 106.0, 79.2, 73.1, 59.8, 55.7, 30.3, 14.5 ppm. HRMS (ESI): calcd for C₁₄H₁₇N₂O₆ [M+H]⁺ 309.1086; found 309.1084.

2-(2-Amino-3-cyano-4H-chromen-4-yl)malononitrile (6a): ¹H NMR (300 MHz, DMSO-d₆): δ = 7.50 (s, 2H), 7.47–7.40 (m, 2H), 7.33–7.23 (m, 1H), 7.17–7.10 (m, 1H), 5.06 (d, J = 3.9 Hz, 1H), 4.59 (d, J = 3.9 Hz, 1H) ppm. ¹³C NMR (75 MHz, DMSO-d₆): δ = 163.9, 150.2, 130.7, 129.4, 125.5, 119.8, 118.5, 116.9, 113.6, 113.4, 49.4, 37.6, 32.9 ppm.

Ethyl 2-amino-4-(1-cyano-2-ethoxy-2-oxoethyl)-4H-chromene-3-carboxylate (6b): ¹H NMR (300 MHz,
CDCl$_3$): $\delta$ = 7.31–7.27 (m, 1H), 7.12–7.05 (m, 3H), 6.81–5.90 (br s, 2H), 4.72 (d, $J$ = 3.0 Hz, 1H), 4.30–4.22 (m, 4H), 3.98 (d, $J$ = 3.0 Hz, 1H), 1.35 (t, $J$ = 7.2 Hz, 3H), 1.28 (t, $J$ = 7.2 Hz, 3H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 168.1, 165.2, 162.6, 150.6, 129.4, 128.3, 124.8, 120.3, 116.7, 115.6, 73.6, 62.8, 60.0, 46.8, 37.0, 14.6, 14.1 ppm.

2-Imino-2H-chromene-3-carbonitrile (Ia): $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 8.29 (s, 1H), 7.77–7.71 (m, 1H), 7.65–7.60 (m, 1H), 7.46–7.39 (m, 2H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 156.4, 154.6, 151.8, 135.6, 129.3, 125.7, 117.5, 117.1, 113.5, 103.4 ppm.

Ethyl 2-imino-2H-chromene-3-carboxylate (Ib): $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 8.53 (s, 1H), 7.70–7.60 (m, 2H), 7.40–7.28 (m, 2H), 4.42 (q, $J$ = 7.2 Hz, 2H), 1.42 (t, $J$ = 7.2 Hz, 3H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 163.1, 156.7, 155.2, 148.5, 134.3, 129.5, 124.8, 118.4, 117.9, 116.8, 62.0, 14.2 ppm.
$^1$H, $^{13}$C NMR Spectra

Compound 4a

$^1$H NMR
300 MHz, CDCl$_3$

$^{13}$C NMR
75 MHz, CDCl$_3$
Compound 4b

$^1$H NMR
300 MHz, DMSO-d$_6$

$^{13}$C NMR
75 MHz, DMSO-d$_6$
Compound 4c

$^1$H NMR
300 MHz, DMSO-d$_6$

$^{13}$C NMR
75 MHz, DMSO-d$_6$
Compound 4d

$^1$H NMR
300 MHz, DMSO-d$_6$

$^{13}$C NMR
75 MHz, DMSO-d$_6$
Compound 4e

$^3$H NMR
300 MHz, DMSO-d$_6$

$^{13}$C NMR
75 MHz, DMSO-d$_6$
Compound 4f

$^1$H NMR
300 MHz, DMSO-$d_6$

$^{13}$C NMR
75 MHz, DMSO-$d_6$
Compound 4g

$^3$H NMR
300 MHz, DMSO-d$_6$

$^{13}$C NMR
75 MHz, DMSO-d$_6$
Compound 5a

$^1$H NMR
300 MHz, CDCl$_3$

$^{13}$C NMR
75 MHz, CDCl$_3$
Compound 5b

$^1$H NMR
300 MHz, CDCl$_3$

$^{13}$C NMR
75 MHz, CDCl$_3$
Compound 5d

$^1$H NMR
300 MHz, CDCl$_3$

$^{13}$C NMR
75 MHz, CDCl$_3$
Compound 5e

$^1$H NMR
300 MHz, CDCl$_3$

$^{13}$C NMR
75 MHz, CDCl$_3$
Compound 5f

$^1$H NMR
300 MHz, CDCl$_3$

$^{13}$C NMR
75 MHz, CDCl$_3$
Compound 5g

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300 MHz, CDCl$_3$

$^{13}$C NMR
75 MHz, CDCl$_3$
Compound 5h

$^1$H NMR
300 MHz, CDCl$_3$

$^{13}$C NMR
75 MHz, CDCl$_3$
Compound 6a

$^1$H NMR
300 MHz, DMSO-$d_6$

$^{13}$C NMR
75 MHz, DMSO-$d_6$
Compound Ia

$^1$H NMR
300 MHz, CDCl$_3$

$^{13}$C NMR
75 MHz, CDCl$_3$
Compound Ib

$^1$H NMR
300 MHz, CDCl$_3$

$^{13}$C NMR
75 MHz, CDCl$_3$
HPLC Profile

Racemic 4a

Enantiomeric enriched 4a
Racemic 4b

![Racemic 4b Chromatogram](image)

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Enantiomeric enriched 4b

![Enantiomeric enriched 4b Chromatogram](image)

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Racemic 4c

Enantiomeric enriched 4c
Racemic 4d

Enantiomeric enriched 4d
Racemic 4e

Enantiomeric enriched 4e
Racemic 4f

Enantiomeric enriched 4f
Racemic 4g

Enantiomeric enriched 4g
Racemic 4h

Enantiomeric enriched 4h
Racemic 5a

Enantiomeric enriched 5a
Racemic 5b

Enantiomeric enriched 5b
Racemic 5c

Enantiomeric enriched 5c
Racemic 5d

Enantiomeric enriched 5d
Racemic 5e

Enantiomeric enriched 5e
Racemic 5e

Enantiomeric enriched 5e (After recrystallization from dichloromethane/n-hexane)
Racemic 5f

![Graph showing the chromatogram of racemic 5f with an area percent report at 15°C.]

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Enantiomeric enriched 5f

![Graph showing the chromatogram of enantiomeric enriched 5f with an area percent report at 15°C.]

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Racemic 5f

Enantiomeric enriched 5f (After recrystallization from dichloromethane/n-hexane)
Racemic 5g

![Graph of racemic 5g with areas and percentages]

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Enantiomeric enriched 5g

![Graph of enantiomeric enriched 5g with areas and percentages]

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Racemic $5h$

Enantiomeric enriched $5h$