Supporting Information

Chiral Organic Base Catalyst with Halogen Bonding Donor Functionality: Asymmetric Mannich Reaction of Malononitrile with N-Boc Aldimines and Ketimines

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1. General

Dry solvents were purchased from commercial suppliers and used without further purification. Analytical thin-layer chromatography (TLC) was performed on glass plates coated with 0.25 mm 230-400 mesh silica gel containing a fluorescent indicator (Merck, #1.05715.0009). Silica gel column chromatography was performed on Kanto silica gel 60 (spherical, 100-210 µm). IR spectra were recorded on JASCO FT/IR-4100 using ATR. $^1$H-NMR spectra were recorded on JEOL ECS-400 (400 MHz), ECA-500 (500 MHz), ECX-400 (400 MHz) spectrometers. Chemical shifts of $^1$H-NMR spectra were reported relative to tetramethyl silane (δ 0). $^{13}$C-NMR spectra were recorded on JEOL ECS-400 (100 MHz), ECA-500 (125 MHz), ECX-400 (100 MHz) spectrometers. Chemical shifts of $^{13}$C-NMR spectra were reported relative to CDCl$_3$ (δ 77.0). $^{19}$F-NMR spectra were recorded on JEOL ECS-400 (376 MHz) spectrometer. Chemical shifts of $^{19}$F-NMR spectra were reported relative to trifluorotoluene (δ ~63.72). Splitting patterns were reported as s, singlet; d, doublet; t, triplet; m, multiplet; br, broad.

$N$-Boc aldimines were synthesized according to known procedure.$^1$ Isatin-derived $N$-Boc ketimines were synthesized according to known procedure.$^{2,3}$

2. Synthesis of chiral halogen-bonding donor/organic base catalyst

A. 2a, 2b, 3a, and 3b

\[
\begin{align*}
\text{F} & \quad \text{OH} \\
\text{F} & \quad \text{F} \\
\text{F} & \quad \text{F} \\
\text{F} & \quad \text{H}_2\text{N} \cdot \text{R}^* \\
\text{Cinchona alkaloid-derived amine} & \quad (1 \text{ equiv}) \\
\text{EDCl-HCl (1 equiv)} & \quad \text{HOBt (3 mol %)} \\
\text{CH}_2\text{Cl}_2 & \quad \text{rt}
\end{align*}
\]

2,3,4,5-Tetrafluoro-6-iodobenzoic acid (0.5 mmol, 1.0 equiv, 0.1 M), cinchona alkaloid-derived amine (0.5 mmol, 1.0 equiv, 0.1 M), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide Hydrochloride (EDCl-HCl) (0.5 mmol, 1.0 equiv, 0.1 M), and 1-hydroxybenzotriazole (HOBt) (0.015 mmol, 0.03 equiv, 0.003 M) were added to a one-necked round flask containing a stir bar under Ar. CH$_2$Cl$_2$ (5 mL) was added to the flask, and the mixture was stirred at room temperature. After being stirred for appropriate time by TLC monitoring, additional CH$_2$Cl$_2$ was added. The organic layer was washed with water and brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. After purification by silica gel column chromatography (hexane/ethyl acetate/Et$_3$N = 1/1/0.03), product was obtained.

2,3,4,5-tetrafluoro-6-iodo-N-((S)-quinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)benzamide (2a)

Cinchonidine-derived amine was used; reaction time: 14 h; white solids (85% yield); $^1$H NMR (400 MHz, CDCl$_3$, 50 °C): δ 8.93 (d, $J = 4.4$ Hz, 1H), 8.40 (d, $J = 8.4$ Hz, 1H), 8.17 (d, $J = 8.4$ Hz, 1H), 7.74 (t, $J = 8.4$ Hz, 1H), 7.62 (t, $J = 8.4$ Hz, 1H), 7.55 (d, $J = 4.4$ Hz, 1H), 5.67 (ddd, $J = 17.6$, 10.0, 7.2 Hz, 1H), 5.45 (br, 1H), 4.98-4.90 (m, 2H), 3.28-3.22 (m, 3H), 2.78-2.72 (m, 2H), 2.33 (br, 1H), 1.73-1.43 (m, 4H), 1.11-1.06 (m, 1H); $^{19}$F NMR (376 MHz, CDCl$_3$): –114.7 (m, 1F), –139.5 (m, 1F), –151.9 (m, 1F), –153.3 (m, 1F); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 162.1, 150.0, 148.8, 147.8, 144.5, 140.9, 140.6, 140.3, 130.6, 129.2, 126.7, 123.4, 114.8, 74.9, 55.9, 40.9, 39.4, 27.8, 27.3, 25.9; IR (neat) 3299, 2945, 1657, 1497, 1457, 1024, 758 cm$^{-1}$; HRMS (ESI+) calcd for C$_{26}$H$_{23}$F$_4$I$_3$N$_3$O [M + H]$^+$ 596.0816: found 596.0807; [α]$_D^{24}$ = +46.2 ($c = 1.0$, CHCl$_3$).

2,3,4,5-tetrafluoro-6-iodo-N-((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)benzamide (2b)
Quinine-derived amine was used; reaction time: 24 h; white solids (57% yield); $^1$H NMR (400 MHz, CDCl$_3$, 50 °C): δ 8.74 (d, $J$ = 4.8 Hz, 1H), 8.05 (d, $J$ = 9.2 Hz, 1H), 7.66 (br, 1H), 7.54 (br, 1H), 7.46 (d, $J$ = 4.8 Hz, 1H), 7.40 (dd, $J$ = 9.6, 2.8 Hz, 1H), 5.69 (ddd, $J$ = 18.0, 10.0, 10.0 Hz, 1H), 5.52 (br, 1H), 4.98-4.92 (m, 2H), 3.98 (s, 3H), 3.26-3.06 (m, 3H), 2.79-2.65 (m, 2H), 2.32 (br, 1H), 1.72-1.65 (m, 3H), 1.49-1.44 (m, 1H), 1.09-1.05 (m, 1H); $^{19}$F NMR (376 MHz, CDCl$_3$): –114.6 (m, 1F), –139.3 (m, 1F), –151.8 (m, 1F), –153.3 (m, 1F); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 162.0, 158.0, 147.7, 147.4, 144.6, 144.4, 141.0, 140.4, 140.2, 131.7, 128.4, 126.6, 121.7, 118.9, 114.8, 101.7, 75.0, 60.8, 55.8, 51.3, 41.0, 39.4, 27.9, 27.3, 25.8; IR (neat) 3279, 2933, 1668, 1455, 1240, 736 cm$^{-1}$; HRMS (ESI+) calcd for C$_{27}$H$_{25}$F$_4$IN$_3$O$_2$ [M + H]$^+$ 626.0922: found 626.0906; [α]$_D^{24}$ = +57.5 (c = 1.0, CHCl$_3$).

2,3,4,5-tetrafluoro-6-iodo-N-((R)-quinolin-4-yl)((1S,2R,4S,5R)-5-vinylquinuclidin-2-yl)methyl)benzamide (3a)

Cinchonine-derived amine was used; reaction time: 12 h; white solids (68% yield); $^1$H NMR (400 MHz, CDCl$_3$, 50 °C): δ 8.90 (d, $J$ = 4.8 Hz, 1H), 8.36 (d, $J$ = 8.8 Hz, 1H), 8.15 (d, $J$ = 8.8 Hz, 1H), 7.76-7.58 (m, 3H), 7.52 (d, $J$ = 4.8 Hz, 1H), 5.96 (ddd, $J$ = 17.6, 10.8, 6.8 Hz, 1H), 5.43 (br, 1H), 5.22-5.12 (m, 2H), 3.03-2.86 (m, 5H), 2.36-2.31 (m, 1H), 1.82 (m, 1H), 1.06-0.99 (m, 1H); $^{19}$F NMR (376 MHz, CDCl$_3$): –114.7 (m, 1F), –139.5 (m, 1F), –152.0 (m, 1F), –153.3 (m, 1F); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 162.1, 149.9, 148.8, 147.9, 144.5, 140.6, 140.4, 140.1, 130.6, 129.2, 126.8, 126.6, 123.4, 115.1, 74.9, 49.2, 47.2, 39.2, 27.4, 26.9, 25.5; IR (neat) 3297, 2939, 1655, 1497, 1456, 1024, 758 cm$^{-1}$; HRMS (ESI+) calcd for C$_{26}$H$_{23}$F$_4$IN$_3$O [M + H]$^+$ 596.0816: found 596.0815; [α]$_D^{24}$ = +46.6 (c = 1.0, CHCl$_3$).

2,3,4,5-tetrafluoro-6-iodo-N-((R)-(6-methoxyquinolin-4-yl)((1S,2R,4S,5R)-5-vinylquinuclidin-2-yl)methyl)benzamide (3b)

Quinidine-derived amine was used; reaction time: 8 h; white solids (75% yield); $^1$H NMR (400 MHz, CDCl$_3$, 50 °C): δ 8.75 (d, $J$ = 4.6 Hz, 1H), 8.04 (d, $J$ = 9.4 Hz, 1H), 7.58 (br, 1H), 7.52 (br, 1H), 7.47 (d, $J$ = 4.6 Hz, 1H), 7.39 (dd, $J$ = 9.4, 2.5 Hz, 1H), 5.97 (ddd, $J$ = 17.4, 11.0, 6.2 Hz, 1H), 5.20-5.10 (m, 2H), 3.98 (s, 3H), 3.10-2.87 (m, 5H), 2.37-2.31 (m, 1H), 1.61-1.44 (m, 4H), 1.11-1.05 (m, 1H); $^{19}$F NMR (376 MHz, CDCl$_3$): –114.6 (m, 1F), –139.4 (m, 1F), –151.9 (m, 1F), –153.3 (m, 1F); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 162.0, 157.9, 147.5, 147.2, 145.0, 144.4, 144.2, 140.5, 140.3, 140.0, 131.4, 128.3, 126.7, 122.2, 122.0, 118.6, 114.7, 101.0, 75.0, 60.8, 55.5, 50.6, 49.0, 46.8, 38.9, 39.4, 27.1, 26.5, 25.3; IR (neat) 3160, 2934, 1670, 1472, 1241, 748 cm$^{-1}$; HRMS (ESI+) calcd for C$_{27}$H$_{25}$F$_4$IN$_3$O [M + H]$^+$ 662.0922: found 662.0906; [α]$_D^{24}$ = +57.5 (c = 20, CHCl$_3$).
S626.0922: found 626.0922; [α]D0° = +44.2 (c = 1.0, CHCl3).

B. 2,3,4,5-tetrafluoro-N-((S)-quinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methylbenzamide (2c)

\[
\begin{align*}
\text{2,3,4,5-Tetrafluorobenzoic acid (0.5 mmol, 1.0 equiv, 0.1 M), cinchonidine-derived amine (0.5 mmol, 1.0 equiv, 0.1 M), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide Hydrochloride (EDCI-HCl) (0.5 mmol, 1.0 equiv, 0.1 M), and 1-hydroxybenzotriazole (HOBt) (0.015 mmol, 0.03 equiv, 0.003 M) were added to a one-necked round flask containing a stir bar under Ar. CH2Cl2 (5 mL) was added to the flask, and the mixture was stirred at room temperature. After 15 h, additional CH2Cl2 was added. The organic layer was washed with water and brine, dried over Na2SO4, and concentrated under reduced pressure. After purification by silica gel column chromatography (hexane/ethyl acetate/Et3N = 1/1/0.03), product 2c was obtained. Pale yellow oil (94% yield); 1H NMR (500MHz, CDCl3, 50 °C) \( \delta \) 8.89 (d, \( J = 4.3 \) Hz, 1H), 8.38 (d, \( J = 8.6 \) Hz, 1H), 8.16-8.14 (m, 2H), 7.72 (t, \( J = 7.2 \) Hz, 1H), 7.61 (t, \( J = 8.0 \) Hz, 1H), 7.56-7.51 (m, 1H), 7.44 (d, \( J = 4.6 \) Hz, 1H), 5.74-5.67 (m, 1H), 5.41 (br, 1H), 4.99-4.93 (m, 2H), 3.30 (dd, \( J = 10.3, 13.8 \) Hz, 1H), 3.18 (br, 1H), 3.08 (br, 1H), 2.80-2.77 (m, 2H), 2.32 (br, 1H), 1.70-1.65 (m, 3H), 1.44-1.42 (m, 1H), 1.04-1.00 (m, 1H); 19F NMR (376 MHz, CDCl3): \( -137.9 \) (m, 1F), \( -139.7 \) (m, 1F), \( -150.2 \) (m, 1F), \( -155.1 \) (m, 1F); \( \{19F\}^{13C} \) NMR (100 MHz, CDCl3): \( \delta \) 170.97, 160.22, 149.95, 148.48, 146.91, 146.14, 142.35, 141.06, 140.46, 130.52, 129.08, 126.72, 122.84, 117.42, 117.38, 114.52, 112.52, 60.22, 55.78, 40.70, 39.43, 27.70, 27.15, 25.78, 20.87, 14.03; IR (neat) 3334, 3077, 2944, 2868, 1670, 1478, 1360, 1244, 1037, 909, 729 cm\(^{-1}\); HRMS (ESI+) calcd for C26H24F4N3O \[\text{[M + H]}^+\]: 470.1850; found 470.1841; [α]D21 = -92.9 (c = 1.0, CHCl3).

C. N-((R)-(6-methoxyquinolin-4-yl)((1S,2R,4S,5R)-5-vinylquinuclidin-2-yl)methyl)acetamide (10)

Quinidine-derived amine (1.0 mmol, 1.0 equiv, 0.1 M) and triethylamine (1.4 mmol, 1.4 equiv, 0.14 M) were dissolved in CH2Cl2 (10 mL). The solution was cooled to 0 °C, and acetyl chloride (1.0 mmol, 1.0 equiv, 0.1 M) was added slowly over 10 min. The reaction mixture was stirred at room temperature for 16 h, and CH2Cl2 was added. The organic layer was washed with sat. NaHCO3 aq, dried over Na2SO4, and concentrated under reduced pressure. After purification by silica gel column chromatography (CHCl3/MeOH = 20/1 to 10/1), product 10 was obtained. White solids (93% yield); 1H NMR (400, Hz, CDCl3, 50 °C): \( \delta \) 8.71 (d, \( J = 4.8 \) Hz, 1H), 8.01 (d, \( J = 9.2 \) Hz, 1H),
7.61 (d, J = 2.8 Hz, 1H), 7.39-7.33 (m, 2H), 6.99 (br s, 1H), 5.95-5.87 (m, 1H), 5.36 (br s, 1H), 5.18-5.12 (m, 2H), 3.98 (s, 3H), 3.08-2.92 (m, 5H), 2.67 (br s, 1H), 2.36-2.30 (m, 1H), 1.97 (s, 3H), 1.68 (br, 1H), 1.64-1.49 (m, 2H), 1.33-1.25 (m, 1H), 1.06-0.99 (m, 1H); \( ^{13} \text{C} \) NMR (100 MHz, CDCl\(_3\)): \( \delta \) 169.9, 157.5, 147.0, 145.4, 144.3, 140.0, 131.1, 121.8, 118.7, 114.5, 101.2, 77.2, 48.9, 46.5, 38.6, 26.9, 26.2, 25.3, 22.7; IR (neat) 3006, 2941, 1653, 1620, 1224, 1083, 908, 664 cm\(^{-1} \); HRMS (ESI+) calcd for C\(_{22}\)H\(_{28}\)O\(_2\)N\(_3\) [M + H]\(^+\) 366.2176: found 366.2169; [\( \alpha \)]\(_D\)^{20} = +188.5 (c = 1.0, CHCl\(_3\)).

D. N-benzyl-2,3,4,5-tetrafluoro-6-iodobenzamide (11)

\[ \text{2,3,4,5-Tetrafluoro-6-iodobenzoic acid (0.5 mmol, 1.0 equiv, 0.1 M), benzyl amine (0.5 mmol, 1.0 equiv, 0.1 M), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide Hydrochloride (EDCl \cdot HCl) (0.5 mmol, 1.0 equiv, 0.1 M), and 1-hydroxybenzotriazole (HOBt) (0.015 mmol, 0.03 equiv, 0.003 M) were added to a one-necked round flask containing a stir bar under Ar. CH\(_2\)Cl\(_2\) (5 mL) was added to the flask, and the mixture was stirred at room temperature. After 17 h, additional CH\(_2\)Cl\(_2\) was added. The organic layer was washed with water and brine, dried over Na\(_2\)SO\(_4\), and concentrated under reduced pressure. The residue was recrystallized from hexane/CH\(_2\)Cl\(_2\) to give product 11. White solids (52% yield); \( ^1 \)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.42-7.31 (m, 5 H), 6.10 (br, 1H), 4.66 (d, J = 5.6 Hz, 2H); \( ^{19} \)F NMR (376 MHz, CDCl\(_3\)): –114.1 (m, 1F), –138.6 (m, 1F), –151.4 (m, 1F), –153.1 (m, 1F); \{ \( ^{19} \)F \} \( ^{13} \)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 162.2, 147.6, 144.1, 140.4, 140.1, 136.6, 128.7, 127.8, 126.6, 74.9, 44.2; IR (neat) 3224, 3060, 1643, 1499, 1453, 744 cm\(^{-1} \); HRMS (ESI+) calcd for C\(_{14}\)H\(_7\)F\(_4\)INO [M - H\(^-\)] 407.9508: found 407.9522. \]

3. General procedure for asymmetric Mannich reaction of malononitrile with N-Boc aldimines

Catalyst 3b (0.6 mg, 0.001 mmol, 0.005 eq) and malononitrile 4 (26.4 mg, 0.4 mmol, 2 eq) were added to a one-necked round flask containing a stir bar under Ar. CHCl\(_3\) (2.0 ml) was added to the flask, and the mixture was stirred at \(-50^\circ\)C. To the resulting suspension, N-Boc imine 5 (0.2 mmol, 1.0 eq) was added. After being stirred for appropriate time, solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 4/1) to afford product. The enantiomeric excesses of the products were determined by chiral stationary phase HPLC using Daicel Chiralcel AD-H, AD-3, OD-H, Chiralpak IA, and IC-3 column.
4. Analytical data for products of enantioselective Mannich reaction of malononitrile with N-Boc aldimines

**tert-butyl (R)-(2,2-dicyano-1-phenylethyl)carbamate (6a)**

Reaction time: 32 h; colorless oil (50.4 mg, 93% yield); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.48 (s, 5H), 5.28 (d, $J = 5.5$ Hz, 1H), 5.08 (t, $J = 5.2$ Hz, 1H), 4.82 (d, $J = 4.30$ Hz, 1H), 1.48 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 154.8, 133.6, 130.2, 129.5, 127.0, 111.1, 110.8, 81.8, 55.6, 29.6, 28.3; IR (neat) 3385, 2979, 2900, 1684, 1508, 1291, 1252, 1165, 757 cm$^{-1}$; HRMS (ESI+) calcd for C$_{15}$H$_{17}$N$_3$NaO$_2$ [M + Na]$^+$ 294.1213: found 294.1208; $[\alpha]_D^{24} = +26.8$ (c = 0.5, CHCl$_3$, 98% ee).

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (hexane:2-propanol = 90:10, 0.5 mL/min, 254 nm); minor enantiomer $t_R = 34.8$ min, major enantiomer $t_R = 20.7$ min, 98% ee.

**tert-butyl (R)-(2,2-dicyano-1-(o-tolyl)ethyl)carbamate (6b)**

Reaction time: 48 h; white solids (51.8 mg, 91% yield); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.55 (br, 1H), 7.35-7.33 (m, 2H), 7.29-7.28 (m, 1H), 5.46 (t, $J = 6.0$ Hz, 1H), 5.14 (d, $J = 5.5$ Hz, 1H), 4.75 (d, $J = 4.9$ Hz, 1H), 2.46 (s, 3H), 1.48 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 154.8, 136.3, 132.7, 131.6, 129.8, 127.2, 125.1, 111.3, 110.8, 81.7, 50.6, 28.6, 28.1, 19.6; IR (neat) 3348, 2900, 1684, 1508, 1366, 1331, 1250, 1163, 794, 607 cm$^{-1}$; HRMS (ESI+) calcd for C$_{16}$H$_{19}$N$_3$NaO$_2$ [M + Na]$^+$ 308.1369: found 308.1365; $[\alpha]_D^{25} = +69.5$ (c = 0.5, CHCl$_3$, 98% ee).

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (hexane:2-propanol = 90:10, 0.3 mL/min, 254 nm); minor enantiomer $t_R = 33.1$ min, major enantiomer $t_R = 34.8$ min, 98% ee.

**tert-butyl (R)-(2,2-dicyano-1-(m-tolyl)ethyl)carbamate (6c)**

Reaction time: 32 h; colorless oil (49.3 mg, 86% yield); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.36-7.21 (m, 4H), 5.32 (br, 1H), 5.06 (t, $J = 6.9$ Hz, 1H), 4.78 (d, $J = 6.0$ Hz, 1H), 2.24 (s, 3H), 1.47 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 154.8, 139.4, 133.6, 130.9, 129.3, 127.6, 124.0, 111.1, 110.8, 81.7, 55.5, 29.6, 28.1, 21.4; IR (neat) 3346, 2979, 2927, 1703, 1509, 1368, 1250, 1159, 772 cm$^{-1}$; HRMS (ESI+) calcd for C$_{16}$H$_{19}$N$_3$NaO$_2$ [M + Na]$^+$ 308.1369: found 308.1362; $[\alpha]_D^{25} = +27.0$ (c = 1.0, CHCl$_3$, 98% ee).

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (hexane:2-propanol = 90:10, 0.5 mL/min, 254 nm); minor enantiomer $t_R = 30.7$ min, major enantiomer $t_R = 17.9$ min, 98% ee.
**tert-butyl (R)-(2,2-dicyano-1-(p-tolyl)ethyl)carbamate (6d)**

![Chemical Structure](image)

Reaction time: 48 h; white solids (51.1 mg, 90% yield); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.36 (d, $J = 8.0$ Hz, 2H), 7.27 (d, $J = 8.6$ Hz, 2H), 5.28 (br, 1H), 5.05 (t, $J = 5.4$ Hz, 1H), 4.79 (d, $J = 4.3$ Hz, 1H), 2.39 (s, 3H), 1.47 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 154.9, 140.3, 130.7, 130.1, 126.9, 111.1, 110.9, 81.7, 55.4, 29.7, 28.1, 21.9; IR (neat) 3347, 2980, 1703, 1508, 1368, 1249, 1161 cm$^{-1}$; HRMS (ESI+) calcd for C$_{16}$H$_{19}$N$_3$NaO$_2$ [M + Na]$^+$ 308.1369: found 308.1362; $\left[\alpha\right]_D^{25} = +33.1$ (c = 0.5, CHCl$_3$, 97% ee).

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (hexane:2-propanol = 90:10, 0.3 mL/min, 254 nm); minor enantiomer $t_R = 49.2$ min, major enantiomer $t_R = 33.9$ min, 97% ee.

**tert-butyl (R)-(2,2-dicyano-1-(2-methoxyphenyl)ethyl)carbamate (6e)**

![Chemical Structure](image)

Reaction time: 24 h; white solids (48.0 mg, 80% yield); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.42-7.38 (m, 1H), 7.33 (d, $J = 7.2$ Hz, 1H), 7.04-7.01 (m, 1H), 6.97 (d, $J = 8.3$ Hz, 1H), 5.83 (d, $J = 9.2$ Hz, 1H), 5.55 (dd, $J = 9.2$, 7.2 Hz, 1H), 4.52 (d, $J = 7.2$ Hz, 1H), 3.91 (s, 3H), 1.47 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 156.4, 154.6, 131.1, 129.2, 122.2, 121.4, 111.33, 111.26, 111.18, 81.1, 55.5, 52.7, 28.9, 28.1; IR (neat) 3384, 2944, 1697, 1512, 1244, 1171 cm$^{-1}$; HRMS (ESI+) calcd for C$_{16}$H$_{19}$N$_3$NaO$_3$ [M + Na]$^+$ 324.1319: found 324.1315; $\left[\alpha\right]_D^{25} = +38.0$ (c = 0.5, CHCl$_3$, 96% ee).

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (hexane:2-propanol = 90:10, 1.0 mL/min, 254 nm); minor enantiomer $t_R = 14.0$ min, major enantiomer $t_R = 16.7$ min, 96% ee.

**tert-butyl (R)-(2,2-dicyano-1-(3-methoxyphenyl)ethyl)carbamate (6f)**

![Chemical Structure](image)

Reaction time: 48 h; colorless oil (53.1 mg, 88% yield); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.36 (t, $J = 8.0$ Hz, 1H), 7.05-6.96 (m, 3H), 5.60 (br, 1H), 5.10 (t, $J = 6.0$ Hz, 1H), 4.76 (d, $J = 4.1$ Hz, 1H), 3.82 (s, 3H), 1.47 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 160.0, 154.8, 135.3, 130.5, 119.0, 115.4, 112.7, 111.2, 110.9, 81.6, 55.4, 55.3, 29.6, 28.1; IR (neat) 3347, 2979, 1703, 1512, 1251, 1161, 1219 cm$^{-1}$; HRMS (ESI+) calcd for C$_{16}$H$_{19}$N$_3$NaO$_3$ [M + Na]$^+$ 324.1319: found 324.1315; $\left[\alpha\right]_D^{25} = +32.3$ (c = 0.5, CHCl$_3$, 97% ee).

Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexane:2-propanol = 90:10, 1.0 mL/min, 254 nm); minor enantiomer $t_R = 27.7$ min, major enantiomer $t_R = 16.6$ min, 97% ee.
**tert-butyl (R)-(2,2-dicyano-1-(4-methoxyphenyl)ethyl)carbamate (6g)**

![Chemical Structure](attachment:image.png)

Reaction time: 48 h; white solids (52.6 mg, 87% yield); \(^1\)H NMR (500 MHz, CDCl\(_3\)): δ 7.41 (d, \(J = 8.6\) Hz, 2H), 6.97 (d, \(J = 8.8\) Hz, 2H), 5.31 (br, 1H), 5.03 (t, \(J = 5.5\) Hz, 1H), 4.80 (d, \(J = 3.4\) Hz, 1H), 3.83 (s, 3H), 1.47 (s, 9H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): δ 160.7, 154.9, 128.3, 125.7, 114.7, 111.2, 110.9, 81.7, 55.3, 55.2, 29.7, 28.1; IR (neat) 3385, 2978, 2910, 1692, 1614, 1506, 1456, 1162, 1112 cm\(^{-1}\); HRMS (ESI+) calcd for C\(_{16}\)H\(_{19}\)N\(_3\)NaO\(_3\) [M + Na\(^+\)] 324.1319: found 324.1312; \([\alpha\] D\(_{25}\) = +33.2 (c = 0.5, CHCl\(_3\), 89% ee).

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (hexane:2-propanol = 90:10, 0.5 mL/min, 254 nm); minor enantiomer \(t_R = 27.4\) min, major enantiomer \(t_R = 13.9\) min, 89% ee.

**tert-butyl (R)-(2,2-dicyano-1-(2-fluorophenyl)ethyl)carbamate (6h)**

![Chemical Structure](attachment:image.png)

Reaction was performed in CHCl\(_3\) (2.7 mL) at −20 °C for 24 h. White solids (49.3 mg, 85% yield); \(^1\)H NMR (500 MHz, CDCl\(_3\)): δ 7.51-7.43 (m, 2H), 7.29-7.26 (m, 1H), 7.21-7.17 (m, 1H), 5.57 (t, \(J = 6.3\) Hz, 1H), 5.47 (d, \(J = 6.3\) Hz, 1H), 4.57 (d, \(J = 5.7\) Hz, 1H), 1.48 (s, 9H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): δ 160.0 (d, \(J_{CF} = 246.8\) Hz), 154.5, 131.9 (d, \(J_{CF} = 8.3\) Hz), 128.5, 125.3 (d, \(J_{CF} = 3.6\) Hz), 121.5 (d, \(J_{CF} = 13.1\) Hz), 116.5 (d, \(J_{CF} = 13.1\) Hz), 110.8, 110.5, 81.9, 50.4, 29.4, 28.1; IR (neat) 3386, 2926, 1685, 1507, 1492, 1168, 1085, 773 cm\(^{-1}\); HRMS (ESI+) calcd for C\(_{15}\)H\(_{16}\)FN\(_3\)NaO\(_2\) [M + Na\(^+\)] 312.1119: found 312.1114; \([\alpha\] D\(_{26}\) = +22.9 (c = 0.5, CHCl\(_3\), 93% ee).

Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (hexane:2-propanol = 70:30, 0.3 mL/min, 254 nm); minor enantiomer \(t_R = 18.0\) min, major enantiomer \(t_R = 20.6\) min, 93% ee.

**tert-butyl (R)-(2,2-dicyano-1-(3-fluorophenyl)ethyl)carbamate (6i)**

![Chemical Structure](attachment:image.png)

Reaction was performed in CHCl\(_3\) (2.7 mL) at −20 °C for 24 h. Colorless oil (43.6 mg, 75% yield); \(^1\)H NMR (500 MHz, CDCl\(_3\)): δ 7.49-7.45 (m, 2H), 7.29-7.26 (m, 1H), 5.27 (br, 1H), 5.11 (t, \(J = 5.4\) Hz, 1H), 5.80 (d, \(J = 3.8\) Hz, 1H), 1.48 (s, 9H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): δ 162.9 (d, \(J_{CF} = 248.0\) Hz), 154.7, 135.9, 131.3 (d, \(J_{CF} = 8.4\) Hz), 122.8, 117.4 (d, \(J_{CF} = 21.5\) Hz), 114.4 (d, \(J_{CF} = 22.7\) Hz), 110.8, 110.5, 82.1, 55.1, 29.5, 28.1; IR (neat) 3339, 2981, 2932, 1703, 1514, 1250, 1220, 1158 cm\(^{-1}\); HRMS (ESI+) calcd for C\(_{15}\)H\(_{16}\)FN\(_3\)NaO\(_2\) [M + Na\(^+\)] 312.1119: found 312.1116; \([\alpha\] D\(_{26}\) = +22.4 (c = 0.5, CHCl\(_3\), 96% ee).

Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (hexane:2-propanol = 90:10, 0.5 mL/min, 254 nm); minor enantiomer \(t_R = 49.2\) min, major enantiomer \(t_R = 25.2\) min, 96% ee.
**tert-butyl (R)-(2,2-dicyano-1-(4-fluorophenyl)ethyl)carbamate (6j)**

reaction time: 36 h; colorless oil (46.4 mg, 80% yield); $^1$H NMR (500 MHz, CDCl$_3$): δ 7.50-7.48 (m, 2H), 7.19-7.16 (m, 2H), 5.22 (br, 1H), 5.08 (t, $J = 5.5$ Hz, 1H), 4.83 (d, $J = 3.2$ Hz, 1H), 4.48 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 163.6 (d, $^1$J$_{CF} = 249.2$ Hz), 154.8, 129.6, 129.1 (d, $^3$J$_{CF} = 8.3$ Hz), 116.7 (d, $^2$J$_{CF} = 22.7$ Hz), 111.9, 110.7, 82.0, 55.1, 29.6, 28.1; IR (neat) 3348, 2982, 2930, 1704, 1509, 1220, 1159 cm$^{-1}$; HRMS (ESI+) calcd for C$_{15}$H$_{16}$FN$_3$NaO$_2$ [M + Na]$^+$ 312.1119: found 312.1117; $[\alpha]_D^{25} = +21.2$ (c = 0.5, CHCl$_3$, 98% ee).

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (hexane:2-propanol = 90:10, 0.5 mL/min, 254 nm); minor enantiomer $t_R = 40.5$ min, major enantiomer $t_R = 20.4$ min, 98% ee.

**tert-butyl (R)-(1-(2-chlorophenyl)-2,2-dicyanoethyl)carbamate (6k)**

reaction time: 26 h; white solids (47.6 mg, 78% yield); $^1$H NMR (400 MHz, CDCl$_3$): δ 7.57-7.55 (m, 1H), 7.50-7.39 (m, 3H), 5.80 (dd, $J = 7.8$, 5.9 Hz, 1H), 5.45 (d, $J = 6.9$ Hz, 1H), 4.66 (d, $J = 5.0$ Hz, 1H), 1.48 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 154.4, 133.0, 132.1, 131.1, 130.6, 128.0, 127.8, 110.9, 110.4, 81.9, 51.8, 28.7, 28.1; IR (neat) 3335, 2979, 1708, 1514, 1369, 1249, 1162, 771 cm$^{-1}$; HRMS (ESI+) calcd for C$_{15}$H$_{16}$ClN$_3$NaO$_2$ [M + Na]$^+$ 328.0823: found 328.0821; $[\alpha]_D^{26} = +22.7$ (c = 0.5, CHCl$_3$, 94% ee).

Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexane:2-propanol = 80:20, 0.5 mL/min, 254 nm); minor enantiomer $t_R = 12.6$ min, major enantiomer $t_R = 18.8$ min, 94% ee.

**tert-butyl (R)-(1-(4-chlorophenyl)-2,2-dicyanoethyl)carbamate (6l)**

reaction was performed in CHCl$_3$ (2.7 mL) at –20 °C for 48 h. White solids (47.5 mg, 78% yield); $^1$H NMR (500 MHz, CDCl$_3$): δ 7.48-7.42 (m, 4H), 5.22 (d, $J = 4.3$ Hz, 1H), 5.07 (t, $J = 5.5$ Hz, 1H), 4.82 (d, $J = 3.7$ Hz, 1H), 1.48 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 154.7, 136.4, 132.1, 129.8, 128.4, 110.9, 110.6, 82.1, 55.2, 29.5, 28.1; IR (neat) 3375, 1693, 1515, 1493, 1246, 1167, 783, 594 cm$^{-1}$; HRMS (ESI+) calcd for C$_{15}$H$_{16}$ClN$_3$NaO$_2$ [M + Na]$^+$ 328.0823: found 328.0822; $[\alpha]_D^{26} = +29.1$ (c = 0.5, CHCl$_3$, 96% ee).

Enantiomeric excess was determined by HPLC with a Chiralpak IC-3 column (hexane:2-propanol = 95:5, 0.5 mL/min, 254 nm); minor enantiomer $t_R = 27.0$ min, major enantiomer $t_R = 21.8$ min, 96% ee.

**tert-butyl (R)-(1-(2-bromophenyl)-2,2-dicyanoethyl)carbamate (6m)**
Reaction time: 48 h; colorless oil (64.0 mg, 91% yield); \(^1\)H NMR (500 MHz, CDCl\(_3\)): δ 7.67 (d, \(J = 8.0\) Hz, 1H), 7.55 (d, \(J = 7.4\) Hz, 1H), 7.46 (t, \(J = 7.4\) Hz, 1H), 7.33-7.30 (m, 1H), 5.79 (dd, \(J = 8.0, 5.2\) Hz, 1H), 5.44 (d, \(J = 6.9\) Hz, 1H), 4.68 (d, \(J = 4.6\) Hz, 1H), 1.48 (s, 9H); \(^13\)C NMR (125 MHz, CDCl\(_3\)): δ 154.4, 133.9, 133.8, 131.3, 128.5, 127.8, 123.3, 110.9, 110.3, 81.9, 53.9, 28.7, 28.1; IR (neat) 3350, 2900, 1684, 1505, 1249, 1151, 754 cm\(^{-1}\); HRMS (ESI+) calcd for C\(_{15}\)H\(_{16}\)BrN\(_3\)NaO\(_2\) [M + Na\(^+\)] 372.0318: found 372.0314; \([\alpha]\)\(_D\)\(^{26}\) = +15.7 (c = 0.5, CHCl\(_3\), 93% ee).

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (hexane:2-propanol = 80:20, 0.3 mL/min, 254 nm); minor enantiomer \(t_R = 20.7\) min, major enantiomer \(t_R = 27.1\) min, 93% ee.

tert-butyl (\(R\))-(1-(4-bromophenyl)-2,2-dicyanoethyl)carbamate (6n)

Reaction was performed in CHCl\(_3\) (2.7 mL) at \(-20\) °C for 24 h. White solids (53.0 mg, 76% yield); Colorless oil (53.1 mg, 88% yield); \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.62 (d, \(J = 8.7\) Hz, 2H), 7.36 (d, \(J = 8.4\) Hz, 2H), 5.23 (br, 1H), 5.08 (t, \(J = 5.5\) Hz, 1H), 4.79 (d, \(J = 3.4\) Hz, 1H), 1.47 (s, 9H); \(^13\)C NMR (125 MHz, CDCl\(_3\)): δ 154.7, 132.7, 132.6, 128.7, 110.8, 110.6, 82.1, 55.2, 29.5, 28.1; IR (neat) 3367, 2915, 1687, 1508, 1246, 1155 cm\(^{-1}\); HRMS (ESI+) calcd for C\(_{15}\)H\(_{15}\)BrN\(_3\)O\(_2\) [M - H\(^-\)] 348.0353: found 348.0360; \([\alpha]\)\(_D\)\(^{26}\) = +29.2 (c = 0.5, CHCl\(_3\), 95% ee).

Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexane:2-propanol = 70:30, 0.3 mL/min, 254 nm); minor enantiomer \(t_R = 28.4\) min, major enantiomer \(t_R = 18.1\) min, 95% ee.

tert-butyl (\(R\))-(2,2-dicyano-1-(2-(trifluoromethyl)phenyl)ethyl)carbamate (6o)

Reaction was performed in CHCl\(_3\) (2.7 mL) at \(-20\) °C for 24 h. Colorless oil (55.2 mg, 81% yield); \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.94-7.44 (m, 4H), 5.66 (br, 1H), 5.32 (br, 1H), 4.73 (br, 1H), 1.47 (s, 9H); \(^19\)F NMR (100 MHz, CDCl\(_3\)): δ 154.3, 133.3, 133.2, 130.1, 128.6, 127.4, 127.0, 123.6, 110.7, 110.4, 82.0, 50.2, 29.2, 28.0; IR (neat) 3346, 2982, 2934, 1704, 1456, 1367, 1312, 1120, 770 cm\(^{-1}\); HRMS (ESI+) calcd for C\(_{16}\)H\(_2\)F\(_3\)N\(_3\)O\(_2\) [M - H\(^-\)] 338.1122: found 338.1118; \([\alpha]\)\(_D\)\(^{17}\) = +19.1 (c = 1.0, CHCl\(_3\), 88% ee).

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (hexane:2-propanol = 95:5, 1.5 mL/min, 254 nm); minor enantiomer \(t_R = 14.9\) min, major enantiomer \(t_R = 45.2\) min, 88% ee.

tert-butyl (\(R\))-(2,2-dicyano-1-(naphthalen-1-yl)ethyl)carbamate (6p)

S12
Reaction time: 48 h; white solids (64.0 mg, 99% yield); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.97-7.94 (m, 3H), 7.75 (d, $J = 5.5$ Hz, 1H), 7.64-7.53 (m, 3H), 6.14 (dd, $J = 5.5$, 4.1 Hz, 1H), 5.39 (d, $J = 5.5$ Hz, 1H), 4.79 (d, 4.1, 1H), 1.48 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 154.8, 134.0, 130.6, 130.2, 130.0, 129.4, 127.6, 126.6, 125.1, 123.9, 121.8, 111.4, 81.8, 50.3, 28.8, 28.1; IR (neat) 3350, 2994, 2898, 1682, 1507, 1330, 1251, 1162, 775 cm$^{-1}$; HRMS (ESI$^+$) calcd for C$_{19}$H$_{19}$N$_3$NaO$_2$ [M + Na]$^+$ 344.1369: found 344.1361; $[\alpha]_{D}^{25}$ = +57.2 (c = 0.5, CHCl$_3$, 98% ee).

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (hexane:2-propanol = 90:10, 1.0 mL/min, 254 nm); minor enantiomer $t_R = 41.6$ min, major enantiomer $t_R = 12.8$ min, 98% ee.

tert-butyl ($R$)-(2,2-dicyano-1-(naphthalen-2-yl)ethyl)carbamate (6g)

Reaction time: 40 h; white solids (52.0 mg, 81% yield); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.94-7.86 (m, 4H), 7.57-7.53 (m, 3H), 5.46 (br, 1H), 5.30-5.28 (m, 1H), 4.86 (d, $J = 3.2$ Hz, 1H), 1.49 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 154.9, 133.7, 132.9, 131.0, 129.6, 128.3, 127.8, 127.3, 127.1, 126.9, 123.7, 111.1, 110.8, 81.8, 55.7, 29.7, 28.1; IR (neat) 3343, 2904, 1687, 1509, 1323, 1244, 1159, 856, 748, 616 cm$^{-1}$; HRMS (ESI$^+$) calcd for C$_{19}$H$_{19}$N$_3$NaO$_2$ [M + Na]$^+$ 344.1369: found 344.1363; $[\alpha]_{D}^{25}$ = +63.9 (c = 0.5, CHCl$_3$, 98% ee).

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (hexane:2-propanol = 90:10, 0.5 mL/min, 254 nm); minor enantiomer $t_R = 54.7$ min, major enantiomer $t_R = 26.6$ min, 98% ee.

tert-butyl ($R$)-(2,2-dicyano-1-(thiophen-2-yl)ethyl)carbamate (6r)

Reaction time: 72 h; white solids (44.5 mg, 80% yield); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.41 (dd, $J = 5.3$, 1.2 Hz, 1H), 7.32 (d, $J = 3.4$ Hz, 1H), 7.09 (dd, $J = 5.0$, 3.6 Hz, 1H), 5.40 (t, $J = 6.0$ Hz, 1H), 5.27 (d, $J = 6.2$ Hz, 1H), 4.79 (d, $J = 3.7$ Hz, 1H), 1.48 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 154.4, 135.5, 127.6, 127.4, 127.0, 110.9, 110.6, 82.1, 51.8, 30.2, 28.1; IR (neat) 3331, 1692, 1510, 1244, 1159, 619 cm$^{-1}$; HRMS (ESI$^+$) calcd for C$_{13}$H$_{15}$N$_3$NaO$_2$S [M + Na]$^+$ 300.0777: found 300.0776; $[\alpha]_{D}^{26}$ = +22.6 (c = 0.5, CHCl$_3$, 73% ee).

Enantiomeric excess was determined by HPLC with a Chiralcel AD-3 column (hexane:2-propanol = 80:20, 0.5 mL/min, 254 nm); minor enantiomer $t_R = 21.6$ min, major enantiomer $t_R = 16.1$ min, 73% ee.

tert-butyl ($R$)-(2,2-dicyano-1-(furan-2-yl)ethyl)carbamate (6s)
Reaction was performed in CHCl₃ (2.7 mL) at –20 °C for 24 h. White solids (36.1 mg, 69% yield); ¹H NMR (400 MHz, CDCl₃): δ 7.50 (d, J = 1.8 Hz, 1H), 6.57 (d, J = 3.2 Hz, 1H), 6.45 (dd, J = 3.4, 2.0 Hz, 1H), 5.44 (d, J = 7.8 Hz, 1H), 5.33 (dd, J = 7.8, 5.2 Hz, 1H), 4.58 (d, J = 5.0 Hz, 1H), 1.48 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 154.4, 146.3, 144.0, 111.0, 110.6, 110.5, 82.0, 49.9, 28.6, 28.1; IR (neat) 3336, 2909, 1687, 1500, 1249, 1156, 1016, 751 cm⁻¹; HRMS (ESI+) calcd for C₁₃H₁₅N₃NaO₃ [M + Na]⁺ 284.1006: found 284.1005; [α]D²⁶ = +2.1 (c = 0.5, CHCl₃, 81% ee).

Enantiomeric excess was determined by HPLC with a Chiralpak IC-3 column (hexane:2-propanol = 70:30, 0.5 mL/min, 220 nm); minor enantiomer tr = 25.7 min, major enantiomer tr = 22.4 min, 81% ee.

tert-butyl (S)-(2,2-dicyano-1-cyclohexylethyl)carbamate (6t)

Reaction was performed with 1 mol % of 1d for 96 h. White solids (40.6 mg, 73% yield); ¹H NMR (400 MHz, CDCl₃): δ 4.79 (d, J = 9.6 Hz, 1H), 4.17 (d, J = 4.4 Hz, 1H), 4.05-3.99 (m, 1H), 1.84-1.63 (m, 6H), 1.47 (s, 9H), 1.37-1.02 (m, 5H); ¹³C NMR (100 MHz, CDCl₃): δ 155.0, 111.4, 111.3, 81.2, 55.8, 39.9, 30.0, 28.4, 28.2, 27.0, 25.60, 25.57, 25.5; IR (neat) 3355, 2931, 2856, 1705, 1516, 1368, 1256, 1170 cm⁻¹; HRMS (ESI+) calcd for C₁₅H₂₃N₃NaO₂ [M + Na]⁺ 300.1682: found 300.1677; [α]D²⁶ = –64.5 (c = 0.5, CHCl₃).

5. Gram-scale synthesis of 6a
Catalyst 3b (31 mg, 0.05 mmol, 0.005 eq) and malononitrile 4 (1.32 g, 20 mmol, 2 eq) were added to a one-necked round flask containing a stir bar under Ar. CHCl₃ (100 ml) was added to the flask, and the mixture was stirred at –50 °C. To the resulting suspension, N-Boc imine 5a (2.16 g, 10 mmol, 1.0 eq) was added. After being stirred for 48 h, solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 4/1 to 0/1) to afford colorless oil 6a (2.57 g, 95% yield, 96% ee). 30 mg of catalyst 3b were recovered after silica gel column chromatography (97% recovery).

6. Transformation of tert-butyl (S)-(2,2-dicyano-1-cyclohexylethyl)carbamate (6t)

Magnesium monoperoxyphthalate hexahydrate (39.0 mg, 0.062 mmol, 0.75 eq) was added to a stirred solution of tert-butyl (S)-(2,2-dicyano-1-cyclohexylethyl)carbamate (6s) (23.0 mg, 0.083 mmol, 1.0 eq) and Li₂CO₃ (9.2 mg, 0.124 mmol, 1.5 eq) in methanol (0.83 ml) at 0 °C. After stirring for 4 h, the reaction mixture was quenched by water and extracted with CH₂Cl₂ three times. The combined organic layers were dried over Na₂SO₄. After removal of Na₂SO₄ by filtration, solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 10/1) to give the product S1 as white solids (16.0 mg, 71% yield).

1H NMR (400 MHz, CDCl₃): δ 5.02 (d, J = 9.2 Hz, 1H), 4.20 (dd, J = 9.2, 5.2 Hz, 1H), 3.73 (s, 3H), 1.77-1.56 (m, 6H), 1.44 (s, 9H), 1.30-1.03 (m, 5H); 13C NMR (100 MHz, CDCl₃): δ 172.9, 155.6, 79.7, 58.2, 52.0, 41.0, 29.4, 28.3, 28.1, 25.9; IR (neat) 3378, 2929, 1744, 1681, 1509, 1152 cm⁻¹; HRMS (ESI+) calcd for C₁₄H₂₅NNaO₄ [M + Na]^+ 294.1676: found 294.1674; [α]D²⁶ = +22.1 (c = 0.5, CHCl₃).

Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane:2-propanol = 99:1, 1.0 mL/min, 220 nm); major enantiomer tr = 26.5 min, minor enantiomer tr = 18.9 min, 94% ee.

7. General procedure for asymmetric Mannich reaction of malononitrile with N-Boc ketimines
Catalyst 3b (1.3 mg, 0.002 mmol, 0.02 eq) and malononitrile (7.3 mg, 0.11 mmol, 1.1 eq) were added to a one-necked round flask containing a stir bar under Ar. CHCl$_3$ (1.0 ml) was added to the flask, and the mixture was stirred at –50 °C. To the resulting suspension, N-Boc imine 7 (0.1 mmol, 1.0 eq) was added. After being stirred for appropriate time, solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 2/1) to afford product. The enantiomeric excesses of the products were determined by chiral stationary phase HPLC using Daicel Chiralcel AD-H, and Chiralpak IC-3 column.

8. Analytical data for products of enantioselective Mannich reaction of malononitrile with N-Boc ketimines

tert-butyl (R)-(3-(dicyanomethyl)-1-methyl-2-oxoindolin-3-yl)carbamate (8a)

![Chemical structure](image)

Reaction time: 20 h; pale pink solids (29.6 mg, 91% yield); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.86 (d, $J$ = 7.8 Hz, 1H), 7.48 (t, $J$ = 7.8 Hz, 1H), 7.21 (t, $J$ = 7.8 Hz, 1H), 6.96 (d, $J$ = 7.8 Hz, 1H), 5.75 (br, 1H), 5.43 (br, 1H), 3.31 (s, 3H), 1.41 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 170.7, 154.5, 143.4, 131.7, 125.5, 124.6, 124.3, 109.7, 109.3, 109.1, 82.3, 60.7, 29.3, 28.0, 26.9; IR (neat) 3284, 2900, 1703, 1613, 1518, 1496, 1470, 1130 cm$^{-1}$; HRMS (ESI+) calcd for C$_{17}$H$_{18}$N$_4$NaO$_3$ [M + Na]$^+$ 349.1271: found 349.1269; $[\alpha]_D^{25}$ = –23.0 (c = 0.01, CHCl$_3$, 82% ee).

Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexane:2-propanol = 90:10, 1.0 mL/min, 254 nm); minor enantiomer $t_R$ = 56.0 min, major enantiomer $t_R$ = 39.2 min, 82% ee.

tert-butyl (R)-(3-(dicyanomethyl)-1,5-dimethyl-2-oxoindolin-3-yl)carbamate (8b)

![Chemical structure](image)

Reaction time: 20 h; pale pink solids (32.1 mg, 94% yield); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.66 (s, 1H), 7.27 (d, $J$ = 8.0 Hz, 1H), 6.84 (d, $J$ = 8.0 Hz, 1H), 5.63 (br, 1H), 5.44 (br, 1H), 3.29 (s, 3H), 2.39 (s, 3H), 1.43 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 170.6, 154.5, 141.0, 134.2, 132.0, 126.2, 124.5, 109.8, 109.2, 109.0, 82.3, 60.8, 29.3, 28.0, 26.9, 21.2; IR (neat) 3288, 2904, 2382, 2349, 1704, 1620, 1502, 1367, 1252, 1164 cm$^{-1}$; HRMS (ESI+) calcd for C$_{18}$H$_{20}$N$_4$NaO$_3$ [M + Na]$^+$ 363.1428: found 363.1425; $[\alpha]_D^{25}$ = –70.7(c = 0.01, CHCl$_3$, 82% ee).

Enantiomeric excess was determined by HPLC with a Chiralpak IC-3 column (hexane:2-propanol = 90:10, 0.3 mL/min, 254 nm); minor enantiomer $t_R$ = 42.8 min, major enantiomer $t_R$ = 39.0 min, 82% ee.

tert-butyl (R)-(3-(dicyanomethyl)-5-methoxy-1-methyl-2-oxoindolin-3-yl)carbamate (8c)
Reaction time: 30 h; pale purple solids (34.8 mg, 97% yield); ¹H NMR (400 MHz, CDCl₃): δ 7.51 (d, J = 2.3 Hz, 1H), 7.98 (dd, J = 8.7, 2.7 Hz, 1H), 6.87 (d, J = 8.7 Hz, 1H), 5.63 (br, 1H), 5.43 (br, 1H), 3.83 (s, 3H), 3.29 (s, 3H), 1.43 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 170.3, 156.9, 154.6, 136.6, 125.6, 116.1, 112.7, 109.9, 109.7, 109.1, 82.4, 60.9, 55.8, 29.2, 28.0, 26.9; IR (neat) 3284, 2901, 2360, 2341, 1704, 1604, 1497, 1366, 1286, 1038 cm⁻¹; HRMS (ESI+) calcd for C₁₈H₂₀N₄NaO₄ [M + Na]⁺ 379.1377: found 379.1374; [α]D₂⁶ = -60.0 (c = 0.001, CHCl₃, 85% ee).

Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexane:2-propanol = 90:10, 1.0 mL/min, 254 nm); minor enantiomer tR = 62.2 min, major enantiomer tR = 45.3 min, 85% ee.

tert-butyl (R)-(3-(dicyanomethyl)-5-fluoro-1-methyl-2-oxindolin-3-yl)carbamate (8d)

Reaction time: 16 h; pale pink solids (33.0 mg, 96% yield); ¹H NMR (400 MHz, CDCl₃): δ 7.69 (dd, J = 7.8, 2.5 Hz, 1H), 7.22-7.17 (m, 1H), 6.91 (dd, J = 8.9, 4.1 Hz, 1H), 5.65 (br, 1H), 5.40 (br, 1H), 3.31 (s, 3H), 1.44 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 170.4, 159.7 (d, ¹JCF = 246.2 Hz), 154.5, 139.4, 125.9 (d, ³JCF = 8.6 Hz), 118.2 (d, ²JCF = 24.0 Hz), 114.4 (d, ²JCF = 26.8 Hz), 110.1 (d, ³JCF = 8.6 Hz), 109.4, 108.8, 82.7, 60.8, 29.1, 28.0, 27.0; IR (neat) 3279, 2923, 2359, 1736, 1687, 1520, 1488, 1372, 1286, 1162 cm⁻¹; HRMS (ESI+) calcd for C₁₇H₁₇FNO₄ [M + Na]⁺ 367.1177: found 367.1175; [α]D₂⁵ = -56.4 (c = 0.02, CHCl₃, 80% ee).

Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexane:2-propanol = 90:10, 1.0 mL/min, 254 nm); minor enantiomer tR = 29.6 min, major enantiomer tR = 22.5 min, 80% ee.

tert-butyl (R)-(5-chloro-3-(dicyanomethyl)-1-methyl-2-oxindolin-3-yl)carbamate (8e)

Reaction time: 16 h; pale pink solids (29.2 mg, 81% yield); ¹H NMR (400 MHz, CDCl₃): δ 7.88 (d, J = 2.1 Hz, 1H), 7.46 (dd, J = 8.4, 2.0 Hz, 1H), 6.90 (d, J = 8.5 Hz, 1H), 5.70 (br, 1H), 5.37 (br, 1H), 3.31 (s, 3H), 1.44 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 170.3, 154.4, 142.0, 131.7, 129.8, 126.3, 126.0, 110.3, 109.4, 108.7, 82.8, 60.7, 29.2, 28.0, 27.0; IR (neat) 3304, 2898, 2361, 2340, 1729, 1685, 1611, 1519, 1368, 1283, 1157, 1103 cm⁻¹; HRMS (ESI+) calcd for C₁₇H₁₇ClN₄O₄ [M + Na]⁺ 383.0881: found 383.0878; [α]D₂⁵ = -32.4 (c = 0.01, CHCl₃, 80% ee).

Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexane:2-propanol = 90:10, 1.0 mL/min, 254 nm); minor enantiomer tR = 27.4 min, major enantiomer tR = 21.1 min, 80% ee.
9. NMR study

(1) $^1$H-NMR analysis on interaction between 10 and malononitrile 4 (1:1 ratio). Chart-a is a $^1$H-NMR spectrum of malononitrile 4 (0.1 M) in CDCl$_3$. Chemical shift of methylene protons is 3.602 ppm. Chart-b is a $^1$H-NMR spectrum of 10 (0.1 M) and malononitrile 4 (0.1 M) in CDCl$_3$. Chemical shift of methylene protons is 3.563 ppm. The acidic methylene protons of malononitrile 4 broadened and shifted up-field by 0.039 ppm.

(2) $^1$H-NMR analysis on interaction between 10 and N-Boc imine 5a (1:1 ratio). Mixing of 10 (0.1 M) and N-Boc imine 5a (0.1 M) in CDCl$_3$ did not produce any obvious changes in the $^1$H-NMR spectrum.

(3) $^1$H-NMR analysis on interaction between 11 and malononitrile 4 (1:1 ratio). Chart-a is a $^1$H-NMR spectrum of malononitrile 4 (0.1 M) in CDCl$_3$. Chemical shift of methylene protons is 3.602 ppm. Chart-c is a $^1$H-NMR spectrum of 11 (0.1 M) and malononitrile 4 (0.1 M) in CDCl$_3$. Chemical shift of methylene protons is 3.589 ppm. The methylene protons of malononitrile 4 slightly shifted up-field by 0.013 ppm.
(4) $^1$H-NMR analysis on interaction between 11 and N-Boc imine 5a (1:1 ratio).
Chart-d is a $^1$H-NMR spectrum of N-Boc imine 5a (0.1 M) in CDCl$_3$. Chemical shift of iminoproton is 8.883 ppm. Chart-e is a $^1$H-NMR spectrum of 11 (0.1 M) and N-Boc imine 5a (0.1 M) in CDCl$_3$. Chemical shift of iminoproton is 8.838 ppm. *Iminoproton of N-Boc imine 5a shifted up-field by 0.045 ppm.*

(5) $^{19}$F-NMR analysis on interaction between 11 and malononitrile 4 (1:10 ratio). Chemical shifts of $^{19}$F-NMR spectra were reported relative to trifluorotoluene ($\delta = -63.72$). Chart-f is a $^{19}$F-NMR spectrum of 11 (0.1 M) in CDCl$_3$. Chemical shift of fluorine atom *ortho* to the iodo group (these appear at roughly $\delta -115$ ppm) is $\delta -114.131$ ppm. Chart-g is a $^{19}$F-NMR spectrum of 11 (0.1 M) and malononitrile 4 (1.0 M) in CDCl$_3$. Chemical shift of the fluorine atom is $\delta -114.380$ ppm. *The fluorine atom ortho to the iodo group of 11 shifted up-field by 0.249 ppm.*
(6) $^{19}$F-NMR analysis on interaction between $\text{11}$ and $N$-Boc imine $\text{5a}$ (1:10 ratio).

Chemical shifts of $^{19}$F-NMR spectra were reported relative to trifluorotoluene ($\delta$ = 63.72). Chart-f is a $^{19}$F-NMR spectrum of $\text{11}$ (0.1 M) in CDCl$_3$. Chemical shift of fluorine atom ortho to the iodo group (these appear at roughly −115 ppm) is −114.131 ppm. Chart-h is a $^{19}$F-NMR spectrum of $\text{11}$ (0.1 M) and $N$-Boc imine $\text{5a}$ (1.0 M) in CDCl$_3$. Chemical shift of the fluorine atom is −114.817 ppm. The fluorine atom ortho to the iodo group of $\text{11}$ shifted up-field by 0.686 ppm.

10. Plausible transition state model

11. Asymmetric Mannich reaction of other nucleophiles with $N$-Boc aldimine
12. $^1$H-NMR and $^{13}$C-NMR spectra
S30
S35
13. HPLC spectra

HPLC spectra were recorded using a Chiralpak IA column (hexane:2-propanol = 90:10, 0.5 mL/min, 254 nm).

Chiralpak IA column (hexane:2-propanol = 90:10, 0.5 mL/min, 254 nm)
Chiralpak IA column (hexane:2-propanol = 90:10, 0.3 mL/min, 254 nm)
Chiralpak IA column (hexane:2-propanol = 90:10, 0.5 mL/min, 254 nm)
Chiralpak IA column (hexane:2-propanol = 90:10, 0.3 mL/min, 254 nm)
Chiralcel AD-H column (hexane:2-propanol = 70:30, 0.5 mL/min, 254 nm)
Chiralcel AD-H column (hexane:2-propanol = 85:15, 1.0 mL/min, 230 nm)
Chiralcel AD-H column (hexane:2-propanol = 85:15, 1.0 mL/min, 230 nm)
Chiralcel AD-H column (hexane:2-propanol = 85:15, 1.0 mL/min, 230 nm)
Chiralcel AD-H column (hexane:2-propanol = 85:15, 1.0 mL/min, 230 nm)
Chiralcel AD-H column (hexane:2-propanol = 85:15, 1.0 mL/min, 230 nm)
Chiralcel AD-H column (hexane:2-propanol = 85:15, 1.0 mL/min, 230 nm)
Chiralcel AD-H column (hexane:2-propanol = 85:15, 1.0 mL/min, 230 nm)
Chiralcel AD-H column (hexane:2-propanol = 85:15, 1.0 mL/min, 230 nm)
Chiralcel AD-H column (hexane:2-propanol = 85:15, 1.0 mL/min, 230 nm)
Chiralpak IA column (hexane:2-propanol = 95:5, 1.5 mL/min, 254 nm)
Chiralpak IA column (hexane:2-propanol = 90:10, 0.3 mL/min, 254 nm)
Chiralpak IA column (hexane:2-propanol = 90:10, 1.0 mL/min, 254 nm)
Chiralcel AD-H column (hexane:2-propanol = 85:15, 1.0 mL/min, 230 nm)
Chiralcel AD-H column (hexane:2-propanol = 85:15, 1.0 mL/min, 230 nm)
Chiralcel AD-H column (hexane:2-propanol = 85:15, 1.0 mL/min, 230 nm)
Chiralcel AD-H column (hexane:2-propanol = 90:10, 1.0 mL/min, 254 nm)
Chiralpak IC-3 column (hexane:2-propanol = 90:10, 0.3 mL/min, 254 nm)
Chiralcel AD-H column (hexane:2-propanol = 90:10, 1.0 mL/min, 254 nm)
Chiralcel AD-H column (hexane:2-propanol = 90:10, 1.0 mL/min, 254 nm)
Chiralcel AD-H column (hexane:2-propanol = 90:10, 1.0 mL/min, 254 nm)