VAPOL Phosphoric Acid Catalysis: The Highly Enantioselective Addition of Imides to Imines

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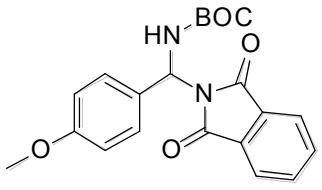
Supplementary Information

General Information: All reactions were carried out in flame-dried or oven-dried screw-cap test tubes and were allowed to proceed under a dry argon atmosphere with magnetic stirring. Ether was purified by passing through a column of activated alumina under a dry argon atmosphere. (*S*)-VAPOL and **PA5** was synthesized according to the literature procedure.[1] *Note: VAPOL phosphoric acid can be purchased from Aldrich or Strem chemicals.* All imines were synthesized according to the literature procedure except Schlenk filtration was required for imines of high purity to be isolated.[2] Phthalimide, Maleimide, 4-Methylphthalimide and 4-Bromophthalimide were purchased from commercial sources and used without further purification. 4-Flurophthalimide, 3-Methylphthalimide, 3-Flurophthalimide and 4-Chlorophthalimide were synthesized according to literature procedure.[3] Substituted BINOL phosphoric acids (**PA2**,[4] **PA3**[5] and **PA4**[6]) were prepared from chiral (*S*)-BINOL according to the known literature procedures. Thin layer chromatography was performed on Merck TLC plates (silica gel 60 F_{254}). Flash column chromatography was performed with Merck silica gel (230-400 mesh). Enantiomeric excess (ee) was determined using a Varian Prostar HPLC with a 210 binary pump and a 335 diode array detector. Optical rotations were performed on a Rudolph Research Analytical Autopol IV polarimeter (λ 589) using a 700-μL cell with a path length of 1-dm. Melting points were determined using a MEL-TEMP 3.0 instrument and are uncorrected. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker Avance DPX-250 (250 MHz) instrument with chemical shifts reported relative to tetramethylsilane (TMS). The HRMS data were measured on an Agilent 1100 LC/MS ESI/TOF mass spectrometer with electrospray ionization. Compounds described in the literature were characterized by comparing their ^{1}H NMR, ^{13}C NMR, and melting point (mp) to the reported values.

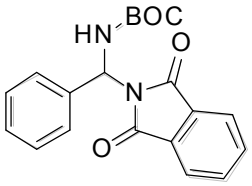
Racemates: All the racemic products were prepared by using Phenylphosphinic acid (30 mol%) as a catalyst and their chiral HPLC retention time data were compared just prior to authentic samples with enantiomeric excess.

General procedure for VAPOL-Phosphoric acid-catalyzed asymmetric addition of imides to imines: In a typical experiment the Boc-imine (0.1 mmol), imide (0.05 mmol) and VAPOL-Phosphoric acid (5 mol%) were weighed into a dry, re-sealable test tube with septa and stir bar. Dry ether (1.0 mL) was added to the mixture via syringe and the resulting mixture was stirred at room temperature overnight. Ether was removed by rotary evaporation to give a crude solid mixture that was purified by column chromatography on silica gel to give the product.



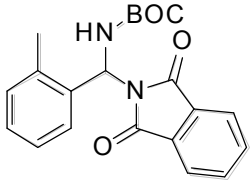
(-)-tert-Butyl (1,3-dioxoisoindolin-2-yl)(4-methoxyphenyl)methylcarbamate, 2a

The reaction was performed in 0.1 mmol scale for 12h using 5 mol% (*S*)-VAPOL-phosphoric acid. The product was obtained by flash chromatography (hexane: acetone = 3:1) as a white solid, 18 mg, 92% yield, 96% ee, mp.: 56-59 °C. HPLC analysis: Chiralcel AD-H (hexane/iPrOH = 80/20, 1.0 mL/min), $t_{\text{r-major}}$ 24.03 min, $t_{\text{r-minor}}$ 30.57 min. $[\alpha]^{20}_{D} = -34.1°$ (c = 0.10, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.45 (s, 9H), 3.78 (s, 3H), 6.30 (s, broad, 1H,) 6.86 (d, *J* = 8.7 Hz, 2H), 7.36 (d, *J* = 9.0 Hz, 2H), 7.70-7.74 (m, 2H), 7.83-7.87 (m, 2H). ^{13}C NMR (62.5MHz, $CDCl_3$): δ 28.25, 28.28, 28.34, 55.31, 59.83, 80.66, 113.91, 114.09, 123.52, 123.61, 127.03, 127.39, 129.43, 131.80, 134.26, 154.31, 159.61, 167.51. MS (ESI): *m/z* = 405 ($[M+Na]^+$). HRMS (ESI) Calcd for $C_{21}H_{22}N_2NaO_5$ ($[M+Na]^+$) m/z 405.1421, Found 405.1436.



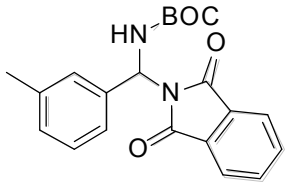
(-)-tert-Butyl (1,3-dioxoisoindolin-2-yl)(phenyl)methylcarbamate, 2e

The reaction was performed in 0.1 mmol scale for 12h using 5 mol% (*S*)-VAPOL-phosphoric acid. The product was obtained by flash chromatography (hexane: acetone = 3:1) as a white solid, 16 mg, 88% yield, 93% ee., mp.: 167-170 °C, HPLC analysis: Chiralcel AD-H (hexane/iPrOH = 80/20, 1.0 mL/min), $t_{\text{r-major}}$ 16.83 min, $t_{\text{r-minor}}$ 15.69 min. $[\alpha]^{20}_{D} = -40.1°$ (c = 0.25, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.45 (s, 9H), 6.30 (s, broad, 1H,), 7.10 (d, *J* =10.0 Hz, 1H), 7.32-7.45 (m, 5H), 7.71-7.74 (m, 2H), 7.84-7.87 (m, 2H). ^{13}C NMR (62.5MHz, $CDCl_3$): δ 28.29, 60.04, 80.75, 123.66, 126.02, 128.51, 128.81, 131.78, 134.32, 137.24, 154.36, 167.46. MS (ESI): *m/z* = 375 ($[M+Na]^+$). HRMS (ESI) Calcd for $C_{20}H_{20}N_2NaO_4$ ($[M+Na]^+$) m/z 375.1315, Found 375.1317.



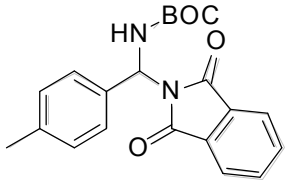
(+)-tert-Butyl (1,3-dioxoisoindolin-2-yl)(o-tolyl)methylcarbamate, 2f

The reaction was performed in 0.1 mmol scale for 12h using 5 mol% (*S*)-VAPOL-phosphoric acid. The product was obtained by flash chromatography (hexane: acetone = 3:1) as a white solid, 17 mg, 94% yield, 99% ee, mp.: 154-156 °C. HPLC analysis: Chiralcel AD-H (hexane/iPrOH = 80/20, 1.0 mL/min), $t_{\text{r-major}}$ 13.35 min, $t_{\text{r-minor}}$ 10.55 min. $[\alpha]^{20}_{D} = 68.2°$ (c = 0.18, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.45 (s, 9H), 2.49 (s, 3H), 6.12 (s, broad, 1H,) 7.19-7.21 (m, 4H), 7.54 (d, *J* =7.5Hz, 1H), 7.70-7.74 (m, 2H), 7.83-7.87 (m, 2H). ^{13}C NMR (62.5MHz, $CDCl_3$): δ 19.47, 28.26, 58.52, 80.62, 123.57, 126.24, 126.30, 128.70, 131.06, 131.78, 134.25, 135.48, 136.11, 154.10, 167.75. MS (ESI): *m/z* = 389 ($[M+Na]^+$). HRMS (ESI) Calcd for $C_{20}H_{20}N_2NaO_4$ ($[M+Na]^+$) m/z 375.1472, Found 375.1457.



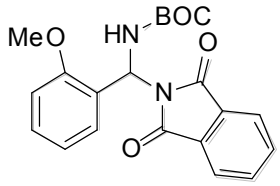
(-)-tert-Butyl (1,3-dioxoisoindolin-2-yl)(m-tolyl)methylcarbamate, 2g

The reaction was performed in 0.1 mmol scale for 12h using 5 mol% (*S*)-VAPOL-phosphoric acid. The product was obtained by flash chromatography (hexane: acetone = 3:1) as a white solid, 16 mg, 86% yield, 90% ee, mp.: 127-129 °C. HPLC analysis: Chiralcel AD-H (hexane/iPrOH = 80/20, 1.0 mL/min), $t_{\text{r-major}}$ 12.12 min, $t_{\text{r-minor}}$ 11.37 min. $[\alpha]^{20}_{D} = -36.1°$ (c = 0.10, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.45 (s, 9H), 2.33 (s, 3H), 6.28 (s, broad, 1H,) 7.04-7.26 (m, 5H), 7.71-7.75 (m, 2H), 7.84-7.87 (m, 2H). ^{13}C NMR (62.5MHz, $CDCl_3$): δ 21.50, 28.29, 60.09, 80.71, 123.05, 123.64, 126.70, 128.71, 129.29, 131.82, 134.27, 137.16, 138.59, 154.36, 167.49. MS (ESI): *m/z* = 389 ($[M+Na]^+$). HRMS (ESI) Calcd for $C_{21}H_{22}N_2NaO_4$ ($[M+Na]^+$) m/z 375.1472, Found 375.1452.



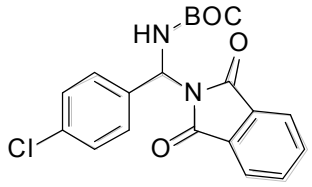
(-)-tert-Butyl (1,3-dioxoisoindolin-2-yl)(p-tolyl)methylcarbamate, 2h

The reaction was performed in 0.1 mmol scale for 12h using 5 mol% (*S*)-VAPOL-phosphoric acid. The product was obtained by flash chromatography (hexane: acetone = 3:1) as a white solid, 17 mg, 90% yield, 94% ee. mp.: 132-135 °C. HPLC analysis: Chiralcel OD-H (hexane/iPrOH = 98/2, 1.0 mL/min), $t_{\text{r-major}}$ 11.89 min, $t_{\text{r-minor}}$ 19.72 min. $[\alpha]^{20}_{D} = -52.3°$ (c = 0.25, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.47 (s, 9H), 2.34 (s, 3H), 6.32 (s, broad, 1H,), 7.07-7.36 (m, 5H), 7.75-7.86 (m, 4H). ^{13}C NMR (62.5MHz, $CDCl_3$): δ 21.10, 28.29, 59.96, 80.66, 123.61, 125.93, 129.46, 131.81, 134.26, 138.33, 154.34, 167.48. MS (ESI): *m/z* = 389 ($[M+Na]^+$). HRMS (ESI) Calcd for $C_{21}H_{22}N_2NaO_4$ ($[M+Na]^+$) m/z 389.1472, Found 389.1467.



(-)-tert-Butyl (1,3-dioxoisoindolin-2-yl)(2-methoxyphenyl)methylcarbamate, 2i

The reaction was performed in 0.1 mmol scale for 12h using 5 mol% (*S*)-VAPOL-phosphoric acid. The product was obtained by flash chromatography (hexane: acetone = 3:1) as a white solid, 17 mg, 91% yield, 93% ee, mp.: 52-54 °C. HPLC analysis: Chiralcel OD-H (hexane/iPrOH = 90/10, 1.0 mL/min), $t_{\text{r-major}}$ 18.32 min, $t_{\text{r-minor}}$ 14.92 min. $[\alpha]^{20}_{D} = -32.3°$ (c = 0.50, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.45 (s, 9H), 3.81 (s, 3H), 6.30 (s, broad, 1H), 6.85-6.96 (m, 2H), 7.27-7.33 (m, 2H), 7.52 (d, *J* = 7.2 Hz, 1H), 7.68-7.72 (m, 2H), 7.81-7.85 (m, 2H). ^{13}C NMR (62.5MHz, $CDCl_3$):δ 28.24, 28.30, 55.61, 110.93, 120.26, 123.43, 125.05, 127.59, 129.90, 131.92, 134.03, 154.17, 156.67, 167.33. MS (ESI): *m/z* = 405 ([M+Na]$^+$). HRMS (ESI) Calcd for $C_{21}H_{22}N_2NaO_5$ ([M+Na]$^+$) m/z 405.1421, Found 405.1412.

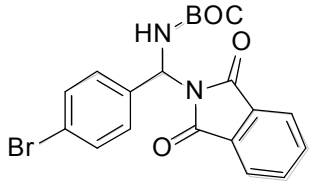


(*R*)-(-)-tert-Butyl (4-chlorophenyl)(1,3-dioxoisoindolin-2-yl)methylcarbamate, 2j

The reaction was performed in 0.1 mmol scale for 12h using 5 mol% (*S*)-VAPOL-phosphoric acid. The product was obtained by flash chromatography (hexane: acetone = 3:1) as a white solid, 18 mg, 93% yield, 93% ee, mp.: 170-172 °C. HPLC analysis: Chiralcel AD-H (hexane/iPrOH = 80/20, 1.0 mL/min), $t_{\text{r-major}}$ 18.04 min, $t_{\text{r-minor}}$ 19.80 min. $[\alpha]^{20}_{D} = -47.3°$ (c = 0.25, $CHCl_3$). The absolute configuration of this compound was determined to be *R* by X-ray crystallographic analysis. See X-ray data in attached file. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.45 (s, 9H), 6.28 (s, broad, 1H,), 7.07 (d, *J* =10.0 Hz, 1H), 7.30-7.39 (m, 4H), 7.73-7.76 (m, 2H), 7.85-7.88 (m, 2H). ^{13}C NMR (62.5MHz, $CDCl_3$): δ 28.27, 59.46, 81.01, 123.75, 127.51, 128.96, 131.67, 134.44, 135.88, 154.25, 167.37. MS (ESI): *m/z* = 409 ([M+Na]$^+$). HRMS (ESI) Calcd for $C_{20}H_{19}ClN_2NaO_4$

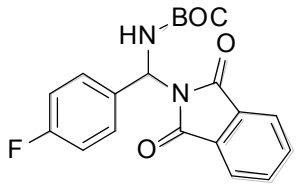
([M+Na]$^+$) m/z 409.0926, Found 409.0910.

Determination of Absolute Stereochemistry by Single X-Ray Crystal Analysis of (2j)



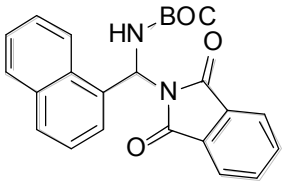
(-)-tert-butyl (4-bromophenyl)(1,3-dioxoisoindolin-2-yl)methylcarbamate, 2k

The reaction was performed in 0.1 mmol scale for 12h using 5 mol% (*S*)-VAPOL-phosphoric acid. The product was obtained by flash chromatography (hexane: acetone = 3:1) as a white solid, 19 mg, 87% yield, 90% ee, mp.: 158-160 °C. HPLC analysis: Chiralcel AD-H (hexane/iPrOH = 80/20, 1.0 mL/min), $t_{\text{r-major}}$ 18.95 min, $t_{\text{r-minor}}$ 22.15 min. $[\alpha]^{20}_{D} = -47.0°$ (c = 0.25, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.46 (s, 9H), 6.30 (s, broad, 1H,), 7.07 (d, *J* =10.0Hz, 1H), 7.30-7.50 (m, 4H), 7.76-7.87 (m, 4H). ^{13}C NMR (62.5MHz, $CDCl_3$): δ 28.27, 59.48, 80.98, 122.59, 123.75, 127.83, 131.65, 131.91, 134.45, 136.42, 154.22, 167.35. MS (ESI): *m/z* = 453 ([M+Na]$^+$). HRMS (ESI) Calcd for $C_{20}H_{19}BrN_2NaO_4$ ([M+Na]$^+$) m/z 453.0420, Found 453.0421.



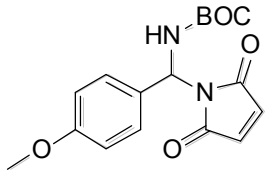
(-)-tert-Butyl (1,3-dioxoisoindolin-2-yl)(4-fluorophenyl)methylcarbamate, 2l

The reaction was performed in 0.1 mmol scale for 12h using 5 mol% (*S*)-VAPOL-phosphoric acid. The product was obtained by flash chromatography (hexane: acetone = 3:1) as a white solid, 17 mg, 90% yield, 93% ee, mp.: 155-157 °C. HPLC analysis: Chiralcel OD-H (hexane/iPrOH = 98/2, 1.0 mL/min), $t_{\text{r-major}}$ 16.28 min, $t_{\text{r-minor}}$ 21.03 min. $[\alpha]^{20}_{D} = -48.9°$ (c = 0.25, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.37 (s, 9H), 6.20 (s, broad, 1H,) 6.92-6.99 (m, 3H), 7.32-7.34 (m, 2H), 7.65-7.68 (m, 2H), 7.77-7.80 (m, 2H). ^{13}C NMR (62.5MHz, $CDCl_3$): δ 28.26, 59.55, 80.89, 115.53, 115.88, 123.71, 127.89, 128.03, 131.70, 133.24, 134.40, 154.24, 160.66, 164.60, 167.41. MS (ESI): *m/z* = 393 ($[M+Na]^+$). HRMS (ESI) Calcd for $C_{20}H_{19}FN_2NaO_4$ ($[M+Na]^+$) m/z 393.1221, Found 393.1220.



(+)-tert-Butyl (1,3-dioxoisoindolin-2-yl)(naphthalen-1-yl)methylcarbamate, 2m

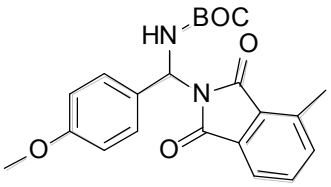
The reaction was performed in 0.1 mmol scale for 12h using 5 mol% (*S*)-VAPOL-phosphoric acid. The product was obtained by flash chromatography (hexane: acetone = 3:1) as a white solid, 17 mg, 86% yield, 91% ee, mp.: 182-184 °C. HPLC analysis: Chiralcel AD-H (hexane/iPrOH = 80/20, 1.0 mL/min), $t_{\text{r-major}}$ 19.76 min, $t_{\text{r-minor}}$ 17.09 min. $[\alpha]^{20}_{D} = 135.6°$ (c = 0.20, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.45 (s, 9H), 3.81 (s, 3H), 6.30 (s, broad, 1H), 7.42-7.70 (m, 6H), 7.81-7.84 (m, 5H), 8.29 (d, *J* = 8.3 Hz, 1H). ^{13}C NMR (62.5MHz, $CDCl_3$): δ 28.30, 58.01, 80.80, 123.29, 123.53, 123.62, 124.36, 124.89, 126.06, 127.01, 128.85, 129.65, 130.37, 131.73, 132.26, 133.87, 134.30, 154.20, 167.75. MS (ESI): *m/z* = 425 ($[M+Na]^+$). HRMS (ESI) Calcd for $C_{24}H_{22}N_2NaO_4$ ($[M+Na]^+$) m/z 425.1472, Found 425.1469.



(-)-tert-Butyl(2,5-dioxo-2H-pyrrol-1(5H)-yl)(4-methoxyphenyl)methylcarbamate,

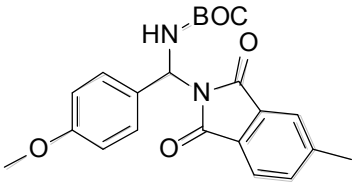
2n

The reaction was performed in 0.1 mmol scale for 12h using 5 mol% (*S*)-VAPOL-phosphoric acid. The product was obtained by flash chromatography (hexane: acetone = 3:1) as a white solid, 14 mg, 82% yield, 92% ee, mp.: 128-130 °C. HPLC analysis: Chiralcel OD-H (hexane/iPrOH = 85/15, 1.0 mL/min), $t_{\text{r-major}}$ 9.24 min, $t_{\text{r-minor}}$ 10.92 min. $[\alpha]^{20}_{D} = -11.5°$ (c = 0.19, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.45 (s, 9H), 3.78 (s, 3H), 6.15 (s, broad, 1H), 6.70-6.88 (m, 5H), 7.28 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (62.5MHz, $CDCl_3$): δ 28.26, 55.32, 59.77, 80.69, 114.12, 127.29, 129.20, 134.24, 154.29, 159.65, 169.89. MS (ESI): *m/z* = 355 ($[M+Na]^+$). HRMS (ESI) Calcd for $C_{17}H_{20}N_2NaO_5$ ($[M+Na]^+$) m/z 355.1264, Found 355.1268.



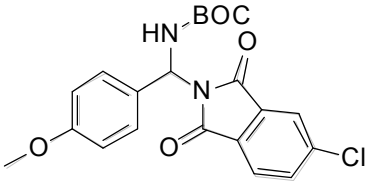
(-)-tert-Butyl(4-methoxyphenyl)(4-methyl-1,3-dioxoisoindolin-2-yl)methylcarbamate, 2o

The reaction was performed in 0.1 mmol scale for 12h using 5 mol% (*S*)-VAPOL-phosphoric acid. The product was obtained by flash chromatography (hexane: acetone = 3:1) as a white solid, 16 mg, 82% yield, 92% ee, mp.: 52-56 °C. HPLC analysis: Chiralcel AD-H (hexane/iPrOH = 80/20, 1.0 mL/min), $t_{\text{r-major}}$ 18.29 min, $t_{\text{r-minor}}$ 23.87 min. $[\alpha]^{20}_{D} = -30.63°$ (c = 0.80, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.45 (s, 9H), 2.68 (s, 3H), 3.77 (s, 3H), 6.31 (s, broad, 1H), 6.85 (d, *J* = 9.0 Hz, 2H), 7.04 (d, *J* = 10.0 Hz, 1H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.44-7.68 (m, 3H). ^{13}C NMR(62.5MHz,$CDCl_3$):δ 17.57, 28.30, 55.29, 59.55, 80.58, 114.06, 121.20, 127.35, 128.43, 129.64, 132.19, 133.75, 136.66, 138.38, 154.35, 159.54, 167.56, 168.27. MS (ESI): *m/z* = 419 ($[M+Na]^+$). HRMS (ESI) Calcd for $C_{22}H_{24}N_2NaO_5$ ($[M+Na]^+$) m/z 419.1577, Found 419.1562.



(-)-tert-Butyl(4-methoxyphenyl)(5-methyl-1,3-dioxoisoindolin-2-yl)methylcarbamate, 2p

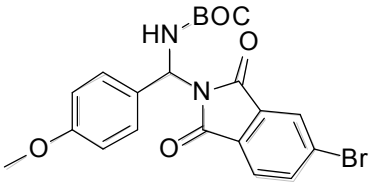
The reaction was performed in 0.1 mmol scale for 12h using 5 mol% (*S*)-VAPOL-phosphoric acid. The product was obtained by flash chromatography (hexane: acetone = 3:1) as a white solid, 22 mg, 90% yield, 92% ee, mp.: 47-49 °C. HPLC analysis: Chiralcel OD-H (hexane/iPrOH = 80/20, 1.0 mL/min), $t_{\text{r-major}}$ 6.72 min, $t_{\text{r-minor}}$ 7.92 min. $[\alpha]^{20}_{D}$ = -33.8° (c = 0.25, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.44 (s, 9H), 2.50 (s, 3H), 3.77 (s, 3H), 6.27 (s, broad, 1H), 6.85 (d, *J* = 4.5 Hz, 2H), 7.01 (d, *J* = 10.0 Hz, 1H), 7.35 (d, *J* = 9.0 Hz, 2H), 7.49-7.73 (m, 3H). ^{13}C NMR (62.5MHz,$CDCl_3$):δ 22.03, 28.24, 28.28, 55.29, 59.73, 80.56, 114.05, 123.51, 124.11, 127.35, 129.19, 129.57, 132.18, 134.81, 145.62, 154.33, 159.55, 167.58, 167.67. MS (ESI): *m/z* = 419 ($[M+Na]^+$). HRMS (ESI) Calcd for $C_{22}H_{24}N_2NaO_5$ ($[M+Na]^+$) m/z 419.1577, Found 419.1568.



(-)-tert-Butyl(5-chloro-1,3-dioxoisoindolin-2-yl)(4-methoxyphenyl)methylcarbamate, 2q

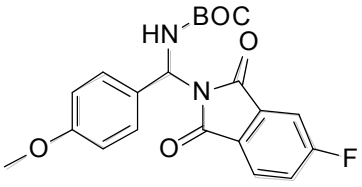
The reaction was performed in 0.1 mmol scale for 12h using 5 mol% (*S*)-VAPOL-phosphoric acid. The product was obtained by flash chromatography (hexane: acetone = 3:1) as a white solid, 19 mg, 92% yield, 93% ee, mp.: 82-85 °C. HPLC analysis: Chiralcel OD-H (hexane/iPrOH = 90/10, 1.0 mL/min), $t_{\text{r-major}}$ 9.72 min, $t_{\text{r-minor}}$ 13.23 min. $[\alpha]^{20}_{D}$ = -24.1° (c = 0.35, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.36 (s, 9H), 3.71 (s, 3H), 6.14 (s, broad, 1H), 6.79 (d, *J* = 8.7 Hz, 2H), 6.93 (d, *J* = 10.0 Hz, 1H), 7.28 (d, *J* = 8.5 Hz, 2H), 7.69-7.73 (m, 3H). ^{13}C NMR (62.5MHz, $CDCl_3$):δ 28.27, 55.33,

60.16, 80.80, 114.15, 124.05, 124.86, 127.39, 129.08, 129.86, 133.48, 134.31, 140.98, 154.26, 159.71, 166.21, 166.53. MS (ESI): *m/z* = 439 ([M+Na]$^+$). HRMS (ESI) Calcd for $C_{21}H_{21}ClN_2NaO_5$ ([M+Na]$^+$) m/z 439.1031, Found 439.1042.



(-)-tert-Butyl(5-bromo-1,3-dioxoisoindolin-2-yl)(4-methoxyphenyl)methylcarbamate, 2r

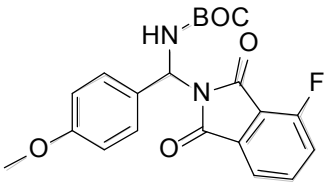
The reaction was performed in 0.1 mmol scale for 12h using 5 mol% (*S*)-VAPOL-phosphoric acid. The product was obtained by flash chromatography (hexane: acetone = 3:1) as a white solid, 19 mg, 84% yield, 90% ee, mp.: 88-90 °C. HPLC analysis: Chiralcel OD-H (hexane/iPrOH = 90/10, 1.0 mL/min), $t_{\text{r-major}}$ 10.19 min, $t_{\text{r-minor}}$ 13.03 min. $[\alpha]^{20}_D$ = -25.1° (c = 0.20, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.44 (s, 9H), 3.78 (s, 3H), 6.21 (s, broad, 1H), 6.86 (d, *J* = 8.7 Hz, 2H), 7.0 (d, *J* = 10.0 Hz, 1H), 7.35 (d, *J* = 8.7 Hz, 2H), 7.69-7.97 (m, 3H). ^{13}C NMR (62.5MHz, $CDCl_3$):δ 28.28, 55.33, 60.14, 80.82, 114.15, 124.97, 126.95, 127.39, 129.06, 129.19, 130.32, 133.44, 137.25, 154.26, 159.70, 166.14, 166.67. MS (ESI): *m/z* = 483 ([M+Na]$^+$). HRMS (ESI) Calcd for $C_{21}H_{21}BrN_2NaO_5$ ([M+Na]$^+$) m/z 483.0526, Found 483.0513.



(-)-tert-Butyl(5-fluoro-1,3-dioxoisoindolin-2-yl)(4-methoxyphenyl)methylcarbamate, 2s

The reaction was performed in 0.1 mmol scale for 12h using 5 mol% (*S*)-VAPOL-phosphoric acid. The product was obtained by flash chromatography (hexane: acetone = 3:1) as a white solid, 17 mg, 87% yield, 91% ee, mp.: 72-76 °C. HPLC analysis: Chiralcel OD-H (hexane/iPrOH = 90/10, 1.0 mL/min), $t_{\text{r-major}}$ 9.40 min, $t_{\text{r-minor}}$ 15.47

min. $[\alpha]^{20}_D$ = -23.5° (c = 0.20, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ 1.44 (s, 9H), 3.78 (s, 3H), 6.22 (s, broad, 1H), 6.87 (d, *J* = 8.7 Hz, 2H), 7.00 (d, *J* = 10.0 Hz, 1H), 7.34-7.53 (m, 4H), 7.84-7.88 (m, 1H). ^{13}C NMR (62.5MHz, $CDCl_3$): δ 28.27, 55.31, 60.14, 80.75, 111.20, 111.60, 114.13, 121.12, 121.50, 125.93, 126.08, 127.39, 127.54, 129.15, 134.57, 134.72, 154.27, 159.69, 164.46, 166.08, 166.42, 168.55. MS (ESI): *m/z* = 423 ($[M+Na]^+$). HRMS (ESI) Calcd for $C_{21}H_{21}FN_2NaO_5$ ($[M+Na]^+$) m/z 423.1327, Found 423.1332.



(-)-tert-Butyl(4-fluoro-1,3-dioxoisoindolin-2-yl)(4-methoxyphenyl)methylcarbamate, 2t

The reaction was performed in 0.1 mmol scale for 12h using 5 mol% (*S*)-VAPOL-phosphoric acid. The product was obtained by flash chromatography (hexane: acetone = 3:1) as a white solid, 17 mg, 84% yield, 89% ee, mp.: 68-71 °C. HPLC analysis: Chiralcel OD-H (hexane/iPrOH = 90/10, 1.0 mL/min), $t_{\text{r-major}}$ 12.47 min, $t_{\text{r-minor}}$ 22.32 min. $[\alpha]^{20}_D$ = -31.7° (c = 1.75, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ 1.45 (s, 9H), 3.78 (s, 3H), 6.24 (s, broad, 1H), 6.87 (d, *J* = 8.0 Hz, 2H), 7.00 (d, *J* = 10.0 Hz, 1H), 7.36-7.70 (m, 5H). ^{13}C NMR (62.5MHz, $CDCl_3$): δ 28.27, 55.32, 60.14, 60.41, 80.77, 114.13, 117.47, 117.67, 119.83, 119.88, 122.51, 122.82, 127.43, 129.08, 133.95, 136.84, 136.96, 154.24, 155.64, 159.70, 159.87, 164.29, 166.26. MS (ESI): *m/z* = 423 ($[M+Na]^+$). HRMS (ESI) Calcd for $C_{21}H_{21}FN_2NaO_5$ ($[M+Na]^+$) m/z 423.1327, Found 423.1315.

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