SUPPORTING INFORMATION

Enantioselective Rhodium Enolate Protonations. A New Methodology for the Synthesis of β^2-Amino Acids

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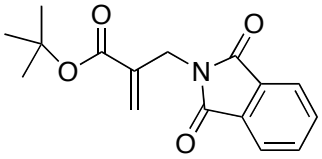
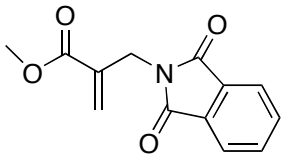
Experimental Procedures. Dioxane was distilled from benzophenone/ketyl prior to use. All the catalysts and ligands were bought from Strem chemicals. The boronic acids were purchased from Lancaster or synthesized via literature procedure.[1] Thin layer chromatographic analysis was performed on silica gel Whatman-60F glass plates and components were visualized by illumination with UV light or by staining with phosphomolybdic acid. Flash chromatography was performed using E. Merck silica gel 60 (230-400 mesh). All glassware was oven dried, assembled hot, and cooled under a stream of dry nitrogen before use.

^{1}H NMR was recorded on a Varian Unity/Inova-500 NB (500 MHz) or Varian Unity/Inova-400 NB (400 MHz). Chemical shifts are reported in parts per million (ppm) down field from TMS, using residual $CDCl_3$ (7.27 ppm) as an internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublets of doublets, t = triplet, tt = triplets of triplets, qu = quintet, m = multiplet), coupling constant(s) and integration. ^{13}C NMR was recorded on a Varian Unity/Inova-500 NB (125 MHz) or Varian Unity/Inova-400 NB (100 MHz) spectrometer using broad band proton decoupling. Chemical shifts are reported in parts per million down field from TMS, using the middle resonance of $CDCl_3$ (77.0 ppm) as an internal standard. HPLC analyses were carried out on a waters 515 HPLC pump and a 2487 dual λ detector connected to a PC with millennium workstation. Melting points are recorded on Fisher-Johns melting point apparatus. Rotations were recorded on a JASCO-DIP-370 instrument. High-resolution mass spectra (HRMS) [ENa$^+$] were obtained at the Ohio State University, Columbus, OH and North Dakota State University, Fargo, ND.

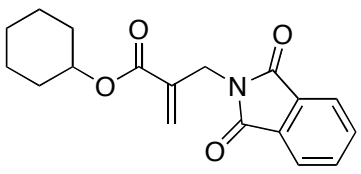
General procedure for the preparation of acrylates (5c-5e): To a solution of the appropriate hydroxymethyl acrylate[2] (50 mmol), PPh_3 (55 mmol) and phthalimide or succinimide (55 mmol) in dry THF (100 mL) was added diisopropyl azodicarboxylate (DEAD) at 0 °C. After complete addition, the mixture was allowed to warm to room temperature and it was stirred overnight. The reaction mixture was extracted with ether and concentrated in vacuum leaving a white solid, which was extracted with hexane/EtOAc solution (7:1) and concentrated. The residue was subjected to column chromatography on silica gel furnishing the desired compound in 75-85% yield. Compounds **5a** and **5b** have been reported in the literature.[4]



2-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-acrylic acid *tert*-butyl ester 5a: Rf= 0.6 (40:60-ethyl acetate: hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47 (s, 9H), 4.49 (t, *J* = 1.4 Hz, 2H), 5.41 (s, 1H), 6.20 (s, 1H), 7.72 (dd, *J* = 5.6, 2.9 Hz, 2H), 7.86 (dd, *J* = 5.3, 2.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.2, 38.6, 81.7, 123.7, 124.7, 132.2, 134.3, 136.1, 164.6, 168.0; HRMS m/z calcd for $C_{16}H_{17}NO_4Na^+$: 310.1049, found: 310.1024.

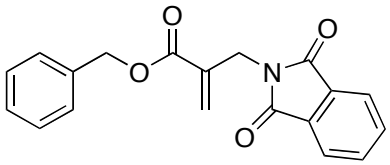


2-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-acrylic acid methyl ester 5b: Rf= 0.6 (40:60-ethyl acetate: hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.79 (s, 3H), 4.56 (t, *J* = 1.39 Hz, 2H), 5.57 (s, 1H), 6.32 (s, 1H), 7.74 (dd, *J* = 5.5, 3.2 Hz, 2H), 7.87 (dd, *J* = 5.4, 3.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 38.5, 52.3, 123.7, 126.3, 132.2, 134.4, 134.6, 165.9, 167.9; HRMS m/z calcd for $C_{13}H_{11}NO_4Na^+$: 268.0580, found: 268.0571.

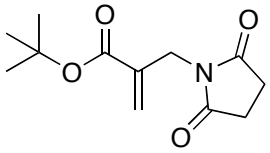


2- (1, 3-Dioxo-1, 3-dihydro-isoindol-2-ylmethyl)-acrylic acid cyclohexyl ester 5c: white solid; mp = 113 °C; Rf= 0.2 (1:5-ethyl acetate: hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24-1.32 (m, 1H), 1.34-1.42 (m, 2H), 1.45-1.57 (m, 3H), 1.72-1.75 (m, 2H), 1.85-1.88 (m, 2H), 4.56 (t, *J* = 1.39 Hz, 2H), 4.85-4.90 (m, 1H), 5.54 (s, 1H), 6.31 (s, 1H), 7.73-7.78 (m, 2H), 7.86-

7.90 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.9, 25.6, 31.7, 38.6, 73.7, 123.7, 123.8, 125.7, 132.2, 134.4, 134.6, 135.3, 164.9, 168.0; HRMS m/z calcd for $C_{18}H_{19}NO_4Na^+$: 336.1206, found: 336.1213.

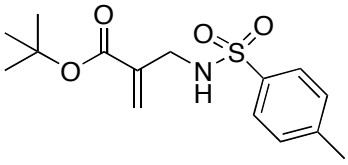


2- (1, 3-Dioxo-1, 3-dihydro-isoindol-2-ylmethyl)-acrylic acid benzyl ester 5d: white solid; mp=96 °C; Rf = 0.6 (1:2.5-ethyl acetate: hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.58 (s, 2H), 5.23 (s, 2H), 5.60 (s, 1H), 6.37 (s, 1H), 7.31-7.37 (m, 5H), 7.73 (dd, *J* = 5.3, 2.9 Hz, 2H), 7.86 (dd, *J* = 5.3, 2.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 38.5, 67.1, 123.7, 126.5, 128.5, 128.8, 132.2, 134.4, 134.6, 135.8, 165.3, 167.9; HRMS m/z calcd for $C_{19}H_{15}NO_4Na^+$: 344.0893, found: 344.0889.



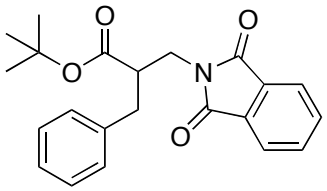
2- (2, 5-Dioxo-pyrrolidin-1-ylmethyl)-acrylic acid *tert*-butyl ester 5e: white solid; mp=135 °C; Rf= 0.1 (1:3-ethyl acetate: hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.50 (s, 9H), 2.77 (s, 4H), 4.34 (s, 2H), 5.37 (t, *J* = 1.4 Hz, 1H), 6.19 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.2, 28.4, 39.3, 81.8, 124.8, 135.4, 164.5, 176.7; HRMS m/z calcd for $C_{12}H_{17}NO_4Na^+$: 262.1049, found: 262.1038.

Procedure for the preparation of acrylate (5f):[3] The solution of corresponding acetoxymethyl acrylate (15 mmol), p-$TsNH_2$ (18 mmol) and DABCO (20 mmol) in dry CH_2Cl_2 (50 mL) was stirred at room temperature overnight. 1N HCl aq. Solution was added and the water layer was extracted three times with CH_2Cl_2. The combined organic layer was washed with sat. brine, dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue oil was subjected to column chromatography on silica gel furnishing the desired compound in 26 % yield.



2- [[[(4-methylphenyl)sulfonyl]amino]methyl])-acrylic acid *tert*-butyl ester 5f: white solid; mp=54 °C; Rf = 0.17 (1:20-ethyl acetate: hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (s, 9H), 2.42 (s, 3H), 3.76 (d, *J* = 6.6 Hz, 2H), 5.09 (t, *J* = 6.6 Hz, 1H), 5.67 (d, *J* = 0.8 Hz, 1H), 6.06 (s, 1H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.72 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 28.2, 45.0, 81.9, 127.1, 127.3, 137.0, 137.5, 143.6, 165.3; HRMS m/z calcd for $C_{15}H_{21}NO_4SNa^+$: 334.1083, found: 334.1087.

General procedure for optimization of the catalyst (Table 1): A 24 mL screw-capped vial equipped with a rubber septum was charged with α,β-unsaturated ester (0.4 mmol), $PhB(OH)_2$ (2 mmol), rhodium-complex (0.008 mmol) and (*S*)-BINAP (0.08 mmol). It was evacuated under vacuum and flushed with nitrogen. Dioxane (1 mL) and water (0.1 mL) were added by a syringe then the mixture was stirred at 50 °C for 20 h. Silica gel (0.5 g) was added and the mixture was concentrated. The resulting powder was subjected to column chromatography on silica gel. The mixture of the desired product and starting unsaturated ester was obtained. The ratio of starting material to product was determined by NMR. The enantiomeric purity was determined by HPLC.

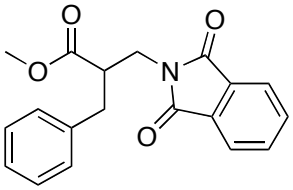


3-Phenyl-2- (1, 3-dioxo-1, 3-dihydro-isoindol-2-ylmethyl)-propionic acid *tert*-butyl ester 6a: colorless oil; Rf= 0.23 (1:5-ethyl acetate: hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (s, 9H), 2.81 (dd, *J* = 14.1, 6.6 Hz, 1H), 3.02 (dd, *J* = 14.1, 8.7 Hz, 1H), 3.23-3.29 (m, 1H), 3.78 (dd, *J* = 13.9, 6.4 Hz, 1H), 4.01 (dd, *J* = 13.8, 8.6 Hz, 1H), 7.11-7.14 (m, 1H), 7.20-7.24 (m, 4H), 7.7 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.82 (dd, *J* = 5.5, 3.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.0, 36.4, 39.9, 46.4, 81.3, 123.4, 126.6, 128.5, 129.1, 132.2, 134.2, 138.5, 168.2, 172.2; HRMS m/z calcd for $C_{22}H_{23}NO_4Na^+$: 388.1519, found: 388.1532; $[\alpha]_D$ –3.95 (*c* 1.90, CH_2Cl_2); HPLC t_r (minor) 30.4 min; t_r (major) 38.0 min [Chiralcel AD (0.46 cm x 50 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 95/5, 0.8 mL/min], 88 %ee.

General procedure for enantioselective Proton transfer reactions using Rhodium catalyst (Table 2):

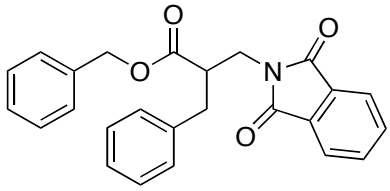
Method A (2-methoxyphenol or 2-acetylphenol as a proton source): A 24 mL screw-capped vial equipped with a rubber septum was charged with α,β-unsaturated ester (0.4 mmol), $PhB(OH)_2$ (2 mmol), rhodium-complex (0.008 mmol) and chiral ligand (0.008 mmol). It was evacuated under vacuum and flushed with nitrogen. Dioxane (1 mL) and 2-methoxyphenol or 2-acetylphenol (0.4 mmol) were added by a syringe then the mixture was stirred at 50 °C for 20 h. Silica gel (0.5 g) was added and the mixture was concentrated. The resulting powder was subjected to column chromatography on silica gel. The mixture of the desired product and starting unsaturated ester was obtained. The ratio of starting material to product was determined by NMR. The enantiomeric purity was determined by HPLC.

Method B (phthalimide as a proton source): A 24 mL screw-capped vial equipped with a rubber septum was charged with α,β-unsaturated ester (0.4 mmol), $PhB(OH)_2$ (2 mmol), phthalimide, rhodium-complex (0.008 mmol) and chiral ligand (0.008 mmol). It was evacuated under vacuum and flushed with nitrogen. Dioxane (1 mL) was added by a syringe then the mixture was stirred at 50 °C for 20 h. Silica gel (0.5 g) was added and the mixture was concentrated. The resulting powder was subjected to column chromatography on silica gel. The mixture of the desired product and starting unsaturated ester was obtained. The ratio of starting material to product was determined by NMR. The enantiomeric purity was determined by HPLC.

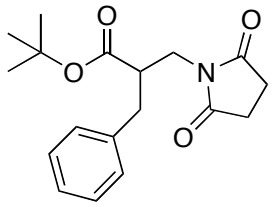


3-Phenyl-2- (1, 3-dioxo-1, 3-dihydro-isoindol-2-ylmethyl)-propionic acid methyl ester 6b: (Mixture, Product: SM = 1:1); Rf= 0.10 (1:5-ethyl acetate: hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.85 (dd, *J* = 14.1, 6.5 Hz, 1H), 3.08 (dd, *J* = 14.1, 9.5 Hz, 1H), 3.24-3.31 (m, 1H), 3.58 (s, 3H), 3.79 (s, 3H, SM), 3.86 (dd, *J* = 13.9, 5.9 Hz, 1H), 4.00 (dd, *J* = 13.9, 8.1 Hz, 1H), 4.56 (s, 2H, SM), 5.58 (s, 1H, SM), 6.32 (s, 1H, SM), 7.11-7.13 (m, 1H), 7.19-7.22 (m, 4H), 7.69 (dd, *J* = 5.5, 3.2 Hz, 2H), 7.74 (dd, *J* = 5.5, 3.0 Hz, 2H, SM), 7.80 (dd, *J* = 5.3, 3.0 Hz, 2H), 7.87 (dd, *J* = 5.3, 3.0 Hz, 2H, SM); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.1,

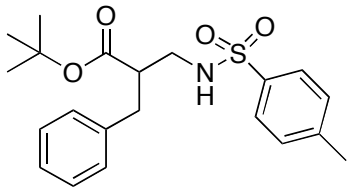
38.5, 39.8, 45.9, 52.2, 52.3, 123.5, 123.7, 123.8, 126.3, 126.7, 128.7, 128.9, 132.1, 132.2, 134.2, 134.4, 134.5, 134.6, 138.2, 157.3, 167.9, 168.2, 173.5; HRMS m/z calcd for $C_{19}H_{17}NO_4Na^+$: 346.1050, found: 346.1043; HPLC t_r (major) 46.7 min; t_r (minor) 61.5 min [Chiralcel OJ (0.46 cm x 50 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 0.8 mL/min], 10 %ee.



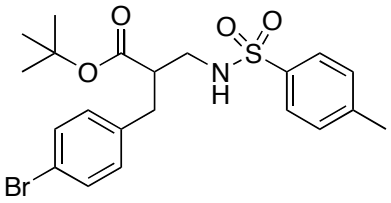
2-Benzyl-3-(1, 3-dioxo-1, 3-dihydro-isoindol-2-yl)-propionic acid benzyl ester 6d: colorless oil; Rf= 0.6 (1:2.5-ethyl acetate: hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.87 (dd, *J* = 14.1, 6.5 Hz, 1H), 3.08 (dd, *J* = 14.1, 8.7 Hz, 1H), 3.32-3.37 (m, 1H), 3.86 (dd, *J* = 13.7, 5.9 Hz, 1H), 4.05 (dd, *J* = 13.7, 8.5 Hz, 1H), 4.99 (s, 2H), 7.11-7.24 (m, 7H), 7.68 (dd, *J* = 5.5, 3.2 Hz, 2H), 7.74-7.78 (m, 3H), 7.87 (dd, *J* = 5.5, 3.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.2, 39.8, 46.0, 67.0, 123.5, 123.8, 126.7, 128.3, 128.4, 128.5, 128.6, 129.0, 132.1, 134.1, 134.5, 138.1, 168.2, 172.9; HRMS m/z calcd for $C_{25}H_{21}NO_4Na^+$: 422.1363, found: 422.1370; HPLC t_r (minor) 42.5 min; t_r (major) 46.1 min [Chiralcel AD (0.46 cm x 50 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 95/5, 1.0 mL/min], 20 %ee.



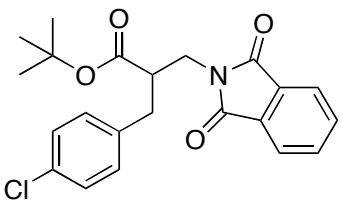
3-Phenyl-2- (2, 5-Dioxo-pyrrolidin-1-ylmethyl)-propionic acid *tert*-butyl ester 6e: colorless oil; Rf= 0.10 (1:5-ethyl acetate: hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (s, 9H), 2.45-2.57 (m, 4H), 2.74 (dd, *J* = 14.3, 7.3 Hz, 1H), 3.01 (dd, *J* = 14.1, 7.9 Hz, 1H), 3.21 (qu, *J* = 7.5 Hz, 1H), 3.66 (dd, *J* = 13.5, 7.2 Hz, 1H), 3.81 (dd, *J* = 13.5, 7.9 Hz, 1H), 7.17-7.20 (m, 3H), 7.25-7.28 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 28.2, 36.6, 40.6, 45.0, 81.4, 126.7, 128.6, 128.9, 138.6, 172.0, 177.1; HRMS m/z calcd for $C_{18}H_{23}NO_4Na^+$: 340.1519, found: 340.1516; HPLC t_r (major) 15.7 min; t_r (minor) 17.6 min [Chiralcel AD (0.46 cm x 50 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 95/5, 1.0 mL/min], 71 %ee.



3-Phenyl-2-[[[(4-methylphenyl)sulfonyl]amino]methyl]-propionic acid *tert*-butyl ester 6f: colorless oil; Rf= 0.14 (1:5-ethyl acetate: hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (s, 9H), 2.42 (s, 3H), 2.71-2.78 (m, 2H), 2.88-2.94 (m, 1H), 2.99-3.07 (m, 2H), 5.02 (t, *J* = 6.4 Hz, 1H), 7.12 (d, *J* = 7.1 Hz, 2H), 7.19-7.22 (m, 1H), 7.27 (dd, *J* = 13.9, 8.1 Hz, 4H), 7.68 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 28.2, 35.9, 43.7, 47.4, 81.9, 126.9, 127.3, 128.7, 129.2, 130.0, 137.1, 138.2, 143.6, 173.4; HRMS m/z calcd for $C_{21}H_{27}NO_4SNa^+$: 412.1552, found: 412.1558; $[\alpha]_D$ –3.52 (*c* 2.78, CH_2Cl_2); HPLC t_r (minor) 37.5 min; t_r (major) 57.5 min [Chiralcel AD (0.46 cm x 50 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 95/5, 1.0 mL/min], 81 %ee.

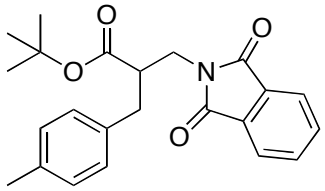


2-(4-Bromo-benzyl)-3-(toluene-4-sulfonylamino)-propionic acid *tert*-butyl ester 6g: colorless oil; Rf= 0.6 (1:2.5-ethyl acetate: hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (s, 9H), 2.42 (s, 3H), 2.65-2.75 (m, 2H), 2.86 (dd, *J* = 13.6, 6.3 Hz, 1H), 2.96-3.03 (m, 2H), 5.02 (t, *J* = 6.1 Hz, 1H), 7.00 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.38 (d, *J* = 8.3 Hz, 2H), 7.67 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 25.6, 28.2, 35.1, 43.4, 47.2, 82.2, 120.7, 127.3, 129.9, 130.9, 131.8, 136.9, 137.2, 143.7, 173.1; HRMS m/z calcd for $C_{21}H_{26}BrNO_4SNa^+$: 490.0658, found: 490.0658; $[\alpha]_D$ –25.0 (*c* 1.42, CH_2Cl_2); HPLC t_r (minor) 22.4 min; t_r (major) 39.9 min [Chiralcel AD (0.46 cm x 50 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min], 84%ee.

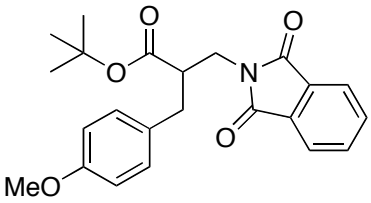


3-(4-Chlorophenyl)-2- (1, 3-dioxo-1, 3-dihydro-isoindol-2-ylmethyl)-propionic acid *tert*-butyl ester 6h: colorless oil; Rf= (1:5-ethyl acetate: hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (s, 9H), 2.77 (dd, *J* = 14.2, 6.5 Hz, 1H), 2.98 (dd, *J* = 14.2, 8.8 Hz, 1H), 3.18-3.24 (m, 1H), 3.78 (dd, *J* = 13.7, 6.5 Hz, 1H), 3.99 (dd, *J* = 13.8, 8.4 Hz, 1H), 7.13 (d, *J* = 8.3 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 2H), 7.71 (dd, *J* = 5.6, 3.0 Hz, 2H), 7.82 (dd, *J* = 5.4, 3.0 Hz, 2H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 28.0, 35.7, 39.8, 46.3, 81.5, 123.5, 128.6, 130.4, 132.1, 132.4, 134.3, 137.0, 168.2, 171.9; HRMS m/z calcd for $C_{22}H_{22}ClNO_4Na^+$: 422.1129, found: 422.1124; $[\alpha]_D$ –9.24 (*c* 1.32, CH_2Cl_2); HPLC t_r (minor) 31.7 min; t_r (major) 39.9 min [Chiralcel AD (0.46 cm x 50 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 95/5, 0.6 mL/min], 84%ee.

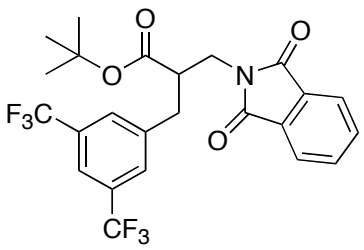


3-(1, 3-Dioxo-1, 3-dihydro-isoindol-2-yl)-2-(4-methyl-benzyl)-propionic acid *tert*-butyl ester 6i: (Mixture, Product: SM = 2:1); Rf= 0.6 (1:2.5-ethyl acetate: hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 9H), 1.47 (s, 4.5 H, SM), 2.19 (s, 3H), 2.71 (dd, *J* = 14.1, 6.9 Hz, 1H), 2.95 (dd, *J* = 14.1, 8.3 Hz, 1H), 3.16-3.24 (m, 1H), 3.72 (dd, *J* = 13.8, 6.4 Hz, 1H), 3.95 (dd, *J* = 13.8, 8.6 Hz, 1H), 4.48 (s, 1H, SM), 5.40 (s, 0.5H, SM), 6.17 (s, 0.5H, SM), 6.95-7.05 (m, 4H), 7.65 (dd, *J* = 5.4, 2.8 Hz, 2H), 7.70 (dd, *J* = 5.4, 2.9 Hz, 1H, SM), 7.76 (dd, *J* = 5.6, 3.0 Hz, 2H), 7.83 (dd, *J* = 5.6, 3.0 Hz, 1H, SM); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 27.9, 28.2, 36.0, 38.6, 39.8, 46.3, 81.2, 81.7, 123.3, 123.6, 124.7, 128.8, 129.1, 130.1, 132.2, 134.1, 134.3, 135.3, 135.9, 136.2, 160.4, 167.9, 168.1, 172.2; HRMS m/z calcd for $C_{23}H_{25}NO_4Na^+$: 402.1676, found: 402.1655; $[\alpha]_D$ –1.20 (*c* 2.41, CH_2Cl_2); HPLC t_r (minor) 30.7 min; t_r (major) 36.2 min [Chiralcel AD (0.46 cm x 50 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 95/5, 0.5 mL/min], 63%ee.

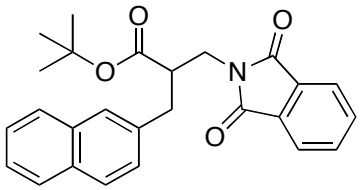


3-(4-Methoxyphenyl)-2- (1, 3-dioxo-1, 3-dihydro-isoindol-2-ylmethyl)-propionic acid *tert*-butyl ester 6j: colorless oil; Rf= 0.17 (1:5-ethyl acetate: hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 1.25 (s, 9H), 2.75 (dd, *J* = 14.1, 6.7 Hz, 1H), 2.96 (dd, *J* = 14.1, 8.5 Hz, 1H), 3.17-3.24 (m, 1H), 3.72 (s, 3H), 3.76 (dd, *J* = 13.7, 6.4 Hz, 1H), 3.99 (dd, *J* = 13.8, 8.6 Hz, 1H), 6.75-6.76 (m, 2H), 7.12 (d, *J* = 8.5 Hz, 2H), 7.70 (dd, *J* = 5.6, 3.0 Hz, 2H), 7.81 (dd, *J* = 5.5, 3.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.0, 35.6, 39.9, 46.6, 55.4, 81.2, 113.9, 123.4, 130.0, 130.5, 132.2, 134.1, 158.4, 168.2, 172.3; HRMS m/z calcd for $C_{23}H_{25}NO_5Na^+$: 418.1624, found: 418.1615; $[\alpha]_D$ –10.86 (*c* 0.93, CH_2Cl_2); HPLC t_r

(minor) 47.8 min; t_r (major) 59.6 min [Chiralcel AD (0.46 cm x 50 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 95/5, 0.5 mL/min], 86 %ee.

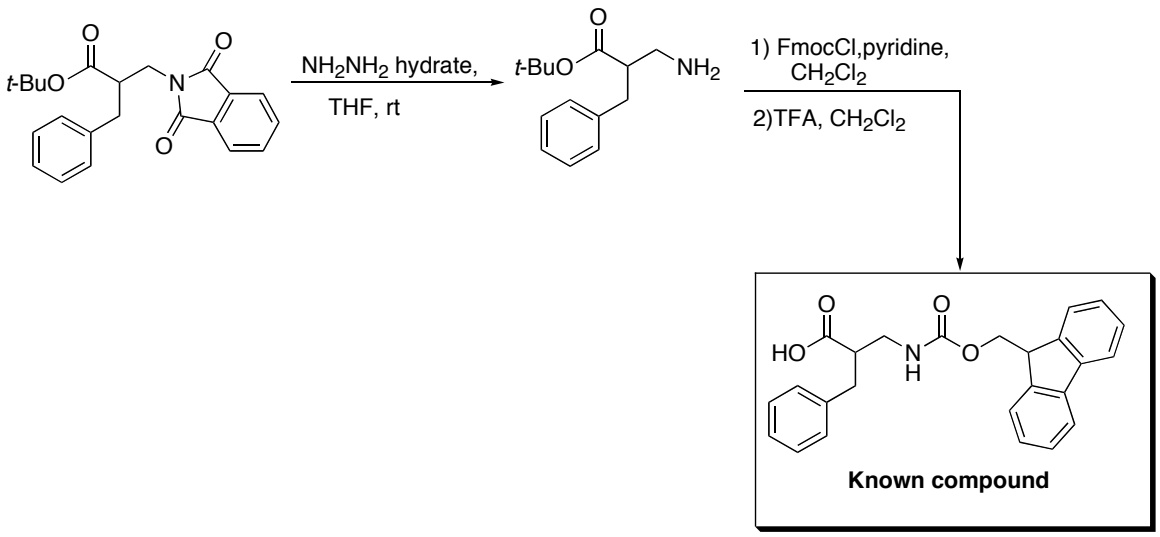


2-(3, 5-Bis-trifluoromethyl-benzyl)-3-(1, 3-dioxo-1, 3-dihydro-isoindol-2-yl)-propionic acid *tert*-butyl ester 6k: (Mixture, Product: SM = 3:1); Rf= 0.6 (1:2.5-ethyl acetate: hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (s, 9H), 1.49 (s, 3H, SM), 2.94 (dd, *J* = 14.1, 5.5 Hz, 1H), 3.14 (dd, *J* = 14.1, 9.7 Hz, 1H), 3.21-3.29 (m, 1H), 3.85 (dd, *J* = 13.9, 6.7 Hz, 1H), 4.05 (dd, *J* = 13.9, 7.7 Hz, 1H), 4.51 (s, 0.6H, SM), 5.43 (s, 0.3H, SM), 6.20 (s, 0.3H, SM), 7.62-7.66 (m, 3H), 7.71 (dd, *J* = 5.5, 3.2 Hz, 2H), 7.73-7.75 (m, 0.6H, SM), 7.82 (dd, *J* = 5.5, 3.2 Hz, 2H), 7.87 (dd, *J* = 5.5, 3.0 Hz, 0.6H, SM); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.8, 28.2, 35.8, 38.6, 39.7, 46.2, 82.1, 120.6, 122.3, 123.6, 123.7, 124.5, 124.7, 129.3, 131.6, 131.9, 132.2, 134.3, 134.4, 136.2, 141.2, 164.6, 167.9, 168.1, 171.2; HRMS m/z calcd for $C_{24}H_{21}F_6NO_4Na^+$: 524.1267, found: 524.1273; $[\alpha]_D$ –8.26 (*c* 0.98, CH_2Cl_2); HPLC t_r (minor) 9.9 min; t_r (major) 11.7 min [Chiralcel AD (0.46 cm x 50 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 97/3, 1.0 mL/min], 90%ee.



3-(2-naphthyl)-2- (1,3-dioxo-1, 3-dihydro-isoindol-2-ylmethyl)-propionic acid *tert*-butyl ester 6l: colorless oil; Rf= 0.23 (1:5-ethyl acetate: hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (s, 9H), 2.97 (dd, *J* = 14.1, 7.0 Hz, 1H), 3.22 (dd, *J* = 14.2, 8.2 Hz, 1H), 3.36-3.42 (m, 1H), 3.85 (dd, *J* = 13.9, 6.8 Hz, 1H), 4.04 (dd, *J* = 13.9, 8.3 Hz, 1H), 7.33-7.43 (m, 3H), 7.61-7.64 (m, 3H), 7.68-7.75 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.0, 36.7, 39.9, 46.0, 81.4, 123.3, 125.5, 126.1, 127.3, 127.5, 127.69, 127.72, 128.2, 132.0, 132.3, 133.6, 134.1, 136.0, 168.3, 172.2; HRMS m/z calcd for $C_{26}H_{25}NO_4Na^+$: 438.1675, found: 438.1649, $[\alpha]_D$ –15.68 (*c* 1.50, CH_2Cl_2); HPLC t_r (minor) 41.6 min; t_r (major) 58.3 min [Chiralcel AD (0.46 cm x 50 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 95/5, 0.5 mL/min], 91 %ee.

Determination of absolute stereochemistry of 6a:



General procedure for hydrazinolysis and preparation of Fmoc derivative of β-amino ester:[4] To a solution of **6a** (0.62mmol) in THF (5 mL) was added hydrazine hydrate (0.4 mL) and the solution was stirred overnight. White precipitates were filtered out and washed with THF successively. The filtrate was concentrated *in vacuo* furnishing the white solid. The solid and FmocCl (0.62 mmol) were dissolved in dry CH_2Cl_2 (8 mL) then the solution was cooled to 0 °C. To the solution at 0 °C, pyridine (0.05 mL/ 0.62 mmol) was added. After the complete addition, the mixture was allowed to warm to room temperature and stirred at room temperature overnight. After the standard workup and purification by flash chromatography, the Fmoc derivative was obtained in 40 % yield (2 steps).

General procedure for the preparation of Fmoc derivative of β amino acid: To the solution of Fmoc derivative of t-butyl ester (0.25 mmol) in dichloromethane (7 mL) at ambient temperature, was added trifluoroacetic acid (0.5 mL) and the solution was stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo* and was purified by flash chromatography on silica gel to furnish the desired compound in 62 % yield. $[\alpha]_D^{25} = +4.5$ (*c* 1.09, $CHCl_3$), lit. $[\alpha]_D^{25} = +8.2$ (*c* 0.91, $CHCl_3$).[5]

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