Mild Conditions for Pd-Catalyzed Carboamination of *N*-Protected Hex-4-enylamines and 1-, 3-, and 4-Substituted Pent-4-enylamines. Scope, Limitations, and Mechanism of Pyrrolidine Formation.

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Supporting Information

Experimental procedures and characterization data for new compounds in Tables 1–5 and equations 2–12 (146 pages).

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General: All reactions were carried out under an argon or nitrogen atmosphere in oven- or flame-dried glassware. All catalysts, reagents, anhydrous DME, and anhydrous dioxane were obtained from commercial sources and were used without further purification. 4-Bromobenzyl acetate,[1] pent-4-enyl-carbamic acid *tert*-butyl ester (**1**),[2] *N*-pent-4-enylacetamide (**3**),[2] (3-methylpent-4-enyl)carbamic acid *tert*-butyl ester (**14**),[2] (1-phenylpent-4-enyl)carbamic acid *tert*-butyl ester (**15**),[2] 4-pentenylamine,[2] (±)–(1*R*,3*S*)-3-(*tert*-butyldimethylsiloxy)-1-nonylpent-4-enylcarbamic acid *tert*-butyl ester (**17**),[3] (*E*)-hex-4-enamide,[4] 2-(2-methylenecyclopentyl)ethanol,[5] and 2-cyclopent-2-enylethyl carbamic acid *tert*-butyl ester (**43**)[2] were prepared according to published procedures. Ratios of regioisomers and/or diastereomers were determined by ^{1}H NMR and/or capillary GC analysis of crude reaction mixtures. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^{1}H NMR, GC, and/or combustion analysis unless otherwise noted. The yields reported in the experimental

section describe the result of a single experiment, whereas the yields reported in Tables 1–5 and equations 2–12 are average yields of two or more experiments. Thus, the yields reported in the experimental section may differ from those shown in Tables 1–5 and equations 2–12. Copies of ^{1}H and ^{13}C NMR spectra for all new compounds are provided in the Supporting Information. Copies of ^{1}H and ^{13}C NMR spectra for compounds **1**–**24**, and **43**–**45** have been published in prior communications,[1,3] and are not included here.

Synthesis of Substrates

4-Bromobenzyl acetate.[6] A flame-dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with 4-bromobenzyl alcohol (4.00 g, 21.4 mmol), acetic anhydride (20 mL), pyridine (20 mL), and DMAP (268 mg, 2.14 mmol, 10 mol %). The tube was purged with nitrogen, and the mixture was stirred at rt for 22 h until the starting material had been consumed as determined by TLC analysis. Water (10 mL) and ethyl acetate (10 mL) were added, and the layers were separated. The organic layer was washed with aq HCl (10 mL, 1 M) and brine (10 mL). The organic layer was then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 5% ethyl acetate/hexanes as the eluent to afford 4.4 g (90%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 8.4 Hz, 2 H), 7.21 (d, J = 8.2 Hz, 2 H), 5.03 (s, 2 H), 2.08 (s, 3 H).

Pent-4-enylcarbamic acid benzyl ester (4).[7] A flame-dried flask was cooled under a stream of nitrogen and charged with a solution of 4-pentenylamine (175 mL, 17.5 mmol, 0.1 M in diethyl ether). Triethylamine (7.4 mL, 52.5 mmol) and benzyl chloroformate (3.8 mL, 26.3 mmol) were added, and the resulting mixture was stirred at rt until the starting material was consumed as judged by TLC analysis (ca. 2 h). A solution of aq HCl (100 mL, 1 M) was added; the mixture was transferred to a separatory funnel, and was extracted with diethyl ether (100 mL). The layers were separated and the organic layer was washed with a solution of saturated aq Na_2CO_3 (100 mL) and brine (100 mL). The organic layer was then dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography using 10% → 15% ethyl acetate/hexanes as the eluent to afford 1.90 g (50%) of the title compound as a

colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.27 (m, 5 H), 5.86–5.70 (m, 1 H), 5.19–4.93 (m, 4 H), 4.92–4.62 (m, 1 H), 3.26–3.08 (m, 2 H), 2.16–2.00 (m, 2 H), 1.67–1.52 (m, 2 H).

3-Methylpent-4-enylcarbamic acid benzyl ester (13). A flame-dried flask was cooled under a stream of nitrogen and charged with 3-methylpent-4-enoic acid[8] (6.85 g, 60 mmol). The flask was purged with nitrogen. Benzene (100 mL) was added and the resulting solution was cooled to ca. 10 °C using an ice water bath. Oxalyl chloride (14 mL, 160 mmol) was added dropwise via syringe to the solution and the resulting mixture was warmed to rt, stirred for 1 h, and then concentrated *in vacuo*. The crude 3-methylpentenoyl chloride product of this reaction was dissolved in THF (100 mL), and slowly added to a separate flask containing aq ammonium hydroxide (100 mL) at 0 °C. The resulting mixture was stirred for 6 h and then concentrated *in vacuo.* The mixture was diluted with H_2O (50 mL) and ethyl acetate (100 mL), the layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 100 mL). The combined organics were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The resulting crude 3-methylpent-4-enylcarboxamide was dissolved in THF (100 mL) and cooled to 0 °C. A solution of LAH in THF (200 mL, 200 mmol, 1.0 M) was added dropwise via syringe. The reaction mixture was warmed to rt and stirred for 36 h, then was cooled to 0 °C, quenched with H_2O (16 mL), and diluted with diethyl ether (200 mL). A solution of aq NaOH (30 mL, 10 M) was added and an insoluble white material precipitated. The organic supernatant was decanted and the precipitate was washed with diethyl ether (100 mL). The combined organics were dried over anhydrous sodium sulfate and filtered to afford a solution of 3-methylpentenylamine in diethyl ether (ca. 0.1 M). The solution of 3-methylpentenylamine (300 mL, 30 mmol, 0.1 M) was cooled to 0 °C, triethylamine (11.5 mL, 90 mmol) and benzyl chloroformate (6.6 mL, 45 mmol) were added and the resulting mixture was stirred at rt until the starting material was consumed as judged by TLC analysis (ca. 16 h). A solution of aq HCl (200 mL, 1 M) was added. The mixture was transferred to a separatory funnel and extracted with diethyl ether (100 mL). The combined organics were washed with saturated aq $NaHCO_3$ (200 mL) and brine (100 mL). The organic layer was then dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography using 5% → 10% ethyl acetate/hexanes as the eluent to afford 1.20 g (17% over the five steps) of the title

compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.26 (m, 5 H), 5.73–5.60 (m, 1 H), 5.16–5.05 (m, 2 H), 5.02–4.90 (m, 2 H), 4.87–4.58 (m, 1 H), 3.27–3.08 (m, 2 H), 2.25–2.11 (m, 1 H), 1.58–1.40 (m, 2 H), 1.00 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 143.6, 136.6, 128.4, 128.1, 128.0, 113.4, 66.5, 39.2, 36.4, 35.6, 20.2; IR (film) 3337, 1706 cm^{-1}. Anal calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.28; H, 8.29; N, 6.08.

1-Phenylpent-4-enylcarbamic acid benzyl ester (16). Treatment of a solution of 1-phenylpent-4-enylamine[1] in diethyl ether (250 mL, 25 mmol, 0.1 M) with triethylamine (9.6 mL, 75 mmol) and benzyl chloroformate (5.5 mL, 37.5 mmol) using a procedure analogous to that described above for the synthesis of **13** afforded 3.86 g (52%) of the title compound as a waxy white solid, m.p. 51–53 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–6.97 (m, 10 H), 5.86–5.65 (m, 1 H), 5.43–5.21 (m, 1 H), 5.14–4.90 (m, 4 H), 4.79–4.47 (m, 1 H), 2.12–1.94 (m, 2 H), 1.92–1.64 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 142.3, 137.4, 136.4, 128.5, 128.4, 128.0, 127.2, 126.3, 115.2, 66.6, 54.9, 35.6, 30.2 (two aromatic carbons are incidentally equivalent); IR (film) 3324, 1710 cm^{-1}. Anal calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.06; H, 7.19; N, 4.69.

(*E*)-*tert*-Butyl hex-4-enylcarbamate (25). A flame-dried round-bottom flask was cooled under a stream of nitrogen and charged with (*E*)-hex-4-enamide[4] (2.83 g, 25 mmol). The flask was purged with nitrogen, THF (100 mL) was added, and the resulting solution was cooled to 0 ^{o}C. A solution of LAH in THF (75 mL, 75 mmol, 1.0 M) was added dropwise. The reaction mixture was warmed to rt and stirred for 21 h, then was cooled to 0 ^{o}C, quenched with H_2O (10 mL), and diluted with diethyl ether (50 mL). A solution of aq NaOH (20 mL, 10 M) was added followed by H_2O (4 mL), and an insoluble white material precipitated. The organic supernatant was decanted and the precipitate was washed with diethyl ether (150 mL). The combined organics were dried over anhydrous Na_2SO_4 and filtered to afford a solution of (*E*)-hex-4-en-1-yl-amine in diethyl ether (ca. 0.1 M), which was used without purification.

A flame-dried flask was cooled under a stream of nitrogen and charged with a solution of (*E*)-hex-4-en-1-yl-amine (250 mL, 25 mmol, 0.1 M). Di-*tert*-butyl dicarbonate (8.20 g, 37.5 mmol) was added, the resulting mixture was stirred for 3 h, and then aq NaOH (200 mL, 1 M)

was added. The biphasic mixture was vigorously stirred for 12 h and then the layers were separated. The aqueous layer was extracted with diethyl ether (3 x 100 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography using 5% → 10% ethyl acetate/hexanes as the eluent to afford 3.56 g (71%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.49–5.36 (m, 2 H), 4.65 (s, br, 1 H), 3.16–3.04 (m, 2 H), 2.03–1.97 (m, 2 H), 1.64 (d, *J* = 5.4 Hz, 3 H), 1.53 (quint, *J* = 7.1 Hz, 2 H), 1.44 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 130.2, 125.4, 78.8, 40.0, 29.7, 28.3, 17.8 (two aliphatic carbons are incidentally equivalent); IR (film) 3351, 1694 cm^{-1}. MS (ESI): 222.1463 (222.1470 calcd for $C_{11}H_{21}NO_2$, M + Na^+).

(*E*)-Benzyl hex-4-enylcarbamate (27). Treatment of a solution of (*E*)-hex-4-en-1-yl-amine (prepared as described above) in diethyl ether (210 mL, 21 mmol, 0.1 M) with triethylamine (8.5 mL, 63 mmol) and benzyl chloroformate (6.0 mL, 42 mmol) using a procedure analogous to that described above for the synthesis of **13** afforded 3.40 g (69%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.27 (m, 5 H), 5.49–5.32 (m, 2 H), 5.17–5.05 (m, 2 H), 4.82 (s, br, 1 H), 3.18 (quint, *J* = 6.8 Hz, 2 H), 2.08–1.95 (m, 2 H), 1.63 (d, *J* = 4.9 Hz, 3 H), 1.54 (quint, *J* = 7.2 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.3, 136.6, 130.1, 128.4, 128.1, 128.0, 125.7, 66.5, 40.5, 29.7, 29.6, 17.8; IR (film) 3336, 1706 cm^{-1}. MS (ESI): 256.1319 (256.1313 calcd for $C_{14}H_{19}NO_2$, M + Na^+).

(*Z*)-*tert*-Butyl hex-4-enylcarbamate (28). A flame-dried flask was cooled under a stream of nitrogen and charged with phthalimide (6.00 g, 41 mmol), triphenylphosphine (7.85 g, 30 mmol), THF (120 mL), and cis-4-hexenol (2.50 g, 25 mmol). The resulting mixture was cooled to 0 ^{o}C and DEAD (4.7 mL, 30 mmol) was added slowly over 15 min. The mixture was allowed to warm to rt and was stirred until the starting material was consumed as judged by TLC analysis (ca. 3 h). The crude reaction mixture was concentrated *in vacuo*, hexanes (500 mL) was then added to the resulting oil and an insoluble white material precipitated. The solution was filtered through a fritted funnel and the residue was rinsed with a solution of 5% ethyl acetate/hexanes (3 x 100 mL). The filtrate was concentrated *in vacuo* and the crude material was purified by flash chromatography using 10%→ 20% ethyl acetate/hexanes as the eluent to afford 4.75 g (83%) of

(*Z*)-2-(hex-4-enyl)isoindoline-1,3-dione[9] as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84–7.79 (m, 2 H), 7.73–7.69 (m, 2 H), 5.51–5.43 (m, 1 H), 5.42–5.35 (m, 1 H), 3.69 (t, *J* = 6.3 Hz, 2 H), 2.11 (q, *J* = 7.3 Hz, 2 H), 1.75 (quint, *J* = 7.6 Hz, 2 H), 1.61–1.57 (m, 3 H).

A flame-dried flask was cooled under a stream of nitrogen and charged with (*Z*)-2-(hex-4-enyl)isoindoline-1,3-dione (4.75 g, 20.7 mmol), ethanol (80 mL), and hydrazine monohydrate (1.26 g, 24.9 mmol). The mixture was heated to reflux with stirring until the starting material was consumed as judged by TLC analysis (ca. 16 h). The reaction mixture was cooled to rt and di-*tert*-butyl dicarbonate (10.4 g, 37.5 mmol) was added. The resulting mixture was stirred at rt for 4 h and then aq NaOH (200 mL, 1 M) was added. The biphasic mixture was vigorously stirred for 12 h and the mixture was concentrated *in vacuo*. The aqueous layer was extracted with diethyl ether (3 x 100 mL), and the combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 10% ethyl acetate/hexanes as the eluent to afford 4.03 g (98%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.53–5.42 (m, 1 H), 5.41–5.32 (m, 1 H), 4.56 (s, br, 1 H), 3.18–3.06 (m, 2 H), 2.07 (q, *J* = 7.2 Hz, 2 H), 1.62–1.58 (m, 3 H), 1.57–1.50 (m, 2 H), 1.44 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 129.5, 124.6, 77.3, 40.2, 29.8, 28.4, 24.1, 12.7; IR (film) 3351, 1694 cm^{-1}. MS (ESI): 222.1471 (222.1470 calcd for $C_{11}H_{21}NO_2$, M + Na^+).

(*Z*)-Benzyl hex-4-enylcarbamate (29). Treatment of a solution of (*Z*)-hex-4-en-1-yl-amine in ethanol (200 mL, 13.7 mmol, 0.07 M) (prepared as described above) with triethylamine (8.5 mL, 63 mmol) and benzyl chloroformate (6.0 mL, 42 mmol) at rt using a procedure analogous to that described above for the synthesis of **13** afforded 3.15 g (99%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.28 (m, 5 H), 5.54–5.42 (m, 1 H), 5.41–5.30 (m, 1 H), 5.19–5.05 (m, 2 H), 4.83 (s, br, 1 H), 3.26–3.11 (m, 2 H), 2.14–2.01 (m, 2 H), 1.66–1.48 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 136.6, 129.3, 128.4, 128.1, 128.0, 124.7, 66.5, 40.7, 29.6, 24.0, 12.7; IR (film) 3334, 1704 cm^{-1}. MS (ESI): 256.1314 (256.1313 calcd for $C_{14}H_{19}NO_2$, M + Na^+).

***tert*-Butyl 4-methylpent-4-enyl carbamate (46).** A flame-dried round-bottom flask was cooled under a stream of nitrogen and charged with 4-methylpent-4-enylamide[10] (965 mg, 8.5 mmol). The flask was purged with nitrogen, THF (20 mL) was added via syringe, and the resulting solution was cooled to 0 ^{o}C. A solution of LAH in THF (35 mL, 35 mmol, 1.0 M) was added dropwise via syringe. The reaction mixture was warmed to rt, and stirred for 20 h, then was cooled to 0 ^{o}C, quenched with H_2O (5 mL), and diluted with diethyl ether (20 mL). An aqueous solution of NaOH (10 mL, 10 M) was added followed by H_2O (2 mL) and an insoluble white material precipitated. The organic supernatant was decanted and the precipitate was washed with diethyl ether (60 mL). The combined organics were dried over anhydrous Na_2SO_4 and filtered to afford a solution of 4-methylpent-4-en-1-yl-amine[11] in diethyl ether (ca 0.1 M), which was used without purification.

A flame-dried flask was cooled under a stream of nitrogen and charged with a solution of 4-methylpent-4-en-1-yl-amine (85 mL, 8.5 mmol, 0.1 M) in diethyl ether. Di-*tert*-butyl dicarbonate (2.80 g, 12.8 mmol) was added to the solution, the resulting mixture was stirred for 4 h, and then aq NaOH (100 mL, 1 M) was added. The biphasic mixture was vigorously stirred for 12 h and the layers were separated. The aqueous layer was extracted with diethyl ether (3 x 75 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography using 5%→ 10% ethyl acetate/hexanes as the eluent to afford 1.10 g (62%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.84 (s, br, 1 H), 4.75–4.67 (m, 2 H), 3.16–3.04 (m, 2 H), 2.03 (t, J = 7.6 Hz, 2 H), 1.72 (s, 3 H), 1.63 (quint, J = 7.6 Hz, 2 H), 1.44 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 144.7, 110.1, 78.6, 40.1, 34.8, 28.2, 27.8, 22.1; IR (film) 3351, 1692 cm^{-1}. MS (ESI): 222.1465 (222.1470 calcd for $C_{11}H_{21}NO_2$, M + Na^+).

Benzyl 4-methylpent-4-enylcarbamate (48). A flame-dried flask was cooled under a stream of nitrogen, charged with a solution of 4-methylpent-4-en-1-yl-amine in ether (87 mL, 8.7 mmol, 0.1 M) (prepared as described above), and cooled to 0 °C. Triethylamine (3.5 mL, 26.2 mmol) and benzyl chloroformate (2.5 mL, 17.5 mmol) were added, and the resulting mixture was stirred at rt until the starting material was consumed as judged by TLC analysis (ca. 24 h). A solution of aq HCl (100 mL, 1 M) was added; the mixture was transferred to a separatory funnel, and was

extracted with diethyl ether (3 x 50 mL). The combined organics were washed with saturated aq $NaHCO_3$ (100 mL) and brine (100 mL). The organic layer was then dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography using 10% ethyl acetate/hexanes as the eluent to afford 1.30 g (64%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.27 (m, 5 H), 5.17–5.06 (m, 2 H), 4.85 (s, br, 1 H), 4.75–4.64 (m, 2 H), 3.24–3.09 (m, 2 H), 2.03 (t, *J* = 7.6 Hz, 2 H), 1.71 (s, 3 H), 1.64 (quint, *J* = 7.6 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.3, 144.8, 136.6, 128.4, 128.1, 128.0, 110.4, 66.5, 40.7, 34.8, 27.7, 22.2; IR (film) 3336, 1699 cm^{-1}. MS (ESI): 256.1307 (256.1313 calcd for $C_{14}H_{19}NO_2$, M + Na^+).

***tert*-Butyl-2-(2-methylenecyclopentyl)ethylcarbamate (49).** A flame-dried flask was cooled under a stream of nitrogen and charged with phthalimide (2.60 g, 17.5 mmol), triphenylphosphine (4.60 g, 17.5 mmol), THF (100 mL), and 2-(2-methylenecyclopentyl)ethanol[5] (1.70 g, 13.5 mmol). The resulting mixture was cooled to 0 ^{o}C, and DEAD (3.5 mL, 17.5 mmol) was added slowly over 15 min. The mixture was allowed to warm to rt and was stirred until the starting material was consumed as judged by TLC analysis (ca. 48 h). The crude reaction mixture was concentrated *in vacuo*, hexanes (500 mL) was added to the crude oil, and an insoluble white material precipitated. The solution was filtered through a fritted funnel and the residue was rinsed with a solution of 5% ethyl acetate/hexanes (3 x 100 mL). The filtrate was concentrated *in vacuo* and the crude material was purified by flash chromatography using 10% ethyl acetate/hexanes as the eluent to afford 2.30 g (67%) of 2-[2-(2-methylenecyclopentyl)ethyl]isoindoline-1,3-dione as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87–7.82 (m, 2 H), 7.75–7.68 (m, 2 H), 4.91–4.88 (m, 1 H), 4.85–4.81 (m, 1 H), 3.75 (t, *J* = 7.4 Hz, 2 H), 2.41–2.24 (m, 3 H), 2.10–1.96 (m, 2 H), 1.79–1.69 (m, 1 H), 1.65–1.48 (m, 2 H), 1.44–1.33 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 155.6, 133.8, 132.1, 123.1, 104.8, 41.5, 36.7, 32.93, 32.89, 32.5, 24.1; IR (film) 1772, 1713 cm^{-1}. MS (ESI): 278.1150 (278.1157 calcd for $C_{16}H_{17}NO_2$, M + Na^+).

A flame-dried flask was cooled under a stream of nitrogen and charged with 2-[2-(2-methylenecyclopentyl)ethyl]isoindoline-1,3-dione (2.30 g, 9.1 mmol), ethanol (45 mL), and hydrazine monohydrate (911 mg, 18.2 mmol). The mixture was heated to reflux with stirring

until the starting material was consumed as judged by TLC analysis (ca. 15 h). The reaction mixture was cooled to rt, diethyl ether was added (200 mL) and the solution was split into two equal portions. Di-*tert*-butyl dicarbonate (10.4 g, 37.5 mmol) was added to one of the portions (120 mL, 4.55 mmol, 0.04 M). The resulting mixture was stirred at rt for 4 h and then aq NaOH (200 mL, 1 M) was added. The biphasic mixture was vigorously stirred for 12 h and the mixture was concentrated *in vacuo*. The aqueous layer was extracted with diethyl ether (3 x 50 mL), and the combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 10% ethyl acetate/hexanes as the eluent to afford 900 mg (87%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90–4.87 (m, 1 H), 4.81–4.77 (m, 1 H), 4.76–4.68 (m, 1 H), 3.21–3.07 (m, 2 H), 2.40–2.21 (m, 3 H), 1.99–1.88 (m, 1 H), 1.84–1.67 (m, 2 H), 1.61–1.49 (m, 1 H), 1.45 (s, 10 H), 1.34–1.23 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 155.8, 104.4, 78.7, 41.4, 39.1, 34.5, 32.8, 32.5, 28.3, 24.0; IR (film) 3350, 1693 cm^{-1}. MS (ESI): 248.1632 (248.1626 calcd for $C_{13}H_{23}NO_2$, $M + Na^+$).

Benzyl 2-(2-methylenecyclopentyl)ethylcarbamate (50). A flame-dried round-bottom flask was cooled under a stream of nitrogen, charged with a solution of 4-methylpent-4-en-1-yl-amine (120 mL, 4.55 mmol, 0.04 M) (prepared as described above), and was cooled to 0 °C. Triethylamine (2.4 mL, 18.3 mmol) and benzyl chloroformate (2.0 mL, 13.7 mmol) were added, and the resulting mixture was stirred at rt until the starting material was consumed as judged by TLC analysis (ca. 22 h). The reaction mixture was concentrated *in vacuo*. A solution of aq HCl (100 mL, 1 M) was added and the mixture was extracted with diethyl ether (3 x 50 mL). The combined organics were washed with saturated aq $NaHCO_3$ (100 mL) and brine (100 mL). The organic layer was then dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography using 10% ethyl acetate/hexanes as the eluent to afford 961 mg (81%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.23 (m, 5 H), 5.21–5.03 (m, 2 H), 5.00–4.91 (m, 1 H), 4.90–4.85 (m, 1 H), 4.81–4.70 (m, 1 H), 3.33–3.10 (m, 2 H), 2.40–2.20 (m, 3 H), 1.97–1.86 (m, 1 H), 1.85–1.75 (m, 1 H), 1.74–1.63 (m, 1 H), 1.58–1.48 (m, 1 H), 1.47–1.34 (m, 1 H), 1.33–1.17 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 155.9, 136.6, 128.4, 128.0, 127.9, 104.5, 66.4, 41.3, 39.6, 34.4, 32.8,

32.5, 24.1; IR (film) 3335, 1699 cm^{-1}. MS (ESI): 282.1472 (282.1470 calcd for $C_{16}H_{21}NO_2$, M + Na^+).

***tert*-Butyl 2-(2-methylenecyclohexyl)ethylcarbamate (51).** A flame-dried flask equipped with magnetic stirbar was charged with 2-(2-methylenecyclohexyl)ethanol[12] (640 mg, 4.6 mmol), triphenylphosphine (1.44 g, 5.5 mmol) and phthalimide (807 mg, 5.5 mmol). The flask was purged with nitrogen, THF (15 mL) was added, and the resulting solution was cooled to 0 °C. DIAD (1.2 mL, 6.1 mmol) was added dropwise, and the resulting yellow-orange solution was allowed to warm to rt. The reaction mixture was stirred until the starting material had been consumed as judged by GC analysis (ca. 4 h). The reaction mixture was concentrated *in vacuo*, and the crude product was purified by flash chromatography using 15% ethyl acetate/hexanes as the eluent to give 1.16 g (94%) of 2-[2-(2-methylenecyclohexyl)ethyl]isoindoline-1,3-dione as a white solid, m.p. 63–65 ^oC. ^1H NMR (500 MHz, $CDCl_3$) δ 7.89–7.80 (m, 2 H), 7.74–7.65 (m, 2 H), 4.71 (s, br, 1 H), 4.69 (s, br, 1 H), 3.76–3.64 (m, 2 H), 2.32–2.23 (m, 1 H), 2.16–2.08 (m, 1 H), 2.08–1.94 (m, 2 H), 1.88–1.77 (m, 1 H), 1.73–1.55 (m, 3 H), 1.55–1.40 (m, 2 H), 1.36–1.26 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 151.5, 133.8, 132.2, 123.1, 106.2, 40.9, 36.5, 34.7, 34.0, 30.8, 28.7, 24.2; IR (film) 1773, 1715 cm^{-1}. MS (ESI): 292.1313 (292.1313 calcd for $C_{17}H_{19}NO_2$, M + Na^+).

A flame-dried flask was charged with 2-[2-(2-methylenecyclohexyl)ethyl]isoindoline-1,3-dione (1.05 g, 3.9 mmol), ethanol (30 mL), and hydrazine monohydrate (300 μL, 6.0 mmol). The mixture was heated to reflux with stirring until the starting material was consumed as judged by TLC analysis (ca. 6 h). The reaction mixture was cooled to rt and di-*tert*-butyl dicarbonate (1.92 g, 8.8 mmol) was added. The resulting cloudy mixture was stirred at rt for 2 h and diluted with diethyl ether (60 mL). A solution of aq NaOH (100 mL, 1 M) was added, and the resulting biphasic mixture was vigorously stirred for 2 h. The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 75 mL). The combined organics were washed with brine (60 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude product was purified by flash chromatography using 10% ethyl acetate/hexanes as the eluent to afford 642 mg (69%) of the title compound as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 4.67

(s, br, 1 H), 4.62 (s, br, 1 H), 4.59 (s, br, 1 H), 3.20–3.05 (m, 2 H), 2.28–2.17 (m, 1 H), 2.15–1.98 (m, 2 H), 1.86–1.70 (m, 2 H), 1.70–1.37 (m, 14 H), 1.34–1.22 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 151.9, 106.0, 78.8, 40.6, 38.9, 34.4, 33.7, 32.2, 28.6, 28.3, 23.9; IR (film) 3351, 1692 cm^{-1}. MS (ESI): 262.1778 (262.1783 calcd for $C_{14}H_{25}NO_2$, M + Na^+).

(*E*)-*tert*-Butyl 4-methylhex-4-enylcarbamate (61). A flame-dried flask equipped with magnetic stirbar was charged with (*E*)-4-methylhex-4-en-1-ol[13] (602 mg, 5.3 mmol), triphenylphosphine (1.69 g, 6.4 mmol) and phthalimide (940 mg, 6.4 mmol). The flask was purged with nitrogen, THF (17 mL) was added, and the resulting solution was cooled to 0 °C. DIAD (1.4 mL, 7.1 mmol) was added dropwise, and the resulting yellow-orange solution was allowed to warm to rt. The reaction mixture was stirred until the starting material had been consumed as judged by GC analysis (ca. 2.5 h). The reaction mixture was concentrated *in vacuo* and the crude product was purified by flash chromatography using 15% ethyl acetate/hexanes as the eluent to give 869 mg (68%) of (*E*)-2-(4-methylhex-4-enyl)isoindoline-1,3-dione[14] as a white solid, m.p. 61–65 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86–7.81 (m, 2 H), 7.74–7.68 (m, 2 H), 5.30–5.18 (m, 1 H), 3.65 (t, *J* = 7.2 Hz, 2 H), 2.05 (t, *J* = 7.6 Hz, 2 H), 1.84–1.74 (m, 2 H), 1.60 (s, 3 H), 1.53 (dd, *J* = 0.8, 6.6 Hz, 3 H).

A flame-dried flask was charged with (*E*)-2-(4-methylhex-4-enyl)isoindoline-1,3-dione (810 mg, 3.3 mmol), ethanol (30 mL), and hydrazine monohydrate (300 μL, 6.0 mmol). The mixture was heated to reflux with stirring until the starting material was consumed as judged by TLC analysis (ca. 7 h). The reaction mixture was cooled to rt and di-*tert*-butyl dicarbonate (2.03 g, 9.3 mmol) was added. The resulting cloudy mixture was stirred at rt for 2 h, then diluted with diethyl ether (60 mL). A solution of aq NaOH (100 mL, 1 M) was added, and the resulting biphasic mixture was vigorously stirred for 2 h. The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 75 mL). The combined organics were washed with brine (60 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude product was purified by flash chromatography using 10% ethyl acetate/hexanes as the eluent to afford 484 mg (68%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.27–5.18 (m, 1 H), 4.60–4.40 (s, br, 1 H), 3.17–2.98 (m, 2 H), 2.02 (t, *J* = 7.5 Hz, 2 H), 1.60

(m, 2 H), 1.59 (s, 3 H), 1.57 (d, J = 8.0 Hz, 3 H), 1.44 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 134.9, 118.9, 79.0, 40.3, 36.8, 28.4, 28.1, 15.5, 13.3; IR (film) 3351, 1692 cm^{-1}. MS (ESI): 236.1630 (236.1626 calcd for $C_{12}H_{23}NO_2$, M + Na^+).

***tert*-Butyl 5-methylhex-4-enylcarbamate (62).** A flame-dried flask equipped with magnetic stirbar was charged with 5-methylhex-4-en-1-ol[15] (1.41 g, 12.3 mmol), triphenylphosphine (3.85 g, 14.7 mmol) and phthalimide (2.16 g, 14.7 mmol). The flask was purged with nitrogen, THF (17 mL) was added, and the resulting solution was cooled to 0 °C. DIAD (3.0 mL, 15.1 mmol) was added dropwise, and the resulting yellow-orange solution was allowed to warm to rt. The reaction mixture was stirred until the starting material had been consumed as judged by GC analysis (ca. 2.5 h). The reaction mixture was concentrated *in vacuo*, and the crude product was purified by flash chromatography using 15% ethyl acetate/hexanes as the eluent to give 2.19 g (73%) of 2-(5-methylhex-4-enyl)isoindoline-1,3-dione as a white solid, m.p. 47–49 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86–7.81 (m, 2 H), 7.73–7.68 (m, 2 H), 5.14–5.07 (m, 1 H), 3.69 (t, J = 7.2 Hz, 2 H), 2.05 (q, J = 7.2 Hz, 2 H), 1.72 (quint, J = 7.6 Hz, 2 H), 1.64 (s, 3 H), 1.59 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 133.8, 132.4, 132.2, 123.2, 123.1, 37.8, 28.5, 25.6, 25.5, 17.7; IR (film) 1770, 1710 cm^{-1}. MS (ESI): 266.1149 (266.1157 calcd for $C_{15}H_{17}NO_2$, M + Na^+).

A flame-dried flask was charged with 2-(5-methylhex-4-enyl)isoindoline-1,3-dione (2.00 g, 8.2 mmol), ethanol (55 mL), and hydrazine monohydrate (550 μL, 11.0 mmol). The mixture was heated to reflux with stirring until the starting material was consumed as judged by TLC analysis (ca. 3 h). The reaction mixture was cooled to rt and di-*tert*-butyl dicarbonate (3.20 g, 14.7 mmol) was added. The resulting cloudy mixture was stirred at rt for 2 h and diluted with diethyl ether (20 mL). A solution of aq NaOH (100 mL, 1 M) was added, and the resulting biphasic mixture was vigorously stirred for 2 h. The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 50 mL). The combined organics were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude product was purified by flash chromatography using 10% ethyl acetate/hexanes as the eluent to afford 1.48 g (84%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.14–5.06 (m, 1 H), 4.55 (s, br, 1 H), 3.18–3.01 (m, 2 H), 2.00 (q, J = 7.2 Hz, 2 H), 1.68 (s, 3 H), 1.60

(s, 3 H), 1.51 (quint, J = 7.2 Hz, 2 H), 1.44 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 132.2, 123.6, 78.9, 40.3, 30.1, 28.4, 25.7, 25.3, 17.6; IR (film) 3354, 1694 cm^{-1}. MS (ESI): 236.1616 (236.1626 calcd for $C_{12}H_{23}NO_2$, M + Na^+).

Synthesis of Functionalized Pyrrolidines via Coupling with Aryl Bromides (Tables 1–5, and Equation 3)

General Procedure for Pd-Catalyzed Carboamination Reactions of Aryl Bromides. A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with the aryl bromide (1.2 equiv), $Pd(OAc)_2$ (2 mol %), Dpe-phos, dppe, (±)–BINAP, or Nixantphos (4 mol %) and Cs_2CO_3 (2.3 equiv). The tube was purged with nitrogen and a solution of the *N*-protected amine substrate (1.0 equiv) in dioxane (5 mL/mmol substrate) was then added. The resulting mixture was heated to 100 °C with stirring until the starting material had been consumed as determined by GC analysis. The reaction mixture was cooled to room temperature and saturated aq NH_4Cl (1 mL) and ethyl acetate (1 mL) were added. The layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 5 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.

Reactions of Terminal Alkene Substrates (Tables 2–3)

2-Napthalen-2-ylmethylpyrrolidine-1-carboxylic acid *tert*-butyl ester (5).[1] The general procedure was employed for the reaction of 2-bromonapthalene (62 mg, 0.30 mmol) with **1** (47 mg, 0.25 mmol) using Dpe-phos as ligand and a reaction time of 15 h. This procedure afforded 58 mg (75%) of the title compound as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85–7.74 (m, 3 H), 7.66–7.60 (m, 1 H), 7.51–7.40 (m, 2 H), 7.40–7.33 (m, 1 H), 4.16– 4.02 (m, 1 H), 3.43–3.21 (m, 3 H), 2.77–2.65 (m, 1 H), 1.83–1.70 (m, 4 H), 1.53 (s, 9 H).

2-(4-*tert*-Butylbenzyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (2). The general procedure was employed for the reaction of 4-*tert*-butyl bromobenzene (52 μL, 0.30 mmol) with

1 (47 mg, 0.25 mmol) using Dpe-phos as ligand and a reaction time of 27 h. This procedure afforded 66 mg (83%) of the title compound as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.26 (m, 2 H), 7.22–7.07 (m, 2 H), 4.12–3.84 (m, 1 H), 3.49–3.23 (m, 2 H), 3.23–2.96 (m, 1 H), 2.60–2.42 (m, 1 H), 1.92–1.67 (m, 4 H), 1.52 (s, 9 H), 1.32 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 148.9, 136.1, 129.1, 125.2, 79.0, 58.8, 46.4, 40.0, 34.3, 31.4, 29.7, 28.6, 22.7; IR (film) 1695 cm^{-1}. Anal calcd for $C_{20}H_{31}NO_2$: C, 75.67; H, 9.84; N, 4.41. Found: C, 75.46; H, 9.88; N, 4.38.

2-(4-Formylbenzyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (6). The general procedure was employed for the reaction of 4-bromobenzaldehyde (89 mg, 0.48 mmol) with **1** (74 mg, 0.40 mmol) using Dpe-phos as ligand, except DME was used in place of dioxane and the reaction was conducted at 85 °C for 20h. This procedure afforded 94 mg (81%) of the title compound as a colorless oil. This compound was found to exist as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 1 H), 7.80 (d, J = 8.0 Hz, 2 H), 7.41–7.29 (m, 2 H), 4.13–3.92 (m, 1 H), 3.46–3.01 (m, 3 H), 2.74–2.58 (m, 1 H), 1.85–1.60 (m, 4 H), 1.49 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.9, 154.4, 146.6, 134.7, 130.1, 129.8, 79.3, 58.4, 46.3, 40.8, 39.9, 29.6, 28.5, 28.3, 23.4, 22.6; IR (film) 1693, 1606 cm^{-1}. Anal calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.45; H, 8.14; N, 4.72.

2-(4-Acetylbenzyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (7). The general procedure was employed for the reaction of 4-bromoacetophenone (120 mg, 0.60 mmol) with **1** (93 mg, 0.50 mmol) using Dpe-phos as ligand, except DME was used in place of dioxane and the reaction was conducted at 85 °C for 18 h. This procedure afforded 118 mg (78%) of the title compound as a white solid, m.p. 63–65 °C. This compound was found to exist as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94–7.85 (m, 2 H), 7.35–7.22 (m, 2 H), 4.11–3.94 (m, 1 H), 3.46–3.04 (m, 3 H), 2.74–2.55 (m, 4 H), 1.85–1.60 (m, 4 H), 1.51 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.9, 197.7, 154.5, 154.4, 145.0, 144.9, 135.3, 135.2, 129.7, 129.5, 128.5, 128.3, 79.4, 79.1, 58.5, 58.3, 46.7, 46.2, 40.6, 39.6, 29.7, 28.9, 28.5, 26.5, 23.4, 22.6; IR (film) 1686, 1607 cm^{-1}. Anal calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.18; H, 8.30; N, 4.60.

***tert*-Butyl 2-[2-(methoxycarbonyl)benzyl]pyrrolidine-1-carboxylate (8).** The general procedure was employed for the reaction of methyl 2-bromobenzoate (65 mg, 0.3 mmol) with **1** (47 mg, 0.25 mmol) using Dpe-phos as ligand and a reaction time of 28 h. This procedure afforded 57 mg (71%) of the title compound as a colorless oil and as a 2:1 mixture of rotamers. The data is for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91–7.79 (m, 1 H), 7.45–7.34 (m, 1 H), 7.32–7.19 (m, 2 H), 4.22–4.10 (m, 1 H), 3.90 (s, 3 H), 3.48–3.21 (m, 3.33 H), 3.09–2.99 (m, 0.66 H), 1.95–1.75 (m, 2.66 H), 1.74–1.62 (m, 1.33 H), 1.52–1.23 (m, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 154.6, 141.0, 131.9, 131.8, 130.4, 130.3, 126.0, 78.9, 58.9, 58.7, 52.0, 46.6, 45.9, 37.6, 36.1, 30.3, 28.5, 28.3, 23.5, 22.7; IR (film) 1719, 1694 cm^{-1}; MS (EI): 342.1674 (342.1681 calcd for $C_{18}H_{25}NO_4$, M^+).

1-[2-(Naphthalen-2-ylmethyl)pyrrolidin-1-yl]ethanone (9).[1] The general procedure was employed for the reaction of 2-bromonapthalene (125 mg, 0.60 mmol) with **3** (64 mg, 0.50 mmol) using Dpe-phos as ligand and a reaction time of 18 h. This procedure afforded 101 mg (80%) of the title compound as a pale yellow oil. This compound was found to exist as a ~ 3:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.74 (m, 3 H), 7.66–7.58 (m, 1 H), 7.51–7.37 (m, 2.3 H), 7.32–7.27 (m, 0.7 H), 4.45–4.37 (m, 0.7 H), 4.17–4.09 (m, 0.3 H), 3.63–3.49 (m, 0.7 H), 3.45–3.32 (m, 2 H), 3.09–3.02 (m, 0.3 H), 2.86–2.69 (m, 1 H), 2.11 (s, 2 H), 2.06 (s, 1 H), 1.96–1.72 (m, 4 H).

1-[2-(4-Nitrobenzyl)pyrrolidin-1-yl]ethanone (10). The general procedure was employed for the reaction of 1-bromo-4-nitrobenzene (97 mg, 0.48 mmol) with **3** (51 mg, 0.4 mmol) using dppe as ligand, except DME was used in place of dioxane and the reaction was conducted at 85 °C for 18 h. This procedure afforded 77 mg (77%) of the title compound as a white solid, m.p. 139–140 °C. This compound was found to exist as a ~ 7:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 8.8 Hz, 0.3 H), 8.12 (d, J = 8.8 Hz, 1.7 H), 7.38 (d, J = 8.8 Hz, 1.7 H), 7.32 (d, J = 8.8 Hz, 0.3 H), 4.34–4.24 (m, 0.85 H), 4.11–4.03 (m, 0.15 H), 3.64–3.51 (m, 0.3 H), 3.50–3.35 (m, 1.7 H), 3.28 (dd, J = 3.4, 13.2 Hz, 0.85 H), 2.97 (dd, J = 5.2, 13.2 Hz, 0.15 H), 2.80 (dd, J = 8.8, 13.6 Hz, 0.15 H), 2.68 (dd, J = 9.2, 13.2 Hz, 0.85 H), 2.07 (s, 2.55 H), 1.99 (s, 0.45 H), 1.94–1.73 (m, 3.15 H), 1.71–1.60 (m, 0.85 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 168.9, 147.0, 146.5, 145.5, 130.2,

130.0, 123.8, 123.5, 59.4, 57.9, 47.8, 45.4, 40.6, 38.8, 30.1, 28.5, 23.7, 22.9 22.0, 21.7; IR (film) 1640, 1516 cm^{-1}. Anal calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.85; H, 6.44; N, 11.08.

2-(Naphthalen-2-ylmethyl)pyrrolidine-1-carboxylic acid benzyl ester (11). The general procedure was employed for the reaction of 2-bromonaphthalene (125 mg, 0.6 mmol) with **4** (110 mg, 0.5 mmol) using Dpe-phos as ligand and a reaction time of 16 h. This procedure afforded 151 mg (88%) of the title compound as a colorless oil. This compound was found to exist as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85–7.63 (m, 3.5 H), 7.56–7.32 (m, 7.5 H), 7.25–7.19 (m, 1 H), 5.27–5.16 (m, 2 H), 4.28–4.12 (m, 1 H), 3.54–3.35 (m, 2.5 H), 3.25–3.16 (m, 0.5 H), 2.82–2.69 (m, 1 H), 1.87–1.72 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 154.8, 137.1, 136.8, 136.5, 136.4, 133.4, 132.1, 128.4, 128.1, 128.0, 127.9, 127.85, 127.79, 127.74, 127.65, 127.6, 127.4, 125.93, 125.86, 125.34, 125.26, 67.0, 66.5, 59.3, 58.8, 46.8, 46.6, 40.8, 39.6, 29.7, 28.9, 23.5, 22.7; IR (film) 1698 cm^{-1}. Anal calcd for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.05. Found: C, 80.01; H, 6.78; N, 4.11.

2-[4-(Methoxycarbonyl)benzyl]pyrrolidine-1-carboxylic acid benzyl ester (12). The general procedure was employed for the reaction of 4-bromobenzoate (129 mg, 0.6 mmol) with **4** (110 mg, 0.5 mmol) using Dpe-phos as ligand, except DME was used in place of dioxane and the reaction was conducted at 85 °C for 18 h. This procedure afforded 152 mg (86%) of the title compound as a pale yellow oil. This compound was found to exist as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98–7.86 (m, 2 H), 7.44–7.23 (m, 6 H), 7.16–7.08 (m, 1 H), 5.22–5.11 (m, 2 H), 4.18–4.02 (m, 1 H), 3.90 (s, 3 H), 3.51–3.31 (m, 2 H), 3.28–3.17 (m, 0.5 H), 3.11–3.00 (m, 0.5 H), 2.76–2.58 (m, 1 H), 1.88–1.61 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 167.0, 154.8, 144.4, 144.3, 137.0, 136.7, 129.64, 129.56, 129.3, 128.5, 128.2, 128.1, 127.9, 127.8, 67.0, 66.5, 58.9, 58.5, 52.0, 46.8, 46.6, 40.7, 39.5, 29.8, 28.9, 23.5, 22.7; IR (film) 1721, 1700 cm^{-1}. Anal calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.15; H, 6.62; N, 4.03.

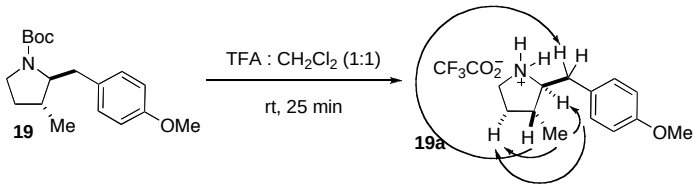
(±)–(2*R*,3*S*)-2-[4-(Acetoxymethyl)benzyl]-3-methylpyrrolidine-1-carboxylic acid benzyl ester (18). The general procedure was employed for the reaction of 4-bromobenzyl acetate (138 mg, 0.6 mmol) with **13** (117 mg, 0.5 mmol) using Dpe-phos as ligand and a reaction time of 20 h. The diastereoselectivity of the transformation was assessed by LAH reduction of the crude product obtained in a duplicate reaction, and was found to be 12:1 dr as judged by ^{1}H NMR analysis. The minor diastereomer was separated upon chromatographic purification to afford 143 mg (82%) of the title compound as a colorless oil with >20:1 dr. Data are for the major diastereomer, which was found to exist as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.29 (m, 5 H), 7.28–7.13 (m, 3 H), 7.09–7.02 (m, 1 H), 5.23–5.10 (m, 2 H), 5.09–5.02 (m, 2 H), 3.73–3.48 (m, 2 H), 3.34–3.18 (m, 1 H), 3.15–3.07 (m, 0.5 H), 3.01–2.92 (m, 0.5 H), 2.82–2.73 (m, 0.5 H), 2.70–2.61 (m, 0.5 H), 2.12–1.99 (m, 4 H), 1.94–1.80 (m, 1 H), 1.50–1.37 (m, 1 H), 0.87 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 155.1, 154.9, 138.8, 137.1, 136.8, 133.9, 133.7, 129.8, 129.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 67.0, 66.5, 66.15, 66.09, 65.9, 65.7, 45.4, 45.2, 39.9, 38.3, 36.8, 35.8, 31.1, 30.2, 21.0, 19.3, 19.1. IR (film) 1740, 1698 cm^{-1}. MS (ESI): 404.1839 (404.1838 calcd for $C_{20}H_{27}NO_4$, M + Na^+).

The stereochemistry of the above compound was assigned based on comparison of ^{1}H and ^{13}C NMR spectra to those obtained for the related product **19**, the stereochemistry of which was elucidated through ^{1}H NMR nOe experiments as described below.

(±)–(2*R*,3*S*)-2-(4-Methoxybenzyl)-3-methylpyrrolidine-1-carboxylic acid *tert*-butyl ester (19). The general procedure was employed for the reaction of 4-bromoanisole (38 μL, 0.3 mmol) with **14** (50 mg, 0.25 mmol) using Dpe-phos as ligand and a reaction time of 16 h. The diastereoselectivity of the transformation was assessed by TFA-mediated deprotection of the crude product obtained in a duplicate reaction, and was found to be 15:1 dr as judged by ^{1}H NMR analysis. The minor diastereomer was separated upon chromatographic purification to afford 58 mg (78%) of the title compound as a pale yellow oil with >20:1 dr. Data are for the major diastereomer, which was found to exist as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the rotamers mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14–7.03 (m, 2 H), 6.86–6.78 (m, 2 H), 3.79 (s, 3 H), 3.63–3.34 (m, 2 H), 3.26–3.06 (m, 1 H), 3.05–2.89 (m, 1 H), 2.75–2.52 (m, 1 H), 2.09–1.95 (m, 1 H), 1.91–1.75 (m, 1 H), 1.51 (s, 9 H), 1.45–1.30 (m, 1 H),

0.85 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 154.7, 131.0, 130.6, 130.3, 113.8, 113.6, 79.2, 78.9, 65.9, 65.5, 55.2, 45.5, 44.9, 39.1, 37.7, 36.7, 35.8, 31.1, 30.3, 28.6, 19.4, 19.2; IR (film) 1692 cm^{-1}. Anal calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59. Found: C, 70.56; H, 8.87; N, 4.60.

The stereochemistry of the above compound was determined by ^{1}H NMR nOe analysis of the product obtained through treatment of **19** with TFA to afford **19a** as shown below.

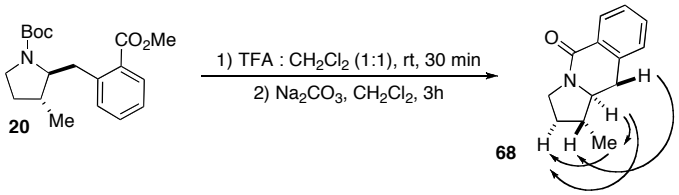


(±)–(2*R*,3*S*)-2-(4-Methoxybenzyl)-3-methylpyrrolidinium-2,2,2-trifluoroacetate (**19a**). A flame-dried flask was cooled under a stream of nitrogen and charged with **19** (42 mg, 0.14 mmol). Dichloromethane (1 mL) was added and the mixture was cooled to 0 °C. Trifluoroacetic acid (1 mL) was then added slowly and the resulting mixture was stirred at rt for 25 min. The crude mixture was concentrated *in vacuo* to afford 41 mg (96%) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.41 (s, br, 1 H), 8.74 (s, br, 1 H), 7.10 (d, J = 8.5 Hz, 2 H), 6.80 (d, J = 8.5 Hz, 2 H), 6.72 (s, br, 1 H), 3.74 (s, 3 H), 3.28–3.18 (m, 1 H), 3.15–3.07 (m, 2 H), 3.00–2.86 (m, 2 H), 2.23–2.15 (m, 1 H), 2.14–2.05 (m, 1 H), 1.66–1.57 (m, 1 H), 0.99 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.5 (q, J = 36.8 Hz), 158.8, 129.9, 127.6, 116.1 (q, J = 290.4 Hz), 114.2, 66.8, 55.1, 43.4, 38.3, 36.0, 32.2, 16.8; IR (film) 3502, 1690 cm^{-1}; MS (ESI): 206.1541 (206.1545 calcd for $C_{13}H_{19}NO$, M + H$^+$).

(±)–(2*R*,3*S*)-*tert*-Butyl-2-[2-(Methoxycarbonyl)benzyl]-3-methylpyrrolidine-1-carboxylate (20). The general procedure was employed for the reaction of methyl-2-bromobenzoate (43 μL, 0.3 mmol) with **14** (50 mg, 0.25 mmol) using Dpe-phos as ligand and a reaction time of 18 h. The diastereoselectivity of the transformation was assessed by TFA-mediated deprotection of the crude product obtained in a duplicate reaction, and was found to be 14:1 dr as judged by ^{1}H NMR analysis. The minor diastereomer was separated upon chromatographic purification to afford 63 mg (75%) of the title compound as a colorless oil with >20:1 dr. This compound was found to exist as a ~2.5:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88–7.79 (m, 1 H), 7.44–7.33 (m, 1 H), 7.30–7.19 (m, 2

H), 3.89 (s, 3 H), 3.78–3.72 (m, 1 H), 3.60–3.50 (m, 0.6 H), 3.47–3.17 (m, 2.8 H), 3.08–3.01 (m, 0.6 H), 2.10–1.96 (m, 2 H), 1.52–1.25 (m, 10 H), 0.93–0.79 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 168.1, 155.0, 154.7, 140.9, 140.5, 131.8, 131.7, 131.6, 130.4, 130.2, 126.0, 125.9, 78.9, 65.8, 52.0, 45.1, 44.4, 37.6, 37.4, 35.9, 30.9, 30.0, 28.5, 28.3, 19.4, 19.3; IR (film) 1723, 1691 cm^{-1}. Anal calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.29; H, 8.12; N, 4.06.

The stereochemistry of **20** was assigned by ^{1}H NMR nOe analysis of the corresponding derivative **68** obtained from treatment of **20** with TFA/dichloromethane, followed by Na_2CO_3, as shown below.

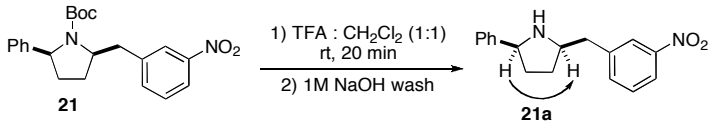


(±)–(1*R*,10a*S*)-1-Methyl-2,3,10,10a-tetrahydropyrrolo[1,2-*b*]isoquinolin-5(1H)-one (**68**). A flame-dried flask was cooled under a stream of nitrogen and charged with **20** (67 mg, 0.2 mmol), and dichloromethane (1 mL). The resulting solution was cooled to 0 °C, trifluoroacetic acid (1 mL) was then added slowly and the resulting mixture was stirred at rt for 30 min. The crude mixture was concentrated *in vacuo*. The crude product was dissolved in dichloromethane (5 mL), and Na_2CO_3 (636 mg, 4 mmol) was added. The resulting mixture was stirred at rt for 3 h, filtered through a plug of celite, and the filtrate was concentrated *in vacuo.* This procedure afforded 37 mg (91%) of the title compound as a white solid, m.p. 152–154 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 1.2, 7.8 Hz, 1 H), 7.41 (dt, *J* = 1.5, 7.3 Hz, 1 H), 7.34 (tt, *J* = 1.2, 7.6 Hz, 1 H), 7.22–7.19 (m, 1 H), 3.86–3.80 (m, 1 H), 3.64–3.57 (m, 1 H), 3.41–3.34 (m, 1 H), 3.05 (dd, *J* = 3.9, 15.1 Hz, 1 H), 2.78 (t, *J* = 3.9 Hz, 1 H), 2.22–2.15 (m, 1 H), 2.09–1.99 (m, 1 H), 1.60–1.50 (m, 1 H), 1.17 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3, 137.3, 131.5, 130.3, 127.6, 127.2, 127.1, 63.0, 44.2, 41.6, 33.6, 31.7, 15.9; IR (film) 1648 cm^{-1}; MS (EI): 201.1151 (201.1153 calcd for $C_{13}H_{15}NO$, M^+).

(±)–(2*R*,5*S*)-2-(3-Nitrobenzyl)-5-phenylpyrrolidine-1-carboxylic acid *tert*-butyl ester (21). The general procedure was employed for the reaction of 1-bromo-3-nitrobenzene (122 mg, 0.6 mmol) with **15** (131 mg, 0.5 mmol) using Dpe-phos as ligand and a reaction time of 16 h. The

diastereoselectivity of the transformation was assessed by TFA-mediated deprotection of the crude product obtained in a duplicate reaction, and was found to be >20:1 dr as judged by ^{1}H NMR analysis. Chromatographic purification afforded 151 mg (79%) of the title compound as a colorless oil with >20:1 dr. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16–8.05 (m, 2 H), 7.72–7.52 (m, 1 H), 7.50–7.44 (m, 1 H), 7.36–7.16 (m, 5 H), 5.08–4.68 (m, 1 H), 4.28–4.09 (m, 1 H), 3.69–3.43 (m, 1 H), 2.88–2.76 (m, 1 H), 2.36–2.24 (m, 1 H), 2.01–1.92 (m, 1 H), 1.91–1.81 (m, 1 H), 1.75–1.66 (m, 1 H), 1.65–1.05 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 148.2, 144.3, 141.1, 135.7, 129.3, 128.2, 126.6, 125.5, 124.1, 121.4, 79.7, 63.0, 60.4, 40.6, 34.3, 28.1 (two aliphatic carbons are incidentally equivalent); IR (film) 1687, 1530 cm^{-1}. Anal calcd for $C_{22}H_{26}N_2O_4$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.97; H, 6.98; N, 7.19.

The stereochemistry of the above compound was determined by ^{1}H NMR nOe analysis of the product obtained through treatment of **21** with TFA, followed by aq NaOH, to afford **21a** as shown below.

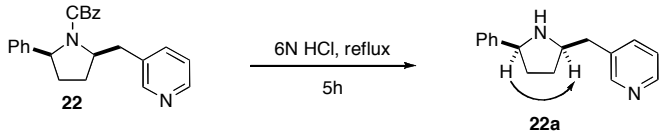


(±)–(2*R*,5*S*)-2-(3-Nitrobenzyl)-5-phenylpyrrolidine (**21a**). Treatment of **21** (100 mg, 0.26 mmol) with TFA/dichloromethane was effected using a procedure analogous to that described above for the preparation of compound **19a**, with the following modification. The crude residue obtained upon removal of TFA/dichloromethane was dissolved in dichloromethane (10 mL), and washed with aq NaOH (10 mL, 1 M). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. This procedure afforded 65 mg (88%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17–8.12 (m, 1 H), 8.09–8.02 (m, 1 H), 7.63–7.57 (m, 1 H), 7.44 (t, *J* = 8.0 Hz, 1 H), 7.40–7.35 (m, 2 H), 7.31 (t, *J* = 7.2 Hz, 2 H), 7.25–7.18 (m, 1 H), 4.15 (t, *J* = 7.4 Hz, 1 H), 3.55–3.44 (m, 1 H), 2.99–2.86 (m, 2 H), 2.20–2.09 (m, 1 H), 2.00–1.91 (m, 1 H), 1.85 (s, 1 H), 1.75–1.55 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 144.9, 142.3, 135.5, 129.1, 128.2, 126.8, 126.5, 123.9, 121.2, 62.2, 59.6, 42.9, 33.9, 30.9; IR (film) 3338, 1526 cm^{-1}; MS (ESI): 283.1435 (283.1447 calcd for $C_{17}H_{18}N_2O_2$, M + H$^+$).

(±)–(2*S*,5*R*)-2-Phenyl-5-(pyridin-3-ylmethyl)pyrrolidine-1-carboxylic acid benzyl ester (22). The general procedure was employed for the reaction of 3-bromopyridine (60 μL, 0.6 mmol) with **16** (148 mg, 0.5 mmol) using Dpe-phos as ligand and a reaction time of 18 h. The

diastereoselectivity of the transformation was assessed by HCl-mediated deprotection of the crude product obtained in a duplicate reaction, and was found to be >20:1 dr as judged by ^{1}H NMR analysis. Chromatographic purification afforded 144 mg (78%) of the title compound as a colorless oil with >20:1 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59–8.31 (m, 2 H), 7.77–6.76 (m, 12 H), 5.29–4.85 (m, 3 H), 4.30–4.09 (m, 1 H), 3.67–3.27 (m, 1 H), 2.77–2.64 (m, 1 H), 2.35–2.24 (m, 1 H), 2.04–1.80 (m, 2 H), 1.76–1.65 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 150.5, 147.9, 143.6, 136.7, 136.5, 134.3, 128.4, 128.3, 127.5, 127.3, 126.8, 125.6, 123.4, 66.7, 63.0, 61.1, 38.1, 34.3, 28.6; IR (film) 1698 cm^{-1}; MS (ESI): 395.1736 (395.1735 calcd for $C_{24}H_{24}N_2O_2$, M + Na^+).

The stereochemistry of the above compound was determined by ^{1}H NMR nOe analysis of the product obtained through treatment of **22** with aq HCl, followed by aq NaOH, to afford **22a** as shown below.

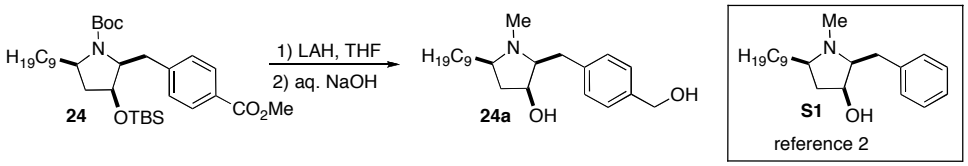


(±)–(2*R*,5*S*)-3-(5-Phenylpyrrolidin-2-ylmethyl)pyridine (**22a**). A flask was charged with **22** (40 mg, 0.11 mmol) and aq HCl (5 mL, 6 M). The mixture was heated to reflux for 5 h, and then was cooled to rt. Water was then added (2 mL), the crude mixture was washed with diethyl ether (3 x 10 mL), and the ether layers were discarded. The aqueous layer was then basified to pH 11 with aq NaOH (1 M) and extracted twice with diethyl ether (10 mL). The combined ether layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography using 5% → 10% methanol/dichloromethane as the eluent to afford 22 mg (87%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55–8.42 (m, 2 H), 7.61–7.55 (m, 1 H), 7.43–7.36 (m, 2 H), 7.34–7.25 (m, 2 H), 7.24–7.17 (m, 2 H), 4.19 (t, *J* = 8.0 Hz, 1 H), 3.56–3.43 (m, 1 H), 3.25–2.89 (m, 1 H), 2.82 (d, *J* = 6.6 Hz, 2 H), 2.23–2.11 (m, 1 H), 2.02–1.90 (m, 1 H), 1.85–1.73 (m, 1 H), 1.72–1.60 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 147.7, 136.6, 135.1, 128.3, 127.1, 126.7, 123.3, 62.3, 60.0, 39.7, 33.3, 30.6 (two aromatic carbons are incidentally equivalent); IR (film) 3410 cm^{-1}; MS (ESI): 239.1537 (239.1548 calcd for $C_{16}H_{18}N_2$, M + H^+).

(±)–(2*S*,3*S*,5*R*)-2-Benzyl-3-(*tert*-butyldimethylsiloxy)-5-nonylpyrrolidine-1-carboxylic acid *tert*-butyl ester (23).[2] The general procedure was employed for the reaction of bromobenzene (26 μL, 0.24 mmol) with **17** (89 mg, 0.20 mmol) using Dpe-phos as ligand and a reaction time of 23 h. ^{1}H NMR analysis of the crude material obtained upon workup showed the formation of the desired product as a >20:1 mixture of diastereomers. This procedure afforded 74 mg (71%) of the title compound as a colorless oil with >20:1 dr. The stereochemistry was assigned by comparison of the ^{1}H NMR spectrum to data previously reported in the literature.[3] This compound was found to exist as a 3:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.06 (m, 5 H), 4.32–4.15 (m, 1.25 H), 4.08–3.95 (m, 0.75 H), 3.83–3.44 (m, 1 H), 3.06–2.96 (m, 1 H), 2.82–2.68 (m, 0.25 H), 2.61–2.47 (m, 0.75 H), 2.32–2.12 (m, 1.75 H), 2.05–1.93 (m, 0.25 H), 1.67–1.54 (m, 1 H), 1.51–1.03 (m, 24 H), 0.97–0.84 (m, 12 H), 0.13– -0.08 (m, 6 H).

(±)–(2*S*,3*S*,5*R*)-3-(*tert*-Butyldimethylsiloxy)-2-(4-methoxycarbonylbenzyl)-5-nonylpyrrolidine-1-carboxylic acid *tert*-butyl ester (24). The general procedure was employed for the reaction of methyl 4-bromobenzoate (52 mg, 0.24 mmol) with **17** (89 mg, 0.20 mmol) using Dpe-phos as ligand and a reaction time of 20 h. The diastereoselectivity of the transformation was assessed by LAH reduction of the crude product obtained in a duplicate reaction, and was found to be >20:1 dr as judged by ^{1}H NMR analysis. Chromatographic purification afforded 83 mg (72%) of the title compound as a colorless oil with >20:1 dr. This compound was found to exist as a 3:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99–7.88 (m, 2 H), 7.39–7.22 (m, 2 H), 4.32–4.19 (m, 1.3 H), 4.07–3.98 (m, 0.7 H), 3.90 (s, 3 H), 3.72–3.51 (m, 1 H), 3.11–3.01 (m, 1 H), 2.87–2.75 (m, 0.3 H), 2.67–2.53 (m, 0.7 H), 2.33–2.12 (m, 1.7 H), 2.07–1.93 (m, 0.3 H), 1.65–1.55 (m, 1 H), 1.46–1.05 (m, 24 H), 0.96–0.81 (m, 12 H), 0.12– -0.12 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 154.8, 145.9, 129.9, 129.4, 127.6, 79.2, 71.4, 62.1, 55.7, 51.9, 38.0, 37.2, 36.3, 31.9, 29.7, 29.6, 29.3, 28.1, 26.5, 25.8, 22.7, 18.1, 14.1, -4.7, -5.0; IR (film) 1726, 1694 cm^{-1}. Anal calcd for $C_{33}H_{57}NO_5Si$: C, 68.82; H, 9.98; N, 2.43. Found: C, 68.43; H, 9.98; N, 2.42.

The stereochemistry of the above compound was determined through LAH reduction of **24** to afford **24a** as shown below. The stereochemistry of **24a** was assigned by comparison of the ^{1}H NMR spectrum of **24** to that previously obtained for the related molecule **S1**.[3]



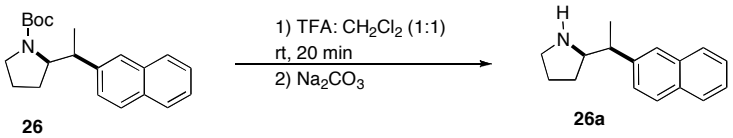
(±)–(2*S*,3*S*,5*R*)-2-(4-Hydroxymethylbenzyl)-1-methyl-5-nonylpyrrolidin-3-ol (24a). A flame-dried flask was cooled under a steam of nitrogen and charged with **24** (70 mg, 0.12 mmol) and THF (3 mL). The resulting solution was cooled to 0 °C and a solution of LAH in THF (1.2 mL, 1.2 mmol, 1.0 M) was added dropwise via syringe. The resulting mixture was heated to reflux until the starting material was consumed as judged by TLC analysis (ca. 21 h). The reaction mixture was cooled to 0 °C, slowly quenched with water (0.3 mL) and diluted with diethyl ether (5 mL). Aqueous NaOH (0.3 mL, 10 M) and water (0.3 mL) were added sequentially and an insoluble white precipitate formed. The organic supernatant was decanted and the precipitate was washed with diethyl ether. The combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude oil obtained was purified by flash chromatography using 10% → 20% methanol/dichloromethane as the eluent to afford 38 mg (91%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.28 (m, 4 H), 4.66 (s, 2 H), 3.83–3.75 (m, 1 H), 2.94–2.80 (m, 2 H), 2.33 (s, 3 H), 2.30–2.03 (m, 5 H), 1.77–1.66 (m, 1 H), 1.46–1.38 (m, 1 H), 1.37–1.15 (m, 15 H), 0.88 (t, *J* = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 129.5, 127.1, 73.7, 70.2, 65.9, 64.9, 39.5, 38.6, 34.7, 33.1, 31.9, 29.9, 29.6, 29.5, 29.3, 26.4, 22.6, 14.1 (two aromatic carbons are incidentally equivalent); IR (film) 3384 cm^{-1}; MS (ESI): 348.2900 (348.2903 calcd for $C_{22}H_{37}NO_2$, M + H$^+$).

Reactions of Hex-4-enylamine Derivatives (Table 4 and eq 3)

(±)–(1*R*,2*S*)-*tert*-Butyl-2-[1-(naphthalen-2-yl)ethyl]pyrrolidine-1-carboxylate (26). The general procedure was employed for the reaction of 2-bromonaphthalene (63 mg, 0.3 mmol) with **25** (50 mg, 0.25 mmol) using Nixantphos as ligand except that 5 mol % palladium and 7.5 mol % of ligand were used. The reaction was complete after 23 h. This procedure afforded 49 mg (60%) of the title compound as a colorless oil. This compound was found to exist as a 1.5:1 mixture of

rotamers as judged by ^{1}H NMR analysis and as a single diastereomer; data are for the mixture of rotamers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84–7.74 (m, 3 H), 7.72–7.61 (m, 1 H), 7.54–7.34 (m, 3 H), 4.24–4.03 (m, 1 H), 3.85–3.71 (m, 0.4 H), 3.66–3.43 (m, 1.6 H), 3.38–3.25 (m, 1 H), 1.87–1.66 (m, 3 H), 1.65–1.53 (m, 1 H), 1.46 (s, 9 H), 1.32 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 153.0, 141.5, 133.4, 132.2, 127.7, 127.5, 126.9, 125.9, 125.3, 79.4, 62.6, 47.7, 47.2, 41.5, 40.5, 28.5, 26.8, 25.9, 24.4, 23.6, 13.2, 12.9; IR (film) 1690 cm^{-1}. MS (ESI): 348.1932 (348.1939 calcd for $C_{21}H_{27}NO_2$, M + Na^+).

The diastereoselectivity of the transformation was assessed by TFA-mediated deprotection of the crude product obtained in a duplicate reaction to provide **26a** as shown below, and was found to be >20:1 dr as judged by ^{1}H NMR analysis.

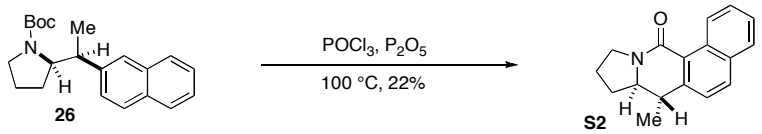


26 **26a**

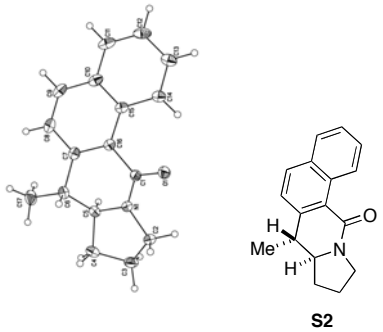
(±)–(1*R*,2*S*)-2-[1-(Naphthalen-2-yl)ethyl]pyrrolidine (26a). A flame-dried flask was cooled under a stream of nitrogen and charged with **26** (33 mg, 0.1 mmol), and dichloromethane (1 mL). The resulting solution was cooled to 0 °C, trifluoroacetic acid (1 mL) was then added slowly and the resulting mixture was stirred at rt for 30 min. The crude mixture was concentrated *in vacuo*. The crude product was dissolved in dichloromethane (5 mL), and Na_2CO_3 (636 mg, 4 mmol) was added. The resulting mixture was stirred at rt for 3 h, filtered through a plug of celite, and the filtrate was concentrated *in vacuo.* This procedure afforded 24 mg (100%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82–7.76 (m, 3 H), 7.67 (s, 1 H), 7.47–7.38 (m, 3 H), 3.22–3.14 (m, 1 H), 2.98–2.92 (m, 1 H), 2.80–2.70 (m, 2 H), 2.06–1.98 (m, 1 H), 1.88–1.72 (m, 2 H), 1.67–1.45 (m, 2 H), 1.34 (d, *J* = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.5, 133.6, 132.3, 128.1, 127.6, 127.6, 125.9, 125.8, 125.2, 65.1, 46.5, 46.1, 30.0, 24.6, 19.7 (two aromatic carbons are incidentally equivalent); IR (film) 3340 cm^{-1}; MS (EI): 226.1591 (226.1596 calcd for $C_{16}H_{19}N$, M $^+$).

The stereochemistry of (±)–(1*R*,2*S*)-*tert*-butyl-2-[1-(naphthalen-2-yl)ethyl]pyrrolidine-1-carboxylate (**26**) was determined through conversion to **S2** via Bischler-Napieralski cyclization.

The stereochemistry of **S2** was assigned on the basis of single crystal x-ray analysis as shown below.



(±)–(10*S*,10a*R*)-10-Methyl-2,3,10,10a-tetrahydropyrrolo[1,2-*b*]isoquinolin-5(1H)-one (S2). A flame-dried flask was cooled under a stream of nitrogen and charged with **26** (70 mg, 0.22 mmol), P_2O_5 (184 mg, 0.65 mmol) and $POCl_3$ (2 mL). The resulting mixture was heated to 100 °C for 13 h. The crude mixture was concentrated *in vacuo* and cooled to 0 °C. The crude material was diluted with water, and saturated aq Na_2CO_3 was added until bubbling stopped. The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organics were then washed with saturated aq Na_2CO_3, brine and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford 12 mg (22%) of the title compound as a white solid, m.p. 135-137 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.39 (d, *J* = 8.8 Hz, 1 H), 7.94 (d, *J* = 8.6 Hz, 1 H), 7.81 (dd, *J* = 0.6, 8.2 Hz, 1 H), 7.60–7.55 (m, 1 H), 7.50–7.44 (m, 2 H), 3.93–3.85 (m, 1 H), 3.79–3.70 (m, 1 H), 3.53–3.44 (m, 1 H), 3.02–2.92 (m, 1 H), 2.44–2.35 (m, 1 H), 2.18–2.09 (m, 1 H), 1.96–1.73 (m, 2 H), 1.46 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 132.8, 132.2, 131.3, 127.8, 127.5, 127.0, 125.7, 121.6, 61.6, 45.6, 39.4, 33.3, 23.3, 14.6 (three aromatic carbons are incidentally equivalent); IR (film) 1639 cm^{-1}. MS (ESI): 274.1202 (274.1208 calcd for $C_{17}H_{17}NO$, M + Na^+).

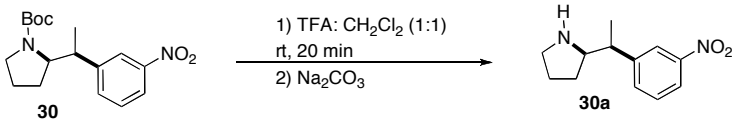


(±)–(1*R*,2*S*)-*tert*-Butyl-2-[1-(3-nitrophenyl)ethyl]pyrrolidine-1-carboxylate (30). The general procedure was employed for the reaction of 1-bromo-3-nitrobenzene (61 mg, 0.3 mmol) with **25** (50 mg, 0.25 mmol) using Nixantphos as ligand, except that 5 mol % palladium and 7.5 mol % of ligand were used. The reaction was complete after 36 h. This procedure afforded 40 mg (50%)

of the title compound as a colorless oil. NMR analysis indicated that the product was obtained as a single diastereomer and an 11:1 mixture of regioisomers. The NMR data is for the major regioisomer, which exists as a 1:1 mixture of rotamers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14–8.02 (m, 2 H), 7.70–7.42 (m, 2 H), 4.10–3.91 (m, 1 H), 3.67–3.39 (m, 2 H), 3.36–3.21 (m, 1 H), 1.88–1.59 (m, 4 H), 1.42 (s, 9 H), 1.29 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 148.1, 146.1, 146.0, 140.3, 134.6, 134.3, 133.4, 133.3, 133.0, 130.3, 129.6, 129.2, 128.9, 123.3, 122.5, 122.12, 122.08, 121.8, 121.7, 121.3, 121.1, 79.6, 79.2, 64.8, 62.3, 47.3, 46.9, 41.5, 40.9, 39.8, 28.5, 28.4, 28.2, 26.9, 26.4, 24.7, 24.2, 23.4, 22.0, 13.5; IR (film) 1691, 1530 cm^{-1}. MS (ESI): 343.1638 (343.1634 calcd for $C_{17}H_{24}N_2O_4$, M + Na^+).

The minor regioisomer (**31**) generated in this reaction has been tentatively assigned as a *N*-boc-2-ethylpyrrolidine bearing a *m*-nitrophenyl group at the 3-, 4-, or 5-position. This assignment was based on the observation of a triplet at 0.9 ppm in the ^{1}H NMR spectrum of the mixture of regioisomers, and on analogy to **33** described below. We were unable to obtain satisfactory MS data for **31** as this isomer failed to separate from the major isomer upon GC/MS analysis.

The diastereoselectivity of the transformation was assessed by TFA-mediated deprotection of the crude product obtained in a duplicate reaction to provide **30a** as shown below, and was found to be >20:1 dr as judged by ^{1}H NMR analysis. The stereochemistry of **30** was assigned based on comparison of ^{1}H and ^{13}C NMR spectra to those obtained for the related product **26**.



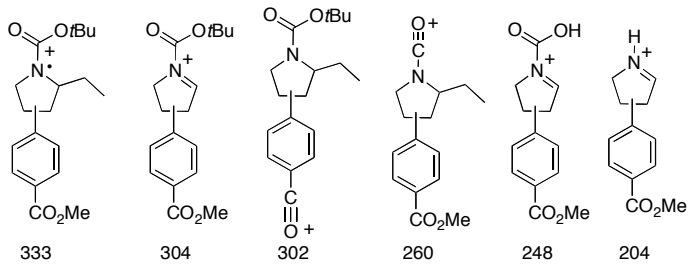
30 **30a**

(±)–(1*R*,2*S*)-2-[1-(4-Nitrophenyl)ethyl]pyrrolidine (30a). A flame-dried flask was cooled under a stream of nitrogen and charged with **30** (18 mg, 0.06 mmol), and dichloromethane (1 mL). The resulting solution was cooled to 0 °C, trifluoroacetic acid (1 mL) was then added slowly and the resulting mixture was stirred at rt for 30 min. The crude mixture was concentrated *in vacuo*. The crude product was dissolved in dichloromethane (5 mL), and Na_2CO_3 (636 mg, 4 mmol) was added. The resulting mixture was stirred at rt for 3 h, filtered through a plug of celite, and the filtrate was concentrated *in vacuo.* This procedure afforded 11 mg (89%) of the title compound as a colorless oil. ^{1}H NMR analysis indicated that the product was obtained as an 11:1

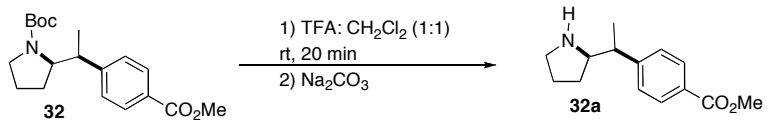
mixture of inseparable regioisomers. The NMR data is for the major regioisomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11–8.03 (m, 2 H), 7.60–7.54 (m, 1 H), 7.45 (t, *J* = 8.0 Hz, 1 H), 3.58–3.47 (m, 1 H), 3.18–3.08 (m, 1 H), 2.95–2.80 (m, 2 H), 2.30–2.20 (m, 1 H), 2.12–2.00 (m, 1 H), 1.98–1.87 (m, 1 H), 1.84–1.71 (m, 1 H), 1.60 (s, br, 1 H), 1.33 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.4, 144.6, 133.5, 129.8, 122.6, 122.2, 65.0, 44.8, 42.7, 29.5, 23.5, 19.8; IR (film) 3412, 1530 cm^{-1}; MS (EI): 221.1290 (221.1290 calcd for $C_{12}H_{16}N_2O_2$, M^+).

(±)–(1*R*,2*S*)-*tert*-Butyl-2-{1-[4-(methoxycarbonyl)phenyl]ethyl}pyrrolidine-1-carboxylate (32). The general procedure was employed for the reaction of methyl 4-bromobenzoate (65 mg, 0.3 mmol) with **25** (50 mg, 0.25 mmol) using (±)-BINAP as ligand, except that 5 mol % palladium and 7.5 mol % of ligand were used. The reaction was complete after 44 h. This procedure afforded 38 mg (46%) of the title compound as a colorless oil and as a 5:1 mixture of regioisomers. The NMR data is for the major regioisomer, which exists as a 1:1 mixture of rotamers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01–7.92 (m, 2 H), 7.41–7.22 (m, 2 H), 4.11–3.95 (m, 1 H), 3.90 (s, 3 H), 3.67–3.54 (m, 1 H), 3.50–3.40 (m, 1 H), 3.33–3.21 (m, 1 H), 1.81–1.55 (m, 4 H), 1.45 (s, 9 H), 1.24 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 166.9, 154.8, 149.4, 130.0, 129.5, 127.9, 127.1, 79.4, 62.4, 52.0, 51.9, 47.5, 47.1, 41.6, 40.8, 28.5, 26.8, 26.1, 24.2, 23.5, 13.1, 9.7; IR (film) 1724, 1693 cm^{-1}. MS (ESI): 356.1838 (356.1838 calcd for $C_{19}H_{27}NO_4$, $M + Na^+$).

The minor regioisomer (**33**) generated in this reaction has been tentatively assigned as a *N*-boc-2-ethylpyrrolidine bearing a *p*-carbomethoxyphenyl group at the 3-, 4-, or 5-position. This assignment was based on the observation of a triplet at 0.9 ppm in the ^{1}H NMR spectrum of the mixture of regioisomers, and on GC/MS analysis of the mixture. Relevant MS fragmentation data for the minor regioisomer is shown below: GC/MS (EI): 333, 304, 302, 260, 248, 204.



The diastereoselectivity of the transformation of **25** to **32** was assessed by TFA-mediated deprotection of the crude product obtained in a duplicate reaction to provide **32a** as shown below, and was found to be >20:1 dr as judged by ^{1}H NMR analysis. The stereochemistry of **32** was assigned based on comparison of ^{1}H and ^{13}C NMR spectra to those obtained for the related product **26**.



(±)–(1*S*,2*R*)-Methyl-4-(1-pyrrolidin-2-yl)ethylbenzoate (32a). A flame-dried flask was cooled under a stream of nitrogen and charged with **32** (15 mg, 0.04 mmol), and dichloromethane (1 mL). The resulting solution was cooled to 0 °C, trifluoroacetic acid (1 mL) was then added slowly and the resulting mixture was stirred at rt for 30 min. The crude mixture was concentrated *in vacuo*. The crude product was dissolved in dichloromethane (5 mL), and Na_2CO_3 (636 mg, 4 mmol) was added. The resulting mixture was stirred at rt for 3 h, filtered through a plug of celite, and the filtrate was concentrated *in vacuo.* This procedure afforded 10 mg (95%) of the title compound as a colorless oil. ^{1}H NMR analysis indicated that the product was obtained as a mixture of 5:1 mixture of regioisomers. The NMR data is for the major regioisomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94–7.85 (m, 2 H), 7.31–7.21 (m, 2 H), 3.87 (s, 3 H), 3.63–3.52 (m, 1 H), 3.10–2.94 (m, 1 H), 2.82–2.69 (m, 2 H), 2.29–2.18 (m, 1 H), 2.05–1.94 (m, 1 H), 1.93–1.82 (m, 1 H), 1.79–1.71 (m, 1 H), 1.60 (s, br, 1 H), 1.27 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 147.8, 130.0, 129.1, 127.4, 64.7, 52.1, 45.0, 43.3, 29.7, 23.6, 20.1; IR (film) 3422, 1721 cm^{-1}; MS (EI): 234.1485 (234.1494 calcd for $C_{14}H_{19}NO_2$, M $^+$).

(±)–(1*R,2S)*-Benzyl-2-{1-[4-(methoxycarbonyl)phenyl]ethyl}pyrrolidine-1-carboxylate (34). The general procedure was employed for the reaction of methyl 4-bromobenzoate (65 mg, 0.3 mmol) with **27** (59 mg, 0.25 mmol) using (±)-BINAP as ligand, except that 5 mol % palladium and 7.5 mol % of ligand were used. The reaction was complete after 42 h. This procedure afforded 39 mg (43%) of the title compound as a colorless oil and as a single diastereomer. This compound exists as a 1.5:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00–7.85 (m, 2 H), 7.41–7.28 (m, 6 H), 7.20–7.13 (m, 1 H), 5.19–5.07 (m, 1.6 H), 5.01–4.93 (m, 0.4 H), 4.18–4.02 (m, 1 H), 3.90 (s, 3 H), 3.71–3.51 (m,

1.6 H), 3.43–3.32 (m, 1.4 H), 1.85–1.57 (m, 4 H), 1.29–1.19 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 155.2, 149.2, 137.0, 136.6, 130.0, 129.4, 129.2, 128.5, 128.1, 127.9, 127.7, 67.1, 66.5, 63.1, 62.6, 52.0, 47.5, 47.4, 41.8, 40.7, 29.7, 26.9, 26.0, 24.3, 23.5, 13.4, 13.1; IR (film) 1719, 1702 cm^{-1}. MS (ESI): 390.1670 (390.1681 calcd for $C_{22}H_{25}NO_4$, M + Na^+).

The stereochemistry of **34** was assigned based on comparison of ^{1}H and ^{13}C NMR spectra to those obtained for the related product **26**.

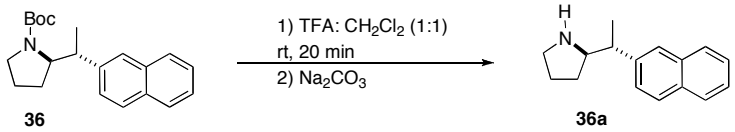
(±)–(1*R*,2*S*)-Benzyl-2-[1-(3-formylphenyl)ethyl]pyrrolidine-1-carboxylate (35). The general procedure was employed for the reaction of 3-bromobenzaldehyde (93 mg, 0.5 mmol) with **27** (59 mg, 0.25 mmol) using (±)-BINAP as ligand except that 10 mol % palladium and 15 mol % of ligand were used. The reaction was complete in 30 h. This procedure afforded 38 mg (45%) of the title compound as a colorless oil. NMR analysis indicated that the product was obtained as a single diastereomer. This compound exists as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.05–9.84 (m, 1 H), 7.83–7.54 (m, 3 H), 7.51–7.28 (m, 6 H), 5.16–4.89 (m, 2 H), 4.19–4.01 (m, 1 H), 3.72–3.54 (m, 1.5 H), 3.46–3.32 (m, 1.5 H), 1.91–1.58 (m, 4 H), 1.32–1.20 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.6, 192.4, 155.2, 144.8, 136.3, 134.5, 134.1, 128.8, 128.5, 128.1, 127.9, 127.7, 67.1, 66.6, 63.1, 62.7, 47.4, 47.3, 41.5, 40.4, 26.9, 26.0, 24.3, 23.5, 13.6, 13.2; IR (film) 1698 cm^{-1}. MS (ESI): 360.1584 (360.1576 calcd for $C_{21}H_{23}NO_3$, M + Na^+).

The stereochemistry of **35** was assigned based on comparison of ^{1}H and ^{13}C NMR spectra to those obtained for the related product **26**.

(±)–(1*R*,2*R*)-*tert*-Butyl-2-[1-(naphthalen-2-yl)ethyl]pyrrolidine-1-carboxylate (36). The general procedure was employed for the reaction of 2-bromonaphthalene (62 mg, 0.3 mmol) with **28** (50 mg, 0.25 mmol) using (±)-BINAP as ligand, except that 5 mol % palladium and 7.5 mol % of ligand were used. The reaction was complete in 27 h. This procedure afforded 50 mg (61%) of the title compound as a colorless oil. NMR analysis indicated that the product was obtained as a single diastereomer. This compound exists as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83–7.73 (m, 3 H), 7.64–7.58 (m, 1 H), 7.49–7.39 (m, 2 H), 7.38–7.29 (m, 1 H), 4.19–4.03 (m, 1 H), 3.54–3.44 (m, 0.5 H), 3.43–3.33 (m, 0.5 H), 3.31–3.18 (m, 1 H), 3.14–2.98 (m, 0.5 H), 2.93–2.82 (m, 0.5 H), 1.79–1.63

(m, 2 H), 1.62–1.47 (m, 10 H), 1.39 (d, *J* = 7.0 Hz, 3 H), 1.31–1.10 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2, 141.2, 133.4, 132.3, 127.8, 127.6, 127.5, 127.4, 127.1, 126.7, 126.6, 126.3, 125.9, 125.8, 125.3, 125.2, 79.4, 79.0, 62.6, 62.5, 46.7, 46.1, 42.6, 41.3, 29.8. 29.7, 28.6, 28.4, 28.2, 27.6, 26.5, 23.5; IR (film) 1690 cm^{-1}. MS (ESI): 348.1626 (348.1939 calcd for $C_{21}H_{27}NO_2$, M + Na^+).

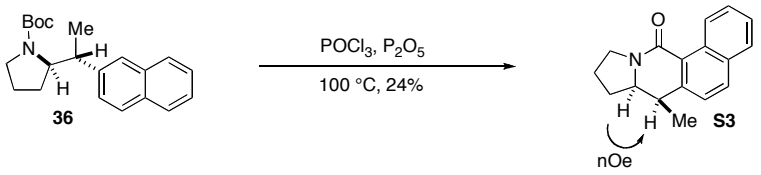
The diastereoselectivity of the transformation was assessed by TFA-mediated deprotection of the crude product obtained in a duplicate reaction to provide **36a** as shown below, and was found to be >20:1 dr as judged by ^{1}H NMR analysis.



36 **36a**

(±)–(1*R*,2*R*)-2-[1-(Naphthalen-2-yl)ethyl]pyrrolidine (36a). A flame-dried flask was cooled under a stream of nitrogen and charged with **36** (40 mg, 0.1 mmol), and dichloromethane (1 mL). The resulting solution was cooled to 0 °C, trifluoroacetic acid (1 mL) was then added slowly and the resulting mixture was stirred at rt for 30 min. The crude mixture was concentrated *in vacuo*. The crude product was dissolved in dichloromethane (5 mL), and Na_2CO_3 (636 mg, 4 mmol) was added. The resulting mixture was stirred at rt for 3 h, filtered through a plug of celite, and the filtrate was concentrated *in vacuo.* This procedure afforded 28 mg (100%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83–7.77 (m, 3 H), 7.65 (s, 1 H), 7.50–7.42 (m, 2 H), 7.35 (dd, *J* = 1.6, 8.6 Hz, 1 H), 5.84 (s, br, 1 H), 3.50–3.42 (m, 1 H), 3.26–3.18 (m, 1 H), 3.16–3.08 (m, 1 H), 3.07–2.98 (m, 1 H), 1.92–1.81 (m, 1 H), 1.80–1.70 (m, 1 H), 1.68–1.58 (m, 1 H), 1.51 (d, *J* = 7.0 Hz, 3 H) 1.49–1.44 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.7, 133.5, 132.4, 128.3, 127.64, 127.60, 126.1, 126.0, 125.6, 125.5, 65.7, 46.0, 44.7, 30.4, 24.5, 20.1; IR (film) 3340 cm^{-1}. MS (EI): 226.1591 (226.1596 calcd for $C_{16}H_{19}N$, M^+).

The stereochemistry of (±)–(1*R*,2*R*)-*tert*-butyl-2-[1-(naphthalen-2-yl)ethyl]pyrrolidine-1-carboxylate (**36**) was determined through conversion to **S3** via Bischler-Napieralski cyclization. The stereochemistry of **S3** was assigned on the basis of comparison of ^{1}H and ^{13}C NMR data with the related compound **S2** (described above) and was confirmed by ^{1}H NMR nOe experiments as shown below.

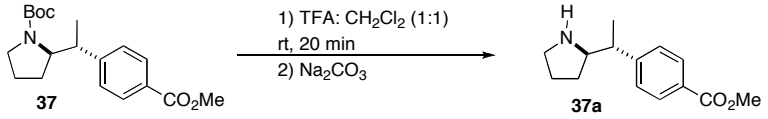


(±)–(10*R*,10a*R*)-10-Methyl-2,3,10,10a-tetrahydropyrrolo[1,2-*b*]isoquinolin-5(1H)-one (S3). A flame-dried flask was cooled under a stream of nitrogen and charged with **36** (64 mg, 0.20 mmol), P_2O_5 (168 mg, 0.59 mmol) and $POCl_3$ (2 mL). The resulting mixture was heated to 100 °C for 13 h. The crude mixture was concentrated *in vacuo* and cooled to 0 °C. The crude material was diluted with water, and saturated aq Na_2CO_3 was added until bubbling stopped. The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organics were then washed with saturated aq Na_2CO_3 (5 mL), brine (5 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford 12 mg (24%) of the title compound as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (d, *J* = 8.8 Hz, 1 H), 7.89 (d, *J* = 8.3 Hz, 1 H), 7.80 (dd, *J* = 0.7, 8.3 Hz, 1 H), 7.60–7.55 (m, 1 H), 7.49–7.45 (m, 1 H), 7.30–7.27 (m, 1 H), 4.09–4.02 (m, 1 H), 3.91–3.84 (m, 1 H), 3.71–3.63 (m, 1 H), 3.10–3.04 (m, 1 H), 2.16–2.07 (m, 2 H), 2.04–1.95 (m, 1 H), 1.94–1.86 (m, 1 H), 1.17 (dd, *J* = 0.7, 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 133.1, 132.4, 131.6, 128.0, 127.5, 126.8, 125.7, 125.1, 58.3, 45.8, 37.7, 28.6, 23.7, 14.9 (three aromatic carbons are incidentally equivalent); IR (film) 1638 cm^{-1}. MS (ESI): 252.1388 (252.1393 calcd for $C_{17}H_{17}NO$, M + H^+).

(±)–(1*R*,2*R*)-*tert*-Butyl-2-{1-[4-(methoxycarbonyl)phenyl]ethyl}pyrrolidine-1-carboxylate (37). The general procedure was employed for the reaction of methyl 4-bromobenzoate (130 mg, 0.6 mmol) with **28** (100 mg, 0.5 mmol) using (±)-BINAP as ligand, except that 5 mol % palladium and 7.5 mol % of ligand were used. The reaction was complete in 21 h. This procedure afforded 98 mg (59%) of the title compound as a colorless oil. NMR analysis indicated that the product was obtained as a single diastereomer. This compound exists as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99–7.93 (m, 2 H), 7.27–7.22 (m, 2 H), 4.10–3.96 (m, 1 H), 3.91 (s, 3 H), 3.52–3.32 (m, 1 H), 3.29–3.13 (m, 1 H), 3.05–2.96 (m, 0.5 H), 2.89–2.80 (m, 0.5 H), 1.81–1.69 (m, 1 H), 1.64–1.45 (m, 11 H), 1.30 (d, *J* = 7.2 Hz, 3 H), 1.20–1.00 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 155.0, 149.0, 129.4, 129.2, 128.3, 128.1, 79.5, 79.1, 62.4, 62.3, 52.0, 46.7, 46.2, 42.4, 40.9, 28.5,

27.3, 26.1, 23.4, 22.5, 17.9, 17.2; IR (film) 1724, 1694 cm^{-1}. MS (ESI): 356.1837 (356.1838 calcd for $C_{19}H_{27}NO_4$, M + Na^+).

The diastereoselectivity of the transformation was assessed by TFA-mediated deprotection of the crude product obtained in a duplicate reaction to provide **37a** as shown below, and was found to be >20:1 dr as judged by ^1H NMR analysis. The stereochemistry of **37** was assigned based on comparison of ^1H and ^{13}C NMR spectra to those obtained for the related product **36**.

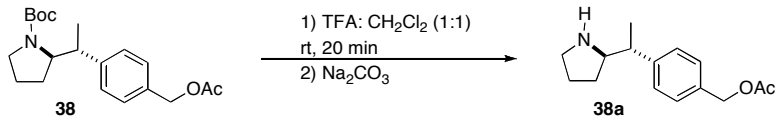


(±)–(1*R*,2*R*)-Methyl-4-(1-pyrrolidin-2-yl-ethyl)benzoate (37a). A flame-dried flask was cooled under a stream of nitrogen and charged with **37** (60 mg, 0.18 mmol), and dichloromethane (2 mL). The resulting solution was cooled to 0 °C, trifluoroacetic acid (2 mL) was then added slowly and the resulting mixture was stirred at rt for 30 min. The crude mixture was concentrated *in vacuo*. The crude product was dissolved in dichloromethane (5 mL), and Na_2CO_3 (1.2 g, 8 mmol) was added. The resulting mixture was stirred at rt for 3 h, filtered through a plug of celite, and the filtrate was concentrated *in vacuo.* This procedure afforded 41 mg (98%) of the title compound as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.2 Hz, 2 H), 7.27 (d, *J* = 8.2 Hz, 2 H), 3.90 (s, 3 H), 3.16–3.09 (m, 1 H), 3.05–2.98 (m, 1 H), 2.97–2.85 (m, 1 H), 2.71–2.62 (m, 1 H), 2.00 (s, br, 1 H), 1.77–1.58 (m, 2 H), 1.55–1.46 (m, 1 H), 1.35 (d, *J* = 6.8 Hz, 3 H), 1.27–1.16 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 151.2, 129.6, 128.1, 127.6, 64.8, 51.9, 46.7, 46.2, 30.3, 25.2, 19.7; IR (film) 3344, 1721 cm^{-1}; MS (EI): 234.1496 (234.1494 calcd for $C_{14}H_{19}NO_2$, M^+).

(±)–(1*R*,2*R*)-*tert*-Butyl-2-{1-[4-(acetoxymethyl)phenyl]ethyl}pyrrolidine-1-carboxylate (38). The general procedure was employed for the reaction of 4-bromobenzyl acetate (69 mg, 0.3 mmol) with **28** (50 mg, 0.25 mmol) using (±)-BINAP as ligand, except that 5 mol % palladium and 7.5 mol % of ligand were used. ^1H NMR analysis of the crude reaction mixture indicated that the reaction proceeded to 94% conversion after 31 h, at which point the reaction was stopped. After purification, 52 mg (60%) of the title compound was obtained as a colorless oil and as a single diastereomer. This compound exists as a 1:1 mixture of rotamers as judged by ^1H NMR analysis; data are for the mixture. ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.24 (m, 2 H),

7.22–7.14 (m, 2 H), 5.08 (s, 2 H), 4.08–3.92 (m, 1 H), 3.44–3.19 (m, 1.5 H), 3.15–2.85 (m, 1.5 H), 2.10 (s, 3 H), 1.78–1.66 (m, 1 H), 1.65–1.45 (m, 11 H), 1.27 (d, J = 7.2 Hz, 3 H), 1.24–1.09 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 155.1, 143.7, 134.0, 133.8, 128.4, 128.2, 128.1, 79.4, 79.0, 66.1, 62.5, 62.4, 46.7, 46.1, 42.1, 41.0, 28.6, 27.5, 26.4, 23.4, 22.6, 21.0, 18.2, 17.7; IR (film) 1742, 1691 cm^{-1}. MS (ESI): 370.1979 (370.1994 calcd for $C_{20}H_{29}NO_4$, M + Na^+).

The diastereoselectivity of the transformation was assessed by TFA-mediated deprotection of the crude product obtained in a duplicate reaction to provide **38a** as shown below, and was found to be >20:1 dr as judged by ^{1}H NMR analysis. The stereochemistry of **38** was assigned based on comparison of ^{1}H and ^{13}C NMR spectra to those obtained for the related product **36**.



(±)–(1*R*,2*R*)-4-(1-Pyrrolidin-2-yl-ethyl)benzyl acetate (38a). A flame-dried flask was cooled under a stream of nitrogen and charged with **38** (25 mg, 0.07 mmol), and dichloromethane (1 mL). The resulting solution was cooled to 0 °C, trifluoroacetic acid (1 mL) was then added slowly, and the resulting mixture was stirred at rt for 30 min. The crude mixture was concentrated *in vacuo*. The crude product was dissolved in dichloromethane (5 mL), and Na_2CO_3 (636 mg, 4 mmol) was added. The resulting mixture was stirred at rt for 3 h, filtered through a plug of celite, and the filtrate was concentrated *in vacuo.* This procedure afforded 30 mg (100%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, J = 8.3 Hz, 2 H), 7.20 (d, J = 8.3 Hz, 2 H), 5.08 (s, 2 H), 3.61–3.54 (m, 1 H), 3.41–3.30 (m, 2 H), 3.09–3.01 (m, 1 H), 2.11 (s, 3 H), 2.08–1.99 (m, 1 H), 1.96–1.85 (m, 1 H), 1.80–1.72 (m, 1 H), 1.67–1.57 (m, 1 H), 1.44 (d, J = 6.8 Hz, 3 H) (the NH proton was not detected due to broadening); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 142.6, 135.1, 128.8, 127.3, 66.2, 65.8, 45.2, 42.7, 30.2, 23.6, 21.0, 20.0; IR (film) 3431, 1678 cm^{-1}; MS (EI): 248.1644 (248.1651 calcd for $C_{15}H_{21}NO_2$, M $^+$).

(±)–(1*R*,2*R*)-*tert*-Butyl-2-(1-pyridin-3-yl-ethyl)pyrrolidine-1-carboxylate (39). The general procedure was employed for the reaction of 3-bromopyridine (48 mg, 0.3 mmol) with **28** (50 mg, 0.25 mmol) using (±)-BINAP as ligand, except that 5 mol % palladium and 7.5 mol % of ligand were used. The reaction was complete in 53 h. This procedure afforded 39 mg (56%) of the title compound as a colorless oil. NMR analysis indicated that the product was obtained as a single

diastereomer. This compound exists as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54–8.37 (m, 2 H), 7.57–7.42 (m, 1 H), 7.25–7.19 (m, 1 H), 4.08–3.95 (m, 1 H), 3.53–3.34 (m, 1 H), 3.31–3.21 (m, 0.5 H), 3.20–3.09 (m, 0.5 H), 3.05–2.95 (m, 0.5 H), 2.91–2.81 (m, 0.5 H), 1.87–1.73 (m, 1.5 H), 1.68–1.48 (m, 10.5 H), 1.31 (d, *J* = 7.2 Hz, 3 H), 1.23–1.13 (m, 0.5 H), 1.11–0.99 (m, 0.5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 150.1, 149.6, 148.0, 147.8, 138.3, 135.5, 135.4, 123.1, 79.6, 79.3, 62.1, 46.8, 46.3, 40.1, 38.3, 28.6, 28.4, 27.3, 25.9, 23.5, 22.6, 17.6, 16.8; IR (film) 1692 cm^{-1}. MS (ESI): 277.1909 (277.1916 calcd for $C_{16}H_{24}N_2O_2$, M + Na^+).

The stereochemistry of **39** was assigned based on comparison of ^{1}H and ^{13}C NMR spectra to those obtained for the related product **36**.

(±)–(1*R*,2*R*)-Benzyl-2-{1-[4-(methoxycarbonyl)phenyl]ethyl}pyrrolidine-1-carboxylate (40). The general procedure was employed for the reaction of methyl 4-bromobenzoate (65 mg, 0.3 mmol) with **29** (59 mg, 0.25 mmol) using (±)-BINAP as ligand, except that 5 mol % palladium and 7.5 mol % of ligand were used. The reaction was complete in 22 h. This procedure afforded 46 mg (50%) of the title compound as a colorless oil. ^{1}H NMR analysis indicated that the product was obtained as a single diastereomer. This compound exists as a 2:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.2 Hz, 2 H), 7.47–7.29 (m, 5 H), 7.24–7.14 (m, 2 H), 5.31–5.14 (m, 2 H), 4.15–4.05 (m, 1 H), 3.91 (s, 3 H), 3.49–3.39 (m, 1 H), 3.38–3.29 (m, 0.66 H), 3.26–3.17 (m, 0.33 H), 3.06–2.91 (m, 1 H), 1.83–1.71 (m, 1 H), 1.67–1.50 (m, 2 H), 1.35–1.23 (m, 3 H), 1.20–1.04 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 155.3, 148.6, 148.5, 137.1, 136.8, 129.4, 129.3, 128.5, 128.3, 128.12, 128.06, 127.9, 127.8, 67.0, 66.6, 63.0, 62.4, 52.0, 46.8, 46.6, 42.1, 40.9, 27.2, 26.1, 23.4, 22.6, 17.7, 17.4; IR (film) 1721, 1702 cm^{-1}. MS (ESI): 390.1670 (390.1681 calcd for $C_{22}H_{25}NO_4$, M + Na^+).

The stereochemistry of **40** was assigned based on comparison of ^{1}H and ^{13}C NMR spectra to those obtained for the related product **36**.

(±)–(1*R*,2*R*)-Benzyl-2-[1-(3-formylphenyl)ethyl]pyrrolidine-1-carboxylate (41). The general procedure was employed for the reaction of 3-bromobenzaldehyde (93 mg, 0.5 mmol) with **29**

(59 mg, 0.25 mmol) using (±)-BINAP as ligand, except that 10 mol % palladium and 15 mol % of ligand were used. The reaction was complete in 53 h. This procedure afforded 39 mg (46%) of the title compound as a colorless oil. NMR analysis indicated that the product was obtained as a single diastereomer. This compound exists as a 2:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.95 (s, 1 H), 7.78–7.61 (m, 2 H), 7.49–7.30 (m, 7 H), 5.33–5.12 (m, 2 H), 4.17–4.07 (m, 1 H), 3.54–3.43 (m, 1 H), 3.42–3.31 (m, 0.66 H), 3.30–3.19 (m, 0.33 H), 3.03–2.88 (m, 1 H), 1.86–1.74 (m, 1 H), 1.67–1.52 (m, 2 H), 1.39–1.25 (m, 3 H), 1.23–1.09 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.6, 155.4, 144.2, 137.1, 136.3, 134.7, 129.2, 128.9, 128.8, 128.7, 128.5, 128.14, 128.14, 128.07, 127.9, 127.8, 67.0, 66.6, 62.8, 62.3, 46.8, 46.6, 41.8, 40.5, 27.3, 26.1, 23.4, 22.6, 17.7, 17.4; IR (film) 1698 cm^{-1}. MS (ESI): 360.1578 (360.1576 calcd for $C_{21}H_{23}NO_3$, M + Na^+).

The stereochemistry of **41** was assigned based on comparison of ^{1}H and ^{13}C NMR spectra to those obtained for the related product **36**.

***tert*-Butyl-2-(2-chlorophenethyl)pyrrolidine-1-carboxylate (42).** The general procedure was employed for the reaction of 2-bromochlorobenzene (48 mg, 0.3 mmol) with **28** (50 mg, 0.25 mmol) using (±)-BINAP as ligand, except that 5 mol % palladium and 7.5 mol % of ligand were used. The reaction was complete in 44 h. This procedure afforded 58 mg (75%) of the title compound as a colorless oil that contained ~8% of an unidentified impurity. This compound exists as a 2:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.02 (m, 4 H), 4.00–3.73 (m, 1 H), 3.48–3.25 (m, 2 H), 2.79–2.62 (m, 2 H), 2.13–1.72 (m, 5 H), 1.69–1.54 (m, 1 H), 1.49–1.37 (m, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 139.5, 133.8, 130.2, 129.5, 127.2, 126.8, 79.1, 56.8, 46.5, 46.1, 34.7, 34.1, 30.5, 29.9, 28.5, 28.4, 23.8, 23.1; IR (film) 1693 cm^{-1}. MS (ESI): 332.1398 (332.1393 calcd for $C_{17}H_{24}ClNO_2$, M + Na^+).

Reactions of 4-Substituted Pent-4-enylamine Derived Substrates (Table 5)

***tert*-Butyl-2-methyl-2-(naphthalen-2-ylmethyl)pyrrolidine-1-carboxylate (47)**. The general procedure was employed for the reaction of 2-bromonaphthalene (63 mg, 0.30 mmol) with **46** (50 mg, 0.25 mmol) using Nixantphos as ligand and a reaction time of 19 h. This procedure

afforded 62 mg (77%) of the title compound as a colorless oil. This compound was found to exist as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84–7.70 (m, 3 H), 7.65–7.56 (m, 1 H), 7.48–7.39 (m, 2 H), 7.36–7.26 (m, 1 H), 3.70–3.64 (m, 0.5 H), 3.47–3.37 (m, 1 H), 3.35–3.26 (m, 0.5 H), 3.19–3.11 (m, 0.5 H), 2.98–2.89 (m, 1.5 H), 2.12–2.03 (m, 1 H), 1.65–1.48 (m, 14 H), 1.23–1.11 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4, 153.8, 136.6, 136.3, 133.4, 132.0, 129.2, 128.9, 128.8, 128.7, 127.6, 127.5, 127.2, 125.8, 125.7, 125.4, 125.2, 79.6, 78.6, 63.6, 63.1, 48.50, 48.46, 44.5, 43.2, 39.0, 37.8, 28.8, 28.7, 27.1, 26.1, 21.7, 21.3; IR (film) 1690 cm^{-1}. MS (ESI): 348.1940 (348.1939 calcd for $C_{21}H_{27}NO_2$, M + Na^+).

***tert*-Butyl-2-methyl-2-(pyridin-3-ylmethyl)pyrrolidine-1-carboxylate (52)**. The general procedure was employed for the reaction of 3-bromopyridine (48 mg, 0.30 mmol) with **46** (50 mg, 0.25 mmol) using Nixantphos as ligand except that 4 mol % palladium and 8 mol % ligand were used. The reaction was complete in 18 h. This procedure afforded 55 mg (80%) of the title compound as a colorless oil. This compound was found to exist as a 1.5:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49–8.40 (m, 2 H), 7.51–7.42 (m, 1 H), 7.23–7.16 (m, 1 H), 3.56–3.50 (m, 0.6 H), 3.48–3.41 (m, 0.4 H), 3.38–3.31 (m, 0.6 H), 3.28–3.21 (m, 0.4 H), 3.18–3.11 (m, 0.4 H), 3.00–2.93 (m, 0.6 H), 2.82–2.73 (m, 1 H), 1.99–1.88 (m, 1 H), 1.70–1.45 (m, 14 H), 1.26–1.15 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.2, 153.7, 151.4, 151.3, 147.8, 147.5, 134.2, 134.0, 123.2, 123.0, 79.8, 78.9, 63.2, 62.7, 48.5, 48.4, 41.6, 40.4, 39.0, 37.6, 28.7, 28.6, 26.9, 25.8, 21.6, 21.2; IR (film) 1687 cm^{-1}. MS (ESI): 299.1738 (299.1735 calcd for $C_{16}H_{24}N_2O_2$, M + Na^+).

***tert*-Butyl-2-(3-methoxybenzyl)-2-methylpyrrolidine-1-carboxylate (53)**. The general procedure was employed for the reaction of 3-bromoanisole (57 mg, 0.30 mmol) with **46** (50 mg, 0.25 mmol) using Nixantphos as ligand and a reaction time of 36 h. This procedure afforded 52 mg (68%) of the title compound as a colorless oil. This compound was found to exist as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (q, J = 7.8 Hz, 1 H), 6.79–6.67 (m, 3 H), 3.78 (s, 3 H), 3.46–3.38 (m, 1 H), 3.36–3.29 (m, 0.5 H), 3.28–3.23 (m, 0.5 H), 3.21–3.13 (m, 0.5 H), 3.09–3.01 (m, 0.5 H), 2.80–

2.69 (m, 1 H), 2.06–1.97 (m, 1 H), 1.60–1.45 (m, 14 H), 1.27–1.13 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 159.3, 154.3, 153.7, 140.6, 140.3, 129.0, 128.7, 123.0, 122.7, 116.1, 115.7, 111.8, 111.5, 79.5, 78.6, 63.5, 63.0, 55.2, 48.6, 48.5, 44.3, 43.2, 39.1, 37.8, 28.73, 28.69, 27.2, 26.0, 21.7, 21.3, 18.6; IR (film) 1693 cm^{-1}. MS (ESI): 328.1881 (328.1889 calcd for $C_{18}H_{27}NO_3$, M + Na^+).

Benzyl 2-(4-*tert*-butylbenzyl)-2-methylpyrrolidine-1-carboxylate (54). The general procedure was employed for the reaction of 4-*tert*-butyl bromobenzene (64 mg, 0.30 mmol) with **48** (50 mg, 0.21 mmol) using Nixantphos as ligand and a reaction time of 19 h. This procedure afforded 58 mg (74%) of the title compound as a colorless oil. This compound was found to exist as a 1.5:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46–7.30 (m, 5 H), 7.27–7.18 (m, 2 H), 7.05–6.95 (m, 2 H), 5.28–5.22 (m, 1.4 H), 5.13–5.05 (m, 0.6 H), 3.53–3.40 (m, 1 H), 3.37–3.31 (m, 0.6 H), 3.26–3.12 (m, 1.4 H), 2.88–2.82 (m, 0.6 H), 2.79–2.73 (m, 0.4 H), 2.08–1.98 (m, 1 H), 1.64–1.53 (m, 2 H), 1.48 (s, 2 H), 1.40 (s, 1 H), 1.34–1.24 (m, 10 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0, 153.8, 149.1, 148.9, 137.5, 135.4, 135.2, 130.1, 129.9, 128.5, 128.4, 128.2, 128.0, 127.8, 127.7, 125.0, 124.8, 67.0, 65.9, 64.2, 63.6, 49.1, 48.1, 43.9, 42.5, 38.9, 37.6, 34.3, 31.4, 31.4, 26.9, 25.7, 21.8, 21.4; IR (film) 1701 cm^{-1}. MS (ESI): 388.2256 (388.2252 calcd for $C_{24}H_{31}NO_2$, M + Na^+).

Benzyl-2-[4-(methoxycarbonyl)benzyl]-2-methylpyrrolidine-1-carboxylate (55). The general procedure was employed for the reaction of methyl 4-bromobenzoate (65 mg, 0.30 mmol) with **48** (59 mg, 0.25 mmol) using Nixantphos as ligand and a reaction time of 20 h. This procedure afforded 63 mg (68%) of the title compound as a colorless oil. This compound was found to exist as a 3:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92–7.84 (m, 2 H), 7.46–7.32 (m, 5 H), 7.16–7.06 (m, 2 H), 5.30–5.20 (m, 1.25 H), 5.12–5.06 (m, 0.75 H), 3.90 (s, 3 H), 3.57–3.51 (m, 0.75 H), 3.50–3.39 (m, 1 H), 3.30–3.25 (m, 0.25 H), 3.23–3.16 (m, 0.25 H), 3.12–3.05 (m, 0.75 H), 2.86–2.79 (m, 1 H), 2.04–1.93 (m, 1 H), 1.67–1.54 (m, 2 H), 1.51 (s, 2.25 H), 1.42 (s, 0.75 H), 1.27–1.13 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 153.9, 144.1, 143.8, 137.3, 130.4, 130.2, 129.4, 129.2, 128.54, 128.45, 128.4, 128.3, 128.1, 128.1, 127.9, 127.8, 67.1, 66.1, 64.0, 63.4, 52.0, 49.1, 48.1, 44.4,

43.0, 39.0, 37.6, 27.2, 26.0, 21.8, 21.4, 18.9; IR (film) 1721, 1698 cm^{-1}. MS (ESI): 390.1683 (390.1681 calcd for $C_{22}H_{25}NO_4$, M + Na^+).

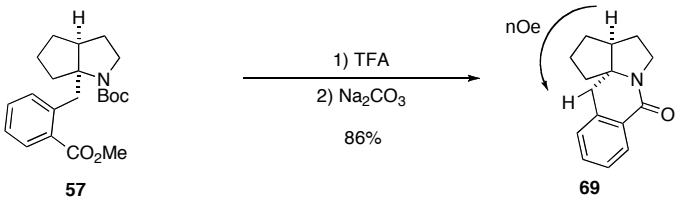
(±)–(3a*S*,6a*R*)-*tert*-Butyl-(biphenyl-4-ylmethyl)hexahydrocyclopenta[*b*]pyrrole-1(2H)-carboxylate (56). The general procedure was employed for the reaction of 4-bromobiphenyl (70 mg, 0.30 mmol) with **49** (57 mg, 0.25 mmol) using Nixantphos as ligand and a reaction time of 25 h. This procedure afforded 83 mg (87%) of the title compound as a colorless oil. This compound was found to exist as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.57 (m, 2 H), 7.53–7.48 (m, 2 H), 7.42 (t, *J* = 7.4 Hz, 2 H), 7.35–7.29 (m, 1 H), 7.26–7.17 (m, 2 H), 3.76 (d, *J* = 13.1 Hz, 0.5 H), 3.57 (d, *J* = 13.3 Hz, 0.5 H), 3.39–3.30 (m, 0.5 H), 3.27–3.18 (m, 0.5 H), 3.17–3.11 (m, 0.5 H), 3.00–2.92 (m, 0.5 H), 2.61 (dd, *J* = 6.1, 13.3 Hz, 1 H), 2.52–2.43 (m, 1 H), 2.42–2.34 (m, 0.5 H), 2.21–2.13 (m, 0.5 H), 1.90–1.77 (m, 2 H), 1.65–1.61 (m, 1 H), 1.59 (s, 5.5 H), 1.52 (s, 4.5 H), 1.39–1.31 (m, 1 H), 1.30–1.18 (m, 1 H), 1.13–0.97 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 153.7, 140.9, 140.8, 138.9, 138.7, 138.4, 137.9, 130.6, 130.5, 128.71, 128.69, 127.1, 127.0, 126.9, 126.7, 126.5, 79.5, 78.7, 74.7, 74.1, 49.0, 47.74, 44.71, 47.6, 43.0, 41.8, 40.7, 39.2, 32.5, 32.3, 28.8, 28.7, 28.3, 27.3, 25.6, 25.4; IR (film) 1689 cm^{-1}. MS (ESI): 400.2251 (400.2252 calcd for $C_{25}H_{31}NO_2$, M + Na^+).

The stereochemistry of **56** was assigned based on comparison of ^{1}H and ^{13}C NMR spectra to those obtained for the related product **57**, the stereochemistry of which was elucidated through ^{1}H NMR nOe experiments as described below.

(±)–(3a*S*,6a*R*)-*tert*-Butyl-[2-(methoxycarbonyl)benzyl]hexahydrocyclopenta[*b*]pyrrole-1(2H)-carboxylate (57). The general procedure was employed for the reaction of methyl 2-bromobenzoate (52 mg, 0.24 mmol) with **49** (43 mg, 0.20 mmol) using Nixantphos as ligand except that 5 mol % palladium and 10 mol % ligand were used. The reaction proceeded to ca. 80% conversion after 42 h, at which point the reaction was stopped. This procedure afforded 49 mg (71%) of the title compound as a colorless oil. This compound was found to exist as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82–7.77 (m, 1 H), 7.42–7.34 (m, 1 H), 7.29–7.15 (m, 2 H), 3.89 (s, 3 H), 3.77–3.72 (m, 0.5 H), 3.63–3.51 (m, 1.5 H), 3.38–3.29 (m, 0.5 H), 3.25–3.16 (m, 0.5 H), 3.11–3.03

(m, 0.5 H), 2.96–2.88 (m, 0.5 H), 2.40–2.26 (m, 1.5 H), 2.17–2.08 (m, 1.5 H), 1.94–1.76 (m, 2 H), 1.70–1.58 (m, 0.5 H), 1.56 (s, 4 H), 1.51 (s, 5 H), 1.33–1.15 (m, 2.5 H), 0.97–0.79 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 168.8, 154.2, 153.7, 140.4, 140.0, 132.6, 132.3, 131.3, 131.2, 131.1, 130.1, 126.0, 125.9, 79.5, 78.7, 75.3, 74.6, 52.1, 52.0, 48.2, 47.6, 47.5, 46.8, 41.2, 39.4, 38.3, 37.3, 32.7, 32.2, 32.1, 28.75, 28.69, 28.4, 28.2, 27.4, 25.6, 25.4; IR (film) 1722, 1689 cm^{-1}. MS (ESI): 382.1998 (382.1994 calcd for $C_{21}H_{29}NO_2$, M + Na^+).

The diastereoselectivity of the transformation was assessed by TFA-mediated deprotection of the crude product obtained in a duplicate reaction, and was found to be >20:1 dr as judged by ^{1}H NMR analysis. The stereochemistry of **57** was established by conversion to **69**, the stereochemistry of which was elucidated through ^{1}H NMR nOe experiments as shown below.



57 **69**

(±)–(4a*S*,12*R*)-2,3,4,4a,5,6-Hexahydro-1*H*-cyclopentapyrrolo[1-*b*]isoquinolin-8(12*H*)-one (69). A flame-dried flask was cooled under a stream of nitrogen and charged with **57** (43.2 mg, 0.11 mmol), and dichloromethane (1 mL). The resulting solution was cooled to 0 °C, trifluoroacetic acid (1 mL) was then added slowly and the resulting mixture was stirred at rt for 30 min. The crude mixture was concentrated *in vacuo*. The crude product was dissolved in dichloromethane (5 mL), and Na_2CO_3 (636 mg, 4 mmol) was added. The resulting mixture was stirred at rt for 3 h, filtered through a plug of celite, and the filtrate was concentrated *in vacuo.* . The crude product was then purified by flash chromatography using 5% methanol/dichloromethane as the eluent to afford 21.7 mg (86%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03–7.99 (m, 1 H), 7.42–7.36 (m, 1 H), 7.35–7.29 (m, 1 H), 7.16 (d, *J* = 7.4 Hz, 1 H), 4.17–4.08 (m, 1 H), 3.46–3.36 (m, 1 H), 3.09 (d, *J* = 15.3 Hz, 1 H), 2.81 (d, *J* = 14.9 Hz, 1 H), 2.53–2.45 (m, 1 H), 2.15–1.97 (m, 2 H), 1.80–1.66 (m, 3 H), 1.60–1.45 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.2, 137.2, 131.4, 129.8, 127.8, 127.6, 127.0, 72.1, 49.9, 44.2, 39.9, 38.0, 32.6, 30.4, 25.4; IR (film) 1646 cm^{-1}. MS (ESI): 227.1313 (227.1310 calcd for $C_{15}H_{17}NO$, M + Na^+).

(±)–(3a*R*,6a*S*)-Benzyl-6a-(3,5-dichlorobenzyl)hexahydrocyclopenta[*b*]pyrrole-1(2*H*)-carboxylate (58). The general procedure was employed for the reaction of 1-bromo-3,5-dichlorobenzene (62 mg, 0.27 mmol) with **50** (63 mg, 0.24 mmol) using Nixantphos as ligand and a reaction time of 20 h. This procedure afforded 77 mg (79%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.18 (m, 6 H), 7.08–6.97 (m, 1.5 H), 6.92–6.85 (m, 0.5 H), 5.36–5.06 (m, 2 H), 3.70 (d, *J* = 13.2 Hz, 1 H), 3.48–3.10 (m, 2 H), 2.63–2.52 (m, 1 H), 2.48–2.10 (m, 2 H), 1.94–1.73 (m, 2 H), 1.72–1.06 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 142.3, 141.8, 137.1, 134.4, 128.6, 128.52, 128.47, 128.38, 128.41, 128.2, 127.8, 127.7, 126.6, 126.4, 75.0, 74.1, 67.2, 66.4, 49.0, 48.2, 47.52, 47.47, 42.9, 41.4, 40.4, 39.2, 32.4, 32.1, 28.5, 27.7, 25.5, 25.3; IR (film) 1701 cm^{-1}. MS (ESI): 426.1000 (426.1004 calcd for $C_{22}H_{23}Cl_2NO_2$, M + Na^+).

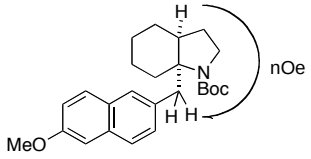
The stereochemistry of **58** was assigned based on comparison of ^{1}H and ^{13}C NMR spectra to those obtained for the related product **57**.

(±)–(3a*R*,7a*S*)-*tert*-Butyl-7a-[3-(trifluoromethyl)benzyl]octahydro-1*H*-indole-1-carboxylate (59). The general procedure was employed for the reaction of 1-bromo-3-(trifluoromethyl)benzene (50 μL, 0.36 mmol) with **51** (71.0 mg, 0.30 mmol) using Nixantphos as ligand and a reaction time of 7 h. This procedure afforded 88 mg (77%) of the title compound as a white solid, m.p. 81–85 °C. This compound was found to exist as ca. 1:1 mixture of rotamers as judged by ^{1}H NMR analysis and as a single diastereomer; data are for the mixture of rotamers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60–7.28 (m, 4 H), 3.76 (d, *J* = 13.5 Hz, 0.7 H), 3.72–3.62 (m, 0.4 H), 3.54–3.43 (m, 0.6 H), 3.39 (d, *J* = 14 Hz, 0.3 H), 2.94 (d, *J* = 14 Hz, 1 H), 2.85–2.75 (m, 0.5 H), 2.38–2.24 (m, 0.5 H), 2.10–1.30 (m, 20 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 154.0, 139.7, 139.3, 133.9, 133.5, 130.4, 129.1, 128.1, 127.8 (q, J_{CF} = 150 Hz), 126.99, 123.1, 122.84, 122.81, 79.7, 78.7, 64.0, 46.6, 46.5, 40.4, 39.8, 38.8, 38.0, 33.5, 32.8, 28.58, 28.53, 28.2, 25.9, 25.7, 25.6, 25.2, 22.6, 21.5, 21.2; IR (film) 1690 cm^{-1}. MS (ESI): 406.1967 (406.1970 calcd for $C_{21}H_{28}F_3NO_2$, M + Na^+).

The stereochemistry of **59** was assigned based on comparison of ^{1}H and ^{13}C NMR spectra to those obtained for the related product **60**, the stereochemistry of which was elucidated through ^{1}H NMR nOe experiments as described below.

(±)–(3a*R*,7a*S*)-*tert*-Butyl-7a-[(6-methoxynaphthalen-2-yl)methyl]octahydro-1*H*-indole-1-carboxylate (60). The general procedure was employed for the reaction of 2-bromo-6-methoxynaphthalene (83 mg, 0.35 mmol) with **51** (70 mg, 0.29 mmol) using Nixantphos as ligand and a reaction time of 7 h. This procedure afforded 96 mg (83%) of the title compound as a white solid, m.p. 48–52 °C. This compound was found to exist as ca. 1:1 mixture of rotamers as judged by ^{1}H NMR analysis and as a single diastereomer; data are for the mixture of rotamers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72–7.60 (m, 2 H), 7.58–7.47 (m, 1 H), 7.32–7.20 (m, 1 H), 7.18–7.10 (m, 2 H), 3.91 (s, 3 H), 3.76 (d, *J* = 13.5 Hz, 0.5 H), 3.66–3.58 (m, 0.5 H), 3.47 (d, *J* = 14 Hz, 0.5 H), 3.47–3.38 (m, 0.5 H), 3.00 (d, *J* = 13.5 Hz, 1 H), 3.00–2.90 (m, 0.5 H), 2.83–2.72 (m, 0.5 H), 2.32–2.22 (m, 0.5 H), 2.13–2.03 (m, 0.5 H), 2.13–1.91 (m, 1 H), 1.90–1.62 (m, 3 H), 1.62–1.32 (m, 15 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 157.1, 154.8, 154.0, 134.0, 133.7, 133.1, 133.0, 129.8, 129.2, 129.0, 128.83, 128.79, 128.6, 126.4, 126.0, 118.6, 118.4, 105.4, 79.5, 78.4, 64.4, 64.3, 55.2, 46.63, 46.55, 40.2, 39.9, 38.7, 38.3, 33.6, 32.9, 28.73, 28.71, 28.4, 26.1, 25.9, 25.8, 25.6, 22.7, 22.68, 22.64, 21.7, 21.5; IR (film) 1689 cm^{-1}. MS (ESI): 418.2350 (418.2358 calcd for $C_{25}H_{32}NO_3$, M + Na^+).

The stereochemistry of **60** was determined by ^{1}H NMR nOe analysis of the product as shown below.



Preparation of Benzocyclobutene 44 or Azabicyclooctane 45 (eq 5–6)

General Procedure. A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with the aryl bromide (1.2 equiv), $Pd(OAc)_2$ (4 mol %), Dpe-phos (8 mol %) and Cs_2CO_3 (2.3 equiv). The tube was purged with nitrogen and a solution of the *N*-protected amine substrate **43** (1.0 equiv) in dioxane (0.25 M) was then added via syringe. The resulting mixture was heated to 100 °C with stirring until the starting material had been consumed as determined by GC analysis. The reaction mixture was cooled to rt and saturated aq NH_4Cl (1 mL) and ethyl acetate (1 mL) were added. The layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 5 mL), and the combined organics were dried

over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel. All reactions provided the benzocyclobutene derivatives with >20:1 dr.

(±)-(1*R*,3a*R*,7b*S*)-2-[6-Phenyl-2,3,3a,7b-tetrahydro-1*H*-cyclopenta[3,4]cyclobuta[1,2]benzen-1-yl]ethyl-carbamic acid *tert*-butyl ester (**44**).[16] The general procedure was employed for the reaction of 4-bromobiphenyl (70 mg, 0.30 mmol) with **43** (53 mg, 0.25 mmol). The reaction was complete in 21 h. This procedure afforded 71 mg (75%) of the title compound as a white solid, m.p. 125–127 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.53 (m, 2 H), 7.46–7.38 (m, 3 H), 7.34–7.27 (m, 2 H), 7.07 (d, *J* = 7.6 Hz, 1 H), 4.56 (s, br, 1 H), 3.85 (d, *J* = 4.6 Hz, 2 H), 3.41–3.28 (m, 1 H), 3.29–3.17 (m, 1 H), 1.95–1.83 (m, 2 H), 1.81–1.59 (m, 4 H), 1.46 (s, 9 H), 1.13–1.02 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 146.3, 144.4, 142.2, 140.4, 128.6, 127.2, 126.8, 122.2, 121.8, 79.0, 50.7, 47.6, 40.2, 38.6, 32.1, 30.2, 28.7, 28.4 (two aromatic carbons are incidentally equivalent); IR (film) 3350, 1700 cm^{-1}. MS (ESI): 386.2092 (386.2096 calcd for $C_{24}H_{29}NO_2$, M + Na^+).

(±)-(3a*R*,6*S*,6a*S*)-6-Biphenyl-4-yl-hexahydrocyclopenta[*b*]pyrrole-1-carboxylic acid *tert*-butyl ester (**45**).[16] The general procedure was employed for the reaction of 4-bromobiphenyl (140 mg, 0.60 mmol) with **43** (106 mg, 0.50 mmol) except that NaO*t*Bu (111 mg, 1.15 mmol) was used as a base instead of Cs_2CO_3 and the reaction was conducted at 90 °C. The reaction was complete in 17 h This procedure afforded 92 mg (51%) of the title compound as a white solid, m.p. 126–128 °C. This compound was found to exist as a ~2:1 mixture of rotamers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.52 (m, 2 H), 7.53–7.45 (m, 2 H), 7.42 (t, *J* = 7.6 Hz, 2 H), 7.28–7.20 (m, 3 H), 4.58–4.48 (m, 0.3 H), 4.43–4.34 (m, 0.7 H), 3.86–3.75 (m, 0.7 H), 3.57–3.45 (m, 0.3 H), 3.39–3.19 (m, 1.3 H), 3.12–3.01 (m, 0.7 H), 3.00–2.81 (m, 1 H), 2.16–2.02 (m, 1 H), 2.01–1.77 (m, 3 H), 1.76–1.62 (m, 2 H), 1.21–0.93 (m, 9 H).

Deuterium-Labeling Experiments

(*E*)-*tert*-Butyl-5-*d*-pent-4-enylcarbamate (63). A flame-dried flask was cooled under a stream of nitrogen and charged with phthalimide (4.80 g, 24 mmol), triphenylphosphine (6.30 g, 24 mmol), THF (125 mL), and 4-pentyn-1-ol (1.70 g, 20 mmol). The resulting mixture was cooled to 0 ^{o}C, and DEAD (4.8 mL, 24 mmol) was added slowly over 15 min. The mixture was allowed to warm to rt and was stirred until the starting material was consumed as judged by TLC analysis (ca. 20 h). The crude reaction mixture was concentrated *in vacuo*. Hexanes (500 mL) was then added to the crude oil and an insoluble white material precipitated. The solution was filtered through a fritted funnel and the residue was rinsed with a solution of 5% ethyl acetate/hexanes (3 x 100 mL). The filtrate was concentrated *in vacuo* and the crude material was purified by flash chromatography using 10% → 20% ethyl acetate/hexanes as the eluent to afford 1.92 g (36%) of 2-(pent-4-ynyl)isoindoline-1,3-dione[17] as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87–7.82 (m, 2 H), 7.75–7.70 (m, 2 H), 3.80 (t, *J* = 7.0 Hz, 2 H), 2.28 (td, *J* = 2.7, 7.2 Hz, 2 H), 1.93 (quint, *J* = 7.0 Hz, 3 H).

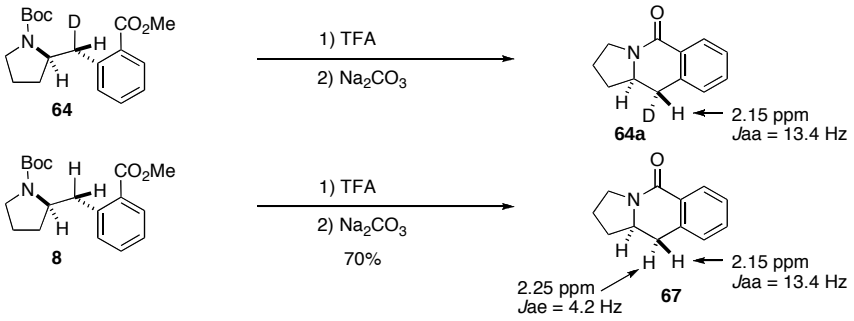
A flame-dried round-bottom flask was cooled under a stream of nitrogen and charged with 2-(pent-4-ynyl)isoindoline-1,3-dione (1.06 g, 4 mmol) and THF (20 mL). The resulting mixture was cooled to 0 ^{o}C, and 9-BBN (24 mL, 12 mmol, 0.5 M in THF) was added slowly. The mixture was allowed to warm to rt and was stirred for 4.5 h. The reaction mixture was then cooled to 0 ^{o}C and a solution of AcOD (4.7 mL, 80 mmol) in THF (4 mL) was added dropwise. The mixture was allowed to warm to rt and was stirred for 1.5 h. The reaction mixture was concentrated *in vacuo* and the crude material was purified by flash chromatography using 5%→10% ethyl acetate/hexanes as the eluent to afford 606 mg (60%) of (*E*)-5-*d*-2-(pent-4-enyl)isoindoline-1,3-dione as a colorless oil with 77% deuterium incorporation as judged by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87–7.80 (m, 2 H), 7.76–7.68 (m, 2 H), 5.88–5.75 (m, 1 H), 5.10–4.94 (m, 1 H), 3.73–3.63 (m, 2 H), 2.16–2.07 (m, 2 H), 1.83–1.74 (m, 2 H). MS (ESI): 216.1005 (216.1009 calcd for $C_{13}H_{12}DNO_2$, M + Na^{+}).

A flame-dried flask was cooled under a stream of nitrogen and charged with (*E*)-5-*d*-2-(pent-4-enyl)isoindoline-1,3-dione (606 mg), ethanol (15 mL), and hydrazine monohydrate (460 mg, 9.2 mmol). The mixture was heated to reflux with stirring until the starting material was consumed as judged by TLC analysis (ca. 24 h). The reaction mixture was cooled to rt, and

diethyl ether (100 mL) and di-*tert*-butyl dicarbonate (3.00 g, 13.8 mmol) were added. The resulting mixture was stirred at rt for 4 h and then aq NaOH (200 mL, 1 M) was added. The biphasic mixture was vigorously stirred for 12 h and the mixture was concentrated *in vacuo*. The aqueous layer was extracted with diethyl ether (3 x 50 mL), and the combined organics were then dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 10% ethyl acetate/hexanes as the eluent to afford 130 mg (17% over two steps) of the title compound as a colorless oil with 75% deuterium incorporation as judged by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85–5.75 (m, 1 H), 5.07–4.96 (m, 1 H), 4.56 (s, 1 H), 3.18–3.05 (m, 2 H), 2.13–2.04 (m, 2 H), 1.58 (quint, J = 7.6 Hz, 2 H), 1.49 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 137.7, 114.8 (t, J_{CD} = 23.9 Hz), 79.0, 40.1, 30.9, 29.2, 28.4; IR (film) 3349, 1693 cm^{-1}. MS (ESI): 209.1369 (209.1376 calcd for $C_{10}H_{18}DNO_2$, M + Na^+).

(±)–(1*R*,2*S*)-*tert*-Butyl-{2*d*-[2-(methoxycarbonyl)phenyl]methyl}pyrrolidine-1-carboxylate (64). The general procedure was employed for the reaction of methyl 2-bromobenzoate (38 mg, 0.17 mmol) with **63** (27 mg, 0.14 mmol) using Dpe-phos as ligand and a reaction time of 20 h. This procedure afforded 30 mg (65%) of the title compound as a colorless oil and as a single stereoisomer. This compound was found to exist as a 2:1 mixture of rotamers, the data is for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91–7.78 (m, 1 H), 7.45–7.33 (m, 1.33 H), 7.30–7.18 (m, 1.66 H), 4.20–4.10 (m, 1 H), 3.89 (s, 3 H), 3.49–3.20 (m, 2.66 H), 3.07–2.97 (m, 0.33 H), 1.95–1.75 (m, 2.66 H), 1.74–1.61 (m, 1.33 H), 1.53–1.17 (m, 9 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 154.6, 141.0, 131.9, 131.7, 130.4, 126.0, 78.9, 58.6, 52.0, 46.6, 45.9, 37.2, 35.7, 30.3 (m), 28.9, 28.5, 28.3, 23.5, 22.7; IR (film) 1723, 1691 cm^{-1}. MS (EI): 343.1741 (343.1744 calcd for $C_{14}H_{24}DNO_4$, M $^+$).

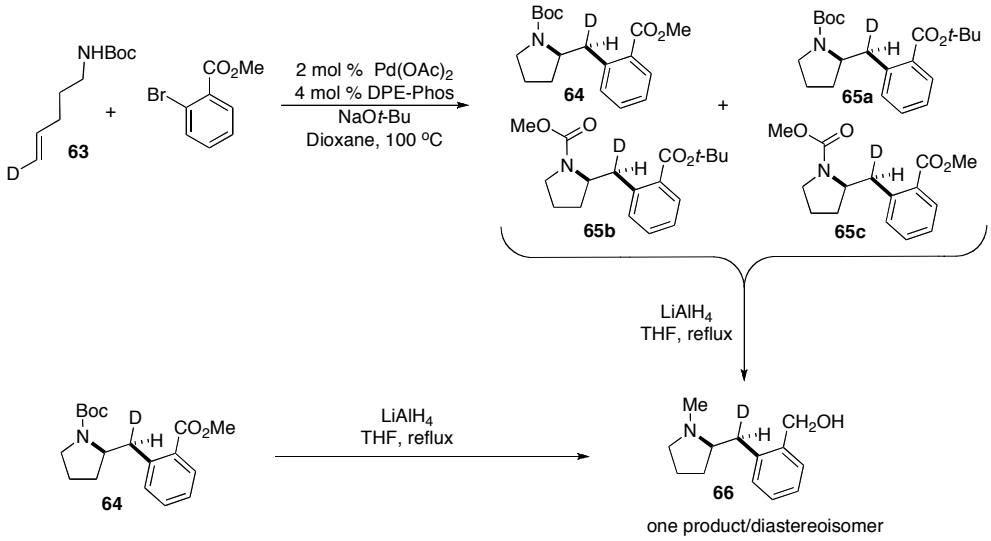
The stereochemistry of this product was established by conversion to **64a** and comparison to all-proteo compound **67** as shown below.



(±)–(10*S*,10a*R*)-10-*d*-2,3,10,10a-Tetrahydropyrrolo[1,2-*b*]isoquinolin-5(1H)-one (64a). A flame-dried flask was cooled under a stream of nitrogen and charged with **64** (30 mg, 0.09 mmol) and dichloromethane (1 mL). The resulting solution was cooled to 0 °C, trifluoroacetic acid (1 mL) was added slowly and the resulting mixture was stirred at rt for 30 min. The crude mixture was concentrated *in vacuo*. The crude product was dissolved in dichloromethane (5 mL), and Na_2CO_3 (636 mg, 4 mmol) was added. The resulting mixture was stirred at rt for 3 h, filtered through a plug of celite, and the filtrate was concentrated *in vacuo.* This procedure afforded 19 mg (100%) of the title compound as a colorless oil with ~80% deuterium incorporation as judged by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, C_6D_6) δ 8.50–8.45 (m, 1 H), 7.09–7.04 (m, 2 H), 6.80–6.75 (m, 1 H), 3.62–3.54 (m, 1 H), 3.45–3.36 (m, 1 H), 3.12–3.08 (m, 1 H), 2.15 (d, J = 13.4 Hz, 1 H), 1.47–1.39 (m, 1 H), 1.36–1.27 (m, 1 H), 1.16–1.04 (m, 1 H), 0.98–0.87 (m, 1 H); ^{13}C NMR (1200 MHz, $CDCl_3$) δ 162.5, 137.8, 131.5, 131.1, 128.2, 127.2, 127.1, 56.4, 44.7, 34.6 (t, J_{CD} = 20 Hz), 33.5, 22.8; IR (film) 1631 cm^{-1}; MS (EI): 343.1741 (343.1744 calcd for $C_{14}H_{24}DNO_4$, M$^+$).

2,3,10,10*a*-Tetrahydropyrrolo[1,2-*b*]isoquinolin-5(1H)-one (67).[18] A flame-dried flask was cooled under a stream of nitrogen and charged with **8** (39 mg, 0.12 mmol) and dichloromethane (1 mL). The resulting solution was cooled to 0 °C, trifluoroacetic acid (1 mL) was then added slowly and the resulting mixture was stirred at rt for 30 min. The crude mixture was concentrated *in vacuo*. The crude product was dissolved in dichloromethane (5 mL), and Na_2CO_3 (636 mg, 4 mmol) was added. The resulting mixture was stirred at rt for 3 h, filtered through a plug of celite, and the filtrate was concentrated *in vacuo*. This procedure afforded 16 mg (70%) of the title compound as a white solid, m.p. 102–104 °C (lit. m.p. 108 °C).[18] ^{1}H NMR (500 MHz, C_6D_6) δ 8.50–8.45 (m, 1 H), 7.09–7.04 (m, 2 H), 6.80–6.75 (m, 1 H), 3.62–3.54 (m, 1 H), 3.45–3.36 (m, 1 H), 3.12–3.08 (m, 1

H), 2.25 (dd, *J* = 4.2, 15.1 Hz, 1 H), 2.15 (dd, *J* = 13.4, 14.7 Hz, 1 H), 1.47–1.39 (m, 1 H), 1.36–1.27 (m, 1 H), 1.16–1.04 (m, 1 H), 0.98–0.87 (m, 1 H).



Pd-Catalyzed Carboamination of 63 With Methyl-2-Bromobenzoate Using NaO*t*Bu as Base.

The general procedure was employed for the reaction of methyl 2-bromobenzoate (65 mg, 0.3 mmol) with **63** (47 mg, 0.25 mmol) except NaO*t*Bu was used as base. The reaction was complete in 20 h. This procedure afforded four isomeric products: **64**, **65a**, **65b**, **65c** in a combined yield of 53%. These four compounds were separated for the purpose of characterization through repeated chromatography; data are provided below. Reduction of these four products with $LiAlH_4$ led to the generation of a single product (**66**). The identity of **66** was confirmed by synthesis of this material through $LiAlH_4$ reduction of a pure sample of **64**.

(±)–(1*R*,2*S*)-*tert*-Butyl-{2*d*-[2-(methoxycarbonyl)phenyl]methyl}pyrrolidine-1-carboxylate (64). This compound was isolated (12 mg, 15%) as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis. Data were identical to those reported above.

(±)–(1*R*,2*S*)-*tert*-Butyl-{2*d*-[2-(*tert*-butoxycarbonyl)phenyl]methyl}pyrrolidine-1-carboxylate (65a). This compound was isolated (12 mg, 14%) as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis. The data is for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81–7.67 (m, 1 H), 7.41–7.34 (m, 1 H), 7.27–7.15 (m, 2 H), 4.19–4.06 (m, 1 H), 3.47–3.21 (m, 2.5

H), 3.02–2.93 (m, 0.5 H), 1.97–1.75 (m, 2.5 H), 1.73–1.65 (m, 1.5 H), 1.59 (s, 9 H), 1.50–1.27 (m, 9 H); MS (EI): 385.2205 (385.2214 calcd for $C_{21}H_{30}DNO_4$, M^+).

(±)–(1*R*,2*S*)-Methyl-{2*d*-[2-(*tert*-butoxycarbonyl)phenyl]methyl}pyrrolidine-1-carboxylate (65b). This compound was isolated (11 mg, 14%) as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis. The data is for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79–7.69 (m, 1 H), 7.41–7.33 (m, 1.5 H), 7.25–7.14 (m, 1.5 H), 4.20–4.10 (m, 1 H), 3.70 (s, 1.5 H), 3.52–3.21 (m, 4 H), 3.09–3.01 (m, 0.5 H), 1.97–1.77 (m, 2 H), 1.76–1.65 (m, 2 H), 1.60 (s, 9 H); MS (EI): 343.1731 (343.1744 calcd for $C_{18}H_{24}DNO_4$, M^+).

(±)–(1*R*,2*S*)-Methyl-{2*d*-[2-(methoxycarbonyl)phenyl]methyl}pyrrolidine-1-carboxylate (65c). This compound was isolated (7 mg, 10%) as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis. The data is for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88–7.81 (m, 1 H), 7.45–7.40 (m, 1 H), 7.38–7.32 (m, 0.5 H), 7.28–7.18 (m, 1.5 H), 4.19–4.14 (m, 1 H), 3.91 (s, 3 H), 3.69 (s, 1.5 H), 3.49–3.19 (m, 4 H), 3.13–3.04 (m, 0.5 H), 1.91–1.76 (m, 2 H), 1.75–1.65 (m, 2 H); MS (EI): 301.1272 (301.1275 calcd for $C_{15}H_{18}DNO_4$, M^+).

(±)–(1*R*,2*S*)-1-[2*d*-(Methylpyrrolidin-2-ylmethyl)phenyl]methanol (66). A flame-dried round-bottom flask was cooled under a stream of nitrogen and charged with **64** (28 mg, 0.09 mmol). The flask was purged with nitrogen, THF (2 mL) was added via syringe and the resulting solution was cooled to 0 ^{o}C. A solution of $LiAlH_4$ in THF (0.5 mL, 0.5 mmol, 1.0 M) was added dropwise via syringe. The reaction mixture was warmed to reflux, and stirred for 21 h, then was cooled to 0 ^{o}C, quenched with H_2O (0.5 mL), and diluted with diethyl ether (2 mL). A solution of aq NaOH (1 mL, 10 M) was added followed by H_2O (0.2 mL), and an insoluble white material precipitated. The organic supernatant was decanted and the precipitate was washed with diethyl ether (6 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 20% methanol/dichloromethane as the eluent to afford 12 mg (67%) of the title compound as a colorless oil with 80% deuterium incorporation as judged by MS analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.17 (m, 4 H), 4.76 (d, J = 11.7 Hz, 1 H), 4.40 (d, J = 11.7 Hz, 1 H), 3.22–3.14 (m, 1 H), 2.96–2.88 (m, 1 H), 2.87–2.79 (m, 1 H), 2.39–2.30 (m, 1 H), 2.14–2.03 (m, 1 H), 1.91

(s, 3 H), 1.87–1.68 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.5, 138.1, 130.5, 130.3, 128.2, 126.7, 67.3, 63.2, 57.4, 42.8, 38.7 (t, J_{CD} = 21.2 Hz), 31.6, 23.9; IR (film) 3361 cm^{-1}. MS (EI): 207.1601 (207.1608 calcd for $C_{13}H_{18}DNO_4$, M^+).

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