Palladium-Catalyzed Tandem *N*-Arylation/Carboamination Reactions for the Stereoselective Synthesis of Pyrrolidines

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Supporting Information

Experimental procedures and characterization data for new compounds in Table 1 and descriptions of stereochemical assignments (15 pages).

General All reactions were carried out under an argon atmosphere in flame-dried glassware. Tris(dibenzylidineacetone)dipalladium(0) and all phosphine ligands were purchased from Strem Chemical Co. and used without further purification. All aryl bromides except for 4-bromobenzoic acid *tert*-butyl ester were obtained from commercial sources (Aldrich Chemical Co. or Acros Chemical Co.) and were used as obtained. 4-Bromobenzoic acid *tert*-butyl ester[1] and 2-allyl-2-methylpent-4-enylamine (**8**)[2] were prepared according to literature procedures. Toluene was purified using a GlassContour solvent purification system. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^{1}H NMR and/or combustion analysis. The yields reported in the supporting information describe the result of a single experiment, whereas the yields reported in Table 1 are average yields of two or more experiments. Thus, the yields reported in the supporting information may differ from those shown in Table 1.

Synthesis of γ-Aminoalkenes

Pent-4-enylamine (1).[4] Neat 4-pentenoyl chloride (16.6 mL, 17.8 g, 150 mmol) was added dropwise via syringe to a solution of 28 % aqueous ammonium hydroxide (400 mL) with stirring. The resulting mixture was stirred at room temperature for 1 h and then was extracted with ethyl acetate (3 x 250 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford 8.5 g (57 %) of pent-4-enoic acid amide[3] as a tan solid, m.p. 102-103 °C (lit m.p. 106 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89–5.81 (m, 1 H), 5.41 (br s, 1 H), 5.32 (br s, 1 H), 5.13–5.02 (m, 2 H), 2.44–2.37 (m, 2 H), 2.36–2.31 (m, 2 H).

A flame-dried round-bottom flask was charged with pent-4-enoic acid amide (8.5 g, 86 mmol) and purged with argon, and then ether (86 mL) was added via syringe. The resulting suspension was cooled to 0 °C and a solution of $LiAlH_4$ in ether (129 mL, 129 mmol, 1.0 M) was added via syringe. The reaction mixture was then warmed to room temperature for 14 h at which time the starting material had been consumed as judged by TLC analysis. The reaction mixture was cooled to 0 °C, diluted with ether (1300 mL), and quenched slowly with aqueous 10 M NaOH until all insoluble material had precipitated. The organic supernatant was decanted to a clean Erlenmeyer flask and the precipitate was washed with ether (200 mL). The combined organic extracts were diluted further with pentane (500 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then fractionally distilled from calcium hydride to afford 4.0 g (55 %) of the title compound[4] as a clear liquid, b.p. 100–105 °C (lit.[5] b.p. 105 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87–5.76 (m, 1 H), 5.06–4.93 (m, 2 H), 2.70 (t, J = 7.2 Hz, 2 H), 2.13–2.06 (m, 2 H), 1.58–1.50 (m, 2 H), 1.07 (br s, 2 H).

1-Phenylpent-4-enylamine (4).[7] A flame-dried round bottom flask was cooled under a stream of argon and charged with 1-phenylpent-4-en-1-one[6] (11.0 g, 69.0 mmol), activated 3 Å molecular sieves (10.0 g), and methanol (200 mL). The mixture was stirred at rt for 5 min and then ammonium acetate (53 g, 690 mmol) and sodium cyanoborohydride (4.3 g, 69.0 mmol) were added. The flask was purged with argon and then stirred at rt for 19 h. Ether (500 mL) was added, the mixture was decanted, and the organic phase was washed with 200 mL of aqueous $NaHCO_3$. The layers were separated, the aqueous phase was extracted with ether (3 x 100 mL), and the combined organic layers were extracted with 1 M aqueous HCl (3 x 100 mL). The organic phase was discarded and the combined acidic aqueous extracts were basicified to pH 10 with 10 M NaOH and extracted with ether (3 x 100 mL). The combined organic extracts were diluted with hexanes (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford 2.1 g (19 %) of the title compound[7] as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.29 (m, 4 H), 7.27–7.21 (m, 1 H), 5.87–5.76 (m, 1 H), 5.05–4.94 (m, 2 H), 3.92–3.87 (m, 1 H), 2.14–1.96 (m, 2 H), 1.84–1.70 (m, 2 H), 1.52 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 138.1, 128.3, 126.8, 126.2, 114.6, 55.2, 38.5, 30.6; IR (film) 3367, 1640 cm^{-1}.

1-But-3-enylpent-4-enylamine (5). A flame-dried round-bottomed flask was charged with 1,8-nonadien-5-ol[8] (210 mg, 1.5 mmol) and THF (5 mL). Triphenylphosphine (470 mg, 1.8 mmol) was added, and the reaction mixture was cooled to 0 °C. Diphenylphosphoryl azide (0.39 mL, 0.50 g, 1.8 mmol) was added slowly, then diisopropyl azodicarboxylate (0.39 mL, 0.40 g, 2 mmol) was added slowly over 5 min. The resulting solution was stirred at 0 °C for 2 h at which point the starting material had been consumed as judged by TLC analysis. The reaction mixture was poured into a biphasic mixture of ether and 5 % aqueous $NaHCO_3$. The layers were

separated, and the organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel to afford 200 mg (81 %) of 5-azidonona-1,8-diene as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82–5.75 (m, 2 H), 5.08–4.99 (m, 4 H), 3.32–3.29 (m, 1 H), 2.24–2.12 (m, 4 H), 1.63–1.59 (m, 4 H).

A flame-dried round-bottom flask was charged with 5-azidonona-1,8-diene (200 mg, 1.2 mmol), ether (2 mL), and THF (2 mL). The solution was cooled to 0 °C, and a solution of $LiAlH_4$ in ether (4 mL, 4 mmol, 1.0 M) was added dropwise. The resulting solution was warmed to room temperature, stirred for 14 h, and then cooled to 0 °C. Water (0.2 mL) was added slowly dropwise followed by 10 M NaOH (1 mL) and additional water (1 mL). The resulting slurry was stirred at room temperature for 5 min until all solids were deposited on the sides of the flask. The solution was decanted, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford 134 mg (80%) of the title compound as pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86–5.78 (m, 2 H), 5.06–4.94 (m, 4 H), 2.76–2.72 (m, 1 H), 2.21–2.06 (m, 4 H), 1.55–1.51 (m, 2 H), 1.39–1.35 (m, 2 H), 1.27 (br, s, 2 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 138.6, 114.5, 50.2, 37.1, 30.4; IR (film) 3325, 1481 cm^{-1}. MS (EI) 140.1432 (140.1439 calcd for $C_9H_{18}N$, $M + H^+$).

3-Phenylpent-4-enylamine (6). A flame-dried round-bottom flask was charged with 3-phenylpent-4-enoic acid amide[9] (1.6 g, 14 mmol), ether (20 mL), and THF (5 mL). The resulting solution was cooled to 0 °C, and a solution of $LiAlH_4$ in ether (28 mL, 28 mmol, 1.0 M) was added dropwise. The mixture was warmed to room temperature, stirred for 14 h, and then cooled to 0 °C. Water (1.5 mL) was added slowly dropwise, followed by 10 M aqueous NaOH (4 mL) and additional water (6 mL). The resulting slurry was stirred at room temperature for 5 min until all solids were deposited on the sides of the flask. The solution was decanted, dried over

anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford 1.0 g (63%) of the title compound as pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.28 (m, 2 H), 7.22–7.18 (m, 3 H), 6.02–5.93 (m, 1 H), 5.08–5.02 (m, 2 H), 3.39–3.34 (m, 1 H), 2.72–2.60 (m, 2 H), 1.93–1.82 (m, 2 H), 1.5 (br, s, 2 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 143.9, 141.9, 128.5, 127.5, 126.3, 114.2, 47.4, 40.1, 39.1; IR (film) 3331, 1576 cm^{-1}. MS (EI) 160.1131 (160.1126 calcd for $C_{11}H_{14}N$, M – H).

3-Methylpent-4-enylamine (7).[10] A flame-dried round-bottom flask was cooled under a stream of nitrogen and charged with 3-methylpent-4-enoic acid amide[9] (5.5 g, 50 mmol). The flask was purged with nitrogen, THF (50 mL) was added, and the resulting solution was cooled to 0 °C. A solution of $LiAlH_4$ in THF (100 mL, 100 mmol, 1.0 M) was added dropwise via syringe. The reaction mixture was warmed to rt and stirred for 16 h. The mixture was then cooled to 0 °C and quenched with a minimal amount of water. Aqueous 10 M NaOH (15 mL) and then H_2O (30 mL) were added until all inorganic materials had precipitated. The organic supernatant was decanted to a clean Erlenmeyer flask, and the precipitate was washed with ether (100 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford 3.5 g (71 %) of the title compound[10] as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67–5.58 (m, 1 H), 4.94–4.84 (m, 2 H), 2.63 (t, J = 7.6 Hz, 2 H), 2.17–2.14 (m, 1 H), 1.41–1.36 (m, 4 H), 0.94 (d, J = 6.8 Hz, 3 H).

General procedures for the one-pot palladium catalyzed synthesis of N-aryl-2-benzylpyrrolidines using two different aryl bromides (Table 1)

Method A. A flame-dried Schlenk tube was cooled under a stream of argon and charged with $Pd_2(dba)_3$ (1 mol % complex, 2 mol % Pd), *t*-Bu_2P(*o*-biphenyl) (**3**) (2 mol %), and NaO*t*-Bu (2.4 equiv). The tube was purged with argon, and toluene (4 mL/mmol amine substrate), the amine

substrate (1.0 equiv), and the first aryl bromide (1.0 equiv) were added via syringe. The mixture was heated to 60 °C with stirring until the starting material had been consumed as judged by GC or ^{1}H NMR analysis. The reaction mixture was heated to 110 °C, and a solution of dppe (2 mol %) in toluene (4 mL/mmol amine substrate) was added to the reaction mixture. After 15 minutes of stirring at 110 °C, the second aryl bromide (1.2 equiv) was added neat. When the intermediate arylamine had been consumed (as judged by GC or ^{1}H NMR analysis), the reaction mixture was cooled to room temperature, quenched with saturated aqueous ammonium chloride (2 mL), and diluted with ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.

Method B. A flame-dried Schlenk tube was cooled under a stream of argon and charged with $Pd_2(dba)_3$ (1 mol % complex, 2 mol % Pd), *rac*-BINAP (**2**) (2 mol %), and NaO*t*-Bu (2.4 equiv). The tube was purged with argon, and toluene (4 mL/mmol amine substrate), the amine substrate (1.0 equiv), and the first aryl bromide (1.0 equiv) were added via syringe. The mixture was heated to 80 °C with stirring until the starting material had been consumed as judged by GC or ^{1}H NMR analysis. The reaction mixture was heated to 110 °C, and the second aryl bromide (1.2 equiv) was added neat. When the intermediate arylamine had been consumed (as judged by GC or ^{1}H NMR analysis), the reaction mixture was cooled to room temperature, quenched with saturated aqueous ammonium chloride (2 mL), and diluted with ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.

2-(4-Methoxybenzyl)-1-phenylpyrrolidine (9). Reaction of 21 mg (0.25 mmol) of pent-4-enylamine (**1**) with bromobenzene (26 μL, 39 mg, 0.25 mmol), 4-bromoanisole (38 μL, 56 mg, 0.3 mmol) and NaO*t*-Bu (58 mg, 0.6 mmol) following Method A afforded 45 mg (67 %) of the title compound as a yellow oil. This compound was obtained as a ca. 30:2:1 mixture of inseparable regioisomers as judged by ^{1}H NMR analysis; data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.30 (m, 2 H), 7.20 (d, *J* = 8.5 Hz, 2 H), 6.91 (d, *J* = 8.5 Hz, 2 H), 6.77–6.72 (m, 3 H), 4.01–3.96 (m, 1 H), 3.85 (s, 3 H), 3.48–3.43 (m, 1 H), 3.25–3.19 (m, 1 H), 3.04 (dd, *J* = 3.0, 13.5 Hz, 1 H), 2.58 (dd, *J* = 9.5, 14.0 Hz, 1 H), 1.98–1.86 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.0, 146.9, 131.5, 130.2, 129.3, 115.4, 113.8, 111.7, 59.8, 55.2, 48.3, 37.6, 29.4, 23.0; IR (film) 1596, 1511 cm^{-1}. Anal calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92. Found: C, 80.87; H, 7.91.

2-(4-Methoxybenzyl)-1-phenylpyrrolidine (9). Reaction of 21 mg (0.25 mmol) of pent-4-enylamine (**1**) with bromobenzene (26 μL, 39 mg, 0.25 mmol), 4-bromoanisole (38 μL, 56 mg, 0.3 mmol) and NaO*t*-Bu (58 mg, 0.6 mmol) following Method B afforded 47 mg (70 %) of the title compound as a yellow oil. This compound was obtained as a ca. 60:4:1 mixture of inseparable regioisomers as judged by ^{1}H NMR analysis.

[4-(2-Naphthalen-1-ylmethylpyrrolidin-1-yl)phenyl]phenylmethanone (10). Reaction of 21 mg (0.25 mmol) of pent-4-enylamine (**1**) with 4-bromobenzophenone (65 mg, 0.25 mmol), 1-bromonaphthalene (42 μL, 62 mg, 0.3 mmol) and NaO*t*-Bu (58 mg, 0.6 mmol) following Method A afforded 71 mg (72 %) of the title compound as a yellow solid, m.p. 68–71 °C. This compound was obtained as a ca. 50:2:1 mixture of inseparable regioisomers as judged by ^{1}H NMR analysis and contained ca. 6% of *N*,*N*-diarylalkylamine impurites. The NMR spectra of the major product were identical to those described below for the synthesis of **10** via Method B.

[4-(2-Naphthalen-1-ylmethylpyrrolidin-1-yl)phenyl]phenylmethanone (10). Reaction of 21 mg (0.25 mmol) of pent-4-enylamine (**1**) with 4-bromobenzophenone (65 mg, 0.25 mmol), 1-bromonaphthalene (42 μL, 62 mg, 0.3 mmol) and NaO*t*-Bu (58 mg, 0.6 mmol) following Method B afforded 90 mg (92 %) of the title compound as a yellow solid, m.p. 68–71 °C. This compound was obtained as a ca. 50:1 mixture of inseparable regioisomers as judged by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.5 Hz, 1 H), 7.90–7.87 (m, 1 H), 7.85 (d, *J* = 9.0 Hz, 2 H), 7.79–7.74 (m, 3 H), 7.57–7.42 (m, 6 H), 7.40–7.37 (m, 1 H), 6.69 (d, *J* = 9.0 Hz, 2 H), 4.43–4.37 (m, 1 H), 3.54–3.48 (m, 2 H), 3.35–3.28 (m, 1 H), 3.16 (dd, *J* = 9.0, 14.5 Hz, 1 H), 2.03–1.83 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.0, 150.2, 139.4, 135.0, 133.8, 133.0, 132.4, 131.0, 129.4, 128.9, 128.0, 127.3, 127.2, 126.0, 125.7, 125.4, 124.5, 123.5, 110.9, 59.0, 48.0, 34.3, 29.5, 22.9; IR (film) 1638, 1594 cm^{-1}. Anal calcd for $C_{28}H_{25}NO$: C, 85.90; H, 6.44; N, 3.58. Found: C, 85.78; H, 6.48; N, 3.52.

1-(4-Methoxyphenyl)-2-(2-methylbenzyl)pyrrolidine (11). Reaction of 21 mg (0.25 mmol) of pent-4-enylamine (**1**) with 4-bromoanisole (31 μL, 47 mg, 0.25 mmol), 2-bromotoluene (36 μL, 51 mg, 0.3 mmol), and NaO*t*-Bu (58 mg, 0.6 mmol) following Method A afforded 12 mg (17 %) of the title compound[11] as a yellow oil. This compound was obtained as a ca. 50:1 mixture of inseparable regioisomers as judged by ^{1}H NMR analysis; data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26–7.14 (m, 4 H), 6.91 (d, *J* = 9.5 Hz, 2 H), 6.67 (d, *J* = 9.0 Hz, 2 H), 4.09–4.03 (m, 1 H), 3.81 (s, 3 H), 3.49 (dt, *J* = 3.0, 7.5 Hz, 1 H), 3.24–3.16 (m, 1 H), 3.12 (dd, *J* = 4.0, 14.5 Hz, 1 H), 2.61 (dd, *J* = 4.5, 9.0 Hz, 1 H), 2.41 (s, 3H), 2.10–1.96 (m, 2 H), 1.90–1.83 (m, 2 H).

(±)-(2*R*,5*S*)-2-(4-Methoxybenzyl)-1,5-diphenylpyrrolidine (12). Reaction of 40 mg (0.25 mmol) of 1-phenylpent-4-enylamine (**4**) with bromobenzene (26 μL, 39 mg, 0.25 mmol), 4-

bromoanisole (38 μL, 56 mg, 0.3 mmol) and NaO*t*-Bu (58 mg, 0.6 mmol) following Method A afforded 59 mg (69 %) of the title compound as a colorless oil. This compound was obtained as a ca. 45:4:1 mixture of inseparable regioisomers as judged by ^{1}H NMR analysis; data are for the major isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.39 (m, 4 H), 7.36–7.30 (m, 3 H), 7.29–7.23 (m, 2 H), 6.98 (d, *J* = 8.4 Hz, 2 H), 6.80–6.74 (m, 1 H), 6.72 (d, *J* = 8.4 Hz, 2 H), 4.79–4.73 (m, 1 H), 4.17–4.09 (m, 1 H), 3.89 (s, 3 H), 3.51 (dd, *J* = 3.2, 14.0 Hz, 1 H), 2.75 (dd, *J* = 10.6, 13.4, 1 H), 2.50–2.41 (m, 1 H), 2.13–1.88 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 147.4, 144.8, 131.5, 130.1, 129.0, 128.6, 126.7, 125.6, 116.4, 114.0, 113.0, 66.0, 63.2, 55.2, 39.9, 35.1, 29.1; IR (film) 1598, 1512, 1502 cm^{-1}. Anal calcd for $C_{24}H_{25}NO$: C, 83.93; H, 7.34; N, 4.08. Found: C, 83.75; H, 7.35; N, 4.07.

(±)-(2*R*,5*S*)-2-Benzyl-1-(4-methoxyphenyl)-5-phenylpyrrolidine (13). Reaction of 40 mg (0.25 mmol) of 1-phenylpent-4-enylamine (**4**) with 4-bromoanisole (31 μL, 47 mg, 0.25 mmol), bromobenzene (32 μL, 47 mg, 0.3 mmol) and NaO*t*-Bu (58 mg, 0.6 mmol) following Method A afforded 58 mg (67 %) of the title compound as a colorless oil. This compound was obtained as a ca. 9:1 mixture of inseparable regioisomers as judged by ^{1}H NMR analysis; data are for the major isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.19 (m, 10 H), 6.81 (d, *J* = 8.8 Hz, 2 H), 6.62 (d, *J* = 8.8 Hz, 2 H), 4.66–4.60 (m, 1 H), 4.07–4.00 (m, 1 H), 3.74 (s, 3 H), 3.52–3.46 (m, 1 H), 2.79–2.71 (m, 1 H), 2.42–2.34 (m, 1 H), 2.03–1.80 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 145.2, 142.2, 139.5, 129.2, 128.6, 128.5, 126.7, 126.3, 125.7, 114.7, 113.8, 66.7, 63.5, 55.8, 41.3, 35.2, 29.3; IR (film) 1510 cm^{-1}. Anal calcd for $C_{24}H_{25}NO$: C, 83.93; H, 7.34; N, 4.08. Found: C, 84.13; H, 7.33; N, 4.07.

(±)-(2*R*,5*R*)-2-But-3-enyl-5-naphthalen-2-ylmethyl-1-phenylpyrrolidine (14). Reaction of 35 mg (0.25 mmol) of 1-but-3-enylpent-4-enylamine (**5**) with bromobenzene (26 μL, 39 mg, 0.25

mmol), 2-bromonaphthalene (62 mg, 0.3 mmol) and NaO*t*-Bu (58 mg, 0.6 mmol) following Method A afforded 59 mg (70 %) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86–7.82 (m, 3 H), 7.71 (s, 1 H), 7.51–7.43 (m, 3 H), 7.33–7.30 (m, 2 H), 6.80–6.75 (m, 3 H), 5.92–5.87 (m, 1 H), 5.08–5.01 (m, 2 H), 4.07–4.01 (m, 1 H), 3.75–3.69 (m, 1 H), 3.41 (dd, *J* = 3.0, 13.5 Hz, 1 H), 2.76 (dd, *J* = 10.0, 13.5 Hz, 1 H), 2.21–2.10 (m, 2 H), 2.09–1.98 (m, 2 H), 1.95–1.77 (m, 3 H), 1.41–1.35 (m, 1 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 147.3, 138.2, 136.9, 133.5, 132.1, 129.2, 127.94, 127.91, 127.63, 127.61, 127.4, 126.0, 125.3, 115.8, 114.7, 112.1, 62.0, 60.3, 41.1, 34.2, 30.7, 29.6, 29.1; IR (film) 1502 cm^{-1}. Anal calcd for $C_{25}H_{27}N$: C, 87.93; H, 7.97; N, 4.10. Found: C, 87.72; H, 7.92; N, 4.15.

(±)-(2*R*,5*R*)-4-(1-Biphenyl-4-yl-5-but-3-enylpyrrolidin-2-ylmethyl)benzoic acid *tert*-butyl ester (15). Reaction of 35 mg (0.25 mmol) of 1-but-3-enylpent-4-enylamine (**5**) with 4-bromobiphenyl (58 mg, 0.25 mmol), 4-bromobenzoic acid *tert*-butyl ester (77 mg, 0.3 mmol) and NaO*t*-Bu (58 mg, 0.6 mmol) following Method A afforded 65 mg (76 %) of the title compound as a colorless oil. This material was obtained as a 10:1 mixture of inseparable regioisomers as judged by ^{1}H NMR analysis; data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.5 Hz, 2 H), 7.62–7.57 (m, 4 H), 7.46–7.43 (m, 2 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 7.31–7.28 (m, 1 H), 6.81 (d, *J* = 8.5 Hz, 2 H), 5.97–5.89 (m, 1 H), 5.13–5.05 (m, 2 H), 4.02–3.98 (m, 1 H), 3.77–3.75 (m, 1 H), 3.29 (dd, *J* = 3.5, 13.5 Hz, 1 H), 2.73 (dd, *J* = 10.0, 13.0 Hz, 1 H), 2.21–2.17 (m, 2 H), 2.09–1.98 (m, 2 H), 1.91–1.77 (m, 3 H), 1.64 (s, 9 H), 1.41–1.35 (m, 1 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 165.7, 146.6, 143.9, 141.1, 138.0, 130.1, 129.5, 129.3, 128.8, 128.6, 127.8, 126.1, 125.9, 114.9, 112.3, 80.7, 61.7, 60.4, 40.8, 34.1, 30.7, 29.5, 29.0, 28.1; IR (film) 1711, 1609 cm^{-1}. Anal calcd for $C_{32}H_{37}NO_2$: C, 82.19; H, 7.97; N, 3.00. Found: C, 81.99; H, 8.02; N, 3.06.

(±)-(2*R*,3*R*)-4-(2-Benzyl-3-phenylpyrrolidin-1-yl)benzonitrile (16). Reaction of 40 mg (0.25 mmol) of 3-phenylpent-4-enylamine (**6**) with 4-bromobenzonitrile (46 mg, 0.25 mmol), bromobenzene (31 μL, 47 mg, 0.3 mmol), and NaO*t*-Bu (58 mg, 0.6 mmol) following Method A afforded 50 mg (59 %) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 9.0 Hz, 2 H), 7.35–7.31 (m, 2 H), 7.28–7.17 (m, 6 H), 6.95 (d, *J* = 7.0 Hz, 2 H), 6.70 (d, *J* = 9.0 Hz, 2 H), 4.23–4.22 (m, 1 H), 3.47–3.43 (m, 2 H), 3.40–3.38 (m, 1 H), 3.08 (dd, *J* = 3.5, 14.0 Hz, 1 H), 2.86 (dd, *J* = 8.5, 14.0 Hz, 1 H), 2.38–2.33 (m, 1 H), 2.04–1.99 (m, 1 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 148.8, 144.2, 137.8, 133.7, 129.3, 128.7, 128.6, 126.7, 126.55, 126.51, 112.1, 97.5, 65.8, 47.12, 47.09, 38.0, 30.7 (one carbon signal is absent due to incidental equivalence); IR (film) 2212, 1606 cm^{-1}. Anal calcd for $C_{24}H_{22}N_2$: C, 85.17; H, 6.55; N, 8.28. Found: C, 85.02; H, 6.70; N, 8.22.

(±)-(2*R*,3*R*)-4-[2-(4-*tert*-Butylbenzyl)-3-phenylpyrrolidin-1-yl]benzoic acid *tert*-butyl ester (17). Reaction of 40 mg (0.25 mmol) of 3-phenylpent-4-enylamine (**6**) with 4-bromobenzoic acid *tert*-butyl ester (64 mg, 0.25 mmol), 1-bromo-4-*tert*-butylbenzene (52 μL, 64 mg, 0.3 mmol), and NaO*t*-Bu (58 mg, 0.6 mmol) following Method A afforded 50 mg (43 %) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 9.0 Hz, 2 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 7.23–7.20 (m, 2 H), 7.17–7.14 (m, 3 H), 6.96 (d, *J* = 7.0 Hz, 2 H), 6.69 (d, *J* = 9.0 Hz, 2 H), 4.24–4.23 (m, 1 H), 3.50–3.38 (m, 3 H), 3.08 (dd, *J* = 3.0, 14.0 Hz, 1 H), 2.81 (dd, *J* = 8.5, 14.0 Hz, 1 H), 2.40–2.34 (m, 1 H), 1.99–1.95 (m, 1 H), 1.60 (s, 9 H), 1.32 (s, 9 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 166.3, 149.3, 149.2, 144.7, 135.1, 131.4, 129.0, 128.6, 126.7, 126.3, 125.4, 118.9, 111.1, 79.7, 65.6, 47.2, 46.9, 37.8, 34.4, 31.3, 31.0, 28.4; IR (film) 1698, 1605 cm^{-1}. Anal calcd for $C_{32}H_{39}NO_2$: C, 81.83; H, 8.37; N, 2.98. Found: C, 81.72; H, 8.49; N, 2.94.

(±)-(2*R*,3*R*)-2-(4-*tert*-Butylbenzyl)-1-naphthalen-1-yl-3-phenylpyrrolidine (18). Reaction of 40 mg (0.25 mmol) of 3-phenylpent-4-enylamine (**6**) with 1-bromonaphthalene (52 mg, 0.25 mmol), 1-bromo-4-*tert*-butylbenzene (52 μL, 64 mg, 0.3 mmol), and NaO*t*-Bu (58 mg, 0.6 mmol) following Method A afforded 58 mg (55 %) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24–8.22 (m, 1 H), 7.88–7.86 (m, 1 H), 7.54–7.48 (m, 3 H), 7.45–7.42 (m, 1 H), 7.36–7.31 (m, 4 H), 7.27–2.23 (m, 1 H), 7.20–7.19 (m, 1 H), 7.13 (d, *J* = 8.5 Hz, 2 H), 6.89 (d, *J* = 8.0 Hz, 2 H), 4.28–4.26 (m, 1 H), 3.95–3.92 (m, 1 H), 3.28–3.19 (m, 2 H), 2.92 (dd, *J* = 6.0, 14.0 Hz, 1 H), 2.63 (dd, *J* = 3.5, 14.0 Hz, 1 H), 2.31–2.27 (m, 1 H), 2.09–2.02 (m, 1 H), 1.30 (s, 9 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 148.4, 146.4, 143.6, 135.2, 134.9, 129.9, 129.5, 128.4, 128.2, 128.0, 126.3, 125.7, 125.6, 124.9, 124.51, 124.46, 121.9, 113.7, 67.5, 55.1, 48.4, 35.1, 34.2, 33.8, 31.4; IR (film) 1574 cm^{-1}. Anal calcd for $C_{31}H_{33}N$: C, 88.73; H, 7.93; N, 3.34. Found: C, 88.54; H, 8.02; N, 3.22.

(±)-(2*R*,3*S*)-4-[2-(4-*tert*-Butylbenzyl)-3-methylpyrrolidin-1-yl]benzonitrile (19). Reaction of 25 mg (0.25 mmol) of 3-methylpent-4-enylamine (**7**) with 4-bromobenzonitrile (46 mg, 0.25 mmol), 1-bromo-4-*tert*-butylbenzene (52 μL, 64 mg, 0.3 mmol), and NaO*t*-Bu (58 mg, 0.6 mmol) following Method A afforded 64 mg (76 %) of the title compound as a colorless oil. This compound was obtained as a ca. 10:1 mixture of diastereomers as judged by ^{1}H NMR analysis; data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 9.0 Hz, 2 H), 7.33 (d, *J* = 8.5 Hz, 2 H), 7.11 (d, *J* = 8.5 Hz, 2 H), 6.59 (d, *J* = 9.0 Hz, 2 H), 3.67–3.64 (m, 1 H), 3.39–3.34 (m, 2 H), 2.95 (dd, *J* = 3.5, 14.0 Hz, 1 H), 2.60 (dd, *J* = 9.0, 14.0 Hz, 1 H), 2.32–2.30 (m, 1 H), 2.13–2.11 (m, 1 H), 1.66–1.64 (m, 1 H), 1.33 (s, 9 H), 0.91 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 149.6, 149.3, 135.2, 133.5, 128.7, 125.4, 120.9, 111.7, 96.6, 66.9,

46.4, 37.5, 36.2, 34.4, 31.3, 29.6, 19.7; IR (film) 2212, 1606 cm^{-1}. MS (EI) 332.2250 (332.2252 calcd for $C_{23}H_{28}N_2$).

(±)-(2*R*,3*S*)-4-(2-Benzyl-3-methylpyrrolidin-1-yl)benzoic acid *tert*-butyl ester (20). Reaction of 25 mg (0.25 mmol) of 3-methylpent-4-enylamine (**7**) with 4-bromobenzoic acid *tert*-butyl ester (64 mg, 0.25 mmol), bromobenzene (31 μL, 47 mg, 0.3 mmol), and NaO*t*-Bu (58 mg, 0.6 mmol) following Method A afforded 38 mg (42 %) of the title compound as a colorless oil. This compound was obtained as a ca. 9:1 mixture of diastereomers as judged by ^{1}H NMR analysis; data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.5 Hz, 2 H), 7.34–7.31 (m, 2 H), 7.27–7.23 (m, 1 H), 7.21–7.20 (m, 2 H), 6.63 (d, *J* = 8.5 Hz, 2 H), 3.70–3.68 (m, 1 H), 3.40–3.37 (m, 2 H), 3.03 (dd, *J* = 3.0, 14.0 Hz, 1 H), 2.65 (dd, *J* = 9.0, 14.0 Hz, 1 H), 2.29–2.26 (m, 1 H), 2.08–2.03 (m, 1 H), 1.63–1.60 (m, 10 H), 0.91 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 166.4, 150.0, 138.8, 131.2, 129.2, 128.5, 126.3, 118.4, 109.8, 79.6, 66.9, 46.5, 38.0, 36.1, 29.8, 28.4, 19.8; IR (film) 1697, 1605 cm^{-1}. Anal calcd for $C_{23}H_{29}NO_2$: C, 78.59; H, 8.32; N, 3.99. Found: C, 78.50; H, 8.50; N, 3.77.

4-Allyl-1-biphenyl-4-yl-4-methyl-2-(2-methylbenzyl)pyrrolidine (21). Reaction of 35 mg (0.25 mmol) of 2-allyl-2-methylpent-4-enylamine (**8**) with 4-bromobiphenyl (58 mg, 0.25 mmol), 2-bromotoluene (36 μL, 51 mg, 0.3 mmol) and NaO*t*-Bu (58 mg, 0.6 mmol) following Method A afforded 48 mg (51 %) of the title compound as a colorless oil. This compound was obtained as a ca. 3:2 mixture of inseparable diastereomers as judged by ^{1}H NMR analysis. The major diastereomer was determined to have a *cis*-relationship between the allyl and benzyl substituents as determined by ^{1}H NMR nOe studies of the mixture of isomers. Characterization data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64–7.56 (m, 4 H), 7.46–7.43 (m, 2 H), 7.32–7.18 (m, 5 H), 6.84–6.81 (m, 2 H), 5.88–5.79 (m, 1 H), 5.15–5.00 (m, 2 H), 4.30–4.26 (m,

1 H), 3.49–3.42 (m, 1.6 H), 3.33 (d, *J* = 4.0 Hz, 0.8 H), 3.21–3.19 (m, 0.6 H), 2.66–2.61 (m, 1 H), 2.45 (s, 3 H), 2.26 (d, *J* = 7.5 Hz, 1.2 H), 2.08 (d, *J* = 7.5 Hz, 0.8 H), 2.03–1.99 (m, 0.4 H), 1.87–1.83 (m, 0.6 H), 1.75–1.71 (m, 0.6 H), 1.66–1.62 (m, 0.4 H), 1.22 (s, 1.2 H), 0.99 (s, 1.8 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 147.1, 146.9, 141.2, 137.4, 137.3, 136.5, 136.4, 135.0, 134.9, 130.28, 130.27, 129.65, 129.62, 128.60, 128.58, 128.54, 127.8, 127.7, 126.18, 126.16, 125.88, 125.85, 125.83, 117.7, 117.4, 113.2, 113.0, 61.5, 60.9, 57.7, 57.1, 44.8, 44.5, 44.1, 43.1, 40.6, 40.4, 36.3, 24.8, 24.7, 20.2 (7 carbon signals are absent due to incidental equivalence); IR (film) 1610 cm^{-1}. Anal calcd for $C_{28}H_{31}N$: C, 88.14; H, 8.19; N, 3.67. Found: C, 88.14; H, 8.28; N, 3.63.

4-(4-Allyl-2-benzyl-4-methylpyrrolidin-1-yl)benzonitrile (22). Reaction of 35 mg (0.25 mmol) of 2-allyl-2-methylpent-4-enylamine (**8**) with 4-bromobenzonitrile (46 mg, 0.25 mmol), bromobenzene (31 μL, 47 mg, 0.3 mmol), and NaO*t*-Bu (58 mg, 0.6 mmol) following Method A afforded 59 mg (75 %) of the title compound as a colorless oil. This compound was obtained as a ca. 3:2 mixture of inseparable diastereomers as judged by ^{1}H NMR analysis. The major diastereomer was determined to have a *cis*-relationship between the allyl and benzyl substituents as determined by ^{1}H NMR nOe studies of the mixture of isomers. Characterization data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.0 Hz, 2 H), 7.34–7.31 (m, 2 H), 7.27–7.26 (m, 1 H), 7.16 (d, *J* = 8.0 Hz, 2 H), 6.67–6.63 (m, 2 H), 5.82–5.67 (m, 1 H), 5.10–4.92 (m, 2 H), 4.17–4.10 (m, 1 H), 3.29 (d, *J* = 10.0 Hz, 0.4 H), 3.21–3.16 (m, 1.6 H), 3.12–3.06 (m, 1 H), 2.69–2.62 (m, 1 H), 2.20–2.17 (m, 1 H), 2.01–1.97 (m, 1.4 H), 1.86–1.82 (m, 0.6 H), 1.78–1.74 (m, 0.6 H), 1.70–1.66 (m, 0.4 H), 1.13 (s, 1.2 H), 0.93 (s, 1.8 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 150.0, 149.7, 137.9, 137.8, 134.4, 134.3, 133.5, 133.4, 129.3, 128.5, 128.4, 126.49, 126.48, 120.7, 118.1, 117.8, 112.5, 112.3, 97.14, 97.11, 60.9, 60.0, 58.7, 58.3, 44.3, 44.2, 43.2,

42.8, 40.6, 40.4, 38.6, 38.5, 24.5, 24.3 (two carbon signals are absent due to incidental equivalence); IR (film) 2212, 1605 cm^{-1}. Anal calcd for $C_{22}H_{24}N_2$: C, 83.50; H, 7.64; N, 8.85. Found: C, 83.27; H, 7.79; N, 8.77.

Assignment of Stereochemistry

2,5-Disubstituted Pyrrolidines

The *cis*-stereochemistry of the 2,5-disubstituted pyrrolidine products was assigned based on analogy to *cis*-2-(4-methoxybenzyl)-1-(4-methoxyphenyl)-5-phenylpyrrolidine, which was previously described by our group.[11]

2,3-Disubstituted Pyrrolidines

The *trans*-stereochemistry of the 2,3-disubstituted pyrrolidine products was assigned *trans*-2-(3-methoxybenzyl)-1-(4-methoxyphenyl)-3-phenylpyrrolidine, which was previously described by our group.[11]

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