Supporting Information

(6 pages including cover)

Suppressed β-Hydride Elimination in Palladium-Catalyzed Cascade Cyclization-Coupling Reactions: An Efficient Synthesis of 3-Arylmethylpyrrolidines

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General

All reactions were conducted under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring. THF was dried over and distilled from sodium metal with benzophenone as the indicator. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS (0 ppm), residual $CHCl_3$ (7.24 ppm) as an internal standard. Allylamine, TsCl, 2,3-dibromopropene, 4-fluorophenylboronic acid, phenylboronic acid, 1-naphthylboronic acid, 3-nitrophenylboronic acid and 4-methoxyphenylboronic acid are commercial products. **1c** and **1d** were synthesized as described in the literature with minor modification.*

***N*-Allyl-4-methylbenzenesulfonamide**

A solution of allylamine (110 mmol) and Et_3N (110mmol) in CH_2Cl_2 is added dropwise to an ice cooled solution of TsCl (100 mmol) in CH_2Cl_2 under nitrogen. After stirring for 12 h at room temperature, the reaction mixture is filtered and solids washed with CH_2Cl_2. The combined organic layers are evaporated to dryness and the resulting solid is used without further purification.^{1}H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 3H), 3.46 (d, *J* = 5.3 Hz, 2H), 5.01 (m, 2H), 5.61 (m, 1H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 45.2, 116.8, 126.6, 129.2, 132.7, 136.5, 142.9.

***N*-Allyl-*N*-(2-bromoallyl)-4-methylbenzenesulfonamide [1a (R´ = H)]**

2,3-Dibromopropene (45 mmol) was added dropwise at room temperature under nitrogen to a mixture of *N*-allyl-4-methylbenzenesulfonamide (35 mmol) and anhydrous K_2CO_3 (70 mmol) in dry toluene (65 mL). The reaction mixture was stirred at reflux for 12 h. The solvent was removed and the crude residue was taken up in CH_2Cl_2 and washed with water. Drying and evaporation of the organic extracts gave an oil, which was purified by flash chromatography (EtOAc/hexane, 10/90; R_f = 0.34) in 96% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.40 (s, 3H), 3.81 (d, *J* = 6.5 Hz, 2H), 4.00 (s, 2H), 5.22 (m, 2H), 5.58 (m, 2H), 5.82 (s, 1H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.70 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 49.9, 53.7, 119.2, 119.9, 127.2, 127.8, 129.6, 131.8, 136.9, 143.5.

***N*-Allyl-*N*-benzyl-2-bromoallylamine (1b)**

According to the procedure of Delgado *et al.*,# allyl bromide (45 mmol) was added dropwise at room temperature under nitrogen to a mixture of *N*-benzyl-2-bromoallylamine (35 mmol) and NEt_3 (70 mmol) in dry acetonitrile (65 mL). The reaction mixture was stirred at room temperature for 18 h. The solvent was removed, and the crude residue was taken up in CH_2Cl_2 and washed with water. Drying and evaporation of the organic extracts gave an oil, which was purified by flash chromatography (EtOAc/hexane, 5/95; R_f =

* Shi, L; Narula, C. K.; Mak, K. T.; Kao, L.; Xu, Y.; Heck, R. F. *J. Org. Chem.* **1983**, *48*, 3894
# Sole, D.; Cancho, Y.; Llebaria, A.; Moretó, J. M.; Delgado, A. *J. Org. Chem.* **1996**, *61*, 5895.

0.29). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.18 (d, *J* = 6.2 Hz, 2H), 3.34 (s, 2H), 3.70 (s, 2H), 5.20-5.31 (m, 2H), 5.65 (s, 1H), 5.89-6.00 (m, 2H), 7.28-7.45 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.0, 57.3, 61.4, 117.7, 118.1, 127.0, 128.2, 128.7, 132.1, 135.2, 139.0.

***N*-(But-3-enyl)-4-methylbenzenesulfonamide**

Prepared similarly as previously in quatitative yield using but-3-enylamine and used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.19 (q, *J* = 6.8 Hz, 2H), 2.41 (s, 3H), 2.98 (q, *J* = 6.7 Hz, 2H), 4.97-5.07 (m, 3H), 5.61 (m, 1H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 33.5, 42.1, 117.7, 125.7, 127.0, 129.6, 134.1, 136.8, 143.2.

***N*-(2-Bromoallyl)-*N*-(but-3-enyl)-4-methylbenzenesulfonamide**

Prepared similarly as previously using *N*-(but-3-enyl)-4-methylbenzenesulfonamide and purified by flash chromatography (EtOAc/hexane, 20/80; R_f = 0.58): 83% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.25 (q, *J* = 7 Hz, 2H), 2.41 (s, 3H), 2.98 (m, 2H), 4.03(s, 2H), 5.01 (m, 2H), 5.63 (m, 2H), 5.87 (d, *J* = 1.2 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.75 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 32.5, 47.5, 55.4, 117.1, 119.1, 127.0, 128.1, 129.5, 134.2, 136.7, 143.4.

***N*-(2-Bromoallyl)-4-methylbenzenesulfonamide**

Prepared similarly as previously using tosylamide and purified by flash chromatography (EtOAc/hexane, 20/80; R_f = 0.21): 34% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (s, 3H), 3.85 (d, *J* = 6.2 Hz, 1H), 5.16 (br s, 1H), 5.48 (s, 1H), 5.81 (s, 1H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.76 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 50.5, 118.5, 126.9, 127.9, 129.6, 136.8, 143.5.

***N*-(2-Bromoallyl)-4-methyl-*N*-(2-methylallyl)benzenesulfonamide [1 (R = H, R´ = Me)]**

Prepared similarly as previously using *N*-(2-bromoallyl)-4-methylbenzenesulfonamide and purified by flash chromatography (EtOAc/hexane, 20/80; R_f = 0.39): 87 % yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62 (s, 3H), 2.41 (s, 3H), 3.81 (s, 2H), 4.04 (s, 2H), 4.83, (s, 1H), 4.91 (s, 1H), 5.54 (m, 1H), 5.75 (m, 1H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.71 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.8, 21.4, 53.3, 53.8, 115.3, 119.4, 125.8, 127.2, 127.6, 129.4, 137.1, 139.3, 143.3.

General procedure of the Pd-catalyzed reactions: To a stirred solution of vinyl bromide (0.5 mmol) in dry THF (6 mL) under N_2 containing $Pd(PPh_3)_2$ (0.025 mmol) was added boronic acid (1 mmol) followed by aqueous sodium carbonate (2 M; 1 mL, 2 mmol), and the mixture was heated by an oil bath at 80 ^{o}C. After overnight, the reaction mixture was cooled and poured into water (30 mL), and the products were extracted

with CH_2Cl_2 (3 x 30 mL). The combined extracts were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography.

3-(4-Fluorobenzyl)-4-methylene-1-(*p*-toluenesulfonyl)pyrrolidine

Using 4-fluorophenylboronic acid and vinyl bromide **1a** (R´ = H), this compound was obtained in 92% yield after purification by flash chromatography (EtOAc/hexane, 10/90; R_f = 0.15).: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.40 (s, 3H), 2.49 (m, 1H), 2.87 (m, 3H), 3.21 (m, 1H), 3.83 (s, 2H), 4.84 (d, *J* = 1.9 Hz, 1H), 4.93 (d, *J* = 1.9 Hz, 1H), 6.90-7.07 (m, 4H), 7.30 (m, 2H), 7.66 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 37.8, 44.5, 52.1, 52.7, 107.4, 115.2 (d, *J* = 21.2 Hz), 127.7, 129.6, 130.1 (d, *J* = 7.7 Hz), 132.6, 134.7 (d, *J* = 3.2 Hz), 143.7, 147.0, 161.5 (d, *J* = 243.1 Hz); FAB- HRMS m/z 346.1280 ($[M + H]^+$, calcd 346.1277).

3-Benzyl-4-methylene-1-(*p*-toluenesulfonyl)pyrrolidine

Using phenylboronic acid and vinyl bromide **1a** (R´ = H), this compound was obtained in 75% yield after purification by flash chromatography (EtOAc/hexane, 10/90; R_f = 0.21).: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.49 (m, 1H), 2.90 (m, 3H), 3.25 (m, 1H), 3.82 (s, 2H), 4.87 (d, *J* = 2.1 Hz, 1H), 4.94 (d, *J* = 2.1 Hz, 1H), 7.10 (d, *J* = 6.7 Hz, 2H), 7.18-7.66 (m, 5H), 7.67 (d, , *J* = 6.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 38.5, 44.5, 52.2, 52.9, 107.2, 126.3, 127.7, 128.5, 128.7, 129.6, 132.5, 139.1, 143.6, 147.2; FAB-HRMS m/z 328.1378 ($[M + H]^+$, calcd 328.1371).

3-Methylene-4-(1-naphthyl)methyl-1-(*p*-toluenesulfonyl)pyrrolidine

Using 1-naphthylboronic acid and vinyl bromide **1a** (R´ = H), this compound was obtained in 88% yield after purification by flash chromatography (EtOAc/hexane, 10/90; R_f = 0.14).: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.92 (m, 1H), 3.08 (m, 3H), 3.38 (m, 1H), 3.91 (m, 2H), 4.97 (d, , *J* = 1.6 Hz, 1H), 5.00 (d, *J* = 1.6 Hz, 1H), 7.23-7.29 (m, 3H), 7.37-7.42 (m, 1H), 7.48-7.53 (m, 2H), 7.65 (d, *J* = 8.2, 2H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.86-7.95 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 35.9, 43.6, 52.2, 53.0, 107.3, 123.2, 125.4, 125.6, 126.0, 126.8, 127.3, 127.7, 128.9, 129.6, 131.5, 132.5, 133.9, 135.1, 143.6, 147.6; FAB-HRMS m/z 378.1536 ($[M + H]^+$, calcd 378.1528).

3-(4-Methoxybenzyl)-4-methylene-1-(*p*-toluenesulfonyl)pyrrolidine

Using 4-methoxyphenylboronic acid and vinyl bromide **1a** (R´ = H), this compound was obtained in 69% yield after purification by flash chromatography (EtOAc/hexane, 10/90; R_f = 0.16).: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.43-2.52 (m, 4H), 2.83 (m, 2H), 2.96 (m, 1H), 3.25 (m, 1H), 3.82 (s, 3H), 3.87 (s, 2H), 4.88 (d, *J* = 1.9 Hz, 1H), 4.95 (d, *J* = 1.9 Hz, 1H), 6.82-6.86 (m, 2H), 7.01-7.05 (m, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.69 (d,

J = 8.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 37.8, 44.7, 52.2, 52.9, 55.2, 107.1, 113.9, 127.8, 129.6, 131.2, 132.8, 143.6, 147.4, 158.2; FAB-HRMS m/z 358.1483 ($[M + H]^+$, calcd 358.1477).

3-Methylene-4-(3-nitrobenzyl)-1-(*p*-toluenesulfonyl)pyrrolidine

Using 3-nitrophenylboronic acid and vinyl bromide **1a** (R´ = H), this compound was obtained in 49% yield after purification by flash chromatography (EtOAc/hexane, 10/90; R_f = 0.06).: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (s, 3H), 2.69 (m, 1H), 2.96 (m, 3H), 3.25 (m, 1H), 3.87 (m, 2H), 4.85 (d, *J* = 1.7 Hz, 1H), 4.99 (d, *J* = 1.7 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.46-7.69 (m, 2H), 7.68 (d, *J* = 8.2 Hz, 1H), 8.0 (s, 1H), 8.07-8.11 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 38.2, 44.1, 51.9, 52.6, 108.0, 121.6, 123.5, 127.7, 129.5, 129.7, 132.6, 135.1, 141.1, 143.8, 146.4, 148.3; FAB-HRMS m/z 373.1239 ($[M + H]^+$, calcd 373.1222).

1-Benzyl-3-(4-fluorobenzyl)-4-methylenepyrrolidine

Using 4-fluorophenylboronic acid and vinyl bromide **1b** (R´ = H), this compound was obtained in 30% yield after purification by flash chromatography (EtOAc/hexane, 10/90; R_f = 0.25).: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31 (m, 1H), 2.66 (m, 1H), 2.79 (m, 1H), 2.95 (m, 2H), 3.15 (m, 1H), 3.37 (m, 1H), 3.56 (m, 1H), 3.68 (m, 1H), 4.87 (d, *J* = 2.0 Hz, 1H), 4.97 (d, *J* = 2.0 Hz, 1H), 6.96-7.02 (m, 2H), 7.14-7.19 (m, 2H), 7.28-7.39 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.1, 44.4, 59.6, 59.8, 60.4, 105.0, 115.0 (d, *J* = 20.9 Hz), 127.0, 128.2, 128.7, 130.1 (d, *J* = 7.7 Hz), 134.2 (d, *J* = 3.2 Hz), 138.7, 151.7, 161.3 (d, *J* = 242.2 Hz); FAB-HRMS m/z 282.1674 ($[M + H]^+$, calcd 282.1658).

***N*-(But-3-enyl)-*N*-[2-(4-fluorophenyl)allyl]-4-methylbenzenesulfonamide**

Using *N*-(2-bromoallyl)-*N*-but-3-enyl-4-methylbenzenesulfonamide and 4-fluorophenylboronic acid, this suzuki coupling product was obtained in 34% yield after purification by flash chromatography (EtOAc/hexane, 20/80; R_f = 0.69): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.15 (m, 2H), 2.45 (s, 3H), 3.09 (m, 2H), 4.20 (sm 2H), 4.92 (m, 2H), 5.25 (s, 1H), 5.46 (s, 1H), 5.56-5.69 (m, 1H), 7.00-7.05 (m, 2H), 7.28- 7.32 (m, 2H), 7.42-7.47 (m, 2H), 7.68 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 29.7, 32.6, 47.0, 52.3, 115.3 (d, *J* = 21.3 Hz), 116.3, 116.8, 127.3, 128.1 (d, *J* = 8.1 Hz), 129.7, 134.1 (d, *J* = 3.8 Hz), 134.7, 136.4, 142.1, 143.3, 162.7 (d, *J* = 245.8 Hz); FAB-MS m/z 360.1432 ($[M + H]^+$, calcd 360.1434).

3-Methylene-1-(*p*-toluenesulfonyl)-1,2,3,6-tetrahydropyridine [3 (R = Ts, R´ = H)]

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3H), 3.75 (m, 2H), 3.84 (s, 2H), 4.93 (m, 2H), 5.73, (m, 1H), 6.17 (m, 1H), 7.31 (m, 2H), 7.69 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 44.7, 48.2, 113.0, 124.7, 127.5, 127.8, 129.6, 133.6, 136.8, 143.6; FAB-MS m/z 250.1 ($[M + H]^+$, calcd 250.1).

5-Methyl-3-methylene-1-(*p*-toluenesulfonyl)-1,2,3,6-tetrahydropyridine [3 (R = Ts, R´ = Me)]

Using the general procedure described above in the absence of a boronic acid, this compound was obtained in 90% yield after purification by flash chromatography (EtOAc/hexane, 10/90; R_f = 0.26).: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.73 (s, 3H), 2.43 (s, 3H), 3.59 (s, 2H), 3.77 (s, 2H), 4.81, (d, *J* = 8.7 Hz, 2H), 5.89 (s, 1H), 7.31 (d, *J* = 7.7 Hz, 2H), 7.68 (d, *J* = 7.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 21.5, 47.8, 48.3, 110.4, 116.5, 123.4, 127.7, 129.5, 133.5, 137.1, 143.5; FAB-HRMS m/z 264.1057 ($[M + H]^+$, calcd 264.1058).