Palladium(II) Catalyzed Intramolecular Aminobromination and Aminochlorination of Olefins

Supplementary Material A

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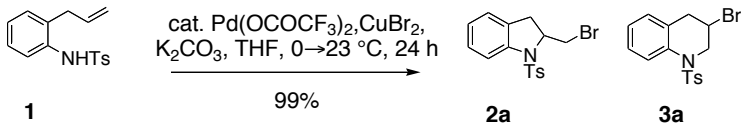
General Experimental Information: All reagents were used out of the bottle as purchased from Aldrich, Acros or Strem. Solvents were purified using a solvent filtration system purchased from Contour Glass Co. (Irvine, California). ^{1}H NMR data were obtained in $CDCl_3$ (using 7.26 ppm for reference of residual $CHCl_3$) at 300, 400 or 500 MHz using Varian instruments. ^{13}C NMR data in $CDCl_3$ (using 77.0 ppm as internal reference) were obtained at 75.5 or 125.7 MHz. IR spectra were obtained from thin films on KBr plates using a Nicolet-Impact 420 FTIR. High resolution mass spectra were obtained at SUNY, Buffalo's Mass Spec. facility on a ThermoFinnigan MAT XL spectrometer purchased by a National Science Foundation grant to the center (NSF CHE0091977).

Experimentals



1 **2a** **3a**

selectivity = 3 : 1

Aminobromination of *O*-Allyl-*N*-tosylaniline 1 (Equation 1).
At 0 °C, a mixture of *O*-Allyl-*N*-tosylaniline **1**[1] (0.050 g, 0.174 mmol, 1 equiv), K_2CO_3 (0.048 g, 0.348 mmol, 2 equiv) and $CuBr_2$ (0.117 g, 0.522 mmol, 3 equiv) in dry THF (3.5 mL) was treated with $Pd(OCOCF_3)_2$ (0.006 g, 0.0174 mmol, 0.1 equiv). A color change from muddy green to rusty orange was observed over the course of the reaction. After allowing the solution to warm to 23 °C over 24 h, the mixture was diluted with Et_2O (3 mL) and was filtered through a pad of celite or SiO_2 with additional Et_2O. Concentration of the filtrate *in vacuo* afforded a crude oil which was purified by chromatography on SiO_2 (5-35% Et_2O/hexanes eluent), yielded 0.0628 g (99%) of a 3 : 1 mixture of **2a** : **3a**. Compounds **2a** and **3a** were poorly separable by flash chromatography. The compounds were best separated by recrystallization (CH_2Cl_2/Hexanes) where **2a** crystallized first.

Data for **2a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, J = 8.0 Hz, 1 H), 7.56 (d, J = 8.0 Hz , 2 H), 7.22 (t, J = 5.6 Hz, 1 H), 7.19 (d, J = 6.4 Hz, 2 H), 7.08-7.02 (m, 2 H), 4.43 (m, 1

H), 3.82 (dd, J = 7.6, 2.8 Hz, 1 H), 3.41 (t, J = 8.0 Hz, 1 H), 2.93-2.91 (m, 2 H), 2.36 (s, 3 H); ^{13}C NMR (75.5 MHz) δ 144.3, 141.1, 134.4, 130.5, 129.7, 127.9, 127.0, 125.2, 124.9, 116.8, 62.1, 35.9, 33.2, 21.5; IR (neat, thin film) υ 3064, 2959, 2923, 1597, 1471, 1357, 1167, 815, 708, 666, 594, 580, 540 cm^{-1}; HRMS, (EI) calcd for [M]$^+$, $C_{16}H_{17}BrNO_2S$: 365.0085, found 365.0085. mp = 135-138 °C.

X-ray Structure of 2a

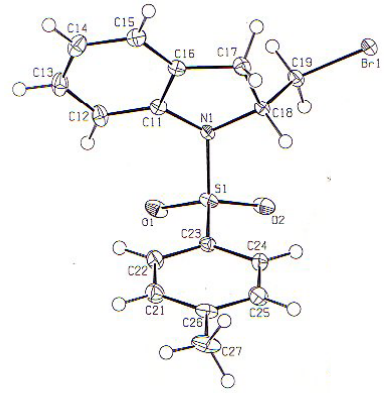
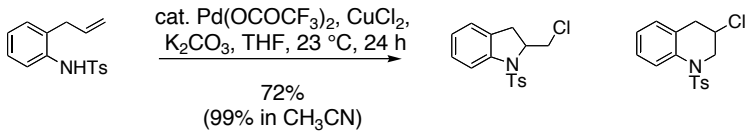


Figure 1. ORTEP diagram (50% thermal ellipsoids at 90K)

Data for **3a** (obtained on a 3.2 : 1 mixture of **3a** : **2a**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 8.5 Hz, 1 H), 7.52 (d, J = 8.5 Hz, 2 H), 7.26-7.22 (m, 3 H), 7.12 (t, J = 7.0 Hz, 1 H), 6.99 (d, J = 7.5 Hz, 1 H), 4.55 (dd, J = 14.0, 3.5 Hz, 1 H), 3.92-3.84 (m, 1 H), 3.62 (dd, J = 14.0, 11.0 Hz, 1 H), 3.12 (dd, J = 16.5, 6.0 Hz, 1 H), 2.93 (dd, J = 16.5, 10.0 Hz, 1 H) 2.40 (s, 3 H); ^{13}C NMR (75.5 MHz) δ 165.0, 144.1, 136.5, 135.5, 129.9, 128.8, 127.3, 127.0, 125.6, 124.7, 52.7, 40.5, 38.0, 21.5; IR (neat, thin film) υ 2923, 2361, 1598, 1488, 1354, 1306, 1165, 1091, 813, 758, 687, 654, 565 cm^{-1}; HRMS (EI) calcd for [M]$^+$ $C_{16}H_{17}BrNO_2S$: 365.0085, found 365.0085.



1 **2b** **3b**

selectivity = 2 : 1

Aminochlorination of *O*-Allyl-*N*-tosylaniline 1 (Equation 2).

O-Allyl-*N*-tosylaniline **1** (0.050 g, 0.174 mmol, 1 equiv) in dry THF (3.5 mL) was treated with K_2CO_3 (0.048 g, 0.348 mmol, 2 equiv) and $CuCl_2$ (0.094 g, 0.696 mmol, 4 equiv). The mixture was treated with $Pd(OCOCF_3)_2$ (0.006 g, 0.0174 mmol, 0.1 equiv). After 24 h at 23 °C, the mixture was diluted with Et_2O (3 mL) and was filtered through a pad of celite with additional Et_2O. Concentration of the filtrate *in vacuo* afforded a crude oil which was purified by chromatography on SiO_2 (5-35% Et_2O/hexanes eluent), yielding the compounds 0.040 g of 2:1 mixture of **2b** and **3b** (72%) and 0.008 g of indole **4** (16%).

Chromatography results in a mixture of **2b** and **3b**. The compounds were ultimately separated by several recrystallizations. Compound **2b** crystallized selectively from the original mixture (1:2 Hexane:CH_2Cl_2). The filtrate was concentrated and then subjected to recrystallization until the stripping liquid eventually became enriched with minor isomer **3b**. With the enriched mixture, **3b** was eluted first on SiO_2 chromatography (0-5% Et_2O/Hexanes). The ^1H NMR of **3b** is contaminated with **2b** in ratio of 3.3 : 1. This procedure was repeated using CH_3CN as the solvent instead of THF, yielding 0.0553 g (99%) of a 2 : 1 mixture of **2b** : **3b**.

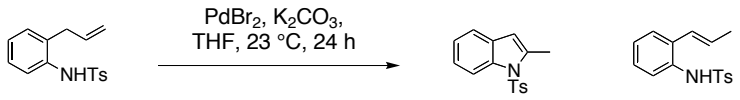
Data for **2b**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J = 8.0 Hz, 1 H), 7.56 (d, J = 8.0 Hz , 2 H), 7.23 (t, J = 7.5 Hz, 1 H), 7.19 (d, J = 8.0 Hz, 2 H), 7.10-7.02 (m, 2 H), 4.41 (m, 1 H), 3.93 (dd, J = 11.0, 3.5 Hz, 1 H), 3.55 (t, J = 10.0 Hz, 1 H), 2.96-2.89 (m, 2 H), 2.36 (s, 3 H); ^{13}C NMR (75.5 MHz) δ 144.3, 141.1, 134.5, 130.7, 129.7, 127.9, 127.0, 125.3, 125.0, 116.9, 62.3, 46.9, 32.2, 21.5; IR (KBr) υ 3854, 3751, 3649, 1700, 1654, 1559, 1541, 1508, 1458, 1168, 666 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{16}H_{17}ClNO_2S$: 321.0590 found 321.0586.

Data for **3b**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 8.0 Hz, 1 H), 7.53 (d, J = 8.0 Hz, 2 H), 7.23 (d, J = 8.0 Hz, 2 H), 7.19 (d, J = 8.0 Hz, 1 H), 7.12 (t, J = 8.0 Hz, 1 H), 7.01 (d, J = 8.0 Hz, 1 H), 4.46 (dd, J = 14.0, 4.5 Hz, 1 H), 3.86 (m, 1 H), 3.53 (t, J = 14.0 Hz, 1 H), 3.03 (dd, J = 17.0, 6.0 Hz, 1 H), 2.77 (dd, J = 17.0, 10.0 Hz, 1 H), 2.40 (s, 3 H); ^{13}C NMR (125 MHz) δ 144.1, 129.9, 129.8, 129.7, 129.1, 127.4, 127.3, 127.0, 125.5, 124.4, 52.2, 50.2, 37.4, 21.6; IR (KBr) υ 3608, 3070, 3649, 1480, 1353, 1166, 1040, 666 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{16}H_{17}ClNO_2S$: 321.0590, found 321.0586.

Structural assignment for 2b and 3b.

The spectral data for aminochloride **2b** correlates very well to that of 5-member aminobromide **2a**, previously determined by x-ray crystallography. Spectral data aminochloride **3b** correlates very well to that of 6-member aminobromide **3a**.

Spectral data for **4** is identical to that reported in literature.[2]



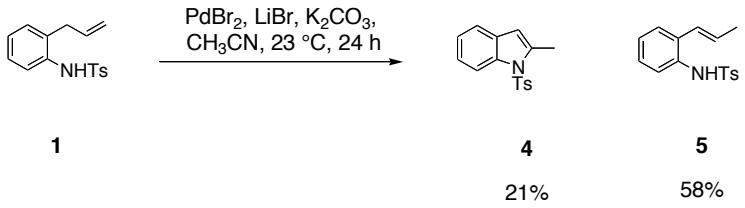
1 **4** **5**

28 % 15%

Procedure used for Equation 3.

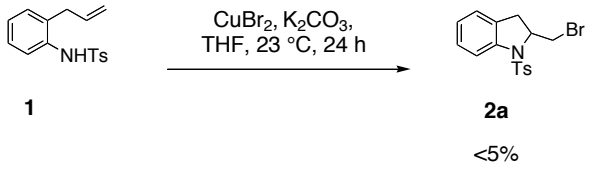
O-Allyl-*N*-tosylaniline **1** (0.050 g, 0.174 mmol) in THF (1.2 mL) was treated with $PdBr_2$ (0.046 g, 0.174 mmol, 1 equiv) and K_2CO_3 (0.024 g, 0.174 mmol, 1 equiv). The mixture was allowed to react for 24 h at 23 °C, then work-up and flash afforded 0.014 g of indole **4** (28%) and 0.0073 g of tosamide **5** (15%).

Spectral data for **4** and **5** is identical to that reported in literature.[2]

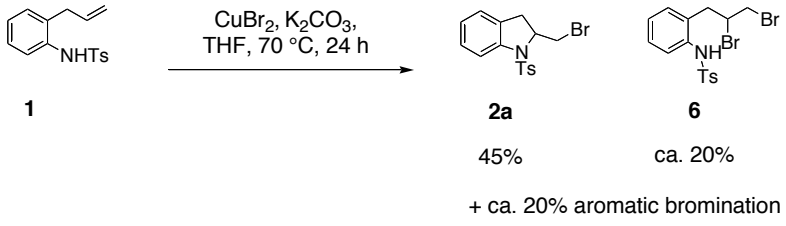


Procedure used for Equation 3.
O-Allyl-*N*-tosylaniline **1** (0.050 g, 0.174 mmol, 1 equiv) in dry CH_3CN (3.5 mL) was treated with K_2CO_3 (0.048 g, 0.348 mmol, 2 equiv) and lithium bromide (0.076 g, 0.87 mmol, 5 equiv). The mixture was treated with $PdBr_2$ (0.046 g, 0.174 mmol, 1 equiv) and allowed to react for 24 h at 23 °C. Work-up and flash chromatography afforded 0.010 g of indole **4** (21%) and 0.029 g of tosamide **5** (58%).
Spectral data for **4** and **5** is identical to that reported in literature.[2]

Table 1 Experimentals

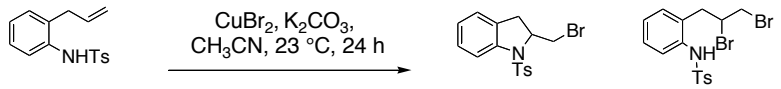


$CuBr_2$ Control Experiment in THF at 23 °C (Table 1, entry 1).
O-Allyl-*N*-tosylaniline **1** (0.050 g, 0.174 mmol, 1 equiv) in dry THF (3.5 mL) was treated with K_2CO_3 (0.048 g, 0.348 mmol, 2 equiv) and $CuBr_2$ (0.117 g, 0.522 mmol, 3 equiv). After 24 h at 23 °C, the mixture was diluted with Et_2O (3 mL) and was filtered through a pad of celite with additional Et_2O. Concentration of the filtrate *in vacuo* afforded a crude oil which yielding **2a** (<5%) and recovered **1** (>95%) by inspection of the crude ^{1}H NMR.



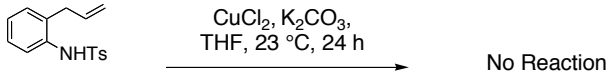
$CuBr_2$ Control Experiment in THF at 70 °C (Table 1, entry 2).
O-Allyl-*N*-tosylaniline **1** (0.057 g, 0.198 mmol, 1 equiv) in dry THF (2.5 mL) was treated with $CuBr_2$ (0.133 g, 0.595 mmol, 3 equiv) and the mixture was heated to 70 °C in a sealed pressure tube. After 24 h at 70 °C, the green mixture was cooled to room temperature and diluted with Et_2O and was filtered through a pad of SiO_2 with additional Et_2O. Concentration of the filtrate *in vacuo* afforded a crude oil which was purified by

chromatography on SiO_2 (5-35% Et_2O/hexanes eluent), yielding 0.032 g of **2a** (44%) and 0.047 g of a mixture composed of approximately 45% dibromoamine **6** (ca. 20% based on **1**), 45% of a compound whose aromatic region showed indications of aromatic bromination and 10% starting **1**.



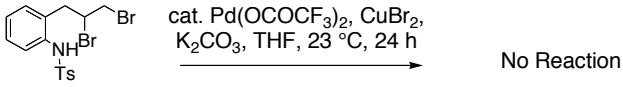
1 **2a** 54% **6** 22%

$CuBr_2$ Control Experiment in CH_3CN at 23 °C (Table 1, entry 3).
O-Allyl-*N*-tosylaniline **1** (0.100 g, 0.348 mmol, 1 equiv) in dry CH_3CN (3.5 mL) was treated with $CuBr_2$ (0.233 g, 1.04 mmol, 3 equiv). After 24 h at 23 °C, the mixture was diluted with Et_2O and was filtered through a pad of celite/SiO_2 with additional Et_2O. Concentration of the filtrate *in vacuo* afforded a crude oil which was purified by chromatography on SiO_2 (5-35% Et_2O/hexanes eluent), yielding 0.069 g of **2a** (54%) and 0.034 g of dibromoamine **6** (22%).



1

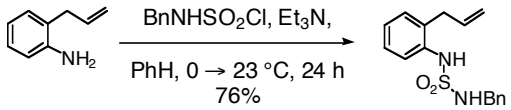
$CuCl_2$ Control Experiment in CH_3CN (Table 1, entry 4).
O-Allyl-*N*-tosylaniline **1** (0.050 g, 0.174 mmol, 1 equiv) in dry THF (2 mL) was treated with K_2CO_3 (0.048 g, 0.348 mmol, 2 equiv) and $CuCl_2$ (0.070 g, 0.522 mmol, 3 equiv). After 24 h at 23 °C, the mixture was diluted with Et_2O and was filtered through a pad of celite with additional Et_2O. Concentration of the filtrate *in vacuo* afforded a crude oil composed only of **1**, as indicated by inspection of the crude ^1H NMR.



6

Procedure used for Equation 5.
Same procedure as seen for equation 1 but used dibromoamine **6** instead of *O*-allyl-*N*-tosylaniline **1**. Concentration of the filtrate *in vacuo* afforded a crude oil composed only of **6**, as indicated by inspection of the crude ^1H NMR.

Table 2 Experimentals

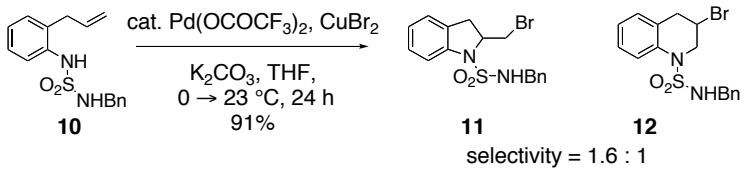


10

Synthesis of sulfamide (10).

O-Allylaniline (0.408 g, 3.06 mmol) in dry benzene (10 mL) was treated with Et_3N (0.85 mL, 6.12 mmol), cooled to 0 °C and benzylsulfonylchloride[3] was added dropwise via an addition funnel over 0.5 h. After 24 h, the reaction mixture was diluted with $NaHCO_3$(aq)(20 mL) and extracted with Et_2O (2 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography of the crude oil on SiO_2 (10-35% Et_2O/hexanes gradient) provided 0.717 g, 76% of sulfamide **10**.

Data for **10**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, J = 8.0 Hz, 1 H), 7.29-7.11 (m, 8 H), 6.43 (s, 1 H), 5.92 (m, 1 H), 5.12 (m, 2 H), 4.67 (m, 1 H), 4.22 (d, J = 6.1 Hz, 2 H), 3.37 (d, J = 6.0 Hz, 2 H); ^{13}C NMR δ (75.5 MHz) 136.0, 135.6, 130.7, 130.7, 129.9, 128.8, 128.1, 127.9, 127.9, 125.2, 121.0, 117.2, 47.6, 36.5; IR (neat, thin film) υ 3302, 1494, 1328, 1152, 919, 751 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{16}H_{18}N_2O_2S$: 302.1089, found 302.1084.



10 **11** **12**

selectivity = 1.6 : 1

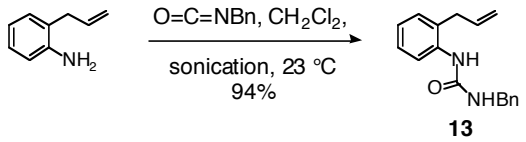
Palladium catalyzed aminobromination of sulfamide 10.

Sulfamide **10** (0.100 g, 0.331 mmol) in dry THF (3.5 mL) was treated with K_2CO_3 (0.091 g, 0.662 mmol, 2 equiv) and $CuBr_2$ (0.185 g, 0.828 mmol, 2.5 equiv). The mixture was cooled to 0 °C and was treated with $Pd(OCOCF_3)_2$ (0.011 g, 0.033 mmol, 0.1 equiv). The solution was allowed to warm to 23 °C gradually (over ca. 4 h). After 24 h, the mixture was diluted with Et_2O (3 mL) and hexanes (1 mL) and was filtered through a pad of celite with additional Et_2O. Concentration of the filtrate *in vacuo* afforded a crude oil which was purified by chromatography on SiO_2 (5-35% Et_2O/hexanes eluent), affording 0.115 g (91% yield) of a 1.6 : 1 mixture of aminobromides **11** and **12**. After several chromatographic separations (Et_2O/hexanes eluent), the minor isomer **12** was crystallized away from the major isomer (Et_2O/CH_2Cl_2/hexanes 1:2:7) for characterization purposes.

Data for Major Aminobromide **11**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.03 (m, 9 H), 4.89 (m, 1 H), 4.51 (m, 1 H), 4.17 (d, J = 6.1 Hz, 2 H), 3.73 (dd, J = 10.1, 3.4 Hz, 1 H), 3.44 (dd, J = 9.4, 9.4 Hz, 1 H), 3.13 (dd, J = 16.8, 9.8 Hz, 1 H), 3.01 (dd, J = 16.5, 3.3 Hz, 1 H); ^{13}C NMR (100 MHz) δ 141.3, 136.1, 129.8, 128.8, 128.1, 127.9, 127.7, 125.3, 124.0, 114.8, 62.6, 47.6, 35.9, 33.4; IR (neat, thin film) υ 3312, 1480, 1345, 1156, 1063 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{16}H_{17}BrN_2O_2S$: 380.0194, found 380.0189.

Data for Minor Aminobromide **12**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, J = 8.5, 1 H), 7.31-7.05 (m, 8 H), 4.74 (t, J = 5.5 Hz, 1 H), 4.47 (m, 1 H), 4.32 (ddd, J = 13.5, 3.6, 0.9 Hz, 1 H), 4.22 (t, J = 5.5 Hz, 2 H), 3.68 (dd, J = 13.4, 9.8 Hz, 1 H), 3.45 (dd, J = 16.8, 5.5

Hz, 1 H), 3.20 (dd, J = 17.0, 9.2 Hz, 1 H); ^{13}C NMR (100 MHz) δ 136.2, 130.6, 129.2, 128.9, 128.2, 128.0, 127.3, 126.4, 124.7, 122.3, 53.0, 47.8, 41.6, 38.2; IR (neat, thin film) υ 3312, 1481, 1456, 1341, 1155, 1063, 1027, 753, 698 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{16}H_{17}BrN_2O_2S$: 380.0194, found 380.0189.

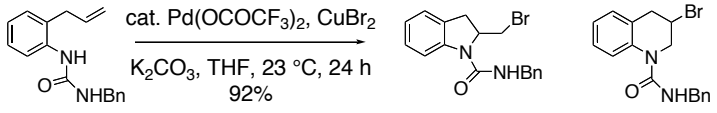


13

Synthesis of Urea 13.

A solution of *o*-allylaniline (0.735 g, 5.51 mmol) in CH_2Cl_2 (6 mL) was treated with a solution of benzylisocyanate (0.734 g, 5.51 mmol) in CH_2Cl_2 at 23 °C. The reaction was sonicated for 1 h, then Amberlyst 15 (500 mg) was added, the solution was sonicated an additional 0.5 h, then was filtered through a scintered glass funnel with copious CH_2Cl_2. The solvent was removed *in vacuo*, affording a white solid. The solid was washed with absolute EtOH and placed in a dessicator overnight, affording 1.38 g (94%) of urea **13**.

Data for **13**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.0 Hz, 1 H), 7.34-7.13 (m, 8 H), 6.14 (bs, 1 H), 5.92 (m, 1 H), 5.08 (d, J = 10.0 Hz, 1 H), 4.97 (d, J = 17.2 Hz, 1 H), 4.43 (s, 2 H), 3.35 (d, J = 5.6 Hz, 2 H); ^{13}C (75.5 MHz, $CDCl_3$) δ 156.5, 138.9, 135.9, 133.9, 130.6, 129.3, 128.6, 127.7, 127.4, 127.3, 126.1, 125.8, 116.4, 44.3, 36.1 IR (neat, thin film) υ 3308, 1631, 1605, 1569, 1478, 1245, 912, 739, 696 cm^{-1}; HRMS (ESI) calcd for $[M + Na]^+$ $C_{17}H_{18}N_2ONa$: 289.1317, found 289.1311.



13 **14** **15**

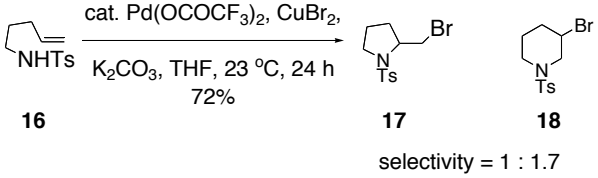
selectivity = 4.4 : 1

Palladium(II) catalyzed aminobromination of urea 13.

Urea **13** (0.050 g, 0.188 mmol) in THF (2 mL) was treated at 23 °C with K_2CO_3 (0.052 g, 0.376 mmol, 2 equiv), $CuBr_2$ (0.105 g, 0.470 mmol, 2.5 equiv) and $Pd(OCOCF_3)_2$ (0.006 g, 0.0188 mmol, 0.1 equiv). After 24 h, the reaction was diluted with Et_2O, filtered through celite and the solvent was removed *in vacuo*. Chromatography of the crude oil on SiO_2 (5-30% EtOAc/hexanes eluent) afforded 11.2 mg of the minor adduct **15** followed by 48.6 mg of the major adduct **14** (92% combined yield).

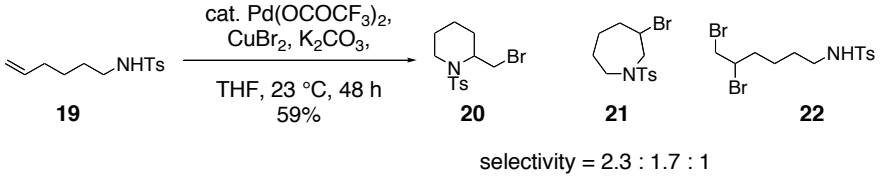
Data for Major Aminobromide **14**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.05 (m, 9 H), 5.57 (bs, 1 H), 4.54 (dd, J = 15.1, 5.9 Hz, 1 H), 4.80-4.41 (m, 2 H), 4.33 (dd, J = 13.6, 3.7 Hz, 1 H), 3.97 (dd, J = 13.5, 7.7 Hz, 1 H), 3.52 (dd, J = 17.2, 5.8 Hz, 1 H), 3.26 (dd, J = 17.2, 7.0 Hz, 1 H); ^{13}C NMR (75.5 MHz) δ 156.1, 138.7, 137.7, 129.9, 128.6, 128.0, 127.6, 127.5, 127.3, 127.2, 124.7, 122.9, 49.9, 45.0, 43.9, 38.2; IR (neat, thin film) υ 3421, 3332, 3010, 2925, 1653, 1488, 1329, 1240, 755 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{17}BrN_2ONa$ $[M + Na]^+$: 367.0422, found 367.0416.

Data for minor aminobromide **15**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.15 (m, 8 H), 6.97 (t, J = 7.3 Hz, 1 H), 5.39 (bs, 1 H), 4.71 (m, 1 H), 4.59 (dd, J = 14.6, 5.5 Hz, 1 H), 4.50 (dd, J = 14.6, 5.5 Hz, 1 H), 3.73 (dd, J = 9.9, 3.3 Hz, 1 H), 3.41-3.33 (m, 2 H), 3.06 (dd, J = 16.9, 1.9 Hz, 1 H); ^{13}C NMR (75.5 MHz) δ 154.6, 141.8, 138.6, 130.3, 128.8, 127.8, 127.7, 127.6, 125.8, 122.9, 113.6, 60.4, 44.8, 34.7, 32.9; IR (neat, thin film) υ 3339, 3025, 2919, 1647, 1513, 1481, 1380, 1284, 750 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{17}BrN_2ONa$ [M + Na]$^+$: 367.0422, found 367.0420.



Palladium(II) catalyzed aminobromination of tosamide 16.
Tosamide **16**[4] (0.0221 g, 0.0923 mmol), $Pd(O_2CCF_3)_2$ (0.0031 g, 0.0093 mmol, 0.1 equiv), $CuBr_2$ (0.0618 g, 0.273 mmol, 3 equiv), and K_2CO_3 (0.0255 g, 0.187 mmol, 2 equiv) were combined in THF (1 mL) and stirred at 23 °C for 24 h. The solution was then diluted with Et_2O, filtered through a pad of SiO_2 with copious Et_2O, dried and concentrated *in vacuo* to afford the crude mixture of products. Flash chromatography on SiO_2 afforded a 1 : 1.7 mixture of aminohalogenation products **17** and **18** (0.0212 g, 72%), and starting material **16** (0.0044 g, 20%). These products could be further separated by careful chromatography on SiO_2 (5-20% Et_2O/hexanes gradient) where **18** eluted first.
Data for 2-Bromomethyl-1-(*p*-toluenesulfonyl)pyrrolidine **17**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.8 Hz, 2 H), 7.33 (d, J = 8.0 Hz, 2 H), 3.85-3.76 (m, 2 H), 3.48 (m, 1 H), 3.35 (t, J = 9.6 Hz, 1 H), 3.14 (m, 1 H), 2.44 (s, 3 H), 1.94 (m, 1 H), 1.85 (m, 1 H), 1.74 (m, 1 H), 1.57 (m, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 143.7, 133.9, 129.8, 127.5, 60.3, 49.7, 36.0, 30.2, 23.7, 21.5. IR (neat) υ 2970, 2860, 1600, 1450, 1345, 1160, 1090 cm^{-1}. HRMS (EI) for [M]$^+$ $C_{12}H_{16}BrNO_2S$ calcd 317.0085, found 317.0088.
Data for 2-Bromo-1-(*p*-toluenesulfonyl)pyridine **18** ^{1}H NMR (400 MHz) δ: 7.65 (d, J = 8.4 Hz, 2 H). 7.34 (d, J = 7.6 Hz, 2 H), 4.07 (m, 1 H), 3.96 (d, J = 12.0 Hz, 1 H), 3.62 (m, 1 H), 2.62 (t, J = 11.2 Hz, 1 H), 2.45 (s, 3 H), 2.27 (m, 1 H), 1.81 (m, 1 H), 1.73-1.61 (m, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 144.3, 136.2, 130.3, 128.1, 54.0, 46.2, 45.6, 35.4, 25.9, 22.0; IR (neat, thin film) υ 2929, 2361, 1337, 1165, 945 cm^{-1}; HRMS (EI) for $C_{12}H_{16}BrNO_2SNa$ [M+Na]$^+$: calcd 339.9985, found 339.9980.

Structural assignment of 17 and 18. The data for compound **17** correlates well with that reported for the corresponding 5-membered iodopyrrolidine.[5]



Aminobromination of Tosamide 19.

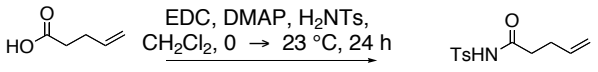
Tosamide **19**[3] (0.0750 g, 0.296 mmol, 1 equiv) in dry THF (3 mL) was treated with K_2CO_3 (0.082 g, 0.592 mmol, 2 equiv) and $CuBr_2$ (0.199 g, 0.888 mmol, 3 equiv). The mixture was treated with $Pd(OCOCF_3)_2$ (0.0100 g, 0.030 mmol, 0.1 equiv). After 48 h at 23 °C, the mixture was diluted with Et_2O (15 mL) and was filtered through a pad of SiO_2 with additional Et_2O. Concentration of the filtrate *in vacuo* afforded a crude oil which was purified by chromatography on SiO_2 (0-50% Et_2O/hexanes eluent), yielding the compounds **20** (0.027 g, 27%), **21** (0.020 g, 20%), and **22** (0.014 g, 12%) where **21** eluted first, followed by **20** and **22**.

Data for **20**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 7.6 Hz, 2 H), 7.30 (d, J = 8.0 Hz , 2 H), 4.27 (m, 1 H), 3.75 (m, 1 H), 3.51 (m, 1 H), 3.42 (dd, J = 10.0, 5.5 Hz, 1 H), 2.94 (ddd, J = 3.0, 14.0, 16.0 Hz, 1 H), 2.43 (s, 3 H), 2.04 (m, 1H), 1.56-128 (m, 5 H); ^{13}C NMR (75 MHz) δ 143.3, 137.9, 129.7, 126.9, 53.3, 41.1, 30.3, 25.1, 24.3, 21.6, 17.9; IR (KBr) υ 2943, 2865, 1342, 1154, 1093, 1055, 924, 816, 666 cm^{-1}; HRMS (ESI) calcd for $[M+1]^+$ $C_{13}H_{19}BrNO_2S$: 332.0321, found 332.0317.

Data for **21**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 8.1 Hz, 2 H), 7.31 (d, J = 7.8 Hz, 2 H), 4.25 (m, 1 H), 4.06 (dd, J = 14.7, 4.8 Hz, 1H), 3.74 (m, 1 H), 2.98 (dd, J = 11.1, 14.1 Hz, 1 H), 2.84 (m, 1 H), 2.43 (s, 3 H), 2.39 (m, 1 H), 1.97-1.58 (m, 5 H); ^{13}C NMR (75 MHz) δ 143.4, 136.3, 129.8, 126.8, 55.0, 50.6, 49.1, 38.5, 28.3, 23.0, 21.5; IR (KBr) υ 2937, 1598, 1444, 1338, 1157, 1092, 1045, 916, 815 cm^{-1}; HRMS (ESI) calcd for $[M+Na]^+$ $C_{13}H_{18}BrNO_2SNa$: 354.0140, found 354.0125.

Data for **22**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8 Hz, 2 H), 7.32 (d, J = 8 Hz , 2 H), 4.60 (m, 1 H), 4.08 (m, 1 H), 3.81 (dd, J = 7.6, 4.4 Hz, 1 H), 3.56 (t, J = 10 Hz, 1 H), 2.96 (m, 2 H), 2.43 (s, 3 H), 2.06 (m, 1 H), 1.76-1.30 (m, 5 H); ^{13}C NMR (75.5 MHz) δ 143.4, 137.0, 129.7, 127.1, 52.3, 42.9, 36.0, 35.4, 28.8, 23.8, 21.5 ; IR (KBr) υ 3854, 3751, 3629.1, 3274, 2944, 1700, 1636, 1559, 1458, 1420, 1323, 1159, 1094, 815, 665 cm^{-1}; HRMS (ESI) calcd for $[M+1]^+$ $C_{13}H_{20}Br_2NO_2S$: 411.9581, found 411.9575.

Structural assignment of 20 and 21. The spectral data for 2-bromomethyl-1-(*p*-toluenesulfonyl)piperidine **20** correlated very well with data of the corresponding 2-iodomethyl--1-(*p*-toluenesulfonyl)piperidine.[5]

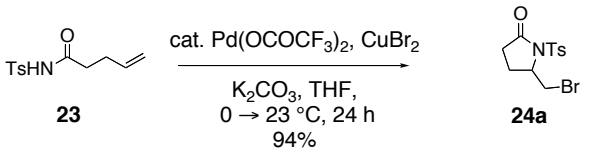


23

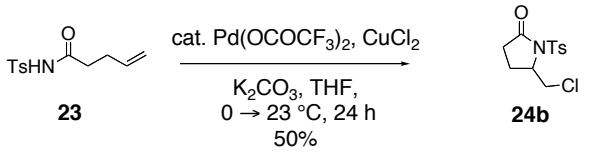
Synthesis of *N*-tosylamide (23).

At 0 °C, 4-pentenoic acid(1 g, 10 mmol, 1 equiv) was added to a solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, EDC (2.5 g, 13 mmol, 1.3 equiv) and DMAP (1.7 g, 14 mmol, 1.4 equiv) in CH_2Cl_2 (25 mL). Then, *p*-toluenesulfonamide (2.1g, 12 mmol, 1.2 equiv) was added to the mixture. The ice bath was removed and warmed to room temperature. After 24 h at 23 °C, the solution was diluted with Et_2O (150 mL) and washed with 1N HCl solution. The aqueous layer was then extracted twice with Et_2O

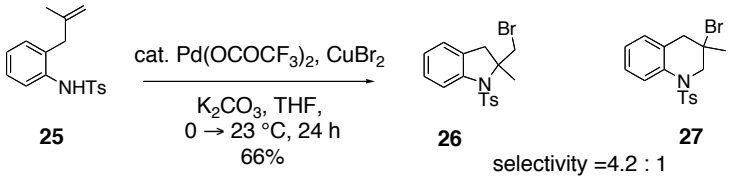
(100 mL). The combined ether layers were dried with Na_2SO_4 and concentrated to yield 2.97 g (98%) of crude tosylamide **23**, which upon flash chromatography (10-40% EtOAc/Hexane) yielded 2.40 g (81%) of **23** as long white needles. Spectral data for **23** was in agreement with the literature data.[6]



Palladium catalyzed aminobromination of *N*-tosylamide 23.
N-tosylamide **23** (0.051 g, 0.202 mmol, 1 equiv) in dry THF (2 mL) was treated with K_2CO_3 (0.056 g, 0.404 mmol, 2 equiv) and $CuBr_2$ (0.135 g, 0.606 mmol, 3 equiv). The mixture was cooled to 0 °C and was treated with $Pd(OCOCF_3)_2$ (0.007 g, 0.020 mmol, 0.1 equiv). The solution was allowed to warm to 18 °C gradually (over ca. 4 h). After 24 h, the mixture was diluted with Et_2O (3 mL) and hexanes (1 mL) and was filtered through a pad of celite with additional Et_2O. Concentration of the filtrate *in vacuo* afforded a crude oil which was purified by chromatography on SiO_2 (5-35% Et_2O/hexanes eluent), affording 0.063 g (94% yield) of aminobromide **24a**.
Data for Aminobromide **24a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, J = 8.5 Hz, 2 H), 7.34 (d, J = 8.5 Hz, 2 H), 4.67 (m, 1 H), 3.84-3.78 (m, 1 H), 3.74-3.70 (m, 1 H), 2.71-2.65 (m, 1 H), 2.44 (s, 3 H), 2.40-2.26 (m, 2 H), 2.10-2.5 (m. 1 H); ^{13}C NMR (125.7 MHz) δ 173.3, 145.4, 135.1, 129.5, 128.5, 58.9, 36.1, 30.6, 23.2, 21.7; IR (neat, thin film) υ 2920, 2361, 1734, 1361, 1168 cm^{-1}; HRMS (EI) calcd for $[M+Na]^+$ $C_{12}H_{14}BrNO_3NaS$: 355.9750, found 355.9761.



Palladium catalyzed aminochlorination of *N*-tosylamide 23.
N-tosylamide **23** (0.052 g, 0.204 mmol, 1 equiv) in dry CH_3CN (2 mL) was treated with K_2CO_3 (0.058 g, 0.408 mmol, 2 equiv) and $CuCl_2$ (0.137 g, 1.02 mmol, 5 equiv). The mixture was cooled to 0 °C and was treated with $Pd(OCOCF_3)_2$ (0.009 g, 0.027 mmol, 0.13 equiv). The solution was allowed to warm to 17 °C gradually (over ca. 4 h). After 24 h, the mixture was diluted with Et_2O (3 mL) and hexanes (1 mL) and was filtered through a pad of celite with additional Et_2O. Concentration of the filtrate *in vacuo* afforded a crude oil which was purified by chromatography on SiO_2 (5-35% Et_2O/hexanes eluent), affording 0.029 g (50% yield) of aminochloride **24b**.
Data for Aminobromide **24b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, J = 8.5 Hz, 2 H), 7.34 (d, J = 8.5 Hz, 2 H), 4.68 (m, 1 H), 4.03-3.98 (m, 1 H), 3.84-3.80 (m, 1 H), 2.70-2.65 (m, 1 H), 2.44 (s, 3 H), 2.44-2.27 (m, 2 H), 2.14-2.10 (m. 1 H); ^{13}C NMR (125.7 MHz) δ 173.4, 145.3, 135.2, 129.5, 128.5, 59.2, 47.2, 30.7, 22.4, 21.7; IR (neat, thin film) υ 2950, 2361, 1735, 1653, 1559, 1457 cm^{-1}; HRMS (EI) calcd for $[M+Na]^+$ $C_{12}H_{14}ClNO_3NaS$: 310.0275, found 310.0277.



Palladium catalyzed aminobromiation of *N*-tosylamide 25.
N-tosylamide **25**[1] (0.069 g, 0.22 mmol, 1 equiv) in dry THF (2.8 mL) was treated with K_2CO_3 (0.06 g, 0.44 mmol, 2 equiv) and $CuBr_2$ (0.153 g, 0.68 mmol, 3 equiv) under argon. The mixture was cooled to 0 °C and was treated with $Pd(OCOCF_3)_2$ (0.007 g, 0.022 mmol, 0.1 equiv). The solution was allowed to warm to 25 °C gradually. After 24 h, the mixture was diluted with Et_2O (10 mL) and was filtered through a pad of celite with additional Et_2O. Concentration of the filtrate *in vacuo* afforded a crude product which was purified by chromatography on SiO_2 (5 % EtOAc/hexanes eluent), affording 0.047 g (54%) of aminobromide **26** (eulutes first) and 0.011 g (12%) of aminobromide **27**, both as white crystalline solids.
Data for major aminobromide **26**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, J = 8.4 Hz, 2 H), 7.42 (d, J = 7.8 Hz, 1 H), 7.26 (m, 2 H), 7.14 (m, 2 H), 6.99 (m, 1 H) 3.94 (dd, J = 9.9, 10.2 Hz, 2 H), 3.50 (d, J = 16.2 Hz, 1 H), 2.92 (d, J = 16.5 Hz, 1 H), 2.39 (s, 3 H), 1.78 (s, 3 H); ^{13}C NMR (125.7 MHz) δ 144.4, 142.3, 139.0, 130.2, 128.3, 128.0, 127.4, 125.5, 123.6, 114.4, 72.0, 43.1, 41.3, 24.9, 22.0; IR (neat, thin film) υ 2925, 1600, 1481, 1461, 1352, 1165, 1091, 999 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{17}H_{18}BrNO_2S$: 379.0236, found 379.0239, mp = 102-104 °C.
Data for minor aminobromide **27**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J = 7.8 Hz, 2 H), 7.56 (d, J = 8.1 Hz, 1 H), 7.27 (d, J = 7.8 Hz, 2 H), 7.15 (m, 1 H), 7.00 (m, 2 H) 4.23 (d, J = 13.2 Hz, 1 H), 4.09 (d, J = 13.2 Hz, 1 H), 3.22 (d, J = 7.5 Hz, 1 H), 2.95 (d, J = 16.5 Hz, 1 H), 2.40 (s, 3 H), 1.89 (s, 2 H); ^{13}C NMR (125.7 MHz) δ 144.4, 137.7, 135.7, 130.2, 129.8, 129.4, 127.9, 127.5, 126.3, 124.5, 121.1, 59.1, 46.2, 31.4, 22.0; IR (neat, thin film) υ 2850, 2359, 1599, 1493, 1458, 1351, 1165, 1091 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{17}H_{18}BrNO_2S$: 379.0236, found 379.0245, mp = 128-130 °C.
Structural assignment of 26. The structure of **26** was assigned by X-ray crystallography, the structure of **27** was assigned by NMR, mass spectroscopy and process of elimination (i.e. it does not correspond to structure **26**).

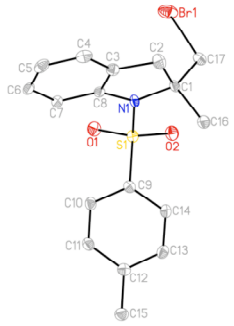


Figure 2. ORTEP structure of aminobromide **26**.

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