Supporting Information for:

Direct Access to Functionalized Azepanes by Cross-Coupling with Alpha-Halo Eneformamides

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Structures

1a; X = Cl
1b; X = Br

3a; Ar = Ph, 3b; Ar = p-F-C₆H₄, 3c; Ar = C₆F₅
3e; R = CO₂Me, 3f; R = CO₂tBu, 3g; R = CONH/iPr, 3h; R = CN
3j; R = OAc, 3k; R = CH₂OAc, 3l; R = OEt, 3m; R = OBu,

Ar

Me

Ph

Me

CO₂Me

3d

3i

3n

R

CHO

8 R = CO₂Me
9; R = CO₂tBu
10; R = CONH/iPr
11; R = CN
12 (75:25, E/Z)

N

CHO

15; R' = Et
16; R' = Bu

17a (Δ²,³), 17b (Δ³,⁴)
17c (Δ⁴,⁵)

R

H (1.5 equiv)

21a; R = Ph, 21b; R = TMS
21c; R = 1-cyclohexenyl
21d; R = -CH₂CH₂CH₂Cl

22; R = Ph
23; R = TMS

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28; X = OMe
29; X = Cl

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2. General Experimental Information & Procedures

All experiments involving palladium precatalysts were carried out under an inert atmosphere of argon or nitrogen. Et$_3$N, MeOH, THF, benzene, toluene, Et$_2$O, and acetonitrile were distilled using the Grubbs solvent system. Anhydrous DMF and 1,4-dioxane were used as purchased. Dichloromethane was distilled from MgSO$_4$. NaTFA, K$_2$CO$_3$, CuI, NaBH$_3$CN, and the boronic acids were used as purchased. The concentration of commercial n-BuLi (solution in hexanes) was determined prior to use by No-D NMR spectroscopy. All alkenes and alkynes were newly purchased and used without further purification. Column chromatography was performed on silica gel (230-400 mesh). Thin-layer chromatography (TLC) was performed on silica plates. Visualization of the TLC plates was aided by UV irradiation at 254 nm or by staining with CAM, p-anisaldehyde, or KMnO$_4$. Unless otherwise indicated, $^1$H, $^{13}$C, DEPT-135, COSY-45, and HMQC NMR spectra were acquired using C$_6$D$_6$ or CDCl$_3$ as solvent at room temperature. Chemical shifts are quoted in parts per million (ppm).

General Procedure A: Synthesis of 2-Halo enamides

To a solution of DMF (60 mmol, 6 equiv) in CH$_2$Cl$_2$ (50 mL) at 0 °C was added dropwise, the corresponding phosphorus oxyhalide (30 mmol, 3 equiv) dissolved in CH$_2$Cl$_2$ (18 mL). The resulting mixture (pale yellow in the case of the chloride or milky white in the case of the bromide) was refluxed for 20 min. A solution of caprolactam (10 mmol, 1 equiv) in CH$_2$Cl$_2$ (50 mL) was added slowly under reflux. After complete addition of the lactam, the mixture was stirred under reflux for the indicated time period (TLC and LC-MS monitoring was used to followed the extent of the reaction). Upon completion, the mixture was allowed to warm to room temperature and then poured into a large flask containing crushed ice. After stirring at rt for 30 min, the layers were separated. Powdered K$_2$CO$_3$ was added slowly to the mixture and the flask was swirled after each addition (Caution: it bubbles vigorously). The addition/swirling was continued until persistent cloudiness was observed. The neutralized/slightly basic mixture was extracted three times with CH$_2$Cl$_2$. The combined organic layer was concentrated to ~100 mL and was dried over Na$_2$SO$_4$ for 30 min. The mixture was filtered and concentrated under reduced pressure to give the desired product as an oil.

Purification: Flash chromatography on silica (pretreated with 1% Et$_3$N) eluting with hexane/EtOAc (80:20).
Caution: The 2-haloenamides are bench stable at room temperature for days but should be stored in the refrigerator either neat or as a solution in benzene.

**General Procedure B: Heck coupling of 2-halo enamides with unactivated alkenes**

To an oven-dried, septum-capped vial equipped with a stir bar, was added the 2-halo enamide (1 mmol, 1.0 equiv) in DMF (2 mL, 0.50 M), Pd(OAc)$_2$ (5 mol%), additive (1 to 2.0 equiv), alkene (2 to 6 equiv) under an argon or nitrogen atmosphere. The mixture was then stirred at 80 °C for the desired length of time (as indicated by TLC and LC-MS, usually 1 h). Upon completion, the mixture was quenched with water and extracted with CH$_2$Cl$_2$. The combined organic layers were concentrated to ~10 mL and dried for ~30 min with Na$_2$SO$_4$. It was filtered and evaporated to give the crude product.

Purification: Flash chromatography on silica eluting with hexane/EtOAc.

*Note:* 1 equiv NaTFA or 2 equiv of K$_2$CO$_3$ were employed. With dioxane as the solvent, longer reaction times (monitoring by TLC and LC-MS, usually 2 h) are required.

**General Procedure C (Sonogashira coupling of 2-halo enamides with terminal alkynes)**

To an oven-dried, septum-capped 2-neck-round bottom flask equipped with a stir bar, was added the 2-halo enamide (1 mmol, 1.0 equiv) in DMF (5 mL) under an argon or nitrogen atmosphere. The desired alkyne (1.2 equiv) was added followed by addition of Et$_3$N (0.7 mL, 5 mmol, 5 equiv). After completely degassing the flask, PdCl$_2$(PPh$_3$)$_2$ (35 mg, 5 mol%) and CuI (2 mg, 1 mol%) were added rapidly and concurrently. The mixture was then stirred at the desired temperature for the desired length of time (as indicated by TLC and LC-MS). Upon completion, the mixture was quenched with water and extracted with CH$_2$Cl$_2$. The combined organic layers were concentrated to ~20 mL and dried with for ~30 min with Na$_2$SO$_4$. It was filtered and evaporated to give the crude product.

Purification: Flash chromatography on silica eluting with hexane/EtOAc.

*Note:* The coupling can be performed in the absence of CuI but longer reaction times (monitoring by TLC and LC-MS) are required.
**General Procedure D (Suzuki coupling of 2-halo enamides with boronic acids)**

To an oven-dried, septum-capped 2-neck-round bottom flask equipped with a stir bar, was added the 2-halo enamide (1 mmol, 1.0 equiv) in DMF (5 mL) under an argon or nitrogen atmosphere. The desired boronic acid (1.2 equiv) was added followed by addition of Et₃N (0.7 mL, 5 mmol, 5 equiv). After completely degassing the flask, PdCl₂(PPh₃)₂ (35 mg, 5 mol%) was added rapidly. The mixture was then stirred at the desired temperature for the desired length of time (as indicated by TLC and LC-MS). Upon completion, the mixture was quenched with water and extracted with CH₂Cl₂. The combined organic layers were concentrated to ~20 mL and and dried with for ~30 min with Na₂SO₄. It was filtered and evaporated to give the crude product.

Purification: Flash chromatography on silica (pretreated with 1% Et₃N) eluting with hexane/EtOAc.

**General Procedure E: Catalytic hydrogenation**

EtOAc was added to a flask containing 10% Pd/C at room temperature. The flask was degassed and placed under an inert atmosphere of nitrogen. A solution of the enamide in EtOAc was added. After complete addition, the nitrogen line was cut off and then replaced with a balloon of hydrogen. After complete consumption of the enamide (based on LC-MS and TLC monitoring), the mixture was filtered through a plug of Celite and concentrated under reduced pressure.

**General Procedure F: N-acyl iminium reduction**

To the N-formyl-substrate (1.0 equiv) dissolved in freshly distilled CH₂Cl₂, was added NaBH₃CN (5 equiv) slowly under nitrogen at 0 °C. TFA (10 equiv) was added slowly and the mixture was stirred for 10 min at 0 °C, then for ~12 h at room temperature (monitoring by LCMS and TLC; the reduced compound is significantly more polar). Upon completion, the reaction was quenched with sat. NaHCO₃. The layers were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, filtered and evaporated to obtain the crude product, which were purified by flash chromatography on silica eluting with hexane/EtOAc.
3. Synthesis of α-Halo Eneformamides

Compound 1a: Prepared using General Procedure A

2 (11.3 g, 100 mmol), POCl₃ (46 g, 28 mL, 300 mmol), DMF (46.3 mL, 600 mmol), Temp = 50 °C, time = 3 h, Purification: Flash chromatography on silica (pretreated with 1% Et₃N) eluting with hexane/EtOAc (80:20). Yield = 14.04 g (97% purity, mixture of rotamers, 85%). "H NMR (400 MHz, C₆D₆) δ 8.40 (1H), 5.36 to 5.31 (1H), 3.28 to 3.20 (2H), 1.58 to 1.51 (2H), 1.31 to 1.24 (2H), 1.02 to 0.93 (2H). "C NMR (101 MHz, C₆D₆) δ 160.89, 130.76, 123.64, 43.48, 28.26, 26.43, 23.41.
Compound 1b: Prepared using **General Procedure A**

2 (1.13 g, 10 mmol), POBr$_3$ (8.6 g, 3.01 mL, 30 mmol), DMF (4.63 mL, 60 mmol), Temp = 50 °C, time = 30 min, Purification: Flash chromatography on silica (pretreated with 1% Et$_3$N) eluting with hexane/EtOAc (80:20). Yield = 1.877 g, 92%. ¹H NMR (400 MHz, C$_6$D$_6$) δ 8.87 (1H), 5.66 to 5.63 (1H), 3.50 to 3.48 (2H), 1.76 to 1.72 (2H), 1.43, 1.41 to 1.37 (2H), 1.20 to 1.14 (2H). ¹³C NMR (101 MHz, C$_6$D$_6$) δ 161.90, 132.10, 126.24, 44.39, 28.44, 27.94, 24.59. HRMS calc for C$_{17}$H$_{10}$BrNO 202.9946, found 202.9945.
4. Alkenylation of 1a

Full Optimization (partial data is included in Table 1)

Note: The choice of base additives was guided by previous reports on the β-alkenylation of piperidine-derived enaminones and enamides.\(^3\)\(^4\)

Prepared using General Procedure B

1a (159.6 mg, 1.0 mmol), Pd(OAc)\(_2\), (11.5 mg, 5 mol%), styrene (0.46 mL, 4 mmol, 4 equiv), NaTFA (136 mg, 1 mmol, 1 equiv), DMF (5 mL), Temp = 80 °C, time = 1 h. Purification: Flash chromatography on silica (pretreated with 1% Et\(_3\)N) eluting with hexane/EtOAc (90:10). Yield = 184 mg, 81%. \(^1\)H NMR (400 MHz, C\(_6\)D\(_6\)) δ 8.19 (1H), 7.32 to 6.89 (5H), 6.63 to 6.45 (2H), 5.51 to 5.35 (1H), 3.52 to 3.26 (2H), 1.88 to 1.74 (2H), 1.64 to 1.50 (2H), 1.18 to 1.01 (2H). \(^1\)H NMR (101 MHz, C\(_6\)D\(_6\)) δ 161.38, 142.29, 136.54, 129.65, 128.54, 128.22, 128.11, 127.93, 127.81, 127.69, 127.57, 127.45, 127.29, 126.70, 42.99, 29.03, 27.11, 24.35. HRMS calc for C\(_{13}\)H\(_{13}\)NO 227.1310, found 227.1309.
Prepared using **General Procedure B**

**1a** (159.6 mg, 1.0 mmol), Pd(OAc)$_2$, (11.5 mg, 5 mol%), 4-fluorostyrene (0.346 mL, 3 mmol, 3 equiv), NaTFA (136 mg, 1 mmol, 1 equiv), DMF (5 mL), Temp = 80 °C, time = 3 h. Purification: Flash chromatography on silica (pretreated with 1% Et$_3$N) eluting with hexane/EtOAc (90:10). Yield = 161.7 mg (96% purity, mixture of rotamers, 72%, contaminated with the Z-isomer). $^1$H NMR (400 MHz, C$_6$D$_6$) $\delta$ 8.18 (1H), 6.86 to 6.65 (5H), 6.33 & 6.31 (1H), 5.46 to 5.43 (1H), 3.46 to 3.43 (2H), 1.85 to 1.78 (2H), 1.59 to 1.51 (2H), 1.16 to 1.07 (2H). $^{13}$C NMR (101 MHz, C$_6$D$_6$) $\delta$ 163.69, 161.39, 161.23, 142.15, 132.71, 132.68, 129.73, 128.29, 128.21, 128.10, 127.92, 127.80, 127.68, 127.56, 127.44, 127.20, 127.08, 127.06, 115.51, 115.30, 115.21, 43.01, 29.01, 27.10, 24.34. HRMS calc for C$_{15}$H$_{16}$FNO 245.1216, found 245.1215.
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Prepared using **General Procedure B**

1a (80 mg, 0.5 mmol), Pd(OAc)$_2$ (6 mg, 5 mol%), pentafluorostyrene (0.139 mL, 1 mmol, 2 equiv), NaTFA (68 mg, 0.5 mmol, 1 equiv), DMF (5 mL), Temp = 80 °C, time = 6 h. Purification: Flash chromatography on silica (pretreated with 1% Et$_3$N) eluting with hexane/EtOAc (70:30). Yield = 100 mg, (99% purity, mixture of rotamers, 63%, *contaminated with the Z-isomer*). $^1$H NMR (400 MHz, C$_6$D$_6$) δ 7.97 (1H), 7.52 & 7.49 (1H), 6.04 & 6.02 (1H), 5.54 to 5.50 (1H), 3.30 to 3.28 (2H), 1.65 to 1.61 (2H), 1.43 to 1.39 (2H), 1.03 to 0.90 (2H). $^{13}$C NMR (101 MHz, C$_6$D$_6$) δ 160.92, 141.59, 134.36, 130.74, 126.40, 123.62, 111.75, 43.47, 28.23, 26.41, 23.39. HRMS calc for C$_{15}$H$_{12}$F$_5$NO 317.0839, found 317.0841.
$^{13}$C NMR (101 MHz, C$_6$D$_6$) δ 160.92, 141.59, 134.36, 130.74, 126.40, 123.62, 111.75, 43.47, 28.23, 26.41, 23.39
Prepared using **General Procedure B**

**1a** (80 mg, 0.5 mmol), Pd(OAc)$_2$ (6 mg, 5 mol%), $\alpha$-methylstyrene (0.26 mL, 2 mmol, 4 equiv), NaTFA (68 mg, 0.5 mmol, 1 equiv), DMF (5 mL), Temp = 80 °C, time = 3 h. Purification: Flash chromatography on silica (pretreated with 1% Et$_3$N) eluting with hexane/EtOAc (70:30). Yield = 93 mg, 95% purity, mixture of rotamers, 73%. $^1$H NMR (400 MHz, C$_6$D$_6$) δ 8.26 (1H, major), 7.81 (1H, minor), 7.45 (2H, both), 7.20 to 7.05 (8H, both), 5.38 to 4.89 (6H both), 3.76 (2H), 3.20 to 3.17 (2H, major), 3.12 (2H, minor), 2.52 to 2.49 (2H, minor), 1.80 to 0.87 (12H, both).

$^{13}$C NMR (101 MHz, C$_6$D$_6$) δ 160.73, 160.11, 144.98, 144.43, 141.88, 140.47, 140.01, 139.97, 128.17, 128.12, 128.04, 127.93, 127.81, 127.69, 127.58, 127.55, 127.45, 127.35, 126.42, 126.30, 124.38, 123.55, 115.64, 114.95, 47.94, 43.95, 42.70, 39.25, 32.08, 28.37, 26.55, 26.44, 24.17, 23.57. HRMS calc for C$_{16}$H$_{19}$NO 241.1466, found 241.1463.
Prepared using **General Procedure B**

1a (159.6 mg, 1.0 mmol), Pd(OAc)$_2$, (11.5 mg, 5 mol%), methyl acrylate (0.554 mL, 6 mmol, 6 equiv), K$_2$CO$_3$ (277 mg, 2 mmol, 2 equiv), DMF (5 mL), Temp = 80 °C, time = 1 h. Purification: Flash chromatography on silica (pretreated with 1% Et$_3$N) eluting with hexane/EtOAc (80:20 to 30:70). Yield = 184.1 mg, 88%, 92:8 dr (E:Z). $^1$H NMR (400 MHz, C$_6$D$_6$) $\delta$ 7.91 (1H), 7.23 & 7.20 (1H), 5.89 & 5.85 (1H), 5.42 to 5.38 (1H), 3.42 (3H), 3.21 to 3.15 (2H), 1.62 to 1.56 (2H), 1.42 to 1.33 (2H), 0.97 to 0.86 (2H). $^{13}$C NMR (101 MHz, C$_6$D$_6$) $\delta$ 166.33, 160.75, 143.01, 140.57, 138.10, 117.58, 50.90, 42.67, 28.70, 27.29, 23.59. HRMS calc for C$_{11}$H$_{15}$NO$_3$ 209.2453, found 209.2451.
Prepared using **General Procedure B**

1a (159.6 mg, 1.0 mmol), Pd(OAc)$_2$ (11.5 mg, 5 mol%), *tert*-butyl acrylate (0.581 mL, 4 mmol, 4 equiv), K$_2$CO$_3$ (277 mg, 2 mmol, 2 equiv), DMF (5 mL), Temp = 80 °C, time = 1 h. Purification: Flash chromatography on silica (pretreated with 1% Et$_3$N) eluting with hexane/EtOAc (90:10 to 50:50). Yield = 211.1 mg, 84%. $^1$H NMR (400 MHz, C$_6$D$_6$) δ 7.93 (1H), 7.26 & 7.22 (1H), 5.93 & 5.90 (1H), 5.44 to 5.40 (1H), 3.22 to 3.19 (2H), 1.62 to 1.36 (13H), 1.01 to 0.86 (2H). $^{13}$C NMR (101 MHz, C$_6$D$_6$) δ 166.12, 161.47, 142.82, 141.42, 138.15, 120.54, 80.56, 43.39, 29.43, 28.49, 27.93, 24.37. HRMS calc for C$_{14}$H$_{21}$NO$_3$ 251.1522, found 251.1520.

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**Experiment:** tbeng_20130904_04  
**Experiment Description:** btk-B-057-f34  
**Sample:**  
**Sample Description:**  
**Data File Name:** C:\LabSolutions\Data\Project1\tbeng\btk-B-057-f34.ldc  
**Sample Location:** Plate Number: 1 - Position: 5  
**Run By:** tbeng  
**Run Started:** Tuesday, September 03, 2013 11:21:57 PM  
**Run Finished:** Tuesday, September 03, 2013 11:29:01 PM  
**Method:** 30.95_8mrun1mLminLowMW(125-625m/z)
Supporting Information

$^1$H NMR [400 MHz, CDCl$_3$] δ 8.78, 8.57, 7.05, 6.25, 5.04, 4.64, 3.43, 2.82, 1.46, 1.21, 1.05

$^{13}$C NMR [101 MHz, CDCl$_3$] δ 166.12, 161.47, 142.82, 141.42, 138.15, 120.54, 80.50, 43.39, 29.43, 28.40, 27.98, 24.37
Prepared using **General Procedure B**

**1a** (159.6 mg, 1.0 mmol), Pd(OAc)$_2$ (11.5 mg, 5 mol%), $N$-isopropyl acrylamide (226.3 mg, 2 mmol, 2 equiv), K$_2$CO$_3$ (277 mg, 2 mmol, 2 equiv), DMF (5 mL), Temp = 80 °C, time = 1 h. Purification: Flash chromatography on silica (pretreated with 1% Et$_3$N) eluting with hexane/EtOAc (50:50 to 25:75). Yield = 189.1 mg, 80%. $^1$H NMR (400 MHz, C$_6$D$_6$) δ 7.97 (1H), 7.52 & 7.49 (1H), 6.78 & 6.76 (1H, coupling across nitrogen very pronounced), 6.05 & 6.02 (1H), 5.54 to 5.50 (1H), 4.40 to 4.35 (1H), 3.30 to 3.28 (2H), 1.65 to 1.61 (2H), 1.43 to 1.39 (2H), 1.18 to 0.90 (8H). $^{13}$C NMR (101 MHz, C$_6$D$_6$) δ 163.98, 161.64, 140.97, 138.27, 135.64, 122.10, 42.85, 41.18, 28.96, 27.13, 23.77, 22.45. HRMS calc for C$_{13}$H$_{20}$N$_2$O$_2$ 236.1525, found 236.1527.
$^{13}$C NMR (101 kHz, CD$_6$): δ 168.98, 161.64, 149.97, 138.27, 135.64, 122.19, 42.86, 41.18, 28.96, 27.13, 23.77, 22.45
Prepared using **General Procedure B**

**1a** (159.6 mg, 1.0 mmol), Pd(OAc)$_2$ (11.5 mg, 5 mol%), acrylonitrile (0.4 mL, 6 mmol, 6 equiv), K$_2$CO$_3$ (277 mg, 2 mmol, 2 equiv), DMF (5 mL), Temp = 80 °C, time = 1 h. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100). Yield = 127 mg, 72%. $^1$H NMR (400 MHz, C$_6$D$_6$) $\delta$ 7.54 (1H), 6.06 & 6.02 (1H), 5.09 to 5.06 (1H), 4.49 & 4.45 (1H), 3.02 to 2.99 (2H), 1.51 to 1.46 (2H), 1.38 to 1.30 (2H), 0.89 to 0.81 (2H). $^{13}$C NMR (101 MHz, C$_6$D$_6$) $\delta$ 161.15, 148.10, 140.65, 139.47, 118.19, 96.89, 43.38, 29.16, 27.87, 24.07. HRMS calc for C$_{10}$H$_{12}$N$_2$O 176.0950, found 176.1002.
Supporting Information

**$^{13}$C NMR (101 MHz, C$_6$D$_6$) δ 161.15, 148.10, 140.65, 139.47, 118.19, 96.89, 43.38, 29.16, 27.87, 24.07**

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**Proton NMR starting parameters: 6/11/03**

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**Carbon NMR starting parameters: 6/11/03**
Note: The product isomerizes after prolonged exposure to silica.
Prepared using **General Procedure B**

1a (159.6 mg, 1.0 mmol), Pd(OAc)$_2$, (11.5 mg, 5 mol%), (E)-methyl crotonate (0.424 mL, 4 mmol, 4 equiv), K$_2$CO$_3$ (277 mg, 2 mmol, 2 equiv), DMF (5 mL), Temp = 80 °C, time = 1 h.

Purification: Flash chromatography on silica (pretreated with 1% Et$_3$N) eluting with hexane/EtOAc (90:10 to 50:50). Yield = 147.4 mg, 80% purity, mixture of rotamers and ~75:25 E/Z mixture, 52%. $^1$H NMR (400 MHz, C$_6$D$_6$) δ 7.93 (1H, minor), 7.83 (1H, major), 5.99 (1H, minor), 5.93 (1H, major), 5.66 to 5.62 (1H, major), 5.33 & 5.32 (1H, minor), 3.40 to 3.16 (10H, major + minor), 2.35 (3H, minor), 2.17 (3H, major), 2.02 to 1.99 (2H, minor), 1.80 to 1.62 (4H, minor + major), 1.47 to 1.39 (2H, major), 1.11 to 0.93 (4H, minor + major). $^{13}$C NMR (101 MHz, C$_6$D$_6$) δ 166.55, 161.28, 150.73, 144.28, 131.56, 116.31, 50.47, 43.01, 28.46, 27.08, 23.62, 14.59. HRMS calc for C$_{12}$H$_{17}$NO$_3$ 223.1208, found 223.1206.
$^{13}$C NMR (101 MHz, C$_6$D$_6$) $\delta$ 166.55, 161.28, 150.73, 144.28, 131.56, 116.31, 50.47, 43.01, 28.46, 27.08, 23.62, 14.59

**Supporting Information**

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Prepared using **General Procedure B**

1a (159.6 mg, 1.0 mmol), Pd(OAc)$_2$, (11.5 mg, 5 mol%), vinyl acetate (0.553 mL, 6 mmol, 6 equiv), NaTFA (136 mg, 1.0 mmol, 1 equiv), DMF (5 mL), Temp = 80 °C, time = 1 h. Purification: Flash chromatography on silica (pretreated with 1% Et$_3$N) eluting with hexane/EtOAc (50:50). Yield = 107.2 mg, 71%. $^1$H NMR (400 MHz, C$_6$D$_6$) δ 8.46 (1H), 5.26 to 5.14 (2H), 4.80 to 4.77 (1H), 4.57 to 4.49 (1H), 3.26 to 3.23 (2H), 1.45 to 1.40 (2H), 1.23 to 1.18 (2H), 0.91 to 0.88 (2H). $^{13}$C NMR (101 MHz, C$_6$D$_6$) δ 161.64, 136.06, 130.32, 124.47, 113.88, 44.21, 28.98, 27.18, 24.15. HRMS calc for C$_9$H$_{13}$NO 151.0998, found 151.2000.
$^{13}$C NMR (101 MHz, C$_6$D$_6$) δ 161.64, 136.06, 130.32, 124.47, 113.88, 44.21, 28.98, 27.18, 24.15
Prepared using General Procedure B

1a (159.6 mg, 1.0 mmol), Pd(OAc)$_2$, (11.5 mg, 5 mol%), allyl acetate (0.432 mL, 4 mmol, 4 equiv), NaTFA (136 mg, 1 mmol, 1 equiv), DMF (5 mL), Temp = 80 °C, time = 1 h. Purification: Flash chromatography on silica (pretreated with 1% Et$_3$N) eluting with hexane/EtOAc (50:50 to 20:80). Yield = 187.6 mg, 97% purity, mixture of rotamers and ~90:10 E/Z mixture, 82%. $^1$H NMR (400 MHz, C$_6$D$_6$) δ 8.04 (1H), 5.95 & 5.92 (1H), 5.53 to 5.29 (2H), 4.38 & 4.37 (2H), 3.31 to 3.28 (2H), 1.75 to 1.62 (5H), 1.49 to 1.44 (2H), 1.07 to 1.01 (2H). $^{13}$C NMR (101 MHz, C$_6$D$_6$) δ 169.44, 161.13, 141.10, 131.91, 129.96, 123.53, 63.52, 42.85, 28.89, 26.84, 24.10, 20.07. HRMS calc for C$_{12}$H$_{17}$NO$_3$ 223.1208, found 223.1210.
$^{13}$C NMR (101 MHz, C$_6$D$_6$) δ 169.44, 161.13, 141.10, 131.91, 129.98, 123.53, 63.52, 42.85, 26.89, 20.84, 24.10, 20.07
Prepared using **General Procedure B**

1a (159.6 mg, 1.0 mmol), Pd(OAc)$_2$ (11.5 mg, 5 mol%), ethyl vinyl ether (0.575 mL, 6 mmol, 6 equiv), NaTFA (136 mg, 1 mmol, 1 equiv), DMF (5 mL), Temp = 60 °C, time = 2 h.

Purification: Flash chromatography on silica (pretreated with 1% Et$_3$N) eluting with hexane/EtOAc (50:10 to 10:90). Yield = 175.7 mg, 96% purity, mixture of rotamers, 86%. $^1$H NMR (400 MHz, C$_6$D$_6$) δ 8.21 (1H), 6.26 to 6.22 (1H), 4.23 (1H), 3.91 (1H), 3.44 to 3.33 (4H), 1.83 to 1.78 (2H), 1.49 to 1.46 (2H), 1.22 to 0.94 (5H). $^{13}$C NMR (101 MHz, C$_6$D$_6$) δ 161.76, 157.93, 139.08, 125.70, 84.14, 63.13, 43.21, 28.92, 26.47, 24.01, 14.10. HRMS calc for C$_{11}$H$_{17}$NO$_2$ 195.1259, found 195.1261.
$^{13}$C NMR (101 MHz, CD$_2$OD) $\delta$ 161.76, 157.93, 139.08, 125.70, 84.14, 63.13, 43.21, 29.92, 26.47, 24.01, 14.10
The following competition experiment revealed that 1a is more reactive than 1b:

Prepared using **General Procedure B**

1a (159.6 mg, 1.0 mmol), Pd(OAc)$_2$ (11.5 mg, 5 mol%), butyl vinyl ether (0.518 mL, 4 mmol, 4 equiv), NaTFA (136 mg, 1 mmol, 1 equiv), DMF (5 mL), Temp = 60 °C, time = 2 h. Purification: Flash chromatography on silica (pretreated with 1% Et$_3$N) eluting with hexane/EtOAc (50:10 to 10:90). Yield = 207.7 mg, 95% purity, mixture of rotamers, 88%. $^1$H NMR (400 MHz, C$_6$D$_6$, mixture of rotamers) δ 8.24 (1H), 6.29 to 6.26 (1H), 4.27 (1H), 3.96 (1H), 3.47 to 3.39 (4H), 1.85 to 1.80 (2H), 1.58 to 1.43 (2H), 1.31 to 1.25 (2H), 1.11 to 1.06
(2H), 0.83 to 0.77 (3H). $^{13}\text{C}$ NMR (101 MHz, C$_6$D$_6$) δ 161.59, 158.02, 139.14, 125.60, 84.09, 67.41, 43.13, 30.97, 28.95, 26.52, 24.04, 19.32, 13.60. HRMS calc for C$_{13}$H$_{21}$NO$_2$ 223.1573, found 223.1571.
Prepared using **General Procedure B**

**1a** (159.6 mg, 1.0 mmol), Pd(OAc)$_2$, (11.5 mg, 5 mol%), cycloheptene (0.467 mL, 4 mmol, 4 equiv), NaTFA (136 mg, 1 mmol, 1 equiv), DMF (5 mL), Temp = 80 °C, time = 1 h. Purification: Flash chromatography on silica (pretreated with 1% Et$_3$N) eluting with hexane/EtOAc (90:10). Yield = 173.3 mg, 79% combined.

Prepared using **General Procedure E**

**17** (22 mg, 0.10 mmol), 10% Pd/C (30 mg), EtOAc (5 mL) temp = 24 °C, time = 22 h. No purification required. Yield = 21.6 mg, 97% (mixture of rotamers). $^1$H NMR (400 MHz, C$_6$D$_6$) δ
8.08 (1H, minor), 7.90 (1H, major), 4.22 to 4.19 (1H, minor), 4.07 to 4.02 (1H, major), 2.77 to 0.78 (46H, both rotamers). $^{13}$C NMR (101 MHz, C$_6$D$_6$) $\delta$ 163.80, 163.45, 62.30, 57.41, 44.85, 44.64, 44.12, 40.45, 33.02, 32.82, 31.54, 31.27, 31.01, 30.98, 30.75, 30.46, 30.08, 29.27, 29.20, 29.09, 28.96, 28.13, 27.21, 27.09, 26.56, 26.42, 25.84, 25.36. HRMS calc for C$_{14}$H$_{25}$NO 223.1946, found 223.1950.
Homocoupling

To an oven-dried, septum-capped vial equipped with a stir bar, was added 1a (159.6 mg, 1.0 mmol), Pd(OAc)$_2$ (23 mg, 10 mol%), K$_2$CO$_3$ (277 mg, 2 mmol, 2 equiv), 1,4-dioxane (5 mL) under an argon or nitrogen atmosphere. The mixture was then stirred at 100 °C for 1 h. The mixture was quenched with water and extracted with CH$_2$Cl$_2$. The combined organic layers were concentrated to ~10 mL and dried for ~30 min with Na$_2$SO$_4$. It was filtered and evaporated to give the crude product (1:1 mixture of 19 & 20). Purification: Slow chromatography on silica eluting with hexane/EtOAc (50:50 to 30:70) affords 20 (16%) as a mixture of rotamers. Flushing the column with EtOAc affords 19 (16%) as a mixture of rotamers.

$^1$H NMR (400 MHz, CDCl$_3$, mixture of rotamers) δ 8.11 (1H, minor), 8.01 (1H, major), 5.98 to 5.73 (2H, both rotamers), 3.76 to 3.29 (4H, both), 2.25 to 2.07 (4H, both), 1.86 to 1.34 (8H,
both. $^{13}$C NMR (101 MHz, CDCl$_3$) δ 163.10, 162.35, 161.80, 141.27, 127.00, 126.62, 124.06, 48.55, 44.11, 43.91, 32.49, 28.85, 28.69, 27.26, 27.20, 26.98, 24.29, 24.18, 23.58. HRMS calc for C$_{14}$H$_{20}$N$_{2}$O$_{2}$ 248.1525, found 248.1524.
\( ^{13}C\) NMR (101 MHz, CDCl\( _3\)) δ 163.10, 162.35, 161.80, 141.27, 127.00, 126.02, 124.06, 48.55, 44.11, 43.91, 32.49, 28.85, 28.69, 27.26, 27.20, 26.90, 24.29, 24.18, 23.58
Obtained in 95% purity as a mixture of rotamers, 15%. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.27 to 8.01 (4H, both rotamers), 6.14 to 5.55 (8H, both rotamers), 3.64 to 3.37 (4H, both), 2.53 to 2.07 (4H, both), 1.93 to 1.35 (4H, both). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 162.34, 161.83, 140.70, 139.36, 135.34, 127.55, 122.32, 115.86, 44.73, 41.87, 41.48, 32.25, 32.01, 28.33, 27.67, 24.16. HRMS calc for C$_{14}$H$_{18}$N$_2$O$_2$ 246.1368, found 246.1365.
Supporting Information

$^1^C$ NMR (101 MHz, CDCl$_3$) $\delta$ 182.34, 161.83, 140.70, 139.36, 135.34, 127.55, 122.32, 115.86, 44.73, 41.87, 41.48, 32.25, 32.01, 28.33, 27.67, 24.10
5. Alkynylation of 1a

Prepared using **General Procedure C**

1a (160 mg, 1.0 mmol), phenyl acetylene (0.132 mL, 1.2 mmol), Temp = 24 °C, time = 30 min. Purification: Flash chromatography on silica (pretreated with 1% Et₃N) eluting with hexane/EtOAc (70:30). Yield = 198 mg, 88%. \(^1\)H NMR (400 MHz, C₆D₆) δ 8.94 (1H), 7.31 to 7.26 (2H), 6.96 to 6.90 (3H), 5.65 to 5.62 (1H), 3.52 to 3.50 (2H), 1.72 to 1.68 (2H), 1.42 to 1.36 (2H), 1.18 to 1.12 (2H). \(^{13}\)C NMR (101 MHz, C₆D₆) δ 161.89, 133.09, 132.26, 132.11, 130.09, 129.70, 129.03, 126.27, 123.04, 90.23, 87.05, 44.39, 28.44, 27.94, 24.59. HRMS calc for C₁₅H₁₅NO 225.1154, found 225.1153.
Prepared using **General Procedure C**

**1a** (160 mg, 1.0 mmol), trimethylsilyl acetylene (0.171 mL, 1.2 mmol), Temp = 24°C, time = 30 min. Purification: Flash chromatography on silica (pretreated with 1% Et<sub>3</sub>N) eluting with hexane/EtOAc (90:10). Yield = 201.5 mg, 91%.<sup>1</sup>H NMR (400 MHz, C<sub>6</sub>D<sub>6</sub>) δ 8.86 (1H), 5.63 to 5.60 (1H), 3.43 to 3.28 (2H), 1.69, 1.68 to 1.63 (2H), 1.38 to 1.28 (2H), 1.16 to 1.04 (2H), 0.19 to 0.16 (9H).<sup>13</sup>C NMR (101 MHz, C<sub>6</sub>D<sub>6</sub>) δ 161.70, 130.45, 126.31, 102.43, 95.25, 44.30, 28.32, 27.80, 24.51, 0.34, 0.05, −0.23. HRMS calc for C<sub>12</sub>H<sub>19</sub>NOSi 221.1236, found 221.1237.
$^{13}$C NMR (101 MHz, CD$_{3}$OD) δ 181.70, 130.45, 126.31, 102.43, 95.25, 44.30, 28.32, 27.80, 24.51, 0.34, 0.05, -0.23.
Prepared using **General Procedure C**

1a (160 mg, 1.0 mmol), 21c (0.141 mL, 1.2 mmol), Temp = 24 °C, time = 30 min. Purification: Flash chromatography on silica (pretreated with 1% Et₃N) eluting with hexane/EtOAc (80:20). Yield = 215.4 mg, 94%. ¹H NMR (400 MHz, C₆D₆) δ 8.98 (1H), 6.05 to 6.02 (1H), 5.61 to 5.57 (1H), 3.52 to 3.49 (2H), 2.04 to 1.99 (2H), 1.79 to 1.65 (4H), 1.42 to 1.12 (8H). ¹³C NMR (101 MHz, C₆D₆) δ 161.95, 136.36, 128.52, 126.76, 120.81, 92.23, 84.67, 44.35, 29.49, 28.46, 27.84, 26.18, 24.69, 22.75, 21.94. HRMS calc for C₁₅H₂₁NO 229.1967, found 229.2009.
Prepared using General Procedure C

1a (160 mg, 1.0 mmol), 21d (0.127 mL, 1.2 mmol), Temp = 24 °C, time = 30 min. Purification: Flash chromatography on silica (pretreated with 1% Et$_3$N) eluting with hexane/EtOAc (90:10).

Yield = 195 mg, 95% purity, mixture of rotamers, 83%. $^1$H NMR (400 MHz, C$_6$D$_6$) δ 8.85 (1H), 5.52 to 5.49 (1H), 3.51 to 3.48 (2H), 3.10 to 3.05 (2H), 2.04 to 2.00 (2H), 1.71 to 1.65 (2H), 1.42 to 1.36 (4H), 1.19 to 1.13 (2H). $^{13}$C NMR (101 MHz, C$_6$D$_6$) δ 161.92, 134.95, 126.32, 89.17, 79.26, 44.34, 43.81, 31.51, 28.39, 27.68, 24.67, 16.90. HRMS calc for C$_{12}$H$_{16}$ClNO 225.0922, found 225.0924.
Experiment: tbeng_20130707_18
Experiment Description: 
Sample: btk-A-076B-f44
Sample Description: 
Data File Name: C:\LabSolutions\Data\Project1\tbeng\btk-A-076B-f44.lcd
Sample Location: Plate Number: 1 - Position: 46
Run By: tbeng
Run Started: Sunday, July 07, 2013 10:12:21 AM
Run Finished: Sunday, July 07, 2013 10:19:27 AM
Method: 30_95_6mrn1mLminLowMW(125-625m/z)

**MS Chromatogram**

Group#1 Scan(+) ESI : TIC
Int

MW 225

RT=0.89
RT=1.18
RT=3.11
RT=5.09

**MS Spectrum**

Group#1 - MS Peak: 3, RT: 2.90 to 3.36 min
Int

MH^+ 226.10

228.10
227.10
267.15
268.20
269.15
289.05
451.20

**NMR Spectrum**

btk-A-076B-12.Lcd
A08-400 ZEO Proton starting parameters 6/11/03 RN

S-59
$^{13}$C NMR (101 MHz, C$_6$D$_6$) 31.61, 92.134, 95, 130.09, 128.63, 128.51, 126.39, 126.27, 126.15, 126.32, 89.17, 79.26, 44.34, 43.81, 31.51, 28.39, 27.68, 24.67, 16.90.
6. Arylation of 1a/b

Prepared using General Procedure D

From 1a (160 mg, 1.0 mmol), phenyl boronic acid (146 mg, 1.2 mmol), temp = 24 °C, time = 18 h. Purification: Flash chromatography on silica (pretreated with 1% Et₃N) eluting with hexane/EtOAc (70:30). Yield = 157 mg, 78%.

And also from 1b (204 mg, 1.0 mmol), phenyl boronic acid (146 mg, 1.2 mmol), temp = 24°C, time = 3 h. Yield = 161 mg, 99% purity, 80%. ¹H NMR (400 MHz, C₆D₆) δ 8.07 (1H), 7.11 to 7.01 (5H), 5.58 to 5.54 (1H), 3.58 to 3.55 (2H), 1.86 to 1.82 (2H), 1.59 to 1.53 (2H), 1.21 to 1.15 (2H). ¹³C NMR (101 MHz, C₆D₆) δ 161.77, 142.97, 138.48, 131.38, 128.56, 125.92, 123.34, 44.19, 28.68, 27.20, 24.07. HRMS calc for C₁₃H₁₅NO 201.1154, found 201.1156.
Prepared using **General Procedure D**

**1a** (160 mg, 1.0 mmol), 1-naphthyl boronic acid (206 mg, 1.2 mmol) Temp = 24 °C, time = 18 h. Purification: Flash chromatography on silica (pretreated with 1% Et₃N) eluting with hexane/EtOAc (70:30). Yield = 189 mg, 75%.

**1H NMR** (400 MHz, C₆D₆) δ 8.07 (1H), 7.91 to 7.86 (1H), 7.61 to 7.51 (2H), 7.31 to 7.09 (4H), 5.21 to 5.19 (1H), 3.92 to 3.86 (2H), 1.97 to 1.91 (2H), 1.67 to 1.61 (2H), 1.46 to 1.40 (2H).

**13C NMR** (101 MHz, C₆D₆) δ 161.68, 141.37, 136.50, 134.05, 131.24, 129.00, 128.64, 126.62, 125.95, 125.17, 124.90, 122.24, 119.16, 44.83, 27.43, 27.11, 24.25. HRMS calc for C₁₇H₁₇NO 251.1310, found 251.1315.
Prepared using **General Procedure B**

**1a** (160 mg, 1.0 mmol), 4-methoxyphenyl boronic acid (183 mg, 1.2 mmol) Temp = 24 °C, time = 18 h. Purification: Flash chromatography on silica (pretreated with 1% Et$_3$N) eluting with hexane/EtOAc (50:50). Yield = 203.5 mg, 91% purity, 80%. $^1$H NMR (400 MHz, C$_6$D$_6$) δ 8.17 (1H), 7.09 to 7.04 (2H), 6.70 to 6.65 (2H), 5.53 to 5.50 (1H), 3.62 to 3.60 (2H), 3.30 (3H), 1.91 to 1.87 (2H), 1.62 to 1.56 (2H), 1.25 to 1.19 (2H). $^{13}$C NMR (101 MHz, C$_6$D$_6$) δ 162.06, 159.90, 142.69, 130.98, 127.92, 121.14, 114.04, 54.51, 44.28, 28.72, 27.17, 24.23. HRMS calc for C$_{14}$H$_{17}$NO$_2$ 231.1256, found 231.1155.
Supporting Information

$^{13}$C NMR (101 kHz, CD$_2$Cl$_2$) δ 182.06, 159.90, 142.68, 130.68, 127.92, 121.14, 114.04, 64.61, 44.28, 28.72, 27.17, 24.28
Prepared using **General Procedure D**

1b (204 mg, 1.0 mmol), 4-chlorophenyl boronic acid (188 mg, 1.2 mmol) Temp = 24 °C, time = 18 h. Purification: Flash chromatography on silica (pretreated with 1% Et₃N) eluting with hexane/EtOAc (80:20). Yield = 165 mg, 95% purity, mixture of rotamers, 67%. ¹H NMR (400 MHz, C₆D₆) δ 7.90 (1H), 7.02 to 6.98 (2H), 6.78 to 6.74 (2H), 5.41 to 5.37 (1H), 3.52 to 3.44 (2H), 1.85 to 1.77 (2H), 1.56 to 1.50 (2H), 1.21 to 1.09 (2H). ¹³C NMR (101 MHz, C₆D₆) δ 162.59, 142.29, 137.45, 134.54, 129.97, 125.05, 117.71, 44.96, 29.68, 27.87, 23.87. HRMS calc for C₁₂H₁₃NOCl 235.0759, found 235.0761.
$^{13}$C NMR (101 MHz, C$_6$D$_6$) δ 162.59, 142.29, 137.45, 134.54, 129.97, 125.05, 117.71, 44.86, 29.68, 27.87, 23.87.
Prepared using General Procedure D

1b (204 mg, 1.0 mmol), 3-chlorophenyl boronic acid (188 mg, 1.2 mmol), temp = 24 °C, time = 18 h. Purification: Flash chromatography on silica (pretreated with 1% Et₃N) eluting with hexane/EtOAc (80:20). Yield = 141 mg, 60%.

\(^1\)H NMR (400 MHz, C₆D₆, mixture of rotamers) δ 7.69 (1H, major) & 7.59 (1H, minor), 7.27 to 6.69 (8H, both), 5.67 to 5.64 (1H, minor), 5.39 to 5.36 (1H, major), 3.34 to 2.64 (4H, both), 2.02 to 0.92 (12H, both).

\(^{13}\)C NMR (101 MHz, C₆D₆) δ 162.62, 141.40, 141.01, 139.84, 129.96, 125.11, 119.73, 116.07, 114.13, 44.43, 28.35, 27.04, 23.66. HRMS calc for C₁₂H₁₃NOCl 235.0759, found 235.0761.
Experiment: tbeng_20131123_03
Experiment Description: tkb-3-040A-2h
Sample: C:\LabSolutions\Data\Project1\tbeng\tkb-3-040A-2h.lcd
Sample Description: Plate Number: 1 - Position: 58
Data File Name: Run By:
Run Started: Saturday, November 23, 2013 5:41:58 PM
Run Finished: Saturday, November 23, 2013 5:53:45 PM
Method: TempPumpAlsoHW10min
Prepared using **General Procedure D**

**1b** (204 mg, 1.0 mmol), 2-chloro-3-pyridylboronic acid (189 mg, 1.2 mmol) Temp = 24 °C, time = 36 h. Purification: Flash chromatography on silica (pretreated with 1% Et$_3$N) eluting with hexane/EtOAc (80:20 to 30:70). Yield = 156 mg, 90% purity, mixture of rotamers, 55%. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.46 (1H), 7.53 to 7.51 (1H), 6.81 to 6.79 (1H), 5.97 to 5.94 (1H), 5.26 to 5.23 (1H), 3.26 to 3.23 (2H), 1.45 to 1.41 (2H), 1.23 to 1.19 (2H), 0.92 to 0.89 (2H). $^{13}$C NMR (101 MHz, C6D6) δ 161.08, 149.60, 141.7, 139.87, 132.78, 132.68, 126.33, 122.62, 45.63, 28.54, 28.10, 24.69. HRMS calc for C$_{12}$H$_{13}$N$_2$Cl 236.0716, found 236.0717.
\[ \text{\textsuperscript{13}C NMR (101 MHz, C, D6)} \text{ \{161.08, 149.60, 141.7, 139.87, 132.78, 132.68, 126.33, 122.62, 45.63, 28.54, 28.10, 24.69.} \]
7. Functionalization of 2-Substituted Eneformamides:

To 1a (160 mg, 1 mmol, 1.0 equiv) dissolved in THF (5 mL) and H₂O (5 mL), was added NIS (270 mg, 1.2 mmol, 1.2 equiv) at room temperature. After complete consumption of the eneformamide (as indicated by TLC and LCMS-monitoring; <10 min), the mixture was diluted with EtOAc (20 mL) and poured into a separating funnel. It was washed with sat. Na₂S₂O₃(aq) and then with brine. The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure to give the product as an oil. ¹H NMR (400 MHz, C₆D₆) δ 9.34 (1H), 4.56 to 4.54 (1H), 4.01 to 3.92 (1H), 3.29 to 3.23 (1H), 1.35 to 0.88 (5H), 0.79 to 0.68 (1H). ¹³C NMR (101 MHz, C₆D₆) δ 172.34, 161.87, 39.14, 32.04, 28.68, 27.53, 26.95. HRMS calc for C₉H₁₄I.NO₃ 266.9756, found 266.9588.
To **1a** (160 mg, 1 mmol, 1.0 equiv) dissolved in THF (5 mL) and ethylene glycol (0.34 mL, 6 mmol, 6 equiv), was added NIS (270 mg, 1.2 mmol, 1.2 equiv) at room temperature. After complete consumption of the eneformamide (as indicated by TLC and LCMS-monitoring; ~30 min), the mixture was diluted with EtOAc (20 mL) and poured into a separating funnel. It was washed with **sat. Na₂S₂O₃(aq)** and then with brine. The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure to give the product as an oil. ¹H NMR (400 MHz, C₆D₆) δ 8.61 (1H), 3.95 to 3.91 (1H), 3.65 to 3.58 (1H), 3.50 to 3.37 (1H), 3.20 to 3.00 (3H), 2.07 to 1.55 (3H), 1.37 to 1.12 (2H), 0.93 to 0.80 (1H). ¹³C NMR (101 MHz, C₆D₆) δ 161.80, 113.55, 65.97, 65.21, 37.85, 37.34, 36.68, 25.94, 25.62. HRMS calc for C₉H₁₄INO₃ 311.0012, found 311.0013.
$^{13}$C NMR (101 MHz, C$_6$D$_6$): 76.18, 113.55, 65.97, 65.21, 37.85, 37.34, 36.68, 25.94, 25.62
To 1a (160 mg, 1 mmol, 1.0 equiv) dissolved in THF (5 mL) and H₂O (5 mL), was added NIS (270 mg, 1.2 mmol, 1.2 equiv) at room temperature. After complete consumption of the 1a (as indicated by TLC and LCMS-monitoring; <10 min), 1 N HCl(aq) was added followed by stirring at room temperature for 1 h. The mixture was diluted with EtOAc (20 mL) and poured into a separating funnel. It was washed with sat Na₂S₂O₃(aq) and then with brine. The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure to give the product as an oil. ¹H NMR (400 MHz, C₆D₆) δ 7.71, 7.70, 7.66, 7.63, 4.22, 4.20, 4.12, 4.03, 4.01, 3.99, 3.98, 3.96, 3.95, 3.92, 3.32, 3.29, 3.27, 3.27, 2.84, 2.83, 2.83, 2.81, 2.80, 2.79, 2.78, 2.76, 2.75, 2.74, 2.19, 2.18, 2.16, 2.14, 1.77, 1.76, 1.75, 1.75, 1.73, 1.73, 1.72, 1.72, 1.71, 1.70, 1.70, 1.69, 1.68, 1.67, 1.66, 1.66, 1.65, 1.64, 1.64, 1.63, 1.63, 1.62, 1.61, 1.61, 1.60, 1.59, 1.59, 1.58, 1.57, 1.56, 1.56, 1.54, 1.01, 0.99, 0.98, 0.97, 0.97, 0.96, 0.95, 0.95, 0.95, 0.94, 0.94, 0.94, 0.93, 0.93, 0.92, 0.91, 0.91, 0.90, 0.90, 0.90, 0.89, 0.89, 0.88, 0.87, 0.87, 0.86, 0.85, 0.85, 0.85, 0.84, 0.84, 0.83, 0.82, 0.82, 0.81, 0.80, 0.79, 0.78, 0.77, 0.76, 0.75, 0.75, 0.74, 0.73, 0.73, 0.72, 0.71, 0.70, 0.70, 0.69, 0.69, 0.68, 0.67, 0.67, 0.66, 0.66, 0.65, 0.65, 0.64, 0.63, 0.62. ¹³C NMR (101 MHz, C₆D₆) δ 171.42, 164.64, 161.12, 52.12, 40.87, 37.39, 35.58, 35.46, 29.94, 28.42, 26.46, 25.88, 20.42, 20.16.
Prepared using **General Procedure E**

26 (40.3 mg, 0.20 mmol), 10% Pd/C (30 mg), EtOAc (5 mL) temp = 24 °C, time = 22 h. No purification required. Yield = 40 mg, 96%. $^1$H NMR (400 MHz, C$_6$D$_6$, mixture of rotamers) $\delta$ 8.02 & 7.97 (2H) 7.19 to 6.86 (10H), 5.44 to 5.40 (1H), 4.27 to 4.22 (1H), 3.99 to 3.94 (1H), 2.83 to 2.77 (1H), 2.60 to 2.51 (1H), 2.31 to 2.25 (2H), 1.94 to 1.86 (2H), 1.68 to 0.72 (10H). $^{13}$C NMR (101 MHz, C$_6$D$_6$) $\delta$ 163.09, 162.85, 143.37, 143.01, 128.58, 128.51, 128.30, 126.88, 126.72, 126.26, 125.47, 60.07, 55.70, 43.98, 40.13, 34.98, 34.31, 32.22, 29.74, 29.16, 28.31, 25.42, 24.97. HRMS calc for C$_{13}$H$_{17}$NO 203.1314, found 203.1316.
To 2-phenylazepane (20.3 mg, 0.1 mmol, 1.0 equiv) dissolved in freshly distilled THF (5 mL) was added \( n \)-BuLi (0.06 mL, 0.12 mmol, 2.0 M in hexanes, 1.2 equiv) at \(-78^\circ C\). After complete deprotection of the enamide (~30 min, as indicated by TLC and LCMS-monitoring), the mixture was quenched with \( H_2O \) and diluted with EtOAc. It was washed with \( sat. NaHCO_3 \) and then with brine. The organic layer was dried over \( Na_2SO_4 \) and concentrated under reduced pressure to give the crude product as an oil.

**Note:** No byproducts of benzylic lithiation were detected after trapping with \( D_2O \).
Prepared using **General Procedure E**

4 (45.4 mg, 0.20 mmol), 10% Pd/C (30 mg), EtOAc (5 mL) temp = 24 °C, time = 22 h. No purification required. Yield = 44 mg, 95%. HRMS calc for C\textsubscript{15}H\textsubscript{17}NO 231.1623, found 231.1626.
Prepared using General Procedure F

22 (56 mg, 0.25 mmol), NaBH₃CN (78 mg, 1.25 mmol, 5 equiv), TFA (0.29 mL, 2.5 mmol, 10 equiv), CH₂Cl₂ (10 mL). Time = 12 h; Purification: Flash chromatography on silica eluting with hexane/EtOAc (80:20 to 40:60). Yield = 42 mg, 74% (mixture of rotamers). ¹H NMR (400 MHz, C₆D₆) δ 8.06 (1H), 7.92 (1H), 7.43 to 7.30 (4H), 7.01 to 6.95 (6H), 5.69 to 5.55 (1H), 4.05 to 3.99 (2H), 3.03 to 2.81 (3H), 1.98 to 0.87 (16H). ¹³C NMR (101 MHz, C₆D₆) δ 162.71, 162.52, 131.69, 131.61, 128.33, 128.27, 128.22, 128.15, 128.12, 123.04, 122.68, 88.20, 88.14, 84.37, 83.34, 49.50, 43.88, 43.77, 40.08, 36.01, 34.03, 30.06, 28.56, 27.36, 27.21, 24.69, 24.10. HRMS calc for C₁₅H₁₃NO 227.1310, found 227.1309.
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