Supporting Information for:

*Iridium-catalyzed α-alkynylation of cyclic nonaromatic eneformamides: Application to the synthesis of azapolycyclic architectures*

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*Contents:*

1. General Experimental Information and Procedures .......................................................... S2
2. Alkynylation of eneformamides with terminal alkynes (Scheme 1) ................................. S3
3. Synthesis of saturated cyclic amines (Scheme 2) .......................................................... S55
4. Synthesis of bicyclic vinylogous lactam 4 (Scheme 3) .................................................... S59
5. Hexannulation of bicyclic vinylogous lactam 4 (Scheme 4) ............................................ S62
6. Synthesis of 2-azabicyclic carbonitriles (Scheme 5) ..................................................... S65
7. References ............................................................................................................................. S73
1. Experimental Section

All experiments involving air- and moisture-sensitive reagents were carried out under an inert atmosphere of nitrogen and using freshly distilled solvents. All alkynes, secondary amines, and electrophiles such as allyltrimethylsilane were newly purchased and used without further purification. Column chromatography was performed on silica gel (230-400 mesh). Thin-layer chromatography (TLC) was performed using Silicycle Siliaplate™ glass backed plates (250 μm thickness, 60 Å porosity, F-254 indicator) and visualized using UV (254 nm) or CAM, p-anisaldehyde, or KMnO₄ stain. All reported temperatures were internal to the reaction vessel. Unless otherwise indicated, ¹H, ¹³C, and DEPT-135, COSY 45, and HMQC (or HSQC) spectra were acquired using C₆D₆ or CDCl₃ as solvent at room temperature. Chemical shifts are quoted in parts per million (ppm). HRMS-EI⁺ data were obtained using either electron spray ionization (ESI) or electron impact (EI) techniques. High-resolution ESI was obtained on an LTQ-FT (ion trap; analyzed using Excalibur). High resolution EI was obtained on an Autospec (magnetic sector; analyzed using MassLynx).

**General Procedure A: Ir-catalyzed alkynylation**

To an oven-dried tube equipped with a stir bar was sequentially added the eneformamide (1 mmol), [IrCp*Cl₂]₂ (2 mol%), AgNTf₂ (10 mol%), NaOAc (20 mol%), Cs₂CO₃ (50 mol%), and AgOAc (2 mmol, 2 equiv). The terminal alkyne (2 mmol, 2 equiv), dissolved in 2-MeTHF/HFIP (4 mL/1 mL) was then introduced by means of a syringe. The resulting reaction mixture was stirred at 90 °C for the desired length of time (GC-MS and TLC monitoring). Upon completion, the contents were diluted with CH₂Cl₂ and filtered through Celite. The solvents were removed in vacuo and the crude product was directly subjected to flash chromatography on silica pretreated with trimethylamine.

**General Procedure B: Catalytic hydrogenation**

EtOAc (8 mL) was added to a flask containing 10% Pd/C (200 mg) at room temperature. The flask was degassed and placed under an inert atmosphere of nitrogen. A solution of the alkynyl enamide (0.5 mmol) in EtOAc (2 mL) 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 C:

Chemoselective reduction to alkenyl eneformamides: To an oven-dried 8 mL reaction vial was added PPh₃ (1.5 equiv), the alkynyl eneformamide (0.5 mmol, 1.0 equiv) dissolved in 2-MeTHF (4 mL) and water (1 mL). The solution was heated to 65 °C and stirred for 22 h. The solvents were removed under reduced pressure, toluene (10 mL) was added, and the solution dried over MgSO₄. The toluene was removed under reduced pressure, and cold Et₂O was added and the solution was filtered over silica. The Et₂O solvent was removed under reduced pressure, and the crude product was advanced to the next step without further purification.

Hexannulation: A vial was flame-dried, evacuated and flushed with nitrogen. A solution of tetracyanoethylene (128 mg, 1.0 mmol, 2 equiv) in 2-MeTHF (2 mL) was added to the vial followed by a solution of crude amino diene (0.5 mmol) in toluene (2 mL). The mixture was stirred for 12 h at room temperature. The crude mixture was concentrated under reduced pressure and purified by flash chromatography on silica (pretreated with 1% Et₃N), eluting with hexane/EtOAc.

![Chemoselective reduction to alkenyl eneformamides](image)

Prepared from 3a (1.0 mmol) and phenylacetylene using General Procedure A. Purification: Flash chromatography on silica (pretreated with 1% Et₃N) eluting with hexane/EtOAc (70:30). Yield = 171 mg, 81%. ¹H NMR (400 MHz, C₆D₆) δ 9.35 (1H), 7.28 to 7.21 (2H), 7.00 to 6.93 (3H), 5.28 to 5.25 (1H), 3.46 to 3.43 (2H), 1.60 to 1.52 (2H), 1.20 to 1.14 (2H). ¹³C NMR (101 MHz, C₆D₆) δ 160.5, 132.0, 129.3, 129.0, 122.7, 121.5, 118.0, 93.39, 83.0, 39.3, 23.5, 20.8. HRMS-EI⁺ (m/z): calc’d for C₁₄H₁₃NO 211.0997; found 211.0993.
Prepared from 1b (1.0 mmol) and phenylacetylene using **General Procedure A**. Purification: Flash chromatography on silica (pretreated with 1% Et₃N) eluting with hexane/EtOAc (70:30).

Yield = 189.5 mg, 84%. Data as previously reported by us.¹

Prepared from 3c (1.0 mmol) and phenylacetylene using **General Procedure A**. Purification: Flash chromatography on silica (pretreated with 1% Et₃N) eluting with hexane/EtOAc (90:10).

Yield = 244 mg, 79%. ¹H NMR (400 MHz, CDCl₃, mixture of rotamers) δ 8.29 & 8.15 (1H, s,s), 7.72 to 7.12 (5H, m), 5.88 to 5.72 (1H, m), 3.76 to 3.65 (2H, t), 2.60 to 2.14 (2H, m), 1.73 to 1.04 (16H, m). ¹³C NMR (101 MHz, CDCl₃) δ 163.1, 162.5, 136.9, 135.68, 135.6, 135.3, 135.2, 135.2, 134.0, 133.1, 132.5, 132.2, 132.1, 132.0, 131.9, 131.7, 131.6, 131.59, 130.3, 129.6, 129.1, 128.8, 128.6, 128.5, 128.4, 128.3, 128.1, 127.9, 127.7, 122.3, 121.8, 95.3, 88.9, 85.4, 85.2, 42.8, 41.3, 36.5, 34.6, 31.4, 29.7, 29.2, 28.6, 28.5, 28.4, 28.2, 28.1, 28.0, 27.9, 27.6, 26.9, 26.8, 26.7, 26.5, 26.4, 26.2, 26.0, 25.9, 25.8, 25.6, 25.5, 25.5, 25.4, 24.9, 24.8, 24.7, 24.5, 23.7, 23.6, 23.6, 23.4. **HRMS-El⁺ (m/z):** calc’d for C₂₁H₂₇NO 309.2093; found 309.2096.
Prepared from 3a (1.0 mmol) and p-methoxyphenylacetylene using **General Procedure A.**

Purification: Flash chromatography on silica (pretreated with 1% Et$_3$N) eluting with hexane/EtOAc (50:50). Yield = 200 mg, 83%. $^1$H NMR (400 MHz, Chloroform-d, mixture of rotamers) $\delta$ 9.06 (1H, s), 7.32 (2H, d), 6.75 (2H, d), 5.59 to 5.57 (1H, t), 3.71 to 3.52 (5H, m), 2.27 to 2.18 (2H, m), 1.88 to 1.73 (2H, m). $^{13}$C NMR (101 MHz, Chloroform-d) $\delta$ 161.3, 160.2, 134.1, 133.1, 128.5, 121.0, 118.0, 114.2, 113.9, 93.0, 80.5, 55.4, 39.1, 23.4, 20.7. **HRMS-EI$^+$ (m/z):** calc’d for C$_{15}$H$_{15}$NO$_2$ 241.1103; found 241.1107.
Prepared from 3b (1.0 mmol) and p-methoxyphenylacetylene using General Procedure A. Purification: Flash chromatography on silica (pretreated with 1% Et₃N) eluting with hexane/EtOAc (50:50). Yield = 247 mg, 97%. ¹H NMR (400 MHz, Benzene-d₆, rotamers) δ 8.94 to 8.37 (1H, s), 7.46 to 7.00 (2H, m), 6.67 to 6.58 (2H, m), 6.06 to 5.72 (1H, t), 3.58 to 3.55 (3H, s), 1.87 to 1.83 (2H, m), 1.51 to 1.38 (2H, m), 1.30 to 1.07 (2H, m). ¹³C NMR (101 MHz, Benzene-d₆) δ 161.4, 160.2, 135.4, 128.8, 125.9, 114.4, 89.9, 85.3, 54.6, 43.9, 28.0, 27.4, 24.1. HRMS-EI⁺ (m/z): calc’d for C₁₆H₁₇NO₂ 255.1259; found 255.1263.
Prepared from 3c (1.0 mmol) and p-methoxyphenylacetylene using **General Procedure A.** Purification: Flash chromatography on silica (pretreated with 1% Et$_3$N) eluting with hexane/EtOAc (50:50). Yield = 285 mg, 84%. $^1$H NMR (400 MHz, CDCl$_3$, mixture of rotamers) $\delta$ 8.31 & 8.13 (1H, s,s), 7.48 to 7.26 (2H, dd), 6.97 to 6.82 (2H, dd), 5.89 to 5.73 (1H, t), 3.86 to 3.66 (5H, m), 2.30 to 2.14 (2H, m), 1.73 to 1.22 (16H, m). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 163.2, 162.1, 160.9, 160.2, 160.1, 159.9, 139.7, 134.9, 134.8, 134.0, 133.2, 133.1, 133.1, 133.0, 132.9, 123.3, 123.3, 119.6, 114.2, 114.1, 114.1, 114.0, 113.9, 113.8, 113.2, 95.3, 88.9, 87.9, 83.9, 81.3, 81.2, 77.5, 77.1, 76.8, 73.0, 60.4, 55.4, 55.3, 47.7, 42.7, 41.2, 29.2, 28.5, 28.5, 28.4, 28.3, 28.2, 28.1, 27.9, 27.6, 26.8, 26.8, 26.7, 26.5, 26.2, 26.0, 25.7, 25.6, 25.5, 25.2, 24.9, 24.8, 24.4, 23.7, 23.6, 23.5, 23.3, 21.1. **HRMS-EI$^+$ (m/z):** calc’d for C$_{22}$H$_{29}$NO$_2$ 339.2198; found 339.2193.
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S-14
Prepared from 3a (1.0 mmol) and p-methylphenylacetylene using **General Procedure A**. Purification: Flash chromatography on silica (pretreated with 1% Et3N) eluting with hexane/EtOAc (50:50). Yield = 203 mg, 80%. **1H NMR** (400 MHz, Chloroform-d) δ 9.06 (1H, s), 7.32 (2H, d), 7.26 (2H, d), 5.59 to 5.57 (1H, t), 3.71 to 3.52 (2H, t), 2.34 to 2.18 (5H, m), 1.81 to 1.76 (2H, m). **13C NMR** (101 MHz, Chloroform-d) δ 161.2, 139.6, 133.1, 132.2, 128.6, 120.9, 118.8, 93.1, 81.1, 39.1, 23.4, 21.6, 20.7. **HRMS-ESI** (m/z): calc’d for C15H15NO 225.1154; found 225.1159.
Prepared from 3b (1.0 mmol) and p-methylphenylacetylene using General Procedure A. Purification: Flash chromatography on silica (pretreated with 1% Et₃N) eluting with hexane/EtOAc (50:50). Yield = 220 mg, 82%. ¹H NMR (400 MHz, Benzene-d6) δ 8.98 (1H, s), 7.89 to 7.21 (2H, d) 6.86 to 6.04 (2H, d), 5.73 to 5.70 (1H, s), 3.58 to 3.55 (2H, t), 2.03 to 1.99 (3H, s), 1.81 to 1.62 (2H, m), 1.49 to 1.37 (2H, t), 1.26 to 1.03 (2H, t). ¹³C NMR (101 MHz, Benzene-d6) δ 161.4, 138.8, 133.9, 129.3, 126.9, 119.5, 90.0, 86.0, 43.8, 27.9, 27.4, 24.1, 21.1. HRMS-El⁺ (m/z): calc’d for C₁₆H₁₇NO 239.1310; found 239.1314.
Prepared from 3c (1.0 mmol) and p-methylphenylacetylene using **General Procedure A.**

Purification: Flash chromatography on silica (pretreated with 1% Et₃N) eluting with hexane/EtOAc (50:50). Yield = 294 mg, 81%. ¹H NMR (400 MHz, CDCl₃, mixture of rotamers) δ 8.29 & 8.05, 7.74 to 7.26 (4H, m), 5.84 to 5.76 (1H, m), 3.84 to 3.66 (2H, m), 2.47 to 2.15 (5H, m), 1.73 to 1.17 (16H, m). ¹³C NMR (101 MHz, CDCl₃, mixture of rotamers) δ 163.2, 162.6, 162.1, 160.9, 140.0, 139.5, 139.3, 139.0, 138.7, 135.3, 135.2, 135.2, 134.9, 134.9, 132.4, 132.2, 132.1, 131.9, 131.8, 131.5, 131.5, 130.5, 130.3, 129.6, 129.3, 129.3, 129.2, 129.1, 128.9, 128.6, 128.5, 128.2, 128.0, 127.7, 127.7, 127.6, 123.2, 119.1, 119.1, 118.8, 114.2, 95.4, 89.1, 88.2, 84.7, 84.6, 81.9, 81.6, 77.5, 77.2, 76.8, 73.5, 55.3, 47.8, 43.3, 42.8, 41.2, 29.8, 29.2, 28.6, 28.5,

**HRMS-EI**<sup>+</sup> <sup>(m/z)</sup>: calc’d for C<sub>22</sub>H<sub>29</sub>NO 323.2249; found 323.2252.
Prepared from 3a (1.00 mmol) and triisopropylsilylethynylacetylene using **General Procedure A**. Purification: Flash chromatography on silica (pretreated with 1% Et$_3$N) eluting with hexane/EtOAc (90:10). Yield = 239 mg, 82%. $^1$H NMR (400 MHz, Chloroform-d) δ 8.99 (s, 1H), 5.54 (t, $J$ = 4.4 Hz, 1H), 3.66 – 3.58 (m, 2H), 2.17 (td, $J$ = 6.3, 4.1 Hz, 2H), 1.78 (m, 4H), 1.05 (m, 21H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 161.0, 120.8, 119.2, 98.8, 95.6, 38.9, 23.2, 20.5, 18.6, 11.4, 11.1, 10.8. **HRMS-ESI** ($m/z$): calc’d for C$_{17}$H$_{29}$NOSi 291.2018; found 291.2022.
Prepared from 3b (1.00 mmol) and triisopropylsilylethylene using General Procedure A. Purification: Flash chromatography on silica (pretreated with 1% Et$_3$N) eluting with hexane/EtOAc (90:10). Yield = 262 mg, 86%. $^1$H NMR (400 MHz, Chloroform-d) $\delta$ 8.59 (s, 1H), 5.84 (t, $J$ = 6.1 Hz, 1H), 3.62 (t, $J$ = 5.9 Hz, 2H), 2.19 (q, $J$ = 5.9 Hz, 2H), 1.72 (p, $J$ = 6.1 Hz, 2H), 1.58 (q, $J$ = 6.1 Hz, 2H), 0.99 (s, 21H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 162.25, 129.90, 125.42, 102.79, 91.85, 44.10, 27.67, 27.50, 24.08, 18.59, 10.87. HRMS-EI$^+$ (m/z): calc’d for C$_{18}$H$_{31}$NOSi 305.5370; found 305.5373.
Prepared from 3c (1.00 mmol) and triisopropylsilylacetylene using **General Procedure A**. Purification: Flash chromatography on silica (pretreated with 1% Et$_3$N) eluting with hexane/EtOAc (90:10). Yield = 316 mg, 81%. $^1$H NMR (400 MHz, Chloroform-$d$, mixture of rotamers) $\delta$ 7.99 (s, 1H), 5.72 (t, $J = 7.2$ Hz, 1H), 3.62 (dt, $J = 20.1$, 5.6 Hz, 2H), 2.20 (q, $J = 6.7$ Hz, 2H), 1.49-1.26 (m, 16H), 1.03 (s, 21H). $^{13}$C NMR (101 MHz, CDCl$_3$, rotamers) $\delta$ 163.00, 161.91, 160.70, 140.10, 135.70, 135.30, 130.83, 128.77, 123.38, 123.19, 118.27, 102.45, 102.30, 99.47, 98.14, 90.93, 89.72, 77.50, 77.18, 76.87, 68.05, 47.59, 42.46, 40.99, 38.75, 30.38, 29.16, 28.94, 28.56, 28.53, 28.43, 28.33, 28.26, 27.84, 27.79, 27.72, 27.66, 27.52, 26.82, 26.79, 26.62, 26.53, 26.13, 26.02, 25.76, 25.46, 25.44, 25.32, 24.99, 24.74, 24.41, 23.76, 23.67, 23.57, 23.45, 23.00, 18.60, 18.59, 14.06, 11.49, 11.21, 11.19, 10.93. **HRMS-EL** ($m/z$): calc’d for C$_{24}$H$_{43}$NOSi 389.3114; found 389.3110.
Prepared from 3a (1.00 mmol) and trimethylsilylacetylene (2 mmol, 2 equiv) using General Procedure B. Purification: Flash chromatography on silica (pretreated with 1% Et$_3$N) eluting with hexane/EtOAc (90:10). Yield = 178 mg, 86%. $^1$H NMR (400 MHz, C$_6$D$_6$) $\delta$ 9.32 (s, 1H), 5.24 to 5.22 (t, 1H), 3.39 to 3.36 (t, 2H), 1.54 to 1.47 (m, 2H), 1.15 to 1.09 (m, 2H), 0.09 (s, 9H). $^{13}$C NMR (101 MHz, C$_6$D$_6$) $\delta$ 160.4, 121.6, 118.6, 98.9, 98.4, 39.2, 23.4, 20.8, 0.1. HRMS-EI$^+$ (m/z): calc’d for C$_{11}$H$_{17}$NOSi 207.1079; found 207.1083.
Prepared from 3a and 1-ethynylcyclohexene (0.24 mL, 2 mmol, 2 equiv) using General Procedure A. Purification: Flash chromatography on silica (pretreated with 1% Et₃N) eluting with hexane/EtOAc (80:20). Yield = 172 mg, 80%. H NMR (400 MHz, C₆D₆) δ 9.39 (1H, s), 6.01 to 5.96 (1H, t), 5.22 to 5.20 (1H, t), 3.46 to 3.43 (2H, t), 1.99 to 1.94 (2H, m), 1.78 to 1.73 (2H, m), 1.57 to 1.46 (2H, q), 1.35 to 1.22 (4H, m), 1.17 to 1.11 (2H, m). C NMR (101 MHz, C₆D₆) δ 160.6, 136.6, 121.9, 120.6, 116.8, 95.3, 80.6, 39.3, 29.3, 26.2, 23.5, 22.7, 21.9, 20.9. HRMS (m/z): calc’d for C₁₄H₁₇NO 215.1310; found 215.1313.
Prepared from 3b and 1-ethynylcyclohexene (0.24 mL, 2 mmol, 2 equiv) using **General Procedure A**. Purification: Flash chromatography on silica (pretreated with 1% Et$_3$N) eluting with hexane/EtOAc (80:20). Yield = 208 mg, 84%. Data as previously reported by us.$^1$

Prepared from 3c (1 mmol) and 1-ethynylcyclohexene (0.24 mL, 2 mmol, 2 equiv) using **General Procedure A**. Purification: Flash chromatography on silica (pretreated with 1% Et$_3$N) eluting with hexane/EtOAc (80:20). Yield = 241 mg, 77%. **HRMS-EI$^+$ (m/z):** calc’d for C$_{21}$H$_{31}$NO 313.2406; found 313.2410.

Prepared from 3a (1.0 mmol) and 1-ethynylcyclopropane (2 mmol, 2 equiv) using **General Procedure A**. Purification: Flash chromatography on silica (pretreated with 1% Et$_3$N) eluting with hexane/EtOAc (80:20). Yield = 156 mg, 79%. 1H NMR (400 MHz, Benzene-d$_6$) $\delta$ 9.45 to 9.12 (1H, s), 5.42 to 5.03 (1H, t), 3.64 to 3.43 (2H, t), 1.77 to 1.52 (2H, m), 1.48 to 0.22 (7H, m). 13C NMR (101 MHz, Chloroform-d) $\delta$ 161.6, 121.2, 117.6, 97.8, 68.7, 39.4, 23.5, 21.1, 9.1, 0.3. **HRMS-EI$^+$ (m/z):** calc’d for C$_{11}$H$_{13}$NO 175.0997; found 175.0993.
Prepared from 3b (1.0 mmol) and 1-ethynylcyclopropane (2 mmol, 2 equiv) using General Procedure A. Purification: Flash chromatography on silica (pretreated with 1% Et$_3$N) eluting with hexane/EtOAc (80:20). Yield = 153 mg, 81%. 1H NMR (400 MHz, Benzene-$d_6$) δ 8.90 to 8.85 (1H, s), 5.60 to 5.37 (1H, t), 3.54 to 3.29 (2H, t), 2.13 to 1.92 (2H, m), 1.77 to 1.41 (2H, m), 1.24 to 1.18 (2H, m), 1.08 to 1.01 (2H, m), 0.85 to 0.26 (4H, m). 13C NMR (101 MHz, Benzene-$d_6$) δ 161.69, 93.78, 73.06, 43.73, 27.87, 27.13, 23.50, 8.43. HRMS-ET$^+$ ($m/z$): calc’d for C$_{12}$H$_{15}$NO 189.1154; found 189.1151.
Prepared from 3c (1 mmol) and 1-ethylcyclopropane (2 mmol, 2 equiv) using **General Procedure A.** Purification: Flash chromatography on silica (pretreated with 1% Et$_3$N) eluting with hexane/EtOAc (80:20). Yield = 208 mg, 76%. **$^1$H NMR** (400 MHz, CDCl$_3$, mixture of rotamers) $\delta$ 8.16 & 7.96 (1H, s,s), 5.80 to 5.57 (1H, t), 3.66 to 3.41 (2H, t), 2.36 to 2.02 (2H, m), 1.73 to 0.98 (17H, m), 0.93 to 0.68 (4H, m). **$^{13}$C NMR** (101 MHz, CDCl$_3$) $\delta$ 163.1, 162.0, 138.8, 134.0, 123.2, 123.1, 99.9, 93.0, 77.4, 77.1, 76.8, 71.7, 68.9, 47.5, 43.1, 42.5, 40.9, 28.8, 28.5, 28.4, 28.2, 28.0, 28.0, 27.9, 27.7, 27.6, 27.5, 26.8, 26.6, 26.4, 26.1, 26.0, 25.9, 25.8, 25.7, 25.6, 25.4, 25.1, 24.9, 24.8, 24.6, 24.4, 23.7, 23.6, 23.5, 23.3, 9.8, 9.6, 9.3, 9.0, 8.7, 8.6, 8.5. **HRMS-EL$^+$ ($m/z$):** calc’d for C$_{18}$H$_{27}$NO 273.2093; found 273.2090.
Prepared from 3a (1.0 mmol) and 5-chloro-1-pentyne (0.21 mL, 2.0 mmol, 2 equiv) using **General Procedure A**. Purification: Flash chromatography on silica (pretreated with 1% Et₃N) eluting with hexane/EtOAc (70:30). Yield = 200 mg, 95%. ¹H NMR (400 MHz, C₆D₆) δ 9.25 (1H, s), 5.14 to 5.11 (1H, t), 3.45 to 3.42 (2H, t), 3.08 to 3.05 (2H, t), 2.02 to 1.98 (2H, t), 1.57 to 1.33 (4H, m), 1.18 to 1.12 (2H, m). ¹³C NMR (101 MHz, C₆D₆) δ 160.5, 121.5, 116.9, 92.5, 75.2, 44.0, 39.3, 31.4, 23.4, 21.0, 16.9. **HRMS-EI⁺** (m/z): calc’d for C₁₁H₁₄ClNO 211.0764; found 211.0769.
$^{13}$C-NMR (161 MHz, CD$_2$D$_6$) δ 180.57, 128.62, 128.38, 128.14, 121.48, 115.94, 52.56, 75.27, 44.03, 39.33, 21.46, 25.49, 21.03, 16.96.
Prepared from 3b (1.0 mmol) and 5-chloro-1-pentyne (0.21 mL, 2.0 mmol) using **General Procedure A.** Purification: Flash chromatography on silica (pretreated with 1% Et₃N) eluting with hexane/EtOAc (90:10). Yield = 203 mg, 90%. Data as previously reported by us.¹

Prepared from 3c (1.0 mmol) and 5-chloro-1-pentyne (0.21 mL, 2.0 mmol) using **General Procedure A.** Purification: Flash chromatography on silica (pretreated with 1% Et₃N) eluting with hexane/EtOAc (90:10). Yield = 281 mg, 91%. ¹H NMR (400 MHz, CDCl₃, mixture of rotamers) δ 8.18 & 7.96 (1H, s,s), 5.85 to 5.77 (1H, t), 3.77 to 3.55 (4H, m), 2.68 to 1.18 (22H, m). ¹³C NMR (101 MHz, CDCl₃, mixture of rotamers) δ 163.1, 162.0, 160.8, 139.2, 135.2, 122.9, 122.6, 94.4, 87.8, 86.8, 77.5, 77.5, 77.4, 77.1, 76.8, 75.0, 47.6, 43.6, 43.6, 43.4, 42.5, 41.0, 31.2, 31.1, 31.0, 28.9, 28.5, 28.4, 28.4, 28.2, 28.1, 28.0, 27.8, 27.6, 27.5, 26.8, 26.7, 26.6, 26.4, 26.3, 26.0, 25.9, 25.7, 25.5, 25.4, 25.2, 24.8, 24.8, 24.6, 24.4, 23.7, 23.6, 23.5, 23.3, 16.8, 16.6, 16.6. **HRMS-ESI⁺ (m/z):** calc’d for C₁₈H₂₈ClNO 309.1859; found 309.1862.
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Prepared from 3a (1.0 mmol) and 6-chloro-1-hexyne (2.0 mmol, 2 equiv) using **General Procedure A**. Purification: Flash chromatography on silica (pretreated with 1% Et₃N) eluting with hexane/EtOAc (90:10). Yield = 196 mg, 87%. ¹H NMR (400 MHz, Benzene-d₆) δ 9.30 to 8.91 (1H, s), 5.22 to 4.71 (1H, t), 3.50 to 3.37 (2H, t), 3.09 to 3.06 (2H, t), 2.01 to 1.88 (2H, m), 1.70 to 1.61 (2H, m), 1.51 to 1.42 (2H, m), 1.32 to 1.20 (2H, m), 1.12 to 0.94 (4H, m). ¹³C NMR (101 MHz, Benzene-d₆) δ 160.1, 121.1, 116.0, 108.3, 93.1, 74.4, 44.0, 38.8, 31.5, 25.4, 23.4, 20.8, 18.2. **HRMS-ESI⁺ (m/z):** calc’d for C₁₂H₁₆ClNO 225.0920; found 225.0923.
Prepared from 3b (160 mg, 1.0 mmol) and 6-chloro-1-hexyne (2.0 mmol, 2 equiv) using General Procedure A. Purification: Flash chromatography on silica (pretreated with 1% Et₃N) eluting with hexane/EtOAc (90:10). Yield = 220 mg, 92%. ¹H NMR (400 MHz, Chloroform-d) δ 8.56 to 8.07 (1H, s), 5.80 to 5.77 (1H, t), 3.80 to 3.41 (2H, t), 2.68 to 2.19 (4H, m), 1.93 to 1.50 (10H, m). ¹³C NMR (101 MHz, Chloroform-d) δ 162.5, 128.8, 125.4, 89.9, 8.1, 44.5, 31.6, 28.7, 27.8, 25.6, 23.6, 18.6. HRMS-ESI⁺ (m/z): calc’d for C₁₃H₁₈ClNO 239.1077; found 239.1074.
Prepared from 3c (243 mg, 1.0 mmol) and 6-chloro-1-hexyne (2.0 mmol, 2 equiv) using General Procedure A. Purification: Flash chromatography on silica (pretreated with 1% Et₃N) eluting with hexane/EtOAc (90:10). Yield = 300 mg, 93%. ¹H NMR (400 MHz, Benzene-d₆, mixture of rotamers) δ 8.30 to 7.87 (1H, s), 5.53 to 5.15 (1H, t), 3.88 to 3.74 (2H, t), 3.24 to 3.06 (2H, m), 2.29 to 0.97 (24H, m). ¹³C NMR (101 MHz, Benzene-d₆) δ 162.2, 161.1, 138.6, 138.2, 133.4, 123.5, 123.3, 95.3, 88.7, 77.7, 75.2, 44.1, 44.0, 42.3, 31.6, 28.5, 27.7, 26.7, 25.8, 25.6, 24.8, 24.5, 23.7, 23.6, 23.4, 18.4. HRMS-ESI⁺ (m/z): calc’d for C₁₉H₃₀ClNO 323.2016; found 323.2020.
Electronic Supplementary Information for New Journal of Chemistry; Beng and Wanjiku

S-50
Prepared from 3b (1.0 mmol) and 4-pentyn-1-ol (2.0 mmol, 2 equiv) using **General Procedure** A. Purification: Flash chromatography on silica (pretreated with 1% Et$_3$N) eluting with hexane/EtOAc (20:80). Yield = 178 mg, 86%. $^1$H NMR (400 MHz, Chloroform-$d$, rotamers) $\delta$ 8.33 (s, 1H), 5.76 (t, $J = 6.1$ Hz, 1H), 3.58 – 3.49 (m, 4H), 3.15 (s, 1H), 2.30 (t, $J = 7.0$ Hz, 2H), 2.09 (p, $J = 6.8, 6.4$ Hz, 2H), 1.58 – 1.49 (m, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 161.61, 134.11, 128.65, 125.42, 90.46, 77.52, 61.08, 48.49, 44.22, 32.18, 31.17, 31.14, 30.96, 27.74, 27.32, 24.15, 23.52, 15.90, 15.76, 15.73. **HRMS-ESI** ($m/z$): calc’d for C$_{12}$H$_{17}$N O$_2$ 207.1259; found 207.1263.
Prepared from 3b (1.0 mmol) and 5-hexyn-1-ol (2.0 mmol, 2 equiv) using **General Procedure A.** Purification: Flash chromatography on silica (pretreated with 1% Et₃N) eluting with hexane/EtOAc (20:80). Yield = 197 mg, 89%. $^1$H NMR (400 MHz, Chloroform-$d$, mixture of rotamers) $\delta$ 8.22 (s, 1H), 5.56 (t, $J = 6.1$ Hz, 1H), 3.58 (s, 1H), 3.44 – 3.33 (m, 4H), 2.15 – 1.95 (m, 4H), 1.42 – 1.26 (m, 8H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 162.63, 161.50, 128.64, 128.51, 128.45, 125.33, 119.61, 90.80, 77.42, 65.56, 62.12, 61.76, 61.72, 61.57, 61.55, 44.14, 31.74, 31.62, 27.63, 27.22, 24.75, 24.69, 24.07, 18.90. **HRMS-ESI** $^{+}$ ($m/z$): calc’d for C$_{13}$H$_{19}$NO$_2$ 221.1416; found 221.1419.
Prepared using **General Procedure B.** Yield = 119 mg, 97%. $^1$H NMR (400 MHz, Chloroform-$d$, mixture of rotamers) $\delta$ 8.20 & 7.98 (s, 1H), 7.17 – 7.01 (m, 4H), 4.36 – 3.98 (m, 1H), 3.47 – 3.34 (m, 1H), 2.72 – 2.43 (m, 3H), 2.31 (s, 3H), 2.15 (dt, $J = 14.7, 7.4$ Hz, 1H), 1.85 – 1.66 (m, 6H), 1.30 – 1.11 (m, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 164.3, 163.6, 138.8, 137.7, 135.7, 135.3, 129.3, 129.1, 128.2, 57.6, 52.3, 44.0, 39.6, 36.7, 36.6, 34.8, 33.3, 32.3, 32.1, 31.8, 30.2, 29.5, 27.6, 24.9, 24.6, 21.0. HRMS-El$^+$ ($m/z$): calc’d for C$_{19}$H$_{23}$NO 245.1780; found 245.1782.
Prepared using **General Procedure B**. Yield = 138 mg, 93%. $^1$H NMR (400 MHz, Chloroform-$d$, mixture of rotamers) $\delta$ 7.82 & 7.80 (s, 1H), 4.11 & 3.94 (dt, $J = 13.7, 3.2$ Hz, 1H), 3.18 – 3.09 (m, 1H), 2.86 – 2.13 (m, 1H), 1.49 – 1.38 (m, 8H), 0.87 – 0.72 (m, 21H), 0.38 – 0.08 (m, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 161.4, 161.3, 58.0, 50.4, 42.6, 36.1, 29.7, 27.4, 26.7, 25.2, 24.9, 23.9, 20.1, 19.7, 18.9, 18.8, 18.7, 18.6, 11.0, 10.9, 10.8, 10.7, 5.9, 5.5. **HRMS-El$^+$** ($m/z$): calc’d for C$_{17}$H$_{35}$NOSi 297.2488; found 297.2491.
Electronic Supplementary Information for New Journal of Chemistry; Beng and Wanjiku
**N-formyl reduction of 2j:** To 2j (291 mg, 1.0 mmol) dissolved in freshly distilled CH₂Cl₂ (10 mL) was added NaBH₃CN (315 mg, 5 mmol, 5 equiv) slowly under nitrogen at 0 °C. TFA (1.14 g, 10 mmol, 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.

**Desilylation:** To all of reduced 2j in THF (10.0 mL) were added CF₃CO₂H (310 mg, 2.7 mmol) and a 1.0 M solution of TBAF (4.0 mL, 4.0 mmol) in THF successively at 0 °C. The resulting reaction mixture was stirred at 0 °C for 3 h. The reaction was quenched with water, and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with water and
brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel to give corresponding desilylated products.

**Hydroboration-oxidation**: To a solution of the crude alkynyl piperidine (1.0 equiv) in freshly distilled CH₂Cl₂ (4 mL) at –78 °C was added dropwise a 2 M solution of BH₃·SMe₂ in THF (500 µL, 1 equiv). After a few minutes, the mixture was warmed to room temperature and stirring was continued for 6 h. It was then cooled to 0 °C and a few drops of 10% NaOH (aq) were added slowly followed by 0.5 mL of 30% H₂O₂. The mixture was returned to room temperature and stirred for 3 h. Water was added and the mixture was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure to afford crude aldehyde as an oil.

**Deformylation**: 6% HCl (1.5 mL) was added to the solution of N-formylated aldehyde (50 mg, 0.18 mmol) in MeOH (10 mL) and the resulting mixture was stirred at room temperature for 18 h. After completion of reaction (monitored by TLC), H₂O was added and the whole mixture was neutralized with aqueous NaHCO₃ and extracted with CH₂Cl₂. The combined organic phase was washed with brine, dried over Na₂SO₄ and evaporated under reduce pressure to give the free piperidinal as an oil.

**Acylation**: The piperidinal was dissolved in dichloromethane (5 mL) and triethylamine (1.0 mL, 7.10 mmol) was added drop-wise at 0 °C, followed by the drop-wise addition of cyanoacetylchloride (727 mg, 7.10 mmol) as a solution in dichloromethane (2 mL). The resulting red solution was stirred at the same temperature for 2 h and then warmed to room temperature for 3 h, at which time saturated aqueous NaHCO₃ (10 mL) was added and volatiles removed in vacuo. The resulting aqueous solution was extracted with ethyl acetate (3 x 10 mL) and the combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. The resulting acylated piperidinal was obtained as a red oil.

**Knoevenagel condensation**: To the acylated piperidinal was added a 20 mM solution of HCl/CH₂Cl₂ (prepared from AcCl/MeOH) and stirring was continued for 12 h at room temperature (TLC monitoring). The solution was diluted with DCM and transferred to a separatory funnel. Sat. aqueous NH₄Cl was added and the layers were separated. The aqueous layer was extracted with DCM and the combined layers were washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo to obtain the bicycle as an oil. ¹H NMR (400 MHz, C₆D₆) δ 6.57 to 6.54 (t, 1H), 4.42 to 4.38 (m, 1H), 2.76 to 2.67 (m, 1H), 2.28 to 2.18 (m, 2H), 1.88, to 1.80 (m, 2H), 1.55
to 0.78 (m, 5H). $^{13}$C NMR (101 MHz, C$_6$D6) $\delta$ 159.15, 152.19, 115.27, 112.15, 53.31, 43.11, 32.60, 30.68, 24.22, 23.22. **HRMS-EI** ($m/z$): calc'd for C$_{10}$H$_{12}$N$_2$O 176.0950; found 176.0955.
A 10 mL microwave vial was flame-dried, evacuated and flushed with nitrogen. A solution of dienophile 4 (176 mg, 1.0 mmol) in toluene (2 mL) was added to the vial under a nitrogen atmosphere followed by a solution of diene 12 (456 mg, 2 mmol) in toluene (2 mL). The mixture was heated to 150 °C under microwave irradiation for 2 h. It was then cooled to room temperature and the toluene was azeotroped off. Purification by flash chromatography on silica (pretreated with 1% Et\textsubscript{3}N) eluting with hexane/EtOAc (80:20) afforded tricycle 13 in 79% yield and >95:5 dr.

Note: It is critical to have absolutely pure starting materials as any minor impurities simply lead to decomposition of the diene. \(^1\)H NMR (400 MHz, Benzene-\textit{d}_6) \(\delta\) 5.66 (ddd, \(J = 10.4, 4.3, 2.9\) Hz, 1H), 5.37 (ddt, \(J = 10.4, 2.0, 1.0\) Hz, 1H), 4.89 (dp, \(J = 13.1, 1.9\) Hz, 1H), 4.12 (ddt, \(J = 4.1, 1.9, 0.9\) Hz, 1H), 3.45 (dd, \(J = 9.9, 6.3\) Hz, 1H), 3.31 (t, \(J = 9.8\) Hz, 1H), 3.09 – 2.84 (m, 5H), 2.78 – 2.62 (m, 1H), 2.29 – 2.04 (m, 3H), 1.45 – 0.87 (m, 24H), 0.02 (s.s, 6H). \(^{13}\)C NMR (101 MHz, C\textsubscript{6}D\textsubscript{6}) \(\delta\) 161.9, 127.4, 123.7, 118.9, 76.7, 62.9, 59.1, 55.3, 49.1, 43.9, 38.0, 33.0, 31.0, 25.6, 25.3, 24.9, 23.3, 17.9, -5.7. **HRMS-\textit{EI}** (m/z): calc’d for C\textsubscript{22}H\textsubscript{36}N\textsubscript{2}O\textsubscript{3}Si 404.2495; found 404.2491.
Prepared using General Procedure C. Yield = 176 mg, 95%. $^1$H NMR (400 MHz, Chloroform-d) δ 8.49 (s, 1H), 7.35 – 7.25 (m, 4H), 5.69 (d, $J = 3.3$ Hz, 1H), 4.49 (d, $J = 3.3$ Hz, 1H), 4.32 (dd, $J = 15.1$, 4.2 Hz, 1H), 3.30 (d, $J = 10.5$ Hz, 1H), 3.03 (t, $J = 12.5$ Hz, 1H), 2.44 (dd, $J = 13.9$, 4.8 Hz, 1H), 2.38 (s, 3H), 2.21 (q, $J = 6.3$ Hz, 1H), 1.98 (d, $J = 33.5$ Hz, 2H), 1.66 (q, $J = 11.5$, 11.1 Hz, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 160.7, 140.9, 137.6, 130.1, 129.9, 129.3, 113.2, 113.1, 111.5, 111.3, 109.7, 109.4, 46.9, 44.7, 43.9, 31.1, 28.6, 26.7, 21.3. HRMS-ESI$^+$ (m/z): calc’d for C$_{22}$H$_{19}$N$_5$O 369.1590; found 369.1593.
Prepared using **General Procedure C**. Yield = 139 mg, 87%. $^1$H NMR (400 MHz, Chloroform-$d$) δ 8.18 (s, 1H), 5.35 (d, $J$ = 2.2 Hz, 1H), 4.15 (dd, $J$ = 14.6, 3.8 Hz, 1H), 3.14 – 3.04 (m, 1H), 2.62 – 2.55 (m, 1H), 2.25 (ddd, $J$ = 10.1, 3.6, 2.1 Hz, 1H), 2.24 – 2.02 (m, 2H), 1.71 – 1.45 (m, 4H), 0.98 (dddd, $J$ = 10.3, 7.7, 4.9, 2.7 Hz, 1H), 0.92 – 0.80 (m, 1H), 0.80 – 0.65 (m, 2H), 0.41 – 0.20 (m, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 160.6, 136.3, 114.8, 111.2, 111.1, 109.3, 108.8, 46.4, 45.9, 44.6, 44.2, 30.4, 29.7, 28.9, 26.9, 13.3, 5.6, 3.5. **HRMS-EI** $(m/z)$: calc’d for C$_{18}$H$_{17}$N$_5$O 319.1433; found 319.1437.
Prepared using **General Procedure C**. Yield = 164 mg, 92%. $^1$H NMR (400 MHz, Chloroform-$d$) δ 8.11 (s, 1H), 7.42 – 7.25 (m, 4H), 5.58 (d, $J = 2.5$ Hz, 1H), 4.46 – 4.36 (m, 1H), 4.32 – 4.24 (m, 1H), 3.00 (ddt, $J = 12.8$, 4.7, 2.3 Hz, 1H), 2.83 – 2.64 (m, 1H), 2.38 (dt, $J = 12.4$, 4.2 Hz, 1H), 2.31 – 2.07 (m, 4H), 1.99 (dp, $J = 13.6$, 3.4 Hz, 1H), 1.68 (ddt, $J = 17.1$, 12.8, 6.5 Hz, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 159.7, 141.0, 136.3, 130.2, 130.1, 130.0, 129.2, 114.4, 111.3, 110.9, 109.8, 108.9, 46.0, 43.7, 43.5, 41.5, 41.4, 41.3, 40.7, 29.4, 24.1, 21.4. **HRMS-ESI** ($m/z$): calc’d for C$_{21}$H$_{17}$N$_5$O 355.1433; found 355.1430.
References