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Note

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CsF-Mediated *In-situ* Desilylation of TMS-Alkynes for Sonogashira Reaction

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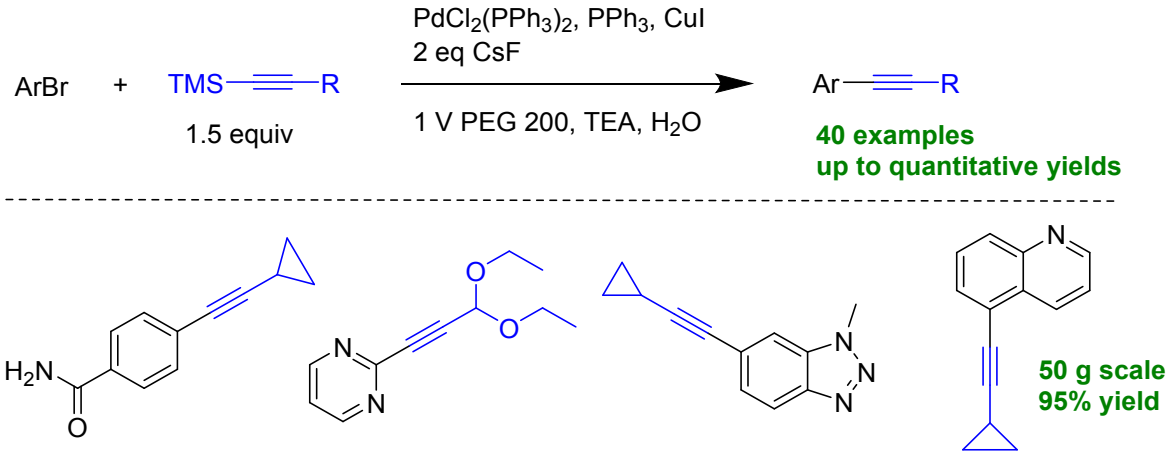
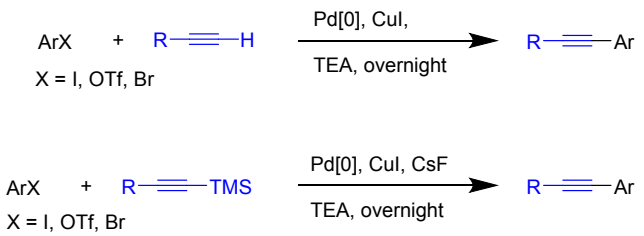
Supporting Information Placeholder



ABSTRACT: A practical, mild set of conditions for the Sonogashira reaction utilizing CsF-mediated *in-situ* TMS-alkyne desilylation followed by Sonogashira coupling has been developed for the synthesis of a variety of alkynyl benzenes and heteroarenes in good to excellent yields. This methodology demonstrates excellent functional group tolerance, and simple purification which allows large-scale industrial application. This one-pot protocol enables a high-yielding Sonogashira coupling with volatile alkynes by avoiding challenging isolation of free alkynes.

The Sonogashira coupling reaction between aryl or alkenyl halides or triflates and terminal alkynes has become one of the most widely used methods in the preparation of conjugated enynes and alkynyl arenes (Scheme 1, top).[1]

Scheme 1. Sonogashira Coupling Reaction (top) and Sila-Sonogashira Reaction investigated in this work (bottom).



One significant drawback associated with the Sonogashira reaction is that low molecular weight alkynes are often highly volatile or gaseous and therefore difficult to handle and isolate. In addition, the Cu-catalyzed homocoupling of terminal alkynes can consume free alkyne in the reaction mixture leading to reduced yields of product.[2] Recently, a number of researchers have addressed these problems by performing an *in-situ* deprotection of trimethylsilyl-alkynes which are then coupled in what has become known as the "Sila-Sonogashira" reaction (Scheme 1). This protocol offers a number of key advantages over the conventional Sonogashira reaction. The TMS-alkynes are readily available both from commercial sources and from literature procedures.[3] It is postulated that the *in-situ* deprotection of TMS-alkynes releases free alkyne for the Sonogashira reaction at a concentration that is sufficiently low to prevent homocoupling of alkyne thereby increasing reaction yields.[4]

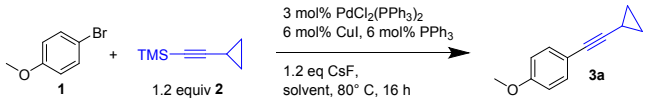
Current methods for *in-situ* deprotection in the Sila-Sonogashira reaction include base-mediated deprotection,[5] catalytic CuCl-mediated transmetallation/deprotecton,[6] tetrabutylammomium chloride deprotection followed by Ag_2CO_3-promoted direct coupling,[7] and tetrabutylammonium fluoride

(TBAF)-mediated deprotection.[8,9] All these examples are limited to active vinyl triflates or aryl iodides. The TBAF-mediated deprotection can lead to difficulties in removal of the tetrabutylammonium ion during purification.[10]

CsF-mediated deprotection has precedence in the literature as a promising method for TMS-group deprotection.[11] We envisioned that the use of CsF as the deprotecting reagent in the Sila-Sonogashira reaction may offer similar efficacy to TBAF. In addition to being more cost effective, the use of CsF would overcome difficulties associated with the removal of the tetrabutylammonium ion[10] through a simple aqueous workup. Here we present a systematic study of the CsF-mediated Sila-Sonogashira reaction, including reaction optimization and substrate scope.

Para-bromo-anisole was chosen as a model substrate for reaction optimization due to its ready availability and its lower reactivity compared to its iodo counterpart. The initial catalyst screening (Supporting Info) revealed the best catalytic system to be $PdCl_2(PPh_3)_2/PPh_3/CuI$, which is consistent with literature reports.[1b] The excess PPh_3 may serve to stabilize the active palladium [0] complex, which leads to dramatic increases in reaction yield (Table 1, entries 1 and 2).[6b]

Table 1. Sila-Sonogashira Solvent Screening



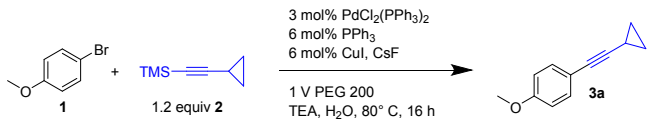
Entry	Solvent(s) (V)[a]	Yield (%)
1	TEA (10)[b,c]	43
2	TEA (10)[c]	70
3	TEA (10), H_2O (0.25)	36
4	TEA (9), H_2O (0.25), PEG 200 (0.5)[d,e]	54
5	TEA (9), H_2O (0.25), PEG 200 (1)	61
6	TEA (9), H_2O (0.5), PEG 200 (1)	75

[a] Parenthetical values denote volume equivalents of solvent (mL/g of substrate). [b] Reaction performed without addition of 6 mol% PPh_3. [c] 1.2 equiv. TBAF added instead of CsF. [d] Poly(ethylene glycol) 200 mw added as phase transfer catalyst (SOURCE). [e] KF (1.2 equiv) used instead of CsF.

With a palladium catalyst selected, we switched our focus towards solvent screening. Initially, poor conversion was observed upon substitution of TBAF with CsF. This decrease may be attributed to the poor solubility of CsF compared to TBAF in triethylamine. There is precedent for the use of phase transfer catalysts to enable the use of fluoride salts as nucleophilic fluoride donors in organic solvents.[12,13] Poly(ethylene glycol) MW 200 (PEG 200) was selected as a phase transfer catalyst based on the work of Fuchigami,[13] as it is inexpensive, and easily removed during aqueous workup. PEG 200 dramatically increased the reaction yields in both CsF and KF mediated Sila-Sonogashira reactions (Table 1, entries 4-6).

With solvent conditions in hand (Table 1, entry 6), we next investigated the identity of the copper catalyst and catalyst loading (SI Table S2). The results were consistent with the literature precedent for the use of CuI as co-catalyst in the Sonogashira reaction in a 2:1 ratio with the palladium catalyst.[1b] With catalyst identity and loading resolved, the final step taken was optimization of reagent stoichiometry.

Table 2. Sila-Sonogashira Stoichiometry Optimization



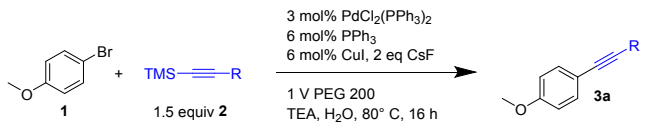
entry	equiv. alkyne	equiv. CsF	Yield (%)
1	1.2	0	3
2	1.2	0[a]	53
3	1.2	1.2	75
4	1.5	2.0	79

[a] Reaction performed using 1.2 eq. K_2CO_3.

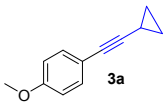
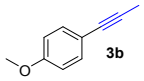
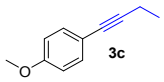
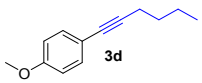
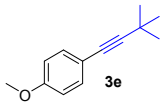
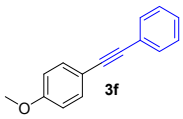
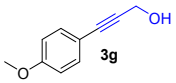
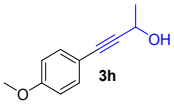
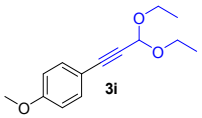
A slight excess of alkyne (1.2 eq) is conventional in Sonogashira reaction protocols.[1] Increased equivalents of both alkyne and CsF leads to a moderate increase in reaction yield (Table 2, entry 4). The boiling point of free cyclopropylacetylene is 51 °C. It is possible that excess alkyne is required in the reaction mixture due to vaporization of the free alkyne into the headspace of the reaction vessel reducing the effective concentration of free alkyne in the reaction mixture. The use of excess alkyne and CsF in the reaction is well tolerated, as both of these components are easily removed during purification, and are both less expensive than the catalysts and aryl halides used in the Sonogashira reaction. The conditions shown in Table 3 were selected as optimal conditions for the CsF mediated Sila-Sonogashira reaction. These conditions offer easier purifications and increased yields compared to TBAF mediated Sila-Sonogashira methods.

The substrate scope of the reaction was assessed following selection of optimized reaction conditions. All reactions were performed on a gram scale[14] to verify the robustness of the conditions, as well as the potential for industrial scale application.

Table 3. Substrate Scope: Trimethylsilyl Alkynes



Product	yield (%)	product	yield (%)

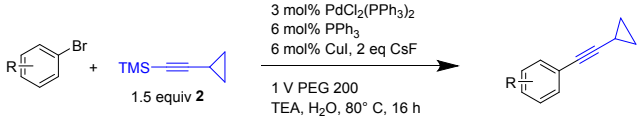
	90		82
	62		62
	93		93
	62		46
	83		

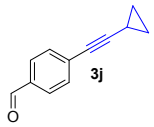
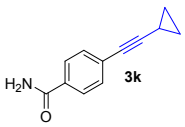
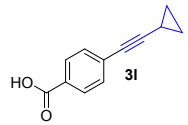
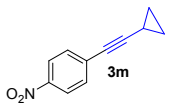
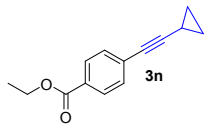
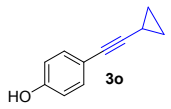
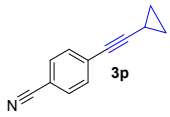
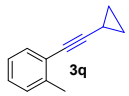
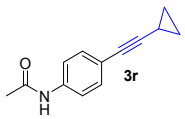
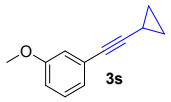
Reactions performed at 1 gram scale. Isolated yields provided.

To assess the scope of this method, the reaction was tried with a variety of TMS-alkynes (Table 3). All of the TMS-alkynes tested were well tolerated, with good to excellent yields. It is possible that the slightly lower yields attributed to alkynes containing hydroxyl groups (products **3g** and **3h**) is due to reduced solubility of the alkyne in triethylamine.

We next assessed the functional group tolerance of the substrates using a number of substituted aryl bromides (Table 4). Para-substitution with an aldehyde, an amide, a carboxyl acid, an ester, a nitro and an acetamido group all gave good to excellent yields. Electron-rich or sterically-hindered aryl bromides give lower yields (products **3o** and **3q**). No product was observed when an aryl choride with a p-cyano group was subjected to our Sila-Sonogashira conditions (product **3p**). Conversely, yields for aryl iodides are higher than aryl bromides (product **3o** and **3p**). These reactivity differences are consistent with known reactivity trends for the Sonogashira reaction.[15]

Table 4. Substrate Scope: Substituted Phenyl Bromides

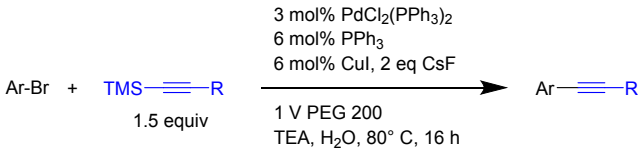


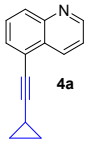
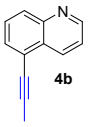
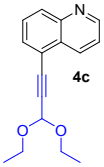
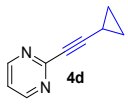
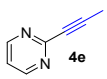
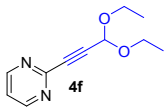
product	yield (%)	product	yield (%)
	100		93
	98		100
	84		51[a] 69[b]
	58[a] 100[b] 0[c]		12[a]
	91		100

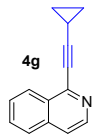
Reactions performed at 1 gram scale. Isolated yields provided. [a] Isolated product contaminated with starting material, yield determined through 1H NMR integration. [b] Reaction performed using aryl iodide. [c] Reaction performed using aryl chloride.

Heterocyclic aromatics have abundant applications in medicinal and agricultural chemistry. Therefore, we chose to apply our Sila-Sonogashira coupling conditions between trimethylsilyl alkynes and a variety of heteroaryl bromides (Table 5) to prepare a variety of useful synthetic intermediates. Almost all of the heteroarenes investigated gave good to excellent yields. Benzofurans gave moderate yields due to their electron-rich character (product **4k** and **4l**). This high-yielding methodology for heteroaryl bromides is particularly advantageous, as their iodo-counterparts are often either expensive or commercially unavailable.

Table 5. Substrate Scope: Bromo-Heteroarenes



Product	yield (%)	product	yield (%)
	81		86
	82		96
	79		92



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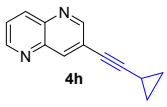

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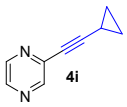

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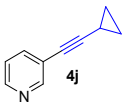

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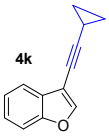

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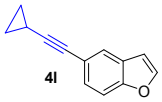

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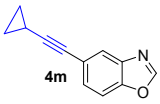

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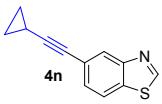

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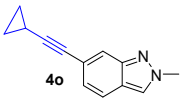

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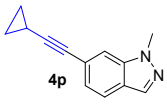

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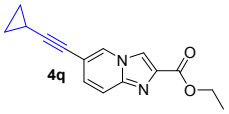
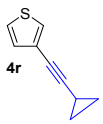
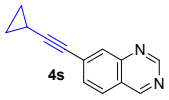


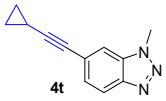
62



91



95



89

Reactions performed at 1 gram scale. Isolated yields provided.

To test the robustness of this protocol for scale-up, 5-bromo-quinoline was subjected these conditions on a 50-gram scale and product **4a** was isolated in 95% yield.

In summary, we have developed a CsF-mediated Sila-Sonogashira reaction protocol for the coupling of TMS-protected alkynes with arylbromides. This protocol exhibits good to excellent yields on over 40 substrates, including synthetically useful heteroaryl bromides, without any modification of the reaction conditions. Our protocol overcomes the difficulties associated with isolation and handling of small/volatile alkynes by *in-situ* desilylation of higher-boiling TMS alkynes followed by a simple aqueous workup. Compared with aryliodines, arylbromides are more attractive from the perspective of cost and commercial availability, which enables the use of this protocol on a wider variety of synthetically useful substrates. All substrates were prepared on a gram scale to verify the robustness of the reaction and its potential for industrial scale application. The high yields achieved on a variety of heterocyclic aromatics demonstrate the potential application of this protocol in drug discovery and agricultural chemistry.

■ EXPERIMENTAL SECTION

All reactions were performed under an atmosphere of nitrogen. All commercial reagents and solvents were used without additional purification. TLC was performed on Uniplate 2.5x10 cm silica gel plates and the spots were visualized by UV light and by treatment with $KMnO_4$ solution. ^1H NMR was recorded using a Bruker Avance 300 (300 MHz) instrument in chloroform-*d* solvent. Proton resonances are recorded in parts per million (ppm) downfield from tetramethylsilane. ^{13}C NMR were recorded at on a Bruker Avance 300 operating at 75 MHz in chloroform-*d* solvent. The following abbreviations were used to explain splitting patterns: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Coupling constants, *J* were reported in Hertz (Hz). Preparative chromatography was performed on ISCO combiflash systems using pre-packed silica gel cartridges. All chromatography was performed using linear gradient elution.

General Experimental Procedure for CsF-Mediated Sila-Sonogashira Coupling of Aryl Halides to Trimethylsilyl Protected Alkynes To a 40 mL pressure vial equipped with stir bar was added copper (I) iodide (6 mol%), bis(triphenylphosphine)palladium (II) dichloride (3 mol%), triphenylphosphine (6 mol%), cesium fluoride (2.0 equiv), aryl halide (1.0 equiv), poly(ethylene glycol) 200 mw (1 vol equiv), triethylamine (9 vol equiv), and water (0.5 vol equiv). The vial was capped and the mixture sparged with nitrogen for 15 minutes while stirring at room temperature. Trimethylsilyl protected alkyne (1.5 equiv) was added to the reaction vessel. The reaction mixture was allowed to stir at 80° C for 16 hours with heating block. Reaction progress was monitored via TLC and LCMS. Upon completion of the reaction, the mixture was cooled to room temperature, and diluted in ethyl acetate. The dilute mixture was washed twice with water, once with brine, dried with magnesium sulfate, filtered, and concentrated under vacuum. The crude product was purified via column chromatography using ethyl acetate/heptane as eluent with 0-100% gradient to afford the corresponding alkynyl arene.

1-(2-cyclopropylethynyl)-4-methoxy-benzene (3a)
The same general procedure was followed. Column chromatography (silica gel, eluting with 0-100% dichloromethane/heptanes gradient) afforded the desired product as a yellow oil (826 mg, 90%). ^1H NMR (300 MHz, Chloroform-*d*) δ 7.31 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 3.79 (s, 3H), 1.51 – 1.36 (m, 1H), 0.89 – 0.74 (m, 4H); $^{13}C\{^1H\}$ NMR (75 MHz, Chloroform-*d*) δ 159.1, 133.1, 116.2, 113.9, 91.9, 75.6, 55.4, 8.6, 0.3. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{13}O$, 173.0966; found, 173.0963.

1-methoxy-4-prop-1-ynyl-benzene (3b)
The same general procedure was followed. Column chromatography (silica gel, eluting with 0-100% dichloromethane/heptanes gradient) afforded the desired product as a colorless oil (644 mg, 82%). Characterization data obtained agrees with literature data.[16] ^1H NMR (300 MHz, Chloroform-*d*) δ 7.34 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 3.78 (s, 3H), 2.04 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, Chloroform-*d*) δ 159.1, 132.9, 116.3, 113.9, 84.2, 79.5, 55.2, 4.3.

1-but-1-ynyl-4-methoxy-benzene (3c)
The same general procedure was followed. Column chromatography (silica gel, eluting with 0-100%

dichloromethane/heptanes gradient) afforded the desired product as a yellow oil (529 mg, 62%). Characterization data obtained agrees with literature data.[6b] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.34 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 3.79 (s, 3H), 2.41 (q, *J* = 7.5 Hz, 2H), 1.23 (t, *J* = 7.5 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 159.1, 133.0, 116.3, 113.9, 90.1, 79.7, 55.3, 14.2, 13.2.

1-hex-1-ynyl-4-methoxy-benzene (3d)

The same general procedure was followed. Column chromatography (silica gel, eluting with 0-100% dichloromethane/heptanes gradient) afforded the desired product as a yellow oil (627 mg, 62%). Characterization data obtained agrees with literature data.[6b] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.33 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 3.79 (s, 3H), 2.39 (t, *J* = 6.9 Hz, 2H), 1.64 – 1.41 (m, 4H), 0.95 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 159.1, 133.0, 116.4, 113.9, 88.9, 80.4, 55.4, 31.1, 22.2, 19.2, 13.8.

1-(3,3-dimethylbut-1-ynyl)-4-methoxy-benzene (3e)

The same general procedure was followed. Column chromatography (silica gel, eluting with 0-100% dichloromethane/heptanes gradient) afforded the desired product as a colorless oil (940 mg, 93%). Characterization data obtained agrees with literature data.[17] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.33 (d, *J* = 8.9 Hz, 2H), 6.80 (d, *J* = 8.9 Hz, 2H), 3.79 (s, 3H), 1.32 (s, 9H); ^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 159.1, 133.0, 116.4, 113.8, 97.0, 78.8, 55.3, 31.3, 28.0.

1-methoxy-4-(2-phenylethynyl)benzene (3f)

The same general procedure was followed. Column chromatography (silica gel, eluting with 0-100% dichloromethane/heptanes gradient) afforded the desired product as an orange solid (1.03 g, 93%). Characterization data obtained agrees with literature data.[17] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.59 – 7.45 (m, 4H), 7.35 (dd, *J* = 6.8, 1.3 Hz, 3H), 6.90 (d, *J* =8.9 Hz, 2H), 3.83 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 159.8, 133.2, 131.6, 128.5, 128.1, 123.8, 115.5, 114.2, 89.6, 88.3, 55.5.

3-(4-methoxyphenyl)prop-2-yn-1-ol (3g)

The same general procedure was followed. Column chromatography (silica gel, eluting with 0-100% EtOAc/heptanes gradient) afforded the desired product as a brown solid (539 mg, 62%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.37 (d, *J* = 8.9 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 4.47 (s, 2H), 3.79 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 159.8, 133.3, 114.7, 114.1, 86.0, 85.7, 55.4, 51.7. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{10}H_{11}O_2$, 163.0759; found, 163.0755.

4-(4-methoxyphenyl)but-3-yn-2-ol (3h)

The same general procedure was followed. Column chromatography (silica gel, eluting with 0-100% EtOAc/heptanes gradient) afforded the desired product as an orange oil (438 mg, 62%). Characterization data obtained agrees with literature data.[18] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.36 (d, *J* = 8.9 Hz, 2H), 6.83 (d, *J* = 8.9 Hz, 2H), 4.74 (qd, *J* = 6.5, 4.9 Hz, 1H), 3.80 (s, 3H), 2.06 (d, *J* = 5.1 Hz, 1H), 1.54 (d, *J* = 6.6 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 159.8, 133.2, 114.8, 114.0, 89.7, 84.1, 59.0, 55.4, 24.6.

1-(3,3-diethoxyprop-1-ynyl)-4-methoxy-benzene (3i)

The same general procedure was followed. Column chromatography (silica gel, eluting with 0-100% EtOAc/heptanes gradient) afforded the desired product as an orange oil (438 mg, 62%). Characterization data obtained agrees with literature data.[19] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.34 (d, *J* = 8.9 Hz, 2H), 6.76 (d, *J* = 8.9 Hz, 2H), 5.41 (s, 1H), 3.83 – 3.67 (m, 5H), 3.59 (dq, *J* = 9.5, 7.1 Hz, 2H), 1.21 (t, *J* = 7.1 Hz, 6H); ^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 160.0, 133.5, 114.0, 114.0, 92.0, 85.4, 83.2, 61.0, 55.3, 15.2.

4-(2-cyclopropylethynyl)benzaldehyde (3j)

The same general procedure was followed. Column chromatography (silica gel, eluting with 0-100% EtOAc/heptanes gradient) afforded the desired product as an amber solid (916 mg, 100%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.93 (s, 1H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.3 Hz, 2H), 1.44 (tt, *J* = 8.2, 5.1 Hz, 1H), 0.95 – 0.75 (m, 4H); ^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 191.4, 134.9, 132.1, 130.5, 129.5, 98.5, 75.4, 9.0, 0.4; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{12}H_{11}O$, 171.0810; found, 171.0807.

4-(2-cyclopropylethynyl)benzamide (3k)

The same general procedure was followed. Column chromatography (silica gel, eluting with 0-100% EtOAc/heptanes gradient) afforded the desired product as an amber solid (863 mg, 93%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 5.90 (d, *J* = 67.5 Hz, 2H), 1.54 – 1.39 (m, 1H), 0.95 – 0.77 (m, 4H); ^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 168.8, 131.9, 131.9 128.1, 127.4, 96.8, 75.3, 8.9, 0.4; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{12}H_{12}NO$, 186.0919, found, 186.0915.

4-(2-cyclopropylethynyl)benzoic acid (3l)

The same general procedure was followed. Column chromatography (silica gel, eluting with 0-100% EtOAc/heptanes gradient) afforded the desired product as a white solid (906 mg, 98%). Characterization data obtained agrees with literature data.[20] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.01 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 7.8 Hz, 2H), 1.48 (tt, *J* = 8.1, 5.1 Hz, 1H), 0.96 – 0.80 (m, 4H); ^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 171.5, 131.7, 130.2, 130.0, 127.9, 97.8, 75.5, 9.0, 0.4.

1-(2-cyclopropylethynyl)-4-nitrobenzene (3m)

The same general procedure was followed. Column chromatography (silica gel, eluting with 0-100% EtOAc/heptanes gradient) afforded the desired product as an orange solid (926 mg, 100%). Characterization data obtained agrees with literature data.[21] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.11 (d, *J* = 9.0 Hz, 2H), 7.46 (d, *J* = 9.0 Hz, 2H), 1.54 – 1.39 (m, 1H), 0.99 – 0.78 (m, 4H); ^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 146.5, 132.2, 131.2, 123.5, 100.1, 74.6, 9.1, 0.4.

Ethyl 4-(2-cyclopropylethynyl)benzoate (3n)

The same general procedure was followed. Column chromatography (silica gel, eluting with 0-100% EtOAc/heptanes gradient) afforded the desired product as a colorless oil (835 mg, 84%). Characterization data obtained agrees with literature data.[21] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.93 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 4.42 – 4.29 (m, 2H), 1.53 – 1.32 (m, 4H), 0.96 –

0.76 (m, 4H); $^{13}C\{^1H\}$ NMR (75 MHz, Chloroform-*d*) δ 166.3, 131.5, 129.5, 129.2, 128.8, 97.0, 75.5, 61.1, 14.4, 8.9, 0.4.

4-(2-cyclopropylethynyl)phenol (30)

The same general procedure was followed. Column chromatography (silica gel, eluting with 0-100% dichloromethane/heptanes gradient) afforded the desired product as a yellow oil (498 mg, 69%). Characterization data obtained agrees with literature data.[22] ^1H NMR (300 MHz, Chloroform-*d*) δ 7.27 (d, *J* = 8.8 Hz, 2H), 6.72 (d, *J* = 8.7 Hz, 2H), 4.83 (s, 1H), 1.42 (tt, *J* = 8.1, 5.1 Hz, 1H), 0.91 – 0.71 (m, 4H); $^{13}C\{^1H\}$ NMR (75 MHz, Chloroform-*d*) δ 155.2, 133.3, 116.4, 115.4, 91.9, 75.5, 8.6, 0.3.

4-(2-cyclopropylethynyl)benzonitrile (3p)

The same general procedure was followed. Column chromatography (silica gel, eluting with 0-100% dichloromethane/heptanes gradient) afforded the desired product as a white solid (728 mg, 100%). 1H NMR (300 MHz, Chloroform-*d*) δ 7.58 – 7.49 (m, 2H), 7.46 – 7.37 (m, 2H), 1.53 – 1.38 (m, 1H), 0.98 – 0.77 (m, 4H); $^{13}C\{^1H\}$ NMR (75 MHz, Chloroform-*d*) δ 132.1, 132, 129.1, 118.8, 110.7, 98.9, 74.7, 9.0, 0.4; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{10}N$, 168.0813; found, 168.0809.

N-(4-(2-cyclopropylethynyl)phenyl)acetamide (3r)

The same general procedure was followed. Column chromatography (silica gel, eluting with 0-100% EtOAc/heptanes gradient) afforded the desired product as a white solid (850 mg, 91%). ^1H NMR (300 MHz, Chloroform-*d*) δ 8.36 (d, *J* = 8.3 Hz, 1H), 7.93 (s, 1H), 7.39 – 7.21 (m, 2H), 6.99 (t, *J* = 7.6 Hz, 1H), 2.22 (s, 3H), 1.54 (tt, *J* = 8.0, 5.0 Hz, 1H), 1.03 – 0.79 (m, 4H); $^{13}C\{^1H\}$ NMR (75 MHz, Chloroform-*d*) δ 168.2, 139.2, 131.8, 128.9, 123.3, 119.1, 112.5, 101.0, 70.9, 25.0, 9.2, 0.3; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{14}NO$, 200.1075; found, 200.1070.

1-(2-cyclopropylethynyl)-3-methoxybenzene (3s)

The same general procedure was followed. Column chromatography (silica gel, eluting with 0-100% dichloromethane/heptanes gradient) afforded the desired product as a yellow oil (920 mg, 100%). Characterization data obtained agrees with literature data.[22] ^1H NMR (300 MHz, Chloroform-*d*) δ 7.17 (dd, *J* = 8.2, 7.7 Hz, 1H), 6.98 (dt, *J* = 7.6, 1.2 Hz, 1H), 6.92 (dd, *J* = 2.7, 1.4 Hz, 1H), 6.82 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 3.78 (s, 3H), 1.53 – 1.38 (m, 1H), 0.94 – 0.75 (m, 4H); $^{13}C\{^1H\}$ NMR (75 MHz, Chloroform-*d*) δ 159.4, 129.3, 125.0, 124.3, 116.5, 114.3, 93.4, 75.8, 55.3, 8.7, 0.3.

5-(2-cyclopropylethynyl)quinoline (4a)

The same general procedure was followed. Column chromatography (silica gel, eluting with 0-100% EtOAc/heptanes gradient) afforded the desired product as an amber oil (781 mg, 84%). ^1H NMR (300 MHz, Chloroform-*d*) δ 8.87 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.54 (ddd, *J* = 8.4, 1.8, 0.9 Hz, 1H), 7.99 (ddd, *J* = 7.6, 2.0, 0.9 Hz, 1H), 7.63 – 7.50 (m, 2H), 7.39 (dd, *J* = 8.4, 4.2 Hz, 1H), 1.62 – 1.47 (m, 1H), 0.96 – 0.83 (m, 4H); $^{13}C\{^1H\}$ NMR (75 MHz, Chloroform-*d*) δ 150.6, 148.0, 134.7, 130.4, 129.4, 128.9, 122.0, 121.5, 99.4, 72.7, 9.0, 0.5; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{12}N$, 194.0970; found, 194.0965.

5-prop-1-ynylquinoline (4b)

The same general procedure was followed. Column chromatography (silica gel, eluting 0-100% EtOAc/heptanes gradient) afforded the desired product as a white solid (692 mg, 86%). ^1H NMR (300 MHz, Chloroform-*d*) δ 8.83 (dd, J = 4.2, 1.8 Hz, 1H), 8.53 (ddd, J = 8.4, 1.8, 0.9 Hz, 1H), 7.97 (ddd, J = 7.9, 1.9, 0.9 Hz, 1H), 7.61 – 7.47 (m, 2H), 7.33 (dd, J = 8.4, 4.2 Hz, 1H), 2.10 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, Chloroform-*d*) δ 150.6, 147.9, 134.6, 130.2, 129.4, 128.8, 128.7, 122.1, 121.4, 91.6, 76.6, 4.5; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{10}N$, 168.0813; found, 168.0809.

5-(3,3-diethoxyprop-1-ynyl)quinoline (4c)

The same general procedure was followed. Column chromatography (silica gel, eluting with 0-100% EtOAc/heptanes gradient) afforded the desired product as a yellow oil (1.008 g, 82%). ^1H NMR (300 MHz, Chloroform-*d*) δ 8.87 (dd, J = 4.2, 1.7 Hz, 1H), 8.54 (ddd, J = 8.5, 1.8, 0.9 Hz, 1H), 8.05 (d, J = 8.5 Hz, 1H), 7.70 (dd, J = 7.2, 1.3 Hz, 1H), 7.58 (dd, J = 8.5, 7.2 Hz, 1H), 7.41 (dd, J = 8.4, 4.2 Hz, 1H), 5.58 (s, 1H), 3.83 (dq, J = 9.5, 7.1 Hz, 2H), 3.68 (dq, J = 9.4, 7.0 Hz, 2H), 1.25 (t, J = 7.1 Hz, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, Chloroform-*d*) δ 150.9, 147.8, 134.4, 131.4, 130.8, 128.7, 128.6, 121.8, 119.9, 91.9, 90.0, 81.9, 61.1, 15.2; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{18}NO_2$, 256.1338; found, 256.1333.

5-(2-cyclopropylethynyl)pyrimidine (4d)

The same general procedure was followed. Column chromatography (silica gel, eluting with 0-100% EtOAc/heptanes gradient) afforded the desired product as a yellow oil (871 mg, 96%). ^1H NMR (300 MHz, Chloroform-*d*) δ 8.88 (s, 1H), 8.51 (s, 2H), 1.38 – 1.23 (m, 1H), 0.79 – 0.62 (m, 4H); $^{13}C\{^1H\}$ NMR (75 MHz, Chloroform-*d*) δ 158.5, 155.8, 120.2, 100.9, 69.0, 8.7, 0.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_9H_9N_2$, 145.0766; found, 145.0762.

5-prop-1-ynylpyrimidine (4e)

The same general procedure was followed. Column chromatography (silica gel, eluting with 0-100% EtOAc/heptanes gradient) afforded the desired product as a white solid (587 mg, 79%). Characterization data obtained agrees with literature data.[23] ^1H NMR (300 MHz, Chloroform-*d*) δ 9.03 (s, 1H), 8.66 (s, 2H), 2.05 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, Chloroform-*d*) δ 158.8, 156.3, 120.5, 93.7, 73.3, 4.5.

2-(3,3-diethoxyprop-1-ynyl)pyrimidine (4f)

The same general procedure was followed. Column chromatography (silica gel, eluting with 0-100% EtOAc/heptanes gradient) afforded the desired product as a yellow oil (1.188 g, 92%). ^1H NMR (300 MHz, Chloroform-*d*) δ 9.07 (s, 1H), 8.73 (s, 2H), 5.43 (s, 1H), 3.66 (ddq, J = 42.1, 9.4, 7.1 Hz, 4H), 1.20 (t, J = 7.1 Hz, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, Chloroform-*d*) δ 159.0, 157.3, 118.5, 91.6, 91.4, 78.2, 61.2, 15.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{11}H_{15}N_2O_2$, 207.1134; found, 207.1129.

1-(2-cyclopropylethynyl)isoquinoline (4g)

The same general procedure was followed. Column chromatography (silica gel, eluting with 0-100% dichloromethane/heptanes gradient) afforded the desired product as a yellow oil (812 mg, 87%). ^1H NMR (300 MHz, Chloroform-*d*) δ 8.36 (d, J = 5.8 Hz, 1H), 8.27 (dd, J = 8.6, 1.1 Hz, 1H), 7.70 – 7.61 (m, 1H), 7.61 – 7.46 (m, 2H), 7.43 (dd, J = 5.8, 0.9 Hz, 1H), 1.62 – 1.48 (m, 1H), 0.97 – 0.85 (m,

4H); $^{13}C\{^1H\}$ NMR (75 MHz, Chloroform-*d*) δ 144.7, 142.6, 135.6, 130.3, 129.1, 127.6, 126.9, 126.6, 119.8, 99.2, 73.7, 9.1, 0.3; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{12}N$, 194.0970; found, 194.0966.

3-(2-cyclopropylethynyl)-1,5-naphthyridine (4h)

The same general procedure was followed. Column chromatography (silica gel, eluting with 0-100% EtOAc/heptanes gradient) afforded the desired product as a brown solid (744 mg, 80%). ^1H NMR (300 MHz, Chloroform-*d*) δ 8.87 – 8.75 (m, 2H), 8.22 (dt, *J* = 4.6, 2.2 Hz, 2H), 7.45 (dd, *J* = 8.6, 4.2 Hz, 1H), 1.42 (td, *J* = 8.2, 4.0 Hz, 1H), 0.82 (tt, *J* = 8.1, 2.7 Hz, 4H); $^{13}C\{^1H\}$ NMR (75 MHz, Chloroform-*d*) δ 153.2, 151.6, 143.0, 142.1, 138.7, 137.0, 124.1, 121.7, 99.0, 72.6, 8.9, 0.3; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{11}N_2$, 195.0922; found, 195.0917.

2-(2-cyclopropylethynyl)pyrazine (4i)

The same general procedure was followed. Column chromatography (silica gel, eluting with heptane/dichloromethane) afforded the desired product as a brown oil (829 mg, 91%). ^1H NMR (300 MHz, Chloroform-*d*) δ 8.57 (d, J = 1.5 Hz, 1H), 8.49 – 8.37 (m, 2H), 1.58 – 1.43 (m, 1H), 0.93 (dddd, J = 7.0, 5.6, 2.9, 1.8 Hz, 4H); $^{13}C\{^1H\}$ NMR (75 MHz, Chloroform-*d*) δ 147.7, 144.3, 142.3, 140.9, 98.9, 73.1, 9.1, 0.3; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_9H_9N_2$, 145.0766; found, 145.0762.

3-(2-cyclopropylethynyl)pyridine (4j)

The same general procedure was followed. Column chromatography (silica gel, eluting with 0-100% EtOAc/heptanes gradient) afforded the desired product as a yellow oil (867 mg, 96%). ^1H NMR (300 MHz, Chloroform-*d*) δ 8.48 (dd, J = 2.1, 0.9 Hz, 1H), 8.33 (dd, J = 4.9, 1.7 Hz, 1H), 7.51 (d, J = 7.9 Hz, 1H), 7.05 (ddd, J = 7.9, 4.9, 0.9 Hz, 1H), 1.41 – 1.26 (m, 1H), 0.82 – 0.65 (m, 4H); $^{13}C\{^1H\}$ NMR (75 MHz, Chloroform-*d*) δ 152.2, 147.6, 138.3, 122.7, 120.9, 97.0, 72.4, 8.6, 0.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{10}H_{10}N$, 144.0813; found, 144.0809.

3-(2-cyclopropylethynyl)benzofuran (4k)

The same general procedure was followed. Column chromatography (silica gel, eluting with 0-100% dichloromethane/heptanes gradient) afforded the desired product as a colorless oil (550 mg, 59%). ^1H NMR (300 MHz, Chloroform-*d*) δ 7.77 (d, J = 1.1 Hz, 1H), 7.71 (dt, J = 6.7, 1.4 Hz, 1H), 7.55 – 7.46 (m, 1H), 7.42 – 7.26 (m, 2H), 1.56 (tt, J = 8.1, 5.0 Hz, 1H), 0.92 (ddt, J = 10.4, 4.9, 2.7 Hz, 4H); $^{13}C\{^1H\}$ NMR (75 MHz, Chloroform-*d*) δ 154.6, 147.2, 128.1, 125.1, 123.2, 120.5, 111.6, 105.0, 98.1, 64.9, 8.8, 0.5; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{11}O$, 183.0810; found, 183.0802.

5-(2-cyclopropylethynyl)benzofuran (4l)

The same general procedure was followed. Column chromatography (silica gel, eluting with 0-100% dichloromethane/heptanes gradient) afforded the desired product as a yellow oil (520 mg, 56%). ^1H NMR (300 MHz, Chloroform-*d*) δ 7.69 – 7.57 (m, 2H), 7.46 – 7.38 (m, 1H), 7.34 (dd, J = 8.5, 1.6 Hz, 1H), 6.71 (dd, J = 2.2, 0.9 Hz, 1H), 1.48 (ddt, J = 8.5, 7.7, 5.1 Hz, 1H), 0.92 – 0.79 (m, 4H); $^{13}C\{^1H\}$ NMR (75 MHz, Chloroform-*d*) δ 154.3, 145.7, 128.2, 127.5, 124.7, 118.5, 111.4, 106.5, 91.9, 76.0, 8.6, 0.3; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{11}O$, 183.0810; found, 183.0803.

5-(2-cyclopropylethynyl)-1,3-benzoxazole (4m)

The same general procedure was followed. Column chromatography (silica gel, eluting with 0-100% dichloromethane/heptanes gradient) afforded the desired product as a yellow oil (745 mg, 81%). ^1H NMR (300 MHz, Chloroform-*d*) δ 8.07 (s, 1H), 7.79 (d, *J* = 0.9 Hz, 1H), 7.46 (dd, *J* = 8.5, 0.7 Hz, 1H), 7.40 (dd, *J* = 8.5, 1.5 Hz, 1H), 1.53 – 1.38 (m, 1H), 0.94 – 0.75 (m, 4H); $^{13}C\{^1H\}$ NMR (75 MHz, Chloroform-*d*) δ 153.2, 149.4, 140.2, 129.6, 123.9, 120.8, 110.9, 93.1, 75.3, 8.7, 0.2; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{10}NO$, 184.0762; found, 184.0758.

5-(2-cyclopropylethynyl)-1,3-benzothiazole (4n)

The same general procedure was followed. Column chromatography (silica gel, eluting with 0-100% EtOAc/heptanes gradient) afforded the desired product as a yellow oil (883 mg, 95%). ^1H NMR (300 MHz, Chloroform-*d*) δ 8.87 (d, *J* = 1.6 Hz, 1H), 8.08 (d, *J* = 1.7 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.38 – 7.29 (m, 1H), 1.47 – 1.32 (m, 1H), 0.77 (ddq, *J* = 6.5, 3.0, 2.0, 1.6 Hz, 4H); $^{13}C\{^1H\}$ NMR (75 MHz, Chloroform-*d*) δ 154.6, 153.1, 132.8, 128.7, 126.4, 121.9, 121.4, 93.9, 75.2, 8.5, 0.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{10}NS$, 200.0534; found, 200.0528.

6-(2-cyclopropylethynyl)-2-methyl-indazole (4o)

The same general procedure was followed. Column chromatography (silica gel, eluting with 0-100% dichloromethane/heptanes gradient) afforded the desired product as a brown oil (874 mg, 94%). ^1H NMR (300 MHz, Chloroform-*d*) δ 7.79 (s, 1H), 7.72 (d, J = 1.3 Hz, 1H), 7.50 (dd, J = 8.7, 0.9 Hz, 1H), 7.03 (dd, J = 8.7, 1.3 Hz, 1H), 4.16 (s, 3H), 1.47 (tt, J = 8.0, 5.2 Hz, 1H), 0.85 (tt, J = 8.0, 2.5 Hz, 4H); $^{13}C\{^1H\}$ NMR (75 MHz, Chloroform-*d*) δ 148.8, 135.1, 131.3, 128.4, 125.2, 123.8, 121.2, 120.6, 119.9, 93.2, 76.7, 40.5, 8.7, 0.4; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{13}N_2$, 197.1079, found, 197.1075.

6-(2-cyclopropylethynyl)-1-methyl-indazole (4p)

The same general procedure was followed. Column chromatography (silica gel, eluting with 0-100% dichloromethane/heptanes gradient) afforded the desired product as a yellow oil (886 mg, 95%). ^1H NMR (300 MHz, Chloroform-*d*) δ 7.91 (d, J = 1.0 Hz, 1H), 7.58 (dd, J = 8.4, 0.9 Hz, 1H), 7.42 (d, J = 1.1 Hz, 1H), 7.12 (dd, J = 8.3, 1.2 Hz, 1H), 4.01 (s, 3H), 1.55 – 1.40 (m, 1H), 0.93 – 0.79 (m, 4H); $^{13}C\{^1H\}$ NMR (75 MHz, Chloroform-*d*) δ 139.7, 132.8, 124.2, 123.1, 121.8, 120.8, 112.1, 93.9, 76.3, 35.5, 8.8, 0.3; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{13}N_2$, 197.1079; found, 197.1075.

Ethyl 6-(2-cyclopropylethynyl)imidazo[1,2-*a*]pyridine-2-carboxylate (4q)

The same general procedure was followed. Column chromatography (silica gel, eluting with 0-100% EtOAc/heptanes gradient) afforded the desired product as a white solid (586 mg, 62%). ^1H NMR (300 MHz, Chloroform-*d*) δ 8.14 (s, 1H), 8.08 (d, *J* = 0.8 Hz, 1H), 7.53 (d, *J* = 9.4 Hz, 1H), 7.14 (dd, *J* = 9.4, 1.6 Hz, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 1.49 – 1.33 (m, 4H), 0.94 – 0.72 (m, 4H); $^{13}C\{^1H\}$ NMR (75 MHz, Chloroform-*d*) δ 163.2, 144.0, 137.4, 129.6, 128.5, 118.5, 116.9, 111.6, 96.2, 71.2, 61.3, 14.5, 8.8, 0.2; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{15}N_2O_2$, 255.1134; found, 255.1128.

3-(2-cyclopropylethynyl)thiophene (4r)

The same general procedure was followed. Column chromatography (silica gel, eluting with 0-100% EtOAc/heptanes gradient) afforded the desired product as a brown oil (831 mg, 91%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.34 (dd, J = 3.0, 1.2 Hz, 1H), 7.21 (dd, J = 5.0, 3.0 Hz, 1H), 7.06 (dd, J = 5.0, 1.2 Hz, 1H), 1.44 (tt, J = 8.1, 5.1 Hz, 1H), 0.90 – 0.76 (m, 4H); ^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 130.1, 127.8, 125.1, 122.9, 92.9, 70.9, 8.6, 0.2; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for C_9H_9S, 149.0425; found, 149.0421.

7-(2-cyclopropylethynyl)quinazoline (4S)

The same general procedure was followed. Column chromatography (silica gel, eluting with 0-100% EtOAc/heptanes gradient) afforded the desired product as a brown oil (890 mg, 95%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.31 (d, J = 8.3 Hz, 2H), 8.01 (s, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.58 (dd, J = 8.4, 1.5 Hz, 1H), 1.53 (tt, J = 8.1, 5.2 Hz, 1H), 1.02 - 0.81 (m, 4H); ^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 159.9, 155.9, 150.1, 131.1, 131.0, 130.5, 127.0, 124.1, 99.2, 75.3, 9.2, 0.5. HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{13}H_{11}N_2$, 195.0917; found, 195.0917.

6-(2-cyclopropylethynyl)-1-methyl-benzotriazole (4t)

The same general procedure was followed. Column chromatography (silica gel, eluting with 0-100% EtOAc/heptanes gradient) afforded the desired product as a brown oil (830 mg, 89%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.94 (dd, J = 8.6, 0.9 Hz, 1H), 7.55 (t, J = 1.1 Hz, 1H), 7.36 (dd, J = 8.6, 1.3 Hz, 1H), 4.27 (s, 3H), 1.57 - 1.45 (m, 1H), 0.98 - 0.81 (m, 4H); ^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 145.1, 133.6, 127.9, 123.5, 119.8, 112.2, 95.4, 75.6, 34.3, 8.9, 0.3; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{12}H_{12}N_3$, 198.1026; found, 198.1026.

ASSOCIATED CONTENT

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Additional optimization tables, and NMR spectra for new and known compounds (PDF).

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Notes

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