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Isocanthine Synthesis via Rh(III)-Catalyzed Intramolecular C—H Functionalization

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Supporting Information Placeholder

ABSTRACT: An efficient synthesis of substituted isocanthines has been achieved using an intramolecular Rh(III)-catalyzed C—H functionalization of alkyne-tethered indoles in the presence of catalytic tris(acetonitrile)pentamethyl-cyclopentadienylrhodium(III) hexafluoroantimonate and stoichiometric copper(II) acetate. This isocanthine synthesis tolerates a variety of electronically diverse 5- or 6-substituted indoles with *N*-tethered alkyne coupling partners and can also be extended to pyrrole derivatives for the synthesis of annulated 5-azaindoles.

INTRODUCTION

Isocanthines are a class of tetracyclic γ -carbolines that have demonstrated widespread clinical use as cardiovascular agents,¹ antiemetic 5-HT₃ receptor antagonists for chemotherapy patients,² as well as potential treatments for CNS disorders.³ Surprisingly, very few syntheses of isocanthines (Scheme 1) have been reported. Typically the reported syntheses employ either thermal cyclization of a 1-azatriene⁴ (Scheme 1, A) or intramolecular hetero-Diels-Alder cycloaddition⁵ of an alkyne-tethered indole oxime (Scheme 1, B).⁶ Unfortunately, these syntheses suffer from very limited scope, the requirement of high reaction temperatures, or low yield over multiple steps.^{4,6} Larock's isocanthine synthesis⁷ employing a Pd-catalyzed intramolecular iminoannulation affords excellent yields with a wide functional group tolerance, but requires pre-installation of a halide, thus is not very efficient (Scheme 1, C). Therefore, a more direct synthesis of isocanthines is highly desirable.

Recently, Rh-catalyzed C—H functionalization reactions⁸ have attracted much attention in the literature and have been employed in synthesizing an array of interesting heterocycles, such as indoles,⁹ isoquinolines,^{10,11} isoquinolones,¹² pyrroles,¹³ pyridines¹⁴ and polyheterocycles.¹⁵ Inspired by Fagnou's isoquinoline synthesis¹⁰ from aryl aldimines and alkynes (eq 1), we envisioned that isocanthines could readily be synthesized by C—H functionalization of alkyne-tethered indole *tert*-

butylimines (Scheme 1, D). Herein, we wish to report an efficient synthesis of substituted isocanthines via intramolecular Rh(III)-catalyzed C—H functionalization of alkyne-tethered indoles.

Scheme 1. Synthetic strategies to Isocanthines

RESULTS AND DISCUSSION

Our investigation commenced with the optimization of 3-*n*-butyl-isocanthine (**1a**) formation from imine **2a** by screening a variety of catalyst and oxidant systems (Table 1). The optimal “standard conditions” employed 2.5 mol % tris(acetonitrile)pentamethylcyclopentadienylrhodium(III) hexafluoroantimonate (**C1**)¹⁶ as the catalyst, 2.1 equiv of Cu(OAc)₂ as the oxidant and the reaction was carried out in dichloroethane (DCE) in a sealed vial at 100 °C for 16 h. Under this set of optimal conditions, the reaction afforded 93% conversion and 73% assay yield based on quantitative

HPLC analysis. The desired product (**1a**) was subsequently isolated in 73% yield (Table 1, entry 1). When the reaction was performed at a lower temperature (83 °C), much lower conversion and assay yield were obtained (Table 1, entry 2). Without Rh complex **C1**, the reaction did not produce any desired product **1a**, which indicates that formation of the isocanthine did not proceed via simple thermal hetero-Diels-Alder cycloaddition and subsequent oxidative aromatization (Table 1, entry 3). Lowering the loading of **C1** to 1 mol % resulted in low conversion and assay yield of product **1a** (Table 1, entry 4). When [Cp*RhCl₂]₂ (**C2**) and [Rh(COD)Cl]₂ (**C3**) were employed, both reactions proceeded with inferior conversion relative to the optimal conditions (Table 1, entries 5–6). Palladium catalysts, such as palladium(II) acetate (**C4**) and palladium(II) trifluoroacetate (**C5**), did not generate significant conversion (Table 1, entries 7–8). Among the oxidants that were screened, Cu(OAc)₂•H₂O which was used in Fagnou's isoquinoline synthesis¹⁰ resulted in 86% conversion and 68% assay yield of the desired product (Table 1, entry 9). The lower yield was possibly due to partial hydrolysis of imine **2a** to the corresponding aldehyde under the reaction conditions since about 8% of the aldehyde was observed upon reaction completion based on HPLC analysis as opposed to <2% of the aldehyde when anhydrous Cu(OAc)₂ was employed. Other oxidants, for example, silver acetate, benzoquinone and (diacetoxyiodo)benzene all produced low assay yield of product **1a** (Table 1, entries 10–12).

Table 1. Optimization of Isocanthine 1a Formation^a

entry	variation from the "standard" conditions	conv (%) ^b	yield (%) ^c	
1	None	93	73(73)	
2	83 °C instead of 100 °C	53	39	
3	no C1	0	0	
4	C1 (1 mol %) as catalyst	20	19	
5	C2 (1.25 mol %) as catalyst	29	25	
6	C3 (1.25 mol %) as catalyst	< 5	< 5	
7	C4 as catalyst	< 5	< 5	
8	C5 as catalyst	< 5	< 5	
9	Cu(OAc) ₂ •H ₂ O as oxidant	86	68	
10	AgOAc as oxidant	30	27	
11	benzoquinone as oxidant	50	<5	
12	PhI(OAc) ₂ as oxidant	61	< 5	
<div style="display: flex; justify-content: space-around; font-size: small;"> [Cp*Rh(MeCN)₃](SbF₆)₂ [Cp*RhCl₂]₂ [Rh(COD)Cl]₂ Pd(OAc)₂ Pd(TFA)₂ </div> <div style="display: flex; justify-content: space-around; font-size: small;"> C1 C2 C3 C4 C5 </div>				

^aAll reactions were performed using 0.50 mmol of **2a** in DCE (3.0 mL) in sealed vials for 16 h. ^bDetermined by HPLC analysis. ^cAssay yields determined by quantitative HPLC analysis. The number in parentheses is the isolated yield.

We next examined the substrate scope and limitations of this Rh(III)-catalyzed isocanthine synthesis. It is worth mentioning that the transformation of the aldehydes to the corresponding *tert*-butylimines is essentially quantitative, thus requiring no further purification and characterization of the starting imines used for the subsequent C–H functionalization.

Indeed, the one-pot imine formation/C–H functionalization process employing aldehyde **3a** afforded the same isolated yield (73%) as that of the step-wise approach (Table 2, entry 1). Therefore, by employing a one-pot protocol, namely imine formation, followed by Rh(III)-catalyzed intramolecular C–H functionalization, we were able to synthesize a variety of substituted isocanthines (Table 2).

The electronic effects of the substituents on the indole ring were first examined. Gratifyingly, both electron-donating and withdrawing substituents are well tolerated on the 5-position of indole. For example, electron-donating methyl and methoxy substituted indoles **3b** and **3c** produced the desired isocanthines (**1b** and **1c**) in 78% and 75% yields, respectively (Table 2, entries 2–3). Indole **3d** substituted with an electron-withdrawing fluorine atom afforded isocanthine **1d** in an excellent 90% yield (Table 2, entry 4). 5-Bromo-substituted indole **3e** also participated in this C–H functionalization reaction, generating a moderate yield (40%) of the desired bromoisocanthine **1e**. (Table 2, entry 5). As expected, indoles substituted with either electron-donating (MeO, **3f**) or electron-withdrawing (CO₂Me, **3g**) groups at the 6-position uneventfully gave the desired products **1f** and **1g** in 78% and 82%, respectively (Table 2, entries 6–7).

Table 2. Scope of Isocanthine Formation^a

entry	indole	product	yield (%) ^b	
1	3a , R = H	1a	73	
2	3b , R = Me	1b	78	
3	3c , R = MeO	1c	75	
4	3d , R = F	1d	90	
5	3e , R = Br	1e	40 ^c	
6	3f , R = OMe	1f	78	
7	3g , R = CO ₂ Me	1g	82	
8	3h , R = CH ₂ OCH ₃	1h	66	
9	3i , R = (CH ₂) ₃ OTHP	1i	85	
10 ^d	3j , R = Ph	1j	<5	
11	3k , R = (CH ₂) ₃ Ph	1k	87	
12	3l , R = H	1l	53	
13	3m , R = CO ₂ Me	1m	71	

^aAll reactions were performed using 0.50 mmol of **3** in *t*-BuNH₂ (3.0 mL) at 80 °C for 2 h, followed by [Cp*Rh(MeCN)₃](SbF₆)₂ (**C1**, 2.5 mol %), Cu(OAc)₂ (2.1 equiv) in DCE (3.0 mL) at 100 °C in sealed vials for 16 h. ^bIsolated yield. ^c30A% of isocanthine **1a** was observed by HPLC. ^dReaction performed at 150 °C.

The substituent effect on the alkyne was then investigated. Indoles with ether substituted alkynes underwent the intramolecular annulation smoothly, giving the desired isocanthine products (**1h** and **1i**) in good yields (Table 2, entries 8–9). Surprisingly, indole **3j** tethered with a phenyl-substituted alkyne failed to produce isocanthine product **1j** even at an elevated temperature 150 °C (Table , entry 10).¹⁷ However, indole **3k** tethered with a phenylpropyl-substituted alkyne uneventfully afforded 87% yield of isocanthine **1k** (Table 2, entry 11). This isocanthine synthesis could also be extended to alkyne-tethered pyrroles for the synthesis of annulated 5-azaindoles. In fact, pyrroles **3l** and **3m** were subjected to the standard reaction conditions, producing 53% and 71% yields of the desired 5-azaindoles (**1l** and **1m**), respectively (Table 2, entries 12–13). Thus, one can envision that this chemistry could be further expanded into a general method for the synthesis of a wide spectrum of annulated 5-azaindoles.

To further demonstrate the synthetic utility of the bromine-functionalized isocanthine, **1d** was converted to cyclopropyl- and 2-furyl-substituted derivatives **4a–b** in moderate to good yields via Suzuki-Miyaura cross-coupling reactions (Scheme 2).¹⁸ The structure of isocanthine **4b** was established unambiguously by single-crystal X-ray diffraction analysis.

Scheme 2. Synthetic Utility of Bromoisocanthine **1d**^a

^aConditions: (**4a**), Pd(OAc)₂ (10 mol %), di(1-adamanyl)-*n*-butylphosphine (15 mol %), Cs₂CO₃ (3.0 equiv), *c*-PrBF₃K (1.5 equiv), PhMe:H₂O (10:1), 100 °C. (**4b**), Pd(dtbpp)Cl₂ (5 mol %), 2-furyl pinacol ester (1.5 equiv), K₃PO₄·H₂O (2 equiv), THF:H₂O (5:1), 65 °C.

We conducted DFT calculations using imine **2a** as an example to assist in understanding the mechanism of this C–H functionalization reaction. The free energy profile of the Rh(III)/Rh(I) catalytic cycle beginning from imine **2a** and rhodacycle **Rh0** is shown in Figure 1. In accord with literature precedent,¹⁰ the mechanism involves an initial imine coordination of **2a** and rhodacycle **Rh0** to form rhodacycle **Int1**, followed by ortho-directed C–H functionalization via concerted metalation deprotonation^{9,12a} (via **Int2**), then alkyne coordination (via **Int3**) and insertion to afford seven-membered rhodacycle **Int4**. **TS1** and **TS2** are the transition states for these two steps, and have barriers of 16.4 and 9.2 kcal/mol, respectively. Rhodacycle **Int4** then undergoes reductive elimination via **TS3** with a barrier of 17.2 kcal/mol to produce intermediate **Int5**. **Int5** then proceeds with *tert*-butyl fragmentation and catalyst regeneration in the presence of 2 equivalents of Cu(OAc)₂ to generate the isocanthine product **1a**, along with byproducts isobutene, acetic acid and Cu(OAc), and catalyst **Rh0**.

CONCLUSIONS

In summary, we have developed a C–H functionalization approach to substituted isocanthines from alkyne-tethered indole-3-carboxaldehydes and *tert*-butylamine using 2.5 mol % of [Cp*Rh(MeCN)₃](SbF₆)₂ as the catalyst and 2.1 equiv of Cu(OAc)₂ as the oxidant in DCE at 100 °C. Both electron-donating and electron-withdrawing substituents are tolerated on the 5- and 6-positions of the indole ring. This chemistry can also be extended to pyrrole derivatives for the synthesis of annulated 5-azaindoles. Bromine substitution on the indole ring allows for further functionalization of the isocanthine framework via Suzuki-Miyaura cross-coupling reactions. Theoretical calculations suggest that the mechanism of this chemistry involves ortho-directed C–H functionalization via a concerted metalation deprotonation pathway, followed by alkyne coordination and insertion, then reductive elimination and *tert*-butyl fragmentation to afford the desired isocanthine product.

Figure 1. (a) Free energy profiles for the mechanism of Rh(III)-catalyzed formation of isocanthine **1a**. (b) Computed configurations of transition states with selected bond distances shown in angstroms (Å). Some hydrogen atoms are omitted for clarity.

EXPERIMENTAL SECTION

Materials and Methods

Unless stated otherwise, reactions were performed in 4-dram vials sealed with Teflon-lined caps. Commercially obtained solvents and reagents were used as received. Thin-layer chromatography (TLC) was performed using glass-backed plates pre-coated with EMD silica gel 60 F₂₅₄ and visualized using UV light (254 nm). ¹H and ¹³C NMR spectra were recorded on 300 or 400 MHz Bruker spectrometer and chemical shifts are reported relative to the residual solvent peak (¹H NMR, δ 7.26 for CDCl₃, ¹³C NMR, δ 77.0 for CDCl₃). ¹H NMR spectral data are reported in terms of: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. ¹³C NMR spectral data are reported in terms of chemical shift (δ ppm). Flash column chromatography was performed using a CombiFlash ISCO instrument, using pre-packed RediSep silica gel columns. HPLC analyses were performed using an Agilent 1290 Infinity Series HPLC instrument. IR spectra were recorded using a Bruker Alpha Platinum-ATR spectrometer and are reported in wavenumbers (cm⁻¹). HRMS data were obtained using a LTQ Orbitrap Discovery (Thermo Fisher Scientific) at Genentech, Inc. Melting points were measured on a Büchi Melting Point B-540 apparatus.

General Experimental Procedure

(8-Chlorooct-4-yn-1-yl)benzene: To a flame-dried 50 mL round-bottom flask was added 5-chloropent-1-yne (0.968 g, 9.44 mmol), followed by THF (9.4 mL), and the mixture was cooled to -78 °C under N₂. *n*-Butyllithium solution (2.5 M in hexanes, 4.2 mL, 1.1 equiv) was then added dropwise, and the mixture was stirred at -78 °C for 30 min before dropwise addition of (3-iodopropyl)benzene (1.5 mL, 9.44 mmol, 1.0 equiv). The mixture was stirred at -78 °C for 30 min, warmed to 23 °C and stirred at 23 °C for 16 h. The reaction was quenched with saturated aqueous ammonium chloride and the aqueous layer was extracted with ethyl acetate (10 mL, ×3). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate (2 g), concentrated in vacuum and purified by silica gel column chromatography using ethyl acetate in hexanes (0–2%) to afford (8-chlorooct-4-yn-1-yl)benzene as a colorless oil (1.27 g, 61%); FTIR (thin film, cm⁻¹)

3026, 2940, 2859, 1603, 1453; ¹H NMR (400 MHz, CDCl₃) δ 7.32 – 7.26 (m, 2H), 7.19 (ddd, *J* = 6.1, 2.1, 1.2 Hz, 3H), 3.67 (t, *J* = 6.4 Hz, 2H), 2.75 – 2.67 (m, 2H), 2.37 (tt, *J* = 6.7, 2.4 Hz, 2H), 2.17 (tt, *J* = 7.1, 2.4 Hz, 2H), 1.95 (quintet, *J* = 6.5 Hz, 2H), 1.87 – 1.75 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 141.9, 128.7, 128.5, 126.0, 81.1, 78.8, 44.0, 35.0, 31.9, 30.8, 18.3, 16.4; HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₄H₁₈Cl 221.1097; Found, 221.1071.

Synthesis of *N*-Alkylated Indole-3-carboxaldehydes

To a 20 mL vial was added indole-3-carboxaldehyde, sodium iodide (1.5 equiv), cesium carbonate (1.5 equiv), and chloroalkyne (1.2 equiv) in acetonitrile (10 mL/g). The vial was then sealed and heated to 80 °C. After 16 h, solids were filtered off and the cake was washed with acetonitrile (2 mL/g, ×3). The combined organic solution was concentrated and purified by silica gel column chromatography with ethyl acetate in hexanes gradient eluent to afford the desired *N*-alkylated indole-3-carboxaldehyde **3**.

1-(Non-4-yn-1-yl)-1*H*-indole-3-carbaldehyde (3a): 1*H*-indole-3-carbaldehyde (1.00 g, 6.89 mmol), sodium iodide (1.55 g, 1.5 equiv), cesium carbonate (3.37 g, 1.5 equiv), 1-chloronon-4-yne (1.31 g, 1.2 equiv) and acetonitrile (10.0 mL) were employed. Upon silica gel column chromatography purification using ethyl acetate in hexanes (0–50%), compound **3a** was isolated as a yellow oil (1.79 g, 97%). FTIR (thin film, cm⁻¹) 2956, 2930, 1655, 1531, 1467; ¹H NMR (300 MHz, CDCl₃) δ 10.02 (s, 1H), 8.35 – 8.28 (m, 1H), 7.77 (s, 1H), 7.47 – 7.28 (m, 3H), 4.35 (t, *J* = 6.7 Hz, 2H), 2.26 – 2.15 (m, 4H), 2.04 (quintet, *J* = 6.4 Hz, 2H), 1.58 – 1.38 (m, 4H), 0.94 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 184.4, 138.9, 137.2, 125.4, 123.9, 122.8, 122.0, 118.0, 110.2, 82.3, 77.8, 45.6, 31.1, 28.7, 22.0, 18.4, 16.0, 13.7; HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₈H₂₂NO 268.1701; Found, 268.1703.

5-Methyl-1-(non-4-yn-1-yl)-1*H*-indole-3-carbaldehyde (3b): 5-methyl-1*H*-indole-3-carbaldehyde (500 mg, 3.14 mmol), sodium iodide (471 mg, 1.5 equiv), cesium carbonate (1.54 g, 1.5 equiv), 1-chloronon-4-yne (598 mg, 1.2 equiv) and acetonitrile (5.0 mL) were employed. Upon silica gel column chromatography purification using ethyl acetate in hexanes (0–50%), compound **3b** was isolated as a yellow oil (857 mg, 97%). FTIR (thin film, cm⁻¹) 2954, 2930, 1652, 1528, 1485; ¹H NMR (300 MHz, CDCl₃) δ 9.98 (s, 1H), 8.12 (s, 1H), 7.72 (s, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.16 (dd, *J* = 8.4, 1.4

Hz, 1H), 4.32 (t, $J = 6.7$ Hz, 2H), 2.49 (s, 3H), 2.25 – 2.13 (m, 4H), 2.02 (quintet, $J = 6.4$ Hz, 2H), 1.57 – 1.38 (m, 4H), 0.94 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 184.4, 138.8, 135.5, 132.6, 125.7, 125.4, 121.8, 117.7, 109.8, 82.3, 77.8, 45.7, 31.1, 28.7, 22.0, 21.4, 18.4, 16.0, 13.6; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{24}\text{NO}$ 282.1858; Found, 282.1861.

5-Methoxy-1-(non-4-yn-1-yl)-1H-indole-3-carbaldehyde (3c): 5-methoxy-1H-indole-3-carbaldehyde (600 mg, 3.43 mmol), sodium iodide (771 mg, 1.5 equiv), cesium carbonate (1.67 g, 1.5 equiv), 1-chloronon-4-yne (653 mg, 1.2 equiv) and acetonitrile (6.0 mL) were employed. Upon silica gel column chromatography purification using ethyl acetate in hexanes (0–50%), compound **3c** was isolated as a white solid (927 mg, 91%). M.p. 61–63 °C; FTIR (thin film, cm^{-1}) 2955, 2930, 1652, 1530, 1389; ^1H NMR (300 MHz, CDCl_3) δ 9.96 (s, 1H), 7.80 (d, $J = 2.5$ Hz, 1H), 7.71 (s, 1H), 7.30 (d, $J = 8.9$ Hz, 1H), 6.97 (dd, $J = 8.9, 2.5$ Hz, 1H), 4.31 (t, $J = 6.7$ Hz, 2H), 3.90 (s, 3H), 2.26 – 2.14 (m, 4H), 2.02 (quintet, $J = 6.5$ Hz, 2H), 1.48 (m, 4H), 0.94 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 184.4, 156.6, 138.8, 132.0, 126.1, 117.8, 114.3, 110.9, 103.4, 82.3, 77.8, 55.7, 45.8, 31.1, 28.7, 22.0, 18.4, 16.0, 13.6; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{24}\text{NO}_2$ 298.1807; Found, 298.1809.

5-Fluoro-1-(non-4-yn-1-yl)-1H-indole-3-carbaldehyde (3d): 5-fluoro-1H-indole-3-carbaldehyde (500 mg, 3.07 mmol), sodium iodide (690 mg, 1.5 equiv), cesium carbonate (1.50 g, 1.5 equiv), 1-chloronon-4-yne (585 mg, 1.2 equiv) and acetonitrile (5.0 mL) were employed. Upon silica gel column chromatography purification using ethyl acetate in hexanes (0–50%), compound **3d** was isolated as a yellow oil (791 mg, 91%). FTIR (thin film, cm^{-1}) 2955, 2930, 1655, 1531, 1392; ^1H NMR (300 MHz, CDCl_3) δ 9.98 (s, 1H), 7.99 (dd, $J = 9.2, 2.5$ Hz, 1H), 7.78 (s, 1H), 7.35 (dd, $J = 9.0, 4.2$ Hz, 1H), 7.07 (td, $J = 9.0, 3.8$ Hz, 1H), 4.34 (t, $J = 6.7$ Hz, 2H), 2.25 – 2.14 (m, 4H), 2.03 (quintet, $J = 6.5$ Hz, 2H), 1.47 (m, 4H), 0.94 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 184.2, 159.7 (d, $J = 319$ Hz), 139.7, 133.6, 125.9 (d, $J = 11.0$ Hz), 117.8 (d, $J = 4.5$ Hz), 112.2 (d, $J = 26.4$ Hz), 111.0 (d, $J = 9.8$ Hz), 107.4 (d, $J = 24.6$ Hz), 82.4, 77.6, 45.9, 31.1, 28.6, 22.0, 18.4, 15.9, 13.6; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{21}\text{FNO}$ 286.1607; Found, 286.1616.

5-Bromo-1-(non-4-yn-1-yl)-1H-indole-3-carbaldehyde (3e): 5-bromo-1H-indole-3-carbaldehyde (500 mg, 2.23 mmol), sodium iodide (501 mg, 1.5 equiv), cesium carbonate (1.09 g, 1.5 equiv), 1-chloronon-4-yne (425 mg, 1.2 equiv) and acetonitrile (5.0 mL) were employed. Upon silica gel column chromatography purification using ethyl acetate in hexanes (0–50%), compound **3e** was isolated as a white solid (678 mg, 88%). M.p. 74–75 °C; FTIR (thin film, cm^{-1}) 2955, 2931, 1662, 1531, 1465, 1401; ^1H NMR (300 MHz, CDCl_3) δ 9.98 (s, 1H), 8.48 (d, $J = 1.9$ Hz, 1H), 7.75 (s, 1H), 7.43 (dd, $J = 8.7, 1.9$ Hz, 1H), 7.30 (d, $J = 8.7$ Hz, 1H), 4.33 (t, $J = 6.7$ Hz, 2H), 2.26 – 2.12 (m, 4H), 2.02 (quintet, $J = 6.4$ Hz, 2H), 1.55 – 1.35 (m, 4H), 0.94 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 184.2, 139.0, 135.8, 127.0, 126.9, 124.8, 117.5, 116.6, 111.5, 82.6, 77.5, 45.9, 31.1, 28.6, 22.0, 18.4, 16.0, 13.6; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{21}\text{BrNO}$ 346.0807; Found, 346.0821.

6-Methoxy-1-(non-4-yn-1-yl)-1H-indole-3-carbaldehyde (3f): 6-methoxy-1H-indole-3-carbaldehyde (296 mg, 1.69 mmol), sodium iodide (380 mg, 1.5 equiv), cesium carbonate (826 mg, 1.5 equiv), 1-chloronon-4-yne (268 mg, 1.0 equiv) and acetonitrile (3.4 mL) were employed. Upon silica gel column chromatography purification using ethyl acetate in hexanes (0–30%), compound **3f** was isolated as a yellow solid (264 mg, 53%); M.p. 38–40 °C; FTIR (thin film, cm^{-1}) 2928, 2858, 1656, 1623, 1578, 1523; ^1H NMR (400 MHz, CDCl_3) δ 9.94 (s, 1H), 8.18 (d, $J = 8.7$ Hz, 1H), 7.66 (s, 1H), 6.96 (dd, $J = 8.7, 2.3$ Hz, 1H), 6.88 (d, $J = 2.1$ Hz, 1H), 4.29 (t, $J = 6.7$ Hz, 2H), 3.89 (s, 3H), 2.25 – 2.14 (m, 5H), 2.10 – 1.96 (m, 2H), 1.54 – 1.38 (m, 4H), 0.93 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 184.6, 157.7, 138.3, 123.1, 119.6, 118.4, 112.0, 94.2, 82.6, 77.9, 77.4, 55.9, 45.7, 31.3, 28.7, 22.2, 18.6, 16.2, 13.8; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{23}\text{NO}_2\text{Na}$ 320.1626; Found, 320.1621.

Methyl 3-formyl-1-(non-4-yn-1-yl)-1H-indole-6-carboxylate (3g): methyl 3-formyl-1H-indole-6-carboxylate (500 mg, 2.46 mmol), sodium iodide (553 mg, 1.5 equiv), cesium carbonate (1.20 g, 1.5 equiv), 1-chloronon-4-yne (468 mg, 1.2 equiv) and acetonitrile (5.0 mL) were employed. Upon silica gel column chromatography purification using ethyl acetate in hexanes (0–50%), compound **3g** was isolated as a yellow oil (578 mg, 72%). FTIR (thin film, cm^{-1}) 2953, 2932, 1711, 1658, 1617, 1529, 1434; ^1H NMR (300 MHz, CDCl_3) δ 10.04 (s, 1H), 8.34 (d, $J = 8.3$ Hz, 1H), 8.18 (s, 1H), 8.00 (dd, $J = 8.4, 1.4$ Hz, 1H), 7.90 (s, 1H), 4.42 (t, $J = 6.6$ Hz, 2H), 3.96 (s, 3H), 2.20 (td, $J = 7.9, 4.7$ Hz, 4H), 2.07 (quintet, $J = 6.6$ Hz, 2H), 1.58 – 1.37 (m, 4H), 0.94 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 184.2, 167.2, 140.7, 136.6, 128.8, 125.5, 123.7, 121.5, 117.9, 112.2, 82.5, 77.5, 52.0, 45.8, 31.0, 28.7, 22.0, 18.3, 15.9, 13.5; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{24}\text{NO}_3$ 326.1756; Found, 326.1764.

1-(6-Methoxyhex-4-yn-1-yl)-1H-indole-3-carbaldehyde (3h): 1H-indole-3-carbaldehyde (1.22 g, 7.61 mmol), sodium iodide (1.71 g, 1.5 equiv), cesium carbonate (3.72 g, 1.5 equiv), 6-chloro-1-methoxyhex-2-yne¹⁹ (1.34 g, 1.2 equiv) and acetonitrile (12.2 mL) were employed. Upon silica gel column chromatography purification using ethyl acetate in hexanes (0–50%), compound **3h** was isolated as a yellow oil (1.83 g, 63%). FTIR (thin film, cm^{-1}) 2932, 2820, 1654, 1530, 1388; ^1H NMR (300 MHz, CDCl_3) δ 10.02 (s, 1H), 8.35 – 8.29 (m, 1H), 7.77 (s, 1H), 7.45 – 7.28 (m, 1H), 4.36 (t, $J = 6.7$ Hz, 2H), 4.12 (t, $J = 2.1$ Hz, 2H), 3.40 (s, 3H), 2.29 – 2.24 (m, 2H), 2.10 (quintet, $J = 6.6$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 184.4, 139.1, 137.1, 125.2, 123.9, 122.7, 121.8, 117.9, 110.2, 84.7, 77.7, 59.9, 57.4, 45.5, 28.2, 15.9; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{18}\text{NO}_2$ 256.1338; Found, 256.1338.

1-(8-(Tetrahydro-2H-pyran-2-yl)oxy)oct-4-yn-1-yl)-1H-indole-3-carbaldehyde (3i): 1H-indole-3-carbaldehyde (1.00 g, 6.89 mmol), sodium iodide (1.55 g, 1.5 equiv), cesium carbonate (3.37 g, 1.5 equiv), 2-((8-chlorooct-4-yn-1-yl)oxy)tetrahydro-2H-pyran²⁰ (2.02 g, 1.2 equiv) and acetonitrile (9.0 mL) were employed. Upon silica gel column chromatography purification using ethyl acetate in hexanes (0–30%), compound **3i** was isolated as a yellow oil (1.26 g, 52%); FTIR (thin film, cm^{-1}) 2942, 1662, 1616, 1533, 1468, 1401; ^1H NMR (400 MHz, CDCl_3) δ 10.02 (s, 1H), 8.35 – 8.27 (m, 1H), 7.78 (s, 1H), 7.45 – 7.39 (m, 1H), 7.37 – 7.28 (m, 2H), 4.60 (dd, $J = 4.3, 2.8$ Hz, 1H), 4.35 (t, $J = 6.7$ Hz, 2H), 3.91 – 3.82 (m, 2H), 3.55 – 3.43 (m, 2H), 2.33 (tt, $J = 7.1, 2.4$ Hz, 2H), 2.22 – 2.13 (m, 4H), 2.10 – 2.00 (m, 2H), 1.88 – 1.77 (m, 3H), 1.72 (tt, $J = 9.1, 3.2$ Hz, 1H), 1.65 – 1.46 (m, 4H); ^{13}C NMR (101 MHz, CDCl_3) δ 184.7, 138.8, 137.3, 125.6, 124.1, 123.1, 122.4, 118.3, 110.2, 99.0, 81.9, 78.2, 66.2, 62.5, 45.9, 30.9, 29.4, 28.7, 25.6, 19.7, 16.2, 15.8; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{22}\text{H}_{28}\text{NO}_3$ 354.2064; Found, 354.2045.

1-(5-Phenylpent-4-yn-1-yl)-1H-indole-3-carbaldehyde (3j): 1H-indole-3-carbaldehyde (200 mg, 1.38 mmol), sodium iodide (310 mg, 1.5 equiv), cesium carbonate (674 mg, 1.5 equiv), (5-chloropent-1-yn-1-yl)benzene^{7a,21} (296 mg, 1.2 equiv) and acetonitrile (2.0 mL) were employed. Upon silica gel column chromatography purification using ethyl acetate in hexanes (0–50%), compound **3j** was isolated as a yellow oil (322 mg, 81%). FTIR (thin film, cm^{-1}) 3103, 3052, 2942, 2809, 2754, 1654, 1530, 1467; ^1H NMR (300 MHz, CDCl_3) δ 10.02 (s, 1H), 8.36 – 8.30 (m, 1H), 7.80 (s, 1H), 7.48 – 7.41 (m, 3H), 7.38 – 7.30 (m, 5H), 4.43 (t, $J = 6.7$ Hz, 2H), 2.45 (t, $J = 6.6$ Hz, 2H), 2.19 (p, $J = 6.6$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 184.5, 138.6, 137.2, 131.6, 128.4, 128.1, 125.5, 124.0, 123.3, 123.0, 122.2, 118.2, 110.1, 87.6, 82.5, 45.7, 28.4, 16.7; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{18}\text{NO}$ 288.1388; Found, 288.1399.

1-(8-Phenylloct-4-yn-1-yl)-1H-indole-3-carbaldehyde (3k): 1H-indole-3-carbaldehyde (1.07 g, 7.36 mmol), sodium iodide (2.00 g, 1.5 equiv), cesium carbonate (4.33 g, 1.5 equiv), (8-chlorooct-4-yn-1-yl)benzene (1.95 g, 1.2 equiv) and acetonitrile (10.0 mL) were employed. Upon silica gel column chromatography purification using ethyl acetate in hexanes (0–30%), compound **3k** was isolated as a yellow oil (1.82 g, 75%); FTIR (thin film, cm^{-1}) 3025, 2935, 1660, 1614, 1576, 1531; ^1H NMR (400 MHz, CDCl_3) δ 10.01 (s, 1H), 8.36 – 8.29 (m, 1H), 7.76 (s, 1H), 7.46 – 7.39 (m, 1H), 7.37 –

7.27 (m, 4H), 7.24 – 7.17 (m, 3H), 4.35 (t, $J = 6.7$ Hz, 2H), 2.75 (dd, $J = 8.3, 6.9$ Hz, 2H), 2.28 – 2.16 (m, 4H), 2.11 – 2.01 (m, 2H), 1.92 – 1.81 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 184.7, 141.7, 138.7, 137.3, 128.6, 128.5, 126.1, 125.6, 124.1, 123.1, 122.3, 118.3, 110.2, 82.0, 78.4, 45.9, 35.1, 30.7, 28.8, 18.4, 16.2; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{24}\text{NO}$ 330.1852; Found, 330.1867.

1-(Non-4-yn-1-yl)-1H-pyrrole-3-carbaldehyde (3l): 1H-pyrrole-3-carbaldehyde (500 mg, 5.26 mmol), sodium iodide (1.18 g, 1.5 equiv), cesium carbonate (2.57 g, 1.5 equiv), 1-chloronon-4-yne (1.00 g, 1.2 equiv) and acetonitrile (5.0 mL) were employed. Upon silica gel column chromatography purification using ethyl acetate in hexanes (0–50%), compound **3l** was isolated as a yellow oil (1.12 g, 98%). FTIR (thin film, cm^{-1}) 2955, 2931, 1664, 1532, 1397; ^1H NMR (300 MHz, CDCl_3) δ 9.74 (s, 1H), 7.30 (t, $J = 1.8$ Hz, 1H), 6.71 – 6.60 (m, 2H), 4.06 (t, $J = 6.7$ Hz, 2H), 2.22 – 2.12 (m, 4H), 1.93 (quintet, $J = 6.6$ Hz, 2H), 1.54 – 1.35 (m, 4H), 0.93 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 185.1, 129.2, 126.4, 123.4, 108.1, 82.0, 77.7, 48.5, 31.0, 30.0, 21.9, 18.3, 15.7, 13.5; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{20}\text{NO}$ 218.1545; Found, 218.1542.

Methyl 4-formyl-1-(non-4-yn-1-yl)-1H-pyrrole-2-carboxylate (3m): methyl 4-formyl-1H-pyrrole-2-carboxylate (500 mg, 3.27 mmol), sodium iodide (735 mg, 1.5 equiv), cesium carbonate (1.60 g, 1.5 equiv), 1-chloronon-4-yne (623 mg, 1.2 equiv) and acetonitrile (5.0 mL) were employed. Upon silica gel column chromatography purification using ethyl acetate in hexanes (0–50%), compound **3m** was isolated as a yellow oil (857 mg, 95%). FTIR (thin film, cm^{-1}) 2955, 2932, 2861, 1713, 1675, 1546, 1419; ^1H NMR (300 MHz, CDCl_3) δ 9.78 (s, 1H), 7.50 (d, $J = 1.9$ Hz, 1H), 7.38 (d, $J = 1.9$ Hz, 1H), 4.48 (t, $J = 6.7$ Hz, 2H), 3.84 (s, 3H), 2.22 – 2.10 (m, 4H), 1.96 (quintet, $J = 6.6$ Hz, 2H), 1.46 (m, 4H), 0.93 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 185.0, 160.8, 133.5, 124.5, 123.7, 117.7, 81.9, 77.9, 51.4, 48.7, 31.0, 29.8, 21.9, 18.3, 15.6, 13.5; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{22}\text{NO}_3$ 276.1600; Found, 276.1610.

Synthesis of Isocanthines

To a 4-dram vial was added indole-3-aldehyde **3** (0.50 mmol), in *tert*-butyl amine (3.0 mL). The vial was then sealed with a Teflon-lined cap, and the mixture was heated to 80 °C for 2 h. After completion of imine formation (>99% conversion observed by ^1H NMR), the reaction mixture was cooled to 23 °C, and concentrated in vacuum. Catalyst $[\text{Cp}^*\text{Rh}(\text{MeCN})_3](\text{SbF}_6)_2$ (**C1**, 2.5 mol %, 10.6 mg), oxidant $\text{Cu}(\text{OAc})_2$ (2.1 equiv, 197 mg) and dichloroethane (DCE, 3.0 mL) were then added. The mixture was heated to 100 °C for 16 h. The mixture was then cooled to 23 °C and quenched with 3 mL of saturated aqueous NaHCO_3 solution. The aqueous layer was extracted with dichloromethane (5 mL $\times$ 3) and the organic layers were combined and concentrated in vacuum. The residue was then purified using column chromatography to give the desired isocanthine **1**.

3-*n*-Butyl-5,6-dihydro-4H-indolo[3,2,1-*ij*][1,6]naphthyridine (1a): 1-(non-4-yn-1-yl)-1H-indole-3-carbaldehyde (134 mg, 0.50 mmol), *tert*-butylamine (3.0 mL), $[\text{Cp}^*\text{Rh}(\text{MeCN})_3](\text{SbF}_6)_2$ (**C1**, 10.6 mg, 2.5 mol %), $\text{Cu}(\text{OAc})_2$ (197 mg, 2.1 equiv) and dichloroethane (3.0 mL) were employed. Upon silica gel column chromatography purification using MeOH in DCM gradient elution (0–10%), compound **1a** was isolated as a yellow solid (97 mg, 73%). M.p. 61–63 °C; FTIR (thin film, cm^{-1}) 2951, 2927, 2857, 1604, 1442; ^1H NMR (300 MHz, CDCl_3) δ 9.07 (s, 1H), 8.11 (d, $J = 7.8$ Hz, 1H), 7.48 (td, $J = 7.6, 1.1$ Hz, 1H), 7.38 (d, $J = 8.1$ Hz, 1H), 7.32 – 7.24 (m, 1H), 4.19 (t, $J = 5.8$ Hz, 2H), 3.03 (t, $J = 6.2$ Hz, 2H), 2.92 (t, $J = 7.9$ Hz, 2H), 2.35 (quintet, $J = 6.0$ Hz, 2H), 1.84 – 1.65 (m, 2H), 1.44 (dq, $J = 14.6, 7.3$ Hz, 2H), 0.96 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 153.0, 142.9, 140.1, 139.5, 125.9, 121.5, 121.0, 120.0, 116.0, 113.1, 108.6, 40.4, 34.1, 32.1, 22.8, 22.1, 21.5, 14.1; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{21}\text{N}_2$ 265.1705; Found, 265.1717.

3-*n*-Butyl-10-methyl-5,6-dihydro-4H-indolo[3,2,1-*ij*][1,6]naphthyridine (1b): 5-methyl-1-(non-4-yn-1-yl)-1H-indole-3-carbaldehyde (141 mg, 0.50 mmol), *tert*-butylamine (3.0 mL), $[\text{Cp}^*\text{Rh}(\text{MeCN})_3](\text{SbF}_6)_2$ (**C1**, 10.6 mg, 2.5 mol %), $\text{Cu}(\text{OAc})_2$ (197

mg, 2.1 equiv) and dichloroethane (3.0 mL) were employed. Upon silica gel column chromatography purification using ethyl acetate in hexanes gradient elution (0–50%), compound **1b** was isolated as a green solid (109 mg, 78%). M.p. 76–78 °C; FTIR (thin film, cm^{-1}) 2951, 2930, 2858, 1632, 1482; ^1H NMR (300 MHz, CDCl_3) 9.03 (s, 1H), 7.59 (d, $J = 2.4$ Hz, 1H), 7.28 (d, $J = 9.0$ Hz, 1H), 7.11 (dd, $J = 8.8, 2.5$ Hz, 1H), 4.15 (t, $J = 5.8$ Hz, 2H), 3.93 (s, 3H), 3.01 (t, $J = 6.2$ Hz, 2H), 2.90 (t, $J = 7.9$ Hz, 2H), 2.33 (quintet, $J = 6.0$ Hz, 2H), 1.82 – 1.67 (m, 2H), 1.44 (dq, $J = 14.6, 7.3$ Hz, 2H), 0.96 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 154.3, 152.9, 143.3, 139.7, 135.2, 122.0, 116.0, 114.9, 113.0, 109.2, 104.1, 56.1, 40.5, 34.2, 32.1, 22.9, 22.2, 21.4, 14.1; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{23}\text{N}_2$ 279.1861; Found, 279.1868.

3-*n*-Butyl-10-methoxy-5,6-dihydro-4H-indolo[3,2,1-*ij*][1,6]naphthyridine (1c): 5-methoxy-1-(non-4-yn-1-yl)-1H-indole-3-carbaldehyde (149 mg, 0.50 mmol), *tert*-butylamine (3.0 mL), $[\text{Cp}^*\text{Rh}(\text{MeCN})_3](\text{SbF}_6)_2$ (**C1**, 10.6 mg, 2.5 mol %), $\text{Cu}(\text{OAc})_2$ (197 mg, 2.1 equiv) and dichloroethane (3.0 mL) were employed. Upon silica gel column chromatography purification using MeOH in DCM gradient elution (0–10%), compound **1c** was isolated as a white solid (111 mg, 75%). M.p. 87–88 °C; FTIR (thin film, cm^{-1}) 2951, 2925, 2857, 1610, 1572, 1483; ^1H NMR (300 MHz, CDCl_3) δ 9.02 (s, 1H), 7.90 (s, 1H), 7.32 – 7.24 (m, 2H), 4.15 (t, $J = 5.8$ Hz, 2H), 3.01 (t, $J = 6.2$ Hz, 2H), 2.89 (t, $J = 7.9$ Hz, 2H), 2.53 (s, 3H), 2.32 (quintet, $J = 6.0$ Hz, 2H), 1.80 – 1.67 (m, 2H), 1.44 (dq, $J = 14.6, 7.3$ Hz, 2H), 0.96 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 152.9, 143.1, 139.6, 138.5, 129.3, 127.1, 121.7, 121.1, 115.8, 113.0, 108.2, 40.4, 34.2, 32.2, 22.9, 22.2, 21.5, 21.4, 14.1; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{23}\text{N}_2\text{O}$ 295.1810; Found, 295.1820.

3-*n*-Butyl-10-fluoro-5,6-dihydro-4H-indolo[3,2,1-*ij*][1,6]naphthyridine (1d): 5-fluoro-1-(non-4-yn-1-yl)-1H-indole-3-carbaldehyde (143 mg, 0.50 mmol), *tert*-butylamine (3.0 mL), $[\text{Cp}^*\text{Rh}(\text{MeCN})_3](\text{SbF}_6)_2$ (**C1**, 10.6 mg, 2.5 mol %), $\text{Cu}(\text{OAc})_2$ (197 mg, 2.1 equiv) and dichloroethane (3.0 mL) were employed. Upon silica gel column chromatography purification using ethyl acetate in hexanes gradient elution (0–50%), compound **1d** was isolated as a white solid (128 mg, 90%). M.p. 101–103 °C; FTIR (thin film, cm^{-1}) 2952, 2929, 2959, 1633, 1572, 1478; ^1H NMR (300 MHz, CDCl_3) δ 9.02 (s, 1H), 7.76 (dd, $J = 8.9, 2.4$ Hz, 1H), 7.31 – 7.25 (m, 1H), 7.20 (td, $J = 8.9, 2.5$ Hz, 1H), 4.16 (t, $J = 5.8$ Hz, 2H), 3.01 (t, $J = 6.2$ Hz, 2H), 2.90 (t, $J = 7.9$ Hz, 2H), 2.34 (quintet, $J = 6.0$ Hz, 2H), 1.79 – 1.67 (m, 4H), 1.44 (dq, $J = 14.6, 7.3$ Hz, 2H), 0.96 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 157.8 (d, $J = 316$ Hz), 153.5, 143.6, 140.0, 136.5, 122.0 (d, $J = 9.8$ Hz), 115.7 (d, $J = 4.1$ Hz), 113.5 (d, $J = 25.5$ Hz), 108.9 (d, $J = 9.2$ Hz), 106.9 (d, $J = 24.2$ Hz), 40.5, 34.2, 32.1, 22.8, 22.1, 21.3, 14.1; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{20}\text{FN}_2$ 283.1611; Found, 283.1622.

10-Bromo-3-*n*-butyl-5,6-dihydro-4H-indolo[3,2,1-*ij*][1,6]naphthyridine (1e): 5-bromo-1-(non-4-yn-1-yl)-1H-indole-3-carbaldehyde (173 mg, 0.50 mmol), *tert*-butylamine (3.0 mL), $[\text{Cp}^*\text{Rh}(\text{MeCN})_3](\text{SbF}_6)_2$ (**C1**, 10.6 mg, 2.5 mol %), $\text{Cu}(\text{OAc})_2$ (197 mg, 2.1 equiv) and dichloroethane (3.0 mL) were employed. Upon silica gel column chromatography purification using ethyl acetate in hexanes gradient elution (0–50%), compound **1e** was isolated as a pale yellow solid (70 mg, 40%). M.p. 96–98 °C; FTIR (thin film, cm^{-1}) 2945, 2851, 1628, 1570, 1450; ^1H NMR (400 MHz, CDCl_3) δ 9.02 (d, $J = 0.7$ Hz, 1H), 8.21 (dd, $J = 2.0, 0.5$ Hz, 1H), 7.55 (dd, $J = 8.6, 1.9$ Hz, 1H), 7.27 – 7.19 (m, 1H), 4.23 – 4.05 (m, 2H), 3.08 – 2.95 (m, 2H), 2.93 – 2.80 (m, 2H), 2.41 – 2.24 (m, 2H), 1.81 – 1.64 (m, 3H), 1.44 (dq, $J = 14.8, 7.3$ Hz, 2H), 0.96 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 153.9, 143.2, 140.0, 138.8, 128.6, 123.8, 123.3, 115.2, 113.3, 112.8, 109.9, 40.6, 34.2, 32.1, 22.9, 22.1, 21.4, 14.1; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{20}\text{BrN}_2$ 343.0810; Found, 343.0826.

3-*n*-Butyl-9-methoxy-5,6-dihydro-4H-indolo[3,2,1-*ij*][1,6]naphthyridine (1f): 6-methoxy-1-(non-4-yn-1-yl)-1H-indole-3-carbaldehyde (149 mg, 0.50 mmol), *tert*-butylamine (3.0 mL), $[\text{Cp}^*\text{Rh}(\text{MeCN})_3](\text{SbF}_6)_2$ (**C1**, 10.6 mg, 2.5 mol %), $\text{Cu}(\text{OAc})_2$ (197 mg, 2.1 equiv) and dichloroethane (3.0 mL) were employed. Upon silica gel column chromatography purification using MeOH in DCM gradient elution (0–10%), compound **1f** was

isolated as a white solid (115 mg, 78%). M.p. 90–92 °C; FTIR (thin film, cm^{-1}) 2952, 2930, 2857, 1609, 1578, 1475; ^1H NMR (300 MHz, CDCl_3) δ 8.96 (s, 1H), 7.96 (d, J = 8.5 Hz, 1H), 6.90 – 6.83 (m, 2H), 4.13 (t, J = 5.8 Hz, 2H), 3.93 (s, 3H), 3.01 (t, J = 6.2 Hz, 2H), 2.89 (t, J = 7.9 Hz, 2H), 2.33 (quintet, J = 6.0 Hz, 2H), 1.72 (m, 2H), 1.44 (dq, J = 14.6, 7.3 Hz, 2H), 0.96 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 159.2, 152.3, 143.2, 141.6, 138.7, 121.7, 116.2, 115.2, 112.9, 108.1, 93.2, 55.7, 40.5, 34.2, 32.2, 22.9, 22.2, 21.5, 14.1; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{23}\text{N}_3\text{O}$ 295.1810; Found, 295.1823.

Methyl 3-*n*-butyl-5,6-dihydro-4*H*-indolo[3,2,1-*ij*][1,6]naphthyridine-9-carboxylate (1g): methyl 3-formyl-1-(non-4-yn-1-yl)-1*H*-indole-6-carboxylate (163 mg, 0.50 mmol), *tert*-butylamine (3.0 mL), $[\text{Cp}^*\text{Rh}(\text{MeCN})_3](\text{SbF}_6)_2$ (**C1**, 10.6 mg, 2.5 mol %), $\text{Cu}(\text{OAc})_2$ (197 mg, 2.1 equiv) and dichloroethane (3.0 mL) were employed. Upon silica gel column chromatography purification using MeOH in DCM gradient elution (0–10%), compound **1g** was isolated as a white solid (133 mg, 82%); M.p. 135–137 °C; FTIR (thin film, cm^{-1}) 3073, 2947, 2865, 2853, 1612, 1567, 1440; ^1H NMR (400 MHz, CDCl_3) δ 9.11 (s, 1H), 8.18 – 8.07 (m, 2H), 7.98 (dd, J = 8.1, 1.5 Hz, 1H), 4.25 (dd, J = 6.3, 5.3 Hz, 2H), 3.99 (s, 3H), 3.05 (t, J = 6.2 Hz, 2H), 2.98 – 2.81 (m, 2H), 2.43 – 2.29 (m, 2H), 1.80 – 1.69 (m, 2H), 1.44 (sextet, J = 7.4 Hz, 2H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 167.6, 154.3, 144.2, 140.7, 139.7, 127.4, 125.5, 121.3, 120.7, 115.5, 113.4, 110.4, 52.3, 40.7, 34.2, 32.1, 22.8, 22.1, 21.5, 14.1; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{23}\text{N}_3\text{O}_2$ 323.1760; Found, 323.1770.

3-(Methoxymethyl)-5,6-dihydro-4*H*-indolo[3,2,1-*ij*][1,6]naphthyridine (1h): 1-(6-methoxyhex-4-yn-1-yl)-1*H*-indole-3-carbaldehyde (128 mg, 0.50 mmol), *tert*-butylamine (3.0 mL), $[\text{Cp}^*\text{Rh}(\text{MeCN})_3](\text{SbF}_6)_2$ (**C1**, 10.6 mg, 2.5 mol %), $\text{Cu}(\text{OAc})_2$ (197 mg, 2.1 equiv) and dichloroethane (3.0 mL) were employed. Upon silica gel column chromatography purification using MeOH in DCM gradient elution (0–10%), compound **1h** was isolated as a yellow solid (83 mg, 66%). M.p. 97–99 °C; FTIR (thin film, cm^{-1}) 2915, 2881, 2801, 1571, 1442; ^1H NMR (400 MHz, CDCl_3) δ 9.11 (s, 1H), 8.14 (dt, J = 7.8, 1.0 Hz, 1H), 7.52 (ddd, J = 8.3, 7.2, 1.2 Hz, 1H), 7.42 (dt, J = 8.2, 0.9 Hz, 1H), 7.31 (ddd, J = 8.1, 7.2, 1.0 Hz, 1H), 4.76 (s, 2H), 4.27 – 4.15 (m, 2H), 3.46 (s, 3H), 3.15 (t, J = 6.2 Hz, 2H), 2.43 – 2.27 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 147.7, 142.9, 140.4, 139.6, 126.4, 121.5, 121.3, 120.3, 117.4, 115.4, 108.8, 73.9, 58.4, 40.7, 22.1, 21.2; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{17}\text{N}_3\text{O}$ 253.1341; Found, 253.1345.

3-(3-(Tetrahydro-2*H*-pyran-2-yl)oxy)propyl)-5,6-dihydro-4*H*-indolo[3,2,1-*ij*][1,6]naphthyridine (1i): 1-(8-(tetrahydro-2*H*-pyran-2-yl)oxy)oct-4-yn-1-yl)-1*H*-indole-3-carbaldehyde (178 mg, 0.50 mmol), *tert*-butylamine (3.0 mL), $[\text{Cp}^*\text{Rh}(\text{MeCN})_3](\text{SbF}_6)_2$ (**C1**, 10.6 mg, 2.5 mol %), $\text{Cu}(\text{OAc})_2$ (197 mg, 2.1 equiv) and dichloroethane (3.0 mL) were employed. Upon silica gel column chromatography purification using ethyl acetate in hexanes gradient elution (0–50%), compound **1i** was isolated as an orange oil (149 mg, 85%). FTIR (thin film, cm^{-1}) 2927, 1605, 1569, 1443, 1355, 1322; ^1H NMR (400 MHz, CDCl_3) δ 9.07 (s, 1H), 8.16 – 8.07 (m, 1H), 7.49 (ddd, J = 8.4, 7.1, 1.2 Hz, 1H), 7.39 (dt, J = 8.0, 0.9 Hz, 1H), 7.33 – 7.28 (m, 1H), 4.66 – 4.55 (m, 1H), 4.26 – 4.17 (m, 2H), 3.95 – 3.78 (m, 2H), 3.48 (dt, J = 9.8, 6.5 Hz, 2H), 3.12 – 2.94 (m, 4H), 2.34 (m, 2H), 2.16 – 2.02 (m, 2H), 1.79 – 1.47 (m, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ 152.6, 143.1, 142.5, 140.3, 139.9, 128.6, 128.4, 126.1, 125.8, 121.7, 121.3, 120.2, 116.3, 113.4, 108.8, 40.7, 36.0, 34.1, 31.5, 22.3, 21.6; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{22}\text{H}_{27}\text{N}_3\text{O}_2$ 351.2067; Found, 351.2054.

3-(3-Phenylpropyl)-5,6-dihydro-4*H*-indolo[3,2,1-*ij*][1,6]naphthyridine (1k): 1-(8-phenyloct-4-yn-1-yl)-1*H*-indole-3-carbaldehyde (165 mg, 0.50 mmol), *tert*-butylamine (3.0 mL), $[\text{Cp}^*\text{Rh}(\text{MeCN})_3](\text{SbF}_6)_2$ (**C1**, 10.6 mg, 2.5 mol %), $\text{Cu}(\text{OAc})_2$ (197 mg, 2.1 equiv) and dichloroethane (3.0 mL) were employed. Upon silica gel column chromatography purification using ethyl acetate in hexanes gradient elution (0–50%), compound **1k** was isolated as an orange oil (142 mg, 87%). FTIR (thin film, cm^{-1}) 2930, 1604, 1570, 1497, 1444, 1321; ^1H NMR (400 MHz, CDCl_3) δ 9.10 (s, 1H), 8.14 (dt, J = 7.8, 1.0 Hz, 1H), 7.51 (ddd, J = 8.3, 7.2, 1.2 Hz, 1H), 7.41 (dt, J = 8.1, 0.9 Hz, 1H), 7.34 – 7.27 (m, 4H), 7.26 – 7.17 (m, 3H),

4.25 – 4.14 (m, 2H), 3.02 – 2.93 (m, 4H), 2.80 – 2.72 (m, 2H), 2.34 (dq, J = 6.8, 5.8 Hz, 2H), 2.19 – 2.08 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 152.6, 143.1, 142.5, 140.3, 139.9, 128.6, 128.4, 126.1, 125.8, 121.7, 121.3, 120.2, 116.3, 113.4, 108.8, 40.7, 36.0, 34.1, 31.5, 22.3, 21.6; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{23}\text{N}_2$ 327.1856; Found, 327.1822.

1-*n*-Butyl-8,9-dihydro-7*H*-pyrrolo[3,2,1-*ij*][1,6]naphthyridine (1l): 1-(non-4-yn-1-yl)-1*H*-pyrrole-3-carbaldehyde (109 mg, 0.50 mmol), *tert*-butylamine (3.0 mL), $[\text{Cp}^*\text{Rh}(\text{MeCN})_3](\text{SbF}_6)_2$ (**C1**, 10.6 mg, 2.5 mol %), $\text{Cu}(\text{OAc})_2$ (197 mg, 2.1 equiv) and dichloroethane (3.0 mL) were employed. Upon silica gel column chromatography purification using ethyl acetate in hexanes gradient elution (0–50%), compound **1l** was isolated as an orange oil (57 mg, 53%); FTIR (thin film, cm^{-1}) 2951, 2928, 2869, 1670, 1619, 1460; ^1H NMR (300 MHz, CDCl_3) δ 8.71 (s, 1H), 7.04 (d, J = 3.1 Hz, 1H), 6.47 (d, J = 3.1 Hz, 1H), 4.12 (t, J = 5.7 Hz, 2H), 2.95 (t, J = 6.2 Hz, 2H), 2.84 (t, J = 7.8 Hz, 2H), 2.27 (quintet, J = 6.0 Hz, 2H), 1.79 – 1.63 (m, 2H), 1.41 (dq, J = 14.6, 7.3 Hz, 2H), 0.94 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 148.1, 140.2, 138.9, 126.9, 121.4, 113.8, 99.9, 43.6, 33.5, 32.3, 22.8, 22.7, 21.3, 14.1; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{19}\text{N}_2$ 215.1548; Found, 215.1556.

Methyl 1-butyl-8,9-dihydro-7*H*-pyrrolo[3,2,1-*ij*][1,6]naphthyridine-5-carboxylate (1m): methyl 4-formyl-1-(non-4-yn-1-yl)-1*H*-pyrrole-2-carboxylate (138 mg, 0.50 mmol), *tert*-butylamine (3.0 mL, 1.50 mL/mmol), $[\text{Cp}^*\text{Rh}(\text{MeCN})_3](\text{SbF}_6)_2$ (**C1**, 10.6 mg, 2.50 mol%), $\text{Cu}(\text{OAc})_2$ (197 mg, 2.1 equiv) and dichloroethane (3.0 mL) were employed. Upon silica gel column chromatography purification using MeOH in DCM gradient elution (0–10%), compound **1m** was isolated as a yellow solid (105 mg, 71%). M.p. 58–60 °C; FTIR (thin film, cm^{-1}) 2953, 2858, 1709, 1614, 1436; ^1H NMR (300 MHz, CDCl_3) δ 8.80 (s, 1H), 7.23 (s, 1H), 4.50 (t, J = 5.8 Hz, 2H), 3.92 (s, 3H), 2.94 (t, J = 6.2 Hz, 2H), 2.85 (t, J = 7.8 Hz, 2H), 2.26 (quintet, J = 6.0 Hz, 2H), 1.70 (m, 2H), 1.41 (dq, J = 14.5, 7.3 Hz, 2H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 162.2, 150.6, 142.7, 140.8, 127.8, 119.7, 114.5, 108.4, 51.7, 43.7, 33.8, 32.1, 22.8, 22.8, 21.2, 14.0; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{21}\text{N}_2\text{O}_2$ 273.1603; Found, 273.1610.

Suzuki-Miyaura Coupling of Bromoisocanthine 1e

3-*n*-Butyl-10-cyclopropyl-5,6-dihydro-4*H*-indolo[3,2,1-*ij*][1,6]naphthyridine (4a): To a 2-dram vial was added bromoisocanthine **1e** (86 mg, 0.25 mmol), potassium cyclopropyltrifluoroborate (45 mg, 1.2 equiv), palladium(II) acetate (5.8 mg, 10 mol %), di-(1-adamantyl)-*n*-butylphosphine (14.2 mg, 15 mol %), Cs_2CO_3 (245 mg, 3.0 equiv), PhMe (1.0 mL) and water (0.10 mL). The mixture was vacuumed and backfilled with nitrogen ($\times 3$) and heated to 100 °C for 16 h. The mixture was cooled to 23 °C, diluted with acetone (10 mL) and concentrated. The residue was purified by silica gel column chromatography using EtOAc in hexanes (0–80%) as eluent to afford compound **4a** as a pale yellow oil (32 mg, 42%). FTIR (thin film, cm^{-1}) 2954, 2927, 2857, 1610, 1575; ^1H NMR (400 MHz, CDCl_3) δ 9.05 (d, J = 0.7 Hz, 1H), 7.82 (dt, J = 1.5, 0.7 Hz, 1H), 7.30 – 7.26 (m, 2H), 4.25 – 4.05 (m, 2H), 3.06 – 2.98 (m, 2H), 2.98 – 2.86 (m, 2H), 2.33 (dq, J = 6.8, 5.8 Hz, 2H), 2.16 – 2.02 (m, 1H), 1.80 – 1.70 (m, 2H), 1.50 – 1.38 (m, 2H), 1.04 – 0.99 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H), 0.80 – 0.74 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 143.4, 139.0, 138.8, 124.9, 121.7, 118.3, 115.9, 113.2, 108.4, 103.2, 40.6, 32.1, 29.7, 22.8, 22.1, 21.5, 15.5, 14.1, 9.0; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{25}\text{N}_2$ 305.2018; Found, 305.2031.

3-Butyl-10-(furan-2-yl)-5,6-dihydro-4*H*-indolo[3,2,1-*ij*][1,6]naphthyridine (4b): To a 2-dram vial was added bromoisocanthine **1e** (50 mg, 0.146 mmol), 2-furyl pinacol boronic ester (42 mg, 1.5 equiv), dichlorobis(di-*t*-butylphenylphosphine)palladium(II) (4.8 mg, 5 mol %), $\text{K}_3\text{PO}_4 \cdot \text{H}_2\text{O}$ (67 mg, 2.0 equiv), THF (0.50 mL) and water (0.10 mL). The mixture was vacuumed and backfilled with nitrogen ($\times 3$) and heated to 65 °C for 5 h. The mixture was cooled to room temperature, diluted with acetone (10 mL) and concentrated. The residue was purified by silica gel column chromatography using EtOAc in hexanes (0–80%) as eluent to afford compound **4c** as a pale yellow solid (38 mg,

79%). M.p. 95–96 °C; FTIR (thin film, cm^{-1}) 3073, 2947, 2865, 1612, 1567, 1440; ^1H NMR (300 MHz, CDCl_3) δ 9.09 (s, 1H), 8.40 (d, J = 1.6 Hz, 1H), 7.79 (dd, J = 8.5, 1.7 Hz, 1H), 7.49 (d, J = 1.8 Hz, 1H), 7.35 (d, J = 8.5 Hz, 1H), 6.67 (dd, J = 3.4, 0.8 Hz, 1H), 6.51 (dd, J = 3.3, 1.8 Hz, 1H), 4.17 (t, J = 5.8 Hz, 2H), 3.02 (t, J = 6.2 Hz, 2H), 2.96–2.77 (m, 2H), 2.34 (p, J = 6.0 Hz, 2H), 1.74 (tt, J = 7.9, 6.5 Hz, 2H), 1.45 (sextet, J = 7.3 Hz, 2H), 0.97 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 154.8, 153.6, 143.4, 141.4, 140.0, 139.5, 123.6, 122.4, 121.9, 116.5, 116.1, 113.2, 111.7, 108.8, 103.6, 40.6, 34.3, 32.1, 22.9, 22.1, 21.5, 14.1; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{22}\text{H}_{23}\text{N}_2\text{O}$ 331.1810; Found, 331.1819.

ASSOCIATED CONTENT

Supporting Information

General calculation information, copies of ^1H NMR and ^{13}C NMR of new compounds, and X-ray crystallographic data of **4b**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

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REFERENCES

- (1) Yanagisawa, H.; Shimoji, Y.; Hashimoto, T. Jpn. Kokai Tokkyo Koho, JP05310738, 1993, Heisei; *Chem. Abstr.* **1994**, *120*, 245056.
- (2) Clark, R. D.; Miller, A. B.; Berger, J.; Repke, D. B.; Weinhardt, K. K.; Kowalczyk, B. A.; Eglen, R. M.; Bonhaus, D. W.; Lee, C.-H.; Michel, A. D.; Smith, W. L.; Wong, E. H. F. *J. Med. Chem.* **1993**, *36*, 2645.
- (3) Costall, B.; Naylor, R. J. *Curr Drug Targets CNS Neurol. Disord.* **2004**, *3*, 27.
- (4) (a) Gilchrist, T. L.; Kemmitt, P. D. *Tetrahedron* **1997**, *53*, 4447. (b) Naik, P. N.; Khan, A.; Kusurkar, R. S. *Tetrahedron* **2013**, *69*, 10733.
- (5) For recent reviews on hetero-Diels-Alder cycloaddition, see: (a) Blond, G.; Gulea, M.; Mamane, V. *Curr. Org. Chem.* **2016**, *20*, 2161. (b) Ishihara, K.; Sakakura, A. In *Comprehensive Organic Synthesis*, 2nd Ed.; Knochel, P.; Molander, G. A. Eds.; Elsevier, **2014**, *5*, 409.
- (6) (a) Snyder, S. A.; Vosburg, D. A.; Jarvis, M. G.; Markgraf, J. H.; *Tetrahedron* **2000**, *56*, 5329. (b) Naik, P. N.; Khan, A.; Kusurkar, R. S. *Tetrahedron* **2013**, *69*, 10733. (c) Eberle, M. K.; Shapiro, M. J.; Stucki, R. J. *Org. Chem.* **1987**, *52*, 4661.
- (7) (a) Zhang, H.; Larock, R. C.; *Org. Lett.* **2002**, *4*, 3035. (b) Zhang, H.; Larock, R. C.; *J. Org. Chem.* **2003**, *68*, 5132.

- (8) For recent reviews on Rh-catalyzed C–H functionalization, see: (a) Dong, Z.; Ren, Z.; Thompson, S. J.; Xu, Y.; Dong, G. *Chem. Rev.* **2017**, *117*, 9333. (b) Yang, Y.; Lan, J.; You, J. *Chem. Rev.* **2017**, *117*, 8787. (c) Ye, B.; Cramer, N. *Acc. Chem. Res.* **2015**, *48*, 1308. (d) Song, G.; Li, X. *Acc. Chem. Res.* **2015**, *48*, 1007. (e) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2012**, *45*, 814.
- (9) (a) Liu, B.; Song, C.; Sun, C.; Zhou, S.; Zhu, J.; *J. Am. Chem. Soc.* **2013**, *135*, 16625. (b) Stuart, D. R.; Alsabeh, P.; Kuhn, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 18326.
- (10) Guimond, N.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 12050.
- (11) (a) Han, W.; Zhang, G.; Li, G.; Huang, H. *Org. Lett.* **2014**, *16*, 3532. (b) Kim, D.; Park, J.; Jun, C. *Adv. Synth. Catal.* **2013**, *355*, 2667. (c) Shi, Z.; Koester, D. C.; Bouladakis-Arapinis, M.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 12204. (d) Zheng, L.; Ju, J.; Bin, Y.; Hua, R. *J. Org. Chem.* **2012**, *77*, 5794. (e) Zhang, X.; Chen, D.; Zhao, M.; Zhao, J.; Jia, A.; Li, X. *Adv. Synth. Catal.* **2011**, *353*, 719. (f) Too, P. C.; Chua, S. H.; Wong, S. H.; Chiba, S. *J. Org. Chem.* **2011**, *76*, 6159. (g) Too, P. C.; Wang, Y.-F.; Chiba, S. *Org. Lett.* **2010**, *12*, 5688. (h) Parthasarathy, K.; Cheng, C. H. *J. Org. Chem.* **2009**, *74*, 9359. (i) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 3645.
- (12) (a) Guimond, N.; Gorelsky, S.; Fagnou, K. *J. Am. Chem. Soc.* **2011**, *133*, 6449. (b) Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6908. (c) Hyster, T. K.; Rovis, T. *Chem. Commun.* **2011**, *47*, 11846. (d) Hyster, T. K.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 10565. (e) Hyster, T. K.; Rovis, T. *Synlett* **2013**, *24*, 1842. (f) Prakash, P.; Jijy, E.; Aparna, P. S.; Radharkrishnan, K. V. *Tetrahedron Lett.* **2014**, *55*, 916.
- (13) Lian, Y.; Huber, T.; Hesp, K. D.; Bergman, R. G.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 629.
- (14) (a) Martin, R. M.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem.* **2012**, *77*, 2501.
- (15) Zheng, L.; Bin, Y.; Wang, Y.; Hua, R. *J. Org. Chem.* **2016**, *81*, 8911. Two examples of 1-methylisocanthines were reported in this study. We initially attempted the C–H functionalization of aldehyde **3a** under conditions described in ref. 15, however, no significant amount of isocanthine **1a** was observed.
- (16) (a) Huestis, M. P. *J. Org. Chem.* **2016**, *81*, 12545. (b) Huestis, M. P.; Chan, L.; Stuart, D. R.; Fagnou, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 1338.
- (17) Further investigations on this reaction are underway. Coincidentally, no phenyl-substituted alkynes were reported in Fagnou's isoquinoline synthesis, see ref. 10.
- (18) For reviews on Suzuki–Miyaura coupling, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.
- (19) Massardo, P.; Bettarini, F.; Bianchini, E.; Piccardi, P. *Gen. Offen.* **1983**, 3307614.
- (20) Ireland, R. E.; Brown Jr., F. R. *J. Org. Chem.* **1980**, *45*, 1868.
- (21) Baker, M. V.; Brown, D. H.; Skelton, B. W.; White, A. H. *J. Chem. Soc., Dalton Trans.* **2000**, 4607.