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J. Org. Chem., Just Accepted Manuscript • DOI: 10.1021/acs.joc.7b02731 • Publication Date (Web): 28 Nov 2017

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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)pentamethylcyclcopentadienylrhodium(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, antiemetic 5-HT3 receptor antagonists for chemotherapy patients, as well as potential treatments for CNS disorders. Surprisingly, very few syntheses of isocanthines (Scheme 1) have been reported. Typically the reported syntheses employ either thermal cyclization of a 1-azatriene (Scheme 1, A) or intramolecular hetero-Diels-Alder cycloaddition of an alkyne-tethered indole oxime (Scheme 1, B). Unfortunately, these syntheses suffer from very limited scope, the requirement of high reaction temperatures, or low yield over multiple steps. Larock’s isocanthine synthesis 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 reactions have attracted much attention in the literature and have been employed in synthesizing an array of interesting heterocycles, such as indoles, isoquinolines, isoquinolones, pyroles, pyridines and polyheterocycles. Inspired by Fagnou’s isoquinoline synthesis from aryl aldimines and alkynes (eq 1), we envisioned that isocanthines could readily be synthesized by C—H functionalization of alkyne-tethered indole tert-butylinmes (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-buty1-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)pentamethylcyclcopentadienylrhodium(III) hexafluoroantimonate (C1) 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*RhCl]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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Variation from the “Standard” Conditions</th>
<th>Conv (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>93</td>
<td>73 (73)</td>
</tr>
<tr>
<td>2</td>
<td>83 °C instead of 100 °C</td>
<td>53</td>
<td>39</td>
</tr>
<tr>
<td>3</td>
<td>no C1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>C1 (1 mol %) as catalyst</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>5</td>
<td>C2 (1.25 mol %) as catalyst</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>6</td>
<td>C3 (1.25 mol %) as catalyst</td>
<td>&lt;5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>7</td>
<td>C4 as catalyst</td>
<td>&lt;5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>8</td>
<td>C5 as catalyst</td>
<td>&lt;5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>9</td>
<td>Cu(OAc)2•H2O as oxidant</td>
<td>86</td>
<td>68</td>
</tr>
<tr>
<td>10</td>
<td>AgOAc as oxidant</td>
<td>30</td>
<td>27</td>
</tr>
<tr>
<td>11</td>
<td>benzoquinone as oxidant</td>
<td>50</td>
<td>&lt;5</td>
</tr>
<tr>
<td>12</td>
<td>PhH(OAc) as oxidant</td>
<td>61</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

*All reactions were performed using 0.50 mmol of 2a in DCE (3.0 mL) in sealed vials for 16 h. *Determined by HPLC analysis. *Assay 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 fluoride 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 unevenly gave the desired products 1f and 1g in 78% and 82%, respectively (Table 2, entries 6–7).

Table 2. Scope of Isocanthine Formation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Indole</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a, R = H</td>
<td>1a</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>3b, R = Me</td>
<td>1b</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>3c, R = MeO</td>
<td>1c</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>3d, R = F</td>
<td>1d</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>3e, R = Br</td>
<td>1e</td>
<td>40</td>
</tr>
<tr>
<td>6</td>
<td>3f, R = OMe</td>
<td>1f</td>
<td>78</td>
</tr>
<tr>
<td>7</td>
<td>3g, R = CO2Me</td>
<td>1g</td>
<td>82</td>
</tr>
<tr>
<td>8</td>
<td>3h, R = CH3OCH3</td>
<td>1h</td>
<td>66</td>
</tr>
<tr>
<td>9</td>
<td>3i, R = (CH3)2OPTH</td>
<td>1i</td>
<td>85</td>
</tr>
<tr>
<td>10</td>
<td>3j, R = Ph</td>
<td>1j</td>
<td>&lt;5</td>
</tr>
<tr>
<td>11</td>
<td>3k, R = (CH3)2Ph</td>
<td>1k</td>
<td>87</td>
</tr>
<tr>
<td>12</td>
<td>3l, R = H</td>
<td>1l</td>
<td>53</td>
</tr>
<tr>
<td>13</td>
<td>3m, R = CO2Me</td>
<td>1m</td>
<td>71</td>
</tr>
</tbody>
</table>
substituted alkyne failed to produce isocanthine product even at an elevated temperature 150 °C (Table 1, entry 10).

Indoles with ether substituted alkynes underwent the intramolecular annulation smoothly, giving the desired functionalized isocanthine, azaindoles. 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,19 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 deprotonation9,12a (via Int2), then alkyn 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-butylation 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 alkynyl-tethered indole-3-carboxaldehydes and tert-butylation using 2.5 mol % of [Cp*Rh(MeCN)3]2(SbF6)3 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 alkyn coordination and insertion, then reductive elimination and tert-butylation fragmentation to afford the desired isocanthine product.
**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). H and 13C NMR spectra were recorded on 300 or 400 MHz Bruker spectrometers and chemical shifts are reported relative to the residual solvent peak (δH 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 Combiblack ISC 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 BN540 apparatus.

**General Experimental Procedure**

(8-Chloro-4-yn-1-yl)benzene: To a flame-dried 50 mL round-bottom flask was added 5-chloro-6-yn-1-yn (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-isopropyl)benzene (1.5 mL, 9.44 mmol, 1.0 equiv). The mixture was then added to 5-MeO-2-NO2 (1.5 mL, 3.0 equiv) and the mixture was stirred at −78 °C for 30 min. The mixture was then added to 8-MeO (1.2 equiv) and acetonitrile (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-chloro-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 (dd, 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, 125.2, 123.9, 122.8, 122.0, 118.0, 110.2, 82.3, 77.8, 45.6, 31.1, 28.7, 22.0, 18.4, 16.4; HRMS (ESI-TOF) m/z: [M + H]⁺ caled for C10H7Cl212.1079; Found, 212.1071.

**Synthesis of 4-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 chloroalkylamine (1.2 equiv) in acetonitrile (10 mL). 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 × 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.

1-(4-yn-1-yl)-1H-indole-3-carboxaldehyde (3a)

To a 20 mL vial was added 1-iodo-2-naphthylamine, sodium iodide (1.5 equiv), cesium carbonate (1.5 equiv), and chloroalkylamine (1.2 equiv) in acetonitrile (10 mL). 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 × 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.

1-(4-yn-1-yl)-1H-indole-3-carboxaldehyde (3a): 1H NMR (400 MHz, CDCl3) δ 7.32 – 7.26 (m, 2H), 7.19 (dd, 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, 125.2, 123.9, 122.8, 122.0, 118.0, 110.2, 82.3, 77.8, 45.6, 31.1, 28.7, 22.0, 18.4, 16.4; HRMS (ESI-TOF) m/z: [M + H]⁺ caled for C10H7Cl212.1079; Found, 212.1071.

1-(4-yn-1-yl)-1H-indole-3-carboxaldehyde (3b)

To a 20 mL vial was added 1-iodo-2-naphthylamine, sodium iodide (1.5 equiv), cesium carbonate (1.5 equiv), and chloroalkylamine (1.2 equiv) in acetonitrile (10 mL). 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 × 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.

1-(4-yn-1-yl)-1H-indole-3-carboxaldehyde (3b): 1H NMR (400 MHz, CDCl3) δ 7.32 – 7.26 (m, 2H), 7.19 (dd, 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, 125.2, 123.9, 122.8, 122.0, 118.0, 110.2, 82.3, 77.8, 45.6, 31.1, 28.7, 22.0, 18.4, 16.4; HRMS (ESI-TOF) m/z: [M + H]⁺ caled for C10H7Cl212.1079; Found, 212.1071.

**Free energy profiles for the mechanism of Rh(III)-catalyzed formation of isocanthine 1.**

**Computed configurations of transition states with selected bond distances shown in angstroms (Å). Some hydrogen atoms are omitted for clarity.**

**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.
5-Methoxy-1-(4-nitro-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-chloronor-4-yn- (53 mg, 1.2 equiv) and acetonitrile (0.6 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, 1562, 1530, 1389; 1H NMR (300 MHz, CDCl3) δ 9.96 (s, 1H), 7.53 (d, J = 2.0 Hz, 1H), 2.70 (t, J = 7.2 Hz, 2H); 13C NMR (75 MHz, CDCl3) δ 184.6, 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: [M + H+] calculated for C19H14NO5; 282.1897; Found, 282.1809.

5-Fluoro-1-(4-nitro-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-chloronor-4-yn- (585 mg, 1.2 equiv) and acetonitrile (0.5 mL) were employed. Upon silica gel column chromatography purification using ethyl acetate in hexanes (0–50%), compound 3d was isolated as a yellow oil (1.26 g, 75%); FTIR (thin film, cm−1) 2925, 2820, 1654, 1530, 1388; 1H NMR (300 MHz, CDCl3) δ 10.02 (s, 1H), 8.35 – 8.29 (m, 1H), 7.77 (s, 1H), 7.45 – 7.38 (m, 3H), 4.36 (t, J = 6.7 Hz, 2H), 4.12 (t, J = 2.1 Hz, 2H), 3.40 (s, 3H), 2.92 – 2.24 (m, 2H), 2.10 (quintet, J = 6.6 Hz, 2H); 13C NMR (75 MHz, CDCl3) δ 184.4, 139.1, 137.1, 125.2, 123.9, 122.7, 118.1, 117.9, 110.2, 84.7, 77.7, 59.7, 54.5, 28.2, 15.9; HRMS (ESI-TOF) m/z: [M + H+] calculated for C19H13FNO5; 265.1383; Found, 265.1383.

1-(5-(4-Methylpent-3-yn-1-yl)-2-pyranoyl)-4-nitro-1H-indole-3-carbaldehyde (3i): 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-methoxy-2-pyranone (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 3i was isolated as a yellow oil (1.25 g, 52%); FTIR (thin film, cm−1) 2924, 1662, 1616, 1543, 1488, 1401; 1H NMR (400 MHz, CDCl3) 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); 13C NMR (100 MHz, CDCl3) δ 184.7, 138.8, 137.3, 125.6, 124.1, 123.1, 122.4, 118.3, 116.2, 89.9, 81.9, 78.2, 78.1, 77.7, 40.6, 38.6, 23.5, 19.6, 12.8; HRMS (ESI-TOF) m/z: [M + H+] calculated for C23H22NO5; 354.2064; Found, 354.2045.

1-(5-(Pyren-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-chloronon-1-yn-1-yl)benzene (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, 2949, 2809, 2754, 1654, 1530, 1467; 1H NMR (300 MHz, CDCl3) δ 10.01 (s, 1H), 8.36 – 8.30 (m, 1H), 7.80 (s, 1H), 7.19 – 7.16 (m, 2H), 7.28 – 7.20 (m, 2H), 7.25 (d, J = 7.6 Hz, 2H), 2.45 (t, J = 6.6 Hz, 2H), 2.19 (p, J = 6.6 Hz, 2H); 13C NMR (75 MHz, CDCl3) δ 184.5, 138.6, 137.2, 131.6, 128.4, 128.1, 125.5, 124.0, 123.3, 123.0, 122.2, 118.7, 86.2, 45.7, 28.4, 16.7; HRMS (ESI-TOF) m/z: [M + H+] calculated for C27H23NO5; 388.1388; Found, 388.1399.

1-(8-(Chloro-4-yn-1-yl)-1H-indole-3-carbaldehyde (3k): 1H-indole-3-carbaldehyde (1.07 g, 7.36 mmol), sodium iodide (2.02 g, 1.5 equiv), cesium carbonate (4.33 g, 1.5 equiv), (8-chloro-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 (0–50%), compound 3k was isolated as a yellow oil (1.81 g, 75%); FTIR (thin film, cm−1) 3025, 2953, 1660, 1614, 1576, 1531; 1H NMR (400 MHz, CDCl3) δ 10.01 (s, 1H), 8.36 – 8.29 (m, 1H), 7.76 (s, 1H), 7.46 – 7.39 (m, 1H), 7.37 –
pletion of imine formation (>99% conversion observed by purified using column chromatography to give the desired isocanN)

tert

HRMS (ESINTOF) m/z: [M + H]\(^+\) calced for C\(_{121}\)H\(_{120}\)N\(_{41}\)O\(_{14}\)S\(_{2}\)Found, 279.1861; Found, 279.1868.

3-n-Butyl-10-methoxy-5,6-dihydro-4H-indolo[3,2,1-j][1,6]naphthyridine (1e): 6-methoxy-1-(non-4-yn-1-yl)-1H-indole-3-carboxylic acid (149 mg, 0.50 mmol), tert-butylamine (3.0 mL), [Cp*Rh(MeCN)]\(_2\)BF\(_4\) (C\(_1\), 10.6 mg, 2.5 mol %), Cu(OAc\(_2\)) (197 mg, 2.1 equiv) and dichloroethane (3.0 mL) were employed.  Upon silica gel column chromatography purification using MeOH in DCN gradient elution (0–10%), compound 1f was isolated as a white solid (111 mg, 75%). M.p. 87–88 \(^\circ\)C; FTIR (thin film, cm\(^{-1}\)) 2955, 2931, 2857, 1610, 1572, 1483; 'HNMR (300 MHz, CDCl\(_3\)) \(\delta\) 9.09 (s, 1H), 7.62 – 7.26 (m, 1H), 5.19 (t, J = 7.3 Hz, 2H), 3.63 (s, 3H), 2.58 (s, 3H), 2.23 (s, 6H), 1.95 (q, J = 6.8 Hz, 2H). FTMS (ESI-SIF) m/z: [M + H]\(^+\) calced for C\(_{120}\)H\(_{120}\)N\(_{41}\)O\(_{14}\)S\(_{2}\)Found, 279.1868.

3-n-Butyl-10-fluoro-5,6-dihydro-4H-indolo[3,2,1-j][1,6]naphthyridine (1d): 6-fluoro-1-(non-4-yn-1-yl)-1H-indole-3-carboxylic acid (143 mg, 0.50 mmol), tert-butylamine (3.0 mL), [Cp*Rh(MeCN)]\(_2\)BF\(_4\) (C\(_1\), 10.6 mg, 2.5 mol %), Cu(OAc\(_2\)) (197 mg, 2.1 equiv) and dichloroethane (3.0 mL) were employed.  Upon silica gel column chromatography purification using MeOH in DCN gradient elution (0–50%), compound 1d was isolated as a white solid (118 mg, 75%). M.p. 101–103 \(^\circ\)C; FTIR (thin film, cm\(^{-1}\)) 2952, 2929, 2959, 1633, 1572, 1478; 'HNMR (300 MHz, CDCl\(_3\)) \(\delta\) 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 (dd, J = 14.6, 7.3 Hz, 2H), 0.96 (t, J = 7.3 Hz, 3H); 'CNMR (75 MHz, CDCl\(_3\)) \(\delta\) 152.9, 143.1, 139.6, 138.5, 129.3, 127.1, 121.1, 115.8, 113.0, 108.2, 40.4, 34.2, 32.2, 22.8, 21.4, 14.1; HRMS (ESI-SIF) m/z: [M + H]\(^+\) calced for C\(_{120}\)H\(_{115}\)N\(_{41}\)O\(_{14}\)S\(_{2}\)Found, 283.1611; Found, 283.1622.

10-Bromo-3-n-butyl-5,6-dihydro-4H-indolo[3,2,1-j][1,6]naphthyridine (1c): 5-bromo-1-(non-4-yn-1-yl)-1H-indole-3-carboxylic acid (173 mg, 0.50 mmol), tert-butylamine (3.0 mL), [Cp*Rh(MeCN)]\(_2\)BF\(_4\) (C\(_1\), 10.6 mg, 2.5 mol %), Cu(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 1c was isolated as a pale yellow solid (70 mg, 40%). M.p. 96–98 \(^\circ\)C; FTIR (thin film, cm\(^{-1}\)) 2945, 2851, 1628, 1570, 1450; 'HNMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.02 (d, J = 0.7 Hz, 1H), 8.21 (dd, J = 2.0, 0.3 Hz, 1H), 7.75 (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 (dd, J = 14.8, 7.3 Hz, 2H), 0.96 (t, J = 7.3 Hz, 3H); 'CNMR (101 MHz, CDCl\(_3\)) \(\delta\) 153.9, 143.2, 140.0, 138.8, 128.6, 128.3, 123.3, 115.2, 113.2, 108.9, 104.6, 34.2, 32.1, 22.1, 21.4, 14.1; HRMS (ESI-SIF) m/z: [M + H]\(^+\) calced for C\(_{120}\)H\(_{115}\)Br\(_2\)N\(_{41}\)O\(_{14}\)S\(_{2}\)Found, 343.0826; Found, 343.0826.

3-n-Butyl-9-methoxy-5,6-dihydro-4H-indolo[3,2,1-j][1,6]naphthyridine (1f): 6-methoxy-1-(non-4-yn-1-yl)-1H-indole-3-carboxylic acid (149 mg, 0.50 mmol), tert-butylamine (3.0 mL), [Cp*Rh(MeCN)]\(_2\)BF\(_4\) (C\(_1\), 10.6 mg, 2.5 mol %), Cu(OAc\(_2\)) (197 mg, 2.1 equiv) and dichloroethane (3.0 mL) were employed.  Upon silica gel column chromatography purification using MeOH in DCN 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, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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: [M + H]^+ calculated for C₁₆H₁₃NO₂ 295.1810; Found, 295.1823.

**Methyl-3-butyl-5,6-dihydro-4H-indole[3,2,1-i][j][1,6]naphthyridine-5-carboxylate (1m):** methyl 3-formyl-(non-4-y-1-yl)-1H-indole-3-carboxylic acid (165 mg, 0.50 mmol), tert-butylamine (3.0 mL), Cu(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 (0–100%), compound 1m was isolated as an orange oil (57 mg, 53%); FTIR (thin film, cm⁻¹) 2951, 2928, 2869, 1670, 1619, 1460; ¹H NMR (300 MHz, CDCl₃) δ 8.81 (s, 1H), 7.04 (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 – 1.93 (m, 2H), 1.41 (dq, J = 14.6, 7.3 Hz, 2H), 0.94 (t, J = 7.3 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 148.1, 140.2, 138.9, 126.9, 121.4, 113.9, 99.9, 43.6, 33.5, 32.3, 22.8, 22.7, 21.3, 14.1; HRMS (ESI-TOF) m/z: [M + H]^+ calculated for C₁₆H₁₃NO₂ 215.1584; Found, 215.1556.

**1-butyl-8,9-dihydro-7H-pyrrolo[3,2,1-i][j][1,6]naphthyridine-5-carboxylate (1m):** methyl 4-formyl-(non-4-y-1-yl)-1H-pyrrole-3-carboxylic acid (138 mg, 0.50 mmol), tert-butylamine (3.0 mL, 1.50 mL/mmol), Cu(OAc)₂ (106 mg, 2.50 mol%), Cu(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 (0–100%), 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, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) δ 162.2, 150.6, 142.7, 148.0, 127.8, 119.7, 114.5, 108.4, 51.7, 43.7, 33.8, 32.1, 22.8, 22.2, 21.2, 14.0; HRMS (ESI-TOF) m/z: [M + H]^+ calculated for C₁₆H₁₃NO₂ 273.1603; Found, 273.1610.

**Suzuki-Miyaura Coupling of Bromosiocanthene 1e**

**3-Butyl-10-cyclopropyl-5,6-dihydro-4H-indole[3,2,1-i][j][1,6]naphthyridine (4a):** To a 2-dram vial was added bromosiocanthene 1e (86 mg, 0.25 mmol), potassium cyclopropylfluoroborate (45 mg, 1.2 equiv), palladium(II) acetate (5.8 mg, 0.10 mol%), di-(1-adamantyl)-n-butylphosphine (14.2 mg, 0.15 mol%), PPh₃ (2.45 mg, 3.0 equiv), PhMe (1.0 mL) and water (0.10 mL). The mixture was vacuumed and backfilled with nitrogen (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, CDCl₃) δ 9.05 (d, J = 0.7 Hz, 1H), 7.82 (d, 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, 1H), 1.50 – 1.38 (m, 2H), 1.04 – 0.99 (m, 2H), 0.70 (t, J = 7.4 Hz, 3H), 0.47 (m, 2H), 0.27 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 143.4, 139.0, 138.8, 124.9, 121.7, 118.3, 115.9, 112.0, 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: [M + H]^+ calculated for C₁₆H₁₃NO₂ 232.0518; Found, 305.2031.

**3-Butyl-10-(furan-2-yl)-5,6-dihydro-4H-indole[3,2,1-i][j][1,6]naphthyridine (4b):** To a 2-dram vial was added bromosiocanthene 1e (50 mg, 0.146 mmol), 2-furfuryl pinacol boronic ester (42 mg, 1.5 equiv), dichlorobis(dii-tert-butylyphosphine)palladium(II) (4.8 mg, 0.05 mol%), K₂PO₄·H₂O (67 mg, 2.0 equiv), THF (0.50 mL) and water (1.0 mL). The mixture was vacuumed and backfilled with nitrogen (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, 60% yield).
ASSOCIATED CONTENT
Supporting Information
General calculation information, copies of ¹H NMR and ¹³C 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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ACKNOWLEDGMENTS
This paper is dedicated to Professor Richard C. Larock, Emeritus Professor of Chemistry at Iowa State University on the occasion of his 73rd birthday. The authors would like to thank Dr. Kevin Kou (University of California, Berkeley) for helpful discussion, Dr. Kenji Kurita (Genentech, Inc.) for collecting HRMS data, Mr. Malcolm Huestis (Genentech, Inc.) for providing catalyst C1, and Dr. Francis Gosselin (Genentech Inc.) for proof-reading the manuscript. AYC, RS and BMS are grateful to the NSF under the CCI Center for Selective C=H Functionalization (CHE-1205646 and CHE-1700982) for support.

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(15) Zheng, L.; Bin, Y.; Wang, Y.; Hua, R. J. Org. Chem. 2016, 81, 8911. Two examples of 1-methilisocanthines 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 isocanthene 1a was observed.
(17) Further investigations on this reaction are underway. Coincidentally, no phenyl-substituted alkynes were reported in Fagnou’s isoquinoline synthesis, see ref. 10.