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

Anthony Y. Chen,[†,‡,§] Qianqian Lu,[¶] Yao Fu,*[,¶] Richmond Sarpong,[‡] Brian M. Stoltz,[§] and Haiming Zhang*[,†]

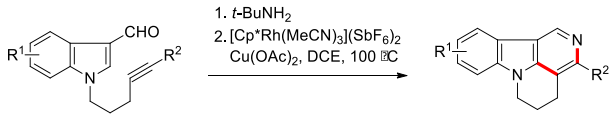
[†]Department of Small Molecule Process Chemistry, Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080, United States

[‡]Department of Chemistry, University of California, Berkeley, CA 94720, United States

[§]Warren and Katherine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA 91125, United States

[¶]Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, China

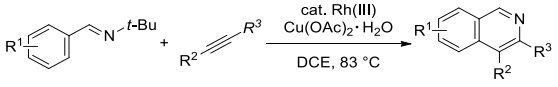
Supporting Information Placeholder



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.

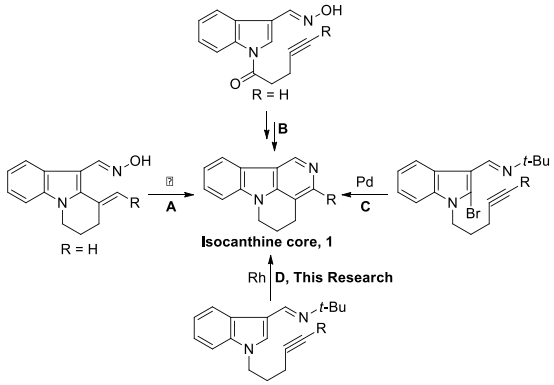
Isocanthines are a class of tetracyclic γ-carbolines that have demonstrated widespread clinical use as cardiovascular agents,[1] antiemetic 5-HT_3 receptor antagonists for chemotherapy patients,[2] as well as potential treatments for CNS disorders.[3] Surprisingly, very few syntheses of isocanthines (**Scheme 1**) have been reported. Typically the reported syntheses employ either thermal cyclization of a 1-azatriene[4] (**Scheme 1, A)** or intramolecular hetero-Diels-Alder cycloaddition[5] 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 synthesis[7] 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[8] 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] pyridines[14] and polyheterocycles.[15] Inspired by Fagnou's isoquinoline synthesis[10] 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.



(1)

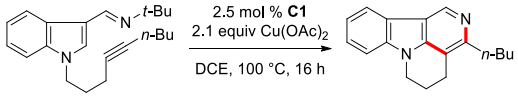
Scheme 1. Synthetic strategies to Isocanthines



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 $[Cp^*RhCl_2]_2$ (**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, $Cu(OAc)_2•H_2O$ which was used in Fagnou's isoquinoline synthesis[10] resulted in 86% conversion and 68% assay yield of the desired product (Table 1, entry 9). The lower yield was probably due to partial hydrolysis of imine **2a** to the corresponding aldehyde under the reaction conditions. 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]



2a 1a

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	$Cu(OAc)_2•H_2O$ as oxidant	86	68
10	AgOAc as oxidant	30	27
11	benzoquinone as oxidant	50	<5
12	$PhI(OAc)_2$ as oxidant	61	< 5

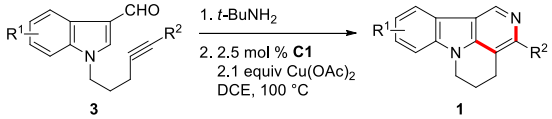
$[Cp^*Rh(MeCN)_3](SbF_6)_2$	$[Cp^*RhCl_2]_2$	$[Rh(COD)Cl]_2$	$Pd(OAc)_2$	$Pd(TFA)_2$
C1	***C2***	***C3***	***C4***	***C5***

[a]All reactions were performed using 0.50 mmol of **2a** in DCE (3.0 mL) in sealed vials for 16 h. [b]Determined by HPLC analysis. [c]Assay yields determined by quantitative HPLC analysis. The number in parentheses is the isolated yield.

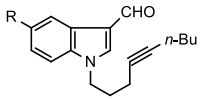
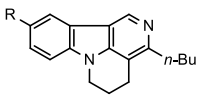
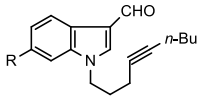
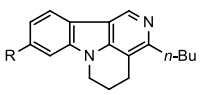
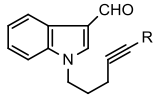
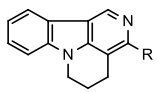
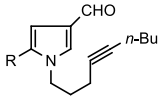
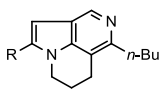
We next examined the substrate scope and limitations of this Rh(III)-catalyzed isocanthine synthesis. It is worth mentioning that the transformation of the aldehydes to the corresponding ***tert***-butylimines is essentially quantitative, thus requiring no further purification and characterization of 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 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 (CO_2Me, **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]



3 1

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_2Me	**1g**	82
			
8	**3h**, R = CH_2OCH_3	**1h**	66
9	**3i**, R = $(CH_2)_3OTHP$	**1i**	85
10[d]	**3j**, R = Ph	**1j**	<5
11	**3k**, R = $(CH_2)_3Ph$	**1k**	87
			
12	**3l,** R = H	**1l**	53
13	**3m,** R = CO_2Me	**1m**	71

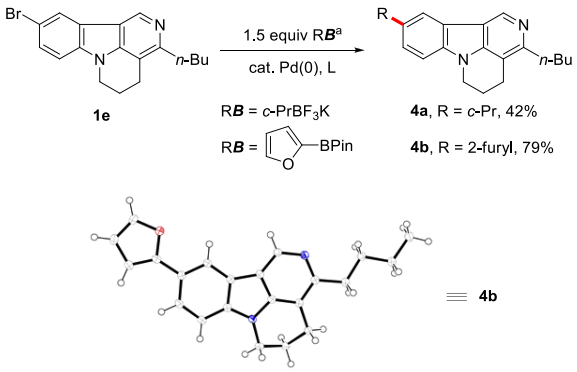
[a]All reactions were performed using 0.50 mmol of **3** in ***t***-$BuNH_2$ (3.0 mL) at 80 °C for 2 h, followed by $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (**C1**, 2.5 mol %), $Cu(OAc)_2$ (2.1 equiv) in DCE (3.0 mL) at 100 °C

in sealed vials for 16 h. [b]Isolated yield. [c]30A% of isocanthine **1a** was observed by HPLC. [d]Reaction 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% yiled of isocanthine **1k** (Table 2, entry 11). This isocanthine synthesis could also be extended to alkyne-tethered pyrroles for the synthesis of annulated 5-azadindoles. 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 strucure of isocanthine **4b** was established unambiguously by single-crystal X-ray diffraction analysis.

Scheme 2. Synthetic Utility of Bromoisocanthine 1d[a]



[a]Conditions: (**4a**), $Pd(OAc)_2$ (10 mol %), di(1-adamanyl)-***n***-butylphosphine (15 mol %), Cs_2CO_3 (3.0 equiv), ***c***-$PrBF_3K$ (1.5 equiv), PhMe:H_2O (10:1), 100 °C. (**4b**), Pd(dtbpp)Cl_2 (5 mol %), 2-furyl pinacol ester (1.5 equiv), K_3PO_4•H_2O (2 equiv), THF:H_2O (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 begining 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**.

In conclusion, 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 $[Cp^*Rh(MeCN)_3](SbF_6)_2$ 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.

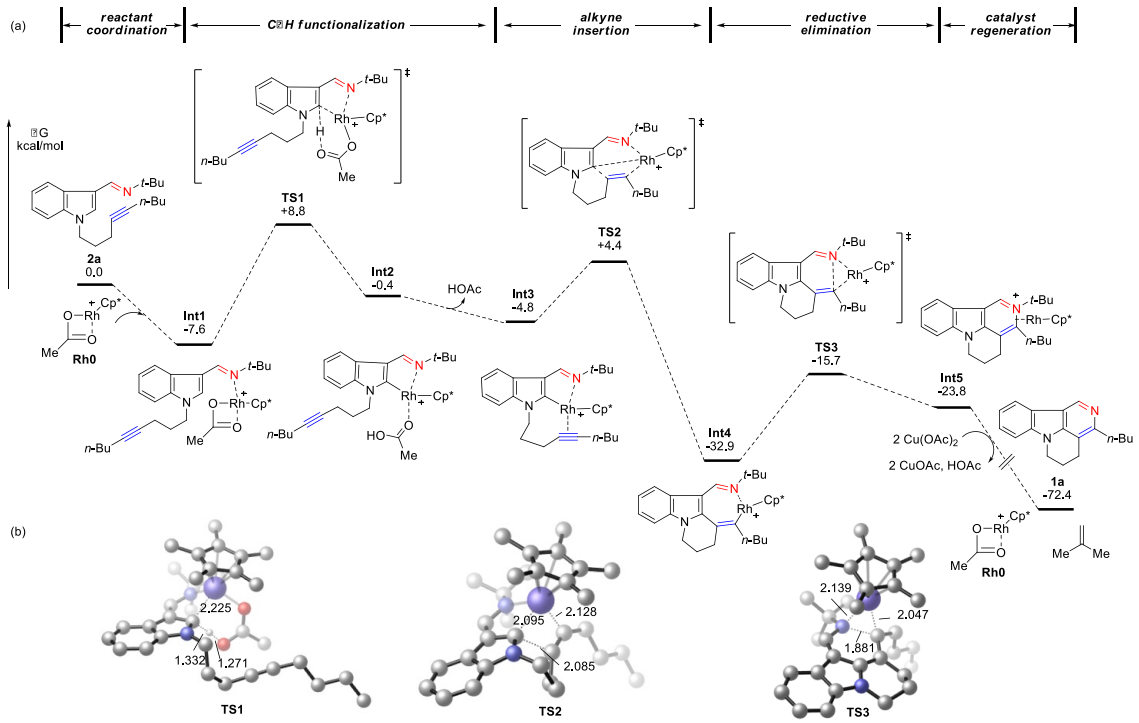


Figure 1. (**a**) Free energy profiles for the mechanism of Rh(III)-catalyzed formation of isocanthine **1a**. (b) Computed configurations of transition states with selected bond distances shown in angstroms (Å). Some hydrogen atoms are omitted for clarity.

ASSOCIATED CONTENT

Supporting Information

General experimental and calculation information, copies of ^{1}H 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.

AUTHOR INFORMATION

Corresponding Author

* Email: fuyao@ustc.edu.cn; zhang.haiming@gene.com

Notes

This research was presented in the Symposium of Applications of C–H Functionalization, Pacifichem, Honolulu, HI in December, 2015. AYC was an undergraduate summer intern at Genentech Inc. where this work was initiated. The authors declare no competing financial interest.

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.

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. (b) Ye, B.; Cramer, N. ***Acc. Chem. Res.*** **2015**, ***48***, 1308. (c) Song, G.; Li, X. ***Acc. Chem. Res.*** **2015**, ***48***, 1007. (d) 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.; Boultadakis-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.