JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
pubs.acs.org/JACS

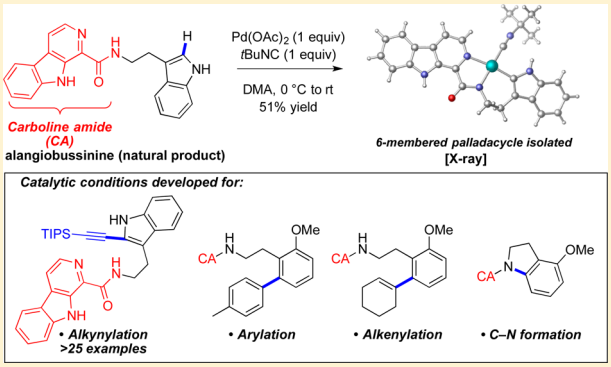
β-Carboline Amides as Intrinsic Directing Groups for C(sp^2)−H Functionalization

Hélène M.-F. Viart,[†] Andreas Bachmann, William Kayitare, and Richmond Sarpong*

Department of Chemistry, University of California, Berkeley, California 94720, United States

Supporting Information

ABSTRACT: Many site-selective palladium-catalyzed C−H functionalization methods require directing groups. We report here β-carboline amides as intrinsic directing groups for C(sp^2)−H functionalization. Various substrates including the natural product alangiobussinine and the marinacarboline core structure were functionalized using carboline-directed δ-C(sp^2)−H alkynylations. This transformation proceeds under mild conditions and is compatible with a wide variety of β-arylethamines. δ-Alkynylation of β-arylethamines via a six-membered palladacycle is favored over γ-C(sp^2)−H bond functionalization when both positions are accessible. The versatility of β-carboline amides as directing groups is evidenced by other δ-C(sp^2)−H functionalizations such as alkenylation, arylation, and C−N bond formation.



1. INTRODUCTION

The emergence of powerful transition metal-catalyzed C−H functionalization methods over the past decade and a half has provided new tools for chemical synthesis. Despite continuing efforts to identify traceless directing groups that can be introduced and removed under the conditions used in the functionalization reaction,[1] most selective C−H functionalization methods exploit intrinsic reactivity differences between C−H bonds in a substrate, coupled with the ability of auxiliaries (directing groups) to direct metalation at specific positions. In the majority of cases, it is necessary to introduce the auxiliary prior to C−H activation and then remove it at the end of the functionalization. Therefore, typical drawbacks of this approach are an increased number of synthetic manipulations, as well as the challenges inherent in introducing and removing the directing group. Generally, directing groups are appended to functional groups common in complex molecules, where C−H functionalization technology is increasingly employed.[2]

Drawing inspiration from substrate-controlled (diastereoselective) processes, where the controlling element for stereoselectivity is inherent to the substrate, we envisioned an analogous scenario for directed C−H functionalization, where the directing group is resident in the substrate and in the product. In this way, the requirement for removing the directing group post C−H functionalization is obviated. For this purpose, we have been especially drawn to directing groups based on pyridine that utilize two-point binding.

The picolinamide and 8-aminoquinoline amide, first reported by Daugulis for the palladium-catalyzed γ- and β-arylation of aliphatic amine and carboxylic acid derivatives, respectively,[3] have emerged as a privileged directing group. However, the removal of these directing groups has historically been challenging. Several solutions to this challenge are beginning to appear. For example, recently, Chen and co-workers reported two variants of the picolinamide and 8-aminoquinoline amide directing groups: the TBS-protected methylene hydroxyl group at the ortho position of the picolinamide (PA),[4] and 8-amino-5-methoxyquinoline (MQ) directing groups,[5] which are easily cleaved through intramolecular acyl transfer under acidic conditions or with ceric ammonium nitrate under mild conditions, respectively.

On the contrary, instances where a picolinamide directing group is employed in C−H functionalization and retained in the targeted product are rare. Only a limited number of examples of bidentate directing groups that are found in or easily derived to afford a target compound have been described. Examples are mostly found for C(sp^3)−H functionalizations in the synthesis and derivatizations of peptides and peptidomimetics, where the auxiliary can be either an amino acid itself[6] or transformed into an amino acid derivative. For instance, the 2-methoxyiminoacetyl (MIA) directing group developed by Fan and Ma has been transformed into a glycine moiety by hydrogenation,[7] and the α-amino oxazolinyl directing group developed by Shi and co-workers was opened and derivatized into amides in a mild, one-pot procedure.[8]

We envisioned β-carboline amides as inherent directing groups that afford many of the advantages of these previously described directing groups. Significantly, β-carbolines and their associated derivatives, which may be accessed in a single step, are found in a number of natural products and pharmaceutically relevant molecules (Figure 1).[9] As such, these "functional

Received: December 6, 2016
Published: January 1, 2017

ACS Publications © 2017 American Chemical Society

DOI: 10.1021/jacs.6b12569
J. Am. Chem. Soc. 2017, 139, 1325−1329

groups" that are innate to the targeted compound may be employed as directing groups for C−H functionalization.

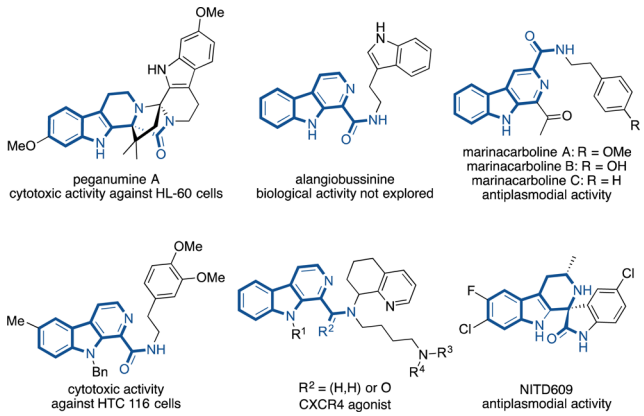
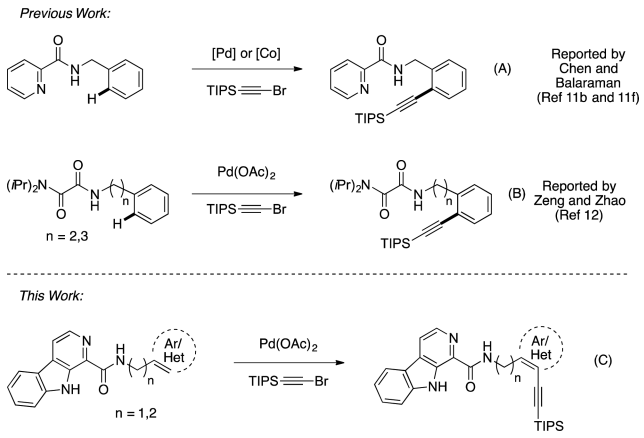


Figure 1. Examples of natural products and biologically active compounds featuring the β-carboline amide motif.

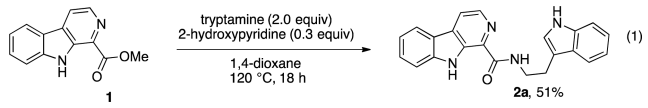
In the context of C−H functionalizations directed by β-carboline amides, we envisioned alkynylations to be particularly useful. Alkynes are versatile building blocks that may be readily transformed into a wide range of functional groups and substituents. Their importance is evidenced by the success of the Sonogashira cross-coupling reaction. Thus, C−H functionalization methods to complement this well-established cross-coupling methodology[10] would be highly useful.



While directed γ-C(sp^2)−H alkynylations abound,[11] to the best of our knowledge, there has only been one report describing the palladium-catalyzed *ortho* C(sp^2)−H alkynylation of aminoalkyl arene derivatives at the δ position, which relies on an oxalylamide directing group.[12] As reported herein, using a β-carboline amide directing group, we have achieved selective palladium-catalyzed γ- and δ-C(sp^2)−H alkynylations via five- and six-membered palladacycle intermediates.[12−14] Our method has been applied to the syntheses of derivatives of the natural products alangiobussinine and marinacarbolines.

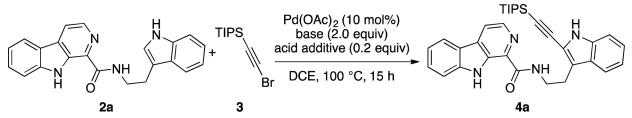
2. RESULTS AND DISCUSSION

Our investigations commenced with studies on the directed alkynylation of alangiobussinine (**2a**), which was prepared in a single step from the known β-carboline-1-methyl ester **1** by activation of the ester moiety using 2-hydroxypyridine under aerobic conditions (eq 1).[15] Our preparation of **2a** from **1** is an improvement in terms of step count and isolated yield over the previously reported synthesis of this natural product.[16] Applying this 2-hydroxypyridine-mediated amidation method, a variety of other β-carboline amide derivatives were accessed in good yields from the corresponding arylethamines. Alternatively, La(OTf)$_3$ could also be employed for the amidation reactions (see the Supporting Information for details).[17]



Alangiobussinine was subjected to the conditions for Pd-catalyzed picolinamide-directed C(sp^2)−H alkynylation reported by Chen and co-workers.[11b] The desired alkynylated product (**4a**) was isolated in 41% yield (Table 1, entry 1). A survey of carboxylic acid additives known to play an important role in the proposed concerted palladation-deprotonation step[18] showed that strong acids were detrimental, whereas acid additives with intermediate pK_a (3.5−5) resulted in increased formation of the alkynylated product. *o*-Phenyl benzoic acid (*o*-PBA) has been shown to be an effective carboxylic acid promoter for C(sp^3)−H arylation reactions. In our hands, *o*-PBA and PivOH led to comparable outcomes (Table 1, entries 2−3 and 18−19).[11b,18] A survey of various bases revealed that the nature of the counterion has a significant impact on the reaction outcome with K_2CO_3 giving the best yield (entries 7−18). Surprisingly, silver salts, which are generally believed to act as halogen scavengers and are often beneficial in metal-catalyzed C−H functionalizations, shut down the reaction (entries 8 and 13). Finally, a clear solvent effect was observed: coordinating

Table 1. Optimization of Reaction Conditions[a]



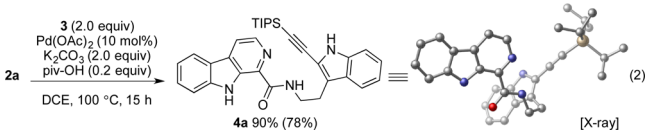
entry	base	additive	yield (%)[b,c]
1[d]	$KHCO_3$	*o*-PBA	41[e]
2	$KHCO_3$	*o*-PBA	72 (18)
3	$KHCO_3$	PivOH	69 (26)
4	$KHCO_3$	AcOH	69 (25)
5	$KHCO_3$	TFA	13 (55)
6	$KHCO_3$	DMBA	65 (22)
7	$KHCO_3$	*o*-MBA	64 (27)
8	AgOAc	*o*-PBA	<5 (>95)
9	NaOAc	*o*-PBA	30 (56)
10	NaOTf	*o*-PBA	7 (64)
11	Cs_2CO_3	*o*-PBA	7 (80)
12	K_2CO_3	*o*-PBA	89 (<5)
13	Ag_2CO_3	*o*-PBA	4 (71)
14	^{t}BuOK	*o*-PBA	23 (68)
15	$NaHCO_3$	*o*-PBA	7 (83)
16	Na_2CO_3	*o*-PBA	63 (28)
17	KOAc	*o*-PBA	77 (15)
18	K_2CO_3	*o*-PBA	89 (5)
19	K_2CO_3	PivOH	90 (4)

[a]Reaction conditions: **2a** (0.05 mmol), **3** (0.1 mmol), Pd(OAc)$_2$ (10 mol %), base (2.0 equiv), acid additive (0.2 equiv), DCE (400 μL), 100 °C. [b]Determined by NMR analysis of the crude mixture using 1,1,2,2-tetrachloroethane as internal standard. [c]Yield of remaining **2a** in parentheses. [d]5 mol % Pd(OAc)$_2$ used instead. [e]Isolated yield. DMBA, 2,6-dimethylbenzoic acid; *o*-MBA, *o*-methylbenzoic acid.

DOI: 10.1021/jacs.6b12569
J. Am. Chem. Soc. 2017, 139, 1325−1329

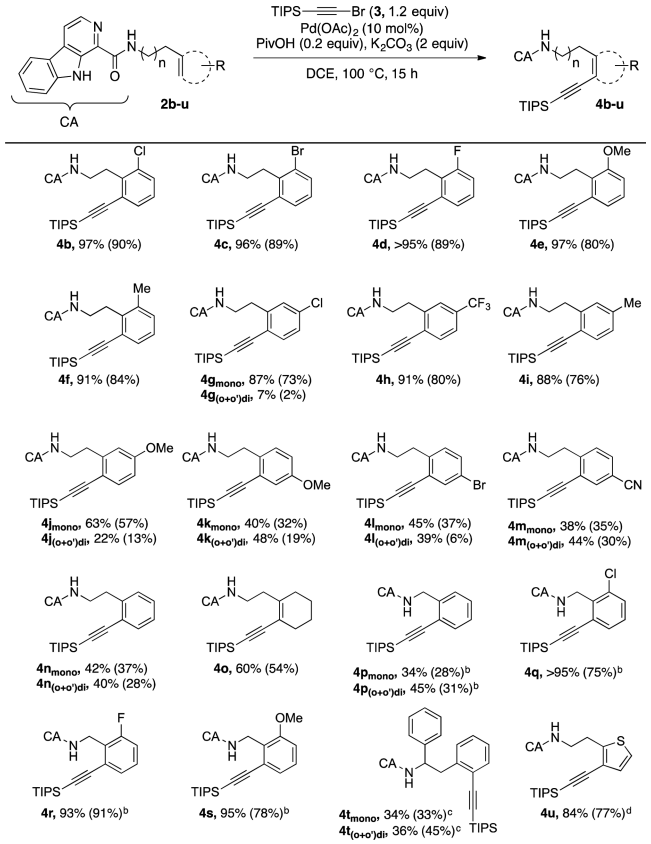
solvents such as DMA, THF, and dioxane impede the reaction, giving moderate yields, whereas chlorinated solvents were superior, with DCE providing the best yields (see the Supporting Information for details).

Under our optimized conditions, alkynylated alangiobussinine derivative **4a** was isolated in 78% yield (eq 2), and its structure was unambiguously confirmed by X-ray crystallographic analysis.[19]



Using the optimized conditions (1.2 equiv of (bromoethynyl)-triisopropylsilane, 10 mol % $Pd(OAc)_2$, 0.2 equiv of PivOH, 2.0 equiv of K_2CO_3, DCE, 100 °C, 15 h),[20] a variety of β-carboline amide derivatives were successfully alkynylated at the δ position (Table 2). Both electron-deficient and electron-rich substrates bearing substituents at the *ortho*- or *meta*- positions were alkynylated in excellent yields favoring the less sterically hindered *ortho*-position (**4b**–**4j**). In some cases, small amounts of dialkynylated products were formed and isolated when *meta*-substituted substrates were employed (see **4g** and **4j**), consistent with observations in other C–H alkynylation reactions.[11c,12]

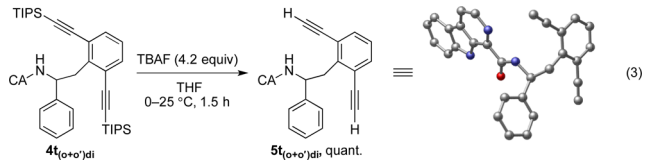
Table 2. Substrate Scope of the Pd-Catalyzed C–H Alkynylation Reaction[a]



[a]Determined by NMR analysis of the crude mixture using 1,1,2,2-tetrachloroethane as internal standard. Isolated yields shown in parentheses. [b]2.0 equiv of **3** used instead at 120 °C for 15 h. [c]At 120 °C for 15 h. [d]3.0 equiv of **3**, 140 °C for 30 min by microwave heating.

Phenethylamine substrates lacking *ortho*- or *meta*-substitution (**4k**–**4n**) gave mixtures of mono- and dialkynylated products under the standard conditions, but selectivity toward the mono- or dialkynylated product could be achieved by varying the equivalents of the bromoalkyne (see the Supporting Information for experiments aimed at the selective synthesis of $\mathbf{4n}_{\mathbf{mono}}$ and $\mathbf{4n}_{(o+o')\mathbf{di}}$). Various functional groups are tolerated under the reaction conditions, including bromide, nitrile, and trifluoromethyl (**4c**, **4l**, **4h**, and **4m**). Therefore, scaffolds displaying a bromide may be further functionalized using Pd^0 cross-coupling processes. Heteroaromatic compounds were alkynylated in good to excellent yields (see **4a**, **4u**). In particular, the presence of a protecting group on the indole nitrogen (see **2a**) is not required, in stark contrast with previously reported alkynylations of tryptamine derivatives.[12]

The vast majority of directed C–H functionalizations, including picolinamide-directed functionalizations, favor γ-functionalization. Presumably, a kinetically favored five-membered palladacycle predominates. However, the β-carboline amide directing group favors functionalization at the δ position via a six-membered palladacycle. We observe selectivity toward δ-functionalization when functionalization via five- and six-membered palladacycles is possible. For example, $\mathbf{4t}_{\mathbf{mono}}$ and $\mathbf{4t}_{(o+o')\mathbf{di}}$ were the sole products of C–H functionalization of the precursor substrate. The identity of the dialkynylated product ($\mathbf{4t}_{(o+o')\mathbf{di}}$) was unambiguously confirmed by X-ray crystallographic analysis of the dialkynylated product after cleavage of the TIPS protecting groups (eq 3).[19] Furthermore, we have found

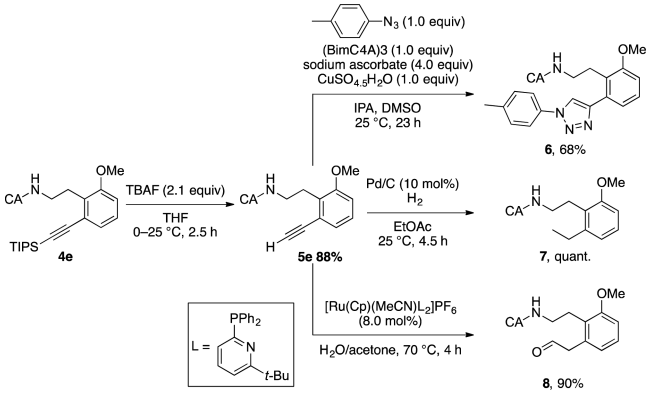


that products that arise from functionalization at the γ position require slightly more demanding conditions (e.g., for **4p**–**4s**, functionalizations occurred at 120 °C instead of 100 °C).

The β-carboline-directed C–H functionalization has proven to be highly general and versatile for $C(sp^2)$–H alkynylation, and has been extended to alkene functionalization (see **4o**).

To highlight the scalability of this reaction, the carboline amide derivative **2e** was alkynylated on 1.0 g (2.90 mmol) scale to afford **4e** in 80% isolated yield. Further derivatizations of **4e** were achieved on terminal alkyne **5e**, obtained in 88% yield by TBAF-mediated cleavage of the TIPS group (Scheme 1). Alkyne **5e** was

Scheme 1. Derivatizations of Alkyne 5e

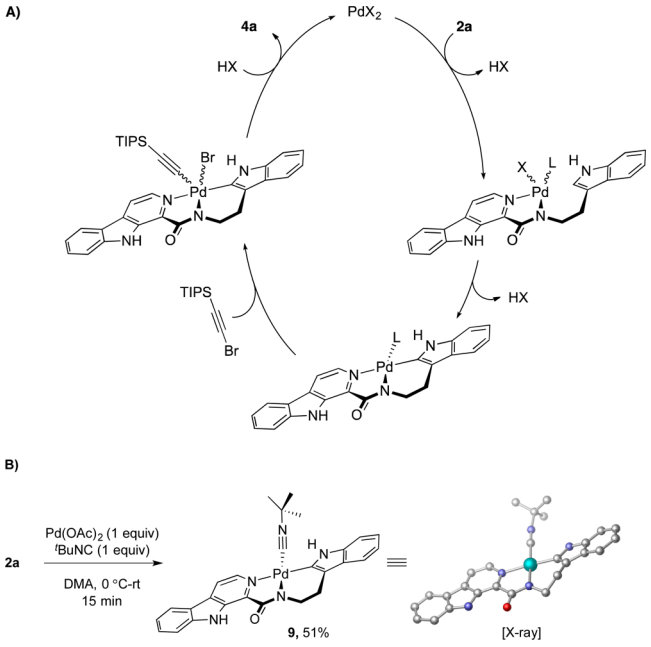


DOI: 10.1021/jacs.6b12569
J. Am. Chem. Soc. 2017, 139, 1325–1329

easily converted to triazole **6** by a copper-catalyzed "click" cycloaddition,[21] hydrogenated to the corresponding alkane (**7**) using Pd/C, and converted to aldehyde **8** through an anti-Markovnikov hydration using Grotjahn's ruthenium complex.[22]

To gain insight into the mechanism of the β-carboline directed functionalization, **2a** was subjected to stoichiometric palladium acetate in DMA in the presence of *tert*-butyl isonitrile. The six-membered palladacycle (**9**) was isolated in 51% yield and unambiguously characterized by X-ray crystallographic analysis (Scheme 2B).[19]

Scheme 2. (A) Proposed Mechanism and (B) Evidence for C−H Activation via Six-Membered Palladacycle

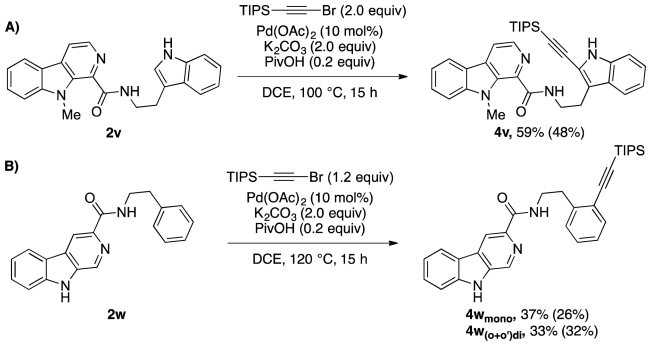


We propose that following C−H activation by a Pd^{II} species to generate a six-membered palladacycle similar to **9**, oxidative addition into the TIPS-protected acetylene bromide generates a Pd^{IV} intermediate, consistent with the observations of Shi and co-workers.[11d] Reductive elimination at this stage provides the alkynylated product. Finally, ligand exchange regenerates the requisite Pd^{II} species to perpetuate the catalytic cycle (Scheme 2A).[23]

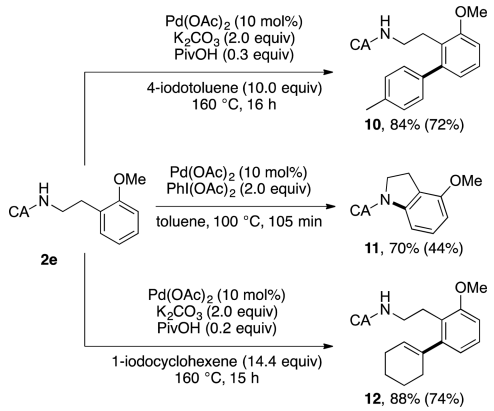
Because a number of pharmaceutically relevant compounds and natural products possess an *N*-alkylated β-carboline-1-carboxylic acid *N*-alkylamide (e.g., **2v**) or β-carboline-3-carboxylic acid *N*-alkylamide (e.g., **2w**) scaffold (see Figure 1), we sought to expand the carboline-directed alkynylations described above to **2v** and **2w** (Scheme 3). Both alkynylated products were successfully isolated. Of note, the presence of the methyl group on the carboline nitrogen slightly decreased the efficiency of the reaction (**4a** vs **4v**), and higher temperatures were required to access **4w** in good yield.

Gratifyingly, the β-carboline amide group directs other C−H functionalization reactions (Scheme 4). For example, using **2e**, arylated and alkenylated products were isolated in high yields, although more vigorous conditions were necessary (see **2e** → **10** and **2e** → **12**). A C−N bond-forming reaction could also be achieved under mild conditions to afford the indoline derivative **11**.

Scheme 3. Expansion of the C(sp^2)−H Alkynylation Reaction to Other β-Carboline Amide Derivatives



Scheme 4. Generalization of β-Carboline Amide as Directing Group for Various C(sp^2)−H Functionalizations



3. CONCLUSION

We report β-carboline amides as a new class of directing groups for a variety of C−H functionalizations that may proceed via five- or six-membered palladacycle intermediates. In particular, we report alkynylation reactions under mild conditions that achieve the functionalization of various β-arylethamine substrates and the natural product alangiobussinine. The synthetic utility of the method was highlighted by the direct derivatization of the alkynylated product into useful groups such as a triazole or aldehyde. The generality of the method is highlighted by the ability of the β-carboline amide to direct other functionalizations such as δ-alkenylation, δ-arylation, and a C−N bond formation to generate an indoline derivative. Finally, we have demonstrated that β-carboline amides can also direct γ-alkynylation, albeit under slightly more demanding conditions, and exclusive δ-alkynylation is achieved in the presence of a more accessible γ-C(sp^2)−H bond.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b12569.

Experimental details and spectroscopic data; procedures, single-crystal X-ray data, and NMR spectra (PDF)
X-ray crystallographic data for sarpong125 (CIF)
X-ray crystallographic data for sarpong136 (CIF)
X-ray crystallographic data for sarpong123 (CIF)

DOI: 10.1021/jacs.6b12569
J. Am. Chem. Soc. 2017, 139, 1325−1329

AUTHOR INFORMATION

Corresponding Author

*rsarpong@berkeley.edu

ORCID

Richmond Sarpong: 0000-0002-0028-6323

Present Address

†The Institute for Neurodegenerative Diseases, University of California, San Francisco, Sandler Neurosciences Center, 675 Nelson Rising Lane, San Francisco, California 94143-0518, United States.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported by the NSF under the CCI Center for Selective C−H Functionalization (CHE-1205646). We are grateful to the Carlsberg Foundation for a postdoctoral scholarship to H.M.-F.V., and to the NSF CCI Center for Selective C−H Functionalization for a summer fellowship for W.K. We thank A. DiPasquale (UC Berkeley) for solving the crystal structures of **4a**, **5**$_{(o+o')\text{di}}$, and **9** (displayed with CYLView), supported by NIH Shared Instrumentation Grant (S10-RR027172).

REFERENCES

(1) (a) Jun, C.-H.; Lee, H.; Hong, J.-B. *J. Org. Chem.* **1997**, *62*, 1200−1201. (b) Mo, F.; Dong, G. *Science* **2014**, *345*, 68. (c) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 112. (d) Lightburn, T. E.; Dombrowski, M. T.; Tan, K. L. *J. Am. Chem. Soc.* **2008**, *130*, 9210. (e) Grünanger, C. U.; Breit, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 7346. (f) Luo, J.; Preciado, S.; Larrosa, I. *J. Am. Chem. Soc.* **2014**, *136*, 4109. (g) Zhang, F.-L.; Hong, K.; Li, T.-J.; Park, H.; Yu, J.-Q. *Science* **2016**, *351*, 252.

(2) For selected reviews and examples of complex molecules synthesis via C−H functionalization, see: (a) Feng, Y.; Chen, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 958. (b) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976. and references therein (c) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885. and references therein (d) Ting, C. P.; Maimone, T. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 3115. (e) Dailler, D.; Danoun, G.; Baudoin, O. *Angew. Chem., Int. Ed.* **2015**, *54*, 4919.

(3) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154.

(4) (a) He, G.; Chen, G. *Angew. Chem.* **2011**, *123*, 5298; *Angew. Chem., Int. Ed.* **2011**, *50*, 5192. (b) He, G.; Zhao, Y.; Zhang, S.; Lu, C.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 3. (c) Zhang, S.-Y.; He, G.; Zhao, Y.; Wright, K.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 7313. (d) Zhang, S.-Y.; He, G.; Nack, W. A.; Zhao, Y.; Li, Q.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 2124.

(5) (a) He, G.; Zhang, S.-Y.; Nack, W. A.; Li, Q.; Chen, G. *Angew. Chem., Int. Ed.* **2013**, *52*, 11124. (b) Wang, B.; Nack, W. A.; He, G.; Zhang, S.-Y.; Chen, G. *Chem. Sci.* **2014**, *5*, 3952. (c) Zhang, S.-Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2015**, *137*, 531.

(6) Gong, W.; Zhang, G.; Liu, T.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 16940.

(7) Fan, M.; Ma, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 12152.

(8) Chen, K.; Li, Z.-W.; Shen, P.-X.; Zhao, H.-W.; Shi, Z.-J. *Chem. - Eur. J.* **2015**, *21*, 7389.

(9) (a) Wang, K.-B.; Di, Y.-T.; Bao, Y.; Yuan, C.-M.; Chen, G.; Li, D.-H.; Bai, J.; He, H.-P.; Hao, X.-J.; Pei, Y.-H.; Jing, Y.-K.; Li, Z.-L.; Hua, H.-M. *Org. Lett.* **2014**, *16*, 4028. (b) Diallo, A. O.; Mehri, H.; Iouzalen, L.; Plat, M. *Phytochemistry* **1995**, *40*, 975. (c) Huang, H.; Yao, Y.; He, Z.; Yang, T.; Ma, J.; Tian, X.; Li, Y.; Huang, C.; Chen, X.; Li, W.; Zhang, S.; Zhang, C.; Ju, J. *J. Nat. Prod.* **2011**, *74*, 2122. (d) Xiao, Z.; Liu, Z.; Lei, C.; Wang, J.; Chen, Z.; Han, G.; Xiao, Y.; He, H.; Chen, S. China Pat. Appl. CN103130800A, June 05, 2013. (e) Clark, M. P.; Lockwood, M. A.; Wagner, F. F.; Natchus, M. G.; Doroh, B. C.; Johnson, T. L.; Tahirovic, Y. A.; Wilson, L.; Wiseman, J. M.; Skudlarek, J. W. PCT Int. Appl. WO2009121063A2, October 01, 2009. (f) Rottmann, M.; McNamara, C.; Yeung, B. K. S.; Lee, M. C. S.; Zou, B.; Russell, B.; Seitz, P.; Plouffe, D. M.; Dharia, N. V.; Tan, J.; Cohen, S. B.; Spencer, K. R.; González-Páez, G. E.; Lakshminarayana, S. B.; Goh, A.; Suwanarusk, R.; Jegla, T.; Schmitt, E. K.; Beck, H.-P.; Brun, R.; Nosten, F.; Renia, L.; Dartois, V.; Keller, T. H.; Fidock, D. A.; Winzeler, E. A.; Diagana, T. T. *Science* **2010**, *329*, 1175.

(10) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. (b) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979. (c) Chinchilla, R.; Nájera, C. *Chem. Soc. Rev.* **2011**, *40*, 5084.

(11) For palladium-catalyzed γ-C(sp^2)−H alkynylations, see: (a) Tobisu, M.; Ano, Y.; Chatani, N. *Org. Lett.* **2009**, *11*, 3250. (b) Zhao, Y.; He, G.; Nack, W. A.; Chen, G. *Org. Lett.* **2012**, *14*, 2948. (c) Ano, Y.; Tobisu, M.; Chatani, N. *Org. Lett.* **2012**, *14*, 354. (d) Ye, X.; Xu, C.; Wojtas, L.; Akhmedov, N. G.; Chen, H.; Shi, X. *Org. Lett.* **2016**, *18*, 2970. For cobalt-catalyzed γ-C(sp^2)−H alkynylations, see:. (e) Sauermann, N.; González, M. J.; Ackermann, L. *Org. Lett.* **2015**, *17*, 5316. (f) Landge, V. G.; Midya, S. P.; Rana, J.; Shinde, D. R.; Balaraman, E. *Org. Lett.* **2016**, *18*, 5252. For ruthenium-catalyzed γ-C(sp^2)−H alkynylations, see: (g) Ano, Y.; Tobisu, M.; Chatani, N. *Synlett* **2012**, *23*, 2763. For rhodium-catalyzed γ-C(sp^2)−H alkynylations, see: (h) Xie, F.; Qi, Z.-S.; Yu, S.-J.; Li, X.-W. *J. Am. Chem. Soc.* **2014**, *136*, 4780. Feng, C.; Loh, T. P. *Angew. Chem., Int. Ed.* **2014**, *53*, 2722. (j) Feng, C.; Feng, D.; Luo, Y.; Loh, T. P. *Org. Lett.* **2014**, *16*, 5956. For nickel-catalyzed γ-C(sp^2)−H alkynylations, see: (k) Liu, Y.-J.; Liu, Y.-H.; Yana, S.-Y.; Shi, B.-F. *Chem. Commun.* **2015**, *51*, 6388. For copper-catalyzed γ-C(sp^2)−H alkynylations, see: (l) Liu, Y.-J.; Liu, Y.-H.; Yin, X.-S.; Gu, W.-J.; Shi, B.-F. *Chem. - Eur. J.* **2015**, *21*, 205.

(12) Guan, M.; Chen, C.; Zhang, J.; Zeng, R.; Zhao, Y. *Chem. Commun.* **2015**, *51*, 12103.

(13) C(sp^3)−H functionalizations via a six-membered Pd-cycle: (a) Subba Reddy, B. V.; Rajender Reddy, L.; Corey, E. J. *Org. Lett.* **2006**, *8*, 3391. (b) He, G.; Zhao, Y.; Zhang, S.; Lu, C.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 3. (c) Nadres, E. T.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 7. (d) Zhang, S.-Y.; He, G.; Nack, W. A.; Zhao, Y.; Li, Q.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 2124. (e) Cui, W.; Chen, S.; Wu, J.-Q.; Zhao, X.; Hu, W.; Wang, H. *Org. Lett.* **2014**, *16*, 4288. (f) Xu, J.-W.; Zhang, Z.-Z.; Rao, W.-H.; Shi, B.-F. *J. Am. Chem. Soc.* **2016**, *138*, 10750.

(14) C(sp^3)−H functionalizations via a six-membered Pd-cycle: (a) Li, J.-J.; Mei, T.-S.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 6452. (b) Jordan-Hore, J. A.; Johansson, C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184. (c) Han, J.; Liu, P.; Wang, C.; Zhao, Y.-S. *Org. Lett.* **2014**, *16*, 5682. (d) Wang, C.; Chen, C.-P.; Zhang, J.-Y.; Yao, Y.-M.; Zhao, Y.-S. *Angew. Chem., Int. Ed.* **2014**, *53*, 9884.

(15) (a) Openshaw, H. T.; Whittaker, N. *J. Chem. Soc. C* **1969**, *89*. (b) Wang, L.-H.; Zipse, H. *Liebigs Ann. Chem.* **1996**, *1996*, 1501.

(16) Baiget, J.; Llona-Minguez, S.; Lang, S.; MacKay, S. P.; Suckling, C. J.; Sutcliffe, O. B. *Beilstein J. Org. Chem.* **2011**, *7*, 1407.

(17) Morimoto, H.; Fujiwara, R.; Shimizu, Y.; Morisaki, K.; Ohshima, T. *Org. Lett.* **2014**, *16*, 2018.

(18) Feng, Y.; Wang, Y.; Landgraf, B.; Liu, S.; Chen, G. *Org. Lett.* **2010**, *12*, 3414 and references therein..

(19) Most H's were removed for clarity. Atoms are shown at the 50% probability level.

(20) While other bromoacetylene derivatives were surveyed, only the use of (bromoethynyl)triisopropylsilane resulted in productive reactivity, consistent with the observations of Chen and Chatani (refs 11b and 11c). Activation/cross-coupling mediated by other metal complexes may be more successful and is currently being investigated.

(21) Rodionov, V. O.; Presolski, S. I.; Gardinier, S.; Lim, Y.-H.; Finn, M. G. *J. Am. Chem. Soc.* **2007**, *129*, 12696−12704.

(22) Grotjahn, D. B.; Lev, D. A. *J. Am. Chem. Soc.* **2004**, *126*, 12232−12233.

(23) Migratory insertion of the bromo-alkyne unit followed by β-Br elimination, as proposed by Chatani (refs 11a and 11b), cannot be discounted.

DOI: 10.1021/jacs.6b12569
J. Am. Chem. Soc. 2017, 139, 1325−1329