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

Cu(II)-Mediated Ortho C−H Alkynylation of (Hetero)Arenes with Terminal Alkynes

Ming Shang,[†] Hong-Li Wang,[†] Shang-Zheng Sun,[§] Hui-Xiong Dai,*[,†] and Jin-Quan Yu*[,†,‡]

[†]State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

[‡]Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, United States

[§]Department of Chemistry, Innovative Drug Research Center, Shanghai University, 99 Shangda Road, Shanghai 200444, China

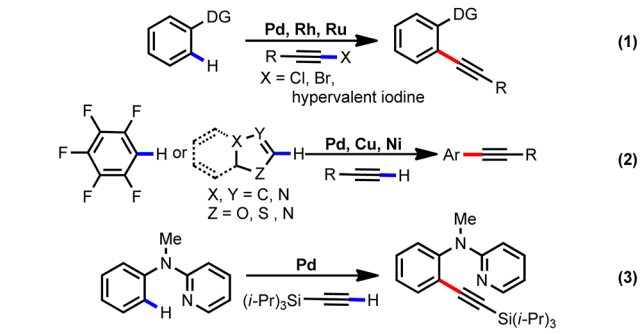
Supporting Information

ABSTRACT: Cu(II)-promoted ortho alkynylation of arenes and heteroarenes with terminal alkynes has been developed to prepare aryl alkynes. A variety of arenes and terminal alkynes bearing different substituents are compatible with this reaction, thus providing an alternative disconnection to Sonogashira coupling.

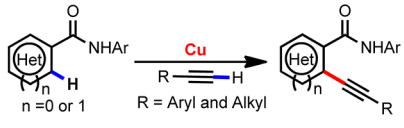
Aryl alkynes are important structural motifs because of their ubiquity in natural products, pharmaceuticals, and materials.[1] Not only are alkynyl groups present in a variety of products with functional significance, but they can also participate in many cross-coupling, metathesis, and cycloaddition reactions.[2] Therefore, the development of efficient synthetic methodologies to construct alkyne motifs is of broad interest. In the past several decades, the Sonogashira coupling reaction has been extensively studied and practiced in both academic and industrial settings.[3]

Recently, with the rapid development of transition-metal-catalyzed C−H functionalization,[4] direct C−H alkynylation of arenes and heteroarenes has received much attention.[5−8] To avoid the homocoupling of terminal alkynes under oxidative conditions,[9] preactivated alkynating reagents such as alkynyl halides[5] and benziodoxolone-based hypervalent iodine reagents[6] have been successfully explored as coupling partners in C−H activation reactions (eq 1). The use of terminal alkynes for alkynylation of highly reactive acidic C−H bonds or electron-rich heteroarenes has also been demonstrated (eq 2).[7] Notably, Chang[10] reported an example of Pd-catalyzed C−H alkynylation of arenes with terminal alkynes bearing a bulky silyl group (eq 3). A Cu-mediated C−H coupling with terminal alkynes was also recently made possible by the use of Daugulis' aminoquinoline directing group.[11] However, this method does not allow for the synthesis of aryl alkynes because of the subsequent cyclization reaction of the amide directing group with the *o*-alkynyl group, thus preventing the broad range of synthetic applications of *o*-alkynylbenzoic acids.[12−19] Moreover, electron-deficient arenes and heteroarenes have not been demonstrated therein. In contrast to the development of other C−H activation transformations, alkynylation of inert aryl C−H bonds with unactivated terminal alkynes remains at an early stage. Herein we detail a Cu(II)-promoted ortho C−H alkynylation of benzamides, including heteroarylamides, with a wide range of terminal alkynes to afford synthetically useful aryl alkynes (eq 4).

Previous work:



This work:

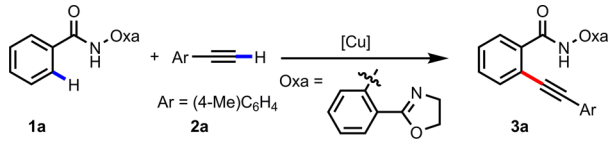


Considering the potential interference of terminal alkynes in the C−H activation step, we anticipated that a highly efficient C−H activation process may be required for the development of alkynylation of aryl C−H bonds. Prompted by our Cu-mediated ortho C−H amination reactions using an amide−oxazoline directing group,[20] we subjected amide **1a** to various conditions in the presence of the alkyne coupling partner *p*-tolylacetylene (**2a**). Encouragingly, we found that C−H alkynylation of *N*-arylbenzamide substrate **1a** with 3 equiv of **2a** proceeded in the presence of 1 equiv of $Cu(OAc)_2$ and 2 equiv of Na_2CO_3 in dimethyl sulfoxide (DMSO) at room temperature to give the desired product **3a** in 5% yield (Table 1, entry 1). Through further evaluation of the reaction conditions, we discovered that the yield was improved to 68% when the reaction temperature was increased to 60 °C (entry 3). Notably, higher reaction temperatures led to substantially lower yields (entries 4 and 5), and thus, 60 °C was found to be the optimal temperature. Monitoring of the reaction at 100 °C by ^{1}H NMR and LC−MS identified a major side product (~60%) formed via cyclization of the amide onto the alkyne, similar to a previous report [see the Supporting Information (SI)].[11] This observation suggests that the high reactivity of this directing group to allow the reaction to proceed at mild temperature is crucial for the formation the aryl

Received: June 2, 2014
Published: August 1, 2014

dx.doi.org/10.1021/ja507704b | J. Am. Chem. Soc. 2014, 136, 11590−11593

Table 1. Optimization of the Reaction Conditions[a,b]



entry	base	temp (°C)	yield (%)[b]	entry	base	temp (°C)	yield (%)[b]
1	Na_2CO_3	rt	5	10	NaOAc	60	75
2	Na_2CO_3	50	42	11	CsF	60	71
3	Na_2CO_3	60	68	12	K_2HPO_4	60	54
4	Na_2CO_3	80	52	13[d]	NaOAc	60	80
5[c]	Na_2CO_3	100	8	14[d,e]	NaOAc	60	60
6	-	60	NR	15[d,f]	NaOAc	60	53
7	K_2CO_3	60	56	16[d,g]	NaOAc	60	NR
8	Cs_2CO_3	60	58	***17***[d,h]	*NaOAc*	***60***	***85***
9	KOAc	60	55	18[d,i]	NaOAc	60	75

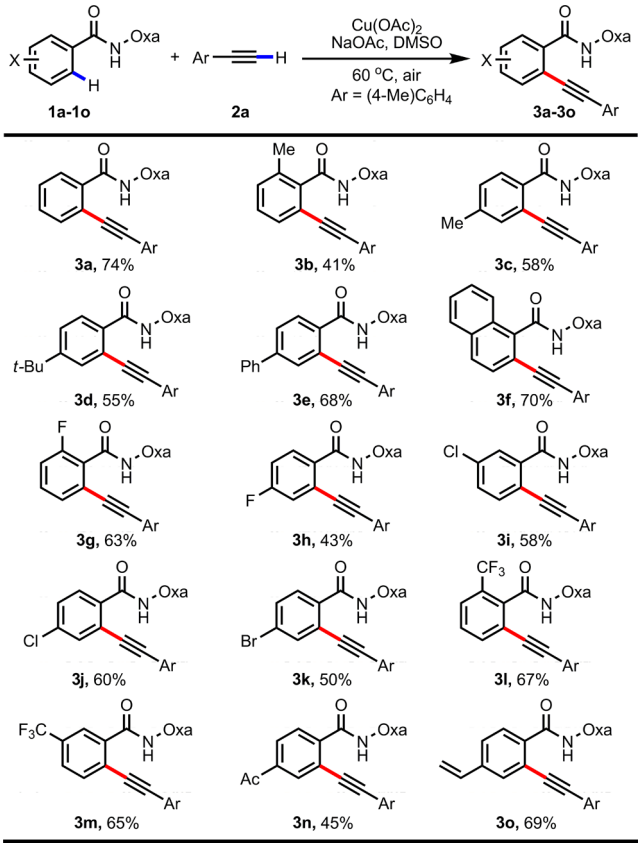
[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.3 mmol), $Cu(OAc)_2$ (0.1 mmol), base (0.2 mmol), DMSO (3.0 mL), air, 12 h. [b]Determined by ^1H NMR analysis of the crude reaction mixtures using CH_2Br_2 as an internal standard. [c]About 60% cyclized byproduct was formed. [d]DMSO (5.0 mL). [e]$Cu(OAc)_2$ (0.06 mmol). [f]$Cu(OAc)_2$ (0.04 mmol). [g]$Cu(OAc)_2$ (0 mmol). [h]NaOAc (0.1 mmol). [i]NaOAc (0.05 mmol).

alkynes without subsequent cyclization. Among the various bases screened, NaOAc gave the highest yield of 75% (entries 6−12). The yield increased to 80% when the reaction was run at lower concentration (entry 13). A variety of copper salts are reactive, with $Cu(OAc)_2$ being the optimal choice (see the SI). Reducing the quantity of $Cu(OAc)_2$ to 40% lowered the yield to 53% (entry 15). The use of 3 equiv of the alkyne is necessary because a substantial amount of alkyne homocoupling occurs under these conditions. Air is a more suitable oxidant than oxygen for this reaction because a high concentration of molecular O_2 promotes ortho hydroxylation as well as alkyne homocoupling (see the SI). It should also be noted that no reactivity was observed in the absence of copper (entry 16). Finally, decreasing the amount of NaOAc to 1 equiv afforded the alkynylation product in 85% yield (entry 17).

With these optimized conditions in hand, we proceeded to examine the substrate scope. As shown in Table 2, a wide variety of substituted benzamides are reactive. Alkynylation of electron-rich methyl-, *tert*-butyl-, and phenyl-substituted arenes gave the corresponding products in 41−68% yield (**3b−e**). Naphthalene substrate **1f** was also alkynylated to give **3f** in 70% yield. Electron-deficient arenes bearing halide, trifluoromethyl, and acetyl groups reacted under these conditions to afford the desired alkynylated products in moderate to good yields (**3g−n**, 43−67% yield). The halogen (**3i−k**) and vinyl (**3o**) substituents in the products are useful handles for further synthetic elaborations.

The scope of terminal alkynes was also extensively examined (Table 3). Alkynylation of **1a** with a variety of substituted phenylacetylenes proceeded to give the desired products in moderate to good yields (**4b−f**, 48−63% yield). Alkyne **2h** bearing a thiophene moiety was also compatible, albeit providing a lower yield (**4g**, 40%). Importantly, aliphatic alkynes, including *n*-pentyl-, *tert*-butyl-, cyclopropyl-, and cyclohexyl-substituted acetylenes, were all compatible (**4h−k**, 46−67% yield). Interestingly, a conjugated enyne also underwent the alkynylation to give the corresponding product in moderate yield, leaving the olefin moiety intact (**4l**, 46% yield), thus introducing a highly functionalizable unit onto the arene.

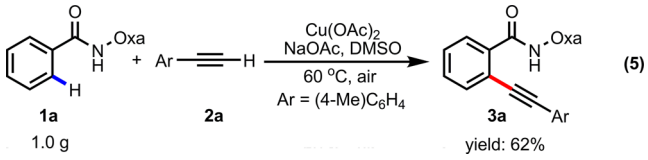
Table 2. Scope of Aromatic Amides[a,b]



[a]Reaction conditions: **1a−o** (0.1 mmol), **2a** (0.3 mmol), $Cu(OAc)_2$ (0.1 mmol), NaOAc (0.1 mmol), DMSO (5.0 mL), 60 °C, air, 12 h. [b]Isolated yields are shown.

To investigate the applicability of this alkynylation reaction in medicinal chemistry, we tested a number of heterocyclic substrates (Table 4).[4f,21−23] Gratifyingly, alkynylation of pyrrole, indole, benzofuran, pyrazole, and imidazole proceeded to give the desired heteroaryl alkynes **3p−t** in synthetically useful yields. The strongly coordinating pyridine-based substrates could also be alkynylated under the developed reaction conditions (**3u−x**, 30−54% yield). Because of the versatility of the alkyne moiety, these alkynylated heteroarenes should be highly useful for medicinal chemistry.[24]

We also conducted the reaction on a gram scale and obtained **3a** in 62% yield (eq 5), thus demonstrating the scalability of this



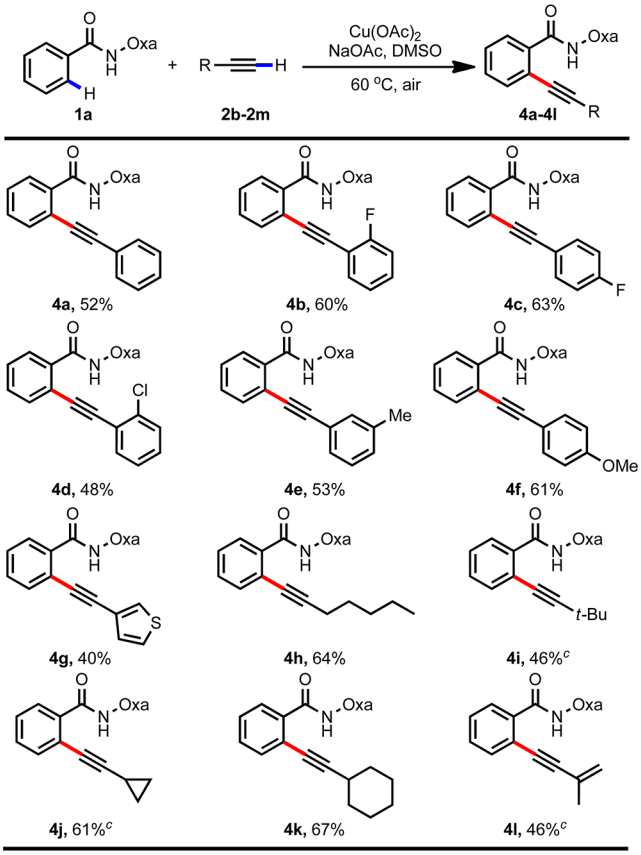
(5)

reaction. The directing group was readily removed by exposing product **3a** to a standard amide hydrolysis sequence to produce the corresponding benzoic acid (Scheme 1).

Alkynylated benzoic acids can be converted to various useful heterocycles and valuable synthons, such as isoindolin-1-ones,[12] isoquinolin-1-ones,[12] pyran-2(2*H*)-ones,[13] furan-2(5*H*)-ones,[13] alkyls,[13] alkenes,[14,15] triazoles,[16] quinoxalines,[17] 1,2-diketones,[17]

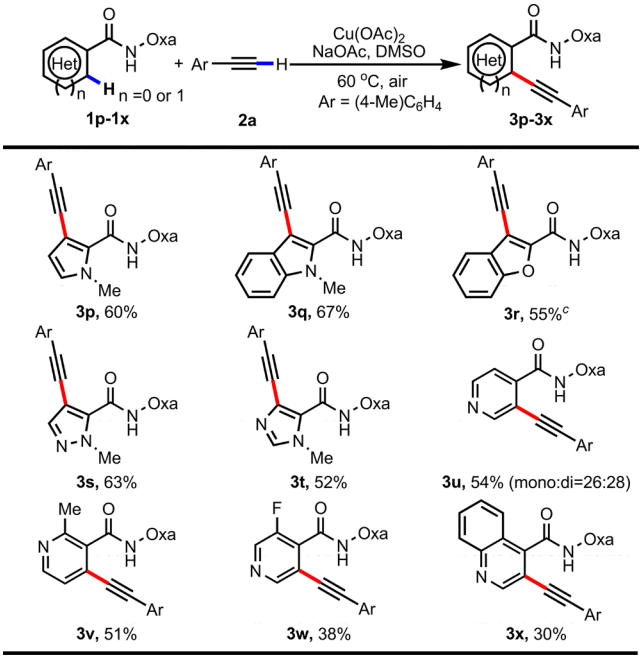
dx.doi.org/10.1021/ja507704b | J. Am. Chem. Soc. 2014, 136, 11590−11593

Table 3. Scope of Terminal Alkynes[a,b]



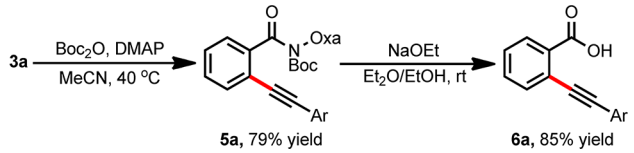
[a]Reaction conditions: **1a** (0.1 mmol), **2b−m** (0.3 mmol), $Cu(OAc)_2$ (0.1 mmol), NaOAc (0.1 mmol), DMSO (5.0 mL), 60 °C, air, 12 h. [b]Isolated yields are shown. [c]Na_2CO_3 (0.2 mmol), 80 °C.

Table 4. Scope of Heteroaromatic Amides[a,b]



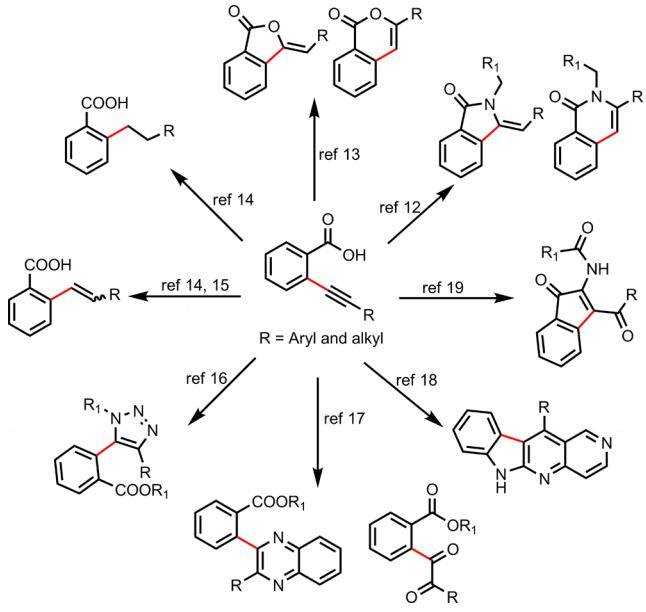
[a]Reaction conditions: **1p−x** (0.1 mmol), **2a** (0.3 mmol), $Cu(OAc)_2$ (0.1 mmol), NaOAc (0.1 mmol), DMSO (5.0 mL), 60 °C, air, 12 h. [b]Isolated yields are shown. [c]80 °C.

Scheme 1. Removal of the Directing Group



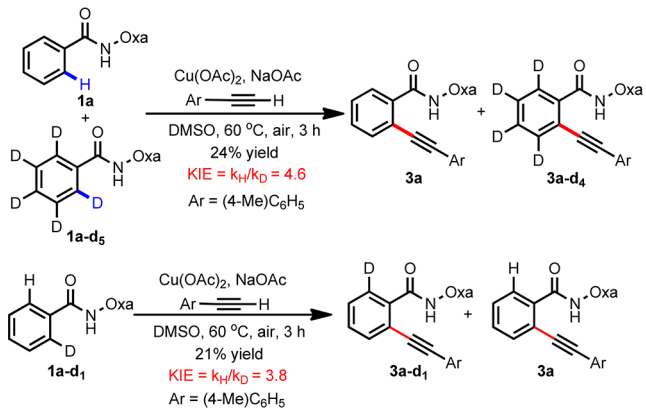
6*H*-indolo[2,3-*b*][1,6]naphthyridines,[18] and indenones[19] (Scheme 2).

Scheme 2. Transformations of *o*-Alkynylbenzoic Acids



Finally, significant inter- and intramolecular isotope effects were observed (Scheme 3), suggesting that a simple electrophilic

Scheme 3. Isotope Effects



aromatic substitution (S_EAr) pathway is unlikely to be involved in this reaction. The lack of H incorporation in **3a-d$_1$** also indicates that the C−H insertion process is not reversible.

In conclusion, we have developed a Cu-promoted C−H alkynylation of arenes and heteroarenes with terminal alkynes. This protocol provides a generally useful method to prepare aryl alkynes as an alternative synthetic disconnection to Sonogashira coupling.

dx.doi.org/10.1021/ja507704b | J. Am. Chem. Soc. 2014, 136, 11590−11593

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

hxdai@sioc.ac.cn

yu200@scripps.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, the CAS/SAFEA International Partnership Program for Creative Research Teams, the Recruitment Program of Global Experts, and The Scripps Research Institute for financial support. This work was supported by NSF under the CCI Center for Selective C−H Functionalization (CHE-1205646).

■ REFERENCES

(1) *Acetylene Chemistry: Chemistry, Biology and Material Science*; Diederich, F., Stang, P. J., Tykwinski, R. R., Eds.; Wiley-VCH: Weinheim, Germany, 2005.

(2) (a) Fürstner, A.; Davies, P. W. *Chem. Commun.* **2005**, 2307. (b) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004. (c) Finn, M. G.; Fokin, V. V. *Chem. Soc. Rev.* **2010**, *39*, 1231. (d) Brand, J. P.; Waser, J. *Chem. Soc. Rev.* **2012**, *41*, 4165. (e) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2014**, *114*, 1783.

(3) (a) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46. (b) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979. (c) King, A. O.; Yasuda, N. *Top. Organomet. Chem.* **2004**, *6*, 205. (d) Doucet, H.; Hierso, J.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 834. (e) Plenio, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6954. (f) Chinchilla, R.; Nájera, C. *Chem. Soc. Rev.* **2011**, *40*, 5084.

(4) For selected reviews of C−H functionalization using transition metals, see: (a) Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62. (b) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (c) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (d) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242. (e) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (f) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (g) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (h) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (i) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281.

(5) For C(sp^2)−H alkynylation with alkynyl halides as alkynylated reagents, see: (a) Kobayashi, K.; Arisawa, M.; Yamaguchi, M. *J. Am. Chem. Soc.* **2002**, *124*, 8528. (b) Seregin, I. V.; Ryabova, V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 7742. (c) Tobisu, M.; Ano, Y.; Chatani, N. *Org. Lett.* **2009**, *11*, 3250. (d) Matsuyama, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 4156. (e) Dudnik, A. S.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2010**, *49*, 2096. (f) Ano, Y.; Tobisu, M.; Chatani, N. *Org. Lett.* **2012**, *14*, 354. (g) Ano, Y.; Tobisu, M.; Chatani, N. *Synlett* **2012**, *23*, 2763.

(6) For C(sp^2)−H alkynylation with hypervalent iodine reagents as alkynylated reagents, see: (a) Brand, J. P.; Charpentier, J.; Waser, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9346. (b) Brand, J. P.; Waser, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 7304. (c) Feng, C.; Loh, T.-P. *Angew. Chem., Int. Ed.* **2014**, *53*, 2722. (d) Xie, F.; Qi, Z.; Yu, S.; Li, X. *J. Am. Chem. Soc.* **2014**, *136*, 4780.

(7) For C−H alkynylation with terminal alkynes, see: (a) Wei, Y.; Zhao, H.; Kan, J.; Su, W.; Hong, M. *J. Am. Chem. Soc.* **2010**, *132*, 2522. (b) Matsuyama, N.; Kitahara, M.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 2358. (c) de Haro, T.; Nevado, C. *J. Am. Chem. Soc.* **2010**, *132*, 1512. (d) Yang, L.; Zhao, L.; Li, C.-J. *Chem. Commun.* **2010**, *46*, 4184. (e) Kim, S. H.; Yoon, J.; Chang, S. *Org. Lett.* **2011**, *13*, 1474. (f) Jie, X.; Shang, Y.; Hu, P.; Su, W. *Angew. Chem., Int. Ed.* **2013**, *52*, 3630.

(8) For C(sp^3)−H alkynylation with alkynyl halides as alkynylated reagents, see: (a) Ano, Y.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 12984. (b) He, J.; Wasa, M.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 3387.

(9) (a) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632. (b) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054.

(10) Kim, S. H.; Park, S. H.; Chang, S. *Tetrahedron* **2012**, *68*, 5162.

(11) Dong, J.; Wang, F.; You, J. *Org. Lett.* **2014**, *16*, 2884.

(12) Zhou, Y.; Zhai, Y.; Li, J.; Ye, D.; Jiang, H.; Liu, H. *Green Chem.* **2010**, *12*, 1397.

(13) Uchiyama, M.; Ozawa, H.; Takuma, K.; Matsumoto, Y.; Yonehara, M.; Hiroya, K.; Sakamoto, T. *Org. Lett.* **2006**, *8*, 5517.

(14) Offermann, D. A.; McKendrick, J. E.; Sejberg, J. J. P.; Mo, B.; Holdom, M. D.; Helm, B. A.; Leatherbarrow, R. J.; Beavil, A. J.; Sutton, B. J.; Spivey, A. C. *J. Org. Chem.* **2012**, *77*, 3197.

(15) Castro, C. E.; Stephens, R. D. *J. Am. Chem. Soc.* **1964**, *86*, 4358.

(16) (a) Röhrig, U. F.; Majjigapu, S. R.; Grosdidier, A.; Bron, S.; Stroobant, V.; Pilotte, L.; Colau, D.; Vogel, P.; Van den Eynde, B. J.; Zoete, V.; Michielin, O. *J. Med. Chem.* **2012**, *55*, 5270. (b) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004.

(17) Liu, Y.; Chen, X.; Zhang, J.; Xu, Z. *Synlett* **2013**, *24*, 1371.

(18) Zhang, Q.; Shi, C.; Zhang, H.-R.; Wang, K. K. *J. Org. Chem.* **2000**, *65*, 7977.

(19) Shimizu, H.; Murakami, M. *Synlett* **2008**, 1817.

(20) Shang, M.; Sun, S.-Z.; Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 3354.

(21) Ritchie, T. J.; Macdonald, S. J. F.; Peace, S.; Pickett, S. D.; Luscombe, C. N. *Med. Chem. Commun.* **2012**, *3*, 1062.

(22) For reviews, see: (a) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (b) Zhu, C.; Wang, R.; Falck, J. R. *Chem.—Asian J.* **2012**, *7*, 1502.

(23) For selected examples of directed C−H functionalizations of heterocycles, see: (a) Wasa, M.; Worrell, B. T.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 1275. (b) Hyster, T. K.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 10565. (c) Takeda, D.; Yamashita, M.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Lett.* **2011**, *40*, 1015. (d) Tran, L. D.; Popov, I.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 18237. (e) Wang, X.-C.; Hu, Y.; Bonacorsi, S.; Hong, Y.; Burrell, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 10326.

(24) (a) Praveen, C.; Ayyanar, A.; Perumal, P. T. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4170. (b) He, Y.; Xu, J.; Yu, Z.-H.; Gunawan, A. M.; Wu, L.; Wang, L.; Zhang, Z.-Y. *J. Med. Chem.* **2013**, *56*, 832. (c) Liu, Y.; Richardson, J.; Tran, T.; Al-Muhtasib, N.; Xie, T.; Yenugonda, V. M.; Sexton, H. G.; Rezvani, A. H.; Levin, E. D.; Sahibzada, N.; Kellar, K. J.; Brown, M. L.; Xiao, Y.; Paige, M. *J. Med. Chem.* **2013**, *56*, 3000.