JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

COMMUNICATION

pubs.acs.org/JACS

An Efficient [2 + 2 + 1] Synthesis of 2,5-Disubstituted Oxazoles via Gold-Catalyzed Intermolecular Alkyne Oxidation

Weimin He, Chaoqun Li, and Liming Zhang*

Department of Chemistry and Biochemistry, University of California, Santa Barbara, California 93106, United States

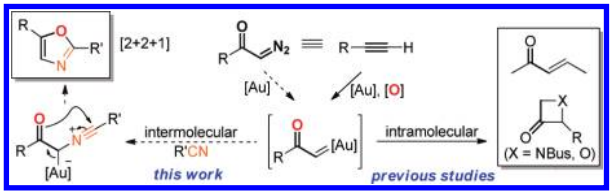
Supporting Information

ABSTRACT: The first efficient intermolecular reaction of gold carbene intermediates generated via gold-catalyzed alkyne oxidation has been realized using nitriles as both the reacting partner and the reaction solvent, offering a generally efficient synthesis of 2,5-disubstituted oxazoles with broad substrate scope. The overall reaction is a [2 + 2 + 1] annulation of a terminal alkyne, a nitrile, and an oxygen atom from an oxidant. The reaction conditions are exceptionally mild, and a range of functional groups are easily tolerated. With complex and/or expensive nitriles, only 3 equiv could be sufficient to achieve serviceable yields in the absence of any solvent and using only 1 mol % BrettPhos-AuNTf$_2$ as the catalyst.

The oxazole ring with its 2- and 5-positions substituted with aryl or alkyl groups is an important structure found in various natural products[1] and compounds with biological activities. These oxazoles can also serve as versatile substrates for various synthetic transformations, including the formation of fully substituted oxazoles.[2] Among many strategies developed for their synthesis,[3,4] one-pot [3 + 2] annulations involving nitriles and α-functionalized ketones are arguably the simplest and most desirable. The α-functionalized ketones can be α-diazoketones[5] or those generated in situ via ketone α-oxidation. However, α-diazoketones are hazardous, potentially explosive, and seldom commercially available, and synthesing and handling them are often challenging. For the in situ generation approach, strong acids (e.g., TfOH)[6] and/or stoichiometric amounts of sometimes toxic metal salts[7] must be used; morever, the reaction scopes are mostly limited to 5-aryloxazoles. Needless to say, there is still much need for a convergent synthesis of 2,5-disubstituted oxazoles from readily available and benign substrates with the following features: exceptionally mild reaction conditions, excellent functional group tolerance, and broad reaction scope. Herein we discolse a gold-catalyzed oxidative approach that largely meets the need via a [2 + 2 + 1] annulation.

We recently showed that stable, benign, and often commercially available alkynes can replace hazardous α-diazoketones for the generation of gold carbene intermediates.[8] These intermediates, generated via gold-catalyzed oxidation[9−11] of alkynes by pyridine/quinoline *N*-oxides, can undergo intramolecular O−H[8a,b] or N−H insertions[8c] and 1,2-C−H insertions[8d] that lead to synthetically useful products (Scheme 1). However, no intermolecular reaction of these gold carbene intermediates has been reported, let alone one that is synthetically efficient. A major concern is that the presence of oxidants and its reduced form would react with the carbene intermediates, leading to unwanted side reactions.[12] We surmised that nitriles,[13] especially when used as the solvent, could react with the gold carbene intermediate rapidly enough that these side reactions would be largely suppressed, therefore allowing the replacement of hazardous α-diazoketones with alkynes in oxazole synthesis;[14] moreover, the overall reaction would be a desirable [2 + 2 + 1] annulation[15] of the alkyne, the nitrile, and an oxygen atom from an oxidant (Scheme 1).

Scheme 1. Gold-Catalyzed Alkyne Oxidation: Application to Intermolecular Oxazole Synthesis



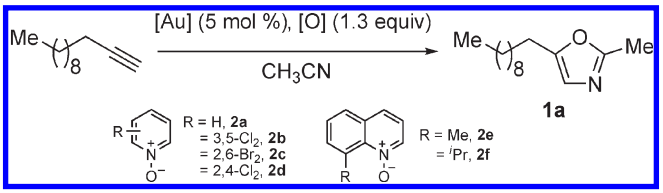
We began the study using acetonitrile as the solvent.[16] To develop conditions that would be highly compatible with various functional groups, acidic additives were avoided in the screening. With $Ph_3PAuNTf_2$[17] as the catalyst, different *N*-oxides were tested at 60 °C (Table 1, entries 1−6). While we were surprised that even commercially available pyridine *N*-oxide worked to some extent (entry 1), 8-methylquinoline *N*-oxide (**2e**) was the best among the oxidants examined (entry 5). Other gold catalysts, though more expensive, worked equally well (entries 7−9). The reaction proceeded very slowly when run at ambient temperature (entry 10); however, it could be accelerated by using MsOH (entry 11), suggesting that 8-methylquinoline may coordinate with the gold catalyst, albeit reversibly. The special catalytic role of gold in this reaction was substantiated by the inability of $AgNTf_2$ and $HNTf_2$ to catalyze this reaction (entries 12 and 13).

The scope of this reaction was then examined (Table 2). First, acetonitrile was used as the nitrile source. As shown in entries 1−10 and 14−18, a range of terminal alkynes were allowed, and the reaction yields were mostly ≥80%. Various functional groups were readily tolerated, including an unprotected HO (entry 2); a free carboxylic acid moiety (entry 5); acid-labile groups such as TBSO (entry 3), THP (entry 4), and Boc (entry 7); an oxidizable PhS group (entry 6); an alkyl chloride (entry 8); and aryl groups having different electronic and steric natures (entries 1 and 15−18). In the case of arylacetylenes, ortho subsitution did decrease the reaction yield substantially, likely due to steric hindrance, although

Received: March 31, 2011
Published: May 12, 2011

dx.doi.org/10.1021/ja2029188 | J. Am. Chem. Soc. 2011, 133, 8482–8485

Table 1. Screening of Gold Catalysts and Reaction Conditions[a]



entry	catalyst	oxidant	conditions	conv. (%)	yield (%)[b]
1	$Ph_3PAuNTf_2$	**2a**	60 °C, 3 h	69	51
2	$Ph_3PAuNTf_2$	**2b**	60 °C, 3 h	54	50
3	$Ph_3PAuNTf_2$	**2c**	60 °C, 3 h	24	13
4	$Ph_3PAuNTf_2$	**2d**	60 °C, 3 h	64	59
5	**$Ph_3PAuNTf_2$**	**2e**	**60 °C, 3 h**	**100**	**98**[c]
6	$Ph_3PAuNTf_2$	**2f**	60 °C, 3 h	100	85
7	$BrettPhosAuNTf_2$	**2e**	60 °C, 3 h	100	90
8	$IPrAuNTf_2$	**2e**	60 °C, 3 h	100	93
9	$(RO)_3PAuNTf_2$[d]	**2e**	60 °C, 3 h	100	98
10	$Ph_3PAuNTf_2$	**2e**	rt, 6 days	92	87
11	$Ph_3PAuNTf_2$	**2e**	rt, overnight, MsOH (1.1 equiv)	100	98
12	$AgNTf_2$	**2e**	60 °C, 3 h	0	0
13	$HNTf_2$	**2e**	60 °C, 3 h	0	0

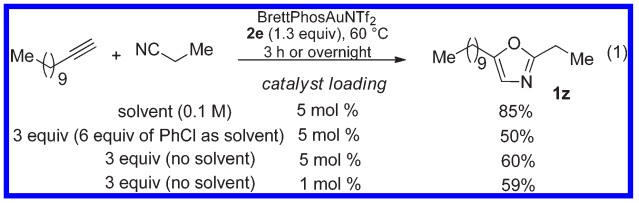
[a] In vial; [**1**] = 0.1 M. [b] Estimated by ^{1}H NMR spectroscopy using diethyl phthalate as an internal reference. [c] Isolated yield of 94%. [d] R = 2,4-(*t*-Bu)$_2$Ph.

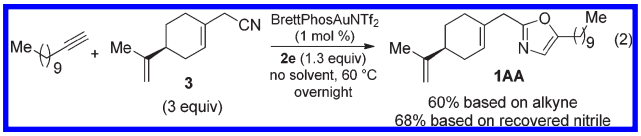
the reaction was still serviceable (entry 18). With propargyl alcohols, their derivatives, and propargyl amides as the alkyne substrates, our previously reported intramolecular trapping of the α-oxo gold carbene intermediates[8a,c] became a major side reaction, resulting in low yields of the desired oxazoles. Similarly, homopropargyl alcohols[8b] were not good alkyne substrates; however, protected ones worked just fine (entry 4). In addition, propargyl bromide and homopropargyl bromide were not good substrates. Interestingly, double annulation occurred smoothly with hepta-1,6-diyne, affording bisoxazole **1o** in 81% yield (entry 14).

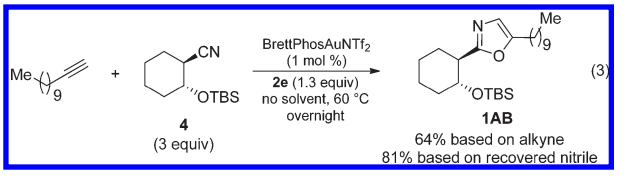
This reaction also permitted the use of acetylenes substituted with a bulky *tert*-butyl group (entry 11), an alkenyl group (entry 12) and a cyclopropyl group (entry 13), and serviceable to good yields were obtained. For these entries, propionitrile or isobutyronitrile was used in order to make the oxazole products less volatile. These cases established that acetonitrile could be readily replaced with another nitrile as the reaction solvent. Indeed, besides these two aliphatic nitriles (entries 11−13, 19, and 20), benzonitrile (entries 21 and 22) and phenylacetonitrile (entry 23) reacted smoothly, affording functionalized oxazoles in good yields. With 1,6-hexanedinitrile as the solvent, a selective monoannulation gave oxazole nitrile **1y** in an acceptable yield (entry 24).

Having demonstrated the broad reaction scope obtained using nitriles as the solvent, our attention turned to situations where the nitrile is expensive and/or not commercially available. We initially used nevertheless cheap propionitrile to probe whether other solvents could be used. With 3 equiv of the nitrile, solvents such as toluene and chlorobenzene at 0.1 M concentration led to poor yields (<20%), but a serviceable yield (50%) was realized with 6 equiv of chlorobenzene as the solvent and $BrettPhosAuNTf_2$[8c,18] as the catalyst (eq 1). Moreover, the reaction yield was improved to a respectable 60% when no solvent was used, which is remarkable considering the high concentrations of **2e** and its reduced form (i.e., 8-methylquinoline). In comparison, the reaction yield was 85% when propionitrile was used as the solvent (alkyne concentration 0.1 M).

These results encouraged us to decrease the loading of the gold catalyst, as its concentration was high with 5% loading in the absence of any solvent. To our delight, a nearly identical yield was realized using only 1 mol % $BrettPhosAuNTf_2$. To test whether this observation could be extended to sophisticated and hence expensive nitriles, we synthesized nitriles **3** and **4**, and they participated in the reaction equally well when only 3 equiv was used in the absence of any solvent (eqs 2 and 3). Moreover, most of the excess nitrile could be recovered, and the reaction yields based on the recovered nitrile were fairly good (68%) to very good (81%). Again, both TBSO and C−C double bonds were readily tolerated under the mild reaction conditions.



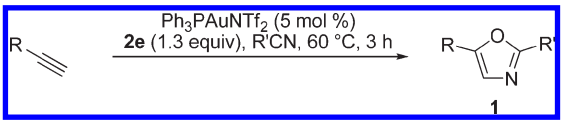


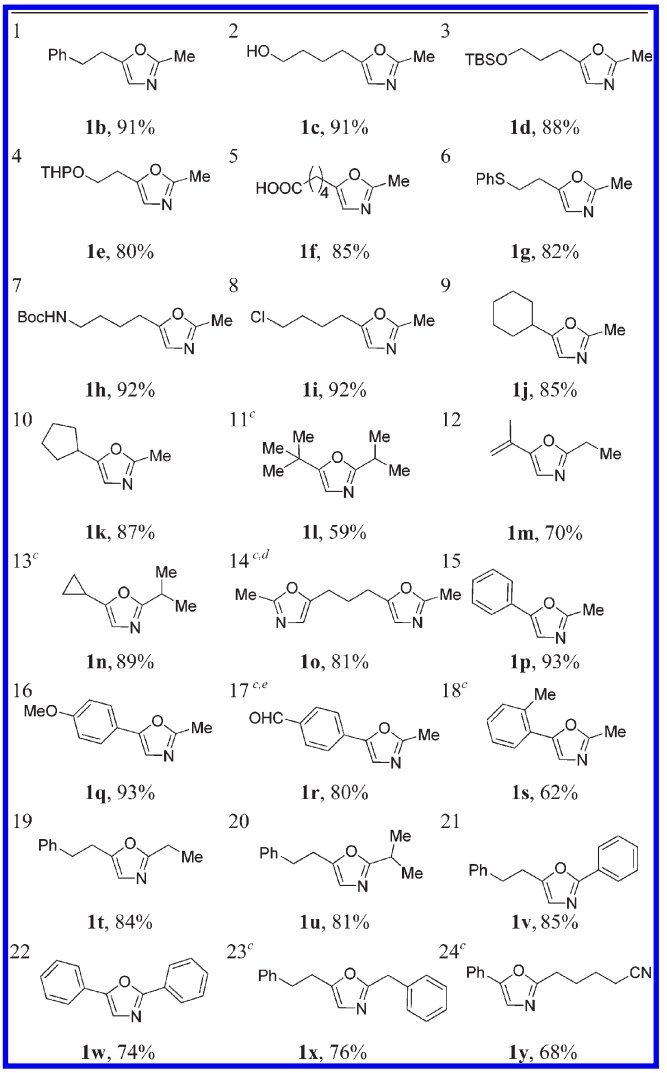


This method provides a facile synthesis[19] of pimprinaphine[1c] from protected 3-ethynylindole **5**[20] and phenylacetonitrile in two steps

dx.doi.org/10.1021/ja2029188 |*J. Am. Chem. Soc.* 2011, 133, 8482–8485

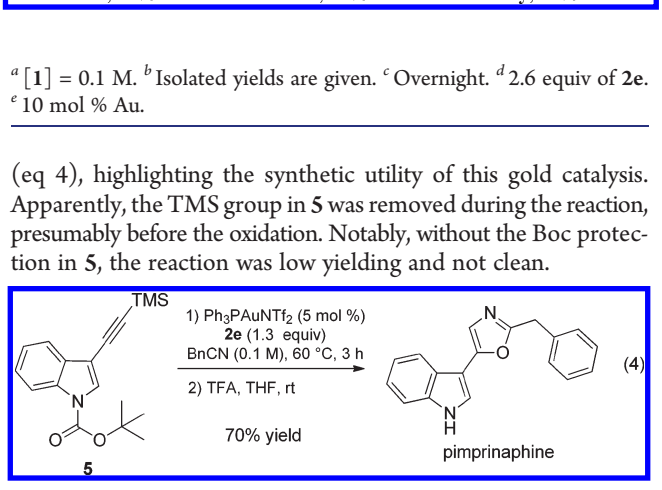
Table 2. Reaction Scope[a,b]





[a] [1] = 0.1 M. [b] Isolated yields are given. [c] Overnight. [d] 2.6 equiv of **2e**. [e] 10 mol % Au.

(eq 4), highlighting the synthetic utility of this gold catalysis. Apparently, the TMS group in **5** was removed during the reaction, presumably before the oxidation. Notably, without the Boc protection in **5**, the reaction was low yielding and not clean.



In summary, we have developed the first intermolecular reaction of α-oxo gold carbenes generated via alkyne oxidation with various nitriles, which affords 2,5-disubstituted oxazoles in mostly good to excellent yields. The reaction scope is broad, and a range of terminal alkynes and nitriles are allowed. For expensive and/or commercially unavailable nitriles, the nitrile does not have to be used as the solvent; use of only 3 equiv of the nitrile is sufficient to obtain a serviceable yield in the absence of any solvent and with only 1 mol % BrettPhosAuNTf$_2$ as the catalyst. The reaction conditions are exceptionally mild, and even sensitive functional groups such as THP and Boc are easily tolerated. The overall reaction is a convergent [2 + 2 + 1] annulation.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
zhang@chem.ucsb.edu

■ ACKNOWLEDGMENT

We thank the NSF (CAREER Award CHE-0969157), Amgen, and UCSB for generous financial support and Sigma-Aldrich for the kind gift of BrettPhos.

■ REFERENCES

(1) For selected examples, see: (a) Debono, M.; Molloy, R. M.; Occolowitz, J. L.; Paschal, J. W.; Hunt, A. H.; Michel, K. H.; Martin, J. W. *J. Org. Chem.* **1992**, *57*, 5200–5208. (b) Crow, W.; Hodgkin, J. *Aust. J. Chem.* **1968**, *21*, 3075–3077. (c) Koyama, Y.; Yokose, K.; Dolby, L. J. *Agric. Biol. Chem.* **1981**, *45*, 1285–1287. (d) Rudi, A.; Stein, Z.; Green, S.; Goldberg, I.; Kashman, Y.; Benayahu, Y.; Schleyer, M. *Tetrahedron* **1994**, *35*, 2589–2592. (e) Fontana, G. *Curr. Bioact. Compd.* **2010**, *6*, 284–308. (f) Davyt, D.; Serra, G. *Mar. Drugs* **2010**, *8*, 2755–2780.

(2) For selected cases, see: (a) Clapham, B.; Sutherland, A. J. *J. Org. Chem.* **2001**, *66*, 9033–9037. (b) Chatani, N.; Fukuyama, T.; Tatamidani, H.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **2000**, *65*, 4039–4047.

(3) For a review, see: Boyd, G. V. *Sci. Synth.* **2001**, *11*, 383–480.

(4) For recent reports of oxazole synthesis, see: (a) Zhang, J.; Coqueron, P.-Y.; Ciufolini, M. A. *Heterocycles* **2011**, *82*, 949–980. (b) Counceller, C. M.; Eichman, C. C.; Proust, N.; Stambuli, J. P. *Adv. Synth. Catal.* **2011**, *353*, 79–83. (c) Cano, I.; Alvarez, E.; Nicasio, M. C.; Perez, P. J. *J. Am. Chem. Soc.* **2011**, *133*, 191–193. (d) Austeri, M.; Rix, D.; Zeghida, W.; Lacour, J. *Org. Lett.* **2011**, *13*, 1394–1397. (e) Wan, C.; Zhang, J.; Wang, S.; Fan, J.; Wang, Z. *Org. Lett.* **2010**, *12*, 2338–2341. (f) Wan, C.; Gao, L.; Wang, Q.; Zhang, J.; Wang, Z. *Org. Lett.* **2010**, *12*, 3902–3905. (g) Saito, A.; Matsumoto, A.; Hanzawa, Y. *Tetrahedron Lett.* **2010**, *51*, 2247–2250. (h) Lai, P.-S.; Taylor, M. S. *Synthesis* **2010**, 1449–1452. (i) Jiang, H.-F.; Huang, H.-W.; Cao, H.; Qi, C.-R. *Org. Lett.* **2010**, *12*, 5561–5563.

(5) For reviews/books on the reactions of α-diazoketones, see: (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley: New York, 1998. (b) Doyle, K. J.; Moody, C. J. *Tetrahedron* **1994**, *50*, 3761–3772. (c) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861–2903. (d) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091–1160.

(6) For examples, see: (a) Ishiwata, Y.; Togo, H. *Tetrahedron* **2009**, *65*, 10720–10724. (b) Varma, R. S.; Kumar, D. *J. Heterocycl. Chem.* **1998**, *35*, 1533–1534.

(7) For examples, see: (a) Lee, J. C.; Hong, T. *Tetrahedron Lett.* **1997**, *38*, 8959–8960. (b) Lee, J. C.; Song, I.-G. *Tetrahedron Lett.* **2000**, *41*, 5891–5894. (c) Nagayoshi, K.; Sato, T. *Chem. Lett.* **1983**, *12*, 1355–1356.

(8) (a) Ye, L.; He, W.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 8550–8551. (b) Ye, L.; Cui, L.; Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 3258–3259. (c) Ye, L.; He, W.; Zhang, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 3236–3239. (d) Lu, B.; Li, C.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 14070–14072.

(9) With various tethered oxidants, gold complexes can catalyze intramolecular oxidations of alkynes, and gold carbene intermediates are typically invoked. For references, see: (a) Li, G.; Zhang, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5156–5159. (b) Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 4160–4161. (c) Yeom, H. S.; Lee, J. E.; Shin, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7040–7043. (d) Cui, L.; Peng, Y.; Zhang, L. *J. Am. Chem. Soc.* **2009**, *131*, 8394–8395. (e) Cui, L.; Zhang, G.; Peng, Y.; Zhang, L. *Org. Lett.* **2009**, *11*, 1225–1228. (f) Yeom, H. S.; Lee, Y.; Lee, J. E.; Shin, S. *Org. Biomol. Chem.* **2009**, *7*, 4744–4752. (g) Davies, P. W.; Albrecht, S. J. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 8372–8375. (h) Cui, L.; Zhang, L. *Chem. Commun.* **2010**in press. (i) Yeom, H. S.; Lee, Y.; Jeong, J.; So, E.; Hwang, S.; Lee, J. E.; Lee, S. S.; Shin, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 1611–1614. (j) Jadhav, A. M.; Bhunia, S.; Liao, H.-Y.; Liu, R.-S. *J. Am. Chem. Soc.* **2011**, *133*, 1769–1771. (k) Yeom, H.-S.; So, E.; Shin, S. *Chem.—Eur. J.* **2011**, *17*, 1764–1767.

(10) For a recent intermolecular case using pyridine *N*-oxide, see: (a) Davies, P. W.; Cremonesi, A.; Martin, N. *Chem. Commun.* **2011**, *47*, 379–381. For an intermolecular gold-catalyzed nitrene transfer, see: (b) Li, C.; Zhang, L. *Org. Lett.* **2011**, 1738–1741.

(11) When sulfoxides are used as external oxidants, the gold carbene intermediates may not be formed. For references, see: (a) Cuenca, A. B.; Montserrai, S.; Hossain, K. M.; Mancha, G.; Lledos, A.; Medio-Simon, M.; Ujaque, G.; Asensio, G. *Org. Lett.* **2009**, *11*, 4906–4909. (b) Li, C.-W.; Pati, K.; Lin, G.-Y.; Sohel, S. M. A.; Hung, H.-H.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2010**, *49*, 9891–9894.

(12) For intermolecular oxidation of gold carbene intermediates, see: (a) Witham, C. A.; Mauleon, P.; Shapiro, N. D.; Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 5838–5839. (b) Taduri, B. P.; Sohel, S. M. A.; Cheng, H.-M.; Lin, G.-Y.; Liu, R.-S. *Chem. Commun.* **2007**, 2530–2532.

(13) For examples of gold catalysis using nitriles as substrates, see: (a) Ramón, R. S.; Marion, N.; Nolan, S. P. *Chem.—Eur. J.* **2009**, *15*, 8695–8697. (b) Ibrahim, N.; Hashmi, A. S. K.; Rominger, F. *Adv. Synth. Catal.* **2011**, *353*, 461–468.

(14) For oxazole synthesis via gold-catalyzed cyclization of propargyl amides, see: (a) Weyrauch, J. P.; Hashmi, A. S. K.; Schuster, A.; Hengst, T.; Schetter, S.; Littmann, A.; Rudolph, M.; Hamzic, M.; Visus, J.; Rominger, F.; Frey, W.; Bats, J. W. *Chem.—Eur. J.* **2010**, *16*, 956–963 and accompanying Supporting Information. (b) Hashmi, A. S. K.; Weyrauch, J. P.; Frey, W.; Bats, J. W. *Org. Lett.* **2004**, *6*, 4391–4394. (c) Hashmi, A. S. K.; Rudolph, M.; Schymura, S.; Visus, J.; Frey, W. *Eur. J. Org. Chem.* **2006**, 4905–4909.

(15) Trisubstituted oxazoles can be formed via annulation of internal alkynes and acetonitrile in the presence of PhTeO(OTf), albeit with a limited scope and moderate efficiencies. See: Fukumoto, T.; Aso, Y.; Otsubo, T.; Ogura, F. *J. Chem. Soc., Chem. Commun.* **1992**, 1070–1072.

(16) For early studies using acetonitrile as the solvent, see: (a) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285–2288. (b) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 11553–11554.

(17) Mézailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133–4136.

(18) Fors, B. P.; Watson, D. A.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 13552–13554.

(19) Roy, S.; Haque, S.; Gribble, G. W. *Synthesis* **2006**, 3948–3954.

(20) Oakdale, J. S.; Boger, D. L. *Org. Lett.* **2010**, *12*, 1132–1134.