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Nickel-Catalyzed Direct Alkynylation of Azoles with Alkynyl Bromides

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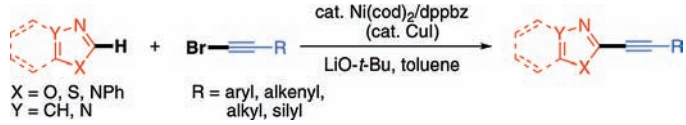
ABSTRACT



The direct C−H alkynylation of azoles with alkynyl bromides proceeds efficiently in the presence of a nickel-based catalyst system. The reaction enables the introduction of various alkynyl groups bearing aryl, alkenyl, alkyl, and silyl substituents to the azole cores. In some cases, addition of a catalytic amount of CuI is observed to accelerate the direct coupling dramatically.

Metal-mediated reactions involving C−H bond cleavage have received significant attention in modern organic chemistry due to their possibilities for transformation of the ubiquitous C−H bonds into diverse functions in one synthetic operation.[1] In particular, catalytic C−C bond formation from unreactive C−H bonds with organic halides or pseudohalides may allow the facile increase of molecular complexity and complement the conventional metal-catalyzed cross-coupling strategies with organometallic compounds.[2] To date, a variety of catalyst systems have been explored for the direct sp^2 C−H arylation and alkenylation. On the other hand, only a few examples of the corresponding sp^2 C−H alkynylation with alkynyl halides have been reported.[3−5] Yamaguchi described the pioneering work, gallium-catalyzed direct alkynylation of phenols and *N*-benzylanilines.[3] Subsequently, Gevorgyan[4a] and Gu[4b] developed palladium-based methods for the alkynylation of highly electron-rich heteroarenes, N-fused heterocycles and indoles, respectively. Very recently, Tobisu and Chatani succeeded in the coordination-assisted ortho-alkynylation of acetanilides under palladium catalysis.[5] Although these processes can compensate for the conventional Sonogashira coupling,[6] the scope and generality are still restricted. Thus, the development of new catalyst systems for this type of transformation is strongly desired.

During our recent studies on the metal-catalyzed direct arylation reaction of heteroarenes, we found the potential catalytic activity of nickel complexes for the direct C2 arylation of azoles with aryl bromides.[7] Here, we report the nickel-catalyzed direct alkynylation of azoles with alkynyl bromides. The nickel-based catalyst enables various alkynyl bromides to serve as promising alkynyl sources to azoles. Additionally, in some cases, addition of a catalytic amount

(1) Recent reviews: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. (c) Campeau, L. C.; Stuart, D. R.; Fagnou, K. *Aldrichchim. Acta* **2007**, *40*, 35. (d) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (e) Park, Y. J.; Park, J.-W.; Jun, C.-H. *Acc. Chem. Res.* **2008**, *41*, 222. (f) Lewis, L. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013. (g) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013.

(2) (a) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004. (b) Tsuji, J. *Palladium Reagents and Catalysts*, 2nd ed.; Wiley: Chichester, UK, 2004. (c) *Cross-Coupling Reactions*; Miyaura, N., Ed. *Topics in Current Chemistry*; Springer: Berlin, Germany, 2002; No. 219.

(3) (a) Kobayashi, K.; Arisawa, M.; Yamaguchi, M. *J. Am. Chem. Soc.* **2002**, *124*, 8528. (b) Amemiya, R.; Fujii, A.; Yamaguchi, M. *Tetrahedron Lett.* **2004**, *45*, 4333.

(4) (a) Seregin, I. V.; Ryabova, V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 7742. (b) Gu, Y.; Wang, X.-m. *Tetrahedron Lett.* **2009**, *50*, 763. Moran also reported the palladium-catalyzed direct alkynylation of *N*-phenyl sydnone with (bromoethynyl)benzene albeit with a low yield (34%). (c) Rodriguez, A.; Fennessy, R. V.; Moran, W. J. *Tetrahedron Lett.* **2009**, *50*, 3942.

(5) Tobisu, M.; Ano, Y.; Chatani, N. *Org. Lett.* **2009**, *11*, 3250.

(6) (a) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46. (b) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979. (c) Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 1566. (d) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874.

(7) (a) Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 1737. See also: (b) Canivet, J.; Yamaguchi, J.; Ban, I.; Itami, K. *Org. Lett.* **2009**, *11*, 1733. (c) Kobayashi, O.; Uraguchi, D.; Yamakawa, T. *Org. Lett.* **2009**, *11*, 2679.

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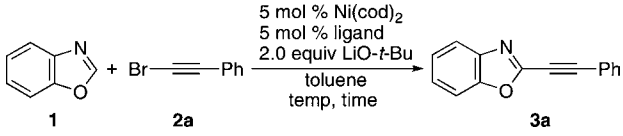
of CuI is observed to enhance the reaction dramatically. As certain alkynyl-substituted azoles work as selective DNA cleavage agents,[8] and azole-containing π-conjugated molecules are found in many natural products, pharmaceuticals, and functional materials,[9] and this transformation appears to be of considerable synthetic utility.

Table 1. Optimization for Nickel-Catalyzed Direct Alkynylation of Benzoxazole (**1**) with (Bromoethynyl)benzene (**2a**)[a]



1 2a 3a

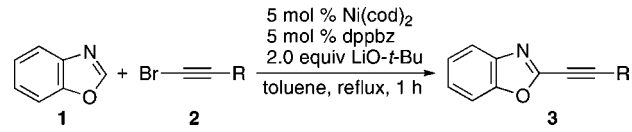
entry	ligand	temp	time (h)	**3a**, yield (%)[b]
1	phen[c]	rt	72	14
2	dppbz	rt	72	29
3	dppp	rt	72	29
4	dppf	rt	72	36
5	PPh_3	rt	72	trace
6	PCy_3	rt	72	2
7	dppbz	reflux	1	76
8	dppp	reflux	6	49
9	dppf	reflux	6	41
10[d]	dppbz	reflux	1	85 (84)
11[d,e]	dppbz	reflux	1	73

[a] A mixture of **1** (0.25 mmol), **2a** (0.25 mmol), $Ni(cod)_2$ (0.013 mmol), ligand (0.013 mmol), and LiO-*t*-Bu (0.50 mmol) was stirred in toluene (2.5 mL). [b] GC yield. Yield of isolated compound is in parentheses. [c] phen = 1,10-phenanthroline. [d] **2a** (0.30 mmol). [e] With $Ni(acac)_2$ (0.013 mmol) and Zn (0.025 mmol) instead of $Ni(cod)_2$.

We initially investigated the effect of various ligands using benzoxazole (**1**) and (bromoethynyl)benzene (**2a**) as model substrates in the presence of 5 mol % of $Ni(cod)_2$ and 2.0 equiv of LiO-*t*-Bu at room temperature (Table 1, entries 1−6). The reaction with our previous optimal ligand, 1,10-phenanthroline (phen),[7a] in toluene afforded the alkynylated product **3a** albeit with only 14% yield (entry 1). The use of P-based bidentate ligands resulted in higher yields of **3a** (entries 2−4), while common monodentate phosphines showed no catalytic activity (entries 5 and 6). Elevating the temperature effectively accelerated the coupling. Especially with the $Ni(cod)_2$/1,2-bis(diphenylphosphino)benzene (dppbz) catalyst system in refluxing toluene, the direct alkynylation was complete within 1 h to furnish **3a** in 76% yield (entry 7). An increase in the amount of **2a** to 1.5 equiv further improved the yield to 84% isolated yield (entry 10). Notably, the combination of bench-stable $Ni(acac)_2$ and Zn instead of air-sensitive $Ni(cod)_2$ was also available for use, providing the desired product **3a** in an acceptable yield (entry 11).

With the optimized conditions in hand, we carried out the direct alkynylation of benzoxazole (**1**) with a variety of

Table 2. Nickel-Catalyzed Direct Alkynylation of Benzoxazole (**1**) with Various Alkynyl Bromides **2**[a]



1 2 3

entry	R in **2**	**3**, yield (%)[b]
1	Ph (**2a**)	**3a**, 84
2	4-MeC_6H_4 (**2b**)	**3b**, 70
3	4-ClC_6H_4 (**2c**)	**3c**, 71
4	4-$CF_3C_6H_4$ (**2d**)	**3d**, 60
5	1-naphthyl (**2e**)	**3e**, 81
6	1-cyclohexenyl (**2f**)	**3f**, 73
7	*n*-C_6H_{13} (**2g**)	**3g**, 60
8	$Si(i\text{-}Pr)_3$ (**2h**)	**3h**, 56

[a] A mixture of **1** (0.25 mmol), **2** (0.30 mmol), $Ni(cod)_2$ (0.013 mmol), dppbz (0.013 mmol), and LiO-*t*-Bu (0.50 mmol) was stirred in boiling toluene (2.5 mL) for 1 h. [b] Yield of isolated compounds.

alkynyl bromides **2** (Table 2). 4-Methyl-, 4-chloro-, 4-trifluoromethyl-substituted (bromoethynyl)benzenes **2b**−**d** reacted with **1** smoothly to give the corresponding alkynylazoles **3b**−**d** in good yields (entries 2−4). The sterically demanding 1-naphthyl group did not interfere with the reaction (entry 5). The conjugated enyne **2f** was transformed to the desired **3f** in 73% yield with the olefin moiety left intact (entry 6). The alkynyl bromide **2g** bearing an aliphatic substituent also participated in the direct coupling. It should be noted that the use of such an aliphatic substrate is not trivial in the catalytic direct alkynylation (entry 7).[10] The introduction of the silylethynyl group, which would be readily further functionalized, to the benzoxazole core was possible (entry 8).

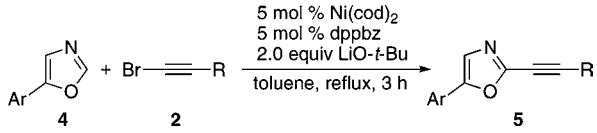
The $Ni(cod)_2$/dppbz system could be applied to the direct alkynylation of 5-aryloxazoles (Table 3). Under reaction conditions similar to those in Table 2, the alkynylation of an array of oxazoles **4a**−**e** with (bromoethynyl)benzene (**2a**) proceeded efficiently to produce the azole core π systems **5aa**−**ea** in good to high yields (entries 1−5). The bulky

(8) Kumar, D.; David, W. M.; Kerwin, S. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2971.

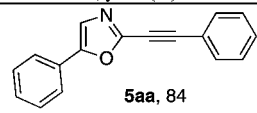
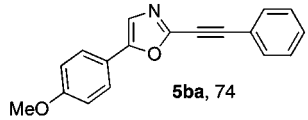
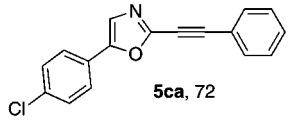
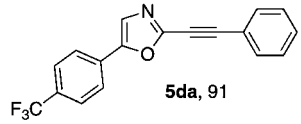
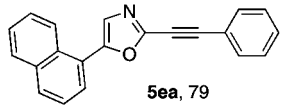
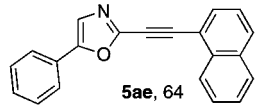
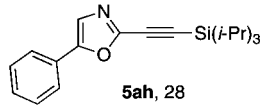
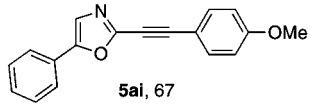
(9) (a) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (b) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651.

(10) Only one precedent, to the best of our knowledge: see ref 4a.

Table 3. Nickel-Catalyzed Direct Alkynylation of Various 5-Aryloxazoles **4** with Alkynyl Bromides **2**[a]



4 **2** **5**

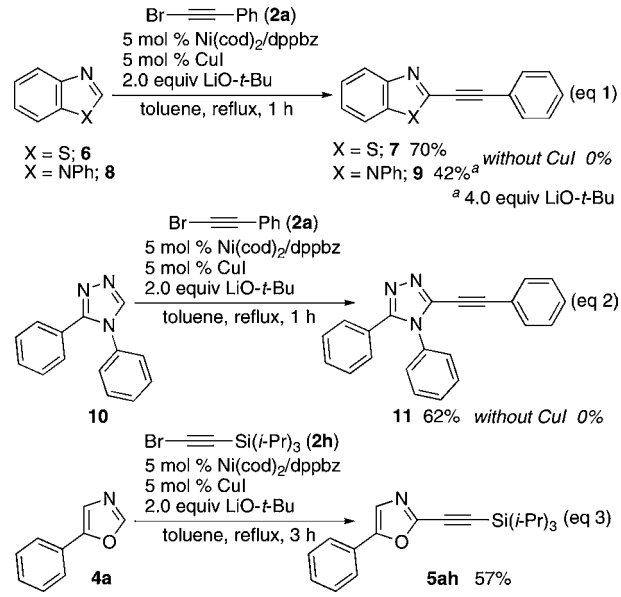
entry	Ar in **4**	R in **2**	**5**, yield (%)[b]
1	Ph (**4a**)	Ph (**2a**)	 **5aa**, 84
2	4-MeOC$_6$H$_4$ (**4b**)	**2a**	 **5ba**, 74
3	4-ClC$_6$H$_4$ (**4c**)	**2a**	 **5ca**, 72
4	4-CF$_3$C$_6$H$_4$ (**4d**)	**2a**	 **5da**, 91
5[c]	1-naphthyl (**4e**)	**2a**	 **5ea**, 79
6	**4a**	1-naphthyl (**2e**)	 **5ae**, 64
7	**4a**	Si(*i*-Pr)$_3$ (**2h**)	 **5ah**, 28
8	**4a**	4-MeOC$_6$H$_4$ (**2i**)	 **5ai**, 67

[a] A mixture of **4** (0.25 mmol), **2** (0.30 mmol), Ni(cod)$_2$ (0.013 mmol), dppbz (0.013 mmol), and LiO-*t*-Bu (0.50 mmol) was stirred in boiling toluene (1.0 mL) for 3 h. [b] Yield of isolated compounds. [c] At 150 °C in *o*-xylene.

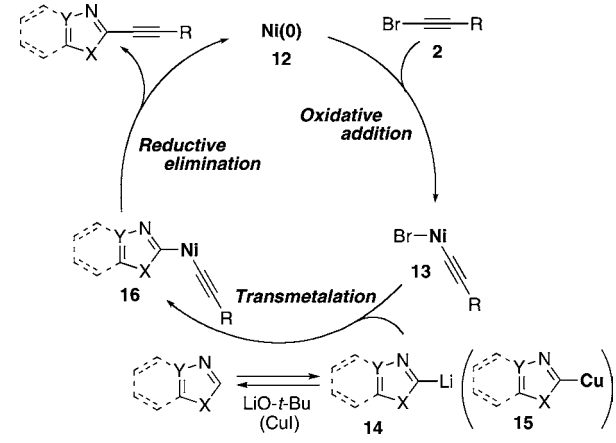
naphthalene motif and electron-donating methoxyphenyl substitution in the alkynyl bromide were tolerant toward the reaction (entries 6 and 8). On the contrary, the coupling with silylethynyl bromide **2h** led to compound **5ah** in a lower yield (entry 7).

Next, we attempted the direct alkynylation of benzothiazole (**6**) with **2a** (Scheme 1, eq 1). On exposure of **6** and **2a** to the standard reaction conditions, however, no expected coupled product was detected. After some additional optimization studies, the addition of 5 mol % of CuI was found to enhance the reaction dramatically,[11] and 2-(phenylethynyl)benzothiazole (**7**) was isolated in 70% yield. Moreover, the Ni/Cu cooperative catalyst system allowed the use of *N*-phenylbenzimidazole (**8**) and 3,4-diphenyl-4*H*-1,2,4-triazole (**10**) (Scheme 1, eq 2) as well, as it improved the reaction efficiency in the coupling of **4a** with **2h** (Scheme 1, eq 3 vs. entry 7 in Table 3).

Scheme 1



Scheme 2



We are tempted to assume the mechanism of the reaction as follows (Scheme 2). Initial oxidative addition of alkynyl bromide **2** to a zerovalent Ni species **12** affords the corresponding (alkynyl)nickel intermediate **13**. Subsequent transmetalation with heteroaryllithium compound **14** generated in situ from heteroarene and LiO-*t*-Bu[12] followed by

(11) A similar effect of CuI was observed in the palladium-catalyzed direct arylation of azoles: Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467.

(12) Deprotonation of heteroarenes with LiO-*t*-Bu: (a) Do, H.-Q.; Khan, M. R. K.; Daugulis, O *J. Am. Chem. Soc.* **2008**, *130*, 15185. (b) Do, H.-Q.; Daugulis, O. *Org. Lett.* **2009**, *11*, 421.

productive reductive elimination furnishes the alkynylated product along with the starting nickel complex to complete the catalytic cycle. Although the exact role of CuI as seen in Scheme 1 is not clear at this stage, the formation of heteroarylcopper **15** would be most plausible.[13] Such species may undergo transmetalation with **13** more readily than the corresponding organolithium.[14]

(13) (a) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404. (b) Ackermann, L.; Potukuchi, H. K.; Landsberg, D.; Vicente, R. *Org. Lett.* **2008**, *10*, 3081. (c) Besselièvre, F.; Piguel, S.; Mahuteau-Betzer, F.; Grierson, D. S. *Org. Lett.* **2008**, *10*, 4029. (d) Yoshizumi, T.; Tsurugi, H.; Satoh, T.; Miura, M. *Tetrahedron Lett.* **2008**, *49*, 1598. (e) Yotphan, S.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2009**, *11*, 1511. (f) Yoshizumi, T.; Satoh, T.; Hirano, K.; Matsuo, D.; Orita, A.; Otera, J.; Miura, M. *Tetrahedron Lett.* **2009**, *50*, 3273. (g) Zhao, D.; Wang, W.; Yang, F.; Lan, J.; Yang, L.; Gao, G.; You, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3296. (h) Kawano, T.; Yoshizumi, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 3072.

(14) Nevertheless, our preliminary investigation indicated that 19% GC yield of **7** was detected only in the presence of a catalytic amount of CuI although the formation of diyne side product predominantly occurred (Scheme 1, eq 1). Further efforts for the clarification of the role of CuI are ongoing.

In summary, we have described an effective nickel-based strategy for the direct alkynylation of azoles with alkynyl bromides. The catalytic system is quite effective for the relatively electron-deficient heteroarenes so as to complement the precedent gallium- and palladium-mediated processes.[3−5] Ongoing work seeks to develop the related C−H cleavage processes by nickel catalysts.

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

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