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Nickel- and Copper-Catalyzed Direct Alkynylation of Azoles and Polyfluoroarenes with Terminal Alkynes under O_2 or Atmospheric Conditions

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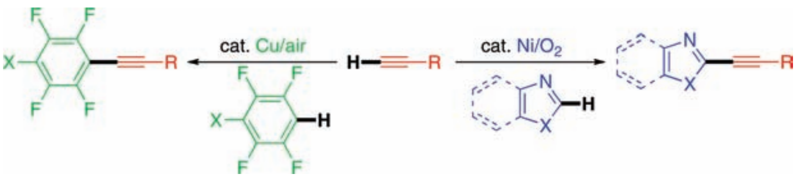
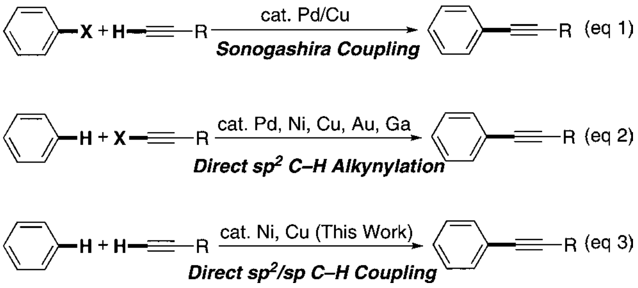
ABSTRACT



The direct C−H alkynylation of azoles with terminal alkynes proceeds efficiently under a nickel/O_2 catalytic system. On the other hand, a copper/air catalyst enables the coupling of polyfluoroarenes with terminal alkynes. These catalyses provide new accesses to arylacetylenes through the formal direct Sonogashira coupling.

Arylacetylenes are among the most fundamental and important π-conjugated systems in the various fields of organic chemistry. A powerful and reliable approach to these molecules is the palladium/copper-catalyzed cross-coupling of aryl halides with terminal alkynes, that is, Sonogashira coupling (Scheme 1, eq 1).[1] On the other hand, the metal-catalyzed direct alkynylation of arene C−H bonds with alkynyl halides or pseudohalides has recently been receiving much attention as a complementary process to Sonogashira coupling (Scheme 1, eq 2).[2] Ultimately, the direct coupling between arenes and terminal alkynes via C−H bond cleavage of both substrates is an ideal goal since no preactivation step is required (Scheme 1, eq 3). However, this type of cross-coupling has been greatly challenging probably due to the difficulties of catalyst control in the sequential activation of two different C−H bonds.

Scheme 1. Approaches to Arylacetylenes



Recently, we found that an appropriate copper species enabled the direct sp^2/sp C−H coupling of heteroarenes involving 5-aryloxazoles and 1,3,4-oxadiazoles.[3] Although the reaction provided the most straightforward access to arylacetylenes, use of a stoichiometric or substoichiometric amount of copper was essential. Thus, the catalytic variants

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(1) (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. (e) Doucet, H.; Hierso, J.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 834. (f) Plenio, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6954.

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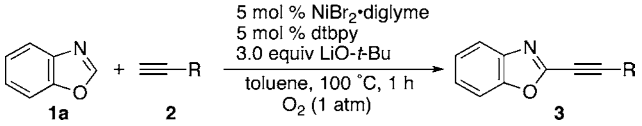
still remain elusive.[4] Herein, we report the nickel- and copper-catalyzed direct alkynylations of azoles and polyfluoroarenes; while the nickel catalyst is effective for the reaction with azoles, the copper one shows unique activity for polyfluoroarenes. Since the acetylenes conjugated with these aromatics are often found in medicinal[5] and material[6] chemistry areas, this transformation appears to be of interest in organic synthesis.

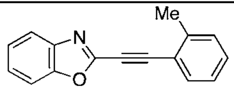
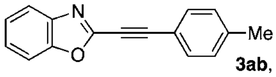
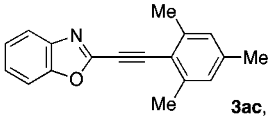
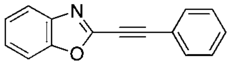
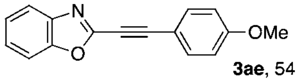
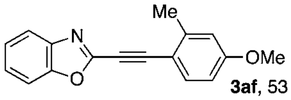
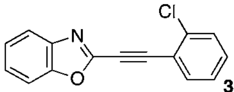
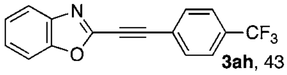
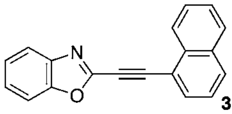
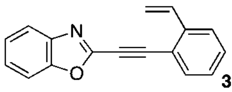
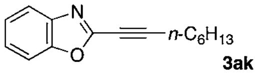
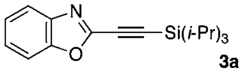
During our recent studies on the nickel-catalyzed direct alkynylation of azoles with alkynyl bromides,[2g] we hypothesized that the replacement of alkynyl bromides with terminal alkynes could be possible and the use of O_2 rendered the reaction catalytic on nickel. Indeed, treatment of benzoxazole (**1a**) with (2-methylphenyl)acetylene (**2a**) in the presence of 5 mol % of NiBr$_2$•diglyme, 5 mol % of 4,4′-di(*tert*-butyl)-2,2′-bipyridine (dtbpy), and LiO-*t*-Bu in toluene at 100 °C under O_2 (1 atm, balloon) gave the direct cross-coupling product **3aa** in 62% yield (Table 1, entry 1).[7] Under similar reaction conditions, arylacetylenes with various substitution patterns participated in the direct coupling (entries 2−8). The naphthylalkynyl moiety could also be introduced to the benzoxazole core (entry 9). The alkyne **2j** reacted with **1a** to afford the corresponding heteroarylacetylene **3aj** in an acceptable yield, leaving the terminal olefin moiety untouched (entry 10). The alkylacetylene **2k** was also available for use by simple temperature control (entry 11). The slow addition of **1a** was beneficial for the reaction with silylacetylene **2l** (entry 12).

The above reaction conditions, with some variations as noted, could be applied to the alkynylation of other azoles (Table 2). The benzoxazoles bearing methyl, phenyl, and chloro substituents at the 5-position coupled with phenylacetylene (**2d**) as well as silylacetylene **2l** to create the heteroarylalkyne conjugations in moderate to good yields (**3bd−dd** and **3bl−dl**). Notably, various 5-aryloxazoles having not only electron-rich **1e−g** but also electron-deficient aryl groups **1h−j** underwent the direct alkynylation with **2l** albeit with the higher catalyst loading (**3el−jl**). The sterically demanding naphthalene motif did not interfere with the

Table 1. Nickel-Catalyzed Direct Alkynylation of Benzoxazole (**1a**) with Terminal Alkynes **2**[a]



1a **2** **3**

entry	Ar **2**	**3a**, yield (%)[b]
1[c]	2-MeC$_6$H$_4$ **2a**	 **3aa**, 62
2	4-MeC$_6$H$_4$ **2b**	 **3ab**, 44
3	2,4,6-Me$_3$C$_6$H$_2$ **2c**	 **3ac**, 45
4	Ph **2d**	 **3ad**, 48
5	4-MeOC$_6$H$_4$ **2e**	 **3ae**, 54
6	4-MeO-2-MeC$_6$H$_3$ **2f**	 **3af**, 53
7	2-ClC$_6$H$_4$ **2g**	 **3ag**, 43
8	4-CF$_3$C$_6$H$_4$ **2h**	 **3ah**, 43
9[d]	1-naphthyl **2i**	 **3ai**, 50
10	2-(CH$_2$=CH)C$_6$H$_4$ **2j**	 **3aj**, 49
11[e]	*n*-C$_6$H$_{13}$ **2k**	 **3ak**, 45
12[f]	Si(*i*-Pr)$_3$ **2l**	 **3al**, 56

[a] A mixture of **1a** (0.50 mmol), **2** (1.0 mmol), NiBr$_2$•diglyme (0.025 mmol), dtbpy (0.025 mmol), and LiO-*t*-Bu (1.5 mmol) was stirred in toluene (2.5 mL) at 100 °C for 1 h under O_2 atmosphere (1 atm). [b] Yield of isolated compounds. [c] With 1.5 mmol of **2** and 2.0 mmol of LiO-*t*-Bu. [d] In 1.5 mL of toluene. [e] At 80 °C. [f] A solution of **1a** in 1.0 mL of toluene was slowly added to a mixture of **2l**, NiBr$_2$•diglyme, dtbpy, and LiO-*t*-Bu in toluene (1.5 mL) over 30 min at 80 °C, and the resulting mixture was stirred for the additional 1.5 h at the same temperature.

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(2) Ga: (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. Pd: (c) Seregin, I. V.; Ryabova, V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 7742. (d) Gu, Y.; Wang, X.-m. *Tetrahedron Lett.* **2009**, *50*, 763. (e) Rodriguez, A.; Fennessy, R. V.; Moran, W. J. *Tetrahedron Lett.* **2009**, *50*, 3942. (f) Tobisu, M.; Ano, Y.; Chatani, N. *Org. Lett.* **2009**, *11*, 3250. Ni: (g) Matsuyama, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 4156. Cu: (h) Besseliévre, F.; Piguel, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 9553. (i) Kawano, T.; Matsuyama, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2010**, *75*, 1764. Au: (j) Brand, J. P.; Charpentier, J.; Waser, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9346. See also: (k) Dudnik, A. S.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2010**, *49*, 2096.

(3) (a) Kitahara, M.; Hirano, K.; Tsurugi, H.; Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 1772. A gold-mediated process is also known: (b) Fuchita, Y.; Utsunomiya, Y.; Yasutake, M. *J. Chem. Soc., Dalton Trans.* **2001**, 2330.

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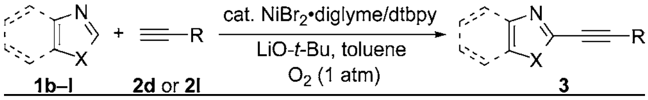
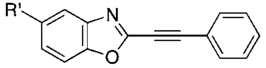
(7) Other N-based ligands such as 1,10-phenanthroline and 2,2′-bipyridine resulted in the lower yield by ca. 10% and had no influence on product selectivity. The combination of toluene and LiO-*t*-Bu was necessary for the reaction. The use of polar solvents and other bases such as Na- or KO-*t*-Bu was detrimental due to the rapid decomposition of the starting materials.

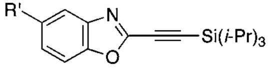
Table 2. Nickel-Catalyzed Direct Alkynylation of Various Azoles **1** with Terminal Alkynes **2d** or **2l**



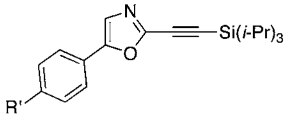
3, % yield[a] (temp, time, conditions[b])



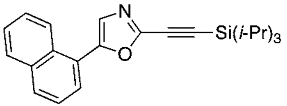
R' = Me; **3bd** 51 (80 °C, 1 h, A)
= Ph; **3cd** 55 (50 °C, 3 h, A)
= Cl; **3dd** 40 (80 °C, 1 h, A)



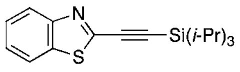
R' = Me; **3bl** 49 (80 °C, 1 h, B)
= Ph; **3cl** 57 (50 °C, 3 h, B)
= Cl; **3dl** 61 (80 °C, 1 h, B)



R' = H; **3el** 40 (120 °C, 1.5 h, C)
= Me; **3fl** 54 (120 °C, 1.5 h, C)
= MeO; **3gl** 45 (120 °C, 1.5 h, C)
= CF_3; **3hl** 56 (120 °C, 1.5 h, C)
= Cl; **3il** 47 (120 °C, 1.5 h, C)
= NO_2; **3jl** 47 (120 °C, 1.5 h, C)



3kl 46 (120 °C, 1.5 h, C)



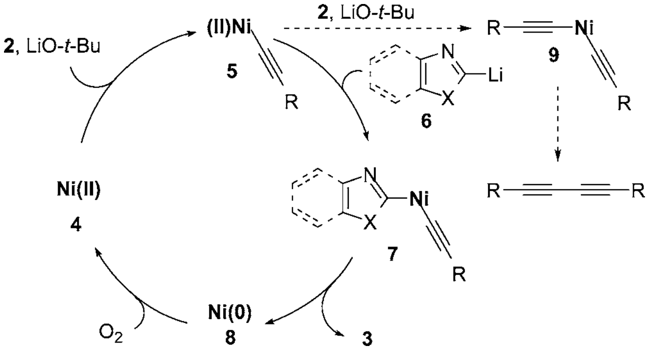
3ll 37 (120 °C, 2 h, D)

[a] Yield of isolated compounds. [b] Conditions A: see Table 1. Conditions B: a solution of **1** (0.50 mmol) in toluene (1.0 mL) was slowly added to a mixture of **2** (1.0 mmol), $NiBr_2$•diglyme (0.025 mmol), dtbpy (0.025 mmol), and LiO-*t*-Bu (1.5 mmol) in toluene (2.5 mL) over 1 h under O_2 atmosphere (1 atm), and the resulting mixture was stirred for the indicated time. Conditions C: a solution of **2** (1.5 mmol) in toluene (1.0 mL) was slowly added to a mixture of **1** (0.50 mmol), $NiBr_2$•diglyme (0.075 mmol), dtbpy (0.075 mmol), and LiO-*t*-Bu (2.0 mmol) in toluene (2.5 mL) over 30 min under O_2 atmosphere (1 atm), and the resulting mixture was stirred for the indicated time. Conditions D: a solution of **2** (1.5 mmol) in toluene (1.0 mL) was slowly added to a mixture of **1** (0.50 mmol), $NiBr_2$•diglyme (0.075 mmol), dtbpy (0.075 mmol), and LiO-*t*-Bu (2.0 mmol) in toluene (2.5 mL) over 1 h under O_2 atmosphere (1 atm), and the resulting mixture was stirred for the indicated time.

reaction (**3kl**). Moreover, the coupling of benzothiazole (**1l**) with **2l** was also possible (**3ll**).

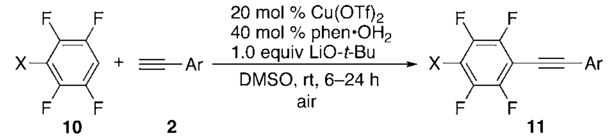
We are tempted to assume the reaction mechanism as follows (Scheme 2). A nickel(II) complex **4** generated in situ initially reacts with terminal alkyne **2** with the aid of LiO-*t*-Bu to generate (alkynyl)nickel intermediate **5**. Subsequently, heteroaryllithium **6** formed through the deprotonation of the relatively acidic sp^2 C−H bond of azole **1**[8] by the action of LiO-*t*-Bu[9] undergoes transmetalation with **5**, and productive reductive elimination provides the cross-coupling product **3** along with the zerovalent nickel complex **8**. The oxidation of **8** with molecular oxygen regenerates **4**, possibly via a Ni(O_2) species,[10−12] to complete the catalytic cycle. If the reaction of **5** with the second alkyne **2** preferably occurred, the undesired diyne would be obtained via formation of bis(alkynyl)nickel **9**. Indeed, a detectable amount of the homocoupling product was often confirmed by GC analysis. The findings and the beneficial effect of the alkyne slow addition technique observed in some cases (Table 2, **3el−3ll**) are consistent with the proposed mechanism.

Scheme 2

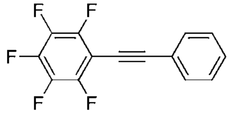


Next, we attempted the direct alkynylation of polyfluoroarenes since the pK_a value of their sp^2 C−H bonds is as high as those of azoles so that the effective activation by nickel catalysts was anticipated.[8] However, pentafluorobenzene (**10a**) showed no activity under the above reaction conditions. Any changes of reaction parameters gave no positive effect. On the basis of our previous observation,[3a] we then turned our attention to the copper catalyst.[4b] To our delight, a combination of $Cu(OTf)_2$/phen•OH_2 (phen =1,10-phenanthroline) in DMSO was found to catalyze without any other additives the direct coupling of **10a** with **2d** even at room temperature under atmospheric conditions to produce **11ad** (Table 3).[13] By using the copper-based catalyst system, the reaction of an array of terminal alkynes **2** with poly-

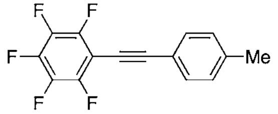
Table 3. Copper-Catalyzed Direct Alkynylation of Polyfluoroarenes **10** with Terminal Alkynes **2**[a]



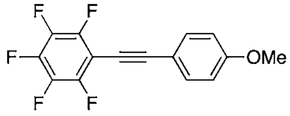
11, yield (%)[b]



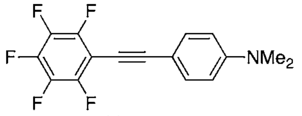
11ad, 60



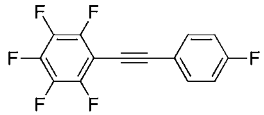
11ab, 68



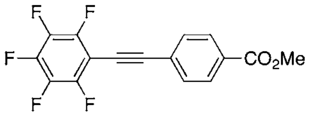
11ae, 76 (52)



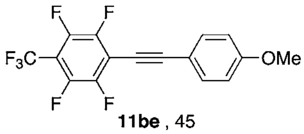
11am, 72



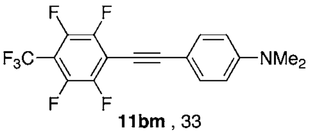
11an, 54



11ao, 25



11be, 45



11bm, 33

[a] A mixture of **10** (1.5 mmol), **2** (0.50 mmol), $Cu(OTf)_2$ (0.10 mmol), phen•OH_2 (0.20 mmol), and LiO-*t*-Bu (0.50 mmol) was stirred in DMSO (1.5 mL) at room temperature under air. Key: **10a**, X = F; **10b**, X = CF_3; **2d**, Ar = Ph; **2b**, Ar = 4-MeC_6H_4; **2e**, Ar = 4-$MeOC_6H_4$; **2m**, Ar = 4-$Me_2NC_6H_4$; **2n**, Ar = 4-FC_6H_4; **2o**, Ar = 4-$MeO_2CC_6H_4$. [b] Yield of isolated compounds. Yield on 5.0 mmol scale is in parentheses.

fluoroarenes **10** was implemented (Table 3). The substitutions of electron-donating groups on the benzene ring at the alkyne terminus increased the yield of the products (**11ab**, **11ae**, and **11am**). On the contrary, the electron-deficient nature of fluoro and methoxycarbonyl groups dropped the reaction efficiency, and the detectable amounts of diyne side products were observed (**11an** and **11ao**). Among other polyfluoroarenes tested, 1,2,4,5-tetrafluoro-3-(trifluoromethyl)benzene (**10b**) was available for use, and the corresponding (polyfluoroaryl)acetylenes **11be** and **11bm** were obtained, albeit with moderate yields.[14] Moreover, a 10-fold larger scale synthesis of **11ae** was possible, indicating the good reliability of the process.

In summary, we have described effective nickel- and copper-based catalyst systems for the direct alkynylation of azoles and polyfluoroarenes with terminal alkynes using molecular oxygen as the sole oxidant, which is quite beneficial from an atom-economical point of view. These strategies are regarded as direct Sonogashira coupling and represent a new, concise avenue to arylacetylenes. Ongoing work seeks to develop the related C−H cleavage processes under the oxidative nickel− or copper−oxygen catalysis.

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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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(10) The isolation of η^2-Ni(O$_2$) complex has been reported. Yao, S.; Bill, E.; Milsmann, C.; Wieghardt, K.; Driess, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7110. (b) In our system, a zerovalent Ni precursor, Ni(cod)$_2$, worked as the catalyst under the conditions in Table 1, which also supports the existence of the η^2-Ni(O$_2$) complex as the active species.

(11) An analogous reaction of the Pd(O$_2$) complex with arylboronic acids: Adamo, C.; Amatore, C.; Ciofini, I.; Jutand, A.; Lakmini, H. *J. Am. Chem. Soc.* **2006**, *128*, 6829.

(12) Generation of the Ni(O$_2$) species from the zerovalent Ni and O$_2$: (a) Wilke, G.; Schott, H.; Heimbach, P. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 92. (b) Otsuka, S.; Nakamura, A.; Tatsuno, Y. *J. Am. Chem. Soc.* **1969**, *91*, 6994. A similar intermediate was proposed in other nickel-catalyzed reaction: (c) Yin, W.; He, C.; Chen, M.; Zhang, H.; Lei, A. *Org. Lett.* **2009**, *11*, 709. Also see: (d) Truong, T.; Alvarado, J.; Tran, L. D.; Daugulis, O. *Org. Lett.* **2010**, *12*, 1200. However, the mechanism involving nucleophilic attack of the nickel acetylide intermediate on azole is not completely discarded: (e) Tobisu, M.; Hyodo, I.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 12070.

(13) The use of dried 1,10-phenanthroline resulted in poor reproducibility. With LiOH instead of LiO-*t*-Bu, which is conceivably generated in situ from LiO-*t*-Bu and H$_2$O, the reaction proceeded to give **11ad** in a somewhat lower yield (ca. 40%). We do not have an explanation for the reason at this stage. The choice of solvent was also crucial. Less polar solvent such as toluene completely failed to lead to the formation of **11ad**.

(14) The reaction with tri- and difluoroarenes or alkylalkynes was unsuccessful probably due to their insufficient acidities of C−H bonds.