ORGANIC LETTERS

2011
Vol. 13, No. 12
3076–3079

Copper-Mediated Annulative Direct Coupling of *o*-Alkynylphenols with Oxadiazoles: A Dehydrogenative Cascade Construction of Biheteroaryls

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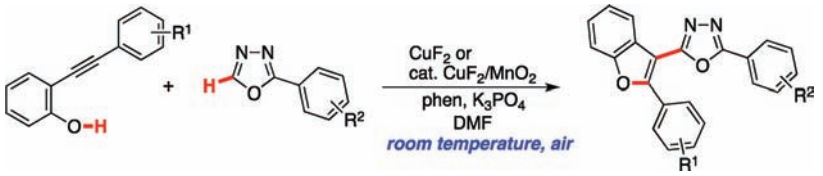
Received April 13, 2011

ABSTRACT



A copper-mediated annulative direct coupling of *o*-alkynylphenols with 1,3,4-oxadiazoles proceeds smoothly even under ambient conditions to afford the corresponding biheteroaryls. The reaction system represents a new avenue for the construction of biheteroaryl molecules of interest in their biological and physical properties.

Various biaryls containing heterocyclic cores constitute an important class of compounds in chemical synthesis owing to their ubiquity in pharmaceuticals, biologically active compounds, and functional materials.[1] In addition to the conventional cross-coupling methodology using organic halides and organometallic reagents, the metal-mediated C−H functionalization has recently received great interest for the synthesis of this type of molecule.[2] In particular, an oxidative, dehydrogenative biaryl coupling is quite attractive because it can avoid the use of halogenated and metalated starting materials. To date, many successful examples based on a combination of palladium catalysts and a stoichiometric amount of external metal oxidants such as copper and silver species have been reported.[3,4] While valuable, these precedents still rely on the precious palladium catalysts. From an economical point of view, further developments of less expensive reaction systems are strongly desired. In this context, we

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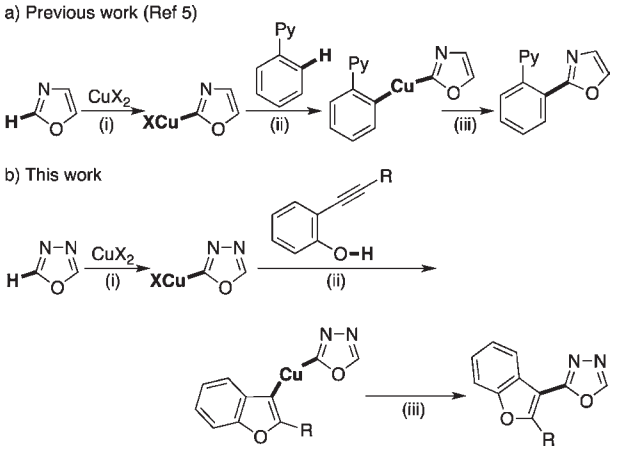
10.1021/ol200975j
Published on Web 05/17/2011

previously succeeded in the palladium-free, copper-mediated intermolecular direct biaryl coupling of azoles with 2-arylazines (Scheme 1 a).[5] The reaction is believed to proceed through (i) direct C−H cupration of azoles,[6] (ii) chelation-assisted second C−H cupration of arylazines,[7] and (iii) productive reductive elimination. In the course of our studies on this chemistry, we envisaged that the second C−H cupration step could be replaced with the annulative cupration of *o*-alkynylphenols (Scheme 1 b).[8] Thus, if the cascade process were feasible, an indirect but formally dehydrogenative biheteroaryl coupling would be realized, leading to a new type of oxidative biaryl construction from nonhalogenated and nonmetalated starting materials.

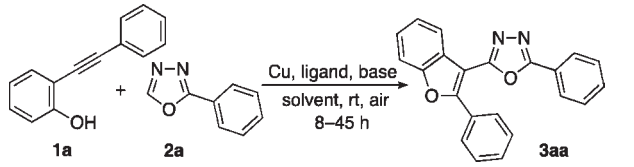
Scheme 1. Oxidative, Dehydrogenative Biaryl Couplings Mediated by Copper (Py = 2-Pyridyl)



Moreover, the expected structures, 1,3,4-oxadiazole-containing biaryls, exhibited a broad spectrum of physical[9] and biological[10] activities so that the reaction appears to be of importance in synthetic chemistry.

Based on the above assumption, we began our optimization studies with 2-(phenylethynyl)phenol (**1a**) and 2-phenyl-1,3,4-oxadiazole (**2a**) as model substrates. In an initial experiment, treatment of **1a** with **2a** in the presence of CuF_2, 1,10-phenanthroline (phen), and K_3PO_4 in *N*,

Table 1. Optimization Studies for Copper-Mediated Dehydrogenative Annulative Coupling of 2-(Phenylethynyl)phenol (**1a**) with 2-Phenyl-1,3,4-oxadiazole (**2a**)[a]



entry	Cu/ligand (ratio)	base	solvent	**3aa**, % yield[b]
1	CuF_2/phen (10:1)	K_3PO_4	DMAc	36
2	CuF_2/phen (10:1)	Cs_2CO_3	DMAc	27
3	CuF_2/phen (10:1)	Na_2CO_3	DMAc	trace
4	$CuBr_2$/phen (10:1)	K_3PO_4	DMAc	5
5	$Cu(OAc)_2$/phen (10:1)	K_3PO_4[c]	DMAc	trace
6	$Cu(acac)_2$/phen (10:1)	K_3PO_4[c]	DMAc	19
7	$Cu(OTf)_2$/phen (10:1)	K_3PO_4	DMAc	0
8	CuF_2/bpy (10:1)	K_3PO_4	DMAc	0
9	CuF_2/TMEDA (10:1)	K_3PO_4	DMAc	4
10	CuF_2/phen (10:1)	K_3PO_4	xylene	0
11	CuF_2/phen (10:1)	K_3PO_4	DMF	47
12	CuF_2/phen (10:1)	K_3PO_4	DMSO	41
13	CuF_2/phen (2:1)	K_3PO_4	DMF	93 (75)
14	CuF_2/phen (1:1)	K_3PO_4	DMF	73
15	CuF_2/none	K_3PO_4[c]	DMF	0

[a] Reaction conditions: Cu (0.60 mmol), ligand, base (0.90 mmol), **1a** (0.30 mmol), **2a** (0.60 mmol), solvent (1.0 or 2.0 mL), rt, 8−45 h, air. [b] The yields are determined by GC method. Yield of isolated product is in parentheses. [c] With 0.60 mmol of K_3PO_4.

(5) Kitahara, M.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2011**, *133*, 2160.

(6) For selected recent examples, see: (a) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404. (b) Yoshizumi, T.; Tsurugi, H.; Satoh, T.; Miura, M. *Tetrahedron Lett.* **2008**, *49*, 1598. (c) Yotphan, S.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2009**, *11*, 1511. (d) Monguchi, D.; Fujiwara, T.; Furukawa, H.; Mori, A. *Org. Lett.* **2009**, *11*, 1607. (e) Yoshizumi, T.; Satoh, T.; Hirano, K.; Matsuo, D.; Orita, A.; Otera, J.; Miura, M. *Tetrahedron Lett.* **2009**, *50*, 3273. (f) Kawano, T.; Yoshizumi, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 3072. (g) Ackermann, L.; Potukuchi, H. K.; Landsberg, D.; Vicente, R. *Org. Lett.* **2008**, *10*, 3081. (h) Zhao, D.; Wang, W.; Yang, F.; Lan, J.; Yang, L.; Gao, G.; You, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3296. (i) Besseliévre, F.; Piguel, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 9553. (j) Kitahara, M.; Hirano, K.; Tsurugi, H.; Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 1772. (k) Kawano, T.; Matsuyama, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2010**, *75*, 1764. (l) Kawano, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2010**, *132*, 6900.

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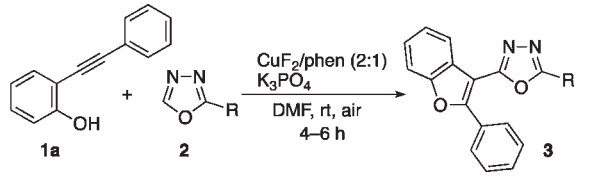
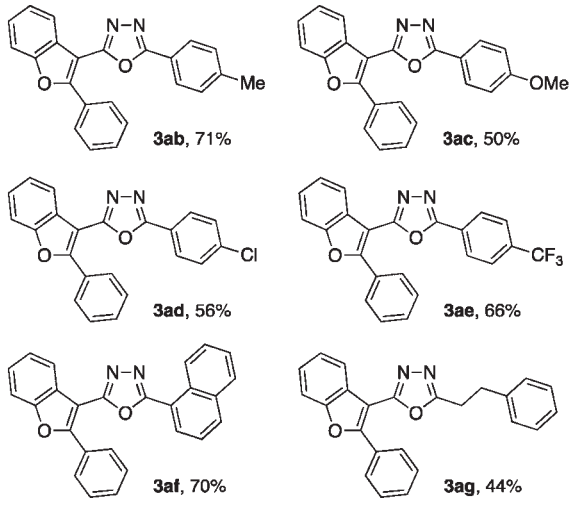
N-dimethylacetamide (DMAc) provided the desired biheteroaryl **3aa** in 36% GC yield (Table 1, entry 1), while with moderate efficiency the reaction proceeded even under ambient conditions (under air at room temperature).[11] With the preliminary result in hand, we investigated various reaction parameters. Replacement of K_3PO_4 with Cs_2CO_3 and Na_2CO_3 (entries 2 and 3) or other copper salts such as $CuBr_2$, $Cu(OAc)_2$, $Cu(acac)_2$, and $Cu(OTf)_2$ (entries 4–7) decreased the reaction efficiency. The change of ligand into bpy and TMEDA also failed to improve the yield (entries 8 and 9). On the other hand, solvent screening revealed that polar, aprotic solvents are essential, with *N*, *N*-dimethylformamide (DMF) proving to be optimal (entries 10–12). Additional optimization indicated that the ratio of Cu/ligand was a crucial factor: a half equivalent of phen (to CuF_2) dramatically increased the yield to 93% GC yield (75% yield after isolation, entry 13). A higher loading gave no longer positive effect on the yield (entry 14), while the absence of phen resulted in no formation of **3aa** (entry 15).

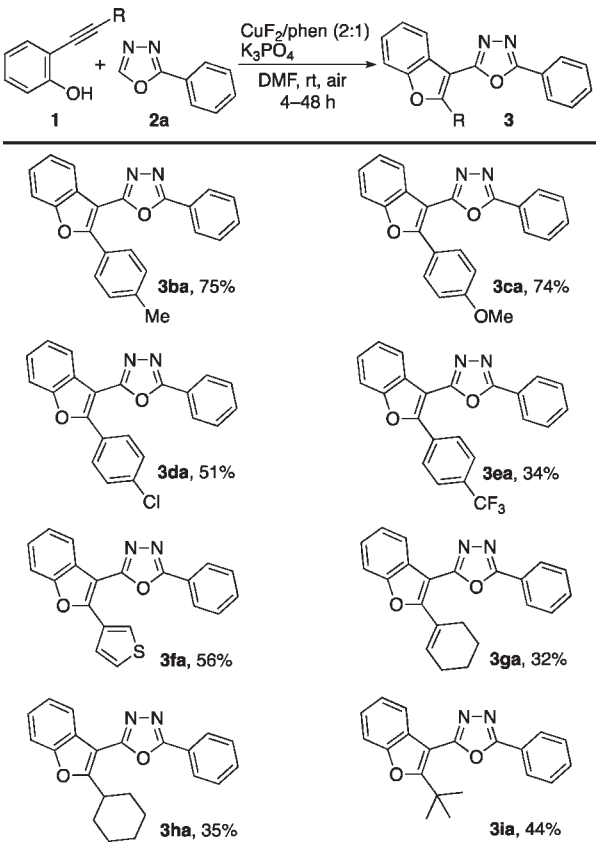
Scheme 2. Copper-Mediated Annulative Direct Coupling of 2-(Phenylethynyl)phenol (**1a**) with Various 2-Substituted-1,3, 4-oxadiazoles **2**





Subsequently, we examined the scope of 1,3,4-oxadiazoles **2** in the annulative coupling (Scheme 2). The substrates bearing electron-donating as well as electron-withdrawing groups showed similar reactivity to create the corresponding benzofuran-oxadiazole linkages in moderate to good yields (**3ab**–**ae**). The sterically demanding naphthyl ring did not interfere with the reaction (**3af**). Moreover, the alkyl-substituted oxadiazole also could be converted to the biheteroaryl **3ag** with the synthetically useful yield.

Scheme 3. Products of the Copper-Mediated Annulative Direct Coupling of Various *o*-Alkynylphenols **1** with 2-Phenyl-1,3, 4-oxadiazole (**2a**)



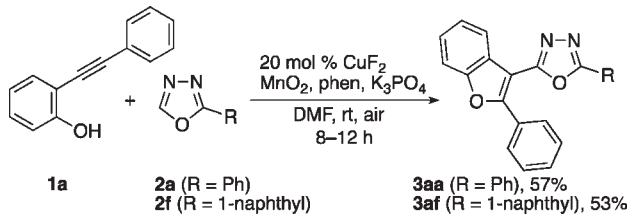
The functional compatibility on the phenols **2** was also investigated. The results are summarized in Scheme 3. While the introduction of electron-rich substituents had no influence on the reaction outcome (**3ba**–**ca**), the chloro and trifluoromethyl groups resulted in somewhat lower efficiency (**3da**–**ea**). In addition to the benzene derivatives, a heteroaryl function, thiophene ring, was also tolerated (**3fa**). The conjugated enyne produced the corresponding **3ga** with the olefinic moiety left intact. Notably, the copper-based process accommodated bulky alkyl substitutions at alkyne terminus (**3ha**–**ia**).

Owing to the inexpensiveness and relatively low toxicity of copper salt, the above reaction system appears to be useful from economical and synthetic points of view despite the inevitable excess amount of copper for the full

(11) The reaction under N_2 and O_2 dropped the yield to 8% and 21% yields, respectively.

(12) MnO_2 for an oxidation of Cu(I) into Cu(II): (a) Zhang, W.; Chemler, S. R. *J. Am. Chem. Soc.* **2007**, *129*, 12948. (b) Sequeira, F. C.; Turnpenny, B. W.; Chemler, S. R. *Angew. Chem., Int. Ed.* **2010**, *49*, 6365.

Scheme 4



conversion. Nevertheless, the catalytic version is much more appealing. Our extensive screening of co-oxidants for CuF_2 revealed that MnO_2 could render the reaction catalytic on copper (Scheme 3).[12] With 20 mol % of CuF_2, 2.0 equiv of MnO_2, and 2.0 equiv of phen, under otherwise identical conditions, the biheteroaryls **3aa** and **3af** were obtained with somewhat lower yields (Scheme 4). Although further improvements are essential, the catalysis shows the high potential of a Cu(II) catalyst for the oxidative, dehydrogenative biaryl coupling.[13]

In conclusion, we have developed a room-temperature, copper-mediated annulative direct coupling of *o*-alkynylphenols with oxadiazoles as a new, unique method for the construction of biheteroaryls. Moreover, the possibility of catalysis using CuF_2/MnO_2 is also described. Detailed mechanistic studies and application to other arene systems[14] are now in progress.

Acknowledgment. This work was partly supported by Grants-in-Aid from MEXT and JSPS, Japan. K.H. acknowledges Kansai Research Foundation for the Promotion of Science.

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.

(13) Without CuF_2, the product was not obtained at all. Under 5 mol % catalyst loading, **3aa** was formed in 10% yield (GC).

(14) Under the present conditions, attempts to apply aniline analogues, benzoxazole, or benzothiazole were unsuccessful. Further optimization and details will be reported in due course.