Bipyridine-Type Bidentate Auxiliary Enabled Copper-Mediated C–H/C–H Biaryl Coupling of Phenols and 1,3-Azoles

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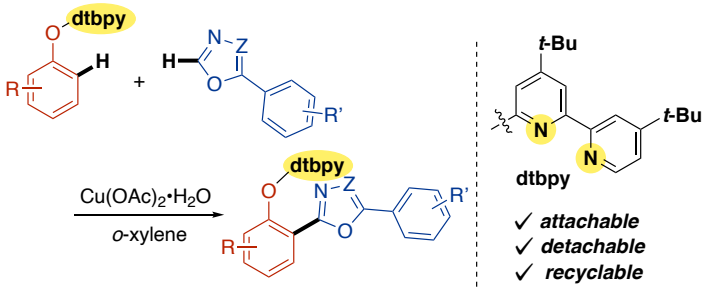
Supporting Information Placeholder



ABSTRACT: A copper-mediated dehydrogenative C–H/C–H biaryl coupling of phenols and 1,3-azoles has been developed. The key to its success is the introduction of a bipyridine-type bidentate auxiliary, 4,4'-di(*tert*-butyl)-2,2'-bipyridine, on the phenol oxygen, which is readily prepared and easily attachable, detachable, and recyclable. The reaction proceeds smoothly in the presence of copper salt alone to form the corresponding phenol-azole heterobiaryls, which are prevalent motifs in functional molecules such as excited-state intramolecular proton transfer materials.

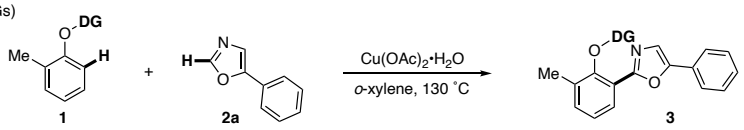
Due to its ubiquity in pharmaceuticals and functional organic materials, construction of the heterobiaryl linkage has been one of the long-standing central topics in synthetic organic chemistry. In addition to the conventional cross-coupling technology using organic halides and organometallic reagents,[1] the metal-promoted C–H activation strategy[2] has recently received a significant amount of attention because of its better step and atom economy. Among them, the dehydrogenative C–H/C–H biaryl coupling is ideal and can streamline the synthesis of the heterobiaryls because preactivation steps, such as stoichiometric halogenation and metalation, of two starting (hetero)arenes can be avoided.[3] There are several successful examples using noble metals (e.g., Pd, Rh, Ir, and Ru)[4] and even earth-abundant base metals (e.g., Ni, Co, Fe, and Cu).[5] However, the applicable combination of two simple (hetero)arenes is still limited. In particular, the phenol–heteroarene direct biaryl coupling is possible only using the noble Cp*Rh(III) catalyst/Ag oxidant system,[4g] despite the fact that the obtained phenol–heteroarene conjugation is frequently occurring in bioactive molecules,[6] organic light-emitting diodes (OLEDs),[7] and excited-state intramolecular proton transfer (ESIPT) materials.[8] A good alternative is the metal-free, electrochemical synthesis developed by Waldvogel, in which the dehydrogenative coupling of phenols and thiophenes is achieved.[9]

Meanwhile, our research group focused on the unique redox activity of Cu salts and developed the Cu-mediated C–H activation reactions involving C–H/C–H couplings.[5d-g] With our continuing interest in this chemistry, we envisioned the dehydrogenative coupling of phenols and heteroarenes. Herein, we report a bipyridine-type bidentate auxiliary-enabled Cu-promoted direct biaryl coupling of phenols and 1,3-azoles. The key to its success is the introduction of a 4,4'-di(*tert*-butyl)-2,2'-bipyridine (dtbpy) auxiliary on the phenol oxygen. The auxiliary can be easily prepared, and its attachment, detachment, and even recycling are feasible. Additionally, the direct substitution via C–O cleavage is also possible. The successful use of 1,3-azoles as the coupling partners is complementary to the reported electrochemical methods.[9]

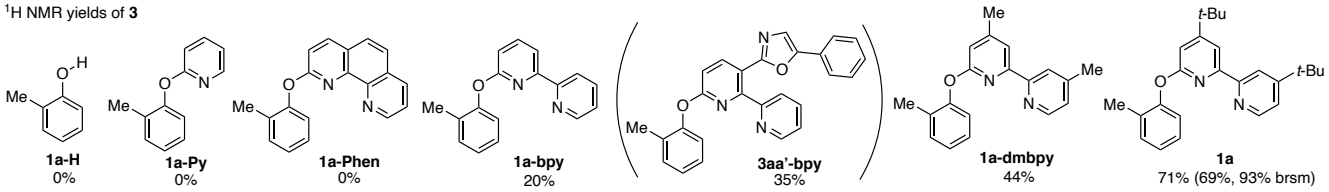
Our initial attempt with the simple *o*-cresol (**1a-H**, 0.10 mmol), 5-phenyloxazole (**2a**, 0.20 mmol), and the $Cu(OAc)_2•H_2O$ promotor (0.30 mmol) remained unsuccessful; no targeted product was detected probably because of rapid oxidative decomposition of the unprotected phenol ring (Scheme 1a). The monodentately coordinating substrate **1a-Py**, which was successfully used during noble transition metal-catalyzed C–H activation,[10] also resulted in no conversion. Thus, we turned our attention to the use of bidentately coordinating phenanthroline auxiliary **1a-Phen**, which was recently originally developed by our group.[11] However, unfortunately, just decomposition of **1a-Phen** was observed. To improve the stability of the starting phenol derivative under the oxidative conditions, we next tested relatively flexible but more robust 2,2'-bipyridine-substitued substrate **1a-bpy**.[12] Gratifyingly, the desired phenol–heteroarene conjugate **3aa-bpy** was

Scheme 1. Investigation of Directing Groups for Cu-Mediated C–H/C–H Coupling of Phenols 1 and 5-Phenyloxazole (2a) and Preparation of the Starting Substrate

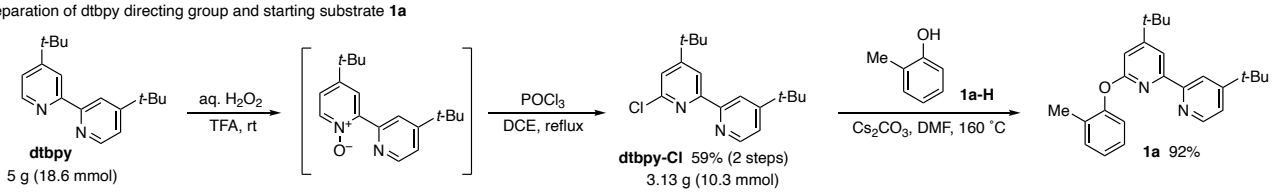
a) investigation of directing groups (DGs)



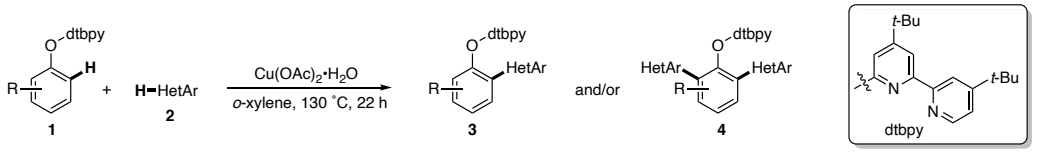
• ^{1}H NMR yields of **3**



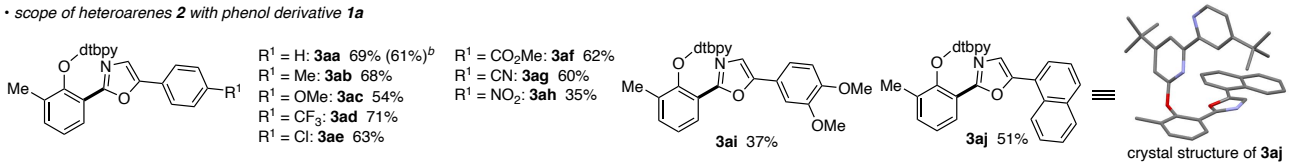
b) preparation of dtbpy directing group and starting substrate **1a**

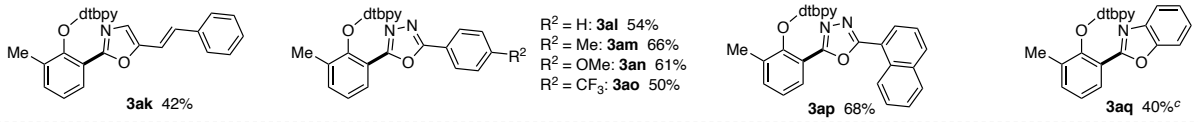


Scheme 2. Copper-Mediated C–H/C–H Biaryl Coupling of Phenols 1 and Heteroarenes 2[a]

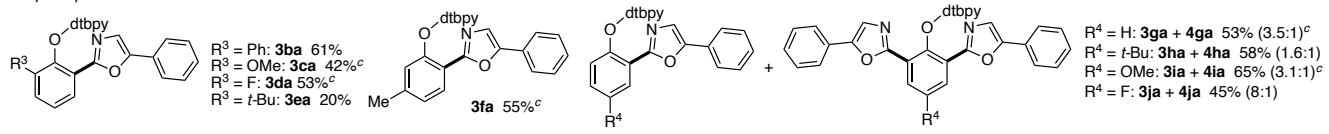


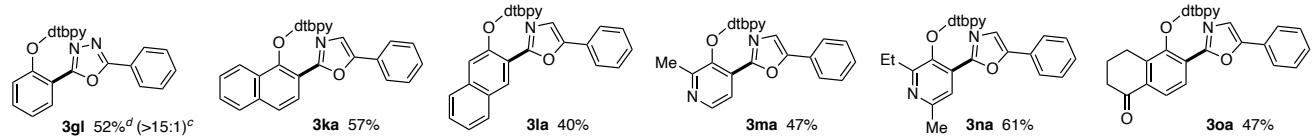
• *scope of heteroarenes **2** with phenol derivative **1a***

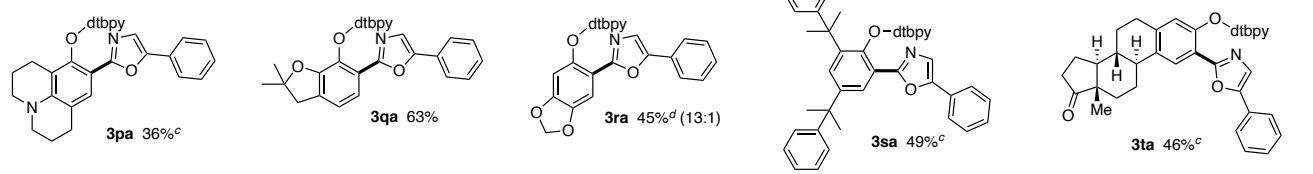




• *scope of phenols **1***







[a] Reaction conditions: $Cu(OAc)_2•H_2O$ (0.30 mmol), **1** (0.10 mmol), **2** (0.20 mmol), *o*-xylene (1.0 mL), 130 °C, 22 h, N_2. Isolated yields are shown. The **3**:**4** ratios are in parentheses. [b] On a 1.0 mmol scale. [c] In toluene. [d] Isolated yields of only monoarylated products.

formed in 20% ^{1}H NMR yield. On the contrary, competitive C–H arylation on the pyridine ring also occurred (**3aa'-bpy**) probably because of the rollover cyclometalation via free rotation of the pyridine–pyridine bond in the bipyridine auxiliary.[13] To suppress the competitive C–H activation on the pyridine ring and enhance its chelating nature, substituents were attached at positions 4 and 4' of the bipyridine moiety. The introduction of methyl groups improved the yield to a 44% ^{1}H NMR yield (**1a-dmbpy**). The *tert*-butyl substituents further increased the yield (**1a**), and targeted **3aa** was isolated in 69% yield with a 26% recovery of unreacted **1a-dtbpy** (93% yield brsm). In this case, the reaction was clean, and any side products corresponding to **3aa'-bpy** were not detected at all (see the Supporting Information for more detailed optimization studies involving attempts to make the reaction catalytic in copper). We believe that the product **3aa** can be a *N,N,N*-tridentately coordinating substrate to the copper to decrease its performance. The starting **1a** was easily prepared by the simple condensation of *o*-cresol (**1a-H**) and 4,4'-di-*tert*-butyl-6-chloro-2,2'-bipyridine (**dtbpy-Cl**), which was readily synthesized on a gram scale from commercially available 4,4'-di-*tert*-butyl-2,2'-bipyridine (**dtbpy**) in two steps (Scheme 1b).

With the optimal auxiliary and reaction conditions in hand, we then examined the substrate scope of heteroarenes **2** (Scheme 2). The copper-mediated conditions were compatible with several electron-rich and -deficient 5-aryloxazoles thar bear methyl (**3ab**), methoxy (**3ac** and **3ai**), trifluoromethyl (**3ad**), chloro (**3ae**), methoxycarbonyl (**3af**), cyano (**3ag**), and nitro (**3ah**) groups. The naphthalene (**3aj**) and styrenyl (**3ak**) substituents were also tolerated. In addition to the oxazole, the electronically and sterically diverse 1,3,4-oxadiazoles were applicable substrates to deliver the corresponding heterobiaryls **3al**–**ap** in acceptable yields. The bicyclic benzoxazole was also a viable substrate (**3aq**). However, attempts to apply other azoles such as thiazole and imidazole remained unsuccessful probably because of their lower acidity of C–Hs at the C2 position (data not shown).[14]

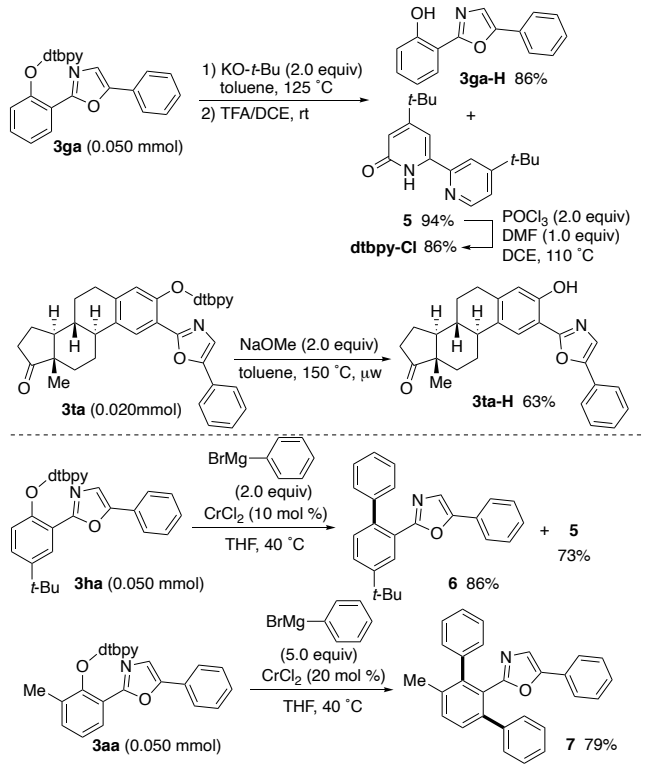
Not only *o*-cresol **1a** but also some *ortho*-substituted phenols underwent the dehydrogenative coupling with **2a** to form **3ba**–**ea** in good yields, except for the *tert*-butyl-substituted hindered **3ea**. The *m*-cresol derivative was arylated selectively at the more sterically accessible *ortho* C–H (**3fa**). In the cases of the parent phenol and *para*-substituted phenols, a mixture of mono- and diarylated products were generally obtained but in synthetically useful combined yields (**3ga**–**ja** and **4ga**–**ja**). Interestingly, when the parent phenol-type substrate **1g** was subjected to reaction conditions with the oxadiazole **1l**, the monoarylated product **3gl** was formed with high selectivity (>15:1 **3gl**:**4gl**). Additionally, naphthols (**3ka** and **3la**) and pyridinols (**3ma** and **3na**) participated in the reaction. Furthermore, the tetralone (**3oa**), julolidine (**3pa**), dihydrobenzofuran (**3qa**), and sesamol (**3ra**) ring systems were accommodated under the standard conditions. The copper-mediated C–H/C–H coupling could also be applied to the modification of a 2,4-bis(α,α-dimethylbenzyl)phenol scaffold (**3sa**), which is the core structure of UV absorption materials, TINUVIN. Particularly notable is the successful use of bioactive estrone, giving heteroarylated **3ta** in a satisfactory yield with high regioselectivity. The structure of **3aj** was unambiguously confirmed by X-ray crystallographic analysis (CCDC 2078754). The reaction was also conducted on a 1.0 mmol scale (**3aa**), thus suggesting the reproducibility and practicality of the process. In some cases, the dtbpy directing group was removed during the reaction, and the formed free phenol underwent decomposition to decrease the mass balance.

The dtbpy auxiliary could be readily removed and recycled from the coupling products **3** (Scheme 3). Treatment of **3ga** with KO-*t*-Bu in heated toluene was followed by TFA to afford the OH-free **3ga-H** in 86% yield along with a 94% yield of pyridone derivative **5**, which was easily converted back into **dtbpy-Cl** by the action of $POCl_3$/DMF. The complex estrone derivative **3ta** also underwent auxiliary removal under microwave-assisted modified conditions (**3ta-H**). The Odtbpy moiety also worked as the good leaving group in the chromium-catalyzed Kumada-Tamao-Corriu coupling. **3ha** reacted with PhMgBr in the presence of the $CrCl_2$ catalyst to furnish arylated **6** and pyridone **5** in 86% and 73% yields, respectively.[15] Intriguingly, in the case of **3aa**, the arylation occurred at the C–H and the C–O,[16] and the corresponding diarylated product **7** was mainly obtained.

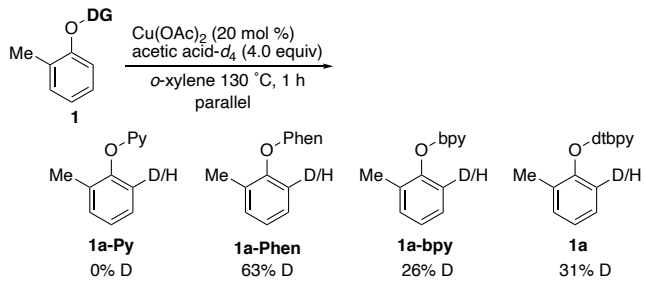
Finally, to compare the directing effect of pyridine, phenanthroline, and bipyridine auxiliaries in the reaction, we performed deuterium incorporation tests (Scheme 4). Each substrate was heated in *o*-xylene with 20 mol % $Cu(OAc)_2$ and 4.0 equiv of acetic acids-d_4, and the recovered starting substrate was analyzed by NMR. Similar to our previous work,[11a] the monodentately coordinating pyridine-ligated **1a-Py** resulted in 0% deuterium content while 63% D was observed in the recovered phenanthroline-substituted **1a-Phen**. However, to our surprise, bpy- and dtbpy-ligated substrates **1a-bpy** and **1a** exhibited lower D contents (26% D and 31% D, respectively). These phenomena suggest that the bidentate coordinating nature of the auxiliary is essential for the C–H activation step, but the directing aptitude cannot be correlated with product formation. Actually, the most productive **1a** showed just a moderate performance in the deuterium incorporation reaction. The highest productivity of the dtbpy bidentate auxiliary might be mainly attributed to its higher stability under the C–H/C–H coupling reaction conditions.[17]

In conclusion, we have developed a Cu-mediated C–H/C–H biaryl coupling of phenols and azoles to form the corresponding heterobiaryls directly. The salient feature is the use of bidentately coordinating auxiliary, 4,4'-di*(tert*-butyl)-2,2'-bipyridine (dtbpy), which is readily prepared from commercial sources and attached on the phenol oxygen. Additionally, the auxiliary is easily removed and recycled after the coupling event, whereas its direct substitution with the aryl functionality is also possible under suitable Cr catalysis. The obtained phenol-heteroarene conjugations are of great interest in pharmaceutical and material chemistry. Additional applications of the dtbpy bidentate auxiliary in C–H activation reactions and development of more robust and selective directing groups are currently underway in our laboratory.

Scheme 3. Removal, Recycling, and Functionalization of an Auxiliary



Scheme 4. Deuterium Incorporation Tests



ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.xxxx.

^{1}H, ^{13}C{^{1}H}, and ^{19}F{^{1}H} NMR spectra, ORTEP drawing, ICP-AES analysis, detailed optimization studies, tentatively proposed mechanisms (PDF)

Accession Codes

CCDC 2078754 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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(14) For pK_a values of C–Hs in representative heteroarens, see: Shen, K.; Fu, Y.; Li, J.-N.; Liu, L.; Guo, Q.-X. What are the pKa values of C–H bonds in aromatic heterocyclic compounds in DMSO? *Tetrahedron* **2007**, *63*, 1568–1576.

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(17) Although still preliminary, on the basis of the literature information the plausible reaction mechanism includes (1) N,N-bidentately coordination-assisted C–H cleavage of **1** with $Cu(OAc)_2$, (2) OAc ligand-promoted cleavage of relatively acidic C–H in the azole **2**, (3) oxidation of Cu(II) to Cu(III) with another Cu(II) (disproportionation), and (4) reductive elimination. See the Supporting Information for more details.