Mild Copper-Mediated Direct Oxidative Cross-Coupling of 1,3,4-Oxadiazoles with Polyfluoroarenes by Using Dioxygen as Oxidant

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In recent decades, significant progress has been made in transition-metal-catalyzed carbon-carbon and carbonheteroatom bond-forming reactions.^[1] Although preactivation by halogenation and/or metalation is commonly required, recent advances in direct metal-catalyzed C-H functionalizations have offered alternative synthetic pathways, which often appear to be more efficient.^[2] Along these lines, various biaryls have been prepared by heteroarene-heteroarene,^[3] heteroarene-arene,^[4] and directed arene-arene^[5] coupling reactions involving C-C bond formation through dual C-H bond cleavage. Unfortunately, many of these procedures require the use of expensive palladium catalysts in combination with toxic reagents and rather harsh reaction conditions. Furthermore, in many cases, the use of stoichiometric amounts of both a suitable metal salt and an oxidant is necessary.^[6] Improved protocols have recently been developed and successful copper-catalyzed direct oxidative C-H/ C-H cross-coupling reactions have been described.^[7] However, those that involve C_{sp^2} -H/ C_{sp^2} -H coupling reactions are still rare.^[8]

1,3,4-Oxadiazoles are important pharmacophoric core structures of compounds exhibiting a broad range of bioactivities. For example, various derivatives of this heterocycle have been found to be fungicidal,^[9] antimicrobial, and antibacterial.^[10] In medicinal chemistry^[11] and applied material sciences relating to electron-transport devices and organic light-emitting diodes (OLEDs),^[12] polyfluorinated biaryls are of high importance. In 1967, Vorozhtsov and co-workers^[13] reported the synthesis of 2-(pentafluorophenyl)-5phenyl-1,3,4-oxadiazole by cyclization of 1-benzoyl-2-pentafluorobenzoylhydrazine (Scheme 1, route a), prepared by treating pentafluorobenzoyl chloride with benzohydrazide. Recently, a series of 2-aryl-5-phenyl-1,3,4-oxadiazoles were synthesized by Miura and co-workers by copper-mediated direct arylation of 1,3,4-oxadiazoles using aryl halides (Scheme 1, route b).^[14]

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Scheme 1. Synthetic approaches to 2-aryl-1,3,4-oxadiazoles.

Noting the significant advances made in C–H functionalizations of 1,3,4-oxadiazoles^[15] and inspired by the recent progress in copper-catalyzed oxidative cross-coupling reactions,^[7,16,17] we decided to investigate the oxidative C5-arylation of 1,3,4-oxadiazoles through C_{sp^2} –H/ C_{sp^2} –H cross-coupling reactions. Herein, we report on copper-mediated reactions between 2-substituted 1,3,4-oxadiazoles and polyfluoroarenes with dioxygen as oxidant at room temperature (Scheme 1, route c).

For the initial screening (Table 1), 2-phenyl-1,3,4-oxadiazole (1a) and pentafluorobenzene (2a) were used as starting materials. After significant experimentation it was found that the desired product **3a** could be obtained in 34% yield when 1a and 2a (0.2 mmol scale) were applied in a 1:5 ratio in the presence of one equivalent of CuBr, three equivalents of tBuOLi, one equivalent of 1,10-phenanthroline, and acetonitrile as solvent under an atmosphere of dioxygen (Table 1, entry 1). Lower yields of **3a** were observed when the reaction was performed in benzonitrile or propionitrile instead of acetonitrile. No product was obtained in other solvents (toluene, DMF, DMSO, NMP, and THF). For further information regarding the optimization process, see the Supporting Information. Because the use of $[PdCl_2(PPh_3)_2]$ or $Pd(OAc)_2$ as catalyst proved ineffective (Table 1, entries 2) and 3), we focused on the application of copper bromide. In its absence, no product formation occurred (Table 1, entry 4).

To reduce the extent of the homocoupling of 1a,^[7a] the loading of 2a was increased to 30 equivalents, which enhanced the yield of 3a significantly to 65% after stirring at room temperature for 14 h (Table 1, entry 5).

The use of bathophenanthroline as an alternative to 1,10phenanthroline was also successful, the product yield remaining almost the same (Table 1, entry 6). In the absence

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Table 1. Direct oxidative cross-coupling reaction of 2-phenyl-1,3,4-oxadiazole (1a) with pentafluorobenzene $(2a)^{[a]}$

$\begin{array}{c} N^{-N} \\ Ph \\ O \\ 1a \\ F \\ 2a \\ F \\ a \\ F \\ 2a \\ F \\ a \\ F \\ F$				
Entry	Metal source	Base	Oxidant	Yield [%]
1	CuBr	tBuOLi	O_2	34
2	$[PdCl_2(PPh_3)_2]$	tBuOLi	O_2	0 ^[b]
3	$Pd(OAc)_2$	tBuOLi	O_2	0 ^[b]
4	-	tBuOLi	O_2	0
5	CuBr	tBuOLi	O_2	65 ^[c]
6	CuBr	tBuOLi	O_2	60 ^[c,d]
7	CuBr	tBuOLi	O_2	24 ^[c,e]
8	CuBr	tBuOLi	$PhI(OAc)_2$	0
9	CuBr	tBuOLi	Selectfluor	0
10	CuBr	tBuOLi	AgOAc	0
11	CuBr	tBuOLi	-	0
12	CuBr	tBuONa	O_2	16
13	CuBr	tBuOK	O_2	12
14	CuBr	tBuOLi	O_2	64 ^[c,f]

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (1.0 mmol), metal source (0.2 mmol), 1,10-phenanthroline (0.2 mmol), base (0.6 mmol), CH₃CN (1.5 mL), RT, 14 h. A balloon of O_2 was used in reactions with dioxygen. [b] Use of 5 mol% of the metal source. [c] Use of 30 equiv of **2a**. [d] Use of bathophenanthroline instead of 1,10-phenanthroline as ligand. [e] No ligand. [f] The purity of CuBr was 99.999%.

of a ligand, the yield of **3a** decreased dramatically (entry 7). Attempts to synthesize **3a** by using other oxidants such as PhI(OAc)₂, Selectfluor, and AgOAc were unsuccessful (entries 8–10). In addition, compound **3a** was not formed in the absence of dioxygen (entry 11). Bases other than *t*BuOLi (*t*BuONa, *t*BuOK, Na₂CO₃, and Cs₂CO₃) were successively tested in this reaction, although the desired product **3a** was obtained in lower yields or only trace amounts. To exclude the possibility of contamination by other catalytically active transition metals, a control experiment was performed by using CuBr with a purity of 99.999 %;^[18] the desired product was obtained in a similarly good yield (entry 14).

With the optimized conditions in hand (see footnote [a] of Table 2), the scope of the reaction was investigated. A broad range of substrates with electron-rich or -deficient aromatic substituents at the 2-position of the 1,3,4-oxadiazole were tolerated (Table 2, entries 1–8). By using ten equivalents of 2a, 2-(3-pyridyl)-1,3,4-oxadiazole (1i) afforded the desired product 3i in 45% yield (1 mmol scale; entry 9). The coupling of benzoxazole (1j) with pentafluorobenzene (2a, 5 equiv) provided the corresponding product 3j in a low yield of 20% (entry 10).

The protocol was also applied to a range of tetrahalo-(het)arenes containing additional substituents (Scheme 2). In these cases, the amount of polyfluoroarene could be reduced to ten equivalents (or less). Tetrafluoroarenes bearing electron-withdrawing substituents efficiently coupled with a variety of 2-aryl-substituted 1,3,4-oxadiazoles, furnishing the corresponding products in good yields. For example, 1-trifluoromethyl-2,3,5,6-tetrafluorobenzene reacted with oxadiazoles **1a-h** to give the products **3k-r** in 50–61% yield. Table 2. Copper-mediated direct arylation of 2-aryl-1,3,4-oxadiazoles (1a-i) and benzoxazole (1j) with pentafluorobenzene (2a).^[a]

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[a] Reaction conditions: heterocycle **1** (0.2 mmol), **2a** (6 mmol), CuBr (0.2 mmol), 1,10-phenanthroline (0.2 mmol), *t*BuOLi (0.6 mmol), O₂ (balloon), CH₃CN (1.5 mL), RT, 14 h. [b] 1 mmol scale; use of 10 equiv of **2a**. [c] 1 mmol scale; use of 5 equiv of **2a**.

By using only five equivalents of 1-cyano-2,3,5,6-tetrafluorobenzene, product **3t** was obtained in 50% yield. With electron-rich 1-methoxy-2,3,5,6-tetrafluorobenzene the yield decreased, product **3s** being obtained in a yield of only 15%. With 1,2,4,5-tetrafluorobenzene (10 equiv) as the coupling partner of **1a**, a mixture of **3u** and **3v** was formed, and the products were isolated in 8 and 9% yield, respectively. With three equivalents of 2,3,5,6-tetrachloropyridine, the crosscoupling reaction with **1a** proceeded smoothly, leading to the formation of **3w** in 35% yield. Attempts to use tri- or difluoroarenes failed, most likely due to the significant difference in acidity between these fluoroarenes and 1,3,4-oxadiazoles.^[7b]

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Scheme 2. Copper-mediated direct arylation of polyhalo(het)arenes with 2-substituted 1,3,4-oxadiazoles. Reagents and conditions: 1,3,4-oxadiazole (0.2 mmol), polyhalo(het)arene (2 mmol), CuBr (0.2 mmol), 1,10-phenanthroline (phen, 0.2 mmol), *t*BuOLi (0.6 mmol), O₂ (balloon), CH₃CN (1.5 mL), RT, 14 h. [a] 1 mmol scale. [b] Use of 5 equiv of polyfluoroarene. [c] Products **3u** and **3v** were obtained as a mixture and isolated in 8 and 9% yield, respectively. [d] 0.5 mmol scale; use of 3 equiv of 2,3,5,6tetrachloropyridine and 4 equiv of *t*BuOLi (0.4 M).

The formation of crystalline structures with relatively high melting transitions (**3t**: 220 °C; **3v**: 201 °C) is another interesting feature of most of the products described here. Furthermore, a dramatic difference between the solubility of **3t** compared with the other products was observed. Although the electron-withdrawing capability of the cyano group and the fluorine atoms is similar, compound **3t** is poorly soluble in a number of polar solvents (EtOAc, CDCl₃, [D₆]DMSO, and CD₃OD), which contrasts with the behavior of the corresponding all-fluoro derivatives such as **3a**.

On the basis of recent reports^[7b] on other copper-catalyzed oxidative cross-coupling reactions and our observations, we postulate the reaction mechanism depicted in Scheme 3. As mentioned above, the copper-catalyzed aerobic cross-coupling proceeds in competition with the formation of homocoupling byproducts.^[7a,c] The desired cross-coupled products would then be formed by reductive elimination of [Cu(azole)(fluoroaryl)L_{n-1}] complex **A**. [Cu(fluoroaryl)₂L_{n-1}] complex **B** and [Cu(azole)₂L_{n-1}] complex **C** result in the formation of the homocoupling products of the polyhaloarene and the azole. Thus, the use of an excess of polyhaloarene suppresses the formation of the azole-derived byproduct (as was also observed experimentally).

In conclusion, we have developed a copper-mediated direct oxidative cross-coupling of 2-(het)aryl-1,3,4-oxadi-



Scheme 3. Proposed reaction mechanism.

azoles with polyhaloarenes by dual C_{sp^2} -H activation. It is noteworthy that the reactions proceed under mild reaction conditions at room temperature by using an inexpensive copper source and dioxygen as oxidant. The process provides a concise access to biaryl structures containing polyhaloarenes, which are of interest to the fields of pharmaceuticals and functional materials. In this particular process, molecular oxygen and acetonitrile play crucial roles. The development of catalytic variants and the application of the strategy to other arene systems are currently underway.

Experimental Section

General procedure for the oxidative cross-coupling-reaction between 2phenyl-1,3,4-oxadiazole (1a) and pentafluorobenzene (2a): A 10 mL oven-dried Schlenk tube equipped with a magnetic stirring bar was charged with CuBr (0.2 mmol, 28.8 mg), 1,10-phenanthroline (0.2 mmol, 36 mg), and tBuOLi (0.6 mmol, 48 mg). The tube was then sealed with a rubber septum and filled with O_2 by using standard Schlenk techniques. After adding CH₃CN (1.5 mL) through a syringe, the reaction mixture was stirred at room temperature (25°C) for 5 min. Then, 2a (6 mmol, 664.1 μ L) and **1a** (0.2 mmol, 29.2 mg) were sequentially added under an atmosphere of oxygen. An oxygen balloon was then connected to the Schlenk tube by a needle and the reaction mixture was stirred at room temperature for 14 h. Then the reaction mixture was diluted with ethyl acetate. The resulting solution was directly filtered through a pad of silica gel and concentrated under reduced pressure. Purification by column chromatography (silica gel, eluent: pentane/ethyl acetate 15:1) afforded product 3a (0.13 mmol, 40.6 mg) as a white solid in 65% yield.

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