

Copper-Mediated Direct Cross-Coupling of 1,3,4-Oxadiazoles and Oxazoles with Terminal Alkynes

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The transition-metal-mediated direct functionalization reactions of C–H bonds have attracted significant interest in modern organic chemistry.^[1] Among them, the direct oxidative cross-coupling reactions utilizing two different C–H bonds, though difficult to achieve in a general way, are quite attractive processes, since the preactivation, such as metalation and halogenation of both coupling components, can be eliminated so that they are economically and environmentally advantageous (Scheme 1). Therefore, many researchers



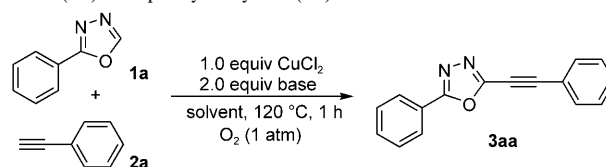
Scheme 1. Transition-metal (M) mediated direct oxidative coupling.

have recently explored this type of transformation, and a number of C–C bond formation reactions between sp^2/sp^2 ,^[2] sp^3/sp^2 ,^[3] sp^3/sp^3 ,^[4] and sp/sp C–H bonds^[5] have become available, in particular under palladium catalysis.^[6] However, the direct cross-coupling with sp^2 and sp C–H bonds, which may be regarded formally as the direct version of Sonogashira type reaction, still remains an important challenge.^[7]

Recently, much attention has been focused on tractable and less expensive copper salts or complexes in oxidative direct C–C coupling reactions.^[8–11] Li described the utility of a copper/peroxide catalyst system in the activation of sp^3 C–H bonds adjacent to olefins, heteroatoms, and carbonyls.^[8]

Kündig^[9a] and Cacchi^[9b] succeeded in the synthesis of oxindoles and indoles, respectively, through an intramolecular direct sp^3/sp^2 C–C coupling mediated by copper salts. Our group also reported the copper-catalyzed oxidative coupling of *N,N*-dimethylanilines with terminal alkynes under molecular oxygen.^[10] These promising examples encouraged us to develop a copper-based process directed toward the coupling between heteroarene sp^2 and alkyne sp C–H bonds as part of our study on the direct functionalization of heterocyclic compounds.^[1b,d,e] We have found that useful heteroarene cores, for example, 1,3,4-oxadiazole and oxazole, efficiently undergo copper-mediated oxidative coupling with terminal alkynes, which is reported herein. As certain 1,3,4-oxadiazole

Table 1. Optimization for the direct cross-coupling of 2-phenyl-1,3,4-oxadiazole (**1a**) with phenylacetylene (**2a**)^[a]



Entry	Base	Solvent	Yield of 3aa [%] ^[b]
1	NaHCO ₃	DMAc	45
2 ^[c]	NaHCO ₃	DMF	45
3 ^[c]	NaHCO ₃	NMP	49
4 ^[c]	NaHCO ₃	DMSO	48
5	KHCO ₃	DMAc	44
6	Na ₂ CO ₃	DMAc	55
7	K ₂ CO ₃	DMAc	55
8	Cs ₂ CO ₃	DMAc	51
9	K ₂ PO ₄	DMAc	32
10 ^[d]	Na ₂ CO ₃	DMAc	65 (64)
11 ^[d,e]	Na ₂ CO ₃	DMAc	12
12 ^[d,f]	Na ₂ CO ₃	DMAc	0

[a] A solution of **2a** (1.0 mmol) in DMAc (2.0 mL) was added over 1 h at 120 °C under O₂ to a mixture of CuCl₂ (1.0 mmol), base (2.0 mmol), and **1a** (2.5 mmol) in DMAc (1.0 mL), (see Experimental Section for the detailed procedure). [b] GC yield. Isolated yield is in parentheses. [c] Slow addition of **2a** over 2 h. [d] **1a** was added in two portions (1.25 mmol × 2) at 0 and 0.5 h. [e] Under air. [f] Under N₂.

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zole derivatives are known to act as ester and amide bioisosteres and π -conjugated systems involving the heterocycle core may have good electron-transporting and hole-blocking abilities, and alkynyl-substituted azoles work as selective DNA cleavage agents, this transformation appears to be also of interest in pharmaceutical and materials chemistry.^[12,13]

In an initial attempt, treatment of 2-phenyl-1,3,4-oxadiazole (**1a**) with phenylacetylene (**2a**, slow addition) in the presence of CuCl₂ and NaHCO₃ in *N,N*-dimethylacetamide (DMAc) at 120 °C under O₂ atmosphere (1 atm, balloon) provided alkynylloxadiazole **3aa** in 45% yield (Table 1, entry 1).^[14] Other solvents such as DMF, NMP, and DMSO resulted in similar yields (entries 2–4). The effect of inorganic bases was also surveyed, with Na₂CO₃ and K₂CO₃ proving to show higher efficiency (entries 5–9). We chose Na₂CO₃ and DMAc as the suitable base and solvent, respectively, due to their good generality and reproducibility in the reaction. The yield further increased by the modification of the addition method of **1a**. Thus, by adding the oxadiazole **1a** in two portions, the desired **3aa** was obtained in 64% isolated yield (entry 10). Notably, the reaction proceeded sluggishly or did not occur under air or N₂ (entries 11 and 12)

We next examined the oxidative coupling of various oxadiazoles **1** with various terminal alkynes **2** under the conditions employed for entry 10 of Table 1 (Table 2). Electron-rich alkynes **2b** and **2c** effectively coupled with **1a** to furnish the corresponding products **3ab** and **3ac**, respectively. A slight decrease of product yield was observed in the reactions of **1a** with electron-deficient **2d** and **2e** leading to **3ad** and **3ae**, because of somewhat faster diyne side-product formation (estimated by GC-MS).^[14] Alkynes bearing a thiophene or naphthalene unit **2f** and **2g** were introduced to the oxadiazole core without any difficulties (**3af** and **3ag**). The reaction of **1a** with conjugated enyne **2h** gave the coupling product **3ah** with the olefin moiety left intact. Moreover, aliphatic alkynes

could be used in the reaction and the product yield was observed to increase with increasing the size of alkyl group on alkyne terminus (**3ai–ak**). The oxadiazoles with various substituents at the 2-position were also available for use. 4-Methyl-, 4-methoxy-, 4-trifluoromethyl-, and 4-chlorophenyl-1,3,4-oxadiazoles **1b–1e** coupled with **2b** to furnish compounds **3bb–3eb**. The reactions of 2-naphthyl- and 2-phenethyl-substituted oxadiazoles **1f** and **1g** with **2b** gave **3fb** and **3fg**, respectively, in substantial yields.

Among other azole compounds, oxazoles were found to be applicable to the present cross-coupling.^[15,16] The optimized conditions mentioned above, however, required some adjustments when 5-aryloxazoles **4** were employed (Table 3).^[17] Thus, the desired 2-alkynyl-5-aryloxazoles **5** were obtained by performing the reaction in a higher 4/2

Table 2. Copper-mediated direct cross-coupling of various 1,3,4-oxadiazoles **1** with terminal alkynes **2**.^[a]

$\text{R}^1\text{-N}_2\text{O} + \text{R}^2\text{-C}\equiv\text{C-H} \longrightarrow \text{R}^1\text{-N}_2\text{O-C}\equiv\text{C-R}^2$			
$\text{R}^1 = \text{Ph}; \mathbf{1a}$ = 4-MeC ₆ H ₄ ; 1b = 4-MeOC ₆ H ₄ ; 1c = 4-CF ₃ C ₆ H ₄ ; 1d = 4-ClC ₆ H ₄ ; 1e = 1-naphthyl; 1f = 2-phenethyl; 1g		$\text{R}^2 = \text{Ph}; \mathbf{2a}$ = 4-MeC ₆ H ₄ ; 2b = 4-MeOC ₆ H ₄ ; 2c = 4-MeO ₂ CC ₆ H ₄ ; 2d = 4-CF ₃ C ₆ H ₄ ; 2e = 3-thienyl; 2f = 1-naphthyl; 2g = 1-cyclohexenyl; 2h = <i>n</i> -C ₈ H ₁₇ ; 2i = <i>c</i> -C ₈ H ₁₇ ; 2j = <i>t</i> -Bu; 2k	
Product	Yield [%] ^[b]	Product	Yield [%] ^[b]
	66		61
	47 ^[c]		45 ^[c]
	51		62
	64		65
	70		74
	50		60
	52		63
	47		43 ^[d]

[a] Reaction conditions: see Table 1, entry 10. [b] Isolated yield. [c] With 1.5 mmol of Na₂CO₃. [d] Slow addition of **2b** over 2 h.

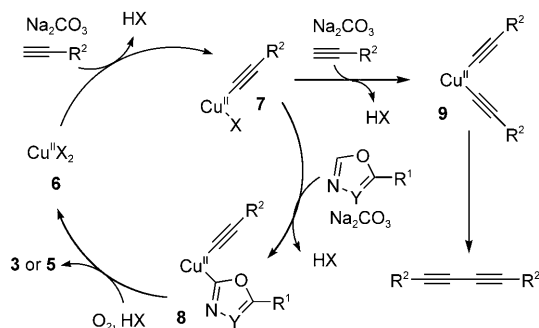
Table 3. Copper-mediated direct cross-coupling of 5-aryloxazoles **4** with terminal alkynes **2**.^[a]

$\text{R}^1\text{-Oxazole} + \text{R}^2\text{-C}\equiv\text{C-H} \xrightarrow[\text{O}_2 (1 \text{ atm})]{\text{1.0 equiv CuCl}_2, \text{2.4 equiv Na}_2\text{CO}_3, \text{DMSO}, 150^\circ\text{C}, 1 \text{ h}} \text{R}^1\text{-Oxazole-C}\equiv\text{C-R}^2$			
Product	Yield [%] ^[b]	Product	Yield [%] ^[b]
	51		58
	50		46
	46		42

[a] A solution of **2** (0.5 mmol) in DMSO (1.0 mL) was added over 1 h to a mixture of CuCl₂ (0.5 mmol), Na₂CO₃ (1.2 mmol), and **4** (2.5 mmol) in DMSO (0.5 mL) at 150 °C under O₂. 5-Aryloxazoles **4**: **4a**, R¹ = Ph; **4b**, R¹ = 4-MeOC₆H₄; **4c**, R¹ = 4-CF₃C₆H₄; **4d**, R¹ = 3,4-(MeO)₂C₆H₃. [b] Isolated yield.

ratio at 150 °C with DMSO as solvent. Despite somewhat lower yields compared to the reaction with the corresponding oxadiazoles, electronically diverse aryl groups at the 5-position of oxazole were tolerable. In addition, a variety of terminal alkynes bearing aryl, alkenyl, and alkyl substituents were compatible under the reaction conditions.

Based on the Stahl's report^[11b] and our observations, we are tempted to assume the reaction mechanism as follows (Scheme 2). Initial ligand exchange between copper(II) spe-

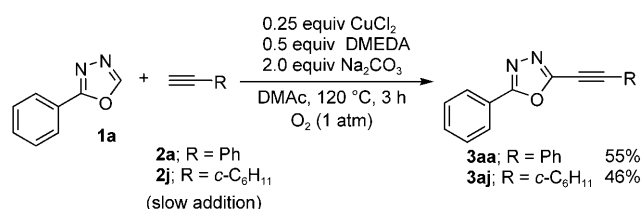


Scheme 2. Plausible mechanism.

cies **6** and a terminal alkyne followed by the cupration of an oxadiazole or oxazole with the aid of Na₂CO₃ affords [Cu^{II}-(alkynyl)(heteroaryl)] (**8**).^[18] Subsequent reductive elimination produces the corresponding product **3** or **5**. The step of going from [Cu^{II}{mono(alkynyl)}] (**7**) to **8** seems to be crucial for this cross-coupling reaction. Thus, the beneficial effect of the slow addition technique is consistent with the mechanism. Namely, the activation of another alkyne molecule with **7** gives [Cu^{II}{bis(alkynyl)}] (**9**), en route to the undesired diyne.^[14,15] Although further studies for clarifying the exact role of O₂ in the reaction are required, it may coordinate to the copper center and enhance the productive reductive elimination from **8** since the N₂ atmosphere failed

to lead to the product even in the presence of a stoichiometric amount of CuCl₂ (Table 1, entry 12).^[19]

If the mechanism mentioned above is reasonable, O₂ would work as an oxidant and render the reaction catalytic in copper. Indeed, a catalyst system of CuCl₂/N,N'-dimethylethylenediamine (DMEDA) was found to show its potential (Scheme 3). Consequently, work is underway toward elucidating the detailed reaction mechanism and making this unique direct methodology more efficient and broad utility with other arene systems.



Scheme 3. Cross-coupling using CuCl₂/DMEDA system.

Experimental Section

Typical procedures—copper-mediated direct cross-coupling of 2-phenyl-1,3,4-oxadiazole (**1a**) with phenylacetylene (**2a**)

Method A (Table 1, entry 10): Under an O₂ atmosphere (1 atm, balloon), CuCl₂ (134 mg, 1.0 mmol), Na₂CO₃ (212 mg, 2.0 mmol), **1a** (183 mg, 1.25 mmol), DMAc (1.0 mL), and 1-methylnaphthalene (ca. 70 mg, internal standard) were placed in a 20 mL two-necked reaction flask equipped with a reflux condenser. The mixture was heated at 120 °C, and the slow addition (over 1 h) of a solution of **2a** (102 mg, 1.0 mmol) in DMAc (1.0 mL) was then started. After a half amount of **2a** was added, an additional portion of **1a** (183 mg, 1.25 mmol) in DMAc (1.0 mL) was added in a single aliquot. After the addition of **2a** was completed, the consumption of **2a** was checked by GC analysis (13% recovery of **1a**). The resulting mixture was allowed to cool to room temperature and then quenched with water. The mixture was extracted with ethyl acetate, and the organic layer was dried over sodium sulfate. Concentration in vacuo followed by silica gel column purification with hexane/ethyl acetate (100:0 to 96:4, v/v) as an eluent gave **3aa** (156 mg, 0.64 mmol) in 64% yield.

Method B (Scheme 3): Under an O₂ atmosphere (1 atm, balloon), CuCl₂ (17 mg, 0.125 mmol), DMEDA (22 mg, 0.25 mmol), Na₂CO₃ (106 mg, 1.0 mmol), **1a** (183 mg, 1.25 mmol), DMAc (1.0 mL), and 1-methylnaphthalene (ca. 50 mg, internal standard) were placed in a 20 mL two-necked reaction flask equipped with a reflux condenser. The mixture was heated at 120 °C, and the slow addition (over 3 h) of a solution of **2a** (51 mg, 0.5 mmol) in DMAc (2.0 mL) was then started. After the addition of **2a** was completed, the consumption of **2a** was checked by GC analysis (32% recovery of **1a**). Product **3aa** (68 mg, 0.28 mmol, 55%) was isolated similarly as above. For product data, see the Supporting Information.

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Keywords: alkynes • copper • direct coupling • heterocycles • oxazoles

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