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Copper-Mediated Direct Arylation of 1,3,4-Oxadiazoles and 1,2,4-Triazoles with Aryl Iodides

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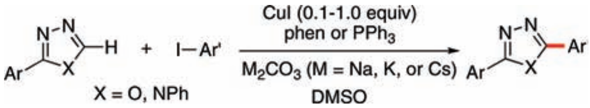
ABSTRACT



The copper-mediated direct arylation of 1,3,4-oxadiazoles and 1,2,4-triazoles with aryl iodides proceeds efficiently in the presence of suitable ligands and bases. This method allows the installation of a variety of aryl moieties bearing a functional group such as ketone, ester, or nitrile so as to enable the facile construction of various functionalized oxadiazole and triazole core π systems.

π-Conjugated molecules containing heterocycles constitute an important class of compounds in material and pharmaceutical chemistry. Among them, 2,5-diaryl-1,3,4-oxadiazoles and 3,4,5-triaryl-1,2,4-triazoles have recently received much attention in the field of organic electronics because of their good electron-transporting and hole-blocking abilities.[1] Examples of such well-known compounds include 2-(4-biphenylyl)-5-(4-*tert*-butylphenyl)-1,3,4-oxadiazole (PBD), 1,3-[bis(4-*tert*-butylphenyl)-1,3,4-oxadiazolyl]phenylene (OXD7), and 3-(4-biphenyl)-4-phenyl-5-*tert*-butylphenyl-1,2,4-triazole (TAZ).[1a,2] Suitably π-conjugated oxadiazole systems may also have multiphoton absorbing properties.[1b] On the other hand, some oxadiazole derivatives are known to work as ester and amide bioisosteres.[3] Therefore, the development of effective methods for their concise synthesis and functionalization is of considerable importance in organic synthesis.

Recently, the metal-mediated direct arylation of heteroarenes has been widely studied and is one of the most attractive approaches to make heteroaryl−aryl linkages.[4,5] While the

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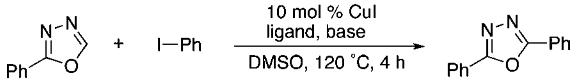
reactions are often carried out by means of palladium catalysis, much less expensive copper salts or complexes may also be used as catalysts or promoters.[6−11] In 2007, Daugulis reported the copper-catalyzed direct arylation of various heterocycles with aryl iodides using LiO-*t*-Bu as a base.[6] Subsequently, Ackermann[7a] and Bergmann and Ellman[7b] described the direct arylation of 1,2,3-triazoles and benzotriazepines, respectively, under similar conditions. Our group also succeeded in performing the direct arylation of azoles mediated by copper salts with the aid of carbonate bases.[8] Gaunt[9] and You[10] expanded the scope of the arylating reagents to the corresponding diaryliodonium(III) salts and aryl bromides, respectively, and in particular, the reaction of the hypervalent iodonium salts with benzanilides was found to induce a unique site selectivity. Given the utilities of copper salts and complexes in this type of transformation, we anticipated that the copper-based strategies could be applied to the reaction with 1,3,4-oxadiazoles and 1,2,4-trizoles. Herein, we report the copper-mediated direct C5 arylation reactions of 2-aryl-1,3,4-oxadiazoles and 3,4-diaryl-1,2,4-triazoles.[12] The methods allow the use of a variety of aryl iodides as the arylating reagents and the facile preparation of various functionalized oxadiazole and triazole core π systems.

Based on our previous work,[8] we initially examined the direct arylation of 2-phenyl-1,3,4-oxadiazole (**1a**) with iodobenzene (**2a**) using CuI (10 mol %), PPh$_3$ (10 mol %), and K$_2$CO$_3$ (2.0 equiv) in DMSO at 120 °C (Table 1, entry 1), and the corresponding arylated product **3aa** was obtained albeit with a low yield. We then screened some nitrogen-based ligands.[6,7,11] While the use of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) and 2,2′-bipyridine (bpy) gave no positive effects (entries 2 and 4), *N*,*N*′-dimethylethylenediamine (DMEDA) and 1,10-phenanthroline (phen) improved the yield, with phen proving to be optimal (entries 3 and 5). The choice of base was also crucial for the reaction. Weaker bases such as Li$_2$CO$_3$ and Na$_2$CO$_3$ were found to dramatically decrease the yield (entries 6−7). Finally, with use of 20 mol % of CuI in the presence of 1.0 equiv of Cs$_2$CO$_3$, the reaction at 100 °C resulted in 83% yield of **3aa** after isolation (entry 8). Unexpectedly, LiO-*t*-Bu completely failed to lead to the formation of **3aa** under the reaction conditions (entry 9).

Table 1. Optimization for Copper-Catalyzed C5 Arylation of 2-Phenyl-1,3,4-oxadiazole (**1a**) with Iodobenzene (**2a**)[a]



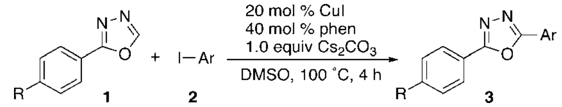
1a **2a** **3aa**

entry	ligand	base	**3aa**, yield[b] (%)
1	PPh$_3$[c]	K$_2$CO$_3$	37
2	TMEDA	K$_2$CO$_3$	18
3	DMEDA	K$_2$CO$_3$	73
4	bpy	K$_2$CO$_3$	33
5	phen	K$_2$CO$_3$	91
6	phen	Li$_2$CO$_3$	7
7	phen	Na$_2$CO$_3$	31
8[d]	phen	Cs$_2$CO$_3$	100(83)
9	phen	LiO-*t*-Bu	0

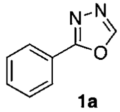
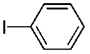
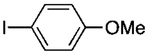
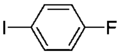
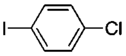
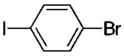
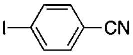
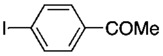
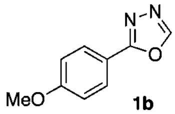
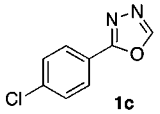
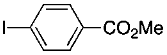
[a] A mixture of **1a** (0.50 mmol), **2a** (0.60 mmol), CuI (0.050 mmol), ligand (0.10 mmol), and base (1.0 mmol) was stirred in DMSO (1.0 mL) for 4 h at 120 °C. [b] GC yield. Isolated yield is in parentheses. [c] PPh$_3$ (0.050 mmol). [d] With CuI (0.10 mmol), phen (0.20 mmol), Cs$_2$CO$_3$ (0.50 mmol), and **2a** (1.0 mmol) at 100 °C.

With the optimized conditions in hand, we carried out the direct arylation using various oxadiazoles **1** and aryl iodides **2** (Table 2). Not only simple iodobenzene (**2a**) but also electron-rich **2b** (entry 2) and electron-deficient **2c** and **2d** (entries 3 and 4) reacted with **1a** effectively. The reaction with **2e** provided the arylated product **3ae** in good yield, leaving the C−Br moiety untouched (entry 5). Taking advantage of the relatively mild reaction conditions, the phenyl groups bearing a cyano or carbonyl function were introduced to the oxadiazole (entries 6 and 7). Methoxy-

Table 2. Copper-Catalyzed Direct Arylation of 2-Aryl-1,3,4-oxadiazole (**1**) with Aryl Iodide (**2**)[a]



1 **2** **3**

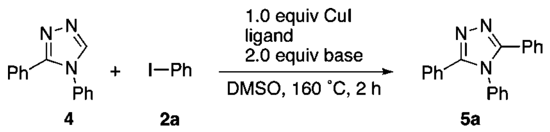
entry	1	2	3, yield (%)[b]
1	 **1a**	 **2a**	**3aa**, 83
2		 **2b**	**3ab**, 65
3		 **2c**	**3ac**, 75
4		 **2d**	**3ad**, 86
5		 **2e**	**3ae**, 84
6		 **2f**	**3af**, 97
7		 **2g**	**3ag**, 65
8	 **1b**	**2b**	**3bb**, 73
9		**2c**	**3bc**, 76
10		**2d**	**3bd**, 79
11		**2e**	**3be**, 93
12		**2f**	**3bf**, 99
13[c]	 **1c**	**2b**	**3cb** (**3bc**), 38
14[c]		**2c**	**3cc**, 63
15[c]		**2d**	**3cd**, 57
16[c]		**2f**	**3cf**, 83
17[c]		 **2h**	**3ch**, 76

[a] A mixture of **1** (0.50 mmol), **2** (1.0 mmol), CuI (0.10 mmol), 1,10-phenanthroline (0.20 mmol), and Cs$_2$CO$_3$ (0.50 mmol) was stirred in DMSO (1.0 mL) at 100 °C for 4 h. [b] Isolated yield. [c] A mixture of **1c** (0.50 mmol), **2** (0.60 mmol), CuI (0.050 mmol), 1,10-phenanthroline (0.10 mmol), and K$_2$CO$_3$ (1.0 mmol) was heated in DMSO (1.0 mL) at 120 °C for 4 h.

substituted oxadiazole **1b** instead of **1a** was available for use. As observed in the reaction with **1a**, an array of aryl iodides took part in the reaction to furnish the corresponding 2,5-diaryl-1,3,4-oxadiazoles **3bb**−**bf** in good to excellent yields (entries 8−12). On the contrary, the oxadiazole **1c** having a chlorine atom on the benzene ring was found to decompose rapidly under the standard reaction conditions. However, the alternative conditions in entry 5 of Table 1 could be applicable to **1c**. A number of aryl iodides coupled with **1c** smoothly to afford the expected products in acceptable yields with the exception of electron-rich **2b** (entries 13−17).

Next, we attempted the direct arylation of 3,4-diphenyl-4*H*-1,2,4-triazole (**4**) as a representative triazole. However, the reaction with **2a** gave no expected coupling product **5a** under the catalytic conditions employed above. Thus, further optimization studies were performed to achieve the arylation (Table 3). According to our previous observation,[8] we tested a stoichiometric amount of CuI/PPh$_3$ in the reaction, and the desired product was obtained in 34% yield with K$_2$CO$_3$ as a base (entry 1). Subsequent additional investigation into the effect of base revealed that the use of Na$_2$CO$_3$ or K$_3$PO$_4$ instead of K$_2$CO$_3$ increased the yield (entries 2 and 3). A decrease in the amount of PPh$_3$ to 0.2 equiv further improved the reaction efficiency to produce **5a** in 75% isolated yield (entry 4). Other typical phosphines such as P(*o*-tolyl)$_3$ and PCy$_3$ showed less efficiency (entries 5 and 6). Even in the presence of a stoichiometric amount of CuI and a suitable base, the addition of PPh$_3$ was essential for a satisfactory yield (entry 7).[13]

Table 3. Optimization for Copper-Promoted C5 Arylation of 3,4-Diphenyl-4*H*-1,2,4-triazole (**4**) with Iodobenzene (**2a**)[a]

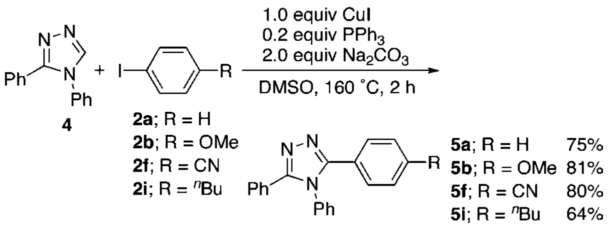


entry	ligand (equiv)	base	**5a**, yield[b] (%)
1	PPh$_3$ (1.0)	K$_2$CO$_3$	34
2	PPh$_3$ (1.0)	K$_3$PO$_4$	50
3	PPh$_3$ (1.0)	Na$_2$CO$_3$	84(62)
4	PPh$_3$ (0.2)	Na$_2$CO$_3$	99(75)
5	P(*o*-tolyl)$_3$ (0.2)	Na$_2$CO$_3$	64
6	PCy$_3$ (0.2)	Na$_2$CO$_3$	47
7	none	Na$_2$CO$_3$	58

[a] A mixture of **4** (0.50 mmol), **2a** (0.60 mmol), CuI (0.50 mmol), ligand, and base (1.0 mmol) was stirred in DMSO (1.0 mL) for 2 h at 160 °C. [b] GC yield. Isolated yield is in parentheses.

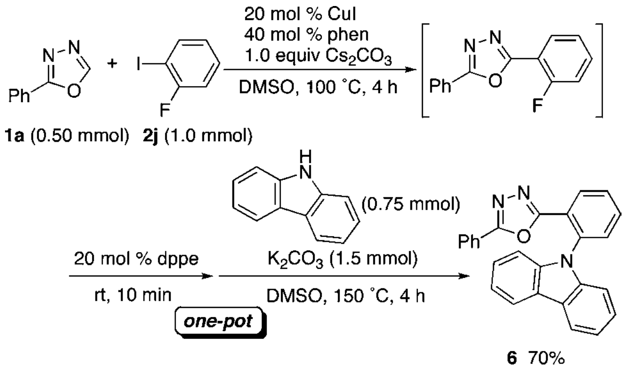
By using the modified conditions, we conducted the reaction of triazole **4** with a number of aryl iodides. As shown in Scheme 1, electron-withdrawing as well as electron-donating groups were compatible under the reaction conditions.

Scheme 1



Finally, we undertook the construction of a carbazole-moiety-containing oxadiazole in a single vessel. Such species have aroused considerable interest in the field of OLEDs (Scheme 2).[14] Treatment of 2-phenyl-1,3,4-oxadiazole (**1a**, 0.50 mmol) with 2-fluoroiodobenzene (**1j**, 1.0 mmol) under copper catalysis followed by the addition of dppe (20 mol %),[15] carbazole (0.75 mmol), and K$_2$CO$_3$ (1.5 mmol) furnished the bipolar π-conjugated compound **6** in 70% overall yield through the direct arylation/S$_N$Ar reaction sequence.

Scheme 2



Although further efforts on the clarification of the reaction mechanism are required, one possibility involves the sequential base-assisted cupration of azole/σ-bond metathesis with aryl iodide. In addition, the pathway including trans-

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(11) Ni catalysis for the direct arylation of azoles: (a) Canivet, J.; Yamaguchi, J.; Ban, I.; Itami, K. *Org. Lett.* **2009**, *11*, 1733. (b) Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 1737.

metalation of CuI with the metalated azole generated in situ by the action of base could not be completely retarded.[6]

In summary, we have described copper-based methods for the effective direct arylation of 1,3,4-oxadiazole and 1,2,4-triazole cores with aryl iodides to give rise to the corresponding π-conjugated compounds. The application to the facile synthesis of the bipolar-type material in a one-pot manner may also demonstrate its synthetic utility.

Acknowledgment. This work was partly supported by Grants-in-Aid from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

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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(12) Daugulis reported one example of the direct arylation with 1-methyl-1*H*-1,2,4-triazole: (a) See ref 6b. Palladium-catalyzed direct arylation of 1,2,3-triazoles: (b) Chuprakov, S.; Chernyak, N.; Dudnik, A. S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 2333. (c) Iwasaki, M.; Yorimitsu, H.; Oshima, K. *Chem. Asian J.* **2007**, *2*, 1430. (d) Ackermann, L.; Vicente, R.; Born, R. *Adv. Synth. Catal.* **2008**, *350*, 741.

(13) Although the exact role of PPh_3 is not clear at this stage, it may work as an initiator rather than a ligand. Namely, PPh_3 could change the association state of CuI via its coordination to the Cu center leading to the monomeric active species.

(14) (a) Guan, M.; Bian, Q.; Zhou, Y. F.; Li, F. Y.; Li, Z. J.; Huang, C. H. *Chem. Commun.* **2003**, 2708. (b) Tao, Y.; Wang, Q.; Yang, C.; Wang, Q.; Zhang, Z.; Zou, T.; Qin, J.; Ma, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 8104.

(15) Without dppe, the copper-catalyzed amination of unreacted **2j** with carbazole predominantly occurred to decrease the yield of **6**. Hence, dppe seemed to deactivate the copper complex for the amination reaction. Other phosphines such as PPh_3, dppp, and dppb were less effective.