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Nickel-Catalyzed Direct Arylation of Azoles with Aryl Bromides

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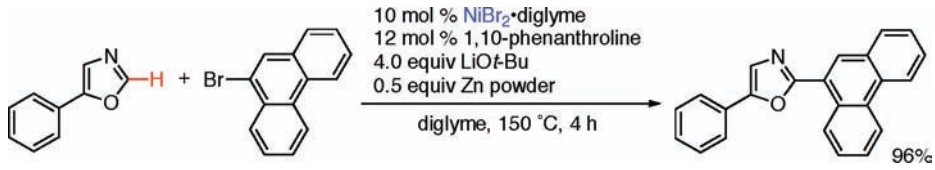
ABSTRACT



Nickel catalyst systems for the direct C2 arylation of oxazoles and thiazoles have been developed. The catalyst systems are cost-efficient and allow the use of various aryl bromides in the C−H arylation of azoles.

Since organic molecules containing heterocycle−aryl linkages are ubiquitously found in many natural products, pharmaceuticals, and functional materials, the arylation methods of heterocycles have received significant attention in organic synthesis.[1] The transition-metal-catalyzed cross-coupling is one of the most reliable approaches to make the linkages.[2] On the other hand, recent advances in the metal-mediated direct arylation of aromatic heterocycles with aryl halides may provide an efficient access to the target molecules because it can eliminate the preactivation steps of the heterocycles.[3] Although palladium[4] and rhodium[5] catalysts are known to catalyze the direct arylation of various heteroerenes, for the realistic catalyst loading, the replacement of these catalysts with other less expensive ones are strongly desired. In 2007, Daugulis reported an effective method for the copper-catalyzed direct arylation of heterocycles with aryl iodides.[6a,b] Subsequently, Ackermann described the copper-catalyzed direct arylation of 1,2,3-triazoles.[6c] Our group also succeeded in the arylation of benzazoles with aryl iodides mediated by copper salts.[7] While these reactions are cost-efficient, compared to the conven-

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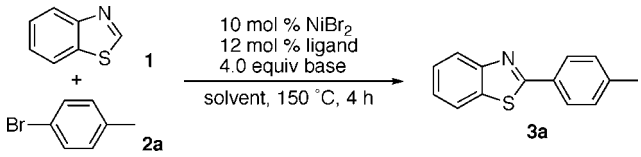
tional palladium- and rhodium-catalyzed processes, the arylating reagents are limited to the corresponding aryl iodides. Therefore, the C−H arylation with less reactive aryl bromides and chlorides using inexpensive catalyst systems still remains a challenge.[8] Herein, we report the nickel-catalyzed direct arylation of azoles. The catalysts comprise common and bench-stable $NiBr_2$ and 1,10-phenanthroline or its derivative and allow the use of aryl bromides as the coupling reagents.

Initially, we chose benzothiazole (**1**), 4-bromotoluene (**2a**), and $NiBr_2$ as model substrates in combination with a nickel source and screened various ligands, solvents, and bases. It was found that treatment of **1** with 1.2 equiv of **2a** in the presence of 10 mol % of $NiBr_2$, 12 mol % of 1,10-phenanthroline, and 4.0 equiv of LiO-*t*-Bu in diglyme at 150 °C for 4 h afforded the C2-arylated benzothiazole **3a** in 73% yield (Table 1, entry 1). Using 5 mol of $NiBr_2$ gave **3a** in 48% yield (entry 2). Other bidentate and tridentate nitrogen ligands such as 2,2′-bipyridine, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), and 2,2′:6′,2″-terpyridine also showed catalytic activities albeit with lower product yields (entries 3−5). The use of a phosphine ligand, 1,2-bis(diphenylphosphino)benzene (dppbz) in *o*-xylene, led to the formation of **3a** in a compatible yield, while it caused the transfer of phenyl group from the phosphorus atom to **1** under the reaction conditions to form undesired 2-phenylbenzothiazole as a byproduct (entry 6).[9] Polar solvents such as NMP and DMAc were ineffective (entries 7 and 8). With other inorganic bases such as NaO-*t*-Bu, KO-*t*-Bu, and Cs_2CO_3, no arylated product was obtained (not shown).

We next examined the direct arylation of benzothiazole (**1**) with a variety of aryl bromides using $NiBr_2$ and 1,10-phenanthroline in diglyme (Table 2). Not only 4- and 3-bromotoluenes (**2a** and **2b**) but also sterically demanding 2-bromotoluene (**2c**) and 1-bromo-2,5-dimethylbenzene (**2d**) reacted with **1** to give the corresponding arylated benzothiazoles in moderate to good yields (entries 1−4). The naphthalene motif could also be introduced to **1** (entry 5).

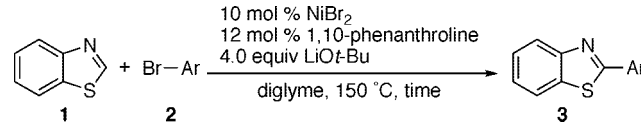
Table 1. Nickel-Catalyzed C2 Arylation of Benzothiazole (**1**) with 4-Bromotoluene (**2a**)[a]

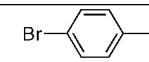
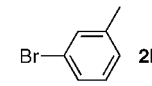
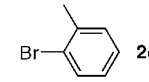
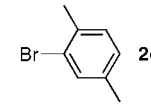
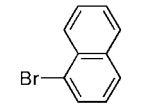
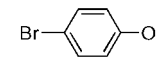
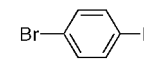
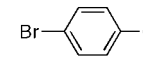
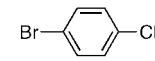
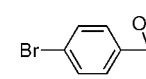


entry	ligand	base	solvent	**3a**, yield[b] (%)
1	1,10-phenanthroline	LiO-*t*-Bu	diglyme	73 (67)
2[c]	1,10-phenanthroline	LiO-*t*-Bu	diglyme	48
3	2,2′-bipyridine	LiO-*t*-Bu	diglyme	21
4	2,2′:6′,2″-terpyridine	LiO-*t*-Bu	diglyme	12
5	TMEDA	LiO-*t*-Bu	diglyme	trace
6[d]	dppbz	LiO-*t*-Bu	*o*-xylene	63[e]
7	1,10-phenanthroline	LiO-*t*-Bu	NMP	0
8	1,10-phenanthroline	LiO-*t*-Bu	DMAc	0

[a] A mixture of **1** (0.50 mmol), **2a** (0.60 mmol), $NiBr_2$ (0.050 mmol), ligand (0.060 mmol), and LiO-*t*-Bu (2.0 mmol) was stirred in solvent (3.0 mL) for 4 h at 150 °C. [b] GC yield. Isolated yield is shown in parentheses. [c] Reaction with $NiBr_2$ (0.025 mmol, 5 mol %) for 6 h. [d] Reaction with $NiBr_2$·diglyme (0.050 mmol). [e] 2-Phenylbenzothiazole was also obtained in 12% yield as a byproduct.

Table 2. Nickel-Catalyzed Direct Arylation of Benzothiazole (**1**) with Various Aryl Bromides (**2**)[a]



entry	**2**	time (h)	**3**, yield[b] (%)
1	 **2a**	4	**3a**, 67
2	 **2b**	4	**3b**, 55
3	 **2c**	4	**3c**, 61
4	 **2d**	4	**3d**, 69
5	 **2e**	4	**3e**, 76
6	 **2f**	4	**3f**, 56
7	 **2g**	4	**3g**, 60
8	 **2h**	4	**3h**, 70
9	 **2i**	4	**3i**, 44
10	 **2j**	4	**3j**, 45[c]
11[d]	**2a**	6	**3a'**, 50

[a] A mixture of **1** (0.50 mmol), **2** (0.60 mmol), $NiBr_2$ (0.050 mmol), 1,10-phenanthroline (0.060 mmol), and LiO-*t*-Bu (2.0 mmol) was stirred in diglyme (3.0 mL) at 150 °C. [b] Isolated yield. [c] Isolation after the removal of acetal protection upon teatment with a catalytic amount of *p*-TsOH in boiling acetone/H_2O (1:1). [d] Reaction with 1.0 mmol of thiazole (**1′**) instead of benzothiazole (**1**) and 0.50 mmol of **2a**.

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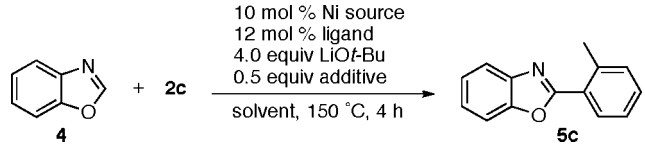
(8) Exceptionally highly reactive aryl bromides such as 2-bromopyridine were available for use in the copper-catalyzed direct arylation. See ref 6b.

(9) The use of other arylphosphines resulted in the same scramble. Trialkylphosphines such as PCy_3 showed no catalytic activities. Dppbz in diglyme was unexpectedly not effective.

Table 3. Nickel-Catalyzed C2 Arylation of Benzoxazole (**1**) with 2-Bromotoluene (**2c**)[a]



entry	Ni source/ligand	additive	solvent	**5c**, yield[b] (%)
1	$NiBr_2$/1,10-phenanthroline	none	diglyme	8
2	$NiBr_2$·diglyme/1,10-phenanthroline	none	*o*-xylene	35
3	$NiBr_2$·diglyme/1,10-phenanthroline	Zn powder	*o*-xylene	44
4	$NiBr_2$·diglyme/2,9-dimethyl-1,10-phenanthroline hydrate	Zn powder	*o*-xylene	73 (53)
5	$NiBr_2$·diglyme/2,9-dimethyl-1,10-phenanthroline hydrate	none	*o*-xylene	58

[a] A mixture of **4** (1.0 mmol), **2c** (0.50 mmol), Ni source (0.050 mmol), ligand (0.060 mmol), LiO-*t*-Bu (2.0 mmol), and additive (0.25 mmol) was stirred in solvent (3.0 mL) for 4 h at 150 °C. [b] GC yield. Isolated yield is in parentheses.

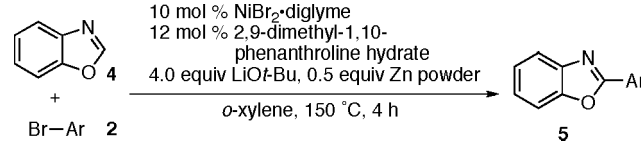
Electron-rich and electron-deficient aryl bromides **2f**−**h** as well as electron-neutral ones participated in the reaction (entries 6−8). Although carbonyl functions except for CN (entry 9) were not tolerant under the basic conditions, acetal protection was compatible, and the coupling product **3k** was obtained (entry 10). Simple thiazole (**1′**) instead of **1** was also arylated (entry 11).

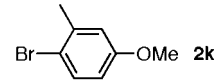
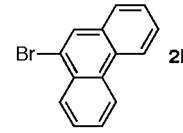
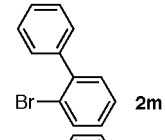
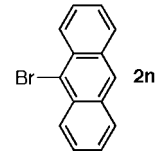
We also attempted the direct arylation of benzoxazole (**4**) with 2-bromotoluene (**2c**). However, the expected coupling product **5c** was obtained in only 8% yield under the standard conditions (Table 3, entry 1). Thus, further optimization studies were performed to achieve the reaction with benzoxazole (**4**). Since the GC analysis confirmed that benzoxazole decomposed at the early stage, the development of the milder reaction conditions would be essential. To our delight, the change of solvent to less polar *o*-xylene suppressed the decomposition of **4**. The improvement of catalyst solubility in *o*-xylene by the replacement of $NiBr_2$ with $NiBr_2$·diglyme increased the yield (entry 2). Moreover, an addition of Zn powder further improved the yield to 44% (entry 3). After some additional ligand investigations, bulkier 2,9-dimethyl-1,10-phenanthroline hydrate was found to be optimal (entry 4). Even in the presence of this ligand, Zn powder was required for satisfactory yield (entry 5). This is probably because the effective generation of zerovalent nickel species would be necessary in the initiation step of the catalytic cycle (vide infra).[10]

By using the modified conditions, we conducted the reaction of benzoxazole (**4**) with an array of aryl bromides (Table 4). As observed in the case of benzothiazole (**1**), various substitution patterns were tolerated toward the arylation. Notably, the reaction with 9-bromophenanthrene (**2l**) proceeded very smoothly to produce the corresponding biaryl **5l** in high yield (entry 5). In addition, the installation of 2-biphenylyl and 9-anthracenyl groups was available (entries 6 and 7).

The nickel/phenanthroline catalyst systems could be applied to the direct arylation of 5-aryloxazoles. Upon treatment of 5-phenyloxazole (**6a**) with 9-bromophenanthrene (**2l**), the corresponding 2,5-diaryloxazole **7al** was formed in excellent

Table 4. Nickel-Catalyzed Direct Arylation of Benzoxazole (**4**) with Various Aryl Bromides (**2**)[a]



entry	**2**	**5**, yield[b] (%)
1	**2c**	**5c**, 53
2	**2d**	**5d**, 66
3	**2e**	**5e**, 62
4		**5k**, 50
5		**5l**, 83
6		**5m**, 60
7		**5n**, 68

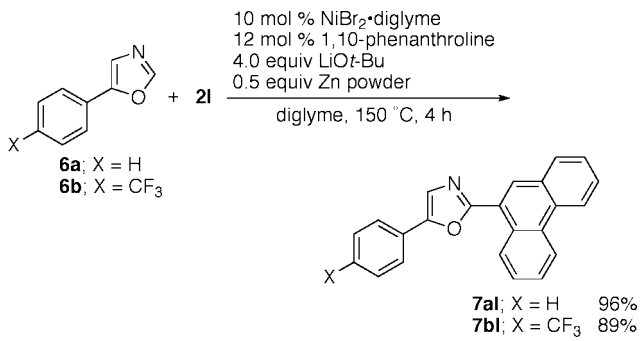
[a] A mixture of **4** (1.0 mmol), **2** (0.50 mmol), $NiBr_2$·diglyme (0.050 mmol), 2,9-dimethyl-1,10-phenanthroline hydrate (0.060 mmol), LiO-*t*-Bu (2.0 mmol), and Zn powder (0.25 mmol) was stirred in *o*-xylene (3.0 mL) for 4 h at 150 °C. [b] Isolated yield.

(10) In the reaction of benzothiazole (**1**), the addition of Zn powder gave no effect on yield. Hence, the combination of **1** and LiO-*t*-Bu in diglyme would reduce the divalent nickel source to the corresponding zerovalent active species effectively (see Scheme 2).

(11) As observed in the reaction of benzoxazole (**4**), the addition of Zn powder improved the yield. For example, without Zn powder, compound **7bl** was obtained in 79% yield.

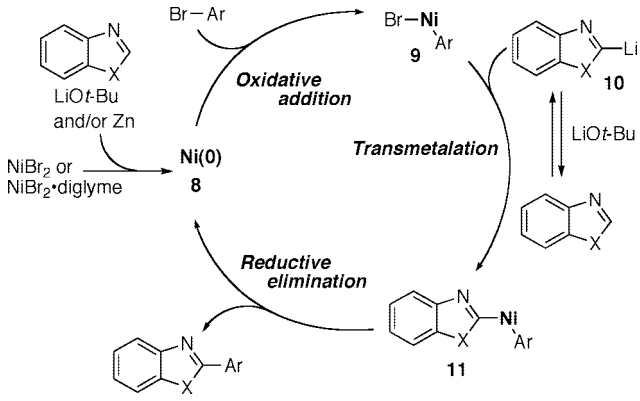
yield (Scheme 1). The oxazole bearing an electron-withdrawing group on the benzene ring **6b** also efficiently reacted with **2l**.[11]

Scheme 1



We are tempted to assume the mechanism of the reaction with benzazoles as follows (Scheme 2). A zerovalent nickel species **8** would be initially generated in situ accompanied by the reduction of $NiBr_2$ with the combination of benzothiazole (**1**) and LiO-*t*-Bu in diglyme.[12] On the contrary, in the case of the reaction with benzoxazole (**4**) in *o*-xylene, the initiation step would be insufficient so that the additional reductant, Zn powder, is required. Subsequent oxidative addition of aryl bromide to the active Ni(0) **8** followed by transmetalation with heteroaryllithium compound **10**[13] gives the corresponding diarylnickel **11**. Productive reductive elimination furnishes the arylated benzazole and regenerates the starting nickel complex **8** to complete the catalytic cycle.

Scheme 2



In conclusion, we have developed the effective and inexpensive nickel catalyst systems for the direct arylation of azoles with aryl bromides. The results show the high potential of nickel catalysts in the direct C−H functionalization of heterocycles. Further elaborations may be expected to make this method of broader utility. The detailed mechanistic studies and the development of related C−H cleavage processes under nickel catalysis are currently underway.

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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) In the reaction mixture, a small amount of the homocoupling product of benzothiazole was detected by GC−MS analysis.

(13) Deprotonation of heterocyclic compounds with LiO-*t*-Bu was suggested. Do, H.-Q.; Daugulis, O. *Org. Lett.* **2009**, *11*, 421 See also ref 6. Nevertheless, at this stage, the pathway involving nickel-assisted proton abstraction mechanism could not be completely excluded.