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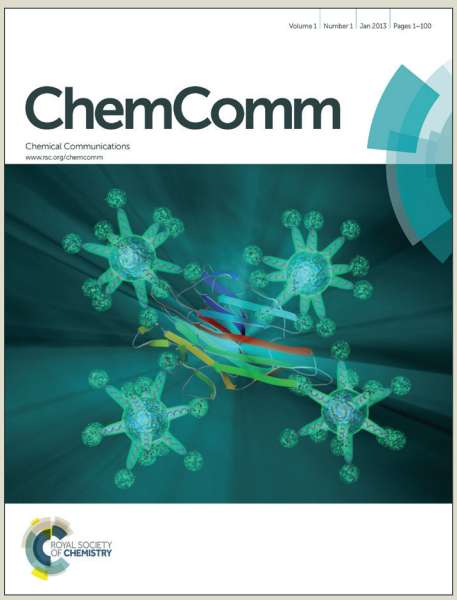

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Room-Temperature Palladium-Catalyzed Direct 2-Arylation of Benzoxazoles with Aryl and Heteroaryl Bromides†

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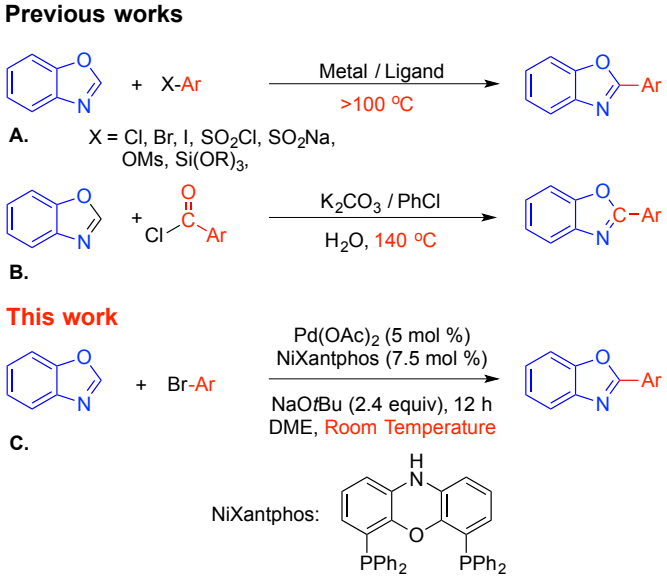
An efficient room-temperature palladium-catalyzed direct 2-arylation of benzoxazoles with aryl bromides is presented. The $Pd(OAc)_2$/NiXantphos-based catalyst enables the introduction of various aryl and heteroaryl groups, via deprotonative cross-coupling process (DCCP) in good to excellent yields (75–99%).

2-Aryl-substituted benzoxazoles are an important class of heterocyclic compounds that are widely found in bioactive molecules,[1] pharmaceuticals[2] and natural products.[3] As such, several strategies for their construction have been reported.[4] Starting from benzoxazoles, the most common approach is the transition metal catalyzed direct arylation with aryl halides (Scheme 1A).[5] 2-Aryl-substitued benzoxazoles can also be prepared by the reaction of benzoxazoles with acyl chlorides or aromatic aldehydes via a ring-opening-ring-closing pathway (Scheme 1B).[6] These protocols *all require high temperatures* (>100 °C), which limits the substrate scope with temperature-sensitive heterocyclic aryl halides, such as furan derivatives. Furthermore, in many cases these reactions were performed in high boiling solvents, such as DMSO, DMF, and NMP, which complicate product isolation. .

Our group has been interested in the functionalization of weakly acidic sp^3 C–H bonds through deprotonative cross-coupling processes (DCCP), wherein the a weakly acidic C–H of the substrate is deprotonated by a base and functionalized in the presence of a transition metal catalyst. Substrates reported to date include chromium-activated benzylic amines,[7] diarylmethanes,[8] allylarenes,[9] amides,[10] sulfones,[11] sulfoxides,[12] imines,[13] phosphine oxides[14] and benzylic phosphonates.[15] We have found that van Leeuwen's NiXantphos[16] (See Scheme 1 for structure) enables a number of these transformations, whereas other ligands are significantly less effective or fail to provide even trace products.[8, 12a, 13] The high reactivity of the NiXantphos-based palladium catalysts may be due to the deprotonation of the ligand N–H under basic reaction conditions.[8a] Based on these studies, we decided to examine DCCP of sp^2 C–H bonds. Given the high temperature for metal-catalyzed direct 2-arylation of benzoxazoles, in combination with the importance of these compounds, we viewed this coupling as an ideal testing ground for NiXantphos-based catalysts. Herein, we report a $Pd(OAc)_2$/NiXantphos-catalyzed direct 2-arylation of benzoxazoles with aryl bromides *at room temperature* (Scheme 1C). Unlike most catalyst systems,[5] this catalyst promotes coupling with heteroaryl bromides.



Scheme 1 Synthesis of 2-arylbenzoxazoles

Our investigations into the direct 2-arylation of benzoxazoles were initiated by testing six bases [LiO*t*Bu, NaO*t*Bu, KO*t*Bu, $LiN(SiMe_3)_2$, $NaN(SiMe_3)_2$ and $KN(SiMe_3)_2$] in THF at 65 °C using benzoxazole **1a** (1.0 equiv) and 1-bromo-4-*tert*-butylbenzene **2a** (1.2 equiv, Table 1, entries 1–6). The nature of the base had a significant impact on the yield under these conditions, with NaO*t*Bu affording the coupling product **3a** in quantitative assay yield after 12 h (Table 1, entry 2). When the reaction temperature was reduced to room temperature, however, the assay yield dropped to 55% (entry 7). We then screened several solvents [DME (1,2-dimethoxyethane), CPME (cyclopentyl methyl ether), toluene and 1,4-dioxane] at rt and obtained 93% assay yield when the reaction was conducted in DME (entry 8). Under these conditions, trace unconverted benzoxazole **1a**

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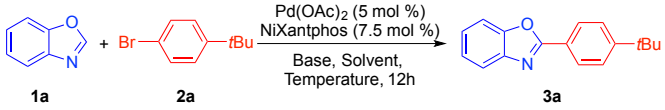
was detected. Using a benzoxazole to aryl bromide ratio of 1.2 : 1.0 at rt, the coupling product **3a** was isolated in 98% yield. When the catalyst/ligand loading was lowered, or the reaction time reduced, the reactions did not go to completion.

Table 1 Optimization of direct 2-arylation of benzoxazole **1a** with 1-bromo-4-*tert*-butylbenzene **2a** [a]



entry	base	solvent	*T* (°C)	yield (%)[b]
1	LiO*t*Bu	THF	65	56
2	NaO*t*Bu	THF	65	100
3	KO*t*Bu	THF	65	98
4	$LiN(SiMe_3)_2$	THF	65	90
5	$NaN(SiMe_3)_2$	THF	65	88
6	$KN(SiMe_3)_2$	THF	65	60
7	NaO*t*Bu	THF	25	55
8	NaO*t*Bu	DME	25	93
9	NaO*t*Bu	CPME	25	72
10	NaO*t*Bu	toluene	25	trace
11	NaO*t*Bu	1,4-dioxane	25	8
12[c]	NaO*t*Bu	DME	25	98[d]

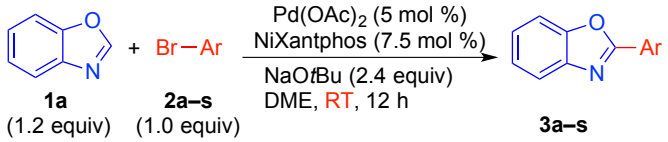
[a] Reactions performed using 1.0 equiv of **1a**, 1.2 equiv of **2a** and 2.0 equiv of base on a 0.1 mmol scale in 12 hours. [b] NMR assay yields. [c] This reaction performed using 1.2 equiv of **1a**, 1 equiv of **2a** and 2.4 equiv of NaO*t*Bu. [d] Isolated yield.

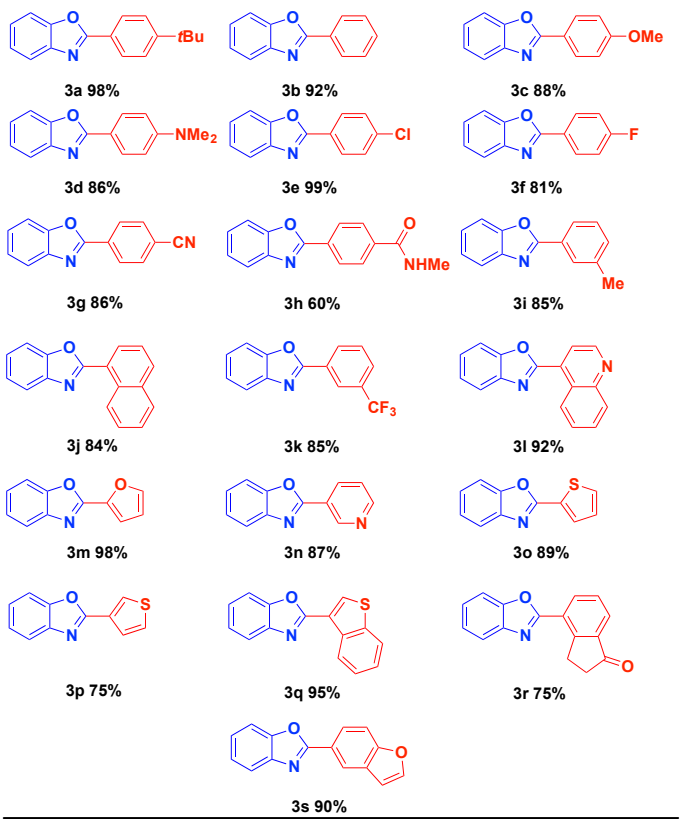
The substrate scope of aryl bromides **2a**–**s** with benzoxazole **1a** was investigated (Scheme 2) with the optimized reaction parameters [benzoxazole **1a** (1.2 equiv), aryl bromide **2** (1.0 equiv), $Pd(OAc)_2$ (5 mol %), NiXantphos (7.5 mol %), and NaO*t*Bu (2.4 equiv) in DME at room temperature for 12 h]. In general, aryl bromides possessing electron-donating, electron-withdrawing and sterically hindered substituents afforded products in good to excellent yields (60–99%).

Electron neutral 4-*tert*-butyl bromobenzene and the parent bromobenzene led to the expected products in 98 and 92% yield, respectively. Aryl bromides bearing 4-methoxy and 4-*N,N*-dimethylamino substituents gave coupling products **3c** and **3d** in 88 and 86% yield, respectively. Electron withdrawing substituents (4-Cl, 4-F, and 4-CN) on the aryl bromide were well tolerated, providing products in 81–99% yield. The most challenging substrate for this system was *N*-(4-bromophenyl)acetamide, with an acidic N–H that could also undergo Buchwald-Hartwig coupling with itself.[17] In this case, the $Pd(OAc)_2$/NiXantphos-based catalyst exhibited good chemoselectivity, generating the 2-aryl benzoxazole product **3h** in 60% yield. Both of 3-bromotoluene and 3-bromobenzotrifluoride provided the coupling products **3i** and **3k** in 85% yield. Sterically hindered 1-bromonaphthylene was a good substrate, furnishing the coupled 2-arylbenzoxazole **3j** in 84% yield.

As mentioned earlier, coupling of heteroaryl bromides is particularly important, but more challenging. To evaluate $Pd(OAc)_2$/NiXantphos-based catalyst, we examined a series of heteroaromatic coupling partners with benzoxazole. The reactions proceeded very well with heteroaryl bromides such as 3-bromopyridine, 2-bromofuran, 2- and 3-bromothiophenes, 4-bromoquinoline, 3-bromobenzothiophene and 5-bromobenzofuran to afford products in 75–98% yield. It should be noted that direct arylation of benzoxazoles with aryl heteroaryl bromides was carried out with excess amounts of heteroaryl bromides due to possible competing Heck-type reactions. Because of high chemoselectivity of the $Pd(OAc)_2$/NiXantphos-based catalyst, we were able to use heteroaryl bromides as a limiting reagent. To the best of our knowledge, this is the first successful coupling with sensitive 2-bromofuran (**2m**).

Scheme 2 Scope of aryl bromides in direct 2-arylation of benzoxazole **1a**





Based on the successful room temperature coupling of benzoxazole with aryl bromides, we briefly explored the scope of substituted benzoxazoles (Scheme 3). In each case, benzoxazoles

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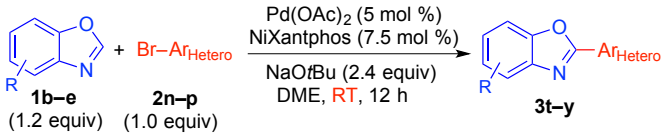
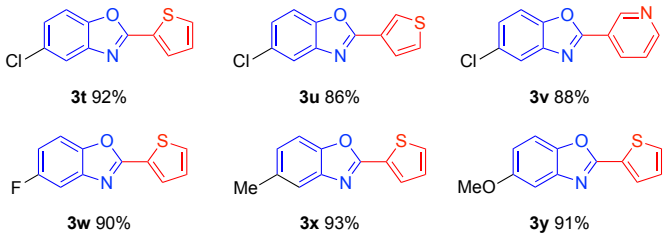
substituted with neutral, electron-rich or electron-withdrawing groups coupled with heterocyclic aryl bromides to generate diheteroaryl products with an average yield of 90%. Benzoxazoles possessing chlorine, fluorine, methyl, or methoxy groups coupled with 2-bromothiophene to provide 2-(thiophen-2-yl)benzoxazoles **3t** and **3w**–**y** in ≥90% yield at room temperature. DCCP of 5-chlorobenzoxazole with 3-bromothiophene or 3-bromopyridine afforded 5-chloro-2-(thiophen-3-yl)benzoxazole **3u** and 5-chloro-2-(pyridin-3-yl)benzoxazole **3v** in 86–88% yield.

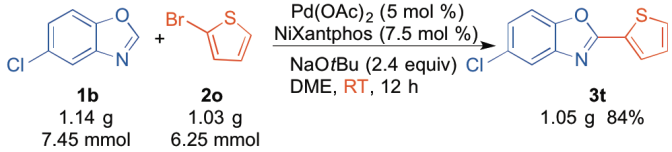
Scheme 3 Scope of substituted-benzoxazoles in the arylation with heteroaryl bromides





We also evaluated the scalability of the DCCP by performing the coupling of 5-chlorobenzoxazole **1b** with 2-bromothiophene **2o** on gram scale. The coupling product, 5-chloro-2-(thiophen-2-yl)benzoxazole **3t** was isolated in 84% yield. This yield is reasonably high, considering that the $Pd(OAc)_2$/NiXantphos-based catalyst can activate aryl chlorides in related reactions.[8a] Surprisingly, however, aryl chlorides were not successful coupling partners with benzoxazoles under these reaction conditions.

Scheme 4 Arylation of 5-chlorobenzoxazole with 2-bromothiophene on gram scale



In summary, we have developed the first room-temperature direct arylation of benzoxazoles with aryl bromides and heteroaryl bromides. The coupling reaction shows good substrate scope and proceeds in high yields (average > 85%). Other catalysts that promote this reaction are typically employed at temperatures >100 °C and exhibit only limited substrate scope. The key to success of our reaction is the $Pd(OAc)_2$/NiXantphos-based catalyst, which operates *via* a deprotonative cross-coupling process. This work is the first demonstration that the $Pd(OAc)_2$/NiXantphos-based catalyst is capable of promoting efficient functionalization of sp^2 hybridized C–H bonds. We expect that this catalyst will be applicable to many of the known arylation reactions that involve deprotonation of substrates possessing weakly acidic sp^2 hybridized C–H's.

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Notes and references

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† Electronic supplementary information (ESI) available. See DOI:

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