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

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Abstract

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 a 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 pharmaceuticals² 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-substituted 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 oxides¹⁴ and benzylic phosphonates.¹⁵ We have found that van Leeuwen's NiXantphos¹⁶ (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

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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 $\text{Pd}(\text{OAc})_2/\text{NiXantphos}$ -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.

Our investigations into the direct 2-arylation of benzoxazoles were initiated by testing six bases [LiOtBu , NaOtBu , KOtBu , $\text{LiN}(\text{SiMe}_3)_2$, $\text{NaN}(\text{SiMe}_3)_2$ and $\text{KN}(\text{SiMe}_3)_2$] 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 NaOtBu 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** 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.

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), $\text{Pd}(\text{OAc})_2$ (5 mol %), NiXantphos (7.5 mol %), and NaOtBu (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 $\text{Pd}(\text{OAc})_2/\text{NiXantphos}$ -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 $\text{Pd}(\text{OAc})_2/\text{NiXantphos}$ -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**).

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 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.

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.

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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A. X = Cl, Br, I, SO₂Cl, SO₂Na, OMs, Si(OR)₃,

B.

This work

C.

Scheme 1.
Synthesis of 2-arylbenzoxazoles

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

Scheme 3.

Scope of substituted-benzoxazoles in the arylation with heteroaryl bromides

Scheme 4.

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

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

entry	base	solvent	<i>T</i> (°C)	yield (%) ^b
1	LiOrBu	THF	65	56
2	NaOrBu	THF	65	100
3	KOrBu	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	NaOrBu	THF	25	55
8	NaOrBu	DME	25	93
9	NaOrBu	CPME	25	72
10	NaOrBu	toluene	25	trace
11	NaOrBu	1,4-dioxane	25	8
12 ^c	NaOrBu	DME	25	98 ^d

^aReactions 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.^bNMR assay yields.^cThis reaction performed using 1.2 equiv of **1a**, 1 equiv of **2a** and 2.4 equiv of NaOrBu.^dIsolated yield.