Direct Oxidative C–H Arylation of Benzoxazoles with Arylsulfonyl Hydrazides Promoted by Palladium Complexes

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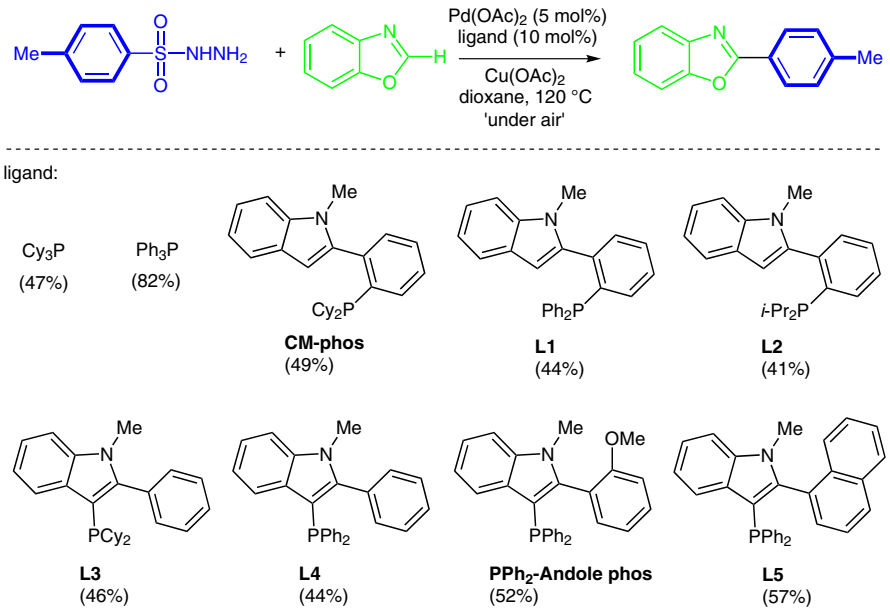
Abstract: This study describes a direct oxidative C-2 arylation of benzoxazoles using arylsulfonyl hydrazides as the aryl sources. A simple catalyst system [$Pd(OAc)_2$ and Ph_3P] allows the reactions to proceed smoothly under oxidative reaction conditions. Other heteroarenes such as caffeine and benzothiazole are also applicable substrates. Notably, this catalytic system tolerates halogen substituents which provides a useful complement to the current cross-coupling reactions which use aryl halides.

Key words: palladium, arylation, arylsulfonyl chlorides, phosphine, benzoxazoles

Cross-coupling protocols have been successful in modern modular organic syntheses for the connection of two different fragments via the formation of carbon–carbon and/or carbon–heteroatom bonds.[1] To prepare useful biaryl motifs,[2] coupling methods such as Hiyama, Kumada, Negishi, Stille and Suzuki–Miyaura coupling have been found to be versatile in the past few decades.[1] Even though these reactions are effective, some intrinsic drawbacks still exist in which the corresponding organometallic nucleophiles must be prepared in situ (e.g. ArMgBr, ArZnCl) or require isolation, in general, prior to the catalysis [e.g. $ArB(OH)_2$]. Thus, the assembling and subsequent disposal of stoichiometric organometallic agents are relatively not desirable. In fact, direct C–H functionalization of heteroarenes is actually more straightforward. This protocol serves as an attractive alternative to conventional coupling protocols in terms of better atom economy, environmental friendliness and more streamlined chemical synthesis.[3,4]

In continuing our research focus of applying arylsulfonyl compounds as effective aryl sources,[5] we envisioned that arylsulfonyl hydrazides could be employed as versatile arylating agents. Indeed, arylsulfonyl hydrazides are stable under air and can be simply prepared in one step from commonly available arylsulfonyl chlorides and hydrazine hydrates. During the process of this work, Tian and coworkers reported the first palladium-catalyzed Heck-type reaction of alkenes with arylsulfonyl hydrazides.[6] To the best of our knowledge, the direct C–H arylation of benzoxazoles remain sporadically studied.[7] In fact, with respect to the reaction of olefins, the arylation of



Scheme 1 A survey of ligand effect in oxidative arylation of benzoxazole

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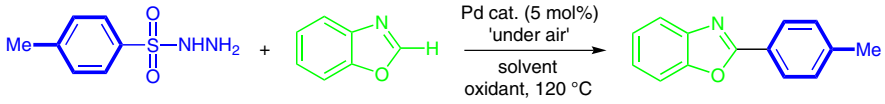
heteroarenes is known to be even more challenging because of the undesirable homocoupling outcome and decomposition of heteroarenes is often observed under oxidative conditions. In continuation of our research program on C-2 functionalization of benzoxazoles,[8] we herein report our efforts in the palladium-catalyzed direct C–H arylation of benzoxazoles using arylsulfonyl hydrazides under oxidative reaction conditions.

We initially probed the efficacy of arylsulfonyl hydrazide as the aryl source in the direct C–H arylation of heteroarenes (Table 1). Benzoxazole and 4-tolylsulfonyl hydrazide were used as benchmark substrates. Among commonly used solvents screened, dioxane provided the best results (entries 1–7). There were little differences in product yield observed in the model reaction when other palladium precursors were investigated (entries 1 and 8–13). The palladium complex associated with triphenylphosphine gave slightly higher yield (entry 9 vs. entry 13). Common inorganic/organic oxidants were also surveyed (entries 1 and 14–21). Copper(II) acetate gave the best results while BQ and O_2 provided inferior product yields. In light of the successful initial results achieved, we next examined the effect of phosphine ligands in this reaction (Scheme 1). Palladium(II) acetate with triphenylphosphine promoted the reaction and gave the highest product yield. Yet, catalytic systems employing our previously developed tunable indolylphosphine ligands **L1**–**L5** showed moderate efficiency (Scheme 1).[9]

With our optimized reaction conditions in hand, we next tested the scope of arylsulfonyl hydrazides (Table 2).[10] The coupling reaction of sterically hindered 2-tolylsulfonyl hydrazide proceeded smoothly (entry 3). Halogen sub-

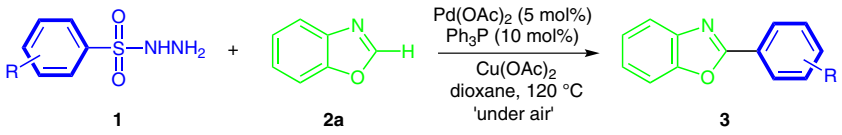
Table 1 Initial Screening of Oxidative Arylation of 4-Methylbenzenesulfonyl Hydrazide and Benzoxazole[a]



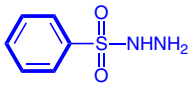
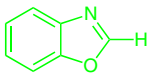
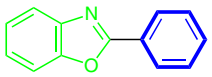
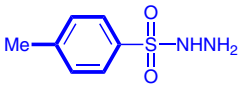
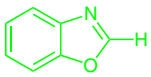
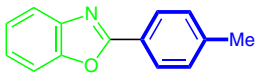
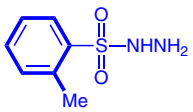
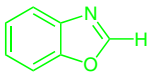
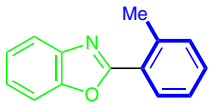
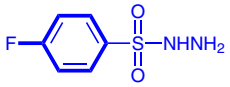
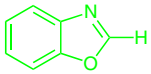
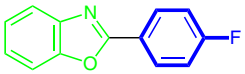
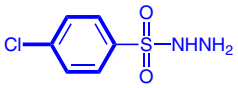
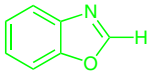
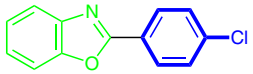
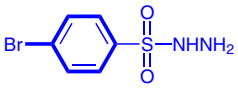
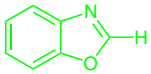
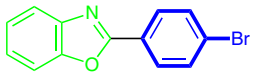
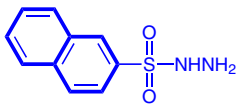
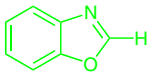
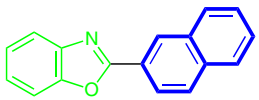
Entry	Pd source	Solvent	Oxidant	Yield (%)[b]
1	$Pd(OAc)_2$	dioxane	$Cu(OAc)_2$	51
2	$Pd(OAc)_2$	DMF	$Cu(OAc)_2$	6
3	$Pd(OAc)_2$	DMA	$Cu(OAc)_2$	39
4	$Pd(OAc)_2$	NMP	$Cu(OAc)_2$	10
5	$Pd(OAc)_2$	DMSO	$Cu(OAc)_2$	34
6	$Pd(OAc)_2$	toluene	$Cu(OAc)_2$	16
7	$Pd(OAc)_2$	H_2O	$Cu(OAc)_2$	0
8	$Pd(TFA)_2$	dioxane	$Cu(OAc)_2$	48
9	$PdCl_2$	dioxane	$Cu(OAc)_2$	52
10	$Pd(acac)_2$	dioxane	$Cu(OAc)_2$	47
11	$PdCl_2(MeCN)_2$	dioxane	$Cu(OAc)_2$	57
12	$PdCl_2(PCy_3)_2$	dioxane	$Cu(OAc)_2$	46
13	$PdCl_2(PPh_3)_2$	dioxane	$Cu(OAc)_2$	54
14	$Pd(OAc)_2$	dioxane	$Cu(OAc)_2{\cdot}H_2O$	36
15	$Pd(OAc)_2$	dioxane	$Cu(acac)_2$	28
16	$Pd(OAc)_2$	dioxane	$CuCl_2$	0
17	$Pd(OAc)_2$	dioxane	$CuBr_2$	0
18	$Pd(OAc)_2$	dioxane	AgOAc	0
19	$Pd(OAc)_2$	dioxane	BQ	0
20	$Pd(OAc)_2$	dioxane	$K_2S_2O_8$	0
21	$Pd(OAc)_2$	dioxane	O_2	0

[a] Reaction conditions: 4-tolylsulfonyl hydrazide (0.45 mmol), benzoxazole (0.3 mmol), Pd catalyst (5 mol%), solvent (3 mL) and oxidant (0.6 mmol) were stirred at 120 °C for 18 h under air.
[b] Calibrated GC yields were reported using dodecane as internal standard.

Table 2 Palladium-Catalyzed Oxidative Arylation of Benzoxazole Using Arylsulfonyl Hydrazides[a]



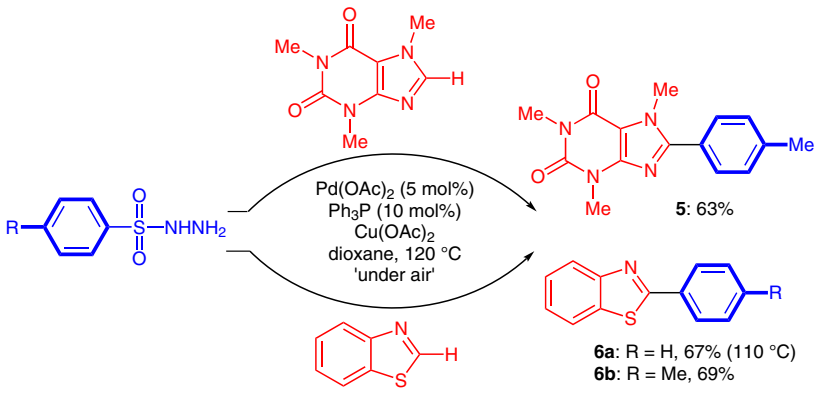
1 2a 3

Entry	$ArSO_2NHNH_2$	Benzoxazole	Product	Yield (%)[b]
1[c]			**3aa** 	76
2			**3ba** 	78
3[d]			**3ca** 	72
4			**3da** 	66
5[c]			**3ea** 	60
6[d]			**3fa** 	59
7			**3ga** 	67

[a] Reaction conditions: arylsulfonyl hydrazide (0.45 mmol), benzoxazole (0.3 mmol), $Pd(OAc)_2$ (5 mol%), Ph_3P (10 mol%), dioxane (3 mL), $Cu(OAc)_2$ (0.6 mmol) were stirred for 18 h at 120 °C under air.
[b] Isolated yields.
[c] The reaction was conducted at 110 °C.
[d] The reaction was conducted at 100 °C.

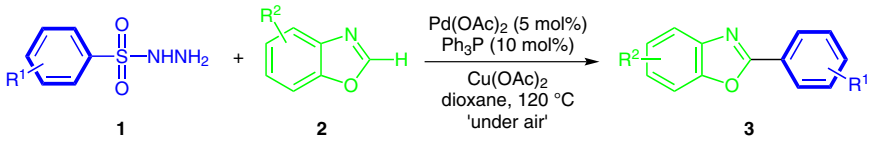
stituents (F, Cl, Br) on the arylsulfonyl hydrazide were found to be compatible under these reaction conditions (entries 4–6). Particularly noteworthy is that the tolerance of chloro and bromo groups can offer an avenue for further versatile functionalization using traditional cross-coupling protocols.[1]

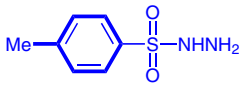
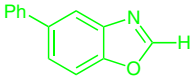
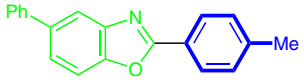
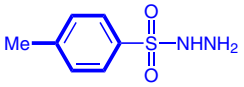
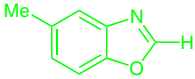
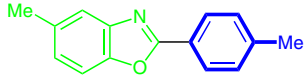
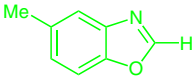
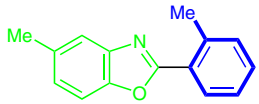
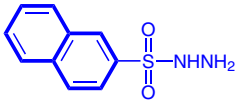
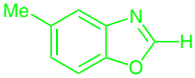
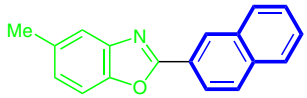
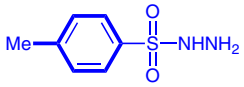
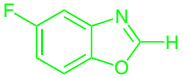
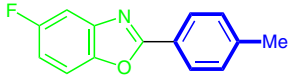
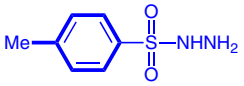
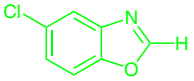
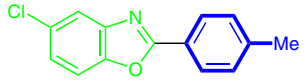
In addition to a variety of arylsulfonyl hydrazides examined, the substituted benzoxazoles were found to be feasible substrates (Table 3). Fluoro and chloro groups remained intact during the course of the reaction (entries 5 and 6). Apart from benzoxazole, other heteroarenes were applicable. Caffeine and benzothiazole could be ap-



Scheme 2 Palladium-catalyzed direct C–H arylation of caffeine and benzothiazole with arylsulfonyl hydrazides

Table 3 Palladium-Catalyzed Oxidative Arylation of Substituted Benzoxazoles with Arylsulfonyl Hydrazides[a]



Entry	$ArSO_2NHNH_2$	Benzoxazole	Product	Yield (%)[b]
1			**3bb** 	70
2			**3bc** 	75
3[c]			**3cc** 	72
4			**3gc** 	67
5			**3bd** 	71
6			**3be** 	72

[a] Reaction conditions: arylsulfonyl hydrazide (0.45 mmol), substituted benzoxazole (0.3 mmol), $Pd(OAc)_2$ (5 mol%), Ph_3P (10 mol%), dioxane (3 mL), $Cu(OAc)_2$ (0.6 mmol) were stirred for 18 h at 120 °C under air.
[b] Isolated yields.
[c] The reaction was conducted at 100 °C.

plied in this catalytic system (Scheme 2). Moderate-to-good product yields were observed. In particular, the product **5** is a useful fluorescent molecule for cell imaging.[11]

In summary, we have reported an oxidative protocol for C-2 arylation of benzoxazoles using readily available and easy-to-handle arylsulfonyl hydrazides as the aryl sources. Particularly noteworthy is that only a simple catalyst system [$Pd(OAc)_2$ and Ph_3P] is required for this coupling reaction. This methodology is a useful complement to the current cross-coupling protocols as it tolerates halogen substituents on both arylsulfonyl hydrazide and heteroarene coupling partners. Detail mechanistic study is currently under way.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(6) (a) Yang, F.-L.; Ma, X.-T.; Tian, S.-K. *Chem.–Eur. J.* **2012**, *18*, 1582. (b) Note: We also presented a very similar Pd-catalyzed arylation of terminal alkenes using arylsulfonyl hydrazides in **2011**, ACP-Lectureship Award, *National University of Singapore, Nanyang Technological University, A*Star Institute*, 6–11th December **2011**, Singapore.

(7) (a) During the preparation of this manuscript, one example of arylation of benzoxazole with 4-tolylsulfonyl hydrazide was reported: Liu, B.; Li, J.; Song, F.; You, J. *Chem.–Eur. J.* **2012**, *18*, 10830. (b) Note: We also presented arylation examples of benzoxazoles and caffeines for this coupling reaction using arylsulfonyl hydrazides, May 8–12, **2012** in Japan (Nagoya University, Kyoto University and Kyushu University).

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(10) **Representative Experimental Procedures**: All reagents were weighted in air and the reactions were performed in an open vessel (60 mL vial equipped with an air condenser). $Pd(OAc)_2$ (0.0034 g, 0.015 mmol), Ph_3P (Pd/L = 1:2), arylsulfonyl hydrazides (0.45 mmol), heteroarenes (0.3 mmol) and $Cu(OAc)_2$ (0.6 mmol) were loaded into a 60 mL vial equipped with a Teflon-coated magnetic stir bar. Dioxane (3 mL) was added at r.t. The vial was fitted with an air condenser and then placed into a preheated oil bath with the reaction temperature indicated in the table and the reaction mixture was vigorously stirred for 18 h. After the completion of reaction, the reaction vial was allowed to cool to r.t. EtOAc (ca. 20 mL) and H_2O (ca. 10 mL) were added. The organic layer was subjected to GC analysis. After analyzing the GC spectra, the crude product in the organic layer was extracted and the vial was washed with EtOAc. The filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (230–400 mesh) to afford the desired product. **2-Phenylbenzoxazole (Table 2, entry1, compound 3aa)**: eluent: EtOAc–hexane (1:20; R_f 0.62) was used for flash column chromatography to provide compound **3aa** (44.5 mg, 76 % yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.40 (m, 2 H), 7.52–7.57 (m, 3 H), 7.58–7.63 (m, 1 H), 7.79–7.83 (m, 1 H), 8.28–8.31 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 110.5, 120.0, 124.5, 125.1, 127.1, 127.6, 128.8, 131.5, 142.0, 150.7, 163.0. MS (EI): *m*/*z* (relative intensity) = 195.0 (100) [M^+], 167.0 (18), 139.0 (3), 92.0 (5), 63.0 (14).

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