

Pd-Catalyzed Oxidative *ortho*-C–H Borylation of Arenes

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Supporting Information

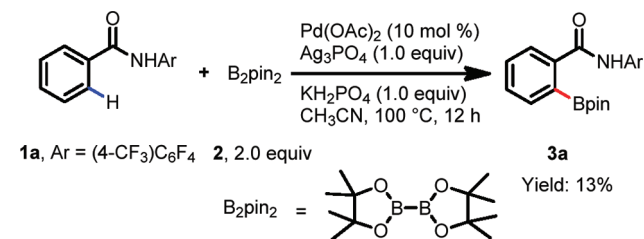
ABSTRACT: The development of a Pd-catalyzed oxidative *ortho*-C–H borylation with *N*-arylbenzamides is reported. A modified dibenzylideneacetone (dba) ligand, a weak base, and a strong oxidant are critical for obtaining good yields. The reaction is tolerant of electron-deficient and electron-rich benzamides derived from readily available benzoic acids. The borylated products can be converted to various synthons via diverse transformations.

Among the various metal-catalyzed C–H functionalization reactions, Pd catalysts have displayed encouraging versatility in terms of the development of diverse carbon–carbon and carbon–heteroatom bond-forming transformations.¹ For instance, the Pd(II)/Pd(0) redox catalytic cycle has been shown to be able to couple C–H bonds with alkyl, aryl, and vinyl organometallic reagents as nucleophiles to forge various carbon–carbon bonds.² Because of the broad utility of arylboron reagents in synthesis, we envision that an aryl C–H borylation reaction using a Pd(II)/Pd(0) catalytic platform would be highly valuable. Prevalent methods for the preparation of arylboronic esters involve the metal-catalyzed borylation of aryl halides^{3,4} or the addition of aryllithium or magnesium species to borates.⁵

Significant progress has been made in the past decade on Ir- and Rh-catalyzed C–H borylation reactions, in which the regioselectivity is controlled by either sterics^{6,7} or a directing group (DG) (eq 1).^{8,9} Two isolated examples of Pd(0)-catalyzed

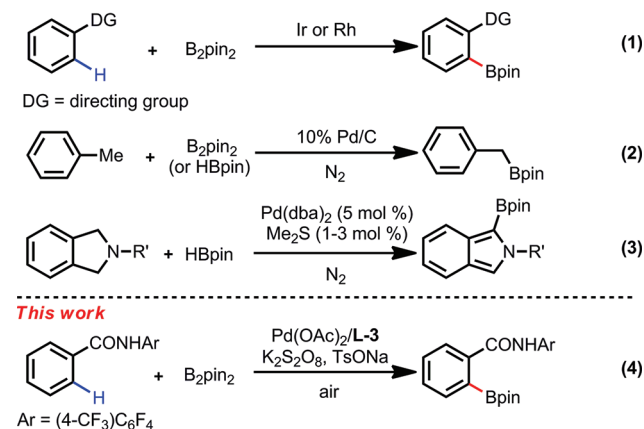
a broad substrate scope. However, a critical challenge in developing this catalytic process is the decomposition of the arylboronic esters via transmetalation between the arylboronic esters and Pd(II) species. Herein we report a Pd-catalyzed oxidative borylation of *N*-arylbenzamides with a diboron reagent via a Pd(II)/Pd(0) manifold (eq 4). The use of a powerful directing group for C–H activation as well as a weak base (TsONa), a strong oxidant (K₂S₂O₈), and a modified dibenzylideneacetone (dba) ligand (**L-3**) are crucial for this transformation. The obtained arylboronic esters are shown to engage in carbon–carbon, carbon–nitrogen, and carbon–halogen bond formation⁵ with various reaction partners, providing access to synthons that currently cannot be obtained using our previously reported Pd-catalyzed C–H activation reactions.²

In our continuing effort to develop synthetically versatile C–H activation reactions, we recently identified –CONHAr [Ar = (4-CF₃)C₆F₄] as a highly efficient auxiliary to assist a diverse range of C–H activation reactions that are otherwise elusive.¹¹ Importantly, this amide auxiliary is applicable to a wide range of carboxylic acids whose carbon skeletons can be mapped onto both drug molecules and natural products.^{11b} We therefore decided to investigate C–H borylation using *N*-arylbenzamide substrate **1a**. We found that C–H borylation of **1a** with 2 equiv of **2** occurred in the presence of 10 mol % Pd(OAc)₂, 1.0 equiv of Ag₃PO₄, and 1.0 equiv of KH₂PO₄ in CH₃CN to give the desired borylation product **3a** in 13% yield (Scheme 1). This initial result suggests

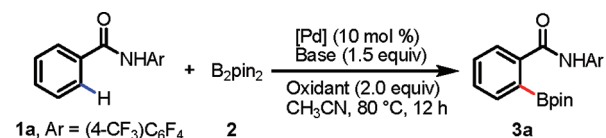
Scheme 1. Pd-Catalyzed Borylation of *N*-Arylbenzamides

that C–H activation could outcompete the decomposition of the diboron by the Pd(II) catalyst.

An extensive screening of bases, oxidants, and solvents showed that the use of K₂S₂O₈ as the oxidant, TsONa as the base, and CH₃CN as the solvent provided **3a** in 53% yield (Table 1, entry 6). Poor yields were obtained with other oxidants [see the Supporting Information (SI)]. The use of a weak base such as TsONa was essential for obtaining good

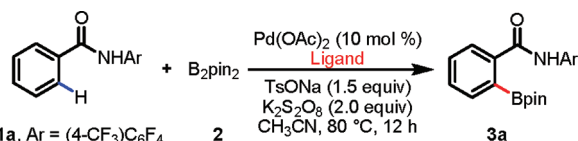


borylation of benzylic or isoindolyl C–H bonds under reducing conditions have also been reported (eqs 2 and 3).¹⁰ Because of the versatile reactivity of Pd(II) catalysts in C–H activation, the development of the oxidative Pd(II)/Pd(0) manifold to effect C–H borylation has the potential to afford

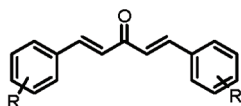
Table 1. Evaluation of Reaction Conditions^a

Entry	[Pd]	Oxidant	Base	Yield (%) ^b
1	Pd(OAc) ₂	K ₂ S ₂ O ₈	K ₃ PO ₄	NR
2	Pd(OAc) ₂	K ₂ S ₂ O ₈	K ₂ HPO ₄	32
3	Pd(OAc) ₂	K ₂ S ₂ O ₈	KH ₂ PO ₄	40
4	Pd(OAc) ₂	K ₂ S ₂ O ₈	CF ₃ CO ₂ Na	26
5	Pd(OAc) ₂	K ₂ S ₂ O ₈	CF ₃ SO ₃ Na	18
6	Pd(OAc)₂	K₂S₂O₈	TsONa	53
7	Pd(OAc) ₂	-	TsONa	12
8	Pd(OAc) ₂	K ₂ S ₂ O ₈	-	24
9	Pd(OAc) ₂	-	-	9
10	-	K ₂ S ₂ O ₈	TsONa	NR
11	Pd(CH ₃ CN) ₂ (OTf) ₂	K ₂ S ₂ O ₈	TsONa	31
12	Pd(CH ₃ CN) ₄ (OTf) ₂	K ₂ S ₂ O ₈	TsONa	24
13	PdCl ₂ (CH ₃ CN) ₂	K ₂ S ₂ O ₈	TsONa	NR
14	Pd(CF ₃ CO ₂) ₂	K ₂ S ₂ O ₈	TsONa	54
15	Pd₂(dba)₃	K₂S₂O₈	TsONa	59
16 ^c	Pd(OAc) ₂	K ₂ S ₂ O ₈	TsONa	31

^aConditions: **1a** (0.1 mmol), **2** (0.2 mmol), Pd catalyst (10 mol %), oxidant (0.2 mmol), base (0.15 mmol), CH₃CN (1.0 mL), 80 °C, 12 h. ^bDetermined by ¹H NMR analysis of the crude product using CH₂Br₂ as an internal standard. ^c**2** (0.1 mmol).

Table 2. C–H Borylation Promoted by dba Ligands^a

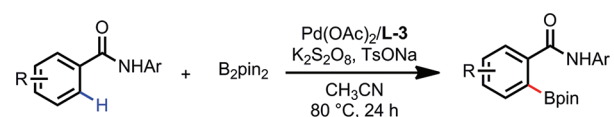
Entry	Ligand	Yield (%) ^b	Entry	Ligand	Yield (%) ^b
1	-	53	7	L-3 (0.3 eq)	67 + 5(di)
2	L-1 (0.1 eq)	48 + 9(di)	8	L-4 (0.3 eq)	53 + 8(di)
3	L-1 (0.2 eq)	51 + 15(di)	9	L-5 (0.3 eq)	58 + 12(di)
4	L-1 (0.3 eq)	55 + 18(di)	10	L-6 (0.3 eq)	59 + 13(di)
5	L-1 (0.5 eq)	51 + 6(di)	11 ^c	L-3 (0.3 eq)	78 + 7(di)
6	L-2 (0.3 eq)	43 + 11(di)	12 ^d	L-3 (0.3 eq)	68 + 15(di)



R = H (dba) **L-1**, 4, 4'-OMe **L-2**,
4,4'-CF₃ **L-3**, 4,4'-Cl **L-4**,
4,4'-F **L-5**, 3,3'-NO₂ **L-6**.

^aConditions: **1a** (0.1 mmol), **2** (0.2 mmol), Pd(OAc)₂ (10 mol %), K₂S₂O₈ (0.2 mmol), TsONa (0.15 mmol), CH₃CN (1.0 mL), 80 °C, 12 h. ^bDetermined by ¹H NMR analysis of the crude products using CH₂Br₂ as an internal standard. ^c24 h. ^d**2** (0.3 mmol).

yields (entries 2–6), as both the diboron reagent and the arylboronate decomposed in the presence of K₃PO₄. While the diboron reagent was stable when TsONa was used, slow decomposition of the arylboronate product still occurred during the reaction. Therefore, the use of 2.0 equiv of the diboron

Table 3. Pd-Catalyzed Borylation Reaction of N-Arylbenzamides^{a,b}

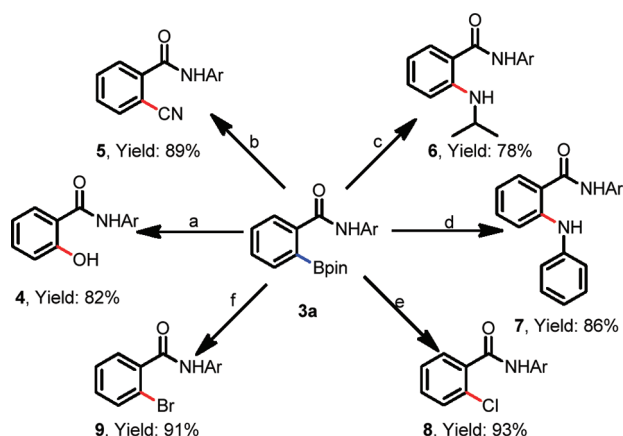
1a-1p, Ar = (4-CF ₃)C ₆ F ₄	2	3a-3p
3a , 71%		3b , 85%
		3c , 82%
		3d , 67%
		3e , 62%
		3f , 61%
		3g , 73%
		3h , 76%
		3i , 75%
		3j , 78%
		3k , 81%
		3l , 77%
		3m , 62% ^c
		3n , 58% ^c
		3o , 46% ^c
		3p , 72%

^aConditions: **1** (0.1 mmol), **2** (0.2 mmol), Pd(OAc)₂ (10 mol %), **L-3** (30 mol %), K₂S₂O₈ (0.2 mmol), TsONa (0.15 mmol), CH₃CN (1 mL), 80 °C, 24 h. ^bIsolated yields are shown. ^c**2** (0.3 mmol).

reagent was beneficial for obtaining good yields (entries 6 and 16) (see the SI).

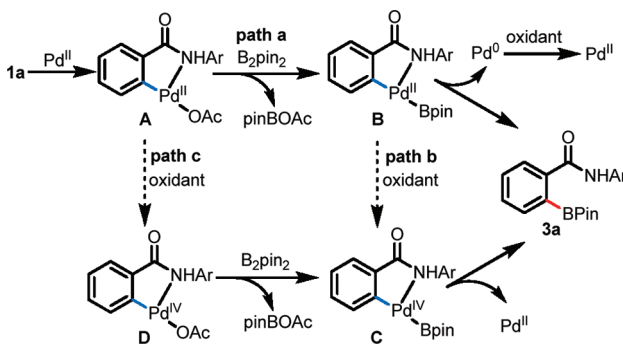
Among various Pd catalysts tested, Pd₂(dba)₃ was found to be equally effective as Pd(OAc)₂ (Table 1, entry 15). Since the electronic properties of substituents on the aryl groups of dba are known to modulate the Suzuki–Miyaura cross-coupling of organohalides with arylboronic acids,¹² we tested a variety of dba analogues in combination with Pd(OAc)₂ to investigate their influence on this reaction (Table 2). While unsubstituted dba had a negligible effect (entries 2–5), the use of electron-deficient dba ligand **L-3** significantly improved the yield of the borylation reaction with good monoselectivity (entry 7). When the reaction time was prolonged to 24 h, the yield was improved to 78% (entry 11). However, the use of 3 equiv of diboron reagent resulted in significant formation of the diborylated product (entry 12).

With these optimized conditions in hand, we surveyed the substrate scope of this borylation reaction (Table 3). Methylated arenes gave yields of 85 and 82% (**3b** and **3c**), whereas MeO- and AcO-substituted arenes afforded lower yields (**3d–f**). Borylation of fluorinated and chlorinated arenes proceeded smoothly to give their corresponding products (**3g–i**) in yields of 73–81%. The presence of an electron-withdrawing CF₃ group on the arene reduced the yield to 62%

Scheme 2. Versatile Transformations of the Borylated Products^a

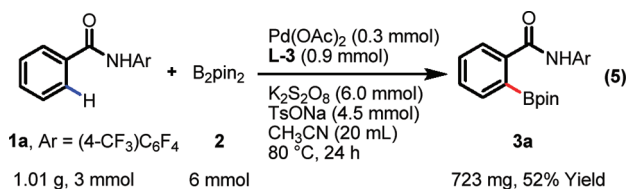
^aConditions: (a) **3a** (0.05 mmol), oxone (0.05 mmol) in H₂O (1.0 mL), acetone (1.0 mL), rt, 2 h. (b) **3a** (0.05 mmol), CuCN (0.05 mmol), K₂CO₃ (0.15 mmol), DMF (1.0 mL), 60 °C, 4 h. (c) **3a** (0.05 mmol), isopropylamine (0.06 mmol), Cu(OAc)₂ (10 mol %), 4 Å molecular sieves (MS), O₂ (1 atm), CH₂Cl₂ (1.0 mL), 40 °C, 12 h. (d) **3a** (0.05 mmol), aniline (0.06 mmol), Cu(OAc)₂ (10 mol %), 4 Å MS, O₂ (1 atm), CH₂Cl₂ (1.0 mL), 40 °C, 12 h. (e) **3a** (0.05 mmol), CuCl₂ (0.15 mmol) in H₂O (1.0 mL), CH₃OH (1.0 mL), 90 °C, 24 h. (f) **3a** (0.05 mmol), CuBr₂ (0.15 mmol) in H₂O (1.0 mL), CH₃OH (1.0 mL), 80 °C, 24 h.

Scheme 3. Proposed Mechanism



(**3m**) and 58% (**3n**). The nitro group was also tolerated as a substituent on the arene ring, providing the borylated product (**3o**) in 46% yield. A good yield was obtained with a naphthalene substrate (**3p**). In the majority of cases, high mono-selectivity (>90%) was observed, and only the monoborylated products were isolated.

To demonstrate the utility of this borylation reaction, we conducted the reaction on gram scale, which provided **3a** in 52% yield (eq 5). Subsequently, we also showed that **3a** can be



converted to a wide range of desirable synthons in excellent yields using known transformations such as hydroxylation,¹³ cyanation,¹⁴ halogenation,¹⁵ and amination¹⁶ with primary alkylamines and arylamines (Scheme 2). The cyanation and

amination reactions are particularly valuable because direct cyanation and amination of C–H bonds still remain a significant challenge.

At this stage, the detailed mechanism of each elementary step remains to be ascertained. Following C–H cleavage by the Pd(II) catalyst, intermediate **A** could undergo transmetalation with the diboron reagent to form the ArPd^{II}B intermediate **B** (Scheme 3). Subsequent C–B reductive elimination would afford the borylated product (path a) and Pd(0). The effectiveness of Pd₂(dba)₃ is consistent with this pathway. Intriguingly, the requirement of a strong oxidant such as K₂S₂O₈ appears to suggest that **B** could be oxidized to Pd(IV) species **C** prior to the C–B reductive elimination (path b). Path c is unlikely to be operative since the formation of the acetoxyated product was not observed, as would be expected from facile C–O reductive elimination of Pd(IV) species **D**.

In summary, we have developed the first Pd-catalyzed borylation of arenes under oxidative conditions. The *N*-arylbenzamides are readily accessible from benzoic acids. The borylated products can be converted to various valuable synthons using known transformations.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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