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

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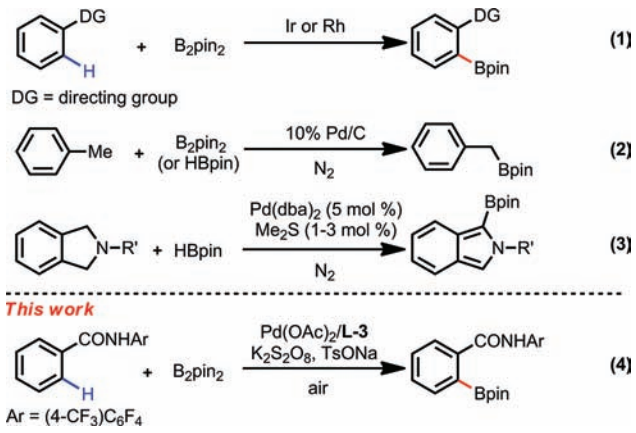
Supporting Information

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]

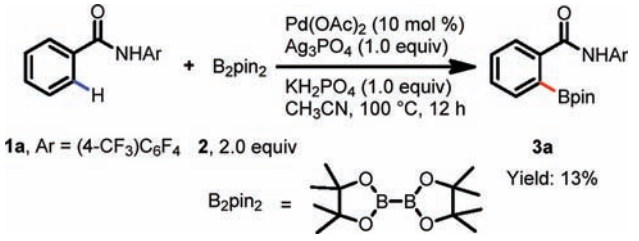
Significant progress has been made in the past decade on Ir- and Rh-catalyzed C−H borylation reactions, in which the regioselectivity is controlled by either sterics[6,7] or a directing group (DG) (eq 1).[8,9] Two isolated examples of Pd(0)-catalyzed



borylation of benzylic or isoindolinyl 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 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 ($K_2S_2O_8$), 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 formation[5] 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 = $(4\text{-}CF_3)C_6F_4$] 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 Ag_3PO_4, and 1.0 equiv of KH_2PO_4 in CH_3CN 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 $K_2S_2O_8$ as the oxidant, TsONa as the base, and CH_3CN 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

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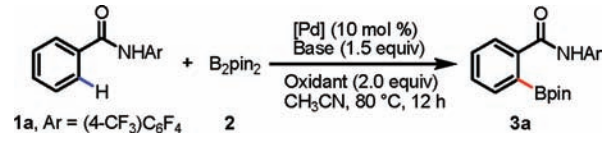
Table 1. Evaluation of Reaction Conditions[a]

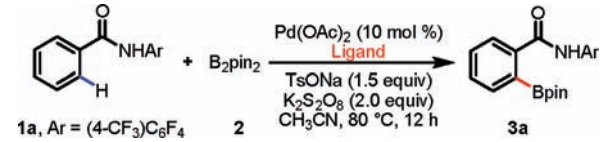


1a, Ar = (4-CF_3)C_6F_4 2 3a

Entry	[Pd]	Oxidant	Base	Yield (%)[b]
1	$Pd(OAc)_2$	$K_2S_2O_8$	K_3PO_4	NR
2	$Pd(OAc)_2$	$K_2S_2O_8$	K_2HPO_4	32
3	$Pd(OAc)_2$	$K_2S_2O_8$	KH_2PO_4	40
4	$Pd(OAc)_2$	$K_2S_2O_8$	CF_3CO_2Na	26
5	$Pd(OAc)_2$	$K_2S_2O_8$	CF_3SO_3Na	18
6	$Pd(OAc)_2$	$K_2S_2O_8$	TsONa	53
7	$Pd(OAc)_2$	-	TsONa	12
8	$Pd(OAc)_2$	$K_2S_2O_8$	-	24
9	$Pd(OAc)_2$	-	-	9
10	-	$K_2S_2O_8$	TsONa	NR
11	$Pd(CH_3CN)_2(OTs)_2$	$K_2S_2O_8$	TsONa	31
12	$Pd(CH_3CN)_4(OTf)_2$	$K_2S_2O_8$	TsONa	24
13	$PdCl_2(CH_3CN)_2$	$K_2S_2O_8$	TsONa	NR
14	$Pd(CF_3CO_2)_2$	$K_2S_2O_8$	TsONa	54
15	$Pd_2(dba)_3$	$K_2S_2O_8$	TsONa	59
16[c]	$Pd(OAc)_2$	$K_2S_2O_8$	TsONa	31

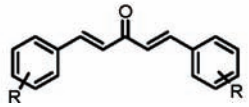
[a]Conditions: **1a** (0.1 mmol), **2** (0.2 mmol), Pd catalyst (10 mol %), oxidant (0.2 mmol), base (0.15 mmol), CH_3CN (1.0 mL), 80 °C, 12 h. [b]Determined by ^1H NMR analysis of the crude productd using CH_2Br_2 as an internal standard. [c]**2** (0.1 mmol).

Table 2. C−H Borylation Promoted by dba Ligands[a]



1a, Ar = (4-CF_3)C_6F_4 2 3a

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'-CF_3 **L-3**, 4,4'-Cl **L-4**, 4,4'-F **L-5**, 3,3'-NO_2 **L-6**.

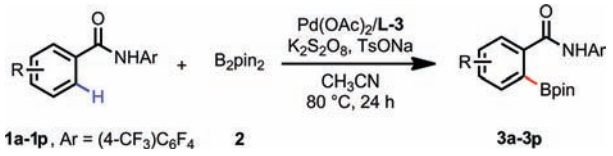
[a]Conditions: **1a** (0.1 mmol), **2** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), $K_2S_2O_8$ (0.2 mmol), TsONa (0.15 mmol), CH_3CN (1.0 mL), 80 °C, 12 h. [b]Determined by ^1H NMR analysis of the crude products using CH_2Br_2 as an internal standard. [c]24 h. [d]**2** (0.3 mmol).

yields (entries 2−6), as both the diboron reagent and the arylboronate decomposed in the presence of K_3PO_4. 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 reagent was beneficial for obtaining good yields (entries 6 and 16) (see the SI).

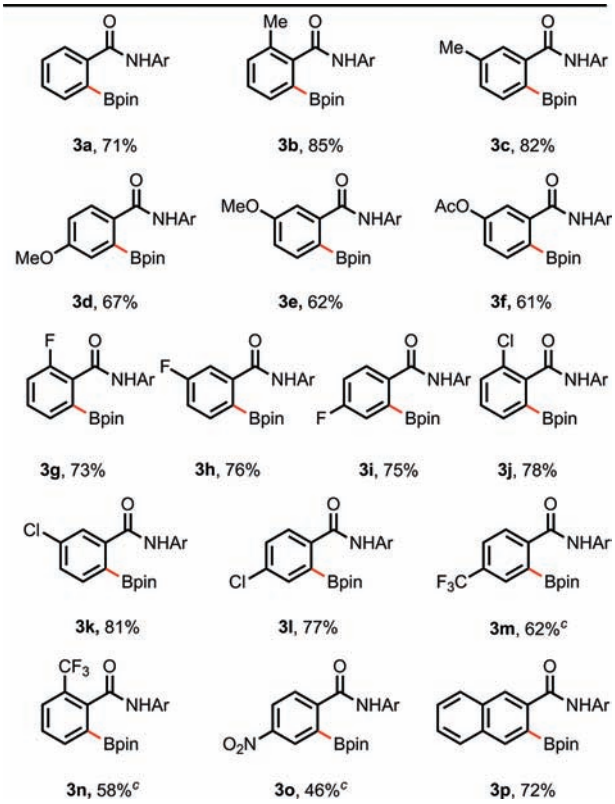
Among various Pd catalysts tested, $Pd_2(dba)_3$ was found to be equally effective as $Pd(OAc)_2$ (Table 1, entry 15). Since the electronic properties of substituents on the aryl groups of dba are known to modulate the Suzuki−Miyaura cross-coupling of organohalides with arylboronic acids,[12] we tested a variety of dba analogues in combination with $Pd(OAc)_2$ to investigate their influence on this reaction (Table 2). While nonsubstituted 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−l**) in yields of 73−81%. The presence of an electron-withdrawing CF_3 group on the arene reduced the yield to 62%

Table 3. Pd-Catalyzed Borylation Reaction of *N*-Arylbenzamides[a,b]



1a-1p, Ar = (4-CF_3)C_6F_4 2 3a-3p



[a]Conditions: **1** (0.1 mmol), **2** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), **L-3** (30 mol %), $K_2S_2O_8$ (0.2 mmol), TsONa (0.15 mmol), CH_3CN (1 mL), 80 °C, 24 h. [b]Isolated yields are shown. [c]**2** (0.3 mmol).

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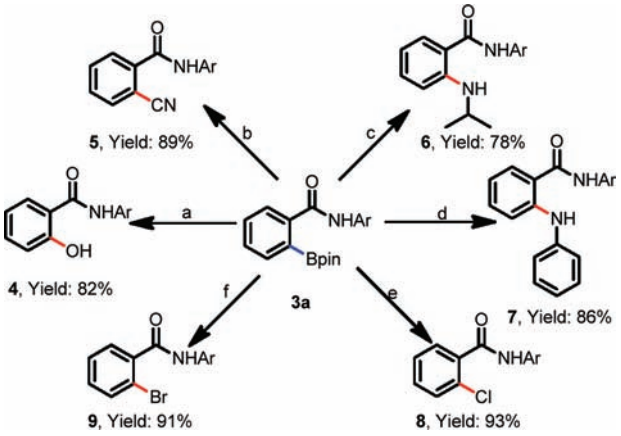
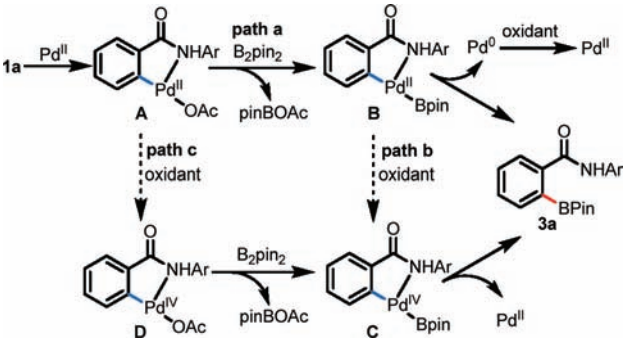
Scheme 2. Versatile Transformations of the Borylated Products[a]



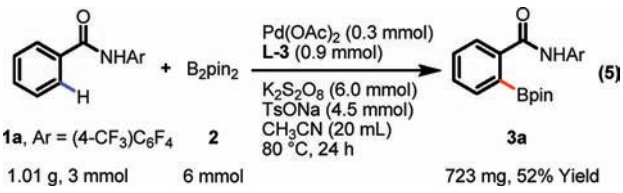
[a]Conditions: (a) **3a** (0.05 mmol), oxone (0.05 mmol) in H_2O (1.0 mL), acetone (1.0 mL), rt, 2 h. (b) **3a** (0.05 mmol), CuCN (0.05 mmol), K_2CO_3 (0.15 mmol), DMF (1.0 mL), 60 °C, 4 h. (c) **3a** (0.05 mmol), isopropylamine (0.06 mmol), $Cu(OAc)_2$ (10 mol %), 4 Å molecular sieves (MS), O_2 (1 atm), CH_2Cl_2 (1.0 mL), 40 °C, 12 h. (d) **3a** (0.05 mmol), aniline (0.06 mmol), $Cu(OAc)_2$ (10 mol %), 4 Å MS, O_2 (1 atm), CH_2Cl_2 (1.0 mL), 40 °C, 12 h. (e) **3a** (0.05 mmol), $CuCl_2$ (0.15 mmol) in H_2O (1.0 mL), CH_3OH (1.0 mL), 90 °C, 24 h. (f) **3a** (0.05 mmol), $CuBr_2$ (0.15 mmol) in H_2O (1.0 mL), CH_3OH (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 monoselectivity (>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 amination[16] 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 ArPdB intermediate **B** (Scheme 3). Subsequent C−B reductive elimination would afford the borylated product (path a) and Pd(0). The effectiveness of $Pd_2(dba)_3$ is consistent with this pathway. Intriguingly, the requirement of a strong oxidant such as $K_2S_2O_8$ 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 acetoxylated 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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