

Base-Free Palladium-Catalyzed Borylation of Aryl Chlorides with Diborons

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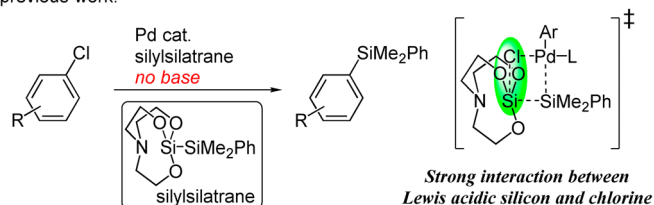
The base-free palladium-catalyzed borylation of aryl chlorides with diborons was achieved. The base-free conditions offered acceptable functional group compatibility. Based on experimental and computational studies, it was shown that smooth boryl transfer from the diborons to the arylpalladium chloride was promoted by strong interaction between the Lewis acidic boron and the chlorine atom on palladium.

Arylboronate esters are versatile reagents for organic synthesis, and they are employed in the preparation of various C–O, C–N, and C–C bonds.^[1] Thus, the development of new methods to synthesize arylboronate esters under mild reaction conditions is important in modern organic chemistry.^[2–19] Accordingly, transition-metal-catalyzed borylation reactions of aryl halides with diborons have emerged as efficient and reliable methods.^[2–4, 5b, 6b, 9f, g, 11] In these catalytic borylation reactions, the presence of a base is essential to activate the diboron for smooth boryl transfer. It would be desirable to develop base-free conditions to achieve the synthesis of arylboronates bearing base-sensitive functional groups.

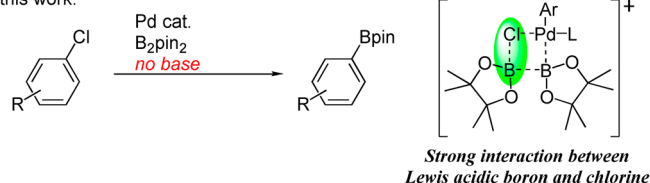
Very recently, we reported the activator-free palladium-catalyzed silylation of aryl chlorides with silylsilatrane, which is a new unsymmetrical disilane having a Lewis acidic silatrane moiety (Scheme 1).^[20] This silylation reaction converts aryl chlorides without the need for a base by taking advantage of the strong interaction between the Lewis acidic silicon and the chlorine atom on the palladium center in the silyl-transfer step. From these results, we envisioned that Lewis acidic diborons could serve as borylating agents under base-free conditions on a mechanistic basis similar to that of silylsilatrane. This is indeed the case, and we describe herein the palladium-catalyzed borylation of aryl chlorides with diborons without the use of any activators.

First, we utilized the reaction conditions of our previous silylation^[20a] for the base-free borylation. Treatment of 4-chloroanisole with B₂pin₂ [bis(pinacolato)diboron, 1.2 equiv.] in the presence of Pd₂(dba)₃ (3 mol%; dba = dibenzylideneacetone)

previous work:



this work:



Scheme 1. Base-free palladium-catalyzed silylation and borylation of aryl chlorides with Lewis acidic bimetallic species.

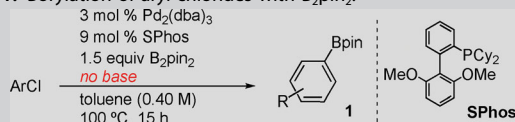
and SPhos (2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, 9 mol%) in toluene at 100 °C (0.33 M) resulted in moderate conversion and afforded the corresponding borylated product in 43% yield. After extensive optimization of the reaction conditions, we discovered that a higher loading of B₂pin₂ (1.5 equiv.), a longer reaction time (15 h), and a higher concentration (0.40 M) led to the highest yield (93%, as determined by NMR spectroscopy) of the desired product (Table 1, entry 1).^[21]

With the optimized conditions in hand, the scope of the borylation reaction was then investigated (Table 1). Interestingly, we applied these base-free conditions to base-sensitive siloxy- and NMeFmoc-substituted aryl chlorides (Fmoc = 9-fluorenylmethoxycarbonyl) without observable deprotection (Table 1, entries 2–4).^[22] As a protecting group of NH₂, phthalimido protection was also tolerated (Table 1, entry 5). Heteroaromatic chlorothiophenes and π -extended chloronaphthalenes also participated in the reaction (Table 1, entries 6–9). Not only *meta*- and *para*-substituted aryl chlorides but also a sterically congested *ortho*-substituted aryl chloride reacted to afford the corresponding products in excellent yields (Table 1, entries 10–12). Electron-deficient substrates such as fluoro-, trifluoromethyl-, ethoxycarbonyl-, and cyano-substituted aryl chlorides reacted smoothly (Table 1, entries 13–16). Unfortunately, our attempts to borylate aryl chlorides bearing acid-sensitive functional groups such as 4-chloroacetophenone, *N*-*tert*-butoxycarbonyl (Boc)-protected 4-chloroaniline, and 4-chlorobenzaldehyde dimethyl acetal failed, probably because of the high Lewis acidity of B-chloropinacolborane. The borylation was efficient enough to borylate 1,4-di- and 1,3,5-trichlorobenzene with a larger amount of the diboron reagent (Scheme 2).

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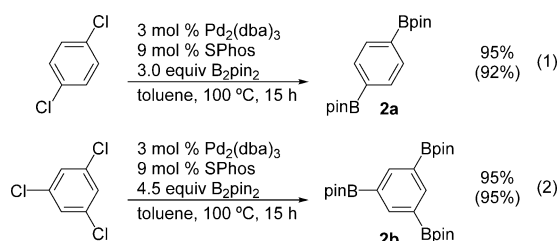
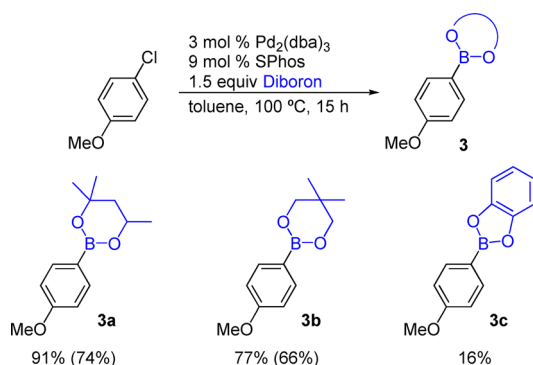
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Table 1. Borylation of aryl chlorides with B_2pin_2 .

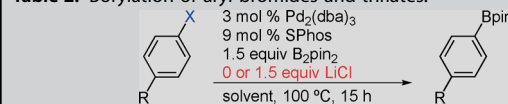
Entry	Ar	1	Yield ^[a] [%]
1	4-MeOC ₆ H ₄	1a	93 (82)
2	4- <i>t</i> BuMe ₂ SiOC ₆ H ₄	1b	92 (86)
3	4-TMSOC ₆ H ₄	1c	87
4	4-FmocMeNC ₆ H ₄	1d	90 (84)
5		1e	96 (91)
6	2-thienyl	1f	90 (79)
7	3-thienyl	1g	86 (76)
8	1-naphthyl	1h	86 (68)
9	2-naphthyl	1i	95 (92)
10 ^[b]	2-MeC ₆ H ₄	1j	83 (82)
11	3-MeC ₆ H ₄	1k	91 (89)
12	4-MeC ₆ H ₄	1l	95 (90)
13	4-FC ₆ H ₄	1m	91 (84)
14	4-F ₃ CC ₆ H ₄	1n	88 (77)
15	4-EtO ₂ CC ₆ H ₄	1o	93 (78)
16	4-NCC ₆ H ₄	1p	94 (92)

[a] Yield was determined by NMR spectroscopy by using 1,1,2,2-tetrachloroethane as an internal standard. Yield of isolated product is given in parentheses and is slightly lower than the corresponding yield determined by NMR spectroscopy owing to the instability of arylboronates on silica gel (see the Supporting Information). [b] $Pd_2(dba)_3$ (5 mol %), SPhos (15 mol %).

**Scheme 2.** Double and triple borylation. Yields of the isolated products are given in parentheses.**Scheme 3.** Scope of the diboron reagents. Yields of the isolated products are given in parentheses.

The scope of the diborons was surveyed (Scheme 3). The reaction proceeded with bis(hexyleneglycolato)diboron to give **3a** in good yield. Bis(neopentyl glycolato)diboron was less reactive yet participated in the borylation with the aid of higher loadings of $Pd_2(dba)_3$ and SPhos. Unfortunately, bis-(catecholato)diboron reacted sluggishly.

Attempted borylation of aryl bromides and triflates (OTf) resulted in sluggish conversions under similar reaction conditions (Table 2, entries 1–4). Similar phenomena were observed

Table 2. Borylation of aryl bromides and triflates.

Entry	R	X	Solvent	LiCl [equiv.]	Yield ^[a] [%]
1	OMe	Br	toluene	0	4
2	OMe	OTf	toluene	0	12
3	CO ₂ Et	Br	toluene	0	1
4	CO ₂ Et	OTf	toluene	0	2
5	OMe	Br	dioxane	1.5	70
6	OMe	OTf	toluene	1.5	79
7	CO ₂ Et	Br	dioxane	1.5	79
8 ^[b]	CO ₂ Et	OTf	toluene	1.5	70

[a] Yield was determined by NMR spectroscopy. [b] $Pd_2(dba)_3$ (5 mol %), SPhos (15 mol %).

in our previous silylation, and we proved that the chloride of the arylpalladium chloride plays a key role in successful silyl transfer to palladium.^[20] To replace the bromide or triflate on the palladium center with chloride after oxidative addition, we added lithium chloride to promote boryl transfer to palladium. The effect of lithium chloride was dramatic in promoting the borylation (Table 2, entries 5–8).^[23,24]

To clarify the positive effect of chloride for boryl transfer, DFT calculations were performed with Gaussian 09.^[25,26] We chose boryl transfer from B_2gly_2 (2,2'-bi-1,3,2-dioxaborolane) to **SM_X** (PhPdX(2-dimethylphosphino-2'-methoxybiphenyl)) as a model reaction for computational simplicity (Figure 1). The oxygen atom on the phosphine ligand in **SM_Cl** weakly coordinates to palladium. Boryl transfer from B_2gly_2 to **SM_Cl** was calculated to proceed concertedly via four-membered transition state **TS_Cl** with an activation barrier of 51.6 kJ mol⁻¹. The lengths of the developing Pd–B bond and the dissociating B–B bond in **TS_Cl** were calculated to be 2.121 and 2.426 Å, respectively. Boryl transfer results in the formation of **Prod_Cl**, in which the chloride atom weakly coordinates to the palladium center and the oxygen atom on the phosphine ligand is dissociated from palladium. The overall reaction is endothermic by 38.8 kJ mol⁻¹. Moreover, the activation energy for boryl transfer from B_2gly_2 to **SM_Br** was calculated to be 80.5 kJ mol⁻¹, and **TS_Br** is more difficult to reach than **TS_Cl** by 28.9 kJ mol⁻¹. The length of the Pd–B bond in **TS_Br** is slightly shorter than that in **TS_Cl** by 0.019 Å, whereas the length of the B–B bond is longer by 0.207 Å. These differences in the bond lengths imply that **TS_Br** is a later transition state than **TS_Cl**. The for-

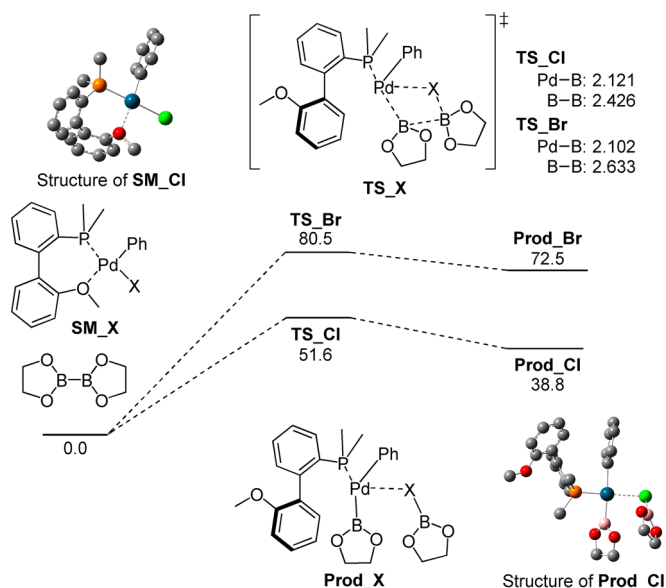
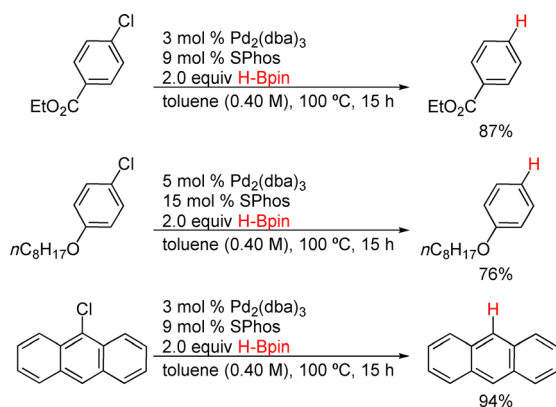


Figure 1. Energy profile of boryl transfer obtained by DFT calculations at the M06-2X/6-31G* + ECP(Pd,P,Cl,Br) level. Energies are in kJ mol^{-1} .

mation of product **Prod_Br** is significantly endothermic (72.5 kJ mol^{-1}), which also correlates with **TS_Br** as a later transition state of higher energy. These results show that the efficient borylation of aryl chlorides is based on an intrinsically strong interaction between the boron and chlorine atoms in the boryl transfer.

We then expected that such a strong boron–chlorine interaction would benefit the base-free reduction of aryl chlorides with pinacolborane (HBpin) by selective hydride transfer. To our delight, palladium-catalyzed hydrodechlorination of electron-deficient, electron-rich, and sterically congested aryl chlorides with HBpin proceeded under conditions similar to those used for borylation with diboron (Scheme 4). To the best of our knowledge, this represents the first example of the base-free palladium-catalyzed hydrodechlorination of aryl chlorides with pinacolborane.^[27]



Scheme 4. Palladium-catalyzed reduction of aryl chlorides with pinacolborane.

In conclusion, we developed the base-free palladium-catalyzed borylation of aryl chlorides with diborons. These borylation reactions allowed the synthesis of arylboronates bearing base-sensitive siloxy and *N*-(9-fluorenylmethoxycarbonyl)-*N*-methyl groups without observable deprotection owing to the absence of a basic activator. Experimental and computational investigations disclosed that the success of the base-free borylation reaction depends on smooth boryl transfer from the diboron reagent to the arylpalladium chloride with the help of the affinity between the chloride atom on the palladium center and the Lewis acidic boron. This concept was applied to the palladium-catalyzed hydrodechlorination of aryl chlorides with pinacolborane. Further studies to realize new base-free reactions are underway in our laboratory.

Acknowledgements

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Keywords: boron • borylation • noncovalent interactions • palladium • transmetalation

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- [21] For details of optimization of conditions, see Table S1 in Supporting Information.
- [22] Admirably, borylations of siloxy- and NMeFmoc-substituted aryl chlorides under Buchwald's protocol using KOAc as a base in Ref. 4c afforded the corresponding borylated products in good yields without observable deprotection.
- [23] This ligand exchange process was confirmed by ³¹P NMR analysis in our previously reported silylation reaction in ref. 20a.
- [24] The borylation of 4-chloroanisole with lithium chloride (1.5 eq) resulted in a lower conversion. This result implies that the chloride ion would not activate the diboron for smooth boron transfer through the formation of chloride-coordinated borate.
- [25] Gaussian 09, rev. C.01, M. J. Frisch, et al., Gaussian, Inc., Wallingford, CT, **2010**. For full citation, see Supporting Information.
- [26] Computational perspectives on the mechanisms of Pd-catalyzed cross-coupling reactions were summarized nicely: a) M. García-Melchor, A. A. C. Braga, A. Lledós, G. Ujaque, F. Maseras, *Acc. Chem. Res.* **2013**, *46*, 2626; b) L. Xue, Z. Lin, *Chem. Soc. Rev.* **2010**, *39*, 1692; c) M. Sumimoto, N. Iwane, T. Takahama, S. Sakaki, *J. Am. Chem. Soc.* **2004**, *126*, 10457. Also see: ref. 4c.
- [27] Palladium-catalyzed hydrodeiodination of aryl iodide with pinacolborane in the presence of base was reported in ref. 7a.

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**Base-Free Palladium-Catalyzed
Borylation of Aryl Chlorides with
Diborons**



B that as it may: The base-free palladium-catalyzed borylation of aryl chlorides with diborons is achieved. The base-free conditions offer acceptable functional group compatibility. Based on experimental and computational

studies, it was shown that smooth boryl transfer from the diborons to the aryl-palladium chloride is promoted by strong interaction between the Lewis acidic boron and the chlorine atom on palladium.