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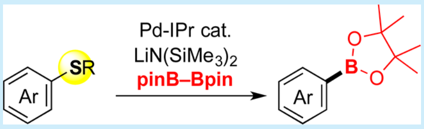
Palladium-Catalyzed *ipso*-Borylation of Aryl Sulfides with Diborons

M. Bhanuchandra, Alexandre Baralle, Shinya Otsuka, Keisuke Nogi, Hideki Yorimitsu,* and Atsuhiro Osuka

Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo-ku, Kyoto 606-8502, Japan

Ⓢ *Supporting Information*

ABSTRACT: A catalytic Miyaura-type *ipso*-borylation of aryl sulfides with diboron reagents has been achieved, providing arylboronate esters of synthetic use. The key conditions to transform inherently reluctant C−S bonds into C−B bonds include a palladium-NHC (N-heterocyclic carbene) precatalyst, bis(pinacolato)diboron, and lithium hexamethyldisilazide. This protocol is applicable to a reasonable range of aryl alkyl sulfides. Twofold borylation was observed in the reaction of diphenyl sulfide.



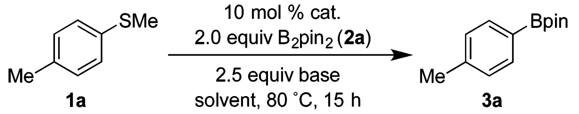
Due to the tremendous versatility of organoboron compounds not only as reagents but also as functional materials and bioactive agents by themselves, new protocols for constructing C−B bonds have long been actively developed.[1] Among them, the Miyaura *ipso*-borylation of aryl halides or pseudohalides represents an important tool.[2,3] While aryl bromides, iodides, and triflates have been widely used as electrophilic partners in this catalytic borylation, less reactive aryl chlorides are now available with the help of electron-rich transition metal catalysts.[4] Further research has now realized catalytic *ipso*-borylation of aryl fluorides[5] and aryl ethers[6] bearing very strong C−F and C−O bonds, respectively.

Aryl sulfides are found widely in nature as well as useful as synthetic intermediates and final products, thus occupying a unique position in organic chemistry.[7] While aryl sulfides may be regarded as surrogates for aryl halides in transition-metal-catalyzed substitution reactions, they have received much less attention.[8,9] This undeveloped situation would be surprising when one considers that aromatic C−S bonds are strong, yet weaker than the corresponding C−F and C−O bonds.[10] Instead, the reluctance of aryl sulfides to catalytic substitution reactions would be explained by the broad recognition that sulfur-containing substrates can serve as catalyst poisons. Even worse, concomitantly formed thiolate anions are much more poisonous.[11] A strong affinity between a transition metal center and the anionic thiolate moiety in an oxidative adduct renders the key transmetalation step highly challenging.

As a part of our research interest in catalytic C−S bond cleavage,[12] we envisioned transforming aryl sulfides to arylboronate esters of synthetic versatility. By overcoming unfavorably strong interactions of organosulfur species with transition metals as well as catalyst deactivation, here we report Miyaura-type catalytic *ipso*-borylation of aryl sulfides.[13]

As a model reaction, the palladium-catalyzed borylation reaction of methyl *p*-tolyl sulfide (**1a**) with bis(pinacolato)-diboron (**2a**, B_2pin_2) was selected (Table 1). To avoid dissociation of ligands on palladium, which results in catalyst deactivation, we chose highly coordinating N-heterocyclic carbenes (NHCs) as promising ligands. Furthermore, to facilitate smooth boryl transfer to reluctant arylpalladium methanethiolate, we presumed the choice of the activator would be crucial. We thus focused on screening Pd-NHC precatalysts and basic activators. As selectively summarized in Table 1, in the presence of $LiN(SiMe_3)_2$ as an activator, a series of palladium precatalysts bearing *N*-2,6-diisopropylphenyl groups (Figure 1) exhibited promising results (entries 1−5).[14,15] Among them, Pd-PEPPSI-IPr[14c−e] was found to be optimal, providing the borylated product **3a** in 81% isolated yield (entry 5). The choice of $LiN(SiMe_3)_2$ is of decisive importance: other hexamethyldisilazides such as the sodium or potassium analogues were far less effective (entries 6 and 7). Other lithium bases including LiO*t*Bu and LiF were totally ineffective (entries 8 and 9). The reactions in other ethereal solvents such as dioxane and 1,2-dimethoxyethane

Table 1. Optimization of Borylation Conditions[a]



entry	catalyst	base	solvent	yield /%[b]
1	SingaCycle-A1	$LiN(SiMe_3)_2$	THF	28
2	SingaCycle-A3	$LiN(SiMe_3)_2$	THF	62
3	[IPrPdCl(π-allyl)]	$LiN(SiMe_3)_2$	THF	64
4	Pd-PEPPSI-SIPr	$LiN(SiMe_3)_2$	THF	75
5	Pd-PEPPSI-IPr	$LiN(SiMe_3)_2$	THF	81[c]
6	Pd-PEPPSI-IPr	$NaN(SiMe_3)_2$	THF	3
7	Pd-PEPPSI-IPr	$KN(SiMe_3)_2$	THF	22
8	Pd-PEPPSI-IPr	LiO*t*Bu	THF	0
9	Pd-PEPPSI-IPr	LiF	THF	0
10	Pd-PEPPSI-IPr	$LiN(SiMe_3)_2$	dioxane	33
11	Pd-PEPPSI-IPr	$LiN(SiMe_3)_2$	DME	59
12	Pd-PEPPSI-IPr	$LiN(SiMe_3)_2$	toluene	8

[a] The reaction was carried out with 0.5 mmol of **1a**. [b] Determined by ^1H NMR experiments using $(CHCl_2)_2$ as an internal standard. [c] Isolated yield.

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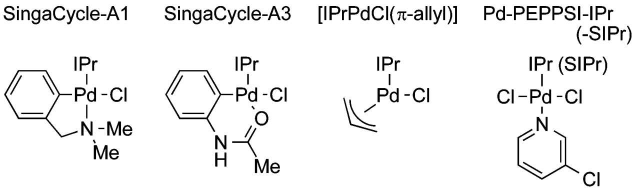
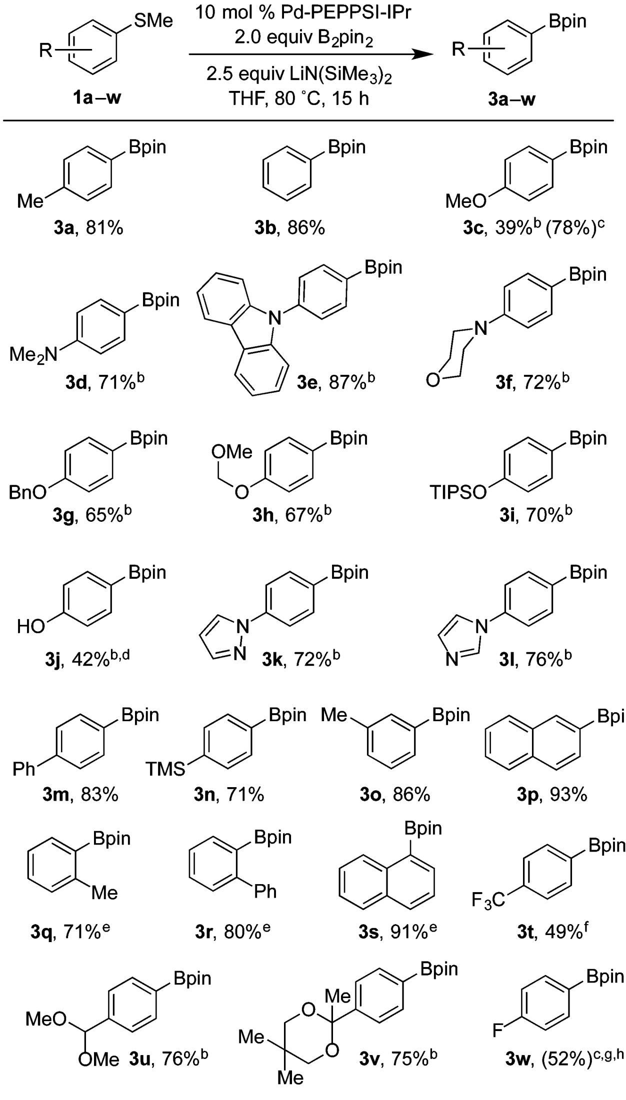


Figure 1. Palladium precatalysts employed in Table 1 (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene; SIPr = 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene).

(DME) gave **3a** in lower yields (entries 10 and 11). Less polar and noncoordinating toluene was an inappropriate solvent (entry 12).

With the optimized conditions (entry 5 in Table 1) in hand, the scope of aryl sulfides was surveyed (Scheme 1). Electronically neutral *para*-substituted aryl sulfides **1a**, **1b**, and **1m** reacted smoothly. Electron-rich sulfides **1c–l** required a larger amount (15 mol %) of the palladium precatalyst and a longer reaction time of 24 h to achieve full conversions. Notably, typical protecting groups such as benzyl, methoxymethyl, and triisopropylsilyl (TIPS) groups in **3g–i** survived under the basic conditions. With 4.5 equiv of $LiN(SiMe_3)_2$, unprotected hydroxythioanisole (**1j**) was borylated, albeit in moderate yield. The azole units in **1k** and **1l** survived under the reaction conditions and did not suppress the borylation. Notably, the borylation proceeded with sterically demanding substrates, including *o*-phenylated thioanisole **1r**, to yield **3q–s** in high yields after 24 h. This offers an advantage for synthetic chemistry because *ortho*-substituted aryl sulfides can be readily synthesized by *ortho*-lithiation of thiophenols.[16] A strongly electron-withdrawing trifluoromethyl group retarded the reaction to yield **3t** in fair yield. While electron-withdrawing carbonyl groups are not compatible under the basic conditions, acetal protections were compatible to obtain **3u** and **3v** in good yields. Unfortunately, carbonyl functionalities including an amide group were not compatible with the borylation conditions. The reaction of 4-$PhCON(Me)C_6H_4SMe$ afforded not only the desired product 4-$PhCON(Me)C_6H_4Bpin$ but also debenzoylated product (4-$MeNHC_6H_4Bpin$) in ca. 20% NMR yields for both (not shown in Scheme 1). Although *para*-fluorinated aryl sulfide **1w** afforded the desired product **3w** in moderate yield, a diborylated compound was also formed in 19% yield through the borylation of the C–F bond. When 4-ClC_6H_4SMe was employed, a mixture of the desired product (4-ClC_6H_4Bpin, 23% NMR yield) and diborylated product (27% NMR yield) was obtained (not shown in Scheme 1). Methyl 2-, 3-, and 4-pyridyl sulfides afforded no borylated products, and the starting materials were decomposed in all cases. Instead of an aryl sulfide, attempted borylation of benzyl methyl sulfide (BnSMe) gave a complex mixture.

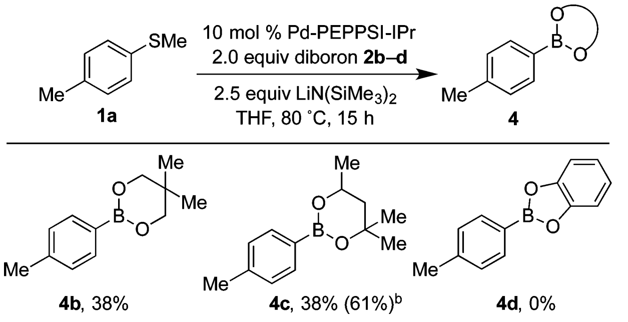
Scheme 1. Palladium-Catalyzed Borylation of Aryl Sulfides with B_2pin_2[a]



[a]Isolated yield. [b]15 mol % Pd-PEPPSI-IPr, 24 h. [c]NMR yield. [d]4.5 equiv of $LiN(SiMe_3)_2$. [e]Reaction time: 24 h. [f]Reaction time: 10 h. [g]Reaction time: 48 h. [h]Diborylated product (4-$pinBC_6H_4Bpin$) was formed in 19% yield.

As the borylating agent, bis(pinacolato)diboron (B_2pin_2) was the best (Scheme 2): Bis(neopentyl glycolato)diboron (**2b**) and bis(hexylene glycolato)diboron (**2c**) were less reactive to give the corresponding *p*-tolylboronate esters **4b** and **4c** in 38% yields, respectively. No borylation took place with bis(catecholato)diboron (**2d**).

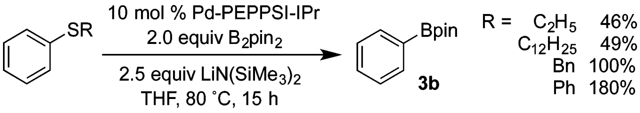
Scheme 2. Scope of Diborons[a]



[a]Isolated yield. [b]NMR yield.

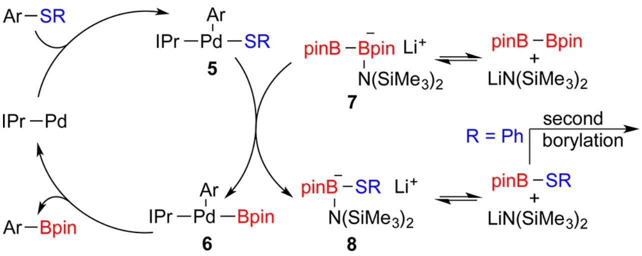
Next we turned our attention to the effect of the leaving sulfanyl groups in the aryl sulfides (Scheme 3, yields determined by NMR). Ethylsulfanyl and dodecylsulfanyl groups were found to be inferior to methylsulfanyl as leaving groups probably because of the more electron-donating character of longer alkyl chains. Benzylsulfanyl showed high leaving group ability, owing to the electron-withdrawing nature

Scheme 3. Effect of Sulfanyl Leaving Groups



of the phenyl ring. Interestingly, a 180% yield of **3b** was obtained when diphenyl sulfide was used as a substrate. This result suggests that the leaving benzenethiolate species should undergo the second borylation with another equivalent of B_2pin_2.

Scheme 4. Plausible Catalytic Cycle



A plausible mechanism is outlined in Scheme 4. The main catalytic cycle can follow the accepted mechanism. The most difficult boryl transfer to **5** would be accomplished by the high reactivity of borate **7**.[17] Considering the bulky structures of pinacolatoboryl and hexamethyldisilazide and the fact that large excesses of diboron and $LiN(SiMe_3)_2$ were necessary, we presume that there would be a dissociation equilibrium of **7**, and **7** would be involved into the boryl transfer with **5**. After the boryl transfer, the resulting thiolate species **8** can dissociate into $LiN(SiMe_3)_2$ and pinB−SR. When R is a phenyl group, the latter would then undergo the second borylation with another equivalent of B_2pin_2 by using $pinB-S^-$ as a good leaving group.

We attempted one-pot Suzuki−Miyaura coupling by adding an aryl iodide or bromide after the borylation reaction. However, no expected biaryl product was obtained. A generated methanethiolate anion through the borylation step would hamper the Suzuki−Miyaura coupling reaction.

In conclusion, we have developed an *ipso*-borylation of inherently reluctant aryl sulfides with diboron under Pd-NHC catalysis. The combined use of a Pd-NHC precatalyst and $LiN(SiMe_3)_2$ is crucial to achieve this borylation. This protocol showed a reasonably wide substrate scope. Twofold borylation was observed in the reaction of diphenyl sulfide, which indicates the reaction mechanism that should involve the eventual formation of pinacolatoboryl thiolate species. Further catalytic transformations of organosulfur compounds are under active investigation in our group.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01305.

Experimental details, characterization data, and NMR spectra of the products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yori@kuchem.kyoto-u.ac.jp.

Notes

The authors declare no competing financial interest.

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(15) Further optimization data is shown in Table S1 in the Supporting Information (SI).

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