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Rh-Catalyzed *Ortho*-Selective C−H Borylation of *N*-Functionalized Arenes with Silica-Supported Bridgehead Monophosphine Ligands

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Supporting Information

ABSTRACT: Supported phosphine-Rh systems, prepared in situ from silica-supported bridgehead monophosphines and $[Rh(OH)(cod)]_2$, have enabled *ortho*-selective C−H borylation for a range of arenes containing nitrogen-based directing groups. The regioselectivity was excellent with various *N*-directing groups, including saturated and unsaturated *N*-heterocycles, *tert*-aminoalkyl groups, and imine-type C−N double bonds. The reaction showed significant tolerance toward steric repulsion around the reacting C−H bond. This Rh catalysis complements the Ir-catalyzed *ortho*-borylation, which is effective for arenes with oxygen-based directing groups.

Arylboronic acids and their derivatives are versatile synthetic intermediates.[1] Among the routes to arylboronic acid derivatives, direct C−H borylation of arenes is the most straightforward and attractive.[2−4] In fact, Ir-catalyzed borylations of arenes with bis(pinacolato)diboron or pinacolatoborane have found wide applications in many fields.[1] While the original Ir-catalyzed borylations showed regioselectivities controlled by steric effects that directed the borylation to positions distal to a substituent,[3] Ir-catalyzed *ortho*-selective borylations have also been developed: Hartwig and co-workers introduced a new *ortho*-directing group, a dialkylhydrosilyl group tethered to an aromatic ring, for Ir catalysis with a 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy) ligand;[5] Ishiyama, Miyaura, and co-workers described *ortho*-borylation of benzoate derivatives catalyzed by the $[3,5\text{-}(CF_3)_2\text{-}C_6H_3]_3P$-Ir system;[6] and our group developed a silica-supported catalyst system that allowed *ortho*-borylation of a wide range of arenes with different directing groups, such as CO_2R, $CONMe_2$, SO_3Me, $CH[O(CH_2)_3O]$, CH_2OMOM, and $OCONEt_2$, as well as a Cl atom.[7] Despite these efforts, nitrogen-based functional groups such as *N*-heterocycles and imino groups have not been used as directing groups.[8]

Herein, we report that immobilized phosphine-Rh systems (P/Rh 1:1), prepared from silica-supported bridgehead monophosphines (Silica-SMAP[9,10] and Silica-TRIP,[11,12] Figure 1) and $[Rh(OH)(cod)]_2$, have enabled *ortho*-selective C−H borylation for a wide range of arenes containing different nitrogen-based directing groups. Furthermore, the reaction showed significant tolerance toward steric hindrance around the reacting C−H bond. Although Rh-catalyzed arene borylations have been described in the literature,[4] they have not been widely applied to organic synthesis because they need relatively harsh reaction conditions compared with the Ir-dtbpy catalytic system.

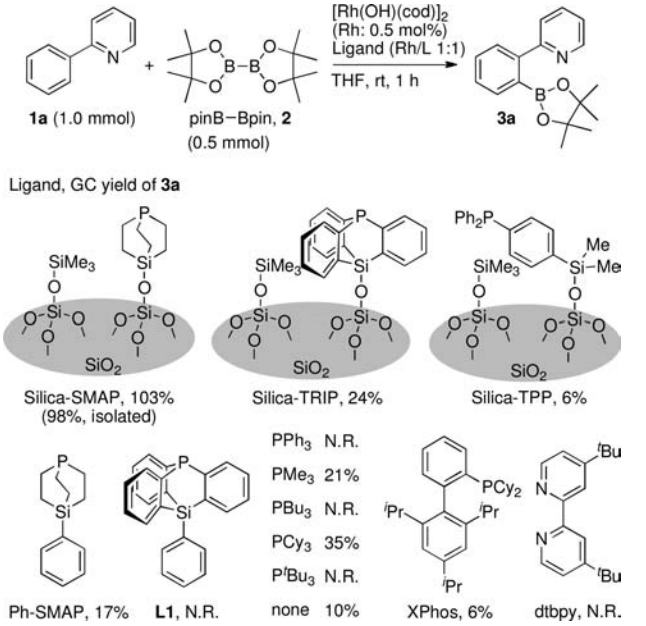


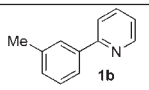
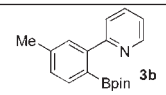
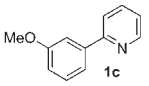
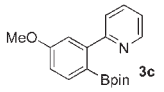
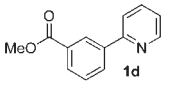
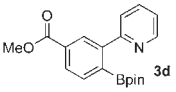
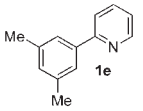
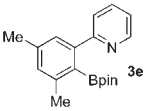
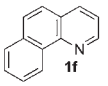
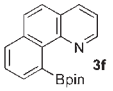
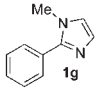
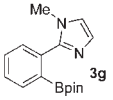
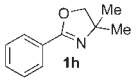
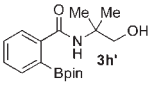
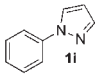
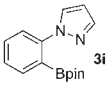
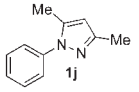
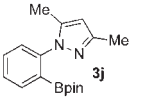
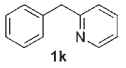
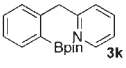
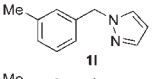
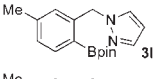
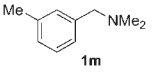
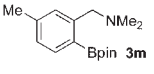
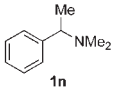
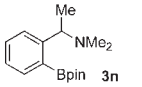
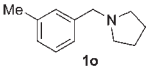
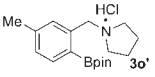
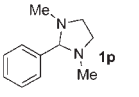
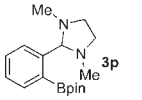
Figure 1. Ligand effects in Rh-catalyzed *ortho*-selective C−H borylation of 2-phenylpyridine (**1a**) with bis(pinacolato)diboron **2**. Conditions: **1a**, 1.0 mmol; **2**, 0.5 mmol; $[Rh(OH)(cod)]_2$ (Rh, 0.0025 mmol); ligand (P, dtbpy, 0.0025 mmol); THF, 1.0 mL; rt, 1 h. Yields based on **2** were determined by GC analysis.

In addition, Rh catalysts have concomitant benzylic borylation activity toward alkylarenes, which is predominant in some cases.[3b,4b,4c]

Ligand effects for Rh-catalyzed borylation of 2-phenylpyridine (**1a**) are summarized in Figure 1. With the immobilized catalyst prepared in situ from Silica-SMAP (0.5 mol%) and $[Rh(OH)(cod)]_2$ (0.5 mol% Rh) (P/Rh 1:1), which appeared to be the most active system, reaction of **1a** (1.0 mmol, 2 equiv relative to **2**) and bis(pinacolato)diboron (pinB-Bpin, **2**, 0.5 mmol) in THF proceeded smoothly at room temperature, and **2** was consumed completely within 1 h to afford the corresponding *ortho*-borylation product **3a** in 103% GC yield based on **2**.[13−16] Neither *meta* nor *para* isomers were detected in the crude mixture. The pyridine ring was not borylated, and no 2′,6′-diborylation occurred. The yield in excess of 100% indicated that byproduct pinB-H also functioned as a reagent, but its reactivity was much lower than that of **2**.[17] To our surprise, *ortho*-borylation occurred

Received: September 5, 2011
Published: November 02, 2011

Table 1. Silica-SMAP-Rh-Catalyzed *Ortho*-Selective C−H Borylation of Arenes 1 Containing a Nitrogen-Based Functional Group with Bis(pinacolato)diboron 2[a]

Entry	Substrate 1	Product 3	Temp. (°C)	Time (h)	Yield[b] (%)
1	 1b	 3b	rt	8	95 (75)[c]
2	 1c	 3c	rt	9	101 (94)[c]
3[d]	 1d	 3d	40	2	99 (96)
4	 1e	 3e	60	1	107 (102)
5[d]	 1f	 3f	rt	6	94 (90)
6	 1g	 3g	rt	1	102 (100)
7[e]	 1h	 3h'	rt	0.5	76 (63)[f,g]
8	 1i	 3i	rt	3	99 (85)[g]
9[e]	 1j	 3j	85	12	126 (117)[g]
10	 1k	 3k	rt	2	109 (96)[g]
11[e]	 1l	 3l	40	4	83[h]
12[d,e]	 1m	 3m	70	1	99 (99)
13[d]	 1n	 3n	40	6	99 (70)
14[d,e]	 1o	 3o'	70	6	99 (93)[i]
15	 1p	 3p	40	0.5	92 (92)[g]

[a] Conditions: **1**, 1.0 mmol; **2**, 0.5 mmol; $[Rh(OH)(cod)]_2$ (Rh, 0.0025 mmol); Silica-SMAP (P, 0.0025 mmol); THF, 1.0 mL. [b] NMR yield (isolated yield in parentheses). [c] Yield for a mixture of isomers: C6′/C2′ 46:1 (entry 1) and 17:1 (entry 2). [d] 1.0 equiv of **1** was used. [e] $[Rh(OMe)(cod)]_2$ and hexane were used in place of $[Rh(OH)(cod)]_2$ and THF. [f] Yield of **3h** determined by NMR. The borylation product was isolated as amide **3h′** (isolated yield in parentheses). [g] Bis-*ortho*-borylation product was detected in the crude mixture: entry 7, 13%; entry 8, 9%; entry 9, 6%; entry 10, 4%; entry 15, 4%. [h] Crude product was a mixture of **3l** (83%), a pyrrazole ring borylation product (22%), and a diborylation product (13%). [i] Yield of **3o** determined by NMR. The borylation product was isolated as hydrochloride salt **3o′**.

even in the absence of a phosphine ligand with exclusive regioselectivity, but the yield was as low as 10% under otherwise identical conditions.[18] The supported triptycene-type bridgehead triarylphosphine (Silica-TRIP hereafter) gave **3a** in only 24% yield. The immobilized but unconstrained triphenylphosphine-type ligand (Silica-TPP)[19] was not effective (6% yield). In contrast to these immobilized ligands, the corresponding homogeneous ligands, Ph-SMAP, **L1**, and PPh_3, induced little or no borylation activity, indicating the importance of phosphine immobilization. Other homogeneous ligands with different steric and electronic natures were also tested. Among those, only PMe_3 and PCy_3 showed some acceleration effects, as judged from the product yields (21% and 35%, respectively), which are higher than the yields obtained in the absence of a ligand.[20] The sterically demanding and electron-rich phosphine XPhos inhibited the reaction, and no reaction occurred with PBu_3, P^tBu_3, and the *N*,*N*-chelating ligand dtbpy.

The Silica-SMAP-Rh catalyst system was applicable to various derivatives of **1a** with different substitution patterns. Furthermore, a wide range of nitrogen-based functional groups appeared to be suitable directing groups. The results are listed in Table 1. Substitution at the 3′-position of 2-phenylpyridine with electron-donating Me or MeO groups did not affect the reactivity of the C−H bond at the *para* position (entries 1 and 2). In turn, an electron-withdrawing CO_2Me substituent slightly reduced the reactivity, but the reaction proceeded smoothly at 40 °C (entry 3). A few features are to be noted for the reactions of monosubstituted 2-phenylpyridines **1b**−**d**: (1) borylation occurred predominantly (≥95:5) at the less hindered position *ortho* to the directing group; (2) the CO_2Me group did not deliver the boron atom to its *ortho* position, whereas it was the strongest directing group in Ir-catalyzed *ortho*-borylation with Silica-SMAP ligand; and (3) no benzylic borylation was observed in the reaction of **1b** despite using the Rh catalyst.[3b,4b,4c]

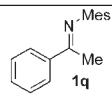
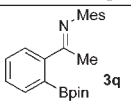
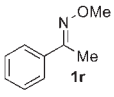
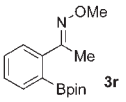
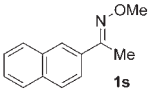
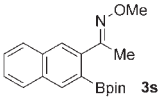
Remarkably, 3′,5′-dimethyl-2-phenylpyridine (**1e**) was a suitable substrate despite the considerable steric hindrance around the reacting C−H bonds. The reaction proceeded smoothly under mild heating conditions (Table 1, entry 4). In contrast, almost no reaction occurred with PCy_3 under the same conditions (data not shown). The borylation of benzo[*h*]quinoline (**1f**) proceeded at room temperature in the same fashion (entry 5).

Unsaturated five-membered *N*-heterocycles featuring a metal-coordinating sp^2 nitrogen atom, such as imidazole, oxazoline, and pyrazole, were also suitable directing groups, as shown in Table 1, entries 6−9. Reaction of 1-methyl-2-phenylimidazole (**1g**) proceeded smoothly at room temperature (entry 6). Reaction of 2-phenyl-5,5-dimethyloxazoline (**1h**) proceeded cleanly at 40 °C, but the borylation product was prone to hydrolyze into amide **3h′**.[21] A pyrazole ring was also a suitable directing group, as shown in the successful conversion of **1i**, despite having potentially reactive heteroaromatic C−H bonds (entry 8). Disubstitution at the 3- and 5-positions of the pyrazole resulted in a significant decrease in reactivity, but borylation did occur at higher temperature (85 °C) (entry 9). Combined with the results from the substituted oxazoline derivative **1h**, successful conversion of the substituted pyrazole **1j** is indicative of a significant tolerance of the Silica-SMAP-Rh system toward sterically demanding directing groups.

The pronounced efficacy of the Silica-SMAP-Rh system enabled *ortho*-borylation of arenes with more flexible directing groups with a distal nitrogen atom. In particular, 2-benzylpyridine (**1k**) and 1-(3-methylbenzyl)pyrazole (**1l**) underwent borylation at room temperature and 40 °C, respectively (Table 1, entries 10 and 11).

dx.doi.org/10.1021/ja208364a |*J. Am. Chem. Soc.* 2011, 133, 19310–19313

Table 2. Rh-Catalyzed *Ortho*-Selective C−H Borylation of Arenes 1 Containing an Imine-Type Functional Group[a]

Entry	Substrate 1	Product 3	Ligand	Temp. (°C)	Time (h)	Yield[b] (%)
1	 1q	 3q	Silica-SMAP	40	6	106 (91)
2			Silica-TRIP	40	5	134
3			PCy_3	40	6	35
4	 1r	 3r	Silica-SMAP	rt	12	15[c]
5			Silica-TRIP	rt	12	102 (90)[d]
6			PCy_3	rt	12	35[e]
7	 1s	 3s	Silica-TRIP	40	5	108 (105)

[a] Conditions: **1**, 1.0 mmol; **2**, 0.5 mmol; $[Rh(OH)(cod)]_2$ (Rh, 0.0025 mmol); ligand (P, 0.0025 mmol); THF, 1.0 mL. [b] NMR yield (isolated yield in parentheses). [c] Low yield of **3r** is due to 2,6-diborylation (19% GC yield) and substantial C=N reduction of **3r**. [d] Diborylation was detected in the crude mixture (19%). [e] 2,6-Diborylation and C=N reduction of **3r** were observed (1% and 5%, respectively).

The reaction of **1k** with PCy_3 afforded only a trace amount of **3k** (data not shown). It should be noted that these types of directing groups have rarely been employed in catalytic C−H functionalizations.[22]

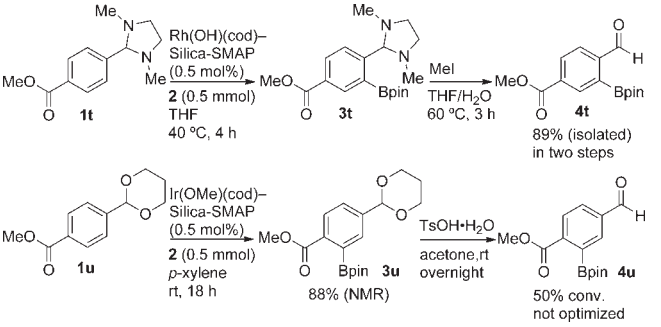
The scope of *ortho*-borylation has further been extended to reaction of arenes with directing groups based on an sp^3 nitrogen atom (Table 1, entries 12−15). This type of directing group has rarely been used in catalytic C−H functionalizations.[23] Specifically, *N*,*N*-dimethylbenzylamine (**1m**,**n**) and *N*-benzylpyrrolidine (**1o**) derivatives as well as 1,3-dimethyl-2-phenylimidazolidine (**1p**) underwent borylation under mild conditions. Importantly, the imidazolidine in **1p** can function as a protecting group for aldehydes (*vide infra*).

We also examined various imine-type functional groups for their suitability as directing groups. It appeared in the initial experiments that concomitant C=N reduction with pinB-H was problematic, but the undesired reaction can be prevented by the choice of *N*-substituents and/or ligands. The results are summarized in Table 2. Specifically, *N*-mesityl acetophenone imine (**1q**) was cleanly converted with Silica-SMAP ligand into the corresponding arylboronate (**3q**, entry 1). Interestingly, we found that borylation of imine **1q** was more efficiently promoted by the Rh complex with the triptycene-type ligand, Silica-TRIP, than by the Silica-SMAP complex (entry 2). The soluble phosphine PCy_3 was also useful for this transformation, but with lower catalytic efficacy (entry 3).

The oxime methyl ether in **1r** also worked as a directing group for *ortho*-borylation, but C=N reduction was significant when Silica-SMAP was used as a ligand (Table 2, entry 4). To our delight, the side reaction could be completely inhibited by the use of Silica-TRIP without changing the high *ortho*-borylation activity (entry 5). The use of PCy_3 resulted in a low yield of **3r** and concomitant reduction of the C=N bonds of **1r** and **3r** (entry 6). Borylation of 2-acetylnaphthalene oxime ether (**1s**) with Silica-TRIP ligand occurred regioselectively at the C3-position (entry 7).

Scheme 1 illustrates the synthetic utility of the complementary catalytic activities of Silica-SMAP-Rh and previously described Silica-SMAP-Ir systems.[7] Thus, we prepared the imidazolidine derivative **1t** and the cyclic acetal **1u** by protecting the aldehyde moiety of methyl 4-formylbenzoate in different ways. Borylation of **1t** with Silica-SMAP-Rh occurred at the position *ortho* to the nitrogen-based directing group with exclusive regioselectivity to afford the boronate **3t**. Subsequent deprotection furnished the 3-borylated 4-formylbenzoate **4t**. On the other hand, Ir-catalyzed borylation of benzoate **1u** with the acetal moiety occurred at the position *ortho* to the ester substituent, again with complete regioselectivity. The resulting arylboronate **3u** was transformed into the 2-borylated 4-formylbenzoate **4u**. Regioselective synthesis of these isomeric arylboronates would be difficult with other methods. This regioselectivity was enabled by the complementary catalytic natures of the supported Rh and Ir catalyst systems combined with their broad substrate scopes.[24]

Scheme 1. Complementary Use of Silica-SMAP-Rh and Silica-SMAP-Ir Systems for Regioselective Borylation of Bifunctional Arenes



Although elucidating the mechanism of the supported phosphine-Rh catalysis demands further studies such as surface analyses and kinetic studies, the critical importance of phosphine immobilization strongly suggests that a rhodium complex that binds only one phosphorus atom provides a vacant coordination site for the nitrogen atom of the directing group. We previously established that each P center of Silica-SMAP independently binds to a Rh center to form a mono(phosphine)-Rh complex selectively; i.e., two or more P centers are not capable of binding to the same Rh center.[9a,b] In fact, the catalytic activity of Silica-SMAP for borylation of **1a** was maintained even when Silica-SMAP was 2 equiv relative to Rh, while addition of 1 equiv of Ph-SMAP to the Silica-SMAP-Rh (P/Rh 1:1) system severely inhibited borylation (23% yield).

The superiority of the constrained phosphines, Silica-SMAP and Silica-TRIP, over unconstrained PPh_3-type immobilized ligand Silica-TPP suggests that reactions of a Silica-TPP-Rh complex encounter significant steric hindrance on the silica surface. This assumption is reasonable because the degree of freedom is higher in Silica-TPP than in the constrained ligands. To shed light on the origins of the differences in the ligand effects of Silica-SMAP and Silica-TRIP, more structure−activity relationship studies must be performed.

In summary, supported bridgehead phosphine-Rh systems have enabled *ortho*-selective C−H borylation of a range of arenes containing nitrogen-based directing groups.[25−27] The regioselectivity was excellent with various *N*-directing groups, and the reaction showed significant tolerance toward steric hindrance around the reacting C−H bond and in the directing groups. This Rh catalysis complements the substrate scope of the Ir-catalyzed *ortho*-borylation, which is effective for arenes with oxygen-based directing groups.

■ ASSOCIATED CONTENT

Supporting Information. Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

This work was supported by Grants-in-Aid for Scientific Research on Innovative Areas "Organic Synthesis Based on Reaction Integration" and a Global COE grant (Project No. B01: Catalysis as the Basis for Innovation in Materials Science), MEXT. S.K. thanks JSPS for scholarship support.

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(13) Other transition metal catalysts based on Ir, Pd, and Pt were not effective under these conditions. See Supporting Information for the screening of metal sources.

(14) Silica-SMAP-Rh catalyst was easily separated from the products by filtration through Celite. Attempts to reuse the catalyst were unsuccessful.

(15) With 1 equiv of **1a**, borylation under otherwise the same conditions afforded **3a** (97%) and 2′,6′-diborylation product (3%).

(16) After the reaction, 1 equiv of pinB-H was detected in the crude mixture by ^{1}H NMR.

(17) Borylation of **1a** with pinB-H proceeded at 60 °C (12 h, 71%).

(18) Reaction under phosphine-free conditions was complete in 12 h to afford **3a** in 106% GC yield. Thus, $[Rh(OH)(cod)]_2$ itself is an effective catalyst precursor for borylation of **1a**. However, the substrate scope of the phosphine-free Rh catalysis appeared to be quite narrow. See Supporting Information for the reaction of various substrates with the phosphine-free Rh catalyst system.

(19) See Supporting Information for the synthesis of Silica-TPP. Details will be reported elsewhere.

(20) See Supporting Information for the reaction of various substrates with the Rh-PCy_3 catalyst system.

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