

Synthesis of Primary and Secondary Alkylboronates through Site-Selective C(sp³)-H Activation with Silica-Supported Monophosphine-Ir Catalysts

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S Supporting Information

ABSTRACT: The site-selective activation and borylation of unactivated C(sp³)-H bonds in 2-alkylpyridines to form primary and secondary alkylboronates was achieved using silica-supported monophosphine-Ir catalysts. This borylation occurs selectively at C-H bonds located γ to the pyridine nitrogen atom. The site-selectivity of this reaction suggests that the C-H bond cleavage occurs with the assistance of a proximity effect due to N-to-Ir coordination.

The transition metal catalyzed direct borylation of unactivated C(sp³)-H bonds offers a versatile and efficient strategy for the synthesis of alkylboronates,¹⁻⁵ which are useful intermediates in organic synthesis.⁶ Pioneering work by the Hartwig group has shown that metal-boryl catalysts based on Re,^{2a} Rh^{2b-d,f} and Ru^{2e} complexes allow the preparation of primary alkylboronates from alkanes through activation of primary C-H bonds at terminal sites on the alkane. The selectivity of this process is controlled by the steric properties of the substrate molecule and hence precludes the efficient borylation of secondary C-H bonds.

Recently, the Hartwig group, as well as our own group, disclosed different catalyst systems that allow the borylation of secondary C(sp³)-H bonds within heterocyclic compounds.^{2g,h} Hartwig et al. used a phenanthroline-Ir system for the borylation of C-H bonds located β to the oxygen atoms of cyclic ethers.^{2g} Our group employed a silica-supported triptycene-type monophosphine-Rh catalyst system (Silica-TRIP-Rh) for the borylation of C-H bond located α to the nitrogen atom of amide, urea and aminopyridine derivatives.^{2h} As a related study, Ohmura, Suginome and co-workers reported more recently Ir-catalyzed C(sp³)-H borylation at the methyl groups of methylchlorosilanes.²ⁱ Although these methods demonstrate a significantly expanded substrate scope, no catalyst has been reported that enables site-selective borylation of electronically unactivated secondary C(sp³)-H bonds in acyclic or carbocyclic systems.

Herein, we report that combinations of silica-supported monophosphines (Silica-SMAP⁷⁻⁹ or Silica-TRIP^{2h}) and [Ir(OMe)(cod)]₂ produce heterogeneous catalyst systems which are effective for the borylation of unactivated primary and secondary C(sp³)-H bonds in pyridine-substituted acyclic or carbocyclic compounds using bis(pinacolato)diboron (**2**). This reaction occurs under relatively mild conditions (0.1–2 mol % Ir, 25–80 °C) with excellent site-selectivity, likely

through C-H bond activation assisted by a proximity effect due to N-to-Ir coordination.

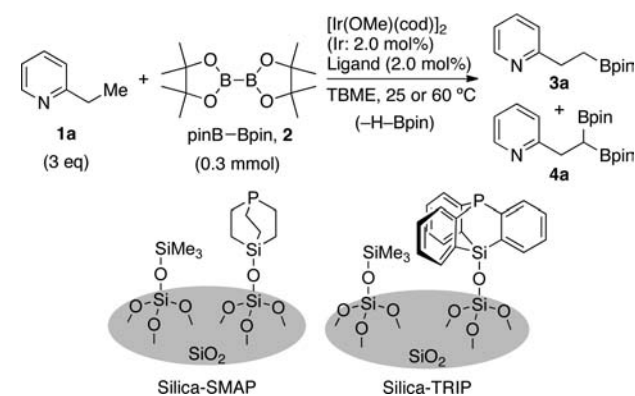
The ligand effects on the Ir-catalyzed borylation of 2-ethylpyridine **1a** (0.9 mmol) with bis(pinacolato)diboron **2** (0.3 mmol) are summarized in Table 1. With the immobilized-catalyst system prepared in situ from Silica-SMAP and [Ir(OMe)(cod)]₂, borylation of the terminal C(sp³)-H bond proceeded over a period of 12 h at 25 °C to give the primary alkylboronate **3a** and the geminal diborylation product **4** in 66% and 21% yields, respectively (based on **2** by ¹H NMR) with complete consumption of the diboron reagent **2** (entry 1).¹⁰⁻¹² Borylation did not occur either on the pyridine ring or at the benzylic position. Entry 2 shows that using 2 equiv of **2** allows the efficient synthesis of the geminal diborylation product **4a**.¹³

The Silica-TRIP-Ir system, which instead uses a silica-immobilized *triaryl*phosphine, also showed catalytic activity at 25 °C, affording **3a** in 46% yield (Table 1, entry 3), although **2** was not consumed completely. Interestingly, changing from Ir to Rh in either the Silica-SMAP or Silica-TRIP catalyst systems resulted in a complete loss of catalytic activity (data not shown). This is the opposite of the phenomenon observed during our previous study on *N*-adjacent C(sp³)-H borylation.^{2h}

The homogeneous SMAP derivative Ph-SMAP did not promote borylation at 25 °C, although the reaction proceeded under mild heating (60 °C) with the partial conversion of **2** (Table 1, entries 4 and 5). These results indicate that the immobilization of the SMAP structure to a solid surface is crucial for the catalytic performance. Other homogeneous monodentate ligands, including PMe₃, PCy₃, P^tBu₃, PPh₃, and XPhos were far less efficient, such that either no reaction or only low conversion reaction occurred even at 60 °C, and reactions were never observed at 25 °C (entries 6–14). The use of the bipyridine-based ligand dtbpy (4,4'-di-*tert*-butylbipyridine) resulted in efficient borylation of the pyridine ring at 25 °C (C4 and C5 positions, 64% and 31% respectively), but did not produce the alkylboronate **3a** at all (entry 15). Surprisingly, **1a** underwent efficient borylation in the absence of any phosphine ligand at 60 °C, with **3a** and **4a** obtained in 99% and 15% yields, respectively (entry 17). This phosphine-free Ir system did not, however, promote borylation at 25 °C, demonstrating the significant ligand effects of Silica-

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Table 1. Ligand Effects in Ir-Catalyzed Borylation of 2-Ethylpyridine (1a) with Bis(pinacolato)diboron (2)^a

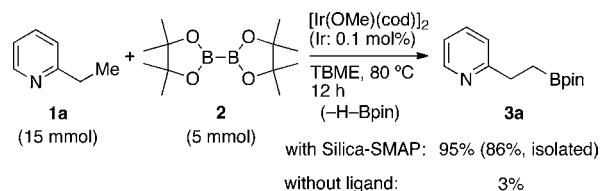
entry	ligand	temp. °C	NMR yield ^b , %	
			3a	4a
1	Silica-SMAP	25	66 (64)	21
2 ^c	Silica-SMAP	25	trace	98 (84)
3	Silica-TRIP	25	46	0
4	Ph-SMAP	25	0	0
5	Ph-SMAP	60	39	12
6	PMe ₃	25	0	0
7	PMe ₃	60	14	4
8	PCy ₃	60	0	0
9	P ^t Bu ₃	25	0	0
10	P ^t Bu ₃	60	14	0
11	PPh ₃	25	0	0
12	PPh ₃	60	10	0
13	XPhos	25	0	0
14	XPhos	60	3	0
15 ^d	dtbpy	25	0	0
16	none	25	0	0
17	none	60	99	15

^aConditions: **1a** (0.9 mmol), **2** (0.3 mmol), [Ir(OMe)(cod)]₂ (Ir: 0.0060 mmol), ligand (0.0060 mmol), *t*-BuOMe (3.0 mL) for 12 h. ^b¹H NMR yield based on **2**. Isolated yields shown in parentheses. ^cConditions: **1a** (0.3 mmol), **2** (0.6 mmol), [Ir(OMe)(cod)]₂ (Ir: 0.0060 mmol), Silica-SMAP (P: 0.0060 mmol), hexane (3.0 mL) for 22 h. ^dRing-borylation products (C4; 64% and C5; 31%) were formed.

SMAP and Silica-TRIP in accelerating the C(sp³)-H borylation (entry 16).

The effect of the Silica-SMAP ligand is also evident in a gram-scale reaction with Ir loading at a level of 0.1 mol %. In the presence of Silica-SMAP, the reaction proceeded smoothly at 80 °C to afford the alkylboronates **3a** and **4a** in 95% and 11% NMR yields, respectively, after a reaction time of 12 h (Scheme 1). In contrast, the phosphine-free Ir catalyst produced only 3% of **3a** under otherwise same conditions.

The Silica-SMAP-Ir system was further found to allow the site-selective C(sp³)-H borylation of a variety of 2-

Scheme 1. Ir-Catalyzed Borylation of 1a on a 5 mmol Scale

alkylpyridine derivatives under mild conditions (Table 2). The reaction with 2-isopropylpyridine **1b** proceeded efficiently

Table 2. Silica-SMAP-Ir Catalyzed C(sp³)-H Borylation of Alkylpyridine Derivatives^a

entry	substrate, 1	product, 3	temp °C	yield ^b %
1 ^c	1b	3b	60	109 (74) ^d
2	1c	3c	60	83 (59) ^e
3	1d	3d	25	82 (53) ^{d,f}
4	1e	3e	60	106 (79) ^e
5	1f	3f	60	102 (82)
6	1g	3g	60	86 (76)
7	1h	3h	60	72 (51) ^e

^aConditions: **1** (0.9 mmol), **2** (0.3 mmol), [Ir(OMe)(cod)]₂ (Ir: 0.0060 mmol), Silica-SMAP (0.0060 mmol), *t*-BuOMe (3.0 mL) for 12–15 h. Conversion of **2** is 100% for all entries. ^b¹H NMR yield based on **2**. Isolated yields are in parentheses. Yield in excess of 100% indicates a minor contribution of the reaction with pinB-H. ^cHexane was used as a solvent. ^dGeminal diborylation products were observed in entries 1 and 3 (14% and 2%, respectively). ^eArylboronates were formed in entries 2, 4, and 7 (2%, 11%, and 3%, respectively). ^fDeoxygenated monoborylation products **3a** (3%) and diborylation product **4a** (5%) were formed. Isolated product is contaminated with a trace of **1d**.

at 60 °C to give the corresponding monoborylation product **3b** with an yield exceeding 100% (109%), along with geminal diboronate **4b** in 14% yield (entry 1).¹⁴ This reaction did not form a 1,3-bisborylation product. The reaction of 2-*tert*-butylpyridine **1c** at 60 °C gave the C(sp³)-H monoborylation product **3c** in 83% yield along with a trace (2%) of a pyridine ring borylation product (entry 2). Substitution with a methoxymethyl ether at the C1 position of 2-ethylpyridine derivative **1d** had virtually no effect on the reactivity of the primary C(sp³)-H bonds toward the borylation, and the primary alkylboronate **3d** was obtained in 82% yield, but it is worth mentioning that small amounts of deoxygenated borylation products **3a** (3%) and **4a** (5%) were also formed as side products (entry 3).

Importantly, the Silica-SMAP-Ir system is capable of functionalizing the internal unactivated C(sp³)-H bonds of 2-alkylpyridine derivatives, allowing the preparation of secondary alkylboronates (Table 2, entries 4–7). The

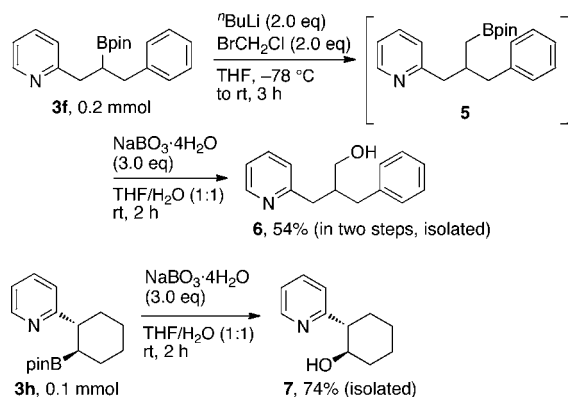
C(sp³)-H borylation occurs with exceptional site-selectivity at the position γ to the pyridine nitrogen atom with minor formation ($\leq 11\%$) of arylboronates due to C(sp²)-H borylation at the pyridine ring. For example, the reaction of 2-pentylpyridine **1e** at 60 °C (15 h reaction with complete conversion of **2**) afforded secondary alkylboronate **3e** in a yield exceeding 100% (79% yield after purification) (entry 4). Alkylboronate isomers resulting from the activation of other C(sp³)-H bonds were not detected by ¹H NMR in the unpurified product mixture. No reaction occurred with the phosphine-free Ir system under otherwise same conditions (see Supporting Information for ligand effects in the reaction of **1e**).

The site-selective secondary C(sp³)-H borylation with the Silica-SMAP-Ir system also proceeded efficiently with 2-(3-phenylpropyl)pyridine (**1f**, 60 °C), giving the corresponding alkylboronates **3f** in 102% yields (Table 2, entry 5). Comparison of the reactivities of **1e** and **1f** indicates that the phenyl substituent in **1f** does not affect the reactivity of the vicinal C-H bonds. It is also noteworthy that the benzylic C-H bonds of **1f** were intact. The reaction of 2-(2-phenylethyl)pyridine (**1g**) proceeded cleanly at 60 °C to afford the benzylic secondary alkylboronate **3g** in 86% yield, no C(sp²)-H borylation at the pyridine ring being observed (entry 6).

The reaction with 2-cyclohexylpyridine (**1h**) provides the first reported instance of the site-selective C(sp³)-H borylation of a carbocyclic system (Table 2, entry 7). The ring borylation proceeded with exceptional stereoselectivity to give the 1,2-disubstituted cyclohexane **3h** in the trans configuration.

Transformations of the pyridine-containing alkylboronates were conducted (Scheme 2). The one-carbon homologation of

Scheme 2. Transformations of Secondary Alkylboronates



the secondary alkylboronate **3f** with a bromochloromethane/BuLi reagent furnished the corresponding β -branched primary alkylboronate **5**.¹⁵ Although isolation of **5** in a pure form was difficult, this compound, prior to purification, was successfully oxidized with NaBO₃ to give the corresponding primary alcohol **6**.¹⁶ In addition, cyclohexylboronate **3h** was converted into the secondary alcohol *trans*-**7**, which has been reported in the literature,¹⁷ through stereospecific, oxidative transformation.

In summary, a combination of the silica-supported cage-shaped trialkylphosphine Silica-SMAP and [Ir(OMe)(cod)]₂ produces a heterogeneous catalyst that enables the pyridine-directed borylation of unactivated primary or secondary C(sp³)-H bonds using bis(pinacolato)diboron. This combination of a reagent and a catalyst provides a new and efficient strategy for the preparation of alkylboronates. The C(sp³)-H borylation occurs with exclusive site-selectivity at the position γ

to the pyridine nitrogen atom, suggesting a proximity effect due to N-to-Ir coordination. The primary C(sp³)-H borylation is also useful as a method for the preparation of geminal diboronates. Even though a phosphine-free catalyst system using solely [Ir(OMe)(cod)]₂ also promoted the primary C(sp³)-H borylation of 2-ethylpyridine, the activity of the heterogeneous catalyst system based on Silica-SMAP was much greater and the use of Silica-SMAP was indispensable for the borylation of secondary C(sp³)-H bonds. In contrast, the application of typical soluble phosphine ligands severely inhibited the Ir catalysis. At present, the exact nature of the catalytically active species in the homogeneous and heterogeneous systems is unclear, but it is likely that the presence of Silica-SMAP creates a favorable environment for the formation of a highly active metal-phosphine species with a significant coordinative vacancy.

■ 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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Notes

The authors declare no competing financial interest.

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