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Directed Ortho Borylation of Functionalized Arenes Catalyzed by a Silica-Supported Compact Phosphine−Iridium System

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The metal catalyzed direct functionalization of aromatic C−H bonds is a straightforward method for the formation of carbon−carbon and carbon−heteroatom bonds in organic synthesis.[1] Generally, the activation of the C−H bond is facilitated by efficient generation of a coordinatively unsaturated metal species, where the sparsity of the vacant coordination site is important for high catalytic activity and a broad substrate scope. We have developed Silica-SMAP, a silica-supported, caged, compact phosphine ligand. Because of its constrained mobility, this ligand selectively forms a monophosphine−metal complex despite its extreme compactness.[2−4] Accordingly, we envisioned that the supported phosphine would be useful in creating a highly active catalytic environment for C−H bond functionalizations.

Herein, we report that a solid-supported monophosphine−Ir system, Silica-SMAP−Ir, which was prepared in situ from $[Ir(OMe)(cod)]_2$ and Silica-SMAP, showed high activities and selectivities for the borylation of aromatic C−H bonds with bis(pinacolato)diboron (**2**).[5−7] This system was effective not only for the borylation of benzene but also for the directed ortho borylation of functionalized arenes.[6,7] The latter showed considerable tolerance toward the steric congestion at the reaction site. Moreover, it was applicable to various arenes with different directing groups, including ester, amide, sulfonate, acetal, alkoxymethyl, and chloro groups.

The reaction of benzene (30 mmol) with **2** (0.5 mmol) in the presence of Silica-SMAP−Ir(OMe)(cod) (0.5 mol %) proceeded smoothly at 80 °C and gave the corresponding monoborylation product in 101% isolated yield (based on **2**, 3 h) together with H−Bpin (Scheme 1).[8] In contrast to Ishiyama and Miyaura's observations for the dtbpy−Ir(OMe)(cod) system,[5d] H−Bpin was not efficiently used for the C−H borylation.

Scheme 1. Borylation of Benzene Catalyzed by the Silica-SMAP−Ir System

Interestingly, benzoate derivatives **1** were more reactive than unsubstituted benzene because of the ortho-directing effect of the ester group (Table 1).[5d,8] The reaction of methyl benzoate (**1a**, 1 mmol) and **2** (0.5 mmol) in hexane in the presence of 0.5 mol % Silica-SMAP−Ir(OMe)(cod) proceeded smoothly at 25 °C and gave the ortho borylation product **3a** in 89% yield based on **2** (101% NMR yield) (Table 1, entry 1).[9] Notably, when the reaction of **1a** was carried out without a solvent at a higher temperature (100 °C) on a larger scale (**1a**, 20.0 mmol; **2**, 10.0 mmol), the Silica-SMAP−Ir system exhibited a much higher turnover number (TON of 20 000) while retaining perfect ortho selectivity (eq 1).[8]

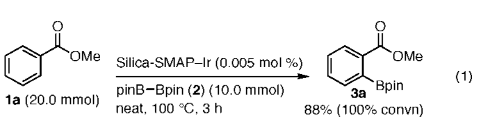
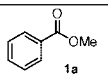
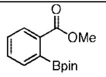
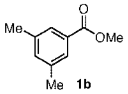
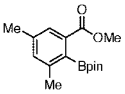
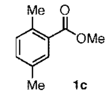
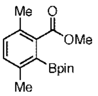
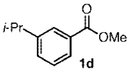
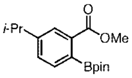
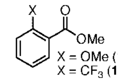
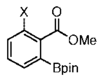
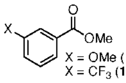
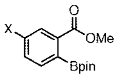
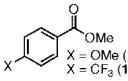
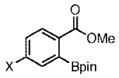


Table 1. Ortho Borylation of Methyl Benzoate Derivatives Catalyzed by the Silica-SMAP−Ir System[a]

entry	benzoate	product		temp (°C)	time (h)	yield[b] (%)
1[c]	 **1a**		**3a**	25	2	89 (101)
2[c]	 **1b**		**3b**	50	3	87 (101)
3	 **1c**		**3c**	50	7	80 (92)
4	 **1d**		**3d**	25	12	89 (93)
5	 X = OMe (**1e**) X = CF_3 (**1f**)		**3e**	25	2	85 (100)
6			**3f**	25	4	108 (108)
7	 X = OMe (**1g**) X = CF_3 (**1h**)		**3g**	40	1	80 (87)
8			**3h**	40	20	89 (115)
9[c]	 X = OMe (**1i**) X = CF_3 (**1j**)		**3i**	40	2	96 (108)
10[c,d]			**3j**	25	15	79 (93)

[a] Conditions: **1** (1.0 mmol), **2** (0.5 mmol), Silica-SMAP−Ir(OMe)(cod) (0.5 mol %), hexane (1.5 mL). [b] Isolated yield of **3** based on **2**. The yield in parentheses was determined by ^1H NMR spectroscopy. [c] A small amount of 2,6-borylation product was detected in the crude mixture (entry 1, 4%; entry 2, 6%; entry 9, 6%; entry 10, 6%). [d] The regiochemistry was assigned on the basis of the J_{C-F} values in the ^{13}C NMR spectrum.

The corresponding homogeneous catalysts that were prepared in situ from $[Ir(OMe)(cod)]_2$ and Ph-SMAP[2a,c] (0.5 mol % Ir, 1:1 or 1:2 Ir/P) afforded only trace conversion at 25 °C, indicating that immobilization of the phosphine is crucial. No reaction took place with other phosphines such as 4-CF_3-Ph-SMAP,[2b] Ph_3P, $(t\text{-}Bu)_3P$, Cy_3P, and Me_3P (1:1 or 1:2 Ir/P) under essentially the same conditions.[10]

The Silica-SMAP−Ir catalyst (0.5 mol %) was applicable to the reaction of various benzoate derivatives **1b**−**j** with one or more additional substituents on the aromatic ring (Table 1, entries 2−10). Remarkably, ortho borylation with 3,5- (**1b**) and 2,5-dimethyl (**1c**) derivatives proceeded at 50 °C regardless of the considerable steric congestion at the reaction site, with no borylation occurring at the

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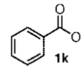
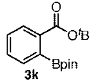
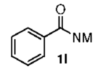
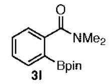
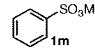
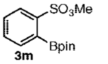
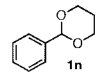
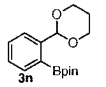
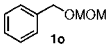
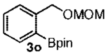
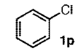
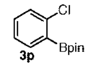
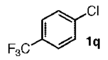
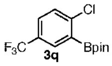
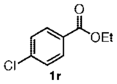
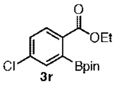
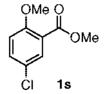
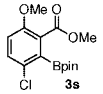
Table 2. Ortho Borylation of Functionalized Arenes Catalyzed by the Silica-SMAP−Ir System[a]

entry	arene	product	temp (°C)	time (h)	yield[b] (%)	ratio of $o/(m+p)$[c]
1	 1k	 3k	50	1	87 (101)	>99:1
2	 1l	 3l	50	3	79 (97)	>99:1
3	 1m	 3m	50	2	89 (103)	>99:1
4	 1n	 3n	70	2	105 (116)	>99:1
5	 1o	 3o	100	6	72 (95)	>99:1
6	 1p	 3p	50	24	50 (71)	92:8
7	 1q	 3q	50	4	75 (83)	>99:1[d]
8	 1r	 3r	70	20	87 (105)	>99:1[d]
9	 1s	 3s	25	4	85 (90)	95:5

[a] Conditions: **1** (1.0 mmol), **2** (0.5 mmol), Silica-SMAP−Ir(OMe)(cod) (0.5 mol %), hexane or octane (1.5 mL). A small amount of 2,6-borylation product was detected in the crude mixture in entries 3−8 (entry 3, 7%; entry 4, 16%; entry 5, 14%; entry 6, 2%; entry 7, 9%; entry 8, 23%).
[b] Isolated yield of **3** based on **2**. The yield in parentheses was determined by ^{1}H NMR spectroscopy.
[c] Determined by ^{1}H NMR spectroscopy.
[d] The regiochemistry was assigned on the basis of the J_{C-F} values in the ^{13}C NMR spectrum.

benzylic positions (entries 2 and 3).[11] The borylation of 3-isopropylbenzoate (**1d**) occurred predominantly at the less hindered C6 position (C6/C2 > 20:1) (entry 4).

Substitution of the aromatic ring of methyl benzoate with either MeO or CF_3 groups caused only marginal and capricious effects on the reactivity (Table 1, entries 5−10).[12] The reaction with 3-methoxybenzoate **1g** afforded the C6-borylation product **3g** and the C2-borylation product in an 84:16 ratio (entry 7).

Functional groups other than methyl ester also served as directing groups. These results are summarized in Table 2.[8] Among the directing groups, *tert*-butyl ester (**1k**), *N*,*N*-dimethylamide (**1l**), and sulfonate (**1m**) seemed to direct the borylation via coordination with their sp^2 oxygen atoms (entries 1−3), while acetal (**1n**) and MOM-protected hydroxymethyl groups (**1o**) directed the borylation via coordination with the sp^3 oxygen atoms (entries 4 and 5).

Notably, the chlorine atom showed a considerable ortho-directing effect. Thus, the reaction of chlorobenzene (**1p**) at 50 °C took place with a reasonably high ortho selectivity [$o/(m+p) = 92:8$] (Table 2, entry 6). Although the directing effect of the chlorine atom is apparently weaker than those of the ester groups, it was strong enough to deliver the boryl group to the ortho position with perfect selectivity in the reaction of 4-chloro-1-trifluorobenzene (**1q**) (entry 7).[12] The borylation of ethyl 4-chlorobenzoate **1r** occurred exclusively at the ortho position of the ester group (entry 8).[12] The reaction of methyl 2-methoxy-5-chlorobenzoate (**1s**) proceeded smoothly at 25 °C and afforded with excellent regioselectivity the highly functionalized, hindered arylboronate **3s**, which is difficult to prepare by other methods (entry 9).

These highly efficient ortho-directing effects probably rely on the monocoordinating feature of the immobilized phosphine ligand. In addition, the sparse nature of the Ir catalytic center, which contains only a single phosphine ligand with extreme compactness, is responsible for the high activity, while electronic effects of the strongly σ-donating SMAP ligand may have an additional influence on the catalytic properties.

In conclusion, a silica-supported, compact phosphine was successfully used in the Ir-catalyzed borylation of arenes. The use of the heterogeneous catalyst system allowed for directed ortho borylation of various functionalized arenes. The application of the immobilized phosphine ligand to other metal catalyzed reactions is under investigation.

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Supporting Information Available: 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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(2) SMAP: silicon-constrained monodentate trialkylphosphine. See: (a) Ochida, A.; Hara, K.; Ito, H.; Sawamura, M. *Org. Lett.* **2003**, *5*, 2671–2674. (b) Ochida, A.; Ito, S.; Miyahara, T.; Ito, H.; Sawamura, M. *Chem. Lett.* **2006**, *35*, 294–295. (c) Ochida, A.; Hamasaka, G.; Yamauchi, Y.; Kawamorita, S.; Oshima, N.; Hara, K.; Ohmiya, H.; Sawamura, M. *Organometallics* **2008**, *27*, 5494–5503.

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(4) For a related study with a self-assembled monolayer of SMAP on a gold surface, see: Hara, K.; Akiyama, R.; Takakusagi, S.; Uosaki, K.; Yoshino, T.; Kagi, H.; Sawamura, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 5627–5630.

(5) For selected papers on the borylation of aromatic C−H bonds with bis(pinacolato)diboron, see: (a) Iverson, C. N.; Smith, M. R., III. *J. Am. Chem. Soc.* **1999**, *121*, 7696–7697. (b) Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E., Jr.; Smith, M. R., III. *Science* **2002**, *295*, 305–308. (c) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390–391. (d) Ishiyama, T.; Takagi, J.; Hartwig, J. F.; Miyaura, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 3056–3058. (e) Boller, T. M.; Murphy, J. M.; Hapke, M.; Ishiyama, T.; Miyaura, N.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 14263–14278.

(6) (a) Ortho borylation of methyl benzoates **1** with **2** (the directing group is CO_2Me) in the presence of $[Ir(OMe)(cod)]_2$ and $P[3,5-(CF_3)_2C_6H_3]_3$ has been presented (e.g., **1f**/**2** = 5:1, 3 mol % Ir, 6 mol % P, octane, 80 °C, 16 h, 98% GC yield of **3f**). See: Isou, H.; Kikuchi, T.; Ishiyama, T.; Miyaura, N. Presented at the 88th Annual Meeting of the Chemical Society of Japan, Tokyo, March 26−30, 2008; 5H3−15. (b) Part of the work has been described in a review: Miyaura, N. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 1535–1541.

(7) For ortho borylation of arenes directed by a Me_2HSi group, see: Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 7534–7535.

(8) In Scheme 1, eq 1, and Tables 1 and 2, H−Bpin seems to have reacted with the arenes to some extent.

(9) ICP-MS analysis of Ir leaching after the reaction (0.5 mol % catalyst loading, Table 1, entry 1, Celite-filtered) detected only 0.05% of the loaded Ir. The catalyst that was recovered by decantation showed decreased activities (∼80%) because of partial decomposition during the recycling process.

(10) Even with 4-CF_3-Ph-SMAP, Ph_3P, $(t\text{-}Bu)_3P$, Cy_3P, or Me_3P (1:1 or 1:2 Ir/P), the borylation of **1a** proceeded at 70 °C (20 h), but **3a** was obtained in low yields or was contaminated with meta and para borylation products (see the Supporting Information).

(11) For benzylic C−H borylation, see: Shimada, S.; Batsanov, A. S.; Howard, J. A. K.; Marder, T. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2168–2171.

(12) The reactions of **1j**, **1q**, and **1r** were carried out with the dtbpy−Ir(OMe)(cod) system under the corresponding conditions shown in Tables 1 and 2. The reaction of **1q** provided **3q** exclusively, but the reactions of **1j** and **1r** did not proceed at all.

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