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Directed Ortho Borylation of Phenol Derivatives Catalyzed by a Silica-Supported Iridium Complex

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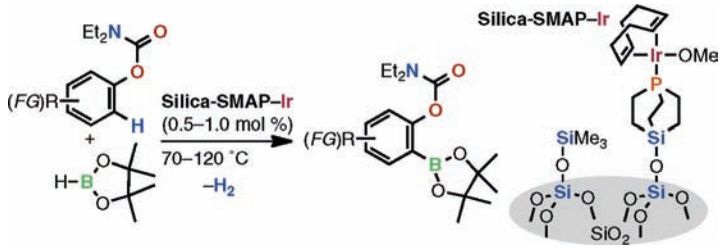
ABSTRACT



The directed ortho borylation of phenol derivatives protected with an *N*,*N*-diethylcarbamoyl group was efficiently catalyzed by an immobilized monophosphine−Ir system, which was prepared in situ from $[Ir(OMe)(cod)]_2$ and a silica-supported, compact phosphine. The utility of the carbamoyloxy group as a leaving group for metal-catalyzed cross-coupling reactions was demonstrated by its utilization in the synthesis of a terphenyl derivative.

Phenol derivatives are fundamental structural components of natural products, pharmaceuticals, ligands for transition-metal complexes, and advanced materials. On the other hand, they are widely used in organic synthesis as an electrophilic cross-coupling partner.[1] Therefore, the development of a new method to functionalize phenol derivatives is highly desirable.

We previously reported that the directed ortho borylation of functionalized arenes with bis(pinacolato)diboron (pinB-Bpin) was efficiently and selectively catalyzed by an immobilized monophosphine−Ir system [Silica-SMAP-Ir (**1**)], which was prepared in situ from a silica-supported, compact monophosphine (Silica-SMAP) and $[Ir(OMe)(cod)]_2$.[2−7] To expand the synthetic utility of the method, we examined the ortho-C−H borylation of phenol derivatives.[8] However, our screening of phenol derivatives revealed that the use of

(1) For nickel-catalyzed Suzuki−Miyaura cross-couplings of pheol derivatives, see: (a) Quasdorf, K. W.; Riener, M.; Petrova, K. V.; Garg, N. K. *J. Am. Chem. Soc.* **2009**, *131*, 17748–17749. (b) Antoft-Finch, A.; Blackburn, T.; Snieckus, V. *J. Am. Chem. Soc.* **2009**, *131*, 17750–17752. (c) Xu, L.; Li, B.-J.; Wu, Z.-H.; Lu, X.-Y.; Guan, B.-T.; Wang, B.-Q.; Zhao, K.-Q.; Shi, Z.-J. *Org. Lett.* **2010**, *12*, 884–887. See also: (d) Knappke, C. E. I.; Jacobi von Wangelin, A. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 3568–3570.

(2) (a) Kawamorita, S.; Ohmiya, H.; Hara, K.; Fukuoka, A.; Sawamura, M. *J. Am. Chem. Soc.* **2009**, *131*, 5058–5059. (b) Kawamorita, S.; Ohmiya, H.; Sawamura, M. *J. Org. Chem.* **2010**, *75*, 3855–3858.

(3) SMAP (silicon-constrained monodentate trialkylphosphine): (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.

(4) For the synthesis and applications of silica-SMAP, see: (a) Hamasaka, G.; Ochida, A.; Hara, K.; Sawamura, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 5381–5383. (b) Hamasaka, G.; Kawamorita, S.; Ochida, A.; Akiyama, R.; Hara, K.; Fukuoka, A.; Asakura, K.; Chun, W. J.; Ohmiya, H.; Sawamura, M. *Organometallics* **2008**, *27*, 6495–6506. (c) Kawamorita, S.; Hamasaka, G.; Ohmiya, H.; Hara, K.; Fukuoka, A.; Sawamura, M. *Org. Lett.* **2008**, *10*, 4697–4700.

(5) For a review on the C−H borylaion of arenes, see: Mkhalid, I. A.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890–931.

(6) For the directed ortho borylation of benzoate derivatives catalyzed by the Ir-P[3,5-$(CF_3)_2C_6H_3]_3$ system, see: Ishiyama, T.; Isou, H.; Kikuchi, T.; Miyaura, N. *Chem. Commun.* **2010**, *46*, 159–161.

(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.

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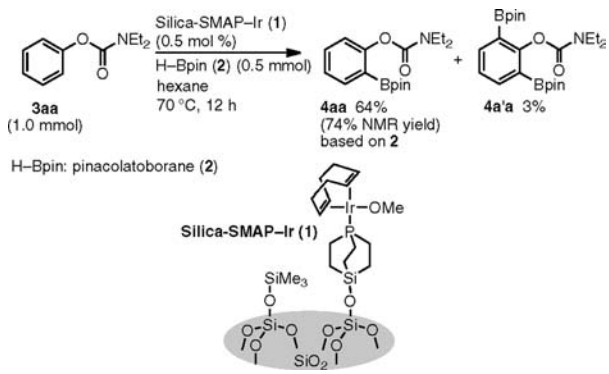
common phenol protecting groups such as acetyl, methoxycarbonyl and *tert*-butoxycarbonyl groups were not effective for the ortho borylation (vide infra). In further investigations, we have found that an *N*,*N*-diethyl-*O*-carbamoyl protecting group can efficiently deliver the boryl group to the ortho-position of phenol derivatives. The utility of *N*,*N*-diethylcarbamoyl phenol derivatives as an electrophilic cross-coupling partner is an attractive feature of this transformation.[1]

The reaction of *O*-phenyl carbamate **3aa** (1 mmol) and pinacolatoborane (H-BPin) **2** (0.5 mmol) in the presence of 0.5 mol % of Silica-SMAP-Ir(OMe)(cod) (**1**) in hexane at 70 °C for 12 h gave the ortho borylation product **4aa** in 64% isolated yield (based on **2**, 74% NMR yield), together with a small amount of bis-ortho-borylation product **4a′a** (3%) (Scheme 1).[9,10] The reaction was completely regioselective,

Scheme 1



delivering the boryl group to the ortho-position. When bis(pinacolato)diboron (pinB-Bpin) was employed instead of H-Bpin, the reaction afforded **4aa** in 113% NMR yield based on pinB-Bpin (70 °C, 8 h, 56% based on B atom): H-Bpin reacted with **3aa** to some extent. Although the reactivity of pinB-Bpin is higher than that of H-Bpin, we mostly used H-Bpin as a boron source for further study in consideration of atom economy.

Table 1 shows that most of the common protecting groups other than the *N*,*N*-dialkylcarbamoyl group were not effective for the ortho borylation of phenol derivatives in terms of the directing power or product yields (0.5 mol % of Silica-SMAP-Ir/**2**/octane/100 °C/24 h). The reactions of anisole (**3ab**) and MOM-protected phenol (**3ac**) were not regioselective (entries 1 and 2). An acetoxy group in acetylphenol

Table 1. Borylation of Phenol Derivatives with Different *O*-Protecting Groups[a]

entry	phenol	product	convn (%)	yield[b] (%)	ratio of *o*/(*m*+*p*)[c]
1	**3ab**	**4ab**	68	61[c]	50:50
2	**3ac**	**4ac**	62	56[c]	19:81
3	**3ad**	**4ad**	37	7[c]	65:35
4	**3ae**	**4ae**	14	9	100:0
5	**3af**	**4af**	48	33	100:0
6	**3ag**	**4ag**	13	7	100:0
7	**3ah**	**4ah**	30	27	100:0

[a] Conditions: **2** (0.5 mmol), **3** (1.0 mmol), Silica-SMAP-Ir(OMe)(cod) (**1**, 0.5 mol %), octane (1.0 mL), 100 °C, 24 h. [b] ^{1}H NMR yield of **4** based on **2**. [c] Total yield of isomeric arylboronates.

(**3ad**) showed only a little directing effect toward the ortho borylation [*o*/(*m* + *p*) 65:35] (entry 3). The reaction stopped at a low conversion of the **3ad**, giving a very low yield of the arylboronates together with a larger amount of phenol (16% based on **3ad**).

Although the methoxycarbonyloxy group induced the ortho borylation with complete selectivity, the conversion stayed very low (Table 1, entry 4). An increase in the steric demand of the carbonate group by changing the Me group to the ^{t}Bu group resulted in an increase in the conversion, but the yield of the ortho borylation product was low (33%, entry 5). Phenyl *N*,*N*,*N*′,*N*′-tetramethylphosphoryldiamide (**3ag**) and phenyl methanesulfonate (**3ah**) also underwent the regioselective ortho borylation (entries 6 and 7), but the conversion and the yield of the boronates were not improved as compared with those in the reaction of the carbonates (**3ae** and **3af**). Our attempt to improve the yields of **4ae**−**4ah** by applying longer reaction time was in vain, indicating that catalyst inactivation was significant. Accordingly, functional groups such as carbonates, phosphorodiamide, and sulfonate seem to be labile under the catalytic conditions.

The Silica-SMAP-Ir catalyst (0.5 mol %) was applicable to the reaction of various aryl carbamate derivatives with one or two additional substituents on the aromatic ring. The results are summarized in Table 2.[9] Although, in most cases, isolated yields of the arylboronates (**4**) were significantly reduced as compared with the ^{1}H NMR yields because of the material loss during distillation or GPC purification, in practice, the crude arylboronates would be usable for further transformation.

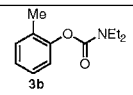
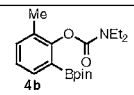
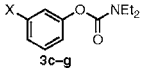
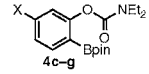
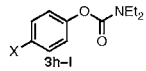
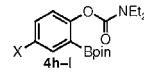
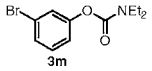
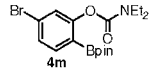
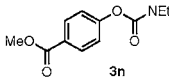
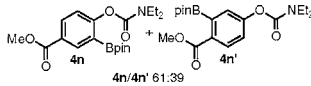
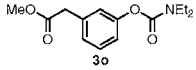
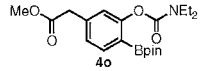
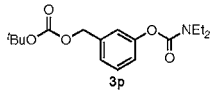
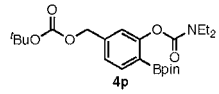
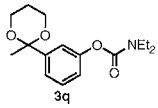
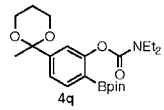
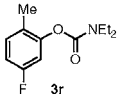
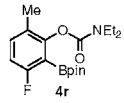
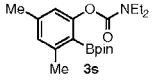
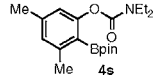
The borylation of isomeric cresol derivatives **3b**,**c**,**h** occurred with high selectivity at the ortho-position of the

(8) For palladium-catalyzed ortho-C−H arylations of phenol derivatives, see: (a) Xiao, B.; Fu, Y.; Xu, J.; Gong, T.-J.; Dai, J.-J.; Yi, J.; Liu, L. *J. Am. Chem. Soc.* **2010**, *132*, 468–469. (b) Zhao, X.; Yeung, C. S.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 5837–5844.

(9) For Scheme 1 and Table 2, unreacted H-Bpin (**2**) was observed in the crude materials (except for Table 2, entries 14, 15, and 18).

(10) The corresponding homogeneous catalysts that were prepared in situ from $[Ir(OMe)(cod)]_2$ and Ph-SMAP (0.5 mol % of Ir, Ir/P 1:1 or 1:2) afforded no borylation compound under otherwise the same reaction conditions, indicating that the phosphine immobilization is crucial. No reaction occured in the absence of a phosphine ligand with any combinations of $[IrX(cod)]_2$ (X = OMe, Cl; 0.5 mol % of Ir) and H-Bpin/pinB-Bpin.

Table 2. Borylation of Phenol Derivatives Catalyzed by the Silica-SMAP-Ir System[a]

entry	carbamate	product	yield (%)[b]
1			66 (68)
2[c]	 X = Me (**3c**)	 **4c**	70 (85)
3[d]	X = OMe (**3d**)	**4d**	63 (74)
4[c]	X = CF_3 (**3e**)	**4e**	55 (70)
5	X = Ph (**3f**)	**4f**	68 (77)
6[c]	X = Cl (**3g**)	**4g**	70 (78)
7[e]	 X = Me (**3h**)	 **4h**	74 (91)
8[e]	X = OMe (**3i**)	**4i**	65 (84)
9[e]	X = CF_3 (**3j**)	**4j**	71 (83)
10[e]	X = Ph (**3k**)	**4k**	41 (76)
11[e]	X = Cl (**3l**)	**4l**	62 (84)
12			51 (70)
13		 4n/4n' 61:39	49 (77)[f]
14[d,g]			88 (99)
15[g]			91 (109)
16[d]			65 (78)
17			71 (86)
18[d,g,h]			48 (67)

[a] Conditions: **2** (0.5 mmol), **3** (entries 1−6, 12, and 14−16, 0.6 mmol; entries 7−11, 13, 17, and 18, 1.0 mmol), Silica-SMAP-Ir(OMe)(cod) (**1**, 0.5 mol %), hexane, 70 °C, 12−24 h. [b] Isolated yield of **4** based on **2**. The yield in parentheses was determined by ^{1}H NMR. [c] A mixture of meta- and para-isomers was detected in the crude mixture (entry 2, 4%; entry 4, 5%; entry 6, 3%). [d] Silica-SMAP-Ir(OMe)(cod) (**1**) (1.0 mol %) was used. [e] Bis-ortho borylation product was detected in the crude mixture (entry 7, 6%; entry 8, 5%; entry 9, 6%; entry 10, 5%; entry 11, 7%; entry 13, 2%). [f] Total yield of isomeric arylboronates. [g] Bis(pinacolato)diboron (pinB-Bpin, 0.5 mmol) was used instead of H-Bpin (**2**). Yield of **4** based on pinB-Bpin. [h] The reaction carried out in octane at 120 °C for 24 h.

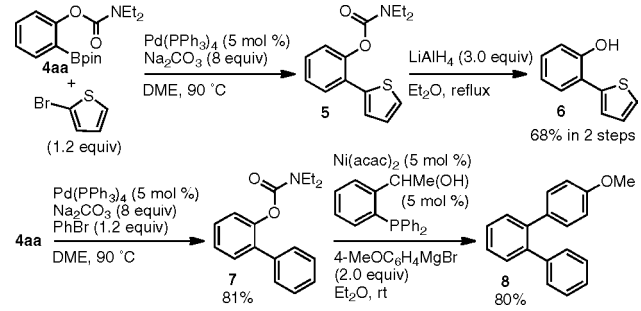
carbamate moiety (Table 2, entries 1, 2, and 7), although the reaction of *o*-cresol **3b** afforded **4b** in a lower yield. The ring substitution with MeO, CF_3, Ph, or Cl groups was tolerated at the meta- and para-positions (entries 3−6 and 8−11). The regioselectivity with the Cl-substituted aryl carbamate (**3g**,**l**) indicates that the carbamoyloxy group is a stronger directing group than the Cl atom (entries 6 and 11). Bromophenol derivative **3m** also underwent the selective ortho borylation to form **4m** with a moderate yield (70% NMR yield), leaving the Br atom untouched (entry 12).

The borylation with *p*-hydroxybenzoate derivative **3n** occurred at the ortho-positions of either the carbamoyl group or the ester group in a 61:39 regioselectivity (**4n**/**4n′**, Table 2, entry 13). Thus, the directing power of the carbamoyl group is estimated to be comparable with that of the methoxycarbonyl group.[2a,b] As shown in entry 14, the ester one carbon distal to the aromatic ring did not direct the ortho borylation. It should be noted that the borylation of the 2-phenylacetate derivative **3o** was successful even in the presence of substantially acidic C−H protons, which are activated by the ester and the aryl groups. As shown in entries 15 and 16, functional groups such as dialkyl carbonates and cyclic acetals were compatible with the ortho borylaton of the phenol derivatives.

More substituted phenol derivatives such as 2-methyl-5-fluorophenol (**3r**) and 3,5-dimethylphenol (**3s**) derivatives were borylated at the sterically hindered position to afford the corresponding arylboronates **4r** and **4s**, respectively, which are difficult to prepare by other methods (Table 2, entries 17 and 18).

Transformations of the borylated aryl *O*-carbamate **4aa** were conducted in two ways to demonstrate its utility (Scheme 2). Suzuki−Miyaura coupling between **4aa** and

Scheme 2. Transformations with Borylated Phenol Derivatives



2-bromothiophene followed by the reductive removal of the carbamate group afforded the thiophene-substituted phenol derivative **6**. On the other hand, we also tried to use the carbamate moiety as a leaving group for metal-catalyzed cross-coupling reactions. Initially, the substituted biphenyl **7**, which was obtained by the cross-coupling between the boronate **4aa** and bromobenzene, was subjected to the Ni-catalyzed aryl−aryl cross-coupling with 4-methoxyphenylboronic acid under the conditions described by Snieckus and Garg,[1] but unfortunately, the reaction resulted in a poor yield. Next we tried the coupling reaction with the corresponding Grignard reagent under Nakamura's conditions [$Ni(acac)_2$ and a hydroxyphosphine ligand].[11] The Ni-catalyzed reaction proceeded at room temperature to furnish the terphenyl derivative **8**. The three-component coupling represents the utility of the directed ortho borylation of the phenol derivatives in the preparation of multiaromatic compounds.

In summary, the directed ortho borylation of phenol derivatives protected with an *N*,*N*-diethylcarbamoyl group was efficiently catalyzed by an immobilized monophosphine−Ir

(11) Yoshikai, N.; Matsuda, H.; Nakamura, E. *J. Am. Chem. Soc.* **2009**, *131*, 9590–9599.

system (Silica-SMAP-Ir). The carbamoyloxy group not only works as a directing group for the ortho borylation but also is usable as a leaving group in the cross-coupling reactions as demonstrated in the synthesis of a terphenyl derivative.

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Supporting Information Available: Experimental procedures and NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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