Letter

Direct Suzuki–Miyaura Coupling with Naphthalene-1,8-diaminato (dan)-Substituted Organoborons

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ACS Catal., **Just Accepted Manuscript** • DOI: 10.1021/acscatal.9b03666 • Publication Date (Web): 11 Oct 2019

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Hiroto Yoshida,*† Michinari Seki,†⊥ Shintaro Kamio,† Hideya Tanaka,† Yuki Izumi,† Jialun Li,† Itaru Osaka,† Manabu Abe,‡ Hiroki Andoh,§⊥ Tomoki Yajima,§ Tomohiro Tani,§ and Teruhisa Tsuchimoto*§

† Department of Applied Chemistry, Graduate School of Engineering, Hiroshima University, Higashi-Hiroshima 739-8527, Japan

‡ Department of Chemistry, Graduate School of Science, Hiroshima University, Higashi-Hiroshima 739-8526, Japan

§ Department of Applied Chemistry, School of Science and Technology, Meiji University, 1-1-1 Higashimita, Tama-ku, Kawasaki 214-8571, Japan

ABSTRACT: The actually direct Suzuki–Miyaura coupling with "protected" R–B(dan) (dan = naphthalene-1,8-diaminato) was demonstrated to smoothly occur without in situ deprotection of the B(dan) moiety. The use of *t*-BuOK ($Ba(OH)_2$ in some cases) as a base under anhydrous conditions is the key to the successful cross-coupling, where R–B(dan) is readily converted into a transmetalation-active borate-form, regardless of the well-accepted diminished boron-Lewis acidity.

KEYWORDS: *boron-Lewis acidity, cross-coupling, direct activation, palladium, protected organoboron*

The cross-coupling reaction of organic electrophiles with organoboron compounds, the Suzuki–Miyaura coupling (SMC), has proven to be one of the most potent and versatile method of constructing carbon frameworks of organic compounds.[1] The less polarized carbon–metal bond of organoboron compounds, compared with those of other organometallic compounds such as Grignard and organozinc reagents, enables the carbon–carbon bond-forming reaction to occur with excellent chemoselectivity and functional-group compatibility. The less nucleophilic character, on the other hand, makes it necessary to activate organoboron compounds with a base in the rate-determining transmetalation;[2] in other words, the Lewis acidity of a boron center holds the key to the smooth progress of SMC. This feature has been well-exemplified by boron-masking strategy, where organoboron compounds can temporarily become inactive toward the transmetalation of SMC by use of a Lewis acidity-diminished, "protected" boron moiety such as B(dan),[3] B(MIDA)[4] or B(aam)[5] (masking) (Figure 1A). The protected boron moieties[6] can be reactivated upon deprotection under certain conditions (unmasking), and these sequential masking–unmasking has been utilized for the iterative SMC (Figure 1B),[3-5] which provides convenient and efficacious approaches to complex oligoarenes and natural products.

In addition to the boron-masking–unmasking strategy, our attention has been continuously devoted to creating another synthetic value by controlling boron-Lewis acidity, especially through the development of new B(dan)-installing reactions and with the resulting dan-substituted organoboron compounds.[7,8] For example, 2-pyridyl–B(dan), available straightforwardly by our copper-catalyzed borylative substitution,[7e,9] becomes significantly resistant to protodeborylation,[10] being in stark contrast to the well-known instability of its $B(OH)_2$- and B(pin)-counterparts with higher Lewis acidity (Figure 2A).[11] Furthermore, unusual regioselectivity has been observed in the B(dan)-installing reactions into unsaturated carbon–carbon bonds; we have disclosed that a boron moiety is attachable to an internal carbon of terminal alkynes with almost perfect regioselectivity (> 94%) in the copper-catalyzed hydroboration[7a] and borylstannylation[7c] (Figure 2B), despite the general tendency that this type of borylations with a usual Lewis acidic boron reagent occur with terminal selectivity (i.e., *anti*-Markovnikov selectivity in hydroboration).[12] Besides these, we have recently clarified that, as a pioneering work, a C(*sp*)–B(dan) bond of alkynyl–B(dan) can directly participate in the SMC (Figure 2C).[8]

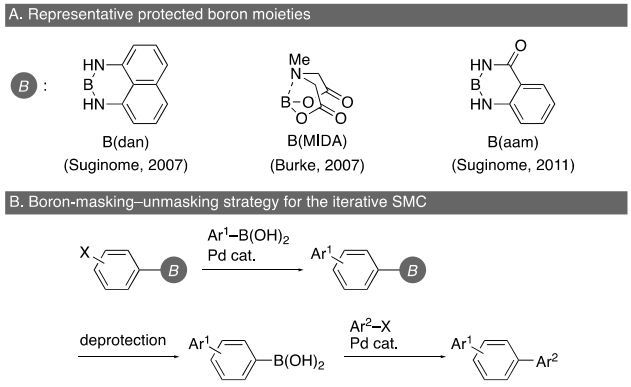


Figure 1. Representative Lewis acidity-diminished, "protected" boron moieties.

In view of the unique synthetic value given by the boron-Lewis acidity-diminishment, an important subject remaining to be addressed would be deprotection-free, *actually* direct

SMC of a much less Lewis acidic and thus very robust C(sp^2)–B(dan),[13] being markedly resistant to the activation by a base toward the transmetalation. This has indeed been demonstrated by their unreactivity even under strongly basic conditions (NaOH aq),[3b,3e] and hence the B(dan) moiety has thus far required the prior deprotection under strongly acidic conditions.[3,7a,7c] Herein we report on the first direct SMC of the C(sp^2)–B(dan) (Figure 3B),[14] which proceeds not through in situ deprotection of the B(dan) moiety, being in sharp contrast to the *formally* direct SMC with R–B(MIDA)[4b-d] or R–B(aam)[10b] via the in situ deprotection (Figure 3A).[15]

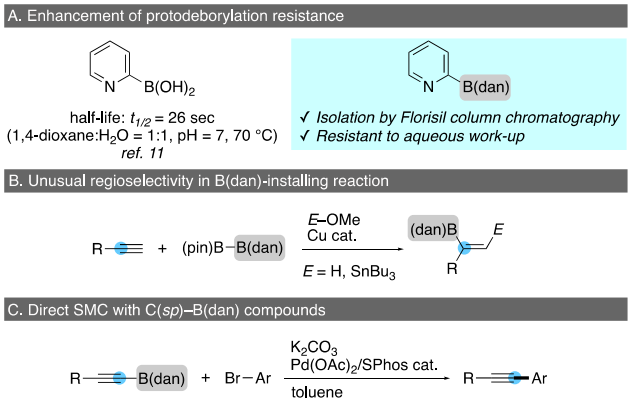


Figure 2. Synthetic value obtained with Lewis acidity-diminished B(dan).

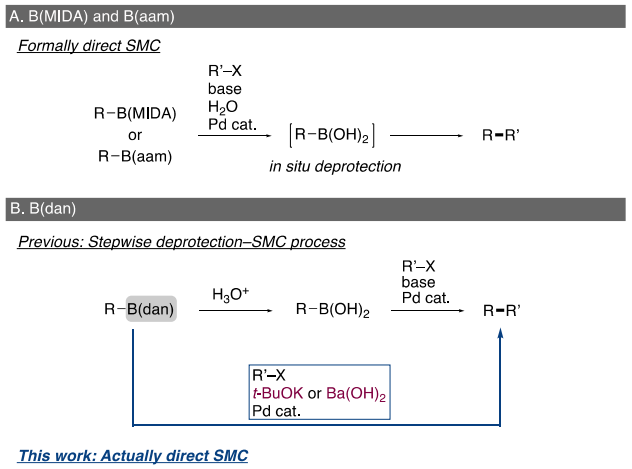
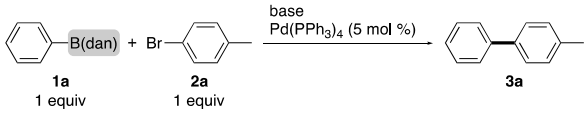


Figure 3. "Direct" SMC with Lewis acidity-diminished organoborons.

Under the assumption that the choice of a base decisively affects the course of SMC, we first carried out the reaction of Ph–B(dan) (**1a**) and 4-bromotoluene (**2a**) in the presence of $Pd(PPh_3)_4$ (5 mol %) using various bases (Table 1). The optimum conditions for the direct SMC with alkynyl–B(dan), unfortunately, did not work well, leaving **1a** almost unchanged (entry 1).[8b] As were the cases in the formally direct SMC with R–B(MIDA)[4b] or R–B(aam),[10b] the use of K_3PO_4 (7.5 equiv) in a water-containing solvent (1,4-dioxane:water = 2:1) was found to give a cross-coupling product (**3a**), albeit with a moderate yield even at an elevated temperature (entries 2 and 3). In addition, the reaction also proceeded with CsOH or Cs_2CO_3 (entries 4 and 5); the concomitant release of 1,8-diaminonaphthalene ($danH_2$) in every run (entries 2–5) implies that the SMC involves the prior hydrolysis of the B(dan) moiety of **1a** under the aqueous conditions, and that the resulting Ph–$B(OH)_2$ should behave as a substrate to directly react with **2a**. In contrast to this formally direct SMC, the reaction with *t*-BuOK (1 equiv) was found to take place smoothly in an anhydrous solvent (1,4-dioxane) at lower reaction temperature (80 °C) without the release of $danH_2$ (entry 6, 95% isolated yield), which strongly suggests the actually direct SMC is operative in this case.[16] It should be noted that the reaction became sluggish as ionic characters of *tert*-butoxides decrease (entries 7 and 8, 50% with *t*-BuONa; 6% with *t*-BuOLi), and furthermore, almost no cross-coupling product was generated with such a weaker base as MeOK, EtOK, KOH or PivOK (entries 9–12), confirming the exceptional activity of *t*-BuOK toward the direct SMC. Moreover, we also established less basic conditions (entry 13, $Ba(OH)_2$, DMF), especially for aryl halides bearing a cyano or carbonyl functionality (*vide infra*).

Table 1. Optimization of Reaction Conditions[a]

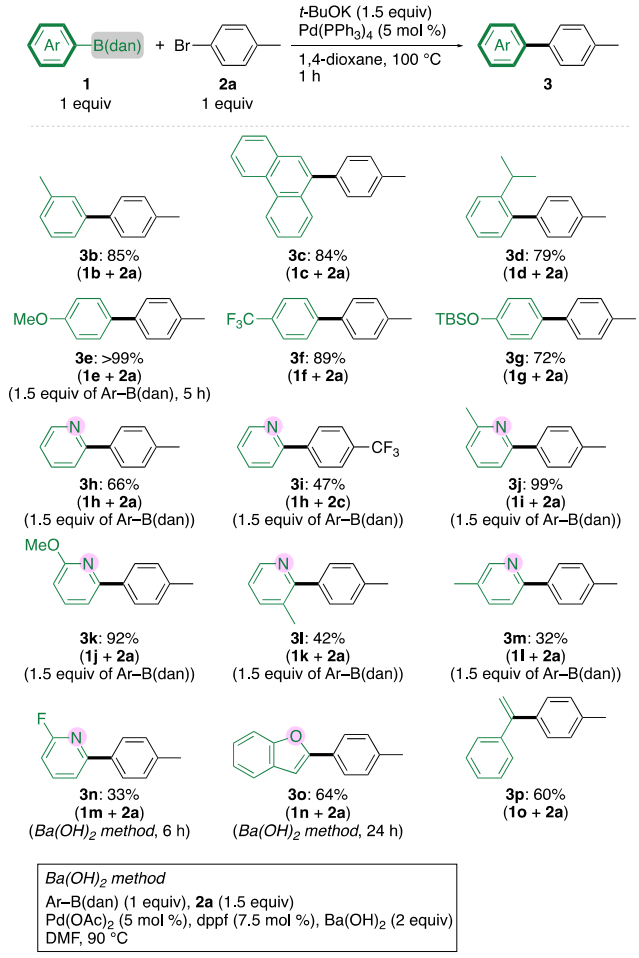


entry	base (equiv)	solvent	temp./time (°C/h)	GC yield (%)
1[b]	K_2CO_3 (3)	toluene	90/6	7[c] ($danH_2$: trace)
2	K_3PO_4 (7.5)	1,4-dioxane/H_2O (2:1)	100/24	10 ($danH_2$: 15)[d]
3	K_3PO_4 (7.5)	1,4-dioxane/H_2O (2:1)	180[e]/4	66 ($danH_2$: 66)[d]
4	CsOH·H_2O (7.5)	1,4-dioxane/H_2O (2:1)	160[e]/4	52 ($danH_2$: 74)[d]
5	Cs_2CO_3 (7.5)	1,4-dioxane/H_2O (2:1)	160[e]/4	30 ($danH_2$: 39)[d]
6	*t*-BuOK (1)	1,4-dioxane	80/21	95[f] ($danH_2$: 0)
7	*t*-BuONa (1)	1,4-dioxane	80/74	50 ($danH_2$: 0)
8	*t*-BuOLi (1)	1,4-dioxane	80/49	6 ($danH_2$: 0)
9	MeOK (3.5)	1,4-dioxane	80/17	5 ($danH_2$: 0)
10	EtOK (5.5)	1,4-dioxane	80/17	0 ($danH_2$: 0)
11	KOH (4)	1,4-dioxane	100/23	7 ($danH_2$: 61)[d]
12	PivOK (7.5)	1,4-dioxane	100/15	3 ($danH_2$: 0)
13[g]	$Ba(OH)_2$ (2)	DMF	90/6	46[c] ($danH_2$: 0)

[a]Reaction conditions: **1a** (0.15 mmol), **2a** (0.15 mmol), base, $Pd(PPh_3)_4$ (5 mol %) and solvent (1 mL). [b]**1a** (0.20 mmol), **2a** (0.20 mmol), $Pd(OAc)_2$ (5 mol %), SPhos (10 mol %) and toluene (0.4 mL). [c]Determined by ^1H NMR using nitromethane as an internal standard. [d]GC yield of 1,8-diaminonaphthalene ($danH_2$) arising from hydrolysis of the B(dan) moiety. [e]Microwave irradiation. [f]Isolated yield. [g]**1a** (0.20 mmol), **2a** (0.20 mmol), $Pd(OAc)_2$ (5 mol %), dppf (7.5 mol %) and DMF (0.4 mL).

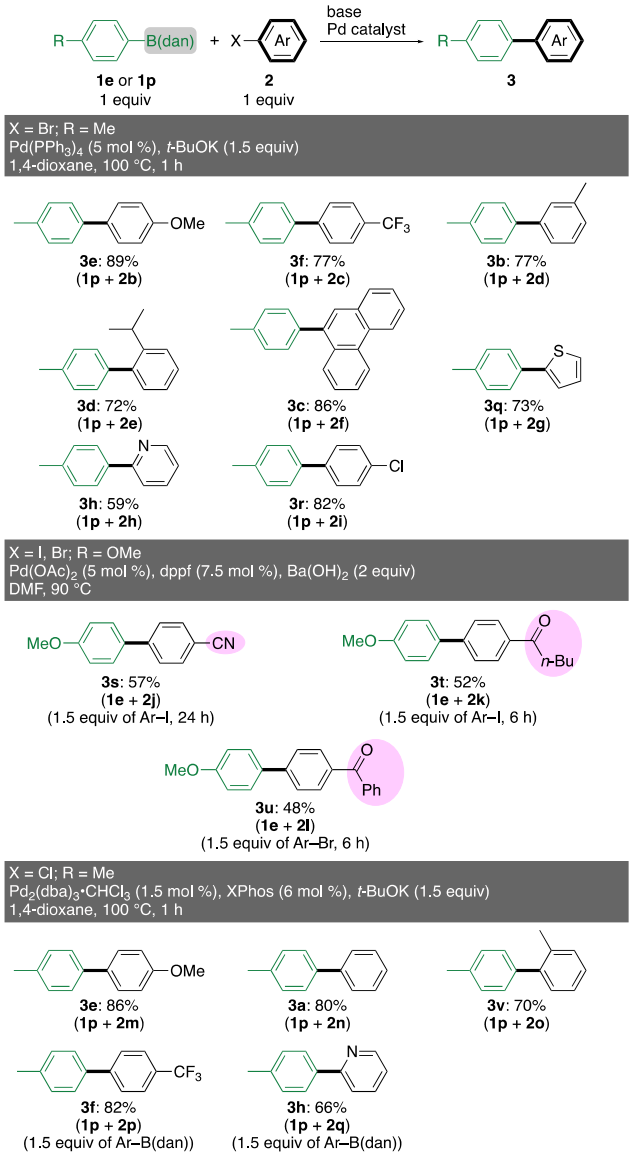
With the slightly modified *t*-BuOK-based conditions (*t*-BuOK 1.5 equiv, 100 °C), a variety of Ar–B(dan) turned out to be facilely coupled with **2a** (Scheme 1): 3-tolyl– (**1b**), 9-

phenanthryl– (**1c**) and even 2-isopropylphenyl–B(dan) (**1d**) provided the respective biaryls (**3b**–**3d**) in high yields (79–85%), despite the steric congestion around the B(dan) moiety. The direct SMC was also applicable to Ar–B(dan) with an electron-donating (**1e**) or -withdrawing group (**1f**), and it should be noted that the acidic deprotection-free procedure allowed TBSO-substituted Ar–B(dan) (**1g**) to be involved in the SMC without damaging the acid-sensitive TBSO moiety.[17] One of the striking features of this SMC is that we can make the most of the stabilizing effect by the B(dan) moiety arising from its diminished Lewis acidity: 2-pyridyl– (**1h**),[4b,4c,10b,18] and substituted 2-pyridyl–B(dan) (**1i**–**1m**),[9] being very prone to protodeborylation in their $B(OH)_2$-forms,[11] could be stably isolated by Florisil or silica gel column chromatography, and were directly convertible into biaryls (**3h**–**3n**). Moreover, 2-benzofuryl– (**1n**) and a branched alkenyl–B(dan) (**1o**), the latter of which is available from our Markovnikov-type hydroboration,[7a] could participate in the SMC to afford **3o** and **3p** in 64% and 60% yield.



Scheme 1. Substrate Scope on C(sp^2)–B(dan)

The substrate scope on aryl halides has proven to be amply broad (Scheme 2): 4-tolyl–B(dan) (**1p**) was successfully cross-coupled with aryl bromides having 4-MeO (**2b**), 4-F_3C (**2c**), 3-Me (**2d**) or 2-*i*-Pr (**2e**), irrespective of their electronic and steric environment. 9-Phenanthryl (**2f**) and heteroaryl (**2g** and **2h**) bromides were also convertible into the respective biaryls (**3b**–**3f**, **3h** and **3q**), and the chemoselective SMC of 4-bromochlorobenzene (**2i**) at the Ar–Br bond over the Ar–Cl bond gave solely **3r**. On the other hand, the reaction of aryl halides having a relatively base-sensitive functionality became unsuccessful (e.g., 22% with 3-bromobenzonitrile), probably owing to the strongly basic conditions required for activating R–B(dan). An alternative set of conditions, which employ less basic $Ba(OH)_2$ (entry 13, Table 1), seems to be suitable for such cases: the reaction of cyano- or carbonyl-substituted aryl–X (**2j**–**2l**, X = I, Br) with Ar–B(dan) in DMF under $Pd(OAc)_2$/dppf (5 mol % on Pd) catalysis provided **3s**–**3u** in 48–57% yields, even under the coexistence of the acidic α-protons (**2k**). Furthermore, the use of XPhos as a supporting ligand enabled electron-rich (**2m**–**2o**) and -deficient (**2p** and **2q**) aryl chlorides to participate in the direct SMC, furnishing good to high yields of **3a**, **3e**, **3f**, **3h** and **3v**.



Scheme 2. Substrate Scope on Aryl Halides

Assuming that the present reaction would proceed through the well-accepted pathway for the usual SMC, ^{11}B NMR experiments on stoichiometric reactions of **1a** with bases were conducted. As shown in Figure 4A, the peak of **1a** at 29.5 ppm was upfield-shifted to –1.1 ppm, being in a typical range of B(sp^3)-hybridized species,[19] upon treatment with *t*-BuOK,

whereas no change was observed at all with *t*-BuOLi or KOH.[20] The upfield peak can be assigned to an arylborate, K^+[Ph–B(dan)O*t*-Bu]$^-$ (**4**), the structure of which would be supported by the theoretical calculation developed recently by Rzepa (Figure 4B),[21] and thus the smooth borate formation with *t*-BuOK would be the key to the successful transmetalation.[22] Although deprotonation of the N–H moiety of Ar–B(dan) might trigger the transmetalation, this pathway would not be operative at all, because the predicted chemical shift of the analogous species was totally different from the observed value (Figure 4B).[23] The direct transmetalation through borate **4** is also evident from the formation of *t*-BuOB(dan) in a crude reaction mixture (**1a** + **2a**),[24] which was easily hydrolyzed to HOB(dan) and (dan)BOB(dan) upon aqueous work-up (Figure 5).[25]

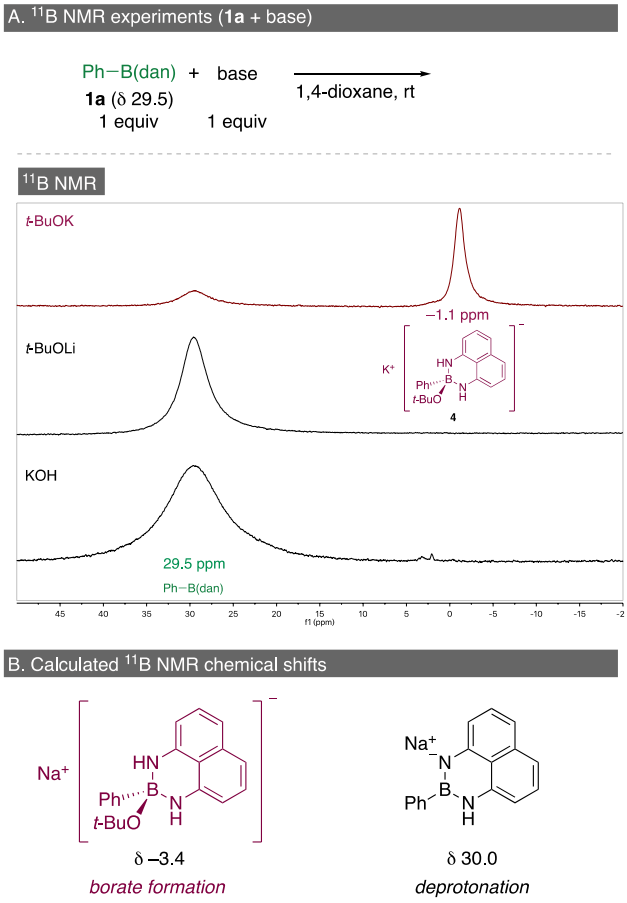


Figure 4. ^{11}B NMR experiments on B(dan) activation.

Due to the intrinsic robust character of the B(dan) moiety derived from its diminished Lewis acidity, a C–B(dan) bond keeps masked unless exposed to the present reaction conditions; base (K_2CO_3)-promoted benzylation of 4-HOC_6H_4–B(dan) (**1q**) with 2-bromobenzyl bromide afforded an 87% yield of **5**, which was chemoselectively converted into **6** (83% yield) by the intramolecular C–H arylation with Fujihara and Tsuji's carboxylic acid[26] under the SMC-like conditions (Scheme 3). The Ar–B(dan) bond remained untouched throughout these transformations, and finally underwent the direct SMC under the present reaction conditions to give **7**.

In summary, we have first demonstrated that a variety of R(sp^2)–B(dan) (R = aryl, alkenyl), which have hitherto been considered to be inactive against the SMC owing to their diminished Lewis acidity, can be efficaciously activated by *t*-BuOK or $Ba(OH)_2$, leading to the actually direct SMC without in situ deprotection of the dan moiety. The ^{11}B NMR experiments revealed the decisive role of *t*-BuOK in generating the borate species, being the key intermediate for the smooth transmetalation. This study, in addition to our precedent on the SMC of alkynyl–B(dan) with the *sp*-hybridized carbon, reveals that we have achieved the SMC of a wide range of sp^2-hybridized carbons connected with the B(dan). Further studies on transition metal-catalyzed carbon–carbon and carbon–heteroatom bond-forming reactions with R–B(dan) depending upon the direct activation method are in progress.

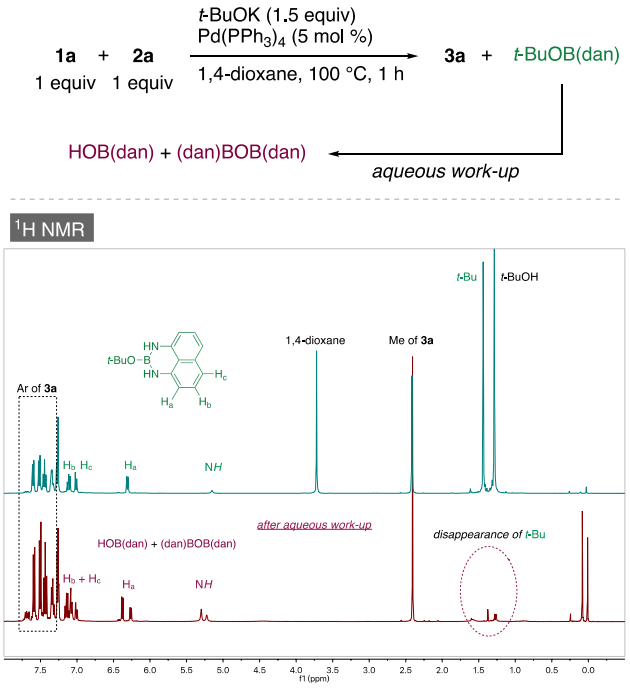
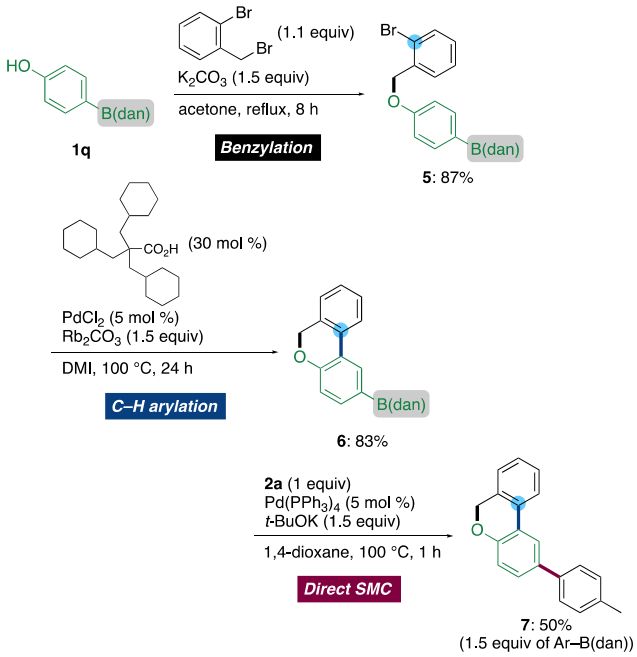


Figure 5. B(dan)-containing by-products in a crude reaction mixture.



Scheme 3. Synthetic Application of Direct SMC

AUTHOR INFORMATION

Corresponding Author

* E-mail: yhiroto@hiroshima-u.ac.jp
* E-mail: tsuchimo@meiji.ac.jp

Author Contributions

⊥These authors contributed equally.

Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, compound characterization data, DFT calculation data for ^{11}B NMR shifts, and copies of NMR spectra (PDF)
Computational data files: input (GJF) and output (OUT)

ACKNOWLEDGMENT

This work was partially supported by JSPS KAKENHI Grant Numbers JP17K05864 (H. Yoshida) and JP19K05484 (T. Tsuchimoto). We thank Profs. Tetsuaki Fujihara and Yasushi Tsuji (Kyoto University) for the generous gift of their carboxylic acid used in the C–H arylation.

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Borylation of Bromoaryl Triflates with Diborons: Chemoselective Replacement of an Ar–Br Bond. *Chem. Lett*. **2018**, *47*, 957–959. (g) Yoshida, H.; Murashige, Y.; Osaka, I. Copper-Catalyzed B(dan)-Installing Allylic Borylation of Allylic Phosphates. *Adv. Synth. Catal.* **2019**, *361*, 2286–2290.

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(9) For a Pd-catalyzed borylative substitution, see: Xu, L.; Li, P. Direct Introduction of a Naphthalene-1,8-diamino boryl [B(dan)] Group by a Pd-Catalysed Selective Boryl Transfer Reaction. *Chem. Commun.* **2015**, *51*, 5656–5659. Although 6-methoxy-2-pyridyl–B(dan) could be synthesized by this method, the reaction of 2-bromopyridine and 2-bromo-6-methylpyridine turned out to be totally unsuccessful. See SI for details.

(10) Similar stabilizing effect has been observed with B(MIDA) and B(aam). For B(MIDA), see: ref. 4b and c. For B(aam), see: (a) Kamio, S.; Kageyuki, I.; Osaka, I.; Hatano, S.; Abe, M.; Yoshida, H. Anthranilamide (aam)-Substituted Diboron: Palladium-Catalyzed Selective B(aam) Transfer. *Chem. Commun.* **2018**, *54*, 9290–9293. (b) Kamio, S.; Kageyuki, I.; Osaka, I.; Yoshida, H. Anthranilamide (aam)-Substituted Arylboranes in Direct Carbon–Carbon Bond-Forming Reactions. *Chem. Commun.* **2019**, *55*, 2624–2627.

(11) Cox, P. A.; Leach, A. G.; Campbell, A. D.; Lloyd-Jones, G. C. Protodeboronation of Heteroaromatic, Vinyl, and Cyclopropyl Boronic Acids: pH–Rate Profiles, Autocatalysis, and Disproportionation. *J. Am. Chem. Soc.* **2016**, *138*, 9145–9157.

(12) Yoshida, H. Borylation of Alkynes under Base/Coinage Metal Catalysis: Some Recent Developments. *ACS Catal.* **2016**, *6*, 1799–1811.

(13) Ph–B(dan) was reported to be much more resistant to aqueous deprotection than its –B(MIDA), –B(aam) and –B(pin) counterparts, which should be attributable to lack of its boron-Lewis acidity. See ref. 5a.

(14) A part of this work was presented at the 99th Chemical Society of Japan Annual Meeting, Kobe, Japan, March 16-19, 2019; Suzuki–Miyaura Cross-Coupling Reaction of dan-Substituted Organoboranes through Direct Activation of the B(dan) Moiety (No. 2H5-03). At the same meeting, Prof. Mutoh and co-workers reported on a closely related reaction; Suzuki–Miyaura Cross-Coupling of Ar–B(dan) (No. 1H5-48).

(15) Actual active species are usually R–$B(OH)_2$ generated in situ by hydrolysis under the SMC conditions.

(16) The reaction in the presence of water under otherwise identical conditions only gave a trace amount of **3a**, which would also rule out a possibility that boronic acids serve as an active species in the present SMC. See SI for details.

(17) Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis,* 4th ed.; John Wiley & Sons, Inc.; Hoboken, 2007; p 994.

(18) For another efficient SMC with 2-pyridylboranes, see: Billingsley, K. L.; Buchwald, S. L. A General and Efficient Method for the Suzuki–Miyaura Coupling of 2-Pyridyl Nucleophiles. *Angew. Chem. Int. Ed.* **2008**, *47*, 4695–4698.

(19) (a) Pietsch, S.; Neeve, E. C.; Apperley, D. C.; Bertermann, R.; Mo, F.; Qiu, D.; Cheung, M. S.; Dang, L.; Wang, J.; Radius, U.; Lin, Z.; Kleeberg, C.; Marder, T. B. Synthesis, Structure, and Reactivity of Anionic sp^2–sp^3 Diboron Compounds: Readily Accessible Boryl Nucleophiles. *Chem. Eur. J.* **2015**, *21*, 7082–7099. (b) Molloy, J. J.; Clohessy, T. A.; Irving, C.; Anderson, N. A.; Lloyd-Jones, G. C.; Watson, A. J. B. Chemoselective Oxidation of Aryl Organoboron Systems Enabled by Boronic Acid-Selective Phase Transfer. *Chem. Sci.* **2017**, *8*, 1551–1559.

(20) The treatment with *t*-BuOLi or KOH might produce the deprotonated species, whose predicted chemical shift would be similar to that of **1a**. But in any event, the borate (**4**) formation would be the key to the smooth SMC.

(21) Rzepa, H. S.; Arkhipenko, S.; Wan, E.; Sabatini, M. T.; Karaluka, V.; Whiting, A.; Sheppard, T. D. An Accessible Method for DFT Calculation of ^{11}B NMR Shifts of Organoboron Compounds. *J. Org. Chem.* **2018**, *83*, 8020–8025.

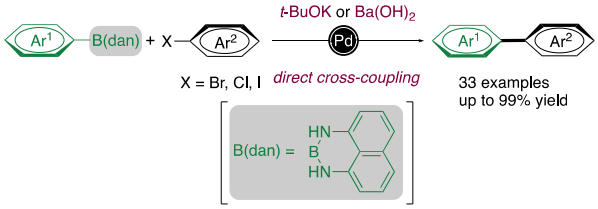
(22) A transmetalation pathway via the reaction of a Pd^{II}-O*t*-Bu complex with a neutral C(sp^2)–B(dan) may also be possible. See: Carrow, B. P.; Hartwig, J. F. Distinguishing Between Pathways for Transmetalation in Suzuki–Miyaura Reactions. *J. Am. Chem. Soc.* **2011**, *133*, 2116–2119.

(23) We have confirmed that an *N*,*N'*-dimethylated Ph–B(dan) derivative [Ph–B(mdan)] underwent the direct SMC under the same reaction conditions, which may support the borate-formation pathway (not deprotonation pathway). This result, however, should be inconclusive, since the smooth reaction also took place even with a weak base (K_3PO_4), possibly indicating that the B(mdan) moiety is sufficiently Lewis acidic to be activated. See SI for details.

(24) *t*-BuOH in the upper ^{1}H NMR spectrum of Figure 5 is thought to be generated from protonation of excess *t*-BuOK with adventitious water during the preparation of an NMR sample.

(25) The reaction with $Ba(OH)_2$ also turned out to proceed directly, where HOB(dan) and (dan)BOB(dan) were formed as the sole boron by-products without the release of $danH_2$. See SI for detailed assignment of the B(dan)-containing by-products.

(26) Tanji, Y.; Mitsutake, N.; Fujihara, T.; Tsuji, Y. Steric Effect of Carboxylate Ligands on Pd-Catalyzed Intramolecular C(sp^2)–H and C(sp^3)–H Arylation Reactions. *Angew. Chem. Int. Ed.* **2018**, *57*, 10314–10317.


Ar1
B(dan)
+ X
Ar2
t-BuOK or Ba(OH)2
Pd
Ar1
Ar2
X = Br, Cl, I
direct cross-coupling
33 examples
up to 99% yield
B(dan) =
HN
B
HN