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COMMUNICATION

Anthranilamide (aam)-substituted arylboranes in direct carbon–carbon bond-forming reactions

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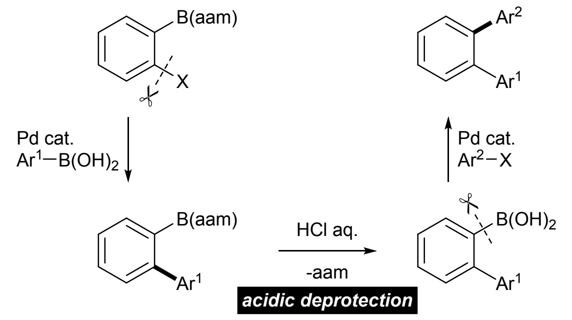
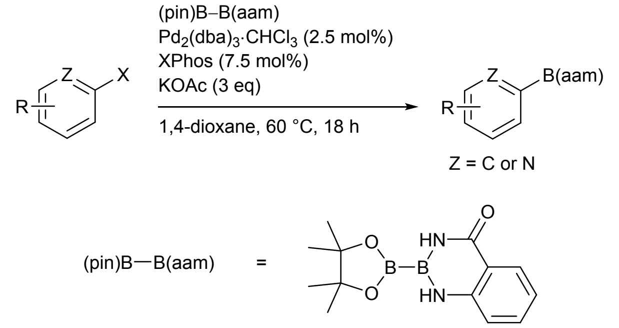
Anthranilamide (aam)-substituted arylboranes, which were reported to serve as masked boranes in the Suzuki–Miyaura coupling, have been found to be directly cross-coupled just by use of an aqueous medium. The excellent stability of 2-pyridyl–B(aam) toward protodeborylation allowed their smooth cross-coupling.

Arylboron compounds with an anthranilamide (aam) substituent on the boron center [Ar–B(aam)][1] have proven to be useful reagents in the Suzuki–Miyaura cross-coupling (SMC): their reactivity toward transmetalation can temporarily be masked,[1-4] thus allowing a C(aryl)–halogen bond in the same molecule to be chemoselectively cross-coupled with another arylboronic acid. The latent reactivity of the remaining C(aryl)–B(aam) bond can then be unmasked by its conversion into the respective boronic acid [C(aryl)–B(OH)$_2$] via acidic deprotection, leading to precise and reliable synthesis of oligoarenes (Scheme 1).

The B(aam) moieties also serve as directing groups for catalytic *ortho*-C(aryl)–H silylation,[1] however the high synthetic potency of Ar–B(aam) was not fully utilized, because they were only accessible by dehydrative condensation of Ar–B(OH)$_2$ with aam. Recently, we have reported that installation of a B(aam) unit into aromatic frameworks becomes feasible by the palladium-catalyzed Miyaura–Ishiyama-type coupling[5] with a new unsymmetrical diboron [(pin)B–B(aam)],[6,7] which expands structural diversity of Ar–B(aam) to be accessed (Scheme 2).



Scheme 1 Reported iterative SMC with Ar–B(aam).



Scheme 2 Miyaura–Ishiyama reaction with (pin)B–B(aam).

Of note is that 2-pyridyl–B(aam), which cannot be synthesized by the dehydrative condensation, become straightforwardly available as open column chromatography-stable compounds, being in stark contrast to the well-accepted propensity of 2-pyridyl–B(OH)$_2$ and –B(pin) to be protodeborylated (*vide infra*).[8,9a] The diminished Lewis acidity of the B(aam) moiety, arising from its planar six-membered-ring configuration as well as effective electron donation from the neighboring nitrogen atoms, would be the key to the stability, and the masked reactivity in SMC is also ascribable to the diminishment. The endowed stabilizing effect by the aam-introduction may provide another option for “2-pyridyl problem”[10] in organoboron chemistry, however, the above acidic deprotection, of course, is not applicable to 2-pyridyl–B(aam), because of the fast protodeborylation,[9] and thus development of direct SMC with Ar–B(aam), that addresses this dilemma, should be of urgent importance. Herein we report

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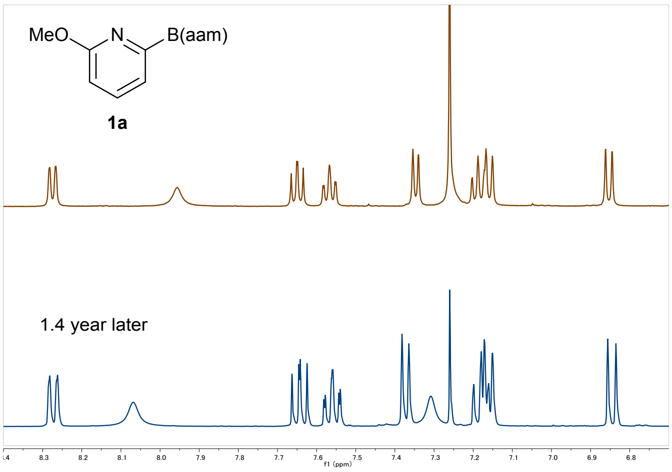
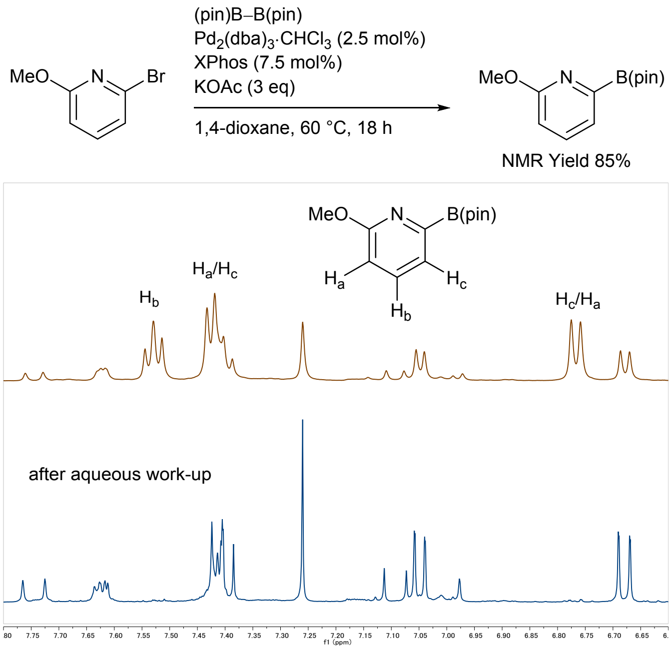


Figure 1 Storability of 6-methoxy-2-pyridyl–B(aam).

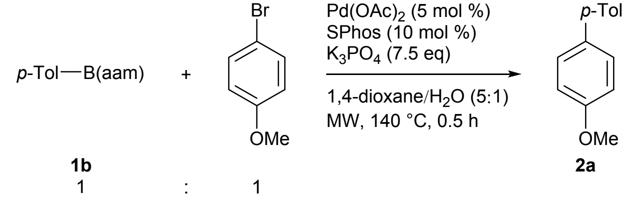


Scheme 3 Protodeborylation of 6-methoxy-2-pyridyl–B(pin).

that Ar–B(aam) facilely undergo direct, acidic deprotection-free SMC just by adding water to the reaction medium.

In addition to the air- and moisture-stability of 2-pyridyl–B(aam),[6] they were found to be sufficiently durable as shown in Figure 1: no trace decomposition of 6-methoxy-2-pyridyl–B(aam) (**1a**) was observed in ^{1}H NMR spectra even 1.4 year after its synthesis without any special care (**1a** was stored in a vial at ambient temperature).[11] In marked contrast, its B(pin)-counterpart, prepared by the Miyaura–Ishiyama reaction with (pin)B–B(pin) (NMR yield 85%, calculated from a crude mixture), instantly disappeared just by aqueous work-up (Scheme 3). Moreover, half-life period of 6-methoxy-2-pyridyl–B(OH)$_2$ was reported to be about 3.5 mins (at pH = 6.86),[9a] demonstrating that the exceptional stability and storability were given by of the aam-introduction.

Table 1 Screening of reaction conditions[a]



Entry	Changes from standard conditions	Yield (%)[b]
1	None	88
2	60 °C, 6 h	89[c,d,e]
3	$Pd_2(dba)_3\cdot CHCl_3$ (5 mol %), XPhos (10 mol %), K_3PO_4 (7.5 eq)	54
4	$PdCl_2(dppf)\cdot CH_2Cl_2$ (2 mol %), K_3PO_4 (3 eq), dry THF, 80 °C, 18 h	4[e]
5	$Pd_2(dba)_3\cdot CHCl_3$ (5 mol %), XPhos (10 mol %), K_2CO_3 (5 eq), $Cu(OAc)_2$ (0.5 eq), DMF/IPA (4:1), 100 °C, 4 h	14[e]
6	$Pd(OAc)_2$ (3 mol %), PPh_3 (6 mol %), KOH aq. (6 eq), 1,4-dioxane	69

[a] Standard conditions: **1b** (0.150 mmol), aryl bromide (0.150 mmol), $Pd(OAc)_2$ (7.50 µmol), SPhos (0.0150 mmol), K_3PO_4 (1.13 mmol), 1,4-dioxane (1.9 mL), H_2O (375 µL), microwave heating, 140 °C, 0.5 h. [b] NMR yield. [c] Isolated yield. [d] **1b** (0.225 mmol). [e] Conventional heating.

Direct, acidic deprotection-free SMC of Ar–B(aam) has been demonstrated to occur efficaciously by simply adding water to a reaction medium. Thus, treatment of *p*-tolyl–B(aam) (**1b**) with 4-bromoanisole in 1,4-dioxane/H_2O (5:1) solvent under palladium catalysis [$Pd(OAc)_2$–SPhos] turned out to afford a biaryl (**2a**) in 88% yield (Table 1, Entry 1), being in contrast to the previous two-step cross-coupling using Ar–B(aam), where prior deprotection of a B(aam) moiety was conducted under acidic conditions.[1] The direct SMC also proceeded in similar yield under conventional heating conditions (Entry 2), showing that microwave irradiation is not always required for the present reaction. The use of XPhos as a supporting ligand resulted in a moderate yield (Entry 3), and the reaction conducted in an anhydrous medium was found to be unsuccessful, which indicates that the use of an aqueous medium is a key to the successful cross-coupling (Entry 4). Addition of copper (II) acetate as a transmetalation promoter in an alcoholic medium, employed in SMC of Ar–B(MIDA),[3b] was not effective (Entry 5), and the yield also decreased in the reaction with a strong base (KOH) (Entry 6).

With the optimized reaction conditions in hand, we next investigated the direct SMC of **1b** with various aryl bromides (Table 2). Electron-rich and -deficient aryl bromides were readily convertible into the respective biaryls (**2a**–**2g**) in high yield within half an hour. Since a weak base (K_3PO_4) suffices for the smooth transformation, a relatively base-sensitive functional group including CO_2Et, CN, Ac or CHO was tolerable (**2h**–**2k**). In addition, heteroaryl bromides with 2-pyridyl, 5-indolyl or 2-thienyl group could also participate in the reaction to provide heterobiaryls (**2l**–**2p**).

It should be noted that the direct SMC turned out to be also applicable to 2-pyridyl–B(aam), resulting in the formation of 2-arylpyridines (**2m**, **2n**, and **2q**) in high yield (Table 3), which provides an alternative approach for “2-pyridyl problem” in

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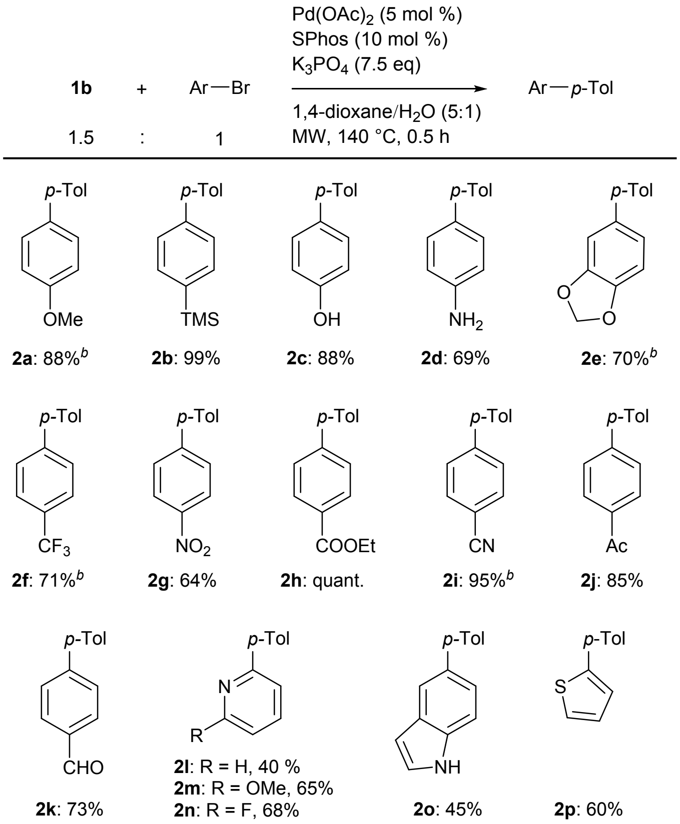
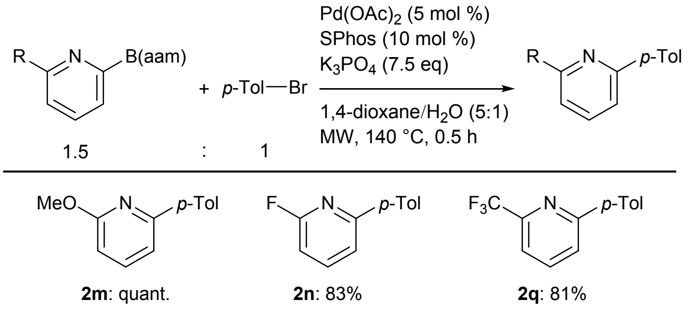
Table 2 Substrate scope on aryl halides[a]



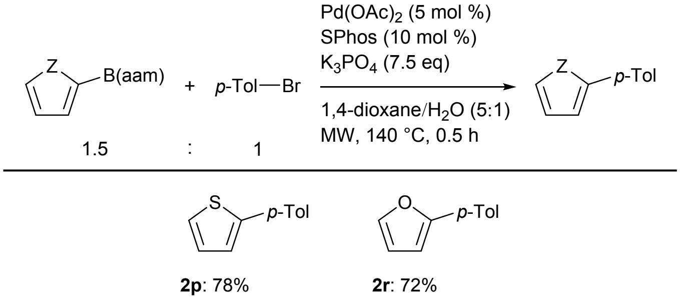
[a]Isolated yield. Conditions: **1b** (0.225 mmol), aryl bromide (0.150 mmol), $Pd(OAc)_2$ (7.50 μmol), SPhos (0.0150 mmol), K_3PO_4 (1.13 mmol), 1,4-dioxane (1.9 mL), H_2O (375 μL), microwave heating, 140 °C, 0.5 h. [b]**1b** (0.150 mmol).

Table 3 Direct SMC of 2-pyridyl–B(aam)[a]

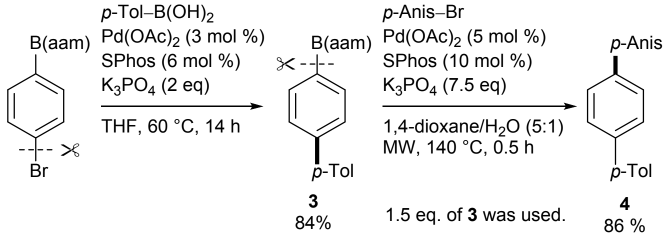


[a]Isolated yield. Conditions: 2-pyridylB(aam) (0.225 mmol), *p*-bromotoluene (0.150 mmol), $Pd(OAc)_2$ (7.50 μmol), SPhos (0.0150 mmol), K_3PO_4 (1.13 mmol), 1,4-dioxane (1.9 mL), H_2O (375 μL), microwave heating, 140 °C, 0.5 h.

Table 4 Direct SMC of 2-(Het)Ar–B(aam)[a]



[a]Isolated yield. Conditions: 2-(Het)Ar–B(aam) (0.225 mmol), *p*-bromotoluene (0.150 mmol), $Pd(OAc)_2$ (7.50 μmol), SPhos (0.0150 mmol), K_3PO_4 (1.13 mmol), 1,4-dioxane (1.9 mL), H_2O (375 μL), microwave heating, 140 °C, 0.5 h.

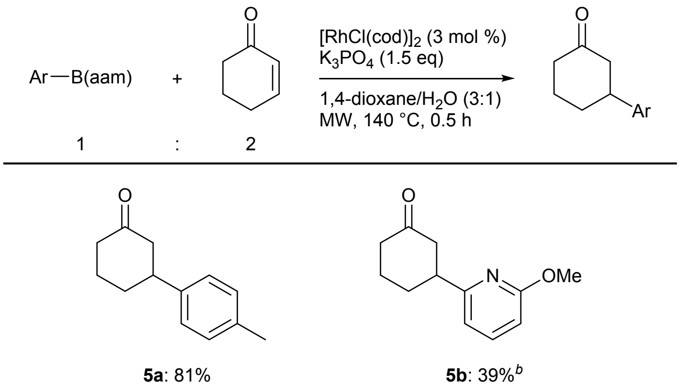


Scheme 4 Iterative SMC with 4-bromophenyl–B(aam).

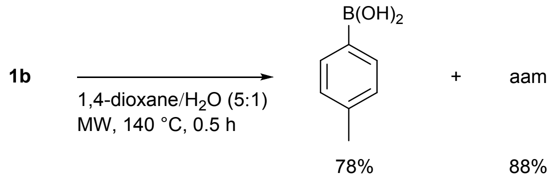
cross-coupling process. Other 2-heteroarylboron compounds, which tend to be protodeborylated, could efficiently be cross-coupled by the aam-substitution; 2-thienyl– and 2-furyl–B(aam) smoothly underwent the direct SMC to give **2p** and **2r** in 78% and 72% yield respectively (Table 4).[12] The successful cross-coupling can obviously be ascribed to their protodeborylation-resistant property as above, and also to in situ-release of cross-coupling-active 2-heteroarylboronic acids at an appropriate pace (*cf*. Scheme 5). In view of the fact that an Ar–B(aam) are unreactive in the cross-coupling under anhydrous conditions,[1] the present results can give another option for the iterative cross-coupling, whose progress is totally controllable by the absence/presence of water, as are the cases with an *N*-methyliminodiacetic (MIDA) boronates.[3,10d] This was well illustrated by the reaction of 4-bromophenyl–B(aam): its C(aryl)–Br bond was chemoselectively convertible into C(aryl)–C(aryl) bond by anhydrous SMC with *p*-tolylboronic acid, giving **3** in 84% yield (Scheme 4). The remaining C(aryl)–B(aam) bond then underwent direct SMC with 4-bromoanisole under the present conditions led to the formation of *p*-teraryl **4**.

The deprotection-free procedure was found to also applicable to rhodium-catalyzed 1,4-addition[10c,13] to 2-cyclohexen-1-one, and *p*-tolyl or 2-pyridyl moity was attached to its β-position to furnish **5a** and **5b** in 81% and 39% yields respectively (Table 5).

Table 5 Rhodium-catalyzed 1,4-addition of Ar–B(aam) to cyclohexenone[a]



[a]Isolated yield. Conditions: Ar–B(aam) (0.150 mmol), cyclohexenone (0.300 mmol), $[RhCl(cod)]_2$ (4.50 μmol), K_3PO_4 (0.225 mmol), 1,4-dioxane (0.50 mL), H_2O (0.13 mL), microwave heating, 140 °C, 0.5 h. [b]H_2O (27 μL).



Scheme 5 Aqueous treatment of **1b**

A control experiment with **1b** under the aqueous conditions gave a 78% yield of *p*-tolylboronic acid which would serve as an actual boron reagent in the direct C–C bond-forming processes, and the facile hydrolysis of the B(aam) moiety is consistent with the previous Suginome's result (Scheme 5).[1]

In conclusion, we have disclosed that direct SMC of Ar–B(aam) smoothly proceeded under aqueous conditions without the need for prior acidic deprotection. In addition to the established procedure, the excellent stability of 2-pyridyl–B(aam) toward protodeborylation provided a promising option for 2-pyridyl problem in SMC. Further studies on direct, catalytic carbon–carbon bond-forming reactions with Ar–B(aam) are in progress.

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Conflicts of interest

There are no conflicts to declare.

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