

Letter

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# Suzuki–Miyaura Cross-Coupling of 1,8-Diaminonaphthalene (dan)-Protected Arylboronic Acids

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**ABSTRACT:** We report a Suzuki–Miyaura cross-coupling reaction of 1,8-diaminonaphthalene (dan)-protected arylboronic acids in the presence of KO*t*-Bu, which does not require the removal of the dan moiety. Notably, the use of aryl-B(dan) in the Suzuki–Miyaura reaction provides a complementary solution to the protodeboronation problems. The base KO*t*-Bu plays a crucial role for the promotion of these cross-coupling reactions as it enables the formation of a borate salt. This reaction protocol was extended to the one-pot sequential Suzuki–Miyaura cross-coupling reaction of 4- [(pin)B]C<sub>6</sub>H<sub>4</sub>–B(dan), wherein the "less reactive" aryl-B(dan) moiety was cross-coupled preferentially.

KEYWORDS: B(dan), borate, boronic acid, cross-coupling, palladium, Suzuki-Miyaura

Suzuki-Miyaura cross-coupling reactions between organoboronic acids and aryl halides represent one of the most useful and straightforward methods to synthesize biaryl compounds.<sup>1</sup> Given the utility of B-protected (masked) boronic acids in iterative Suzuki-Miyaura reactions,<sup>2</sup> it is not surprising that substantial research efforts have been devoted to the development of a diverse range of effective protecting (masking) groups.<sup>2</sup> Among these, much attention has been focused on nitrogenprotective groups,<sup>2a-c</sup> containing particularly the naphthalene-1,8-diaminato (dan) group,<sup>3,4</sup> as aryl-B(dan) derivatives are stable toward protodeboronation under aqueous basic conditions.<sup>4-6</sup> Yet the removal of the dan group from Ar-B(dan) under acidic conditions is necessary to provide the latent boronic acids that engage in the subsequent Suzuki-Miyaura reaction.<sup>2,4a,b,e</sup>

38 The direct use of Ar-B(dan) derivatives in 39 Suzuki-Miyaura cross-coupling reactions would thus be 40 highly desirable in terms of step- and atom-economy,7 41 which would help to streamline the synthesis of complex 42 molecules. Moreover, it would contribute to a significant 43 broadening of the utility of Ar-B(dan) derivatives, which 44 could provide a complementary solution to the 45 problems protodeboronation known the as 46 "polyfluorophenyl<sup>8</sup> and 2-pyridyl<sup>9</sup> problems". Although 47 palladium- or copper-catalyzed reactions of alkynyl-B(dan),  $RC \equiv C - B(dan)$ , with aryl halides have been 48 reported,<sup>10</sup> examples of the formation of carbon-carbon 49 bonds via direct cross-coupling reactions of Ar-B(dan) 50 derivatives remain elusive.<sup>11</sup> Herein, we report 51 Suzuki-Miyaura cross-coupling reaction of Ar-B(dan) 52 derivatives with aryl halides, where the removal of the dan 53 moiety is not required.<sup>12</sup> The key to the success of these 54 cross-coupling reactions is the use of KOt-Bu as the base, 55 as KOt-Bu enables the formation of an active borate, 56 which was characterized by NMR spectroscopy and 57 single-crystal X-ray diffraction analysis. 58

Initially, we examined the impact of various bases on the reaction of Ph–B(dan) (**1a**) and 4-iodoanisole (**2a**) in the presence of Pd-PEPPSI-IPr<sup>13</sup> at 70 °C in toluene (Table 1). When KOt-Bu was used as the base, the crosscoupled product (**3aa**) was obtained in 95% yield (entry 1). When NaOt-Bu or LiOt-Bu were used, the crosscoupling of **1a** and **2a** did not proceed (entries 2 and 3). Other basic potassium salts were also examined, but only KOt-Bu promoted the desired reaction in high yield (entries 4–6). Subsequently, we varied the amount of KOt-Bu and discovered that 2.5 equiv of the base was optimal for this reaction (entries 7–9). The addition of water, which is essential to promote the Suzuki–Miyaura cross-coupling of R–B(pin) (pin = pinacolato), inhibited the reaction (entry 10).

# Table 1. Impact of the Nature of the Base on thePalladium-Catalyzed Cross-Coupling of 1a and 2a<sup>a</sup>

<b>1a</b> (1.25 equ	(dan) + 2a iiv) (1.0 equiv) Pd-PEPPSI-I base toluer 70 °C, 2	Pr (2.0 mol %	o) Jaa Jaa
entry	base	equiv	yield (%) <sup>b</sup>
1	1.0 M KO <i>t</i> -Bu/THF	3.0	95
2	1.0 M NaOt-Bu/THF	3.0	trace
3	1.0 M LiO <i>t</i> -Bu/THF	3.0	no reaction
4	KO <i>t</i> -Bu	3.0	95
5	KOEt	3.0	28
6	KF	3.0	no reaction
7	1.0 M KO <i>t</i> -Bu/THF	3.75	99
8	1.0 M KO <i>t</i> -Bu/THF	2.5	99
9	1.0 M KO <i>t</i> -Bu/THF	1.25	40
10 <sup>c</sup>	1.0 M KO <i>t</i> -Bu/THF	2.5	trace

<sup>a</sup>General reaction conditions: **1a** (1.25 equiv), **2a** (1.0 equiv), Pd-PEPPSI-IPr (2.0 mol %), toluene ([**2a**]<sub>0</sub> = 0.05 M). <sup>b</sup>Isolated yield. <sup>c</sup>A mixture of toluene/H<sub>2</sub>O (5:1, v/v) was used as the solvent.

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Subsequently, we briefly screened various palladium complexes for the Suzuki–Miyaura cross-coupling of **1a** and **2a** in the presence of KOt-Bu in toluene (Table 2). The use of Pd-PEPPSI-IPr as the catalyst is not mandatory. When other palladium(II) complexes such as  $[PdCl_2(dppf)] \cdot CH_2Cl_2$  and  $[PdCl_2(PPh_3)_2]$  were employed, the cross-coupling reaction proceeded smoothly (entries 1–3). A combination of  $[Pd(OAc)_2]$  and XPhos<sup>14</sup> also provided **3aa** in high yield (entry 4). The cross-coupling reaction also proceeded in the presence of common palladium(0) complexes such as  $[Pd_2(dba)_3] \cdot CHCl_3/PPh_3$ and  $[Pd(PPh_3)_4]$  (entries 5 and 6). These results demonstrate that common palladium-based catalyst systems can be used for the cross-coupling of Ar–B(dan).

# Table 2. Screening of Palladium Complexes for the Cross-Coupling of 1a and 2a in the Presence of KO*t*-Bu<sup>a</sup>

(1.25	B(dan) + 1a 2a equiv) (1.0 equiv)	[Pd] (2.0 mol %) additive 1.0 M KO <i>t</i> -Bu/THF ( toluene 70 °C, 24 h	2.5 equiv)	3aa
entry	[Pd] complex	additive	yield (%	) <sup>b</sup>
с	Pd-PEPPSI-IPr	-	99	
2	[PdCl₂(dppf)]·CH₂C	Cl <sub>2</sub> -	95	
3	[PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> ]	-	91	
ł	[Pd(OAc) <sub>2</sub> ]	XPhos <sup>d</sup>	97	
5	[Pd₂(dba) <sub>3</sub> ]·CHCl <sub>3</sub>	PPh <sub>3</sub> <sup>d</sup>	97	
6	[Pd(PPh <sub>3</sub> ) <sub>4</sub> ] <sup>e</sup>	-	94	
n(ry  c } } }	$[Pd] complex$ $Pd-PEPPSI-IPr$ $[PdCl_{2}(dppf)] \cdot CH_{2}C$ $[PdCl_{2}(PPh_{3})_{2}]$ $[Pd(OAc)_{2}]$ $[Pd_{2}(dba)_{3}] \cdot CHCl_{3}$ $[Pd(PPh_{3})_{4}]^{e}$	$ \begin{array}{c} -\\ Cl_2 -\\ -\\ XPhosd\\ PPh_3d\\ -\\ -\\ \end{array} $	99 95 91 97 97 94	

<sup>a</sup>General reaction conditions: **1a** (1.25 equiv), **2a** (1.0 equiv), [Pd] (2.0 mol %), KO*t*-Bu (2.5 equiv), toluene ([**2a**]<sub>0</sub> = 0.05 M). <sup>b</sup>Isolated yield. <sup>c</sup>Taken from entry 8 in Table 1. <sup>d</sup>4 mol % of the additive were used. <sup>e</sup>Purified by recrystallization prior to use.

Then, we investigated the substrate scope of this Suzuki-Miyaura cross-coupling reaction under the established optimal conditions (Table 3). When 4substituted phenyl-B(dan) (1b-f) and 4-iodoanisole (2a) were used, the corresponding biaryls (3ba-fa) were obtained in high yield. Notably, the cross-coupling of the B(dan) group in benzenediboronic acid derivative 1e proceeded selectively to afford 3ea in 89% yield, which shows that the B(pin) group in 1e remains unaffected under the established cross-coupling conditions, and that 3ea should be susceptible to further functionalization of the  $C(sp^2)-B(pin)$ bond under conventional Suzuki-Miyaura coupling conditions. Although the reactivity of Ar-B(dan) derivatives with silvlether and cyclic ether moieties (1f and 1g) are low, biaryls 3fa and 3ga were obtained in high yield when XPhos was used as the ligand. Moreover, the bromo functionality in Ar-B(dan) substrates 1h and 1i is tolerated in this cross-coupling reaction, and the corresponding products (3ha and 3ia)

were obtained regardless of the position of the bromine atom on the benzene ring. These results suggest that the products should be readily amenable to further functionalization of the  $C(sp^2)$ -Br bond. Sterically demanding 2,4,6-trimethylphenyl-B(dan) (**1j**) reacted with **2a** using XPhos as the ligand, and **3ja** was isolated in 75% yield.

To investigate the "polyfluorophenyl and 2-pyridyl problems" in these Suzuki-Miyaura cross-coupling reactions, polyfluorophenyl-B(dan) derivatives **1k** and **1l** and a 2-pyridyl-B(dan) derivative **1m**,<sup>4c</sup> which are stable and can be easily purified by column chromatography, were subjected to the established cross-coupling protocol. When the reactions of **1k** and **1l** were carried out in the presence of a reduced amount (1.25 equiv) of KO*t*-Bu, the corresponding polyfluorobiaryls **3ka** and **3la** were isolated in high yield. The reaction of **1m** with **2a** provided coupling product **3ma** in 92% yield. These results indicate that the cross-coupling using **1k-m** complements the previous solutions<sup>15-18</sup> for the "polyfluorophenyl and 2-pyridyl problems".

Table 3. Substrate Scope of the Suzuki–Miyaura Cross-Coupling Reaction Between Ar–B(dan) (1) and ArX (2).

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#### **ACS** Catalysis



<sup>a</sup>General reaction conditions: 1 (1.25 equiv), 2a (1.0 equiv), [Pd<sub>2</sub>(dba)<sub>3</sub>]·CHCl<sub>3</sub> (2.0 mol %), PPh<sub>3</sub> (4.0 mol %), KOt-Bu (2.5 equiv), toluene ([2a]<sub>0</sub> = 0.05 M). <sup>b</sup>THF was used as the solvent. <sup>c</sup>XPhos (4.0 mol %) was used instead of PPh<sub>3</sub>. <sup>d</sup>The reaction was carried out at 110 °C. e1.25 equiv of KOt-Bu was used.

We also briefly explored the scope with respect to aryl halides (2) in these cross-coupling reactions. Various substituted iodobenzene derivatives (2b-e) were tested, and, as expected, the corresponding coupling products (3ab-ae) were obtained in high yield, regardless of the substituents and their positions on the benzene ring. Finally, 4-bromo- and 4-chloroanisole were used in the cross-coupling of 1a, which afforded 3aa, albeit slightly modified reaction conditions were required.

To gain insight into the mechanism underlying the Suzuki-Miyaura cross-coupling of Ar-B(dan), we carried out several control experiments (Scheme 1). The crosscoupling of **1a** and **2a** in

Scheme 1. Preliminary Mechanistic Studies



(c) Formation and molecular structure<sup>a</sup> of the borate K[1a(Ot-Bu)]



(d) Stoichiometric reaction of K[1a(Ot-Bu)] with [Pdl(4-MeOC<sub>6</sub>H<sub>4</sub>)(PPh<sub>3</sub>)<sub>2</sub>]



<sup>a</sup>For clarity, only one of the repeat units of the onedimensional coordination polymer of {[K(thf)][1a(Ot-Bu)]} is shown. Thermal ellipsoids are shown at 50% probability and only selected atoms are labeled.

the presence of radical scavengers such as TEMPO and 1,4-benzoquinone afforded 3aa in moderate yields, while the reaction in the absence of a palladium complex did not which renders single-electron-transfer proceed, pathways<sup>19</sup> unlikely (Scheme 1a). Moreover, in the presence of 18-crown-6, the reaction of 1a and 2a afforded 3aa only in 25% yield (Scheme 1b),20 indicating that the potassium ion is of crucial importance for this reaction.<sup>21</sup> Subsequently, we examined the chemical species present in the reaction mixture. When a toluene solution of 1a was treated for 10 min at room temperature with a THF solution of KOt-Bu, the <sup>11</sup>B{<sup>1</sup>H} NMR spectrum of the resulting colored reaction mixture showed the complete conversion of **1a** ( $\overline{\delta}_{11B}$ : 29 ppm) into a new boron compound ( $\overline{\delta}_{11B}$ : -1.9 ppm) (Scheme 1c).<sup>22</sup> The molecular structure of this boron compound was unambiguously determined as potassium borate K[**1a**(Ot-Bu)] by a singlecrystal X-ray diffraction study. As evident from the <sup>11</sup>B{<sup>1</sup>H} NMR spectra, treatment of **1a** with LiOt-Bu or NaOt-Bu did not afford the corresponding borate (Figure S29). The stoichiometric reaction between K[**1a**(Ot-Bu)] and [Pdl(4-MeOC<sub>6</sub>H<sub>4</sub>)(PPh<sub>3</sub>)<sub>2</sub>] at 70 °C furnished cross-coupled product **3aa** in 92% yield (Scheme 1d),<sup>23</sup> which indicates that the formation of the potassium borate should be responsible for the present cross-coupling reaction.

Given the stoichiometric reaction of the borate salt from **1a** and the use of common palladium(0) complexes as the catalysts, the present cross-coupling reaction probably proceeds via a catalytic cycle that is generally accepted for Suzuki-Miyaura cross-coupling reactions (Scheme 2). Initially, the oxidative addition of haloarene **2** to

## Scheme 2. A Plausible Reaction Pathway



the palladium(0) species affords arylpalladium(II) **A**, which may undergo ligand exchange<sup>24</sup> with KOt-Bu to yield butoxide complex (X = Ot-Bu). Subsequently, transmetalation (step **B**) between **A** and K[1(Ot-Bu)], which is generated from **1** and KOt-Bu, would deliver diarylpalladium(II) **C** and K[BX(Ot-Bu)(dan)]. The high basicity of KOt-Bu enables the delivery of the borate salt. Moreover, the potassium ion may serve as the template to accelerate the transmetalation step **B**,<sup>20,21</sup> possibly through a cation- $\pi$  interaction.<sup>25</sup> Finally, the reductive elimination of **C** affords biaryl **3** under concomitant regeneration of the palladium(0) catalyst.

Finally, we extended the present reaction to a one-pot sequential Suzuki-Miyaura cross-coupling reaction, wherein the "less reactive" aryl-B(dan) moiety was cross-

coupled first (Scheme 3).26,27 The

# Scheme 3. One-Pot Iterative Suzuki-Miyaura Cross-Coupling via a B(dan)-B(pin) Sequence



reaction of 4-[(pin)B]C<sub>6</sub>H<sub>4</sub>B(dan) (**1e**) with **2a** generated **3ea** as the initial product under the previously established cross-coupling conditions. The reaction mixture containing **3ea** was subsequently treated with 4-iodotoluene (**2i**), KOt-Bu, and H<sub>2</sub>O. The reaction mixture was stirred for 24 h at 70 °C, and terphenyl derivative **4** was isolated in 80% yield. This procedure provides a complementary method to the previously reported synthesis of oligo(arene)s by sequential or iterative cross-coupling reactions.<sup>2,4a,b,e</sup> Moreover, this reaction is step-and pot-economic, a feature that has received much attention in recent years.<sup>7</sup>

In conclusion, we have developed a Suzuki–Miyaura cross-coupling protocol for Ar–B(dan) derivatives that proceeds without removal of the dan moiety. The use of KO*t*-Bu as a base is of crucial importance to deliver the borate that readily undergoes the transmetalation, and the formation of the borate was unequivocally confirmed by NMR spectroscopy and X-ray diffraction analysis. This study opens up new possibilities for the use of R–B(dan) substrates in various coupling reactions.<sup>28</sup>

### ASSOCIATED CONTENT

### **Supporting Information**

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

Experimental procedures and characterization data (PDF)

X-ray crystallographic data for 1k and  $[\{K(thf)\}\{1a(Ot\text{-}Bu)\}]_n$  (CIF)

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