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Highly practical boronic acid surrogates for the Suzuki–Miyaura cross-coupling

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ABSTRACT

Boronic acids and esters are well known substrates for the Suzuki–Miyaura cross-coupling. Yet their isolation can sometimes be tedious. We report here that the use of aryl dioxazaborocanes afford a simple isolation procedure while keeping a high efficiency in the cross-coupling process.

The Suzuki–Miyaura reaction (SMR) is among the most popular palladium-catalyzed reactions, as it proved almost unrivaled both in terms of its scope and efficiency.[1] It has been applied in a wide variety of applications including organic synthesis, materials, medicinal chemistry, etc.[2–5] Nevertheless, it still represents an area of intense research efforts. Numerous ligands have been developed and there are now systems of high efficiency, tolerating both bulk and various functionalities.[6,7] In contrast, the organic partners involved in these cross-couplings have been incredibly less studied. Although the impact of catalytic species in a catalytic reaction is obvious, the stoichiometric reagents should not be neglected. An efficient and quite universal access to nucleophilic coupling partners has thus become an important field of interest.[8–12]

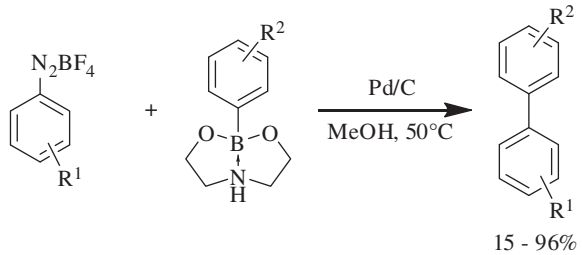
We have recently reported the facile synthesis and use of solid, stable, and self-activated precursors, namely dioxazaborocanes, for palladium-catalyzed cross-coupling reactions with tetrafluoroborate diazonium salts (Scheme 1).[13,14] These compounds, arising from the addition of diethanolamine to boronic acids or esters, were indeed shown to be the first boronic esters able to couple with diazonium salts without external activation of the boronic moiety.

Others have also reported that condensing diethanolamine with boronic acid offered some significant interest in the field of propargylation and allylation,[15–18] and in the borylation of α,β unsaturated ketones, esters, and derivatives.[19]

Despite these, diethanolamine esters have demonstrated exceptional stability, and ease of purification and handling,[20] and their use in the SMR with aryl halides is quite rare and almost exclusively limited to the coupling of pyridyl dioxazaborocanes.[21–26] We report here that aryl derivatives are also good boronic acid surrogates for Suzuki–Miyaura cross-coupling reactions with halogenated compounds under well defined conditions.

We first synthesized an array of dioxazaborocanes using our previously established procedure (Scheme 2).[27] This protocol was successfully extended to the synthesis of 4-(1,3,6,2-dioxazaborocan-2-yl)-N,N-disubstituted anilines in moderate to good yields.

Conditions of cross-couplings were then established on a model substrate as depicted in Table 1.



R^1 = 4-NO_2, 4-OMe, 4-Br, 4-I, 3-Br, 2-Br, 2-CF_3
R^2 = H, 4-OMe, 4-CHO, 4-CN, 4-OH, 3-CHO, 2-F-3-OMe

Scheme 1. Base-free cross-coupling of dioxazaborocanes with aryl diazonium salts.

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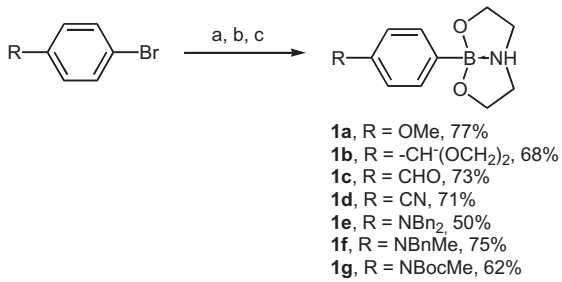


Scheme 2. Preparation of aryl dioxazaborocanes **1a–g**. Reagents and conditions: (a) *n*-BuLi, Et_2O, −78 °C; (b) B(O*i*-Pr)$_3$, Et_2O, −78 °C; (c) diethanolamine, *i*-PrOH, Et_2O.

The conditions previously established for the coupling of diazonium salts with dioxazaborocanes proved their inability to perform the cross-coupling even after extended reaction times (entries 1 and 2). Switching to more conventional catalysts for the classical SMR was beneficial and allowed the isolation of the desired cross-coupled product in moderate yields (entry 3). Moving from a biphasic system (toluene/water) to a homogeneous and polar one (DMF/water) not only enhanced the yield but also shortened the reaction time required for full conversion (entry 4).

In the absence of a copper salt, a significant decrease of the reaction rate was observed, the full conversion being achieved in 5 h instead of one (entry 5 vs 4). Yet the isolated yield remains unaltered. The copper might be involved in the transmetallation step of the SMR catalytic cycle either by facilitating the Pd–B transmetallation as already observed in Stille couplings[28–30] or by chelating the nitrogen atom of the diethanolamine part of the molecule. When using palladium acetate as a catalyst precursor, we observed some beneficial effect in using strongly donating ligands such as tricyclohexylphosphine (entry 6) or N-heterocyclic carbenes (entry 7). Introducing chlorides on the catalyst source slightly pushed the reaction toward a quantitative isolated yield (entry 8), which was finally achieved with simple $PdCl_2(PPh_3)_2$ (entry 9). We have then clearly established that the presence of water is strictly required in a homogeneous reaction mixture (entries 10 and 11). The hydrolysis of the dioxazaborocane in the presence of water at 100 °C cannot be excluded, and the possible in situ formation of the boronic acid is currently under investigation in our laboratory. It is noticeable that the cross-coupling reaction conditions have been optimized, not only in terms of isolated yields, but also by the fact that only 1.2 equiv of the boronic partner is introduced. This clearly contrasts with the usual excess of boronic derivatives involved in the SMR (1.5–2 equiv).

With the established optimized conditions and having an array of dioxazaborocanes in hand, we then explored the scope of these conditions to form disubstituted biaryl adducts and aryl-heteroaryl adducts.[31]

Concerning biaryl synthesis (Table 2), excellent yields were achieved with both electron rich and electron poor

Table 2
Scope of cross-coupling reactions using aryl dioxazaborocanes and aryl bromides under the optimized conditions

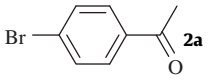
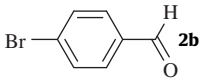
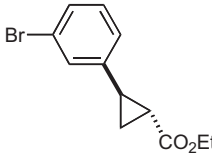
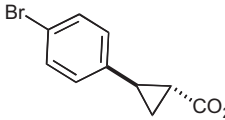
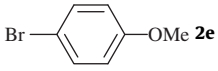
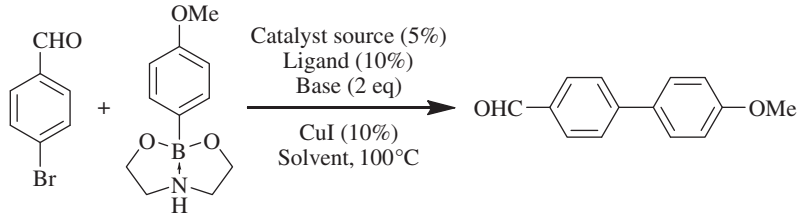
Entry	Dioxazaborocane	Aryl bromide	Isolated yield (%)
1	**1a**	 **2a**	100
2	**1b**	 **2b**	93
3	**1c**	**2a**	87
4	**1d**	**2b**	95
5[b]	**1d**	 **2c**	65
6	**1d**	 **2d**	40
7	**1d**	 **2e**	0

Table 1
Optimization of conditions for SMR with 4-metoxyphenyldioxazaborocane as a model substrate and 4-bromobenzaldehyde



Entry	Catalyst source	Ligand	Base	Solvent	Time (h)	Isolated yield (%)
1	Pd/C	None	Na_2CO_3	EtOH/H_2O	24	0
2	Hermann catalyst[a]	None	K_3PO_4	DMF/H_2O	48	0
3	$Pd(OAc)_2$	PPh_3	K_3PO_4	Tol./H_2O	3.5	63
4	$Pd(OAc)_2$	PPh_3	K_3PO_4	DMF/H_2O	1	88
5[b]	$Pd(OAc)_2$	PPh_3	K_3PO_4	DMF/H_2O	5	89
6	$Pd(OAc)_2$	PCy_3	K_3PO_4	DMF/H_2O	1	93
7	$Pd(OAc)_2$	SIMes[c]	K_3PO_4	DMF/H_2O	3.5	95
8	$PdCl_2$dppf	PPh_3	K_3PO_4	DMF/H_2O	4.5	98
9	$PdCl_2(PPh_3)_2$	PPh_3	K_3PO_4	DMF/H_2O	1	100
10	$PdCl_2(PPh_3)_2$	PPh_3	K_3PO_4	Tol./H_2O	24	9
11	$PdCl_2(PPh_3)_2$	PPh_3	K_3PO_4	DMF	16	45

[a] Hermann catalyst = [Pd(μ-OAc)$_2$(κ$_2$-P(*o*-tolyl)$_3$)$_2$].
[b] No copper iodide was used.
[c] SIMes = 1,3-bis(2,4,6-trimethylphenyl)-2-pentafluorophenyl imidazolidine.

dioxazaborocanes in reactions with electron deficient bromoarenes (entries 1–4).

Coupling with more electron rich aryl bromides proved less efficient as shown by the results obtained in the coupling reaction of 4-(1,3,6,2-dioxazaboracan-2-yl)-benzonitrile with trans ethyl-2-(3-bromophenyl)cyclopropanecarboxylate and trans ethyl-2-(4-bromophenyl)cyclopropanecarboxylate (entries 5 and 6). Expectedly, no epimerization of the 1,2-disubstituted cyclopropanes occurred under these reaction conditions. It is noticeable that these examples represent a straightforward access to biologically-active cyclopropanated biaryls recently described in the patent literature (Fig. 1).[32–34]

Introducing a methoxy group at the *para* position of the bromobenzene moiety proved to be deleterious, mainly yielding degradation of starting material (entry 7).

Finally, the cross-coupling of aryl dioxazaborocanes with heteroaryl bromides could also be achieved in moderate to very good yields (Table 3).

This approach provides a fairly straightforward route to 2-(4-aminophenyl)benzothiazole derivatives, which have been described as antitumor agents.[35–37] Moreover, there is a strong interest for this type of substrate for early detection of Alzheimer's disease β-amyloid peptide deposits by mean of Positron Emission Tomography (PET).[38–40] The coupling of differently substituted benzothiazoles with various N-protected anilines bearing a dioxazaborocane moiety in the *para* position have been carried out. Doubly benzylated anilines **1e** always achieved lower yields in cross-couplings (entries 1 and 2) compared to **1f** (entries 3 and 4). This might be seen as the consequence of a higher enrichment of the aromatic ring (bulk induced by two benzyl groups force the nitrogen in a sp^2 hybridization), which can lower the transmetallation step by increasing the carbon–boron bond strength. On the other side, deactivation of the nitrogen lone pair by a Boc group as in **1g** does not appear to influence the reaction efficiency (entries 6–8).

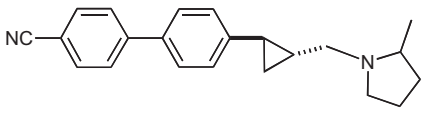
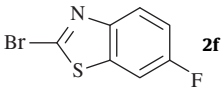
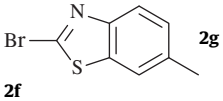
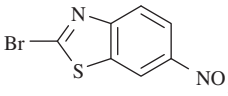
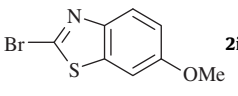


Figure 1. Patented cyclopropane-substituted biaryl.

Table 3
Scope of cross-coupling reactions using aryl dioxazaborocanes and heteroaryl bromides under the optimized conditions

Entry	Dioxazaborocane	Heteroaryl bromide	Isolated yield (%)
1	**1e**	 **2f**	52
2	**1e**	 **2g**	51
3	**1f**	**2f**	63
4	**1f**	**2g**	81
5[b]	**1f**	 **2h**	50
6	**1g**	**2f**	82
7	**1g**	**2g**	75
8	**1g**	 **2i**	71

In conclusion, we have demonstrated that aryl dioxazaborocanes represents good boronic acid surrogates for the Suzuki–Miyaura cross-coupling reaction. From a practical point of view, these compounds are easy to synthesize and isolate in a very pure fashion. As previously highlighted, they are highly stable, exhibiting a bench life time of many years without noticeable degradation. Because of their high stability, they do not require the use of a large excess of the boron partner which represents a significant advantage. Moreover the best reaction conditions require a catalyst source that is easily accessible. We do consider that all these practical features are of primary interest and will make these compounds attractive to both the academic and industrial communities.

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27. *Typical experimental procedure for the synthesis of aryl dioxazaborocane*: To 1 equiv of bromoaryl in THF (1 mmol/mL) under Argon at −78 °C is added dropwisely 1 equiv of *n*-BuLi. After 10 min at −78 °C neat $B(O\text{-}iPr)_3$ is dropwisely added. The resulting mixture is stirred for 1 h while allowed to warm to room temperature. Diethyl ether and a saturated solution of ammonium chloride are then added, and the resulting mixture is stirred for 30 min. The organic and aqueous phases are separated, the aqueous phase is then extracted with ether, and the organic phases are washed with brine. The organic phase is dried over $MgSO_4$ and filtered. The diethanolamine solution (*i*-PrOH, 3 M, 1 equiv) is added under stirring. A solid precipitates instantly. The mixture is filtered, and the solid is washed with ether and dried under vacuum. Spectroscopic data for selected dioxazaborocanes:
4,5,7,8-Tetrahydro-2-(4′-methoxyphenyl)-6H-[1,3,6,2]dioxazaborocane: ^{1}H NMR (DMSO-d_6, 300 MHz), δ = 7.34 (d, J = 8.5 Hz, 2H), 6.76 (d, J = 8.5 Hz, 2H), 3.89–3.81 (td, J = 9.2 Hz, J = 5.4 Hz, 2H), 3.79–3.73 (m, 2H), 3.70 (s, 3H), 3.12–3.00 (tdd, J = 11.7 Hz, J = 9.0 Hz, J = 6.9 Hz, 2H), 2.85–2.77 (m, 2H). ^{13}C NMR (DMSO-

d_6, 75.5 MHz), δ = 158.9, 134.2, 112.8, 63.4, 55.2, 51.1, C in α position of the boron not detected. ^{11}B NMR (DMSO-d_6, 96.3 MHz), δ = 10.8. MS (DCI–NH_3, MeCN) m/z: 239.4 $[M-NH_4]^+$. EA: C = 59.43%, H = 7.32%, N = 6.21% (calculated for $C_{11}H_{16}BNO_3$, C = 59.77%, H = 7.30%, N = 6.34%). IR, KBr (cm^{-1}): 3137 (br), 3031, 2879, 2836, 1600, 1282, 1220, 1174, 1080, 1065, 818.

4,5,7,8-Tetrahydro-2-(4′-cyanophenyl)-6H-[1,3,6,2]dioxazaborocane: lithiation and addition of $B(O^iPr)_3$ were done at −100 °C. ^{1}H NMR (DMSO-d_6, 300 MHz), δ = 7.61 (s, 4H), 3.93–3.85 (td, J = 9.2 Hz, J = 5.4 Hz, 2H), 3.83–3.76 (m, 2H), 3.16–3.05 (tdd, J = 11.8 Hz, J = 9.2 Hz, J = 6.9 Hz, 2H), 2.92–2.86 (m, 2H). ^{13}C NMR (DMSO-d_6, 75.5 MHz), δ = 133.9, 130.7, 120.3, 109.5, 63.4, 51.3, C in α position of the boron not detected. ^{11}B NMR (DMSO-d_6, 96.3 MHz), δ = 10.8. MS (DCI–CH_4): 217.1 $[MH]^+$. EA: C = 59.49%, H = 6.13%, N = 12.59% (calculated for $C_{11}H_{13}BN_2O_2 + 0.33H_2O$: C = 59.52%, H = 6.20%, N = 12.62%). IR, KBr (cm^{-1}): 3138 (br), 3040, 2865, 2218, 1466, 1279, 1236, 1072, 823, 786. Characterization of other dioxazaborocanes can be found in Ref. 11.

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31. *Typical experimental condition for cross coupling reaction between dioxazaborocanes and brominated aromatics*: aryldioxazaborocane (1.2 equiv), arylbromide (1 equiv) $PdCl_2(PPh_3)_2$ (5 mol %), PPh_3 (10 mol %) and copper iodide (10 mol %) in a 4:1 DMF/water mixture (0.2 mmol/mL) under Argon are brought to 100 °C until no more aryl bromide is detected. After cooling to RT, water and Et_2O are added. The organic and aqueous phases are separated, the aqueous phase is then extracted with ether, and the organic phase is washed with brine, then dried over $MgSO_4$, and filtered. After evaporation the residue is purified by flash column chromatography. Spectroscopic data for selected biaryls:

4′-acetyl-4-methoxy-biphenyl (Table 2, entry 1): flash chromatography eluant: DCM/C_6H_{12}: 70:30. ^{1}H NMR ($CDCl_3$, 300 MHz), δ = 8.04 (d, J = 8.5 Hz, 2H), 7.67 (d, J = 8.5 Hz, 2H), 7.61 (d, J = 8.9 Hz, 2H), 7.03 (d, J = 8.9 Hz, 2H), 3.89 (s, 3H), 2.66 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz), δ = 197.8, 160.0, 145.4, 135.3, 132.3, 129.0, 128.4, 126.6, 114.5, 55.4, 26.7. MS (DCI–NH_3): 245.1 $[M+NH_4]^+$. mp = 155–156 °C. R_f = 0.37.

2-[3′-(4-cyanophenyl)phenyl]cyclopropane ethyl carboxylate (Table 2, entry 5): flash chromatography eluant: DCM/C_6H_{12}: 70:30. ^{1}H NMR ($CDCl_3$, 300 MHz), δ = 7.76 (d, J = 8.5 Hz, 2H), 7.69 (d, J = 8.5 Hz, 2H), 7.45–7.36 (m, 3H), 7.18 (td, J = 6.5 Hz, J = 2.0 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 2.63 (ddd, J = 9.3 Hz, J = 6.5 Hz, J = 4.2 Hz, 1H), 2.00 (ddd, J = 8.5 Hz, J = 5.2 Hz, J = 4.2 Hz, 1H), 1.69 (ddd, J = 9.3 Hz, J = 5.2 Hz, J = 4.7 Hz, 1H), 1.40 (ddd, J = 8.5 Hz, J = 6.5 Hz, J = 4.7 Hz, 1H), 1.33 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz), δ = 173.2, 145.5, 141.2, 139.6, 132.6, 129.3, 127.8, 126.3, 125.5, 125.4, 118.9, 111.1, 60.9, 26.1, 24.3, 17.1, 14.3. MS (DCI–NH_3): 309.3 $[M+NH_4]^+$. HRMS (DCI–NH_3) 309.1597 (calculated for $C_{19}H_{21}N_2O_2$: 309.1998).

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