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Silyl-protected dioxaborinanes: application in the Suzuki cross-coupling reaction†

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The synthesis of a range of novel silyl-protected dioxaborinanes as a column- and bench-stable boron reagent were found to be advantageous to achieving good yields in palladium-catalysed cross-coupling reactions under standard conditions.

For Suzuki cross-coupling reactions, boronic acids are the coupling partners of choice in the majority of applications. However, boronic acids can be difficult to synthesise and there can often be issues with purification and manipulation. Also, an excess of the boronic acid has to be used due to the competing formation of trimeric cyclic anhydrides (boroxines) and protodeboronation processes, leading to difficulties in being able to accurately measure reaction stoichiometry.[1] A number of elegant solutions to these problems have been presented involving the use of preformed borate and boronate reagents that can be isolated and stored prior to use (Fig. 1). These include tris(hydroxy)borates,[2] lithium trimethoxyborate species,[3] trifluoroborate salts[4] and *N*-methyliminodiacetic acid (MIDA) boronates.[5] An important addition to this range of donors is the cyclic triolborates synthesised by Miyaura.[6] These borate reagents are reported to be stable in air and water and more soluble in organic solvents than potassium trifluoroborates. Recently, we described the synthesis of silyl-protected dioxaborinanes and exemplified their use as a coupling partner in the enantioselective synthesis of 4-aryl-chroman-2-ones.[7] In this paper we describe an alternative procedure to the synthesis of silyl-protected dioxaborinanes and demonstrate their use as a boron reagent within the Suzuki cross-coupling reaction.

Previously, we reported that heating boronic acids with 1,1,1-tris(hydroxymethyl)ethane **1**, under Dean-Stark conditions gives the dioxaborinane intermediate prior to silylation.[7] Alternatively, stirring the boronic acid with the triol at room temperature in dichloromethane leads to the formation of the same intermediate without losing any boronic acid to boroxine formation. Following work-up, treatment with chlorotrimethylsilane in the presence of triethylamine gives the silyl-protected dioxaborinane in improved yields (Scheme 1). Also, the concentration of the reaction mixture for both reactions was found to be important in order to gain optimum yields *via* the telescoped procedure. Purification can be achieved through standard column chromatography to afford the desired protected boron species. Once synthesised and purified, silyl-protected dioxaborinanes are stable on a bench-top for several months without any decomposition being observed.

The synthesis was then applied to a wide range of commercially available boronic acids and the corresponding silyl-protected dioxaborinanes were obtained in all cases (Table 1). Simple aryl boronic acids gave excellent yields over the two steps but yields decreased somewhat for both electron-withdrawing aryl boronic acids as well as sterically demanding

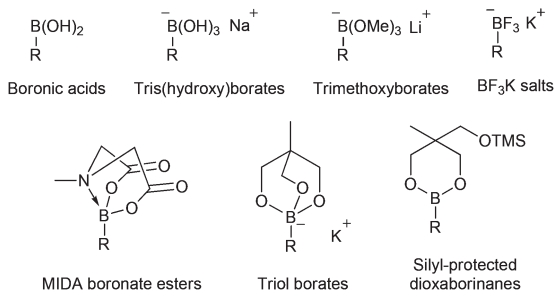
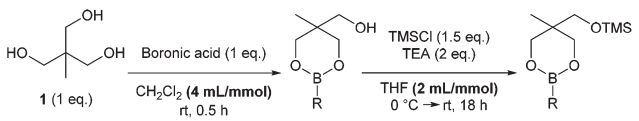


Fig. 1 Organoboron reagents.



Scheme 1 General procedure for the synthesis of silyl-protected dioxaborinanes.

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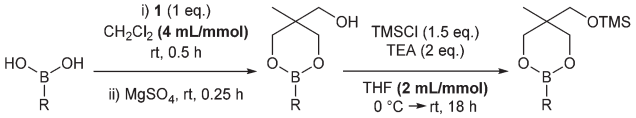
†Electronic supplementary information (ESI) available: Experimental procedures, characterisation data, copies of NMR spectra for compounds synthesised. CCDC 944020. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ob42099j

Table 1 Results of boronic acid protection[a]



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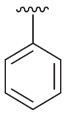
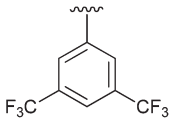
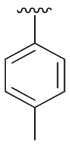
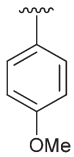
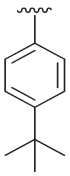
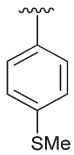
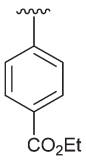
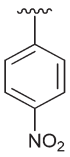
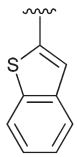
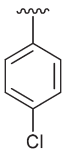
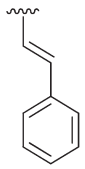
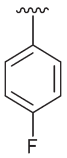
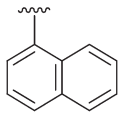
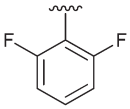
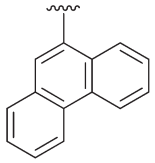
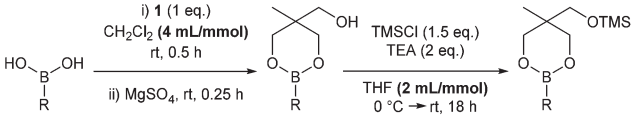
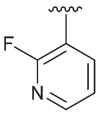
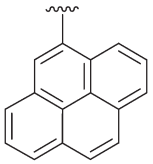
1	**2a**		96	10	**2j**		63
2	**2b**		95	11	**2k**		94
3	**2c**		49	12	**2l**		37
4	**2d**		56	13	**2m**		17
5	**2e**		70	14	**2n**		57
6	**2f**		98	15	**2o**		38
7	**2g**		97	16	**2p**		59
8	**2h**		15	17	**2q**		28

Table 1 *(Contd.)*



Entry		R	Yield[b] (%)	Entry		R	Yield[b] (%)
9	**2i**		37	18	**2r**		27

[a] Reaction conditions: boronic acid (8 mmol) suspended in anhydrous CH_2Cl_2 (4 mL $mmol^{-1}$) under N_2. Tris(hydroxymethyl)ethane (1 eq., 8 mmol) was then added and stirred until homogeneous (~0.5 h), then $MgSO_4$ added and stirred for an additional (0.25 h). Filtration and concentration gives crude intermediate. Redissolved in anhydrous THF (2 mL $mmol^{-1}$) under N_2 and TEA (2 eq. 16 mmol) was added. At 0 °C, TMSCl (1.5 eq., 12 mmol) added and left to stir overnight. Purification *via* silica gel column chromatography (hexane 8–2 EtOAc). [b] Isolated yields over two steps.

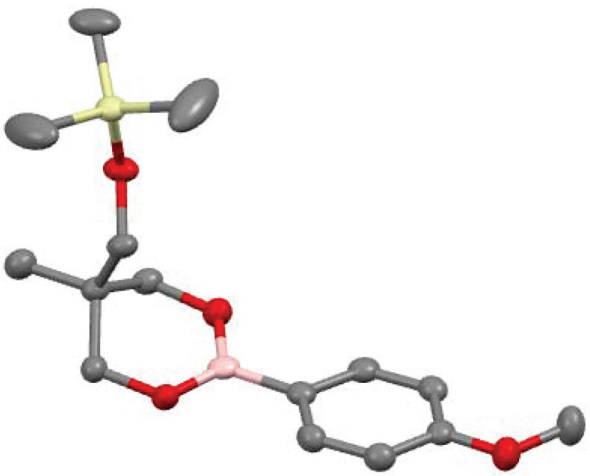


Fig. 2 ORTEP drawing of **2k**. Hydrogen atoms omitted for clarity.

substrates. Pleasingly, heteroaromatics were also tolerated under the reaction conditions. The structure of silyl-protected dioxaborinane **2k** was confirmed by X-ray crystallography (Fig. 2).

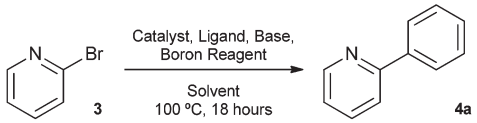
Previously, we have shown that silyl-protected dioxaborinanes provide superior yields as a boron reagent than boronic acids, trifluoroborates and triol borates within rhodium-catalysed conjugate addition reactions to arylidene Meldrum's acids.[7] We therefore attempted to extend the application of the silyl-protected dioxaborinanes by utilising them in Suzuki cross-coupling reactions.

The Suzuki cross-coupling reaction between boronic acids and aryl halides has developed into one of the most important cross-coupling reactions and is a powerful and general method for the formation of carbon–carbon bonds.[8] In particular, the construction of carbon–carbon bonds between hetero-aromatics is of great interest as a variety of pharmaceutical compounds are structured around heteroaryl motifs, often containing a pyridine moiety.[9] With this in mind, we decided to choose 2-bromopyridine as the substrate for Suzuki cross-coupling reactions with our silyl-protected dioxaborinanes to identify any potential benefit the protecting group has over standard boronic acids. Typically, a combination of solvents, bases and ligands are required to obtain high yields in Suzuki cross-coupling reactions, especially with difficult substrates.[10] Therefore, a common set of conditions were chosen to identify the optimum conditions for the cross-coupling reaction with our dioxaborinanes (Table 2).

Surprisingly, when using conditions pioneered by Fu *et al.*, that can deliver excellent yields using aryl chlorides as substrates at room temperature, the Suzuki cross-coupling failed to give any of the desired product (Table 2, entry 1).[11] Conditions typified by Buchwald *et al.*, afforded 2-phenylpyridine **4a** only in a modest yield (Table 2, entry 2).[12] However, when using standard Suzuki cross-coupling conditions of 1 mol% $Pd(PPh_3)_4$ in ethanol, a near quantitative yield was obtained (Table 2, entry 4). Lowering the catalytic loading and dropping the equivalents of dioxaborinane only lead to a drop-off in yield. Comparatively, when using the same conditions but using phenylboronic acid as the coupling partner, a lower yield was obtained (Table 2, entry 5). This interesting result prompted a further study to compare the advantage silyl-protected dioxaborinanes may have over boronic acids and other boronic acid ester derivatives using a more challenging substrate.

The construction of carbon–carbon bonds between two heteroaryl reagents can be problematic for palladium-catalysed coupling reactions due to hetero-atom lone pairs being able to coordinate to the metal centre and subsequently poison the catalyst.[13] Benzo[*b*]thiophen-2-ylboronic acid, its neopentyl glycol and pinacol derivatives, along with silyl-protected dioxaborinane derivative **2n**, were therefore chosen as boron reagents in the Suzuki cross-coupling with 2-phenylpyridine under our optimised conditions (Table 3).

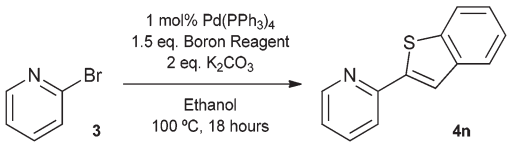
Table 2 Optimisation of the Suzuki cross-coupling reaction[a]

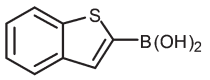
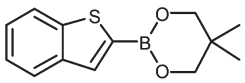
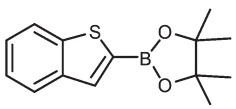


Entry	Catalyst	Base	Boron reagent	Solvent	Yield[j] (%)
1	Pd_2dba_3 [b]	K_3PO_4 [c]	**2a** (1 eq.)	Dioxane 2–1 H_2O	0
2	$Pd(OAc)_2$ [d]	K_3PO_4 [e]	**2a** (0.8 eq.)	DMF 9–1 H_2O	77
3	$Pd(PPh_3)_4$ [f]	K_2CO_3 [g]	**2a** (1.5 eq.)	Ethanol	70
4	$Pd(PPh_3)_4$ [h]	K_2CO_3 [g]	**2a** (1.5 eq.)	Ethanol	98
5	$Pd(PPh_3)_4$ [h]	K_2CO_3 [g]	Ph-$B(OH)_2$ [i]	Ethanol	74
6	$Pd(PPh_3)_4$ [h]	K_2CO_3 [g]	**2a** (1.3 eq.)	Ethanol	73
7	$Pd(PPh_3)_4$ [h]	K_2CO_3 [g]	**2a** (1.1 eq.)	Ethanol	70

[a] Reaction conditions: catalyst, ligand and base dissolved in solvent under argon. Boron reagent in solvent then added followed by 2-bromopyridine (1 mmol). Reaction mixture then stirred for 18 hours at 100 °C. Purification *via* silica gel column chromatography (EtOAc 5–95 hexane). [b] 2.5 mol% Pd_2dba_3, 5 mol% PCy_3. [c] 1.7 eq. [d] 2.5 mol% $Pd(OAc)_2$, 5 mol% SPhos. [e] 3 eq. [f] 0.5 mol% $Pd(PPh_3)_4$. [g] 2 eq. [h] 1 mol% $Pd(PPh_3)_4$. [i] 1.5 eq. [j] Isolated yields.

Table 3 Comparative study of silyl-protected dioxaborinanes with other boron reagents[a]



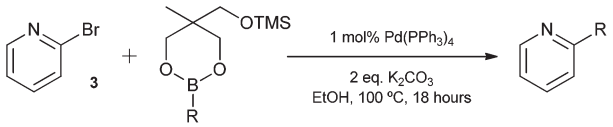
Entry	Boron reagent	Yield[b] (%)
1		50
2		67
3		91
4	**2n**	92

[a] Reaction conditions: $Pd(PPh_3)_4$ (0.01 mmol, 1 mol%), K_2CO_3 (2 mmol, 2 eq.) dissolved in ethanol (2 mL) under argon. Boron reagent (1.5 mmol, 1.5 eq.) in ethanol (2 mL) was added followed by 2-bromopyridine (1 mmol, 1 eq.). Reaction mixture stirred for 18 hours at 100 °C. Purification *via* silica gel column chromatography (hexane 95–5 EtOAc). [b] Isolated yields.

The unprotected boronic acid delivered only a moderate yield of product **4n**, whilst the neopentyl glycol protected species provided just a slight improvement. Surprisingly, the structurally similar protecting group of the silyl-protected dioxaborinane provided a far superior yield in comparison. This leads us to believe that the –OTMS group is playing a role within the reaction mechanism. Recent investigations into the rate of hydrolysis of boronic acid protecting groups have revealed that a 'slow-release' mechanism from the protected species to the free boronic acid suppresses the formation of competing side-products.[14] The silyl-protected dioxaborinanes could be operating in a similar fashion and slowly releasing the boronic acid under mild conditions for Suzuki cross-coupling reactions without the need for additional water to be added. However, it is also plausible that under basic conditions, the trimethylsilyl group is removed leading to the formation of a triol borate, which is a known active species formed prior to oxidative insertion. Further investigations are underway to determine the precise mechanism of the silyl-protected dioxaborinanes with coupling reactions. The pinacol-protected benzothiophene derivative also furnished a high yield of **4n** showing that the silyl-protected dioxaborinane competes favourably with existing protecting groups, and offers an alternative option for the preparation of a stable boron protecting group that has high reactivity in carbon–carbon bond forming reactions.

Having found the optimum conditions for the Suzuki cross-coupling using the silyl-protected dioxaborinane, the scope of the reaction was then explored (Table 4). Pleasingly, the desired product was obtained with all the dioxaborinanes that were screened against 2-bromopyridine. Electron-donating substituents on the aryl ring of the dioxaborinane gave near quantitative yields of the bis-aryl compound (Table 4, entries 2, 11, 12). This is as expected as increased nucleophilicity of the aryl ring accelerates transfer to the palladium catalyst during the transmetallation step of the catalytic cycle.[15] The alkenyl dioxaborinane **2o** also gave a near quantitative yield of 2-styrylpyridine, a result which is in accordance with Suzuki and Miyaura's findings in their seminal publication.[16] Generally, aryl halides were tolerated giving good yields in some cases (Table 4, entries 6, 7), but electron-withdrawing substituents on the aryl ring caused a decrease in yields (Table 4, entries 4, 5, 8, 9). Heteroaromatics were also tolerated giving good yields (Table 4, entries 13, 14) but bulkier groups and larger aromatics gave decreased yields due to sterics. The use of silyl-protected dioxaborinanes with 2-bromopyridine in Suzuki cross-coupling reactions allows for the efficient formation of 2-substituted pyridines; products which can be

Table 4 Scope of Suzuki cross-couplings with silyl-protected borinanes[a]



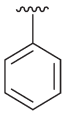
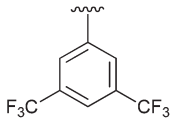
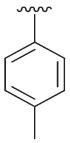
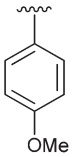
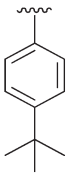
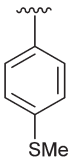
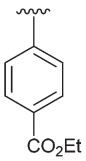
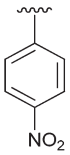
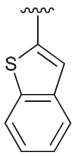
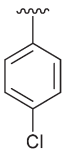
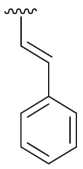
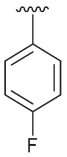
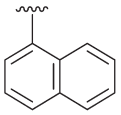
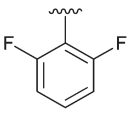
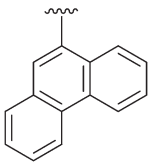
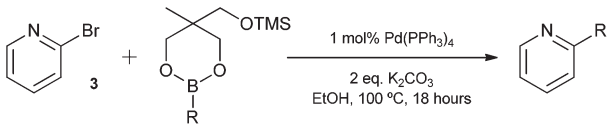
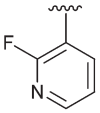
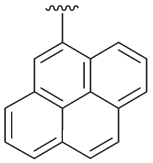
Entry		R	Yield[b] (%)	Entry		R	Yield[b] (%)
1	**4a**		98	10	**4j**		88
2	**4b**		96	11	**4k**		97
3	**4c**		80	12	**4l**		98
4	**4d**		48	13	**4m**		79
5	**4e**		67	14	**4n**		92
6	**4f**		87	15	**4o**		99
7	**4g**		98	16	**4p**		77
8	**4h**		42	17	**4q**		47

Table 4 *(Contd.)*



Entry		R	Yield[b] (%)	Entry		R	Yield[b] (%)
9	**4i**		9	18	**4r**		20

[a] Reaction conditions: $Pd(PPh_3)_4$ (0.01 mmol, 1 mol%), K_2CO_3 (2 mmol, 2 eq.) dissolved in ethanol (2 mL) under argon. Silyl-protected dioxaborinane (1.5 mmol, 1.5 eq.) in ethanol (2 mL) was added followed by 2-bromopyridine (1 mmol, 1 eq.). Reaction mixture stirred for 18 hours at 100 °C. Purification *via* silica gel column chromatography (hexane 95–5 EtOAc). [b] Isolated yields.

further functionalised *via* C–H activation methodology due to the directing group nature of the pyridine moiety.

Conclusions

In conclusion, we have shown that a wide range of silyl-protected dioxaborinanes can be prepared on a gram-scale in a mild and simple manner from their parent boronic acid. They are both column- and bench-stable and we have also shown that these dioxaborinanes perform exceptionally well in palladium-catalysed cross-coupling reactions. In the scenario presented here, this allowed for the efficient construction of highly functional bis(hetero)aryl compounds in very good yields from basic starting materials. Mechanistic studies are underway to understand the unique properties of silyl-protected dioxaborinanes within coupling reactions and their application to other reactions are also in progress.

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