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Zirconium-catalyzed Nagata reaction for the synthesis of 2-aryl-1,3,2-aryldioxaborins via a mild three-component condensation of phenols, aldehydes, and boronic acid

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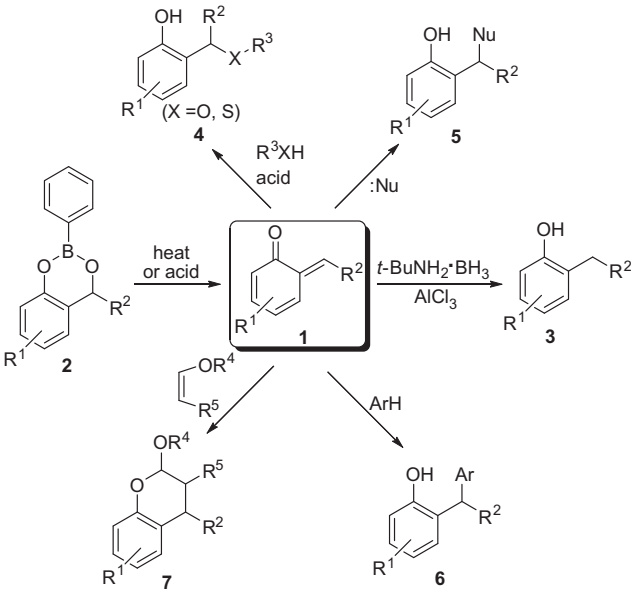
ABSTRACT

An efficient $ZrCl_4$ catalyzed *ortho*-hydroxyalkylation of phenols with aldehydes promoted by 3,5-bis (trifluoromethyl)phenyl boronic acid, leading to the formation of 2-aryl-1,3,2-aryldioxaborins was investigated and optimized. The reaction afforded the desired aryldioxaborins in good to excellent yields under mild conditions at room temperature. The electron-deficient boronic acid promoter was essential. Electron-rich phenols react faster, and both alkyl and aryl aldehydes are suitable substrates. The resulting aryldioxaborins can be further elaborated to produce substituted saligenols, 2-ethoxy chromans and 2-substituted phenols.

ortho-Quinone methides **1** (Scheme 1) are versatile motifs in organic synthesis, as they are known to be very reactive intermediates with applications in the total synthesis of natural products.[1] Following their generation, *ortho*-quinone methides (**1**) can undergo a wide variety of chemical transformations. For instance, they can be reduced to give *o*-alkylphenols **3**;[2b] or they can be trapped by alcohols/thiols and carbon nucleophiles to generate phenol derivatives **4** and **5**.[2a,b] A Friedel–Crafts reaction between **1** and aromatic compounds furnished the corresponding phenols **6**.[2a] Moreover, intermediates **1** can also be fused with different dienophiles inter- and intramolecularly to deliver the Diels–Alder cycloadducts **7**.[2b] A major issue with *ortho*-quinone methides **1** is their high reactivity, therefore, they are usually produced from a stable precursor in situ and used directly in the synthesis. 2-Aryl-1,3,2-aryldioxaborins (**2**) are very stable at room temperature, however, they can generate *ortho*-quinone methides (**1**) under thermolytic or acidic conditions.[2] Surprisingly, only a few approaches for the preparation of 2-aryl-1,3,2-aryldioxaborins **2** have been reported until now. The Peer group synthesized **2** from the three-component condensation of phenylboronic acid, phenol and paraformaldehyde by employing a carboxylic acid as the catalyst under reflux in benzene.[3] The Nagata group later modified the reaction conditions (refluxing toluene) to extend the substrate scope to various aldehydes.[4] The harsh reaction conditions, however, hampered further applications to sensitive, polymerizable aldehydes. Dufresne and co-workers developed a novel dichlorophenylborane as the phenylboronic acid surrogate to perform this reaction smoothly at 0 °C or room temperature.[5] The high cost and sensitivity to humidity of this surrogate limited its general application. Recently, Naimi-Jamal et al. reported that microwave irradiation can promote the transformation to **2** on the surface of acidic alumina, which results in environmentally harmful acidic alumina waste.[6] An effective approach to synthesize **2** under simple and practical conditions at room temperature was envisioned.



Scheme 1. 2-Aryl-1,3,2-aryldioxaborin **2** as versatile synthetic intermediates.

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As part of our program aimed at exploring the use of boronic acids as catalysts and promoters for amidation[7] and cycloadditions,[8] we herein report an efficient construction of 2-aryl-1,3,2-aryldioxaborin (**2**) catalyzed by $ZrCl_4$ under mild ambient conditions.

Initially, different arylboronic acids were screened. Interestingly, 3,5-bis(trifluoromethyl)phenylboronic acid (**8**) was identified as the most active one amongst over 70 boronic acids. It reacted with phenol and hexanal to deliver the desired aryldioxaborin **2a** in 10% yield promoted by propionic acid at 50 °C with 4 Å molecular sieves.[9] Inspired by this intriguing result, we examined different reaction conditions. Representative results are summarized in Table 1.[10] Several common dehydrating additives were selected to scavenge the water produced from the condensation reaction (Table 1, entries 1–3), and $MgSO_4$ led to the best yield of product **2a** at 25 °C. Unfortunately, the reaction was not Brønsted acid dependent so that the reaction yield could not be improved by changing different Brønsted acids (Table 1, entries 3–5). It is assumed that the reaction mechanism involves a [3,3]-sigmatropic rearrangement pathway (**A**, Fig. 1).[4] Lewis acid catalyzed [3,3]-sigmatropic rearrangements are well documented in the literature.[11] In the event, $Cu(OTf)_2$ was found to improve the reaction yield (Table 1, entry 6), and dichloromethane was found to give the best result after further screening of various solvents (Table 1, entries 7–10). Different Lewis acids were tested to further improve the reaction rate at room temperature (Table 1, entries 11–21). To our satisfaction, zirconium tetrachloride $ZrCl_4$ (5 mol %) gave the best yield (60%), and it also was found that excess hexanal (3.0 equiv) was essential to drive the reaction to completion (Table 1, entry 22). Control experiments showed that no desired product was formed in the absence of Lewis acid or **8** as the reactant. The detailed mechanism towards how the Lewis acid catalyzes the formation of 2-aryl-1,3,2-aryldioxaborins **2** is unclear. This reaction is proposed to proceed through a closed six-membered chairlike transition state **B** (Fig. 1), which is based on our previous mechanistic studies of Lewis acid-catalyzed allylboration.[12] In this transition state, the electron-deficient aryl substituent of **8** combines with Lewis acid coordination to render the boron atom more electrophilic and further favor aldehyde activation.

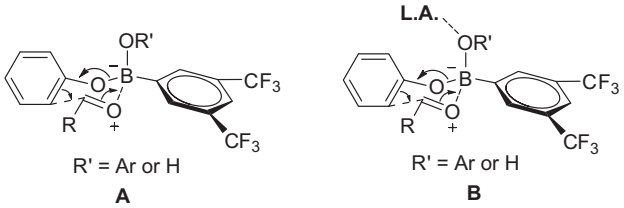
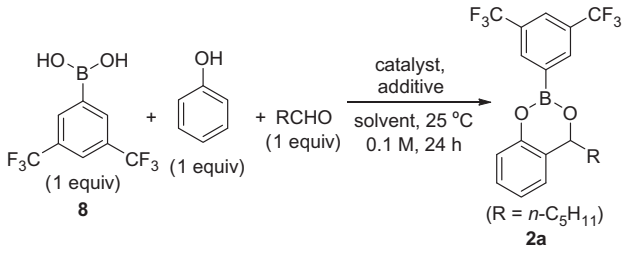


Figure 1. Proposed intermediates **A** (left, without Lewis acid catalysis) and **B** (right, with Lewis acid catalysis) for the formation of 2-aryl-1,3,2-aryldioxaborins **2**.

With the optimized conditions in hand,[13] more synthetically useful phenols and aldehydes were investigated (Table 2). Aliphatic, and electron-poor aromatic aldehydes are tolerated (Table 2, entries 1–3 and entries 5–8). Linear aldehydes proceeded

Table 1
Optimization of reaction conditions for three-component condensation[a]



Entry	Additive	Solvent	Catalyst[b]	Yield[c] (%)
1	M.S.[d]	Toluene	C_2H_5COOH	0
2	Na_2SO_4	Toluene	C_2H_5COOH	Trace
3	$MgSO_4$	Toluene	C_2H_5COOH	10
4	$MgSO_4$	Toluene	CCl_3COOH	13
5	$MgSO_4$	Toluene	CF_3COOH	ND[e]
6	$MgSO_4$	Toluene	$Cu(OTf)_2$	30
7	$MgSO_4$	EtOH	$Cu(OTf)_2$	0
8	$MgSO_4$	EtOAc	$Cu(OTf)_2$	Trace
9	$MgSO_4$	Et_2O	$Cu(OTf)_2$	5
10	$MgSO_4$	CH_2Cl_2	$Cu(OTf)_2$	33
11	$MgSO_4$	CH_2Cl_2	$ZnBr_2$	Trace
12	$MgSO_4$	CH_2Cl_2	$SnCl_2$	6
13	$MgSO_4$	CH_2Cl_2	$Yb(OTf)_3$	42
14	$MgSO_4$	CH_2Cl_2	CuBr	13
15	$MgSO_4$	CH_2Cl_2	$ZrCl_4$	53
16	$MgSO_4$	Toluene	$ZrCl_4$	48
17	$MgSO_4$	EtOH	$ZrCl_4$	Trace
18	$MgSO_4$	EtOAc	$ZrCl_4$	7
19	$MgSO_4$	Et_2O	$ZrCl_4$	Trace
20	M.S.[d]	CH_2Cl_2	$ZrCl_4$	Trace
21	Na_2SO_4	CH_2Cl_2	$ZrCl_4$	31
22[f]	**$MgSO_4$**	**CH_2Cl_2**	**$ZrCl_4$**	**60**

[a] Reaction conditions: the mixture of phenol (1.0 mmol), 3,5-bis(trifluoromethyl)phenylboronic acid (1.0 mmol), hexanal (1.0 mmol), 4 Å molecular sieves (1.0 g) or other additives (5.0 mmol) and catalyst (0.05 mmol or 0.3 mmol) in the given solvent was stirred at 25 °C for 24 h.

[b] For Brønsted acids, 30 mol % catalyst loading was used. For Lewis acids, 5 mol % catalyst loading was used.

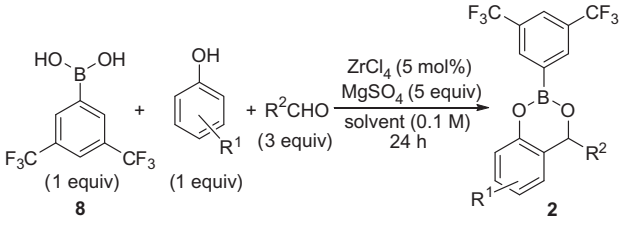
[c] Isolated yields of product purified by recrystallization of crude mixture from diethyl ether/*n*-pentane (1:3).

[d] M.S.: 4 Å molecular sieves.

[e] A complex mixture was obtained.

[f] 3.0 mmol (3 equiv) hexanal was used.

Table 2
Substrate scope studies for $ZrCl_4$-catalyzed three-component condensation[a]



Entry	R^1 =	R^2 =	Solvent[b]	Temp (°C)	Prdt	Yield[c] (%)
1	H	n-C_5H_{11}	CH_2Cl_2	25	**2a**	60
2	H	$PhCH_2CH_2$	CH_2Cl_2	25	**2b**	68
3	H	$(C_2H_5)_2CH$	DCE	50	**2c**	63
4	H	$(CH_3)_3C$	DCE	50	**2d**	0
5	H	Ph	DCE	50	**2e**	36
6	H	2-$NO_2C_6H_4$	CH_2Cl_2	25	**2f**	76
7	H	3-$NO_2C_6H_4$	CH_2Cl_2	25	**2g**	58
8	H	4-$NO_2C_6H_4$	CH_2Cl_2	25	**2h**	71
9	H	4-$MeOC_6H_4$	DCE	50	**2i**	Trace
10	Naph[d]	$PhCH_2CH_2$	CH_2Cl_2	25	**2j**	80
11	Naph[e]	$PhCH_2CH_2$	CH_2Cl_2	25	**2k**	75
12	2-CH_3	$PhCH_2CH_2$	CH_2Cl_2	25	**2l**	70
13	4-CH_3	$PhCH_2CH_2$	CH_2Cl_2	25	**2m**	78
14	2-OMe	$PhCH_2CH_2$	CH_2Cl_2	25	**2n**	83
15	4-OMe	$PhCH_2CH_2$	CH_2Cl_2	25	**2o**	87
16	4-Cl	$PhCH_2CH_2$	DCE	50	**2p**	53
17	4-NO_2	$PhCH_2CH_2$	DCE	50	**2q**	0

[a] Reaction conditions: the mixture of phenols (1.0 mmol), 3,5-bis(trifluoromethyl)phenylboronic acid (1.0 mmol), aldehydes (3.0 mmol), $MgSO_4$ (5.0 mmol) and $ZrCl_4$ (0.05 mmol) in the given solvent was stirred at the given reaction temperature for 24 h.

[b] DCE: 1,2-dichloroethane.

[c] Isolated yields of product purified by recrystallization of crude mixture from diethyl ether/*n*-pentane (1:3).

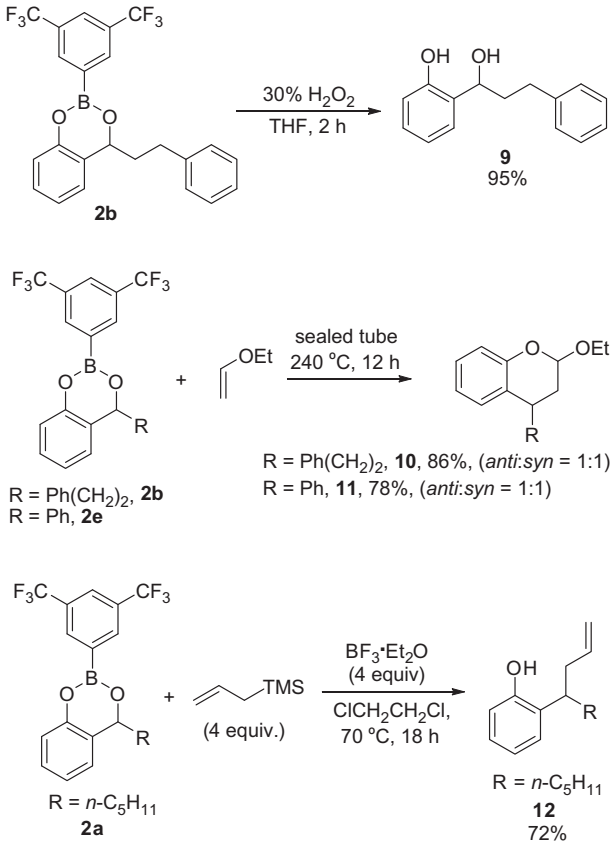
[d] Substituted phenol: 1-naphthol.

[e] Substituted phenol: 2-naphthol.

to react smoothly under optimized conditions (Table 2, entries 1 and 2). For the more hindered aldehyde, it was necessary to use 1,2-dichloroethane as a solvent at elevated temperature (50 °C) (Table 2, entry 3). No desired product was observed with pivalaldehyde neither in the crude reaction mixture nor after work up (Table 2, entry 4). This lack of reactivity is likely as a result of steric hindrance. Compared to aliphatic aldehydes, benzaldehyde gave the desired product **2e** in moderate yield even at 50 °C (Table 2, entry 5). It was found that the electronic properties of substituents played an important role for the reactivity. Thus, electron-withdrawing aromatic aldehydes delivered products **2f**–**h** in good yields under optimized conditions (Table 2, entries 6–8), and electron-donating aromatic aldehydes showed lower reactivity (Table 2, entry 9).

We next examined the substrate scope of this methodology with a panel of substituted phenols in the presence of hydrocinnamaldehyde. 1-Naphthol and 2-naphthol gave the aryldioxaborins **2j** and **2k** in good yields (Table 2, entries 10 and 11). Interestingly, only one regioisomer was obtained with 2-naphthol both in crude reaction mixture and after work up, which revealed that the 1-position of 2-naphthol is more reactive than the 3-position. The reactivity of substituted phenols was found to be dependent on the electronic properties of the substituents. Electron-rich phenols gave the desired aryldioxaborins **2l**–**o** in excellent yields (Table 2, entries 12–15). Halogen (Cl) substituted phenol gave the desired product **2p** in good yield under elevated temperature (Table 2, entry 16). The electron-poor 4-nitro-phenol however, showed no reactivity (Table 2, entry 17).

Further applications of 2-aryl-1,3,2-aryldioxaborin **2** to the preparation of more synthetically and biologically useful derivatives are shown in Scheme 2. The substituted saligenol **9** was obtained by hydrolytic oxidation (30% H_2O_2) of dioxaborin **2b** in excellent yield.[2] Thermolysis of the dioxaborin **2b** or **2e** gave the corresponding *ortho*-quinone methides **1** as the intermediates, which were trapped by ethyl vinyl ether to afford the desired 2-ethoxy chromans **10** or **11** in good yields.[2] Michael addition of allyl trimethylsilane to the *ortho*-quinone methide generated in situ from dioxaborin **2a** in the presence of boron trifluoride etherate at 70 °C gave the desired 2-substituted phenol **12** in good yield.[2]



Scheme 2. Synthetic applications of 2-aryl-1,3,2-aryldioxaborin **2**.

Although the underlying mechanism of this new catalytic process remains to be elucidated, it can be concluded that the electronic properties of substituents have a large impact on the reactivity of all three reactants. The electron-withdrawing CF_3 groups make boronic acid **8** more acidic, thus favoring the formation of six-membered chair-like transition state **B** (Fig. 1). The improved nucleophilicity of the phenols by electron-donating groups and the increased electrophilicity of the aldehydes decorated with electron-withdrawing groups favor the [3,3]-sigmatropic rearrangement process.

In summary, we have identified a mild and effective approach for the preparation of aryldioxaborins **2** using $ZrCl_4$ as the catalyst and electron-deficient boronic acid **8** as the promoter. A wide range of aldehydes and phenols are suitable as substrates. Further studies of this reaction process will be aimed at clarifying the mechanism, developing a chiral Lewis for producing optically pure aryldioxaborins, and its application to the total synthesis of biologically important molecules.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures, NMR spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.035.

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9. For detailed information about the screening of arylboronic acids, see Supplementary data Section 2.1.

10. For detailed information about the screening of reaction conditions, see Supplementary data Section 2.
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13. *Typical experimental procedure for $ZrCl_4$ catalyzed synthesis of 2-aryl-1,3,2-aryldioxaborins via a three-component condensation*: a mixture of 3,5-bis(trifluoromethyl)phenylboronic acid (258 mg, 1.0 mmol), phenol (94 mg, 1.0 mmol), hexanal (300 mg, 3.0 mmol), $MgSO_4$ (600 mg, 5.0 mmol) and $ZrCl_4$ (12 mg, 0.05 mmol) in dichloromethane (10 mL) was stirred at 25 °C for 24 h. The reaction mixture was filtered to remove $MgSO_4$. The filtrate was diluted with dichloromethane (30 mL) and washed with H_2O (30 mL). The aqueous phase was further extracted with dichloromethane (2 × 20 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The residue was recrystallized from diethyl ether/*n*-pentane (1:3) to afford the title 2-aryl-1,3,2-aryldioxaborin **2a** (250 mg, 60%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 2H), 8.00 (s, 1H), 7.28 (t, J = 7.7 Hz, 1H), 7.15–7.08 (m, 2H), 7.06 (d, J = 7.6 Hz, 1H), 5.33 (dd, J = 7.2, 4.2 Hz, 1H), 2.02–1.81 (m, 2H), 1.60–1.44 (m, 2H), 1.42–1.26 (m, 4H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 134.2, 131.0 (q, J_{C-F} = 32.8 Hz), 128.9, 126.0, 125.5, 124.9, 123.7, 123.6 (q, J_{C-F} = 272.9 Hz), 118.0, 73.6, 39.4, 31.6, 23.9, 22.6, 14.0; ^{11}B NMR (128 MHz, $CDCl_3$) δ 26.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.3; IR (Microscope, cm^{-1}) 3053, 2956, 2935, 2861, 1618, 1590; HRMS (EI) for $C_{20}H_{19}BF_6O_2$: calcd 416.13824; found 416.13754.