

Reactivity Insights of Methoxyphenyl Boronic Acids in Rieche Formylation Reaction

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In this study, mono- or poly-methoxylated phenyl boronic acids, were subjected to Rieche formylation. Unexpectedly the corresponding *ipso*-substituted aryl aldehydes were obtained in excellent yields and, for some of these substrates, the

formylated arylboronic acids were also synthesized in moderate yields. These findings provide new insights into the general reactivity and versatility of arylboronic acids.

Introduction

To date, the formylation of aromatic compounds has been extensively studied, and a wide variety of reagents are available for the aromatic electrophilic formylation. Classical methods to prepare aryl aldehydes, such as the Reimer-Tiemann, Vielsmeier-Haack, Gattermann-Koch, and Duff reactions,^[1] or through aryl halides,^[2] generally involve the use of large amounts of reagents and multi-step sequences, resulting in the generation of side products.

These features raise significant environmental concerns and limit the practical application in industrial settings. Moreover, the harsh reaction conditions employed in these methods are often incompatible with sensitive functional groups, and the lack of regioselectivity presents a challenge for achieving milder and more selective formylation reactions.

Notably, recent advancements in borylation methods have made aryl boronic acids readily accessible and widely utilized as versatile building blocks in organic synthetic transformations. These substances exhibit unique reactivity, enabling various carbon-carbon coupling reactions such as the well-known Suzuki coupling,^[3] as well as carbon-heteroatom bond formations utilizing transition metal complexes.^[4] These transformations encompass the introduction of oxygen,^[5] nitrogen,^[6] halogen,^[7] as well as alkyl, alkynyl, alkenyl, and aryl moieties.^[8] However, to the best of our knowledge, there are limited examples of formylation reactions specifically involving arylboronic acids.^[9]

In this study, we present a simple, convenient, and mild method for the formylation of arylboronic acids based on the Rieche conditions.^[10] This approach utilizes Lewis acids (AgOTf, AlCl₃, or FeCl₃) and dichloromethyl methyl ether (Cl₂CHOCH₃) as the formylating agent in dichloromethane at room temperature.

Results and Discussion

The formylation of various arylboronic acids was initially attempted using AgOTf^[10a] under mild conditions, as depicted in Scheme 1.

No reaction was observed in the presence of electron-withdrawing group (EWG) (CN, CHO, CF₃, NO₂, SO₂Me), or halogens (F, Cl, Br), even at higher temperatures or longer reaction times.

Surprisingly, 4-methoxyphenyl boronic acid **1** resulted in a 75:25 mixture of 4- and 2-methoxybenzaldehyde.

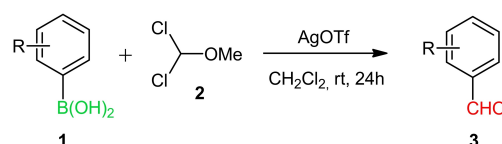
Motivated by this intriguing outcome, we proceeded to investigate this reaction using different Lewis acids. The results are summarized in Table 1. Formylation of **1a** using AgOTf (**method A**) led to a 3:1 ratio of the 4-/2-regioisomers **3a**:**3a'**, whereas AlCl₃ (**method B**) or FeCl₃ (**method C**) exclusively yielded the *ipso*-formylated product **3a**. It is noteworthy that when 4-methoxybenzene was subjected to formylation with AgOTf^[10a] or AlCl₃,^[10c] a mixture of regioisomers **3a**:**3a'** was obtained in a 1:1.5 or 1:1.2 ratio, respectively. The improved regioselectivity observed for 4-methoxyphenyl boronic acid

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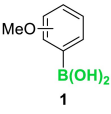
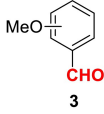
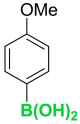
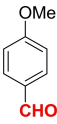
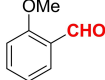
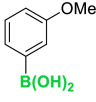
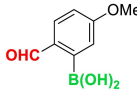
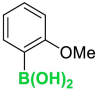
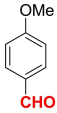
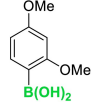
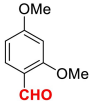
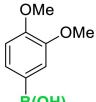
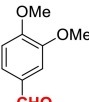
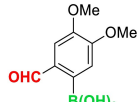
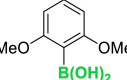
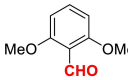

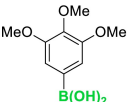
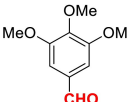
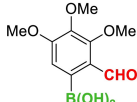
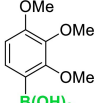
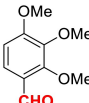
R = H, 4-Br, 4-SO₂Me, 4-CHO, 3-Cl, 3-CN,
3-CF₃, 3-NO₂, 3-F, 3,5-diF, 3,5-diBr

no reaction

R = 4-OMe

4-: 2-isomers 75:25

Scheme 1. Formylation of aryl boronic acids with AgOTf.

Table 1. Formylation of aryl boronic acids 1. ^[a]						
Entry	Substrate 1	Method	Product 3 (%) ^[b] and/or 3' (%) ^[b] and/or 4 (%) ^[b]			
						
1	 1 a	A B C	 3 a	75 100 92	 3 a'	25 0 0
2	 1 b	A B C			 4 b	18 58 56
3	 1 c	A B C	 3 a	21 13 48		
4	 1 d	A B C	 3 d	99 25 98		
5	 1 e	A B C	 3 e	87 88 85	 4 e	0 12 15
6	 1 f	A B C	 3 f	0 16 0	 3 d	85 59 60
7	 1 g	A B C	 3 g	ND 8 0	 4 g	ND 7 82
8	 1 h	A B ^[c] C	 3 h	100 0 100		

[a] Reaction conditions: **method A** (AgOTf, 1.0 eq., 1–3 h) or **method B** (AlCl₃, 1.2 eq., 24 h) or **method C** (FeCl₃, 1.0 eq., 24 h), from 0 °C to rt. [b] Yields of isolated compounds. [c] 1,2,3-trimethoxybenzene was obtained in quantitative yield.

prompted us to extend this reaction to various mono- and poly-methoxyphenyl boronic acids.

Herein, 3-methoxy- and 2-methoxyphenylboronic acids **1b** and **1c** were subjected to the same reaction conditions (Table 1, entries 2 and 3). Surprisingly, formylation of 3-methoxy phenylboronic acid **1b** (entry 2) yielded **4b**, a formylated boronic acid, as the exclusive product with a modest yield. On the other hand, formylation of 2-methoxy phenylboronic acid **1c** (entry 3) resulted in the formation of 4-methoxybenzaldehyde **3a**, deviating from the expected mixture of regioisomers **3a**:**3a'**.

Furthermore, the formylation of 2,4-dimethoxyphenylboronic acid **1d** (entry 4) led to the *ipso*-formylation product **3d** with moderate to excellent yield, where both substituents occupied the *ortho*- and *para*-positions relative to the formyl group. In the case of compound **1e** (entry 5) containing both *para* and *meta* substituents, the reaction produced aldehydes **3e** as the primary product, along with **4e**.^[11] Notably, 2,6-dimethoxyphenylboronic acid **1f** (entry 6) predominantly yielded the regioisomer **3d**, which, in this case, could be attributed to steric hindrance at the *ipso*-position.

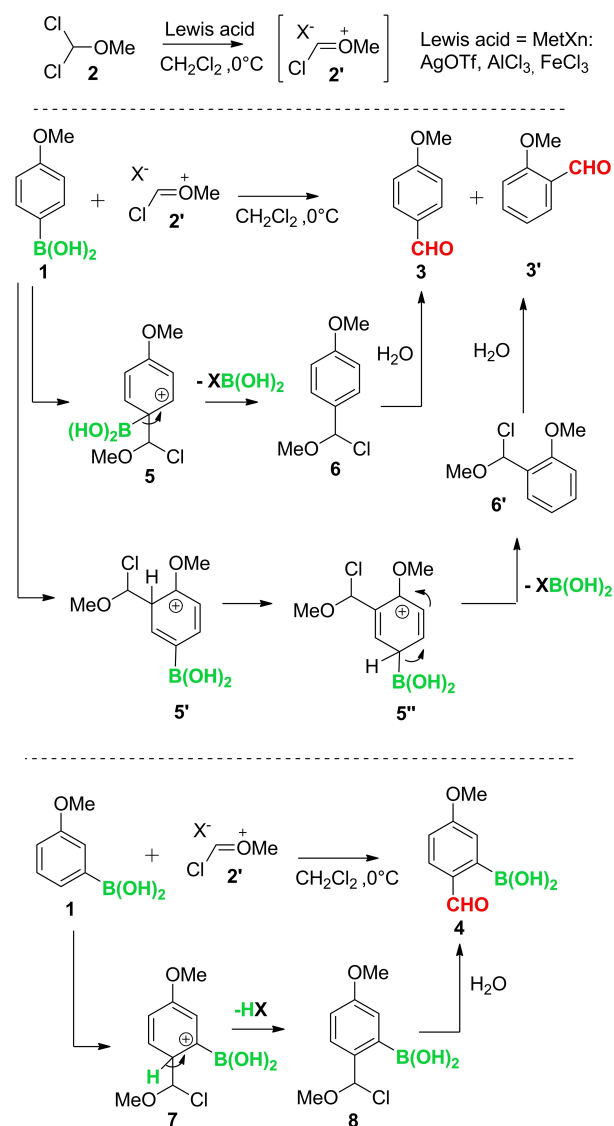
The Rieche reaction performed on the 3,4,5-trimethoxy derivative **1g** (entry 7) yielded both compounds **3g** and **4g** in varying ratios depending on the reaction conditions. In contrast, the isomeric 2,3,4-trimethoxyphenylboronic acid **1h** quantitatively formed the *ipso*-formylated compound **3h** using methods A and C, while the corresponding protodeboronated 1,2,3-trimethoxybenzene was obtained when AlCl₃ was used as the Lewis acid (method B, entry 8).

In order to extend the scope of these methodologies others electron-rich phenyl boronic acids and some heteroaryl boronic acids were subjected to the Reiche formylation reaction (see table 2).

The formylation of boronic acids bearing the 2-OH and 2-CH₂OH groups, compounds **5** and **6**, resulted in substrate degradation (Table 2, entries 1 and 2). The formylation carried out on compounds **7** and **9**, bearing a 4-*t*Bu or 4-Ph groups (Table 2, entries 3 and 5) resulted in both cases, in the exclusive formation of the protodeboronation products **17** and **19**, while 4-MeS-phenyl boronic acid **8** furnished the desired formylated compound **18** with 75% yield (Table 2, entry 4).

Heteroaryl boronic acids as the 3-pyridine derivative, compound **10**, was found to be completely unreactive under the investigated reaction conditions (Table 2, entry 6) while those containing oxygen, 3-furyl and 2-benzofuryl boronic acids, **11** and **12**, did not result in the expected formylated but rather in the degraded substrates (Table 2, entries 7 and 8). On the other hand, sulfur-containing heteroarenes such as 2-thiophenyl and 3-thiophenyl boronic acids, compounds **13** and **14**, resulted as unreactive compounds while the 2-benzothiophenyl and 3-benzothiophenyl derivatives, compounds **15** and **16**, provided both the formylated compound **20** with 56% and 95% yield (Table 2, entries 11 and 12, respectively).

Considering that the position and nature of the substituents influenced both the yield and regioselectivity of the phenylboronic acid formylation, an electrophilic aromatic substitution mechanism can explain the observed results. A plausible mechanism is proposed in Scheme 2. Electron-rich aryl boronic



Scheme 2. Proposed mechanism for the formylation of 4-OMe- and 3-OMe-phenyl boronic acids.

acids exhibited regioselective formation of *ipso*-substituted aryl aldehydes when the boronic moiety was located at an activated position. Regioisomers could arise from the addition of the electrophile 2' at other mesomeric-activated positions. Subsequently, the hydrogen shift on the carbon bearing the boron allows protodeboronation. Infact no traces of precursors with simultaneous co-presence of the boronic and formyl moieties on the ring were detected, as well as simply protodeboronated compounds. When the boronic moiety was located in a deactivated position, formylated phenylboronic acids were observed.

It appears that AgOTf is the most reactive system, as it generally provides higher yields and shorter reaction time, although with lower regioselectivity when compared to other systems. On the other hand, AlCl₃ generally resulted in poor reaction yields and required longer reaction times; however, it exhibited better regioselectivity. Finally, FeCl₃ emerged as the


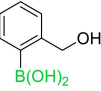
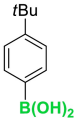
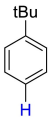
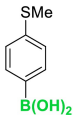
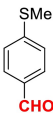
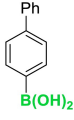
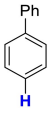
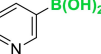
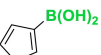
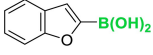
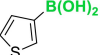
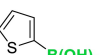
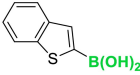
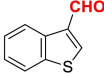
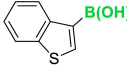
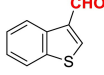
Table 2. Formylation of aryl boronic acids. ^[a]			
Entry	Substrate	Method	Product (%) ^[b]
	$\text{Ar}-\text{B}(\text{OH})_2 / \text{Het}-\text{B}(\text{OH})_2$		
1		A C	degradation
5			
2		A C	degradation
6			
3		C	 17 (90)
7			
4		C	 18 (75)
8			
5		C	 19 (87)
9			
6		A C	/
10			
7		A C	degradation
11			
8		A C	degradation
12			
9		C	/
13			
10		C	/
14			

Table 2. continued			
Entry	Substrate	Method	Product (%) ^[b]
	$\text{Ar}-\text{B}(\text{OH})_2 / \text{Het}-\text{B}(\text{OH})_2$		
11		C	 20 (56)
15			
12		C	 20 (95)
16			
[a] Reaction conditions: method A (AgOTf, 1.0 eq., 1–3 h) or method C (FeCl ₃ , 1.0 eq., 24 h), from 0 °C to rt. [b] Yields of isolated compounds.			

most efficient Lewis acid, displaying both high regioselectivity and good to excellent yields.

Conclusions

The synthesis of electron-rich benzaldehydes was accomplished through regioselective Rieche formylation using FeCl₃ under mild reaction conditions, leading to excellent yields. It is worth noting that electron-poor arylboronic acids exhibit low reactivity under these specific conditions. Moreover, the regioselectivity of the reaction depends on the positions of the substituents on the arylboronic acids and the choice of the Lewis acid, providing a straightforward method to obtain formylated arylboronic acids. This study enhances our understanding of the reactivity of arylboronic acids and highlights their versatility in synthetic applications.

Experimental Section

The experimental procedure for method A and B: A suspension of substrate **1** (1.00 mmol, 1 eq.) and AgOTf (1.00 mmol, 1 eq., **method A**) or AlCl₃ (1.2 mmol, 1.2 eq., **method B**) in dry DCM (4 mL/mmol) was stirred at 0 °C under argon atmosphere, after 10 min Cl₂CHOCH₃ **2** (1.00 mmol, 1 eq.) was added dropwise, after being stirred at room temperature for 1–3 h (**method A**) or 24 h (**method B**) the reaction mixture was quenched with saturated aqueous NaHCO₃. The reaction mixture was filtered through a pad of Celite. The organic layer was separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine and dried with Na₂SO₄. The crude was concentrated *in vacuo* and purified by flash column chromatography on silica gel (hexane: EtOAc 8:2 or DCM: MeOH 9:1) to afford the benzaldehyde **3** or **4**. All compounds **3** and **4**, as well as compounds **17–20**, are known and several commercially available except for compound **4g**. ¹H NMR (400 MHz, CDCl₃): δ 4.02 (s, 9H, OCH₃), 7.58 (s, 1H, Ar–H), 10.29 (s, CHO), ¹³C NMR (100 MHz, CDCl₃): δ 56.17, 60.90, 61.63, 116.71, 126.61, 136.00, 143.25, 158.72, 160.18,

194.75. Anal. Calcd for C₁₀H₁₃BO₆: C, 50.04; H, 5.46. Found: C, 50.10; H, 5.51.

The experimental procedure for method C. To a solution of **1** (1.0 mmol, 1 eq.) in DCM (4 mL/mmol), FeCl₃ (1.0 mmol, 1.2 eq.) was added, after stirring for 10 min at 0 °C and under argon atmosphere, Cl₂CHOCH₃ **2** (1.0 mmol, 1 eq.) was dropwise added, after 24 h stirred at room temperature the reaction mixture was quenched with HCl 10%. The organic layer was separated and the aqueous layer was extracted twice with DCM. The combined organic layers were washed with NaHCO₃ and brine, dried with Na₂SO₄, filtered and concentrated *in vacuo*. The resulting residue was purified by column chromatography on silica gel (hexane: EtOAc 8:2 or DCM: MeOH 9:1) to afford the desired benzaldehyde **3** or **4**.

Supporting Information Summary

In the supporting information section reader can see copy of ¹H NMR spectra of **3a**, **3a'**, **3d**, **3e**, **4e**, **3h**, **18**, **20** and copy of ¹H NMR and ¹³C NMR spectra of **4g**.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Keywords: benzaldehyde derivatives · electron-rich arylboronic acids · formylated boronic acids · Lewis acid · Rieche formylation

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