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Aryl *gem*-Difluorovinyl Pinacolboronates: Synthesis and Utility for Suzuki-Miyaura Coupling Reaction

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Aryl *gem*-Difluorovinyl Pinacolboronates: Synthesis and Utility for Suzuki-Miyaura Coupling Reaction

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The synthesis of unstable aryl difluorovinyl pinacolboronates was achieved by the dehydrofluorination of α-trifluoromethyl arylmethyl pinacolboronates with LDA. These aryl difluorovinyl pinacolboronates can be used for Suzuki-Miyaura coupling with various aryl halides under Pd-catalysis to furnish diaryl *gem*-difluorovinyl compounds.

Keywords: *gem*-difluorovinyl | pinacolboronates | Suzuki-Miyaura coupling

In recent decades, organofluorine compounds have been the subject of intense research activity because of their pharmaceutical and agrochemical applications.[1] The efficacy of such molecules in these fields of study/research is rigorously related to the remarkable physical and chemical properties created by fluoro-functional groups such as trifluoromethyl (CF_3), difluoromethyl (CF_2H), trifluoromethylthio (SCF_3), pentafluorosulfanyl (SF_5) and others in their structures.[1,2] Among distinctly varying fluoro-functional groups, the *gem*-difluorovinyl group ($C=CF_2$) is particularly attractive synthetically[3-7] since the *gem*-difluorovinyl moiety is exceptionally reactive towards nucleophiles, allowing it to be efficiently transformed into other fluorinated functional groups such as CF_3,[4] *gem*-difluoromethylene (R-CF_2R'),[5] monofluoroalkene (C=CFR, C=CFAr),[6] and even non-fluorinated functional groups of carboxylic acids and esters.[7] The *gem*-difluorovinyl moiety is also a known bioisostere for a carbonyl group.[8] Moreover, the high electrophilicity of the $C=CF_2$ group is attractive for the design of biologically active molecules, including enzyme inhibitors,[9] pesticides,[10] and others[11] (Figure 1).

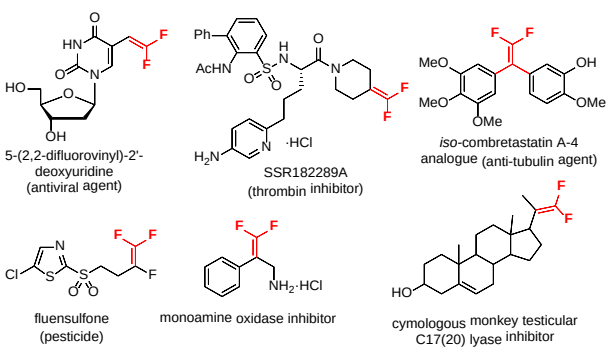
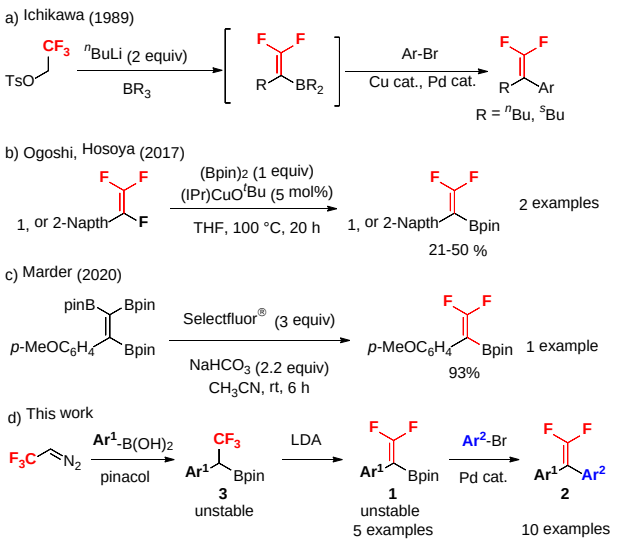


Figure 1. Examples of biologically active molecules with a *gem*-difluorovinyl unit.

The *gem*-difluorovinyl compounds have been traditionally synthesized from carbonyl compounds by the Wittig reaction,[12] Julia-Kocienski cross-coupling,[13] Horner-Wadsworth-Emmons reactions,[14] and others.[15] Nowadays, vast synthetic approaches for *gem*-difluorovinyl compounds have emerged.[16] Despite the tremendous methodologies for synthesizing *gem*-difluorovinyl compounds,[3,12-16] we noticed that the Suzuki-Miyaura cross-coupling reaction of aryl *gem*-difluorovinyl boronates ($R_2B(Ar)C=CF_2$) with aryl halides has never appeared in the literature, except for Ichikawa's seminal work in 1989.[17] Ichikawa and co-workers reported the synthesis of 2-alkyl-2-aryl-substituted *gem*-difluorovinyl compounds by the coupling reaction of aryl bromides and *gem*-difluorovinyl alkyl boranes ($R_2B(R)C=CF_2$, R = ^{n}Bu, ^{s}Bu) generated *in situ* from 2,2,2-trifluoromethyl *p*-toluene sulfonate with trialkyl boranes *via* a one-pot transformation (Scheme 1a). Although this method is efficient, the *gem*-difluorovinyl boranes are limited to alkyl-aryl-substituted molecules ($Ar(R)C=CF_2$). Thus, diaryl *gem*-difluorovinyl molecules ($Ar'(Ar)C=CF_2$) cannot be accessed.

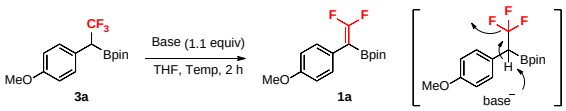


Scheme 1. *gem*-Difluorovinyl boronates and their reaction. a) Coupling reaction of alkyl *gem*-difluorovinyl boronates with aryl bromides. b) First report of aryl *gem*-difluorovinyl boronates. c) Second report of aryl *gem*-difluorovinyl boronates. d) The preparation of aryl *gem*-difluorovinyl boronates and their application for coupling reaction (this work).

We envisaged that if the aryl *gem*-difluorovinyl boronates ($R_2B(Ar)C=CF_2$) could be synthesized, then Ichikawa's methodology would become a standard for the synthesis of both alkyl-aryl and diaryl *gem*-difluorovinyl compounds by

the Suzuki-Miyaura coupling reaction. When we started this work in 2016,[18] aryl *gem*-difluorovinyl boronates ($R_2B(Ar)C=CF_2$) were completely unknown in the SciFinder® database. In 2017, Ogoshi, Hosoya, and co-workers reported the first preparation of *gem*-difluorovinyl pinacolboronates having a naphthyl group (pinB(Napth)C=CF_2) by regioselective monodefluoroborylation of trifluoroalkenes under Cu-catalysis, with 21-50% yield (two examples) (Scheme 1b).[19] In 2020, Marder et al. disclosed a single example of the synthesis of *p*-methoxyphenyl *gem*-difluorovinyl pinacolboronate (pinB(*p*-MeOC_6H_4)C=CF_2) by difluorination of 1,1,2-triborylalkene by Selectfluor® with 93% yield (one example) (Scheme 1c).[20] However, there is no report of their use for any coupling reaction. Moreover, their methods are limited (total 3 examples), and the preparation of the corresponding starting materials requires steps. Thus, the development of a novel synthetic method for the aryl *gem*-difluorovinyl boronates remains a challenge. Herein, we report the concise synthesis of aryl *gem*-difluorovinyl pinacolboronates (pinB(Ar)C=CF_2, **1**) and their application for the Suzuki-Miyaura cross-coupling reaction to access the unsymmetrical diaryl *gem*-difluorovinyl compounds (Ar'(Ar)C=CF_2, **2**). The key to preparing aryl g*em*-difluorovinyl pinacolboronates **1** is the dehydrofluorination of unstable α-trifluoromethyl-α-arylmethyl pinacolboronates **3** by treatment with LDA. While the aryl *gem*-difluorovinyl pinacolboronates **1** were also found to be unstable, the following Suzuki-Miyaura cross-coupling reaction of **1** with aryl bromides **4** proceeded smoothly to provide the desired diaryl-*gem*-difluorovinyl compounds **2** in moderate overall yields. Our method for the preparation of aryl gem-difluorovinyl pinacolboronates **1** is very different form previous two approaches.[19,20] Besides, in our knowledge, this is the first example of Suzuki-Miyaura cross-coupling reaction of aryl g*em*-difluorovinyl pinacolboronates **1**.

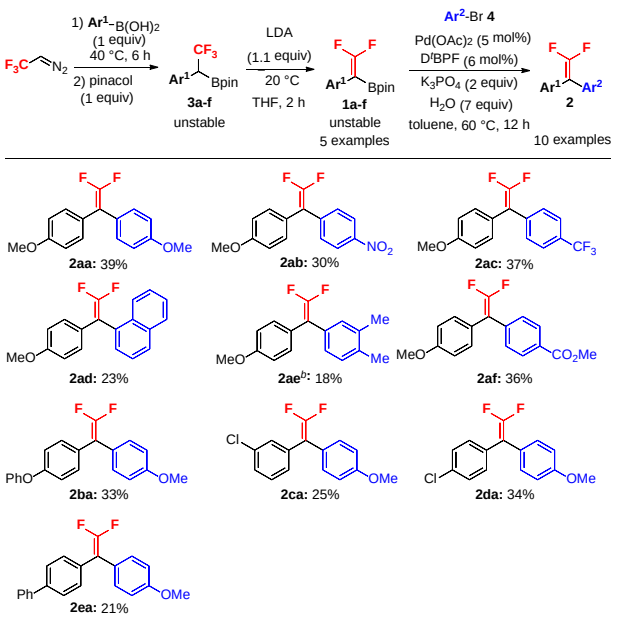
Table 1. Optimization of dehydrofluorination reaction conditions of **3a**[a]



Entry	Base	Temp	Yield (%)[a]
1	^{n}BuLi	rt	N.D.
2	LiHMDS	rt	7
3	KHMDS	rt	9
4	LDA	rt	30
5	LDA	−20 °C	62

[a] Isolated yield

Molander and co-workers reported the synthesis of α-trifluoromethyl-α-arylmethyl pinacolboronates **3** from 2,2,2-trifluorodiazoethane ($CF_3CH=N_2$) and aryl boronic acids (Ar^1-$B(OH)_2$).[21] We imagined that the treatment of pinacolboronates **3** with a base should induce dehydrofluorination triggered by negative hyperconjugation of the CF_3 group,[22] resulting in the targeted aryl *gem*-difluorovinyl pinacolboronates **1** (Table 1). Our study commenced by optimizing the dehydrofluorination of α-trifluoromethyl pinacolboronates **3**. We selected α-trifluoromethyl-*p*-methoxyphenylmethyl pinacolboronate **3a** as a model substrate. According to Molander's protocol, **3a** was prepared from $CF_3CH=N_2$ and *p*-MeOC_6H_4-$B(OH)_2$.[21] Using α-CF_3-pinacolboronate **3a**, we examined the base-mediated dehydrofluorination of **3a** to **1a**. The results of a brief screening of bases are summarized in Table 1. The use of ^{n}BuLi at room temperature did not afford the desired dehydrofluorination product **1a** (entry 1). On the other hand, LiHMDS or KHMDS gave the desired dehydrofluorinated product **1a** with low yield (entries 2 and 3). The use of LDA at room temperature provided **1a** in 30% yield (entry 4). Yield improved to 62% when the reaction was performed at −20 °C (entry 5). Starting material **3a** is unstable, and a couple of byproducts were observed in the reaction mixture, but we could not identify them. While the dehydrofluorinated product **1a** could be isolated, **1a** slowly decomposed during the purification on silica-gel column chromatography.



Scheme 2. Substrate scope of the Suzuki-Miyaura coupling reaction of aryl *gem*-difluorovinyl pinacolboronates **1** with aryl bromides **4**[a]

[a]Isolated yield was calculated according to aryl boronic acid (Ar^1-$B(OH)_2$). See the details of experimental procedure for **2** in supporting information (SI). [b]Commerical grade of 4-bromo-*o*-xylene (**4e**) (contaminated with 3-bromo-*o*-xylene) was used.

With the desired **1a** in hand, we examined the Suzuki-Miyaura cross-coupling of **1a** with aryl bromides. Since both pinacolboronate **1a** and precursor **3a** are unstable, we decided to examine the reaction from the start without purification in each step (Scheme 2). After the initial screening of reaction conditions focusing on the Suzuki-Miyaura coupling reaction,

we found that $Pd(OAc)_2$, 1,1'-bis(di-tert-butylphosphino)ferrocene (D^tBPF), K_3PO_4, and H_2O in toluene at 60 °C provided the desired coupling product **2aa** in 39% overall yield. With these optimized reaction conditions, the substrate scope for aryl bromides **4** was investigated. Taking into consideration the instability and purification difficulty of pinacol boronates **1** and **3**, a stoichiometric amount of aryl boronic acid (Ar^1-$B(OH)_2$) was used as starting material to proceed with the subsequent reactions to afford coupling products **2**. When using **1a**, electron-donating and -withdrawing groups substituted aryl bromides **4a-c** were well-tolerated in the coupling reaction to provide the corresponding diaryl *gem*-difluorovinyl products **2** in good yields (**2aa–ac**). Besides, 1-bromonaphthalene (**4d**) with **1a** also proceeded with the coupling reaction under optimal reaction conditions to afford the corresponding diaryl-*gem*-difluorovinyl-product (**2ad:** 23%). 4-Bromo-*o*-xylene (**4e**) with **1a** gave the desired product in lower yield (**2ae**: 18%). The aryl bromide with a methyl ester moiety **4f** was also tolerated and accepted for the coupling reaction with **1a** to furnish product **2af** in 36% yield. We further examined the substrate scope on *gem*-difluorovinyl boronates **1**. Electron-donating phenoxy-substituted *gem*-difluorovinyl boronates **1b**, electron-withdrawing chloro-substituted **1c**, **1d**, and aryl-substituted **1e** were transformed with *p*-methoxyphenyl bromide (**4a**) into the corresponding unsymmetrical diaryl *gem*-difluorovinyl compounds **2ba, 2ca, 2da** and **2ea** at an acceptable overall yield of 21-34%, independent of the substitution of the Ar^1 group of **2**.

In summary, we report a feasible method for the synthesis of aryl *gem*-difluorovinyl boronates **1**, and subsequent access to unsymmetrical diaryl *gem*-difluorovinyl products **2** via the Pd-catalyzed Suzuki-Miyaura cross-coupling reaction. While the aryl *gem*-difluorovinyl pinacolboronates **1** were found to be unstable, they can be straightforwardly synthesized from readily available trifluorodiazoethane and aryl boronic acids followed by LDA treatment. The wide synthetic application of aryl *gem*-difluorovinyl boronates **1** for a variety of coupling reactions is expected.

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Supporting Information is available on http://dx.doi.org/10.1246/cl.******.

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