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COMMUNICATION

Synthesis of fluorovinyl aryl ethers by a three-component reaction of *gem*-difluoroalkenes with arylboronic acids and oxygen

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Mingjin Wang, Fang Liang, Yang Xiong and Song Cao*

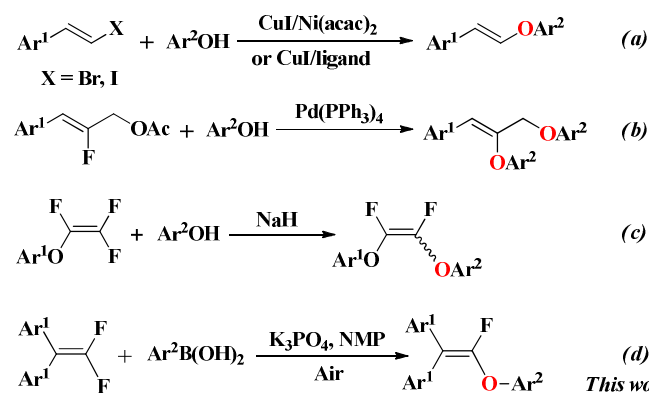
A novel and efficient three-component reaction for the synthesis of fluorovinyl aryl ethers from *gem*-difluoroalkenes, arylboronic acids and oxygen under metal-free conditions is described.

Vinyl ethers or fluorovinyl ethers are often found as structural frameworks in material chemistry and medicinal chemistry.¹ They also serve as versatile building blocks and intermediates in organic synthesis for the preparation of complex molecules.² A facile method for the synthesis of vinyl ethers is transition metal catalyzed cross-coupling of vinyl halides (RX, X = Cl, Br, I) and phenols (Scheme 1, *a*).³ More recently, Kawatsura reported an efficient protocol for the synthesis of vinyl aryl ether catalyzed by Pd(PPh₃)₄ via carbon–fluorine bond activation (Scheme 1, *b*).⁴

gem-Difluoroalkenes possess remarkable reactivity toward nucleophiles due to the high polarization of the carbon–carbon double bond caused by the two fluorine atoms.⁵ Thus, a straightforward method for the synthesis of fluorovinyl aryl ethers is by the reaction of *gem*-difluoroalkenes with phenols in presence of base via nucleophilic substitution of the vinylic fluorine (Scheme 1, *c*).⁶ However, the major drawback of this approach is the formation of the undesired addition or disubstitution byproducts.⁷ Therefore, the development of a facile and efficient approach for the synthesis of fluorovinyl aryl ethers from *gem*-difluoroalkenes is still highly desirable. In continuation of our efforts on the functionalization of carbon–fluorine bonds in *gem*-difluoroalkenes,⁸ we herein describe a new and facile approach to fluorovinyl aryl ethers through a three-component reaction of *gem*-difluoroalkenes, arylboronic acids and oxygen with the assistance of K₃PO₄ (Scheme 1, *d*).

It is well-known that the hydroxylation of arylboronic acids to phenols usually occurred readily under various reaction conditions.⁹ In addition, the formation of phenols from the corresponding arylboronic acids was reported as side reaction of the palladium-catalyzed Suzuki–Miyaura cross-coupling reaction.¹⁰ In our recent publication, we have reported the synthesis of polyfluoro-substituted unsymmetrical biaryl ethers via a novel Ni-catalyzed reaction of

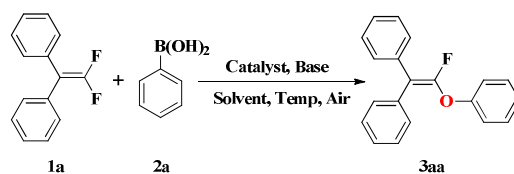
Scheme 1 Synthesis of vinyl aryl ethers or fluorovinyl aryl ethers



polyfluoroarenes with arylboronic acids and oxygen.¹¹ Encouraged by the results obtained with the polyfluoroarenes, we wondered if this strategy could be further extended into the formation of fluorovinyl aryl ether from *gem*-difluoroalkenes. To test our assumption, the investigation of the reaction conditions was commenced using (2,2-difluoroethene-1,1-diyl)dibenzene **1a** and phenylboronic acid **2a** as the model substrates, as shown in Table 1.

Initially, the reaction was performed in the presence of NiCl₂ or Ni(acac)₂ using K₃PO₄ as base. Solvent screening (entries 1–7) showed that aprotic polar solvent NMP were most suitable reaction media while nonpolar solvent, such as THF was not effective. To our delight, the desired product **3aa** was obtained in excellent yield using K₃PO₄ as base and NMP as solvent at 100 °C for 24h in absence of Ni catalyst (entry 8). Decreasing the reaction temperature from 100 to 80 °C would result in lower yields (entries 9 and 10). The yield of product **3aa** was promoted to 93% when the amount of phenylboronic acid **2a** was increased to 2.0 equiv (entries 8, 11–13). Moreover, the use of two equivalent of base was proven to be essential for the success of the transformation (entries 14–19).

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Table 1 Optimization of the reaction conditions^a

Entry	Catalyst (5 mol %)	2a (equiv)	Base (2.0 equiv)	Solvent	Temp (°C)	Yield of 3aa(%) ^b
1	NiCl ₂	2.0	K ₃ PO ₄	THF	80	10
2	NiCl ₂	2.0	K ₃ PO ₄	Dioxane	100	33
3	NiCl ₂	2.0	K ₃ PO ₄	DMSO	100	36
4	NiCl ₂	2.0	K ₃ PO ₄	NMP	100	83
5	Ni(acac) ₂	2.0	K ₃ PO ₄	DMSO	100	50
6	Ni(acac) ₂	2.0	K ₃ PO ₄	DMF	100	66
7	Ni(acac) ₂	2.0	K ₃ PO ₄	NMP	100	92
8	none	2.0	K ₃ PO ₄	NMP	100	93
9	none	2.0	K ₃ PO ₄	NMP	90	79
10	none	2.0	K ₃ PO ₄	NMP	80	70
11	none	1.5	K ₃ PO ₄	NMP	100	65
12	none	1.2	K ₃ PO ₄	NMP	100	48
13	none	1.0	K ₃ PO ₄	NMP	100	33
14	none	2.0	none	NMP	100	0
15	none	2.0	Et ₃ N	NMP	100	0
16	none	2.0	Na ₂ CO ₃	NMP	100	71
17	none	2.0	KOH	NMP	100	86
18	none	2.0	<i>t</i> BuOK	NMP	100	92
19	none	2.0	Cs ₂ CO ₃	NMP	100	91
20	none ^c	2.0	K ₃ PO ₄	NMP	100	48

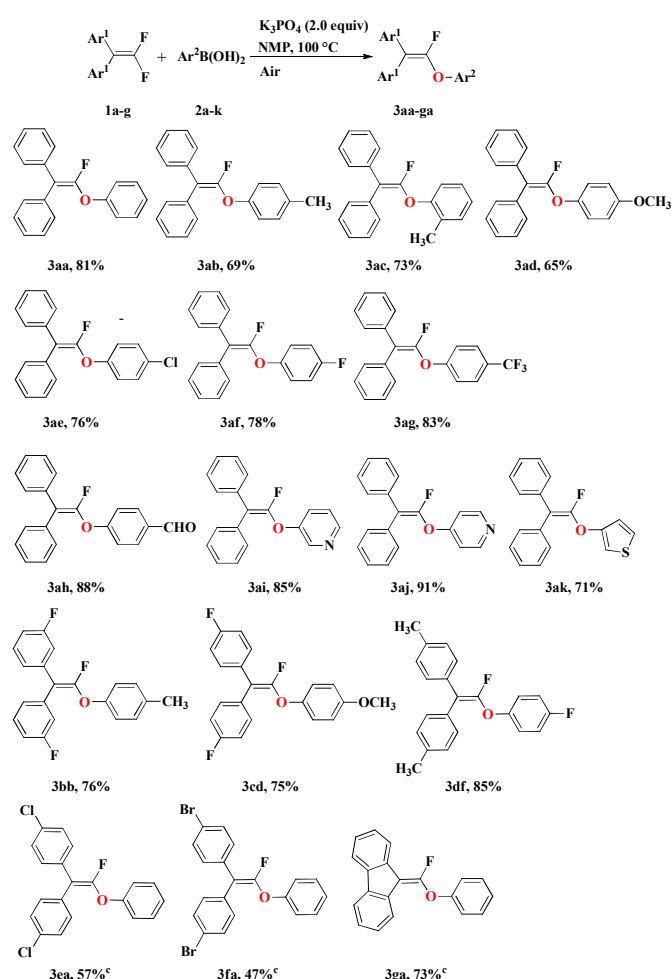
^aReaction conditions: *gem*-difluoroalkenes **1a** (1.0 mmol), solvent (2 mL), 24 h, under air atmosphere. ^bYields determined by GC analysis.

^cUnder an argon atmosphere.

No detectable product was observed when performing the reaction in the absence of base (entry 14). Among all the tested bases, K₃PO₄ provided the most optimal yield of 93% (entry 8). When *t*BuOK and Cs₂CO₃ were employed, comparable yields to K₃PO₄ were obtained (entries 18–19). Finally, when the reaction was performed under argon, only 48% the expected product was produced (entry 20). It indicated that the atmospheric oxygen plays a key role in the reaction. The formation of **3aa** (48% yield) under an argon atmosphere is due to the existence of small amounts of oxygen in the reaction system.

To survey the generality of this novel three-component reaction, a number of different symmetrical *gem*-difluoroalkenes was allowed

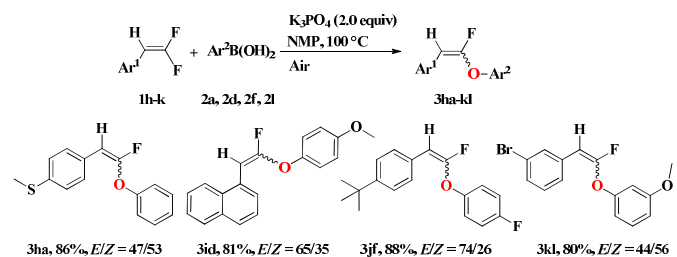
to react with a wide array of arylboronic acids under the optimized conditions (Table 1, entry 8). The results are elucidated in Table 2. As can be seen from Table 2, in most cases the desired fluorovinyl aryl ethers could be obtained in moderate to good yields. Arylboronic acids bearing electron-withdrawing group (**3ag** and **3ah**) gave the desired products in higher yields than substrates bearing electron-donating groups (**3ab** and **3ad**). The presence of electron-donating group on the benzene ring of symmetrical *gem*-difluoroalkenes was found to be advantageous over other *gem*-difluoroalkenes (**3df** versus **3af**). Interestingly, arylboronic acid having sensitive functional group such as aldehyde group remains intact under the optimized conditions (**3ah**).

Table 2 Reactions of various symmetrical *gem*-difluoroalkenes with aryl boronic acids ^{a, b}

^aReaction conditions: *gem*-difluoroalkenes **1a–d** (1.0 mmol), ArB(OH)₂ **2a–k** (2.0 mmol), K₃PO₄ (2.0 mmol), NMP (2 mL), 24 h, under air atmosphere. ^bIsolated yields. ^cReaction conditions: *gem*-difluoroalkenes **1e–g** (1.0 mmol), PhB(OH)₂ **2a** (2.0 mmol), Ni(acac)₂ (5 mol%), Cs₂CO₃ (2.0 mmol), toluene (2 mL), 24 h, O₂ balloon was applied.

Treatment of the heteroarylboronic acids such as pyridin-3-ylboronic acid **2i**, pyridin-4-ylboronic acid **2j** and thiophen-3-ylboronic acid **2k** with (2,2-difluoroethene-1,1-diyl)dibenzene **1a** afforded the corresponding products in good to high yields (**3ai–ak**). The synthesis of **3ai–ak** is particularly useful and could be applied to prepare some special fluorovinyl aryl ethers when the corresponding phenols such as thiophen-3-ol are unstable or unavailable.

The 4,4'-(2,2-difluoroethene-1,1-diyl)bis(chlorobenzene) **1e**, 4,4'-(2,2-difluoroethene-1,1-diyl)bis(bromobenzene) **1f** and 9-(difluoromethylene)-9H-fluorene **1g** were not good substrates for this reaction under the optimized conditions due to their low reactivities towards ArO[−]. According to our previous report,¹¹ Ni catalyst could accelerate the releasing of aryloxy anion (ArO[−]). Therefore, we reinvestigated the reaction conditions. It was found that the addition of 5 mol% Ni(acac)₂ could improved the yield obviously. Furthermore, performing the reaction under an oxygen atmosphere (balloon) resulted in a higher yield of the expected product than when the reaction was performed under air (see Table 2, note c).

Table 3 Reactions of unsymmetrical difluoroalkenes with aryl boronic acids ^{a, b, c}

^aReaction conditions: unsymmetrical difluoroalkenes **1h–k** (1.0 mmol), ArB(OH)₂ **2a, 2d, 2f, 2l** (2.0 mmol), K₃PO₄ (2.0 mmol), NMP (2 mL), 24 h, under air atmosphere. ^bIsolated yields of an inseparable *E/Z* mixture of the products. ^c*E/Z* selectivity was determined by ¹⁹F NMR spectra. The configurations of *E*- and *Z*-isomers were determined by their ³J_{HF} coupling constants in ¹H NMR spectra.

For the unsymmetrical difluoroalkenes **1h–k** (one is hydrogen and the other is aryl group), the reactions also gave the corresponding products **3ha–kl** in good to high yields but with low *E/Z*-selectivity under the optimized conditions. The results are summarized in Table 3. Unfortunately, the *E* and *Z* isomers of **3ha–kl** are inseparable by column chromatography.

On the basis of the experimental results and our previous work,¹¹ we suggest that the mechanism is analogous to those reported by Ichikawa and co-workers,^{5d} *gem*-Difluoroalkenes undergo nucleophilic vinylic substitution (S_NV) with aryloxy anion (ArO[−]) in the presence of K₃PO₄ via addition–elimination processes to afford fluorovinyl aryl ethers. The oxidation of arylboronic acids with oxygen to generate the corresponding aryloxy anion is essential for the efficient aryloxylation of *gem*-difluoroalkenes. It is reasonable to assume that the highly electron-deficient *gem*-difluoroalkenes are more efficient for trapping aryloxy anion generated from arylboronic acid than poly-fluorinated aromatic compounds.

In summary, we have developed an efficient three-component reaction for the preparation of fluorovinyl aryl ethers from *gem*-difluoroalkenes, arylboronic acids and oxygen using simple and commercially available K₃PO₄ as base under metal-free conditions. This reaction proceeds well for a wide variety of arylboronic acids including heteroarylboronic acids and tolerates several electron-donating as well as electron-withdrawing functional groups. It provides an alternative approach to access fluorovinyl aryl ethers.

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Shanghai Key Laboratory of Chemical Biology, School of Pharmacy, East China University of Science and Technology (ECUST), Shanghai 200237, China

*Corresponding author. Tel: +86-21-64253452; fax: +86-21-64252603 E-mail address: scao@ecust.edu.cn

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