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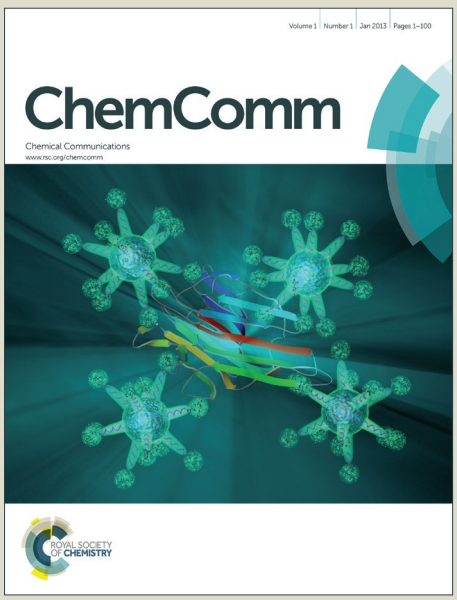

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Pd-Catalyzed *gem*-Difluoroallylation of Arylboronic Acids with γ, γ-Difluoroallylic Acetates

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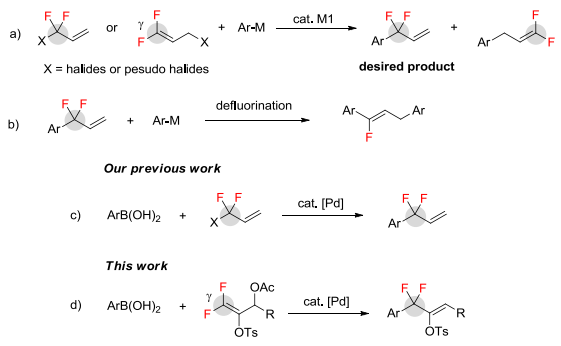
Bo Zhang[a] and Xingang Zhang*[a]

A highly regio- and stereo-selective palladium-catalyzed *gem*-difluoroallylation of arylboronic acids with γ, γ-difluoroallylic acetates has been described. The method allows the synthesis of a variety of *gem*-difluoroallylated arenes with a tosyloxy group on the C=C double bond, thus providing a good opportunity for the down-stream transformations.

As a distinct class of organic compounds in pharmaceuticals and agrochemicals, difluoroalkylated arenes have been received great attentions recently.[1,2] This is because the introduction of difluoromethylene (CF_2) group at benzylic position can dramatically improve the metabolic stability and change the physiological activity of the bioactive molecules.[3] Among the numerous difluoroalkylated arenes, *gem*-difluoroallylic arenes represent one of the extremely appealing compounds owning to their important applications in medicinal chemistry[4] and versatile synthetic utility of the C=C double bond. The most common approach to prepare such a valuable structural motif relies on the Wittig reaction or HWE reaction from aryldifluoromethylated aldehydes or ketones.[5] Despite the utility of this approach, multiple steps were required to prepare the difluoroalkylated starting materials, which restricts its widespread synthetic applications. In particular, this approach is not suitable for the late stage synthesis of difluoroalkylated complexes due to the requirement of difluoroalkylated precursors. From the point of view of synthetic simplicity and generality, a direct introduction of *gem*-difluoroallyl group onto aromatic rings would be an attractive alternative (Scheme 1a).[6,7] However, the regiochemical selectivity of this synthetic strategy and suppressing undesired defluorination side reaction resulted from *gem*-difluoroallylated products remain the synthetic challenges thus far.[7]

Several years ago, a palladium catalyzed reaction of 3,3-difluoro-2-propen-1-ol acetate with phenylzinc chloride was reported by Shi.[6a] Although a high γ-substitution regioselectivity was observed, an undesired defluorination of resulting *gem*-difluoroallylic product occurred (Scheme 1b). In this context, a sterically hindered 1-substituted 3-bromo-3,3-difluoropropene (BDFP) was used as a substrate, leading to *gem*-difluoroallylic product in high regioselectivity without observation of defluorination side reaction.[7] However, the reaction of BDFP with phenylzinc chloride or tributylphenyltin still resulted in defluorinated product. To address this crucial issue, very recently, a highly efficient method to prepare *gem*-difluoroallylated arenes through palladium-catalyzed reaction of organoborons with bromodifluoromethylated alkenes has been developed by us,[8] which represents a first example to prepare such a kind of structure catalyzed by transition-metal (Scheme 1c). Inspired by this preliminary study, we questioned that whether γ,γ-difluoroallylic electrophiles can also serve as a suitable coupling partner to prepare *gem*-difluoroallylated arenes (Scheme 1d). Herein, we described a Pd-catalyzed *gem*-difluoroallylation of arylboronic acids with γ,γ-difluoroallylic acetates. The method provides a facile access to a variety of *gem*-difluoroallylated arenes with high *regio*- and *stereo*-selectivity.



Scheme 1. Strategies for regio-selective synthesis of *gem*-difluoroallylated arenes

[a] *Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China. E-mail: xgzhang@mail.sioc.ac.cn*
Fax: +86 (21) 64166128; Tel: +86 (21)54925333

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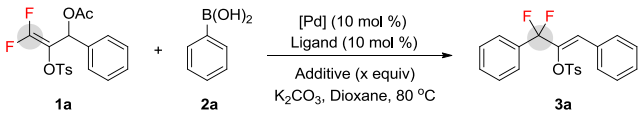
We began our studies by choosing 3,3-difluoro-1-phenyl-2-(tosyloxy) allyl acetate **1a** and phenyl boronic acid **2a** as model substrates (Table 1). The use of **1a** is because it can be easily prepared from low-cost and widely available 2,2,2-trifluoroethanol.[9] In addition, the transformations of tosyloxy group on the C=C double bond can easily lead to a variety of difluoroalkylated arenes.[10] To our delight, a 37% yield of the desired product **3a** with high stereoselectivity (Z/E > 20:1, determined by ^{19}F NMR) was obtained when the reaction was carried out with **1a** (1.0 equiv), **2a** (1.5 equiv), $Pd(PPh_3)_4$ (10 mol %), K_2CO_3 (2.0 equiv) in dioxane at 80 °C (entry 1). Notably, no branched γ,γ-difluoroallylic isomer and defluorinated side product were observed in the reaction process. We reasoned that this is probably because of the steric effect of the substituent. Further optimization of the reaction conditions by examining the phosphine ligands (entries 2-8) revealed that the bidentate ligand Xantphos[11] was the best ligand, providing **3a** in 57% yield (entry 8). The dppf and the monodentate ligand Me-Phos also provided moderate yields, but other ligands showed less activity (entries 3 and 6).

Table 1 Representative results for optimization of Pd-catalyzed *gem*-difluoroallylation of **2a** with **1a**[a]



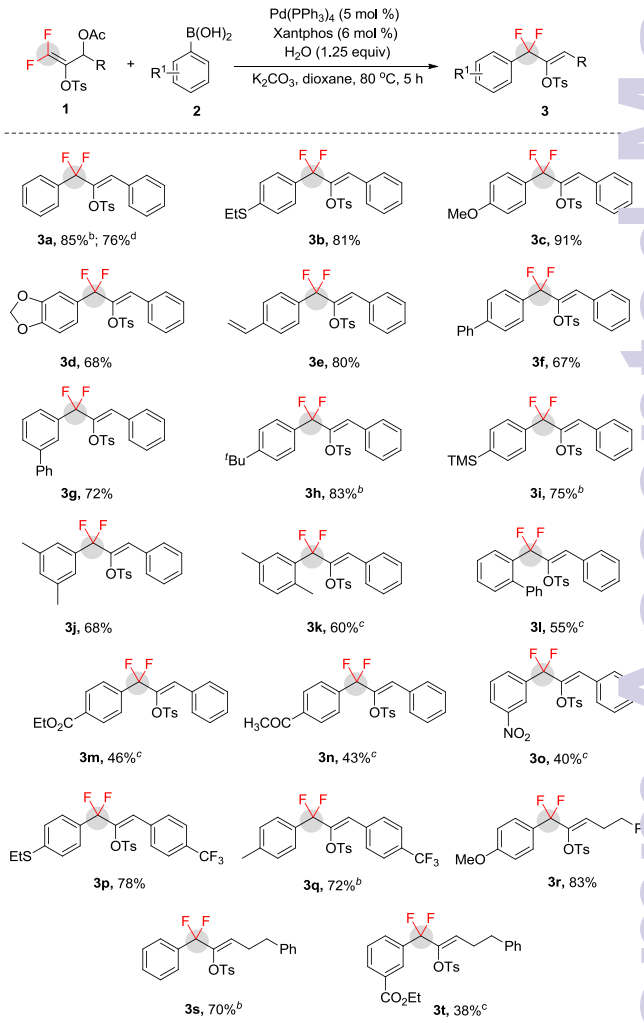
entry	[Pd]	Ligand	Additive	yield (%)[b]
1	$Pd(PPh_3)_4$	--	--	37
2	$Pd(PPh_3)_4$	PPh_3	--	42
3	$Pd(PPh_3)_4$	Me-Phos	--	53
4	$Pd(PPh_3)_4$	S-Phos	--	45
5	$Pd(PPh_3)_4$	dppe	--	18
6	$Pd(PPh_3)_4$	dppf	--	50
7	$Pd(PPh_3)_4$	BINAP	--	43
8	$Pd(PPh_3)_4$	Xantphos	--	57
9	$Pd_2(dba)_3$	Xantphos	--	49
10	$Pd(OAc)_2$	Xantphos	--	ND
11[c]	$Pd(PPh_3)_4$	Xantphos	--	64
12[d]	$Pd(PPh_3)_4$	Xantphos	--	72 (68)
13[e]	$Pd(PPh_3)_4$	Xantphos	--	30
14[d]	$Pd(PPh_3)_4$	Xantphos	H_2O (1.25)	71 (72)
15[d]	$Pd(PPh_3)_4$	Xantphos	CuI (0.06)	89 (84)

[a]Reaction conditions (unless otherwise specified): **1a** (0.2 mmol, 1.0 equiv), **2a** (0.3 mmol, 1.5 equiv), dioxane (1.5 mL) , K_2CO_3 (2.0 equiv), 5 h under N_2. [b]Determined by ^{19}F NMR using fluorobenzene as an internal standard and number in parenthesis is isolated yield. *Z*/*E* > 20:1, determined by ^{19}F NMR. [c]$Pd(PPh_3)_4$ (5 mol %), Xantphos (5 mol %). [d]$Pd(PPh_3)_4$ (5 mol %), Xantphos (6 mol %). [e]$Pd(PPh_3)_4$ (1 mol %), Xantphos (1.2 mol %).

Encouraged by these results, a survey of the reaction parameters, such as palladium sources, bases, and solvents were conducted (entries 8-10, for details, see the Supporting Information). The combination of $Pd(PPh_3)_4$, dioxane, and K_2CO_3 remained the optimal choice (entry 8). Decreasing the loading amount of $Pd(PPh_3)_4$ from 10 mol % to 5 mol % with a ratio of Xantphos/$Pd(PPh_3)_4$ = 1.2 benefited the reaction efficiency, providing **3a** in 68% yield upon isolation (entry 12). However, in the meanwhile, the homocoupling of **2a** and defluorination of **3a** were also observed. Taking into account the fact that the addition of H_2O or CuI can facilitate the transmetalation step of the Suzuki reaction,[12] H_2O and CuI were employed as additives to improve the reaction efficiency further. A best yield of **3a** (84% upon isolation) was obtained when CuI (6 mol %) was used (entry 15). H_2O also showed beneficial effect, but led to slightly lower yield (72% upon isolation, entry 14).

To demonstrate the substrate scope of this method, a variety of arylboronic acids were examined to react with **1a** (Table 2).

Table 2 Pd-catalyzed *gem*-difluoroalkylation of arylboronic acids **2** with **1**[a]

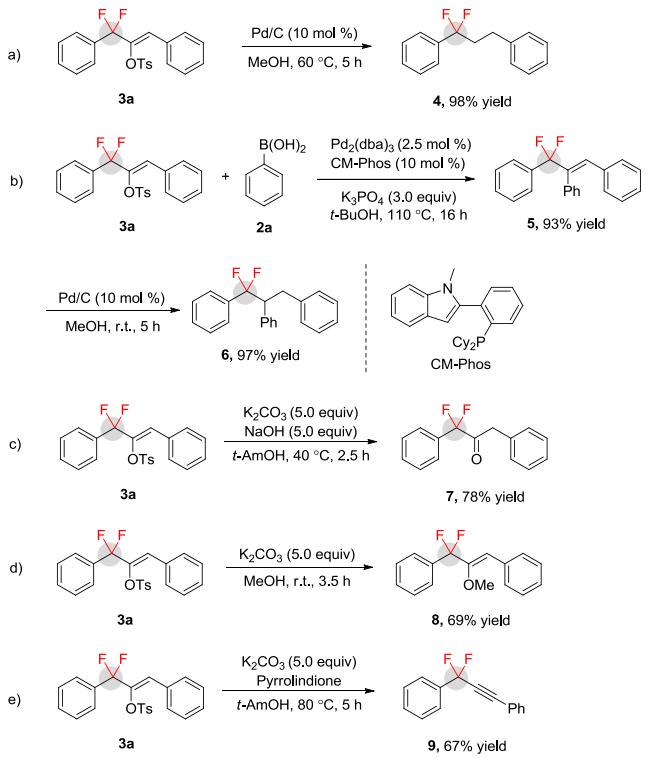


[a]Reaction conditions (unless otherwise specified): **1a** (0.4 mmol, 1.0 equiv), **2** (0.6 mmol, 1.5 equiv), , K_2CO_3 (2.0 equiv) and dioxane (3 mL) All reported yields are isolated yields and the stereoselectivity of **3** is *Z*/*E* > 20:1. [b]CuI (6 mol%) instead of H_2O was used. [c]Reaction ran for 15 h. [d]Reaction run on a gram-scale.

Generally, moderate to high yields of **3** were obtained without observation of branched isomers and electron-rich arylboronic acids provided higher yields than that from electron-deficient ones. Most importantly, the tosyloxy group was compatible with the reaction without formation of diarylated byproducts, thus providing a good opportunity for downstream

transformations. However, it should be mentioned that in most of the cases, H_2O was proved to be an optimal additive. Versatile functional groups, such as vinyl, silyl, ester, enonlizable ketone, and nitro, showed good tolerance (**3e**, **3f**, **3i**, and **3m**-**o**). The sterically hindered substrates were also applicable to the reaction, providing the corresponding products in moderate to good yields (**3k** and **3l**). The reaction can also be extended to other functionalized γ,γ-difluoroallylic acetates **1**, in which the substituents R did not interfere with the reaction efficiency. Notably, high yields of **3r** and **3s** were also obtained when R is an alkyl group, thus highlighting the generality of this method. It was also possible to synthesize compounds **3** on a gram-scale. A good yield of **3a** (76%) was obtained on a gram-scale synthesis, thus demonstrating the reliability of current reaction.

To demonstrate the utility of this method, the transformations of *gem*-difluoroallylated arene **3a** were performed.



Scheme 2 Transformations of compound **3a**

As shown in Scheme 2a, hydrogenation of **3a** provided difluoroalkylated arene **4** in excellent yield. Suzuki cross-coupling of **3a** with phenylboronic acid **2a** also underwent smoothly and provided trisubstituted **5** in 93% yield, which was further hydrogenated to produce compound **6** with high efficiency (Scheme 2b). This is noteworthy as difluoroalkylated arenes have important applications in medicinal chemistry.[13] Compound **3a** can also be converted into difluoroalkylated ketone **7** smoothly, thus providing an alternative approach to prepare such a kind of fluorinated compound (Scheme 2c). Interestingly, the tosyloxy group can be easily substituted by methoxy group when compound **3a** was treated with MeOH under basic condition at room temperature (Scheme 2d). Unexpectedly, extension of this strategy to replace tosyloxy group with amide group produce an unstable enamine intermediate, which subsequently eliminated under basic condition to afford an useful *gem*-difluoropropargylated arene **9** (Scheme 2e), thus demonstrating the versatility of the compounds **3**.

In conclusion, we have developed an efficient and alternative strategy to prepare *gem*-difluoroallylated arenes through palladium-catalyzed reaction between arylboronic acids and γ,γ-difluoroallylic acetates with high *regio*- and *stereo*-selectivity. Application of the method led to different difluoroalkylated arenes efficiently, which may have potential applications in medicinal chemistry. The reason for high regiochemical selectivity of current reaction is probably because the reductive elimination of aryl(γ,γ-difluoroallyl)palladium complex prefers generating of linear product due to the steric effect of the substituents.[14] However, for the detailed reaction mechanism, it remains a point of discussion.

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