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Palladium-catalysed difluoroolefination of benzyl tosylates toward the synthesis of *gem*-difluoro-2-trifluoromethyl styrene derivatives†

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We have presented an efficient method to access *gem*-difluoro-2-trifluoromethyl styrene derivatives via palladium catalysis. This method features mild reaction conditions, broad substrate scope and good product yields. Moreover, gram-scale reactions demonstrated the robustness and potential of this method. Control experiments revealed that the $-\text{CF}_3$ group was essential to the success of this transformation. Finally, the practicality of this method was successfully proven by three synthetic applications.

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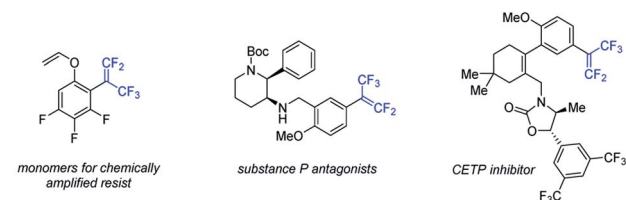
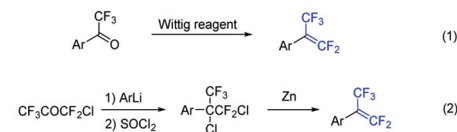
Introduction

Fluorinated compounds have found wide applications in various fields due to their unique properties.¹ Among them, *gem*-difluorostyrenes have been frequently used in the design of potential enzyme inhibitors.² Introducing α - CF_3 group into *gem*-difluoroolefins could not only retain its high electrophilicity towards many nucleophiles at the terminal carbon, but also increase the biological activity of the molecules (Fig. 1a).³

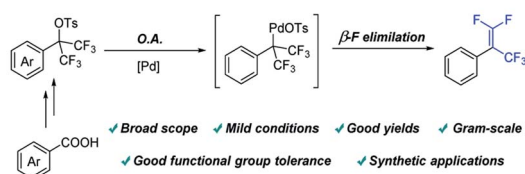
Compared with considerable efforts devoted to the development of *gem*-difluorostyrenes,^{4,5} the synthesis of *gem*-difluoro-2-trifluoromethyl styrenes is less investigated. The most common method is Wittig *gem*-difluoroolefination of trifluoroacetophenone (Fig. 1b(1)).⁶ Another pathway is a multi-step strategy involving nucleophilic addition of an aryl metallic reagent to chloropentafluoroacetone, $\text{S}_{\text{N}}2$ type substitution of chloride anions and dechlorination with Zn (Fig. 1b(2)).⁷ However, stoichiometric phosphine oxide as a by-product, utilization of organometallic reagents and multistep operation have greatly restricted substrate scope and applications of the methods above. Therefore, it is of great significance to develop a complementary method for the synthesis of *gem*-difluoro-2-trifluoromethyl styrenes.

On the other hand, transition-metal catalysis plays an irreplaceable role in modern organic synthesis.⁸ We hypothesize that a method including two elementary reactions to access

gem-difluoro-2-trifluoromethyl styrenes from trifluoromethyl-substituted benzyl tosylate by transition metal catalysis could be developed (Fig. 1c). From the perspective of elementary reactions, the oxidative addition of palladium catalyst into $\text{Csp}^3\text{-O}$ bond⁹ and $\beta\text{-F}$ elimination of palladium complex¹⁰ have been realized in different transformations in the reported work respectively. Therefore, the key to success of this strategy is to find a suitable catalyst system which is compatible with the two elementary reactions above.

 a) Biologically active compounds containing *gem*-difluoro-2-trifluoromethyl olefin moiety.

 b) Previous pathways to access *gem*-difluoro-2-trifluoromethyl olefins.


c) Our strategy (this work)


 Fig. 1 Importance of *gem*-difluoro-2-trifluoromethyl olefins and synthetic strategy.

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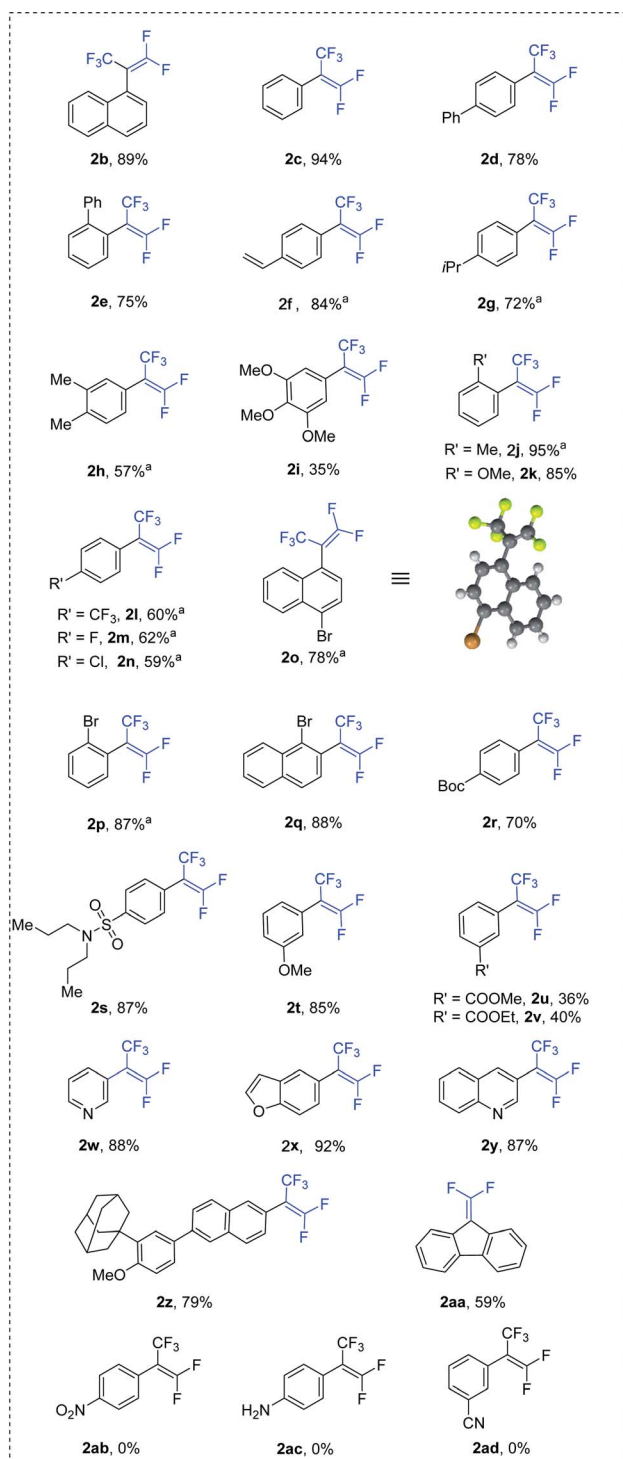
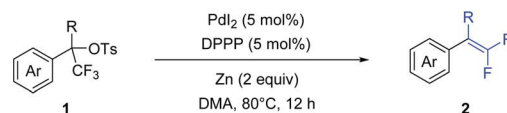
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Results and discussion

To demonstrate our hypothesis, we began the study by evaluating *gem*-difluoroolefination of trifluoromethyl-substituted benzyl tosylate (**1a**) via palladium catalysis (Table 1). Compound **1a** could be easily synthesized from corresponding aryl carboxylic acid.¹¹ After evaluation of all reaction parameters, reaction conditions which could provide a high yield of **2a** was identified. The optimum reaction conditions consisted of PdI₂ (5 mol%) with bidentate ligand DPPPP (5 mol%) as catalyst, zinc (2.0 equiv.) as reductant, and DMA as solvent at 80 °C (entry 1). Using other palladium sources as catalyst resulted in lower yields (entries 2–5). Variation of monodentate and other bidentate phosphine ligands from DPPPP led to moderate yields of **2a** (entries 6–11), while nitrogen ligands would inhibit the reaction with the majority of **1a** unconverted (entries 12–13). Solvents screening revealed that DMA was the best choice for this transformation (entries 14–18). Lastly, reaction temperature investigation suggested that the desired product **2a** could be formed in the highest yield at 80 °C, although the yield was acceptable at 40 °C (entries 19–21).

With the optimized conditions in hand, the substrate scope of this transformation was investigated and the results are summarized in Scheme 1. Initially, substrates with electron-



Scheme 1 Substrate scope. ^aThe temperature is 100 °C and PdI₂ (10 mol%), DPPPP (10 mol%) were used.

Table 1 Optimization of the reaction conditions^a

Entry	Variation from std. conditions	Yield of 2a ^b
1	None	93% (90%) ^c
2	Pd(dba) ₂ instead of PdI ₂	60%
3	PdCl ₂ instead of PdI ₂	61%
4	Pd(acac) ₂ instead of PdI ₂	86%
5	Pd(PPh ₃) ₂ Cl ₂ instead of PdI ₂	82%
6	PPh ₃ instead of DPPPP	64%
7	PCy ₃ instead of DPPPP	68%
8	(<i>n</i> -Bu)P(ad) ₂ instead of DPPPP	65%
9	DPEPhos instead of DPPPP	27%
10	DPPF instead of DPPPP	43%
11	XantPhos instead of DPPPP	73%
12	1,10-Phenanthroline instead of DPPPP	9%
13	2,2-Bipyridine instead of DPPPP	20%
14	DMF instead of DMA	54%
15	MeCN instead of DMA	57%
16	THF instead of DMA	34%
17	Toluene instead of DMA	29%
18	1,4-Dioxane instead of DMA	31%
19	100 °C instead of 80 °C	85%
20	60 °C instead of 80 °C	86%
21	40 °C instead of 80 °C	75%

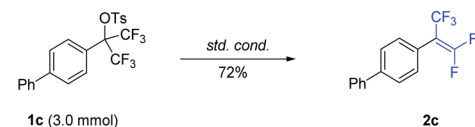
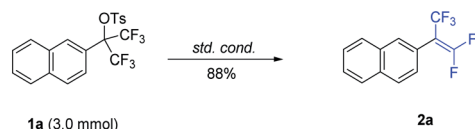
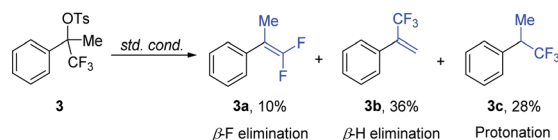
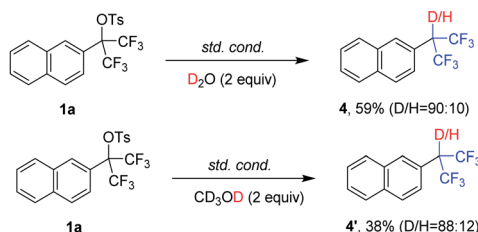
^a Standard reaction conditions: **1a** (0.2 mmol), PdI₂ (5 mol%), DPPPP (5 mol%), Zn (2 equiv.), DMA (1.0 mL), 80 °C, 12 h. ^b Yields were determined by GC analysis using dodecane as an internal standard. ^c Isolated yield in the parenthesis.

neutral aryl groups, such as naphthalene ring and benzene ring, were examined. The reactions proceeded smoothly and produced the corresponding *gem*-difluoroolefins in excellent

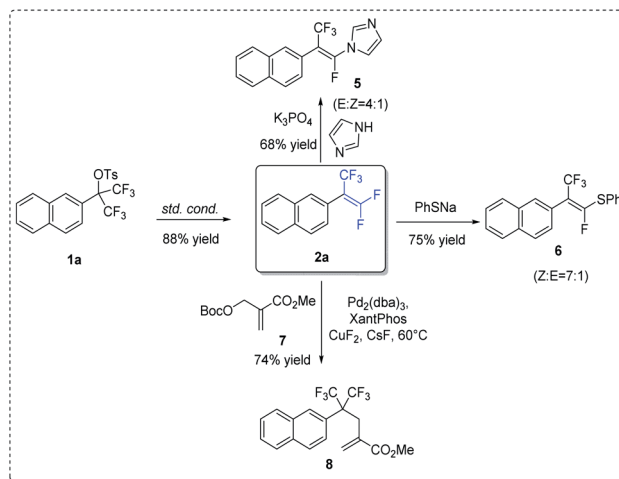


yields (**2b–2c**). Benzene ring bearing a phenyl substituent at the *para* and *ortho* position also afforded the corresponding products in good yields (**2d–2e**). In addition, vinyl group were also well tolerated (**2f**). Next, compounds with electron-rich substituents were evaluated. The usage of isopropyl-, methyl-, methoxy-substituted substrates led the formation of corresponding products in moderated to good yields (**2g–2k**). Various electron-poor substrates were also investigated. Compounds containing halogen and trifluoromethyl groups in *para* position were adapted to the reactions and gave desired products in moderate yields (**2l–2o**). The configuration of compound **2o** was confirmed by X-ray crystallography.¹² Notably, aryl ring bearing bromide at the *ortho* position had positive hindrance effect on the reaction, resulting in good yields (**2p–2q**). In addition, both Boc- and sulfonamide-substituted tosylates were tolerated, giving the corresponding products **2r** and **2s** in 70% and 87% yields respectively. Aryl ring containing methoxy at the *meta* position (**2t**) obtained 85% yield, while substrate with an ester group (**2u–2v**) led to a lower yield. Pleasingly, the reaction was compatible with a range of heterocycles, as demonstrated by the excellent yields obtained for a series of substrates containing pyridine, furan and quinoline ring (**2w–2z**). Lastly, diaryl-trifluoromethyl tosylate could also be converted to corresponding *gem*-difluorostyrene (**2aa**) in moderate yield. Unfortunately, nitro (**2ab**), amino (**2ac**) and cyano (**2ad**) groups were found to unsuitable for the reaction.

a) Gram-scale reactions.

b) Effect of CF₃ group.c) D₂O and CD₃OD quenching reaction.

Scheme 2 Gram-scale reactions and control experiments.



Scheme 3 Synthetic applications.

The robustness and potential of this method have also been successfully demonstrated by **2a** (88% yield) and **2c** (72% yield) in gram-scale reactions (Scheme 2a). Next, the effect of –CF₃ group was investigated (Scheme 2b). Mono-CF₃-substituted benzyl tosylate **3** was subjected to the standard conditions, resulting in β-F elimination product **3a** (10%), β-H elimination product **3b** (36%) and protonated product **3c** (28%). To gain more insight into the mechanism, a control experiment was carried out (Scheme 2c). The reaction was carried out in the presence of D₂O (2.0 equiv.) or CD₃OD (2.0 equiv.) under the standard conditions, leading to the formation of protonated product D-4 or D-4'. This result indicated that Pd(0) was oxidatively added into C–OTs bond rather than C–F bond.

To illustrate synthetic utility of this methodology, previously synthesized **2a** was subjected to subsequent transformations (Scheme 3). Firstly, the reaction of compound **2a** with imidazole in the presence of K₃PO₄ could provide the *N*-(α-fluorovinyl)azole product **5**.^{13,15} Likewise, treatment of **2a** with sodium phenyl thiolate in THF at room temperature for 12 h resulted in the formation of vinyl sulfide **6** (Z : E = 7 : 1) in 75% yield.^{14,15} Lastly, in the presence of palladium catalyst, allylic alkylation between **2a** and allyl *tert*-butyl carbonate **7** could take place, in which the nucleophilic addition of external fluoride onto *gem*-difluoroalkenes was the initial step.¹⁶

Conclusions

In conclusion, we have developed an efficient pathway to access *gem*-difluoro-2-trifluoromethyl styrene derivatives *via* palladium catalysis. This transformation features mild reaction conditions, broad functional group tolerance and good yields. Gram-scale reactions have demonstrated the robustness and potential of this method, and various synthetic applications have proved the practicality of this strategy.

Conflicts of interest

There are no conflicts to declare.



Acknowledgements

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