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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.

## Introduction

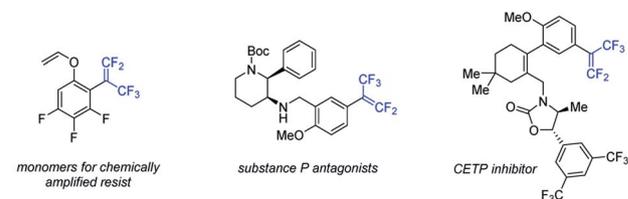
Fluorinated compounds have found wide applications in various fields due to their unique properties.<sup>1</sup> Among them, *gem*-difluorostyrenes have been frequently used in the design of potential enzyme inhibitors.<sup>2</sup> Introducing  $\alpha$ - $\text{CF}_3$  group into *gem*-difluoroolefins 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).<sup>3</sup>

Compared with considerable efforts devoted to the development of *gem*-difluorostyrenes,<sup>4,5</sup> the synthesis of *gem*-difluoro-2-trifluoromethyl styrenes is less investigated. The most common method is Wittig *gem*-difluoroolefination of trifluoroacetophenone (Fig. 1b(1)).<sup>6</sup> 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)).<sup>7</sup> 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.

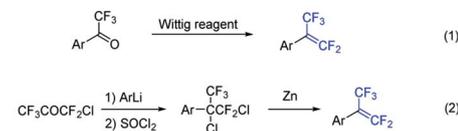
On the other hand, transition-metal catalysis plays an irreplaceable role in modern organic synthesis.<sup>8</sup> We hypothesize that a method including two elementary reactions to access

*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  $\text{Csp}^3\text{-O}$  bond<sup>9</sup> and  $\beta$ -F elimination of palladium complex<sup>10</sup> 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.

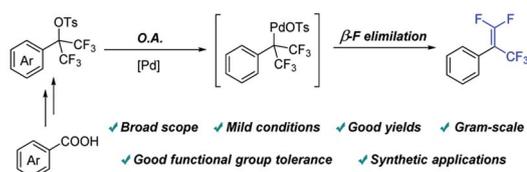
a) Biologically active compounds containing *gem*-difluoro-2-trifluoromethyl olefin moiety.



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



c) Our strategy (this work)



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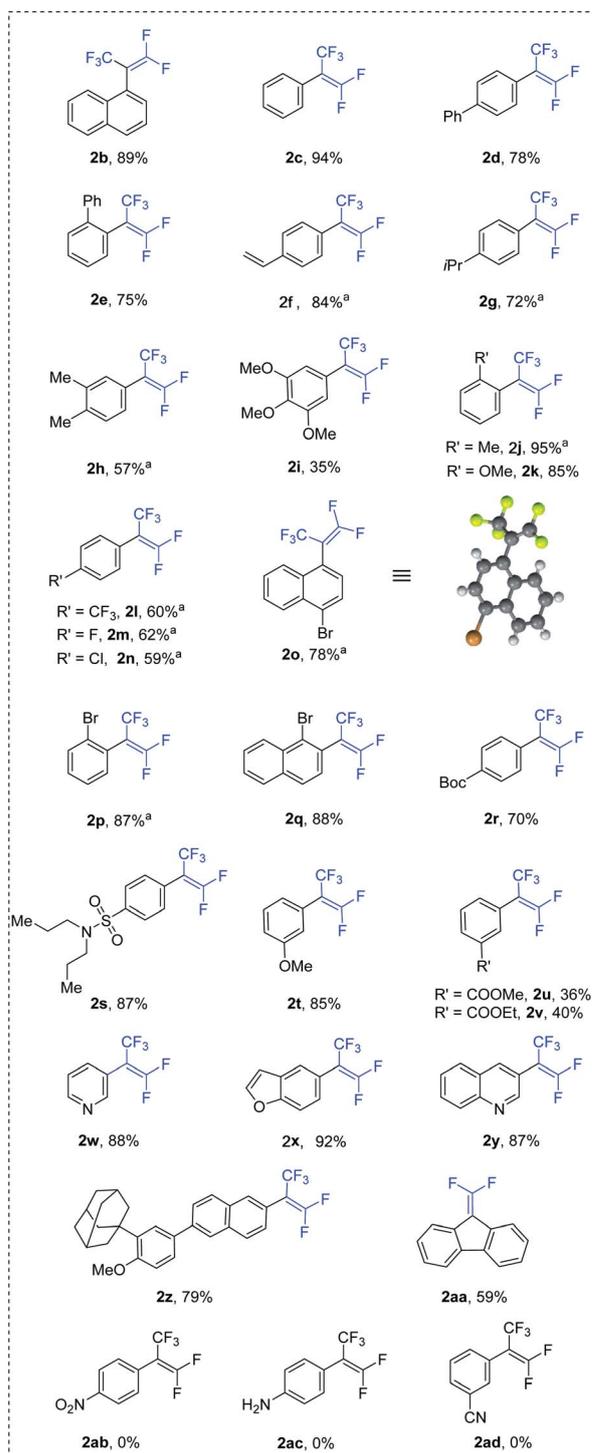
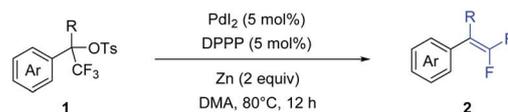
Fig. 1 Importance of *gem*-difluoro-2-trifluoromethyl olefins and synthetic strategy.



## 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.<sup>11</sup> After evaluation of all reaction parameters, reaction conditions which could provide a high yield of **2a** was identified. The optimum reaction conditions consisted of PdI<sub>2</sub> (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. <sup>a</sup>The temperature is 100 °C and PdI<sub>2</sub> (10 mol%), DPPPP (10 mol%) were used.

Table 1 Optimization of the reaction conditions<sup>a</sup>

Entry	Variation from std. conditions	Yield of <b>2a</b> <sup>b</sup>
1	None	93% (90%) <sup>c</sup>
2	Pd(dba) <sub>2</sub> instead of PdI <sub>2</sub>	60%
3	PdCl <sub>2</sub> instead of PdI <sub>2</sub>	61%
4	Pd(acac) <sub>2</sub> instead of PdI <sub>2</sub>	86%
5	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub> instead of PdI <sub>2</sub>	82%
6	PPh <sub>3</sub> instead of DPPPP	64%
7	PCy <sub>3</sub> instead of DPPPP	68%
8	( <i>n</i> -Bu)P(ad) <sub>2</sub> 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%

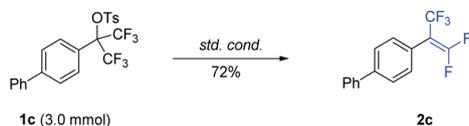
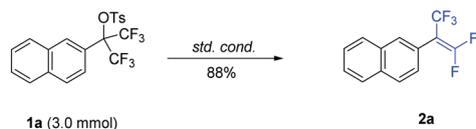
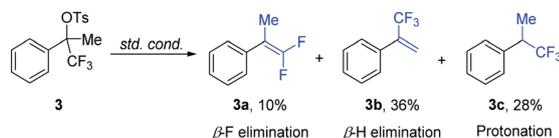
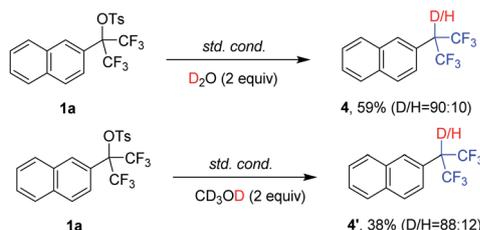
<sup>a</sup> Standard reaction conditions: **1a** (0.2 mmol), PdI<sub>2</sub> (5 mol%), DPPPP (5 mol%), Zn (2 equiv.), DMA (1.0 mL), 80 °C, 12 h. <sup>b</sup> Yields were determined by GC analysis using dodecane as an internal standard. <sup>c</sup> Isolated yield in the parenthesis.

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

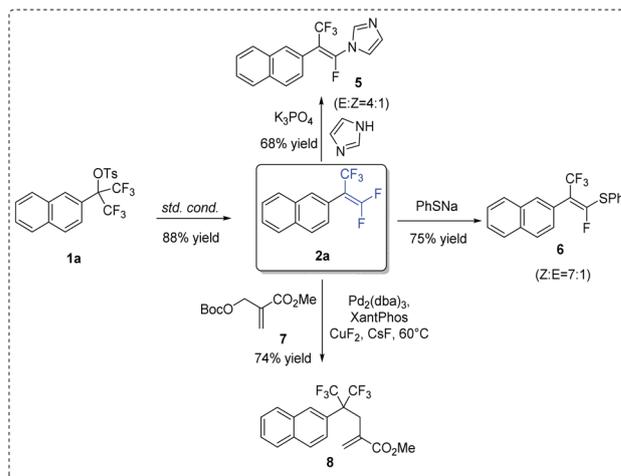


yields (**2b–2c**). Benzene ring bearing a phenyl substituent at the *para* and *ortho* position also afforded the corresponding products in good yields (**2d–2e**). In addition, vinyl group were also well tolerated (**2f**). Next, compounds with electron-rich substituents were evaluated. The usage of 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.<sup>12</sup> 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 CF<sub>3</sub> group.c) D<sub>2</sub>O and CD<sub>3</sub>OD 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 –CF<sub>3</sub> group was investigated (Scheme 2b). Mono-CF<sub>3</sub>-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 D<sub>2</sub>O (2.0 equiv.) or CD<sub>3</sub>OD (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 K<sub>3</sub>PO<sub>4</sub> could provide the *N*-(α-fluorovinyl)azole product **5**.<sup>13,15</sup> 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.<sup>14,15</sup> 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.<sup>16</sup>

## 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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