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

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We have presented an efficient method to access *gem*-difluoro-2-trifluromethyl 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 $-CF_3$ 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.[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-trifluromethyl styrenes is less investigated. The most common method is Wittig *gem*-difluoroolefination of trifluoroacetophenone (Fig. 1b(1)).[6] Another pathway is a multistep strategy involving nucleophilic addition of an aryl metallic reagent to chloropentafluoroacetone, S_N2 type substitution of chloride anions and dechlorination with Zn (Fig. 1b(2)).[7] However, stochiometric 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-trifluromethyl 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-trifluromethyl 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 Csp^3–O bond[9] and β–F elimination of palladium complex[10] 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.

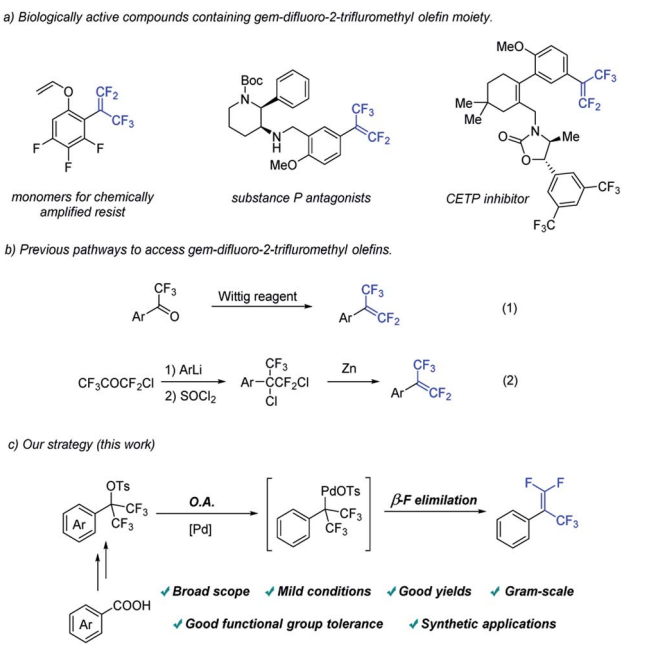

Fig. 1 Importance of *gem*-difluoro-2-trifluoromethyl olefins and synthetic strategy.

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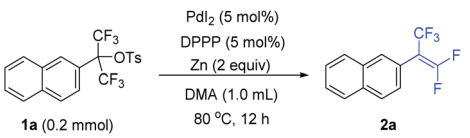
Results and discussion

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 PdI_2 (5 mol%) with bidentate ligand DPPP (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 DPPP 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).

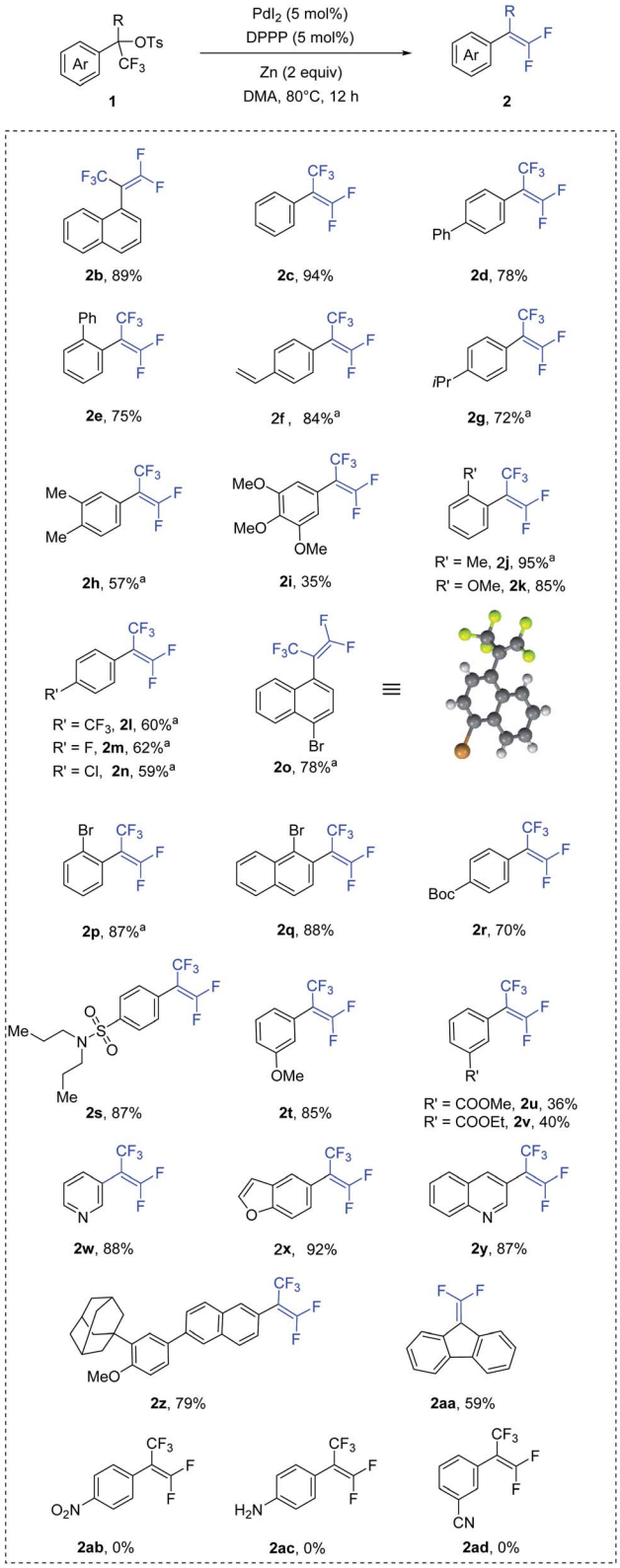
With the optimized conditions in hand, the substrate scope of this transformation was investigated and the results are summarized in Scheme 1. Initially, substrates with electron-neutral aryl groups, such as naphthalene ring and benzene ring, were examined. The reactions proceeded smoothly and produced the corresponding *gem*-difluoroolefins in excellent

Table 1 Optimization of the reaction conditions[a]



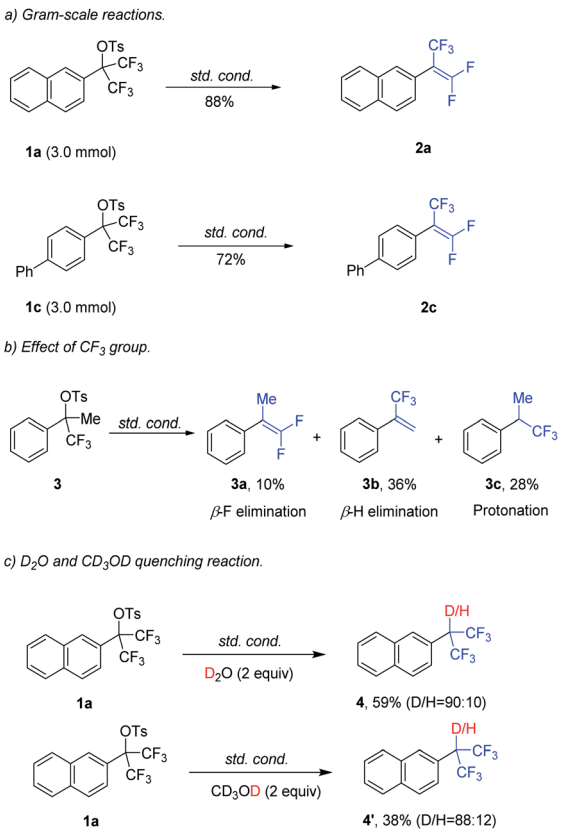
Entry	Variation from std. conditions	Yield of **2a**[b]
1	None	93% (90%)[c]
2	$Pd(dba)_2$ instead of PdI_2	60%
3	$PdCl_2$ instead of PdI_2	61%
4	$Pd(acac)_2$ instead of PdI_2	86%
5	$Pd(PPh_3)_2Cl_2$ instead of PdI_2	82%
6	PPh_3 instead of DPPP	64%
7	PCy_3 instead of DPPP	68%
8	(*n*-Bu)P(ad)$_2$ instead of DPPP	65%
9	DPEPhos instead of DPPP	27%
10	DPPF instead of DPPP	43%
11	XantPhos instead of DPPP	73%
12	1,10-Phenanthroline instead of DPPP	9%
13	2,2-Bipyridine instead of DPPP	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), PdI_2 (5 mol%), DPPP (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.

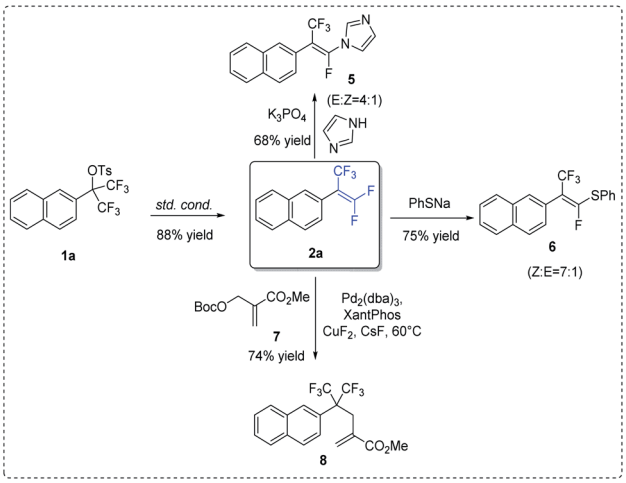


Scheme 1 Substrate scope. [a]The temperature is 100 °C and PdI_2 (10 mol%), DPPP (10 mol%) were used.

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, diaryltrifluoromethyl 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.



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 $-CF_3$ group was investigated (Scheme 2b). Mono–CF_3–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_2O (2.0 equiv.) or CD_3OD (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_3PO_4 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-trifluromethyl 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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