Synthetic Methods

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Pd-Catalyzed Regioselective Activation of *gem*-Difluorinated Cyclopropanes: A Highly Efficient Approach to 2-Fluorinated Allylic Scaffolds**

*Jun Xu, Ebrahim-Alkhalil Ahmed, Bin Xiao, Qian-Qian Lu, Yun-Long Wang, Chu-Guo Yu, and Yao Fu**

Abstract: *An unprecedented Pd-catalyzed regioselective activation of gem-difluorinated cyclopropanes induced by C–C bond cleavage is reported. It provides a general and efficient access to a variety of 2-fluoroallylic amines, ethers, esters, and alkylation products in high Z-selectivity, which are important skeletons in many biologically active molecules. In addition, the transformation represents the first general application of gem-difluorinated cyclopropanes as reaction partners in transition-metal-catalyzed cross-coupling reaction.*

Fluorinated allylic scaffolds, as an important class of fluorinated molecules,[1] have been examined for potential applications as enzyme inhibitors,[2] peptide isosteres,[3] in liquid-crystalline materials[4] as well as substrates for generating more complex fluorinated molecules[5] (Figure 1). Due to the broad utilities, it has been of great interest to develop efficient methods for the construction of diverse fluorinated alkene derivatives.[6] In this context, the pioneering studies mainly focused on various noncatalytic reactions, for example, classical olefination reactions such as the Peterson reaction,[7] the aldol condensation,[8] and the Horner–Wadsworth–Emmons reaction.[2d] Nevertheless, these methods usually suffer from relatively harsh reaction conditions and limited substrate scope. To overcome these problems, recent research has paid more attention to the transition-metal-catalyzed allylic selective C–F bond activation of polyfluorinated molecules.[9] For example, Fujii[10] and co-workers once described an interesting chemo- and stereoselective synthesis of (*Z*)-fluoroalkenes through Pd-catalyzed allylic C–F bond activation of allylic *gem*-difluoride, whereas Paquin[11] et al. reported the palladium-catalyzed allylic amination of 3,3-difluoropropenes toward the synthesis of 3-fluoroallylic amines (Scheme 1 a). Note that both of the above processes initiate with the oxidative addition of an allylic C–F bond to a palladium(0) catalyst, and thus is limited by the high C–F bond energies.[12] Notwithstanding the impressive advances, these reactions still suffer from major drawbacks including limited substrates scope as a result of using 3,3-difluoropropene derivatives as substrates which are difficult to be synthesized, and the nucleophiles are also limited to highly nucleophilic organometallic reagents and amines. Therefore, the general synthesis of fluorinated allylic structural motifs in a well-defined manner is still highly desirable.

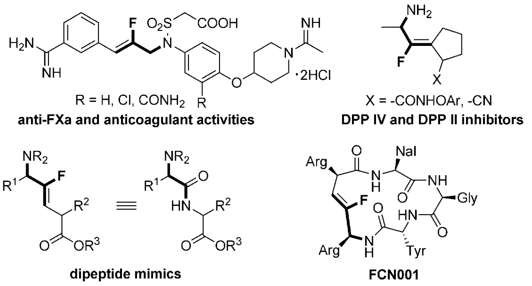
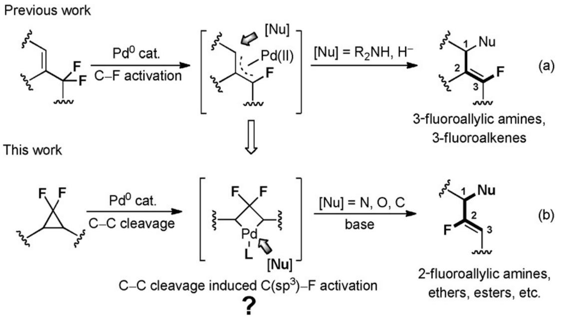


Figure 1. Important fluorinated allylic scaffolds.



Scheme 1. Synthesis of fluorinated allylic structural motifs.

Herein, we report our preliminary findings on a unique Pd-catalyzed regioselective activation of *gem*-difluorinated cyclopropanes[13] (Scheme 1 b), providing 2-fluoroallylic amines, ethers, esters, and alkylation products in high *Z*-selectivity, which would be difficult to synthesize by known methods.[13a] The advantages of this method include: 1) It represents the first Pd-catalyzed regioselective activation of

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[*] J. Xu,[+] E.-A. Ahmed,[+] B. Xiao, Q.-Q. Lu, C.-G. Yu, Prof. Y. Fu
iChEM, CAS Key Laboratory of Urban Pollutant Conversion
Department of Chemistry
University of Science and Technology of China
Hefei 230026 (China)
E-mail: fuyao@ustc.edu.cn
J. Xu,[+] Y.-L. Wang
School of Medical Engineering, Hefei University of Technology
Hefei 230009 (China)

[+] These authors contributed equally to this work.

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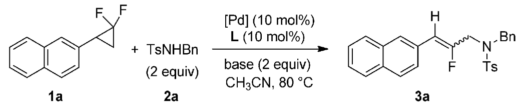
gem-difluorinated cyclopropanes which is induced by C−C bond cleavage and subsequent β-F elimination. 2) Although great progress has been made on the development of synthetic methods for the construction of *gem*-difluorinated cyclopropanes,[14] their catalytic transformation for more complex fluorinated compounds has been much less examined.[14a,b] The present method expands the utility of *gem*-difluorinated cyclopropanes as building blocks in organic synthesis. 3) Compared with previous methods,[10,11,13] our new method starts from simpler and readily available substrates (easily derived from simple alkenes and difluorocarbene precursors,[14]) and shows better functional group tolerance. Besides, the use of N, O, and even C as nucleophiles would provide the unique and valuable strategy for preparation of 2-fluorinated allylic amines, ethers, esters, and alkylation products, which are themselves valuable synthetic building blocks for further transformations. Furthermore, the present process also exhibits a good tolerance to moisture and thus eliminates the necessity for strict anhydrous operation (for details, see the Supporting Information, SI). Therefore, the present protocol represents a general and efficient method for the synthesis of diverse fluoroallylic scaffolds.

The optimization was initiated by employing 2-(2,2-difluorocyclopropyl)naphthalene (**1a**) and *N*-benzyl-4-methylbenzenesulfonamide (**2a**) as test substrates (Table 1), which were subjected to conditions similar to those describe by Paquin and co-workers[11a] in their previous study on the allylic C−F activation of 3,3-difluoropropenes (entries 1 and 2). However, the desired product **3a** could not be detected. Therefore, further tests were conducted to improve the conditions. Firstly, the evaluation of various other Pd catalysts (entries 3–5) showed that Pd(OTFA)$_2$ can afford the desired product in low yield with moderate selectivity. Meanwhile, it was found that the ligand significantly influences the reaction efficiency.[15] The reactions with sterically hindered monodentate P-ligands led to higher yields of **3a** (entries 7–9) than those obtained with the bidentate P-ligands (entries 5 and 6); Further improvement was obtained by changing the base from K$_3$PO$_4$ to K$_2$CO$_3$ (entry 10), whereas the use of a stronger base *t*BuOK, did not afford the desired product **3a** (entry 11). Finally, the desired product cannot be detected in the absence of Pd catalyst and ligand, even at a higher temperature (entry 12).

With the optimized conditions established, preliminary investigation of the scope of N-nucleophiles was then performed (Table 2). A variety of sulfonamides, amides, and secondary amines reacted successfully to give the desired 2-fluorinated allylic amines in good to excellent yield and generally high selectivity for the *Z*-type products. Besides the protected benzylamines could be used as nucleophiles (**3a**, **3b**), protected aromatic amines also gave the desired product in good yields (**3c**, **3d**). Both the linear (**3e**, **3f**) and cyclic (**3g**–**3m**) secondary amines are suitable nucleophiles. Six-membered cyclic amines with different substituents at the 4-

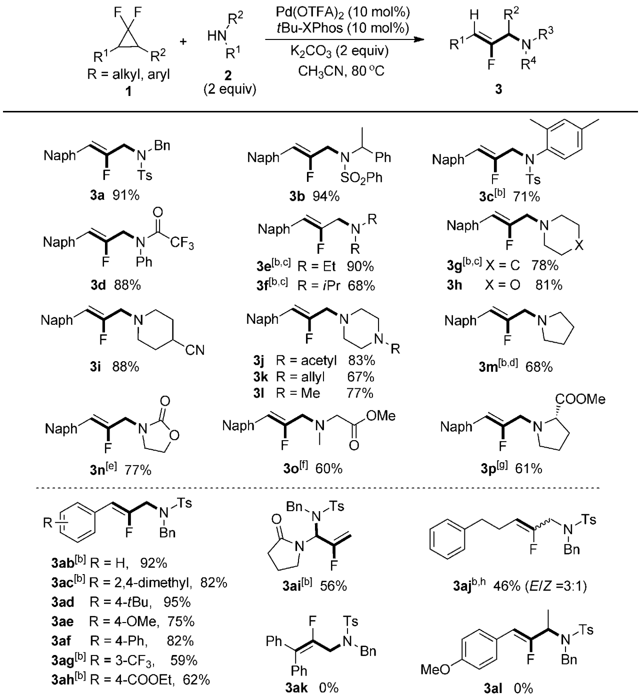
Table 1: Optimization of the reaction conditions.[a]



Entry	[Pd]	Ligand **L**	Base (2 equiv)	Yield of **3a** [%][b]	*Z*/*E*[c]
1	[Pd(dppf)Cl$_2$]	–	–	0	–
2	[Pd(dppf)Cl$_2$]	–	K$_3$PO$_4$	0	–
3	Pd(dba)$_2$	dppf	K$_3$PO$_4$	0	–
4	Pd(OAc)$_2$	dppf	K$_3$PO$_4$	14	5:1
5	Pd(OTFA)$_2$	dppf	K$_3$PO$_4$	18	8:1
6	Pd(OTFA)$_2$	Xantphos	K$_3$PO$_4$	41	>10:1
7	Pd(OTFA)$_2$	S-Phos	K$_3$PO$_4$	72	>10:1
8	Pd(OTFA)$_2$	X-Phos	K$_3$PO$_4$	82	>10:1
9	Pd(OTFA)$_2$	*t*Bu-XPhos	K$_3$PO$_4$	90	>30:1
10	**Pd(OTFA)$_2$**	***t*Bu-XPhos**	**K$_2$CO$_3$**	**96 (91)[d]**	**>30:1**
11	Pd(OTFA)$_2$	*t*Bu-XPhos	*t*BuOK	trace	–
12[e]	–	–	K$_2$CO$_3$	0	–

[a] Reactions were carried out with **1a** (0.2 mmol), **2a** (0.4 mmol), base (2 equiv), [Pd] (10 mol%), and **L** (10 mol%) in CH$_3$CN (1 mL) at 80°C for 16 h. [b] Yields were determined by ^{19}F NMR spectroscopy using PhF as the internal standard. [c] The ratio of *Z*/*E* isomer was determined by ^{19}F NMR spectroscopy. [d] Yield of isolated product in the parenthesis. [e] the reaction was conducted at 110°C. dba = dibenzylideneacetone, OTFA = trifluoroacetate, dppf = 1,1′-bis(diphenylphosphino)ferrocene. dppp = 1,3-bis(diphenylphosphanyl)propane, dppe = 1,2-bis(diphenylphosphanyl)ethane, Xantphos = 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene, S-Phos = 2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl, X-Phos = 2-(dicyclohexylphosphin-o)-2′,4′,6′-triisopropylbiphenyl, *t*Bu-XPhos = 2-di-*tert*-butylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl.

Table 2: Substrate scope of reaction partners.[a]



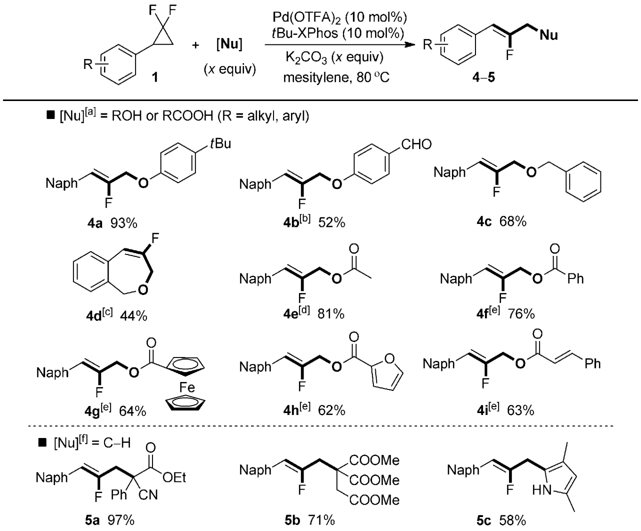
[a] Isolated yields on 0.2 mmol scale, Naph = 2-naphthyl. [b] Mesitylene as the solvent. [c] without the addition of K$_2$CO$_3$. [d] Pd(OTFA)$_2$ (20 mol%), *t*Bu-XPhos (20 mol%), **2m** (1equiv), K$_3$PO$_4$ (1 equiv), 100°C. [e] Et$_3$N (2 equiv) as base. [f] K$_2$CO$_3$ (4 equiv) as base. [g] Cs$_2$CO$_3$ (4 equiv) as base. [h] Pd(OAc)$_2$ (10 mol%), *t*Bu-XPhos (10 mol%), Cs$_2$CO$_3$ (2 equiv).

position (**3h**–**3l**), such as cyano, *N*-acyl, *N*-allyl, and oxygen were equally compatible. Additionally, simple cyclic amines with different ring sizes were successfully incorporated (**3m, 3n**). Amine hydrochloride salts could also be employed as nucleophiles in the reaction by increasing the amount of additional base to capture the excess HCl. Thus, both sarcosine methyl ester hydrochloride salt and L-proline methyl ester hydrochloride reacted successfully to afford the corresponding 2-fluorinated allylic amines (**3o**, **3p**).

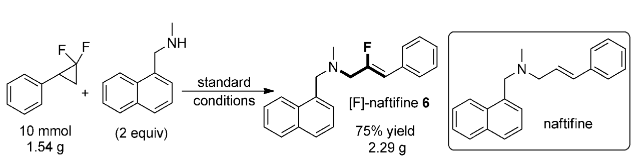
Examining the scope of *gem*-difluorinated cyclopropane coupling partners, we found that various substituted *gem*-difluorinated cyclopropanes bearing different functional groups were found to undergo the desired reaction successfully (Table 2). Both, electron-donating methyl, methoxy, *t*Bu, and Ph groups (**3ab**–**3af**) as well as electron-withdrawing CF_3 and ester groups (**3ag**–**3ah**) on arene rings are well tolerated in the reaction. In most of these reactions, the linear products (i.e., **3ab**–**3ah**) constitute the major products, and the branched byproducts are generated only in trace amounts. An exceptional substrate is **1i**, which mainly generates the branched product **3ai** in moderate yield (b/l = 10:1). Finally, a but-3-en-1-ylbenzene derived *gem*-difluorinated cyclopropane lead to significantly lower *Z*/*E* selectivity (**3aj**). Although the cause of this result is unclear at present, a general observation is that the steric bias of substrate is responsible for high *Z*/*E* selectivity. Notably, terminal *gem*-difluorinated cyclopropanes with one substituent at the 1-position are viable substrates, whereas 1,1-disubstituted and internal *gem*-difluorinated cyclopropanes cannot be converted by the present protocol (**3ak**, **3al**) even at higher reaction temperature.

After this proof of the concept, effort was then made to expand our system to synthesize more diverse 2-fluorinated allylic scaffolds by investigating the use of other simple nucleophiles (e.g., phenols, alcohols, carboxylate salts, and even simple C–H bonds; see Table 3). With slightly modified reaction condition, we were delighted to find that not only phenols are suitable nucleophiles (**4a**–**4b**), but also the benzyl alcohol is adequately reactive, and could undergo the reaction smoothly to give the 2-fluorinated allylic ethers (**4c**). A fluorinated seven-membered ring can also be formed by intramolecular reaction, albeit in relatively lower yield (**4d**). An array of carboxylates bearing alkyl, aryl, and alkenyl substituents reacted smoothly to afford diverse 2-fluorinated allylic esters (**4e**–**4i**), which are difficult to obtain by other methods. Besides, reactive acidic C–H bonds of ethyl 2-cyano-2-phenylacetate (**5a**) and 2-methoxycarbonylsuccinic acid dimethyl ester (**5b**) are also good nucleophiles. Therefore, the reaction provides a new route for the construction of complicated fluorinated quaternary carbon centers, and makes an asymmetric transformation feasible. It is noteworthy that the use of a pyrrole derivative as nucleophile, only yielded C-2-fluorinated allylation product in moderate yield (**5c**), whilst the N–H bond was kept intact.

Table 3: Substrate scope of other nucleophiles.



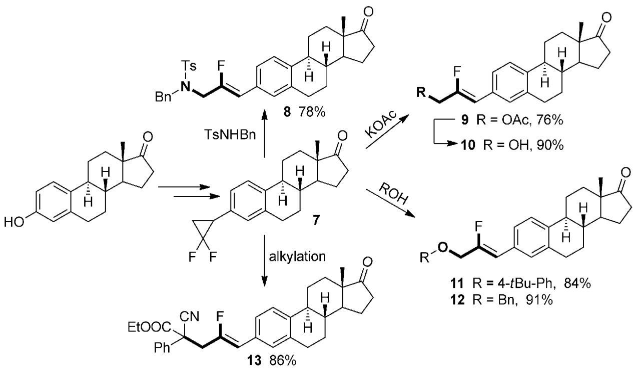
[a] **1a** (0.2 mmol), ROH (1 equiv), K_2CO_3 (1 equiv). 16 h, yields of isolated products. [b] **1a** (0.4 mmol), ROH (0.2 mmol), K_2CO_3 (1 equiv). [c] $Pd(OAc)_2$ as catalyst and $NaHCO_3$ (1 equiv) as base. [d] KOAc as nucleophile and without the addition of K_2CO_3. [e] **1a** (0.2 mmol), RCOOH (2 equiv), K_2CO_3 (2 equiv), 24 h. [f] **1a** (0.2 mmol), [Nu] (1 equiv), K_2CO_3 (1 equiv), 16 h, yields of isolated products.



Scheme 2. Gram-scale synthesis of [F]-naftifine.

This Pd-catalyzed C–F bond activation reaction could be conducted at gram scale, and is thus promising for practical applications (Scheme 2). For instance, the reaction of 1.54 g of (2,2-difluorocyclopropyl)benzene proceeded smoothly under the standard conditions, producing [F]-naftifine **6** in 75% yield (2.29 g) in one step, which is a potential antifungal drug.[16]

To further demonstrate the utility of our newly developed strategy in natural products derivation, a range of more complex estrone derivatives were synthesized.[17] As shown in Scheme 3, the estrone derivatives **7** can easily undergo amination, esterification, etherification, and alkylation to form the corresponding 2-fluorinated allylic scaffolds **8**–**13** in excellent yield. These functionalized estrone derivatives are



Scheme 3. Representative derivatizations of biologically active compounds.

otherwise difficult to prepare by previous methods, and the availability of these compounds may facilitate structure modification and structure–activity relationship studies in natural products.

Preliminary experiments and DFT calculations were performed to investigate the reaction mechanism. The radical capture and inhibition experiment of substrate **1a** (conducted with the addition of 1,1-diphenylethylene or TEMPO, see SI for more details) results in the desired product **3a** in 94 % and 91 % ^{19}F NMR yield respectively. These results are inconsistent with the free radical mechanism, and thus preclude the possibility of the radical intermediate.[18] On this basis, two possible mechanisms were proposed. As shown in Figure 2, path I and II are initiated by the oxidative addition of C–F and C–C[19] bonds to Pd^0, respectively. Thereafter, either the isomerization[19a] on **A** (in path I) or the β-F elimination[19b] on **B** (in path II) might occur to result in the 2-fluorinated palladium π–allyl complex **C**. In other words, these two mechanisms converge at **C**, from which the external nucleophilic attack occurs at the sterically less hindered C1 atom and affords the desired 2-fluorinated allylic scaffolds **D**. According to the DFT calculation results, the oxidative addition of the C–F bond in path I has a high energy barrier of +46.5 kcal mol^{-1} (path I), whereas the energy barrier for C–C bond oxidative addition in path II is much lower (+7.9 kcal mol^{-1}). Meanwhile, the subsequent steps in path II are also facile, and the rate-determining step is the nucleophilic attack (with an overall energy barrier of 29.4 kcal mol^{-1}, see SI for more details). Therefore, the preliminary DFT calculations indicate that path II is more plausible than path I. Note that the C–C oxidative addition is supported by previous observations on the lengthened C_1–C_3 bond in the *gem*-difluorinated cyclopropane system.[14a] In addition, the calculated overall energy barrier (29.4 kcal mol^{-1}) is reasonably consistent with the reaction temperature (80 °C).

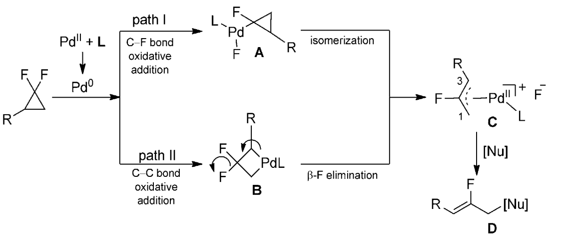


Figure 2. Plausible reaction mechanisms.

In conclusion, we have reported a general and efficient Pd-catalyzed regioselective activation of *gem*-difluorinated cyclopropanes, and afforded the 2-fluoroallylic amines, ethers, esters, and alkylation products with high *Z*-selectivity. It represents the first general application of *gem*-difluorinated cyclopropanes as the reaction partners in transition-metal-catalyzed cross-coupling reactions. In addition, mechanistic understanding from this endeavor indicates that the reaction favorably proceeds through a four-membered-ring palladacycle and subsequent β-F elimination process. The application of such a strategy to the synthesis of highly complex biologically relevant skeletons has also been demonstrated.

Keywords: C(sp^3)–F activation · C–C bond cleavage · fluorinated compounds · *gem*-difluorinated cyclopropanes · palladium

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