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Palladium-Catalyzed Defluorinative Alkylation of *gem*-Difluorocyclopropanes: Switching Regioselectivity via Simple Hydrazones

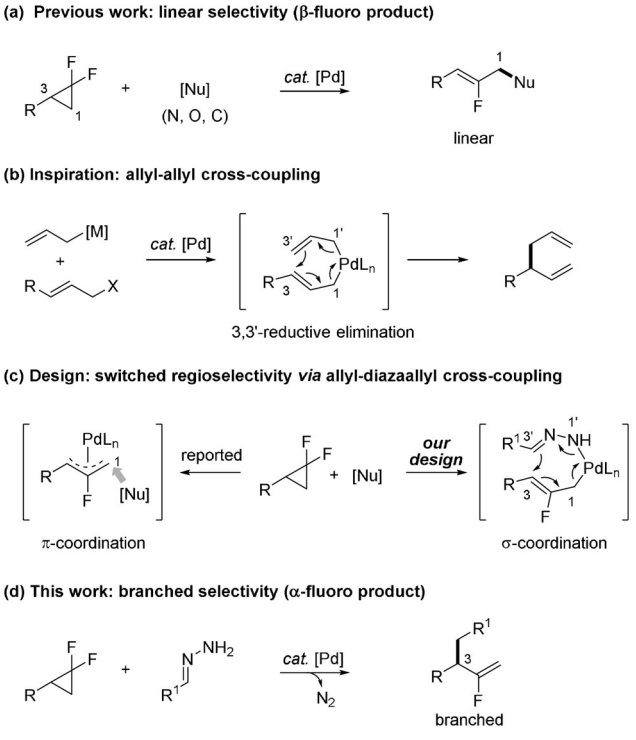
Leiyang Lv and Chao-Jun Li**

Abstract: *Conventional approaches for Pd-catalyzed ring-opening cross-couplings of gem-difluorocyclopropanes with nucleophiles predominantly deliver the β-fluoroalkene scaffolds (linear selectivity). Herein, we report a cooperative strategy that can completely switch the reaction selectivity to give the alkylated α-fluoroalkene skeletons (branched selectivity). The unique reactivity of hydrazones that enables analogous inner-sphere 3,3′-reductive elimination driven by denitrogenation, as well as the assistance of steric-embedded N-heterocyclic carbene ligand, are the key to switch the regioselectivity. A wide range of hydrazones derived from naturally abundant aryl and alkyl aldehydes are well applicable, and various gem-difluorocyclopropanes, including modified pharmaceutical and biological molecules, can be efficiently functionalized with high value alkylated α-fluorinated alkene motifs under mild conditions.*

Introduction

The introduction of fluorine atoms or fluorine-containing scaffolds into molecules can provide unique chemical or physical properties and significant improvement in their biological and pharmacological activities, which has been widely utilized in medicinal chemistry and drug-discovery research.[1,2] In this context, mono-fluoroalkenes have been drawing increasing interest, owing to their potential use as amide bond isosteres or mimics of enols, as well as their far-reaching applications in materials science and synthetic organic chemistry.[3] Typical protocols for the preparation of mono-fluoroalkenes include addition,[4a] olefination,[4b] elimination,[4c] and transition-metal-catalyzed cross-coupling reactions.[4d–f] Although many efforts have been made in this field,[5] several problems such as precise control of the regio- and stereo-selectivity and functional group compatibility still exist. Therefore, the general and practical synthesis of high value mono-fluorinated alkene structures in a well-defined manner remains highly desirable.

Gem-difluorocyclopropanes are readily available (easily prepared from simple alkenes and difluorocarbene precursors), structurally unique (the C–C bond being highly polarized) and versatile fluoroalkylating reagents.[6] By taking advantage of transition-metal-catalyzed ring-opening strategy, Fu and co-workers[7] reported the first Pd-catalyzed C–C activation/C–F cleavage[8] of *gem*-difluorocyclopropanes with various nucleophiles (N, O) to construct mono-fluorinated alkene skeletons with high regioselectivity (linear product) and stereoselectivity (*Z*-configuration) (Scheme 1a). This strategy was further extended to prepare an array of appealing β-fluoroalkene structures integrated with C–C, C–N or C–S bond formations.[9] Very recently, Xia and co-workers reported an elegant Rh-catalyzed C–H allylation of arenes with *gem*-difluorocyclopropanes.[10] Mechanistically, those external nucleophiles (whether interact with the metal center or not) preferentially attack at the sterically less hindered C1 atom, and the linear fluorinated allylic scaffolds (β-fluoroal-



Scheme 1. Functionalization of *gem*-difluorocyclopropanes to synthesize mono-fluorinated alkene scaffolds and the strategy to switch the regioselectivity.

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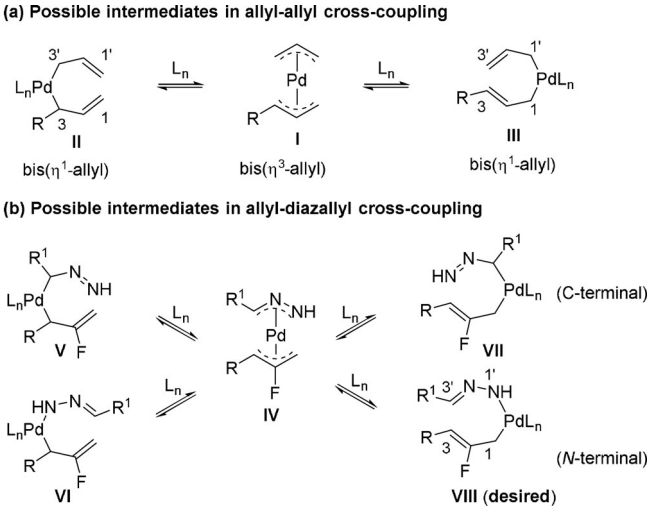
kenes) were obtained predominantly (Scheme 1c, left) via the π-coordination.

As is well-known, rationally manipulating reaction selectivity for regio-divergent synthesis by utilizing and/or overcoming the intrinsic electronic and steric bias is a perpetual subject for chemists.[11] In view of the privileged significance of α-fluoroalkene motifs in drugs, agrochemicals and materials, we wondered if we could overcome the innate reactivity to gain high level of branch-enriched fluorinated allylic skeletons also from the same *gem*-difluorocyclopropane precursors via the σ-coordination.

Inspired by Echavarren[12] and Morken's elegant works[13] on the regio-controlled allyl-allyl cross-couplings via 3,3′-reductive elimination pathway (Scheme 1b), and combined with our expertise on hydrazones acting as alkyl carboanion equivalents in the nucleophilic additions[14] and cross-coupling reactions,[15] we hypothesized that *gem*-difluorocyclopropane could be used as allyl electrophile with simple hydrazone as diazaallyl partner.[16] The readily formed putative allyl, diazaallyl-palladium intermediate would allow for the analogous inner-sphere 3,3′-reductive elimination, thus ensuring the nucleophiles to attack at the sterically more hindered C3 atom (Scheme 1c, right). Besides, based on the literature[17] and our previous work on Pd-catalyzed hydroalkylation of methylenecyclopropanes with hydrazones as pronucleophiles,[15e] we also reasoned that a subsequent denitrogenation activity might take place, which in turn would accelerate the 3,3′-reductive elimination process cooperatively. Assuming that our proposal is viable, there comes with an affiliated benefit that alkyl groups could be incorporated into the monofluoroalkene scaffolds, which is potentially complementary to the Au-catalyzed hydrofluorination reaction of terminal alkyne.[4a] With this design in mind, herein we wish to report that a switched regioselectivity of Pd-catalyzed defluorination alkylation of *gem*-difluorocyclopropanes was enabled by simple hydrazones, and the branch-enriched monofluorinated alkene products were obtained selectively (Scheme 1d).



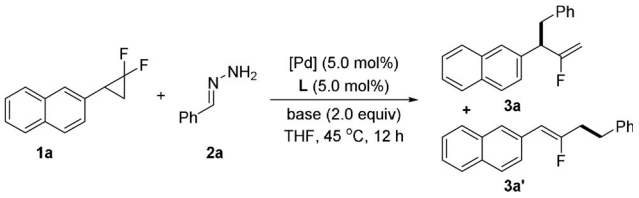
Scheme 2. Possible intermediates encountered in the allyl-(diaza)allyl cross-couplings.

Results and Discussion

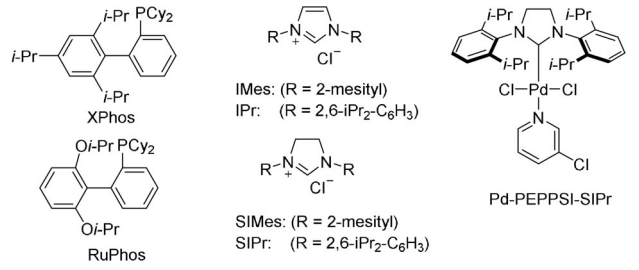
To realize this hypothesis, several challenges must be taken into consideration (Scheme 2). Firstly, to make the reaction operate via a 3,3′-reductive elimination, the coordination ligand must play a key role, which should render both (aza)allyl groups to adopt η^1-bonding mode (**II** or **III**) other than the more common η^3-bonding mode (**I**). Secondly, two kinds of bis(η^1-allyl) bonding modes are available when the substitution (R) is present, and the sterically less hindered bis(η^1-allyl) species (**III**) is supposed be predominant to favor 3,3′-reductive elimination (the direct elimination from intermediate **II** is less likely[18]) relative to the 1,1′-path. As revealed by Morken's work,[19] small-bite-angle bidentate phosphine ligands could effectively increase both the C1-C1′ separation and promote the formation of desired bis(η^1-allyl) bonding mode. Whether it also works or not in our system, the general principle to choose appropriate ligands is well applicable. Thirdly, considering the analogous allyl-diazaallyl cross-coupling, the ambident nucleophilic sites (C-terminal and *N*-terminal)[20] in hydrazone part may result in additional bis(η^1-allyl) bonding modes (**V**, **VI** and **VII**), which are detrimental to the designed regioselectivity. Last but not the least, different from allyl-allyl cross-coupling, an appended denitrogenative event is expected to complete the ring opening-alkylation process.

With these concerns in mind, a palladium/bidentate phosphine system was initially adopted to start our study with the model reaction of 2-(2,2-difluorocyclopropyl)naphthalene (**1a**) and phenyl hydrazone (**2a**) (Table 1). However, no expected product **3a** was obtained with small bite-angle bidentate phosphine ligand, which indicated that the allyl-(diaza)allyl cross-coupling might be quite different from the previous allyl-allyl one. We then reanalyzed the possible intermediates (**V**–**VIII**) in Scheme 2 and envisioned that in order to make the least hindered bis(η^1-allyl) species **VIII** favorable, the steric-embedded coordination ligand might be beneficial due to its repulsion to the substituents (R or R^1). Therefore, a series of bulky ligands, such as PCy_3, P^tBu_3, RuPhos, Xphos and NHCs (*N*-heterocyclic carbenes) were examined accordingly (entries 1–8). We were pleased to find that the anticipated branched fluoroalkene product **3a** could be selectively obtained in 97% yield when the carbene ligand precursor SIPr·HCl [1,3-bis(2,6-diisopropylphenyl)imidazolium chloride] was used in presence of KOH in THF at 45 °C for 12 h (entry 8). In order to simplify the experimental procedure, the air-stable and commercially-available Pd-PEPPSI-SIPr catalyst was employed and **3a** was afforded in comparable yield and regioselectivity (entry 9). Base was utilized to mediate the hydrazone deprotonation, and its choice was also crucial to facilitate the final denitrogenation. No desired product was observed when strong bases such as KO^{t}Bu and LiO^{t}Bu were tested, owing to the dominant Wolff–Kishner reduction of hydrazone (entries 10 and 11). Organic base DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) did not work for the defluorination alkylation reaction (entry 12). Relatively

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



Entry	[Pd]	L	Base	Yield[b] **3a** [%]	**3a**/**3a'**[c]
1	$Pd(OAc)_2$	PCy_3	KOH	N.D.	–
2	$Pd(OAc)_2$	P^tBu_3	KOH	N.D.	–
3	$Pd(OAc)_2$	XPhos	KOH	34	3:1
4	$Pd(OAc)_2$	Ruphos	KOH	42	60:1
5	$Pd(OAc)_2$	IMes·HCl	KOH	trace	–
6	$Pd(OAc)_2$	SIMes·HCl	KOH	trace	–
7	$Pd(OAc)_2$	IPr·HCl	KOH	91	33:1
8	$Pd(OAc)_2$	SIPr·HCl	KOH	97	80:1
9[d]	Pd-PEPPSI-SIPr	–	KOH	97 (94)	80:1
10	Pd-PEPPSI-SIPr	–	KO^{t}Bu	N.D.	–
11	Pd-PEPPSI-SIPr	–	LiO^{t}Bu	N.D.	–
12	Pd-PEPPSI-SIPr	–	DBU	N.D.	–
13	Pd-PEPPSI-SIPr	–	K_3PO_4	73	18:1
14	Pd-PEPPSI-SIPr	–	Cs_2CO_3	91	27:1
15	–	SIPr·HCl	KOH	N.D.	–
16	$Pd(OAc)_2$	–	KOH	N.D.	–



[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), palladium catalyst (5.0 mol%), ligand (5.0 mol%), base (0.2 mmol), THF (1.0 mL), 45 °C, 12 h under N_2 unless otherwise noted. [b] NMR yields were based on **1a** and determined by ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard. [c] The **3a**/**3a'** ratio was determined by ^{1}H NMR analysis of the crude mixtures. [d] Isolated yield in parenthesis. N.D. = not detected.

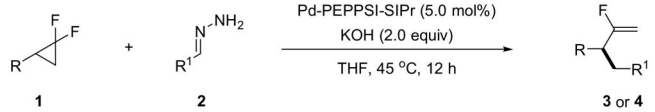
weak bases such as K_3PO_4 and Cs_2CO_3 could deliver the product **3a** in good yields yet with diminished regioselectivity (entries 13 and 14). One explanation may be that the slower deprotonation of hydrazone resulted in the shift of its coordination site with palladium to the C-terminal. Control experiments revealed that no desired product **3a** was obtained in the absence of either the palladium catalyst or a ligand (entries 15 and 16).

With an effective tactic to control the regioselectivity in allyl-diazaallyl cross-coupling reactions in hand, the substrate scope with respect to various easily available hydrazones and *gem*-difluorocyclopropanes was investigated, and the results were shown in Table 2. An array of simple hydrazones (derived from naturally abundant aryl and alkyl aldehydes) bearing either electron-donating or electron-withdrawing groups regardless of the *para*-, *meta*- or *ortho*-substitutions on the aromatic rings, were all competent reaction partners to afford the branched monofluoroalkene products **3b**–**n** in 84–95% yields. The reaction efficiency was almost not hampered even with the sterically bulky hydrazone that prepared from mesitaldehyde (**3e**, 87%). Various functional groups, for example, methoxy (**3g**), methylenedioxy (**3h**), methylthio (**3i**), trifluoromethoxy (**3j**), fluoro (**3k**, **3l**) and trifluoromethyl (**3m**), were well tolerated under the optimized conditions. In the presence of sensitive ester group, a slightly modified reaction conditions (Cs_2CO_3 used instead of KOH) was employed to maintain the efficient reactivity (**3n**, 84%). Hydrazones that prepared from polycyclic aromatic aldehydes such as 1-naphthaldehyde and 2-naphthaldehyde were also suitable substrates (**3o**, **3p**). Notably, heterocyclic-containing hydrazones including furan, pyrrole and carbazole also reacted smoothly, delivering the desired products **3q**–**s** in 82–95% yields. Due to the lack of stabilization from the aromatic ring, hydrazones that derived from aliphatic aldehydes were typically unreactive or less efficient in most of the previously reported cross-coupling reactions. To our delight, this drawback was successfully overcome with the Pd/NHC catalytic system, and the desired alkylated monofluoroalkene products **3t**–**y** were obtained in 85–92% yields (Table 2b). Moreover, aliphatic hydrazones bearing ether, protected alcohol (-OTBS) or amines (-NBoc, -NCbz) could also deliver the desired products **3z**–**3ac** in moderate to excellent yields. To this end, hydrazones behaved as not only the limited benzylation reagents but also the more general alkylation reaction partners.

Next, we surveyed the substrate scope with respect to *gem*-difluorocyclopropanes (Table 2c). It was found that diverse electronic or steric biased substituents attached to the *gem*-difluorocyclopropanes were well accommodated under the standard conditions. Both electron-donating groups such as methyl (**4b**), *tert*-butyl (**4c**), methoxy (**4e**) and benzyloxy (**4f**) as well as the electron withdrawing groups such as fluoro (**4g**), ester (**4h**) and tosyl (**4i**) on the arene rings were tolerated, affording the corresponding products in 86–96% yields. The 2,5-dimethyl substituted difluorocyclopropyl benzene also gave the expected product **4d** in 94% yield. The chloro substituent on the arene (**4j**) could not survive due to its facile interaction with palladium catalyst. Reaction with *gem*-difluorinated cyclopropane that derived from but-3-en-1-ylbenzene (**4k**) was also successful. When the *gem*-difluorinated substrate prepared from 1-vinylpyrrolidin-2-one was tested under optimal conditions, the branched product **4l** was generated exclusively in a 32% yield, possibly due to deactivation of the metal catalyst by the coordination of amide group.[17] It should be noted that this transformation was observed to be quite sensitive to the steric bias on the cyclopropane part. For example, only *gem*-difluorinated cyclopropanes with one substituent at the terminal position (e.g., those derived from mono-substituted alkenes with difluorocarbene precursors) were viable substrates, whereas *gem*-disubstituted difluorocyclopropanes as well as the internal ones were not applicable with this protocol.

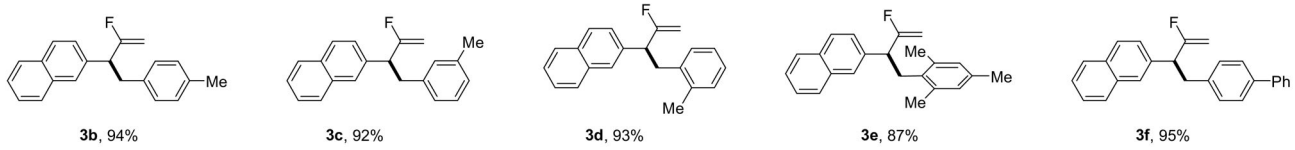
To further exemplify the value of this palladium-catalyzed regioselective defluoroalkylation protocol, the biologically and pharmaceutically related substrates were evaluated. As shown in Table 2d, a series of bioactive molecules assembled

Table 2: Scope of substrates.[a]

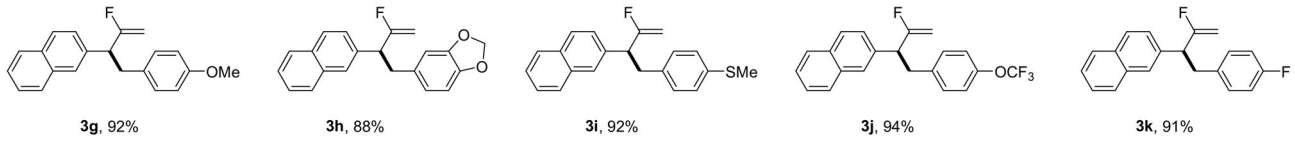


1 **2** **3** or **4**

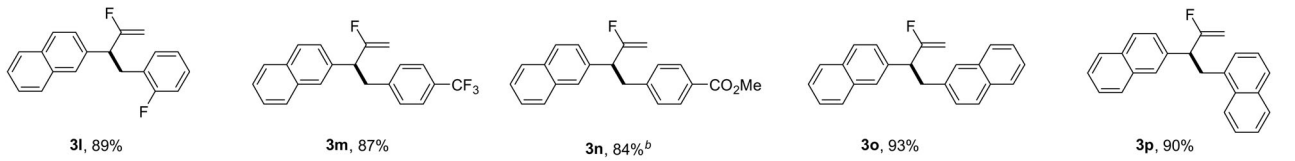
(a) Scope of aromatic hydrazones



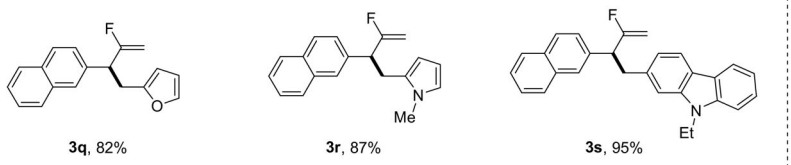
3b, 94% **3c**, 92% **3d**, 93% **3e**, 87% **3f**, 95%



3g, 92% **3h**, 88% **3i**, 92% **3j**, 94% **3k**, 91%

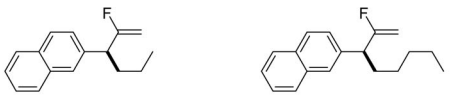


3l, 89% **3m**, 87% **3n**, 84%[b] **3o**, 93% **3p**, 90%

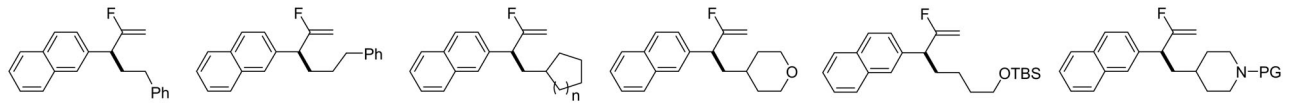


3q, 82% **3r**, 87% **3s**, 95%

(b) Scope of aliphatic hydrazones

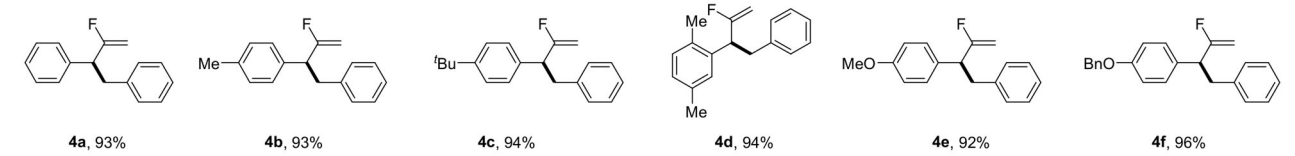


3t, 88% **3u**, 92%

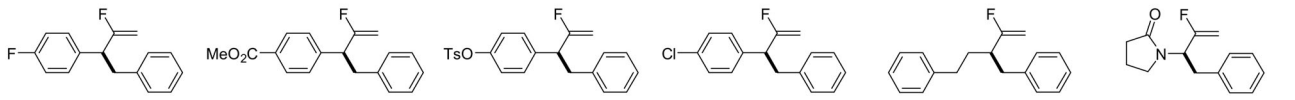


3v, 87% **3w**, 88% **3x**, 85% (n = 1) **3y**, 89% (n = 2) **3z**, 65%[c] **3aa**, 43%[c] **3ab**, 58% (PG = Boc) **3ac**, 94% (PG = Cbz)

(c) Scope of *gem*-difluorocyclopropanes

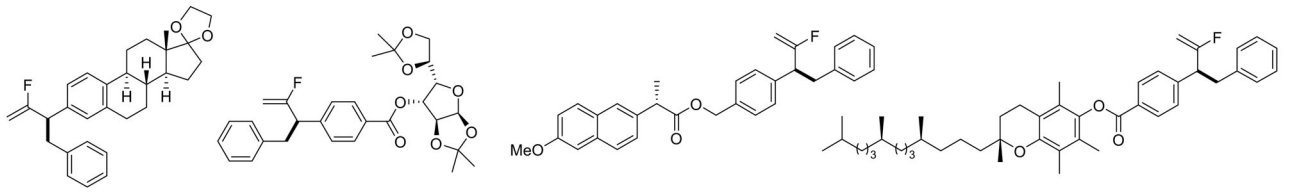


4a, 93% **4b**, 93% **4c**, 94% **4d**, 94% **4e**, 92% **4f**, 96%



4g, 95% **4h**, 86% **4i**, 93% **4j**, 0 **4k**, 81% **4l**, 32% (92%)[d]

(d) Derivative of bioactive molecules



From estrone **4m**, 86% (dr = 1:1)[e]

From diacetone-D-glucose **4n**, 82% (dr = 1:1)[b,e]

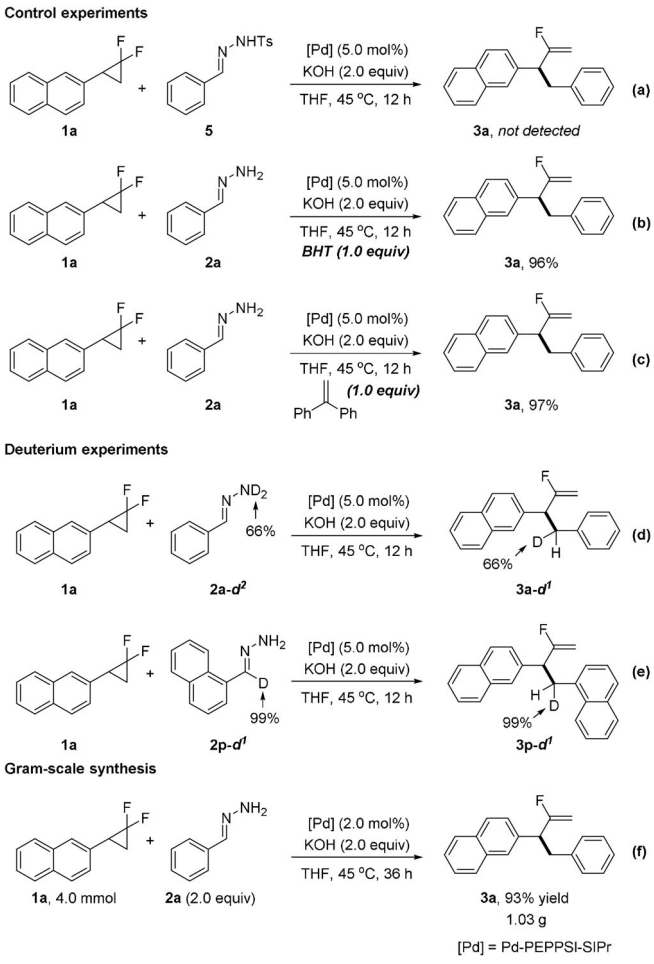
From naproxen **4o**, 92% (dr = 1:1)[b,e]

From α-tocopherol **4p**, 86% (dr = 1:1)[b,e]

[a] Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), Pd-PEPPSI-SIPr (5.0 mol%), KOH (0.2 mmol), THF (1.0 mL), 45 °C, 12 h under N_2. Reported yields are the ones of the isolated products, the branched:linear ratio was more than 20:1 unless otherwise noted. [b] Cs_2CO_3 was used instead of KOH. [c] 60 °C. [d] The yield in parenthesis was calculated based on recovered starting material. [e] The diastereoselectivity in parentheses was determined by ^{1}H NMR analysis of the crude mixtures. PG = protecting group.

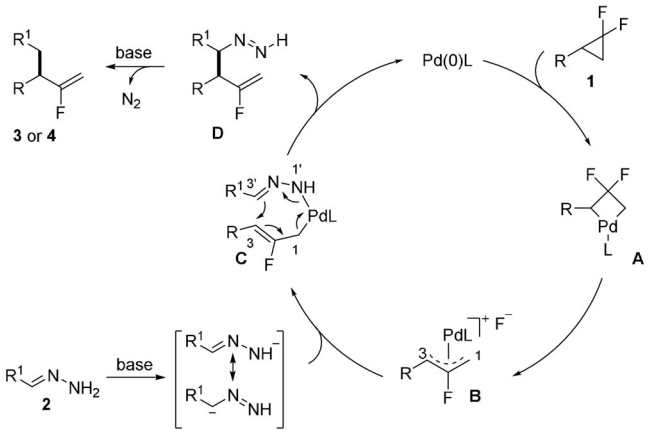
with the α-fluoroalkene motif, including estrone derivative (**4m**), diacetone-D-glucose derivative (**4n**), naproxen derivative (**4o**) as well as α-tocopherol derivative (**4p**), were obtained with this method in good yields (>80%) with 1:1 diastereoisomers. These examples highlighted the broad applicability and compatibility of the current approach, meanwhile enriched the toolbox of chemists for the equipment of bioactive molecules with α-fluoroalkene scaffolds. Notwithstanding, the lack of stereo-control is the limitation of the reaction at this stage.

To gain preliminary insight into the reaction mechanism, several control and deuterium experiments were then carried out (Scheme 3). When *N*-tosylhydrazone **5**, commonly utilized as the carbene precursor, was tested instead of hydrazone to react with **1a** under the standard conditions, no desired product **3a** was detected. This outcome indicated the unlikely involvement of a carbene process in this transformation [Scheme 3, Eq. (a)]. When the reaction was carried out in the presence of radical inhibitors such as butylated hydroxytoluene (BHT) or 1,1-diphenylethylene, the yield of **3a** was not affected, which precluded the possibility of a radical mechanism [Scheme 3, Eqs. (b) and (c)]. Deuterium-labeling experiment with **2a**-d^2 (66%) showed that deuterium were exclusively incorporated into the benzyl position in **3a**-d^1, which suggested that hydrazone served as both the alkyl nucleophile and hydrogen donor [Scheme 3, Eq. (d)]. When deuterated hydrazone **2p**-d^1 was conducted with **1a** under optimal conditions, the aldehydic hydrogen was preserved completely in **3p**-d^1 and no observation of H/D scrambling between benzylic and other moiety. This result revealed that there were no C–H activation of hydrazone or generation of Pd-H species during this transformation [Scheme 3, Eq. (e)]. Besides, to explore the practicality of this defluorination alkylation method, the reaction of 2-(2,2-difluorocyclopropyl)naphthalene (**1a**) with phenyl hydrazone (**2a**) was carried out in gram-scale. Gratifyingly, the desired product **3a** was obtained in excellent yield (93%, 1.03 g) even with a reduced palladium loading (2.0 mol%) [Scheme 3, Eq. (f)].



Scheme 3. Control and deuterium experiments and gram-scale synthesis.

Based on these results and our previous work, a plausible reaction mechanism is proposed (Scheme 4). Initially, oxidative addition of the strained C–C bond in **1** gives the intermediate **A**, upon which β-F elimination occurs to afford the 2-fluorinated palladium π-allyl complex **B**. Then transmetallation of **B** with amphipathic nucleophile that derived from deprotonated hydrazone **2** delivers the key sterically less hindered bis(η^1-allyl) species **C**, which undergoes regioselective 3,3′-reductive elimination to afford the intermediate **D** and regenerate Pd catalyst. Finally, decomposition of **D** via deprotonation and N_2 extrusion releases the desired product **3** or **4**.



Scheme 4. Proposed reaction mechanism.

Conclusion

In summary, we have developed a highly effective and regioselective Pd-catalyzed defluorinative alkylation of *gem*-difluorocyclopropanes with simple hydrazones. This reaction proceeds smoothly under mild reaction conditions to deliver a series of high value α-fluorinated alkene scaffolds complimentary to the previously documented β-fluorinated ones in good to excellent yields. The unique trifunctional reactivity of hydrazones is crucial for the success of this transformation and can be ascribed as follows: 1) assisting inner-sphere 3,3′-reductive elimination via forming putatively allyl, diazaallyl-

palladium complex; 2) accelerating the reductive elimination process through loss of nitrogen gas; 3) acting as alkylating reagents. Moreover, the cooperation of palladium with sterically hindered NHC ligand is also indispensable to ensure the switched regioselectivity. Last but not the least, this protocol displays great compatibility with various functional groups, thus providing a straightforward access to incorporate α-fluoroalkene unit into pharmaceutically relevant molecules that may be useful in drug discovery. Further studies to elucidate the mechanism and asymmetric synthesis are ongoing in our lab.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkylation · defluorination · fluoroalkenes · *gem*-difluorocyclopropane · hydrazones

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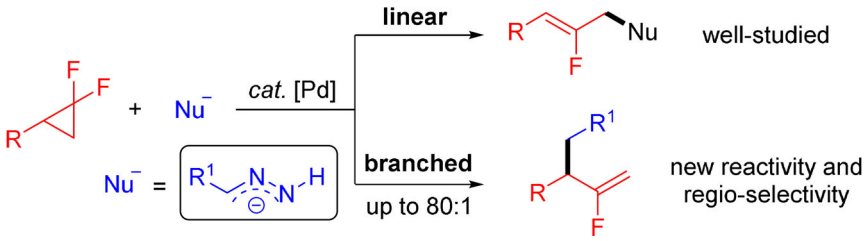
Research Articles

Synthetic Methods

L. Lv,* C.-J. Li* _____ ■■■■–■■■■

Palladium-Catalyzed Defluorinative Alkylation of *gem*-Difluorocyclopropanes: Switching Regioselectivity via Simple Hydrazones



A highly effective Pd-catalyzed defluorinative alkylation of *gem*-difluorocyclopropane with branched selectivity was achieved by using a cooperative strategy that integrated the unique trifunctional character of hydrazones with Pd/NHC catalysis.