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Conformational control of nonplanar free base porphyrins: towards bifunctional catalysts of tunable basicity

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COMMUNICATION

Synthesis of Remote Fluoroalkyated Alkenes by Palladium-Catalyzed Relay Heck-Type Reaction

Lixin Li,*[a] Zhengguang Zhao,[a] Jing Xu,*[a] Haotian Luo,[a] Yong Li,[a] Xiantao Ma,[a] Lin Tang,[a] Bo Ren,[a] Xinhua Cao[a] and Yan-Na Ma[b]

**Herein, we report a palladium-catalyzed relay Heck-type reaction of fluoroalkyl bormide and terminalalkenes. The reaction involves fluoroalkylationof alkenes and migrationof double bondsvia 1,5-hydrogen atom transfer strategy.Through this method, a series of remote fluoroalkylated alkenes were obtainedunder mild conditions.**

Fluoroalkyl groups have profound impact on physicochemical and biological properties, that exhibits to improve the absorption, distribution, metabolism, and excretion properties of compounds in the drugs discovery.[1]Therefore, the introduction of fluoroalky groups into organic molecules has attracted considerable research attention. Fluoroalkyl alkenes are useful building blocks for the synthesis of a wide range of fluorinated compounds.[2] Many strategies have been developedin the past decade: in particularly transition-metal catalyzed direct C-H fluoroalkylation of alkenes[3] has emerged as a powerful tool for the synthesis of corresponding fluoroalkylated alkenes (Scheme 1, a). For example, Buchwald[4] and Cho[5] groups reported the synthesis of trifluoromethyl alkenes with Togni, Umemoto's reagent and CF_3X as CF_3 sources. Furthermore, inexpensive and commerciallyavailable fluoroalkyl halides[6] have also been exploited in the Heck-type reaction, which appears to be an appealing and straightforward pathway for the synthesis of fluoroalkyl alkenes. Zhang's groups realized the synthesis of fluoroalkylated alkenes by Palladium/Xantphos catalyzed Heck-type reaction of fluoroalkyl bromides. [7]Subsequently, Wang and coworkers reported C-H difluoroalkylation and perfluoroalklation of alkenes and hetero-arenes via Cu-PMEDA catalyst system.[8] In addition, the Ir- or Ru-catalyzed fluoroalkylation of alkenes[9]

under visible light condition were also developed. To the best of our knowledge, however, only vicinal fluoroalkyated alkenes can be obtained through these methods. To date, transition-metal-catalyzed Heck-type reaction for the synthesis of remote fluoroalkyl alkenes remains a great challenge.
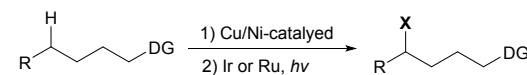
Scheme 1 Methods for the synthesis of fluoroalkyl alkenes

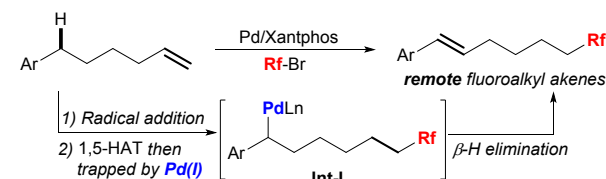a) Synthesis of vicinal fluoroalkyl alkenes
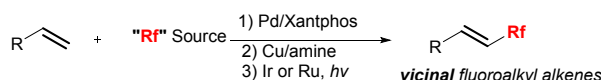
Rf source: Togni, Umemoto's regent, Rf-Br etc.

b) Remote C-H functionalization *via 1,5-HAT* strategy

DG = RN-H, RN-F, double bond etc.
X = C, N, O etc.

c) This work

• High C-H site selective • Mild reaction condition •via Pd(0)/Pd(I)/Pd(II) pathway

Over the past years, 1,5-hydrgogen atom transfer (HAT) has been proven as a powerful strategy for the remote functionalization of inert C(sp³)-H bonds and construction of structurally diverse compounds (Scheme 1, b).[10] Various functional groups have been introduced into target molecules efficiently to realize C-O, C-C, C-N and C-X bond formation under mild conditions. Base on the fact, our group[11] developed photoredox-catalyzed remote difunctionalization of alkenes for synthesisof fluoroalkyl ketones via 1,5-HAT strategy. Therefore, we envisioned that 1,5-HAT strategy could be used into relay Heck-type reaction to construct the remote fluoroalkylated alkenes (Scheme 1, c). First, the addition of fluoroalky radical to alkenes which is initiated by [Pd(0)Ln]

a. College of Chemistry and Chemical Engineering, Xinyang Normal University, Xinyang, Henan 464000, China.lilixin@xynu.edu.cn, xujing@xynu.edu.cn
b. College of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang, Henan 453007, China.

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produces an alkyl radical.Subsequently a key benzyl radical is formed via 1,5-HAT, which can be trapped by [Pd(I)L$_n$] to provide the key alkyl-palladium species **Int-I**. Finally, **Int-I** undergos β–hydride elimination to deliver the desired remote fluoroalky alkenes.

**Table 1**Optimization of the reaction conditions
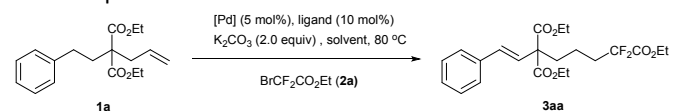
Entry	[Pd]/Ligand	Solvent	Yield(%)[b]
1	Pd(PPh$_3$)$_2$Cl$_2$/ Xantphos	THF	37
2	Pd(PPh$_3$)$_2$Cl$_2$/ Xantphos	DCE	33
3	Pd(PPh$_3$)$_2$Cl$_2$/ Xantphos	DCM	48
4	Pd(PPh$_3$)$_2$Cl$_2$/ Xantphos	Dioxane	39
5	Pd(PPh$_3$)$_2$Cl$_2$/ Xantphos	CH$_3$CN	72
6	Pd(PPh$_3$)$_2$Cl$_2$/ Xantphos	PhCH$_3$	33
7	Pd(PPh$_3$)$_2$Cl$_2$/ Xantphos	MeOH	NR[c]
8	Pd(CH$_3$CN)$_2$Cl$_2$/Xantphos	CH$_3$CN	37
9	Pd$_2$(dba)$_3$/ Xantphos	CH$_3$CN	30
10	[Pd(allyl)Cl]$_2$/ Xantphos	CH$_3$CN	20
11	Pd(TFA)$_2$/ Xantphos	CH$_3$CN	25
12	Pd(PPh$_3$)$_4$/ Xantphos	CH$_3$CN	42
13	Pd(PPh$_3$)$_2$Cl$_2$/ DPEphos	CH$_3$CN	22
14[d]	Pd(PPh$_3$)$_2$Cl$_2$/ Xantphos	CH$_3$CN	trace
15[e]	Pd(PPh$_3$)$_2$Cl$_2$/ Xantphos	CH$_3$CN	trace

[a] Reaction condition: **1a** (0.1 mmol), **2a** (0.2 mmol), [Pd] (5 mol %), ligand (10 mol%), Base (0.2 mmol),solvent (1.0 mL), under N$_2$, 80°C, 24h. [b] Yield determined by ^{19}F NMP using PhCF$_3$ as an internal standard. [c] NR = no reaction [d] at 25 ^{o}C. [e] Under 12 W blue LED.

To validate our hypothesis, we commenced our study by attempting the proposed relay Heck-type reaction between diethyl 2-allyl-2-phenethylmalonate (**1a**) and ethyl bromodifluoroacetate (**2a**) with Pd(PPh$_3$)$_2$Cl$_2$ as catalyst, tetrahydrofuran (THF) as solvent, K$_2$CO$_3$ as base under 80 ^{o}C. Studies of the reaction parameters revealed that reaction efficiently run is highly dependent on the phosphine ligands. No reaction occurred when other phosphine ligands except Xantphos and DPEphos (see supporting information), which is contributed to the large bite angle of bidentate phosphine Xanthphos when binds with palladium.[7a] To our delight, when Xantphos was used as ligand under the above conditions, the desired product **3aa** was obtained in 37% yield (Table1, entry 1). Encouraged by these results, a series of solvents were examined, which revealed that CH$_3$CN was the best choice and **3aa** was gained in 72% yield, Presumably, CH$_3$CN can be as ligand to stabilize the palladium complex (Table1, entry 1-7). It should be pointed out that no reaction occurred when protonic solvent MeOH was used. The yields of **3a**reduced dramatically when the pre-Pd catalyst was swtiched from Pd(PPh$_3$)$_2$Cl$_2$ to other palladium catalyst (Table 1, entry 9-12). The species of base also influenced the reaction efficiency, various inorganicbase and organic base were optimized (see

supporting information), and the best yield was observed when K$_2$CO$_3$was used. Only trace of desired product was obtained when the reaction temperature was reduced to room temperature (Table1, entry 14). Notably, It should be noticed that the result of this relay Heck-type reaction was messy under 12 W blue LED and only trace amount of **3aa** was obtained (Table1, entry 15). This result revealed that Pd-catalyzed Heck-type reaction under thermal conditions has distinct difference compared with visible light-irradiated condition.

Scheme 2 Scope of Alkenes[a]
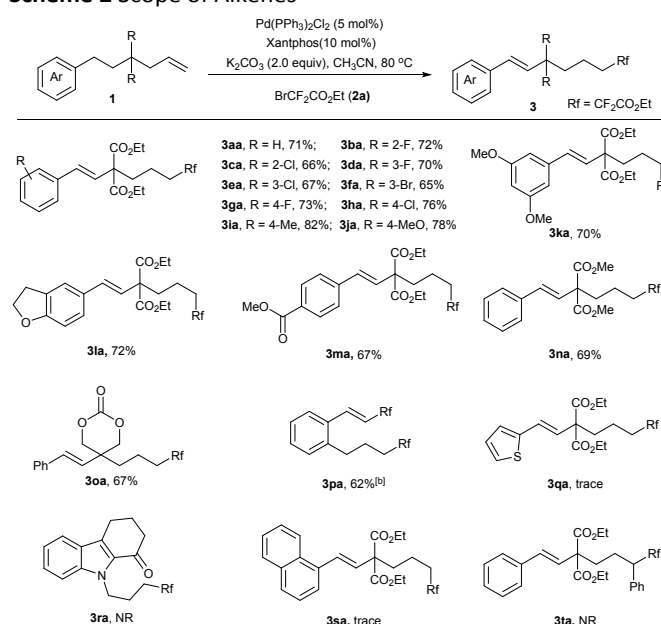
[a] Reactions were performed on a 0.2mmol scale under standard conditons, and isolated yields are given. [b] BrCF$_2$CO$_2$Et (0.4 mmol).

With the optimized conditions in hand, we explored the substrate scope of alkenes with different substituents (Scheme 2). Firstly, a series of alkenes bearing different substituents on the remote aromatic ring were examined (Scheme 2, **3aa–3la**), which revealed that electron-withdrawing group (-F, -Cl, -Br) and electron-donating group (-Me, -OMe) at both the *ortho*, *meta*, and *para* position of aromatic ring were all suitable for this transformation, and the reaction proceeded smoothly to provide corresponding products in moderate to good yields. It is noteworthy that the bromide group can also be tolerated to avoid that oxidative addition of Pd(0) species (Scheme 2, **3fa**). The desired product **3ka** was obtained in 70% yield whenthe remote aromatic rings contains two substituents. The heterocycle substituted alkene was also subjected to the reaction conditions to affaord the target product **3la** in 72% yield. When a carbonyl-containing functional group was introduced into aromatic ring, **3ma** was obtained in 67% yield. Switching *gem*-substituent from ethyl ester to methyl ester groups on the aliphatic chain was well accommodated in this transformation to furnish the corresponding product **3na** in 69% yield. Additionally, when the substituent was carbonate ester, the product **3oa** was also produced in 67% yield. To our surprise, two fluoroalkyl groups were introduced when 1-allyl-2-ethylbenzene was used as substrate and the desired product

3pa was obtained in 62% yield (Scheme 2). No reaction occurred or trace product was observed when heterocycles such as indole-, thiophene- and1-naphthalene alkene(Scheme 2, **3qa–3sa**) were used as substrate respectively. The internal alkene was also not suitable to this reaction because steric effect (see supporting information).

Next, we studied different fluoroalkyl sources (Scheme 3). As expected, the bromodifluoroacetamide derivatives could also be subjected for the palladium-catalyzed relay Heck-type reaction, particularly naked bromodifuoroacetamide, to give corresponding products in moderate yields (**3ab-3af**). It is noteworthy that monofluoroalkyl bromide was also suitable for this transformation under the optimal reaction conditions and generated product **3ag** in 43% yield. The desired product **3ah** was obtained in 76% yield when methyl bromodifluoroacetate was used. Additionally, perfluorohexyl and perfluorooctyl bromides could also be used into this reaction to produce desired products in moderate yields (Scheme 3, **3ai, 3aj**) (see supporting information).

Scheme 3 Scope of Fluoroalkyl Sources[a]
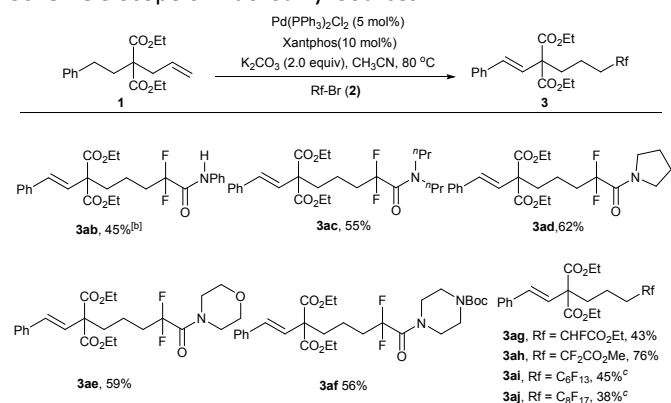
[a] Reaction were performed on a 0.2mmol scale under standard conditions, and isolated yields are given. [b] Rf-Br (0.3 mmol). [c] Yield determined by ^{19}F NMP using PhCF$_3$ as an internal standard.

Scheme 4 Reaction of Alkenyl Alcohol **1b**
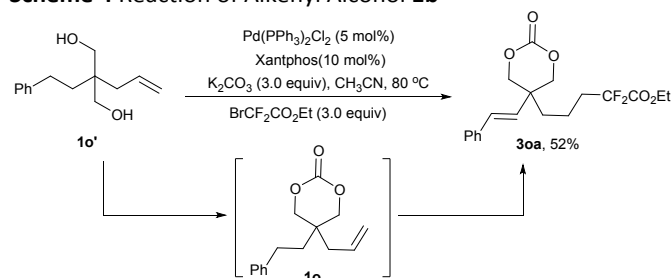
Interestingly, when 2-allyl-2-phenethylpropane-1,3-diol (**1o'**) was used as substrate, the remote difluoroalky alkene containing cyclic carbonate structure was obtained in 52% yield (Scheme 4). In this process,[12] consecutive nuclephilic acyl substitution reaction occurred between hydroxyl groups and ethyl bromodifluoroacetate, ethoxy group and -CF$_2$Br act as leaving group in the formation of **1o**, then undergo relay Heck-type reaction to give the desired product in one pot.

To examine the practicality of this method, a gram-scale reaction was explored between **1a** and **2a**, and the

corresponding product was obtained in 67% yield under the standard conditions (Scheme 5).

Scheme 5 Gram-Scale Reaction for the Synthesis of **3aa**
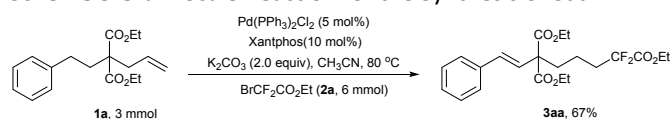
To gain insight into the reaction mechanism, some control experiments were conducted (scheme 6). First, the radical scavenger 2,2,6,6-tetramethyl-1-piperidinoxyl (TEMPO, 4.0 equiv) was added to the standard reaction system, which completely inhibited the reaction. Instead of forming **3a**, the radical adduct TEMPO-CF$_2$CO$_2$Et **4** was detected by HRMS (scheme 6, 1). Furthermore, ethyl 2-(4-phenyl-3,4-dihydronaphthalen-1-yl)acetate **6** and ethyl 2,2-difluoro-4,4-diphenylbut-3-enoate **8** were detected by HRMS when (1-(2-phenylcyclopropyl)vinyl)benzene **5**and 1,1-diphenylethene**7** were explored as the radical trapping agents, respectively (scheme 6, 2). The results suggested that • CF$_2$CO$_2$Et may be existed during the reaction, and participated in relay Heck-type reaction.

On the basis of the results mentioned above and previous report, a plausible mechanism was proposed (Scheme 6, 3). First, the fluoroalkyl radical generates by Pd(0)/Xantphos complex through single electron transfer (SET) with BrCF$_2$CO$_2$Et and at the same time forms a Pd(I) species. Subsequently addition of the fluoroalkyl radical to the double bond produces alkyl radical **Int-III**. Then a more stable benzyl radical **Int-II** is formed via 1,5-HAT. At this point, **Int-II** is trapped by Pd(I) species to afford a new Pd-alkyl species, which undergoesβ-H elimination to give the desired product **3aa**. With the assistance of base, the Pd-H species is transformed to Pd(0) to achieve the catalyst cycle.

Scheme 6 Control Experiments and Proposed Mechanism

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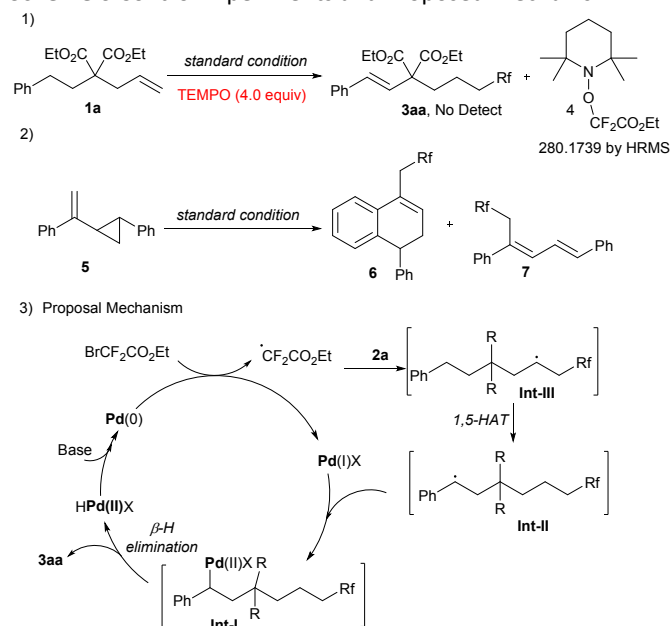
In summary, we have developed a protocol for palladium-catalyzed relay Heck-type reaction of fluoroalkyl bromides to synthesize remote fluoroalkyl alkenes via 1,5-HAT strategy. This method provides a direct way for highly site selective remote C-H activation and highly efficient access to 1,5-fluoroalkyl alkenes in moderate to good yields. Further investigation of remote functionalization of alkenes via 1,5-HAT strategy with [Pd/Xantphos] complex through a SET pathway is underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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