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Fluoroalkylation

Palladium-Initiated Radical Cascade Stereoselective Iodofluoroalkylation/Cycloisomerization of Ene-vinylidenecyclopropanes

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Abstract: A novel and convenient palladium-initiated radical cascade stereoselective iodofluoroalkylation/cycloisomerization of ene-vinylidenecyclopropanes with fluoroalkyl iodides has been developed. The reaction proceeds under mild reaction conditions with high atom economy and stereoselectivity, thereby allowing an efficient access to a variety of difluoromethylated or perfluoroalkylated pyrrolidines tethered with an alkyl iodide. Two plausible radical pathways for the transformation have been proposed on the basis of the results of control experiments and previous reports, which in one case it was thought that palladium(0) was an initiator rather than a catalyst.

Organofluorine compounds are widely used in medicine, agriculture, and also in life and material sciences because of their unique metabolic stability, lipophilicity, and biological properties (Figure 1).[1] Therefore, the development of new synthetic methods for the incorporation of fluorine or fluorinated moieties into organic molecules is of significant importance. Numerous methods for the incorporation of fluoroalkyl motifs have been extensively investigated in the past decades.[2]

As ubiquitous feedstock materials and good radical receptors, reacting enynes with fluoroalkyl halides (Br or I) has been achieved before using a radical initiator, such as AIBN,[3] Et_3B,[4] $Na_2S_2O_4$,[5] or light.[6] At the same time, transition-metal-mediated or catalyzed fluoroalkylation has emerged as a highly efficient alternative pathway to fluorination for the introduction of fluorine-containing structural motifs into organic molecules in recent years.[7] Despite significant advances in this area,[8] more concise, mild, and atom-economical fluoroalkylation methods for synthesizing complex organic compounds remain highly desired.

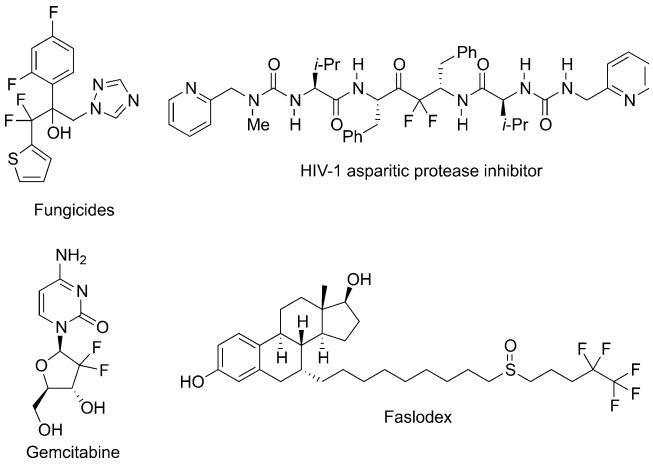
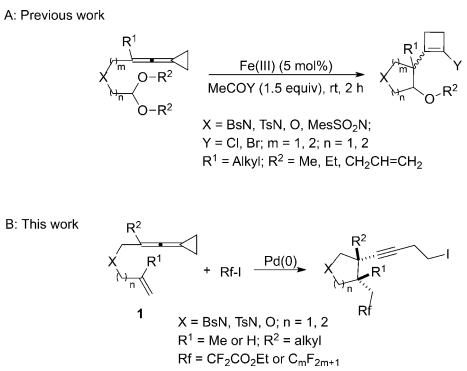


Figure 1. Representative fluorine containing drugs and bioactive molecules.

During our ongoing investigation on the chemistry of vinylidenecyclopropanes (VDCPs),[9] we have developed the Fe^{III}-catalyzed intramolecular cycloisomerization of acetal-VDCPs to construct a series of halogenated 1,2-disubstituted cyclobutenes tethered with a tetrahydropyrrole (Scheme 1 A).[9b] Combined with our previous work on metal-mediated transformations of VDCPs, we envisaged that ene-VDCPs could be excellent candidates for the exploration of new reaction method in fluoroalkylation because of their multiple reaction sites. Herein, we wish to report an intriguing new palladium-initiated radical cascade iodofluoroalkylation/cycloisomerization of ene-VDCPs with fluoroalkyl iodide, which affords an easy and efficient



Scheme 1. A) Fe^{III}-catalyzed cycloisomerization of acetal-vinylidencyclopropanes and B) the current work.

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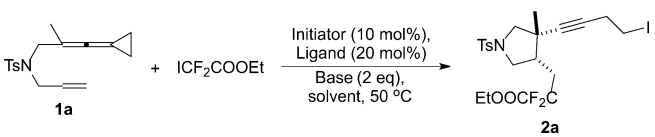
access to iodine/fluoroalkylation pyrrolidines tethered with an alkyl iodide and other five- or six-membered-ring heterocyclic derivatives (Scheme 1 B).

Our initial studies focused on the palladium-initiated reaction of readily available ethyl difluoroiodoacetate with ene-VDCP **1a**. The use of ethyl difluoroiodoacetate is of interest because of its applications arising in various areas, including medicinal chemistry. For instance, the difluoromethylene moiety (CF_2R, CF_2H) has been recognized as a potential bioisostere of hydroxy[10] or thiol[11] groups, and acts as a lipophilic hydrogen-bond donor.[12] To our delight, an expected product **2a** was isolated in 58% yield as a single stereoisomer after 12 h, in the presence of $PdCl_2(PPh_3)_2$ (10 mol%), DPEPhos (20 mol%), and Cs_2CO_3 (2.0 equiv) in 1,4-dioxane (1.0 mL) at 50 °C under an argon atmosphere (Table 1, entry 1). The structure of **2a** was unambiguously assigned by X-ray diffraction.[13,14] Inspired by this result, different palladium catalysts were evaluated for this transformation. In contrast to $PdCl_2(PPh_3)_2$, other catalysts failed to show higher catalytic ability (Table 1, entries 2–4). Among the ligands surveyed, we found that Xantphos was the most efficient one, promoting an increasing yield to 69% (Table 1, entries 5–8). A subsequent survey on several representative bases and solvents indicated that Cs_2CO_3 and 1,4-dioxane were still the best choice (Table 1, entries 9–16). Pleasingly, an improvement was achieved by decreasing the concentration of **1a** to 0.05 mol/L, giving **2a** in 78% yield (Table 1, entry 17). However, further decrease of the concentration did not raise the yield of product **2a**. Additionally, no product was formed without palladium catalyst or ligand (Table 1, entry 20). Interestingly, the yields of **2a** decreased distinctly if the reaction was conducted without Cs_2CO_3 or phosphine ligands (Table 1, entries 21 and 22). It has been reported that Cs_2CO_3 alone is sufficient to activate fluoroalkyl iodides at 60 °C, leading to the formation of fluoroalkyl radicals.[7g] Thus, we thought that Cs_2CO_3 alone could activate fluoroalkyl iodides in this reaction to give the desired product. Finally, the use of **1a** (1.0 equiv), $PdCl_2(PPh_3)_2$ (10 mol%), Xantphos (20 mol%), and Cs_2CO_3 (2.0 equiv) with ethyl difluoroiodoacetate (2.0 equiv) in the presence of dioxane (2.0 mL) under an argon atmosphere at 50 °C for 12 h was considered as the optimal reaction conditions.

Table 1. Screening conditions for iododifluoromethylation/cycloisomerization of ene-VDCP **1a**.

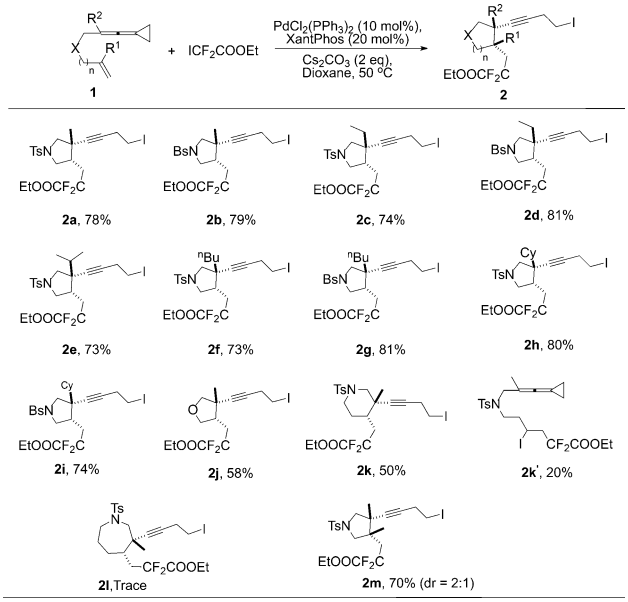


1a 2a

Entry[a]	Initiator	Ligand	Base	Solvent	Yield[%][b]/**2a**
1	$PdCl_2(PPh_3)_2$	DPEPhos	Cs_2CO_3	dioxane	58
2	$Pd(OAc)_2$	DPEPhos	Cs_2CO_3	dioxane	42
3	$PdCl_2$	DPEPhos	Cs_2CO_3	dioxane	47
4	$Pd(PPh_3)_4$	DPEPhos	Cs_2CO_3	dioxane	53
5	$PdCl_2(PPh_3)_2$	JohnPhos	Cs_2CO_3	dioxane	27
6	$PdCl_2(PPh_3)_2$	Xantphos	Cs_2CO_3	dioxane	69
7	$PdCl_2(PPh_3)_2$	DPPF	Cs_2CO_3	dioxane	60
8	$PdCl_2(PPh_3)_2$	(±)-BINAP	Cs_2CO_3	dioxane	33
9	$PdCl_2(PPh_3)_2$	Xantphos	K_2CO_3	dioxane	trace
10	$PdCl_2(PPh_3)_2$	Xantphos	Na_2CO_3	dioxane	30
11	$PdCl_2(PPh_3)_2$	Xantphos	NaOAc	dioxane	complex
12	$PdCl_2(PPh_3)_2$	Xantphos	Cs_2CO_3	DMF	complex
13	$PdCl_2(PPh_3)_2$	Xantphos	Cs_2CO_3	MeCN	40
14	$PdCl_2(PPh_3)_2$	Xantphos	Cs_2CO_3	Toluene	trace
15	$PdCl_2(PPh_3)_2$	Xantphos	Cs_2CO_3	DCE	35
16	$PdCl_2(PPh_3)_2$	Xantphos	Cs_2CO_3	DCM	52
17	***$PdCl_2(PPh_3)_2$***	***Xantphos***	***Cs_2CO_3***	***dioxane***	***78***
18[d]	$PdCl_2(PPh_3)_2$	Xantphos	Cs_2CO_3	dioxane	72
19[c,e]	$PdCl_2(PPh_3)_2$	Xantphos	Cs_2CO_3	dioxane	52
20	–	–	Cs_2CO_3	dioxane	trace
21	$PdCl_2(PPh_3)_2$	Xantphos	–	dioxane	51
22	$PdCl_2(PPh_3)_2$	–	Cs_2CO_3	dioxane	31
23[f]	$PdCl_2(PPh_3)_2$	–	Cs_2CO_3	dioxane	64

[a] Reaction conditions: **1a** (0.1 mmol), ethyl difluoroiodoacetate (2.0 equiv), catalyst (10 mol%), ligand (20 mol%), base (2.0 equiv) and solvent (1.0 mL) were used. [b] Yield of isolated product. [c] 2.0 mL dioxane was employed. [d] 3 mL dioxane was employed. [e] ICF_2CO_2Et (4 equiv) was employed. [f] 1.0 equiv $PdCl_2(PPh_3)_2$ was employed.

To demonstrate the substrate scope of this method, a variety of ene-VDCPs were examined and the results are shown in Scheme 2. With ene-VDCPs **1b–i** as the substrates (R = primary or secondary alkyl groups; X = TsN or BsN anchor), the desired products **2b–i** were obtained in good yields ranging from 73% to 81% with good stereoselectivity. When ene-VDCP **1j**, with O as an anchor, was used as substrate, the yield of desired product **2j** slightly decreased to 58%. Extending the carbon chain to alkene moiety as a $(CH_2)_2$ tether, the desired product **2k** could be given in 50% with 20% byproduct **2k′**. Notably, **2k′** may be the precursor of **2k**. However, when ene-VDCP **1l**, bearing a $(CH_2)_3$ carbon chain to the alkene moiety, was employed, no reaction occurred under the standard conditions. The inferior results for **1k** and **1l** are presumably due to the fact that forming six or seven-membered rings is difficult

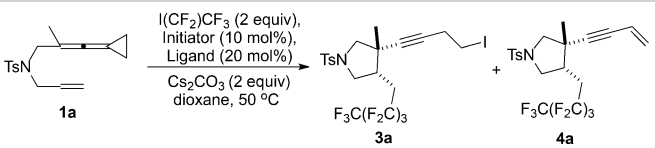


Scheme 2. Substrate scope of the iododifluoromethylation/cycloisomerization of ene-VDCPs. Reaction conditions: **1** (0.2 mmol), ethyl difluoroiodoacetate (2 equiv), $PdCl_2(PPh_3)_2$ (10 mol%), Xantphos (20 mol%), Cs_2CO_3 in dioxane (4.0 mL) at 50 °C for 10–20 h, yield of isolated product.

and needs higher energy than that of five-membered ring. In all these cases, the desired products were isolated as a single stereoisomer. Interestingly, when ene-VDCP **2m** (R^1 = Me) was applied under the standard conditions, the corresponding product **2m** could be obtained in 70% yield. It was notable that the product **2m** contains a pair of diastereoisomers with a 2:1 ratio and the relative configuration of syn-**2m** was determined by nuclear Overhauser effect spectroscopy (see the Supporting Information).

To further investigate the practicability of this reaction, other fluoroalkyl iodides were surveyed as well. Gratifyingly, we found that when perfluorobutyl iodide was used, the corresponding perfluoroalkylated product **3a** was successfully obtained in 37% yield along with 17% of byproduct **4a** (Table 2, entry 1). The structure of **4n** ($R_f = C_6F_{13}$) was unambiguously assigned by X-ray diffraction.[13,14] To improve the reaction selectivity and yield of **3a**, different palladium catalysts, bases, solvents, and additives were surveyed. Detailed results are briefly summarized in Table 2 (for more details, see the Supporting Information, Table S1). We found that $Pd(PPh_3)_4$ and (±)-BINAP were superior to other palladium catalysts and ligands (Table 2, entries 1–5). Interestingly, the addition of 10.0 equiv of deionized water to the reaction mixture leads to selective formation of **3a** in 85% yield (Table 2, entry 6). However, increasing the employed amount of water further did not give a better result (Table 2, entry 7). Besides, the addition of 4 Å molecular sieves did not improve the yield of **4a**. The role of water cannot be clearly explained at the present stage, but it seems that the dehydroiodination process was inhibited. It has been reported that bulky ligands and other additives could suppress β-hydride elimination from alkylpalladium halides.[15] When 10 equiv of LiCl was added, only trace of **3a** could be detected on the basis of monitoring with thin-layer chromatography (Table 2, entry 8). Moreover, the yield of **3a** decreased in the absence of ligand (Table 2, entry 10).

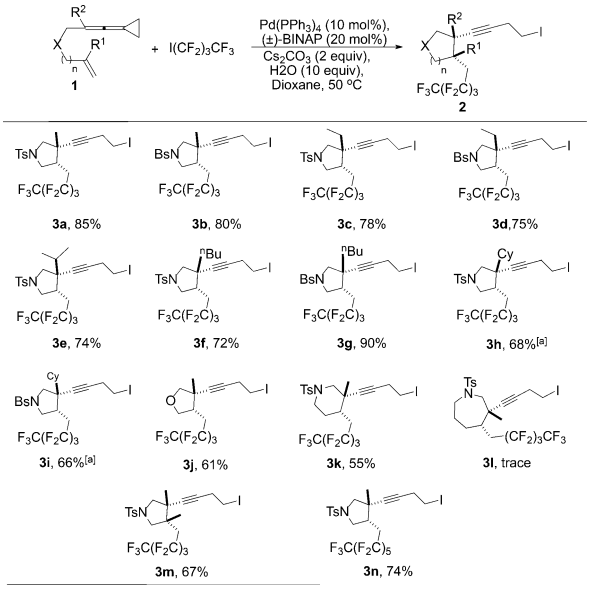
Table 2. Screening conditions for iodoperfluoroalkylation/cycloisomerization of ene-VDCP **1a**.



Entry[a]	Initiator	Ligand	Additive (equiv)	Yield[%][b] / **3a**:**4a**[c]
1	$PdCl_2(PPh_3)_2$	Xantphos	–	54 (2.1:1)
2	$Pd(PPh_3)_4$	Xantphos	–	67 (3.5:1)
3	$PdCl_2$	DPEPhos	–	73 (3.3:1)
4	$Pd(PPh_3)_4$	dppf	–	62 (3.7:1)
5	$Pd(PPh_3)_4$	(±)-BINAP	–	79 (4.2:1)
6	***$Pd(PPh_3)_4$***	***(±)-BINAP***	***H_2O (10)***	***85 (> 20:1)***
7	$Pd(PPh_3)_4$	(±)-BINAP	H_2O (100)	81 (> 20:1)
8	$Pd(PPh_3)_4$	(±)-BINAP	LiCl (5)	trace
9[d]	$Pd(PPh_3)_4$	(±)-BINAP	4 Å	69 (1.2:1)
10	$Pd(PPh_3)_4$	-	H_2O (10)	60 (> 20:1)

[a] Reaction conditions: **1a** (0.02 mmol), $I(CF_2)_3CF_3$ (2 equiv), catalyst (10 mol%), ligand (20 mol%), Cs_2CO_3 (2.0 equiv) and dioxane (2.0 mL) were used. [b] Yield of isolated **3a** and **4a**. [c] Determined by ^{19}F NMR spectroscopy. [d] 4 Å molecular sieve (50 mg) was added.

With the optimized reaction conditions in hand, the reactions of fluoroalkyl iodides with other ene-VDCPs **1** were then carried out to define the generality of this procedure, and the results are shown in Scheme 3. Similarly, using ene-VDCPs **1b**–**1j** as the substrates, the desired perfluoroalkylated products **3b**–**3g** were obtained in good to excellent yields, ranging from 72% to 90%. When R^2 was bulky cyclohexyl, $PdCl_2(MeCN)_2$ was employed as the initiator and the corresponding products **2h** and **2i** could also be afforded in 68% and 66% yields, respectively. A moderate yield was obtained when ene-VDCP **1j** was used as substrate. Satisfactorily, **3k** and **3m** could be smoothly afforded as single diastereoisomers in 55% and 67% yields under the standard conditions, respectively. However, none of the desired seven-membered-ring product was formed when **1l** was employed as substrate. A different perfluoroalkyl iodide was also investigated. When perfluoro-1-iodohexane was utilized in this reaction, the desired product **3n** was produced in 74% yield. In all these cases, the desired products were isolated as a single stereoisomer.

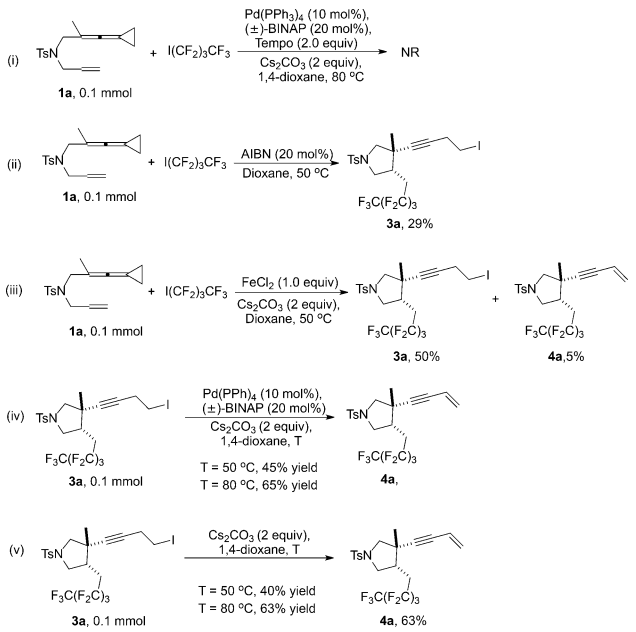


Scheme 3. Substrate scope of the iodoperfluoroalkylation/cycloisomerizations of ene-VDCPs. Reaction conditions: **1** (0.2 mmol), $I(CF_2)_3CF_3$ (2 equiv), $Pd(PPh_3)_4$ (10 mol%), (±)-BINAP (20 mol%), Cs_2CO_3 and H_2O (10 equiv), in Dioxane (2.0 mL) at 50 °C for 10–20 h, yield of isolated product.
[a] $Pd(MeCN)_2Cl_2$ (10 mol%) was employed.

In the previous reports with regard to the Pd-catalyzed similar fluoroalkylation/cycloisomerization, iodofluoroalkyl alkene intermediates were involved in the related transformation.[7b–d] Thus, it is worth considering that the exist of (alkyl)PdI intermediates may produce the target products via reductive eliminations. Although iodinated alkylpalladium(II) complexes have recently become synthetically useful for constructing carbon–carbon bonds and carbon-heteroatom bonds through transition-metal-catalyzed cross-coupling reactions.[16] However, the

iodinated alkylpalladium complex is believed to be highly reactive owing to the absence of stabilizing electronic interaction with metal d-orbitals.[17] The fast and thermodynamically favored β-hydride elimination is the predominant process for the (alkyl)PdI species. Only a few examples of reductive elimination of iodinated alkylpalladium-containing *syn*-β-hydrogen atoms have been reported.[16a,18] In general, the formation of (alkyl)PdI intermediates not seems to be possible in this case.

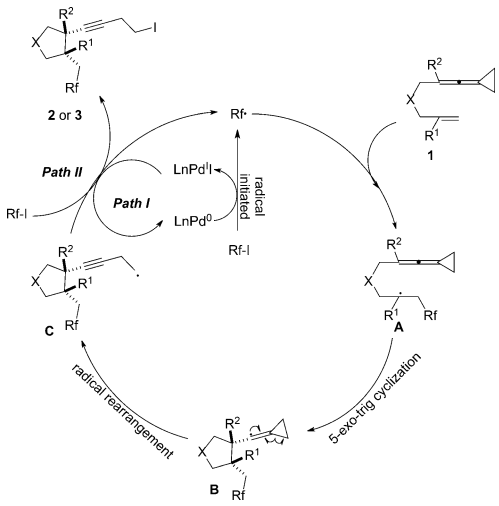
To gain more mechanistic insight into the present reaction, several control experiments were performed (Scheme 4).



Scheme 4. Control experiments for mechanistic studies.

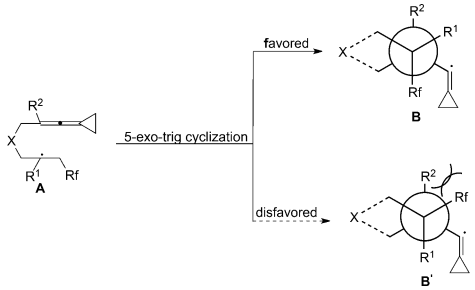
When a reaction mixture of **1a** and perfluorobutyl iodide was treated under the standard conditions in the presence of the radical scavenger TEMPO (2,2,6,6-tetramethylpiperidinyloxy) (2.0 equiv), no product was detected, implying that a SET process is involved in the catalytic cycle. When $Pd(PPh_3)_4$ was replaced by AIBN or $FeCl_2$,[7f] the reaction also proceeded very well and afforded **3a** in 46% and 55% yields, respectively, rendering the involvement of a radical process. However, only $FeCl_2$ (20 mol%) could not initiate this reaction if without the use of Cs_2CO_3 (Supporting Information, Table S2). Furthermore, when **3a** (0.1 mmol) was used as substrate directly in the presence of $Pd(PPh_3)_4$ (10 mol%), (±)-BINAP (20 mol%), and Cs_2CO_3 (2.0 equiv) in 1,4-dioxane (1.0 mL) at 50 °C or 80 °C, **4a** could be obtained in 45% or 65% yields respectively. In the absence of $Pd(PPh_3)_4$ and (±)-BINAP however, the transformation of **3a** proceeded smoothly to afford **4a** in a similar yield. Thus, **4a** was believed to be formed by a base-assisted dehydroiodination instead of the β-H elimination of alkylpalladium iodide intermediate. These results shed some lights on the insight into the mechanism of this Pd initiated reactions.

On the basis of the above experiments and the relevant results reported, two of the plausible pathways for the Pd-initiated radical cascade iodofluoroalkylation/cycloisomerization of ene-VDCPs with fluoroalkyl iodides are presented in Scheme 5. In one mechanism (path I), a fluoroalkyl radical $R_f^{\cdot}$ and a Pd^I specie are generated through a single electron transfer (SET) between R_f-I and Pd^0. Then, the addition of the $R_f^{\cdot}$ radical to the double bond of ene-VDCP generates the radical intermediate **A**. Subsequently, a 5-*exo*-trig cyclization occurs to afford methylenecyclopropane (MCP) radical intermediate **B**, which undergoes an intramolecular radical rearrangement with the ring-opening of cyclopropane to give the corresponding radical intermediate **C**. Finally, the intermediate **C** is able to abstract the iodide from $LnPd^I$I, thus leading to the formation of product and regeneration of Pd^0.[19] Besides, another plausible mechanism has been also proposed (path II). The same intermediate **C** is produced after an intramolecular radical rearrangement. However, this intermediate **C** reacts with R_f-I to generate the $R_f^{\bullet}$ radical again and produce the corresponding iodofluoroalkylation product **2** or **3**. In this radical process, Pd^0 acts as an initiator rather than a catalyst.



Scheme 5. An outline of two plausible mechanisms for the formation of **2** or **3**.

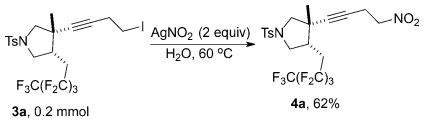
As for the observed high diastereoselectivities, a hypothesis based on steric hindrance has been proposed in Scheme 6. Placing the alkyl substituent R^2 and R_f away from each other minimizes steric interactions and provides intermediate **B** as *syn*-configuration. Furthermore, it is also possible that the $LnPd^I$I species or Cs_2CO_3 may be involved in the 5-*exo*-trig cyc-



Scheme 6. Hypothesis for the diastereoselectivity of the cycloisomerization.

lization process by activating VDCP moiety, which might have an influence on the observed excellent diastereoselectivities.

Nitroalkanes are one of the fundamental classes of substances in organic synthesis. The conversion of alkyl halides to nitro compounds is one of the most used methods for the preparation of nitroalkanes. Using $AgNO_2$ (2 equiv), **3a** could be easily transformed to perfluoroalkylated pyrrolidine tethered with nitroalkane **4a** in 62% yield (Scheme 7).[20]



3a, 0.2 mmol **4a**, 62%

Scheme 7. Further transformation of **3a**.

In conclusion, we have developed a palladium-initiated radical cascade stereoselective iodofluoroalkylation/cycloisomerization of ene-vinylidenecyclopropanes with fluoroalkyl iodides, which can efficiently synthesize a variety of useful iododifluoromethylated or iodoperfluoromethylated pyrrolidines tethered with an alkyl iodide and other five or six-membered heterocyclic derivatives. These five or six-membered fluorine-containing heterocyclic compounds may be used as potential intermediates in organic synthesis and medicinal chemistry. Beside, two plausible mechanisms were proposed based on the results of control experiments and relevant previous reports. Further work will be devoted to applying this new method to synthesize biologically active products.

Acknowledgements

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Keywords: alkyl iodides · cyclopropane · difluoromethylation · ene-vinylidenecyclopropanes · palladium

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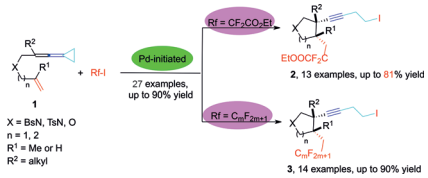
A radical cascade stereoselective iodofluoroalkylation/cycloisomerization of ene-vinylidenecyclopropanes with fluoroalkyl iodides and initiated by palladium has been developed. This method affords a variety of difluoromethylated or perfluoroalkylated pyrrolidines tethered with an alkyl iodide.



Fluoroalkylation

*S. Yang, Q. Xu, M. Shi**

■■ – ■■

Palladium-Initiated Radical Cascade Stereoselective Iodofluoroalkylation/Cycloisomerization of Ene-vinylidenecyclopropanes