Synthetic Methods

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A General Synthesis of Fluoroalkylated Alkenes by Palladium-Catalyzed Heck-Type Reaction of Fluoroalkyl Bromides**

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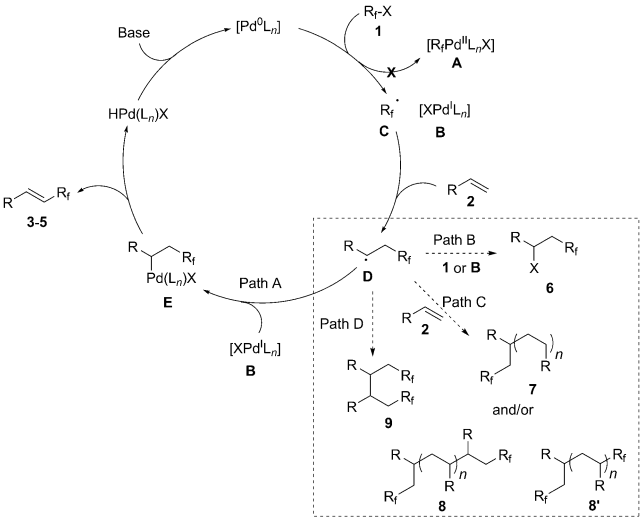
Abstract: *An efficient palladium-catalyzed Heck-type reaction of fluoroalkyl halides, including perfluoroalkyl bromides, trifluoromethyl iodides, and difluoroalkyl bromides, has been developed. The reaction proceeds under mild reaction conditions with high efficiency and broad substrate scope, and provides a general and straightforward access to fluoroalkylated alkenes which are of interest in life and material sciences.*

The development of new methods to introduce fluorinated functional groups into organic molecules has become an intensive topic of synthetic organic chemistry because of the importance of fluorinated compounds in agrochemicals, pharmaceuticals, and functional materials.[1] To date, there have been substantial efforts on fluoroalkylation of aromatic compounds,[2] but alkenes containing fluorinated functional groups are less studied owning to the lack of efficient and general strategies. Usually, fluoroalkylated alkenes can be prepared through cross-coupling of fluoroalkyl metal species with alkenyl halides,[3] or stepwise procedures of addition of fluoroalkyl free radical to alkenes, followed by base-assisted elimination.[4] However, such processes suffer from the use of stoichiometric amounts of a transition metal and/or the requirement of multiple steps, in particular for preparation of alkenyl halides and fluoroalkyl radical precursors. To circumvent these issues, transition-metal-catalyzed fluoroalkylation of alkenes through Heck-type reactions appears to be an appealing and straightforward alternative. Furthermore, using low-cost and widely available fluoroalkyl halides (R_f–X), in particular fluoroalkyl bromides (R_f–Br), in the Heck-type reactions would make the synthesis routine cost-efficient for practical applications.[5] To date, however, the preparation of fluoroalkylated alkenes through transition-metal-catalyzed Heck-type reactions remains challenging. Herein, we disclose the first example of a palladium-catalyzed Heck-type reaction of perfluoroalkyl bromides. The reaction can also be extended to trifluoromethyl iodide and other functionalized difluoromethyl bromides, thus providing a facile and general access to a wide range of fluoroalkylated alkenes. The notable features of this approach are its synthetic simplicity, broad substrate scope, high efficiency, and excellent functional-group compatibility.

We began our study based on the fact that the addition of the fluoroalkyl radical **C** to the alkenes **2** is kinetically favorable compared with insertion of the palladium complex $[R_fPd^{II}L_nX]$ (**A**) to **2** (Scheme 1).[6,7] Therefore, if **C**, instead of **A**, is initiated by reaction of $[Pd^0L_n]$ with fluoroalkyl halides



Scheme 1. Proposed mechanism for palladium-catalyzed fluoroalkylation of alkenes with fluoroalkyl halides.

(**1**; R_f–X),[7,8] then the recombination of the newly formed alkyl radical **D** with $[XPd^{I}L_n]$ (**B**) would provide the key palladium species $[(alkyl)Pd^{II}L_nX]$ (**E**; Scheme 1, Path A).[5] As a consequence of β-hydride elimination of **E**, the desired fluoroalkylated alkenes **3**–**5** would be delivered. To facilitate the catalytic cycle, however, the competitive reactions between the formation of **E** and the side product alkyl halides **6** (Scheme 1, Path B) are a concern, because it has been demonstrated by Chen et al. that among the fluoroalkyl halides, perfluoroalkyl iodides, the most commonly used radical precursors, are prone to yielding **6** in the presence of a $[Pd^0L_n]$ catalyst.[7] In addition, other competitive side reactions, such as oligomerization of **2** with **D** (Scheme 1, Path C) and dimerization of **D** (Scheme 1, Path D), are also hurdles to realizing such a Heck-type reaction. To the best of our knowledge, no successful example of transition-metal-catalyzed perfluoroalkylation of alkenes through Path A (Scheme 1) has been reported thus far.[9]

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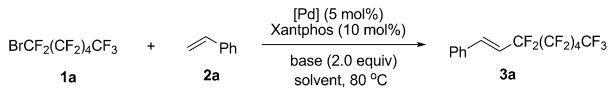
Accordingly, we chose perfluorohexyl bromide (**1a**) as our initial substrate based on the following considerations: 1) The C–Br bond is stronger than the C–I bond; as a result, the generation of the side products **6–9** through Paths B–D (Scheme 1) from perfluoroalkyl bromides would be slower than that from perfluoroalkyl iodides. Although perfluoroalkyl bromides have been demonstrated to be poor fluoroalkyl radical precursors,[7] we envisioned that if a suitable phosphine ligand in combination with a palladium catalyst could induce perfluoroalkyl bromides to generate fluoroalkyl radicals and accelerate Path A, it will benefit the formation of desired products. 2) Perfluoroalkyl bromides are one of the cheapest and most widely available fluorinated sources. However, the transition-metal-catalyzed fluoroalkylation reactions with perfluoroalkyl bromides remain underdeveloped, and represent a challenge because of their inert reactivity. Therefore, it is of great interest to develop new and efficient catalytic system for their wide applications in life and materials sciences.

Initially, the coupling of **1a** with styrene (**2a**) was examined by using bidentate phosphine Xantphos as a ligand which binds palladium with a large bite angle[10] (Table 1). The use of Xantphos was inspired by our very recent investigations into the palladium-catalyzed direct difluoroalkylation of organoborons, in which a single-electron transfer (SET) from a Pd^0/Xantphos complex to difluoroalkyl bromides initiated the catalytic cycle and gave difluoroalkyl radicals.[11] To our delight, when the reaction was carried out with Xantphos (10 mol%) in the presence of $[PdCl_2(PPh_3)_2]$ (5 mol%), and K_2CO_3 (2.0 equiv) in 1,4-dioxane at 80°C, 39% yield of **3a** was obtained without observation of the by-products **6–9** (entry 1). Switching the pre-palladium catalyst from $[PdCl_2(PPh_3)_2]$ to $[Pd(PPh_3)_4]$ dramatically improved the yield to 62% (entry 2). Encouraged by these results, several reaction parameters were investigated to improve the reaction efficiency further (for details, see the Supporting Information). It was found that 1,2-dichloroethane (DCE) was the optimal solvent, and a higher yield (68%) was obtained when the reaction was catalyzed by $[PdCl_2(PPh_3)_2]$ in DCE (entry 3). Other palladium sources also catalyzed the reaction, but led to lower yields (entries 4–8). The choice of base also influenced the reaction efficiency, and the best yield (89% upon isolation) was obtained with Cs_2CO_3 as a base (entry 10). However, no reaction occurred when other phosphine ligands other than Xantphos were used, thus demonstrating the essential role of Xantphos in the catalytic cycle (for details, see the Supporting Information). It should be mentioned that the diminished yields were observed by reducing the ratio of Pd/Xantphos from 1:2 to 1:1 (entries 11 and 12). In addition, neither the product nor by-products were observed in the absence of the palladium sources or the base (entries 13 and 14). Thus, these findings implied that the tetraphosphine-ligated Pd^0 species plays a crucial role in the promotion of the reaction. Whereas no **3a** was observed when perfluorohexyl iodide (**1a′**) was tested under optimized reaction conditions, a mixture of oligomerized by-products (**7a**; Path C, Scheme 1), the dimer **9a** (Path D), and other uncertain by-products were provided as major products (for details, see the Scheme S1 in the Supporting Information). Furthermore, only a small amount of benzyl iodide derivative **6a** (Path B) was observed in this reaction (for details, see the Scheme S1 in the Supporting Information). We reasoned that it is probably because of the high reactivity of Pd^0/Xantphos complex which may generate perfluoroalkyl radical from perfluoroalkyl iodides faster than that from perfluoroalkyl bromides, thus initiating different side reactions.

Table 1: Representative results for optimization of palladium-catalyzed Heck-type reaction of **1a** with styrene (**2a**).[a]



Entry	[Pd]	Solvent	Base	Yield [%][b]
1	$[PdCl_2(PPh_3)_2]$	1,4-dioxane	K_2CO_3	39
2	$[Pd(PPh_3)_4]$	1,4-dioxane	K_2CO_3	62
3	$[PdCl_2(PPh_3)_2]$	DCE	K_2CO_3	68
4	$Pd(OAc)_2$	DCE	K_2CO_3	35
5	$PdCl_2$	DCE	K_2CO_3	49
6	[PdCl$_2$(dppf)]	DCE	K_2CO_3	39
7	$[PdCl_2(MeCN)_2]$	DCE	K_2CO_3	39
8	$[Pd(PPh_3)_4]$	DCE	K_2CO_3	30
9	$[PdCl_2(PPh_3)_2]$	DCE	Cs_2CO_3	79 (81)
10[c]	$[PdCl_2(PPh_3)_2]$	DCE	Cs_2CO_3	(89)
11[d]	$[PdCl_2(PPh_3)_2]$	DCE	Cs_2CO_3	63
12[e]	$[PdCl_2(PPh_3)_2]$	DCE	Cs_2CO_3	34
13	none	DCE	Cs_2CO_3	n.r.
14	$[PdCl_2(PPh_3)_2]$	DCE	none	n.r.

[a] Reaction conditions (unless otherwise specified): **1a** (0.6 mmol, 2.0 equiv), **2a** (0.3 mmol, 1.0 equiv), solvent (2 mL), 24 h. [b] Determined by ^{19}F NMR spectroscopy using fluorobenzene as an internal standard and yield within parentheses is that of the isolated product. [c] DCE (3 mL). [d] 7.5 mol% Xantphos was used. [e] 5 mol% Xantphos was used. DCE = 1,2-dichloroethane, dppf = 1,1′-bis(diphenylphosphino)ferrocene, n.r. = no reaction, Xantphos = 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene.

A variety of styrene derivatives could be fluoroalkylated with **1a** through this method (Table 2). Versatile functional groups, such as alkoxycarbonyl and formyl were quite well-tolerated (**3h**,**i**). In particular, the heterocyle thiazole furnished the corresponding product in a synthetically useful yield (**3j**). Branched alkenes were also applicable to the reactions. Good yield was obtained, when cyclic alkene 1,2-dihydronaphthalene (**2k**) was examined (**3k**). As for a terminal branched alkene bearing an alkyl group, the double bond migrated product was the only product obtained (**3l**), thus providing an alternative strategy to access fluoroalkylated allylic compounds. It is noteworthy that the conjugated alkene underwent the reaction smoothly, thus providing **3m** in good yield without observation of other by-products. The alkenes were not restricted to styrenes, as an enamide was also a suitable substrate, thus providing perfluorohexylated alkene with 81% yield (**3o**). In addition, the successful fluoroalkylation of dihydropyran makes it possible to rapidly access fluorinated gylcomimetics for carbohydrate-based studies (**3n**).[12] However, aliphatic alkenes were not suitable substrates. Internal linear alkenes also failed to provide products because of steric effects.

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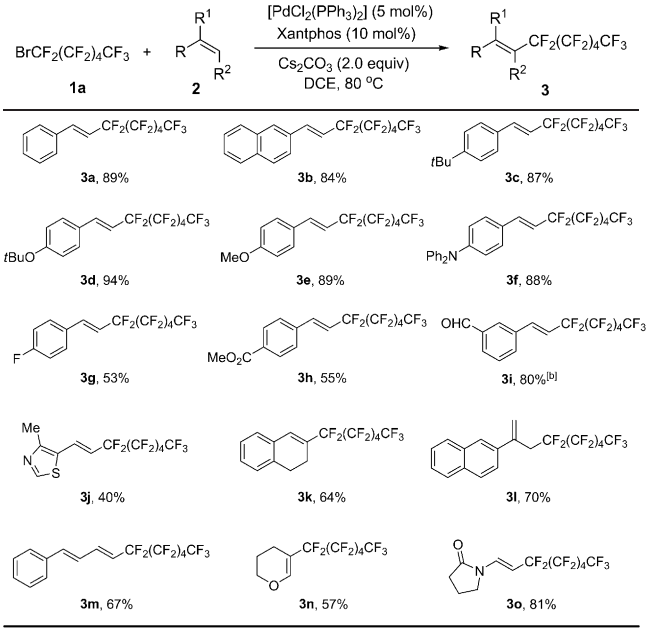
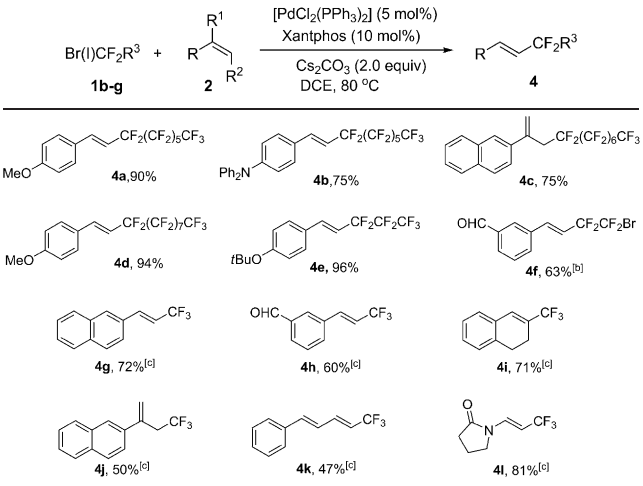
Table 2: Palladium-catalyzed Heck-type reaction of perfluorohexyl bromide with alkenes.[a]



[a] Reaction conditions (unless otherwise specified): **1a** (0.6 mmol, 2.0 equiv), **2** (0.3 mmol, 1.0 equiv), DCE (3 mL), 24 h. All reported yields are those of isolated products. [b] Reaction was conducted at 120 °C.

To demonstrate the generality of this catalytic system, other perfluoroalkyl bromides were also explored (Table 3). Overall, perfluoroalkyl bromides containing seven to nine carbon atoms all let to good yields (**4a**–**d**). In particular, excellent yield (96%) was obtained when perfluoropropyl bromide was tested (**4e**). 1,2-Dibromotetrafluoroethane was also applicable to the reaction, and afforded the monoalkenylated product in moderate yield with one bromide intact

Table 3: Palladium-catalyzed Heck-type reaction of perfluoroalkyl bromides and trifluoromethyl iodide with alkenes.[a]

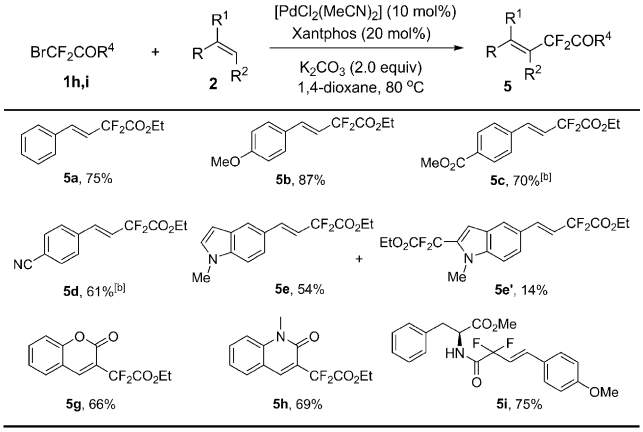


[a] Reaction conditions (unless otherwise specified): **1** (0.6 mmol, 2.0 equiv), **2** (0.3 mmol, 1.0 equiv), DCE (3 mL), 24 h. All reported yields are those of isolated products. [b] $[PdCl_2(MeCN)_2]$ (10 mol%), Xantphos (20 mol%), K_2CO_3 (2 equiv), 1,4-dioxane (2 mL). [c] 4.0 equiv of CF_3I was used.

(**4f**), thus providing good opportunities for downstream transformations. Importantly, some styrene derivatives and enamide were also suitable substrates for trifluoromethyl iodide, thus leading to trifluoromethylated alkenes with high efficiency (**4g**–**l**). However, it should be mentioned that the reaction efficiency highly depends on the nature of the substrates. Styrene gave a mixture of complexes, and only a poor yield (16%) of trifluoromethylated alkene was observed. *para*-Substituted styrenes, such as 1-methoxy-4-vinylbenzene (**2e**) and methyl 4-vinylbenzoate (**2h**), also afforded their corresponding products in low yields (**2e**, 31%; **2h**, 15%) (for details, see the Scheme S2 in the Supporting Information), along with the by-products **8 or 8′** (Path C, Scheme 1) and **9** (Path D).[13]

The reaction can also be extended to bromodifluoroacetate (**1h**).[14] A series of difluoroacetylated alkenes were obtained through this method with high efficiency and excellent functional-group tolerance (Table 4). But in these

Table 4: Palladium-catalyzed Heck-type reaction of bromodifluoroacetate and its derivative with alkenes.[a]



[a] Reaction conditions (unless otherwise specified): **1** (0.6 mmol, 2.0 equiv), **2** (0.3 mmol, 1.0 equiv), 1,4-dioxane (2 mL), 24 h. All reported yields are those of isolated products. [b] Molecular sieves (3 Å) were used.

cases, $[PdCl_2(MeCN)_2]$ instead of $[PdCl_2(PPh_3)_4]$ showed good activity. Interestingly, when indole derivative **2q** was subjected to the reaction, besides the desired product **5e**, a small amount of **5e′**, with a second difluoroacetyl group installed at C2, was also isolated (**5e** and **5e′**). We supposed that the formation of **5e′** was ascribed to the reaction of the indole ring with free difluoroacetyl radical which was generated by Pd/Xantphos/base with **1h**. Most remarkably, chromenone and quinolinone underwent the reactions smoothly with the difluoroacetyl group exclusively introduced at C3 position (**5g** and **5h**). This reactivity is noteworthy as chromenone and quinolinone are important scaffolds of natural products and display various biological activities.[15] Therefore, this method is a valuable strategy for chromenone and quinolinone modification and for the discovery of new interesting molecules. Furthermore, the phenylalanine derived bromodifluoroamide **1i** also afforded fluorinated alkene in good yield, thus providing a facile access to complex fluorinated compounds (**5i**).

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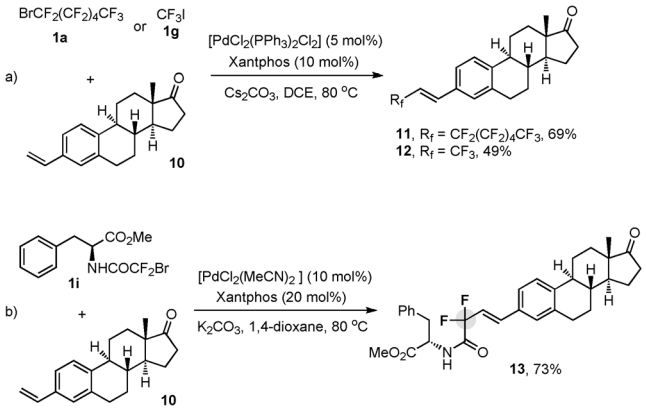
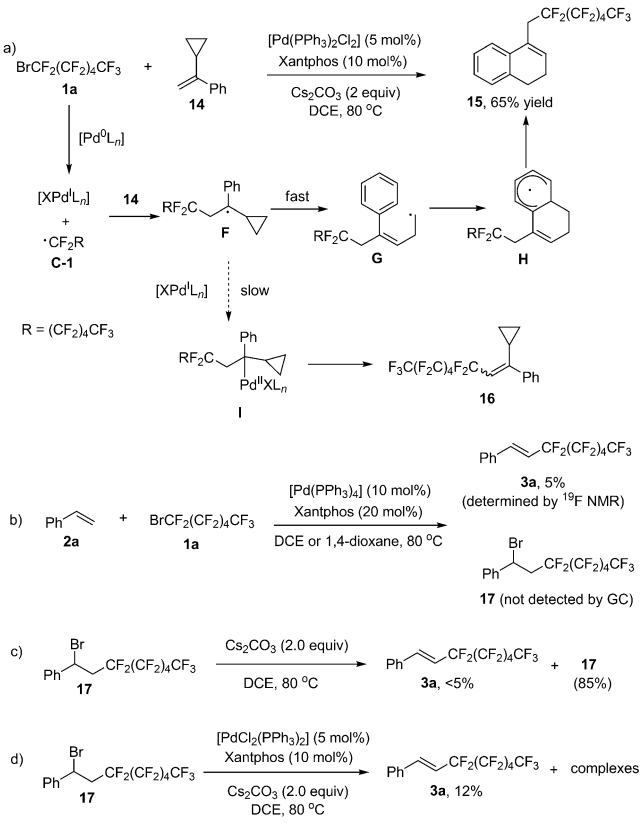


Scheme 2. Synthesis of fluorinated biologically active compounds.



Scheme 3. Experiments for mechanistic studies.

The importance of this protocol can also be featured by the late-stage fluoroalkylation of bioactive molecules. As shown in Scheme 2, treatment of the estrone-derived alkene **10** with **1a**, **1g**, and **1i** afforded the corresponding fluoroalkylated alkenes **11**–**13** with high efficiency, thus providing a facile access to diversified fluorinated bioactive molecules from one key structure through present process.

To gain some mechanistic insight into the present reaction, radical inhibition experiments were performed (for details, see the Supporting Information). When a reaction mixture of **1a** and **2a** was treated with the electron-transfer scavenger 1,4-dinitrobenzene[16] or the radical inhibitor hydroquinone in the presence of $[PdCl_2(PPh_3)_2]$ (5 mol%), Xantphos (10 mol%), and Cs_2CO_3 in DCE, the yield of **3a** was significantly decreased, thus implying that a SET pathway via a perfluorohexyl radical is involved in the catalytic cycle.

To further confirm that a free fluoroalkyl radical existed in the reaction, a radical-clock experiment was conducted. As illustrated in Scheme 3a, when compound **14**, which is known to participate in radical rearrangements,[17,18] was treated with **1a** under the standard conditions, the compound **15** (65% yield), instead of normal Heck-type product **16**, was obtained. This finding demonstrated that a perfluorohexyl free radical was indeed generated in the reaction, because it has been shown that if a free-radical species exists in the reaction, the ring-opening products would be delivered with use of α-cyclopropylstyrene.[18] What is more, this result also suggested that the formation of the radical species **G** from **F** was faster than the generation of key intermediate palladium complex **I**. Additionally, to confirm that the fluoroalkylated alkenes were not generated by a bromine-atom transfer radical addition to an alkene (Path B, Scheme 1), followed by base-assisted elimination of the resulting benzyl bromides, the reaction of styrene with **1a** in the presence of $[Pd(PPh_3)_4]$ and Xantphos without the base was conducted (Scheme 3b). We found that the benzyl bromide **17** was not generated (detected by GC). Instead, the perfluorohexylated alkene **3a** was observed in 5% yield (determined by ^{19}F NMR spectroscopy). This result is in sharp contrast to the result illustrated in Table 1 entry 2, because if Path B was feasible in the reaction, a high yield of **17** should be observed in the absence of base. Thus, the formation of fluoroalkylated alkenes by the above-mentioned two-stepwise process (Path B) could be ruled out. This was further confirmed by the following experiments. As shown in Scheme 3c, when **17** was treated with Cs_2CO_3 at 80 °C, only less than 5% yield of **3a** was observed and 85% of **17** was recovered. Furthermore, treatment of **17** in the presence of $[PdCl_2(PPh_3)_2]$ and Xantphos under standard conditions led to **3a** in low yield (12%), along with some uncertain by-products as major products (Scheme 3d). Thus, these results demonstrated that the proposed mechanism (Path A) illustrated in Scheme 1 is reasonable.

In conclusion, we have demonstrated the first example of palladium-catalyzed Heck-type fluoroalkylation of alkenes with perfluoroalkyl bromides. The reaction can also be extended to trifluoromethyl iodide, and other functionalized difluoromethyl bromides. The method allows fluoroalkylation of a variety of alkenes with high efficiency, in which the bidentate ligand Xantphos is essential for the reaction. A notable feature of this protocol is the late-stage fluoroalkylation of bioactive compounds in good yields, thus providing an efficient and straightforward route for application in drug discovery and development. Mechanistic studies reveal that the free fluoroalkyl radicals initiated by a $[Pd^0$/Xantphos] complex through a SET pathway is involved in the Heck-type catalytic cycle.

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