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Palladium/acetic acid-catalyzed fluoroalkylation of alkynes with monofluorinated sulfones as pronucleophiles

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ABSTRACT

A facile palladium-catalyzed fluoroalkylation of alkynes with monofluorinated sulfones in the presence of acetic acid has been achieved. By using different α-substituted fluoro(phenylsulfonyl)methane derivatives, a variety of allylated monofluoromethyl compounds were obtained with high regio- and stereoselectivity. Substrate scope and limitation were also examined, and it was found that the reaction was amenable to both 1-aryl-substituted propynes and 3-aryl-substituted propynyl ethers.

The development of efficient methods for the incorporation of fluorine atom(s) or fluorinated functional group(s) into organic molecules has become a fast-growing research field in modern organic chemistry, since fluorinated compounds play an increasingly important role in life science- and materials science-related applications.[1] Many studies have shown that fluorine-containing organic molecules can exhibit unique properties such as the enhancement of metabolic stability, lipophilicity, and bioavailability, an increase of binding affinity, as well as an improvement of membrane permeability by the perturbation of pK_a.[2] Among the fluoroalkyl groups, the monofluoromethyl group has attracted much attention in isostere-based drug design,[3] and a number of nucleophilic monofluoromethylation reactions with monofluorinated carbanions have been developed in recent years.[4,5]

In 2006, we reported for the first time that fluoromethyl phenyl sulfone could act as a fluoromethide equivalent in diastereoselective nucleophilic monofluoromethylation of aldimines[4a], and more recently, we extended this method to ketimines.[4b] In the course of our study on nucleophilic fluoroalkylation of epoxides with fluorinated sulfones, we found that fluorobis(phenylsulfonyl)methane (**1**) could readily undergo nucleophilic fluoroalkylation reactions with epoxides.[4c] Compound **1** has also been independently reported by Prakash, Shibata, and us as a robust reagent for the transfer of a monofluoromethyl group to alcohols,[4d] alkyl and benzyl halides,[4f] allylic acetates,[4g] α-amido sulfones,[4h] arynes,[4j] and for the 1,4-addition reactions to various Michael acceptors.[4e,i,j] It should be noted that most of these reactions were conducted under basic conditions and a base was generally required to generate the fluorobis(phenylsulfonyl)methyl anion species as a real fluoromethylating agent.[4a–c,e–j]

The palladium-catalyzed allylic alkylation reaction has been recognized as one of the most useful synthetic methods for the construction of carbon-carbon bond.[6] The transformation typically involves the reaction between a pronucleophile and an allyl compound with a proper leaving group under basic conditions.[6] Recently, due to the high importance of fluorinated molecules in many applications, some fluorinated pronucleophiles such as compound **1**,[4g] 2-fluoromalonate,[7a] ethyl 2-fluoroacetoacetate,[7b] and fluorinated silyl enols[7c] have been used in the palladium-catalyzed allylic fluoroalkylations. However, these reactions were carried out in the presence of a stoichiometric amount of base to generate fluorinated nucleophiles and a stoichiometric amount of leaving group was released. The allylation reaction of nonfluorinated pronucleophiles with alkynes catalyzed by palladium/carboxylic acid provides an eco-chemical protocol toward the formation of C–C,[8a–e] C–O,[8f–h] and C–N[8i,j] bonds. As Yamamoto and co-workers have proposed,[8a] the mechanism for these type of reactions involves two catalytic cycles with hydridopalladium species being the active catalyst: one is the isomerization of alkyne to allene, and the other is the nucleophilic addition of allene by a nucleophile via allyl palladium intermediates. The fluorinated carbanions are usually generated under basic conditions and they are commonly recognized as thermally unstable species, for they readily undergo self-decomposition at elevated temperatures.[4g,j] Nucleophilic fluoroalkylation under acidic conditions is rare, with the only two re-

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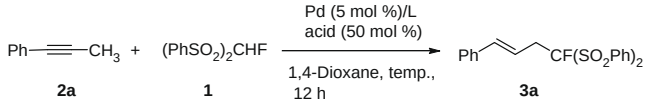
Table 1
Effect of various parameters on the allylation of $(PhSO_2)_2CFH$



Entry	Pd source	Ligand (mol %)	Acid additive	Temp (°C)	Yield[a] (%)
1	$Pd(PPh_3)_4$	/	HOAc	100	100 (97)[b]
2	$Pd(PPh_3)_4$	/	HOAc	50	4
3	$Pd(PPh_3)_4$	/	PhCOOH	100	96 (95)[b]
4	$Pd(PPh_3)_4$	/	CF_3COOH	100	0
5	$Pd(PPh_3)_4$	/	HCl	100	0
6	$Pd_2(dba)_3{\cdot}CHCl_3$	PPh_3 (20)	HOAc	100	90[c]
7	$Pd_2(dba)_3{\cdot}CHCl_3$	dppf (10)	HOAc	100	10
8	$Pd_2(dba)_3{\cdot}CHCl_3$	/	HOAc	100	0
9	$[Pd(allyl)Cl]_2$	PPh_3 (20)	HOAc	100	10[d]
10	$[Pd(allyl)Cl]_2$	dppf (10)	HOAc	100	40[d]

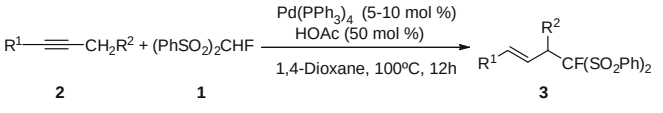
[a] Yield was determined by ^{19}F NMR analysis based on the unreacted **1**.
[b] The number in parentheses refers to the isolated yield.
[c] Trace amount of branched product was detected.
[d] The allylated product $[C_3H_5CF(SO_2Ph)_2]$ was formed as by-product.

ports of the trifluoromethylation of imines and enamines with Me_3SiCF_3 in the presence of HF of which we are aware.[9] In continuation of our research on selective nucleophilic fluoroalkylations with fluorinated sulfones,[4a–c,j] we wish to report herein a palladium-catalyzed allylic monofluoromethylation reaction between functionalized monofluorinated sulfones and simple alkynes in the presence of acetic acid at high temperatures.

We began our investigation with the reaction between fluorobis(phenylsulfonyl)methane (**1**) and 1-phenyl-1-propyne (**2a**) in the presence of a palladium catalyst and an acid additive in dioxane (Table 1). When $Pd(PPh_3)_4$ (5 mol %) was used as a catalyst and acetic acid (50 mol %) was used as an additive, the reaction could proceed smoothly at 100 °C to give the linear allyl monofluoromethylated product (*E*)-**3a** as the sole product in excellent yield (entry 1). However, when reaction temperature was decreased to 50 °C, the reaction became very sluggish (entry 2). Among the four acid additives that were tested, acetic acid proved to be the best one. Although the use of PhCOOH (instead of HOAc) could also provide (*E*)-**3a** in high yield, fluorobis(phenylsulfonyl)methane could not be completely consumed (entry 3). Both trifluoroacetic acid and HCl could not promote the reaction (entries 4 and 5). Subsequently, the influence of different palladium catalysts and phosphine ligands was examined. It was found that although the $Pd_2(dba)_3{\cdot}CHCl_3/PPh_3$ combination possesses the similar catalytic power as $Pd(PPh_3)_4$, trace amount of branched product was detected (entry 6). When a bidentate ligand was used, the $Pd_2(dba)_3{\cdot}CHCl_3$/dppf combination made the reaction proceed very slowly and the conversion of fluorobis(phenylsulfonyl)methane was only 10% after heating at 100 °C for 12 h (entry 7). The reaction could not proceed at all in the absence of a ligand (entry 8). When $[Pd(allyl)Cl]_2$ was used, the bidentate ligand dppf showed higher reactivity than the monodentate ligand PPh_3 (entries 9 and 10). However, owing to the formation of the allyl-substituted by-product and low efficiency, it was not a proper palladium source.

After a survey on the influences of different acid additives, palladium sources, and phosphine ligands with 1-phenyl-1-propyne

Table 2
Pd/HOAc-catalyzed allylation of $(PhSO_2)_2CFH$ with simple alkynes



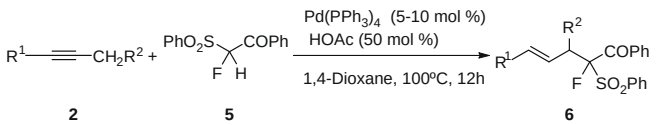
Entry[a]	R^1	R^2	Alkyne	Product	Yield[b] (%)
1	C_6H_5	H	**2a**	**3a**	97
2	4-Cl–C_6H_4	H	**2b**	**3b**	91
3	4-Me–C_6H_4	H	**2c**	**3c**	93
4	4-MeO–C_6H_4	H	**2d**	**3d**	95
5	C_6H_5	MeO	**2e**	**3e**	91 (50[c])
6	C_6H_5	BnO	**2f**	**3f**	72
7	4-Cl-C_6H_4	MeO	**2g**	**3g**	98
8	4-MeO–C_6H_4	MeO	**2h**	**3h**	82

[a] Reaction condition: entries 1–4, **2** (1 equiv), **1** (1 equiv), $Pd(PPh_3)_4$ (5 mol %), HOAc (50 mol %); entries 5–8, **2** (2 equiv), **1** (1 equiv), $Pd(PPh_3)_4$ (10 mol %), HOAc (50 mol %).
[b] Isolated yield.
[c] ^{19}F NMR yield when 1 equiv of **2e** was used.

as the model substrate, we finally chose the $Pd(PPh_3)_4$/HOAc combination as the catalytic system for the allylic monofluoromethylation reaction with various alkynes (Table 2). It was found that the reaction was also amenable to methoxyphenyl-, chlorophenyl-, and methylphenyl-substituted propynes **2b–d** (entries 2–4). When 1.0 equiv of alkyne was used as the allylation reagent with a catalyst loading of $Pd(PPh_3)_4$ (5 mol %)/HOAc (50 mol %), reactions could proceed smoothly to afford the desired fluorobis(phenylsulfonyl)methylated products **3b–d** in excellent yields (entries 2–4). However, the reaction of propargyl ether derivative **2e** with **1** in a molar ratio of 1:1 gave the monofluoromethylated allyl ether **3e** only in moderate yield (entry 5), which is caused by the partial isomerization of **2e** under acidic conditions. The cinnamaldehyde **4** was obtained as a by-product. The possible pathway for this side reaction is proposed in Scheme 1.

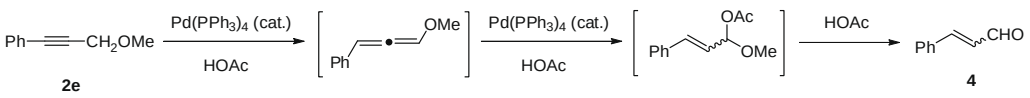
We also tried to inhibit the undesired isomerization by lowering the amount of acetic acid; however, the reaction became more sluggish and stopped to some extent. It seems that the nucleophilic attack of the allyl palladium intermediate by HOAc is competitive to the desired fluoroalkylation reaction. When an excess amount of **2e** (2.0 equiv) was used, fluromethylated ether **3e** could be obtained as a single isomer in 91% yield (Table 2, entry 5). Similarly, the reaction of fluorobis(phenylsulfonyl)-methane with 2.0 equiv

Table 3
Pd/HOAc-catalyzed allylation of $PhSO_2CFHCOPh$ with simple alkynes

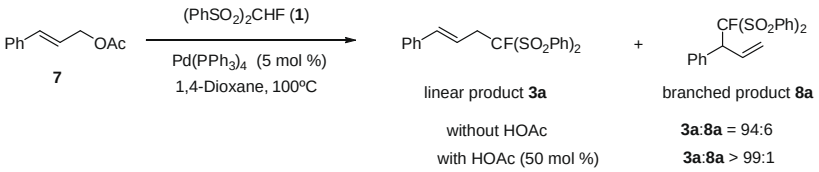


Entry[a]	R^1	R^2	Alkyne	Product	Yield[b] (%)
1	C_6H_5	H	**2a**	**6a**	89
2	4-Me–C_6H_4	H	**2c**	**6b**	92
3	4-MeO–C_6H_4	H	**2d**	**6c**	94
4	C_6H_5	MeO	**2e**	**6d**	97

[a] Reaction condition: entries 1–3, **2** (1 equiv), **5** (1 equiv), $Pd(PPh_3)_4$ (5 mol %), HOAc (50 mol %); entry 4, **2** (2 equiv), **5** (1 equiv), $Pd(PPh_3)_4$ (10 mol %), HOAc (50 mol %).
[b] Isolated yield.



Scheme 1. Possible pathway for the side reaction of **2e**.



Scheme 2. Allylic monofluoromethylation with cinnamyl acetate **7**.

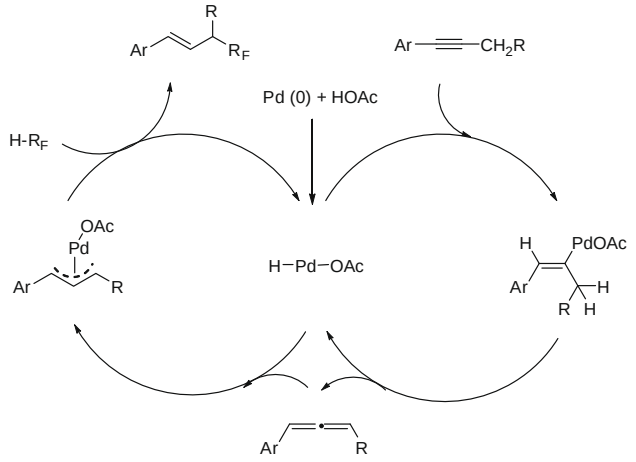
of other propargyl ether derivative **2f–h** provided the allyl fluromethylated ether **3f–h** in good to excellent yields, respectively (entries 6–8).

Attempts to extend this monofluoromethylation method to other disubstituted propynes such as 1-phenyl-1-butyne (**2i**) and 1,3-diphenylpropyne (**2j**) failed. In the case of substrate **2i**, only trace amount of desired product was formed and most of the alkyne was isomerized to 1,3-diene. In the case of substrate **2j**, although no by-product was detected, the hindered phenyl group made it less reactive and the reaction proceeded very slowly. It is obvious that the R^2 substituent can significantly influence the reaction.

On the basis of above-mentioned results, we further extended this methodology to the allylation of other fluorinated pronucleophiles such as α-fluoro-β-ketosulfone **5** with simple alkynes. Similar to the previous case, the reactions with ketosulfone **5** could also proceed smoothly to afford the fluorinated homoallyl ketones **6a–d** in high yields (Table 3, entries 1–4).

It is worthwhile to note that the above-mentioned allylic monofluoromethylation reaction with aryl-substituted propyne and propargyl ether gave the corresponding products in high regio- and stereoselectivity. It is well known that vinyl acetate can be formed from the addition of HOAc to alkyne under palladium-catalyzed condition.[8f] To gain some insights into the cause of the high regioselectivity of the reaction, we conducted the allylic monofluoromethylation with cinnamyl acetate **7** as a substrate. Much to our delight, we found that the linear/branched product ratio could be significantly improved when acetic acid was added (Scheme 2). It seems that the acidic media can keep the in situ-generated $(PhSO_2)_2CF^-$ species in low concentration, which is beneficial for the regioselectivity.

Concerning the mechanism of this palladium-catalyzed fluoroalkylation of alkynes with monofluorinated sulfones, it is similar to the one proposed earlier by Yamamoto and co-workers in the case of nonfluorinated ones,[8f] which is shown in Scheme 3.



Scheme 3. Proposed mechanism for palladium-catalyzed fluoroalkylation of alkynes

In conclusion, we have accomplished a facile palladium-catalyzed fluoroalkylation of alkynes with fluorinated sulfones in the presence of acetic acid. By using different α-substituted fluoro(phenylsulfonyl)methane derivatives, a variety of allylated monofluoromethyl compounds were obtained in high regio- and stereoselectivity. Substrate scope and limitation were also examined, and it was found that the reaction was amenable to both 1-aryl-substituted propynes and 3-aryl-substituted propynyl ethers.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and spectroscopic data for all isolated new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.126.

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