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Authors: Guosheng Liu, Xiaoxu Qi, and Pinhong Chen

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Catalytic Oxidative Trifluoromethoxylation of Allylic C-H Bonds using a Palladium Catalyst

Xiaoxu Qi, Pinhong Chen, and Guosheng Liu*

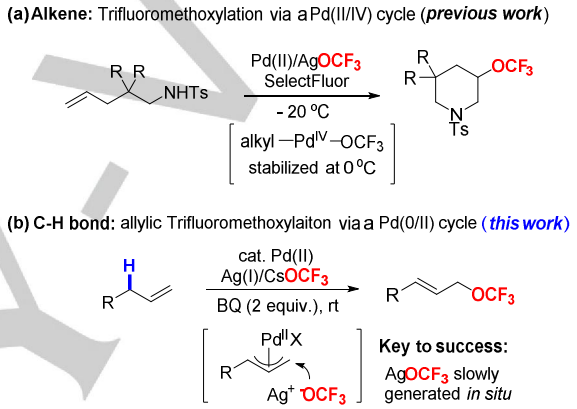
State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

Supporting Information

Abstract: A novel catalytic intermolecular allylic C-H trifluoromethoxylation of alkenes has been developed using a palladium catalyst, in which $CsOCF_3$ was employed as the trifluoromethoxide source and BQ as the oxidant. This reaction provides an efficient route for directly accessing allylic trifluoromethoxy ether derivatives with excellent regioselectivities from terminal alkenes via an allylic C-H bond activation process.

The selective transformations of C-H bonds have emerged as an efficient and atom-economical tool for the organic transformations,[1] and tremendous efficient methods have been reported.[2] Due to the importance of organofluorine compounds in pharmaceutical, agrochemicals, and material science,[3] the direct oxidative fluorination, [4] trifluoromethylation,[5] and trifluoromethylthiolation [6] of C-H bonds have received much attention.[7] Distinct from these reactions, the easy decomposition property of an OCF_3 anion and limited range of trifluoromethoxide reagents cause the extreme difficulty to carry out catalytic trifluoromethoxylation reaction.[8] Recently, we reported the first catalytic oxidative trifluoromethoxylation of alkenes through a Pd(II/IV) cycle at -20 °C (Scheme 1a).[9] However, unlike those difunctionalization reactions of alkenes which take place under mild conditions,[10] most of C-H bond functionalizations often proceed under harsh reaction conditions,[2,4-6] which significantly impede applying instable CF_3O reagents for the new catalytic design. Thus, the oxidative trifluoromethoxylation of C-H bonds remains intact so far. Herein, we reported our success on the catalytic allylic C-H oxidative trifluoromethoxylation using a palladium catalyst. The slow generation of $AgOCF_3$ from an easily synthesized and thermo-stable $CsOCF_3$[11] is crucial for the reaction (Scheme 1b).

In the last decade, groundbreaking achievement on the palladium-catalyzed oxidative functionalization of allylic C-H bonds has been obtained, and most of reactions proceed smoothly



Scheme 1. Catalytic Oxidative Trifluoromethoxylations.

under the mild condition (room temperature).[12] Considering the nature of trifluoromethoxide, we reasoned that, compared to other reactions, palladium-catalyzed allylic C–H activation of alkenes might be a suitable mode reaction to test the possibility of C-H trifluoromethoxylation. Distinct from previous trifluoromethoxylation involving a high-valent palladium species,[9] however, allylic C-H functionalization generally undergoes a Pd(0/II) catalytic cycle. Vicic and coworkers demonstrated that low-valent $(NHC)Cu^{I}OCF_3$ and $(NHC)Au^{I}OCF_3$ complexes are extremely unstable.[13] Thus, the question is that how fast trifluoromethoxide decomposes within a Pd(0/II) cycle, and how to retard this side reaction?

In fact, fast $AgOCF_3$ decomposition was observed in our initial reaction of **1a** with $Pd(OAc)_2/AgOCF_3$/BQ system at room temperature, accompanied with a small amount of desired product **2a** (table 1, entry 1). Although Szabó and coworkers reported that a Pd(II/IV) catalytic cycle is good for allylic acetoxylation,[12g] but similar reaction conditions are failed in this trifluoromethoxylation. None or trace product **2a** (< 3%) was detected in the presence of strong oxidants, such as SelectFluor, NFSI, I(III) reagents (see SI). Catalysts screening revealed that $PdCl_2(MeCN)_2$ was superior to other Pd catalysts to give product **2a** in 20% yield (entries 2-3). Due to the fast decomposition of $AgOCF_3$, further optimizing reaction condition was failed to improve the reaction yield, along with the side fluorination product. Furthermore, other OCF_3 sources, such as $CsOCF_3$, Me_4NOCF_3 and $TASOCF_3$,[14] were ineffective (entries 4-6). These observations indicated that silver plays an important role in the trifluoromethoxylation, in spite of a heavy side decomposition of $AgOCF_3$. In order to alleviate this side reaction, we surmised that slowly generating $AgOCF_3$ *in situ* from poor soluble OCF_3 salts might be beneficial. After extensive screening, the combination of $AgBF_4$ (1.2 equiv.) and $CsOCF_3$ (3.0

[*] X. Qi, Dr. P. Chen, Prof. Dr. G. Liu
State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences
345 Lingling Road, Shanghai, 200032 (China)
E-mail: gliu@mail.sioc.ac.cn
Homepage: http://guoshengliu.sioc.ac.cn/

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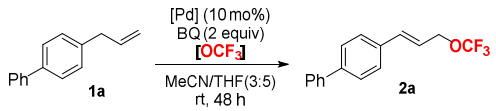
equiv.) provided a better result to generate **2a** in 39% yield (entries 7-8). Meanwhile, owing to the equilibrium in eq 1,[11a] we reasoned that the addition of extraneous AgF might be helpful to retard the decomposition in a sealed bottle. Indeed, the reaction yield was increased to 46% by adding AgF (entry 9). Furthermore, the yield could be slightly increased to 51% by increasing the amount of $CsOCF_3$ to 3.5 equivalents (entry 10). Adding catalytic amount of carboxylic acid (**A1**) and slightly increasing the palladium catalyst loading (15 mol %) were beneficial to the reaction (76% yield, entries 11-12); Alternative 2,4,6-trimethylbenzoic acid (**A2**) gave a slightly better yield (78%, entry 13). The addition of 2,4,6-trimethylbenzoic acid **A2** could accelerate the reaction rate (See the Supporting Information). Finally, the best yield was given by increasing the reaction concentration with $PdCl_2(PhCN)_2$ (entries 14-15). Notably, the trifluoromethoxylation reaction did not occur in the absence of either Pd(II) catalyst or BQ (entries 16-17). It is worth noting that, all of these reactions exhibited excellent regio- and stereoselectivity to give linear product *E*-**2a** at room temperature.

$$AgOCF_3 \rightleftharpoons COF_2 + AgF \qquad (1)$$

Table 1. Optimization of reaction conditions.[a,b]

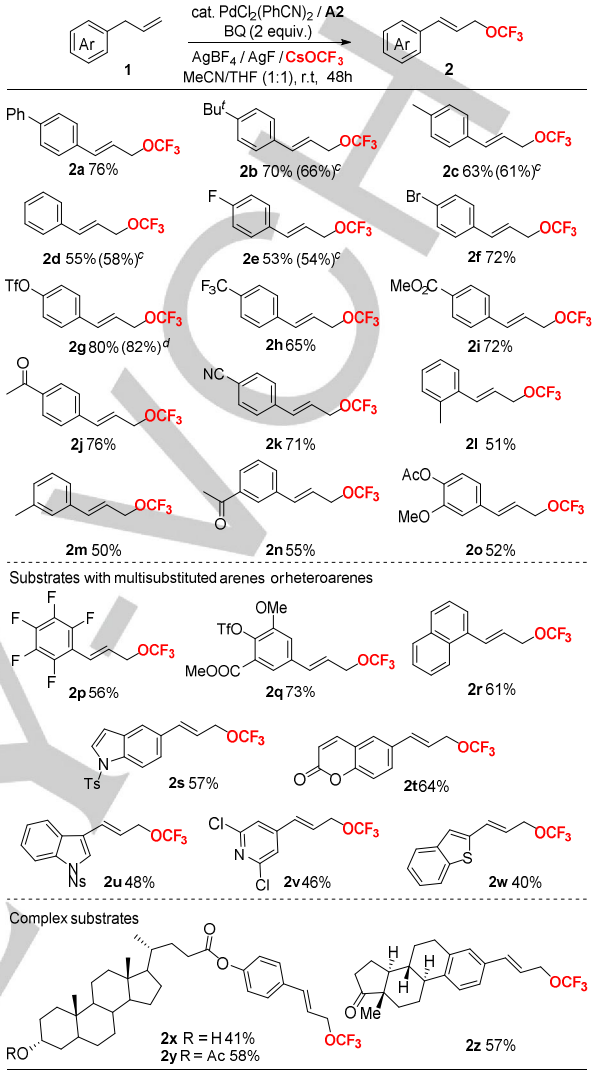


entry	Pd catalyst	[OCF_3] (equiv)	Yield (%)[b]
1	$Pd(OAc)_2$	$AgOCF_3$ (3.0)	12
2	$Pd(OTFA)_2$	$AgOCF_3$ (3.0)	9
3	$PdCl_2(MeCN)_2$	$AgOCF_3$ (3.0)	20
4	$PdCl_2(MeCN)_2$	$CsOCF_3$ (3.0)	trace
5	$PdCl_2(MeCN)_2$	Me_4NOCF_3 (3.0)	trace
6	$PdCl_2(MeCN)_2$	$TASOCF_3$ (3.0)	trace
7	$PdCl_2(MeCN)_2$	$AgBF_4$ (1.2) + $CsOCF_3$ (3.0)	39
8	$PdCl_2(MeCN)_2$	$AgBF_4$ (1.2) + Me_4NOCF_3 (3.0)	19
9[c]	$PdCl_2(MeCN)_2$	$AgBF_4$ (1.2) + $CsOCF_3$ (3.0)	46
10[c]	$PdCl_2(MeCN)_2$	$AgBF_4$ (1.2) + $CsOCF_3$ (3.5)	51
11[c,d]	$PdCl_2(MeCN)_2$	$AgBF_4$ (1.2) + $CsOCF_3$ (3.5)	65
12[c,d,e]	$PdCl_2(MeCN)_2$	$AgBF_4$ (1.2) + $CsOCF_3$ (3.5)	76
13[c,e,f]	$PdCl_2(MeCN)_2$	$AgBF_4$ (1.2) + $CsOCF_3$ (3.5)	78
14[c,e,f,g]	$PdCl_2(MeCN)_2$	$AgBF_4$ (1.2) + $CsOCF_3$ (3.5)	80
15[c,e,f,g]	$PdCl_2(PhCN)_2$	$AgBF_4$ (1.2) + $CsOCF_3$ (3.5)	82
16[c,f,g]	---	$AgBF_4$ (1.2) + $CsOCF_3$ (3.5)	0
17[c,e,f,g,h]	$PdCl_2(MeCN)_2$	$AgBF_4$ (1.2) + $CsOCF_3$ (3.5)	0

[a]All reactions were run at 0.1 mmol scale in mixture solvent (0.6 mL). [b]^{1}H-NMR yield was obtained using CF_3-DMA as internal standard. [c]AgF(1.5 equiv.) was added. [d]2-F-4-methylbenzoic acid (**A1**, 20 mol %) as additive. [e][Pd] 15 mol%. [f]2,4,6-trimethylbenzoic acid (**A2**, 20 mol %) as additive. [g]MeCN/THF(1:1, 0.2 mL). [h]Reaction carried out without BQ.

With the optimized reaction conditions in hand, the substrate scope was examined, and the results were summarized in Table 2. A variety of allyl arenes bearing both electron-rich (**1a-1c** and **1l-1m**) and electron-poor (**1e-1k**) substituents on the aryl ring were suitable to afford the corresponding linear *E*-configuration products **2a-2k** in moderate to good yields with excellent regio- and stereo-selectivities. In addition, various functional groups on the aryl ring, such as halogen (**2e**, **2f**), triflate (**2g**), trifluoromethyl (**2h**), carboxylic ester (**2i**), ketone (**2j**) and nitrile (**2k**), were tolerated under the reaction conditions. The compatible aryl bromide (**2f**) and aryl triflate (**2g**) also provided opportunities for further transformations. For the multi-substituted allyl arenes, the reactions also proceeded smoothly to afford products (**2o-2q**) in satisfactory

Table 2. Substrate scope of allylic C-H trifluoromethoxylation.[a]

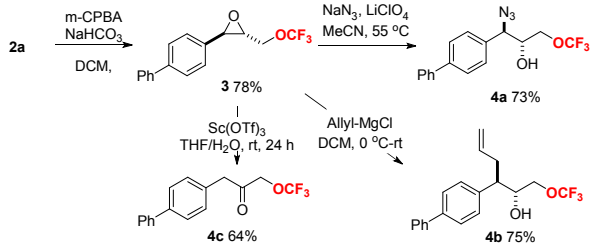


[a]All reactions were conducted on 0.2 mmol sale: Pd catalyst (15 mol %), **A2** (20 mol %), BQ (2 equiv.), $AgBF_4$ (1.2 equiv.), AgF (1.5 equiv.), $CsOCF_3$ (3.5 equiv.) and **1** (0.2 mmol) in the mixture solvent of MeCN and THF (v/v 1:1, 0.4 mL). [b]Isolated yields. [c]0.5 mmol scale. [d]5.5 mmol scale.

yields. Notably, the reaction of substrate bearing pentafluorophenyl provided product **2p** in 56% yield, and product **2q** containing OTf moiety allows for the further transformation. In addition to allyl benzene derivatives, allyl naphthalene, indole, coumarin and other heteroarenes such as pyridine and benzothiophene were proved as suitable substrates to give products **2r-2w** in moderate yields (40-64%). Finally, more complex molecules were also evaluated. For example, substrates bearing steroid scaffold with free-alcohol (**1x**) or protected ester (**1y**) were compatible with the reaction condition, and provided products **2w** (41%) and **2x** (58%), respectively. Meanwhile, when substrate **1z** with estrone moiety was subjected to the standard reaction conditions, product **2z** was obtained in good yield (57%). It is noteworthy that, the reaction could be scaled up to provide product **2g** in excellent yield (82% in 5.5 mmol, 1.58 g). Unfortunately, this transformation is limited on the allyl arene substrates. Other terminal alkenes and cyclic aliphatic alkenes, such as 1-octene or cyclohexene were ineffective to give trace amount of the desired products with substrate remained.

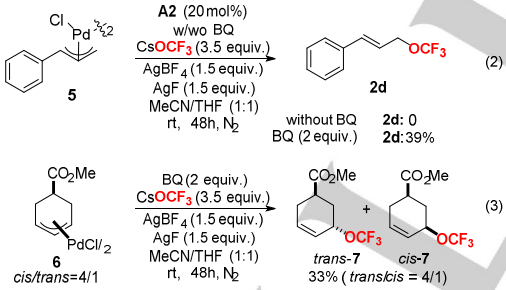
To demonstrate potential application of these allylic

trifluoromethoxylation products, as shown in Scheme 2, the epoxidation of product **2a** was achieved with *m*-CPBA to provide a single isomer *E*-**3** in 78% yield, which could act as a valuable OCF_3-containing synthon to access a wide array of trifluoromethoxylated building blocks. For instance, the epoxide could be attacked by either azide or Grigard reagent to give single isomers **4a** (73% yield) or **4b** (75% yield) stereosepcifically. Meanwhile, treatment by strong Lewis acid $Sc(OTf)_3$, the epoxide compound **3** could be efficiently converted to product α-OCF_3 ketone **4c** in 64% yield.

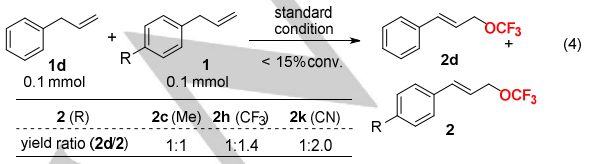


Scheme 2. Further transformations.

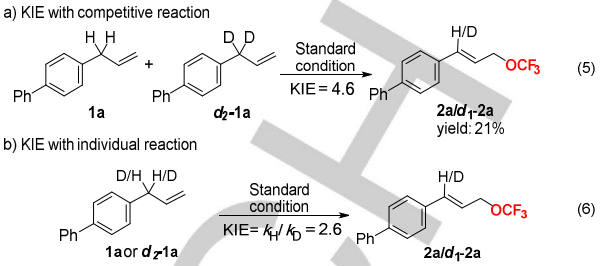
To get more insight into the reaction mechanism, π-allyl-Pd dimer **5** was synthesized and treated with $AgBF_4$/$CsOCF_3$/AgF. Similar to the catalytic reaction, the reaction only took place in the presence of BQ (eq 2). This observation indicated that BQ should act as a π-acceptor ligand to activate π-ally-Pd intermediate, promoting the fast nucleophilic attack by OCF_3 anion.[15] Meanwhile, π-allyl-Pd complex **6** (*cis*/*trans* = 4/1) was applied to address the stereochemistry. As shown in eq 3, the trifluoromethoxylation reaction of **6** afforded major *trans*-**7** (*cis*/*trans* = 1/4), suggesting a stereo-configuration inversion pathway. Although the detailed mechanism is still unclear, we believe that the C-OCF_3 bond formation might occur *via* an outer-sphere nucleophilic substitution pathway by $AgOCF_3$. However, an alternative intermolecular bimetallic pathway with another π-allyl-Pd(OCF_3) complex cannot be excluded.[16]



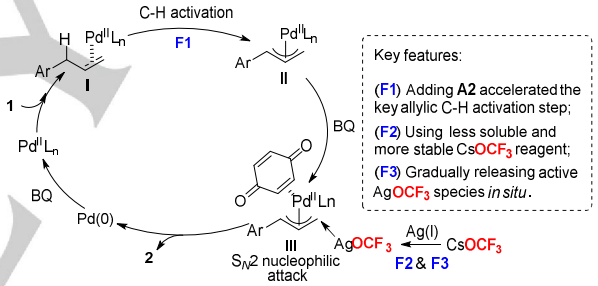
Furthermore, the competitive reactions between allyl benzene (**1d**) and *para*-substituted allyl benzenes (**1c**, **1h** or **1k**) were conducted, and the results indicated that electron-poor substrates (**1h**, **1k**) were preferred to give major products **2h** and **2k** (eq 4). This observation indicated that the allylic C-H activation is prior to occur at an allylic carbon center with more acidic proton.



In addition, the competitive deuterium kinetic isotopic effects (KIE) study, using a mixture of **1a** and d_2-**1a**, revealed a significant KIE (k_H/k_D) of 4.6 (eq 5). On the other hand, independent measurement of the reaction rate of these two substrates still provided a large KIE (k_H/k_D = 2.6, eq 6). These values suggest that allylic C(sp^3)–H bond activation contributes to the turnover-limiting step.



Based on the above analysis, a proposed mechanism was shown in Scheme 3. First, the reaction was initiated by a Pd(II)-catalyzed allylic C-H bond activation to give an π-allyl-Pd(II) intermediate **II** followed by a S_N2 nucleophilic attack by trifluoromethoxide to give the desired trifluoromethoxylation products, which was promoted by BQ coordination. The released Pd(0) catalyst was oxidized by BQ to regenerate Pd(II) catalyst.[17] Herein, the rate-determining allylic C-H bond activation resulted in a competitive decomposition of $AgOCF_3$ in the presence of Pd (II) catalyst. To alleviate this side reaction, two key features were crucial for the success of this transformation: (1) the addition of carboxylic acid **A2** can accelerate allylic C-H activation step (see SI); (2) employing poorly soluble and stable $CsOCF_3$ can gradually release active trifluoromethoxide reagent $AgOCF_3$, which could lower its concentration to slow down the decomposition step.



Scheme 3. Plausible reaction mechanism.

In conclusion, the first allylic C-H trifluoromethoxylation reaction has been developed by using a palladium catalyst, which provides a new approach to synthesize OCF_3-containing organic molecules efficiently. Importantly, the current study reveals that the catalytic trifluoromethoxylation could be achieved through a Pd(0/II) catalytic cycle under room temperature. Moreover, the slowly releasing key $AgOCF_3$ reagent is vital. Further exploration of new trifluoromethoxylation reaction is ongoing in our laboratory

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Keywords: alkenes • trifluoromethoxylation • C-H activation • palladium catalyzed

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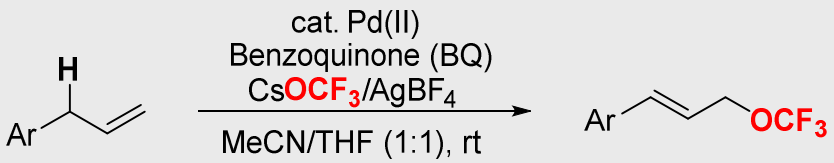

Catalytic C-H Trifluoromethoxylation
High regio- and stereoselectivity

*X. Qi, P. Chen, G. Liu **

Page No. – Page No.

Title: Catalytic Oxidative Trifluoromethoxylation of Allylic C-H Bonds using a Palladium Catalyst

A novel catalytic intermolecular allylic C-H trifluoromethoxylation of alkenes has been developed using a palladium catalyst, in which $CsOCF_3$ was employed as the trifluoromethoxide source and BQ as the oxidant. This reaction provides an efficient route for directly accessing allylic trifluoromethoxy ether derivatives with excellent regioselectivities from terminal alkenes via an allylic C-H bond activation process.