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Communication

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Palladium-Catalyzed Intermolecular Ditrifluoromethoxylation of Unactivated Alkenes: CF_3O-palladation Initiated by Pd(IV)

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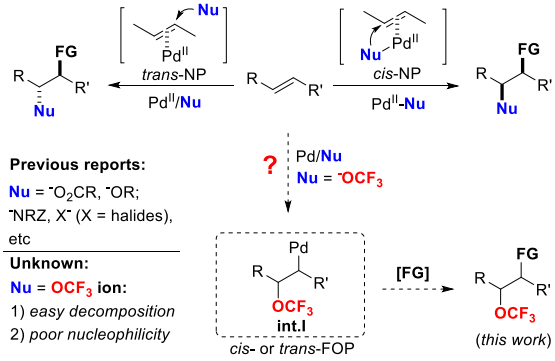
Supporting Information

ABSTRACT: A novel palladium-catalyzed intermolecular ditrifluromethoxylation of unactivated alkenes has been developed, using a new electrophilic reagent, Selectfluor[CN], as a strong oxidant, and $AgOCF_3$ as a trifluoromethoxide source. Preliminary mechanistic studies revealed that the reaction was possibly initiated by Pd(IV) species, and an unusual *cis*-addition of CF_3O-Pd(IV) into the double bond leads to the formation of the first C-OCF_3 bond; in addition, the second C-OCF_3 bond was produced through reductive elimination at high-valent palladium center.

Palladium-catalyzed difunctionalizations of alkenes (DFAs) represents one of the most efficient approaches to organic molecules bearing two vicinal carbon-heteroatom bonds.[1] Among them, most reactions were generally initiated through nucleopalladation (**NP**), and followed by a sequential oxidative cleavage of alkyl-Pd(II) species. In addition, the *cis*- or *trans*-NP with various stable nucleophiles, such as carboxylates, alcohols, amides, sulfonamides and halides, have been extensively studied to give the corresponding products (Scheme 1, top).[2] However, compared to the intramolecular reactions, the intermolecular nucleopalladation (NP) of alkenes is more kinetically-unfavorable and harsh reaction conditions are often required.[3]

Considerable effort has been directed toward incorporation of fluorine and fluorine-containing groups into organic molecules in the last decades, and transition metal catalysis was considered as one of most prevalent and efficient methods.[4] Unfortunately, the direct introduction of the trifluoromethoxy (OCF_3) moiety into molecules is extremely difficult and challenging, because the trifluoromethoxide (OCF_3^-) is easily decomposed,[5] especially in presence of low-valent metal catalysts.[6] Inspired by the above-mentioned NP strategy, we reasoned that, if a trifluoromethoxide is suitable to undergo NP process, the unprecedented trifluoromethoxypalladation (**FOP**) could deliver a key alkyl-Pd species **int.I** containing the OCF_3 moiety, which might provide a variety of OCF_3-containing products (Scheme 1, bottom). Notably, if possible, this FOP process will present an efficient and straightforward way to introduce OCF_3 into unsaturated C-C bonds. However, compared to the previously reported NP with stable nucleophiles, the easy decomposition property of trifluoromethoxide makes this intermolecular FOP of alkenes extremely challenging. In order to diminish the decomposition of

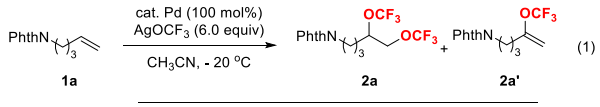


Scheme 1. Pd-Catalyzed Intermolecular Difunctionalization Reactions of Alkenes (NP = nucleopalladation; FOP = trifluoromethoxypalladation).

OCF_3 anions, decreasing reaction temperature is beneficial to the desired trifluoromethoxylation. However, as we discussed above, decreasing reaction temperature is not good for the intermolecular NP process.[3] We assumed that, if palladium catalysts possessing strong Lewis acidity, for example, high-valent palladium species, was used as catalyst; the Pd-coordination on the alkenes should be much easy, which makes the process of nucleopalladation feasible.[7] Herein, we reported the first intermolecular FOP of alkenes, which provides a series of ditrifluoromethoxylation products. Preliminary mechanistic studies revealed that the reaction started with a *cis*-FOP process, occurring at a Pd(IV) center.

As part of our effort to develop catalytic trifluoromethoxylation of alkenes, we have disclosed two catalytic reactions, in which the C-OCF_3 bond can be formed either by nucleophilic trifluoromethoxylation of π-allylic-Pd(II) species[8] or reductive elimination of alkyl-Pd(IV)OCF_3 intermediates.[9] Notably, these two reactions were conducted at room temperature and low temperature, respectively. In order to address the possibility of the FOP process, the reaction of **1a** with stoichiometric amounts of palladium catalysts was performed at -20 °C. As shown in eq 1, when a series of Pd(II) catalysts were employed, the reactions did not provide any trifluoromethoxylation products. Pleasingly, the reaction, in the presence of Pd(IV) catalysts, gave two different OCF_3-containing products, the major ditrifluoromethoxylated product **2a** in 36% yield, as well as the Wacker-type product **2a'**

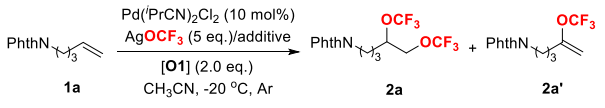
in 16% yield. These results suggested that the reaction much likely started with Pd(IV) catalysts,[10] and the FOP process would result in a key Pd(IV) intermediate **int.I**, which underwent reductive elimination and β-H elimination to give the products **2a** and **2a'** respectively.[11]



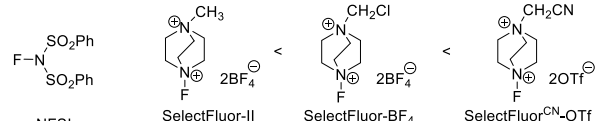
		2a	2a'
Pd(II)	$Pd(CH_3CN)_2Cl_2$ $Pd(CH_3CN)_4(BF_4)_2$ Na_2PdCl_4	0	0
Pd(IV)	K_2PdCl_6	36%	16%

Inspired by these results, thus we selected SelectFluor as a strong oxidant for the catalytic ditrifluoromethoxylation reaction. The initial screening on the palladium catalyst revealed that $Pd(^{i}PrCN)_2Cl_2$ was the best catalyst, delivering the desired difluoromethoxylation product **2a** in 40% yield, along with the Wacker-type product **2a'** in 11% yield (Table 1, entry 1). No reaction occurred in the absence of palladium catalyst (entry 2). Meanwhile, other strong oxidants, such as $PhI(OAc)_2$, Oxone and benzoquinone (BQ), failed to provide the trifluoromethoxylation products (entry 3). In addition, $AgOCF_3$ was essential to the reaction, but $CsOCF_3$ or Me_4NOCF_3 were not suitable (entries 4-5).[12] Notably, the yield of **2a** could be increased to 51% by adding 2,6-difluoropyridine to the reaction (entry 6). Slightly increasing the catalyst loading and amounts of the oxidant could improve the yield of **2a** to 56% (entry 7). Furthermore, adding small amounts of $^{i}PrCN$ and Tf_2O (trifluoromethanesulfonic anhydride) could further increase the yield of **2a** to 62% (entry 8). Finally, a series of other electrophilic fluorinating reagents were investigated; NFSI and SelectFluor-II [O2] with lower oxidative potential were not suitable for the reaction (entries 9-10), but $SelectFluor^{CN}$ [O3] with higher oxidative potential provided **2a** in 70% yield (entry 11).[13] Unfortunately, further optimizing reaction conditions failed to inhibit or decrease the side Wacker-type product **2a'**.

Table 1. Optimization of the Reaction Conditions.[a,b]



Entry	Varified from standard condition	Additive	Yield (%)[b] 2a	2a'
1	standard (see above)	--	40%	11%
2	no Pd catalyst	--	0	0
3	$PhI(OAc)_2$, Oxone, or BQ instead of [O1]	--	0	0
4	$CsOCF_3$ instead of $AgOCF_3$	--	8%	6%
5	Me_4NOCF_3 instead of $AgOCF_3$	--	7%	5%
6	standard (see above)	2,6-F_2-Py[c]	51%	17%
7	Pd (15%)/$AgOCF_3$ (7.5 eq.)/[O1] (3 eq.)	2,6-F_2-Py[c]	56%	18%
8	Pd (15%)/$AgOCF_3$ (7.5 eq.)/[O1] (3 eq.)	2,6-F_2-Py[c]/$^{i}PrCN$[d]/Tf_2O[e]	62%	25%
9	Pd (15%)/$AgOCF_3$ (7.5 eq.)/[O2] (3 eq.)	2,6-F_2-Py[c]/$^{i}PrCN$[d]/Tf_2O[e]	29%	4%
10	Pd (15%)/$AgOCF_3$ (7.5 eq.)/NFSI (3 eq.)	2,6-F_2-Py[c]/$^{i}PrCN$[d]/Tf_2O[e]	0	0
11	Pd (15%)/$AgOCF_3$ (7.5 eq.)/[O3] (3 eq.)	2,6-F_2-Py[c]/$^{i}PrCN$[d]/Tf_2O[e]	70%	23%



[a]Reaction conditions: **1a** (0.1 mmol), Pd catalyst (10 mol %), [O1] (0.2 mmol), $AgOCF_3$ (0.5 mmol) in CH_3CN at -20 °C, under Ar atmosphere. [b] ^1H NMR yield with CF_3-DMA as internal standard. [c]2,6-F_2Py (2,6-difluoropyridine, 75 mol %). [d] $^{i}PrCN$ (50 μL). [e] Tf_2O (1.0 eq.).

With the optimized reaction conditions in hand, the scope of unactivated alkenes was examined. As revealed in Table 2, aliphatic terminal alkenes reacted smoothly to yield the corresponding ditrifluoromethoxylated products **2a-3b** in moderate to good yields. In addition, a variety of functional groups, such as the imide (**2a-2c**), ester (**2d**, **2j**, **2k**, **2l**, **2w**), nitro (**2f**), halide (**2h-2i**), ether (**2m-2r**), nitrile (**2u**) and phosphate ester moieties (**2v**), remain intact under the mild reaction conditions. In particular, the substrates bearing oxidatively sensitive functional groups, such as alcohol (**2g**) and aldehyde (**2s**), are still suitable to yield the desired products in good yields, even in the presence of the very strong oxidant, $SelectFluor^{CN}$. However, substrates bearing the ketone moiety is not compatible. Interestingly, when ketone was protected as ketal (**1t**), the reaction proceeded very well, followed by a subsequent deprotection to provide the product **2t** in 72% yield. Furthermore, for substrates bearing good leaving groups, such as tosylate (**2d**) and bromide (**2h** and **2i**), the direct nucleophilic substitution reaction did not occur, which also demonstrates the weak nucleophility of the OCF_3 anion. More importantly, the reaction of substrates containing both the internal and terminal C=C bonds exclusively took place at the terminal C=C bond to give the product **2x** in 47% yield. Notably, only terminal alkenes can be conducted in the current reaction conditions, whereas internal alkenes only afforded trace amounts of the desired products but with most of alkenes remained.

We then turned our attention to complex substrates. For instance, substrates bearing heterocycles, such as indole (**3c**), coumarin (**3d**), and carbazole (**3e**) are also suitable for the reaction, affording the corresponding products in 46%-62% yields. Furthermore, more complex substrates bearing the ibuprofen (**3f**), bicyclic amine (**3g**) and sugar (**3h**) moieties also proceeded smoothly to deliver trifluoromethoxylated products in moderate to good yields (47-75%). Interestingly, the reaction of the substrate **1ai** bearing estrone gave the ditrifluoromethoxylated product **3i** in 44% yield, in which the cyclohexane ring was also simultaneously dehydrogenated. Moreover, the reaction is amenable to larger scale (1 – 3 mmol) synthesis without decreasing of reaction yield (products **3d** and **3f** in table 2). The structure of **3c** was confirmed by X-Ray (Figure 1).

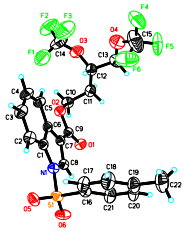
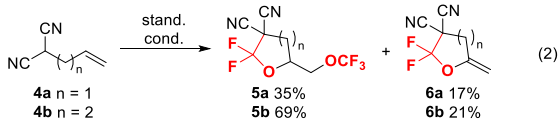


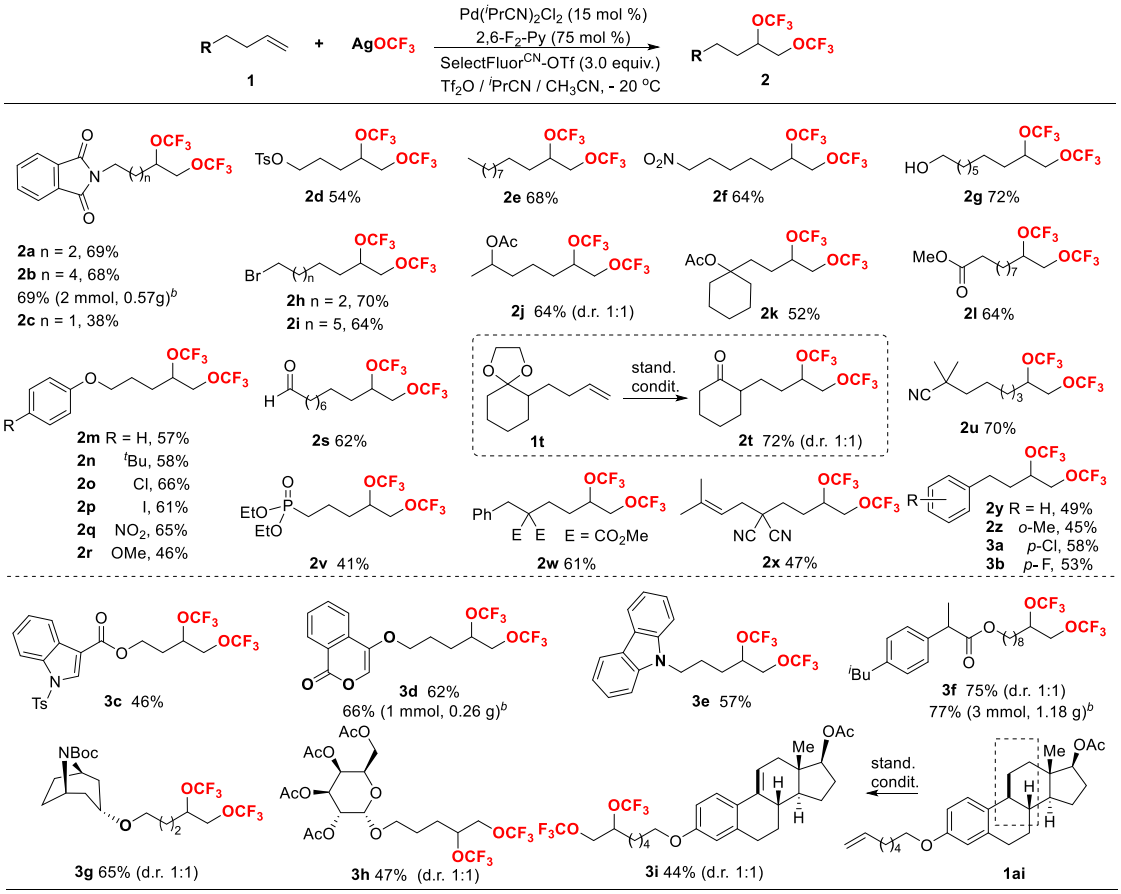
Figure 1. X-Ray of compound **3c**.

More importantly, when the substrates **4a** and **4b** derived from malononitrile were treated under standard conditions, the novel cyclic products **5a** and **5b** were obtained in moderate to good yields (35% and 69% respectively), along with small amounts of the *exo*-cyclic alkene products **6a** and **6b** (eq 2). These products might be generated through an oxidative trifluoromethoxylation/nucleophilic cyclization sequence.



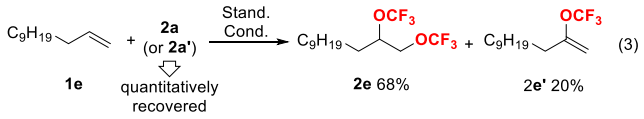
To gain some insight into the plausible reaction mechanism, some control experiments were carried out. First, the products **2a** or **2a'** was subjected to the reaction of **1e** under standard condition

Table 2. Substrate Scope.[a]

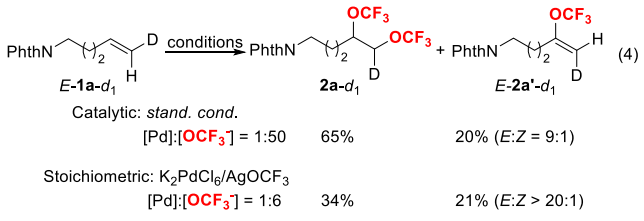


[a]All the reactions were conducted in 0.2 mmol scale, isolated yields. [b]Reaction was conducted in large-scale.

respectively, the compound **2a** (or **2a'**) was quantitatively recovered, and the interconversion between **2a** and **2a'** was not observed, suggesting that the trifluoromethoxylated products **2a** and **2a'** were generated independently of each other in the reaction (eq 3).



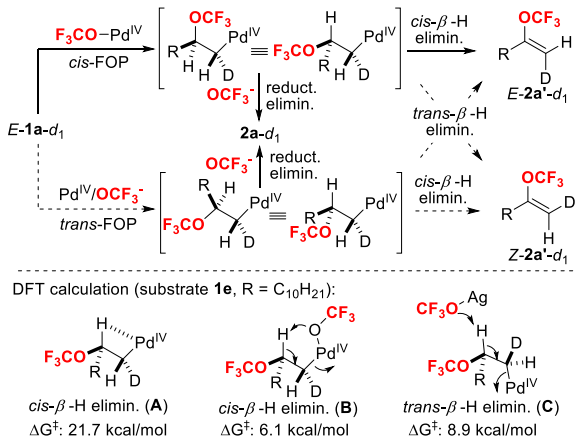
Second, when the deuterium-labeled substrate *E*-**1a**-d_1 was treated under the catalytic reaction conditions (Table 1, entry 11), the reaction provided the product **2a**-d_1 (configuration not determined),[14] along with the β-hydride elimination product *E*-**2a'**-d_1 with a 9:1 *E*/*Z* ratio. The reaction of the substrate *E*-**1a**-d_1 in the presence of stoichiometric amounts of Pd(IV) species provided similar results, but giving the β-hydride elimination product as a single isomer *E*-**2a'**-d_1 (> 20:1 *E*/*Z* ratio, eq 4).



For the selective formation of *E*-**2a'**-d_1, there are two possible pathways (Scheme 2, top). First, our previous studies revealed that a trifluoromethoxide could be stablized by Pd(IV) species. Thus, the reaction is possibly initiated by a CF_3O-Pd(IV) complex via a *cis*-FOP process to form an alkyl-Pd(IV) intermediate, which could undergo reductive elimination to generate the major product **2a**-d_1. In addition, this Pd(IV) species could also undergo side *cis*-β-hydride elimination to give *E*-**2a'**-d_1. Alternatively, the side Wacker-type product *E*-**2a'**-d_1 would also be formed through a *trans*-FOP/*trans*-β-hydride elimination sequence. In the latter case, increasing the amounts of $AgOCF_3$ should facilitate the *trans*-β-hydride elimination which would enhance the E/Z ratio of **2a'**-d_1. However, a lower *E*/*Z* ratio (9:1) of **2a'**-d_1 was observed under the catalytic reaction conditions in which the amounts of the trifluoromethoxide is 50 times more than that of the palladium catalyst (eq 4). These results indicated that the latter case is less likely than the former one.

For the *cis*-β-hydride elimination, recent studies revealed that this process is difficult to occur at a Pd(IV) center owing to the lack of open coordination sites.[15] However, DFT calculations (Scheme 2, bottom) demonstrated that a concert model **B** (a barrier of 6.1 kcal/mol) via intramolecular hydride abstraction using the internal base OCF_3, is more favorable than the direct cis-β-hydride elimination process (model **A** with a barrier of 21.7 kcal/mol). In addition, this favorable model **B** also exhibits a lower energy barrier than that of the *trans*-β-hydride abstraction

process which is driven by $AgOCF_3$ (model **C** with a barrier of 8.9 kcal/mol).



Scheme 2. Proposed mechanism on the stereochemistry**.**

In summary, we have developed a novel process of palladium-catalyzed ditrifluoromethoxylation of terminal unactivated alkenes. The reaction itself features high functional group tolerance, broad substrate scope and mild reaction conditions. Preliminary mechanistic studies demonstrated that the intermolecular reaction was possibly initiated by a high-valent Pd(IV) catalyst possessing strong Lewis acidity, which allows the intermolecular *cis*-trifluoromethoxypalladation (FOP) process under much mild conditions, avoiding the decomposition of trifluoromethoxide. Further applications of this strategy are in progress.

Supporting Information

Synthetic procedures, characterization, mechanistic study data and additional data. This material is available free of charge via the Internet at http://pubs.acs.org.

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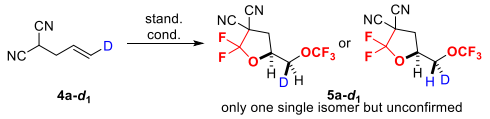
(13) The stronger oxidant SelectFluor^{CN} provided better yields, indicating a more likely pathway initiated by a Pd(IV) catalyst. In addition, DFT calculation reveals the *cis*-CF_3O-palladation process has a low energy barrier of 4.0 kcal/mol, which is consistent with our reaction condition at -20^{o}C. For details, see the Supporting Information.

(14) When the deuterium-labeled substrate ***E*-4a-*d*$_1$** was used, the reaction provided a single isomer of **5a-*d*$_1$**, which was determined by NMR spectra; however, the relative stereo-configuration of **5a-*d*$_1$** is still unknown. For details, see SI.



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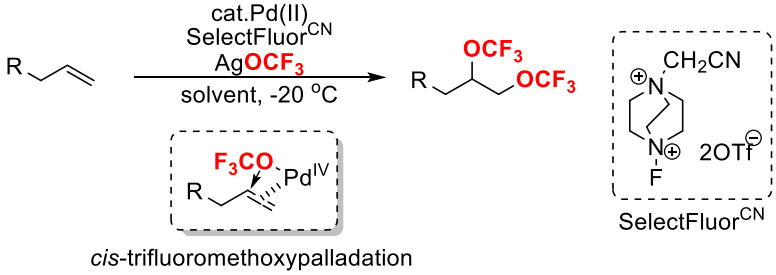

cis-trifluoromethoxypalladation