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Palladium-Catalyzed Intramolecular Aminotrifluoromethoxylation of Alkenes

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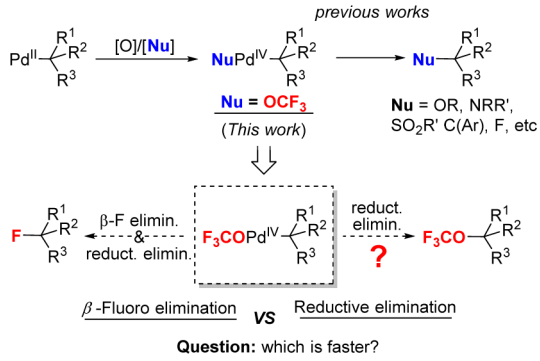
Supporting Information

ABSTRACT: The first catalytic trifluoromethoxylation of unactivated alkenes has been developed, in which $Pd(CH_3CN)_2Cl_2$ was used as catalyst, $AgOCF_3$ as trifluoromethoxide source, and Selectfluor-BF_4 as oxidant. A variety of 3-OCF_3 substituted piperidines were selectively obtained in good yields. Direct evidence was provided to address the facile reductive elimination of Pd^{IV}–OCF_3 complex to form sp^3 C–OCF_3 bond.

Incorporation of fluorine atom into drugs often leads to a significant improvement of their medicinal properties, resulting in a revolution of the pharmaceutical industry during the last several decades.[1] Among them, OCF_3-containing organofluorines have received intensive attention in the recent years.[2] However, due to the lack of efficient synthetic methodology, the related studies of these compounds are quite limited, with the trifluoromethoxy group being the least well understood.[3] Thus, exploration of a new approach for the efficient synthesis of OCF_3-containing organofluorines is urgent.

For the synthesis of OCF_3-containing organofluorines, most of efforts were focused on the chlorine/fluorine exchange of trichloromethoxylated precursors.[2,4] An alternative approach involving trifluoromethylation of alcohols or phenols has also been investigated.[5] Compared with the above methods, the direct trifluoromethoxylation reaction is much more attractive and much more challenging.[6] Transition-metal-catalyzed reactions have been demonstrated as powerful tools for the construction of C–F,[7] C–CF_3,[8] and C-SCF_3[9] bonds. However, due to the nature of easy decomposition of the OCF_3 anion, there have been no reports on catalytic methods for transferring the trifluoromethoxy group from metal center to organic compounds.[10] Vicic et al. recently reported well-defined N-heterocyclic carbene (NHC)-stabilized metal complexes (NHC)CuOCF$_3$ and (NHC)AuOCF$_3$ only at −30 °C.[11] However, these complexes were prone to decomposition at elevated temperature. To achieve the target on the trifluoromethoxylation, the reductive elimination of metal complex should proceed much faster than the related β-fluoride elimination or OCF_3 decomposition. Recent studies revealed that the reductive elimination in the high-valent palladium center is much more favored, and β-hydride elimination is disfavored owing to the lack of open coordination site at high-valent Pd center.[12] In line with the property of high-valent Pd complex, we speculated that if the β-fluoride elimination at high-valent Pd center is slower than that of reductive elimination, the alkyl–OCF_3 bond formation might be expected, which is beneficial for the catalytic reaction (Scheme 1). Herein, we report the first catalytic trifluoromethoxylation reaction by using a catalytic amount of palladium catalyst under mild reaction conditions. Various 3-trifluoromethoxylated piperidines were regioselectively obtained from *N*-toslate alkenylamines in moderate to good yields. Preliminary mechanistic studies provided the evidence to support the reductive elimination of a high-valent palladium complex to form the C–OCF_3 bond.

Scheme 1. Pathways for the Oxidative Reaction via an Alkyl–Pd(IV) Intermediate



Palladium-catalyzed oxidative intramolecular difunctionalization of alkenes presented an array of efficient transformations for the synthesis of vicinal carbon–heteroatom bonds.[12a,e] Our group has recently developed intramolecular aminochlorination,[13a] aminofluorination,[13b] and aminooxygenation[13c,d] of alkenes to build up various functionalized nitrogen-containing heterocycles, in which the related final carbon–heteroatom bonds were derived from a high-valent palladium center. Thus, we believed that intramolecular oxidative amination of alkenes might be a good model to test our hypothesis on the trifluoromethoxylation. Inspired by our previous aminofluorination condition,[13b] the initial investigation was focused on the substrate **1a** with the Pd(II)/I(III)/$AgOCF_3$ oxidative system. As shown in Table 1, we were delighted to find that the reaction of **1a** indeed provided a small amount of desired product **2a** at room temperature, but also with a side aminofluorination product **3a** in 10% yield (entry 1). However, the fluoroformylation of sulfonylamide proceeded as a major reaction to give RTsNCOF, which was derived from

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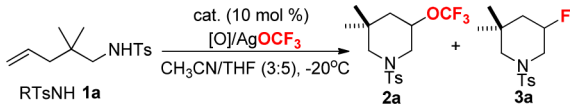
Table 1. Optimization of Reaction Conditions[a]



entry	cat.	[O] (2 equiv)	yield[b] 2a (%)	3a (%)	RTsNCOF (%)
1[c]	$Pd(OAc)_2$	$PhI(OPiv)_2$	8	10	69
2[c]	$Pd(CH_3CN)_2Cl_2$	$PhI(OPiv)_2$	21	17	40
3[d]	$Pd(CH_3CN)_2Cl_2$	$PhI(OAc)_2$	15	19	34
4[d]	$Pd(CH_3CN)_2Cl_2$	$PhI(OBz)_2$	33	11	32
5[d,e]	$Pd(CH_3CN)_2Cl_2$	$PhI(OBz)_2$	52	8	13
6[d,e]	$Pd(CH_3CN)_2Cl_2$	$PhI(O_2CAr)_2$	60	8	10
7	$Pd(CH_3CN)_2Cl_2$	$PhI(O_2CAr)_2$	70	7	6
8	$Pd(CH_3CN)_2Cl_2$	oxone	3	12	0
9	$Pd(CH_3CN)_2Cl_2$	BQ	0	0	0
10	$Pd(CH_3CN)_2Cl_2$	NFSI	13	6	2
11	**$Pd(CH_3CN)_2Cl_2$**	**SelectFluor-BF_4**	**77**	**4**	**trace**
12	$Pd(CH_3CN)_2Cl_2$	PyF·OTf	3	0	11
13[f]	$Pd(CH_3CN)_2Cl_2$	SelectFluor-BF_4	10	0	0
14[g]	$Pd(CH_3CN)_2Cl_2$	SelectFluor-BF_4	11	0	0
15	$Pd(CH_3CN)_2Cl_2$	–	0[h]	0	87
16	–		0	0	69
17	$CuCl_2$	$PhI(O_2CC_4H_6CF_3$-*m*$)_2$	0	0	49
18	$PtCl_2$	or	0	0	62
19	$AuCl_3$	SelectFluor-BF_4	0	0	18
20	MnF_2		0	0	87

[a]Reaction condition: **1a** (0.1 mmol), catalyst (0.01 mmol), $AgOCF_3$ (0.3 mmol), [O] (0.2 mmol) in the mixture of solvent of CH_3CN and THF at −20 °C. [b]^1H NMR yield with 2,2,2-trifluoro-*N*,*N*-dimethylacetamide as internal standard. [c]In pure CH_3CN at room temperature. [d]In the mixture of solvent of CH_3CN/THF (1:1). [e]At −10 °C. [f]$CsOCF_3$ (3 equiv) instead of $AgOCF_3$. [g]Me_4NOCF_3 (3 equiv) instead of $AgOCF_3$. [h]RTsNCOF as major product. Ar = $C_4H_6CF_3$-*m*. NFSI = *N*-fluorodibenzenesulfonimide.

COF_2. We reasoned that, if the related aminopalladation of **1a** is slow, the fast decomposition of $AgOCF_3$ could occur to provide COF_2 in the presence of Pd(II) catalyst.[14] Further screening of palladium catalysts and hypervalent iodine reagents showed that the combination of $PdCl_2(CH_3CN)_2$ and $PhI(O_2CC_6H_4CF_3$-*m*$)_2$ could promote the fast aminopalladation of alkene to give aminofluoromethoxylation product **2a** in 60% yield (entries 2−6). Importantly, lowering the reaction temperature was obviously beneficial for the aminotrifluoromethoxylation due to the reduction of the side fluoroformylation reaction, and the best yield (70%) was obtained at −20 °C (entries 5−7). Next, some other oxidants were also surveyed. We found that benzoquinone (BQ) was inert to promote the reaction, and other strong oxidants, such as oxone, NFSI, and *N*-fluoropyridine salt were ineffective (entries 8−10 and 12). Gratifyingly, oxidant SelectFluor-BF_4 presented the best efficiency to provide **2a** in 77% yield, combined with trace amounts of **3a**. Importantly, the corresponding fluoroformylation reaction was suppressed (entry 11). For the source of OCF_3 group, both $CsOCF_3$ and Me_4NOCF_3 provided the desired product, but with much lower efficiency than $AgOCF_3$ (entries 13 and 14). Finally, some control experiments revealed that both palladium catalyst and oxidant were necessary for the successful transformation (entries 15−16). Other Lewis acids, such as $CuCl_2$, $PtCl_2$, $AuCl_3$ and MnF_2, were ineffective for the trifluoromethoxylation, which exclude the possibility of electrophilic pathway (entries 17−20).

With the optimized reaction condition in hand, substrate scope was examined, and the results are summarized in Table 2. First, substrates with different sulfonyl groups on nitrogen were surveyed. Substrates **1a−c** were suitable for transformation to give 6-*endo* products **2a−c** in good yields (72−78%, entries 1−3). However, substrate **1d** with *p*-nitrobenesulfonyl (Ns) group was less effective and gave **2d** in 30% yield (entry 4). However, substrate **1e** with benzyl (Bn) protecting group were ineffective (entry 5). Furthermore, various *gem*-disubstituted substrates (**1f−j** and **1l−m**) were suitable for the reaction to provide corresponding products in moderate to good yields (55−80%, entries 6−10, 12−13). But substrate **1k** with bis-ester group yielded **2k** in low yield (37%, entry 11). Interestingly, the trifluoromethoxylated *spiro*-products **2n−p** could be obtained in moderated to good yields (60−71%, entries 14−16). Furthermore, when a substituent was introduced to the carbon adjacent to nitrogen, the reaction also proceeded very well to produce desired products **3q−r** in good yields with excellent regioselectivities, but with poor diastereoselectivities (entries 17−18). Similarly, the substrate with substituents on allylic position was also compatible to the reaction conditions, affording product **2s** in 62% yield with slightly better diastereoselectivity (5.3:1, entry 19). Finally, for the cyclic substrates *trans*-**1t** and *cis*-**1t**, both reactions proceeded very well to give the corresponding products **2t** and **2u** in good yields, and *cis*-**1t** provided a better diastereoselectivity (entries 20−21). It is worth noting that a significant Thrope-Ingold effect was observed in this transformation, and the linear substrate *N*-Ts-4-pentenylamine failed to produce the desired aminotrifluoro-methoxylation product. The configuration of product **2f** and **2r** was determined by X-ray analysis (Figure 1).

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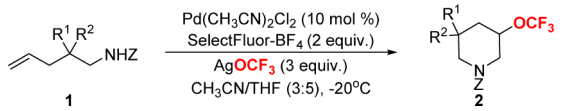
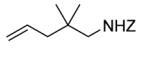
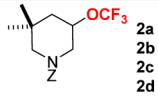
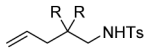
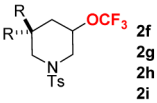
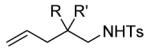
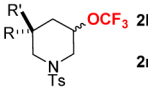
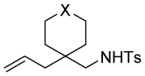
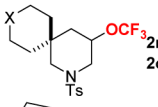
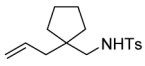
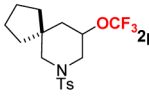
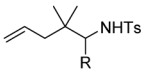
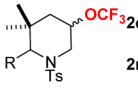
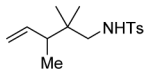
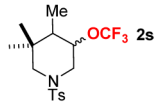
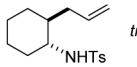
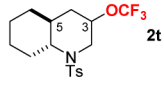
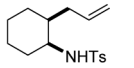
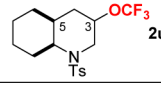
Table 2. Substrate Scope of Alkenes[a]



Entry	Alkene		Product	Yield[b]
1		**1a** Z = Ts	 **2a**	72%
2		**1b** Ps	**2b**	76%
3		**1c** PMPs	**2c**	78%
4		**1d** Ns	**2d**	30%
5		**1e** Bn	**2e**	0
6		**1f** R = Ph	 **2f**	80%
7		**1g** *o*-MeC$_6$H$_4$	**2g**	60%
8		**1h** *m*-MeC$_6$H$_4$	**2h**	63%
9		**1i** *p*-MeC$_6$H$_4$	**2i**	70%
10		**1j** CH$_2$Ph	**2j**	71%
11		**1k** COOMe	**2k**	37%
12		**1l** R = Me, R' = Ph	 **2l**	60% (3.4:1)[c]
13		**1m** R = Cy, R' = Ph	**2m**	55% (1.1:1)[c]
14		**1n** X = C	 **2n**	60%
15		**1o** X = O	**2o**	71%
16		**1p**	 **2p**	68%
17		**1q** R = Me	 **2q**	82% (1.6:1)[c]
18		**1r** R = n-C$_4$H$_9$	**2r**	72% (1.6:1)[c]
19		**1s**	 **2s**	62% (5.3:1)[c]
20		*trans*-**1t**	 **2t**	76% (1:1.4)[d]
21		*cis*-**1t**	 **2u**	77% (3.6:1)[d]

[a]Reactions were conducted at 0.2 mmol scale. [b]Isolated yield. [c]Ratio of *trans* and *cis* isomers. [d]Ratio of 3,5-*cis* and 3,5-*trans* isomers. Ps = phenylsulfonyl, PMPs = *para*-methoxyphenylsulfonyl, Ns = *para*-nitrophenylsulfonyl.

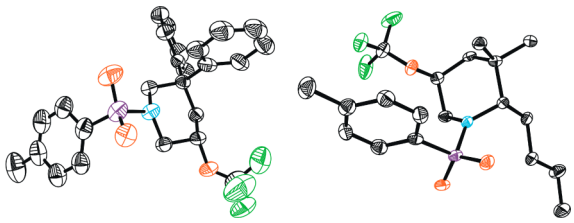
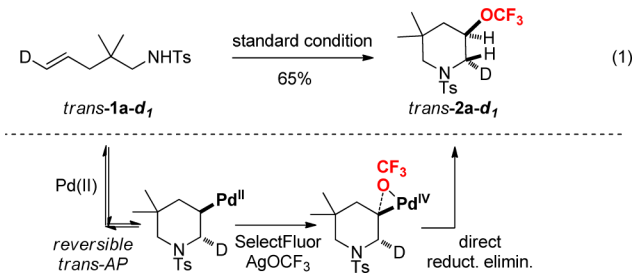


Figure 1. X-ray structure of product **2f** (left) and **2r** (right).

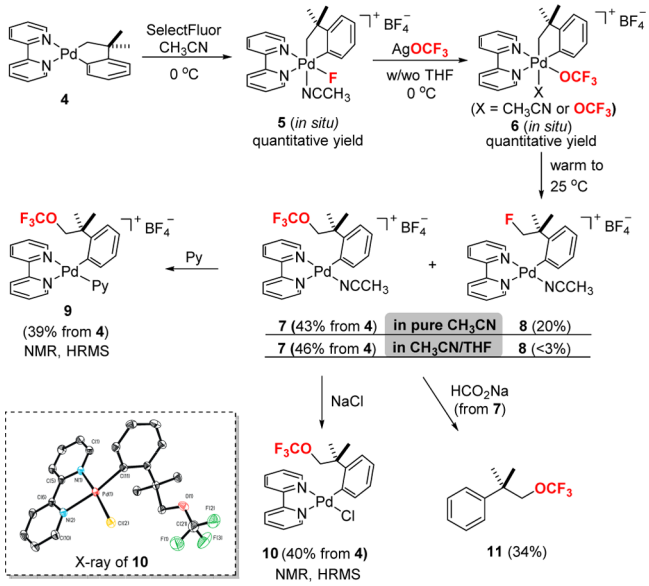
To illustrate the mechanism of aminotrifluoromethoxylation reaction, the stereochemistry was first investigated by employing deuterium-labeled substrates *trans*-**1a**-d_1. The reaction afforded *trans*-**2a**-d_1 as a single isomer, which is similar to the previous aminochlorination[13a] and aminoacetoxylation[13d] reactions (eq 1). We believed that the reaction could involve a reversible *trans*-aminopalladation, and the formed secondary alkyl-Pd intermediate was oxidized to give a high-valent alkyl-Pd(OCF$_3$)



complex, which undergoes direct reductive elimination to yield *trans*-**2a**-d_1.

In order to gain direct evidence on the reductive elimination of high-valent palladium complex for the C−OCF$_3$ bond formation, palladium complex **4** was synthesized and employed to the trifluoromethoxylation reaction (Scheme 2).[15] First, treatment

Scheme 2. Trifluoromethoxylation of Palladium Complex 4



by SelectFluor at 0 °C, Pd^{IV}F complex **5** was formed in quantitative yield.[15a] After addition of AgOCF$_3$ into system, the signals of **5** (at −334.8 ppm for ^{19}F-NMR, 4.2 and 4.8 ppm for ^{1}H NMR) were diminished immediately, and a new broad signal at −31.4 ppm (^{19}F-NMR) and two new methylene signals at 4.0 and 4.6 ppm (^{1}H NMR) were observed, possibly belonging to the Pd^{IV}OCF$_3$ complex **6**. Interestingly, when the solution of complex **6** in pure CH$_3$CN was warmed to room temperature, the reductive elimination proceeded to generate the desired sp^3 C-OCF$_3$ bond, and the related Pd(II) complex **7** was observed in 43% yield. In addition, the reaction also provided a small amount of Pd(II) complex **8** bearing C−F bond (20% yield),[15a] which derived from the sequential *β*-fluoride elimination and reductive elimination. Very interesting, when the reaction of **6** was conducted in the mixture solvent of CH$_3$CN and THF, the formation of complex **8** was significantly diminished, which is consistent with the results in the catalytic reaction. These observations indicated that the high-valent palladium exhibited better stability than that of the low-valent metal,[14] and the reductive elimination of RPd^{IV}OCF$_3$ is indeed faster than *β*-fluoride elimination. The structure of palladium complexes **7** was unambiguously determined by following experiments:[16] (1) treatment of palladium complex **7** by HCO$_2$Na, the related

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hydrogenation product **11** was obtained; and (2) in order to get single crystal of palladium complex, pyridine and chloride were added, respectively, to provide palladium complexes **9** and **10**, which were characterized by NMR as well as high-resolution mass spectroscopy. After several tentative efforts, we were delighted to obtain the single crystal of complex **10**, which confirmed its structure by X-ray spectroscopy.

In conclusion, we have developed a novel palladium-catalyzed intramolecular aminotrifluoromethoxylation reaction of unactivated alkenes. A variety of 3-trifluoromethoxylated piperidines were selectively obtained in good yields. Mechanistic study revealed that involvement of a high-valent palladium intermediate was likely in the catalytic system. The related $Pd^{IV}OCF_3$ exhibited better stability, and its facile reductive elimination over β-fluoride elimination led to the formation of C−OCF_3 bond. Further exploration of new trifluoromethoxylation reaction is in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b10971.

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Notes

The authors declare no competing financial interest.

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