

Palladium-Catalyzed Oxidative Aryltrifluoromethylation of Activated Alkenes at Room Temperature

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Supporting Information

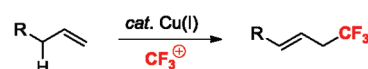
ABSTRACT: A palladium-catalyzed intramolecular oxidative aryltrifluoromethylation reaction of activated alkenes has been explored. The reaction allows for an efficient synthesis of a variety of CF₃-containing oxindoles. Preliminary mechanistic study indicated that the reaction involves a C_{sp}³–Pd^{IV}(CF₃) intermediate, which undergoes reductive elimination to afford a C_{sp}³–CF₃ bond.

The trifluoromethyl group is prevalent in pharmaceuticals, agrochemicals, and functional materials.^{1,2} The unique properties of trifluoromethylated molecules, such as elevated electronegativity, hydrophobicity, metabolic stability, and bio-availability, attract intensive attention to the development of practical methods to synthesize such compounds.³ Among them, transition metal-mediated or -catalyzed trifluoromethylation reactions have proved to be an efficient strategy to introduce a CF₃ moiety into aromatic compounds.^{3d,4} For instance, trifluoromethylation of aryl iodides or arylboronic acids can be achieved by employing stoichiometric⁵ or catalytic amounts⁶ of copper salts. For less reactive aryl chlorides, Pd-catalyzed trifluoromethylation was developed by Buchwald and co-workers. In their reaction, sterically hindered phosphine ligand Brettphos promotes reductive elimination from L_nPd(CF₃)Aryl.⁷ Yu and co-workers explored Pd-catalyzed trifluoromethylation of arene C–H bonds using electrophilic Umemoto's reagent as CF₃ source.^{8,9} However, these two reported trifluoromethylations were required expensive CF₃ reagents at relatively high temperature.

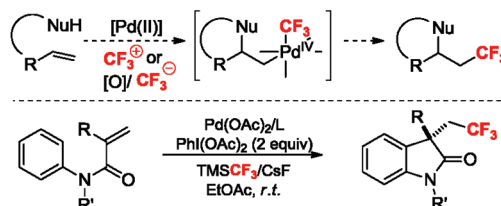
Transition metal-catalyzed selective trifluoromethylation of alkenes is quite rare. Very recently, Buchwald,^{10a} Liu,^{10b} and Wang^{10c} independently reported Cu-catalyzed allylic C–H trifluoromethylation reactions (Scheme 1a).¹⁰ It is known that Pd-catalyzed oxidative difunctionalization of alkenes provides an efficient strategy to construct two vicinal chemical bonds.¹¹ Reactions such as aminooxygenation,¹² diamination,¹³ dioxygenation,¹⁴ and fluoroamination¹⁵ have been shown to involve a Pd(II/IV) mechanistic pathway. We hypothesize that, if a trifluoromethylation catalytic system can be applied in the alkene difunctionalization, a variety of CF₃-containing aliphatic compounds should be easily available (Scheme 1b, top). Herein, we report a novel Pd-catalyzed oxidative aryltrifluoromethylation of activated alkenes using easily available, inexpensive TMSCF₃ as trifluoromethyl source at room temperature (Scheme 1b, bottom).¹⁶ It is worth noting that this method represents one of most efficient ways to synthesize

Scheme 1. Transition Metal-Catalyzed Trifluoromethylation of Alkenes

a) Allylic C–H trifluoromethylation (Buchwald, Liu and Wang):



b) Difunctionalization of Alkenes: trifluoromethylation (this work)



various CF₃-substituted oxindoles, which are important in natural products and biologically active compounds.^{17,18}

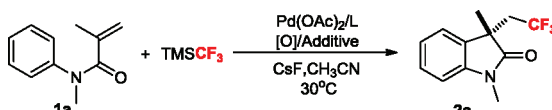
To test our hypothesis, the initial investigation focused on the reaction of substrate **1a** with various CF₃⁺ reagents, such as Togni's reagent **3** and Umemoto's reagent **4**, using Pd(OAc)₂ catalyst. However, none of the desired product was observed under these reaction conditions (Table 1, entries 1 and 2). Inspired by our previous work on fluoroamination of alkenes,¹⁴ we tested a catalytic system combining hypervalent iodine reagent and CF₃[–]. Interestingly, a significant amount of aryltrifluoromethylation product **2a** was observed with high regioselectivity when the reaction employed TMSCF₃ and CsF to generate CF₃[–] *in situ* and PhI(OAc)₂ oxidant (entry 3). Screening of nitrogen-containing ligands **L1**–**L5** showed that **L5** gave the best yield. A similar ligand, **L6**, bearing a cyclopropane group gave worse results (entries 4–9). Exploration of oxidants revealed that only hypervalent iodine reagents are reactive, and PhI(OAc)₂ afforded the best result (entries 8, 10–12). Subsequently, a series of Lewis acids were screened (entries 13–16). The best yield (75%) was obtained in the presence of Yb(OTf)₃ (20 mol %, entry 15). No significant effect for the addition of radical scavenger TEMPO indicates that a radical process is less likely (entry 17). Finally, the highest yield was achieved in the reaction with EtOAc as solvent (entry 18).¹⁹

With the optimized reaction conditions, the substrate scope was then investigated as shown in Table 2. Substrates **1a**–**1c** bearing alkyl, aryl, or silyl protecting groups on the nitrogen

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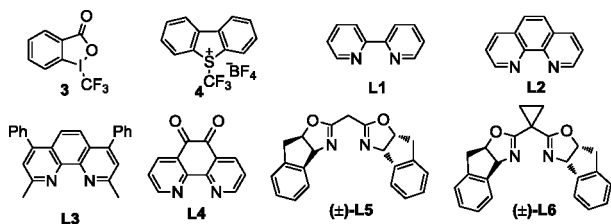
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Table 1. Optimization of the Reaction Conditions^a


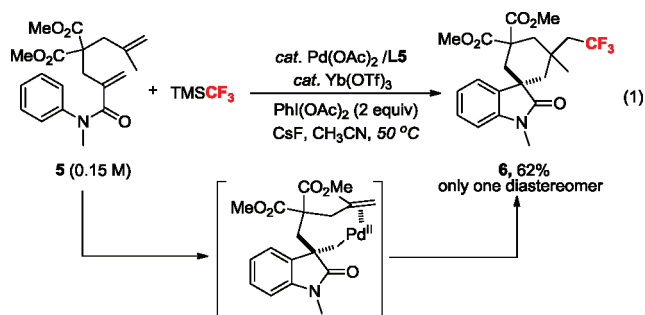
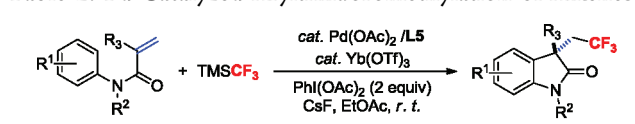
entry	ligand (15 mol %)	additive	oxidant	yield (%) ^b
1 ^c			3	0
2 ^c			4	0
3			PhI(OAc) ₂	24
4	L1		PhI(OAc) ₂	25
5	L2		PhI(OAc) ₂	26
6	L3		PhI(OAc) ₂	34
7	L4		PhI(OAc) ₂	30
8	L5		PhI(OAc) ₂	55
9	L6		PhI(OAc) ₂	21
10	L5		PhI(OPiv) ₂	38
11	L5		PhI(TFA) ₂	0
12	L5		PhI=O	0
13 ^d	L5	HOTf	PhI(OAc) ₂	62
14 ^d	L5	TFA	PhI(OAc) ₂	46
15 ^d	L5	Yb(OTf) ₃	PhI(OAc) ₂	75
16 ^d	L5	Sc(OTf) ₃	PhI(OAc) ₂	60
17 ^{d,e}	L5	Yb(OTf) ₃	PhI(OAc) ₂	70
18 ^f	L5	Yb(OTf) ₃	PhI(OAc) ₂	81 (78) ^g

^aReaction conditions: **1a** (0.1 mmol), Pd(OAc)₂ (10 mol %), CsF (0.4 mmol), TMSCF₃ (4 equiv), PhI(OAc)₂ (0.2 mmol) in 1.0 mL of CH₃CN at room temperature (30 °C) for 6 h. ^b¹⁹F NMR yield. ^cCF₃⁺ reagent was used, without TMSCF₃/CsF and oxidant. ^dLewis acid (20 mol %). ^eTEMPO (1 equiv) ^fEtOAc as solvent. ^gIsolated yield.



were good for this transformation, but tosylated substrate **1d** failed to give the desired product. A variety of anilines substrates **2e–2r** were next determined. The position of the substituents has no significant influence on the efficiency. The substrates bearing electron-withdrawing or electron-donating groups always afforded the desired products **2e–2n** in good to excellent yields. Notably, halides were tolerated and furnished the corresponding products **2k–2o** in excellent yields. Substrates having two substituents on the phenyl rings provided the products **2p–2r** in good yields. However, the reaction afforded the mixture of **2r** and **2r'** with moderate regioselectivity (1:3 ratio). Finally, substrates with different substituents on olefin were examined. No reaction occurred in the case of mono-substituent olefin (R₃ = H). However, a series of α -substituted olefins bearing different functional group, such as aryl (**1s**), alcohol (**1t**), ester (**1u**), ether (**1v**, **1w**), and phthalimide (**1x**), are compatible with this catalytic system, and all reactions produced desired products **2s–2x** in moderate to good yields. It is remarkable that only one isomer, **2w**, was obtained in the reaction of **1w** with excellent diastereoselectivity.

To evaluate the aryltrifluoromethylation reaction further, diene **5** was subjected to the reaction conditions at 50 °C (eq 1). This tandem cyclization afforded spirocyclic product **6** as a single diastereomer in 62% yield, but its relative stereoconfiguration was

Table 2. Pd-Catalyzed Aryltrifluoromethylation of Alkenes^a


2a 78%	2b 82%	2c 66%	2d 0%
2e R = OMe 68%	2f Me 76%	2g NO ₂ 84%	2h OCF ₃ 72%
2i 81%	2j 78%	2k X = F 83%	2l Cl 88%
2m Br 82%	2n I 89%	2o 79%	2p R = Me 61%
2q R = F 71%	2r 83% (1:3)	2s 58%	2t 43%
2u 81%	2v 68%	2w 72% ^b	2x 70%

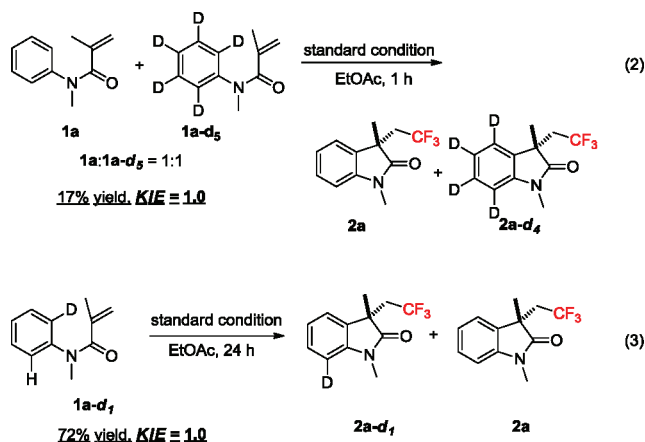
^aAll reactions were conducted at 0.2 mmol scale: Pd(OAc)₂ (10 mol %), L5 (15 mol %), Yb(OTf)₃ (20 mol %), PhI(OAc)₂ (2 equiv), TMSCF₃ (4 equiv), and CsF (4 equiv) in EtOAc (1 mL). Isolated yield are given.

^bOnly one isomer was obtained.

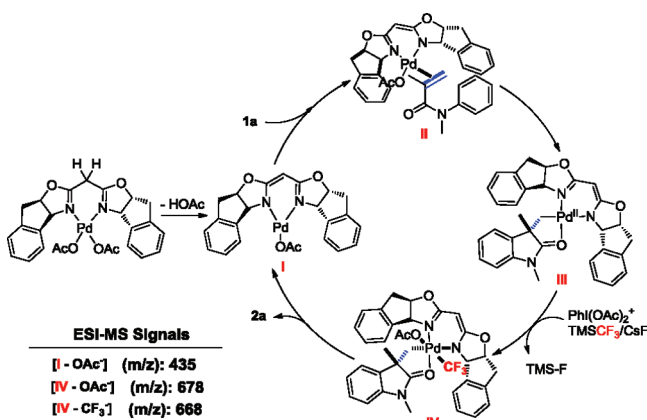
not confirmed at this stage. This result is consistent with a mechanism of arylpalladation of alkene to give a C_{sp}³-Pd(II) intermediate, which undergoes sequential alkene insertion and oxidative trifluoromethylation to form product **6**.

The formation of **2** indicates that a C–H bond functionalization of aniline is involved in the reaction. To probe the mechanism of C–H bond cleavage, a mixture of substrates **1a** and **1a-d₅** in a 1:1 ratio was used to determine the intermolecular isotope effect, and substrate **1a-d₁** was used for the intramolecular isotope effect. No kinetic isotope effect (*k_H*/*k_D* = 1.0, eqs 2 and 3) was observed.²⁰ The absence of an intramolecular isotope effect suggests that the arylation step may involve an electrophilic aromatic substitution process.²¹

Mass spectrometry experiments provided further insights into the catalytic cycle of the trifluoromethylation. First, ESI-MS showed a peak at *m/z* 435, which corresponds to the mass of [I – OAc]⁺,²² in the mixture of Pd(OAc)₂, L5, and **1a** in



Scheme 2. Proposed Mechanism for Aryltrifluoromethylation



CH₃CN. The intermediate I is generated from the (L5)Pd(OAc)₂ complex by loss of HOAc.²³ In the standard catalytic reaction, we are delighted that two signals at *m/z* 668 and 678, which are related to the masses of [IV - CF₃]⁺ and [IV - OAc]⁺, were observed (Scheme 2).²⁴ In addition, stoichiometric reaction gave a ¹⁹F NMR signal at -27.1 ppm, which is consistent with the data of aryl-Pd^{IV}CF₃ species reported by Sanford.^{9c,d} The above observations provide support that this aryltrifluoromethylation may involve a C_{sp}³-Pd^{IV}CF₃ intermediate, IV.

Based on the above analysis, a possible catalytic cycle is shown in Scheme 2. The reaction is initiated by coordination of the olefin to Pd(II) complex I. Nucleophilic attack of the tethered arene affords Pd complex III. This species undergoes oxidation by PhI(OAc)₂/TMSCF₃ to form a C_{sp}³-Pd^{IV}(CF₃) intermediate IV, which generates a C_{sp}³-CF₃ bond via reductive elimination and releases Pd catalyst I.²⁵

In summary, we have developed a novel Pd-catalyzed oxidative aryltrifluoromethylation of activated alkenes using TMSCF₃/CsF as trifluoromethyl group source and PhI(OAc)₂ as oxidant. Preliminary mechanistic studies indicate that the reaction proceeds through initial arylpalladation of alkene, followed by sequential oxidation and reductive elimination of C_{sp}³-Pd^{IV}CF₃ species to provide the products in good yields. This reaction creates an opportunity to construct a variety of bioactive molecules containing trifluoromethylated oxindole moieties. Further investigation of this transformation is in progress.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

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- (24) For detailed analysis, see the Supporting Information.
- (25) Other mechanistic pathways cannot be excluded at this point. Further investigations are ongoing.