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Palladium-Catalyzed Oxidative Aryltrifluoromethylation of Activated Alkenes at Room Temperature

Xin Mu,[†] Tao Wu,[†] Hao-yang Wang,[‡] Yin-long Guo,[‡] and Guosheng Liu*,[†]

[†]State Key Laboratory of Organometallic Chemistry and [‡]Shanghai Mass Spectrometry Center, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

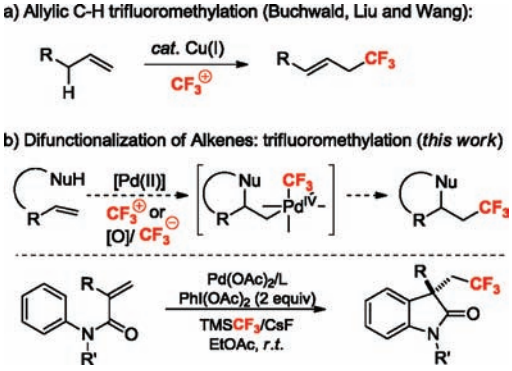
Supporting Information

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 CF_3-containing oxindoles. Preliminary mechanistic study indicated that the reaction involves a C_{sp^3}–$Pd^{IV}(CF_3)$ intermediate, which undergoes reductive elimination to afford a C_{sp^3}–CF_3 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 bioavailability, 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 CF_3 moiety into aromatic compounds.[3d,4] For instance, trifluoromethylation of aryl iodides or arylboronic acids can be achieved by employing stoichiometric[5] or catalytic amounts[6] 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 $L_nPd(CF_3)Aryl$.[7] Yu and co-workers explored Pd-catalyzed trifluoromethylation of arene C–H bonds using electrophilic Umemoto's reagent as CF_3 source.[8,9] However, these two reported trifluoromethylations were required expensive CF_3 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 fluoroamination[15] 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 CF_3-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 $TMSCF_3$ 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 various CF_3-substituted oxindoles, which are important in natural products and biologically active compounds.[17,18]

Scheme 1. Transition Metal-Catalyzed Trifluoromethylation of Alkenes



To test our hypothesis, the initial investigation focused on the reaction of substrate **1a** with various CF_3^+ 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 CF_3^-. Interestingly, a significant amount of aryltrifluoromethylation product **2a** was observed with high regioselectivity when the reaction employed $TMSCF_3$ and CsF to generate CF_3^- *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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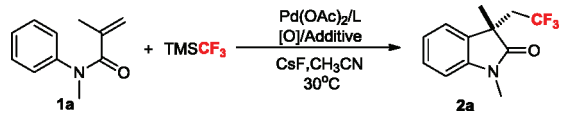
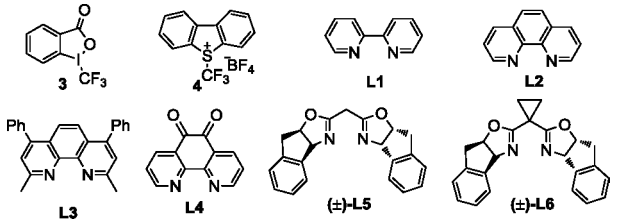
Table 1. Optimization of the Reaction Conditions[a]



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]

[a]Reaction conditions: **1a** (0.1 mmol), $Pd(OAc)_2$ (10 mol %), CsF (0.4 mmol), $TMSCF_3$ (4 equiv), $PhI(OAc)_2$ (0.2 mmol) in 1.0 mL of CH_3CN at room temperature (30 °C) for 6 h. [b]^{19}F NMR yield. [c]CF_3^+ reagent was used, without $TMSCF_3$/CsF and oxidant. [d]Lewis acid (20 mol %). [e]TEMPO (1 equiv) [f]EtOAc as solvent. [g]Isolated 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 monosubstituent olefin (R_3 = 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

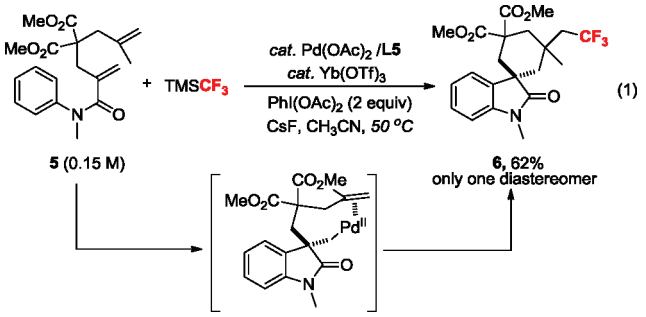
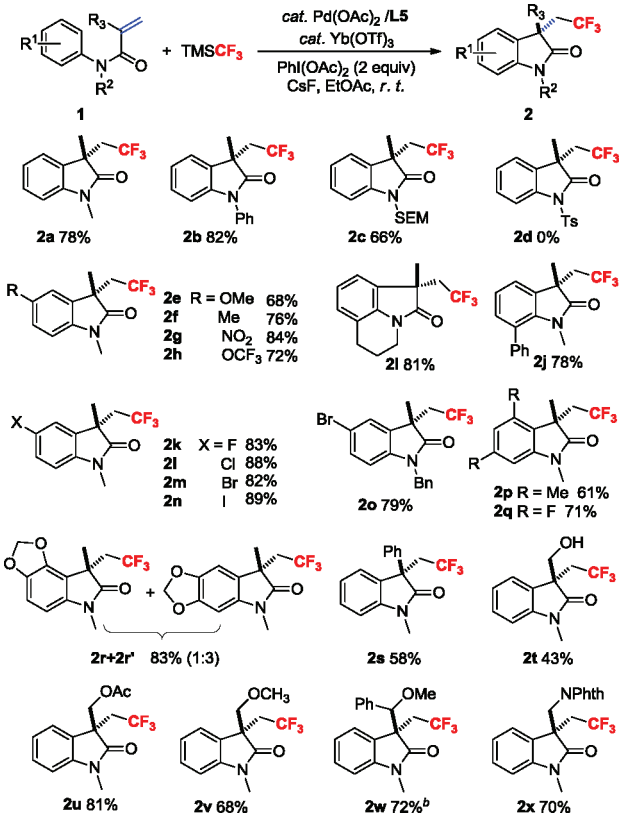


Table 2. Pd-Catalyzed Aryltrifluoromethylation of Alkenes[a]



[a]All 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), $TMSCF_3$ (4 equiv), and CsF (4 equiv) in EtOAc (1 mL). Isolated yield are given. [b]Only 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**-d_5 in a 1:1 ratio was used to determine the intermolecular isotope effect, and substrate **1a**-d_1 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 $[\mathbf{I} - OAc]^+$,[22] in the mixture of $Pd(OAc)_2$, **L5**, and **1a** in

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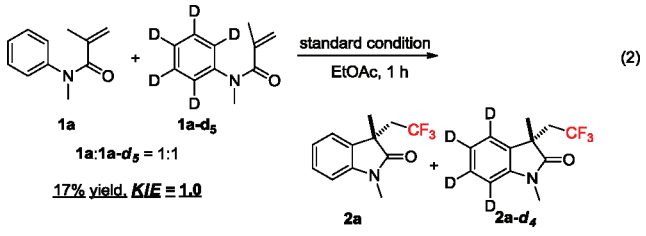
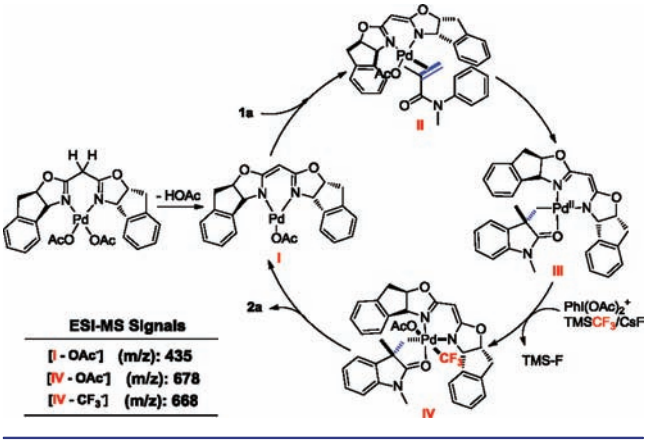


Scheme 2. Proposed Mechanism for Aryltrifluoromethylation



CH_3CN. 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 $[\mathbf{IV} - CF_3]^+$ and $[\mathbf{IV} - OAc]^+$, were observed (Scheme 2).[24] In addition, stoichiometric reaction gave a ^{19}F NMR signal at −27.1 ppm, which is consistent with the data of aryl−$Pd^{IV}CF_3$ species reported by Sanford.[9c,d] The above observations provide support that this aryltrifluoromethylation may involve a C_{sp^3}−$Pd^{IV}CF_3$ 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 $PhI(OAc)_2/TMSCF_3$ to form a C_{sp^3}−$Pd^{IV}(CF_3)$ intermediate **IV**, which generates a C_{sp^3}−CF_3 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 $TMSCF_3$/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}−$Pd^{IV}CF_3$ 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

Corresponding Author

gliu@mail.sioc.ac.cn

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(19) In the absence of Pd catalyst, the reaction affords aryltrifluoromethylation product in 31% yield (24 h), and 27% yield with 1 equiv of TEMPO. It is possible that this transformation is promoted by $PhI(OAc)_2$. For some selective examples of hypervalent iodine-promoted olefin functionalization, see: (a) Röben, C.; Souto, J. A.; González, Y.; Lishchynskyi, A.; Muñiz, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 9478. (b) Kang, Y.-B.; Gade, L. H. *J. Am. Chem. Soc.* **2011**, *133*, 3658. (c) Lovick, H. M.; Michael, F. E. *J. Am. Chem. Soc.* **2010**, *132*, 1249.
(20) For the reaction in eq 1, no H/D scrambling was observed in the recovered starting material **1a** and **1a-*d*$_5$**. For details, see the Supporting Information.
(21) For the corresponding KIE value of the electrophilic aromatic substitution process, see: (a) Tunge, J. A.; Foresee, L. N. *Organometallics* **2005**, *24*, 6440−6444. (b) Taylor, R. *Electrophilic Aromatic Substitution*; John Wiley & Sons Inc.: New York, 1990; pp 25−57.
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(23) Compared to noneffective bis-nitrogen ligands **L1**−**L4** and **L6**, ligand **L5**, which contains an acid proton, is easy to transform into a monoionic ligand.
(24) For detailed analysis, see the Supporting Information.
(25) Other mechanistic pathways cannot be excluded at this point. Further investigations are ongoing.