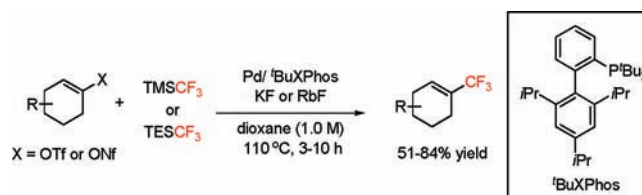


The Palladium-Catalyzed
Trifluoromethylation of Vinyl SulfonatesEun Jin Cho[†] and Stephen L. Buchwald*Department of Chemistry, Massachusetts Institute of Technology, 77 Massachusetts
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ABSTRACT

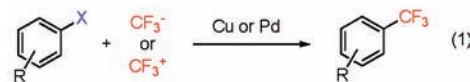


A method for the palladium-catalyzed trifluoromethylation of cyclohexenyl sulfonates has been developed. Various cyclohexenyl triflates and nonaflates underwent trifluoromethylation under mild reaction conditions using a catalyst system composed of Pd(dba)₂ or [(allyl)PdCl]₂ and the monodentate biaryl phosphine ligand ^tBuXPhos. The trifluoromethyl anion (CF₃⁻) or its equivalent for the process was generated *in situ* from TMSCF₃ in combination with KF or TESCF₃ in combination with RbF.

The development of methods for the trifluoromethylation of organic compounds is of great importance since the introduction of a trifluoromethyl (CF₃) group can dramatically change the physical and biological activities of a molecule. In many instances, inclusion of a CF₃ group increases the metabolic stability, lipophilicity, bioavailability, and binding selectivity of a pharmaceutical candidate.¹ Notably, many top-selling pharmaceuticals as well as agrochemicals contain a trifluoromethyl group.^{1a,c}

While a variety of processes for the construction of sp³ carbon-CF₃ bonds have been reported (using electrophilic, nucleophilic, and radical-based reagents),² processes for the construction of sp² carbon-CF₃ bonds are rarer. Traditional methods for the formation of benzotrifluorides require harsh reaction conditions such as the use of HF and SbF₅ at high temperature,³ precluding the use of highly functionalized substrates. In contrast, cross-coupling processes can facilitate the construction of sp² carbon-CF₃

Aryl trifluoromethylation



Vinyl trifluoromethylation

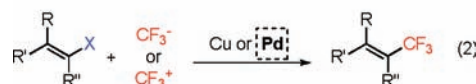


Figure 1. Construction of sp² carbon-CF₃ bonds.

bonds under milder reaction conditions, rendering them more amenable to the late-stage modification of highly functionalized molecules.⁴ Toward this end, a variety of copper⁵- and palladium⁶-mediated reactions have recently been developed [Figure 1, reaction 1]. These transition-metal-catalyzed trifluoromethylations, however, are mainly limited to the installation of aryl-CF₃ groups.

Trifluoromethylated alkenes are key structural components of many biologically active compounds and are featured in pharmaceuticals and agrochemicals such as panomifene⁷ and bifenthrin.⁸ Despite the importance of these

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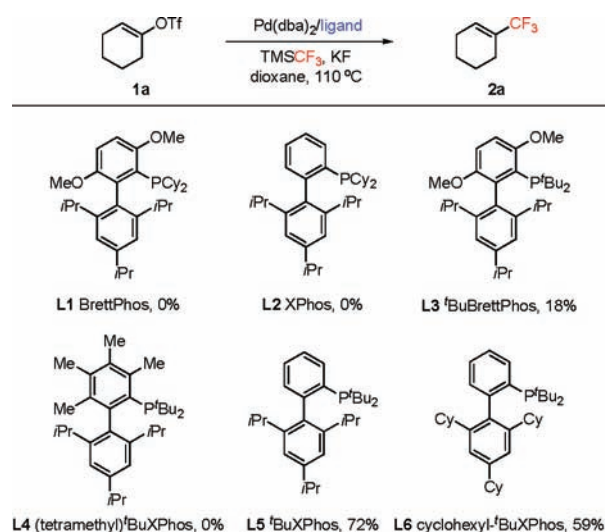
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vinyl-CF₃ moieties, processes for their direct installation have not been well developed [Figure 1, reaction 2]. Typically, trifluoromethylated alkenes are generated from aldehydes, ketones, or alkynes via several synthetic manipulations.⁹ Regarding copper-mediated coupling processes, trifluoromethylations of vinylboronic acids were reported recently. However, the process reported by Chu and Qing^{5c} required the use of a stoichiometric quantity of copper with sensitive reagents and the process by Liu and Shen^{5g} produced a mixture of alkene stereoisomers. Herein, we report the first palladium-catalyzed process for the trifluoromethylation of cyclohexenyl triflates and nonaflates into trifluoromethylated alkenes under mild conditions. We found the use of Pd(dba)₂ or [(allyl)PdCl]₂ as the palladium source in conjunction with the electron-rich bulky biphenyl based ligand ^tBuXPhos provided the optimal results.

Our studies of the vinyl trifluoromethylation reaction began by evaluating various monodentate biaryl phosphine ligands (Scheme 1). 1-Cyclohexenyl trifluoromethanesulfonate **1a** was used as a test substrate with 5 mol % Pd(dba)₂ and 10 mol % ligand in dioxane at 110 °C. Trifluoromethyltrimethylsilane (Ruppert's reagent, TMSCF₃)¹⁰ was used as the trifluoromethyl anion (CF₃⁻) source in combination with KF as an activator. Interestingly, the cyclohexyl-substituted biaryl phosphine ligand **L1** (BrettPhos), which was found to be the optimal ligand for the palladium-catalyzed trifluoromethylation of aryl chlorides under similar conditions,^{6d} was unsuccessful in providing any of the desired trifluoromethylated alkene **2a**. In fact, only catalysts based on ligands with *tert*-butyl substitution on phosphorus were successful in promoting this transformation. In addition, it

Scheme 1. Ligand Screen for the Trifluoromethylation of Vinyl Triflate **1a**^{a,b}



^a Reaction conditions: **1a** (0.3 mmol), Pd(dba)₂ (5 mol %), ligand (10 mol %), TMSCF₃ (0.6 mmol), KF (0.6 mmol), dioxane (0.3 mL), 110 °C, 5 h. ^b The yield was determined by ¹⁹F NMR spectroscopy with 4-fluorotoluene as an internal standard.

was found that catalysts based on ligands lacking substitution at the 3-position of the upper aromatic ring (**L5** and **L6**) were the most effective in generating the desired trifluoromethylated alkene products. Specifically, the use of ligand **L5** (^tBuXPhos) provided the best results for this transformation and was chosen for further study.

We next investigated the substrate scope for the coupling process using various 4-phenyl-substituted cyclohexenyl halides and sulfonates with ligand **L5** (Table 1). Both vinyl triflates and nonaflates (–ONf = OSO₂CF₂CF₂CF₂CF₃) participated in the reaction to give the desired trifluoromethylated alkene **2b** (entries 4–12). In contrast, the trifluoromethylation of a vinyl chloride (entry 1) or bromide (entry 2) did not occur under these conditions.

The source of the trifluoromethyl anion or its equivalent was also examined with several combinations of TMSCF₃ or TESCf₃ (trifluoromethyltriethylsilane) and metal fluoride activators as shown in Table 1. The rate of *in situ* CF₃⁻ generation is crucial, since it decomposes readily to difluorocarbene (F₂C:) and fluoride (F⁻).¹¹ We found that the highest yield of product was obtained by using TMSCF₃ and KF for triflate electrophiles (entry 4), while the use of TESCf₃ and RbF gave better results for nonaflate electrophiles (entry 10). Additionally, we found that switching the palladium source from Pd(dba)₂ to [(allyl)PdCl]₂ increased the yield of product for vinyl nonaflate substrates (entry 11).

With the optimized conditions in hand, we investigated the substrate scope of the vinyl trifluoromethylation reaction (Scheme 2). TMSCF₃ was employed with KF as the activator for the reactions of vinyl triflates while the

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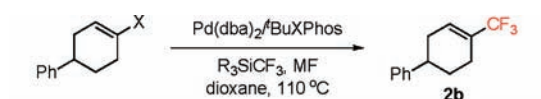
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Table 1. Optimization of the Trifluoromethylation of Vinyl Substrates^{a,b}



entry	X	R ₃ SiCF ₃	MF	¹⁹ F-NMR yield
1	Cl	TMSCF ₃	KF	0%
2	Br	TMSCF ₃	KF	0%
3	OTf	TMSCF ₃	NaF	0%
4	OTf	TMSCF ₃	KF	71%
5	OTf	TMSCF ₃	RbF	49%
6	OTf	TESCF ₃	KF	55%
7	OTf	TESCF ₃	RbF	39%
8	ONf	TMSCF ₃	KF	29%
9	ONf	TESCF ₃	KF	22%
10	ONf	TESCF ₃	RbF	43%
11 ^c	ONf	TESCF ₃	RbF	65%
12	ONf	TESCF ₃	CsF	14%

^a Reaction conditions: RX (0.2 mmol), Pd(dba)₂ (5 mol %), ^tBuXPhos (10 mol %), TMSCF₃ (0.4 mmol), KF (0.4 mmol), dioxane (0.2 mL), 110 °C, 5 h. ^b The given yield was determined by ¹⁹F NMR spectroscopy with 4-fluorotoluene as an internal standard. ^c 2.5 mol % [(allyl)PdCl]₂ was used as the palladium source.

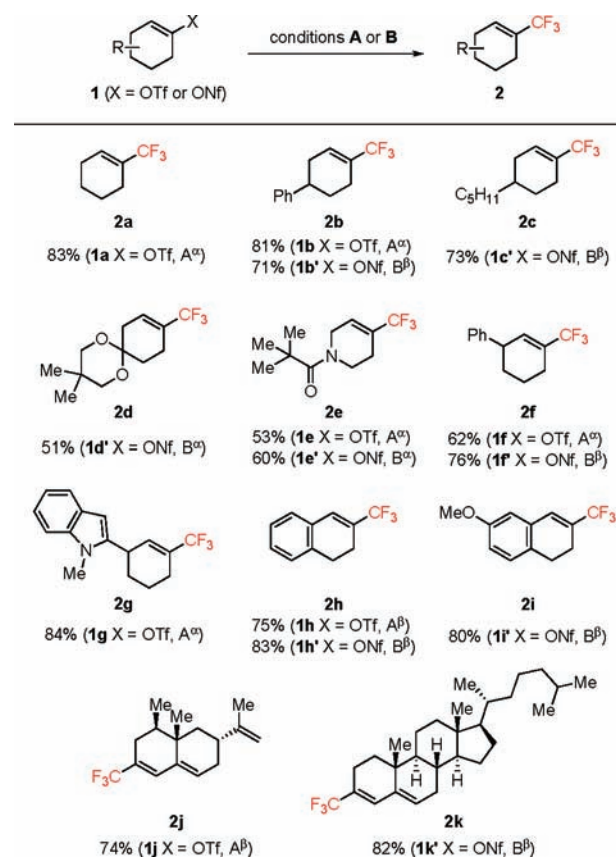
TESCF₃/RbF system was used for reactions of vinyl nonaflates. Generally, 5 mol % palladium [5% Pd(dba)₂ or 2.5% [(allyl)PdCl]₂] was used with 10 mol % ^tBuXPhos in dioxane at 90 to 110 °C with a reaction time of 3 h. A variety of six-membered vinyl triflates and vinyl nonaflates were transformed into trifluoromethylated alkenes in modest to high yields. Additionally, minor amounts (1–5%) of reduced starting materials (vinyl-H) were usually observed. Several functional groups are tolerated under the reaction conditions including ketals (**2d**), amides (**2e**), and heteroaromatic rings (**2g**).¹² Conjugated alkenyl sulfonates such as those derived from 2-tetralone (**2h**, **2i**), (+)-nootkatone (**2j**), and cholesterol (**2k**) also underwent the transformation, producing the corresponding trifluoromethylated alkenes in high yield. The reaction conditions also proved applicable to larger scale reactions, and trifluoroalkene products **2a** and **2b** were prepared on a 5 mmol scale in yields similar to those reported for the 1 mmol scale reactions. Conversely, we found that reactions of triflates conducted on a smaller scale (less than 0.5 mmol) with TMSCF₃ and KF gave the desired products in yields 10–20% lower than those from reactions conducted on a larger scale.¹³

While 3- or 4-alkyl substituted cyclohexenyl substrates work well in this reaction, cyclohexenyl sulfonates with substitution at the 2-position were less successful substrates. Though several 2-methyl-substituted substrates did undergo the trifluoromethylation under optimized conditions, these reactions proceeded slowly (Scheme 3).

(12) Substrates bearing aldehydes, ketones, and unprotected OH or NH groups are not suitable for this process.

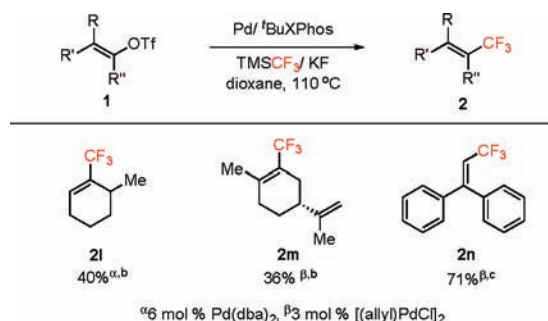
(13) The reason is unclear at the moment. The change of either concentration or surface area of the reaction did not affect the results.

Scheme 2. Scope of the Palladium-Catalyzed Trifluoromethylation of Vinyl Triflates and Vinyl Nonaflates^{a,b}



^a Reaction conditions: The exact amount of Pd catalyst used for each substrate is described in the Supporting Information. (A) ROTf (1.0 mmol), 4–6 mol % Pd(dba)₂^α or [(allyl)PdCl]₂^β, 8–12 mol % ^tBuXPhos (Pd/L = 1:2), TMSCF₃ (2.0 mmol), KF (2.0 mmol), dioxane (1.0 mL), 90–110 °C, 3–10 h. (B) RONf (1.0 mmol), 4–6 mol % Pd(dba)₂^α or [(allyl)PdCl]₂^β, 8–12 mol % ^tBuXPhos (Pd/L = 1:2), TESCF₃ (1.5 mmol), RbF (1.5–2.0 mmol), dioxane (1.0 mL), 90–110 °C, 3–10 h. ^b The given yields are isolated yields based on an average of at least two runs except **2a**. The yield of **2a** was determined by ¹⁹F NMR spectroscopy using 4-fluorotoluene as an internal standard due to its volatility.

Scheme 3. Trifluoromethylation of 2-Alkyl Substituted Cyclohexenyl Triflates^{a,b}



^a Reaction conditions: ROTf (1.0 mmol), 6 mol % Pd^α or ^β, 12 mol % ^tBuXPhos, TMSCF₃ (2.0 mmol), KF (2.0 mmol), dioxane (1.0 mL), 110 °C, 4–10 h. ^b The given yields are determined by ¹⁹F NMR spectroscopy. ^c The given yields are isolated and based on an average of two runs.

Longer reaction times failed to improve yields significantly due to a competing triflate decomposition pathway under these conditions. Interestingly, we found that a 2,2-disubstituted triflate was a competent substrate, with trifluoromethyl alkene **2n** produced in 71% yield.

Compared to six-membered fluoroalkylsulfonates, the analogous five-membered substrates demonstrated significantly reduced reactivity. For example, trifluoromethylation of cyclopentenyl fluoroalkylsulfonates did not go to completion even after being subjected to higher temperatures and catalyst loadings. Current efforts seek to develop suitable conditions for these more challenging substrates. In the case of reactions of larger cyclic (> 7-membered rings) or acyclic systems, alkyne or allene side products were observed as the major products. Further investigations revealed that the formation of alkynes or allenes was slow and did not go to completion in the absence of a palladium catalyst, while in the presence of palladium these products were obtained in quantitative yields in just 1 h. These findings suggest that these side processes proceed

primarily via competitive β -hydride elimination of alkenyl-Pd oxidative addition complexes. These results indicate that relatively slow transmetalation compared to β -hydride elimination likely results in this distribution of products.

We have developed a palladium-catalyzed trifluoromethylation of vinyl triflates and nonaflates, providing a direct method to access trifluoromethylated alkenes from vinyl electrophiles. A variety of trifluoromethylated cyclohexenes were generated under mild reaction conditions.

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Supporting Information Available. Experimental procedures and spectral data for products. This material is available free of charge via the Internet at <http://pubs.acs.org>.