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Palladium-Catalyzed Fluorination of Cyclic Vinyl Triflates: Effect of $TESCF_3$ as an Additive

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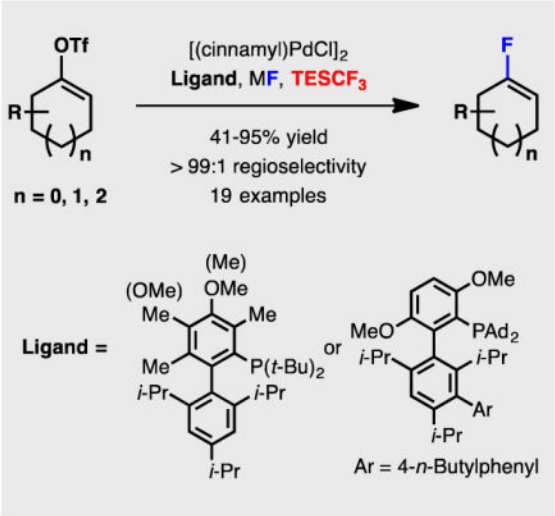
Abstract

A method for the palladium-catalyzed fluorination of cyclic vinyl triflates has been developed. As with several previous palladium-catalyzed fluorination reactions using fluoride salts, controlling the regioselectivity was nontrivial and presented a challenge in developing a practical synthetic procedure. The addition of triethyl(trifluoromethyl)silane ($TESCF_3$) was found to effectively address this problem and resulted in dramatically improved regioselectivities in this palladium-catalyzed fluorination reaction. This discovery, along with the use of a new biarylphosphine ligand, allowed for the development of an efficient and highly regioselective protocol for the fluorination of vinyl triflates. This method is compatible with a range of sensitive functional groups and provides access to cyclic (five, six, and seven-membered) vinyl fluorides

Graphical Abstract



A technique for the palladium-catalyzed fluorination of cyclic vinyl triflates has been developed. The reaction exhibited good functional group tolerance and proceeded efficiently for five, six and seven-membered vinyl triflate substrates, as well as a few acyclic substrates. The addition of

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triethyl(trifluoromethyl)silane ($TESCF_3$) was found to effectively address the problem of regioisometric side product generation and resulted in dramatically improved regioselectivities in this method.

Keywords

palladium; cross-coupling; fluorination; fluoroalkene

Fluorine-substituted olefins constitute a valuable class of compounds of interest for medicinal chemistry and chemical biology (Figure 1).[1,2] The alkenyl fluoride group resembles an amide linkage in terms of both steric demand and charge distribution,[3] but fluoroalkenes exhibit substantially enhanced stability towards hydrolysis compared to amides. Moreover, in contrast to amides, which often exist as equilibrating s-*cis* and s-*trans* rotamers, fluoroalkenes are configurationally stable. As a result, they have been investigated as amide bioisosteres with improved lipophilicity and metabolic stability in pharmaceutical applications and as tools for probing the conformational properties of biologically active amides.[4] In addition to these applications, fluoroalkenes also serve as versatile starting materials for a variety of transformations, including the Diels-Alder reaction,[5a] cyclopropanation,[5b,5c] and epoxidation,[5d] allowing for the construction of other classes of fluorine-containing molecules.

Despite considerable potential, fluoroalkenes are underutilized due to challenges in their synthesis. Current approaches for their preparation generally require multistep functional group manipulations or the use of harsh reaction conditions, which limit the functional group compatibility of these techniques. [6–11] The development of a mild and general method for fluoroalkene synthesis would therefore be highly desirable. Due to the challenge of preparing suitable precursors, cyclic fluoroalkenes are particularly difficult to access using existing methods, and new methods that provide access to these compounds would be especially useful.

In this context, the palladium-catalyzed coupling of cyclic vinyl triflates with simple metal fluoride salts represents a particularly attractive strategy to access fluoroalkenes. In 2009, we reported a palladium(II)-catalyzed fluorination of aryl triflates using a bulky biaryl monophosphine ligand (*t*-BuBrettPhos).[12a] Since then, more effective catalysts based on AdBrettPhos and HGPhos were developed and the fluorination of aryl bromides was achieved.[12b,12c] However, the generation of regioisomeric side products in these reactions remained an unsolved problem.[12d] Recently, a new fluorinated biaryl phosphine ligand (AlPhos) was developed to improve the rate and regioselectivity in the fluorination of aryl triflates and bromides.[12e] However, as described below, direct application of these new ligands and reaction conditions to cyclic vinyl triflate substrates afforded the corresponding vinyl fluoride products in low yield and as mixtures of regioisomers. Herein, we report the development of a highly regioselective palladium(II)-catalyzed reaction for the fluorination of cyclic vinyl triflates. High regioselectivity was realized through the development of a new biaryl phosphine ligand (**L8**) and the serendipitous discovery of triethyl(trifluoromethyl)silane ($TESCF_3$) as an additive.

We commenced our study using 4-phenylcyclohexenyl triflate (**1a**) as the model substrate (Table 1). Preliminary ligand evaluation showed that catalysts based on *t*-BuBrettPhos (**L1**), AdBrettPhos (**L2**), HGPhos (**L3**) or AlPhos (**L4**), which were effective ligands for the fluorination of aryl eletrophiles,[12a–c] provided low yields of the desired vinyl fluoride **2a** and a substantial amount of the undesired regioisomer **3a** (close to 1:1 ratio, entry 1–4). Replacing the 6-methoxyl group of the ligand with a methyl substituent (**L5** and **L6**) led to improved yields, indicating that ligand rigidity may be important in this transformation (entry 5–6).[13] After further evaluation of ligands possessing a trimethylmethoxy-substituted top ring (**L7** and **L8**),[14] a novel biarylphosphine ligand **L8** was found to provide **2a** in moderate combined yield (58%) though still with poor regioselectivity (1.8:1) (entry 7–8).

During our investigation of the palladium-catalyzed trifluoromethylation of vinyl sulfonates,[15b] we made the serendipitous discovery that the corresponding vinyl fluoride was formed as a side product with relatively high regioselectivity (6.3:1, Scheme 1). We hypothesized that the presence of trifluoromethylsilanes, which were used as CF_3^- sources in trifluoromethylation reactions, might be responsible for the improved regioselectivity of the fluorination process. Indeed, the use of $TMSCF_3$, $TESCF_3$ or $TIPSCF_3$ as substoichiometric additives (30 mol%) drastically improved the regioselectivity (34:1, 73:1, and 4.7:1, respectively) (Table 1, entry 9–11). Although catalyst based on **L6** and **L8** gave comparable results in the absence of the trifluoromethyl silane additive, the yield and regioselectivity obtained with **L8** were considerably higher when $TESCF_3$ (30 mol%) was added (entries 6, 8, 10 and 12). Finally, performing the reaction in 2-MeTHF at 90 °C with **L8** as the supporting ligand, along with a substoichiometric amount of $TESCF_3$ afforded the desired product **2a** in 74% yield with excellent regioselectivity (>99:1) (entry 13). In addition to this significant improvement in regioselectivity, the addition of the $TESCF_3$ additive also allowed the reaction to be conducted at a lower temperature (entry 13 vs. entry 14).

We subsequently examined the substrate scope using these optimized reaction conditions, and found this protocol to be applicable to the fluorination of a variety of 1,2-disubstituted cyclic vinyl triflates (Table 2). In addition, the fluorination of 1,2,2-trisubstituted vinyl triflates, for which regioisomer formation is not an issue,[12d] was possible with **L3** as the ligand and CsF as the fluoride source. $TESCF_3$ was not required for these processes. Interestingly, our new ligand (**L8**) developed for vinyl triflate **1a**, did not perform well for 1,2,2-trisubstituted vinyl triflates, which likely stems from its sterically encumbered nature.

1-Cyclohexenyl triflates with substituents at the 4- (**2a** and **2c**), 3- (**2e**) or 2- (**2b**) position were all excellent substrates (Table 2, $n = 1$). Benzofused (**2f**) and oxygen-containing six-membered cyclic triflates (**2g**) were compatible as well. Moreover, the method could be used to access fluorinated analogues of biologically active terpene and steroid derivatives (**2h**, **2i** and **2j**). In the case of **1j**, isomerization of the terminal double bond to the more thermodynamically stable internal position occurs under these reaction conditions.

In general, the fluorination of 1-cyclopentenyl triflates was more difficult, presumably due to the higher energy barrier for C-F reductive elimination from the respective palladium(II)

complex (Table 1, $n = 0$).[16] Thus, vinyl triflate **1k** without additional substitution on the double bond provided the desired cyclopentenyl fluoride in low yield. However, substrates possessing an additional substituent at the 2-position reacted efficiently to provide the corresponding cyclic vinyl fluorides in good to excellent yield (**2l**, **2m** and **2n**).

Although 1-cycloheptenyl triflate **1o** was fully consumed under these conditions, the fluorinated product was not obtained (Table 1, $n = 2$). GC/MS analysis of the crude reaction mixture indicated the formation of the corresponding alkyne or allene product, implying that the vinyl triflate starting material decomposed through β-hydrogen elimination. Consistent with this hypothesis, seven-membered cyclic vinyl triflates without β-hydrogen atoms were fluorinated in good yields (**2p**, **2q** and **2r**).

A variety of functional groups were tolerated in this transformation, including an acetal (**2d**), a nitrile (**2l**), a trifluoromethyl group (**2m**), an amide (**2n**) and a nitro group (**2r**). Heterocycles, including an indole (**2e**), a pyrimidine (**2q**) and a pyridine (**2p**) were also compatible.

The fluorination of acyclic 1-substituted vinyl triflates **1s** was unsuccessful, presumably as a result of competitive β-hydrogen elimination. More highly substituted vinyl triflates without β-alkenyl hydrogen atoms were successfully fluorinated (**1t** and **1u**).

The formation of side-products is an important factor affecting the synthetic utility of a fluorination reaction due to the challenges often encountered during the separation of fluorinated products from side-products with similar physical properties. Thus, careful analysis of the crude reaction mixture in this fluorination protocol was performed. Generally speaking, the corresponding reduction product was formed in less than 0.5% in all cases while the corresponding vinyl chloride was formed in 2.5%–0.5%. Although the entries in Table 2 could all be purified to >99.5% purity by column chromatography, conditions that would avoid the formation of the vinyl chloride side product would significantly simplify purification of the desired vinyl fluoride.

Towards this goal, the use of precatalysts of the form [(1,5-cyclooctadiene)$(LPd)_2$] that activate with minimal generation of reactive or other undesired byproducts were investigated. In the case of vinyl triflates for which regioisomer formation is not a concern, the use of the **L3**-derived precatalysts of this type in place of **L3**/[(cinnamyl)$PdCl]_2$ was found to provide comparable or superior yields without formation of vinyl chloride (Table 4, **2m** and **2p**). However, because of the large size of **L8**, the corresponding precatalysts based on **L8** could not be prepared. Therefore, for fluorination reactions employing **L8**, a modified reaction protocol employing a “sacrificial” vinyl triflate was developed. We found that preheating the reaction mixture with cyclohexenyl triflate (**2v**) (50 mol%) as the “sacrificial” vinyl triflate for one hour prior to the addition of the vinyl triflate starting material led to improved yields (Table 4, **2a**, **2f**, **2i**). The volatile fluorination and chlorination products derived from **2v** could be easily removed *in vacuo*. Using this protocol, the corresponding vinyl chloride coming from the vinyl triflate starting material was not detected by GC analysis of the crude reaction mixtures. Moreover, yields obtained using this protocol were generally higher than those obtained previously.

In summary, we have developed a method for palladium-catalyzed fluorination of vinyl triflates for the synthesis of cyclic fluoroalkenes. High levels of regiochemical fidelity of this reaction were achieved by employing a new biarylphosphine ligand **L8** and $TESCF_3$ as a crucial additive. The reaction exhibited good functional group tolerance and proceeded efficiently for five, six and seven-membered vinyl triflate substrates, as well as a few acyclic substrates. As the synthesis of cyclic vinyl fluorides using existing methods is problematic due to the lack of availability of starting materials and limited functional group compatibility of the existing methods, our palladium-based protocol is complementary to these previously developed processes.[7m,7n,7o] The intriguing "$TESCF_3$ effect" has provided us with a new tool for addressing the problem of the formation of regioisomers in palladium-catalyzed fluorination reactions of vinyl triflates. Studies are undergoing to gain a detailed mechanistic understanding of this phenomenon.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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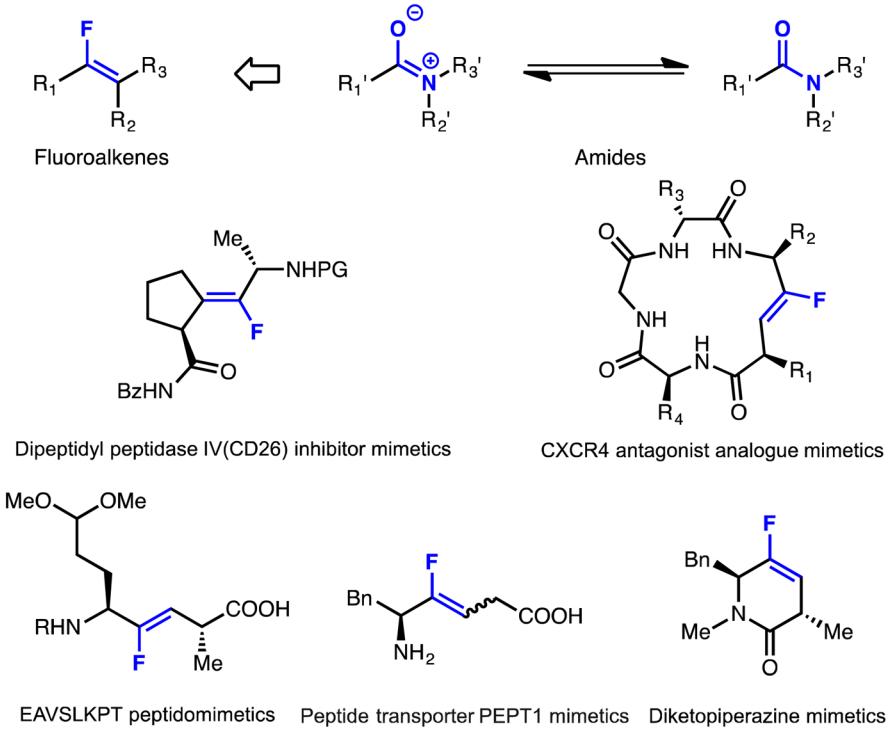
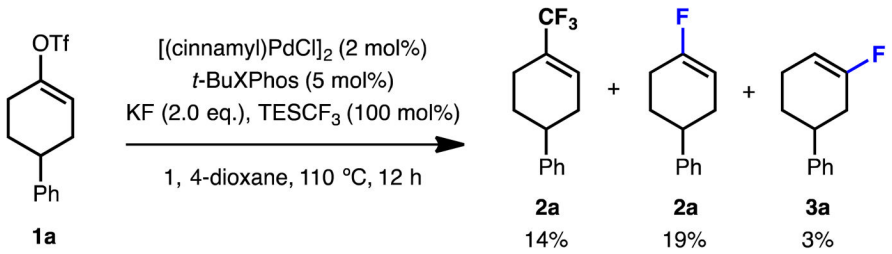


Figure 1.
Representative fluoroalkenes as peptidomimetics.

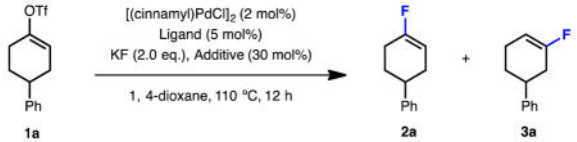


Scheme 1.

Fluorinated side products generated in the palladium-catalyzed trifluoromethylation reaction.

Table 1

Reaction optimization studies.



entry	ligand	additive	2a (%)	3a (%)	2a : 3a
1	**L1**		23	21	1.1 : 1
2	**L2**		18	18	1.0 : 1
3	**L3**		11	13	0.8 : 1
4	**L4**		19	19	1.0 : 1
5	**L5**		27	20	1.4 : 1
6	**L6**		37	19	1.9 : 1
7	**L7**		23	20	1.2 : 1
8	**L8**		37	21	1.8 : 1
9	**L8**	$TMSCF_3$	68	2	34 : 1
10	**L8**	$TESCF_3$	73	1.0	73 : 1
11	**L8**	$TIPSCF_3$	47	10	4.7 : 1
12	**L6**	$TESCF_3$	57	5.0	11 : 1
13[b]	**L8**	$TESCF_3$	74	0.4	>99 : 1
14[b]	**L8**		7	4	1.8 : 1

[a] Reactions were run at 0.1 mmol scale. Yields were determined by ^{19}F NMR analysis of the crude reaction mixture using 1-fluoronaphthalene as an internal standard.

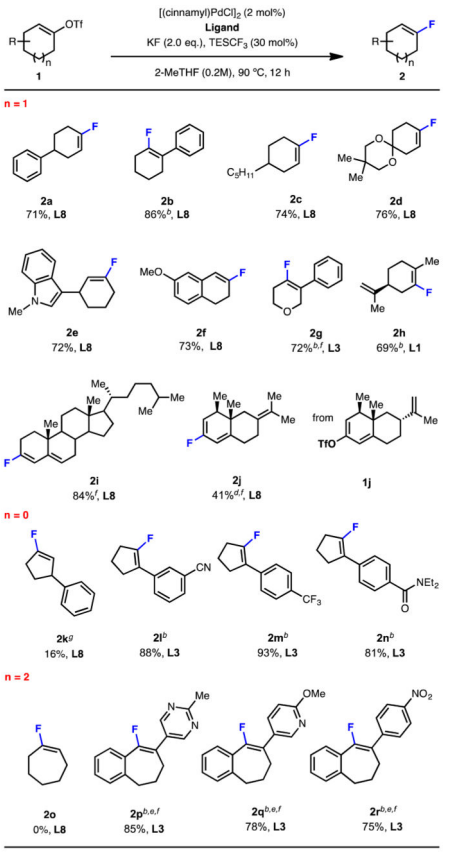
[b] 2-MeTHF, 90 °C.

L1: R^1 = OMe, R^2 = *t*-Bu, R^3 = *i*-Pr, R^4 = H (*t*-BuBrettPhos)
L2: R^1 = OMe, R^2 = Ad, R^3 = *i*-Pr, R^4 = H (AdBrettPhos)
L3: R^1 = OMe, R^2 = Ad, R^3 = *i*-Pr, R^4 = 4-*n*-BuPh (HGPhos)
L4: R^1 = H, R^2 = Ad, R^3 = *i*-Pr, R^4 = 2, 3, 5, 6-F_4-*n*-BuPh (AlPhos)
L5: R^1 = Me, R^2 = *t*-Bu, R^3 = *i*-Pr, R^4 = H
L6: R^1 = Me, R^2 = *t*-Bu, R^3 = Cy, R^4 = H

L7: R^4 = Ad, R^5 = Cy
L8: R^4 = *t*-Bu, R^5 = Cy

Table 2

Palladium-catalyzed fluorination of cyclic vinyl triflates.



[a] Isolated yields are reported as an average of two runs on a 1.0 mmol scale.

[b] Reaction conditions: [(cinnamyl)PdCl]$_2$ (2 mol%), ligand (5 mol%), CsF (2.0 eq.), 2-MeTHF, 90 °C, 12 h.

[c] *t*-BuBrettPhos as the ligand.

[d] In 1,4-dioxane.

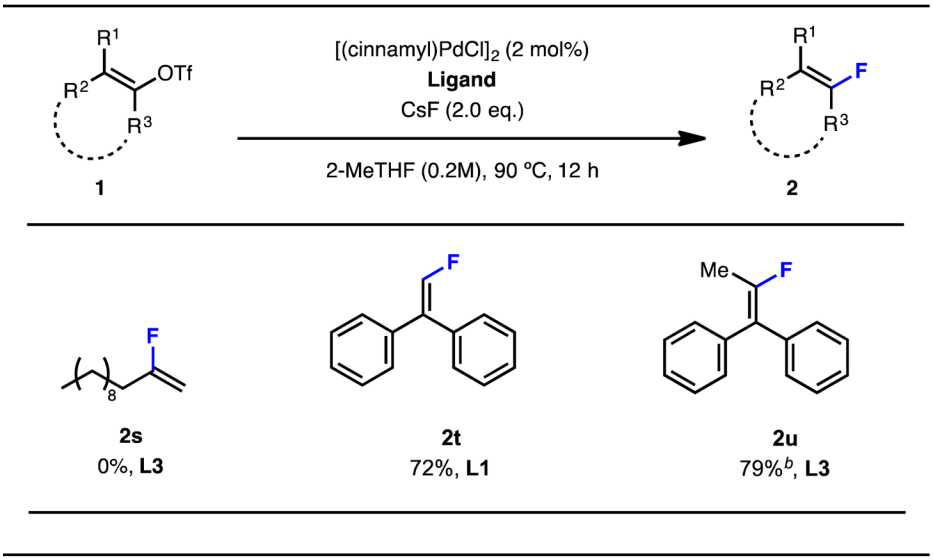
[e] In toluene.

[f] 110 °C.

[g] 130 °C.

Table 3

Palladium-catalyzed fluorination of six-membered vinyl triflates.

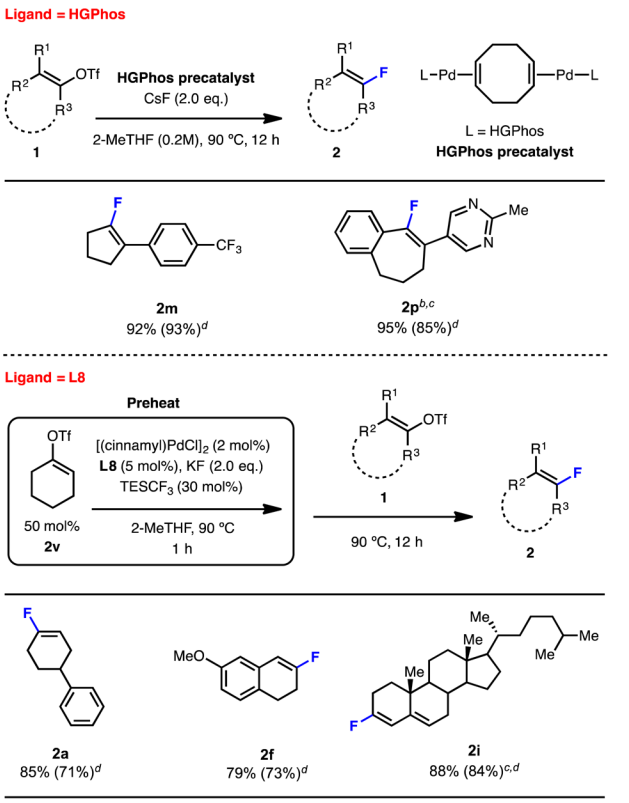


[a] Isolated yields are reported as an average of two runs on a 1.0 mmol scale.

[b] 110 °C.

Table 4

Modified fluorination reaction protocol without the generation of chlorination side products.



[a] Isolated yields are reported as an average of two runs on a 1.0 mmol scale.

[b] In toluene.

[c] 110 °C.

[d] Yield when conducted under previous reaction conditions.