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Palladium-Catalyzed Allylic C−H Fluorination

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Supporting Information

ABSTRACT: The first catalytic allylic C−H fluorination reaction using a nucleophilic fluoride source is reported. Under the influence of a Pd/Cr cocatalyst system, simple olefin substrates undergo fluorination with $Et_3N{\cdot}3HF$ in good yields with high branched:linear regioselectivity. The mild conditions and broad scope make this reaction a powerful alternative to established methods for the preparation of allylic fluorides from prefunctionalized substrates.

Substituting a C−F bond for a C−H bond in a target molecule has emerged as a powerful strategy for the optimization of pharmaceuticals, agrochemicals, and performance materials.[1] Accordingly, methods that enable access to these valuable fluorinated structures by the direct transformation of a C−H bond to a C−F bond are of high synthetic value. The last 10 years have witnessed notable advances in the development of such catalytic methods for C_{sp^2}−H fluorination,[2] but examples of catalytic fluorination of aliphatic C−H bonds have only recently emerged. In 2012, Sanford and co-workers reported a strategy relying on the use of a directing group for Pd-catalyzed nucleophilic fluorination of benzylic C−H bonds.[2a,3] Concurrent with this work, both Groves and Lectka described versatile radical C−H abstraction/fluorination methods for aliphatic and benzylic fluorination using Mn,[4,5] Cu,[6] and Fe[7] catalysts. Despite these important advances, numerous challenges remain, including the identification of methods that demonstrate unique selectivity, improved operational convenience, and expanded substrate scope. Herein we report a strategically distinct approach to aliphatic C−H fluorination: a Pd(II) catalyst is shown to enable the branched-selective synthesis of allylic fluorides from simple olefin substrates using an inexpensive nucleophilic fluoride source.

The allylic fluoride motif is featured in a range of medicinal and imaging agents and also serves as a versatile building block for the construction of numerous aliphatic fluorine-containing structures.[8] Synthetic methods for the preparation of allylic fluorides currently require substrate prefunctionalization (Figure 1). For example, our group,[9] Gouverneur and Brown,[10] Nguyen,[11] Wu,[12] and recently Liu[13] have demonstrated that allylic fluorides may be accessed through transition-metal-catalyzed fluorination of allylic halides, *p*-nitrobenzoates, trichloroacetimidates, and phosphorothioates. Although these methods exhibit high levels of reactivity, functional group compatibility, and regioselectivity, they suffer from limitations due to poor atom economy and multistep preparation of substrates.

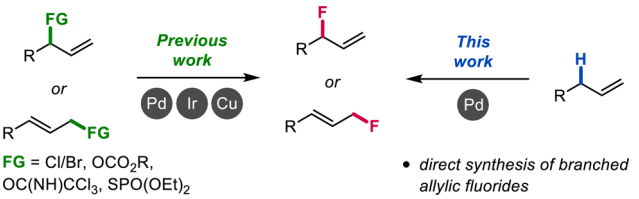

Figure 1. Catalytic synthesis of allylic fluorides by functional group exchange or C−H activation approaches.

In an effort to identify a synthesis of allylic fluorides that would obviate the need for substrate prefunctionalization, we considered whether allylic fluorination could proceed instead by C−H activation of simple olefin substrates. We recognized that the electrophilic Pd(II)−sulfoxide catalyst system developed by White and co-workers for allylic C−H functionalization might provide such a platform[14] while retaining the high functional group tolerance and selectivity of the programmed methods. This system has proven remarkably general for allylic C−H functionalization, enabling allylic esterification, amination, alkylation, Heck addition, and dehydrogenation of terminal olefins via a π-allylpalladium intermediate.[15] However, it was apparent at the outset of our studies that the adaptation to allylic fluorination would present several challenges. First, although phosphine ligands were necessary to impart reactivity and selectivity in the conversion of prefunctionalized substrates to allylic fluorides in the previously described methodologies using Pd catalysts, these and other Lewis basic ligands are typically not compatible with Pd(II)-mediated electrophilic C−H cleavage.[16] Furthermore, many fluoride sources show strong Lewis basicity that might interfere with C−H activation or lead to elimination rather than nucleophilic substitution at the π-allylpalladium intermediate. It has also been shown that under certain conditions, the targeted allylic fluoride products can themselves undergo reaction with palladium(0) to form π-allyl complexes, thereby leading to product decomposition or isomerization.[17]

With these considerations in mind, our investigation began with an examination of the allylic C−H fluorination of 1-decene (**1**) using the White catalyst, benzoquinone (BQ) as an oxidant, and a series of fluoride sources (Table 1). In our previously described Pd-catalyzed enantio- and regioselective allylic fluorination of allylic halides, AgF was uniquely effective as a fluoride source;[9] however, its use for allylic C−H fluorination of **1** resulted in no detectable product formation (entry 1). Reactions with alkali-metal fluorides such as potassium fluoride

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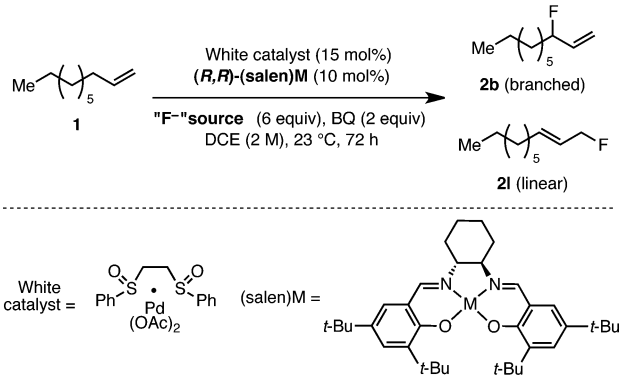
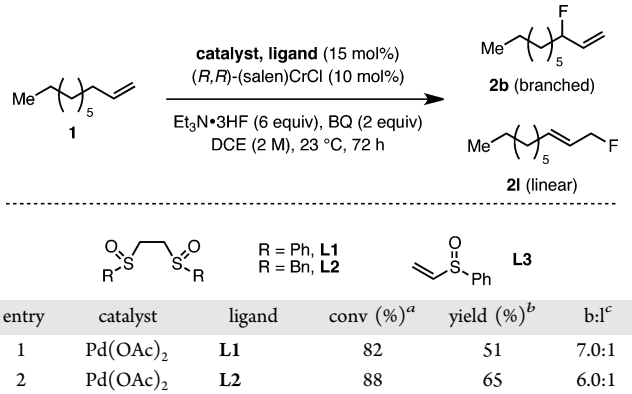
Table 1. Fluoride Source and Cocatalyst Optimization



entry	"F⁻" source	M	conv (%)[a]	yield (%)[b]	b:l[c]
1	AgF	–	100	0	nd[d]
2[e]	KF	–	12	0	nd[d]
3	KHF_2	–	40	0	nd[d]
4	Pyr·9HF	–	81	0	nd[d]
5	$Et_3N{\cdot}3HF$	–	38	33	6.6:1
6	**$Et_3N{\cdot}3HF$**	**CrCl**	**82**	**51**	**7.0:1**
7	$Et_3N{\cdot}3HF$	CoCl	37	6	7.9:1
8	$Et_3N{\cdot}3HF$	MnCl	35	14	7.2:1
9	$Et_3N{\cdot}3HF$	AlCl	33	8	8.2:1
10	$Et_3N{\cdot}3HF$	CrF	47	28	5.3:1

[a]Determined by GC using dodecane as an internal standard for reactions carried out on a 0.2 mmol scale in a polypropylene vial. [b]Combined GC yields of **2b** and **2l**. [c]Based on GC analysis of the unpurified reaction mixture and not corrected for small response variations. [d]Not determined. [e]Reaction carried out at 1 M.

Table 2. Catalyst and Ligand Optimization



entry	catalyst	ligand	conv (%)[a]	yield (%)[b]	b:l[c]
1	$Pd(OAc)_2$	**L1**	82	51	7.0:1
2	$Pd(OAc)_2$	**L2**	88	65	6.0:1
3	$Pd(OAc)_2$	**L3**[d]	23	9	6.6:1
4	$Pd(OAc)_2$	DMSO[d]	38	1	nd[e]
5	$Pd(TFA)_2$	**L1**	96	58	7.4:1
6	**$Pd(TFA)_2$**	**L2**	**94**	**70**	**7.3:1**
7[f]	$Pd(TFA)_2$	**L2**	33	0	nd[e]
8	–	**L2**	7	0	nd[e]

[a]Determined by GC using dodecane as an internal standard for reactions carried out on a 0.2 mmol scale in a polypropylene vial. [b]Combined GC yields of **2b** and **2l**. [c]Based on GC analysis of the unpurified reaction mixture and not corrected for small response variations. [d]1.4 equiv. [e]Not determined. [f]Reaction carried out without BQ.

(KF) were similarly unsuccessful, instead affording byproducts from elimination or acetoxylation of the allylpalladium intermediate (entry 2). Since nucleophiles bearing acidic X–H bonds have been most successful for the Pd(II)–sulfoxide catalyst system, we next turned our attention to the evaluation of HF-containing fluoride reagents. While KHF_2 and Olah's reagent[18] were ineffective (entries 3 and 4), $Et_3N{\cdot}3HF$ provided allylic fluoride **2** in 33% yield with high branched:linear (b:l) selectivity (6.6:1) and minimal formation of these byproducts (entry 5). This fluoride source has the benefit of being inexpensive and commercially available, but to the best of our knowledge, it has never been employed for Pd-catalyzed fluorinations.

In an effort to improve the yield of this promising result, we turned our attention to the inclusion of Lewis acid cocatalysts, a strategy that was previously delineated by White and coworkers for the purpose of activating the putative π-allylpalladium–BQ intermediate toward nucleophilic functionalization.[19] A variety of metal–salen complexes were evaluated (Table 1, entries 6–9). Most notably, addition of catalytic amounts of (salen)CrCl (10 mol %) gave the desired fluorinated product **2** in an enhanced 51% yield while maintaining high levels of regioselectivity (entry 6). Our observation that (salen)CrF was less reactive than (salen)CrCl (entry 10) suggests that this cocatalyst does not play the role of a fluoride delivery agent.[20]

Further optimization studies evaluated the influence of the sulfoxide ligand and the identity of the Pd precatalyst on the reaction outcome using cocatalytic (salen)CrCl (Table 2). Whereas monosulfoxide ligands provided poorer conversions (entries 3 and 4), the bis(benzyl sulfoxide) ligand **L2**[14,21] induced allylic C–H fluorination of **1** in improved yield (entry 2). Additionally, a brief survey of Pd(II) catalysts revealed that $Pd(TFA)_2$ was superior to $Pd(OAc)_2$, affording **2** in 70% yield with 7.3:1 b:l selectivity (entry 6). On the other hand, changing the solvent and reaction temperature had no beneficial impact on the reaction yield. Notably, control experiments determined that allylic fluoride **2** is not produced in the absence of the Pd(II) catalyst or BQ (entries 7 and 8).[22]

Having established conditions suitable for the allylic fluorination of 1-decene, we proceeded to examine the substrate scope of the methodology (Table 3). Olefins bearing a broad range of oxygen- and nitrogen-containing functional groups were found to be competent substrates, delivering products with benzyl ethers (**3**), esters (**4**), amides (**5**), and phthalimides (**6**) (entries 2–5). Tolerance of the method to N-containing heterocycles such as pyridines (**7**) and acidic heteroatom–H bonds (**8** and **9**) is particularly significant given the importance of these motifs in medicinal chemistry (entries 6–8). An alkyl bromide-containing olefin was also well-tolerated, underscoring the mildness of the nucleophilic fluorination conditions (entry 9). In addition, fluorination of arene- and alkyne-containing olefins afforded allylic fluorides **11** and **12** as the exclusive fluorine-containing products in 64 and 47% yield, respectively (entries 10 and 11); these findings are noteworthy because chemoselectivity for allylic over benzylic or propargylic fluorination is not observed in the other reported methods for aliphatic C–H fluorination. An additional feature that distinguishes this C–H fluorination is that the reactions can be conducted under air using wet solvents.

Overall, the scope and accompanying regioselectivity of the method compare favorably to those described for alternative syntheses of allylic fluorides. The yields are modest but synthetically useful, especially given the accessibility of the starting materials. For example, whereas the terminal olefin precursor to **10** in Table 3 is commercially available,

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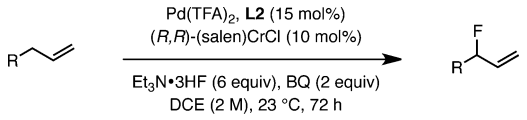
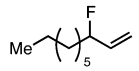
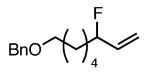
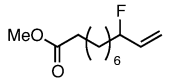
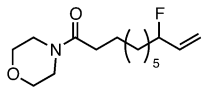
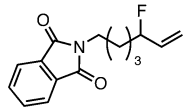
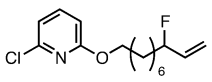
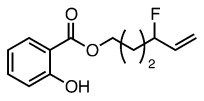
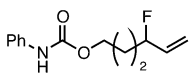
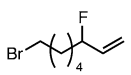
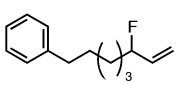
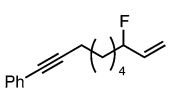
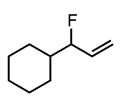
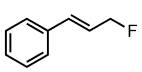
Table 3. Scope of the Allylic C−H Fluorination



entry	major product		yield (%)[a]	b:l[b]
1		**2**	56	7.0:1
2		**3**	59	6.9:1
3		**4**	53	7.5:1
4		**5**	53	7.0:1
5		**6**	51	6.7:1
6		**7**	54	7.8:1
7		**8**	68	7.4:1
8		**9**	67	6.5:1
9		**10**	54	7.0:1
10		**11**	64	7.0:1
11		**12**	47	7.5:1
12[c]		**13**	33[d]	2.0:1
13		**14**	16[d]	-
14		**15**	18[d]	1:20

[a]Combined isolated yields of branched and linear isomers for reactions carried out on a 0.4 mmol scale in a polypropylene vial (averages of two runs). [b]Based on ^{19}F NMR analyses of the purified products (averages of two runs). [c]Reaction conducted in dioxane. [d]Determined by ^{19}F NMR analysis using fluorobenzene as a quantitative internal standard.

preparation of the allylic chloride substrate previously necessary to access this allylic fluoride requires seven steps.[9] Moreover, the C−H fluorinations proceed to complete conversion with minimal diene generation, enabling straightforward product isolation.[23] Nevertheless, certain limitations were identified: cyclic alkenes and olefins with substitution at the homoallylic position, such as allylcyclohexane, were found to undergo fluorination with significantly depressed yields (33% and 16%; entries 12 and 13). Furthermore, allylbenzene proved to be a poor substrate, providing exclusively the linear product **15** in 18% yield (entry 14);[24] the reported instability of **15** at high concentrations may explain this result.[25]

C−H activation approaches can be particularly useful when applied to the direct functionalization of bioactive natural products or drug candidates. In these targets, allylic C−H bonds can be metabolic hotspots;[26] since fluorination is a common strategy used in medicinal and agrochemistry to block such sites, a direct allylic fluorination may prove quite useful. To demonstrate this potential, we subjected the complex steroid scaffold **16** to the Pd-catalyzed allylic C−H fluorination conditions (Figure 2). In the event, allylic fluoride **17** was isolated from this reaction in 59% yield with good regioselectivity (b:l = 8.0:1).[27]

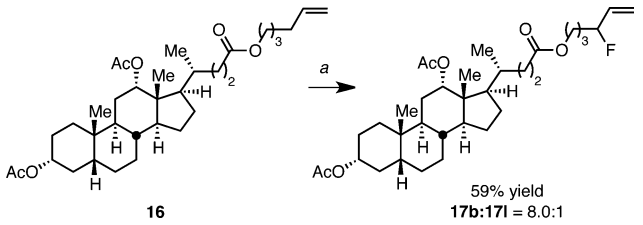


Figure 2. Late-stage functionalization of a natural product derivative via direct allylic C−H fluorination. Conditions: (a) $Pd(TFA)_2$ (15 mol %), **L2** (15 mol %), [(*R*,*R*)-salen]CrCl (10 mol %), $Et_3N{\cdot}3HF$ (6.0 equiv), BQ (2.0 equiv), DCE (2 M), 23 °C, 72 h.

In conclusion, we have demonstrated the first example of a direct allylic C−H fluorination reaction using a simple nucleophilic fluoride reagent. The methodology furnishes a diverse collection of synthetically valuable fluorinated products under mild and operationally simple conditions. Furthermore, in comparison with reported methods for C−H fluorination, this approach exhibits chemoselective allylic functionalization. Our future investigations will focus on elucidating the mechanism of this reaction and rendering it enantioselective.[28]

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, additional reaction optimization, and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(28) Allylic fluoride **3** was obtained as a racemic mixture under the optimized conditions.