Communication

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Highly Selective Pd-Catalyzed Intermolecular Fluorosulfonylation of Styrenes

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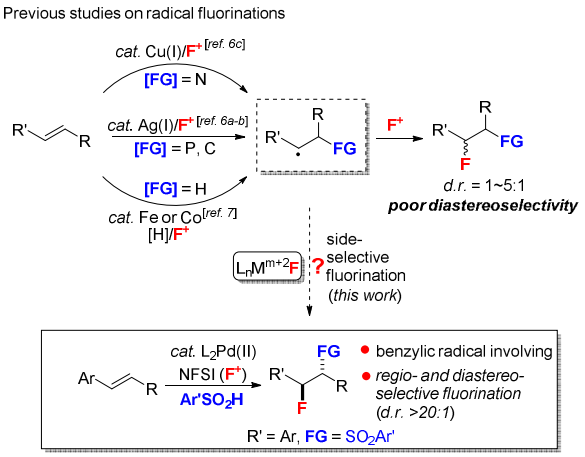
Supporting Information

ABSTRACT: A novel palladium-catalyzed intermolecular regio- and diastereoselective fluorosulfonylation of styrenes has been developed under mild conditions. This reaction exhibits a wide range of functional-group tolerance in styrenes as well as arylsulfinic acids to afford various *β*-fluoro sulfones. Preliminary mechanistic study reveals an unusual mechanism, in which a high-valent $L_2Pd^{III}F$ species side-selectively reacts with benzylic carbon radical to deliver C-F bond. This pathway is distinct from previously reported radical fluorination reaction.

As basic structural moieties, sulfones are widely existed in bioactive natural products and pharmaceuticals.[1] Representative compounds, such as Eletriptan and [2H]-SB-3CT, have been used for treatment of migraine headaches, or as a potent non-selective MMP-2 and MMP-9 inhibitor to inhibit human prostate cancer growth.[2] Therefore, efficient incorporation of sulfonyl group into organic molecules has drawn much attention.[3] Recently, the flourishing organofluorine chemistry and its widespread application in scientific research and industry have demanded more synthetic approaches towards the C-F bond formation.[4] We speculated that, if both fluorine atom and sulfonyl group can be simultaneously installed into the C=C bond, a variety of *β*-fluorinated sulfones could be easily accessed from simple alkenes.

Recently, radical fluorination has been explored to achieve the efficient fluorination of alkanes.[5] This strategy was also applied for the difunctionalization of alkenes (Scheme 1a).[6] For instance, Li and coworkers disclosed a powerful silver catalytic system for the efficient fluorination of unactivated alkenes by using SelectFluor as fluorine atom donor.[6a-b] Zhang and coworkers reported a Cu-catalyzed aminofluorination of styrenes using NFSI as both fluorine and nitrogen source.[6c] With respect to the radical fluorination process, hydrofluorination of alkenes with Fe and Co catalyst were developed by Boger[7a] and Hiroya[7b] respectively. All of these reactions exhibited excellent regioselectivity, however, *poor diastereoselectivity was obtained due to the nature of carbon radical intermediate*. To overcome these limitations, we hypothesized that, if carbon radical could side-selectively react with a high-valent metal fluoride complex, the highly diastereoselective fluorination might be expected. Recently, Groves demonstrated that the high-valent $(TMP)Mn^{V}F$ species can react with alkyl radical to generate C-F bond with good diastereoselectivity (around 10:1).[8] Herein, we reported the first intermolecular *anti*-specific fluorosulfonylation of styrenes using palladium catalyst to deliver vicinal F-substituted sulfones

Scheme 1. Metal-catalyzed Radical Fluorination of Alkenes.



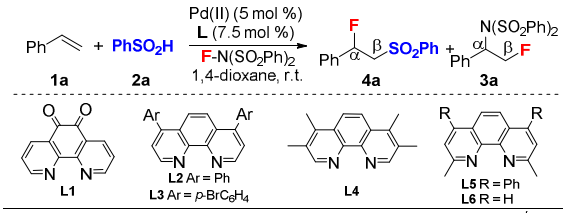
with excellent regio- and diastereoselectivity, in which a benzylic carbon radical was involved for the C-F bond formation but not via previous radical fluorination process.

With our continuing interest in transition metal-catalyzed difunctionalization of alkenes containing fluorination,[9] we recently reported a Pd-catalyzed intermolecular fluoroamination and fluoroesterification of styrenes.[10] During the studies, when CF_3CO_2H was replaced by phenylsulfinic acid as an additive under standard condition with $[Pd(O_2CCF_3)_2$/**L1**$]$,[10b] the reaction afforded fluoroamination product **3a** in low yield (entry 1 in Table 1). However, when ligand **L1** was switched to electron-rich phenanthroline (Phen) and **L2**, the reaction gave a major fluorosulfonylation product **4a** with an opposite regioselectivity as **3a** (entries 2-3). Different with previous fluoropalladation pathway,[10] we believed that the opposite regioselectivity might be stemed from the property of $ArSO_2H$, which can be easily oxidized to give active $ArSO_2$ radical species, resulting rapid addition to styrenes.

Further screening of palladium catalysts revealed that other Pd(II) catalysts, such as $Pd(OAc)_2$, $PdCl_2$ and $Pd(acac)_2$, gave comparable or worse yields than $Pd(O_2CCF_3)_2$ (entries 4-6). However, cationic palladium catalysts, such as $[Pd(CH_3CN)_4]X_2$ (X = BF_4 and OTf), were more reactive to afford product **4a** in good yields, and formation of the side product **3a** was completely inhibited (entries 7-8). Encouraged by these results, more bidentate nitrogen-containing ligands were tested, and phenanthroline type ligands **L3** and **L4** exhibited a slightly better

reactivity (entries 9-10). However, steric hindered ligands **L5-L6** bearing *ortho*-methyl group were ineffective (entries 11-12). Compared with dioxane, reaction carried out in THF provided a better reproducible result (entry 13). Finally, no reaction ocurred in the absence of palladium catalyst or ligand (entries 14-15). Notably, the reaction also afforded small amount of side products $PhSO_2F$ and β-sulfonylstyrene.

Table 1. Optimization of the Reaction Condition.[a]



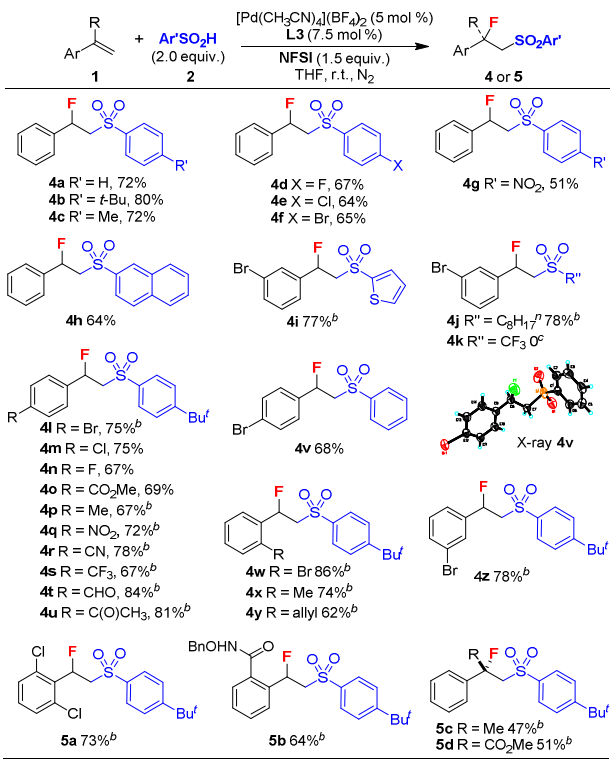
Entry	palladium catalyst	Ligand	Yield (%)[b] 4a	3a
1	$Pd(OCCF_3)_2$	**L1**	0	20
2	$Pd(OCCF_3)_2$	**Phen**	18	3
3	$Pd(OCCF_3)_2$	**L2**	36	7
4	$Pd(OAc)_2$	**L2**	33	3
5	$PdCl_2$	**L2**	0	0
6	$Pd(acac)_2$	**L2**	24	2
7	$[Pd(CH_3CN)_4](BF_4)_2$	**L2**	69	0
8	$[Pd(CH_3CN)_4](OTf)_2$	**L2**	65	0
9	$[Pd(CH_3CN)_4](BF_4)_2$	**L3**	73	0
10	$[Pd(CH_3CN)_4](BF_4)_2$	**L4**	72	0
11	$[Pd(CH_3CN)_4](BF_4)_2$	**L5**	0	0
12	$[Pd(CH_3CN)_4](BF_4)_2$	**L6**	0	0
13[c]	**$[Pd(CH_3CN)_4](BF_4)_2$**	**L3**	**75**	**0**
14	--	**L3**	0	0
15	$[Pd(CH_3CN)_4](BF_4)_2$	**--**	0	0

[a] All reactions were conducted in 0.2 mmol. [b] ^{19}F NMR yield with $PhCF_3$ as internal standard. [c] THF as solvent. Phen = 1,10-phenanthroline.

With the optimized condition in hand, the scope of sulfinic acids was investigated**.** As shown in Table 2, gratifyingly, a series of arylsulfinic acids bearing both electron-donating groups (R = ^{t}Bu, Me) and electron-withdrawing groups (R = F, Cl, Br, NO_2) were compatible to the reaction condition providing the desired products **4b-4g** in satisfactory yields. However, electron-rich arylsulfinic acid presented higher reactivity than electron-poor substrates. Moreover, 2-naphthylsulfinic acid was also effective to give the corresponding product **4h** (64%). Additionally, thiophenyl sulfinic acid (for **4i**) and aliphatic sulfinic acid (for **4j**) were also suitable for this reaction. Unfortunately, combination of CF_3SO_2Na and HOAc failed to generate product **4k**. Subsequently, a range of styrenes were surveyed under standard reaction condition. Both electron-rich and electron-poor styrenes were viable to produce **4l-5b** in good yields. Most importantly, a series of functional groups, such as halides, ester, aldehyde, ketone, amide, nitrile, nitro, and CF_3, were compatible for the reaction condition. Notably, the allyl group in styrene also survived to give product **4y** in 62% yield. Finally, 1,1-disubstituted styrenes were also tested, and these substrates had moderate reactivity to give desired products **5c-5d** in satisfactory yields. However, unactivated substrate 1-octene was ineffective, and only trace amount of the desired product was detected.

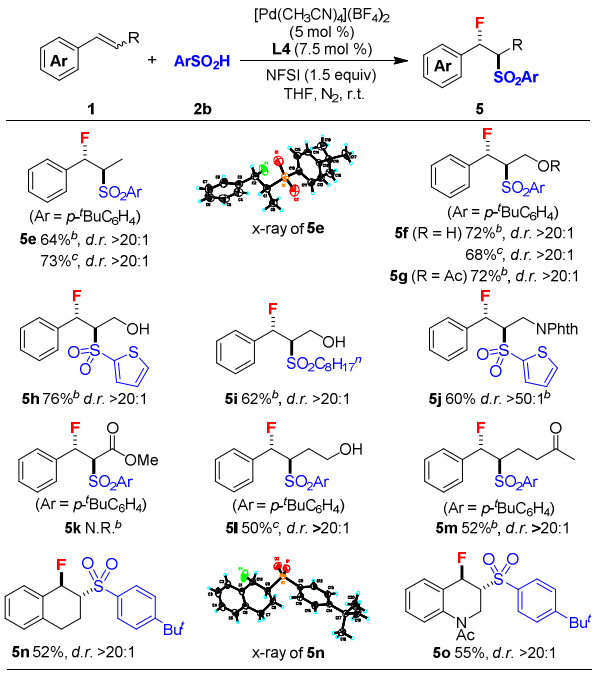
Next, we turned our attention to more challenging internal alkenes. *E*- and *Z*-(β)- methyl styrenes were initially surveyed and both reactions proceeded smoothly to give *anti*-specific fluorosulfonylation product **5e** in good yields with excellent diastereoselectivity, which is obviously distinct from previous

Table 2. Substrate Scope.[a]



[a] Reaction condition: **1** (0.20 mmol), **2** (0.40 mmol), NFSI (0.30 mmol), [Pd] (5 mol%), **L3** (7.5 mol%) in THF (1 mL) under N_2 at r.t., isolated yield (average of two runs). [b] **L4** instead of **L3**; [c]Combination of CF_3SO_2Na and HOAc.

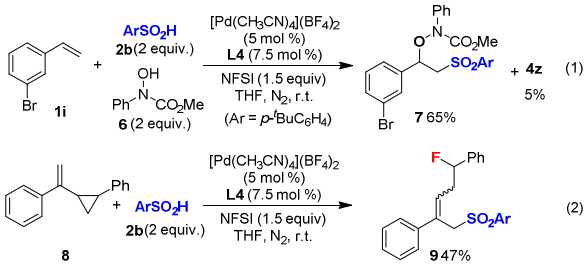
Table 3. The Fluorosulfonylation of Internal Alkenes.[a]



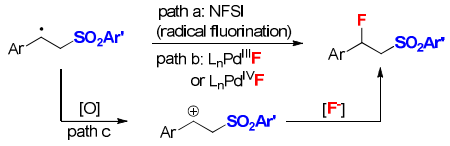
[a] Reaction condition: **1** (0.20 mmol), **2** (0.40 mmol), NFSI (0.30 mmol), catalyst (5 mol%), **L4** (7.5 mol%) in THF (1 mL) at r.t. under N_2; isolated yield (average of two runs). [b] From *E*-substrate. [c] From *Z*-substrate.

radical fluorination.[11] Furthermore, similar results were obtained in the reactions of *E*- and *Z*-cinnamyl alcohol to deliver product *anti*-**5f** efficiently with an intact hydroxyl group. In addition, cinnamyl alcohol, acetate and imide were also suitable to react with various sulfinic acids to produce *anti*-**5g-5j** in good yields. In

contrast, electron-deficient cinnamyl ester was ineffective toward the fluorosulfonylation reaction. Furthermore, the reaction with homoallylic alcohol and homoallylic ketone also provided *anti*-**5l** and *anti*-**5m** in moderate yields with excellent *d.r.* ratio. Finally, the cyclic alkene substrates were studied, and we are delighted to find that the desired products *anti*-**5n** and *anti*-**5o** could be synthesized efficiently with high diastereoselectivity in satisfactory yields. The configurations of products **5e** and **5n** were confirmed by single crystal X-ray crystallography.[12]



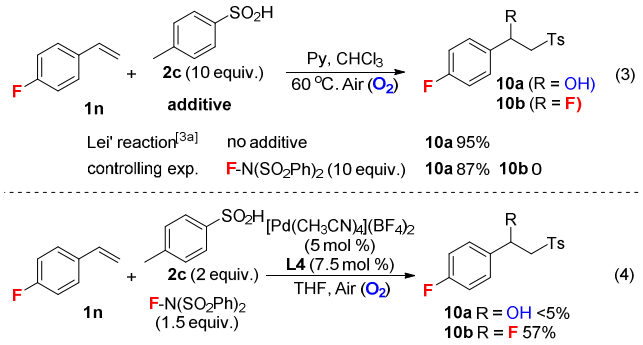
As mentioned above, single isomers *anti*-**5e** and *anti*-**5f** were obtained from the reactions of *Z*- and *E*-styrenes (Table 3), which reveals the reaction should involve a benzylic radical or carbon cation intermediate. To test the possibility of radical intermediate, compound **6** was introduced to the standard reaction condition as a radical scavenger. The fluorosulfonylation reaction was significantly suppressed. Instead, sulfonyloxygenation product **7** was obtained as major product in 65% yield (eq 1). In addition, when the radical clock substrate **8** was treated under standard reaction condition, the cyclopropyl group was completely opened to give product **9** (eq 2). These observations implied that *the reaction could involve a benzylic radical species*. Based on above analysis, there are three scenarios to address the final C-F bond formation (Scheme 2): (1) a radical pathway involving a carbon radical to attack $\mathbf{F}^+$ reagent NFSI (path a); (2) a high-valent palladium fluoride involved as the electrophilic fluorine reagent to react with benzylic radical (path b); (3) a benzylic carbon cation involved as key species to react with F^- to give C-F bond (path c).



Scheme 2. The possible mechanism for C-F bond formation.

In order to differentiate these three possibilities, the electronic effect of styrenes was further evaluated under standard condition. A much small Hammett ρ-value -0.029 (see the SI) was observed, which implied that the carbon cation pathway (path c) is less likely.

Lei and coworkers recently proved that a benzylic radical intermediate can be trapped by dioxygen to provide β-hydroxysulfones (eq 3).[3a] We hypothesized that, if the radical fluorination process was responsible for the C-F bond formation in current transformation (path a),[5] addition of extraneous NFSI to Lei's reaction should also afford the fluorosulfonylation product. However, the reaction only afforded oxygenation product **10a**, but without fluorination product **10b** (eq 3). This result addressed that either path a is not involved, or trapping of benzylic radical by O_2 is much faster than NFSI. If the latter is true, the fluorosulfonylation reaction should be inhibited in the presence of O_2. In fact, the fluorosulfonylation of styrene under aerobic condition did afford product **10b** in 57% yield, combined with only trace amount of product **10a** (eq 4), which argues against this possibility. In addition, the classic free radical fluorination process generally exhibits a poor diastereoselectivity (range from 1:1 to 4:1).[6,7] The excellent *d.r.* ratio in current reaction also ruled out the possibility of the radical fluorination pathway.



In order to gain further insights on the mechanism, the catalytic reaction was monitored by ESI-MS spectroscopy. We are delighted to find that two signals at *m/z* 289 and 446.5, corresponding to the mass of $[(\mathbf{L4})_2Pd]^{2+}$ and $[(\mathbf{L4})_2Pd(F)N(SO_2Ph)_2]^{2+}$, were detected.[12] Furthermore, the reaction rate was highly dependent on the ratio of **L4** and Pd catalyst (range from 1:1 to 4:1). In addition, $[(\mathbf{L4})_2Pd]^{2+}(OTf)_2$ was also an efficient catalyst,[13] and the reaction gave the identical rate with the catalyst of **Pd**:**L4** = 1:2 (Figure 1, left). Thus, we believed that cationic $[(\mathbf{L4})_2Pd]^{2+}$ should be the catalytically active species, thus Pd catalysts having coordinative X-type ligands (OAc, Cl) may impede the formation of such active species, meanwhile **L5-L6** bearing *ortho*-methyl group also prevent the formation of bis-bidentate Pd species $[(\mathbf{L})_2Pd]^{2+}$.

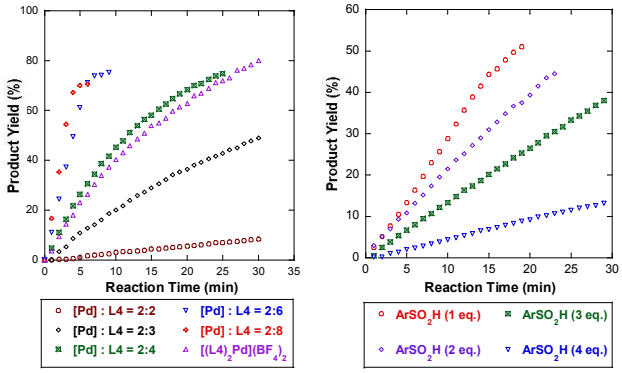


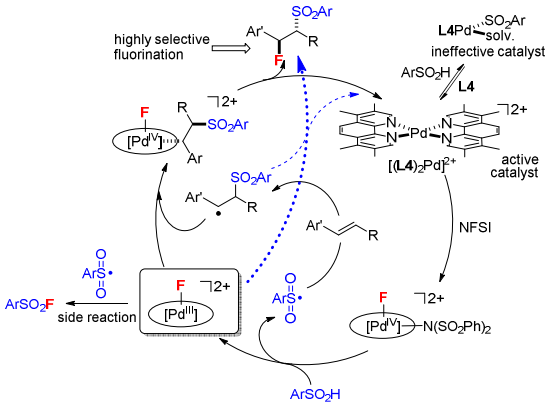
Figure 1. The effect on the reaction of **1n** and $ArSO_2H$ (Ar = ^{t}BuC$_6$H$_4$): Left, **L4**/[Pd] ratio effect, [Pd] = $[Pd(CH_3CN)_4](BF_4)_2$ (2 mol %), **L4** (2-8 mol%); Right, $[ArSO_2H]$ effect.

Further kinetic studies exhibited a first order dependence on the concentration of $[(\mathbf{L4})_2Pd]^{2+}(OTf)_2$ and NFSI, and zeroth order dependence on the styrene (see the SI).[12] Surprisingly, the reaction rate was inverse dependence on the concentration of arylsulfinic acid (Figure 1, right). NMR studies clarified that $[(\mathbf{L4})_2Pd]^{2+}(OTf)_2$ catalyst could convert to ineffective $[(\mathbf{L4})Pd(SO_2Ar)_n]$ (n = 1 or 2) species and release ligand **L4** in the presence of $ArSO_2H$, but could be further regenerated in the presence of excess amount of ligand **L4** (see the SI). These

observations implied that the sulfonylpalladation of styrenes should not be involved in the catalytic cycle.

Based on above analysis, the proposed mechanism was illustrated in Scheme 3: the initial oxidation of cationic $[(\mathbf{L4})_2Pd]^{2+}$ by NFSI provided $[(\mathbf{L4})_2Pd(F)N(SO_2Ph)_2]^{2+}$, which could react with arylsulfinic acid via a SET process to generate $ArSO_2$ radical and $(\mathbf{L4})_2Pd^{III}F$ species.[14,15] The former could react with styrene to give benzylic radical species, which directly attack $Pd^{III}F$ complex to give the fluorination product (dash line). Alternatively, the benzylic radical could also be trapped by $Pd^{III}F$ complex to give alkyl-$Pd^{IV}F$ species, which undergoes direct reductive elimination to form C-F bond selectively (plain cycle). The first order on the [Pd] and NFSI revealed that the oxidation of palladium catalyst occurs as turn-over limiting step. For the C-F bond forming step, it is difficult to differentiate above two possible mechanisms at this stage. Compared to good diastereoselectivity (*d.r.* ~10:1) from high-valent $(TMP)Mn^{V}F$ species,[8] Governeur recently demonstrated that a tandem stereospecific *cis*-hydropalladation and direct reductive elimination of $Pd^{IV}(F)R$ complex for hydrofluorination of styrenes could dilever excellent diastereoselectivity (*d.r.* >20:1).[16,17] Thus, we though the current fluorosulfonylation reaction is more likely to involve a $(\mathbf{L4})_2Pd^{IV}(F)R$ species for highly selective fluorination, and the benzylic radical is possibly trapped by Pd^{III} species on the opposite side of sulfonyl group with high selectivity due to the steric hindrance of ligand **L4**.

Scheme 3. Proposed Mechanism.



In conclusion, we have developed a Pd-catalyzed *anti*-selective intermolecular fluorosulfonylation of styrenes. The reaction exhibits excellent regio- and diasteroselectivity to provide various vicinal fluorinated sulfone products. Preliminary mechanistic study reveals that the radical species is involved, but significantly different with previous radical fluorination process. Instead, the side-selectively combination of benzylic carbon radical with Pd^{III} complex and the direct reductive elimination of $L_2Pd^{IV}(F)R$ intermediate was proposed to address the high diastereoselectivity. We envisioned that this unusual pathway may be operational in other alkene difunctionalization reactions.

Supporting Information

Synthetic procedures, characterization and additional data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) For the internal substrates, ligand **L4** provided a better yield than **L3**. For product **5e,** 57% yield was given by **L3**, and 64% by **L4**.

(12) See the Supporting Information (SI) for detail.

(13) With $[(\mathbf{L4})_2Pd]^{2+}(OTf)_2$ (3 mol %) as catalyst, the reactions afforded product **4j** in 80% yield, **5g** in 65% yield (>20:1 *d.r.*) and **5h** in 60% yield (>20:1 *d.r.*). For more detail, see the SI.

(14) For the oxidation of L_2Pd^{II} by NFSI and from Pd^{IV} to Pd^{III} via SET process, see: a) Mazzotti, A. R.; Campbell, M. G.; Tang, P.; Murphy, J. M.; Ritter, T. *J. Am. Chem. Soc.* **2013**, *135*, 14012. b) Boursalian, G. B.; Ngai, M.-Y.; Hojczyk, K. N.; Ritter, T. *J. Am. Chem. Soc.* **2013**, *135*, 13278.

(15) In this reaction, the $ArSO_2$ radical is efficiently generated in the presence of palladium catalyst. For more discussions, see the SI.

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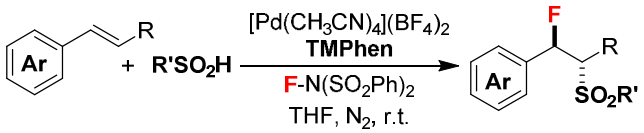

regioselective
anti-specific addition
Benzylic radical involved