JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Highly Selective Pd-Catalyzed Intermolecular Fluorosulfonylation of Styrenes

Zheliang Yuan,[†] Hao-Yang Wang,[‡] Xin Mu,[†] Pinhong Chen,[†] Yin-Long Guo,[‡] and Guosheng Liu*[,†]

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

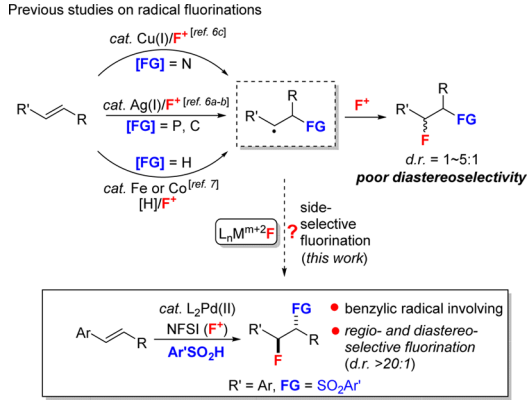
Supporting Information

ABSTRACT: A novel Pd-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 and 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 a benzylic carbon radical to deliver a C−F bond. This pathway is distinct from a previously reported radical fluorination reaction.

As basic structural moieties, sulfones widely exist 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 nonselective MMP-2 and MMP-9 inhibitor to inhibit human prostate cancer growth.[2] Therefore, efficient incorporation of a 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 toward the C−F bond formation.[4] We speculated that, if both the 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 1).[6] For instance, Li et al. disclosed a powerful Ag catalytic system for the efficient fluorination of unactivated alkenes by using SelectFluor as the fluorine atom donor.[6a,b] Zhang et al. reported a Cu-catalyzed aminofluorination of styrenes using NFSI as both the fluorine and nitrogen source.[6c] With respect to the radical fluorination process, hydrofluorination of alkenes with Fe and Co catalysts 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 the carbon radical intermediate*. To overcome these limitations, we hypothesized that, if the carbon radical could side-selectively react with a high-valent metal fluoride complex, the highly diastereoselective fluorination might be expected. Recently, Groves et al. demonstrated that the high-valent (TMP)$Mn^{V}F$ species can react with an alkyl radical to generate a C−F bond with good diastereoselectivity (~10:1).[8] Herein, we reported the first intermolecular *anti*-specific fluorosulfonylation of styrenes using a Pd catalyst to deliver vicinal F-substituted sulfones with excellent regio- and diastereoselectivity, in which a benzylic carbon radical was involved in the C−F bond formation but not via a previous radical fluorination process.

Scheme 1. Metal-Catalyzed Radical Fluorination of Alkenes



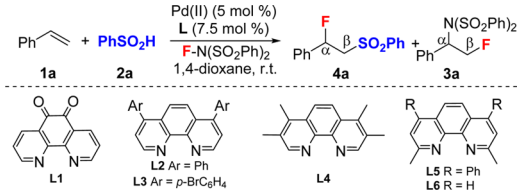
With our continuing interest in transition-metal-catalyzed difunctionalization of alkenes containing fluorination,[9] we recently reported a Pd-catalyzed intermolecular fluoroamination and -esterification of styrenes.[10] During the studies, when CF_3CO_2H was replaced by phenylsulfinic acid as an additive under standard conditions with [$Pd(O_2CCF_3)_2$/**L1**],[10b] the reaction afforded fluoroamination product **3a** in low yield (entry 1, 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 from the previous fluoropalladation pathway,[10] we believed that the opposite regioselectivity might stem from the property of $ArSO_2H$, which can be easily oxidized to give active $ArSO_2$ radical species, resulting in rapid addition to styrenes.

Further screening of Pd 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 Pd 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 N-containing ligands were tested, and phenanthroline

Received: December 26, 2014
Published: February 4, 2015

DOI: 10.1021/ja5131676
J. Am. Chem. Soc. 2015, 137, 2468−2471

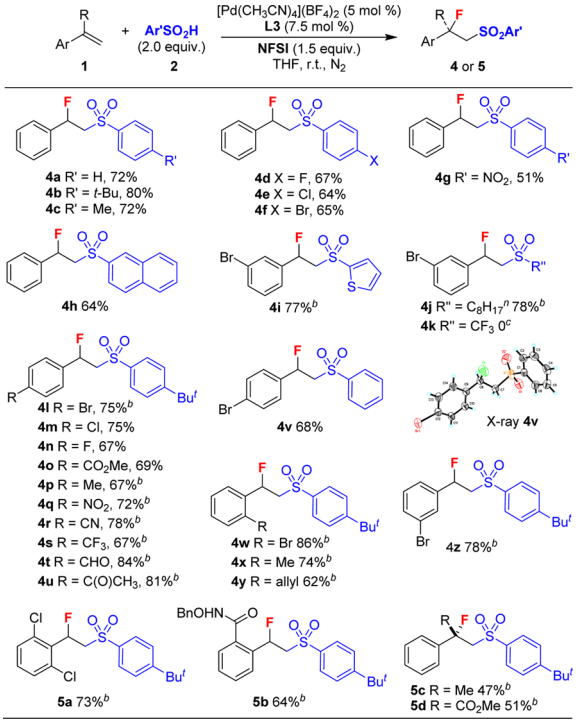
Table 1. Optimization of the Reaction Conditions[a]



entry	Pd 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 scale. [b]^{19}F NMR yield with $PhCF_3$ as internal standard. [c]THF as solvent. Phen = 1,10-phenanthroline.

Table 2. Substrate Scope[a]



[a]Reaction conditions: **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 rt, isolated yield (average of two runs). [b]**L4** instead of **L3**. [c]Combination of CF_3SO_2Na and HOAc.

type ligands **L3** and **L4** exhibited slightly better reactivity (entries 9−10). However, sterically hindered ligands **L5**−**L6** bearing an *ortho*-methyl group were ineffective (entries 11−12). Compared with dioxane, a reaction carried out in THF provided a better reproducible result (entry 13). Finally, no reaction occurred in the absence of a Pd catalyst or ligand (entries 14−15). Notably, the reaction also afforded a small amount of side products $PhSO_2F$ and β-sulfonylstyrene.

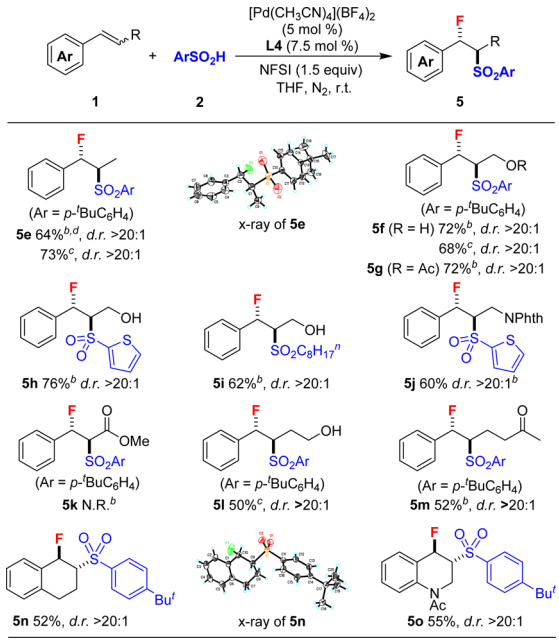
With the optimized conditions in hand, the scope of sulfinic acids was investigated. As shown in Table 2, gratifyingly, a series of arylsulfinic acids bearing both electron-donating (R = ^{t}Bu, Me) and electron-withdrawing groups (R = F, Cl, Br, NO_2) were compatible with the reaction conditions providing 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, the combination of CF_3SO_2Na and HOAc failed to generate product **4k**. Subsequently, a range of styrenes were surveyed under standard reaction conditions. Both electron-rich and -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 with the reaction conditions. 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 a trace amount of the desired product was detected.

Next, we turned our attention to more challenging internal alkenes. *E*- and *Z*-(β)-methylstyrenes 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 radical fluorinations. 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 (for **5k**) 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 an 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.

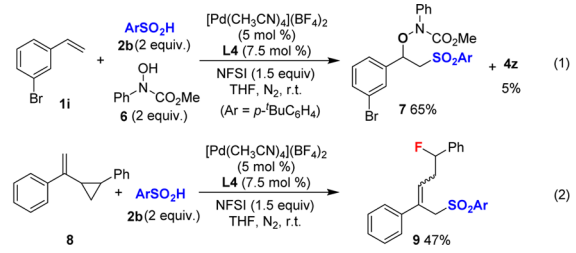
As mentioned above, single isomers *anti*-**5e** and *anti*-**5f** were obtained from the reactions of *Z*- and *E*-styrenes (Table 3), which reveals the reaction should involve a benzylic radical or carbon cation intermediate. To test the possibility of a radical intermediate, compound **6** was introduced to the standard reaction conditions as a radical scavenger. The fluorosulfonylation reaction was significantly suppressed. Instead, sulfonyloxygenation product **7** was obtained as a major product in 65% yield (eq 1). In addition, when the radical clock substrate **8** was treated under standard reaction conditions, the cyclopropyl group was completely opened to give product **9** (eq 2). These observations implied that *the reaction could involve a benzylic*

DOI: 10.1021/ja5131676
J. Am. Chem. Soc. 2015, 137, 2468−2471

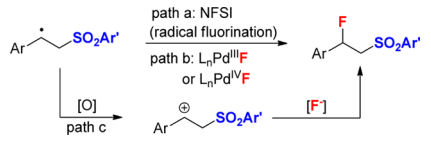
Table 3. Fluorosulfonylation of Internal Alkenes[a]



[a]Reaction conditions: **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.



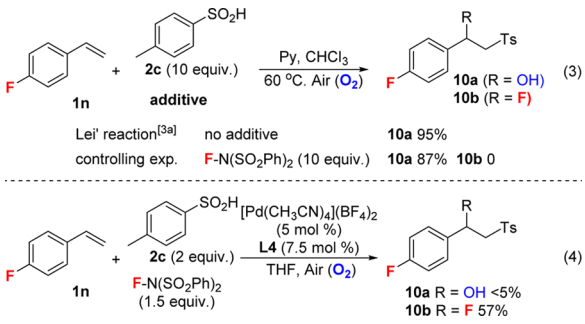
Scheme 2. Possible Mechanism for C−F Bond Formation



radical species. Based on the 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 F^+ reagent NFSI (path a); (2) a high-valent palladium fluoride involved as the electrophilic fluorine reagent to react with a benzylic radical (path b); (3) a benzylic carbon cation involved as the key species to react with F^- to give the C−F bond (path c).

In order to differentiate these three possibilities, the electronic effect of styrenes was further evaluated under standard conditions. 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 et al. 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 the 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 conditions did afford product **10b** in 57% yield, combined with only a trace amount of product **10a** (eq 4), which argues against this possibility. In addition, the classic free radical fluorination process generally exhibits poor diastereoselectivity (from 1:1 to 4:1).[6,7] The excellent *d.r.* ratio in the current reaction also ruled out the possibility of the radical fluorination pathway.

In order to gain further insights into 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. Furthermore, the reaction rate was highly dependent on the ratio of **L4** and Pd catalyst (from 1:1 to 4:1). In addition, $[(\mathbf{L4})_2Pd]^{2+}(OTf)_2$ was also an efficient catalyst, and the reaction gave the identical rate with the catalyst **Pd**:**L4** = 1:2 (Figure 1, left). Thus, we believed that cationic

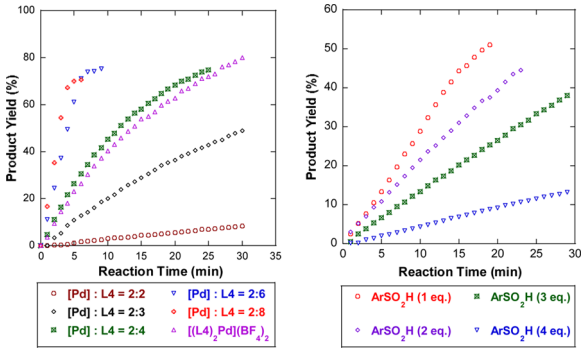


Figure 1. Effect on the reaction of **1n** and $ArSO_2H$ (Ar = ^{t}BuC$_6$H$_4$): Left, **L4**/[Pd] ratio effect, [Pd] = $[Pd(CH_3CN)_4](BF_4)_2$ (2 mol %), **L4** (2−8 mol %); Right, $[ArSO_2H]$ effect.

$[(\mathbf{L4})_2Pd]^{2+}$ 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 an *ortho*-methyl group also prevent the formation of bis-bidentate Pd species $[(\mathbf{L})_2Pd]^{2+}$.

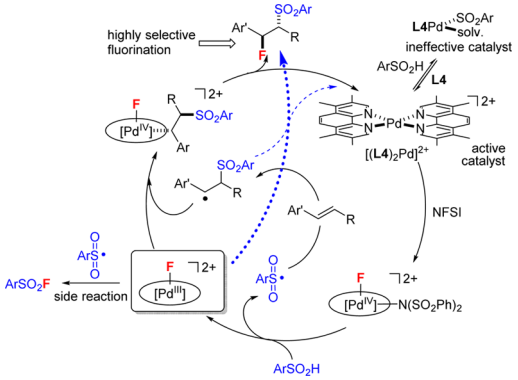
Further kinetic studies exhibited a first-order dependence on the concentration of $[(\mathbf{L4})_2Pd]^{2+}(OTf)_2$ and NFSI, and zeroth-order dependence on the styrene (see the SI). Surprisingly, the reaction rate exhibited an inverse dependence on the concentration of arylsulfinic acid (Figure 1, right). NMR studies clarified that the $[(\mathbf{L4})_2Pd]^{2+}(OTf)_2$ catalyst could convert to ineffective $[(\mathbf{L4})Pd(SO_2Ar)_n]$ (n = 1 or 2) species and release

DOI: 10.1021/ja5131676
J. Am. Chem. Soc. 2015, 137, 2468−2471

ligand **L4** in the presence of $ArSO_2H$, but could be further regenerated in the presence of an 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

Scheme 3. Proposed Mechanism



$[(\mathbf{L4})_2Pd]^{2+}$ by NFSI provided $[(\mathbf{L4})_2Pd(F)N(SO_2Ph)_2]^{2+}$, which could react with arylsulfinic acid via an SET process to generate the $ArSO_2$ radical and $(\mathbf{L4})_2Pd^{III}F$ species.[11] The former could react with styrene to give benzylic radical species, which directly attack the $Pd^{III}F$ complex to give the fluorination product (dash line). Alternatively, the benzylic radical could also be trapped by the $Pd^{III}F$ complex to give the alkyl-$Pd^{IV}F$ species, which undergoes direct reductive elimination to form the C−F bond selectively (plain cycle). The first order dependence on the [Pd] and NFSI revealed that the oxidation of the Pd catalyst occurs as the turnover 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 the $Pd^{IV}(F)R$ complex for hydrofluorination of styrenes could deliver excellent diastereoselectivity (*d.r.* > 20:1).[12] Thus, we thought the current fluorosulfonylation reaction is more likely to involve an $(\mathbf{L4})_2Pd^{IV}(F)R$ species for highly selective fluorination, and the bezylic radical is possibly trapped by the Pd^{III} species on the opposite side of the sulfonyl group with high selectivity due to the steric hindrance of ligand **L4**.

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 from the previous radical fluorination process. Instead, the side-selective combination of a benzylic carbon radical with a Pd^{III} complex and the direct reductive elimination of an $L_2Pd^{IV}(F)R$ intermediate was proposed to address the high diastereoselectivity. We envisioned that this unusual pathway may be operational in other alkene difunctionalization reactions.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Synthetic procedures, characterization, and additional 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

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support from the 973 program (No. 2011CB808700), and NSFC (Nos. 21225210, 21202185, 21421091, and 21472219).

■ REFERENCES

(1) (a) Fromtling, R. A. *Drugs Future* **1989**, *14*, 1165. (b) Oida, S.; Tajima, Y.; Konosu, T.; Nakamura, Y.; Somada, A.; Tanaka, T.; Habuki, S.; Harasaki, T.; Kamai, Y.; Fukuoka, T.; Ohya, S.; Yasuda, H. *Chem. Pharm. Bull.* **2000**, *48*, 694.

(2) (a) Willems, E.; De Vries, P.; Heiligers, J. P.; Saxena, P. R. *Naunyn Schmiedeberg's Arch. Pharmacol.* **1998**, *358*, 212. (b) Lee, M.; Ikejiri, M.; Klimpel, D.; Toth, M.; Espahbodi, M.; Hesek, D.; Forbes, C.; Kumarasiri, M.; Noll, B. C.; Chang, M.; Mobashery, S. *ACS Med. Chem. Lett.* **2012**, *3*, 490.

(3) For some recent examples, see: (a) Liu, Q.; Zhang, J.; Wei, F.; Qi, Y.; Wang, H.; Liu, Z.; Lei, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 7156. (b) Liu, Q.; Zhang, J.; Zhao, G.; Qi, Y.; Wang, H.; Liu, Z.; Lei, A. *J. Am. Chem. Soc.* **2013**, *135*, 11481. (c) Shen, T.; Yuan, Y.; Song, S.; Jiao, N. *Chem. Commun.* **2014**, *50*, 4115. (d) Tang, X.; Huang, L.; Xu, Y.; Yang, J.; Wu, W.; Jiang, H. *Angew. Chem., Int. Ed.* **2014**, *53*, 4205.

(4) (a) Hiyama, T. *Organofluorine Compounds: Chemistry and Applications*; Springer: Berlin, 2000. (b) Ojima, I. *Fluorine in Medical Chemistry and Chemical Biology*; Wiley-Blackwell: U.K., 2009.

(5) For radical fluorination process, see: (a) Sibi, M. P.; Landais, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 3570. (b) Xia, J.-B.; Zhu, C.; Chen, C. *J. Am. Chem. Soc.* **2013**, *135*, 17494. (c) Rueda-Becerril, M.; Sazepin, C. C.; Leung, J. C. T.; Okbinoglu, T.; Kennepohl, P.; Paquin, J.-F.; Sammis, G. M. *J. Am. Chem. Soc.* **2012**, *134*, 4026. (d) Bloom, S.; Pitts, C. R.; Miller, D. C.; Haselton, N.; Holl, M. G.; Urheim, E.; Lectka, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 10580.

(6) (a) Zhang, C.; Li, Z.; Zhu, L.; Yu, L.; Wang, Z.; Li, C. *J. Am. Chem. Soc.* **2013**, *135*, 14082. (b) Li, Z.; Song, L.; Li, C. *J. Am. Chem. Soc.* **2013**, *135*, 4640. (c) Zhang, H.; Song, Y.; Zhao, J.; Zhang, J.; Zhang, Q. *Angew. Chem., Int. Ed.* **2014**, *53*, 11079.

(7) (a) Barker, T. J.; Boger, D. L. *J. Am. Chem. Soc.* **2012**, *134*, 13588. (b) Shigehisa, H.; Nishi, E.; Fujisawa, M.; Hiroya, K. *Org. Lett.* **2013**, *15*, 5158.

(8) (a) Liu, W.; Huang, X.; Cheng, M.-J.; Nielsen, R. J.; Goddard, W. A., III; Groves, J. T. *Science* **2012**, *337*, 1322. (b) Huang, X.; Liu, W.; Ren, H.; Neelamegam, R.; Hooker, J. M.; Groves, J. T. *J. Am. Chem. Soc.* **2014**, *136*, 6842.

(9) (a) Liu, G. *Org. Biomol. Chem.* **2012**, 6243. (b) Wu, T.; Yin, G.; Liu, G. *J. Am. Chem. Soc.* **2009**, *131*, 16354. (c) Wu, T.; Cheng, J.; Chen, P.; Liu, G. *Chem. Commun.* **2013**, *49*, 8707. (d) Zhu, H.; Liu, G. *Acta Chim. Sinica.* **2012**, *70*, 2404.

(10) (a) Qiu, S.; Xu, T.; Zhou, J.; Guo, Y.-L.; Liu, G. *J. Am. Chem. Soc.* **2010**, *132*, 2856. (b) Peng, H.; Yuan, Z.; Wang, H.-Y.; Guo, Y.-L.; Liu, G. *Chem. Sci.* **2013**, *4*, 3172.

(11) For the oxidation of L_2Pd^{II} by NFSI and from Pd^{IV} to Pd^{III} via the 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.

(12) Emer, E.; Pfeifer, L.; Brown, J. M.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2014**, *53*, 4181 And the reference therein.

DOI: 10.1021/ja5131676
J. Am. Chem. Soc. 2015, 137, 2468−2471