Organofluorine Chemistry

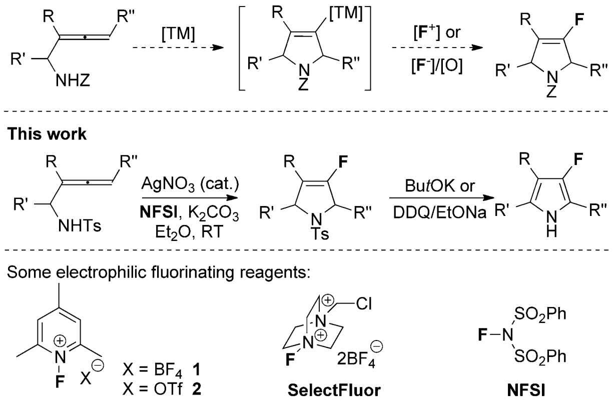
DOI: 10.1002/anie.201103225

# Silver-Catalyzed Intramolecular Aminofluorination of Activated Allenes**

*Tao Xu, Xin Mu, Haihui Peng, and Guosheng Liu**

The replacement of hydrogen by fluorine in organic molecules frequently leads to dramatic changes of their properties, such as solubility, metabolic stability, and bioavailability.[1] Among these organofluorine molecules, fluorinated heterocycles have been extensively used as important building blocks for the synthesis of anticholinergic, antiemetic, and antispastic drugs as well as enzyme inhibitors.[2] Thus, the efficient synthesis of these fluorinated heterocycles has attracted more attention.[3,4]

Recently, several research groups have described methods for the efficient synthesis of aryl fluoride using transition-metal catalysts.[5,6] For instance, Buchwald and co-workers reported a palladium-catalyzed cross-coupling reaction of aryl triflate and CsF.[5a] The groups of Sanford and Yu explored the palladium-catalyzed oxidative fluorination of arenes through C–H bond activation by using electrophilic fluorinating reagents **1** or **2** (Scheme 1).[5b–c] Ritter and co-workers reported a silver-catalyzed fluorination of aryl stannanes with SelectFluor.[6] Meanwhile, Au complexes have been applied to catalyze the fluorination of alkynes.[7] Sadighi and co-workers documented the hydrofluorination of alkynes,[7a] and the groups of Gouverneur[7b] and Nevado[7c–d] each reported the fluorination of alkynes to create vinyl C–F bond. This approach involved an oxidative fluorination of vinyl–Au species bearing an adjacent carbonyl group using SelectFluor as fluorinating reagent.

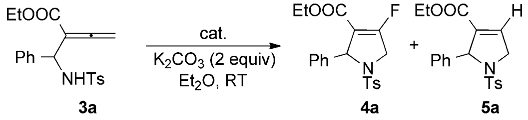


**Scheme 1.** The concept of aminofluorination of allenes. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

Recent studies on intramolecular aminofluorination of alkenes by our group demonstrated that the $C_{sp^3}$–F bond formation can be achieved through oxidative cleavage of the $C_{sp^3}$–Pd bond.[8] Thus, we decided to investigate the reactivity of allenes toward aminofluorination, which not only represents an efficient strategy to build up a heterocyclic skeleton bearing a vinyl fluoride moiety, but also provides a good opportunity to study the oxidative fluorination of vinyl C–M species.[9] Herein, we reported a novel silver-catalyzed intramolecular aminofluorination of allenes for the synthesis of 4-fluoro-2,5-dihydropyrroles, in which the vinyl C–Ag bond is cleaved using NFSI to afford vinyl C–F bonds.[10,11] In addition, further convenient aromatization of fluorinated dihydropyrroles readily afforded the corresponding 4-fluoropyrrole derivatives (Scheme 1).

The initial investigation focused on the cyclization of allene **3a** using a Pd catalyst. Unfortunately, no desired fluorinated product **4a** was observed under our previous reaction condition AgF/PhI(OPiv)$_2$, and only a trace amount of hydoramination product **5a** was detected (Table 1,

**Table 1:** Screening results of reaction conditions.[a]



| Entry | Catalyst (mol %) | [F]/[O] (equiv) | **4a** [%][b] | **5a** [%][b] |
|---|---|---|---|---|
| 1 | Pd(OAc)$_2$ (10) | AgF (2)/PhI(OPiv)$_2$ (2) | 0 | 7 |
| 2[c] | Pd(OAc)$_2$ (10) | NFSI (3) | 0 | 0 |
| 3 | Pd(OAc)$_2$ (10) | AgF (2)/NFSI (3) | 8 | 57 |
| 4 | – | AgF (2)/NFSI (3) | 84 | 1 |
| 5 | AgF (10) | NFSI (3) | 5 | 4 |
| 6 | AgNO$_3$ (10) | NFSI (3) | 84 | 1 |
| 7 | AgNO$_3$ (20) | NFSI (1.5) | 88 | 1 |
| 8[d] | AgNO$_3$ (20) | NFSI (1.5) | 0 | 5 |
| 9 | – | NFSI (1.5) | 0 | 0 |
| 10 | AgNO$_3$ (20) | SelectFluor (1.5) | 17 | 53 |
| 11 | AgNO$_3$ (20) | XeF$_2$ (1.5) | 5 | 69 |
| 12 | AgNO$_3$ (20) | **1** (1.5) | 0 | 26 |
| 13 | AgNO$_3$ (20) | **2** (1.5) | 0 | 80 |

[a] Reactions were conducted on a 0.1 mmol scale. [b] Yield determined by $^1$H NMR spectroscopy with *N*,*N*-dimethyl trifluoroacetamide as an internal standard. [c] Bathocuproine (15 mol %) as ligand. [d] Without K$_2$CO$_3$. Piv = pivaloyl, TS = 4-toluenesulfonyl.

---

[*] T. Xu, X. Mu, H. Peng, Prof. Dr. G. Liu
State Key Laboratory of Organometallic Chemistry
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
354 Fenglin Road, Shanghai, 200032 (China)
E-mail: gliu@mail.sioc.ac.cn

[**] We are grateful for the financial support from the Chinese Academy of Science, the National Natural Science Foundation of China (20821002, 20872155, 20972175, and 20923005), the National Basic Research Program of China (973-2011CB808700), and the Science and Technology Commission of the Shanghai Municipality (08dj1400100).

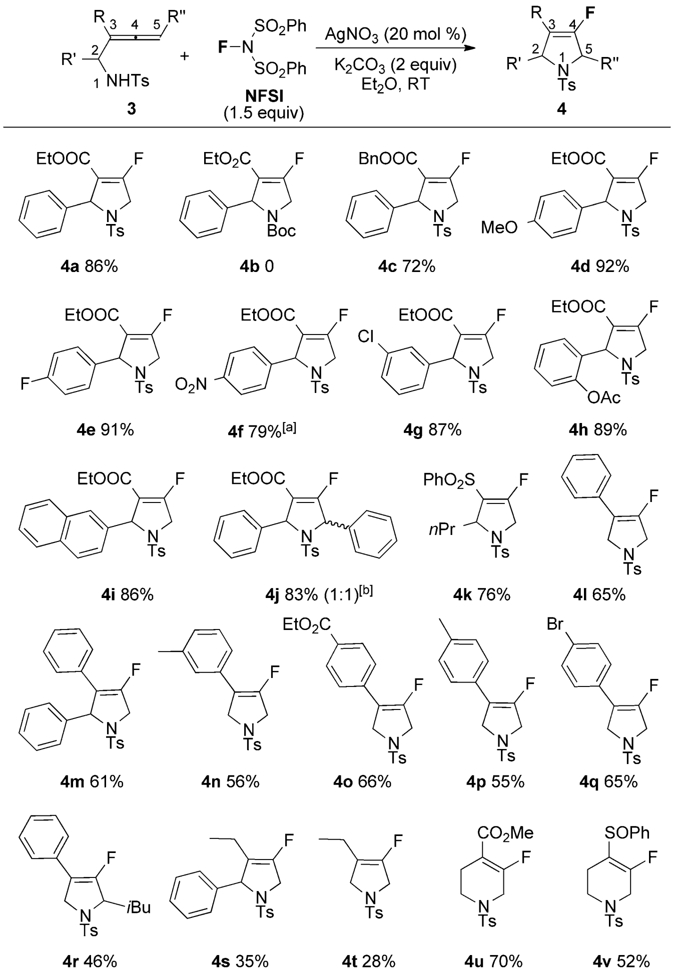
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201103225.

entry 1).[8] An application of an alternative catalytic system for aminofluorination of styrenes using NFSI[12] also failed to proceed (entry 2). Combination of the above two reaction systems using NFSI instead of $PhI(OPiv)_2$ as the oxidant, afforded a small amount of aminofluorination product **4a** (entry 3). Surprisingly, control experiment in the absence of Pd catalyst significantly improved the yield of **4a** to 84 % yield and the hydroamination reaction was inhibited (entry 4). These results indicate that the reaction is mediated by a stoichiometric amount of AgF rather than Pd complex. Further studies on the catalytic reaction were carried out. The use of $AgNO_3$ (20 mol %) proved to give the best yield (entries 5–7). Notably, both $AgNO_3$ and $K_2CO_3$ are crucial for the successful transformation (entries 8 and 9).[13] Other electrophilic fluorinating reagents, such as SelectFluor, $XeF_2$, and *N*-fluoropyridinium **1** and **2**, were ineffective for aminofluorination.[14] Instead, the hydroamination product was the dominated product (entries 10–13). Although formation of the vinyl C−F bond mediated by $Ag^I$ has been reported, the fluorination only occurs with toxic vinyl stannanes using expensive $XeF_2$ as the fluorinating reagent.[15]

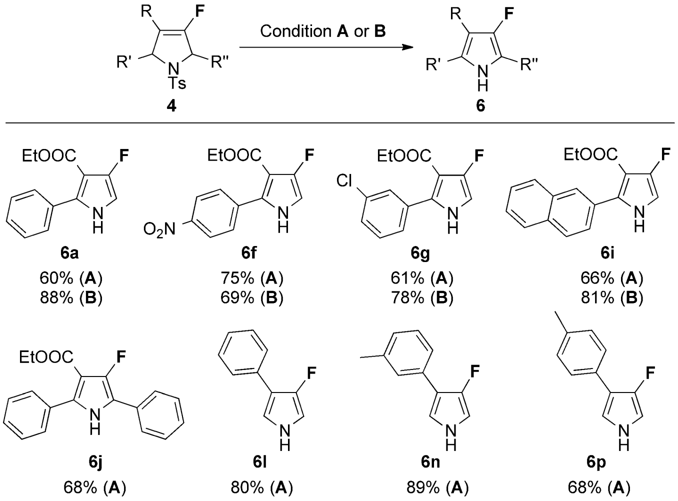
Under standard condition, the substrate scope of the aminofluorination reaction was investigated (Scheme 2). The effect of having a protection group on the nitrogen atom was firstly examined. Compared to allene **3a** with a 4-toluenesulfonyl protecting group, the substrate having carbamate did not yield aminofluorination product **4b**. The substrates with various substituents at the C3-position were further studied. The results in Scheme 2 show that substrates possessing an electron-withdrawing or aromatic group are suitable reactants (**4c**–**4r**). Meanwhile the allene substrates with alkyl group (**4s**–**4t**) gave low yields (35 % and 28 %, respectively).[16] Among them, the allene substrates with an electron-withdrawing group at C3 exhibited very good reactivity, and those reactions afforded the corresponding products **4c**–**4k** in good to excellent yields. In addition, a substrate with three substituents still had a very good reactivity to generate fluorinated product **4j** in 83 % yield. In contrast, the substrates with the aryl group at C3 also smoothly underwent aminofluorination to generate products **4l**–**4r** but in moderate yields. Finally, when the substrates bearing one more tethered carbon atom between the allene and amine, the reactions also proceeded very well and afforded six-membered products **4u** and **4v** in 70 % and 52 % yield, respectively.

Subsequently, a study on the aromatization of 4-fluoro-2,5-dihydropyrrole compounds were undertaken to synthesize fluorinated pyrrole derivatives.[17,18] Results shown in Scheme 3 suggest that the aminofluorination products **4** can be efficiently converted into 4-fluoropyrroles **6** by treatment with the strong base KO*t*Bu, or sequential oxidation by DDQ and removal of the protecting group by EtONa—no defluorination reaction was observed in these reactions.

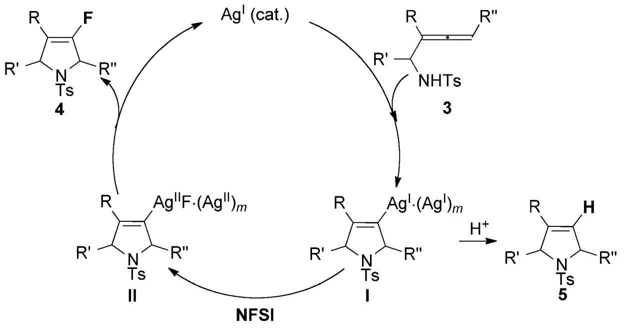
Owing to the rarity of silver-catalyzed redox catalytic system,[6,19] mechanistic details of this aminofluorination remains elusive at the moment. However, our preliminary



***Scheme 2.*** Silver-catalyzed aminofluorination of allenes. Reaction conditions were the same as for Table 1, entry 7. The yields of isolated product are given. [a] NFSI (3 equiv) and $K_2CO_3$ (4 equiv). [b] Starting material **3j** is a mixture of two isomers (d.r. 1:1). Bn = benzyl, Boc = *tert*-butoxycarbonyl.

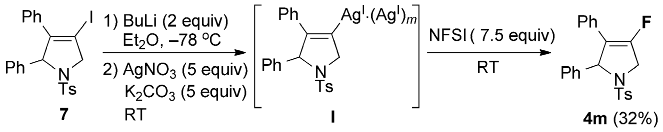


***Scheme 3.*** The aromatization of 4-fluoro-2,5-dihydropyrolles. Condition A: KO*t*Bu (3 equiv), DMSO, RT or 50 °C for 2 h; Condition B: 1) DDQ (3 equiv), benzene, 110 °C, 5 h; 2) EtONa (5 equiv), EtOH, 30 °C, 1 h. The yields of isolated product are given.



*Scheme 4.* The proposed mechanism for silver(I)-catalyzed aminofluorination of allenes.

study shows that oxidative cleavage of the vinyl C–Ag bond may be involved in the C–F bond formation (Scheme 4). During optimization of the reaction condition, the observations of aminofluorination and hydroamination product formation suggest that the reaction might involve a vinyl–sliver intermediate **I** generated from silver-catalyzed amination of allene. To probe the mechanism of C–F bond formation, a vinyl–silver complex **I** that is generated in situ from substrate **7** by treatment with *n*BuLi and $AgNO_3$,[20] was treated with NFSI in the presence of $K_2CO_3$, and aminofluorination product **4m** was formed in 32% yield [Eq. (1)].[21] This result indicates that vinyl C–F bond formation possibly undergoes an oxidation of the vinyl–Ag$^I$ intermediate **I** by NFSI to afford a vinyl–Ag$^{II}$ fluoride **II**,[22] and subsequent reductive elimination. Based on recent studies on oxidative fluorination of aryl stannanes,[6] a multinuclear silver complex may be involved to facilitate one-electron redox chemistry.[6a] Moreover, addition of 2,6-di-*tert*-butylphenol or 2,2,6,6-tetramethylpiperidine-1-oxyl as free radical scavengers did not obviously influence the fluorination,[23] thus suggesting that a radical pathway is unlikely.



(1)

In conclusion, a novel silver-catalyzed intramolecular oxidative aminofluorination of allenes has been reported, in which NFSI functioned as the fluorinating reagent. This methodology provided an efficient route to synthesize 4-fluoro-2,5-dihydropyrrole compounds, and this type of product can be conveniently converted into fluorinated pyrrole derivatives. Further mechanistic study is in progress.

Received: May 11, 2011

**Keywords:** allenes · aminofluorination · fluorinated heterocycles · oxidation · silver

---

[1] a) R. Filler, Y. Kobayashi in *Biomedicinal Aspects of Fluorine Chemistry*, Elsevier, Amsterdam, **1982**; b) *Fluorine in Bioorganic Chemistry* (Eds.: J. T. Welch, S. Eswarakrishman), Wiley, New York, **1991**.

[2] *Organofluorine Chemistry: Principles and Commercial Applications* (Eds.: R. E. Banks, B. E. Smart, J. C. Tatlow), Plenum, New York, **1994**.

[3] For reviews on fluorination of organic compounds, see: a) P. T. Nyffeler, S. G. Duron, M. D. Burkart, S. P. Vincent, C.-H. Wong, *Angew. Chem.* **2005**, *117*, 196–217; *Angew. Chem. Int. Ed.* **2005**, *44*, 192–212; b) M. Shimizu, T. Hiyama, *Angew. Chem.* **2005**, *117*, 218–234; *Angew. Chem. Int. Ed.* **2005**, *44*, 214–231; c) P. M. Pihko, *Angew. Chem.* **2006**, *118*, 558–561; *Angew. Chem. Int. Ed.* **2006**, *45*, 544–547.

[4] For reviews on the synthesis of fluorinated heterocycles, see: a) V. A. Petrov in *Fluorinated Heterocyclic Compounds: Synthesis, Chemistry, and Applications*, Wiley, Hoboken, **2009**; b) E. V. Nosova, G. N. Lipunova, V. N. Charushin, O. N. Chupakhin, *J. Fluorine Chem.* **2010**, *131*, 1267–1288; c) S. Zhu, Y. Wang, W. Peng, L. Song, G. Jin, *Curr. Org. Chem.* **2002**, *6*, 1057–1096; d) M. J. Silvester, *Aldrichimica Acta* **1991**, *24*, 31–38; for some selective examples, see: e) P. Kwiatkowski, T. D. Beeson, J. C. Conrad, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2011**, *133*, 1738–1741; f) Y. Kishi, H. Nagura, S. Inagi, T. Fuchigami, *Chem. Commun.* **2008**, 3876–3878; g) S. Fustero, S. Catalan, M. Sanchez-Rosello, A. Simon-Fuentes, C. del Pozo, *Org. Lett.* **2010**, *12*, 3484–3487.

[5] For palladium-catalyzed coupling reaction of aryl triflates with CsF, see: a) D. A. Watson, M. Su, G. Teverovskiy, Y. Zhang, J. García-Fortanet, T. Kinzel, S. L. Buchwald, *Science* **2009**, *325*, 1661–1664; for palladium-catalyzed fluorination of C–H bonds of arenes, see: b) K. L. Hull, W. Q. Anani, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, *128*, 7134–7135; c) X. Wang, T.-S. Mei, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 7520–7521; for mechanistic studies, see: d) N. D. Ball, M. S. Sanford, *J. Am. Chem. Soc.* **2009**, *131*, 3796–3797; e) T. Furuya, T. Ritter, *J. Am. Chem. Soc.* **2008**, *130*, 10060–10061; for palladium-mediated fluorination of aryl borate, see: f) T. Furuya, H. M. Kaiser, T. Ritter, *Angew. Chem.* **2008**, *120*, 6082–6085; *Angew. Chem. Int. Ed.* **2008**, *47*, 5993–5996; for palladium-catalyzed allylic fluorination, see: g) M. H. Katcher, A. G. Doyle, *J. Am. Chem. Soc.* **2010**, *132*, 17402–17404; h) C. Hollingworth, A. Hazari, M. N. Hopkinson, M. Tredwell, E. Benedetto, M. Huiban, A. D. Gee, J. M. Brown, V. Gouverneur, *Angew. Chem.* **2011**, *123*, 2661–2665; *Angew. Chem. Int. Ed.* **2011**, *50*, 2613–2617.

[6] For silver-catalyzed fluorination reactions, see: a) P. Tang, T. Furuya, T. Ritter, *J. Am. Chem. Soc.* **2010**, *132*, 12150–12154: for silver-mediated reaction, see: b) T. Furuya, A. E. Strom, T. Ritter, *J. Am. Chem. Soc.* **2009**, *131*, 1662–1663; c) T. Furuya, T. Ritter, *Org. Lett.* **2009**, *11*, 2860–2863.

[7] For gold-catalyzed fluorination of alkyne, see: a) J. A. Akana, K. X. Bhattacharyya, P. Muller, J. P. Sadighi, *J. Am. Chem. Soc.* **2007**, *129*, 7736–7737; b) M. Schuler, F. Silva, C. Bobbio, A. Tessier, V. Gouverneur, *Angew. Chem.* **2008**, *120*, 8045–8048; *Angew. Chem. Int. Ed.* **2008**, *47*, 7927–7930; c) T. de Haro, C. Nevado, *Chem. Commun.* **2011**, *47*, 248–249; d) T. de Haro, C. Nevado, *Adv. Synth. Catal.* **2010**, *352*, 2767–2772.

[8] T. Wu, G. Yin, G. Liu, *J. Am. Chem. Soc.* **2009**, *131*, 16354–16355.

[9] For some reviews on the reaction of allenes catalyzed by transition metals, see: a) R. Zimmer, C. U. Dinesh, E. Nandanan, F. Ahmed Khan, *Chem. Rev.* **2000**, *100*, 3067–3126; b) L. K. Sydnes, *Chem. Rev.* **2003**, *103*, 1133–1150; c) S. Ma, *Chem. Rev.* **2005**, *105*, 2829–2872; d) T. Bai, S. Ma, G. Jia, *Coord. Chem. Rev.* **2009**, *253*, 423–448; for selective examples of

amination of allenes involved a vinyl–metal intermediates, see: e) S. Ma, W. Gao, *Org. Lett.* **2002**, *4*, 2989–2992; f) G. Liu, X. Lu, *Org. Lett.* **2001**, *3*, 3879–3882; g) R. K. Dieter, H. Yu, *Org. Lett.* **2001**, *3*, 3855–3858.

[10] Generally, the C–Ag bond is inclined to protonolysize, for details, see: a) Y. Yamamoto, *Chem. Rev.* **2008**, *108*, 3199–3222; b) M. Álvarez-Corral, M. Muñoz-Dorado, I. Rodríguez-García, *Chem. Rev.* **2008**, *108*, 3174–3198; c) M. Naodovic, H. Yamamoto, *Chem. Rev.* **2008**, *108*, 3132–3148; for selective examples on silver-catalyzed hydroamination of allenes, see: d) Y. Koseki, S. Kusano, T. Nagasaka, *Tetrahedron Lett.* **1998**, *39*, 3517–3520; e) R. Lok, R. E. Leone, A. J. Williams, *J. Org. Chem.* **1996**, *61*, 3289–3297; f) Q. H. Huang, J. A. Hunter, R. C. Larock, *J. Org. Chem.* **2002**, *67*, 3437–3444; g) R. Kinsman, D. Lathbury, P. Vernon, T. Gallagher, *J. Chem. Soc. Chem. Commun.* **1987**, 243–244; h) R. K. Dieter, N. Chen, V. K. Gore, *J. Org. Chem.* **2006**, *71*, 8755–8760; i) D. Lathbury, T. Gallagher, *J. Chem. Soc. Chem. Commun.* **1986**, 1017–1018.

[11] For an example on the cleavage of a C–Ag bond using NCS to form a C–Cl bond, see: J. Meijer, K. Ruitenberg, H. Westmijze, P. Vermeer, *Synthesis* **1981**, 551–554.

[12] For palladium-catalyzed fluorination of alkene and alkyne using NFSI as the fluorinating reagent, see: a) S. Qiu, T. Xu, J. Zhou, Y. Guo, G. Liu, *J. Am. Chem. Soc.* **2010**, *132*, 2856–2857; b) H. Peng, G. Liu, *Org. Lett.* **2011**, *13*, 772–775.

[13] Other transition-metal complexes, such as CuBr, $[(PPh_3)AuCl]$ and $[Ni(PPh_3)Cl_2]$, were ineffective.

[14] For metal-free fluorination of allenes using SelectFluor as a strong electrophilic fluorinating reagent, see: a) C. Zhou, Z. Ma, Z. Gu, C. Fu, S. Ma, *J. Org. Chem.* **2008**, *73*, 772–774; b) B. Lü, C. Fu, S. Ma, *Org. Biomol. Chem.* **2010**, *8*, 274–281; c) H. Cui, Z. Chai, G. Zhao, S. Zhu, *Chin. J. Chem.* **2009**, *27*, 189–194.

[15] For the silver-mediated fluorination of vinyl stannanes, see: a) M. A. Tius, J. K. Kawakami, *Synth. Commun.* **1992**, *22*, 1461–1471; b) M. A. Tius, J. K. Kawakami, *Synlett* **1993**, 207–208; c) M. A. Tius, J. K. Kawakami, *Tetrahedron* **1995**, *51*, 3997–4010.

[16] Only a trace amount aminofluorination product was obtained in the reaction of substrate *N*-(4-*p*henylbuta-2,3-dienyl)-*N*-tosylamine.

[17] For synthesis of fluoropyrroles, see: a) R. Surmont, G. Verniest, F. Colpaert, G. Macdonald, J. W. Thuring, F. Deroose, N. De Kimpe, *J. Org. Chem.* **2009**, *74*, 1377–1380; b) R. Surmont, G. Verniest, N. De Kimpe, *Org. Lett.* **2009**, *11*, 2920–2923; c) Y. Wu, S. Zhu, *Org. Lett.* **2003**, *5*, 745–748; d) J. Wang, I. A. Scott, *J. Chem. Soc. Chem. Commun.* **1995**, 2399–2400.

[18] Fluoropyrroles have been used as building block to design some leader compounds for biological studies in pharmaceutical and agriculture sciences, see: a) T. Taniguchi, A. Kawada, M. Kondo, J. F. Quinn, J. Kunitomo, M. Yoshikawa, M. Fushimi, US 20100197651, **2010**; b) S. P. Mercer, A. J. Roecker, T. Williams, X.-F. Zhang, WO 2010124055, **2010**; c) H. Nishida, Y. Arikawa, I. Fujimori, WO 2010024451, **2010**; d) K. Liu, W. Shi, J. Qie, S. Feng, Q. Jia, S. Jiang, WO 2009155789, **2009**; e) M. Sakagami, H. Hashizume, S. Tanaka, T. Okuno, H. Yari, K. Tonogaki, N. Kouyama, WO 2009131096, **2009**.

[19] For silver-catalyzed nonradical oxidative reactions, see: a) K. Burgess, H. J. Lin, A. M. Prote, G. A. Sulikowski, *Angew. Chem.* **1996**, *108*, 192–194; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 220–222; b) H. V. R. Dias, R. G. Browning, S. A. Polach, H. V. K. Diyabalanage, C. J. Lovely, *J. Am. Chem. Soc.* **2003**, *125*, 9270–9271; c) Y. Cui, C. He, *J. Am. Chem. Soc.* **2003**, *125*, 16202–16203; d) Y. Cui, C. He, *Angew. Chem.* **2004**, *116*, 4306–4308; *Angew. Chem. Int. Ed.* **2004**, *43*, 4210–4212; e) W. Liu, H. Jiang, L. Huang, *Org. Lett.* **2010**, *12*, 312–315; f) J. Llaveria, Á. Beltrán, M. M. Díaz-Requejo, M. I. Matheu, S. Castillón, P. J. Pérez, *Angew. Chem.* **2010**, *122*, 7246–7249; *Angew. Chem. Int. Ed.* **2010**, *49*, 7092–7095.

[20] The vinyl C–Ag complex can be generated in situ from a vinyl C–Li complex and a $Ag^I$ complex by transmetalation, for details see: a) G. M. Whitesides, C. P. Casey, *J. Am. Chem. Soc.* **1966**, *88*, 4541–4544; b) G. M. Whitesides, C. P. Casey, J. K. Krieger, *J. Am. Chem. Soc.* **1971**, *93*, 1379–1389.

[21] The reaction also afforded the desired aminofluorination product **4m** in the absence of $K_2CO_3$, but in lower yield (17%). In addition, no fluorinated product **4m** was observed in the absence of $AgNO_3$. For details, see the Supporting Information.

[22] The electrophilic fluorinating reagents can be used as fluorinating resource, as well as oxidant, see the following review: K. M. Engle, T.-S. Mei, X. Wang. J.-Q. Yu, *Angew. Chem.* **2011**, *123*, 1514–1528; *Angew. Chem. Int. Ed.* **2011**, *50*, 1478–1491.

[23] Reactions of **3l** afforded aminofluorination product **4l** in 57% or 50% yield in the presence of BHT (1 equiv) or TEMPO (1 equiv), respectively.