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# Palladium-Catalyzed Allylic Fluorination of Cinnamyl Phosphorothioate Esters

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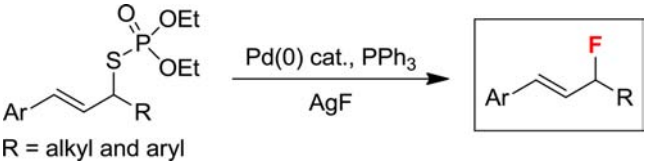
## ABSTRACT

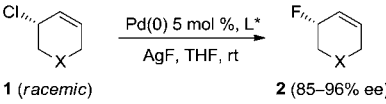



**A highly regioselective, Pd-catalyzed allylic fluorination of phosphorothioate esters is reported. This chemistry addresses several limitations of previously reported methods in which elimination and lack of reactivity were problematic. Preliminary mechanistic investigations reveal that these reactions are stereospecific and provide fluorinated products with net retention of stereochemical configuration. In analogy to other Pd-catalyzed allylic substitution reactions, this process likely proceeds through a palladium $\pi$-allyl intermediate.**

Fluorinated compounds are extremely important in medicinal chemistry.[1] For instance, fluorination of some drugs can impart substantially improved metabolic stability. These therapeutics often exhibit unique pharmacokinetic properties. Fluorine also plays a prominent role in medical imaging technologies. For instance, $^{18}$F is the preferred nucleus in positron emission tomography (PET).[2] Because the half-life of $^{18}$F is about 110 min, its rapid incorporation into PET tracers is critical.

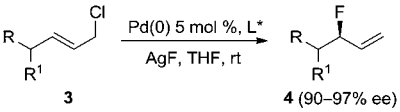
Notwithstanding the importance of fluorine in medicine, the synthesis of C–F bonds remains an underdeveloped area. Noncatalyzed fluorination reactions have been known for a long time.[3] In contrast, only recently has there been significant progress in the development of methods for the transition metal-catalyzed construction of C–F bonds at either sp$^2$- or sp$^3$-hybridized carbon centers.[4,5] Catalytic *nucleophilic* fluorinations at the sp$^3$ centers are quite rare.[6] Furthermore, there have been only a handful of publications describing the transition metal-catalyzed nucleophilic fluorination of allylic substrates.[7] These are summarized in eqs 1–4.

***Doyle et al.*** (*J. Am. Chem. Soc.* **2010**)



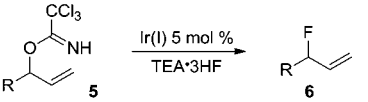

**1** (*racemic*) **2** (85–96% ee) (1)

***Doyle et al.*** (*J. Am. Chem. Soc.* **2011**)



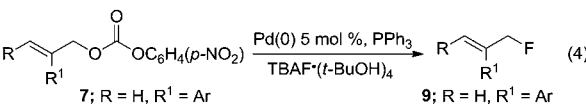

**3** **4** (90–97% ee) (2)

***Nguyen et al.*** (*J. Am. Chem. Soc.* **2011**)




**5** **6** (3)

***Brown and Gouverneur*** (*Angew. Chem., Int. Ed.* **2011**)




**7**; R = H, R$^1$ = Ar
**8**; R = Ar, R$^1$ = H
**9**; R = H, R$^1$ = Ar
**10**; R = Ar, R$^1$ = H (4)

In 2010, Doyle and co-workers reported the Pd-catalyzed dynamic kinetic asymmetric transformation (DYKAT) of racemic cyclic allylic chlorides (eq 1).[8] Soon

(1) (a) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (c) Qui, X.-L.; Xu, X.-H.; Qing, F.-L. *Tetrahedron* **2010**, *66*, 789. (d) Kirk, K. L. *Org. Process. Res. Dev.* **2008**, *12*, 305.

(2) (a) Miller, P. W.; Long, N. J.; Vilar, R.; Gee, A. D. *Angew. Chem., Int. Ed.* **2008**, *47*, 8998. (b) Ametamey, S. M.; Honer, M.; Schubiger, P. A. *Chem. Rev.* **2008**, *108*, 1501. (c) Adam, M. J.; Wilbur, D. S. *Chem. Soc. Rev.* **2005**, *34*, 153.

(3) For leading references, see: (a) Yin, J.; Zarkowsky, D. S.; Thomas, D. W.; Zhao, M. M.; Huffman, M. A. *Org. Lett.* **2004**, *6*, 1465. (b) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574.

(4) For reviews of catalytic fluorination reactions, see: (a) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470. (b) Lectard, S.; Hamashima, Y.; Sodeoka, M. *Adv. Synth. Catal.* **2010**, *352*, 2708.

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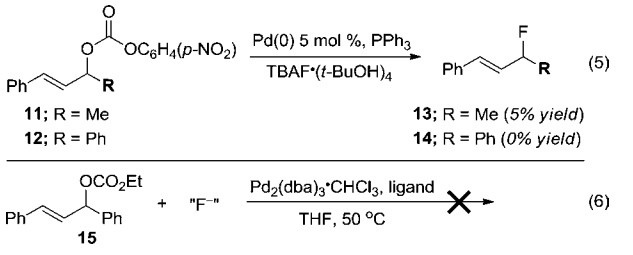
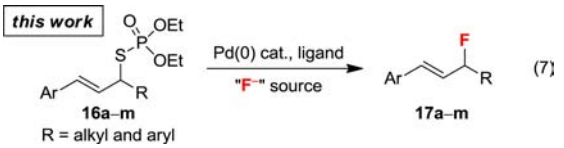
afterward, they described the conversion of acyclic chlorides to enantioenriched branched allylic fluorides (eq 2).[9] Nguyen and co-workers discovered that Ir(I) complexes can catalyze the conversion of trichloroacetimidates to similar fluorinated products (eq 3).[10] Finally, Brown and Gouverneur reported the Pd-catalyzed fluorination of primary allylic *p*-nitrobenzoates (eq 4).[11]

Despite these elegant advances in the transition metal-catalyzed construction of C−F bonds at $sp^3$ centers, numerous challenges remain. One notable limitation is that the attempted fluorination of **11** furnished the desired product in only 5% yield (Scheme 1, eq 5).[11] The formation of diene byproduct is evidently quite problematic for substrates in which $\beta$ hydrogens are present. Also, fluorination of **12** was not possible (Scheme 1, eq 5). In fact, a study by Hintermann and co-workers regarding the Pd-catalyzed fluorination of related substrate **15** resulted in none of the expected fluorinated product (Scheme 1, eq 6).[12] Referring to **15**, Hintermann suggested that under their reaction conditions, "straightforward allylic fluorination in a catalytic manner is thus not feasible."[12]

**Scheme 1.** Limitations of Prior Art




Herein, we report the successful Pd-catalyzed fluorination of secondary allylic phosphorothioate esters **16** (eq 7). In all but two of these substrates, $\beta$ hydrogens to the leaving group are present. This chemistry is complementary to known methods in that it provides access to fluorinated compounds previously unattainable by other transition metal-catalyzed processes.




Recently, our group has been exploring the chemistry of phosphorothioate esters.[13] We have demonstrated that their use can afford complementary selectivity as compared to the utilization of more conventional electrophiles. Because of our ongoing interest in this rather unusual functional group, we began our investigation with **16a** (Table 1).

Several palladium complexes furnished diene **3** as the major product (Table 1, entries 1−3). However, the use of $Pd(PPh_3)_4$ as the Pd(0) catalyst led to increased reactivity and a 60% isolated yield of the desired allylic fluoride **17a** with only 24% of the elimination product (entry 4). We could further improve upon the yield of **17a** by employing 8 mol % $Pd(dba)_2$ in conjunction with $PPh_3$ as the ligand (entry 6). Bidentate phosphine ligands were also investigated; however, poor reactivity was observed (entries 3, 7, and 8). Of several fluoride sources surveyed, only AgF was effective in promoting the desired reaction (entries 9−12). As expected, a control experiment in which the palladium catalyst was omitted resulted in no reaction (entry 13).

Notably, the application of the optimized conditions (entry 6) to two of the compounds reported by Brown and Gouverneur resulted in 1) mostly elimination (only ~10% fluorinated product) for **11** and 2) no reaction in the case of **12**. These data support the notion that the phosphorothioate ester functional group is critical for successful fluorination of these types of substrates.

There are also practical advantages of using phosphorothioate esters over the corresponding allylic halides. For instance, secondary allylic halides (and phosphates), especially those which can form stabilized carbocations after ionization, are often thermally unstable and incompatible with silica gel chromatography.[14] In contrast, the corresponding allylic phosphorothioate esters are stable to moisture, air, and chromatography. They can be stored for extended periods of time at room temperature without any noticeable decomposition.

With optimized reaction conditions in hand, we proceeded to explore its scope with several phosphorothioate

(5) For leading references, see: (a) Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; García-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009**, *325*, 1661. (b) Noël, T.; Maimone, T. J.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8900. (c) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134. (d) Racowski, J. M.; Gary, J. B.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3414. (e) Wang, X.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 7520. (f) Chan, K. S. L.; Wasa, M.; Wang, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 9081. (g) Tang, P.; Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 12150. (h) Furuya, T.; Kaiser, H. M.; Ritter, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5993. (i) Furuya, T.; Strom, A. E.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 1662. (j) Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2008**, *130*, 10060. (k) Yandulov, D. V.; Tran, N. T. *J. Am. Chem. Soc.* **2007**, *129*, 1342. (l) Grushin, V. V. *Chem.—Eur. J.* **2002**, *8*, 1006. (m) Wu, T.; Yin, G.; Liu, G. *J. Am. Chem. Soc.* **2009**, *131*, 16354. (n) Qiu, S.; Xu, T.; Zhou, J.; Guo, Y.; Liu, G. *J. Am. Chem. Soc.* **2010**, *132*, 2856. (o) Xu, T.; Mu, X.; Peng, H.; Liu, G. *Angew. Chem., Int. Ed.* **2011**, *51*, 8176.

(6) (a) Kalow, J. A.; Doyle, A. G. *J. Am. Chem. Soc.* **2010**, *132*, 3268. (b) Haufe, G.; Bruns, S. *Adv. Synth. Catal.* **2002**, *344*, 165. (c) Bruns, S.; Haufe, G. *J. Fluorine. Chem.* **2000**, *104*, 247.

(7) For a review of noncatalyzed methods for preparing allylic and propargylic fluorides, see: Pacheco, M. C.; Purser, S.; Gouverneur, V. *Chem. Rev.* **2008**, *108*, 1943.

(8) Katcher, M. H.; Doyle, A. G. *J. Am. Chem. Soc.* **2010**, *132*, 17402.

(9) Katcher, M. H.; Sha, A.; Doyle, A. B. *J. Am. Chem. Soc.* **2011**, *133*, 15902.

(10) Topczewski, J. J.; Tewson, T. J.; Nguyen, H. M. *J. Am. Chem. Soc.* **2011**, *133*, 19318.

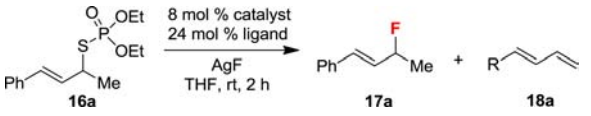
(11) Hollingworth, C.; Hazari, A.; Hopkinson, M. N.; Tredwell, M.; Benedetto, E.; Huiban, M.; Gee, A. D.; Brown, J. M.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2011**, *50*, 2613.

(12) Hintermann, L.; Läng, F.; Maire, P.; Togni, A. *Eur. J. Inorg. Chem.* **2006**, 1397.

(13) (a) Lauer, A. M.; Mahmud, F.; Wu, J. *J. Am. Chem. Soc.* **2011**, *133*, 9119. (b) Han, X.; Zhang, Y.; Wu, J. *J. Am. Chem. Soc.* **2010**, *132*, 4104. (c) Robertson, F. J.; Wu, J. *J. Am. Chem. Soc.* **2012**, *134*, 2775. (d) Robertson, F. J.; Wu, J. *Org. Lett.* **2010**, *12*, 2668. (e) Han, X.; Wu, J. *Org. Lett.* **2010**, *12*, 5780.

(14) (a) Dieter, R. K.; Gore, V. K.; Chen, N. *Org. Lett.* **2004**, *6*, 763. (b) Yasui, K.; Fugami, K.; Tanaka, S.; Tamaru, Y. *J. Org. Chem.* **1995**, *60*, 1365. (c) Carrillo-Marquez, T.; Caggiano, L.; Jackson, R. F. W.; Grabowska, U.; Rae, A.; Tozer, M. J. *Org. Biolmol. Chem* **2005**, *3*, 4117.

**Table 1.** Reaction Optimization Studies




| entry | catalyst | ligand | "F⁻" | yield **17a** (%)[a] | yield **18a** (%)[a] |
|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ | $PPh_3$ | AgF | < 5 | 15 |
| 2 | $Pd(Pt\text{-}Bu_3)_4$ | --- | AgF | < 5 | < 5 |
| 3 | $Pd(dppf)Cl_2$ | --- | AgF | < 5 | 25 |
| 4 | $Pd(PPh_3)_4$ | --- | AgF | 60[b] | 24 |
| 5 | $PdCl_2$ | $PPh_3$ | AgF | < 5 | < 5 |
| 6 | $Pd(dba)_2$ | $PPh_3$ | AgF | 71[b] | 9 |
| 7 | $Pd(dba)_2$ | dppf[c] | AgF | < 5 | < 5 |
| 8 | $Pd(dba)_2$ | DPEphos[c] | AgF | < 5 | < 5 |
| 9 | $Pd(dba)_2$ | $PPh_3$ | KF | no rxn | --- |
| 10 | $Pd(dba)_2$ | $PPh_3$ | CsF | no rxn | --- |
| 11 | $Pd(dba)_2$ | $PPh_3$ | TBAF | decomp | --- |
| 12 | $Pd(dba)_2$ | $PPh_3$ | TBAF•(*t*-BuOH)$_4$ | decomp | --- |
| 13 | none | --- | AgF | none | --- |

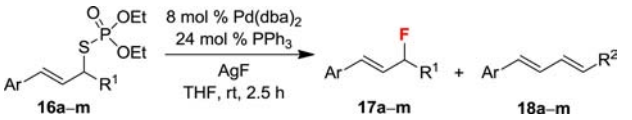
[a] As determined by $^1$H NMR spectroscopy. [b] Isolated yield. Purified product was contaminated with diene as they coelute on silica gel chromatography. Reported yield is of **17a** only and was calculated on the basis of the ratio of **17a** versus **18a**, as determined by $^1$H NMR spectroscopy. [c] Used 16 mol % of ligand.

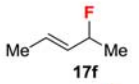
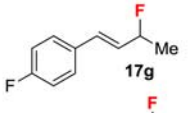
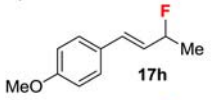
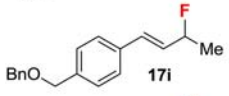
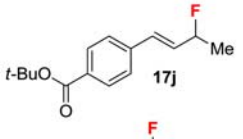
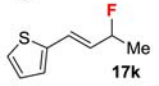
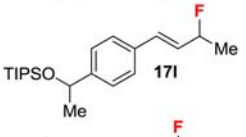
esters (Table 2). For most substrates, optimal yields were obtained using 8 mol % of $Pd(dba)_2$; however, compounds **17a** and **17g** were isolated in good yield with only 2 mol % of catalyst (entry 1 and 7). In all cases, fluorination was accompanied by dienes **18a**−**m** as minor products. Sterically hindered phosphorothioate esters also gave good yields for the desired allylic fluoride (entries 3 and 4). In addition, excellent regioselectivity was observed for all cases with the exception of the *tert*-butyl substrate (entry 4). Fluorination was amenable to electron-withdrawing and electron-donating substituents (entries 7, 8, 10, 11, and 13). The reaction was also compatible with various functional groups. These include esters, ethers, and thiophene (entries 8−11). Notably, a TIPS (triisopropylsilyl) ether remained intact during the reaction (entry 12), further highlighting the mildness of this method. This methodology is most suited to cinnamyl-derived phosphorothioate esters since we believe that the aromatic group is instrumental in dictating the formation of the observed regioisomer of the product.

It should be noted that in their neat forms, many allylic fluorides, especially those possessing $\gamma$ substituents that can stabilize carbocations, are sensitive to acid and in some cases even to borosilicate glass.[15] It is therefore possible that some of the yields in Table 2 may be diminished as a result of the isolation process.

(15) Lee, E.; Yandulov, D. V. *J. Fluorine Chem.* **2009**, *130*, 474.
(16) Obtained via preparatory SFC separation using a Chiralcel AD-H column (performed by Lotus Separations, Princeton, NJ).

**Table 2.** Scope of Allylic Fluorination

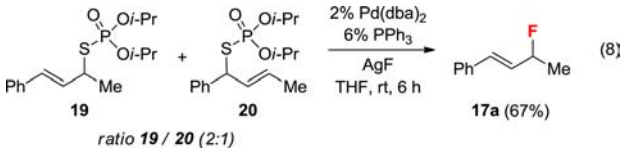



| entry | product | **17**:**18**[a] | yield of **17** (%)[e] |
|---|---|---|---|
| 1[c] | **17a**; R = Me | 88:12 | 75 |
| 2 | **17b**; R = Et | 84:16 | 63 |
| 3 | **17c**; R = *i*-Pr | 84:16 | 68 |
| 4 | **17d**; R = *t*-Bu | – | 74[d] |
| 5 | **17e**; R = Ph | – | 67 |
| 6 |  **17f** | – | 50[b] |
| 7[c] |  **17g** | 83:17 | 66 |
| 8 |  **17h** | 81:19 | 65 |
| 9 |  **17i** | 84:16 | 60 |
| 10 |  **17j** | 84:16 | 53 |
| 11 |  **17k** | 84:16 | 65 |
| 12 |  **17l** | 84:16 | 79 |
| 13 |  **17m** | 82:18 | 66 |

[a] As determined by $^1$H NMR spectroscopy of unpurified reaction mixture, [b] Due to volatility and instability of the product, the yield was determined via $^1$H NMR spectroscopy of the crude reaction mixture using 1,2-dimethoxypropane as an internal standard. [c] 2 mol % of $Pd(dba)_2$ and 6 mol % of $PPh_3$ [d] Isolated as a 1:1 mixture of regiosomers. [e] Purified products were contaminated with varying amounts of diene (coelutes with product). Reported yields are of the fluorinated products and were calculated based on the ratio of product vs diene, as determined by $^1$H NMR spectroscopy.

Several experiments were performed to gain some mechanistic insight. First we subjected a 2:1 mixture of phosphorothioate esters **19** and **20** to the optimized conditions (eq 8). This reaction provided allylic fluoride **17a** as the exclusive regioisomer. The formation of only **17a** suggests a mechanism wherein a Pd $\pi$-allyl complex undergoes rapid $\pi-\sigma-\pi$ isomerization. This is

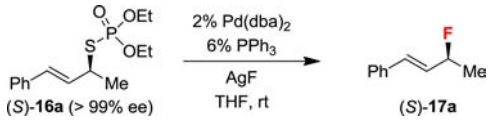
consistent with other Pd-catalyzed mechanisms for allylic substitution.



(8)

Using enantiopure phosphorothioate (*S*)-**16** (>99% ee),[16] compound (*S*)-**17a** was generated in only 60% ee (Table 3, entry 1). However, at partial conversion, the enantioenrichment of **17a** was substantially improved (92% ee, entry 2). Longer reaction times did not further diminish its enantioenrichment or have an appreciable effect on yield (entry 3).

**Table 3.** Stereospecific Allylic Fluorinations




| entry | time (h) | ee (%)[a] | yield (%)[b] |
|---|---|---|---|
| 1 | 5.5 | 60 | 65 |
| 2[c] | 1 | 92 | 37 |
| 3 | 12 | 58 | –[d] |

[a] As determined by HPLC analysis with a Chiralcel OD-H column. [b] Isolated yields. [c] Reaction halted at partial conversion of (*S*)-**16a**. [d] Not determined.

The fluorination products for all three entries in Table 3 were produced with net retention of stereochemical configuration. This is opposite to the predictive model invoked by Trost and co-workers for hard and/or unstabilized nucleophiles.[17] It is unclear how or why fluoride, which is widely regarded as a hard nucleophile,[18] would exhibit this mode of reactivity. However, these results are consistent with what Doyle and co-workers observed in their studies of the enantioselective fluorination of allylic chlorides.[8]

Preliminary data suggest that silver coordination may play an important role in these reactions. While AgF itself is sparingly soluble in THF, the addition of phosphorothioate ester **16a** promotes a noticeable increase in solubility of the silver salt. Furthermore, the $^{19}F$ and $^{31}P$ NMR spectra of a mixture of **16a** and AgF indicate the presence of a new species. The addition of $PPh_3$ to AgF had no visible effect on solubility or the $^{19}F$ and $^{31}P$ NMR spectra. We believe this NMR data is suggestive of some type of coordination between AgF and **16a**. This interaction may facilitate the requisite ionization of the phosphorothioate ester.

In summary, we have reported a highly regioselective Pd-catalyzed allylic fluorination of phosphorothioate esters. This chemistry addresses several limitations of previously reported methods in which diene formation and lack of reactivity were problematic. The mildness of the reaction conditions are demonstrated by its functional group tolerance.

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**Supporting Information Available.** Experimental procedures and spectra for all previously unreported compounds.This material is available free of charge via the Internet at http://pubs.acs.org.

(17) (a) Trost, B. M.; Machacek, M. R.; Aponick, A. *Acc. Chem. Res.* **2006**, *39*, 747. (b) Trost, B. M.; Zhang, T.; Sieber, J. D. *Chem. Sci.* **2010**, *1*, 427. (c) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (d) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258.

(18) Parr, R. G.; Pearson, R. G. *J. Am. Chem. Soc.* **1983**, *105*, 7512.

The authors declare no competing financial interest.