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Palladium-Catalyzed Asymmetric Synthesis of Allylic Fluorides

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Abstract: The enantioselective fluorination of readily available cyclic allylic chlorides with AgF has been accomplished using a Pd(0) catalyst and Trost bisphosphine ligand. The reactions proceed with unprecedented ease of operation for Pd-mediated nucleophilic fluorination, allowing access to highly enantioenriched cyclic allylic fluorides that bear diverse functional groups. Evidence that supports a mechanism in which C−F bond formation occurs by an S_N2-type attack of fluoride on a Pd(II)-allyl intermediate is presented.

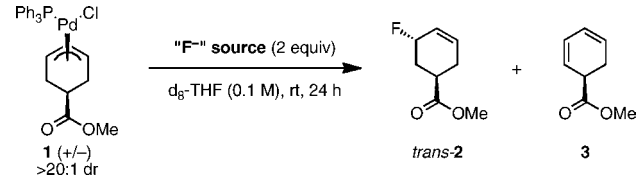
The extension of palladium-catalyzed cross coupling to the formation of carbon−fluorine bonds is of widespread interest due to the growing need for versatile, mild, and selective methods in the preparation of organofluorine compounds.[1] While aryl fluoride bond formation has been intensively investigated in this context,[2] the preparation of aliphatic C−F bonds by palladium catalysis remains relatively unexplored.[3] Our lab has initiated a program aimed at the development of asymmetric catalytic methods for nucleophilic fluorination.[4,5] As part of this program, we sought a method for the enantioselective synthesis of allylic fluorides by palladium-catalyzed nucleophilic substitution. Although allylic fluorides are key components of bioactive molecules and serve as versatile synthetic intermediates,[6,7] only one direct asymmetric catalytic method has been identified for their preparation.[8] Herein, we report that a chiral bisphosphine-ligated palladium complex catalyzes the enantioselective fluorination of allylic chlorides with AgF. We propose that a unique mechanism for C−F bond formation is operative, which enables allylic fluorination to take place at room temperature with high enantioselectivity and broad functional group compatibility.

Scheme 1. Mechanisms for C−F Bond Formation from Pd(II)

Two strategies for palladium-mediated C_{sp^2}−F bond formation have been described previously, both involving discrete palladium fluoride intermediates. In the most widespread approach, methods for C−H and C−B fluorination have been identified that proceed through high-valent palladium fluoride complexes, accessed by oxidation of Pd(II) with electrophilic "F^+" sources.[2a−d,f] In contrast, C−F bond formation by reductive elimination from Pd(II)ArF intermediates, generated from Pd(II) precursors with nucleophilic "F^-" reagents, has proven more challenging.[9] The recent identification of a Pd(0)-catalyzed methodology for the fluorination of aryl triflates with CsF at elevated temperature (80−120 °C) is the only successful example to date.[2e]

We hypothesized that efficient and mild allylic C−F bond formation could proceed by a distinct mechanism: the nucleophilic attack of fluoride on an electrophilic Pd(II)-allyl intermediate (Scheme 1). This elementary step is well-established for Pd-catalyzed allylic alkylations with various carbon- and heteroatom-centered nucleophiles[10] but, to the best of our knowledge, has no precedent for fluoride anion.[11,12] We reasoned that accessing allylic fluorides in this manner would provide a platform for the design of a broadly useful catalyst-controlled enantio-, diastereo-, and regioselective methodology that uses readily available and inexpensive fluoride sources.[13]

Table 1. Reaction of Palladium Complex **1** with Various Fluoride Sources



entry	"F^-" source	conv. (%)[a]	yield **2** (%)[a]	yield **3** (%)[a]
1	KF	77	0	14
2	CsF	96	0	24
3	TBAT	72	10[b]	19
4	AgF	100	49[b]	4
5	CuF_2	36	0	1

[a] Determined by ^{1}H NMR using methyl benzoate as a quantitative internal standard; reactions were conducted in the presence of dimethyl fumarate (1.2 equiv) to complex residual Pd(0). [b] >20:1 dr as determined by ^{19}F NMR.

To evaluate this proposal, we investigated the reaction of known Pd(II)-allyl complex **1**[14] with representative "F^-" sources (Table 1). Consistent with the documented Brønsted basicity of alkali metal fluorides, reactions with KF and CsF led predominantly to elimination, providing diene **3** as the major observable product (entries 1 and 2).[11] With the less basic fluoride source tetrabutylammonium difluorotriphenylsilicate (TBAT),[15] allylic fluoride *trans*-**2** was formed, albeit in 10% yield (entry 3). A more promising result was obtained from the reaction of complex **1** with AgF, which gave the desired product in almost 50% yield with minimal (<5%) diene production (entry 4). The selective formation of *trans*-**2** in this reaction indicates that reductive elimination occurs with inversion of configuration, consistent with nucleophilic attack of fluoride on the allyl ligand of **1**.[10,16] Notably, the efficacy of AgF does not appear to be tied solely to its potential redox activity since other transition metal fluorides tested, such as CuF_2, were ineffective as fluoride sources (entry 5).[17]

After establishing the feasibility of the critical C−F bond-forming event, we pursued a catalytic variant of the allylic fluorination. Remarkably, substrates possessing traditional leaving groups for Pd-catalyzed allylic alkylation, such as allylic acetates and carbonates, were unreactive in the presence of a Pd(0) catalyst and AgF (Table 2, entries 1 and 2). Instead, efficient C−F bond formation

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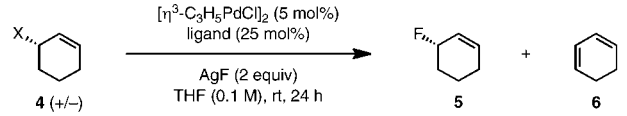
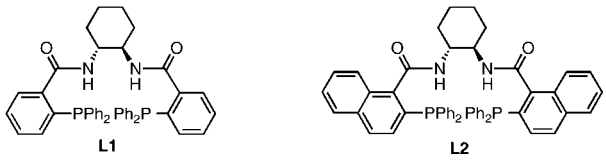
Table 2. Identification of a Catalytic Allylic Fluorination Protocol





entry	X	ligand	yield **5** (%)[a]	ee **5** (%)[b]	yield **6** (%)[a]
1	OAc (**4a**)	PPh_3	0	–	1
2	OCO_2Et (**4b**)	PPh_3	1	–	0
3	Cl (**4c**)	PPh_3	64	–	15
4[c]	Cl (**4c**)	none	8	–	1
5[d]	Cl (**4c**)	**L1**	85	88	4
6[d]	Cl (**4c**)	**L2**	70	74	5

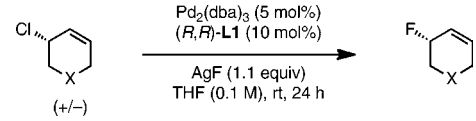
[a] Determined by GC using decane as a quantitative internal standard. [b] Determined by chiral GC using a commercial chiral column. [c] Reaction conducted with AgF (1.1 equiv) in the absence of a Pd catalyst. [d] Using $Pd_2(dba)_3$ (5 mol %), **L1** or **L2** (10 mol %), AgF (1.1 equiv).

was observed when allylic chloride **4c** was employed as a substrate (entry 3).[18,19] We propose that **4c** and Pd(0) combine to generate an intermediate analogous to **1**, from which precipitation of AgCl provides a driving force for C−F bond formation. Although **4c** reacts with AgF in the absence of palladium,[20] background reaction is suppressed at room temperature and in nonpolar solvents (entry 4).[21] Evaluation of chiral ligands under these conditions revealed that the commercially available Trost ligand **L1**[22] imparts high levels of enantioinduction in the production of allylic fluoride **5** (85% yield, 88% ee, entry 5). Control experiments demonstrated that the enantioenriched allylic fluoride product does not decompose or epimerize under the reaction conditions, despite reports documenting the instability of certain allylic fluorides toward Pd(0).[11,23]

We have found that the identified procedure provides a versatile protocol for enantioselective allylic fluorination of six-membered cyclic allylic chlorides.[24] The transformation is tolerant of substrates bearing common functional groups, including ethers, amines, esters, and amides (Table 3, entries 2−6). Less than 10% diene is observed in most cases, and the nonvolatile allylic fluorides can be isolated in moderate to good yields with excellent enantioselectivities.[25] Moreover, good levels of efficiency and enantioselectivity are maintained in the presence of traditionally fluoride-sensitive silyl ethers (entry 7) and unprotected alcohols (entry 8). These two examples underscore the mildness of the reaction conditions and the synthetic utility of the process; by contrast, the synthesis of enantioenriched allylic fluorides by dehydroxyfluorination with (diethylamino)sulfur trifluoride (DAST) is typically incompatible with these substituents and can suffer from poor stereoselectivity.[6,26] Moreover, unlike Ar−F bond formation from Pd(II)F intermediates,[2e,27] the allylic fluorinations are conducted under ambient conditions and without rigorous exclusion of moisture or air.[28]

Since allylic carbonates and acetates were unreactive under the conditions described in Table 2, we anticipated that fluorination of bifunctional substrate *cis*-**12** would proceed in a chemoselective manner. In the event, fluoroallylic carbonate *cis*-**13** was formed in 80% yield as the only detectable fluorine-containing product (eq 1). Since preferential Pd-catalyzed allylic substitution of allylic carbonates over allylic fluorides has been reported,[23b] the catalytic

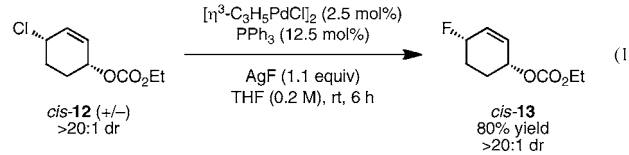
Table 3. Palladium-Catalyzed Fluorination of Allylic Chlorides



entry	product[a]	yield (%)[b]	ee (%)[c]	dr[d]
1	**5**	85[e]	88	N/A
2[f]	**7**	62[e]	90	N/A
3[f,g]	**8**	74	96	N/A
4[g,h]	*trans*-**2**	68	90	14:1
5	*cis*-**2**	70	91 (85)[i]	3:1[j]
6	**9**	85	85	>20:1
7	**10**	56	93 (88)[i]	7:1
8	**11**	59	87	20:1[j]

[a] Absolute configuration of **8** assigned by X-ray crystallography; other products assigned by analogy. [b] Isolated yield for reactions carried out on a 0.5 mmol scale. [c] Determined by chiral GC or HPLC using commercial chiral columns. [d] Determined by ^1H NMR; dr's were unchanged from starting material to product. [e] Determined by GC using octane as an internal quantitative standard. [f] Using commercial **L2** instead of **L1**. [g] Reaction conducted in toluene with 2.0 equiv of AgF. [h] Reaction conducted with $[\eta^3\text{-}C_3H_5PdCl]_2$ (5 mol %) and **L1** (15 mol %). [i] ee of minor diastereomer in parentheses. [j] dr of the allylic chloride was 5:1.

fluorination accesses a product primed for diversification by sequential Pd-catalyzed substitutions.



Notably, the allylic fluorinations in Table 3 and eq 1 deliver fluoride to the same diastereotopic face as that of the chloride leaving group in the substrate. To account for this outcome, we propose that Pd(0) oxidatively adds to the allylic chlorides by an S_N2-type reaction with inversion of configuration.[29] Chloride abstraction by Ag^+ prior to or concurrent with an outer-sphere attack of fluoride on the allyl-Pd intermediate would deliver fluoride with

an overall retention of configuration. As support for this proposal, and in line with our stoichiometric studies in Table 1, fluorination of an **L1**-ligated analog of **1** provided *trans*-**2** in 53% yield and 88% ee (compare to Table 3, entry 4; see Supporting Information for more details). In addition, the observation that the absolute configuration of the allylic fluorides is in accord with the predictive model developed by Trost for Pd-catalyzed asymmetric allylic alkylations with soft nucleophiles provides circumstantial evidence for an analogous mechanism.[30]

In summary, we have described a new methodology for the enantioselective synthesis of allylic fluorides by Pd(0)-catalyzed C−F bond formation with AgF. Our future efforts will be directed toward elucidating the full synthetic scope of the reaction. Additionally, studies to understand how a classically hard nucleophile plays the role of a soft nucleophile in this process are underway.[31]

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Supporting Information Available: Experimental procedures, details of mechanistic experiments and optimization studies, and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For a recent review, see: Furuya, T.; Klein, J. E. M. N.; Ritter, T. *Synthesis* **2010**, 1804–1821.
(2) (a) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134–7135. (b) Furuya, T.; Kaiser, H. M.; Ritter, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5993–5996. (c) Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2008**, *130*, 10060–10061. (d) Wang, X.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 7520–7521. (e) Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; García-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009**, *325*, 1661–1664. (f) Furuya, T.; Benitez, D.; Tkatchouk, E.; Strom, A. E.; Tang, P.; Goddard, W. A., III; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 3793–3807.
(3) (a) Hamashima, Y.; Sodeoka, M. *Synlett* **2006**, 1467–1478. (b) Wu, T.; Yin, G.; Liu, G. *J. Am. Chem. Soc.* **2009**, *131*, 16354–16355. (c) Qiu, S.; Xu, T.; Zhou, J.; Guo, Y.; Liu, G. *J. Am. Chem. Soc.* **2010**, *132*, 2856–2857.
(4) Kalow, J. A.; Doyle, A. G. *J. Am. Chem. Soc.* **2010**, *132*, 3268–3269.
(5) For recent reviews of asymmetric catalytic C−F bond formation using electrophilic and nucleophilic fluorine sources, see: (a) Cahard, D.; Xu, X.; Couve-Bonnaire, S.; Pannecoucke, X. *Chem. Soc. Rev.* **2010**, *39*, 558–568. (b) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1–PR43.
(6) For a review, see: Pacheco, M. C.; Purser, S.; Gouverneur, V. *Chem. Rev.* **2008**, *108*, 1943–1981.
(7) For examples of allylic fluoride motifs in pharmaceutical or imaging agents, see: (a) Khan, M. O. F.; Lee, H. J. *Chem. Rev.* **2008**, *108*, 5131–5145. (b) Stehouwer, J. S.; Daniel, L. M.; Chen, P.; Voll, R. J.; Williams, L.; Plott, S. J.; Votaw, J. R.; Owens, M. J.; Howell, L.; Goodman, M. M. *J. Med. Chem.* **2010**, *53*, 5549–5557.
(8) (a) Ishimaru, T.; Shibata, N.; Horikawa, T.; Yasuda, N.; Nakamura, S.; Toru, T.; Shiro, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4157–4161. For an indirect method to acyclic allylic fluorides by asymmetric organocatalytic α-fluorination, followed by homologation, see: (b) Jiang, H.; Falcicchio, A.; Jensen, K. L.; Paixão, M. W.; Bertelsen, S.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2009**, *131*, 7153–7157.
(9) (a) Grushin, V. V. *Chem.—Eur. J.* **2002**, *8*, 1006–1014. (b) Yandulov, D. V.; Tran, N. T. *J. Am. Chem. Soc.* **2007**, *129*, 1342–1358. (c) Grushin, V. V. *Acc. Chem. Res.* **2010**, *43*, 160–171.
(10) For reviews, see: (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395–422. (b) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258–297. (c) Trost, B. M.; Zhang, T.; Sieber, J. D. *Chem. Sci.* **2010**, *1*, 427–440.
(11) For an unsuccessful investigation, see: Hintermann, L.; Läng, F.; Maire, P.; Togni, A. *Eur. J. Inorg. Chem.* **2006**, 1397–1412.
(12) A computational investigation has been reported that supports the feasibility of allylic C−F bond formation from a π-allyl palladium complex: Hagelin, H.; Åkermark, B.; Norrby, P.-O. *Chem.—Eur. J.* **1999**, *5*, 902–909.
(13) For a discussion of the relative advantages and disadvantages of nucleophilic and electrophilic fluorine sources, see: Furuya, T.; Kuttruff, C. A.; Ritter, T. *Curr. Opin. Drug Discovery Dev.* **2008**, *11*, 803–819, and references therein.
(14) Kurosawa, H.; Kajimaru, H.; Ogoshi, S.; Yoneda, H.; Miki, K.; Kasai, N.; Murai, S.; Ikeda, I. *J. Am. Chem. Soc.* **1992**, *114*, 8417–8424.
(15) Pilcher, A. S.; Ammon, H. L.; DeShong, P. *J. Am. Chem. Soc.* **1995**, *117*, 5166–5167.
(16) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730–4743.
(17) CoF_2, MnF_2, AgF_2, and several other transition metal fluorides were found to be ineffective as fluoride sources under catalytic conditions similar to those described in Table 2.
(18) Allylic chlorides can be prepared from allylic alcohols in one step. See Supporting Information for details.
(19) Togni and Mezzetti have reported a ruthenium complex that promotes Br/F exchange between alkyl, allyl, and benzyl bromides and TlF; see: (a) Barthazy, P.; Hintermann, L.; Stoop, R.; Wörle, M.; Mezzetti, A.; Togni, A. *Helv. Chim. Acta* **1999**, *82*, 2448–2453. (b) Barthazy, P.; Togni, A.; Mezzetti, A. *Organometallics* **2001**, *20*, 3472–3477.
(20) Finkelstein reactions between allylic halides and silver fluoride have been reported. For an example, see: Bannai, K.; Toru, T.; Oba, T.; Tanaka, T.; Okamura, N.; Watanabe, K.; Hazato, A.; Kurozumi, S. *Tetrahedron* **1986**, *42*, 6735–6746.
(21) Among the solvents tested, toluene and THF were optimal. Reactions conducted above room temperature or in more polar solvents showed increased background reactivity, presumably due in part to the enhanced solubility of AgF under these conditions.
(22) Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327–9343.
(23) (a) Narumi, T.; Tomita, K.; Inokuchi, E.; Kobayashi, K.; Oishi, S.; Ohno, H.; Fujii, N. *Org. Lett.* **2007**, *9*, 3465–3468. (b) Hazari, A.; Gouverneur, V.; Brown, J. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 1296–1299. (c) Pigeon, X.; Bergeron, M.; Barabé, F.; Dubé, P.; Frost, H. N.; Paquin, J.-F. *Angew. Chem., Int. Ed.* **2010**, *49*, 1123–1127.
(24) We have found that five- and seven-membered allylic chlorides undergo fluorination with reduced efficiency and enantioselectivity. An acyclic allylic chloride, (*E*)-6-chloronon-4-ene, also reacted with low enantioselectivity. See Supporting Information for details.
(25) Allylic fluorides **2** and **5** are unstable to borosilicate glass in neat form. See: Lee, E.; Yandulov, D. V. *J. Fluorine Chem.* **2009**, *130*, 474–483.
(26) (a) Singh, R. P.; Shreeve, J. M. *Synthesis* **2002**, 2561–2578. (b) Bresciani, S.; Slawin, A. M.; O'Hagan, D. *J. Fluorine Chem.* **2009**, *130*, 537–543.
(27) Pilon, M. C.; Grushin, V. V. *Organometallics* **1998**, *17*, 1774–1781.
(28) Allylic fluorinations set up under an inert atmosphere, with rigorous exclusion of air and moisture, proceed with comparable % yield and % ee.
(29) Oxidative addition of Pd(0) to allylic chlorides with inversion of configuration has been documented. See ref 14.
(30) Trost, B. M.; Machacek, M. R.; Aponick, A. *Acc. Chem. Res.* **2006**, *39*, 747–760.
(31) Parr, R. G.; Pearson, R. G. *J. Am. Chem. Soc.* **1983**, *105*, 7512–7516.

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