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Palladium-Catalyzed Regio- and Enantioselective Fluorination of Acyclic Allylic Halides

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Supporting Information

ABSTRACT: This report describes the Pd(0)-catalyzed fluorination of linear allylic chlorides and bromides, yielding branched allylic fluorides in high selectivity. Many of the significant synthetic limitations previously associated with the preparation of these products are overcome by this catalytic method. We also demonstrate that a chiral bisphosphine-ligated palladium catalyst enables highly enantioselective access to a class of branched allylic fluorides that can be readily diversified to valuable fluorinated products.

Allylic fluorides occur in a range of pharmaceutical agents, PET tracers, and agrochemicals.[1] Moreover, in much the same way that allylic alcohols are versatile intermediates in chemical synthesis,[2] chiral allylic fluorides can serve as building blocks for the preparation of valuable fluorine-containing synthons. This privileged functionality is usually assembled by allylic substitution; however, achieving high regio- and stereoselectivity in such processes has been a longstanding challenge. The synthesis of *linear* allylic fluorides by nucleophilic displacement of halides or activated alcohols with metal or ammonium fluorides typically proceeds with high regioselectivity, including in a recent Pd-catalyzed example (eq 1).[3] Alternatively, the method of choice for the production of *branched* allylic fluorides is deoxyfluorination of allylic alcohols with diethylaminosulfur trifluoride (DAST) or its derivatives (eq 2).[4] Unfortunately, many of these reactions proceed with only marginal bias for the branched regioisomer. In addition, fluorinations of chiral allylic alcohols lead to erosion in regio- and enantiopurity through S_N1 and S_N2' pathways, and the reactions are intolerant of common organic functional groups (alcohols, aldehydes, ketones).[5] To address some of these limitations, Gouverneur and co-workers have identified an alternative approach to the synthesis of these products by fluorodesilylation of allylsilanes.[6,7] Although the reactions are highly branched-selective, asymmetric catalytic variants are almost completely undeveloped.[8]

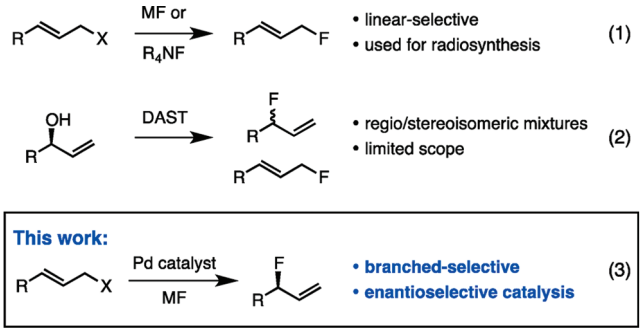
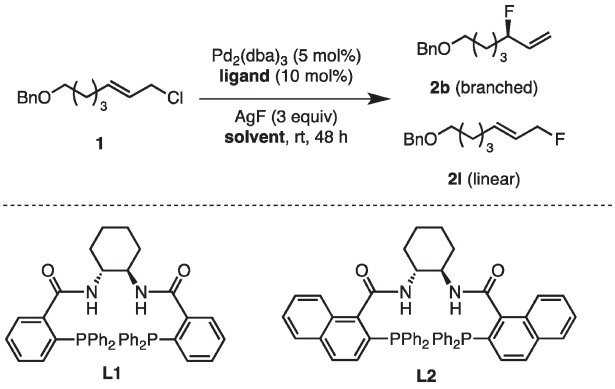


Table 1. Optimization of Branched-Selective Fluorination



entry	ligand[a]	solvent	yield[b]	b:l[b]
1	PPh_3[c]	toluene	70	6:1
2	dppe	toluene	21	2:1
3	dppf	toluene	20	2:1
4	DPEphos	toluene	24	4:1
5	**L1**	toluene	23	3:1
6	Xantphos	toluene	55	7:1
7	**L2**	toluene	76	>20:1
8	**L2**	THF	22	1:1
9	**L2**	CH_2Cl_2	26	2:1
10	**L2**	CH_3CN	6	1:4

[a] Bite angles for bidentate ligands:[9] dppe (86°), dppf (99°), DPEphos (104°), **L1**[10] (107°), Xantphos (108°). [b] Determined by GC using dodecane as a quantitative internal standard. [c] Using 30 mol % ligand.

Recent work from our laboratory has demonstrated that a chiral bisphosphine-ligated palladium catalyst promotes enantioselective fluorination of cyclic allylic chlorides with AgF.[11] Mechanistically, these reactions proceed in a manner analogous to asymmetric allylic alkylations with stabilized nucleophiles:[12] namely, by outer-sphere attack of fluoride on a Pd π-allyl intermediate. We sought to extend this catalytic system to branched-selective allylic fluorination of acyclic substrates and report herein that high regio- and enantioselectivity can be obtained for the preparation of branched allylic fluorides using Pd(0) catalysis (eq 3). The methodology addresses many of the current limitations for the synthesis of this motif, furnishing a diverse collection of synthetically valuable fluorinated products under

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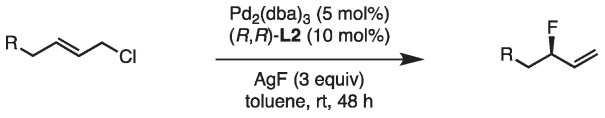
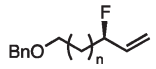
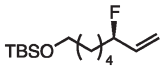
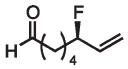
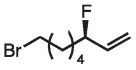
Table 2. Scope of Regioselective Allylic Fluorination



entry	product		yield (%)[a]	b:l[b]	ee (%)[c]
1		**2** (n = 3)	78	>20:1	58
2		**3** (n = 1)	83	>20:1	21
3		**4**	84	>20:1	58
4[d]		**5**	67	>20:1	71
5[e]		**6**	66	>20:1	nd[f]

[a] Isolated yields (combined branched and linear isomers) for reactions carried out on a 0.5 mmol scale. [b] Determined by GC analysis of crude reaction mixtures. [c] Determined by GC or HPLC using commercial chiral columns. [d] Reaction conducted with $Pd(dmdba)_2$ (10 mol %) for ease of purification. [e] Reaction conducted in benzene. [f] Not determined.

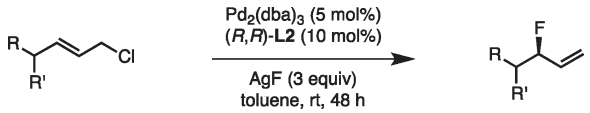
mild conditions, using commercial and bench-stable reagents and catalysts.

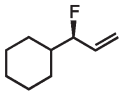
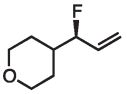
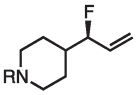
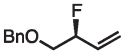
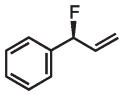
We began our investigation using acyclic chloride **1** as a substrate for allylic fluorination with AgF in the presence of $Pd_2(dba)_3$ and various ligands.[13] Notably, promising levels of regioselectivity (6:1 branched:linear) were obtained simply by employing PPh_3 as a ligand (Table 1, entry 1); in contrast, preparation of **2** utilizing DAST affords an inseparable mixture of isomers in a 2:1 b:l ratio.[14]

A number of bidentate phosphines were next examined. We found that those with larger bite angles induced higher regioselectivity (entries 2−6), with the commercial Trost naphthyl ligand **L2** delivering product in a >20:1 b:l ratio (entry 7).[15] Similar bite angle trends have been described for Pd-catalyzed allylic substitution with outer-sphere nucleophiles,[16] but reactions with acyclic, unsymmetrical substrates usually afford low-to-moderate regioselectivity in favor of the branched isomer.[17−19] We hypothesize that the enhanced selectivity with fluoride arises in part from its small size, which would facilitate nucleophilic addition at the more hindered terminus of the Pd π-allyl intermediate.[20] Furthermore, **L2** may direct regioselective allylic substitution by hydrogen-bond donation to the nucleophile, as proposed by Lloyd-Jones and Norrby in their stereochemical model of Pd-catalyzed asymmetric allylic alkylations.[21] As such, the selectivity with fluoride could also be ascribed to its strong hydrogen-bond acceptor properties.[22] As would be expected based on this proposal, nonpolar solvents such as toluene afforded optimal regioselectivities (entries 7−10). Use of toluene also suppresses an unselective background reaction on account of the low solubility of AgF in this solvent.

The broad substrate scope and ease of operation of the optimized process are highlights of the catalytic methodology. As outlined in Table 2, substrates containing benzyl and silyl ethers undergo reaction with high regioselectivity to afford **2**−**4** in 78−84% yield (entries 1−3).[23,14] The mild reaction

Table 3. Enantioselective Synthesis of Branched Allylic Fluorides



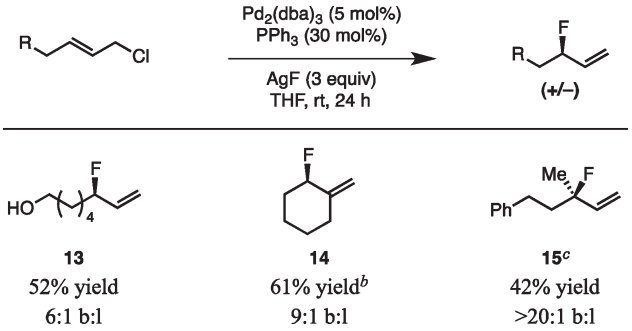
entry	product[a]		yield (%)[b]	b:l[c]	ee (%)[d]
1		**7**	84[e]	>20:1	90
2[f]		**8**	62	>20:1	97
3[f, g]		**9** (R = Boc)	85	10:1	93
4[g]		**10** (R = Cbz)	88	10:1	93
5		**11**	50	16:1	90
6		**12**	77[e]	1:4	0

[a] Absolute configuration of **7** assigned by derivatization to a compound with known stereochemistry; other products assigned by analogy. [b] Isolated yields (combined branched and linear isomers) for reactions carried out on 0.5−1.0 mmol scale. [c] Determined by GC or NMR analysis of crude reaction mixtures. [d] Determined by GC or HPLC using commercial chiral columns. [e] Determined by GC using dodecane as a quantitative internal standard. [f] Reaction conducted with $Pd(dmdba)_2$ (10 mol %) for ease of purification. [g] Reaction conducted with allylic bromide as starting material.

conditions are also tolerant of aldehydes and alkyl bromides (entries 4 and 5). These products bear synthetically useful functional groups, most of which are incompatible with alternative protocols for the preparation of allylic fluorides.[4,7a] Furthermore, the Pd-catalyzed method affords minimal diene byproducts (<5%), as determined by GC analysis of the crude reaction mixtures.

A current limitation of the reactions in Table 2 is that, in contrast to our previous results with cyclic allylic chlorides, moderate to low enantioselectivity is attained with these acyclic substrates. We reasoned that substrates possessing allylic substituents of greater steric or electronic bias might afford higher asymmetric induction under the fluorination conditions. In the event, we were pleased to find that various allylic chlorides and bromides bearing α-branching or heteroatom substituents undergo fluorination with 90−97% ee (Table 3, entries 1−5).[24] Ethers and protected amines are well-tolerated, and motifs such as a β-fluoroether (**11**) can be accessed in 90% ee and 16:1 b:l selectivity. In contrast to these results, the synthesis of **9** by the reaction of an enantiopure branched allylic alcohol with DAST proceeds with significant erosion in enantiopurity (>99% ee to 49% ee) and 2:1 b:l selectivity.[14] The Pd-catalyzed method affords mainly linear product using cinnamyl chloride as substrate, with the minor branched isomer formed in 0% ee (entry 6).

Scheme 1. Regioselective Fluorination with PPh_3 as Ligand[a]



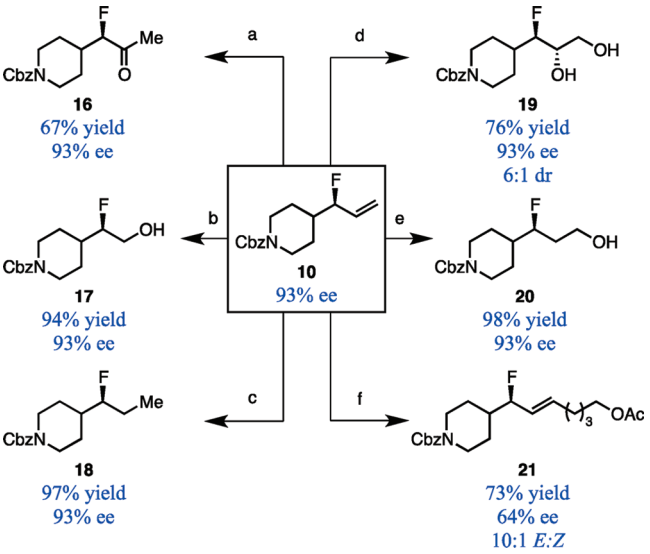
[a] Isolated yields (combined branched and linear isomers) for reactions carried out on 0.5 mmol scale. b:l ratios determined by GC analysis of crude reaction mixtures. [b] Determined by GC using dodecane as a quantitative internal standard. [c] Reaction conducted in benzene.

Preference for this regioisomer has also been reported by Gouverneur and co-workers in their Pd-catalyzed fluorination of cinnamyl 4-nitrobenzoates[3] and is commonly found for Pd-catalyzed allylic alkylations with cinnamyl substrates.[12,17b]

Despite the broad functional group tolerance of the fluorinations in Tables 1 and 2, we have discovered that certain substrates perform poorly with **L2** as ligand. For example, allylic fluoride **13** and the structurally distinct **14** and **15** are formed in low b:l selectivity (1:1, 1:1, and 7:1, respectively).[14] This problem can be circumvented through the use of PPh_3 as ligand, which provides **13**−**15** in 6:1 to >20:1 b:l selectivity (Scheme 1).[15] In comparison with alternative protocols for allylic fluorination, this catalytic method is unique in its ability to tolerate an unprotected alcohol. Nevertheless, **13** is produced in only moderate yield due to competitive intramolecular allylic etherification.[14] Exocyclic methylene-containing allylic fluorides such as **14**, generated in a 9:1 b:l ratio, represent a common motif found in non-natural vitamin D analogs.[25] For tertiary allylic fluoride **15**, formation of a fully substituted carbon center at the electrophile by Pd-catalyzed allylic substitution is noteworthy.[26] However, competitive diene formation (20−30%) erodes the efficiency of this reaction, as well as that for the synthesis of **14**. A final limitation is that the fluorinations with either **L2** or PPh_3 are not compatible with secondary alkyl amines as these substrates undergo competitive *N*-alkylation.

Overall, access to fluorine-containing products by asymmetric allylic substitution provides an opportunity to rapidly generate a wide array of fluorinated synthons from a common, bench-stable precursor. To illustrate this point, we elaborated allylic fluoride **10** via Wacker oxidation,[27] ozonolysis/reduction, hydrogenation, diastereoselective dihydroxylation,[28] hydroboration/oxidation, and cross-metathesis.[29] Despite the versatility of the allyl functional group, some of the transformations in Scheme 2 have never been carried out on allylic fluorides, and most have not been performed on enantioenriched material due to the paucity of methods for their synthesis. Excellent stereofidelity is observed in each of the transformations, with the exception of the cross-metathesis reaction, which results in erosion from 93 to 64% ee due to the forcing conditions required for productive bond construction. Motifs such as those found in enantioenriched β-fluoroalcohol **17**[30] and internal allylic fluoride **21**[31] may now be prepared by both asymmetric catalytic electrophilic and nucleophilic fluorination. Notably, products that are otherwise difficult

Scheme 2. Derivatization of Allylic Fluoride 10[a,b]



[a] Reagents and conditions: (a) Pd(quinox)Cl_2, $AgSbF_6$, TBHP, CH_2Cl_2, 0 °C to rt; (b) O_3, then $NaBH_4$, CH_2Cl_2/MeOH, −78 °C to rt; (c) NBSH, Et_3N, CH_2Cl_2, 0 °C to rt; (d) AD-mix β, $NaHCO_3$, *t*-BuOH/H_2O, 0 °C to rt; (e) 9-BBN, 0 to 40 °C, then NaOH, H_2O_2, THF rt; (f) Hoveyda−Grubbs II, 5-hexenyl acetate, CH_2Cl_2, 100 °C. [b] Isolated yields for reactions carried out on a 0.2 mmol scale. ee's determined by HPLC using commercial chiral columns.

or impossible to access in enantioenriched form, such as acyclic α-fluoroketone **16**,[32] aliphatic fluoride **18**, diol **19**,[28] and γ-fluoroalcohol **20**, can be prepared in one step from allylic fluoride **10**.

In conclusion, we have developed a new approach to the highly regioselective synthesis of branched allylic fluorides that is operationally trivial and displays unprecedented functional group tolerance. The utility of this transformation has been highlighted via the expedient synthesis of a wide range of valuable fluorine-containing building blocks. Since $Ag^{18}F$ is readily available,[33] we intend to optimize the process for future applications in the production of radiotracers for PET imaging.[34] Our future investigations will also focus on elucidating the origin of the noteworthy ligand-dependent regioselectivity observed in this Pd-catalyzed process and extending the approach to non-allylic C−F bond formation.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, additional reaction optimization, X-ray crystallographic structure of **10**, and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) To the best of our knowledge, the bite angle of **L2** has not been reported. The bite angle of an **L1**−Pt complex has been computationally estimated at 107°: (a) Ohshima, T.; Miyamoto, Y.; Ipposhi, J.; Nakahara, Y.; Utsunomiya, M.; Mashima, K. *J. Am. Chem. Soc.* **2009**, *131*, 14317–14328. For a crystal structure of a ligand related to **L1** and **L2**, see:(b) Trost, B. M.; Breit, B.; Peukert, S.; Zambrano, J.; Ziller, J. W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2386–2388.

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(13) Highly branched-selective allylic substitution can be achieved with other transition metal catalysts, including Ir, Mo, and Cu (see ref 12); however, we found that these metals provided low regioselectivity for fluorination with allylic chlorides.

(14) See Supporting Information.

(15) We do not yet fully understand why PPh_3 provides superior selectivity to many of the bidentate ligands in Table 1 and to **L2** for products **13**−**15** in Scheme 1. However, π-acceptor ligands have been shown to induce high b:l selectivity in other Pd-catalyzed allylic substitution reactions: (a) Åkermark, B.; Zetterberg, K.; Hansson, S.; Krakenberger, B.; Vitagliano, A. *J. Organomet. Chem.* **1987**, *335*, 133–142. Since PPh_3 is a better π-acceptor than many of the bidentate ligands in Table 1, this electronic effect may account for the higher regioselectivity. Additionally, the P−Pd−P angle in a $[(PPh_3)_2Pd$-(cinnamyl)$]BF_4$ complex is 104°, similar in magnitude to the larger bite angles of the bidentate ligands of Table 1: (b) Baize, M. W.; Blosser, P. W.; Plantevin, V.; Schimpff, D. G.; Gallucci, J. C.; Wojcicki, A. *Organometallics* **1996**, *15*, 164–173.

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(17) See ref 15a and: (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545–4554. (b) Trost, B. M.; Ariza, X. *J. Am. Chem. Soc.* **1999**, *121*, 10727–10737.

(18) For examples where this selectivity has been overcome with biased substrates, see: (a) Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968–5976. (b) Trost, B. M.; Osipov, M.; Dong, G. *J. Am. Chem. Soc.* **2010**, *132*, 15800–15807.

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(22) Clark, J. H. *Chem. Rev.* **1980**, *80*, 429–452.

(23) Synthesis of **2**−**4** using DAST provides 2:1 b:l selectivity. Fluorinations with PPh_3 as ligand provide **2**−**6** in <7:1 b:l selectivity.

(24) Allylic bromides were used as substrates when the rate of reaction and selectivity were inferior with allylic chlorides.

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