

Palladium-Catalyzed Enantioselective 1,1-Fluoroarylation of Aminoalkenes

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S Supporting Information

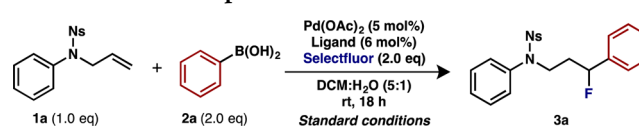
ABSTRACT: The development of an enantioselective palladium-catalyzed 1,1-fluoroarylation of unactivated aminoalkenes is described. The reaction uses arylboronic acids as the arene source and Selectfluor as the fluorine source to generate benzylic fluorides in good yields with excellent enantioselectivities. This transformation, likely proceeding through an oxidative Heck mechanism, affords 1,1-difunctionalized alkene products.

The unique properties engendered by fluorine¹ have inspired a number of strategies for the enantioselective construction of C–F bonds employing either electrophilic or nucleophilic fluorine sources.^{2–5} The difunctionalization of alkenes has emerged as an attractive strategy for the simultaneous formation of C–F and C–X (X = C, N, P, etc.) bonds.^{6,7} However, while great progress has been made in fluorocyclization of alkenes,⁸ intermolecular difunctionalization of alkenes as a means for enantioselective construction of C–F bonds remains challenging.⁹ We recently reported a palladium-catalyzed asymmetric 1,2-fluoroarylation of styrenes with boronic acids and Selectfluor as the fluorine source (Figure 1a).¹⁰ Key to this transformation was the placement of

alkenes with arylstannanes (Figure 1b) in the absence of a directing group on the alkene.¹³ Inspired by these reports, we have developed a catalytic enantioselective 1,1-arylfuorination of alkenes with arylboronic acids and Selectfluor (Figure 1c).

On the basis of the interest in fluorine-containing amines,¹⁴ we began our investigation by examining the fluoroarylation of protected allylamine **1a** with phenylboronic acid (**2a**). Using these substrates, conditions similar to those previously employed in the 1,2-fluoroarylation of styrenes¹⁰ afforded the 1,1-fluoroarylation product **3a**, albeit with moderate yield (Table 1, entry 1). Notably, the product derived from the

Table 1. Selected Optimization of Reaction Conditions^a



entry	variation from "standard conditions"	yield (%) ^b
1	none	50
2	2,2'-bipyridine as ligand	44
3	NFSI instead of Selectfluor	trace
4	Ts instead of Ns in 1a	44
5	Mbs instead of Ns in 1a	40
6	Ms instead of Ns in 1a	42
7	no water	
8	no catalyst or no ligand	
9	MeCN (0.1 mL) as additive	75 ^c

^aReaction conditions: all reactions were run on 0.1 mmol scale with respect to **1a**. Ligand: 4,4'-*tert*-butyl-2,2'-bipyridine; CH₂Cl₂, 1.0 mL; H₂O, 0.2 mL. ^b¹H NMR yield using 1,3,5-trimethoxybenzene as internal standard. ^cIsolated yield. Ns = 4-nitrobenzenesulfonyl, Ts = 4-methylbenzenesulfonyl, Mbs = 4-methoxybenzenesulfonyl, Ms = methanesulfonyl.

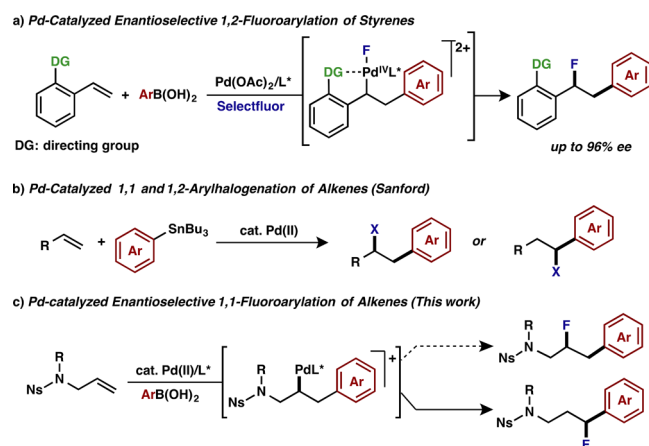


Figure 1. Pd-catalyzed arylhalogenation of alkenes.

a directing group on the alkene, which disfavored the oxidative Heck reaction¹¹ and allowed for C–F bond formation via a high-valent palladium intermediate.¹² In contrast, Sanford has described the 1,2 or 1,1-arylchlorination/bromination of

1,2-fluoroarylation of **1a** was not observed.¹⁵ Encouraged by this discovery, we set out to further optimize the reaction conditions. Modification of the ligand afforded little change in the yield (Table 1, entry 2). The use of *N*-fluorobenzenesulfonamide (NFSI) as an alternative source of fluorine resulted in only trace yield of **3a** (Table 1, entry 3). Changing the nitrogen protecting group did not have a dramatic impact on the yield of this transformation (Table 1, entries 4–6). No 1,1-fluoroarylated product was formed when water (Table 1, entry 7),

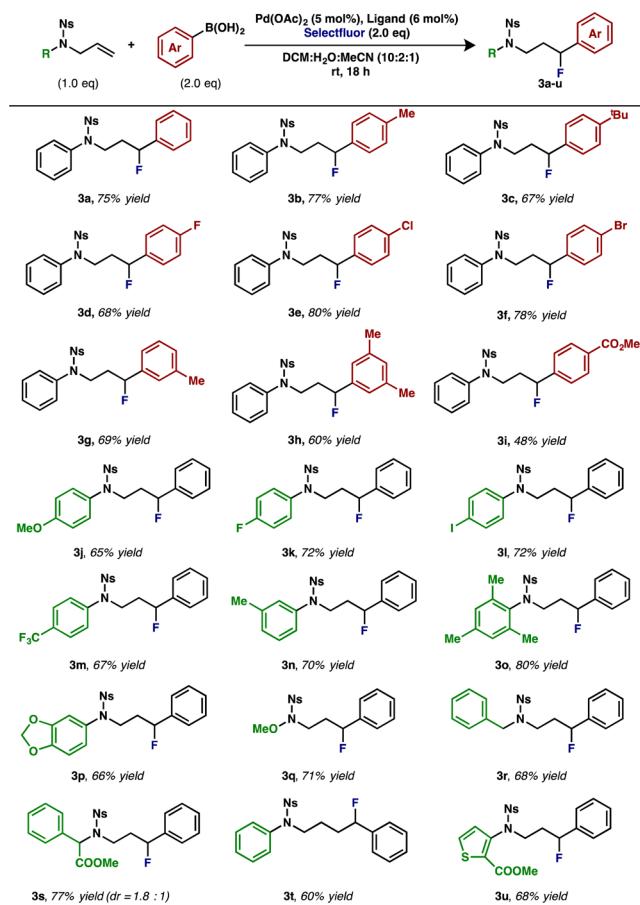
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ligand, or palladium (Table 1, entry 8) were removed from the reaction. However, the addition 0.1 mL of MeCN resulted in an increase in yield to 75% (Table 1, entry 9).

With the optimized conditions in hand, we investigated the scope of the palladium-catalyzed 1,1-arylfuorination (Table 2).

Table 2. Substrate Scope^a



^aReaction conditions: alkene (0.1 mmol), boronic acid (0.2 mmol), Selectfluor, (0.2 mmol), ligand: 4,4'-ditert-butyl-2,2'-bipyridine; CH_2Cl_2 , 1.0 mL; H_2O , 0.2 mL; MeCN, 0.1 mL; yield of isolated products.

The reaction was amenable to halogen and alkyl substitution in the *para*- and *meta*-positions of the arylboronic acids (3a–3h). Additionally, the coupling of an arylboronic acid substituted with an electron-withdrawing ester group afforded benzyl fluoride 3i in 48% yield. With respect to the alkene scope, substitution at nitrogen with aryl moieties bearing either electron-donating or electron-withdrawing groups in the *para*- or *meta*-position was well tolerated (3j–3n). Notably, γ -fluoroamine 3l was also obtained in good yield, leaving the *iodo* group intact for further transformations. Moreover, substrates derived from hindered anilines proved competent in this transformation (3o and 3p). The reaction was not limited to aniline derived substrates. Substrates with alkyl, *O*-alkyl, and heteroaryl-substitution at nitrogen also furnished the desired products in good yields (3q, 3r, and 3u).

Use of a substrate derived from (\pm)-2-phenylglycine provided the corresponding product in excellent yield and a modest diastereomeric ratio (1.8:1) (3s). A longer chain alkene was also effective in the 1,1-fluoroarylation reaction, affording the desired δ -fluoroamine (3t) in 60% yield.¹⁶

Table 3. Selected Optimized Conditions of Enantioselective 1,1-Fluoroarylation^a

Reaction scheme for Table 3: $\text{N-allyl-N-phenylamine} + \text{Ar-B(OH)}_2 \xrightarrow[\text{solvent:H}_2\text{O:nitrile (8:8:1), rt, 18 h}]{\text{Pd}^{II} (10 \text{ mol\%}), \text{ligand (13 mol\%)}, \text{Selectfluor (3.0 eq)}} \text{1,1-arylfuorinated amine}$

entry	Pd	ligand	solvent	nitrile	% ee ^b (yield ^c)
1	Pd(OAc)_2	L1	$\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$		(trace)
2	$\text{Pd(MeCN)}_2\text{Cl}_2$	L1	$\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$		(trace)
3	$\text{Pd(MeCN)}_2\text{Cl}_2$	L1	$\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$	MeCN	66 (68%)
4	$\text{Pd(MeCN)}_2\text{Cl}_2$	L1	$\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$	^t PrCN	82
5	$\text{Pd(MeCN)}_2\text{Cl}_2$	L1	$\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$	BnCN	84
6	$\text{Pd(MeCN)}_2\text{Cl}_2$	L2	$\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$	BnCN	81
7	$\text{Pd(MeCN)}_2\text{Cl}_2$	L3	$\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$	BnCN	55
8	$\text{Pd(MeCN)}_2\text{Cl}_2$	L1	CH_2Cl_2	BnCN	80
9	$\text{Pd(MeCN)}_2\text{Cl}_2$	L1	benzene/ H_2O	BnCN	87
10 ^d	$\text{Pd(MeCN)}_2\text{Cl}_2$	L1	benzene/ H_2O	BnCN	90 (46%)

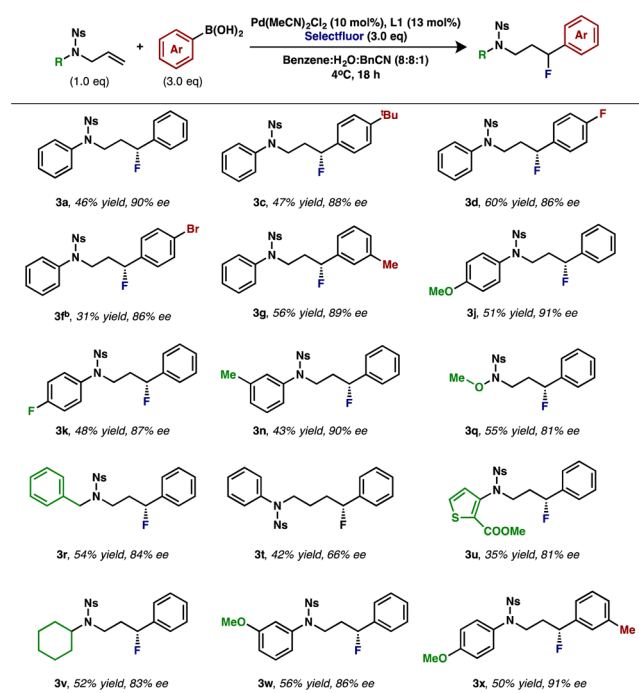
Ligand structures: L1 (4,4'-ditert-butyl-2,2'-bipyridine), L2 (4,4'-diisopropyl-2,2'-bipyridine), L3 (4,4'-diisopropyl-2,2'-bipyridine with a methyl group at the 2-position).

^aReaction conditions: 1a (0.1 mmol), 2a (0.3 mmol), Selectfluor (0.3 mmol); Cat., 10 mol %; ligand, 13 mol %; solvent, 0.8 mL; H_2O , 0.8 mL; nitrile, 0.1 mL; rt, 18 h. ^b% ee determined by chiral HPLC. ^c¹H NMR yields in parentheses. ^dThe reaction was carried out at 4 °C for 18 h, isolated yield in parentheses.

In light of the described results, we investigated the enantioselective palladium-catalyzed 1,1-fluoroarylation. Selected optimization studies are shown in Table 3 (for additional details, see the Supporting Information). Both Pd(OAc)_2 and $\text{Pd(MeCN)}_2\text{Cl}_2$ gave disappointing results without added nitrile (Table 3, entries 1 and 2); however, the reaction proceeded smoothly in the presence of acetonitrile as an additive, affording γ -fluoroamine 3a in 68% yield and 66% ee (Table 3, entry 3). On the basis of this initial result, examination of a variety of nitriles (see Supporting Information for full details) revealed that use of benzyl nitrile as an additive produced the desired product with the highest enantioselectivity (Table 3, entries 4 and 5). We then surveyed the effect of ligand, solvent, and temperature on the reaction and found that the enantiomeric excess of 3a was improved to 90% ee when using a solvent mixture of benzene/water at 4 °C for 18 h (Table 3, entries 6–10).¹⁷

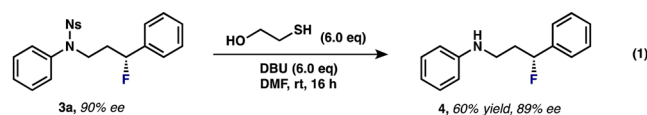
The substrate scope of the enantioselective transformation was explored under these optimized conditions. The reaction tolerated substitution in both the *para*- and *meta*-positions of the boronic acid coupling partner, producing the corresponding fluoroamines in 86–91% ee (Table 4, 3a–3g, 3x). With respect to the substitution at nitrogen, aniline-derived substrates bearing electron-donating or electron-withdrawing groups at the *para*- and *meta*-positions furnished the corresponding products in good to excellent enantioselectivities (3j–3n, 3w). Additionally, a heteroaryl group on nitrogen was also tolerated under the enantioselective conditions, affording the 1,1-fluoroarylation adduct 3u in 81% ee, albeit in 35% yield. Substrates with *O*-methyl and alkyl groups on nitrogen also provided the products in 81% ee to 84% ee (3q, 3r, and 3v); however, when a longer chain alkene was used, the product (3t) was obtained in 66% ee.

To demonstrate potential application of these chiral benzylic fluorides, removal of the nosyl group of 3a was carried out. The deprotection proceeded smoothly at room temperature,

Table 4. Substrate Scope of Enantioselective 1,1-Fluoroarylation^{ab18}

^a% ee determined by chiral HPLC, isolated yield; absolute configuration assigned by analogy to that of 3x, which was determined to be (R) by single-crystal X-ray diffraction (see Supporting Information for details). ^bRun at room-temperature in CH₂Cl₂:H₂O (1:1).

affording γ -fluoroamine in 60% yield while maintaining the enantiomeric excess; see eq 1:



In conclusion, we have disclosed a palladium-catalyzed 1,1-fluoroarylation of unactivated amino-alkenes by a three-component coupling of alkenes, arylboronic acids, and Selectfluor. Moreover, the reaction was extended to an asymmetric transformation that generated chiral benzylic fluorides in good to excellent enantioselectivities. This method promises to serve as a powerful strategy for the difunctionalization of alkenes to provide chiral fluorinated molecules.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b07795.

Crystallographic data (CIF)

Experimental procedures; compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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(15) The observance of no product derived from the 1,2-fluoroarylation of **1a** is believed to be a result of the sparing solubility of Selectfluor in organic solvents. The low concentration of Selectfluor in organic solvents allows β -hydride elimination and reinsertion to form the palladium-benzyl intermediate to outcompete oxidation. A mechanism involving β -hydride elimination and reinsertion is supported by literature precedent (ref 13b) and deuterium labeling experiments (see [Supporting Information](#)).

(16) Substrates bearing longer methylene tethers (those derived from pent-4-en-1-amine and hex-5-en-1-amine) furnished the 1,1-fluoroarylation adducts in low yield (<20%).

(17) The major byproduct in this case was the corresponding styrene derived from an oxidative Heck reaction.

(18) Substitution in the *ortho*-position of the phenylboronic acids (e.g., *o*-chlorophenyl and *o*-tolyl)boronic acid) gave low yields of the desired product under both the racemic and asymmetric reaction conditions.