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Palladium-Catalyzed Enantioselective 1,1-Fluoroarylation of Aminoalkenes

Ying He,[†,‡,§] Zhenyu Yang,[†,§] Richard T. Thornbury,[†] and F. Dean Toste*[,†]

[†]Department of Chemistry, University of California, Berkeley, California 94720, United States
[‡]Institute of Chemistry and BioMedical Science, Nanjing University, Nanjing 210046, China

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 fluorine[1] 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 a directing group on the alkene, which disfavored the oxidative Heck reaction[11] 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 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-arylfluorination of alkenes with arylboronic acids and Selectfluor (Figure 1c).

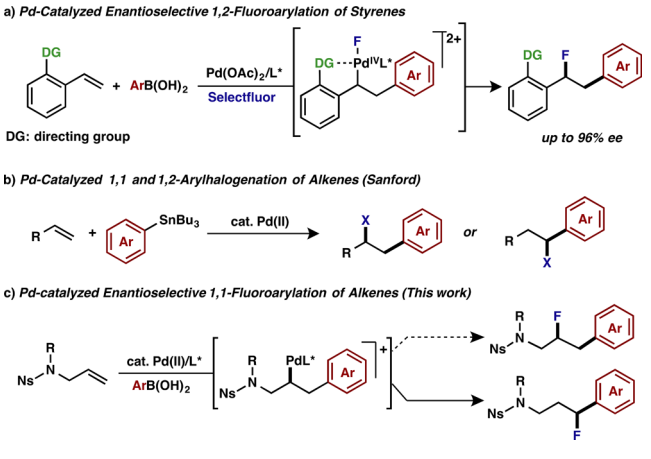
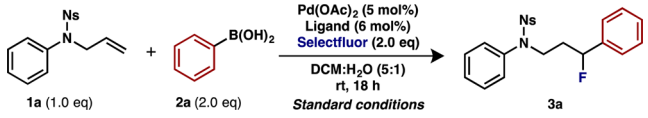


Figure 1. Pd-catalyzed arylhalogenation of alkenes.

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 styrenes[10] afforded the 1,1-fluoroarylation product **3a**, albeit with moderate yield (Table 1, entry 1). Notably, the product derived from the 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*-fluorobenzenesulfonimide (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),

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]

[a]Reaction conditions: all reactions were run on 0.1 mmol scale with respect to **1a**. Ligand: 4,4′-di*tert*-butyl-2,2′-bipyridine; CH_2Cl_2, 1.0 mL; H_2O, 0.2 mL. [b]^1H NMR yield using 1,3,5-trimethoxybenzene as internal standard. [c]Isolated yield. Ns = 4-nitrobenzenesulfonyl, Ts = 4-methylbenzenesulfonyl, Mbs =4-methoxybenzenesulfonyl, Ms = methanesulfonyl.

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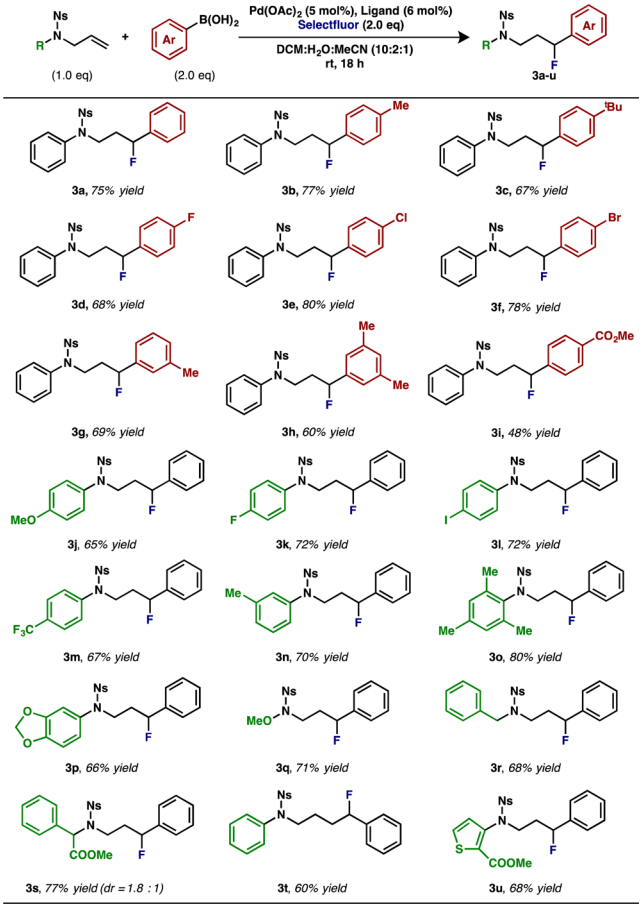
ligand, or palladium (Table 1, entry 8) were removed from the reaction. However, the addition 0.1 mL of MeCN resulted in an increase in yield to 75% (Table 1, entry 9).

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

Table 2. Substrate Scope[a]

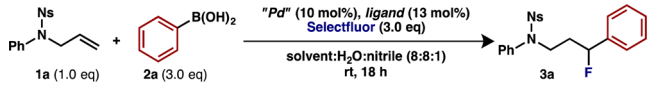


[a]Reaction conditions: alkene (0.1 mmol), boronic acid (0.2 mmol), Selectfluor, (0.2 mmol), ligand: 4,4′-di*tert*-butyl-2,2′-bipyridine; CH_2Cl_2, 1.0 mL; H_2O, 0.2 mL; MeCN, 0.1 mL; yield of isolated products.

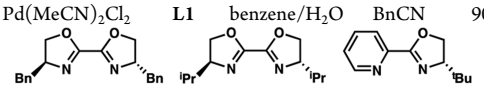
The reaction was amenable to halogen and alkyl substitution in the *para*- and *meta*-positions of the arylboronic acids (**3a**–**3h**). Additionally, the coupling of an arylboronic acid substituted with an electron-withdrawing ester group afforded benzyl fluoride **3i** in 48% yield. With respect to 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 (±)-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]



entry	Pd	ligand	solvent	nitrile	% ee[b] (yield[c])
1	$Pd(OAc)_2$	**L1**	CH_2Cl_2/H_2O		
2	$Pd(MeCN)_2Cl_2$	**L1**	CH_2Cl_2/H_2O		(trace)
3	$Pd(MeCN)_2Cl_2$	**L1**	CH_2Cl_2/H_2O	MeCN	66 (68%)
4	$Pd(MeCN)_2Cl_2$	**L1**	CH_2Cl_2/H_2O	^{i}PrCN	82
5	$Pd(MeCN)_2Cl_2$	**L1**	CH_2Cl_2/H_2O	BnCN	84
6	$Pd(MeCN)_2Cl_2$	**L2**	CH_2Cl_2/H_2O	BnCN	81
7	$Pd(MeCN)_2Cl_2$	**L3**	CH_2Cl_2/H_2O	BnCN	55
8	$Pd(MeCN)_2Cl_2$	**L1**	CH_2Cl_2	BnCN	80
9	$Pd(MeCN)_2Cl_2$	**L1**	benzene/H_2O	BnCN	87
10[d]	$Pd(MeCN)_2Cl_2$	**L1**	benzene/H_2O	BnCN	90 (46%)



[a]Reaction 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. [c]^{1}H NMR yields in parentheses. [d]The 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 $Pd(MeCN)_2Cl_2$ 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,

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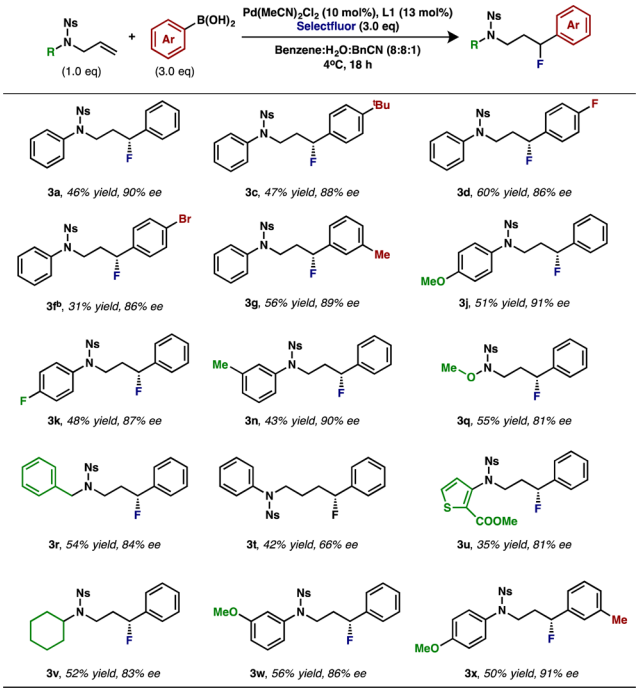
Table 4. Substrate Scope of Enantioselective 1,1-Fluoroarylation[ab18]



[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). [b]Run at room-temperature in CH_2Cl_2:H_2O (1:1).

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

(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 enantioselectivies. 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)

■ AUTHOR INFORMATION

Corresponding Author

*fdtoste@berkeley.edu

Author Contributions

§Y.H. and Z.-Y.Y. contributed equally to this work.

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.

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