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Asymmetric Palladium-Catalyzed Directed Intermolecular Fluoroarylation of Styrenes

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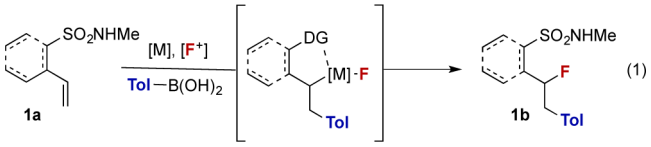
Supporting Information

ABSTRACT: A mild catalytic asymmetric direct fluoroarylation of styrenes has been developed. The palladium-catalyzed three-component coupling of Selectfluor, a styrene and a boronic acid, provides chiral monofluorinated compounds in good yield and in high enantiomeric excess. A mechanism proceeding through a Pd(IV)-fluoride intermediate is proposed for the transformation and synthesis of an sp^3 C−F bond.

Fluorine substituents have become widespread in their use in drugs,[1] their presence in a plethora of agrochemicals[2] and in high-performance materials. The introduction of fluorine affects a multitude of properties, and it is well-known that $C-(F)_x$ substituents can induce conformational changes, alter pK_a and dipole moments, increase the lipophilicity, and beneficially alter the oral bioavailability of a drug.[2,3] Given this perspective, their introduction has attracted considerable attention from the synthetic community, and the safe and selective introduction of these moieties into the desired scaffold is key to the further expansion in these areas of research. The asymmetric synthesis of sp^3 C−F bonds[4] is most commonly achieved through α-fluorination of ketones and aldehyde derivatives with the use of organocatalysts,[5] phase transfer catalysis,[6] or by way of ring-opening of strained heterocycles.[7] Few examples of enantioselective transition-metal-catalyzed fluorination exist, and where they do, the metal generally serves as a Lewis acid.[8] Herein, we report a palladium-catalyzed arylative fluorination and its application toward the enantioselective construction of sp^3 C−F bonds.

During the course of our studies on the Selectfluor promoted gold-catalyzed intramolecular aminoarylation of styrene **1a** with *p*-tolylboronic acid,[9] we noted that small amounts of benzylic fluoride **1b** was formed when bimetallic gold−palladium complexes were employed as catalysts. Switching to palladium chloride as a catalyst and employing bipyridine (BiPy) as a ligand allowed for **1b** to be formed as the major product. We envisioned that this product arose from a pathway in which the sulfonamide[10] served as chelating group, rather than a nucleophile, to a high-valent palladium intermediate (eq 1).

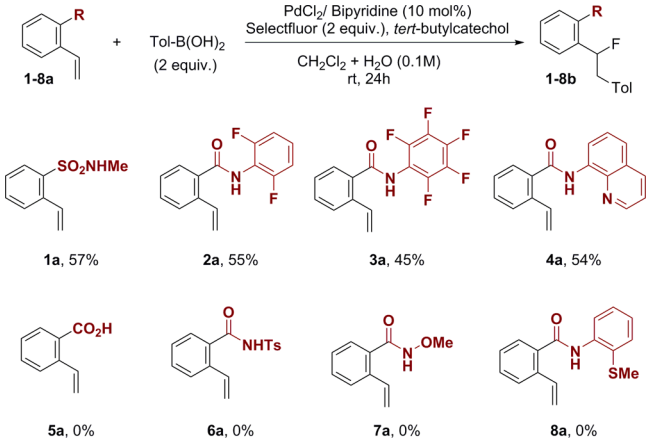


(1)

We had previously shown that sp^3 C−F occurred from gold(III)-fluorides[11] and Ritter and Sanford have elegantly demonstrated that C−F bonds could be generated from the reductive elimination of high-valent palladium.[12] Therefore, we reasoned that the directing group could control the regioselectivity and stabilize the high-valent metal intermediate in conjunction with the bipyridine ligand, diverting it from an oxidative Heck-type coupling reaction toward C−F bond formation.[13]

On the basis of this hypothesis, and starting from commercially available 2-vinylbenzoic acid, we sought an effective directing group (DG) that could provide the desired control of regiochemistry and product distribution. The $PdCl_2$/BiPy-catalyzed reaction of **1a** with *p*-tolylboronic acid and Selectfluor,[14] in wet CH_2Cl_2[15] containing *tert*-butylcatechol,[16] afforded the benzylic fluoride **1b** in 57% yield (Scheme 1).

Scheme 1. Screening of Suitable Directing Group[a]



[a]Yields after chromatographic purification.

Moreover, we were pleased to observe that under identical conditions, the desired fluorinated product was formed when the DG was 2,6-difluoroaniline, pentafluoroaniline,[17] or 8-aminoquinoline[18] (**2a**−**4a**, Scheme 1). In contrast, no product was detected with **5a**, and only cyclized nonarylated isoxindole-type products were observed with **6a** and **7a**. Finally, decomposition and trace of product was observed with **8a**, likely a result of competing oxidation of the arylthioether.

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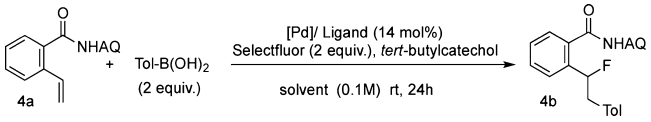
With these results in hand, we decided to focus our investigation using 8-aminoquinoline (AQ) as the directing group. This versatile directing group had proven easy to remove and offered more flexibility to extend the chemistry.[18] Screening of several palladium sources revealed $Pd(OAc)_2$ as the optimal choice, with $Pd(TFA)_2$, $PdCl_2$, and $PdBr_2$ all producing increased amounts of the undesired competing oxidative Heck process (see Supporting Information for product distribution) at the expensive of the desired fluoride (Table 1, entries 1–4). *N,N*-

Table 1. Optimization of Fluoroarylation of Styrene 4a



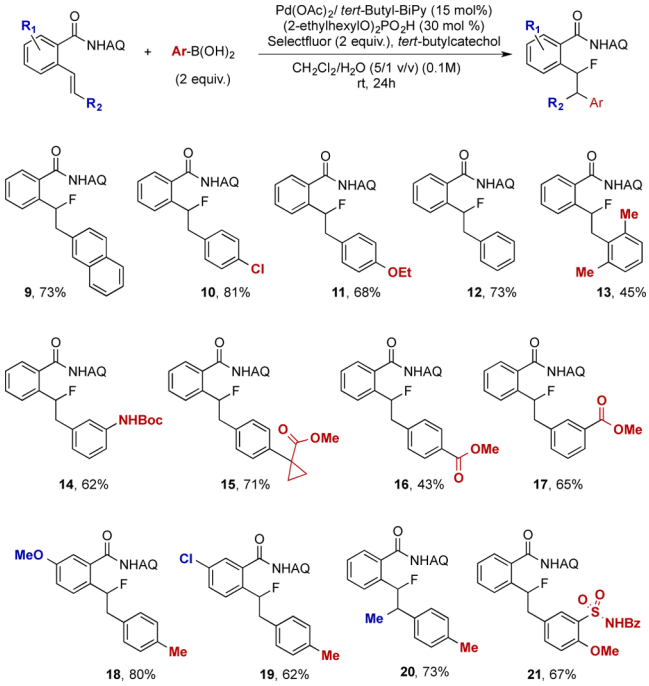
entry	catalyst	ligand[c]	solvents	additive[d]	yield 4b[a]
1	$PdCl_2$	L1	CH_2Cl_2/H_2O (1/0.1)	none	54
2	$Pd(OAc)_2$	L1	CH_2Cl_2/H_2O (1/0.1)	none	67
3	$PdBr_2$	L1	CH_2Cl_2/H_2O (1/0.1)	none	54
4	$Pd(TFA)_2$	L1	CH_2Cl_2/H_2O (1/0.1)	none	61
5	$Pd(OAc)_2$	–	CH_2Cl_2/H_2O (1/0.1)	none	0
6	$Pd(OAc)_2$	L2	CH_2Cl_2/H_2O (1/0.1)	none	56
7	$Pd(OAc)_2$	L3	CH_2Cl_2/H_2O (1/0.1)	none	76
8	$Pd(OAc)_2$	L3	CH_2Cl_2	none	23
9	$Pd(OAc)_2$	L3	CH_2Cl_2/H_2O (1/0.2)	none	82
10	$Pd(OAc)_2$	L3	CH_2Cl_2/H_2O (1/0.2)	P1: 30 mol %	91 (86)[b]
11	$Pd(OAc)_2$	L5	CH_2Cl_2/H_2O (1/0.2)	P1: 50 mol %	82
12	$Pd(OAc)_2$	L3	CH_2Cl_2/H_2O (1/0.2)	P2: 30 mol %	74

[a]Determined by correlation between HPLC-MS and crude 1H-NMR analysis. [b]Value in parentheses reflects isolated yield. [c]L1: bipyridine; L2: 4,4′-dimethoxy-2,2′-bipyridine, L3: 4,4′-di-*tert*-butyl-2,2′-bipyridine. [d]P1: bis(2-ethylhexyl) hydrogen phosphate; P2: dibenzyl hydrogen phosphate.

Bipyridine-type ligands were vital to achieving the fluorinative reaction manifold, with 4′4-di-*tert*-butylpyridine proving optimal (entry 7); absence of coordinating ligand produced solely the conventional Heck product (entry 5).[19] Solvent affects were dramatic with methylene chloride being the solvent of choice; no coupling products were formed in toluene, DMF, THF, CH_3CN, and EtOAc. Water was found to increase the reaction rate, and therefore the ideal solvent consisted of a biphasic mixture of 1.0:0.2 CH_2Cl_2:water (entries 7–9). Addition of an organic phosphate (30 mol %) as a phase transfer catalyst further increased the rate of the fluoroarylation and diminished the impurities seen in the reaction.[18k] Under the optimized reaction conditions, the palladium-catalyzed oxidative arylation of styrene **4a** furnished fluoride **4b** in 86% isolated yield after 24 h at room temperature (entry 10).

Having the optimized conditions in hand, a range of boronic acids[19] were subjected to the oxidative conditions using Selectfluor in CH_2Cl_2/water (5/1:v/v) to evaluate the scope of the reaction. As shown in Scheme 2, this protocol was efficient with various arylboronic acids bearing electron-donating groups

Scheme 2. Substrate Scope for AQ Directing Group[a]



[a]Yields after chromatographic purification.

such as methyl, methoxy, and amino afforded the corresponding coupling products in good yields. Benzylic fluoride **13** was generated in 45% yield after 24h with 2,6-dimethylphenylboronic acid as the substrate, indicating that steric hindrance has an effect on the reaction. The inductive electron-withdrawing/mesomerically donating chloro group was also well tolerated, and **10** was formed in 81% yield after 13h. Electron-poor ester-substituted boronic acids reacted slowly but still afforded the desired fluorides in modest to good yields. It should also be noted that reaction of *p*-tolylboronic acid and Selectfluor under the optimal conditions with the (*E*)-propenyl amide (R_2 = Me) yielded **20** as a single diastereoisomer. On the other hand, the palladium-catalyzed reaction of alkynyl, alkenyl, or alkyl boronic acids failed to deliver the desired product.[20]

In light of the above results, having defined conditions to control the regiochemistry and product distribution, we undertook the evaluation of a range of different *N,P*- and *N,N*-chiral ligands. Unfortunately, using these ligands resulted in erosion of the yield and slow conversion to the desired product; attempting to heat the reaction failed to increase the conversion. The most encouraging *N,N*-chiral ligand (pyridyl-oxazolidine ligand **L***) in combination with the quinolone-based directing, afforded **4b** in good enantiomeric excess (81%; er 90.5:9.5) but at the expense of yield (15%) (Scheme 3). Given the issues that were emerging using the quinolone-based directing group in conjunction with the *N,P*- and *N,N*-chiral ligands, we reinvestigated the requirements of our directing group. To that end, we were encouraged to find that the palladium-catalyzed enantioselective fluoroarylation of the 2,6-difluoroanilide and the 2,4,6-trimethylphenyl derivatives gave a much improved yield without significant changes to perturbing the enantioselectivity. The dramatic improvement was seen with the simplified anilides; an aromatic group with no *ortho*-substituent or even a simple methylamide now gave ee in excess of 90% and with the 4-methoxyanilide directing group giving fluororide **27** in 74% yield

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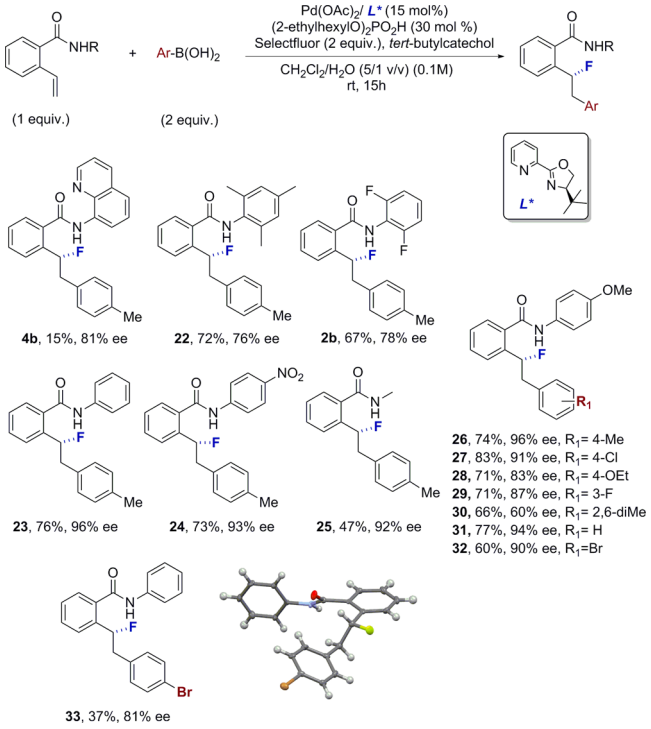
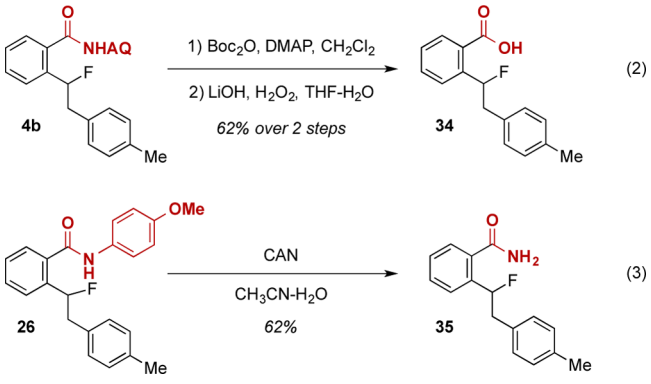
Scheme 3. Substrate Scope for Enantioselective Fluoroarylation[a]



[a]Yields after chromatographic purification and enantioselectivities determined by chiral SFC or HPLC. Absolute Configuration assigned by analogy to X-ray structure of **33**.

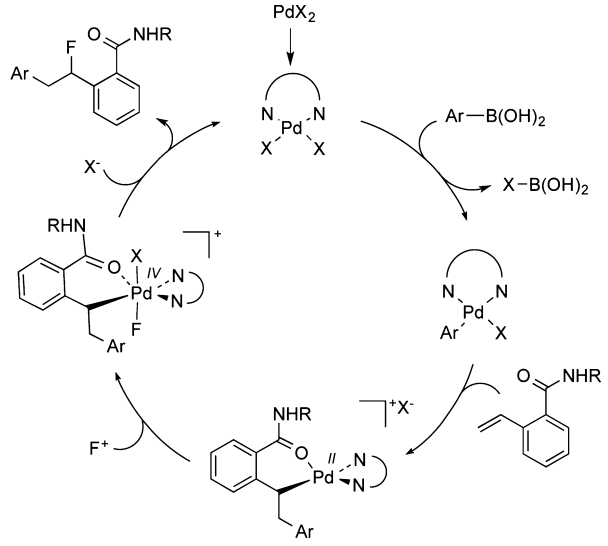
and 96% ee. Following these results, a range of boronic acids were tested on the 4-methoxyaniline substrate, and pleasingly, desired products (**26**–**32**) were obtained in good yield and high ee with the exception of the bulky 2,6-dimethylboronic acid.

To demonstrate the potential of this fluorinated compound as a useful precursor for synthesis, deprotection of the amino-quinoline **4b** was achieved using Boc anhydride with DMAP, followed by mild deprotection with LiOH and hydrogen peroxide in water/THF to give the desired acid **34** in 62% yield over two steps (eq 2).[18h] Additionally, the 4-methoxyanilide directing group employed in the enantioselective variant was converted to amide **35** be reaction with ceric ammonium nitrate (CAN) (eq 3).



A proposed mechanism for the reaction is outlined in Scheme 4. As already noted, fluoroarylation was only achieved in the presence of an *N,N*-ligand; thus, the catalytic cycle is initiated through formation of an *N,N*-ligated palladium(II) intermedi-

Scheme 4. Proposed Mechanism for the Directed Fluoroarylation of Styrene



ate.[21] Transmetalation with the boronic acid and thereafter coordination and insertion yields a β-arylated Pd(II) species. The regiocontrol of insertion is provided by the directing group coordination and the electronics of the substrate. The coordination of the directing group and the *N,N*-ligand may also stabilize this intermediate and retard the competing β-hydride elimination process thereby promoting oxidation.[22] Oxidation to the high-valent Pd(IV) intermediate is achieved using Selectfluor. Reductive elimination yields the desired monofluorinated product and the catalytic [N–N–Pd$^{(II)}$] complex.

In conclusion, using amide-based directing groups, we have developed a palladium-catalyzed fluoroarylation of styrenes. The reaction allows for the synthesis of a range of enantioenirched benzylic fluorides by a three-component coupling of styrenes, Selectfluor, and boronic acids.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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