Synthetic Methods

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Enantioselective Palladium-Catalyzed Oxidative β,β-Fluoroarylation of α,β-Unsaturated Carbonyl Derivatives

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Abstract: *The site-selective palladium-catalyzed three-component coupling of deactivated alkenes, arylboronic acids, and N-fluorobenzenesulfonimide is disclosed herein. The developed methodology establishes a general, modular, and step-economical approach to the stereoselective β-fluorination of α,β-unsaturated systems.*

Fluorine plays a decisive role in medicinal chemistry, having led to remarkable breakthroughs in the field.[1] Despite its widespread distribution in nature, the presence of fluorine in natural organic molecules is scarce, and most of the fluorine-containing organic molecules are synthetic.[2] Given this perspective, the development of new methodologies which gain access to new fluorinated derivatives is always in great demand, particularly those enabling selective fluorination on specified positions of an organic framework.

Among current strategies for the asymmetric construction of C(sp^3)−F bonds,[3] α-fluorination of carbonyl derivatives is the strategy most commonly exploited. Distinct approaches, including organocatalysis,[4] chiral anion phase-transfer catalysis,[5] ring-opening of strained heterocycles,[6] and transition-metal-catalyzed fluorinations[7] have been devised. In the last case, C−F reductive elimination[8] is usually accomplished from high-valent electron-deficient species,[9] since fluoride, as a hard base, is well suited for stabilizing highly oxidized metal centers.[10]

While great progress has been made in the assembly of C−F bonds adjacent to an electron-withdrawing group, just a few protocols incorporating fluorine at the β-position of a carbonyl derivative have been reported, and most of them are racemic. Seminal contributions entailed prior installation of a functional group, for example, alcohols, halides, sulfonates, or boronates, and further conversion into the corresponding β-fluorinated carbonyl compounds using either nucleophilic or electrophilic fluorinating reagents (Figure 1 a).[11] The enantioselective variant has recently been achieved through a fluorinative semipinacol rearrangement (Figure 1 b).[12] Recently reported methods explored selective C−H (Figure 1 c)[13] and C−C (Figure 1 d)[14] activation as a means to guide C(sp^3) fluorination.

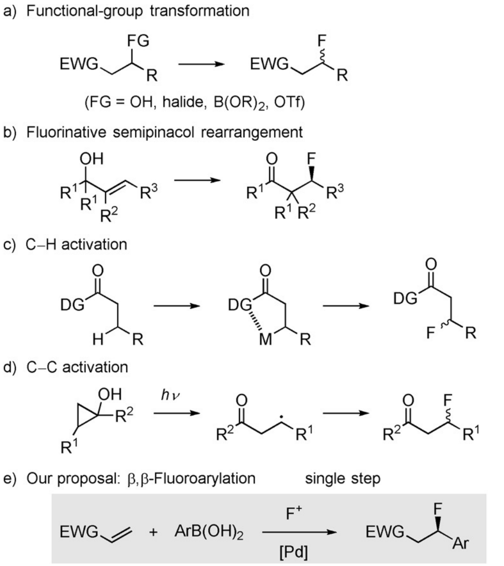

Figure 1. Strategies to access to β-fluorocarbonyl-derived systems. DG = directing group, EWG = electron-withdrawing group, FG = functional group, Tf = trifluoromethanesulfonyl.

On the basis of the limited reported oxidative transition-metal-catalyzed fluorinations[9,15] and inspired by the latest examples on palladium-catalyzed 1,1-difunctionalizations,[15b,16] we envisioned access β-fluorinated carbonyl derivatives by a single-step three-component Heck arylation/oxidative fluorination cascade reaction (Figure 1 e).

Under this scenario, we decided to test our hypothesis by examining the fluoroarylation of ethyl acrylate (**1a**) with 4-tolylboronic acid (**2a**) as a model reaction, under reaction conditions similar to those previously employed in the 1,2-fluoroarylation of styrenes[15a] (Table 1). Thus, **1a** was initially treated with **2a** (2 equiv), $Pd(OAc)_2$ (15 mol %), 1,10-phenanthroline (15 mol %), and 4-*t*Bu-catechol (4 mol %) in DCM/H_2O using Selectfluor as the electrophilic fluorine source. However, after 20 hours only trace amounts of the ester **3a** were detected, with the major product resulting from the undesired competing oxidative Heck reaction (entry 1). Pleasantly, switching the $(N-F)^+$ source to NFSI had a dramatic effect, thus giving rise to the exclusive formation of **3a**

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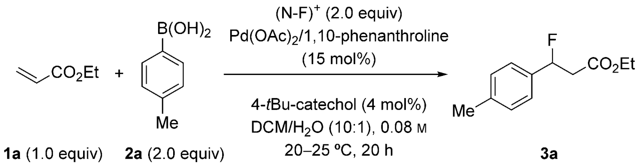
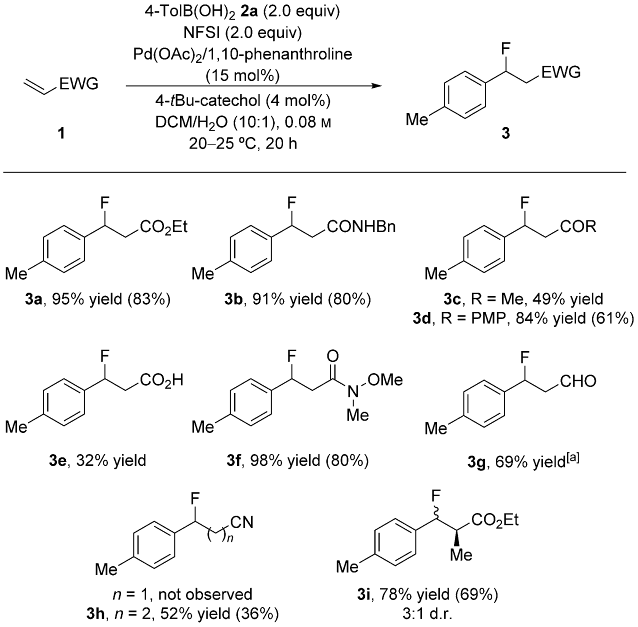
Table 1: Optimization of the reaction conditions.



Entry	Variant conditions	Yield [%]
1	$(N{-}F)^+$ = Selectfluor	trace
2	$(N{-}F)^+$ = NFSI	95
3	without degassing	–
4	without water	–
5	without 1,10-phenanthroline	–
6	without 4-*t*Bu-catechol	trace

[a] Reaction conditions: all reactions were run on 0.055 mmol scale with respect to **1a**. [b] Yields determined by ^{19}F NMR spectroscopy by utilizing fluorobenzene as internal standard. DCM = dichloromethane, NFSI = *N*-fluorobenzenesulfonimide.



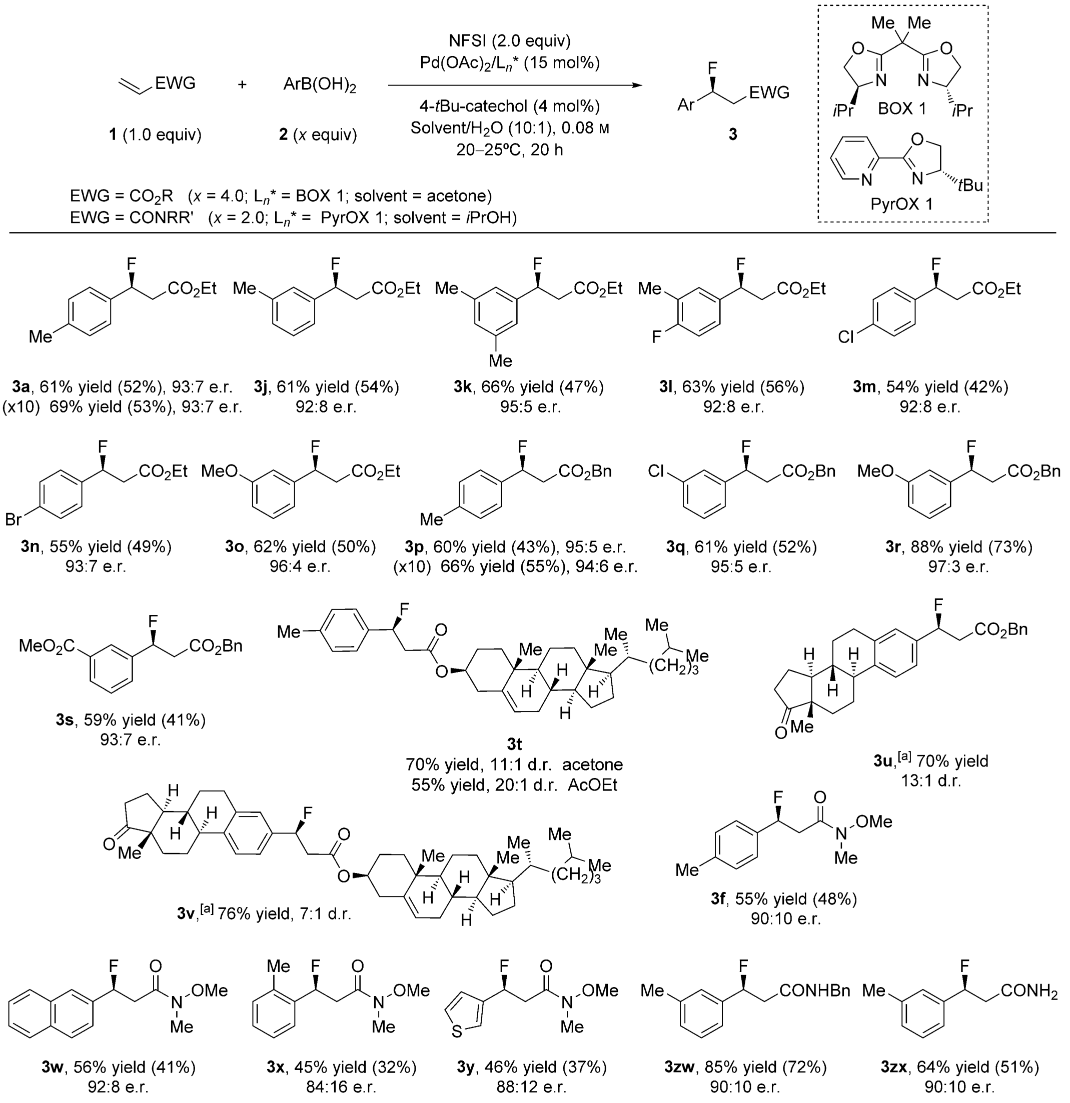
Scheme 1. Substrate scope for the non-enantioselective process. Reaction conditions: alkene (0.11 mmol), boronic acid (0.22 mmol), NFSI (0.22 mmol); $Pd(OAc)_2$/1,10-phenanthroline (15 mol%); DCM, 1.4 mL; H_2O, 0.14 µL; RT, 20 h. Yield determined by ^{19}F NMR spectroscopy by utilizing fluorobenzene as an internal standard. Yield of isolated product given within parentheses. [a] Yield after two steps: 1) β,β-fluoroarylation of **1 f** and 2) reduction of **3 f**. See the Supporting Information. PMP = *p*-methoxyphenyl.

in high yield (entry 2), with complete exclusion of styrene formation. Notably, degassing of the system was necessary to avoid oxidation of the boronic coupling partner (entry 3). Moreover, the reaction did not proceed in the absence of water (entry 4). Likewise, the presence of both a bipyridine-type ligand (entry 5), and a radical scavenger to preclude alternative radical pathways involving the arylboronic acid (entry 6), was critical to access the fluorinative reaction manifold.[17]

With these optimized reaction conditions, the scope of the β,β-fluoroarylation protocol was evaluated (Scheme 1). We were pleased to observe that under optimized reaction conditions acrylic esters, amides, and ketones smoothly provided the racemic β-fluoro derivatives **3a–d** in good to excellent yields.[18] Nevertheless, acrylic acid furnished the benzylic fluoride **3e** in diminished yield, despite increasing the number of equivalents of arylboronic acid. Diminished yields obtained for methyl vinyl ketone (**3c**) offers an interesting mechanistic insight into the reaction manifold. We hypothesized that this result was an indication of the likely role displayed by the chelating carbonyl group prompting insertion while backing up the stabilization of the palladium intermediate species. In agreement with this hypothesis, the highly activated 4-methoxyphenyl vinyl ketone **1d** afforded **3d** in a satisfactory 84% yield. The Weinreb amide **1 f** underwent smooth β,β-fluoroarylation in 98% yield. This result, besides widening the scope with respect to the ketones, indirectly opens access to aldehyde derivatives (**3g**) and, in turn, to over-reduced 3,3-fluoroaryl alcohols.[19] In contrast, the use of a nitrile-substituted substrate provided the γ-fluoronitrile **3h** in modest yield, but the nitrile moiety had to be placed in a more distant position. The α-substituted ethyl methacrylate **1i** provided the corresponding product **3i** in good yield and modest diastereoselectivity, but β-substituents were not tolerated.

Having achieved proof-of-principle for the β,β-fluoroarylation reaction, the enantioselective version was examined next. To this end, we undertook the evaluation of a range of various bidentate diimine chiral ligands (see the Supporting Information). Among them, BOX 1 and PyrOX 1 were identified as the most encouraging ligands for acrylates and acrylamides, respectively. Attempts to increase the e.r. value by cooling failed, but in a survey of the solvent effects, coordinating solvents such as AcOEt, ROH, and acetone were identified as superior in terms of enantioselectivity. Nevertheless, the improvement in selectivity was reached at the expense of yield, as previously observed in the reported Heck–Matsuda arylation/Miyaura borylation cascade.[16d] Finally, acetone and *i*PrOH were the solvents of choice for esters and amides, respectively, providing a good compromise in terms of selectivity and yield. Notably, the major byproduct in the stereoselective reactions was the corresponding styrene, that is, selected reaction conditions result in significant termination by β-hydride elimination.

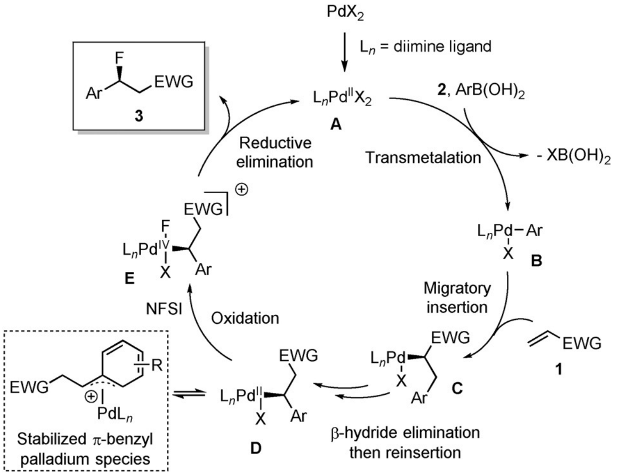
With the optimized reaction conditions in hand, a range of boronic acids was tested (Scheme 2). To our delight the desired β-fluoroesters and β-fluoroamides **3** were obtained in synthetically useful yields and good enantiomeric ratios. As shown in Scheme 2, this procedure was efficient with non-electronically biased arylboronic acids. The β-fluorocarbonyls **3j** and **3x** were formed in 61 and 45% yield, respectively, thus indicating that steric hindrance did not significantly impact the reaction. Whereas steric effects did not have a deleterious effect on the efficiency of the process, 3-substituted arylboronic acids provided higher e.r. values. Electron-rich 4-methoxyphenylboronic acid gave trace amounts of the desired product, most likely because of the general incompatibility of the anisole ring with strongly oxidative species



Scheme 2. Scope of the enantioselective process. Reaction conditions: all reactions were run on 0.11 mmol scale with respect to alkene **1**. Enantiomeric ratio (e.r.) determined by chiral-phase HPLC. Yield determined by ^{19}F NMR spectroscopy utilizing fluorobenzene as an internal standard. Yield of isolated product within parentheses. [a] 0.04 M.

such as NFSI.[9b,20] The less activated 3-methoxyphenylboronic acid afforded the desired products **3o** and **3r** in comparably good yields and good e.r. values. In contrast, highly deactivated arylboronic acids such as 4-CF_3-phenylboronic acid, failed to provide the desired β-fluorocarbonyl adducts, but underwent the Heck coupling. Presumably, electron-withdrawing substituents compromise the stability of the proposed cationic π-benzyl palladium species **D** (see Scheme 3), driving 1,1-difunctionalization. Additionally, the reaction was amenable to halogen substitution (**3l–n**, **3q**), leaving chlorine, bromine, and even iodine[21] moieties intact for further transformations. The protocol was also compatible with heteroarylboronic acids, thus rendering product **3y** in 46% yield and 88:12 e.r. Notably, the ester group did not have a dramatic effect on the enantioselectivity (**3p**), thus providing good levels of stereoselectivity, also when more challenging steroid-derived acrylates (**3t**) were used. Molecular complexity was also tolerated at the aryl coupling partner (**3u**), thus showcasing that this chemistry may add to the repertoire of late-stage functionalization methods and even to the ready generation of fluoro bioconjugates (**3v**). Moreover, the protocol was applicable to primary (**3zx**), secondary (**3zw**), and tertiary amides (**3f**). Notably, stereochemical integrity of the products was preserved after several weeks of storage at room temperature.[22] Moreover, when this protocol was scaled up ten times, the catalytic charge (5 mol%) and the amount of $ArB(OH)_2$ (2.0 equiv) were reduced without affecting either yields or e.r. values (**3a**, **3p**).

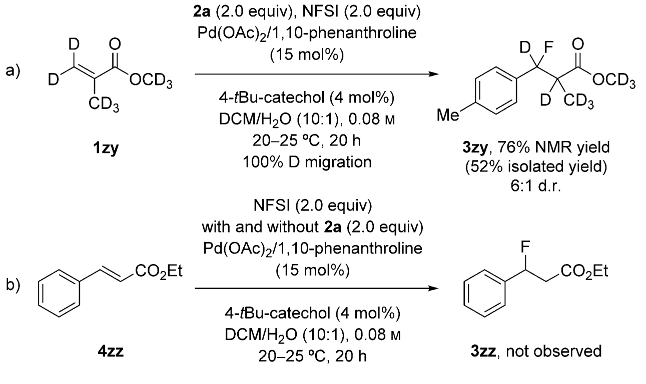
A mechanistic proposal for this reaction is outlined in Scheme 3. As noted above, the presence of a diimine ligand is crucial for achieving the desired reaction manifold. An N,N-ligated palladium(II) complex (**A**) is likely the catalytically active species. Transmetalation with the arylboronic acid and subsequent migratory insertion generates the β-arylated α-palladium(II) intermediate **C**. Sequential β-hydride elimination and reinsertion steps yield the enantioenriched



Scheme 3. Mechanistic proposal.

π-benzyl palladium complex **D**. Oxidation by NFSI gives rise to the high-valent palladium(IV) fluoride **E**, which is now poised to undergo reductive elimination to yield the final β-fluorocarbonyl derivative **3** and regenerate **A**.

Deuterium-labeling experiments carried out with the substrate **1zy**, corroborated the proposed 1,1-difunctionalization mechanism disclosed above, that is, β-deuteride elimination and subsequent palladium deuteride reinsertion (Scheme 4a). Additionally, the β-fluoride ester was not observed when the reaction conditions were examined with the Heck-type byproduct **4zz**, thus eliminating a pathway involving β-fluoride addition to the unsaturated ester (Scheme 4b).



Scheme 4. Mechanistic experiments.

In conclusion, we have disclosed a novel strategy to access β-fluorocarbonyl-derived systems by a mild catalytic direct 1,1-difunctionalization of α,β-unsaturated systems. In analogy to reported transformations, the reaction is likely to proceed through the intermediacy of a high-valent palladium(IV) fluoride species in an oxidative Heck-type mechanism. The method broadens the limited number of reported strategies for the still challenging enantioselective construction of C(sp^3)–F bonds β to electron-withdrawing groups.

Acknowledgments

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[17] Remarkably, the product derived from the 1,2-fluoroarylation of **1a** was not observed.

[18] Regiochemistry of 1,1-difunctionalization was confirmed by two-dimensional NMR studies on **3b**.

[19] See SI-3 in the Supporting Information.

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[21] See SI-5 in the Supporting Information.

[22] See HPLC data for **3p** at the Supporting Information.

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