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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.

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A modular and step-economical method for the direct β,β -fluoroarylation of conjugated carbonyl derivatives is reported. This methodology provides access to a range of enantioenriched β -fluorinated carbonyl derivatives in good yields.

Keywords

β -fluorination; fluoroarylation; carbonyl derivatives; difunctionalization; oxidative coupling

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 that 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 sp^3 C-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, e.g. alcohols, halides, sulfonates, or boronates, and further conversion into the corresponding β -fluorinated carbonyl compounds using either nucleophilic or electrophilic fluorinating reagents (Figure 1a).^[11] The enantioselective variant has recently been achieved through a fluorinative semipinacol rearrangement (Figure 1b).^[12] Recently reported methods explored selective C-H (Figure 1c)^[13] and C-C (Figure 1d)^[14] activation as a means to guide sp^3 fluorination.

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 to access β -fluorinated carbonyl derivatives via a single-step three-component Heck arylation-oxidative fluorination cascade reaction (Figure 1e).

Under this scenario, we decided to test our hypothesis by examining the fluoroarylation of ethyl acrylate **1a** with 4-tolylboronic **2a** acid as a model reaction, under similar conditions to those previously employed in the 1,2-fluoroarylation of styrenes^[15a] (Table 1). Thus, compound **1a** was initially treated with **2a** (2 equiv), Pd(OAc)₂ (15 mol %), 1,10-phenanthroline (15 mol %) and 4-^tBu-catechol (4 mol %) in DCM:H₂O using Selectfluor as the electrophilic fluorine source. However, after 20 h only trace amounts of ester **3a** were detected, with the major product resulting from the undesired competing oxidative Heck reaction (Table 1, entry 1).

Pleasantly, switching the (N-F)⁺ source to NFSI had a dramatic effect, giving rise to the exclusive formation of 1,1-fluoroarylated product **3a** in high yield (Table 1, entry 2), with complete exclusion of styrene formation. Notably, degassing of the system was necessary to avoid oxidation of the boronic coupling partner (Table 1, entry 3). Moreover, the reaction did not proceed in the absence of water (Table 1, entry 4). Likewise, the presence of both a bipyridine-type ligand (Table 1, entry 5), and a radical scavenger to preclude alternative radical pathways involving the arylboronic acid (Table 1, entry 6), was critical to access the fluorinative reaction manifold.^[17]

With these optimized conditions, the scope of the β,β -fluoroarylation protocol was evaluated next (Scheme 1). We were pleased to observe that, under optimized conditions, acrylic esters, amides and ketones smoothly provided racemic β -fluoro derivatives **3a-d** in good to excellent yields.^[18] Nevertheless, acrylic acid furnished benzylic fluoride **3e** in diminished yield, despite increasing 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, highly activated 4-methoxyphenyl vinyl ketone **1d**, afforded β -fluoroketone **3d** in a satisfactory 84% yield. Weinreb amide **1f** underwent smooth β,β -fluoroarylation in 98% yield. This result, besides widening the ketones' scope, indirectly opens access to aldehyde derivatives (**3g**) and, in turn, to over-reduced 3,3-fluoroaryl alcohols.^[19] On the other hand, the use of a nitrile-substituted substrate provided γ -fluoro nitrile **3h** in modest yield, but the nitrile moiety had to be placed in a more distant position. α -Substituted ethyl methacrylate **1i** provided the corresponding product **3i** in good yield and modest diastereoselectivity, whereas 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 Supporting Information). Among them, **BOX 1** and **PyrOX 1** were identified as the most encouraging ligands for acrylates and acrylamides, respectively. Whereas attempts to increase *er* by cooling failed, when surveying the solvent effect, 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 reaction.^[16d] Finally, acetone and *t*-PrOH were the solvents of choice respectively, providing a good compromise in terms of selectivity and yield. Notably, the major byproduct in the stereoselective reactions was the corresponding styrene, i.e. selected conditions result in significant termination via β -hydride elimination.

With the optimized conditions in hand, a range of boronic acids was tested (Scheme 2). To our delight the desired β -fluoroesters and amides **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. β -Fluorocarbonyls **3j** and **3x** were formed in 61% and 45% yield, respectively, 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 *er*(s). 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 such as NFSI.^[9b,20] Less activated 3-methoxyphenylboronic acid afforded the desired products **3o** and **3r** in comparably good yields and good *er*(s). On the other hand, highly deactivated arylboronic acids such as 4-CF₃-phenylboronic acid, failed to provide the desired β -fluoro carbonyl adducts, but formed the Heck coupling. Presumably, electron-withdrawing substituents compromise the stability of the proposed cationic π -benzyl palladium species (**D**, 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, rendering product **3y** in 46% yield and 88:12 *er*. Notably, an ester group did not have a dramatic effect on the enantioselectivity (**3p**), 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**), 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 $\text{ArB}(\text{OH})_2$ (2.0 equiv) were reduced without affecting either yields or er (**3a**, **3p**).

A mechanistic proposal for this reaction is outlined in Scheme 3. As noted above, the presence of a diimine ligand is crucial to achieve the desired reaction manifold. An *N,N*-ligated Pd(II) complex **A** is the likely catalytically active species. Transmetalation with the arylboronic acid and subsequent migratory insertion generates β -arylated- α -Pd(II) intermediate **C**. Sequential β -hydride elimination and reinsertion steps yield enantioenriched π -benzyl palladium complex **D**. Oxidation by NFSI gives rise to a high-valent Pd(IV)-fluoride **E**, now poised to undergo reductive elimination yielding the final β -fluorocarbonyl derivative **3** and regenerating Pd(II) complex **A**.

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

In conclusion, we have disclosed a novel strategy to access β -fluorocarbonyl derived systems via 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 Pd^{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 $\text{sp}^3\text{-C-F}$ bonds β to electron-withdrawing groups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- [1]. a) Wang J, Sánchez-Roselló M, Aceña JL, del Pozo C, Sorochinsky AE, Fustero S, Soloshonok VA, Liu H, Chem. Rev 2014, 114, 2432–2506; [PubMed: 24299176] b) Zhou Y, Wang J, Gu Z, Wang S, Zhu W, Aceña JL, Soloshonok VA, Izawa K, Liu H, Chem. Rev 2016, 422–518. [PubMed: 26756377]
- [2]. Jaivel N; Uvarani C; Rajesh R; Velmurugan D; Marimuthu PJ Nat. Prod 2014, 77, 2–8.
- [3]. Champagne PA; Desroches J; Hamel J-D; Vandamme M; Paquin J-F Chem. Rev 2015, 115, 9073–9174. [PubMed: 25854146]

- [4]. Selected examples: Ishimaru T, Shibata N, Horikawa T, Yasuda N, Nakamura S, Toru T, Shiro M, *Angew. Chem. Int. Ed.* 2008, 47, 4157–4161; *Angew. Chem.* 2008, 120, 8171–8175; Lozano O, Blessley G, Martínez del Campo T, Thompson AL, Giuffredi GT, Bettati M, Walker M, Borman R, Gouverneur V, *Angew. Chem. Int. Ed.* 2011, 50, 8105–8109; *Angew. Chem.* 2011, 123, 8255–8259; Kwiatkowski P, Beeson TD, Conrad JC, MacMillan DWC, *J. Am. Chem. Soc.* 2011, 133, 1738–1741. [PubMed: 21247133]
- [5]. Rauniyar V, Lackner AD, Hamilton GL, Toste FD, *Science*, 2011, 334, 1681–1684. [PubMed: 22194571]
- [6]. a) Kalow JA, Doyle AG, *J. Am. Chem. Soc.* 2010, 132, 3268–3269; [PubMed: 20163118] b) Kalow JA, Doyle AG, *J. Am. Chem. Soc.* 2011, 133, 16001–16012; [PubMed: 21863842] c) Zhu J, Tsui GC, Lautens M, *Angew. Chem. Int. Ed.* 2012, 51, 12353–12356; *Angew. Chem.* 2012, 124, 12519–12522; d) Kalow JA, Doyle AG, *Tetrahedron*, 2013, 69, 5702–5709.
- [7]. a) Hamashima Y, Yagi K, Takano H, Tamás L, Sodeoka M, *J. Am. Chem. Soc.* 2002, 124, 14530–14531; [PubMed: 12465951] b) Katcher MH, Doyle AG, *J. Am. Chem. Soc.* 2010, 132, 17402–17404; [PubMed: 21087003] c) Katcher MH, Sha A, Doyle AG, *J. Am. Chem. Soc.* 2011, 133, 15902–15905. [PubMed: 21894884]
- [8]. For the feasibility of C-F reductive elimination from transition metal complexes, see: Grushin VV, *Chem. Eur. J.* 2002, 8, 1006–1014; [PubMed: 11891886] Grushin VV, *Acc. Chem. Res.* 2010, 43, 160–171. [PubMed: 19788304]
- [9]. a) Furuya T, Kaiser HM, Ritter T, *Angew. Chem. Int. Ed.* 2008, 47, 5993–5996; *Angew. Chem.* 2008, 120, 6082–6085; b) Furuya T, Ritter T, *J. Am. Chem. Soc.* 2008, 130, 10060–10061; [PubMed: 18616246] c) Ball ND, Sanford MS, *J. Am. Chem. Soc.* 2009, 131, 3796–3797; [PubMed: 19249867] d) Furuya T, Benitez D, Tkatchouk E, Strom AE, Tang P, Goddard WA III, Ritter T, *J. Am. Chem. Soc.* 2010, 132, 3793–3807. [PubMed: 20196595]
- [10]. Riedel S, Kaupp M, *Coord. Chem. Rev.* 2009, 253, 606–624.
- [11]. a) Kim K-Y, Kim BC, Lee HB, Shin H, *Org. HJ. Chem.* 2008, 73, 8106–8108; b) Bonaccorso HG, Porte LMF, Navarini J, Paim GR, Luz FM, Oliveira LM, Whietan CW, Martins MAP, Zanatta N, *Tetrahedron Lett.* 2011, 52, 3333–3335; c) Zhang M, Gong Y, Wang W, *Eur. J. Org. Chem.* 2013, 7372–7381; d) Li Z, Wang Z, Zhu L, Tan X, Li C, *J. Am. Chem. Soc.* 2014, 136, 16439–16443. [PubMed: 25350556]
- [12]. a) Wang M, Wang BM, Shi L, Tu YQ, Fan C-A, Wang SH, Hu XD, Zhang SY, *Chem. Commun.* 2005, 5580–5582; b) Romanov-Michailidis F, Guénée L, Alexakis A, *Angew. Chem. Int. Ed.* 2013, 52, 9266–9270; *Angew. Chem.* 2013, 125, 9436–9440; c) Romanov-Michailidis F, Pupier M, Guénée L, Alexakis A, *Chem. Commun.* 2014, 50, 13461–13464.
- [13]. a) Zhu R-Y, Tanaka K, Li G-C, He J, Fu H-Y, Li S-H, Yu J-Q, *J. Am. Chem. Soc.* 2015, 137, 7067–7070; [PubMed: 26001406] Zhang Q, Yin X-S, Chen K, Zhang S-Q, Shi B-F, *J. Am. Chem. Soc.* 2015, 137, 8219–8226; [PubMed: 26067591] Zhu Q, Ji D, Liang T, Wang X, Xu Y, *Org. Lett.* 2015, 17, 3798–3801; [PubMed: 26172446] Miao J, Yang K, Kurek M, Ge H, *Org. Lett.* 2015, 17, 3738–3741; [PubMed: 26205696] Xia J-B, Ma Y, Chen C, *Org. Chem. Front.* 2014, 1, 468–472; [PubMed: 24976971] Bloom S, Pitts CR, Woltornist R, Griswold A, Holl MG, Lectka T, *Org. Lett.* 2013, 15, 1722–1724; [PubMed: 23527764] Bloom S, Sharber A, Holl MG, Knippel JL, Lectka T, *J. Org. Chem.* 2013, 78, 11082–11086. [PubMed: 24073747] Metal-free C(sp³)-H fluorinations: Pitts CR, Ling B, Woltornist R, Liu R, Lectka T, *J. Org. Chem.* 2014, 79, 8895–8899; [PubMed: 25137438] Bloom S, Knippel JL, Lectka T, *Chem. Sci.* 2014, 5, 1175–1178; Halperin SD, Fan H, Chang S, Martin RE, Britton R, *Angew. Chem. Int. Ed.* 2014, 53, 4690–4693; *Angew. Chem.* 2014, 126, 4778–4781; Kee CW, Chin KF, Wong MW, Tan C-H, *Chem. Commun.* 2014, 50, 8211–8214; Xia J-B, Zhu C, Chen C, *J. Am. Chem. Soc.* 2013, 135, 17494–17500; [PubMed: 24180320] Bloom S, McCann M, Lectka T, *Org. Lett.* 2014, 16, 6338–6341. [PubMed: 25493423]
- [14]. Bloom S, Bume DD, Pitts CR, Lectka T, *Chem. Eur. J.* 2015, 21, 8060–8063. [PubMed: 25877004]
- [15]. a) Talbot EPA, de A. Fernandes T, McKenna JM, Toste FD, *J. Am. Chem. Soc.* 2014, 136, 4101–4104; [PubMed: 24617344] b) He Y, Yang Z, Thornbury RT, Toste FD, *J. Am. Chem. Soc.* 2015, 137, 12207–12210. [PubMed: 26378886]

- [16]. a)Liao L, Jana R, Urkalan KB, Sigman MS, J. Am. Chem. Soc 2011, 133, 5784–5787; [PubMed: 21449562] b)Saini V, Sigman MS, Am MSJ. Chem. Soc 2012, 134, 11372–11375;c)Saini V, Liao L, Wang Q, Jana R, Sigman MS, Org. Lett 2013, 15, 5008–5011; [PubMed: 24047468] d)Nelson HM, Williams BD, Miró J, Toste FD, J. Am. Chem. Soc 2015, 137, 3213–3216; [PubMed: 25723255] e)Kalyani D, Satterfield AD, Sanford MS, J. Am. Chem. Soc 2010, 132, 8419–8427; [PubMed: 20515033] f)Kalyani D, Sanford MS, J. Am. Chem. Soc 2008, 130, 2150–2151. [PubMed: 18229926]
- [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 substrate 3b.
- [19]. See SI-3 at the Supporting Information.
- [20]. a)Stavber G, Zupan M, Jereb M, Stavber S, Org. Lett 2004, 6, 4973–4976; [PubMed: 15606113] b)Furuya T, Ritter T, Org. Lett 2009, 11, 2860–2863. [PubMed: 19507870]
- [21]. See SI-5 at the Supporting Information.
- [22]. See HPLC data for 3p at the Supporting Information.

(a) Functional group transformation

(b) Fluorinative semipinacol rearrangement

(c) C-H activation

(d) C-C activation

(e) Our proposal: β,β -Fluoroarylation **Single step**

Figure 1.

Strategies to access to β -fluoro carbonyl derived systems. EWG = electron-withdrawing group. FG = functional group. DG = directing group.

Scheme 1.

Non-enantioselective substrate scope.^[a,b,c] [a] 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; H₂O, 0.14 μL; rt, 20 h. [b] Yield determined by ¹⁹F-NMR utilizing fluorobenzene as internal standard. [c] Isolated yield in brackets. [d] Yield for two steps: 1) β,β-fluoroarylation of **1f** and 2) reduction of **3f**. See supporting information. PMP = *p*-methoxyphenyl.

Scheme 2.

Enantioselective scope.^[a,b,c] [a] Conditions: all reactions were run on 0.11 mmol scale with respect to alkene **1**. [b] Enantiomeric ratio (er) determined by chiral phase HPLC. [c] Yield determined by ¹⁹F-NMR utilizing fluorobenzene as internal standard. [d] Isolated yield in brackets. [e] 0.04M.

Scheme 3.
Mechanistic proposal.

Scheme 4.
 Mechanistic experiments.

Table 1.

Optimization of the reaction conditions.

Entry	Variant conditions	Yield (%)
1	(N-F) ⁺ = Selectfluor	Trace
2	(N-F) ⁺ = NFSI	95
3	w/o degassing	-
4	w/o water	-
5	w/o 1,10-phenanthroline	-
6	w/o 4- <i>t</i> Bu-catechol	Trace

^[a] Conditions: all reactions were run on 0.055 mmol scale with respect to **1a**.

^[b] Yields determined by ¹⁹F-NMR utilizing fluorobenzene as internal standard. NFSI = *N*-fluorobenzenesulfonimide.