C–C Coupling

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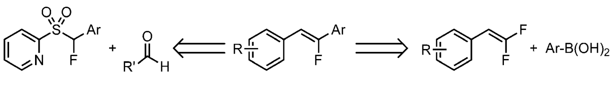
Palladium-Catalyzed Defluorinative Coupling of 1-Aryl-2,2-Difluoroalkenes and Boronic Acids: Stereoselective Synthesis of Monofluorostilbenes

*Richard T. Thornbury and F. Dean Toste**

***Abstract:** The palladium-catalyzed defluorinative coupling of 1-aryl-2,2-difluoroalkenes with boronic acids is described. Broad functional-group tolerance arises from a redox-neutral process by a palladium(II) active species which is proposed to undergo a β-fluoride elimination to afford the products. The monofluorostilbene products were formed with excellent diastereoselectivity (≥50:1) in all cases, and it is critical, as traditional chromatographic techniques often fail to separate monofluoroalkene isomers. As a demonstration of this method's unique combination of reactivity and functional-group tolerance, a Gleevec® analogue, using a monofluorostilbene as an amide isostere, was synthesized.*

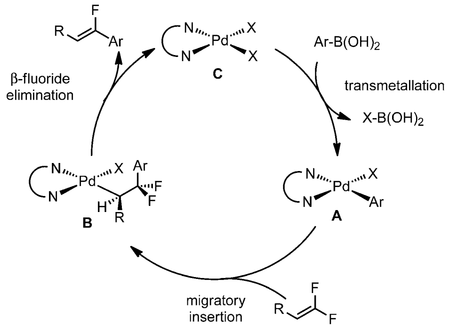
The amide bond is an ubiquitous structural motif found in medicinal chemistry, and consequently much effort has been made to develop peptide-bond mimics known as amide isosteres.[1] Some important properties, which might be conferred by amide isosteres, include enhanced stability to peptidases, increased lipophilicity, conformational stability, and improved recognition.[1] Monofluoroalkenes have emerged as a useful peptide mimic which exhibits a similar steric and electronic profile to amides, and consequently have been used extensively as amide isosteres.[1,2] While a wide variety of methods have been developed to access different classes of monofluoroalkenes, modular synthesis and stereoselective synthesis remain outstanding challenges.[3] Moreover, traditional chromatographic techniques, including preparative HPLC, often fail to separate *E* and *Z* isomers of monofluoroalkenes, thus highlighting the importance of stereoselective methods.[4]

Hu and co-workers have recently developed a Julia–Kocienski olefination procedure which utilizes a selective decomposition strategy of sulfinate intermediates to isolate the *E* and *Z* isomers by extraction (Scheme 1).[4] While the procedure allowed isolation of both fluoroalkenes stereoisomers from the same reaction, the issue of selective synthesis remains unsolved. Additionally, this protocol required the synthesis of a new olefination reagent for each derivative, an impediment to modularity which is inherent to olefination strategies for monofluoroalkene synthesis.[3] As an alternative, Cao and co-workers have recently reported a nickel-catalyzed Suzuki-type coupling of boronic acids and difluorostyrenes, which afforded monofluorostilbenes stereoselectively (Scheme 1).[5] They proposed that the reaction proceeds through oxidative addition of the alkene C–F bond,[6,7] followed by cross-coupling with an aryl boronic acid. While a cross-coupling strategy provides the opportunity for more rapid diversification, the high temperature and reactive catalysts required for C–F bond activation resulted in limited functional-group tolerance. We hypothesized that a mechanistically distinct cross-coupling strategy, not requiring oxidative addition into a C–F bond and tolerant of the functional groups relevant to pharmaceutical, agrochemical, and material sciences, would be required.[8] Herein we report the development of a palladium-catalyzed defluorinative coupling reaction to access single isomers of monofluorostilbenes under mild reaction conditions (Scheme 1).



Scheme 1. Synthesis of monofluorostilbenes.

Our group's recent interest in interrupted Heck reactions led us to wonder if stereoselective fluoro-olefin synthesis might be achieved by a defluorinative coupling reaction with difluoroalkenes.[9–11] We envisioned a scenario as outlined in Scheme 2, wherein insertion of a difluoroalkene into the palladium–aryl bond of **A** would lead to the alkylpalladium intermediate, **B**. In an analogous fashion to β-hydride elimination in the Heck reaction, β-fluoride elimination would lead to formation of the alkene product. The resulting palladium(II) species, **C**, could readily transmetallate with an aryl boronic acid to close the catalytic cycle. β-Fluoride elimination from organometallic intermediates is not without



Scheme 2. Proposed reactivity manifold.

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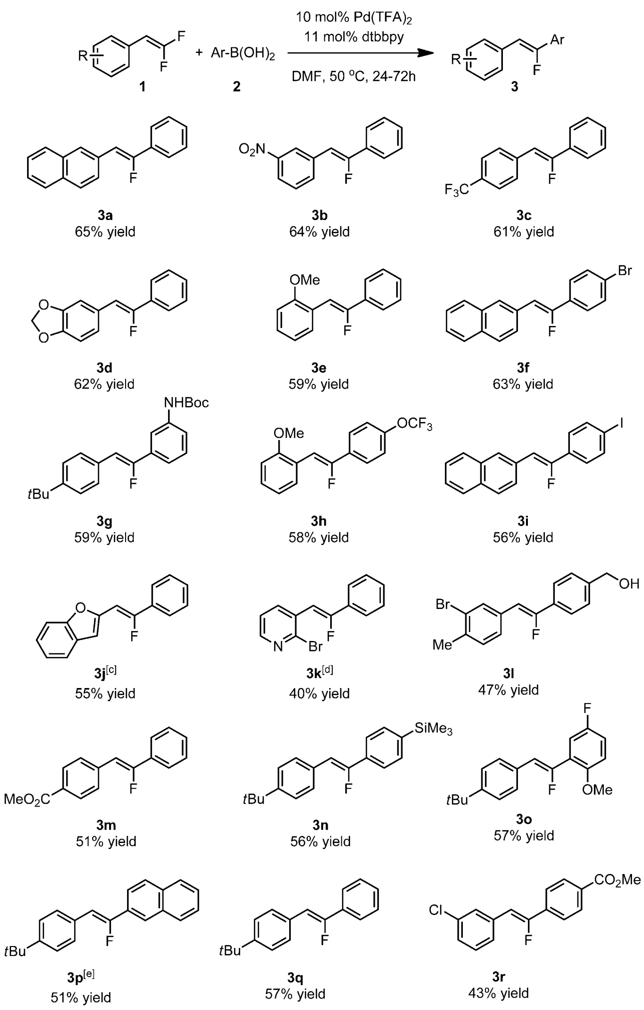
precedent, however it is infrequently incorporated into catalytic transformations.[12] Importantly, such a process circumvents the generation of palladium(0) and is a redox neutral process, thus not requiring the use of external oxidants or added base. These aspects would be expected to help minimize issues with functional-group compatibility.

Difluoroalkenes are a readily accessible class of substrates.[13] While a variety of methods exist for their synthesis, perhaps the most notable is through a Julia–Kocienski olefination protocol utilizing commercially available difluoromethyl 2-pyridyl sulfone (Hu's reagent) and aldehydes or ketones, which we found to be useful for our purposes.

With a variety of difluoroalkenes and boronic acids on hand, reaction conditions for a palladium-catalyzed defluorinative coupling were sought (see the Supporting Information). The optimization efforts revealed palladium(II) trifluoroacetate as a palladium source, with 4,4′-di-*tert*-butyl-2,2′-bipyridine as a ligand in *N*,*N*-dimethylformamide (DMF) at 50 °C. The scope of the reaction under these reaction conditions is detailed in Scheme 3. In all cases the monofluorostilbene products were formed in a greater than or equal to 50:1 diastereomeric ratio. With respect to the difluoroalkene, a wide variety of functional groups were tolerated including alkyl, ester, nitro, trifluoromethyl, ether, and halogen substituents, and substitution at *ortho*-, *meta*-, and *para*-positions of the aromatic ring. The reaction also tolerated a variety of functional groups on the boronic acid coupling partner, including halogens, ester, methoxy, trifluoromethoxy, trimethylsilyl, free alcohol, and protected amine substituents, as well as substitution at *ortho*-, *meta*-, and *para*-positions. Some heteroarene-substituted difluoroalkenes were compatible as well, albeit with extended reaction times and/or elevated temperature (Scheme 3, footnotes [c] and [d]). Both the benzofuran product **3j** and pyridine **3k** were synthesized, thus increasing the diversity of molecules accessible by this method.

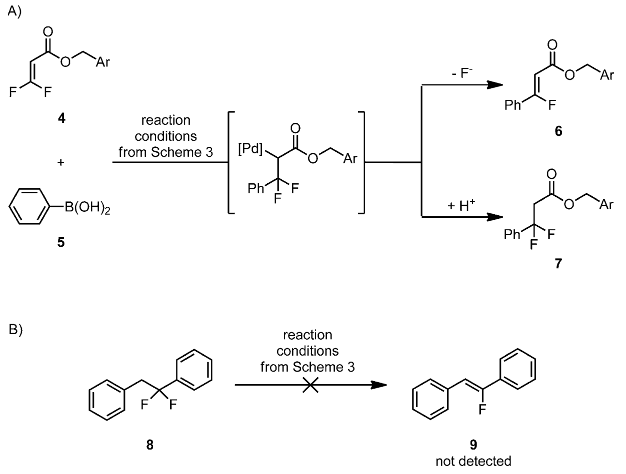
The reaction developed herein exhibits some interesting chemoselectivity and functional-group tolerances worth further comment. First, in addition to being highly stereoselective, the reaction was also highly selective for monocoupled products. Only in the case of **3m**, did we observe over-coupled side products (Scheme 3). However, this undesired reactivity was easily remedied by reduction of boronic acid loading to near stoichiometric quantities, and **3m** was isolated in moderate yield. Second, the reaction conditions are uniquely suited to boron-based nucleophiles, including boronic acids and potassium tetrafluoroborate salts (Scheme 3, footnote [e]), although boronic esters react sluggishly. Interestingly, we found that arylstannanes and arylsilanes were inert under our reaction conditions both with and without added equivalents of fluoride, thus affording the opportunity for orthogonal cross-coupling.[14]

Finally, a variety of functional groups were tolerated and might be useful for further synthetic manipulations. Importantly, arylhalides were tolerated under these reaction conditions, including chlorides, bromides, and iodide. Even a substrate bearing a 2-bromopyridine was tolerated. In no case was there cross-coupling with these functional groups, and it stands in stark contrast to the previously described nickel-catalyzed procedure which also produced competitive aryl halide cross-coupling, even with arylchlorides.[5] These results strongly suggest that our process does not involve formation of palladium(0), and supports the initial mechanistic hypothesis, and demonstrates that the distinct reactivity manifold enables significant expansion of functional group tolerance.



Scheme 3. Scope of the defluorinative coupling. [a] Standard reaction conditions: 0.2 mmol **1**, 1.05–2.0 equiv **2**, 10 mol% Pd(TFA)$_2$, 11 mol% 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbbpy), 0.5 mL DMF, 50 °C. Completion of reaction was monitored by thin-layer chromatography. [b] Yield of isolated product. [c] Reaction run for 5 days. d) Reaction run at 85 °C for 4 days. [e] 47% yield when corresponding potassium trifluoroborate salt is employed in place of the boronic acid. TFA = trifluoroacetate.

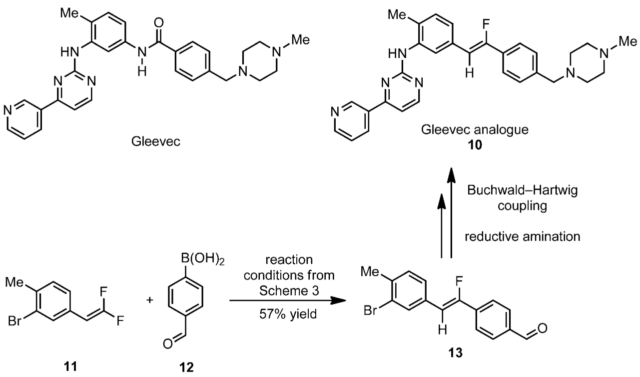
In an effort to lend further support to the mechanistic hypothesis, the difluoroacrylate **4** was subjected to reaction conditions. Analysis of the proton and fluorine NMR spectra revealed a mixture of the defluorocoupled product **6** and 1,4-conjugate addition product **7** (Scheme 4a). Formation of **7** presumably proceeds through a palladium alkyl intermediate,[15] and further supports the proposal that the reaction proceeds through a migratory insertion, β-fluoride elimination pathway. Although analogous protonolysis products were not observed for the difluorostyrene substrates, observation



Scheme 4. Mechanistic probes. Ar = p-BrC_6H_4.

of **7** led us to consider whether protonolysis followed by base-catalyzed elimination might be responsible for the formation of the monofluorostilbenes. To test for this possibility, 1,1-difluoro-1,2-dipheneylethane (**8**) was subjected to standard reaction conditions (Scheme 4b). The corresponding monofluoroalkene **9** was not observed, thus suggesting that the β-fluoride elimination is not simply base-mediated and likely occurs from a palladium alkyl intermediate.

To demonstrate the utility of this palladium-catalyzed defluorinative coupling the methodology was applied to the synthesis of a Gleevec® isostere. Gleevec® is a tyrosine kinase inhibitor, and the first of its class to be approved for the treatment of a variety of cancers.[16] Gleevec® contains a benzamide moiety (Scheme 5), and we sought to substitute it with a monofluoroalkene moiety. Crystallographic studies suggest that the benzamide moiety adopts a *trans* geometry in the enzyme binding site, thus making our stereoselective method particularly useful for accessing a conformationally locked analogue of Gleevec®.[17] From commercially available 3-bromo-4-methyl-benzaldehyde, the difluoroalkene **11** was synthesized using Hu's reagent, and then subjected to the standard reaction conditions in the presence of 4-formylphenylboronic acid. Gratifyingly, the defluoro-coupled product **13** was obtained in 57% yield. Reductive amination with 1-methylpiperazine and subsequent palladium-catalyzed Buchwald–Hartwig coupling with commercially available 4-(3-pyridinyl)-2-pyrimidine amine afforded the monofluoroalkene derivative of Gleevec® **10** in two additional steps (see the Supporting Information for details).[18] Critical to the synthesis was the compatibility of functional groups such as the benzaldehyde moiety and the aryl bromide to the palladium-catalyzed coupling.



Scheme 5. Synthesis of Gleevec® analogue.

In conclusion, the palladium-catalyzed defluorinative coupling of 1-aryl-2,2-difluoroalkenes with boronic acids to afford a monofluoroalkenes with high diasteroselectivity is described. The reaction is proposed to proceed through a rare example of a β-fluoride elimination of a palladium(II) intermediate in a catalytic process. This distinct mechanistic manifold and the resulting mild reaction conditions allow the incorporation of a variety of synthetically useful functional groups into the coupling partners. The utility of this method and the monofluoroalkene building blocks was demonstrated by the synthesis of a Gleevec® amide isostere.

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Keywords: alkenes · C–C coupling · fluorine · palladium · synthetic methods

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