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Letter

Synthesis and Reactions of 3,3-Difluoro-2-*exo*-methylidene Indolines

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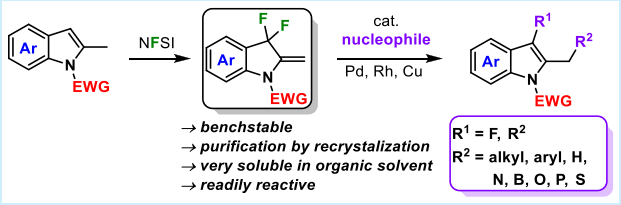
ABSTRACT: A dearomative electrophilic fluorination of 2-methylindoles is reported, delivering 3,3-difluoroindolines bearing an exomethylidene. The model substrate was synthesized on up to a 20 mmol scale and was purified by a practical recrystallization as a crystalline bench-stable, yet reactive solid. The olefin is amphoteric and can react both as a nucleophile and as an electrophile. A wide range of metal-free, palladium, rhodium, and copper reactions was explored, forming new C−H, C−B, C−C (alkyl and aryl), C−N, C−O, C−P, and C−S bonds.

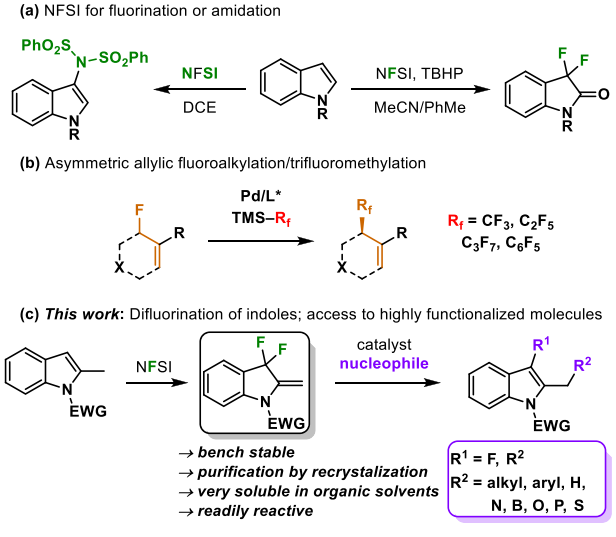


Fluorine-containing molecules continue to account for a disproportionate number of pharmaceuticals and agrochemicals due to an increase in solubility, lipophilicity, and biological stability against oxidation as compared to the C−H counterparts.[1] Additionally, the benefits of fluorine incorporation are extended to other stages of API development. For example, the nuclei can be used to track compounds *in vitro* or *in vivo* by NMR or MRI, respectively.[2] Finally, ^{18}F is the most commonly used radioisotope in positron emitting tomography due to its convenient half-life (110 min) and its low positron energy (635 keV).[3]

Diverse strategies have been employed for fluorine incorporation, including the use of catalysts, nucleophilic reagents, electrophilic reagents, and radical additions.[4] One of the most commonly used electrophilic sources of fluorine is *N*-fluorobenzenesulfonimide (NFSI) due to its shelf-stability, controlled reactivity, modest cost, ability to vary its electronic properties, and the availability of a ^{18}F variant.[5] NFSI has been shown to be a versatile reagent capable of fluorine or sulfonamide transfer to heterocycles, typically by modifying the solvent (Scheme 1a).[6] The incorporation of fluorine proved to be a useful method to rapidly access functionalized isatin analogues.[6e,7]

Functionalization of allylic and propargylic fluorides has been studied with various nucleophiles, metal catalysts, and organocatalysts.[8] Reactions catalyzed by palladium and platinum have been investigated in detail, and in some cases, the reactivity is found to be superior compared to many commonly used oxygen-based leaving groups.[8i,j] Recently, the Trost group developed an asymmetric palladium-catalyzed trifluoromethylation of allylic fluorides using chiral Trost ligands (Scheme 1b).[9] In our attempts at a dearomative fluorination of 2-alkylindoles with NFSI, we isolated 3,3-*gem*-difluoroindoline bearing an exocyclic double bond (Scheme 1c). Herein, we report a scalable synthesis of these scaffolds and their modular functionalization. They behave as nucleophiles, electrophiles, and as substrates for metal-catalyzed transformations of the allyl fluoride moiety, allowing

Scheme 1. Use of NFSI for Electrophilic Fluorination of Indoles and Allylic Fluoride Substitutions



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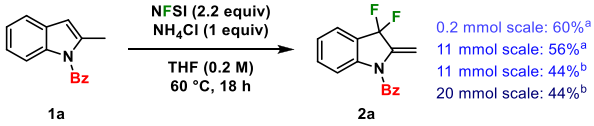
access of highly substituted indoles and indolines. We were able to successfully form new C−C (aryl/alkyl), C−H, C−N, C−B, C−O, C−P, and C−S bonds.

An optimization of solvent, temperature, and concentration found that the reaction improved in polar solvents such as THF as well as with increased concentration and milder temperatures (see Supporting Information, section 3.1). Additionally, NH_4Cl (1 equiv) was found to benefit the reaction, presumably by either activating NFSI or quenching byproducts of the reaction. The fluorination of 2-methylindole (**1a**, 0.2−20 mmol) with NFSI (2.2 equiv) delivered exomethylidene containing indoline **2a** as a crystalline, bench stable product (Scheme 2).[10] The reaction could be scaled to 20 mmol and purified without the need for column chromatography, as the product could be crystallized from pentanes.

Scheme 2. Dearomative Fluorination of 2-Methylindole on Various Scales

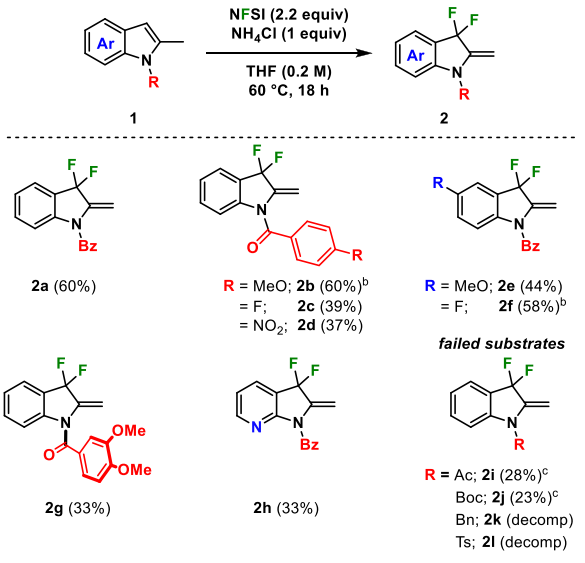


[a]Using column chromatography purification. [b]Using one round of recrystallization

Next, we investigated the impact of the protecting group on nitrogen as well as a few substituents on the indole backbone (Scheme 3).

The substrate bearing an electron-rich benzoyl group delivered product **2b** in comparable yield. However, electron-withdrawing groups had a negative effect on yield, with the strong π-withdrawing nitro group having the greatest impact (**2c** and **2d**). The opposite trend was found when introducing electronic perturbations at the 5-position of the indole; MeO- functionalized indole (**2e**) provided the product in slightly diminished yield, and F-containing indole (**2f**) was accessed in good yield. Dimethoxy containing indoline **2g** was isolated in low yield; however, an interesting restrictive rotation around the C−N bond was elucidated by NMR, suggesting *meta*-functionalized benzoyl groups are too sterically bulky for the reaction. Azaindole derivative produced **2h** in modest yield, which proved to be unstable and decomposed during storage. A carbonyl moiety on the nitrogen was necessary as only acetyl (**2i**) and Boc (**2j**) protected indoles gave the desired product (^{1}H NMR and ^{19}F NMR), accompanied by inseparable byproducts. Benzyl (**2k**) and tosyl (**2l**) protected indoles decomposed upon reaction with NFSI. Extending the carbon chain at the 2-position led to no desired product.

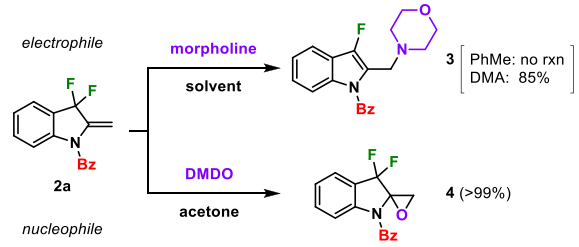
Scheme 3. Nitrogen-Protecting Group and Electronic Perturbation Screening[a]



[a]Reactions run on a 0.2 mmol scale. [b]Reaction run on a 1 mmol scale. [c]Separation difficult, NMR yield using trifluorotoluene as an internal standard.

With an efficient medium-scale synthesis of indoline **2a** in hand, we sought to evaluate the reactivity of these interesting exomethylidene-containing fluorinated scaffolds. First, we aimed to study the electronic properties of the olefin as it appears there is potential for amphoteric reactivity as there are σ-bond withdrawing fluorine atoms as well as weak π-donation from the nitrogen atom (Scheme 4).

Scheme 4. Nucleophilic and Electrophilic Reactivity of Product 2a



We found that the olefin could participate in an S_N2' reaction with morpholine acting as the nucleophile.[11] The reaction required DMA as no product was isolated in toluene, in contrast to the outcome using palladium (*vide infra*). Rapid and quantitative epoxidation with DMDO was also achieved with preservation of the fluorine moiety.

We aimed to further elucidate the electrophilic nature of these indolines as potential substrates in palladium-allylation chemistry with various nucleophiles (Scheme 5).[8k,12]

Phenylsilane, a mild hydride source, delivered 3-fluoroindole **5** in quantitative yield.[13] When reactions were run with 1.5 equiv of morpholine at 60 °C, we obtained a 4:1 mixture favoring **3** over **6**.[14] However, using a larger excess of morpholine (5 equiv) and running the reaction at 100 °C led to an 80% yield of **6**. In a similar manner, sulfonylation of **2a** led to the product of double addition (**7**), which upon treatment with LiOH led to cleavage of the labile benzoyl moiety.[15] A clean phosphorylation reaction was observed using dialkylphosphite as a nucleophile, producing product **8** in good yield.[16] Finally, using sodium dimethylmalonate, according to the literature procedure, the difunctionalized product **9** was isolated in excellent yield.[8j,17]

We sought to investigate the order of events in the double addition reaction and in particular the site of the first amination under palladium catalysis (Scheme 6).

With this goal in mind, we subjected **3** to the higher temperature reaction conditions (see Scheme 5) and observed no reaction, which implies that **3** is not the species that leads to

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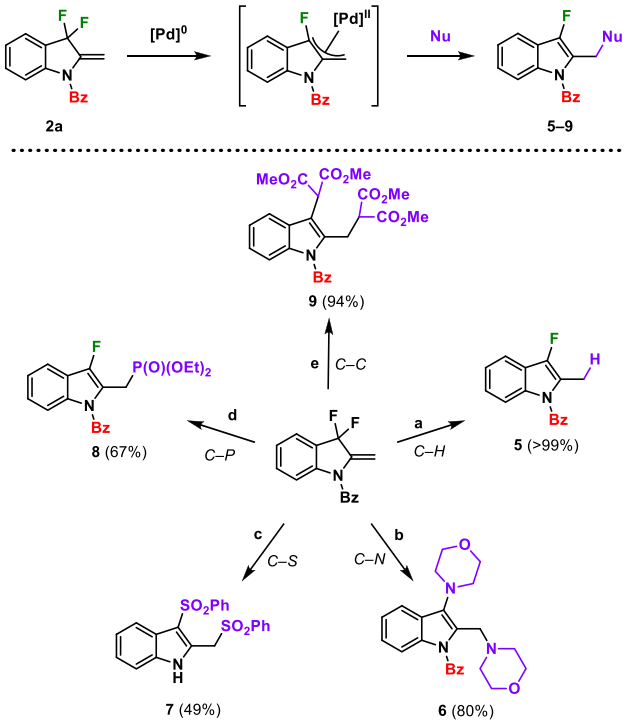
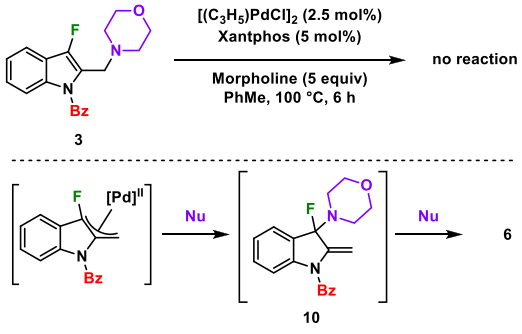
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 5. Palladium-Catalyzed Allylic Functionalizations[a]



[a]Unless otherwise stated, reactions were run on a 0.1 mmol scale using $[(C_3H_5)PdCl]_2$ (2.5–5 mol %) and xantphos (5–10 mol %). Reaction conditions: (a) XPhos (5 mol %) instead of xantphos, $PhSiH_3$ (2 equiv), Et_3N (1 equiv), EtOH, 50 °C, 6 h. (b) Morpholine (5 equiv), PhMe, 100 °C, 6 h. (c) Sodium phenylsulfinate (5 equiv), PhMe, 100 °C, 18 h, then LiOH (2 M), 2 h. (d) $HP(O)(OEt)_2$ (2 equiv), CsF (1 equiv), PhMe, 70 °C, 18 h. (e) Sodium dimethylmalonate (5 equiv), 15-crown-5 (5 equiv), DCM, r.t., 2 h.

Scheme 6. Investigation of the Mechanism for the Double Addition Reaction of Morpholine

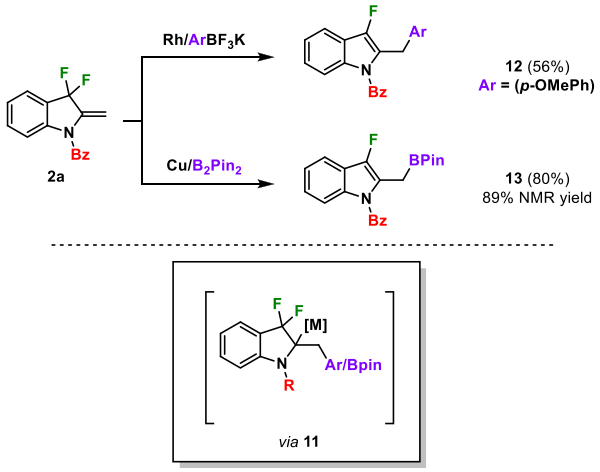


6. Instead it appears that reaction occurs *via* the π-allyl intermediate to give **10** which undergoes an amine-assisted ionization and amination or a second palladium-mediated ionization and amination.[14] All attempts to observe **10** have met with failure, so for the moment, this is a proposal that requires confirmation.

We also explored the viability of metal-catalyzed addition to the olefin through a sterically congested metal complex **11** which could undergo a β-fluoride elimination (Scheme 7).[18]

The rhodium-catalyzed arylation/β-fluoride elimination of **2a** provided monoarylated product **12** in good yield and maintained a fluoride within the product. Similarly, the copper-

Scheme 7. Cu and Rh Addition/β-Fluoride Elimination



catalyzed borylation/β-fluoride elimination provided product **13**, which possesses two handles for future transformations.

In conclusion, we developed an efficient and scalable protocol for the synthesis of a *gem*-difluoroindoline bearing an exocyclic and allylic olefin without the need for column chromatography. These scaffolds are versatile building blocks capable of acting in an amphoteric sense as well as with various Pd/Cu/Rh reactions forming new C–H, C–B, C–C, C–N, C–O, C–P, and C–S bonds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01175.

Experimental procedures, optimization, mechanistic studies, characterization data, X-ray data, and $^1H/^{13}C/^{19}F/^{31}P$ NMR spectra (PDF)

Accession Codes

CCDC 1956222 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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