Modular synthesis of α-fluorinated arylmethanes via desulfonylative cross-coupling

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α-Fluoromethylarenes are common substructures in pharmaceuticals and agrochemicals, with the introduction of fluorine often resulting in improved biological activity and stability. Despite recent progress, synthetic routes to α-fluorinated diarylmethanes are still rare. Herein we describe the Pd-catalyzed Suzuki-Miyaura cross-coupling of α-fluorinated benzylic triflones with arylboronic acids affording structurally diverse α-fluorinated diarylmethanes. The ease of synthesis of fluorinated triflones as the key starting materials enables powerful late-stage transformations of known biologically active compounds into fluorinated analogs.
The strategic substitution of fluorine for hydrogen is an important strategy to improve the stability of materials and pharmaceuticals against metabolic or oxidative degradation (Fig. 1a). Transition metal-catalyzed cross-coupling reactions of arené derivatives with fluorinated alkyl electrophiles or nucleophiles are among the most valuable methods to form aryl–fluoroalkyl bonds under mild conditions without the use of toxic or hazardous reagents. However, despite these recent advances, α-fluorinated diarylmethanes are still prepared by classical methods including deoxyhalogenation of diarylmethanols or diarylketone derivatives. Important advances from the Zhang and Szymczak groups have begun to address these issues, but still require difluoromethylenes as starting materials, which can be of limited availability (Fig. 1b, c). In an alternative approach, Chen has described the photolytic fluorination of benzyl C–H bonds, which enables the selective synthesis of mono- and difluorinated products; however, this reaction was demonstrated only for simple diphenylmethanes. Considering the potential importance of fluorinated molecules in drug discovery, the modular and selective synthesis of α-fluorinated diarylmethanes from readily available reagents remains a real challenge. Routes that enable late-stage transformation of existing biomolecules are even more impactful.

Fluorophosphine derivatives are emerging as important electrophiles in transition-metal-catalyzed transformations. Unlike other electrophiles, which serve only as a leaving group, the sulfonyl group also activates adjacent protons, enabling facile α-functionalizations such as fluorination, in advance of any cross-coupling reactions. This enables the modular and straightforward synthesis of complex structures from simple, readily prepared starting materials. Utilizing this unique reactivity of sulfones, our group has developed Pd- and Ni-catalyzed reactions of benzylic sulfone derivatives that afford compounds which are difficult to prepare by other methods. The Baran group has also employed this functional group to enable the Nicatalyzed radical cross-coupling of alkyl or fluoroalkylsulfones with arylzinc reagents (Fig. 1d).

We describe herein the Pd-catalyzed desulfonylative cross-coupling of α-fluorinated benzyltrifluorides with aryloboronic acids, which enables the generation of a range of structurally diverse mono- and difluorinated diarylmethanes not described using the Baran approach (Fig. 1e). Notably, fluorinated benzyltrifluoride substrates were readily prepared by α-fluorination using an inexpensive fluorinating agent and mild base. This strategy takes advantage of the properties of the sulfone as an activator for fluorination and a leaving group for cross-coupling reactions.

![Fig. 1 Synthesis of α-fluoromethylenes.](image-url)

**Results**

Optimization of desulfonylative coupling. Di- and monofluorinated starting materials 1 and 2 were readily prepared by the use of N-fluorobenzenesulfonylimide (NFSI) as an inexpensive fluorinating agent. Difluorination was readily accomplished with excess NFSI and K3PO4, giving a difluorobenzyltrifluoride 1 in high yield. Monofluoro derivatives 2 were prepared by deprotonation of benzyltrifluorides with one equivalent of NaHMDS followed by the addition of NFSI. These procedures enabled the facile synthesis of 1 and 2 bearing a variety of functional groups (see Supplementary Information).

We began our investigation of the desulfonylative cross-coupling reaction using tert-butyl-α-difluorobenzyltrifluoride 1a as the electrophile and phenylboronic acid 3a as the nucleophile. The choice of substituent on the sulfonil group was found to be crucial (Fig. 2). Replacing the trifluoromethyl substituent phenyl (5), 3,5-bis(trifluoromethyl)phenyl (6), 2-pyridyl (7), 2-benzothiazolyl (8), or 1-phenyl-1H-tetrazol-5-yl (9) shut down the cross-coupling reaction. This suggests that the strongly electron-withdrawing triflyl group is critical for the C–SO2 bond activation process.

Optimized conditions were found to be the following: the use of DavePhos as ligand, Pd(OAc)2 as catalyst, K3PO4 as base in THF at 60 °C, which afforded 4aa in 90% isolated yield (Table 1, entry 1). Representative alkylphosphines were inactive (Table 1, entries 2–3), while other Buchwald ligands displayed lower activity.
reactivities (Table 1, entries 4–7). The use of Na₂CO₃ instead of K₃PO₄ decreased the yield of product (Table 1, entry 8). The synthetically useful boronic acid pinacol ester was also applicable in this reaction (Table 1, entry 9).

These conditions were less effective for electron-deficient substrates such as ester-substituted difluorobenzyltriflate 1b (Table 1, entry 10). However, di(1-adamantyl)-n-butylphosphine (P(Ad)₂Bu)¹⁷ was employed in DME at 90 °C, and gave the cross-coupling product in good yield (Table 1, entry 11). The related α-mono­fluorobenzyltriflate 2a did give α-fluoro­diarylmethane 10aa under standard conditions, but the yield was relatively low (Table 1, entry 12). Anticipating that the presence of the acidic benzylic proton in 2a might be incompatible with strong base, we employed Na₂CO₃ as a milder base, which gave the desired 10aa in 82% yield (Table 1, entry 13). In no case was benzotri­fluoride, which can be potentially generated by the arylation of SO₂–CF₃ bond, observed.

**Substrate scope of desulfonylative Suzuki–Miyaura cross-coupling.** With the optimized conditions for the cross-coupling in hand, we then investigated the substrate scope (Fig. 3).

First, we examined the reaction of 1a with a range of arylboronic acids. Arylboronic acids (3) bearing electron-donating and electron-withdrawing groups were well tolerated, and useful functional groups such as acetyl, cyano, formyl, ester, nitro, and vinyl groups were compatible, affording the corresponding products 4 in good yields. The sterically hindered o-tolyloboronic acid (3j) displayed decreased reactivity, while π-extended 1-naphthylboronic acid (3k) showed good reactivity. Although heteroarylboronic acids (3l–3n) were less reactive under standard conditions, increasing the catalyst loading and reaction temperature improved product yields. Some π-extended arenes (1b, 1c) and heteroarenes, such as indole (1d) and azole (1e), could be introduced in good yields. Gram-scale synthesis was successfully achieved in the preparation of 4bh.

Electron-deficient benzylic sulfones were smoothly reacted under the modified conditions (P(Ad)₂Bu instead of DavePhos) as shown in Table 1. Under these conditions, sulfone substrates bearing ester (1f), cyano (1g), nitro (1h), benzoyl (1i), and benzyloxy (1j) groups underwent cross-coupling, affording the

![Substituent effect of sulfonyl group on desulfonylative cross-coupling reaction.](image)

**Fig. 2** Substituent effect of sulfonyl group on desulfonylative cross-coupling reaction. Reactions were carried out on a 0.1 mmol scale. Yields were determined by GC using dodecane as an internal standard.

| Sulfone | Entry | Variation from the standard conditions | Product | Yield (%)² |
|---------|-------|----------------------------------------|---------|------------|
| 1a      | 1     | None                                   | 4aa     | 93 (90)    |
|         | 2     | PCy₃·HBF₄, instead of DavePhos          |         | 0          |
|         | 3     | P(Ad)₂Bu·HI, instead of DavePhos       |         | 0          |
|         | 4     | CyJohnPhos, instead of DavePhos        |         | 30         |
|         | 5     | XPhos, instead of DavePhos             |         | 39         |
|         | 6     | SPhos, instead of DavePhos             |         | 59         |
|         | 7     | PhDavePhos, instead of DavePhos        |         | 7          |
|         | 8     | Na₂CO₃, instead of K₂PO₄               |         | 19         |
|         | 9     | PhB(pin), instead of PhB(OH)₂          |         | 74         |
| 1b      | 10    | None                                   | 4ba     | 20         |
|         | 11    | P(Ad)₂Bu·HI, instead of DavePhos       |         | 80 (77)    |
| 2a      | 12    | None                                   | 10aa    | 90 (90)²   |
|         | 13    | Na₂CO₃, instead of K₂PO₄               |         |            |

Conditions: 1 or 2 (0.1 mmol), 3a (2.0 equiv), Pd(OAc)₂ (5 mol %), ligand (15 mol %), K₂PO₄ (3.0 equiv), THF (0.25 M)

¹Yields were determined by GC using dodecane as an internal standard

²Isolated yield (0.2 mmol scale)

³Reaction conducted in DME at 90 °C

⁴Yields were determined by ¹⁹F NMR spectroscopy using 4-fluorotoluene as an internal standard
desired products. As an illustration of the ease with which heteroaromatics can be incorporated, α,α-di-fluoro(di(heteroaryl)methane 4kn could be prepared in high yield. The present Pd-catalyzed cross-coupling is limited to benzylic substrates. Thus α,di-fluoroalkyltriflones such as 1,1-di-fluoro-3-phenylpropyl triflone are not viable substrates (see Supplementary Fig. 3).

Arylation of α-mono-fluorinated benzylic sulfones 2 also proceeded under the standard conditions, affording the corresponding mono-fluorinated diarylmethanes 10 in high yields. As in the difluorinated series, a variety of functional groups on sulfone and arylboronic acid substrates were compatible with this protocol (Fig. 3).

Desulfonylation of α-fluorobenzyl triflones 1 and 2. In addition to their use as partners in cross-coupling chemistry, 1 and 2 are also precursors to the pharmaceutically relevant difluoromethyl- and difluoromethylarenes (11, 12) (Fig. 4). Using typical procedures with Mg or SmI as reducing agents, desulfonylation proceeded smoothly to give the corresponding CF$_2$H or CFH$_2$-containing species in good yields. This desulfonylation approach is complimentary to other cross-coupling reactions using mono- and difluoromethylating agents for the selective synthesis of mono- and difluoromethylarenes.

Mechanistic investigations. Experimental and theoretical studies were carried out to gain mechanistic insights into the desulfonylative cross-coupling reaction. Reaction mechanisms involving radical intermediates appear likely in cross-coupling reactions using fluoroalkyl halides 17; thus, we conducted preliminary experiments to determine whether similar radical species are generated in this case. When the reactions of 1a with 3a were conducted under standard conditions in the presence of typical radical inhibitors, such as TEMPO and BHT, or 1,4-dinitrobenzene as an electron-transfer inhibitor, yields of 4aa were not significantly affected (Fig. 5a). This suggests that the present cross-coupling reaction does not likely involve the generation of free difluorobenzyl radical species in the catalytic cycle, and likely occurs via the similar catalytic cycle as the Suzuki–Miyaura cross-coupling reaction (see Supplementary Fig. 4).
Next, we explored the mechanism and the dramatic substituent effects of sulfonyl groups on the reactivity of cross-coupling by theoretical calculations. Gibbs free energies were obtained from single point calculations on optimized geometries with thermal correction and solvation effects considered. The energy profile is summarized in Fig. 5b for α,α-difluorobenzyltrifluorobenzyl (14CF3, α,α-difluorobenzyl phenyl sulphone 14Ph, and 3,5-bis(trifluoromethyl) phenyl difluorobenzyl sulphone 14ArCF3). The C–SO2 activation step should occur through the formation of a n2-arene complex 15 between Pd(DavePhos) 13 and sulfones (14CF3, 14Ph, or 14ArCF3), and then the three-membered transition state (TS15–16) to afford the Pd(II) complex.

16. The Gibbs activation energies of ΔG‡SO2CF3 ΔG‡SO2Ph, and ΔG‡SO2ArCF3 were calculated to be 18.2, 27.7, and 24.2 kcal/mol, respectively. In addition, the Gibbs reaction energy for the cross-coupling of 16CF3 (−28.8 kcal/mol) was more exergonic than that of 16Ph (−14.5 kcal/mol) or 16ArCF3 (−19.3 kcal/mol), indicating that C–SO2 activation of 14CF3 is thermodynamically favorable, consistent with our experimental results for these sulfones.

Synthetic applications. A significant advantage of this method is that the triaryl group can be easily installed through the late-stage transformation of any benzylic methyl group or indeed any benzylic C–H group (Fig. 6a). For example, the methyl group on 6-methyllavone could be converted into the triaryl trifluoromethyl group (Fig. 6a). In addition, the reaction process energy for the cross-coupling of 16CF3 (−28.8 kcal/mol) was more exergonic than that of 16Ph (−14.5 kcal/mol) or 16ArCF3 (−19.3 kcal/mol), indicating that C–SO2 activation of 14CF3 is thermodynamically favorable, consistent with our experimental results for these sulfones.

by the cross-coupling of α,α-difluoro-2-naphthylmethyl trifluorobenzyl (1c with 3,4,5-trimethoxylphenylboronic acid 3u) (Fig. 6b).

ABT-518 has been developed as an inhibitor of matrix metalloproteinases, which are key species implicated in tumor growth and metastasis.44,45. We have successfully prepared the analog of ABT-518 (26) in which the diaryl ether unit is replaced by a diarylCF2 unit (Fig. 6c). The key intermediate α,α-difluorodiarylmethane 23 was synthesized from the cross-coupling of α,α-difluoro-4-methanesulfonylbenzyl triflone 11 and 4-(trifluoromethyl) methoxyphenylboronic acid 3v. According to the previous procedure, vinyl sulfone 25 could be isolated. Finally, the conjugated addition of hydroxylamine to 25 followed by N-formylation using formic acid-acetic anhydride mixture gave 26 in seven steps from 11. These results illustrate that our robust method will expand the utility of CF3 units as bioisosters, which are difficult to introduce by existing methods, leading to accelerated generation of previously unknown pharmaceuticals.

In conclusion, we have established a versatile synthetic route for the synthesis of structurally diverse α-fluorinated and α,α-difluorinated molecules through the Pd-catalyzed Suzuki–Miyaura cross-coupling reaction of α-fluorinated benzyltriflones with arylboronic acids. In addition to cross-coupling, desulfonylation can be carried out to provide medicinally important fluoromethyl- and difluoromethylarenes in good yields. The ability to convert aromatic methyl groups to reactive sulfones is particularly exciting for late-stage functionalization approaches to the synthesis of fluorinated analogs of biomolecules. These reactions not only provide facile access to α-fluorinated arylmethanes from stable and readily available...
Methods

Cross-coupling of triflones 1 with arylboronic acids 3. A 10-mL scalable glass vessel containing a magnetic stirring bar was flame-dried under vacuum and filled with argon after cooling to room temperature. The tube was charged with Pd(OAc)2 (3.3 mg, 0.015 mmol), base (0.9 mmol) and arylboronic acid (0.4 mmol), K3PO4 (127 mg, 0.6 mmol), and THF (0.4 mL). The vial was capped with a Teflon cap and dry THF (1.5 mL) was added, under argon. This mixture was stirred at 60 °C for 16 h. The reaction was then allowed to cool to room temperature, quenched with 3–4 drops of sat. NH4Cl aq and the mixture was passed through a pad of silica gel with copious washings with EtOAc (~10 mL). The filtrate was concentrated under reduced pressure. The crude product was purified by preparative thin-layer chromatography (PTLC) or preparative recycling HPLC (GPC) to afford diaryl-α,α-difluoromethane 4.

Cross-coupling of triflones 2 with arylboronic acids 3. An oven-dried 1-dram vial equipped with a magnetic stirring bar was charged with Pd(OAc)2 (3.3 mg, 0.015 mmol) and DavePhos (17.7 mg, 0.045 mmol). The vial was capped with a Teflon cap and dry THF (1.5 mL) was added, under argon. This mixture was stirred for 30 min. Another vial containing a stirring bar was charged with α-fluorobenzyl triflone 2 (0.3 mmol), base (0.9 mmol) and arylboronic acid 3 (0.6 mmol). The vial was sealed under argon atmosphere, and the solution containing the catalyst was added to it. The resulting mixture was heated at 60 °C for 18–24 h, under stirring. After cooling to room temperature, the mixture was filtered through a plug of silica and washed with DCM/EtOAc (4:1). The crude product was purified by column chromatography or PTLC to afford diarylfluoromethane 10.

Data availability

The authors declare that the data supporting the findings of this study are available within the article and Supplementary Information file, or from the corresponding authors (M.N. and C.M.C.) upon reasonable request. The X-ray crystallographic coordinates for structure of compound 19 reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition numbers 1890466. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Author contributions
M.N. and C.M.C. devised the project. M.N. and C.M.C. performed the experiments, compound characterization and data analysis. M.N. and D.Y. performed the computational studies. All authors contributed to the overall experiment design, discussions and manuscript preparation. The manuscript was written by M.N. and C.M.C. with assistance from co-authors.

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