The chemistry of ferrocenesulfonyl fluoride revealed
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The first general route toward polysubstituted ferrocenesulfonyl fluorides is described. Merging deprotometallations, ‘halogen dance’ reaction, Sonogashira, Suzuki-Miyaura and Negishi cross-couplings with SuFEx chemistry allowed original ferrocenes of an unprecedented diversity to be obtained.

Aromatic sulfonyl fluorides have been known for almost a century with the studies of Steinkopf on their chemical properties. Furthermore, their biological properties were early recognized, leading to the wide use of AEBSF and PMSF in biochemistry as non-specific serine protease inhibitors. A major development in this field resulted from Sharpless’ seminal article, which introduced the concept of sulfur(VI) fluoride exchange (SuFEx), establishing sulfonyl fluorides as click-reactants. The unique chemical reactivity properties of this functional group result from its resistance to reduction, its high thermodynamic stability, the exclusive substitution at sulfur and the specific fluoro-proton interactions required for SuFEx.

As a result, sulfonyl fluorides are stable under a wide range of reaction conditions but, if properly activated, can react with a nucleophile. Since then, a number of applications of these compounds have been reported, mainly in material science and chemical biology to achieve covalent inhibitors. The fluorosulfonyl group acting as a warhead.

While ferrocene is one of the most important organometallic scaffolds with multiple applications, only two ferrocenesulfonyl fluoride derivatives (1'-carbomethoxyferrocenesulfonyl and 1'-carboxyferrocenesulfonyl fluorides) have been reported. Due to our interest in ferrocenesulfonamides and sulfonates, we decided to explore the chemistry of these unique three-dimensional compounds which might have unique properties when compared with flat aromatics.

Figure 1. Examples of biologically active arenesulfonyl fluorides.

Among the many substrates that can lead to sulfonyl fluorides, we selected ferrocenesulfonyl chloride (1), easily available on a gram scale from ferrocene, to explore the nucleophilic substitution approach. We initially evaluated the biphasic system reported by Barbasiwicz and reacted 1 with potassium bifluoride in the presence of tetrabutylammonium bromide in a water-acetonitrile mixture. A modest 32% yield of ferrocenesulfonyl fluoride (2) was obtained and crystals suitable for X-ray analysis were obtained (Scheme 1). The yield was improved to 63% under anhydrous conditions but after prolonged heating (see SI). Although the use of “naked” fluoride (KF in the presence of 18-crown-6) is one of the most accepted procedures, its cost would become problematic to access large quantities of 2. Therefore, we reassessed the reaction conditions described by Nesmeyanov in 1959, and reacted 1 with KHF2 in acetic acid at 25°C for 14 h and isolated 2 in 52% yield (see SI). We found that heating the reaction mixture at 60 °C considerably fastened the reaction, complete in only 30 min, and that it was possible to scale up the reaction to 100 mmol (63% yield).

With large quantities of 2 now available, we explored its functionalization toward polysubstituted ferrocenes.

Scheme 1. Synthesis of 2. Reaction conditions: a) KHF2 (3.0 equiv), AcOH, 60 °C, 30 min.

In 2019, Barbasiwicz reported the use of lithium disopropylamide to perform the ortho-deprotometallation of arenesulfonyl fluorides. Indeed, the use of alkylolithiums resulted in fluorne nucleophilic substitution, leading to the corresponding sulfone. Ferrocene being more electron-rich and bulkier than benzene, it might act as an electronic and steric shield for the sulfonyl fluoride group, making 2 compatible with simple alkylolithiums. Therefore, the substrate 2 was reacted with nBuLi in tetrahydrofuran (THF) at -85 °C for 30 min before addition of trimethylchlorosilane (Scheme 2). The silylated derivative 3a was isolated in 75% yield, highlighting the marked reactivity difference between arene- and ferrocenesulfonyl fluoride. Upon scaling up the reaction, the reproducibility was improved by performing the deprotometallation at -95 °C for 15 min, allowing 3a to be isolated in 80% yield on a 10 mmol scale. The use of iodine and N-fluorobenzenesulfonyl (NFSI) as electrophiles similarly afforded the compounds 3b and 3c, isolated in 76 and 48% yields, respectively. It was also possible to transmetalate the ferrocenyl lithium into the corresponding ferrocenylzinc derivative by using ZnCl2-TMEDA (TMEDA: N,N,N',N’-tetramethylethylenediamine) and perform a Negishi cross-coupling with 3-iodopyridine in the presence of palladium dichloride and 1,1’-bis(diphenylphosphino)ferrocene (dppf) (compound 3d; 64% yield).
As demonstrated by Seebach and Corey, 13, 35, 36 aromatic iodides are easily functionalized by lithium/halogen exchange toward a range of derivatives depending on the electrophile used to intercept the lithiated intermediate. To reach other valuable 1,3-disubstituted ferrocenes, we treated the compound 6a with an excess of tBuLi in THF at -90 °C before addition of Eschenmoser’s salt or methyl chloroformate (Scheme 4). The dimethylaminomethyl and methyl ester derivatives 7a and 7b were thus isolated in 68% and 73% yields, respectively.

The orthogonal reactivity of ferrocenesulfonyl fluoride was further demonstrated in Sonogashira and Suzuki-Miyaura cross-couplings. While aresenylsulfonyl fluorides have been previously shown to be compatible with the former reaction, only tertiary amines were used as reagents. 37 We were eager to see if diisopropylamine could be compatible, and therefore selected the conditions reported by Albrecht and Long. 38 The compound 3b was therefore reacted with trimethylsilylacetylene in the presence of catalytic bis(tri-tert-butylphosphine)palladium and copper iodide in a THF-diisopropylamine mixture (Scheme 5).

After 14 h at 25 °C, the title 1,2-disubstituted ferrocene 8a was isolated in 90% yield without evidence of reaction between the excess of amine and the sulfonyle fluoride. Pleasingly, it was also possible to isolate the 1,3-disubstituted isomer 8b in a similar yield from the substrate 6a. Mild deprotection of the alkylene was possible by using TBAF in THF at 0 °C, affording the isomeric compounds 9a,b in 83% and 58% yields, respectively. Aresenylsulfonyl fluorides are known to be compatible with Suzuki-Miyaura cross-coupling conditions using ligand-free or palladium-ligand combinations in water, 39, 40 water-dioxane 41 or anhydrous dimethylformamide. 42 In the presence of Pd(dba) 2 (dba: dibenzylideneacetone) and 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos), 43 2-iodoferrocenesulfonyl fluoride (3b) was reacted with 4-fluorophenylboronic acid while its 3-iodinated isomer 6a was reacted with either 4-(trifluoromethyl)- or 2,6-(dimethoxy)phenylboronic acids. 44 After 14 h at 110 °C in toluene, the desired arylated ferrocenes 10a-c were isolated in 86%, 79% and 94% yields, respectively (Scheme 5, bottom).
occurred at higher temperatures. Li recently reported the amidation of arenesulfonyl fluoride by using a catalytic amount of hydroxybenzothiazole (HOBt) in the presence of 1,1,1,3,3-tetramethyldisiloxane in dimethyldisulfide (DMSO) at 25 °C. In our case, the reduced reactivity of 2 required the use of an excess of both HOBt and triethylsilane at 50 °C for 72 h to deliver (N-morpholinosulfonyl)ferrocene (13a) in 61% yield. The more reactive imidazole was successfully reacted with 2 toward (N-imidazolosulfonyl)ferrocene (13b; 91% yield) in the presence of cesium hydride at 25 °C. In 2019, De Borggraewe reported the reaction between amides and arenefluorosulfonates in the presence of sodium hydride at 25 °C. In our hands, the use of acetamide in the presence of NaNH at 50 °C afforded the N-acetylsulfonylamide 13c in a moderate 63% yield (22% of 2 recovered). Ferrocenesulfonates can also be obtained from 2 by reaction with phenols in the presence of cesium fluoride (compound 13d; 93% yield) or with aliphatic alcohols in the presence of sodium hydride (compound 13e; 99% yield). Sulfones can be prepared by reacting arenesulfonyl fluorides with either organolithium reagents or electron-rich aromatics in the presence of aluminium trichloride. Therefore, we treated ferrocenesulfonyl fluoride (2) with phenyllithium in THF at 0 °C. Complete conversion was reached after 15 min, and the phenylferrocenesulfone 13f was isolated in 72% yield. Finally, the reaction between 2 and 1,4-dimethoxybenzene in the presence of AlCl₃ furnished the sulfone 13g in 91% yield. It was, of interest to extend the SuFEx reaction to a substituted ferrocenesulfonyl fluoride. Therefore, the iodinated derivative 6a was reacted with morpholine in the presence of HOBt and Et₃SiH toward the sulfonamide 13h, isolated in 76% yield after 16 h at 60 °C. When compared with the parent compound 2 (61% after 72 h, Scheme 7), this represents a considerable reactivity enhancement which can be linked with the moderate electron withdrawing properties of the iodine atom. However, when the substrate 6a was reacted with sodium isopropoxide, the sulfonate 13i was isolated in 89% yield (Scheme 8, right), slightly lower than the one recorded for the sulfonate 13e (99%, Scheme 7).

To the best of our knowledge, there is only one report of a nickel-catalyzed Negishi coupling of an iodinated zinc reagent and no example under palladium catalysis. Thus, we were eager to see if the iodo substituent of 3b could be tolerated in such a reaction. It was treated by LiTMP in THF at -50 °C in the presence of the ZnCl₂:TMEDA in situ trap and the resulting ferrocenylzinc intermediate was reacted with 3-iodopyridine in the presence of PdCl₂ and dppf (Scheme 6). Pleasingly, the 1,2,3-trisubstituted ferrocene 11 was isolated in 41% yield, its structure being unambiguously assigned by X-ray diffraction. It was further engaged into Suzuki-Miyaura coupling toward the bis-arylated ferrocenesulfonyl fluoride 12 (75% yield).

Having established the robustness of ferrocenesulfonyl fluoride in various reaction conditions, we investigated its behaviour in SuFEx reactions. Indeed, one can expect a decrease in electrophilicity of the sulfonyl fluoride from benzene to ferrocene due to the electron-rich core of the latter. Therefore, the reactivity of 2 toward morpholine was first evaluated in the presence of cesium carbonate in acetonitrile. However, no desired product was observed at 25 °C and decomposition of hydroxybenzothiazole (HOBt) in the presence of 1,1,1,3,3-tetramethyldisiloxane in dimethyldisulfide (DMSO) at 25 °C. In our case, the reduced reactivity of 2 required the use of an excess of both HOBt and triethylsilane at 50 °C for 72 h to deliver (N-morpholinosulfonyl)ferrocene (13a) in 61% yield. The more reactive imidazole was successfully reacted with 2 toward (N-imidazolosulfonyl)ferrocene (13b; 91% yield) in the presence of cesium hydride at 25 °C. In 2019, De Borggraewe reported the reaction between amides and arenefluorosulfonates in the presence of sodium hydride at 25 °C. In our hands, the use of acetamide in the presence of NaNH at 50 °C afforded the N-acetylsulfonylamide 13c in a moderate 63% yield (22% of 2 recovered). Ferrocenesulfonates can also be obtained from 2 by reaction with phenols in the presence of cesium fluoride (compound 13d; 93% yield) or with aliphatic alcohols in the presence of sodium hydride (compound 13e; 99% yield). Sulfones can be prepared by reacting arenesulfonyl fluorides with either organolithium reagents or electron-rich aromatics in the presence of aluminium trichloride. Therefore, we treated ferrocenesulfonyl fluoride (2) with phenyllithium in THF at 0 °C. Complete conversion was reached after 15 min, and the phenylferrocenesulfone 13f was isolated in 72% yield. Finally, the reaction between 2 and 1,4-dimethoxybenzene in the presence of AlCl₃ furnished the sulfone 13g in 91% yield. It was, of interest to extend the SuFEx reaction to a substituted ferrocenesulfonyl fluoride. Therefore, the iodinated derivative 6a was reacted with morpholine in the presence of HOBt and Et₃SiH toward the sulfonamide 13h, isolated in 76% yield after 16 h at 60 °C. When compared with the parent compound 2 (61% after 72 h, Scheme 7), this represents a considerable reactivity enhancement which can be linked with the moderate electron withdrawing properties of the iodine atom. However, when the substrate 6a was reacted with sodium isopropoxide, the sulfonate 13i was isolated in 89% yield (Scheme 8, right), slightly lower than the one recorded for the sulfonate 13e (99%, Scheme 7).
In conclusion, a gram scale synthesis of ferrocenesulfonyl fluoride permitted its functionalization toward original derivatives. The unique properties of ferrocenesulfonyl fluoride allowed widely available butyllithium to be used for its irreversible, efficient deprotonation when hindered lithium amides are required to deprotonate their benzene counterpart. The orthogonal reactivity of sulfonil fluoride was demonstrated in lithium/iodine exchange reactions as well as in Sonogashira, Suzuki-Miyaura and Negishi cross-couplings. Finally, the usefulness of ferrocenesulfonyl fluoride was demonstrated in SuFEx chemistry as a general entry toward various sulfur-functionalized groups. Considering the wide range of sulfonil fluoride applications in material science and chemical biology, the chemical diversity of ferrocenesulfonyl fluorides now accessible, it makes little doubt that this new scaffold is promised to a bright future.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

16. During the evaluation of this manuscript, the deprotonetallation of ferrocenesulfonyl fluoride using a lithium amide has been reported, see: G. M. Romero Boston, H. M. Philipp and H. Butenschön, Eur. J. Inorg. Chem., DOI: 10.1002/ejc.202100785.
41. T. S.-B. Lou and M. C. Willis, Tetrahedron, 2020, 76, 130782.
44. In our hands, the Suzuki-Miyaura coupling required an excess of boronic acids to maximise the product yield and overcome the decomposition of boronic acids, especially fluorinated ones.