Synthesis L. Wang et al. Special Topic

Validation of Arylphosphorothiolates as Convergent Substrates for Ar-SF_4Cl and Ar-SF_5 Synthesis

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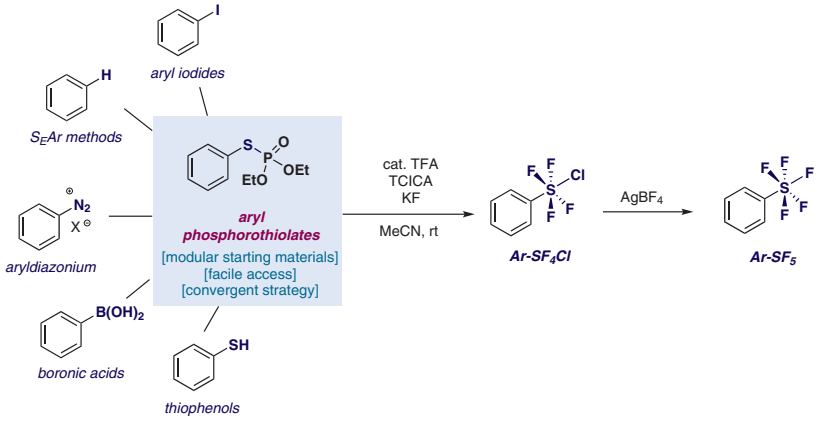

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Abstract In this manuscript we describe the oxidative fluorination of aryl phosphorothiolates to access Ar-SF_4Cl compounds. These compounds serve as precursors for the highly coveted Ar-SF_5 compounds. The use of phosphorothiolates as starting materials permits access to Ar-SF_4Cl from a wide variety of available starting materials, namely boronic acids, diazonium salts, aryl iodides, thiophenols, or simple arenes. The protocol has been demonstrated for >10 examples and showed good tolerance to various functional groups. Finally, we demonstrated that $AgBF_4$ can be used as a fluorinating agent, affording good yields of an Ar-SF_5.

Key words fluorine, phosphorus, sulfur, pentafluorosulfanylation, isosteres

Nearly a quarter of the pharmaceuticals in the market contain at least one fluorine atom in their structure.[1] The impact of fluorine in drug discovery campaigns has been remarkable and methods to create X-F bonds in organic molecules are highly coveted.[2] In this context, chemists have identified groups of fluorinated functionalities which have had a dramatic impact on the ADME (i.e. Absorption, Distribution, Metabolism and Excretion) properties of certain biologically active compounds.[3] For example, CF_3,[4] OCF_3,[5] SCF_3,[6] CF_2H,[7] CFH_2,[8] and trifluorocyclopropyl[9] have all been studied as bioisosteres of CH_3, OCH_3, and ^{t}Bu groups. In recent years, a related fluorinated functionality has also been identified as a bioisostere of the CF_3 and ^{t}Bu groups: the pentafluorosulfanyl group (SF_5).[10] This hypervalent sulfur moiety is characterized by an octahedral arrangement of the F atoms around the S(VI) atom, resulting in high electronegativity[11] (Scheme 1A). Compared to its CF_3 analog, the SF_5 group is more hydrophobic and is robust when confronted to harsh acidic or basic conditions (for Ph-SF_5).[12]

With the volume comparable to a ^{t}Bu group and the electronegativity resembling a NO_2 group, the introduction of SF_5 into lead compounds has captivated the interest of medicinal chemists. For example, analogues of mefloquine (antimalarial) or bosentan (pulmonary arterial hypertension) bearing an SF_5 group have shown to be more potent than its CF_3 analog, highlighting some of the potential applications of the pentafluorosulfanyl group (Scheme 1A).[13] Despite the interesting chemical properties of this group, its synthesis and strategies for its straightforward introduction are still somewhat limited. Although early examples using Cl_2, F_2, or XeF_2 are known, limitations in functional group tolerance, scope, and practicality have prevented their adoption by organic chemists.[14] In groundbreaking work, Pitts, Santschi, Togni, and co-workers reported a practical variation of the Umemoto process,[14d] which enabled the synthesis of a wide variety of Ar-SF_5 compounds in a simple and straightforward manner.[15] The strategy consists of the oxidation of aryl disulfides (from thiols) with TCICA (tetrachloroisocyanuric acid) in the presence of an excess of KF, to forge the key intermediate Ar-SF_4Cl (Scheme 1B). Simple Cl-F exchange then leads to Ar-SF_5. It is important to mention that such a strategy has also been used in the oxidation of other chalcogens and even organophosphorus compounds.[16] Our group has recently contributed to this area reporting the possibility to use aryl sulfenylphthalimides as precursors, which can be obtained from the parent Ar-ZnX compounds (Scheme 1B).[17] Despite these advances, the current methodologies are still restricted to thiophenols and organozinc reagents as precursors. With

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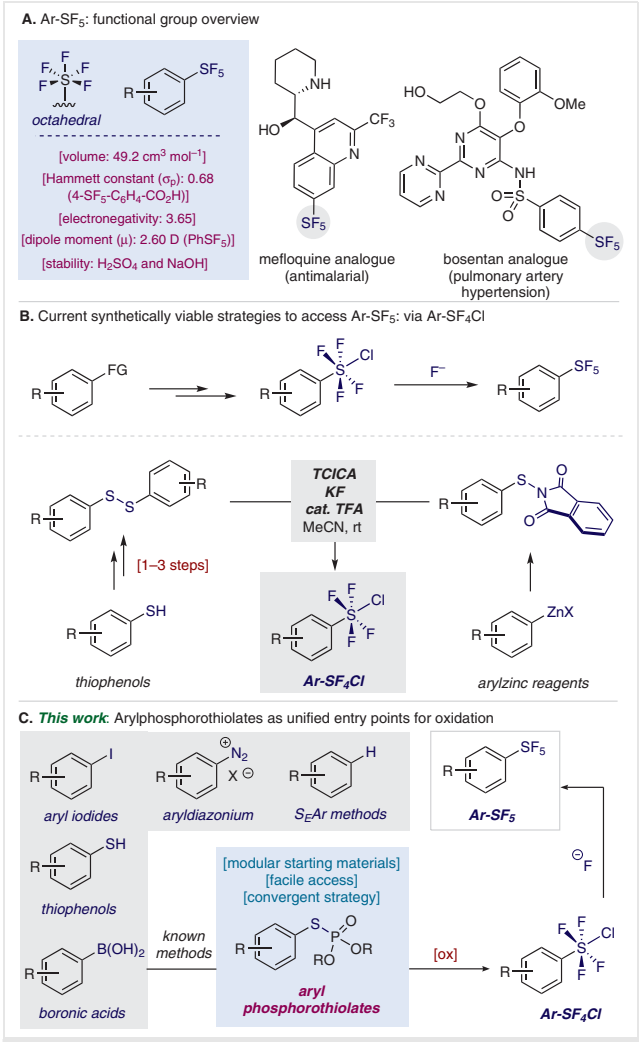
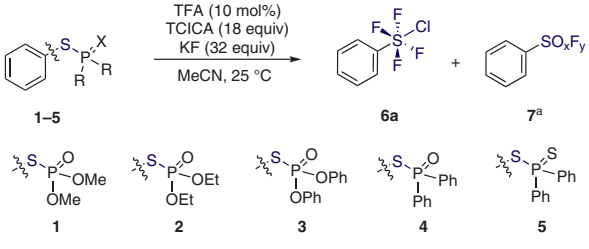


Scheme 1 (A) Physical and chemical properties of Ar-SF_5; (B) Current strategies to access Ar-SF_4Cl; (C) Use of aryl phosphorothiolates in oxidative fluorination

the aim of expanding the palette of opportunities in terms of a wider spectrum of precursors, we focused our attention on the oxidative fluorination of aryl phosphorothiolates, *en route* to valuable Ar-SF_4Cl (Scheme 1C).

Indeed, aryl phosphorothiolates can be accessed through a variety of different starting materials and their synthesis has been widely explored. For example, Ar-S-P(O)$(OR)_2$ can be easily accessed in one step from thiophenols by the simple reaction with H-P(O)$(OR)_2$ or Cl-P(O)$(OR)_2$.[18] Schoenebeck has recently shown that Ar-S-P(O)$(OR)_2$ can also be easily accessed via palladium catalysis from the parent aryl iodides.[19] Additionally, Gooßen and Tang have developed protocols which enable the synthesis of aryl phosphorothiolates through S_EAr from electron-rich arenes or via Cu-catalyzed/mediated cross-coupling from the corresponding diazonium salt or boronic acid.[20] The possibility to access these compounds from a myriad of diverse starting materials further supports the consideration of Ar-S-P(O)$(OR)_2$ as convergent linchpin reagents. In this work, we demonstrate that oxidation of Ar-S-P(O)$(OR)_2$ with TCICA in the presence of KF delivers Ar-SF_4Cl in good yields with a variety of substitution patterns at the aryl moiety (Scheme 1C). Additionally, we also demonstrate that Ar-SF_4Cl can be converted into the corresponding Ar-SF_5 via the use of $AgBF_4$.

Optimization of the oxidative fluorination started by the testing of various phenyl phosphorothiolates. As shown in Scheme 2, when a mixture of TCICA and KF is used in MeCN at room temperature, phenyl phosphorothiolates bearing OMe (**1**) or OEt (**2**) led to good yields of **6a** (entries 1 and 2). However, side products were also observed, which were identified to be mainly the S(IV) product Ph-SF_3 and the partially hydrolyzed S(VI) product Ph-SOF_3 (shown together as **7**). When the alkoxy groups in the phosphorus ester are replaced by phenoxy (**3**), the yields dramatically decreased, resulting in only 25% overall yield with almost no selectivity for Ar-SF_4Cl (entry 3). When the P(O)$(OR)_2$ group is replaced by P(O)Ph_2 (**4**), good yields were also obtained in high selectivity (entry 4). Finally, the replacement of P=O by P=S reduced the yield of the desired product **6a**, presumably through the undesired oxidation of the terminal sulfide group (entry 5). Although slightly better yields were obtained for compound **4**, we selected compound **2** as our phosphorothiolate of choice, because of the wider availability of methods to access this particular moiety. Although several protocols can lead to Ar-S-P(O)$(OEt)_2$, we utilized the methods reported by Gooßen and Zhao to access our starting materials **2b**–**m**.[20]

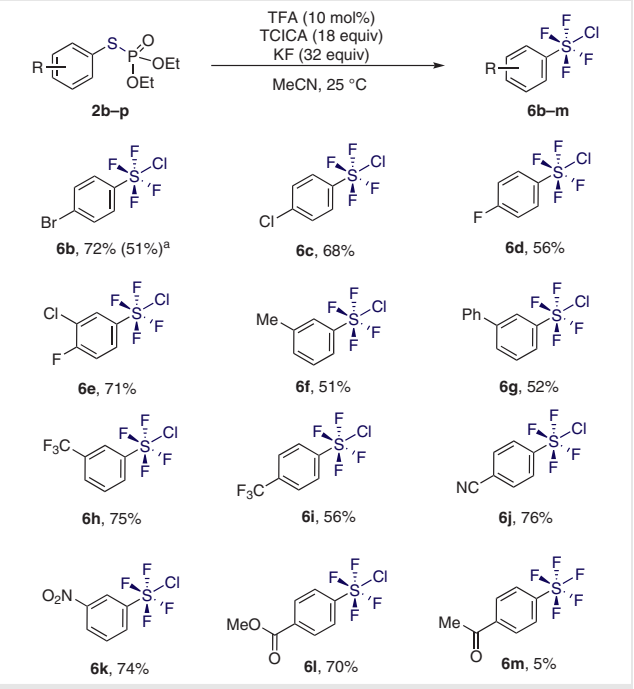


entry	starting Ar-S-PR_3	yield (%)[b] (**6a**+**7**)	ratio[b] (**6a**/**7**)
1	**1**	>99	71:28
2	**2**	>99	75:25
3	**3**	25	<5:24
4	**4**	>99	82:18
5	**5**	86	43:43

Scheme 2 Optimization of the reaction conditions. [a] Combined integration for Ph-SF_3 and Ph-SOF_3. [b] Yields determined by ^{19}F NMR spectroscopy with α,α,α-trifluorotoluene as internal standard.

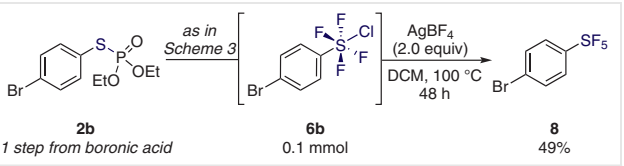
With this optimization in hand, we scrutinized the scope of this transformation. As depicted in Scheme 3, the method functioned well in the presence of halogens. For example, aryl groups substituted with *p*-Br (**6b**), *p*-Cl (**6c**), *p*-F (**6d**), or multiple halogens (**6e**) afforded good yields of the

corresponding Ar-SF_4Cl **6**. Product **6f** with an alkyl groups in the *meta* position of the ring was smoothly obtained in 51% yield. Aromatic substituents were also tolerated, as exemplified by **6g** (52%). The presence of other electron-withdrawing substituents such as CF_3 both in the *meta* (**6h**) and *para* (**6i**) positions did not present any hurdles in the oxidative fluorination. When CN or NO_2 groups are attached to the aryl ring, good yields of the desired Ar-SF_4Cl products **6j** and **6k** were also obtained. Interestingly, the presence of an ester did not pose any hurdle, affording **6l** in excellent yield. Unfortunately, the methodology met its limitations when alkyl aryl ketones are present, affording only traces of **6m**. This is probably due to side reactions on the α-carbon. As noticed in previous works, Ar-SF_4Cl compounds are highly reactive and their isolation is extremely challenging. Therefore, the yields were calculated by ^{19}F NMR spectroscopy by using an internal standard.



Scheme 3 Scope of the reaction for aryl tetrafluorosulfanyl chlorides. *Reagents and conditions*: Ar-S-P(O)$(OEt)_2$ (0.2 mmol, 1.0 equiv), trichloroisocyanuric acid (TCICA, 18 equiv), rigorously dried KF (32 equiv), 0.1 M TFA in MeCN (0.2 mL), MeCN (2 mL), in a PTFE vessel, 25 °C, under argon, 24 h; yields calculated by ^{19}F NMR using α,α,α-trifluorotoluene as reference. [a] Reaction performed on 1.0 mmol scale.

Having shown the viability of aryl phosphorothiolates as precursors to access Ar-SF_4Cl, we decided to explore whether the protocol was suited for the formation of Ar-SF_5. It is important to mention that the byproducts formed during oxidative fluorination are P(V) fluoro compounds, which could potentially affect the Cl-F exchange and generate side reactions through the additional fluorides required.[21] With these potential issues in mind, we developed a proof-of-concept protocol for the Cl-F exchange using BF_4 anions. To exemplify this possibility, compound **6b** was mixed with $AgBF_4$ (2.0 equiv) in DCM at 100 °C; **8** was smoothly formed in 49% yield from **2b**, which is obtained from (4-bromophenyl)boronic acid (Scheme 4). Although this process resembles the silver-induced self-immolative protocol using Ag_2CO_3, more information is required to provide a full mechanistic rationale by which this last Cl-F exchange occurs.[22]



Scheme 4 Cl-F exchange protocol based on $AgBF_4$ to access Ar-SF_5

In conclusion, we have developed an oxidative fluorination protocol that converts Ar-S-P(O)$(OR)_2$ to Ar-SF_4Cl in a practical manner. This new protocol broadens the palette of starting materials to access Ar-SF_5 compounds, whose practical synthesis is still highly coveted by practitioners in medicinal and agrochemical sciences. Although these results are still far from ideal, we believe that they provide a step forward in the field and will be an incentive for the development of even more practical methods, finally leading to routine investigations of Ar-SF_5 compounds in drug discovery campaigns.

Unless stated otherwise, all manipulations were performed using standard Schlenk techniques under anhydrous argon in flame-dried glassware. Anhydrous solvents were distilled from appropriate drying agents and were transferred under argon: MeCN (CaH_2), DCM (CaH_2), hexane (Na/K), Et_3N (MS). Unless stated otherwise, all chemicals were purchased from Sigma-Aldrich, Alpha Aesar, and TCI and used without prior drying or purification. $Cu(OTf)_2$ (34946-82-2) and Cs_2CO_3 (534-17-8) were purchased from Sigma-Aldrich and stored under argon. Trichloroisocyanuric acid (TCICA, powder, 87-90-1) was purchased from Alpha Aesar and transferred in an argon-filled glovebox before usage. Potassium fluoride (KF, powder, 7789-23-3) was purchased from Sigma-Aldrich, rigorously dried under high vacuum (10^{-6} mbar) at 120 °C for 24 h, and stored under argon. Flash chromatography was performed on Merck silica gel 60 (40–63 μm). GC-MS (FID) was carried out on a GC-MS-QP2010 equipped instrument (Shimadzu Europe Analytical Instruments). NMR spectra were recorded using a Bruker Avance VIII-300 spectrometer. ^1H NMR spectra (300.13 MHz) were referenced to the residual protons of the deuterated solvent used. All ^{19}F NMR spectra were acquired on a 300 MHz spectrometer. For ^{19}F NMR yield determination, α,α,α-trifluorotoluene was used as internal standard (^{19}F, δ = –63.10 in CD_3CN). $^{13}C\{^1H\}$ NMR spectra (75.47 MHz) were referenced internally to the D-coupled ^{13}C resonances of the NMR solvent. The 12 mL PTFE vials were purchased from AHF Analysentechnik in Tübingen, Germany.

Ar-SF_4Cl 6; General Procedure

In a glovebox under argon, the appropriate Ar-S-P(O)$(OEt)_2$ precursor **2** (0.2 mmol, 1 equiv), TCICA (840 mg, 3.6 mmol, 18 equiv), and rigorously dried KF (372 mg, 6.4 mmol, 32 equiv) were added to an oven-dried 12 mL PTFE reaction vial equipped with a stir bar. Under vigorous stirring, anhydrous and degassed MeCN (2.0 mL) was added to the mixture, followed by the addition of a 0.1 M solution of TFA in MeCN (0.2 mL). Then the vial was sealed with a septum-pad cap and the reaction was stirred at rt in the glovebox for 24 h. After this time, the atmosphere in the vial was vented carefully and the internal standard α,α,α-trifluorotoluene was added into the mixture. After 10 min of stirring, an aliquot of the resulting solution was filtered under argon. The NMR sample was prepared with the filtered aliquot (0.4 mL) and CD_3CN (0.1 mL) for ^{19}F NMR yield determination. Please note that, although Ar-SF_4Cl is not too sensitive to moisture, the use of dry reaction vials and anhydrous solvent, as well as carrying out the experiment and workup under argon benefited the reaction. See Supporting Information for NMR analysis.

4-BrC_6H_4-SF_5 (8)

4-BrC_6H_4-SF_4Cl (**6b**) was synthesized according the general procedure described above. Upon the completion of the reaction, the atmosphere in the vial was vented carefully and the suspension was transferred to a flame-dried Schlenk tube under argon. Then the solvent and other volatile constituents were evaporated carefully under vacuum at 0 °C. To the residue, an anhydrous and degassed mixture of hexane/DCM (9:1) was added to extract the Ar-SOF_3 compound (3 × 4 mL). The resulting solution was filtered in two batches of ca. 6 mL under argon followed by concentration of the filtrate under vacuum. The crude product of Ar-SF_4Cl was used immediately for the next step. (Please note, some kinds of Ar-SF_4Cl are very volatile. Even at low temperature, the concentration led to significant loss of Ar-SF_4Cl). The crude product of Ar-SF_4Cl (ca. 0.1 mmol, 1 equiv) was dissolved in 1 mL of dry and degassed DCM followed by the addition of $AgBF_4$ (0.2 mmol, 2 equiv) under argon. The mixture was stirred at 100 °C for 48 h. Upon completion of the reaction, the resulting solution was then concentrated and further purified by column chromatography (silica gel, pentane/EtOAc, 20:1); this gave **8**; yield: 19 mg (49%).

^1H NMR (298 K, 300 MHz, $CDCl_3$): δ = 7.55–7.48 (m, 4 H).

$^{19}F\{^1H\}$ NMR (298 K, 282 MHz, $CDCl_3$): δ = 83.5 (m, 1 F), 63.0 (d, *J* = 150.3 Hz, 4 F).

^{13}C NMR (298 K, 75 MHz, $CDCl_3$): δ = 152.6 (m), 131.9, 127.6 (quin, *J* = 4.7 Hz), 126.1.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1706039.

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