Straightforward Pentafluorosulfanylation for Molecular Design

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Abstract:
Pentafluorosulfanylation is a powerful boost of molecular properties for many applications. In order to leverage its full potential, a direct and high-yielding synthetic strategy is in great demand. We report here how the discovery of a direct pentafluorosulfanylation of thiolated arenes led to a generalized synthetic approach toward aryl– and heteroaryl pentafluorosulfanyl (SF_5) compounds from various common building blocks. The combination of onium halides with silver(II) fluoride (AgF_2) provided drastically enhanced oxidative fluorination conditions that enabled the single-step conversion of various thiophenol derivatives to SF_5-compounds in high yields and broad scope. The particularly high reaction rate is accounted to an onium fluoroargentate(II)-mediated fluorination mechanism. The recycling potential of inorganic silver byproducts furthermore offers an avenue into industrial-scale production.

One-Sentence Summary: The efficient installation of pentafluorosulfanyl (SF_5) groups from various precursors enable advanced shaping of molecular properties.

Main Text

Fluorination technology is a core component of modern and future advances in medicine, crop protection, materials and energy conversion.(*1*) While the implementation of trifluoromethyl (CF_3) groups has become very popular, the less common derivatization with pentafluorosulfanyl (SF_5) groups – also referred as a *super-trifluoromethyl* group –very often results in superior molecular properties. In comparison to CF_3, the SF_5 group exhibits enhanced characteristics,(*2–4*) such as larger size, higher electronegativity and electron-withdrawing capacity, increased lipophilicity and can also improve hydrolytic stability (Fig. 1A). Thus, prominent examples for aryl SF_5-compounds (Ar-SF_5) outperforming their CF_3-analogs can be found in all fields of molecular design, e.g. for catalysts,(*5*) agrochemicals,(*6*) materials such as liquid crystals,(*7*) and in pharmaceutical chemistry.(*2*) Despite the advantages of Ar-SF_5 compounds, however, their widespread application is severely hampered by the cumbersome and low-yielding synthetic methodology of pentafluorosulfanylation. Initial synthetic approaches in the 1960s by Sheppard involved the direct fluorination of aryl disulfides (Ar_2S_2) with silver(II) difluoride (AgF_2) resulting in low yield and chemoselectivity.(*8*) Modern protocols proceed via a stepwise oxidative fluorination sequence involving an arylsulfur chlorotetrafluoride (Ar-SF_4Cl) intermediate, which must be isolated and further converted into the SF_5-product via a separate Cl-F exchange reaction (Fig. 1B, top). The oxidative fluorination is achieved either with chlorine gas as the stoichiometric oxidant in the

presence of KF, introduced by Umemoto et al.(*9*, *10*) or with solid chlorinating reagent TCICA, as reported by Togni and Shibata.(*11*, *12*) Due to these advances, the interest of the synthetic organic community in pentafluorosulfanylation and its related chemistry has been re-ignited recently(*13–21*) and novel SF_5-pharmaceuticals have appeared in clinical trials and patents.(*22–24*) However, the total efficiency of the current synthetic route toward Ar-SF_5 compounds remains unsatisfactory due to several associated problems: a multi-step synthetic sequence; overall low to moderate yields; difficulty in handling of intermediates due to strong smell and/or moisture sensitivity; limitations in substrate scope (e.g. for certain heterocycles and generally electron-rich arenes); long reaction time and harsh reaction conditions; limited set of available and applicable starting materials.

Given the modern challenges in public health, global food supply, environmental protection and energy efficiency, creating better molecules is imperative and we believe it is essential to make the SF_5 group a prevalent part of the molecule design toolbox. In order to ensure wide and easy accessibility, SF_5 compounds should be obtainable from a variety of starting materials in a synthetically efficient manner. Herein, we report how the discovery of a single-step perfluorosulfanylation of thiophenol derivatives gave rise to a convenient and generalized synthetic strategy for aryl– and heteroaryl SF_5 compounds from common building blocks, such as aryl fluorides, bromides, iodides and diazonium salts, through a thiolation cross-coupling (Step 1) and oxidative fluorination (Step 2) sequence (Fig. 1B, bottom).

As the initial puzzle piece toward our goal to increase the synthetic efficiency of pentafluorosulfanylation (Step 2), we first successfully developed a single-step oxidative fluorination of diphenyldisulfide (Ph_2S_2, **1**) to pentafluorosulfanylbenzene (Ph-SF_5, **2**) using the combination of AgF_2 and NEt_4Cl. Our reaction development is summarized in Figure 2A. Weak oxidants (Me-NFPy, NFSI, DBI, TBCA) did not provide sufficient reactivity and the use of Cl-NFPy, Select-F, AgF_2(*25*), XeF_2(*26*) and Br_2/KF(*27*) only gave phenylsulfur(IV) trifluoride (Ar-SF_3). Thus, as reported in literature, the oxidative fluorination to phenylsulfur(VI) requires stronger oxidants, TCICA(*11*), Cl_2/KF(*9*), [NEt_3Me][ClF_4](*28*) and XeF_2/NEt_4Cl(*29*) providing Ph-SF_4Cl as the main product. The use of XeF_2 with a soluble tetraalkylammonium salt results in stark increase in reactivity providing **2** in up to 20% yield. The use of AgF_2 as the stoichiometric oxidant, as originally reported, afforded **2** from **1** only in up to 15% yield at 120 °C in 48 h.(*8*) In contract, we found in this study that treatment of **1** with two equivalents NEt_4Cl in the presence of an excess amount of AgF_2 in acetonitrile (MeCN) provides **2** in nearly quantitative yield within a short reaction time (<1 h) at room temperature. No other products except for traces (<2%) of hydrolyzed sulfur compounds (Ph-SO_2F, PhSOF) were detected. In place of NEt_4Cl, other onium salts such as Bu_4NCl, Et_4NBr and Ph_4PX (X = F, Cl, and Br) are also effective to give **2** in very high yields (see SI for details). The silver(I) byproducts (AgF, AgCl) can easily be filtered off and fluorinated back to AgF_2 with industrial F_2 gas.(*30*) Thus, the recycling of inorganic silver salts offers the potential to render the process net catalytic in AgF_2 using F_2 gas as the stoichiometric oxidant and fluorine source. The use of AgF_2 was key for our success as the re-evaluation of suitable reagents demonstrated to us and also other high-valent metal–fluorides (e.g. CoF_3, MnF_3, etc.) proved to be ineffective.

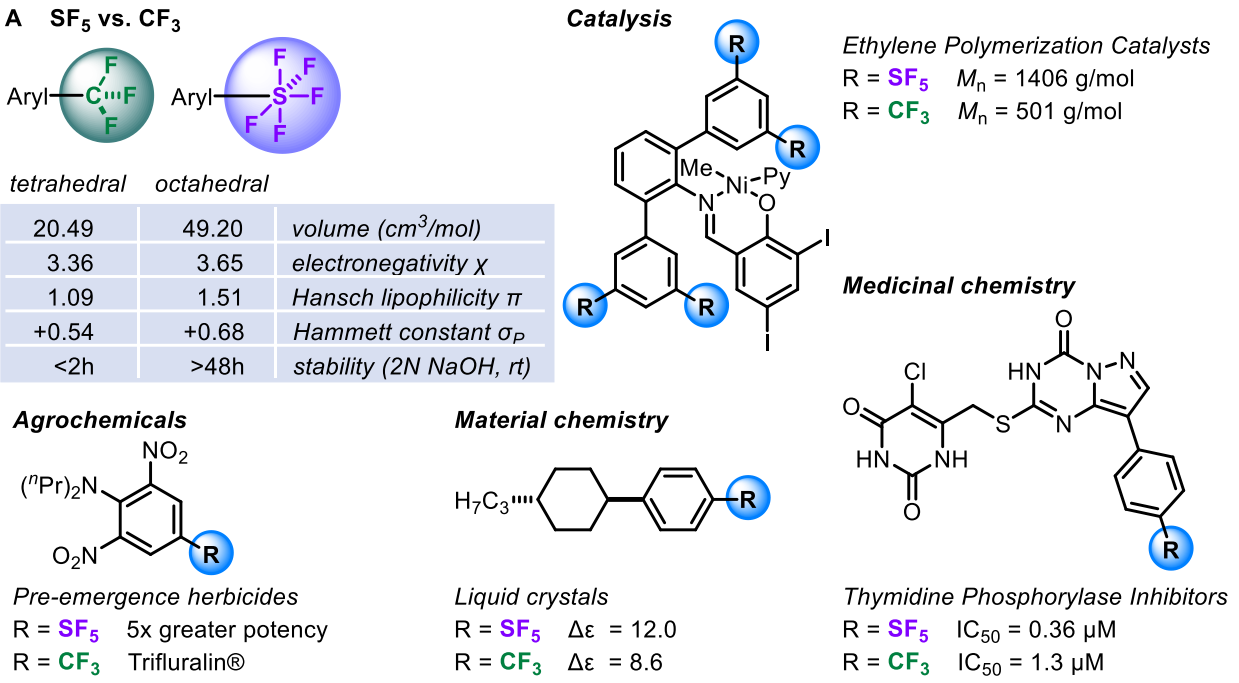

Fig. 1. Pentafluorosulfanyl (SF_5) group properties and synthesis. (**A**) Comparison of characteristics for the pentafluorosulfanyl (SF_5) and trifluoromethyl (CF_3) group and advantages of the SF_5 group in various applications. (**B**) Conventional synthetic route to pentafluorosulfanylation vs. our two-step thiolation/oxidative fluorination strategy. The first step comprises of a Cu- or Pd-catalyzed thiolation cross-coupling of aryl halides or diazonium salts to suitable thiophenol derivatives. In the second step, the thiolated arenes are converted to aryl SF_5 compounds by direct oxidative fluorination. FG, functional group; KSR, potassium sulfuration reagent.

The equally high yield for **2** from thiophenol with slight modification of the reaction conditions (see SI for details) allowed us to investigate the substrate scope for both aryl disulfides and aryl thiols. Excellent yields for halogenated (F, Cl, Br), alkylated (Me, ^{t}Bu, CF_3) or ester-containing SF_5 products (**3**–**25**) pointed to a high functional group compatibility. In contrast to previous methodologies,(*9*, *11*) both electron-rich and electron-deficient aryl disulfides reacted equally well and gave both **3** (4-NO_2) and **26** (4-OMe) in very high yields. Electron-rich thiophenols typically required longer reaction time for high yields and we account the generation of an equivalent of bifluoride (HF_2^-) in the reaction medium for the deceleration the oxidative fluorination. Both *para*- and *meta*-substitution patterns were well tolerated, while *ortho*-substituted substrates showed diminished reactivity for the oxidation of sulfur(IV) to sulfur(VI) as observed in previous reports. The *o*-nitro derivative **24** was nevertheless obtained in 13% yield (86% Ar-SF_3) under preliminary conditions, while *o*-fluoro derivative **25** as well as the mixed SF_3/SF_5 product **45** showed high yields. To identify suitable protecting groups, we tested several phenol- and aniline disulfide derivatives. For phenols, benzyl (Bn, **28**) and methoxymethyl (MOM, **29**) protections give high yields, while for anilines phthalimides (Phth, **27**) and *tert*-butyloxycarbonyl (Boc, **33**) are compatible. When investigating *N*-heterocyclic thiols, we could obtain SF_5–quinoline **37** and several 2-SF_5 pyridine derivatives (**38**–**41**) in good to excellent yields. With increasing electron-deficiency (**41, 42**) we detected an increasing amount of 2-fluorination instead of pentafluorosulfanylation, which we account to a nucleophilic aromatic substitution (S_NAr) side reactions. To obtain compounds with multiple SF_5 groups, we tested several aryl di- or tri-thiols and obtained the *bis*- and *tris*-pentafluorosulfanylated product (**43**–**47**, **49**) in good to excellent yields. Bis-SF_5 compound **47** is a frequently employed SF_5-synthon for the synthesis of SF_5-NaBArF,(*31*) as well as several pentafluorosulfanylated catalysts.(*5*, *32*, *33*) To evaluate scalability, we reacted nitro-substituted disulfide **50** on a 4 mmol scale (1.2 g) and obtained SF_5-aniline **51** in 84% over two steps in a total of 1.5 h reaction time (Fig. 2C). **51** is the intermediate for the synthesis of the SF_5-lefluamide,(*34*, *35*) which displayed two-fold greater potency than its original, commercialized CF_3-version, and the antimalarial drug DSM265 (*22*–*24*) – the first SF_5-compound in clinical development.

In order to connect this reaction to a wider set of building blocks, we next searched for suitable thiophenol derivatives that could be obtained through cross-coupling chemistry while also directly yield $ArSF_5$ compounds in the oxidative fluorination (Fig. 2D). We identified the thiotrityl (STr) and thiobenzoyl (SBz), as well as thiophthalimide (S-Phth), recently utilized by Cornella and coworkers,(*13*) as suitable groups converting to SF_5 with high efficiency (>95%). Other thiophenol derivatives would either only partially (tertbutyl thioether, up to 41% yield) or not at (allyl or benzyl thioethers) liberate the protecting group, decompose (silicon-containing groups and thioacetate) or give only unsatisfactory yields (thiocyanate, up to 68% yield).

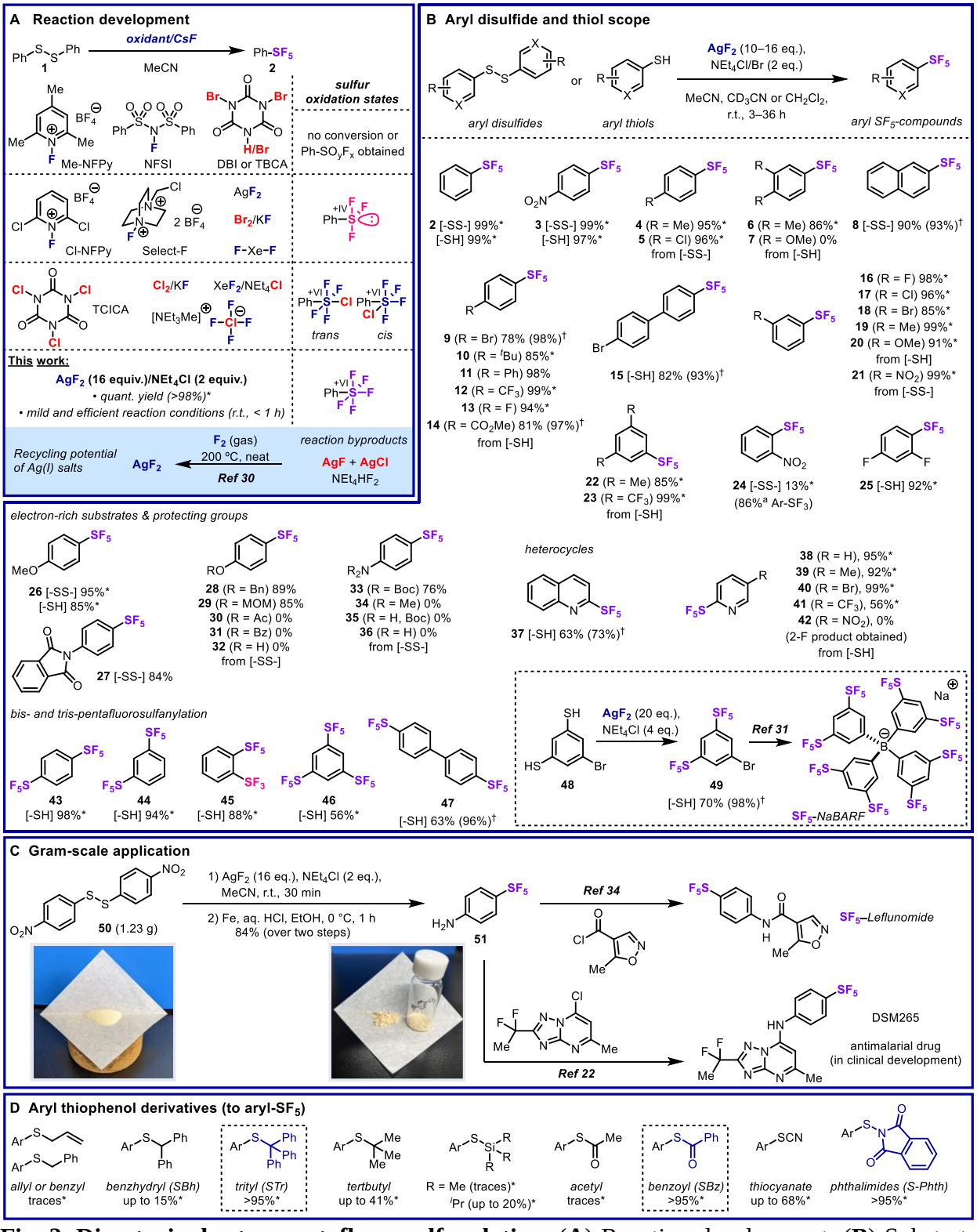

Fig. 2. Direct, single-step pentafluorosulfanylation. (**A**) Reaction development. (**B**) Substrate scope for the oxidative fluorination of aryl disulfides and thiolphenols. (**C**) Gram-scale oxidative fluorination on a 4 mmol scale for the synthesis of compound **51**. (**D**) Evaluation of suitable aryl thiophenol derivatives obtainable via cross-coupling methods. Unless otherwise indicated, yields are isolated. *Yields of volatile pentafluorosulfanylated products are reported based on ^{19}F NMR

integration of reaction mixtures with internal standard. †NMR yield from reaction mixture prior to isolation. See supplementary materials for detailed reaction conditions; MeCN, acetonitrile. Boc, tert-butoxycarbonyl group, [-SS-] refers to aryl disulfide as starting material, [-SH] refers to aryl thiol as starting material.

Subsequently, a generalized pentafluorosulfanylation approach was completed with the development of cross-coupling methods for the synthesis of thiobenzoates and trityl thioethers (Step 1 in Fig. 1B). Although precedence exists, the cross-coupling reactions of these thio-moieties were highly underdeveloped.(*36*–*39*) Aryl iodides and diazonium salts could effectively be converted to aryl thiobenzoates through Cu(I) catalysis using (phen)CuSBz (**cat 1**, pre-formed or generated *in situ*) in good to excellent yields (see SI for details). For aryl bromides, we identified Pd(II) pre-catalysts [Pd(cinnamyl)(tBuXPhos)]OTf (**cat 2**) and [Pd(allyl)(AlPhos)]OTf (**cat 3**) to obtain aryl trityl thioethers in high yields (see SI for details). Nucleophilic aromatic substitution (S_NAr) with potassium thiotritylate (KSTr) furthermore opened an avenue for the utilization of electron-deficient aryl fluorides. Our efforts conclude with a greatly expanded access of aryl– and heteroaryl SF_5 compounds through the generalized utilization of aryl fluorides, bromides, iodides and diazonium salts (Fig. 3). The oxidative fluorination of thiobenzoates and trityl thioethers proceeded smoothly in the presence of a variety of functional groups (**26**, **52–71**) as well as oxygen- or nitrogen-containing heterocycles (**57**, **59**, **65**) in good to excellent yields. The double pentafluorosulfanylation of an aryl bis-thiobenzoate toward valuable SF_5-synthon **49** proceeded in good yield (70%). With highly electron-rich substrates (one to three OMe groups) we detected decreasing yields for products **26**, **69**, **70** with increasing electron-density due to side-reactions, pointing to a limitation of the current reaction conditions. For 3-substituted thiolated (SBz or STr) pyridines (**60**, **67**), we observed C−H fluorination in the 2-position in addition to pentafluorosulfanylation.(*40*) Finally, we utilized our strategy for an improved synthesis of the SF_5-liquid crystal **74** (*7*) from the corresponding aryl bromide **72** in a high yielding two-step reaction sequence.

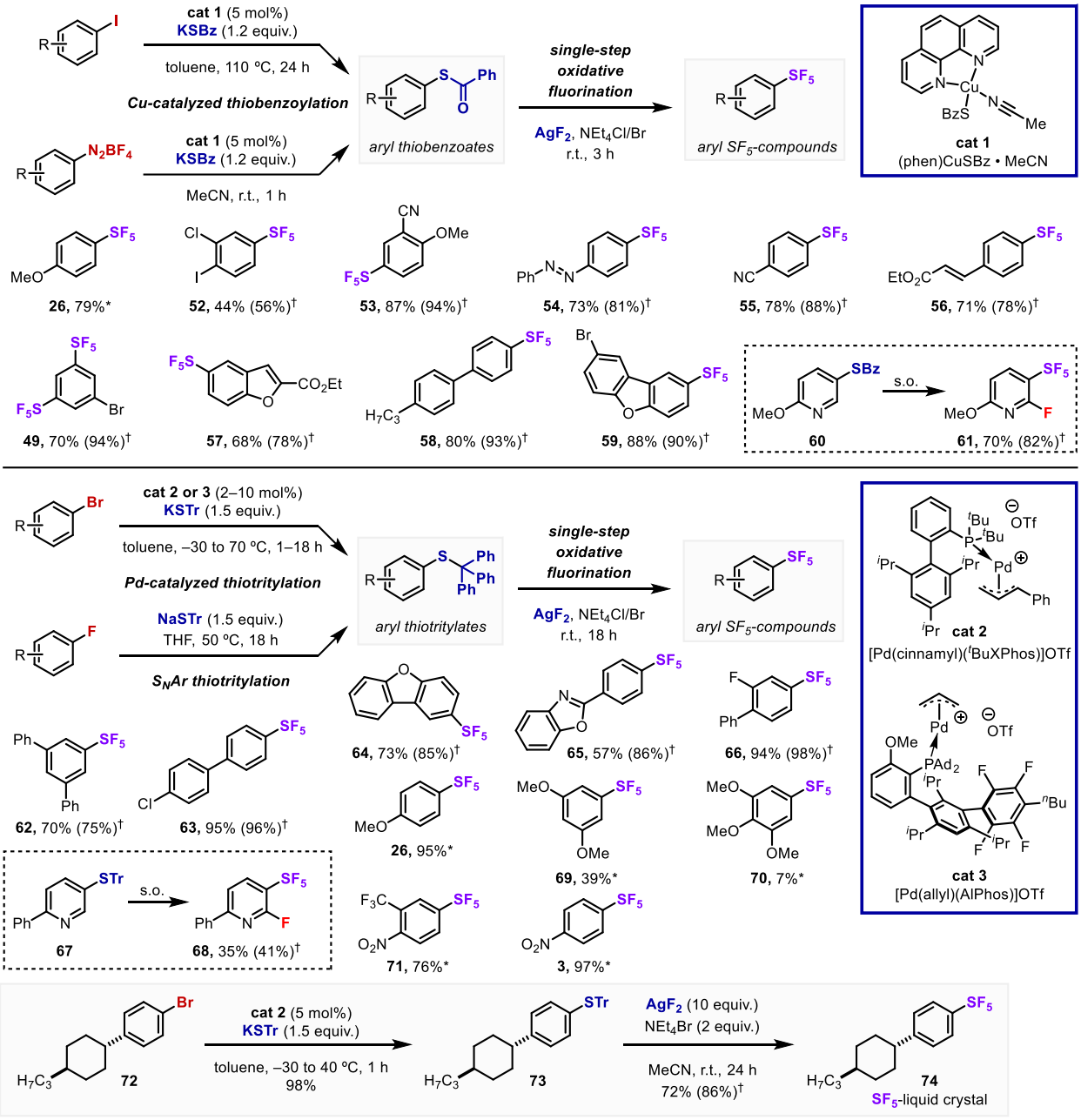

Fig. 3 Generalized pentafluorosulfanylation strategy. Substrate scope of Ar-SF_5 compounds from thiobenzoates and trityl thioethers. Thiobenzoates were synthesized from aryl diazonium salts and iodides via Cu-catalysis. Trityl thioethers were obtained from aryl bromides and fluorides through either S_NAr reactions or Pd-catalyzed thiolation cross-coupling. All yields correspond to the oxidative fluorination reaction on the basis of the isolated thiobenzoate and trityl thioether intermediates. Unless otherwise indicated, yields are isolated. *Yields of volatile pentafluorosulfanylated products are reported based on ^{19}F NMR integration of reaction mixtures with internal standard. †NMR yield from reaction mixture prior to isolation. See supplementary materials for detailed reaction conditions.

The remarkably high efficiency of the pentafluorosulfanylation prompted us to investigate the reaction mechanism and our findings are depicted in Figure 4 (see SI for details). Previous approaches to SF_5-compounds are characterized by requiring particularly high temperatures for pentafluorosulfanylation to occur (e.g. 120 °C, AgF, 48 h from Ar-SF_4Cl).(*11*, *25*) In sharp contrast, experiments in a shorter reaction time revealed that **2** was already formed in near quantitative yield after 15 min at room temperature (Fig. 4A-i). Furthermore, testing various tetraalkylammonium or phosphonium salts showed that besides the corresponding chlorides and bromides, also bench-stable tetraphenylfluorophosphane (PPh_4F)(*41*) was effective (Fig. 4A-ii). Although the yield was lower, also non-halogen anion, azide (NBu_4N_3) afforded the desired product. These findings indicate a pentafluorosulfanylation mechanism that does not involve chlorinated or brominated intermediates. Instead, we propose the formation of soluble fluoroargentates(II) from the complexation of Lewis acidic AgF_2 by onium salts acting as the active fluorinating species. In NMR experiments, the reaction of PPh_4F with AgF_2 afforded a red solution with yellow AgF precipitate showing a characteristic ^{19}F NMR doublet of doublet at −242 ppm (Fig. 4B, left top). We ascribe this signal to a fluoroargentate(II) complex, such as $AgF_3[X](PPh_4)_n$, where the AgF_2 is coordinated by one or more equivalents of fluoride from PPh_4F ([X] indicating potential additional ligands). The complex is stable in the presence of an excess of AgF_2 for a few hours, but decomposes over time through the fluorination of the solvent CD_3CN. The reaction could also be followed by ^{31}P NMR indicating a broad signal at 14.5 ppm for $AgF_3[X](PPh_4)_n$ and a sharp singlet at 23.3 ppm for PPh_4DF_2(*42*) formed after decomposition of the complex (Fig. 4B, right). Upon mixing AgF_2 and NEt_4Cl, a very similar signal was observed by ^{19}F NMR indicating that the same fluoroargentate(II) with a different countercation, described as $AgF_3[X](NEt_4)_n$, was generated through the precipitation of AgCl (Fig. 4B, left bottom). Although fluoroargentates(II) such as $KAgF_3$, K_2AgF_4 or $K_3Ag_2F_7$ are known,(*43–47*) solution-phase fluoroargentate(II) complexes have no precedence in the literature to the best of our knowledge. Consequently, we formulate in Figure 4C a plausible reaction mechanism with PPh_4F as the additive. The reaction starts with the fluorination of **1** or other aryl thiol derivatives to an aryl sulfur (IV) trifluorides (Ar-SF_3), which even proceeds with AgF_2 in the absence of any additive. Due to the nature of silver(II) as a one-electron oxidant, an oxidative fluorine-atom transfer from the fluoroargentate(II) complex would produce aryl tetrafluorosulfur radical intermediates (Ar-SF_4•), which have been studied for their stability and propensity to olefin additions.(*48–50*) In a second fluorine-atom transfer step, Ar-SF_4• would be further fluorinated to the SF_5-product. Besides precipitation of AgF, the PPh_4F could be regenerated *in situ* and further coordinate AgF_2. Importantly however, the correct stoichiometry of PPh_4F and other onium salts is crucial for the full conversion of all intermediates to the SF_5-product (Fig. 4A-ii). Catalytic conditions do not result in high yields and the appropriate amounts also depend on the type of starting material used (see SI for details). The oxidative fluorination is eventually terminated through fluorination of the solvent (observed for CD_3CN, MeCN, DCM and others) and the strong tendency to form bifluoride (HF_2^-) salts likely prevents further AgF_2 complexation.

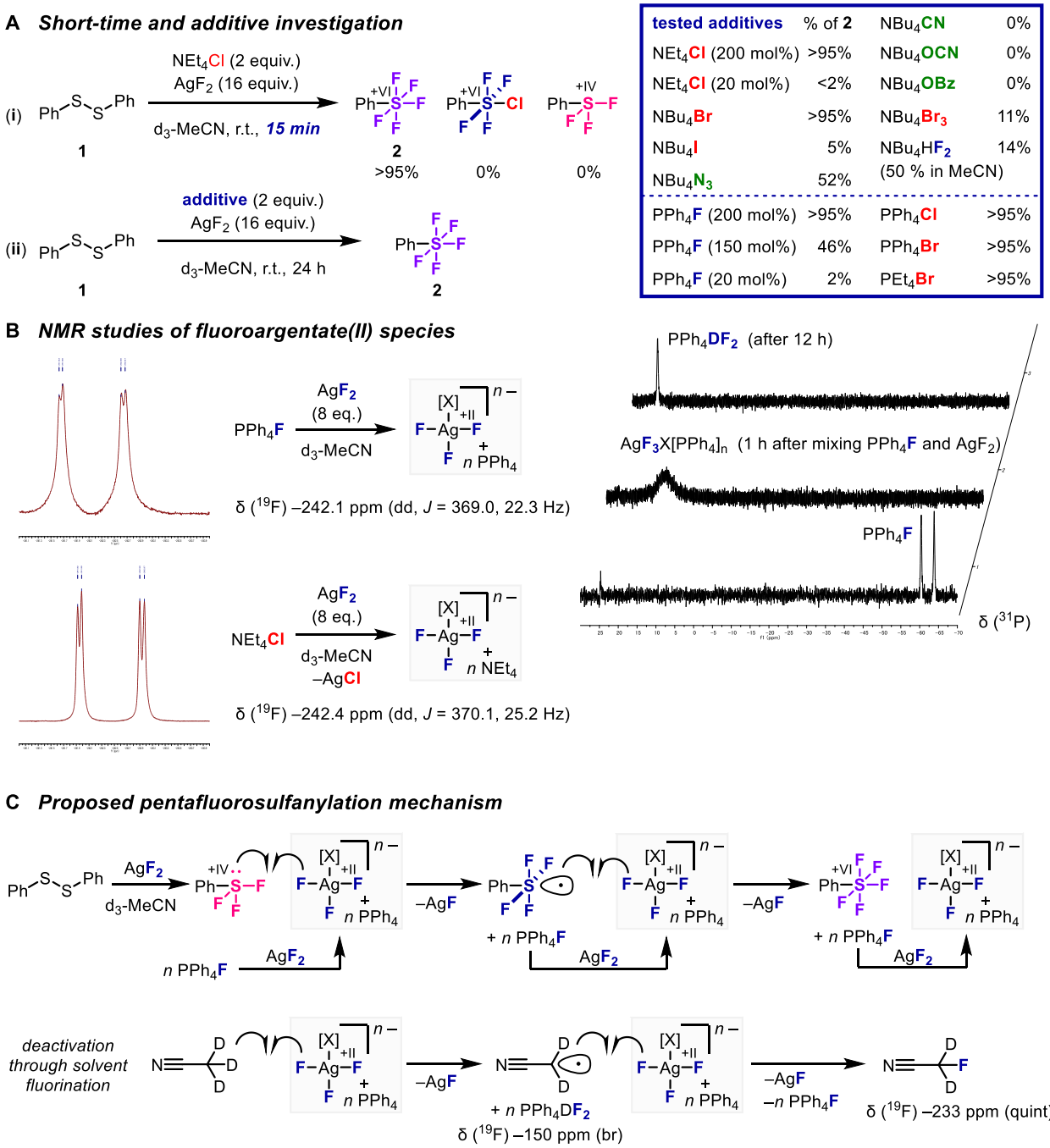

Fig. 4 Mechanistic proposal. (**A**) Investigation of ammonium and phosphonium additives in the oxidative fluorination with AgF_2. (**B**) *in situ*-formed onium fluoroargentate(II) species and NMR characterization. (**C**) Proposed mechanism for the oxidative fluorination to $ArSF_5$ compounds mediated by onium fluoroargentate(II) complexes.

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Competing interests: We have filed patents on pentafluorosulfanylation and thiolation reactions including: WO2022/186304A1, 2021; WO2022/186305A1, 2021.

Data and materials availability: All data is presented in the main text and the supplementary materials.

Supplementary Materials

Materials and Methods

Supplementary Text

Figs. S1 to S4

Tables S1 to S9

References (51–74)