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RESEARCH ARTICLE

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N-Heteroaromatic Fluoroalkylation through Ligand Coupling Reaction of Sulfones

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Abstract: Ligand coupling on hypervalent main group elements has emerged as a pivotal methodology for the synthesis of functionalized *N*-heteroaromatic compounds in recent years due to the avoidance of transition metals and the mildness of the reaction conditions. In this direction, the reaction of *N*-heteroaryl sulfur(IV) and *N*-heteroaryl phosphorus(V) compounds has been well studied. However, the ligand coupling of sulfur(VI) is still underdeveloped and the reaction of alkyl *N*-heteroarylsulfones is still elusive, which does not match the high status of sulfones as the chemical chameleons in organic synthesis. Here we present a ligand coupling-enabled formal SO_2 extrusion of fluoroalkyl 2-azaheteroarylsulfones under the promotion of Grignard reagents, which not only enriches the chemistry of sulfones, but also provides a novel and practical synthetic tool towards *N*-heteroaromatic fluoroalkylation.

Introduction

Exploring novel fluorination and fluoroalkylation methods for the efficient synthesis of organofluorine compounds has stimulate the interest in developing new strategy, new type of reaction and efficient group-transfer reagents.[1-5] In this area, extensive research on the coupling of fluoroalkyls (CF_3, CF_2H, CF_2R and CH_2F) with aromatic rings has grown tremendously in recent years,[6-9] delivering fluoroalkyl groups to structurally diverse organic molecules to meet the needs of favorable physicochemical attributes of organofluorine compounds in biological domains.[10-13] The fluoroalkylated *N*-heteroarenes (such as pyridine) are pharmacophores with wide application in recent drug development, with examples being shown in Figure 1A.[14-16] The fluoroalkyl motif not only modifies the basicity of the *N*-heteroaromatic ring, but also improves the metabolic stability of the benzylic position.[10] Moreover, a difluoromethyl group can serve as the hydrogen-bonding donor.[7] Remarkable advances in aromatic fluoroalkylation have provided state-of-the-art methods for the efficient synthesis of fluoroalkylated *N*-heteroaromatics,[6-9] which mainly rely on transition-metal-mediated coupling of prefunctionalized *N*-heteroaromatics or C-H fluoroalkylation of *N*-heteroarenes by using external fluoroalkylation reagents (Figure 1B).[1,17] However, these synthetic protocols still suffer from drawbacks such as the dependence on transition-metals, high cost of reagents, and poor site-selectivity, which limit their practical applications in large-scale synthesis in pharmaceutical industry.[18] To address the challenges voiced by the industry, a sustainable fluoroalkylation method should be able to accomplish precise fluoroalkylation in a safe, practical, cost-effective and environmentally benign manner.[1]

Ligand coupling reaction is featured by the contractive coupling of two substituents on a hypervalent valence-shell-expanded atom center (such as phosphorous, sulfur, iodine, etc.), which is usually triggered through substitution of a σ-ligand with a nucleophile or the addition of a nucleophile on a π-ligand.[19] Since its first proposal in 1980s,[20] this methodology has found extended synthetic applications in heteroaryl-involved $C(sp^2)$-$C(sp^2)$ and $C(sp^2)$-$C(sp^3)$ couplings based on the reaction of hypervalent sulfur(IV) and phosphorous(V) intermediates, owing to its high efficiency and transition-metal-free feature in the construction of complex *N*-heteroaromatics.[17,19,21-25] However, sulfur-mediated ligand couplings mainly focus on the nucleophilic activation of *N*-heteroarylsulfoxides. The $C(sp^2)$-$C(sp^3)$ ligand coupling reaction of hypervalent sulfur(VI) intermediates derived from *N*-heteroarylsulfones has been elusive[19,26] due to the high tendency of the competitive nucleophilic aromatic substitution (S_NAr) reaction of alkyl *N*-heteroarylsulfones.[27] Considering that organofluorine compounds often exhibit unusual properties in comparison with nonfluorinated parent compounds,[28] one may envision that fluoroalkyl *N*-heteroarylsulfones, with the sulfonyl group being activated by the electron-withdrawing fluoroalkyl substituent,[29] should be able to undergo the attack of a nucleophile at sulfur center to furnish the pentacoordinate sulfur(VI) intermediates that are suitable for *N*-heteroaryl-fluoroalkyl couplings (Figure 1C). Herein we describe our discovery and development of *N*-heteroaromatic fluoroalkylation through ligand coupling-enabled

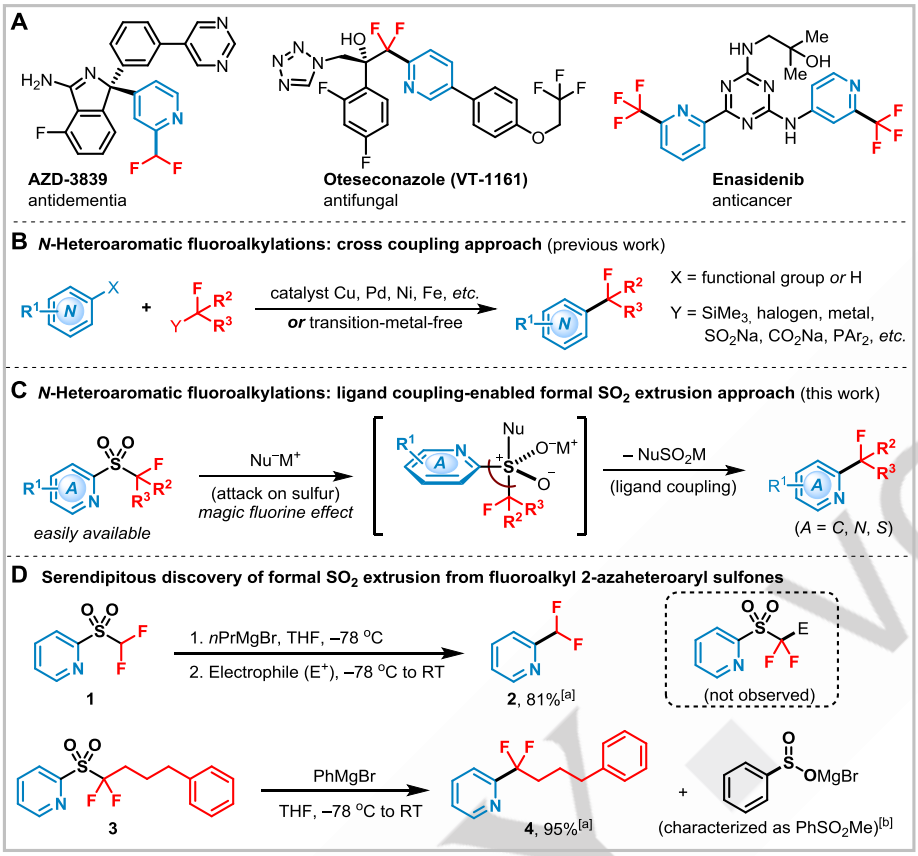

Figure 1. Important fluoroalkylated *N*-heteroaromatic compounds and *N*-heteroaromatic fluoroalkylation strategies. (A) Medicinally relevant compounds containing fluoroalkylated *N*-heteroaryls. (B) Conventional *N*-heteroaromatic fluoroalkylations via intermolecular cross coupling approach. (C) Working hypothesis for *N*-heteroaromatic fluoroalkylations via sulfone-based ligand coupling. (D) Initial study leading to the discovery a novel sulfone-based ligand coupling reaction approach. [a] Yields determined by ^{19}F nuclear magnetic resonance (NMR) with (trifluoromethyl)benzene as an internal standard. [b] See the Supporting Information for experimental details. R^1, R^2 and R^3 denote general organic groups; Nu^- denotes a nucleophile; M^+ denotes a metal cation; THF, tetrahydrofuran.

formal SO_2-extrusion of fluoroalkyl 2-azaheteroarylsulfones under the promotion of Grignard reagents, which affords an operationally simple, efficient and practical protocol for the coupling of 2-azaheteroaryl with difluoromethyl, difluoroalkyl and perfluoroalkyl groups using sulfone as the modular platform.[30] Since the fluoroalkyl 2-azaheteroarylsulfones are readily prepared from commodity chemicals and have been well recognized as versatile fluoroalkylation reagents,[31-37] this transition-metal-free reaction with fluoroalkyl 2-azaheteroarylsulfones should be of great significance for the synthesis of fluoroalkylated *N*-heteroarenes in both academia and industry.

Results and Discussion

Initial Discovery and Reaction Development

The discovery was made by serendipity when we attempted to deprotonate difluoromethyl 2-pyridyl sulfone (2-$PySO_2CF_2H$, **1**) with a Grignard reagent as the base for nucleophilic fluoroalkylation reactions (Figure 1D). To our great surprise, when **1** was treated with propylmagnesium bromide (*n*PrMgBr) in THF at temperatures ranging from –78 °C to room temperature, the complete consumption of **1** led to 2-$PyCF_2H$ (**2**) as the product. An examination of the reactivity of 2-$PySO_2CF_2(CH_2)_3Ph$ (**3**) towards phenylmagnesium bromide (PhMgBr) gave similar result. The "SO_2" moiety was combined with PhMgBr and released in the form of sulfinate salt. Based on these preliminary results, we soon realized that the fluoroalkyl-heteroaryl coupling via the formal SO_2-extrusion should be a general transformation with fluoroalkyl heteroarylsulfones. Considering that metal-free nucleophilic fluoroalkylation of prefunctionalized heteroaromatics via ipso-S_NAr reaction is not trivial due to the liability and limited reactivity of the anionic fluoroalkyl species,[1] we decided to develop this unprecedented coupling between fluoroalkyl and heteroaryl to a practical method for heteroaromatic fluoroalkylations.

Initially, we chose sulfone **1** as a model substrate to investigate the suitable reaction conditions (Table S1 in the Supporting Information). The reaction was conducted by adding a nucleophilic reagent to the solution of **1** at varying temperatures. We were delighted to find that a series of Grignard reagents (such as MeMgBr, CH_2=CHMgBr and PhMgBr) effectively promoted the reaction in tetrahydrofuran

(THF) to give **2** in good to excellent yields at room temperature. Moreover, the reaction could complete in a short time (2 minutes for 1 mmol scale). Other nucleophilic reagents such as butyllithium (*n*BuLi), potassium *tert*-butoxide (*t*BuOK) and phenylzinc bromide (PhZnBr) were inefficient due to either the competitive deprotonation of **1** or their inertness towards **1**.

Substrate Scope and Synthetic Applications

We next synthesized a series of difluoromethyl and perfluoroalkyl heteroarylsulfones with various substituents at the heteroaromatic ring to examine the scope of this reaction (Figure 2, A-B). Generally, these fluorinated sulfones were easily prepared through fluoroalkylation of heteroaryl thiophenols (Het-SH) with cost-effective fluorochemicals such as sodium chlorodifluoroacetate, chlorodifluoromethane, and perfluoroalkyl iodides followed by oxidation (see section 3.2 in the Supporting Information). The heteroaryl thiophenols were normally obtained via thiolation of the corresponding heteroarylhalides with sodium bisulfide or thiourea.

For the difluoromethyl-heteroaryl coupling, the results are given in Figure 2A. Vinylmagnesium bromide (CH_2=CHMgBr) was normally used as the optimal reagent duo to its moderate basicity in comparison with methylmagnesium bromide (MeMgBr). A wide range of heteroaryl rings including pyridine (**2** and **6**-**24**), quinolone (**25**), isoquinoline (**26**), pyridazine (**27**), pyrimidine (**28)** and pyrazine (**29**) are amenable to the reaction. An exhaustive investigation on the reaction of pyridylsulfones showed that both 2-pyridyl (**2** and **6**-**23**) and 4-pyridyl (**24**) can undergo coupling with difluoromethyl, with the former being more effective. Electron-donating groups can be present at each position on the 2-pyridyl ring; however, substitution at the 6-position possesses a negative effect (**21**), which made the coupling process sensitive towards temperature. Mono- and dihalogenated 2-pyridylsulfones are also viable substrates, whose coupling products were obtained in moderate to good yields with the chlorine and bromine substituents remaining intact (**14**-**18**). The lack of debromination side products is probably due to the following reasons: (a) relatively low reactivity of the C–Br bond; (b) short reaction time; and (c) low reaction temperature. Moreover, strong electron-withdrawing groups such as trifluoromethyl group, cyano group and aminocarbonyl group can be tolerated at the pyridyl ring, as is demonstrated by the successful synthesis of 2-difluoromethylpyridines bearing such groups at 4- or 5-positions (**10**-**13**). In these cases, moderate to good yields were gained by suppressing the competitive nucleophilic aromatic substitution (S_NAr) reaction at low temperatures ranging from −40 °C to 0 °C. However, substrates bearing cyano group at 3-position were less productive than the 4-substituted one owing to the competitive S_NAr reaction even at −40 °C (see section 3.8 in the Supporting Information). Besides, a comparison with sulfoxides (see section 5.1 in the Supporting Information) shows that sulfones are more suitable for the 2-azaheteroaryl-fluoroalkyl coupling.

For the perfuoroalkyl-heteroaryl coupling, the results are given in Figure 2B. The scope of *N*-heteroaromatics is broader than that that of the difluoromethylation (**30**-**48**); 3-cyano-2-pyridyl-, benzothiazolyl- and tetrazolylsulfones are also suitable substrates due to the suppression of S_NAr reaction (**38**, **39**, **45**-**48**). Nevertheless, there are two major differences between trifluoromethylation and difluoromethylation. First, the trifluoromethylation prefers phenylmagnesium bromides containing one or two MeO groups at the *ortho*-positions of phenyl group (**30**-**48**); the ligation of MeO with magnesium is believed to improve the stability of the pentacoordinate sulfur(VI) intermediate, thus inhibiting the loss of the CF_3 ligand. Second, electron-neutral and electron-rich pyridyl groups are much more difficult to couple with CF_3 (**30**, **31**, **33**, **37** and **40**), but electron-withdrawing groups on the pyridine ring can promote the coupling (**32**, **34**, **35**, **36**, **38** and **39**). In addition, *ortho*-methoxyphenylmagnisium bromide is also beneficial for the incorporation of C_2F_5 (**49**). However, longer perfluoroalkyl chains such as perfluoropropyl and perfluorobutyl do not need further coordination, and are compatible with simple Grignard reagent CH_2=CHMgBr (**50**-**52**). Interestingly, it seems that the demanding of further coordination with magnesium is in accordance with the thermal instability of the perfluoroalkylmetal species.[38]

Difluoromethyl- and trifluoromethylpyridines substituted with halides are useful building blocks for the construction of complex molecules. Previously, their synthesis mainly relies on metal catalyzed cross coupling with expensive fluoroalkyl sources,[1,3] deoxofluorination with dangerous reagents (such as diethylaminosulfur trifluoride and sulfur tertrafluoride),[39a] or selective hydrodefluorination of the pre-prepared trifluoromethylpyridines.[39b] This sulfone-based ligand coupling reaction provides an operationally simple and practical alternative to make these compounds, which is showcased by the large scale synthesis of 5-bromo-2-(difluoromethyl)pyridine (**15**) from 2,5-dibromopyridine and sodium chlorodifluoroacetate in 54% overall yield (the yield of the sulfone was 76%).

To further illustrate the utility and functional group tolerance of the method, we investigated the synthesis of substituted fluoroalkylpyridines via palladium-catalyzed cross coupling of brominated fluoroalkylsulfones with various arylboronic acids followed by ligand coupling (Figure 2C). The high chemoselectivity for fluorinated sulfone makes this chemistry tolerant of functional groups such as methanesulfonyl (**22**), ester (**60**), amide (**62**) and alcohols (**64**). And the electronic nature of the aryl substituents on the pyridyl ring has little influence on the ligand coupling process (**54**, **56**, **58**, **60** and **62**). The results also demonstrate that fluoroalkyl heteroarylsulfones possess orthogonal reactivity towards the two couplings, indicating their potential use as masked fluoroalkylpridines in other transformations, which would exaggeratedly expand the synthetic value of this fluoroalkylation protocol. Besides, performing the ligand coupling reaction at a late stage of multiple-step synthesis can make a full use of the crystallinity of sulfones to simplify the purification process.

Next, we synthesized difluoroalkyl heteroarylsulfones via functionalization of the corresponding difuoromethyl sulfones at the CF_2 position (**31**) or electrophilic difluorination of the nonfluorinated precursors[40a] (see section 3.4 in the Supporting

Information) to study their compatibility with this reaction (Figure 3, A-C). As shown in Figure 3A, simple Grignard reagents such as methyl- and vinylmagnesium reagents efficiently promote the coupling reaction of a wide range of *α,α*-difluoroalkyl heteroarylsulfones, including those with electron-rich and electron-deficient heteroaryl substituents on the difluoroalkyl chains (**4** and **75**-**99**). Note that difluoroalkylation at the 4-position of pyridine rings is also a highly feasible transformation (**82** and **99**). Active C–H bonds vicinal to C-SO_2 bonds exhibit a high stability in this reaction (**4** and **75**-**79**). Potentially reactive functionalities are also tolerated, such as hydroxyl group at the β-position of fluoroalkyls (**83**-**94**), the deprotonated form of which would readily take part in Smiles rearrangements at room temperature.[40b] In our hand, only the extremely sterically hindered alcohol was detected to undergo

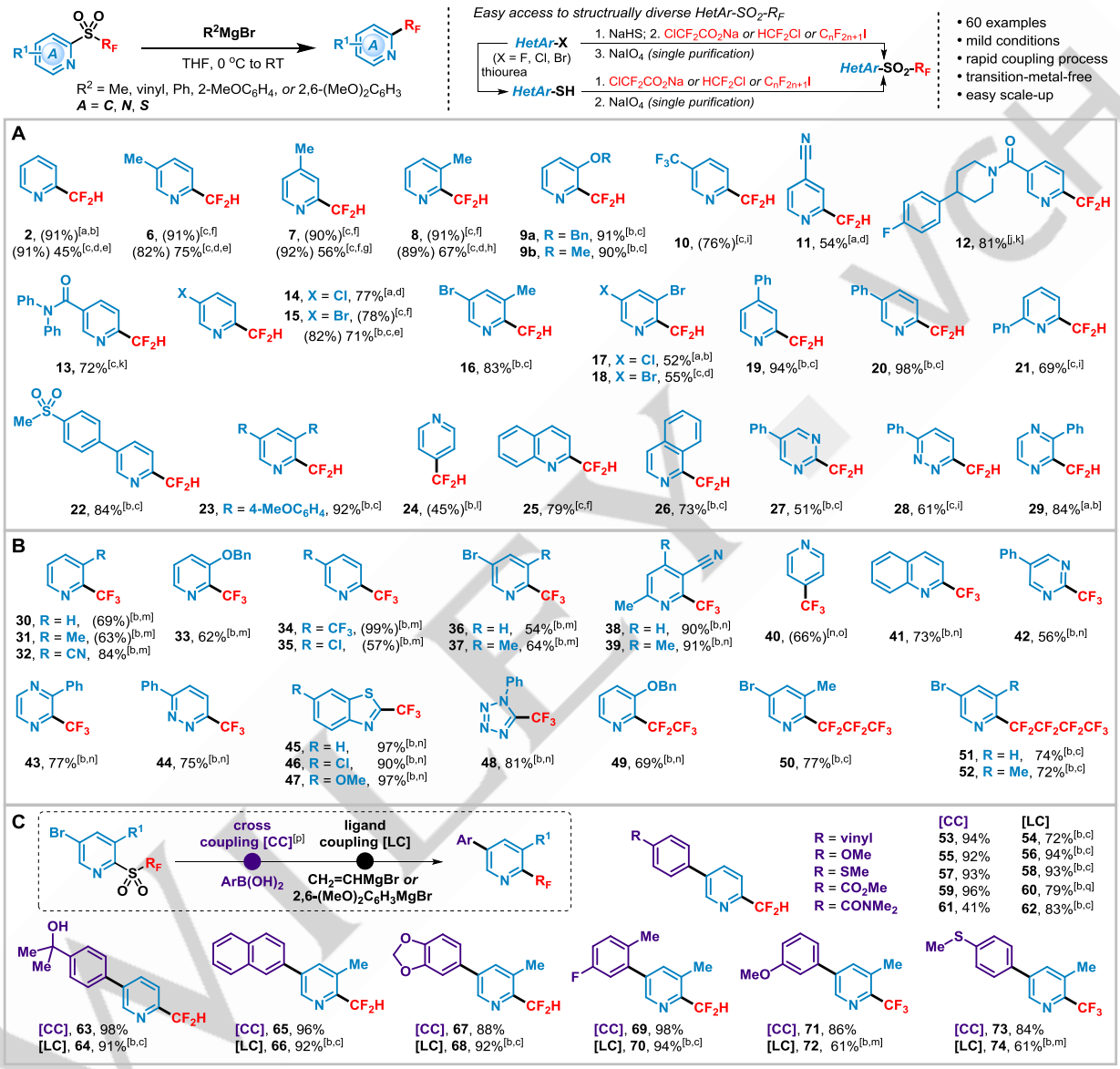

Figure 2. Scope of *N*-heteroarylsulfones with difluoromethyl and perfluoroalkyl groups. Conditions: Sulfone (0.2 mmol to 1.5 mmol, 1.0 equiv.), R^2MgBr (2.0 to 4.0 equiv.) in THF for 2 minutes to 45 minutes. Experimental details are provided in the Supporting Information. Isolated yields. Yields determined by ^{19}F NMR analysis with (trifluoromethyl)benzene or (trifluoromethoxy)benzene as an internal standard are shown in the parentheses. (A) Difluoromethyl group. (B) Trifluoromethyl and other perfluoroalkyl groups. (C) Orthogonal coupling with brominated heteroarylsulfones. [a] 2.0 equiv. MeMgBr. [b] room temperature. [c] 2.0 equiv. CH_2=CHMgBr. [d] 0 °C. [e] 100 mmol scale. [f] 0 °C to room temperature. [g] 10 mmol scale. [h] 15 mmol scale. [i] –40 °C to room temperature. [j] 2.5 equiv. PhMgBr. [k] –45 °C. [l] 2.0 equiv. PhMgBr. [m] 4.0 equiv. 2,6-$(MeO)_2C_6H_3MgBr$. [n] 4.0 equiv. 2-$MeOC_6H_4MgBr$. [o] –78 °C to room temperature. [p] Brominated sulfone (1.0 equiv.), $ArB(OH)_2$ (1.0 to 2.0 equiv.), $Pd(PPh_3)_4$ (10 mol%), Na_2CO_3 in $PhCH_3$-EtOH-H_2O at 90 °C. [q] 3.0 equiv. CH_2=CHMgBr. R_F denotes an alkyl group that contains at least one fluorine substitution at the *α*-position. HetAr, heteroaryl.

such a reaction to some extent (**89**),[41] probably due to a relatively slow attack on sulfone by the Grignard reagent, and protection of the hydroxyl group led to an immediate and productive coupling (**90**). The potential to conduct the reaction with chiral substrates has been demonstrated by the efficient preparation of *α*-(2-pyridyl)difluoromethylated amines with complete stereoretention at the chiral carbons (**95**-**98**).[41]

This sulfone-based ligand coupling reaction opens a door to a new approach for nucleophilic (heteroaryl)difluoromethylation,[42] that is, tethering the heteroaryl group and difluoromethyl group using "SO_2" as a "built-in" traceless activating group to facilitate the deprotonative functionalization of difluoromethylheteroarenes (Figure 3B). The strategic application of this approach was showcased with the efficient nucleophilic *α*-difluoro(2-pyridyl)methylation of the antipsychotic drug daloperidol, an easily enolizable ketone that is difficult to undergo efficient reaction with 2-PyCF_2H[42a] under the promotion of a base (**100**). Additional experiments on the reaction of aromatic aldehydes also support the advantages of

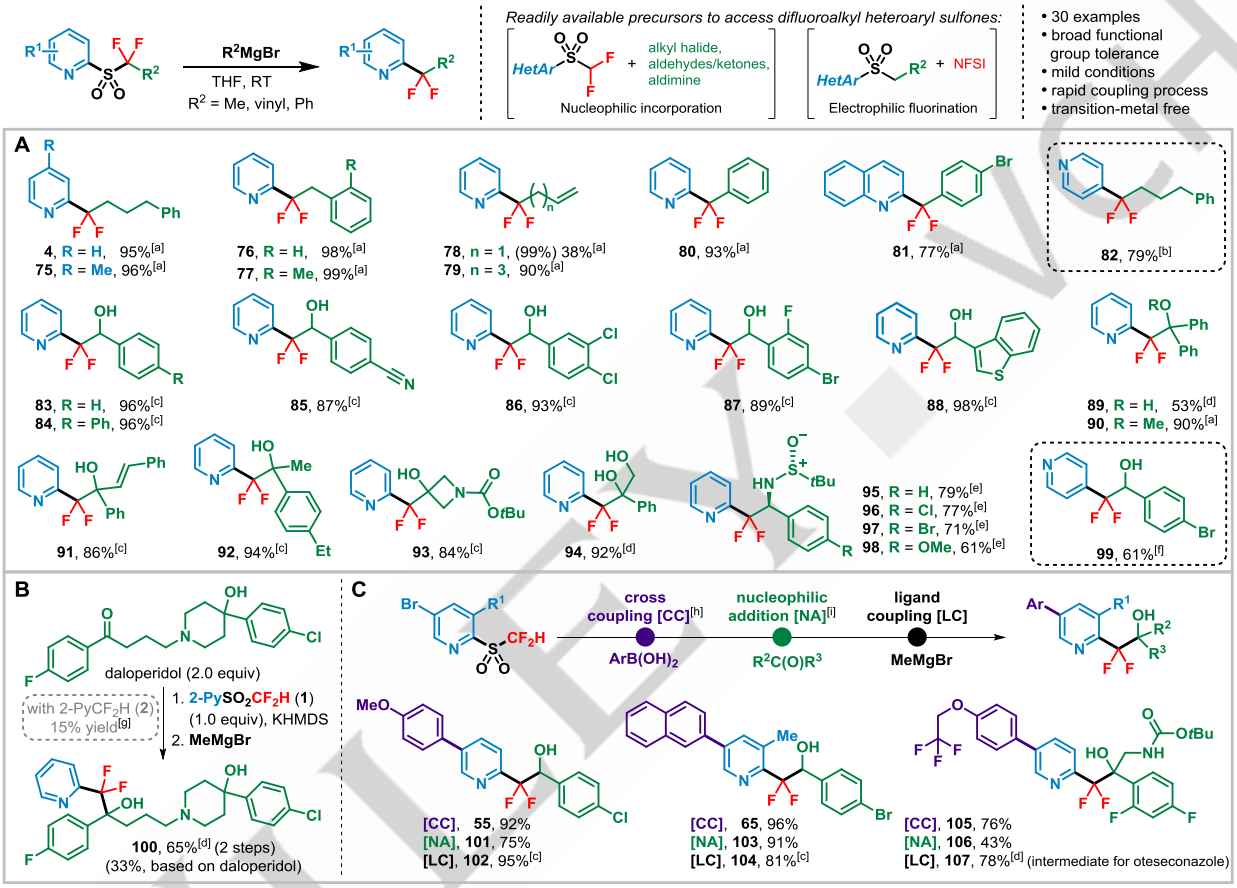

Figure 3. Scope of *N*-hetroarylsulfones with functionalized difluoroalkyl groups. Conditions: Sulfone (0.1 mmol to 2.0 mmol, 1.0 equiv.), R^2MgBr (2.0 to 5.0 equiv.) in THF at room temperature for 2 minutes to 10 minutes. Experimental details are provided in the Supporting Information. Isolated yields. Yields determined by ^{19}F NMR with (trifluoromethyl)benzene as an internal standard are shown in the parentheses. (A) Diversity of heteroaryl and functionalized difluoroalkyl groups. (B) Efficient late-stage modification of a drug via sulfone-enabled nucleophilic difluoro(2-pyridyl)methylation reaction. (C) Sequential cross coupling, nucleophilic addition, and ligand coupling using difluoromethylsulfones as a modular platform. [a] 2.0 equiv. CH_2=CHMgBr. [b] 10.0 equiv. MeMgBr. [c] 4.0 equiv. MeMgBr. [d] 5.0 equiv. MeMgBr. [e] 4.0 equiv. PhMgBr. [f] –40 °C to room temperature, 30 minutes. [g] Yield based on the substrate. Details are provided in the Supporting Information. [h] Brominated sulfone (1.0 equiv.), $ArB(OH)_2$ (1.0 to 2.0 equiv.), $Pd(PPh_3)_4$ (10 mol%), Na_2CO_3 in $PhCH_3$-EtOH-H_2O at 90 °C. [i] Difluoromethylsulfone obtained in the previous step (1.0 equiv.), aldehyde or ketone (1.0 to 2.0 equiv.), *t*BuOK in THF-DMF at –78 °C. 2-Py, 2-pyridyl; HetAr, heteroaryl; KHMDS, potassium bis(trimethylsilyl)amide; DMF, *N*,*N*-dimethylformamide.

this "SO_2"-activation strategy (see 5.2 in the Supporting Information). Moreover, the ability for heteroaromatic functionalization of 2-azaheteroarylsulfones adds a new dimension to the utility of this chemistry. As demonstrated in Figure 3C, sequential cross coupling/nucleophilic addition/ligand coupling transformation of the readily available difluoromethyl bromoheteroarylsulfones affords a straightforward means to pyridine-ring-modified difluoro(2-pyridyl)methylated complex molecules (**102**, **104** and **107**). After removal of the *N*-*tert*-butoxycarbonyl (Boc) group from compound **107**, the free amine is a key intermediate for the synthesis of oteseconazole,[43] an antifungal drug currently under phase III clinical trials.[15]

Extension to the Ligand Coupling of Dipyridyl Sulfones

There has been no report on the ligand coupling reaction of diheteroaryl sulfones. In this context, we extended our methodology to the synthesis of bipyridine compounds from dipyridyl sulfones. The sulfones can be easily prepared from pyridyl thiols and pyridyl halides such as pyridyl iodides via nucleophilic aromatic substitution followed by oxidation. Our preliminary results showed that both symmetrical and unsymmetrical dipyridyl sulfones **S94** could smoothly undergo the Grignard reagent-promoted coupling reaction to afford the corresponding 2,2'-bipyridines **S95** in moderate yields (Fig. S10 in the supporting information). Considering the easy scale-up synthesis of the sulfones, we believe that this protocol will provide a novel solution for the efficient cross-coupling of pyridine compounds under completely metal free conditions.

Mechanistic Investigation

Mechanistic investigations were conducted with 2-pyridylsulfones to gain more insights into the present ligand coupling reaction. First, the possibility of a radical process was ruled out by analyzing the chemical outcome of the reaction of a difluoroalkylsulfone containing a terminal alkene functionality. If a fluoroalkyl radical is involved, the cyclized product would be formed. However, in the case of sulfone **108**, neither **109** nor **110** was detected as the side product (Figure 4A). Second, the cross-over experiment of two difluoroalkylsulfones of similar reactivity yet with different pyridyl and fluoroalkyl groups showed that no cross-over products were formed (Figure 4B), which suggests that the coupling between the heteroaryl group and the fluoroalkyl group is an intramolecular process. Third, the reaction between a difluoromethylsulfone bearing a methyl-substituted 2-pyridyl group and a Grignard reagent bearing unsubstituted 2-pyridyl group gave only trace intermolecular fluoroalkylation product (Figure 4C), and the interchange of the two 2-pyridyl groups afforded no intermolecular fluoroalkylation product. These results can lead to the following conclusions: (1) the coupling reaction of sulfone-derived pentacoordinate sulfur(VI) intermediate proceeds with high chemoselectivity, with the intrinsic heteroaryl group being selectivity coupled with the fluoroalkyl group; (2) the ligand coupling takes place

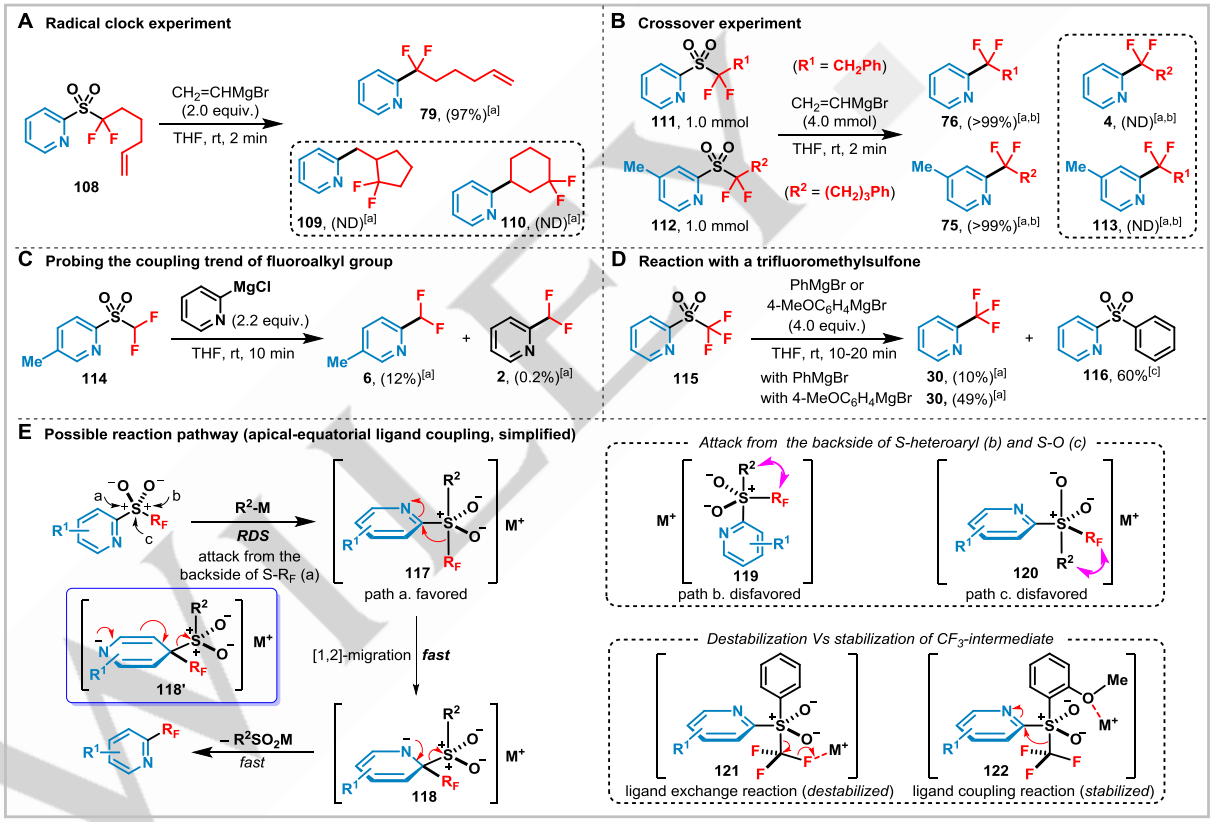

Figure 4. Mechanism consideration. (A) Radical clock experiment ruled out the involvement of a fluoroalkyl radical pathway. (B) Crossover experiment confirmed that the coupling reaction proceeded intramolecularly. (C) The selective coupling of difluoromethyl group with the intrinsic heteroaryl group indicates that the external ligand and the fluoroalkyl ligand adopt apical positions in the pentacoordinate sulfur(VI) intermediates. (D) Reactions of a trifluoromethylsulfone with PhMgBr and 4-MeOC$_6$H$_4$MgBr indicate that the fluorine-metal interaction can affect the ligand coupling reaction. (E) The proposed reaction pathways. The nucleophilic attack step is the rate determining step (RDS), which was evidenced by the slow consumption of the sulfone at low temperatures such as –40 °C. According to the attack direction of the carbanion, three kinds of hypervalent sulfur(VI) intermediates would be formed. In the case of trifluoromethylsulfones, additional chelation of magnesium is important for the stabilization of the hypervalent intermediate. [a] Yields determined by ^{19}F NMR with (trifluoromethyl)benzene as an internal standard. [b] Confirmed by gas chromatography-mass spectrometry (GC-MS) analysis. [c] Isolated yield. ND = Not detected; M = metal; RDS = rate determining step.

immediately after the attack of a nucleophile on sulfone, and the topological transformations such as the Berry pseudorotation is difficult to occur. Fourth, the possible role of the methoxy group on the aryl ring of the magnesium reagent was probed by conducting the reaction of trifluoromethylsulfone **115** with PhMgBr and 4-$MeOC_6H_4MgBr$. In the former case, ligand-coupling product **30** was detected in only 10% yield, with the formation of aryl-CF_3 exchange product **116** as the major product. In the latter case, the ligand coupling product **30** was formed in much higher yield (Figure 4D), proving that the methoxy group can chelate with magnesium, and the chelation with magnesium is important in precluding the loss of a highly electronegative fluoroalkyl ligand via ligand exchange.

Based on above results and discussion, a plausible mechanism for the sulfone-based ligand coupling reaction with Grignard reagents is provided in Figure 4E. Nucleophilic attack of a carbanion on sulfone from the backside[44] of sulfur-fluoroalkyl bond affords a trigonal bipyramidal pentacoordinate sulfur(VI) intermediate **117** (Figure 4E, path a), where the incoming nucleophile and the fluoroalkyl substituent occupy two apical positions, and the two oxygen atoms occupy the equatorial positions. The arrangement of the fluoroalkyl group and the oxygen atoms are consistent with the preferred positions of the CF_3 groups and oxygen atoms in a structurally well-defined hypervalent sulfur(VI) compound $[(CF_3)_3SO_2]^-[K(18\text{-crown-6})]^+$.[45] Then apical-equatorial 1,2-migration[19] of the more electronegative ligand fluoroalkyl from sulfur to the less electronegative ligand 2-azaheteroaryl gives the Meisenheimer-type intermediate **118**, which goes on to form the 2-azaheteroaryl-fluoroalkyl coupling product, with the release of a sulfinate salt as the byproduct. The ligand coupling of a fluoroalkyl group with 4-pyridyl group may proceed similarly via intermediate **118'**. The attacks of the carbanion on sulfone from the backside of sulfur-heteroaryl bond (Figure 4E, path b) and the sulfur-oxygen bond (Figure 4E, path c) are disfavored probably due to the electrostatic repulsion between the incoming nucleophile and the negative charge on the fluoroalkyl group (**119** and **120**). As for magnesium cation, we believe that it can interact with fluorine atom on the fluoroalkyl group to destabilize the pentacoordinate sulfur(VI) intermediate to some extent. And this destabilization effect is more significant in the case of a CF_3-intermediate such as **121**, where the strong Mg-F interaction can induce the leaving of the CF_3-substitutent through the formation of stable difluorocarbene, thus leading to the ligand exchange product such as **116**. The presence of a methoxy group on the *ortho*-position of the aryl substituent can coordinate with magnesium to weaken the interaction between magnesium and one of the α-fluorine atom of CF_3 (**122**),[38] thus improving the stability of the pentacoordinate intermediate and facilitating the heteroaryl-CF_3 coupling reaction.

Conclusion

In summary, an unprecedented ligand coupling of fluoroalkylsulfones has been developed for the efficient synthesis of fluoroalkyl *N*-heteroarenes. The starting materials are cheap and easily available and the coupling process is operationally simple, rapid and transition metal free, which is especially suitable for scale-up synthesis of fluoroalkylated *N*-heteroarenes. This transformation also enables the use of difluoromethyl 2-azaheteroarylsulfones as the traceless activated difluoromethyl heteroarenes in nucleophilic (heteroaryl)difluoromethylation reactions. Moreover, compared with sulfoxides (section 5.1 in the Supporting Information), sulfones are more suitable for the 2-azaheteroaryl-fluoroalkyl coupling. Further exploration of the fluoroalkylative ligand coupling of hypervalent sulfur(VI) compounds and its synthetic applications are underway in our laboratory.

Supporting Information

The authors have cited additional references within the Supporting Information.[46-96]

Acknowledgements

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Keywords: Fluoroalkylation • 2-Azaheteroaryl sulfone • Ligand coupling • Fluorine • Organic synthesis

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[42] (a) For an example on nucleophilic (heteroaryl)difluoromethylation via deprotonation of difluoromethyl pyridines, see: L. Santos, A. Panossian, M. Donnard, J.-P. Vors, S. Pazenok, D. Bernier, F. R. Leroux, *Org. Lett.* **2020**, *21*, 8741–8745; (b) for an example on radical (heteroaryl)difluoromethylation via C-F activation of trifluoromethyl pyridines, see Ref. 39(b).

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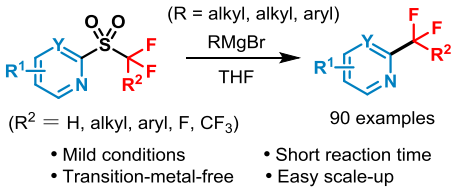

Fluoroalkylated *N*-heteroarenes are efficiently synthesized from fluoroalkyl 2-azaheteroarylsulfones via Grignard reagent-promoted formal SO_2 extrusion reaction. The reaction proceeds through the ligand coupling of a pentacoordinate sulfur(VI) intermediate and exhibits the unique fluorine effect.