4-Pyridyl perfluoroalkyl sulfide as a practical nucleophilic perfluoroalkylation reagent

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Abstract

The incorporation of perfluoroalkyl groups into molecules leads to unique properties, and perfluoroalkylation reagents play a vital role in facilitating this process. Although various types of perfluoroalkylation reagents have been developed, the established nucleophilic perfluoroalkylation reagents have faced certain limitations. This work aims to address these challenges by introducing a novel nucleophilic perfluoroalkylation reagent, known as 4-pyridyl perfluoroalkyl sulfide (4-PySR$_f$), which demonstrates a distinctive mechanism of perfluoroalkyl anion release based on the *N*-boryl pyridyl anion chemistry developed in our research group. In the presence of a diboron(4) compound and an alcoholate base, the 4-PySR$_f$ reagent efficiently undergoes perfluoroalkyl transfer reactions with a range of electrophiles. Unique to this reagent, compared to established nucleophilic perfluoroalkylation reagents, is its suitability for the effective transfer of functionalized perfluoroalkyl groups, as well as for intramolecular perfluoroalkylation reactions. Meanwhile, the 4-PySR$_f$ reagent exhibits excellent chemical stability, making it an ideal precursor for multi-step synthetic sequences. These attributes offer a robust strategy for synthesizing complex molecules incorporating perfluoroalkyl groups. Detailed mechanistic studies strongly support the nucleophilic nature of the perfluoroalkyl transfer reactions involving the 4-PySR$_f$ reagent. The present work expands the synthetic potential of the *N*-boryl pyridyl anion chemistry, and broadens the scope of nucleophilic perfluoroalkylation reactions.

Introduction

Fluorinated compounds play important roles in various fields. For example, by introducing fluorine atoms or fluorinated substituents, the lipophilicity, solubility, acidity, and basicity of a molecule can be effectively improved,[1] thus enabling their unique applications in pharmaceutical chemistry, [1-4] materials chemistry,[5] and agriculture[6] (Fig. 1a). As the application of fluorinated organic compounds continues to expand, their synthesis has become a research focus in the field of organic chemistry, with fluoroalkylation reactions being an important topic in this area.

In fluoroalkylation reactions, perfluoroalkylation reagent is a key to introduce a perfluoroalkyl group into the substrate molecule. Various organic perfluoroalkylation reagents featuring electrophilic,[7] radical,[8] and

nucleophilic[9] characters have been invented to meet the demands of perfluoroalkylation for different substrate types (Fig. 1b). Among these reagents, significant advancements have been made in the development of electrophilic and radical perfluoroalkylation reagents. For nucleophilic perfluoroalkylation, although the research field had an early development, to achieve versatile perfluoroalkylation remains highly challenging.

Perfluoroalkyl metal species have been recognized as a typical nucleophilic perfluoroalkylation reagent in the past two decades. Perfluoroalkyl titanium,[10] indium,[11] and zinc[12,13] reagents were developed by Mikami,[10-12] Uchiyama,[13] and other groups. These organometallic reagents exhibit good reactivity towards electrophiles, though most of them are not bench-stable and need to be prepared prior to use. Alternatively, the groups of Powelke,[14] Petrov[15] and others[16,17] explored the use of tetrakis(*N*,*N*-dimethylamino)ethylene (TDAE) as a reducing agent to promote the transformation of perfluoroalkyl anion from perfluoroalkyl iodide, enabling smooth nucleophilic perfluoroalkylation reactions with a variety of electrophiles. This protocol was proved most suitable for CF_3I and C_2F_5I, while more advanced perfluoroalkyl iodides exhibited significantly decreased reactivity.[17] Perfluoroalkyl transfer reagents provide another access to nucleophilic perfluoroalkylation. (Trifluoromethyl)trimethylsilane ($TMSCF_3$) and related perfluoroalkyltrimethylsilane ($TMSR_f$), developed by Ruppert,[18] Prakash,[19,20] and others,[21,22] were proved practical nucleophilic perfluoroalkylation reagents in the presence of a catalytic amount of base. Langlois and co-workers introduced a trifluoromethyl substituted silyl hemiaminal as a trifluoromethyl anion equivalent after treatment with base.[23,24] The Prakash group also discovered that, trifluoromethyl sulfone or sulfoxide could be used as nucleophilic trifluoromethyl transfer reagent in the presence of base.[25] Similarly, the Beier group developed a trifluoromethylphosphonate reagent that can be used in nucleophilic trifluoromethylation reactions upon base activation.[26] Compared with the organometallic perfluoroalkyl reagents, these bench-stable perfluoroalkyl transfer reagents are easy to store and use (Fig. 1c).

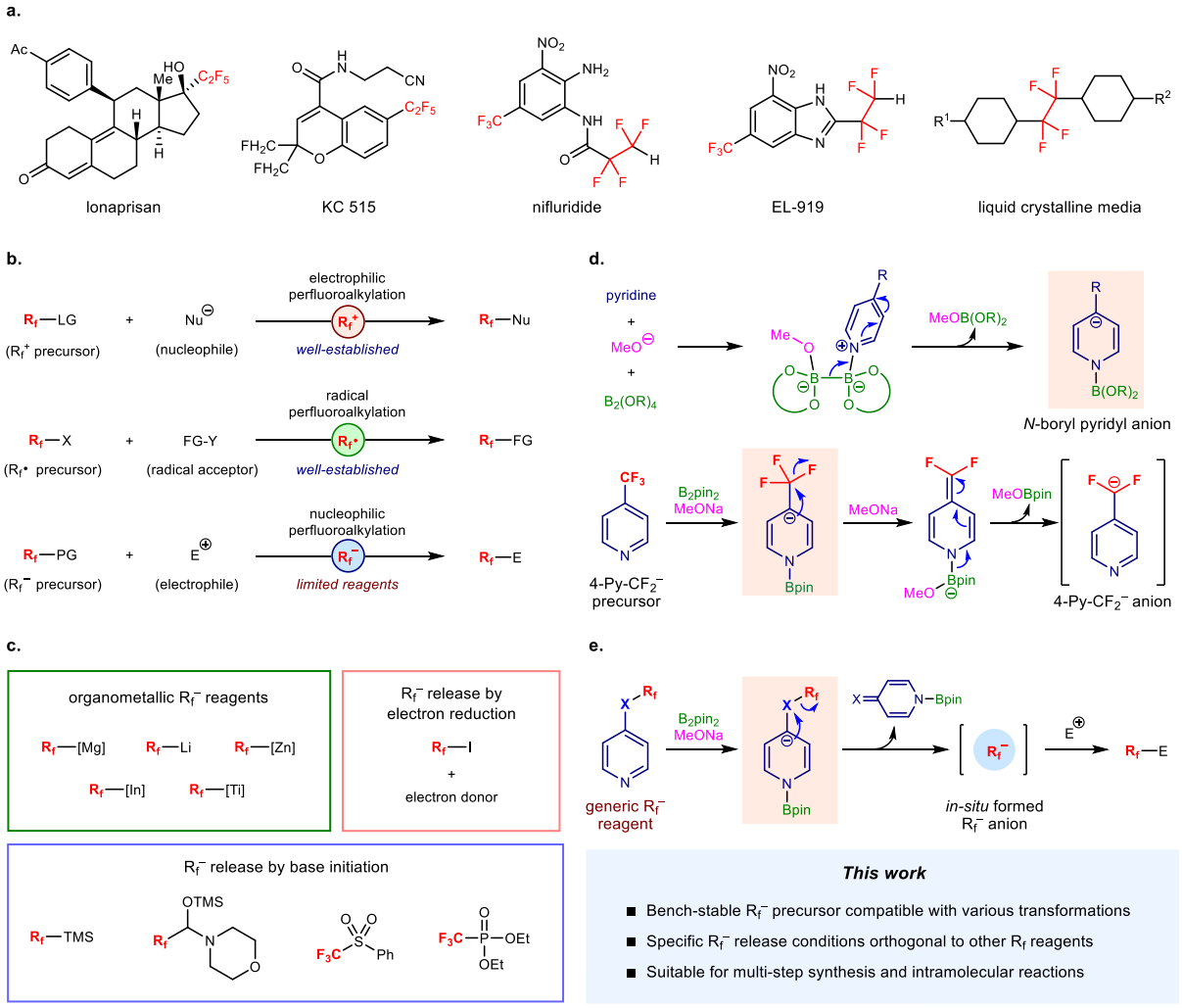

Fig. 1 | Perfluoroalkylation reactions and related reagents. a, Representative functional molecules containing perfluoroalkyl groups. **b,** Categories of perfluoroalkylation reactions. **c,** Representative nucleophilic perfluoroalkylation reagents. **d,** Formation of 4-pyridyldifluoromethyl anion via the *N*-boryl pyridyl anion intermediate reported in our previous work. **e,** Design of nucleophilic perfluoroalkylation reagent based on *N*-boryl pyridyl anion chemistry (this work).

Despite these advances, the established protocols for nucleophilic perfluoroalkylation are associated with certain limitations. While these methods enable efficient transfer of simple perfluoroalkyl groups, especially the trifluoromethyl group, the perfluoroalkylation reagents with functionalized perfluoroalkyl moieties are not easily prepared. Furthermore, the implementation of intramolecular perfluoroalkylation is usually difficult, because the established perfluoroalkyl anion precursor could hardly survive the reaction conditions required for multi-step synthesis of the corresponding substrates.

In this work, we aim to design a new type of nucleophilic perfluoroalkylation reagent based on our previous findings in *N*-boryl pyridyl anion chemistry. We discovered that, the reaction between a diboron(4) compound, a pyridine derivative, and an alkyloxide base could form an *N*-boryl pyridyl anion intermediate,[27-29] which is strongly electron-rich and nucleophilic.[30,31] In our previous work, we demonstrated that 4-trifluoromethylpyridine could undergo fluoride elimination to form a difluoromethylpyridyl anion

intermediate (4-PyCF$_2^-$) as a nucleophile for difluoroalkylation (Fig. 1d).[32] Encouraged by this finding, we further envisioned to insert an X atom between the pyridine moiety and the fluoroalkyl group to form 4-PyXR$_f$, expecting to use it as a generic perfluoroalkylation reagent without constraint on the perfluoroalkyl moiety. We expected that, by treatment of base and diboron(4), the corresponding *N*-boryl pyridyl anion may be generated and then elimination could occur to produce a perfluoroalkyl anion (Fig. 1e). The proposed 4-PyXR$_f$ reagent would be a bench stable precursor that releases perfluoroalkyl anion only under specific conditions, and its chemical stability made it particular suitable for the transfer of complex functionalized perfluoroalkyl groups and intramolecular perfluoroalkylation reactions, which makes an important addition to the nucleophilic perfluoroalkylation reagent toolbox.

Results and Discussion

Preliminary computational and experimental assessment. In order to achieve the proposed reactivity of 4-PyXR$_f$ reagents, the choice of a suitable atom X is critical. The atom should be at least divalent, serving as a bridge between the pyridine and perfluoroalkyl units; the R$_f$-X bond strength should be appropriate to facilitate the heterolytic cleavage; the preparation of the PyXR$_f$ should be easily implemented from readily available perfluoroalkyl source. Taking these factors into account, we focused on three atoms: oxygen, carbon, and sulfur (Fig. 2a).

We commenced our research with DFT computational investigations (Fig. 2a). The possibility for R$_f$-X bond heterolysis in the corresponding *N*-boryl pyridyl anion intermediates **Int-A** to **Int-C** was first investigated. It was found that, the heterolytic cleavage of the R$_f$-O, R$_f$-C and R$_f$-S bonds were all thermodynamically favorable, with Gibbs free energy changes of -30.6 kcal/mol, -34.2 kcal/mol, and -25.0 kcal/mol, respectively. However, further analysis on the molecular orbital interaction within these intermediates revealed dramatic differences. According to the frontier molecular orbital (FMO) theory, the R$_f$-X heterolysis relies on the interaction of the electron-rich *N*-boryl pyridyl anion orbital (the donor orbital) with the R$_f$-X σ* antibonding orbital (the acceptor orbital), and strong donor-acceptor interaction corresponds to facile R$_f$-X heterolytic cleavage. Interestingly, natural bond orbital (NBO) calculations showed that, the donor-acceptor interaction energy in **Int-C** (X = S) is much greater than those in **Int-A** (X = O) and **Int-B** (X = C). This is in agreement with the calculated orbital coefficients, where the R$_f$-X σ* antibonding orbital resides more on the side of X atom in **Int-C** than in **Int-A** and **Int-B**. Finally, the calculated bond cleavage transition states indicated that R$_f$-S heterolytic cleavage exhibited a significantly lower Gibbs free activation energy, consistent with the result of orbital interaction analysis.

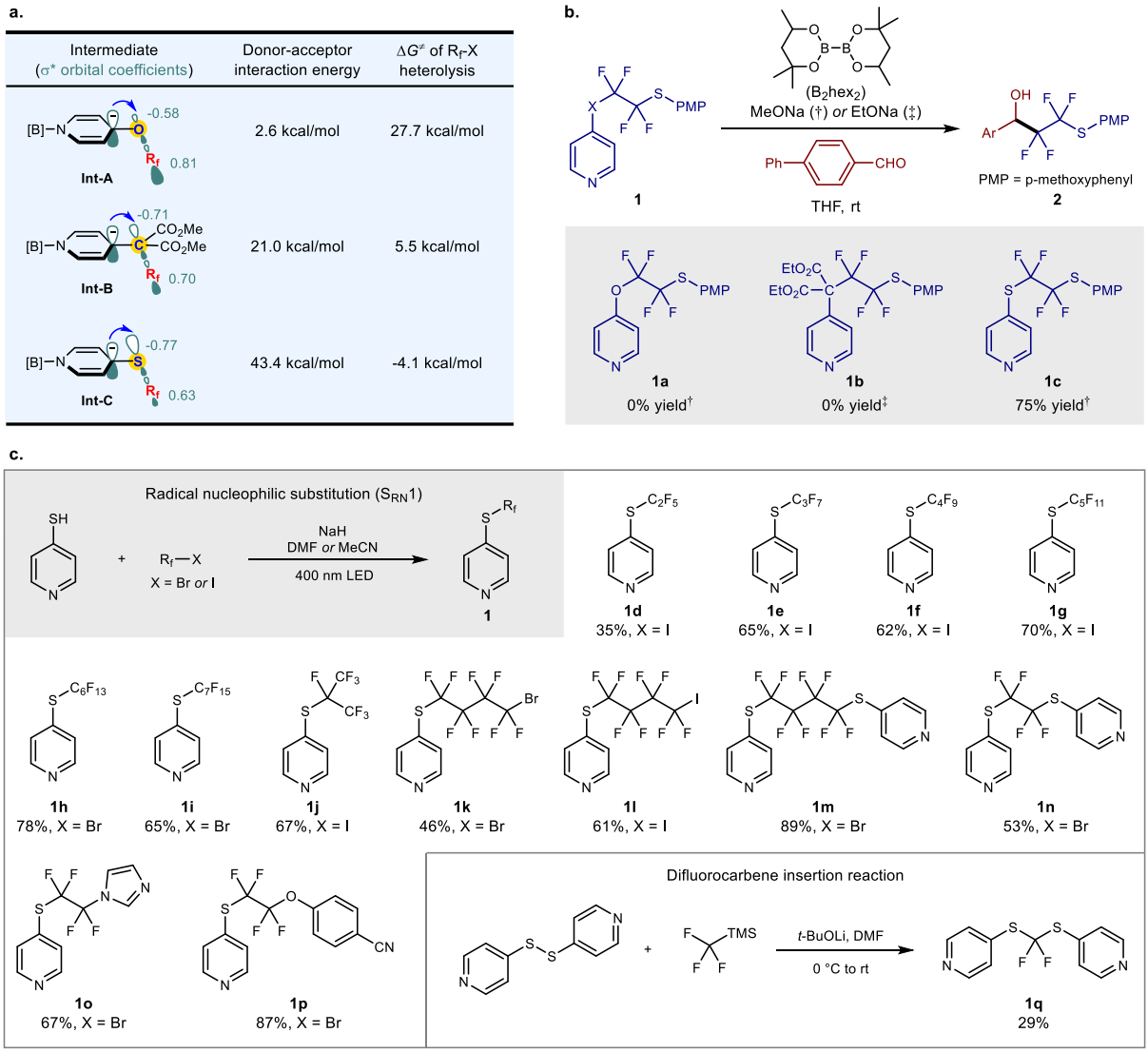

Fig. 2 | Preliminary computational and experimental assessments of the designed perfluoroalkylation reaction. a, DFT calculated σ* orbital coefficients, donor-acceptor interaction energies, and activation Gibbs free energies of R_f-X heterolysis of *N*-boryl pyridyl anion intermediates, where [B] = Bpin, R_f = *n*-C_3F_7. **b,** Reactivity profile of oxygen-, carbon-, and sulfur-tethered $PyXR_f$ molecules in perfluoroalkylation reaction. **c,** Preparation of structurally diverse 4-$PySR_f$ reagents.

The preliminary computational study figured out 4-pyridyl perfluoroalkyl sulfide (4-$PySR_f$) as a most promising candidate for nucleophilic perfluoroalkylation reagent. Experimental study was subsequently performed to verify the reactivity profile of oxygen-, carbon-, and sulfur-tethered pyridyl perfluoroalkyl molecules **1a-c** in nucleophilic perfluoroalkylation.

With the encouraging computational results, we prepared $PyXR_f$ molecules **1a**, **1b** and **1c** with different tether atoms for experimental assessment (Fig. 2b). We selected 4-phenylbenzaldehyde as the electrophile, and the desired perfluoroalkylation reactions were performed in the presence of B_2hex_2 and sodium alkoxide (NaOMe or NaOEt) in tetrahydrofuran (THF) under room temperature. We were delighted to find that, 4-$PySR_f$ molecule **1c** could indeed undergo the designed perfluoroalkyl transfer reaction, delivering product **2** in 75% yield. Conversely, the reactions involving oxygen- and carbon-tethered molecules **1a** and **1b** resulted

in much inferior results, in accordance with the computational analysis above. Although our calculation predicted that the X-R_f bond cleavage in oxygen- and carbon-tethered *N*-boryl pyridyl anion is not entirely impossible, the experimental findings that **1a** and **1b** were mostly intact in the reaction indicated that the formation of the *N*-boryl pyridyl anion intermediate could be difficult for these substrates.

Subsequently, we explored the preparation of various perfluoroalkyl pyridyl sulfides as perfluoroalkylation reagents (Fig. 2c). To our delight, the 4-PySR_f reagents could be readily synthesized from commercially available pyridine-4-thiol and perfluoroalkyl halides under basic conditions via the radical nucleophilic substitution ($S_{RN}1$) reaction.[33] In the presence of base and 400 nm light-emitting diode (LED) irradiation, various perfluoroalkyl bromides and iodides with different chain lengths afforded the desired 4-PySR_f reagents in decent yields. Normally, *N*,*N*-dimethylformamide (DMF) was used as the solvent with perfluoroalkyl bromides, while MeCN was used as the solvent with perfluoroalkyl iodides. Interestingly, selective activation of a single site or both sites of dihaloperfluorobutane was viable, affording **1k**/**1l** as functionalized perfluoroalkylation reagent and **1m**/**1n** as bis-perfluoroalkylation reagent. Notably, perfluoroalkyl halides with different substituents were also competent to deliver complex 4-PySR_f reagents **1o** and **1p** in good yields. Finally, by using a difluorocarbene insertion reaction with bis(4-pyridyl)disulfide, 1,1-bis(4-pyridylthio)difluoromethane **1q** could be obtained. The successful preparation of these structurally diverse 4-PySR_f reagents laid the foundation for generic and diversified perfluoroalkylation reaction.

Single-step perfluoroalkylation. 4-phenylbenzaldehyde was employed as a model substrate to explore the scope of the viable 4-PySR_f reagent (Fig. 3a). Since previous studies mainly focused on trifluoromethylation protocols, methods suitable for nucleophilic perfluoroalkylation with longer chains are relatively limited.[34] With an array of easily accessible 4-PySR_f reagents in hand, we assessed their potential in diverse perfluoroalkylation reactions. Gratifyingly, this type of reagent was found efficient in perfluoroalkylation with different chain lengths ranging from C2 to C7 (**1d-i**), affording addition products **4** and **5a-e**. Reagent **1j** with a branched heptafluoroisopropyl group could also afford the perfluoroalkyl addition product **5f**, albeit in a diminished yield. Other electrophiles, including unsaturated aldehyde, alkyl aldehyde, ketoesters, ketimide, and heteroaromatic aldehyde, were all compatible to afford high yields of perfluorobutyl addition products **5g-k** with reagent **1f**.

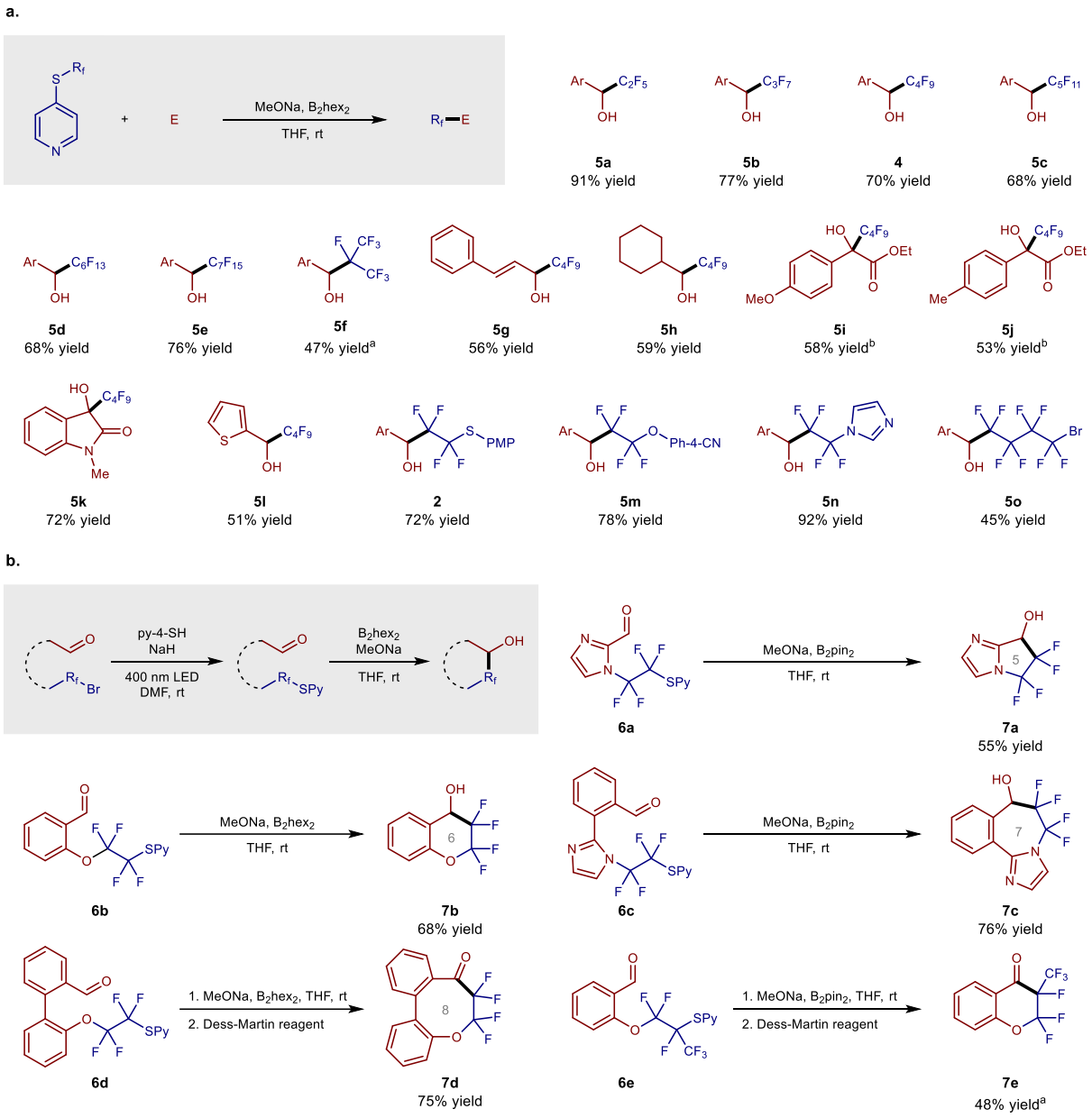

Fig. 3 | Perfluoroalkylation reactions with 4-PySR$_f$ reagents. a, Intermolecular reactions, where Ar = 4-phenylphenyl. **b,** Intramolecular reactions leading to fluorine-substituted cycles. [a]B_2pin_2 was employed instead of B_2hex_2. [b]EtONa was employed instead of MeONa.

One significant advantage of the perfluoroalkyl pyridyl sulfide reagent is its ability to transfer functionalized perfluoroalkyl groups. When implementing this type of reaction, traditional nucleophilic perfluoroalkylation protocols often encounter side reactions that lead to low yields of the desired products or difficulties in purification.[35] Gratifyingly, the 4-PySR$_f$ reagents exhibited excellent potential for this task. In addition to successful 2-arylthioperfluoroethylation using reagent **1c** to form adduct **2**, 2-phenoxylperfluoroethyl and 2-imidazoylperfluoroethyl could also be transferred from reagents **1o** and **1p** to the aldehyde substrate (products **5m** and **5n**). Notably, it was previously found that 2-imidazole substituted perfluoroethyl Grignard reagent displayed a tendency to undergo intramolecular proton transfer from the

imidazole C(1)-H position,[36] while in the present reaction this side reaction was absent, ensuring a high yield of addition product **5n**. Additionally, it is worth mentioning that the bromine-substituted 4-PySR$_f$ reagent **1k** smoothly underwent the perfluoroalkylation reaction to produce adduct **5o** while retaining the bromide moiety. In contrast, the perfluoroalkyl bromide moiety is prone to react under the conventional metal exchange conditions.[35]

Compared with the intermolecular perfluoroalkylation, the intramolecular approach for constructing cyclized fluoroalkyl frameworks is more intriguing but relatively underexplored.[37-39] These structures pose a significant challenge when using conventional perfluoroalkylation methods, while our reagent demonstrated remarkable capability for achieving this goal (Fig. 3b). A series of 4-PySR$_f$ molecules **6a-e** featuring an intramolecularly tethered aldehyde moiety were synthesized using the $S_{RN}1$ reaction. By simply treating them with diboron(4) and MeONa, intramolecular perfluoroalkyl addition product with complex fluorine-containing molecular frameworks could be obtained. The reaction was competent for the formation of five-, six-, seven-, and eight-membered rings (**7a-d**), and the product with a branched perfluoro moiety could be produced in a moderate yield (**7e**). Overall, this approach demonstrates promising potential for the synthesis of diverse and intricate fluorine-containing molecules.

Multi-step synthetic sequence. The 4-PySR$_f$ reagents have demonstrated remarkable potential in single-step nucleophilic perfluoroalkylation reactions. Given their good stability and distinctive activation conditions that are orthogonal to most chemical transformations, the 4-PySR$_f$ structure could be used as a robust precursor of fluoroalkyl anion that can be introduced at the very early stage of synthesis. This provides an intriguing opportunity for the synthesis of complex molecules incorporating perfluoroalkyl groups through multi-step reactions (Fig. 4a), which is a formidable challenge for the current nucleophilic perfluoroalkylation protocols.

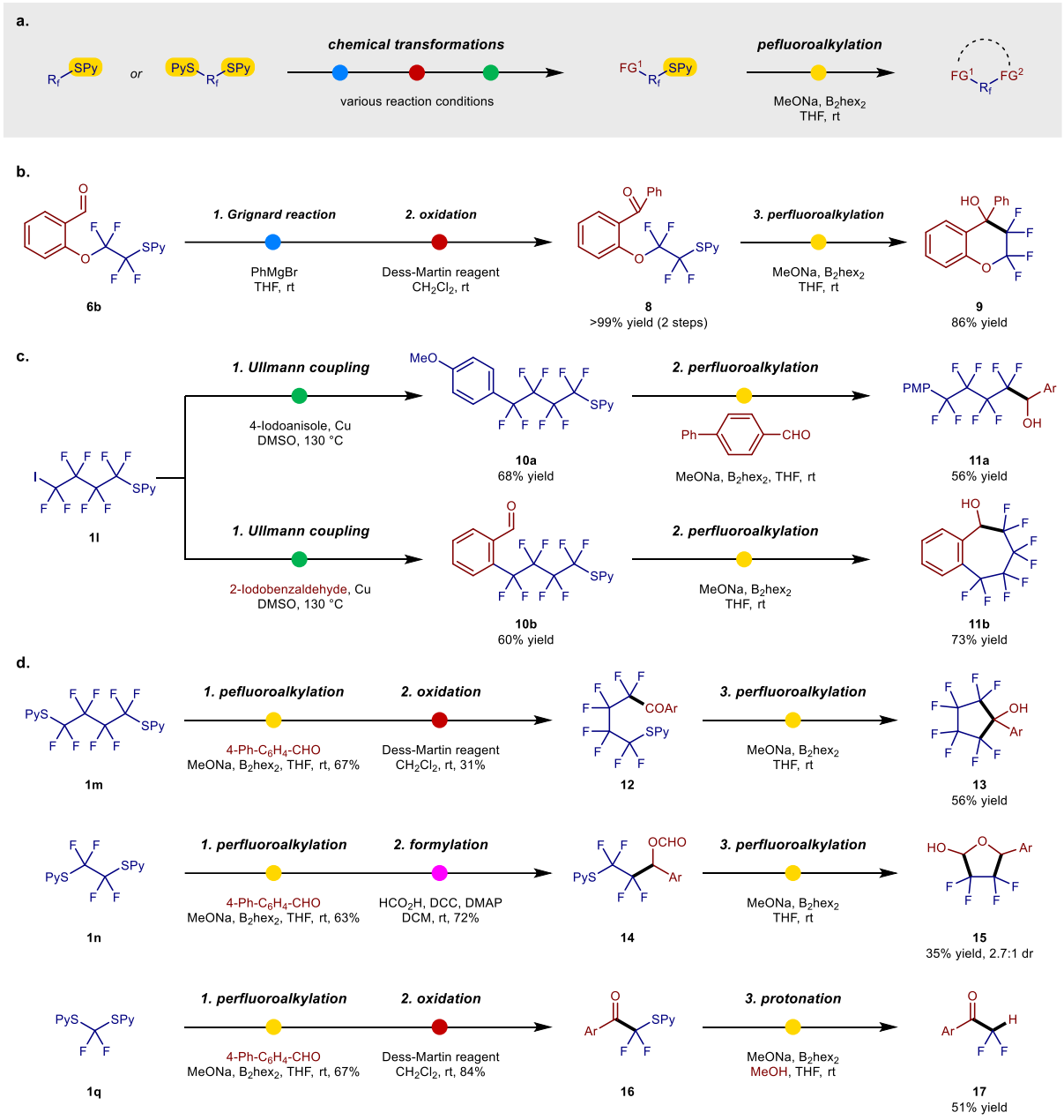

Fig. 4 | 4-PySR$_f$ reagent as a starting material in multi-step synthesis. a, The stability of 4-PySR$_f$ reagent allows for various chemical transformation to be done prior to perfluoroalkylation. **b,** The Grignard reaction-oxidation-perfluoroalkylation sequence. **c.** The Ullmann coupling-perfluoroalkylation sequence. **d,** Stepwise activation and transformations of bis(4-pyridylthio)perfluoroalkyl reagents.

We demonstrate that, the 4-PySR$_f$ unit in substrate **6b** could survive Grignard reaction and Dess-Martin oxidation conditions, and the product **8** underwent the final intramolecular perfluoroalkylation to afford **9** in a high yield (Fig. 4b). On the other hand, Cu-catalyzed Ullmann coupling[40] of iodine-substituted 4-PySR$_f$ reagent **1l** with iodoarenes proceeded smoothly to give **10a** and **10b** in good yields. Subsequent inter- or intramolecular perfluoroalkylation afforded products **11a** and **11b** in good yields (Fig. 4c). It is noteworthy that, the present chemistry allowed for stepwise activation of the bis(4-pyridylthio)perfluoroalkyl reagents by applying appropriate reaction time and loadings of diboron and base (Fig 4d). For 1,4-bis(4-

pyridylthio)perfluorobutane (**1m**), first perfluoroalkyl transfer and subsequent oxidation afforded compound **12**, which underwent an intramolecular perfluoroalkylation by the second activation to produce a cyclized fluoroalkyl compound **13**. For 1,2-bis(4-pyridylthio)perfluoroethane (**1n**), first-round perfluoroalkylation and subsequent formylation afforded formate **14**, which upon treatment with diboron(4) and base generated a fluorinated five-membered sugar-like compound **15**. Interestingly, in the case of 1,1-bis(4-pyridylthio)difluoromethane (**1q**), stepwise difluoromethylation could still occur. Through consecutive fluoroalkylation-oxidation, intermediate **16** was obtained, and the second activation resulted in the formation of difluoromethylation product **17**. This three-step sequence enabled the reagent to serve as an equivalent for difluoromethyl anion. The ability of the 4-PySR$_f$ reagent to participate in various multi-step synthetic sequences extended the scope of this chemistry.

Reaction mechanism. In addition to its synthetic potential, we were curious to reveal the perfluoroalkyl transfer mechanism of the 4-PySR$_f$ reagent. To this end, Hammett analysis[41] was performed by running intermolecular competition experiments between benzaldehyde and a series of *para*-substituted benzaldehydes employing pyridyl *n*-perfluorobutyl sulfide (**1f**) as the perfluoroalkylation reagent (Fig. 5a). It was found that, under the standard reaction conditions, the electron-deficient benzaldehydes were more reactive than the electron-rich ones, exhibiting a ρ value of +0.93 with excellent linearity. This indicated the accumulation of partial negative charge at the carbonyl carbon in the transition state (TS) of perfluoroalkyl transfer, which was in line with a nucleophilic addition mechanism.[42] Interestingly, by switching the base from MeONa to MeOK, the observed ρ value increased to +1.19, in consistent with the general trend that less oxophilic contercation (K^+) results in more negative charge accumulation at the reaction center in the nucleophilic addition TS.

In order to get a more comprehensive understanding on the mechanism of this reaction, we performed Hammett analysis on the reaction between *n*-$C_4F_9SiMe_3$ and *para*-substituted benzaldehydes (Fig. 5b). Since CF_3^- anion has been identified as a key intermediate in the trifluoromethyl transfer reaction of trifluoromethylsilane,[43] comparison of the results from *n*-perfluorobutylsilane and *n*-perfluorobutyl 4-pyridyl sulfide could provide some hint for the reaction mechanism of the latter. It was found that, under the standard reaction conditions employing tetrabutylammonium fluoride as the base to activate the *n*-$C_4F_9SiMe_3$, the reaction was more sensitive to electronic effect of the aldehyde, exhibiting a ρ value of +1.85. Interestingly, when MeONa was used as the base activator, a remarkably decreased ρ value of +1.22 was observed. This phenomenon was also in agreement with a nucleophilic perfluoroalkylation mechanism. Although this slope (+1.22) did not perfectly match that of the 4-PySR$_f$ reagent (+0.93), given their same general trend towards counteraction and the complexity of the reaction system, we reasoned that it is very likely that the perfluoroalkylation reaction with the 4-PySR$_f$ reagent proceeds through perfluoroalkyl anion.

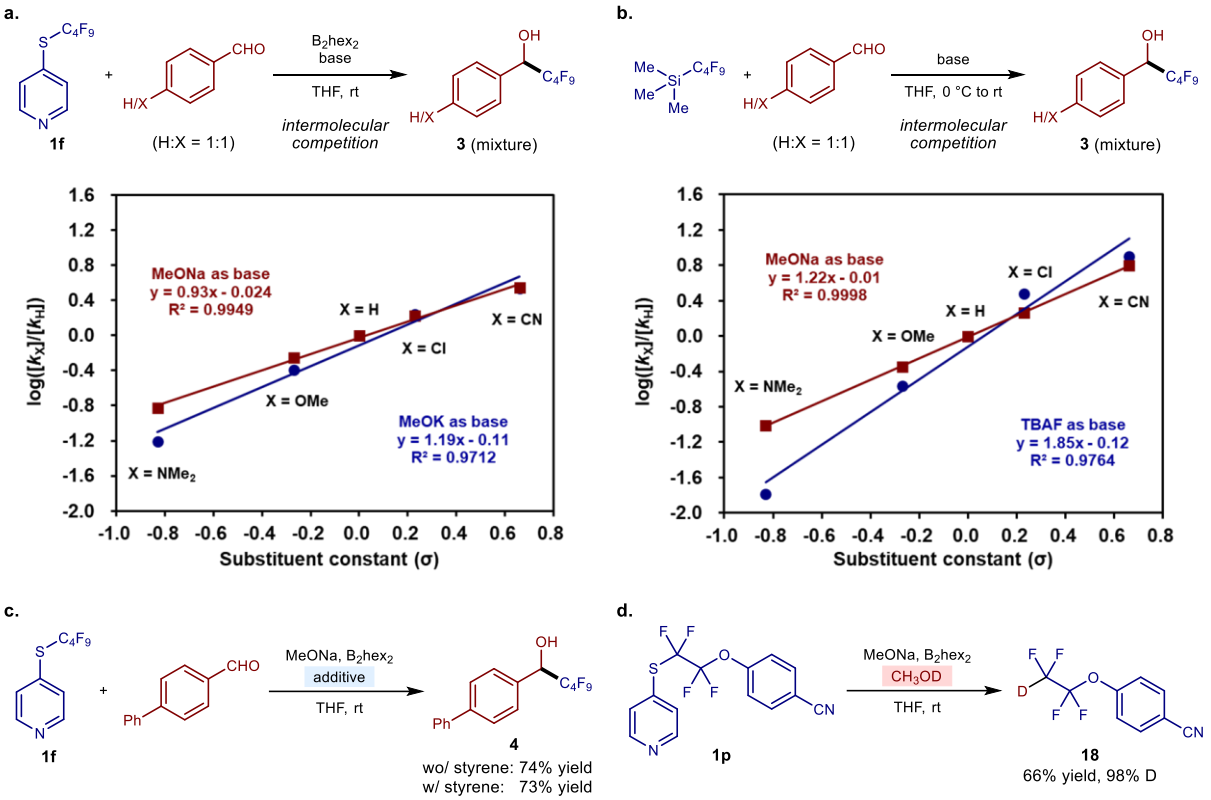

Fig. 5 | Mechanistic investigations. a, Hammett plot of the perfluoroalkylation reactions between **1f** and *para*-substituted benzaldehyde. **b,** Hammett plot of the perfluoroalkylation reactions between trimethylperfluorobutylsilane and *para*-substituted benzaldehyde. **c,** Radical trapping experiment using styrene. **d,** Trapping of the perfluoroalkyl anion by using methanol-d_1.

A further experiment was performed to probe the intermediacy of perfluoroalkyl radical in the perfluoroalkyl transfer reaction of 4-PySR$_f$. To this end, the reaction between reagent **1f** and *para*-phenylbenzaldehyde was conducted in the presence of styrene as a perfluoroalkyl radical trapping reagent (Fig. 5c).[44-46] If the perfluoroalkyl transfer proceeded through perfluoroalkyl radical, the presence of styrene could suppress the formation of product **4**. The fact that the addition of styrene to the reaction had no obvious impact one reaction indicated that a radical mechanism was unlikely to operate.

Finally, to further confirm that the nucleophilic nature of the *in-situ* generated perfluoroalkylation reagent, a deuteration experiment was performed with reagent **1p** in the presence of CH_3OD (Fig. 5d). The expected product **18** with a deuteroperfluoroalkyl group was obtained in a decent yield and excellent deuterium incorporation. This result not only supported the formation of a nucleophilic perfluoroalkyl reagent, but also served as a practical method for the preparation of functionalized hydro(deutero)perfluoroalkyl products.

Conclusion

In this study, we have designed and synthesized a novel class of nucleophilic perfluoroalkylation reagents, 4-pyridyl perfluoroalkyl sulfide. These reagents exhibit remarkable structural versatility, enabling efficient nucleophilic perfluoroalkylation reactions on a wide range of substrates in the presence of diboron and base.

This includes substrates that are typically challenging to handle using conventional methods. These reagents enable intramolecular fluoroalkylation and demonstrates excellent compatibility with various other transformations. The findings in this work represents an unprecedented approach to the formation of nucleophilic perfluoroalkyl species, and the versatility demonstrated by this new reagent surpasses many previous methods, showcasing its exceptional performance. In particular, this reagent offers a distinct advantage with its unique and mild perfluoroalkyl anion releasing conditions that are orthogonal to most synthetic conditions, enabling its integration into complex multi-step synthetic sequence at an early stage. The present this work holds great promise for expanding the realm of perfluoroalkylation chemistry, and we expect that this chemistry exhibits potential for various synthetic applications in diverse research directions.

Acknowledgements

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