ARTICLE

A General Photocatalytic Hydrodefluorination and Defluoroalkylation of Electronically-Variable $ArCF_3$ by Changing Commercially-Available Arenethiolates

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Although defluorinative functionalization of trifluoromethylarenes has been studied by several research groups, different kinds of catalysts are requested accordingly based on specific substrate families to obtain corresponding RCF_2Ar compounds. Herein, we report a general photocatalytic approach for selective hydrodefluorination (HDF) and defluoroalkylation (DFA) of $ArCF_3$. Using electronically-different arenethiolates as photosensitizer, 88 α, α-difluoromethyl compounds were synthesized from a broad range of electronically-variable trifluoromethylarenes, including natural products and bioactive molecules. Our mechanistic studies uncovered photo-induced Electron Donor-Acceptor (EDA) complexation followed by the silane-assisted C-F bond activation.

Introduction

To activate inert bonds and to render them synthetic valuable, direct functionalization is attractive. One example of such inert bonds is the C−F bond of trifluoromethyl groups ($-CF_3$), which have a high bond dissociation energy (128 kcal/mol, HCF_3). In this context, direct C−F functionalization of trifluoro-methylarenes ($ArCF_3$) is an ideal route to access α, α-difluorobenzylic compounds (RCF_2Ar) because of widely available materials.[1] Fluoroalkylated motifs are increasingly found in medicinal molecules, and although compounds containing -CF_3 groups are most common, those containing -CF_2R units are becoming more widely incorporated as new synthetic methodologies are developed for their incorporation. Given the prevalence of $ArCF_3$ compounds, new methods that enable the direct functionalization of $ArCF_3$ to RCF_2Ar variants will further enlarge the drug pool.[2] Several strategies for the direct C-F bond activation of $ArCF_3$ have been recently developed.[3] One of remarkable breakthroughs in C-F activation relies on single electron transfer (SET) via either photoredox catalysis[4] or electrochemistry.[5] Despite these impressive advancements, limitations on substrate scope are often observed and several challenges still remain. For instance, reactivity of photosensitizer is substrate dependent. Photosensitizers with high excited-state redox potential are only suitable for electron-withdrawing substrates, such as **PC1**,[6] **PC2**,[7] **PC3**[8] (Scheme 1A). Recently, the Jui group has shown a high excited-state redox potential, **PC4**,[9] catalyzes substrates with electron donating groups, although elevated temperatures are required. In order to activate substrates containing electron-donating functional groups, a low excited-state redox potential of photosensitizers **PC5**[10] and **PC6**[4b,11] must be used for C-F bond reduction. However, those photosensitizers are not only expensive and challenging to synthesize, but also lack generality and substrate scope. In order to functionalize both electron-donating and electron withdrawing substrates on $ArCF_3$, two or more very different classes of catalysts are inevitable, limiting generality. Apart from photochemical methodology approaches, electrochemical approaches have achieved the reductive defluorination of trifluoromethyl aromatics by a Ni cathode.[5a] Moreover, silylium-ion-promoted C(sp^3)−F bonds activation are successfully employed in defluorinative functionalization, because of Lewis acidity of silylium ions and also silicon's affinity for fluoride.[12] However, over functionalization of C-F bonds is commonly observed because monofunctionalized products ($ArCF_2H$) have a lower bond dissociation energy and higher reactivity than starting $ArCF_3$; therefore, a cascade reaction occurs. In addition to inherent challenges in defluorination selectivity, purification is often challenging because the polarity of by-products are often very similar. Therefore, obtaining both a broader range of RCF_2Ar from $ArCF_3$ using one class of catalysts and being capable of controlling regioselectivity in the defluorination functionalization remain an unsolved challenge.

Typically, current methods for hydrodefluorination (HDF) and defluoroalkylation (DFA) employ formates as the hydrogen source, which also generates $CO_2^{\bullet-}$ ($E_{1/2}$ ($CO_2/CO_2^{\bullet-}$) = −2.2 V vs SCE).[9,13] The anionic free radical $CO_2^{\bullet-}$ interferes with selective defluorination,

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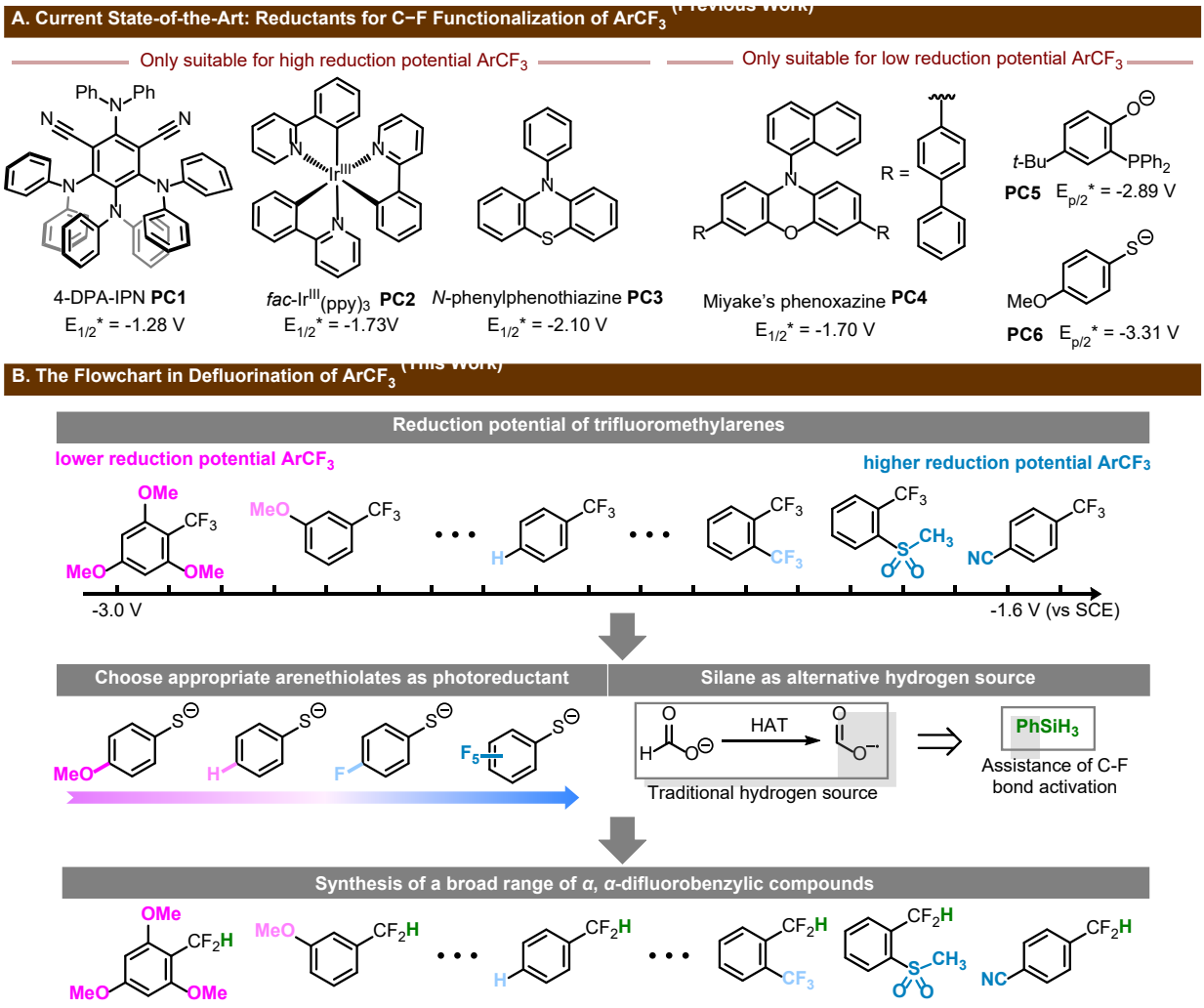
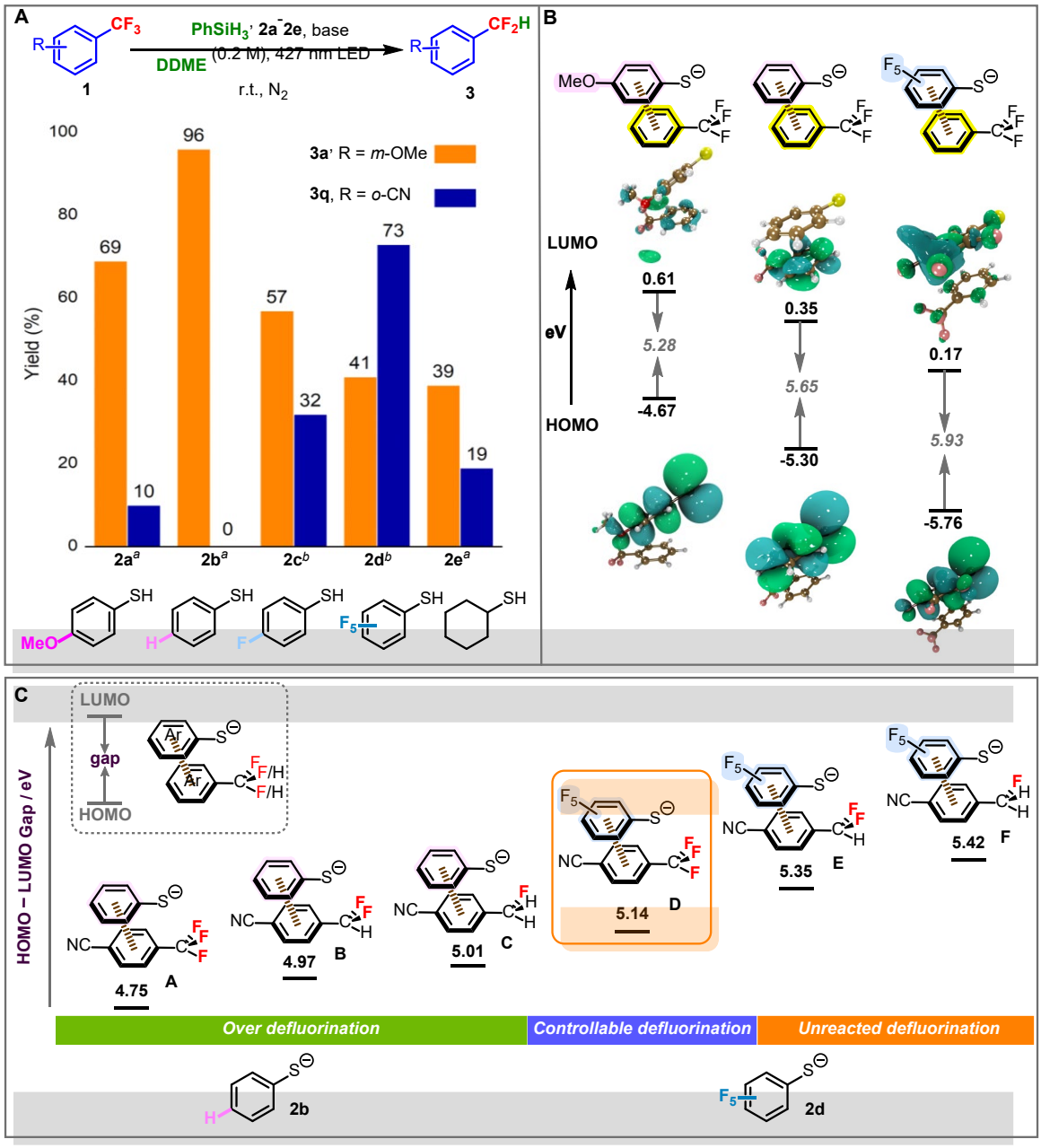


Scheme 1. Radical C−F functionalization of $ArCF_3$ substrates via photoredox catalysis

particularly with substrates containing electron withdrawing groups, and causes over reduction, giving poor selectivity and low yields. In this article, we address this challenge by using simple silanes as an alternative hydrogen source to eliminate over reduction of CF_3, leading to only mono defluorinated regiospecific products. Also of note, inspired by the photo-induced Electron Donor-Acceptor (EDA) strategy,[14] we envisaged the development of a defluorinative functionalization of C(sp^3)-F bonds. The selection of electronically-different thiolate-based photosensitizers could be employed to achieve a precise and specific C-F bond defluorination of a broad range of trifluoromethylarenes (Scheme 1B).

Results and Discussion

The reduction potentials of trifluoromethylarenes are an important parameter to describe thermodynamic requirements for C-F reduction. However, only select examples have been measured in literature.[5a,15] To the convenience of audiences and researchers, we measured the half-peak potentials of 34 $ArCF_3$ substrates via cyclic voltammetry, in which all of the values were obtained with a saturated calomel electrode (SCE) as the reference electrode. (See Supporting Information Section 4 for more details). Expectedly, the reduction potential window of a set range of arene electronics is rather broad. In particular, when there are two or more electronically different substituents connected to the aromatic rings of $ArCF_3$, the half-peak potentials are unpredictable. Thus, we anticipate these values might enable rational selection of reagents for selective defluorination of $ArCF_3$ compounds using electronically distinct arenethiolates according to their reduction potentials. Accordingly, we selected both electron-donating substrate 3-methoxybenzotrifluoride (**1c**), and electron-withdrawing substrate 2-cyanobenzotrifluoride (**1aa**) as models to evaluate the feasibility of the conceived the hydrodefluorination (Scheme 2A). Meanwhile, given the hypothesis that thiophenol serves a key role to dictate the selective defluorination of $ArCF_3$, Density Functional Theory (DFT) calculations were performed (Scheme 2B and 2C). Firstly, control experiments revealed that for the electron-donating substrate (**1c**), which has a reduction potential of $E_{p/2}$ = -2.63 V, thiophenol **2b** (E_{ox}* = -3.31 V) with a reduction capability of exhibits optimal catalysis for C-F bond reduction. When **2b** was used, the HDF product from **1c** was obtained with 96% yield. However, the yield of the products decreases using thiophenols either with stronger reducing agent (**2a**)

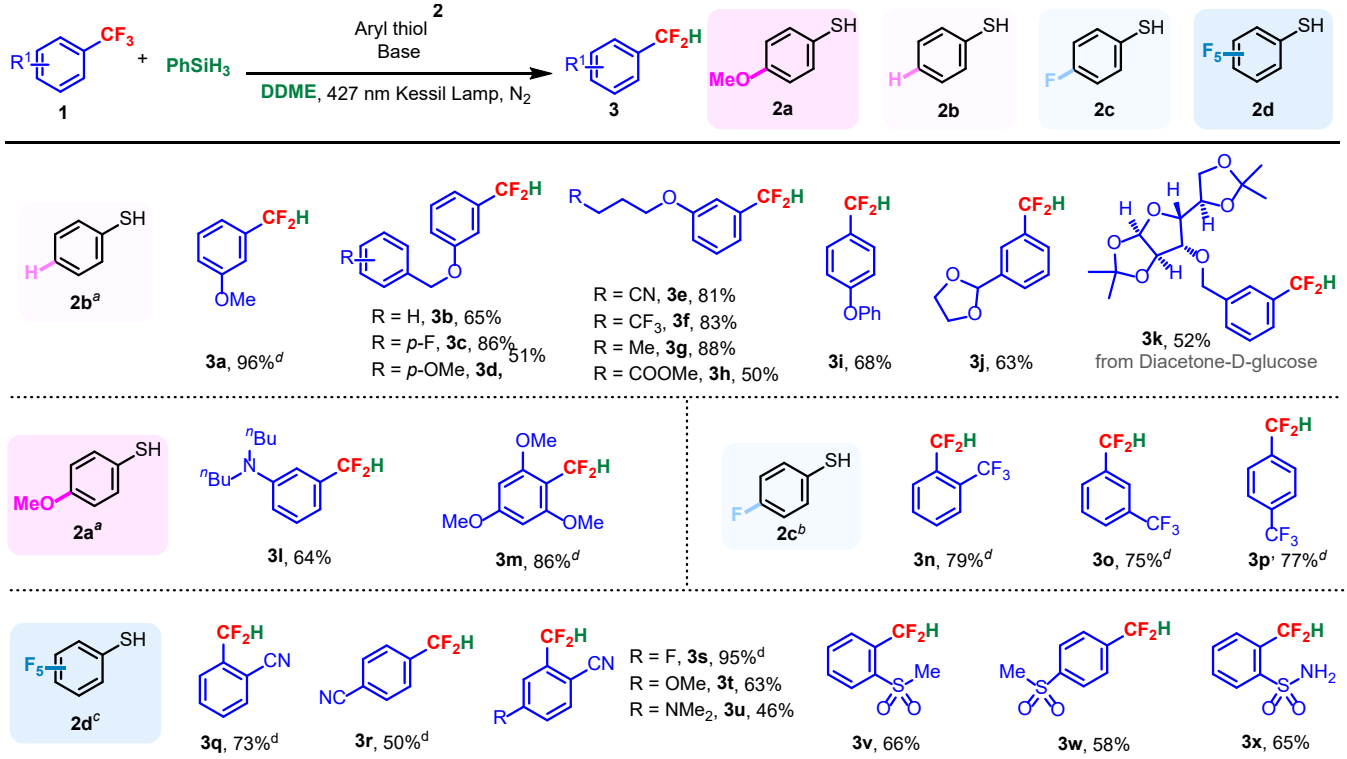


Scheme 2. Control Experiments and DFT (Density Functional Theory) Computations. A. Optimization of Thiols in Hydrodefluorination of Trifluoromethylarenes. B. Frontier molecular orbitals (HOMO and LUMO) of EDA complex ($PhCF_3$ with different ArSH). C. HOMO–LUMO gap of EDA complex (4-cyanobenzotrifluoride with different arene thiolates). Computational results were obtained from the [SMD(DME)-M06-2X-D3/ma-Def2-TZVP] optimizations.

or weaker reducing agents (**2c**, **2d**, **2e**). DFT computations from [SMD(DME)-M06-2X-D3/ma-Def2-TZVP] (DME = DimethoxyEthane) show that the electron-rich thiophenol anion (**2b**) has a lower HOMO-LUMO gap with benzotrifluoride (5.65 eV, Scheme 2B left), making it easier for single electron transfer (SET) to occur. In contrast, a larger HOMO-LUMO gap (5.93 eV, Scheme 2B right) was observed when using the electron-deficient pentafluorobenzenethiolate anion and benzotrifluoride, prohibiting the SET process. Compared to the wavelength (427 nm) of light used, the relatively high HOMO-LUMO gaps were obtained from the current computations. It was caused by the high percentage of HF in the M06-2X functional (54%), since functionals with high percentage of HF usually present high values of HOMO-LUMO gaps.[16] It is worth noting that the trend, instead of the absolute values, HOMO-LUMO gaps could provide more reliable conclusions from the DFT computations. Compared to the electron-donating groups, $ArCF_3$ with electron-withdrawing group (**1aa**, 2-cyanobenzotrifluoride) have relatively higher reduction potentials ($E_{p/2}$ = -1.87 V) and are easier to be reduced. However, the issue of over defluorination inevitably exists. Combined with the DFT computational results (Scheme 2C), thiophenol anion **2b** is found to produce difluoromethyl compound, which could be further reduced into monofluoromethyl species under the reaction condition.

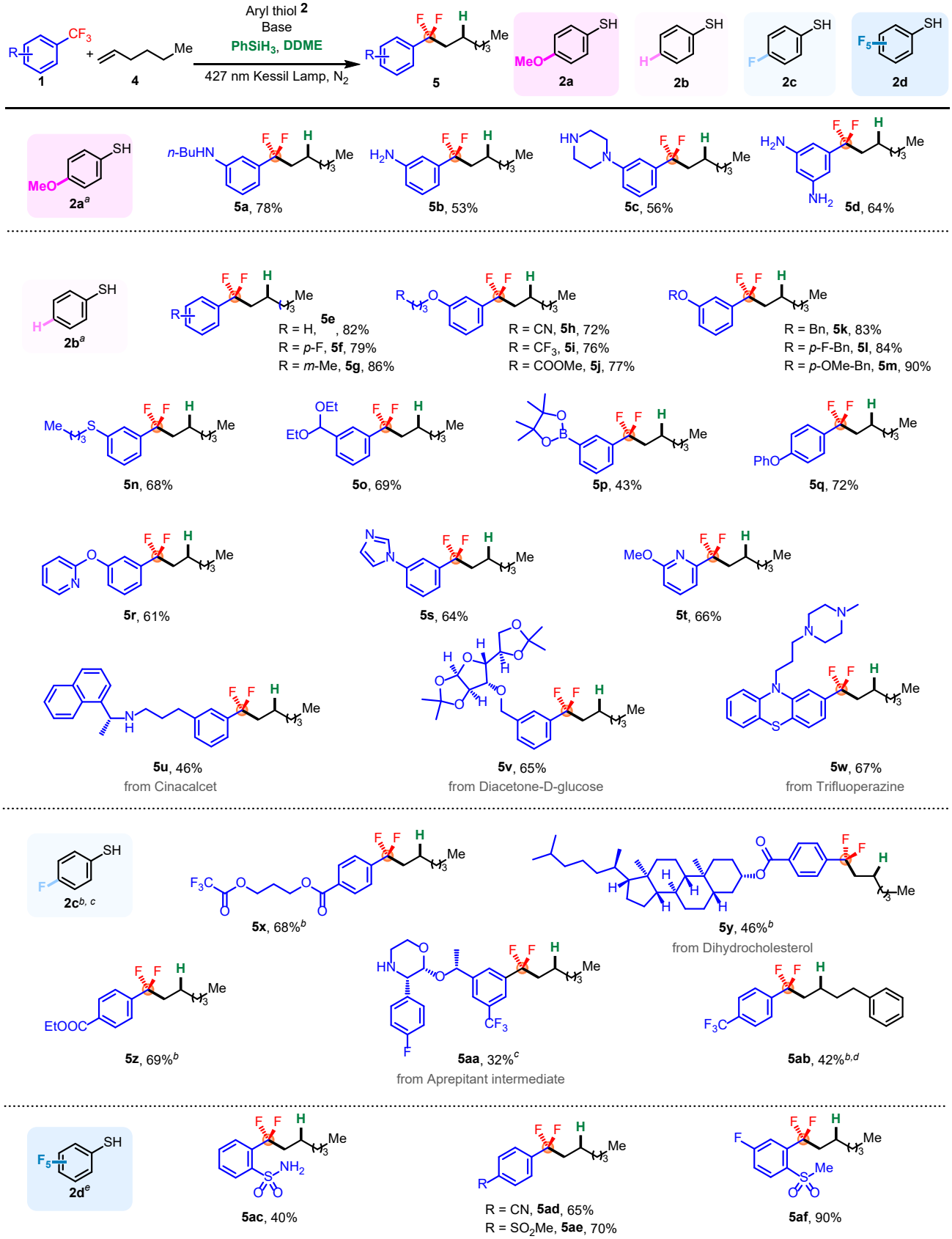
However, the energy gap between the pentafluorothiophenol anion (**2d**) and 4-cyanobenzotrifluoride (**1af**) is too large for the over reduction to occur. As a result, in the corresponding HDF reactions, no over-defluorinated products were obtained to achieve higher selective mono defluorination than previous literatures[6] (Scheme 2C, complex **D**). However, when the aromatic thiol was replaced with an alkyl thiol (cyclohexanethiol; **2e**), we observed low yields of products independent of either electron-donating or electron-withdrawing groups (**3a** and **3q**). We attribute this result to p-π interactions between alkyl thiolate anion and the aromatic ring of $ArCF_3$,[17] wherein the p-π interaction is weaker than π-π interactions. The above experimental observations and DFT computational results further successfully demonstrate the advantages and feasibility of our "tailor strategy".

With the established protocol and methodology, we initially focused on the reaction generality with respect to $ArCF_3$ containing electron-donating groups (Scheme 3, top). The results indicated that the target products **3a**-**3d** could be obtained in 51-96% yields. Apart from that, $ArCF_3$ with alkoxy chains on the ring can also achieve an excellent activation effect, and the nature of the substituent attached to the chain end has little effect on the reaction, such as cyano (**3e**), trifluoromethyl (**3f**), methyl (**3g**) and ester (**3h**). All of these substrates were nicely compatible to give the corresponding products in 50%−88% yields. Substrates with *p*-phenoxy and *m*-acetal groups on the aromatic rings were found to function well, delivering the hydrodefluorination products **3i** and **3j** in 68% and 63% yields, respectively. It's worth mentioning that a diacetone-D-glucose-derived trifluoromethylarenes was also investigated, which was also successfully converted to the desired product **3k** in 52% yield. In order to activate deeper reduction potential substrates, such as trimethoxy-substituted substrates (**1a**, $E_{p/2}$ = -2.92 V vs. SCE) and amino-substituted substrates (**1b**, $E_{p/2}$ = -2.72 V vs. SCE), the lowest potential reduction photosensitizer **2a** was found to be the most efficient. The desired products **3l** and **3m** were observed in 64% and 86% yields, respectively. For bistrifluoromethylarenes, the initial CV test revealed that **2c** was the optimal reducing agent for this reaction. The expected products **3n**-**3p** could be achieved in 75%−79% yields. Notably, the results evidenced promising chemoselectivity as the over reduction of C-F bond was inhibited after the first hydrodefluorination. Next, with respect to other substrates with electron-deficient groups on the aromatic ring, **2d** was more applicable to the hydrodefluorination. Reactions of substrates possessing cyano or sulfone group at *ortho*- or *para*- position on the aromatic ring proceeded smoothly, providing the target products **3q**, **3r**, **3v** and **3w** in moderate to good yields. Next, we tested the substrate with both an electron-donating group and an electron-withdrawing group attached to aromatic ring of $ArCF_3$ (**3s**-**3u**), and it is evident from the experimental results that good yields can be obtained with the dominant role of electron-withdrawing substituents. Moreover, the desired product **3x** was also isolated in 65% yield, when a substrate with a sulfonamide at the *ortho*-position of the aromatic ring was employed. Through the above series of substrate tests, it can be demonstrated that our "tailor strategy" can achieve precise defluorination, the reaction of thiophenol with trifluoromethyl aromatics by modulating different electrical properties.



Scheme 3. Investigation on the Trifluoromethylarenes Scope of Hydrodefluorination of Trifluoromethylarenes. [a]Reaction conditions (unless otherwise specified): **1** (0.6 mmol), **2** (0.3 mmol), $PhSiH_3$ (3.6 mmol), NaOH (1.2 mmol), DDME (Diethylene Glycol Dimethyl Ether) (3 mL), 427 nm Kessil Lamp, r.t., 12 h, N_2 atmosphere, isolated yields; [b]**1** (0.2 mmol), **2c** (0.08 mmol), $PhSiH_3$ (1.2

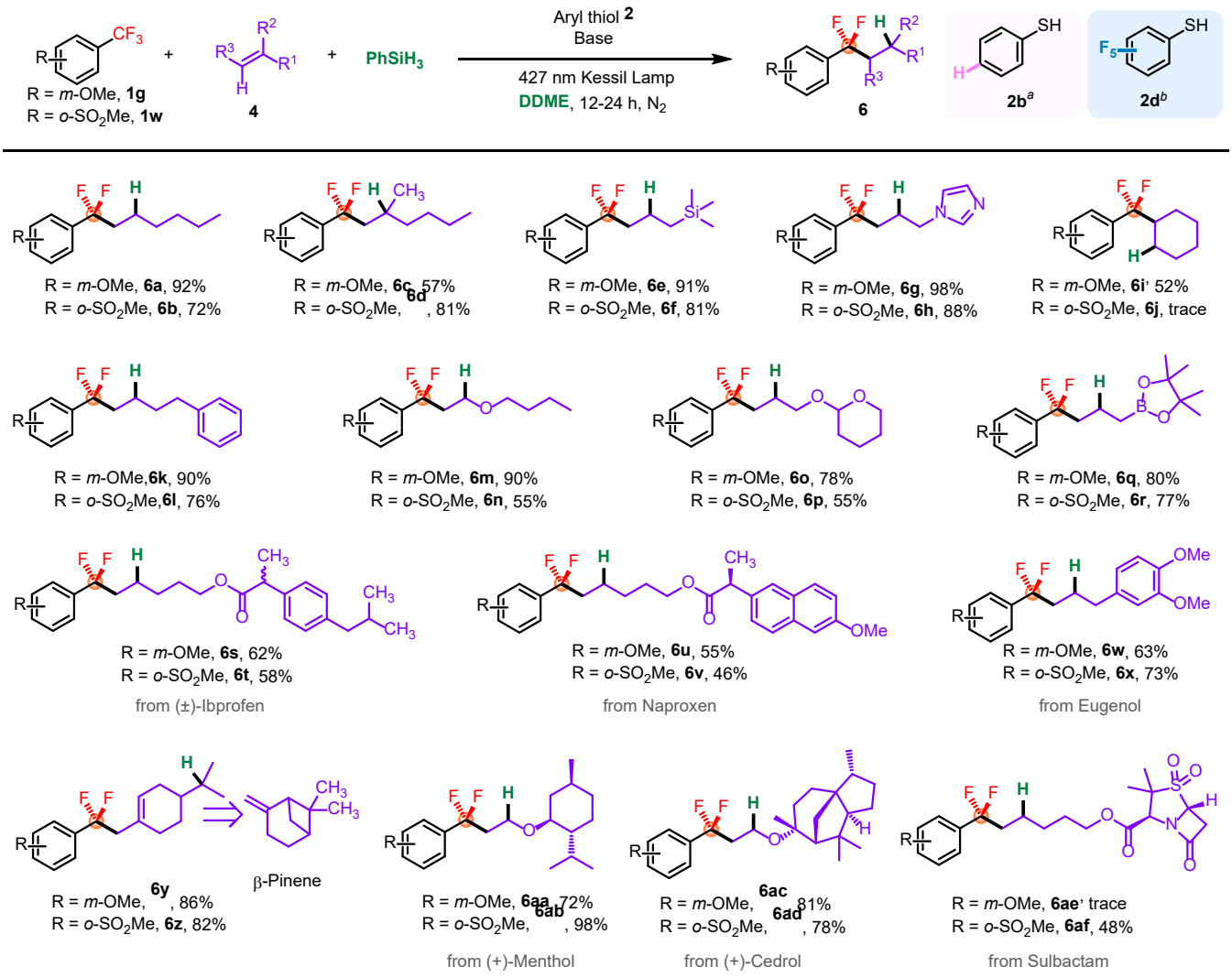
mmol), Na_2CO_3 (0.8 mmol), 24 h; [c]**1** (0.1 mmol), **2d** (0.02 mmol), $PhSiH_3$ (0.6 mmol), TMP (0.2 mmol), PMP (0.4 mmol), 24 h; [d]Determined by ^{19}F NMR using (trifluoro-methoxy)benzenes as an internal standard.



Scheme 4. Investigation on the Trifluoromethylarenes Scope of Defluoroalkylation of Trifluoromethylarenes. [a]Reaction conditions

(unless otherwise specified): **1** (0.6 mmol), **2** (0.3 mmol), **4** (3.0 mmol), $PhSiH_3$ (3.6 mmol), NaOH (1.2 mmol), DDME (3 mL), 427 nm Kessil Lamp, r.t., 12 h, N_2 atmosphere, isolated yields; [b]**1** (0.1 mmol), **2c** (0.04 mmol), **4** (0.6 mmol), $PhSiH_3$ (0.6 mmol), TMP (0.2 mmol), PMP (0.4 mmol), 24 h; [c]**1** (0.2 mmol), **2c** (0.08 mmol), **4** (1.2 mmol), $PhSiH_3$ (1.2 mmol), Na_2CO_3 (0.8 mmol), 24 h; [d]4-phenyl-1-butene as olefin; [e]**1** (0.1 mmol), **2d** (0.02 mmol), **4** (0.6 mmol), $PhSiH_3$ (0.6 mmol), TMP (0.2 mmol), PMP (0.4 mmol), 24 h.

According to the above results, when different substituted aryl thiols were used as reducing agents to participate in the hydrodefluorination, it can not only achieve an excellent activation effect, but also gain high expected yield. Consequently, we further attempted to apply this protocol to the defluoroalkylation of $ArCF_3$ (Scheme 4). A range of amino- substituted substrates, such as 1°, 2°, 3° amines and even diamino-substituted, engaged in this reaction smoothly to afford the expected products **5a**-**5d** in 53%-78% yields. $ArCF_3$ with electron-donating groups at different positions of the phenyl ring could also furnish this reaction successfully, providing the target products **5e**-**5q** in 43-90% yields. In addition, it is necessary to mention that acetal or boronate substituted substrates were also adaptable, delivering the corresponding products **5o** and **5p** in 69% and 43% yields, respectively. Meanwhile, $ArCF_3$ with heterocycles (pyridine, imidazole) were also examined to evaluate the generality of this defluoroalkylation, which could be smoothly converted into the corresponding products **5r**-**5t** in 61%-66% yields. Furthermore, several biologically active skeletons could be introduced to the $ArCF_3$ with moderate yields. Using cinacalcet (**5u**), derived glucose (**5v**) and trifluoroperazine (**5w**), we could easily alkylate them to their derived products in 46%, 65% and 67% yield, respectively. Their biological effects of different functionalizations have never been studied, but could have promising results with the increasing drug pools to potentially overcome drug resistance and to further achieve different functionalization of biological active molecules. As a general observation, the scope was also evaluated by decorating the phenyl ring with an array of electron-withdrawing substituents. The results indicated that various substituents were all applicable in this approach, and the effective defluorinated alkylation is performed in moderate to high yields, further highlighting the generality of this methodology (**5x**-**5af**).



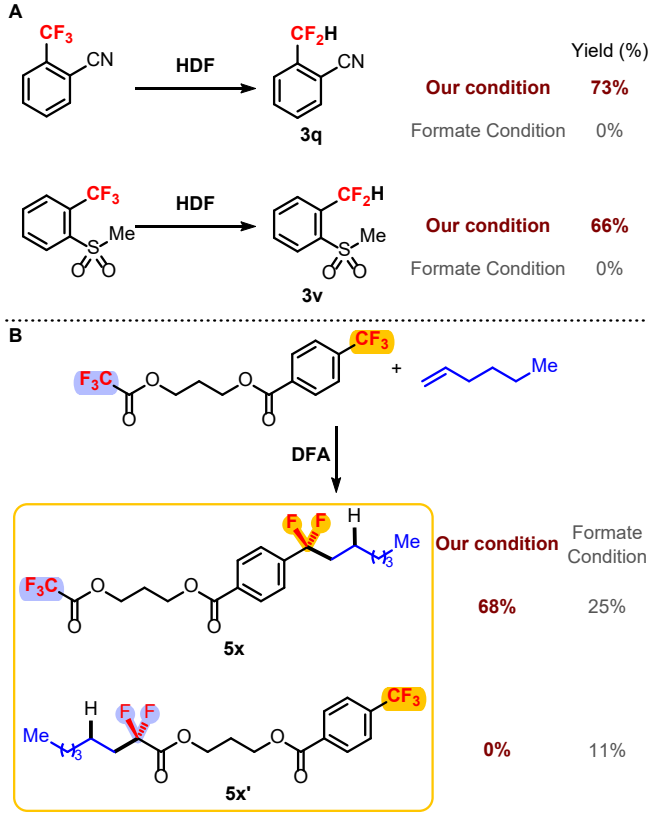
Scheme 5. Investigation on the Alkene Scope of the Defluoroalkylation of Trifluoromethylarenes. [a]Reaction conditions (unless

otherwise specified): **1** (0.6 mmol), **2b** (0.3 mmol), **4** (3.0 mmol), $PhSiH_3$ (3.6 mmol), NaOH (1.2 mmol), DDME (3 mL), 427 nm Kessil Lamp, r.t., 12 h, N_2 atmosphere, isolated yields; [b]**1** (0.1 mmol), **2d** (0.02 mmol), **4** (0.6 mmol), $PhSiH_3$ (0.6 mmol), TMP (0.2 mmol), PMP (0.4 mmol), 24 h.

Remarkably, dihydrocholesterol, as an important bioactive steroid, derivative of which could participate well in this defluoroalkylation process leading to target product **5y** in moderate yield. Aprepitant precursor could also proceed this protocol, allowing the facile formation of the defluoroalkylated product **5aa** in acceptable yield.

To further illustrate the utility of this defluoroalkylation protocol, the scope of olefins **4** was examined carefully using **1c** as an electron-donating substrate and **1ac** as an electron-withdrawing substrate (Scheme 5). Gratifyingly, inactive mono-substituted and disubstituted alkenes reacted with the trifluoromethylarenes delivered the desired products **6a**-**6d** in 57%-92% yields. TMS- or imidazole-substituted alkenes were also well tolerated, leading to the desired products **6e**-**6h** in 81-98% yield. Then, cyclohexene, as an internal cyclic alkene, was reacted with trifluoromethylarenes bearing *m*-methoxyl on the aromatic ring to afford the target product **6i** in 52% yield. When using the trifluoromethylarenes bearing *o*-sulfonyl on the aromatic ring as the substrate (**6j**), the results displayed unsatisfactory result, probably because of its steric hindrance. Homoallylbenzene has also proven to be a suitable partner for this defluoroalkylation, which could transfer to the corresponding products **6k** and **6l** in 76-90% yields. Several alkenyl ethers were also performed well, and the corresponding products **6m**-**6p** were isolated in 55–90% yields. The boronate group is a useful building block in organic synthesis, which could be compatible in the defluoroalkylation to access smoothly products **6q** and **6r** in 80% and 77% yields, respectively. Giving the significance of potential late-stage functionalization, we next turned our attention to drug fragments and natural product derivatives. The alkenyl moieties tethered to complex derived from (±)-ibuprofen,naproxen, eugenol, β-pinene, (+)-menthol and (+)-cedrol were smoothly transformed into the desired products **6s**-**6ad** in moderate to high yields. Notably, the reaction of *β*-pinene produced ring-opening products **6y** and **6z** in high yields, supporting the generation of *α*, *α*-difluoromethyl radical species. Although sulbactam is not ideal for electron-donating substrates due to the strong alkaline environment, the electron-withdrawing substrates can still be smoothly converted to 48% yield (**6af**). Among all of the substrates studied, over reduction has never been observed, indicating the chemospecificity of thiophenol based C-F bond reduction.

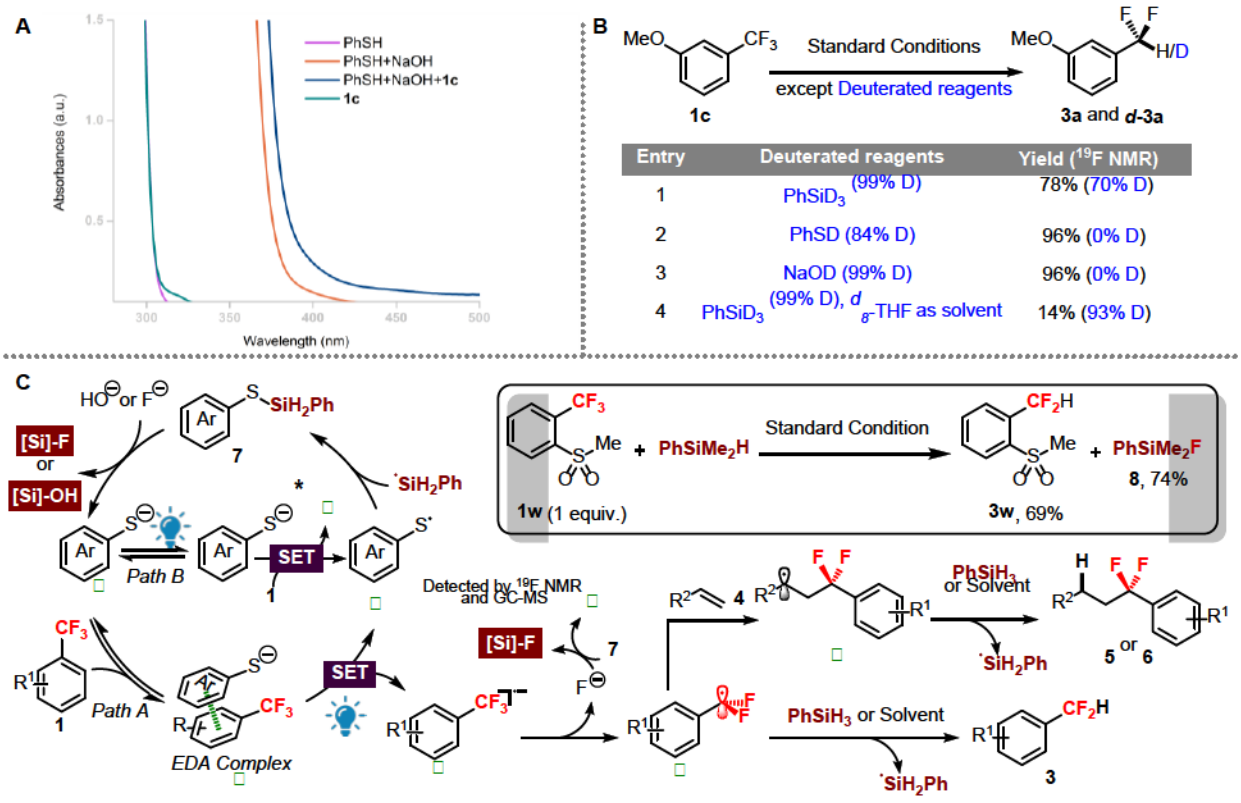
Although the arenethiolates have been studied to activate the C(sp^3)-F bonds to undergo hydrodefluorination (HDF) and defluoroalkylation (DFA),[13b] our method exhibits much broader substrate scopes and unique selectivity on the defluorination. As tabulated in Scheme 6, comparison experiments were be conducted. Gratifyingly, substrates with electron-deficient groups on the aromatic ring proceeded smoothly, providing the target products **3q** and **3v** in good yields. However, previous method's condition,[13b] using formate as the hydrogen source, did not provide any product **3q** and **3v** (Scheme 6A). affording over reduced products. Moreover, in previous literature,[13b] poor regioselectivity is observed between trifluoromethyl groups on aryl moiety (**5x**) and trifluoroacetate motif (**5x'**) in the defluoroalkylation process as both of them occur simultaneously in 25% and 11% respectively. In comparison, using 4-fluorobenzenethiol (**2c**) as the catalyst in our system, the trifluoromethyl on aryl moiety can only selectively defluorinated, retaining CF_3 group on the trifluoroacetate motif (**4x**) in 68% yield (Scheme 6B).



Scheme 6. Comparison experiments between this work and previous method on HDF and DFA reaction

The electron transfer process between arenethiolate (PhS^-) and **1c** was explored by UV-visible spectroscopic measurements (Scheme 7A). Absorption spectra of benzenethiol or substrate **1c** showed bands in the UV region (<300 nm). Moreover, PhS^- was observed to absorb light at 390 nm, performing a further significant redshift after the addition of **1c**. These results might support the formation of EDA charge-transfer complexes in this process. The similar result was also confirmed by our recent work.[18] Next, to gain more insights into the source of hydrogen, several deuteration experiments were conducted (Scheme 7B). When running the reaction with **1c** and $PhSiD_3$, the product *d*-**3a** with 70% D was observed in 78% yield. Additionally, the deuterated product *d*-**3a** was not observed when using neither PhSD nor NaOD to evaluate hydrogen sources. It is noteworthy that the deuterated rate was greater than 93% when both d_8-THF and $PhSiD_3$ were employed. The above experiments indicated that the hydrogen in the reaction comes from $PhSiH_3$ or solvent. Si-F bond related products could be observed through ^{19}F NMR and GC-MS using $PhSiMe_2H$ as the hydrogen source, which showed that silane might play a role in C(sp^3)–F bond cleavage of the reaction.[19] On the basis of the aforementioned results and previous reports, a plausible mechanistic pathway for this transformation is outlined in Scheme 7C. Initially, assisted by a base, ArS^- **I** was

generated, and reacted with $ArCF_3$ **1** to obtain EDA complex **II** (Path A). In spite of this, we cannot exclude the possibility of excited state chemistry (Path B). The thiyl radical **III** and aryldifluoromethyl radical anion **IV** were generated from EDA complex **II** via single electron transfer (SET) process with the irradiation of blue light. Next, the thiyl radical **III** was trapped by silyl radical to produce $ArSSiH_2Ph$ **7**, following regeneration of ArS^- **I** under the base condition. Thus, the by-products of Si-F bond product and Si-OH bond product were formed and identified by GC-MS and ^{19}F NMR spectrum (see Supporting Information Section 6.3 for more details). Subsequently, for the hydro-defluorination process, the α, α-difluoromethyl radical **V** could be directly captured by $PhSiH_3$ or solvent to obtain the target product **3**; for the defluoroalkylation process, the benzyl radical **VI** was generated by the capture of the α, α-difluoromethyl radical **V** by olefin **4**, followed by the reaction with $PhSiH_3$ or solvent, as H-atom donor, to access the target products **5** or **6**.



Scheme 7. Mechanism experiments

Conclusions

The half-peak potentials of 34 representative trifluoromethylarenes were obtained via cyclic voltammetry. Based on these data, a blueprint of different reduction potential thiophenols were selected accordingly to accomplish mono defluorination of trifluoromethylarenes via the photo-induced EDA strategy. Of note, an alternative hydrogen source of silane was investigated to overcome the existing limitation of formate. A variety of electron-donating and electron-withdrawing functional groups were well tolerated in this transformation. In particular, the precision of defluorination selectivity is efficient and effective, and almost no over-defluorination occurs. In this paper, 88 α, α-difluoromethyl compounds were synthesized. Mechanistic studies revealed that silane not only acts as a source of protons, but also assists the defluorination process. Aside from that, ether solvents can also be used as proton sources.

Author Contributions

S. Guo conceived the project. Y. Y. Jiang and C. X. Han performed the experiments. Z. P. Guo and G. C. Liang was responsible for DFT calculations. Y. Y. Jiang and C. X. Han analysed and interpreted the experimental data. All the authors discussed the results and contributed to the preparation of the final manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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