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Synthetic Methods

Iron-Catalyzed Fluoroalkylation of Arylborates with Sulfone Reagents: Beyond the Limitation of Reduction Potential

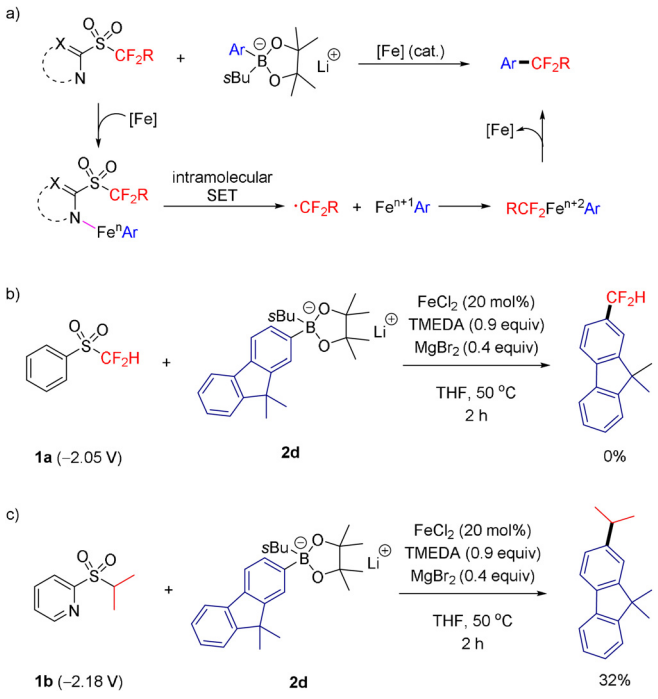
Zhiqiang Wei, Wenjun Miao, Chuanfa Ni, and Jinbo Hu**

Abstract: *The iron-catalyzed alkyl–aryl coupling reaction between sulfones and arylboron compounds has remained a challenge. We report the first iron-catalyzed radical difluoroalkylation of arylborates with N-heteroaryl sulfones. The coordination between the iron catalyst and the nitrogen atom of N-heteroaryl sulfones was identified to be important in overcoming the reduction potential limitation of sulfones in the intermolecular single-electron-transfer process, which enables both fluoroalkyl N-heteroaryl sulfones (with relatively high reduction potentials) and nonfluorinated alkyl N-heteroaryl sulfones (with low reduction potentials) to serve as powerful alkylation reagents.*

Single electron transfer (SET) reduction is a powerful approach to generate organic radical intermediates from various neutral organic substrates that are capable of accepting electrons, and has been extensively used in modern organic synthesis.[1] To facilitate the SET reduction of challenging systems, common strategies include modifying the electronic properties of the substrates or the reductants and taking advantage of ligand effect to modify the redox potential of the metal catalyst.[2] In addition, proton-coupled electron transfer (PCET) catalysis is also operative to promote the SET reduction of substrates that are otherwise difficult to reduce, and recently has been developed into a general mode of substrate activation.[3] However, the SET reduction of challenging substrates through their activation by coordination with metal catalyst has been little explored in organic synthesis,[4] despite the fact that a linkage between the oxidant and reductant reactants by a bridging ligand can accelerate the electron transfer reactions.[5]

Fluoroalkyl sulfones, a class of stable and easily accessible organofluorine compounds, have been widely used in selective fluoroalkylation of organic molecules.[6] In 2016, we reported the first example of using fluoroalkyl sulfones as fluoroalkyl radical precursors for efficient fluoroalkylation.[7] In 2018, we reported an iron-catalyzed radical difluoromethylation of diarylzincs using difluoromethyl 2-pyridyl sulfone.[8] Almost at the same time, the Baran group reported nickel-catalyzed fluoroalkylation of aryl zinc chlorides using 1-phenyl-1*H*-tetrazol-5-yl sulfones as fluoroalkyl radical precursors.[9] Nevertheless, the SET reduction of sulfones via metal coordination has never been revealed.

Difluoroalkylated compounds are widely used in the development of agrochemicals, pharmaceuticals, and other biologically important molecules,[10] and transition metal-catalyzed aromatic difluoroalkylation reactions have been emerging.[7–9,11–14] However, although arylboron compounds have been widely used in organic synthesis, metal- catalyzed difluoroalkylation of arylboron compounds has remained a challenging task.[8,9,15] With these considerations in mind, we aimed at developing an iron-catalyzed cross coupling between arylboron compounds and difluoroalkyl sulfones to address the synthetic challenge and to probe the role of metal coordination in the SET reduction of sulfones. We envisioned that if we enable an N-Fe coordination by using a difluoroalkyl *N*-heteroaryl sulfone (Scheme 1 a), an intramolecular SET



Scheme 1. Proposed single electron reduction of sulfones and proof-of-concept experiments.

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process from iron to sulfur could readily occur to give difluoroalkyl radical species ($^{\bullet}CF_2R$), which reacts with aryliron ($Fe^{n+1}Ar$) to form $RCF_2Fe^{n+2}Ar$. The latter intermediate undergoes reductive elimination to afford product Ar-CF_2R. Herein, we report our results on the first iron-catalyzed difluoroalkylation of arylborates with *N*-heteroaryl sulfones, which is facilitated by an additional coordination of sulfone to iron.

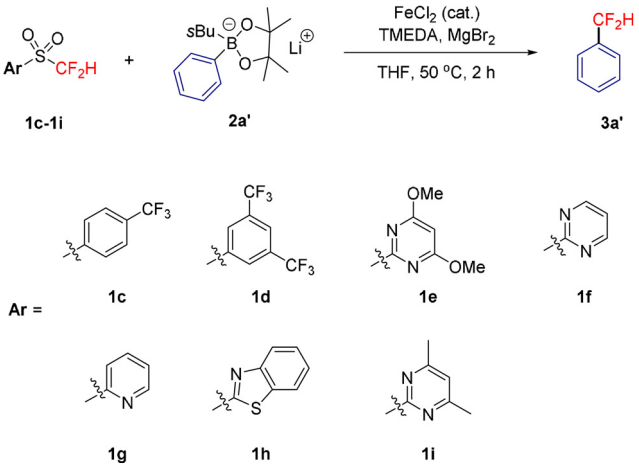
Initially, we attempted iron-catalyzed difluoromethylation of arylborates **2d** with difluoromethyl phenyl sulfone ($PhSO_2CF_2H$), no desired product was observed and $PhSO_2CF_2H$ (**1a**) remained (Scheme 1b).[16] However, in the case of isopropyl 2-pyridyl sulfone (**1b**), the reduction potential of which (−2.18 V vs. Ag/AgCl) is lower than that of $PhSO_2CF_2H$ (−2.05 V vs. Ag/AgCl),[17] the cross coupling product can be obtained in 32% yield (Scheme 1c). It indicates that this kind of cross coupling reaction goes beyond the limit of reduction potential of sulfones, which is distinctly different from our previously reported one-electron reduction of sulfones by the photocatalyst.[7] In other words, under certain conditions, a sulfone with lower reduction potential can undergo better radical cross coupling reaction than another sulfone with higher reduction potential does.

Next, we set out to synthesize various difluoromethyl (hetero)aryl sulfones **1c**–**1i**, and screened their reactivity in the iron-catalyzed cross-coupling reaction with lithium phenylborate **2a′** (Table 1; for more details, see SI).[18] It should be noted that in all cases, lithium phenylborate **2a′** is compatible with difluoromethyl sulfones **1**, and there was no observable consumption of **1** in the absence of $FeCl_2$ catalyst. In general, the yields are more closely related to the structure of *N*-heteroaryl moieties, but remarkably, much less related to the reduction potentials of sulfones **1c**–**1i**. For instance, the reduction potentials of sulfones **1c** (−1.68 V) and **1i** (−1.67 V) are almost the same, but their chemical behaviors are significantly different (Table 1, entries 1 and 7). Under the same conditions, the reaction with sulfone **1c** gave 15% yield of product **3a′** (with 43% of **1c** being recovered; entry 1), while that with sulfone **1i** gave 80% yield of **3a′** (with full consumption of **1i**; entry 7).[19] As their reduction potentials are similar, the reactivity difference between sulfones **1c** and **1i** supports our assumption that intermolecular N-Fe coordination (*yes* for **1i**, but *no* for **1c**) can play an important role in enhancing the intramolecular SET reactivity between iron and sulfur (as depicted in Scheme 1a).

With the standard reaction conditions in hand (Table 1, entry 7), we examined the substrate scope of this iron-catalyzed fluoroalkylation protocol. As shown in Scheme 2, under the iron catalysis, (fluoro)alkyl 4,6-dimethylpyrimidin-2-yl sulfones **1i**–**1o** were able to undergo efficient aromatic difluoromethylation, difluoroalkylation, and even non-fluorinated alkylation of lithium arylborates **2**, giving the corresponding (fluoro)alkylated products **3**. The reactions with lithium arylborates bearing *meta*- and *para*-substituents on the aryls gave good to excellent yields (**3a**–**3g**, **3q** and **3r**), whereas reactions with those bearing *ortho*-substituents on aryls gave medium yields of the corresponding products (**3s**). This reaction was also amenable to polysubstituted or fused ring-containing arylborates (**3e** and **3h**). Furthermore, lithium arylborates bearing morpholine (**3k**), amide (**3m**), C=C double bond (**3o**) and OTBS (**3g**) are all applicable in this iron-catalyzed reaction. This sulfone-mediated cross coupling reaction proceeds smoothly with substrates bearing a range of heterocyclic motifs, including benzpyrole (**3l**) and carbazole (**3i**). More importantly, this iron-catalyzed fluoroalkylation protocol enabled the difluoromethylation of biologically relevant compounds such as the estradiol (**3n**), *S*-citronellol (**3o**), and Vitamin E (**3p**). Previously, the Genicot group synthesized ^{18}F-labeled difluoromethyl benzothiazolyl sulfone, and used the sulfone reagent in ^{18}F-labeled difluoromethylation of aryl-substituted heterocycles.[20] We found that our iron-catalyzed fluoroalkylation reaction basically completed in about 1 h, and when the temperature rose to 60 °C, the yield did not change significantly. Hence, it is promising that our method can be expanded to synthesize ^{18}F-labeled products.

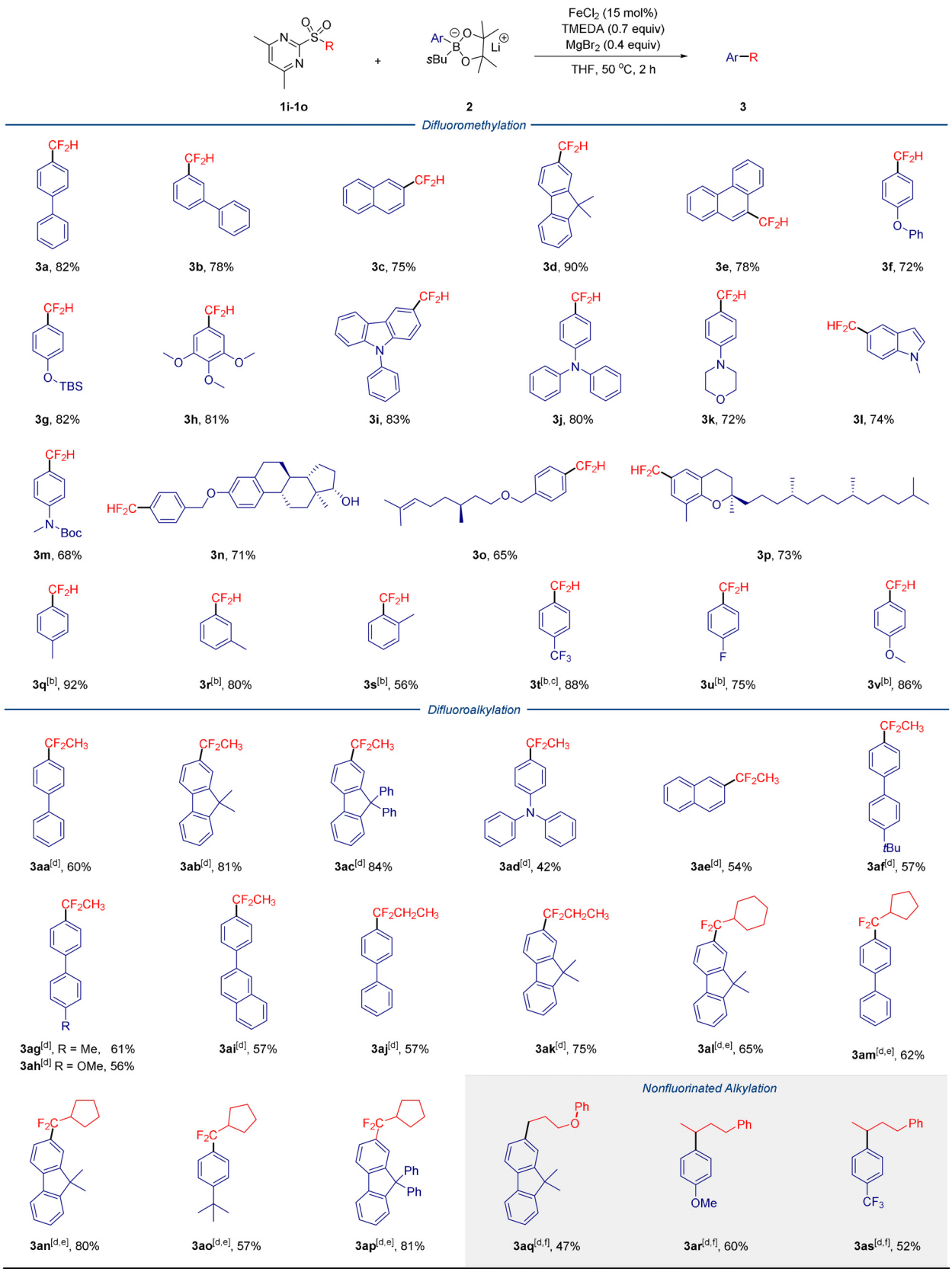
In addition to difluoromethyl (CF_2H) group, other difluoroalkyl groups are also useful for biologically important molecules. For instance, difluoroethyl (CF_2CH_3) moiety has been recognized as a bioisostere of the methoxy group.[21] Hence, we synthesized difluoroethyl 4,6-dimethylpyrimidin-2-yl (**1i**; for details, see SI) and successfully applied it in aromatic 1,1-difluoroethylation (**3aa**–**3ai**). Similarly, we also prepared other functionalized 1,1-difluoroalkyl 4,6-dimethylpyrimidin-2-yl sulfones (for details, see SI), and was pleased

Table 1: Screening the reactivity of various (hetero)aryl sulfones with different reduction potentials.[a]



Entry	1	*E* (V vs. Ag/AgCl)[b]	Yield [%][c]	Conversion of 1 [%][c]
1	**1c**	−1.68	15	57
2	**1d**	−1.48	37	>99
3	**1e**	−1.73	52	70
4	**1f**	−1.57	71	>99
5	**1g**	−1.80	54	75
6	**1h**	−1.27	51	>99
7	**1i**	−1.67	80	>99

[a] Reaction conditions: **1** (0.5 mmol, 1.0 equiv), **2a'** (0.85 mmol, 1.7 equiv), $FeCl_2$ (0.15 equiv), TMEDA (0.7 equiv), $MgBr_2$ (0.4 equiv), THF (10.0 mL). [b] E refers to the reduction potential using Ag/AgCl as reference. [c] Determined by ^{19}F NMR spectroscopy using trifluoromethoxybenzene as an internal standard.



Scheme 2. Iron-catalyzed alkylation of lithium arylborates with 4,6-dimethylpyrimidin-2-yl sulfones.[a] [a] Unless otherwise mentioned, the yields refer to isolated yields, and the reaction conditions are: **1i** (0.5 mmol, 1.0 equiv), **2** (0.85 mmol, 1.7 equiv), and THF (10.0 mL). [b] Determined by ^{19}F NMR spectroscopy using trifluoromethoxybenzene as an internal standard. [c] Reaction time was 3 h. [d] **1j–1n** (0.3 mmol, 1.0 equiv), **2** (0.6 mmol, 2.0 equiv), THF (6.0 mL). [e] The reaction was stirred at 40 °C for 4 h. [f] 20 mol% of $FeCl_2$ and 0.9 equiv of TMEDA were used.

to find that these sulfone reagents were able to undergo efficient aromatic 1,1-difluoroalkylations (**3aj**–**3ap**). To our surprise and joy, we found that this iron-catalyzed, and 4,6-dimethylpyrimidin-2-yl sulfone-enabled method was also able to install *nonfluorinated* alkyl groups onto aromatic rings (**3aq**–**3as**), which features the broad applicability of this new synthetic method.

To gain mechanistic insights into this reaction, we carried out several experiments to probe the N-Fe coordination between the iron catalyst and 4,6-dimethylpyrimidin-2-yl reagents. Firstly, NMR study was conducted on difluoromethyl 4,6-dimethylpyrimidin-2-yl sulfone (**1i**) in the presence of $FeCl_2$. One equivalent of **1i** was added into the pregenerated 1:1 complex of TMEDA and $FeCl_2$ in dichloromethane. After removal of the volatile in vacuo and washing with hexane, the residue was purified by dissolving in $CDCl_3$, filtering to remove solid impurities, and removing $CDCl_3$ in vacuo to give a white solid. Its $CDCl_3$ solution is very sensitive towards air, leading to the ready formation of a brown solid and free **1i**. Fortunately, it can be characterized by NMR spectroscopy in a well-sealed NMR tube. ^{1}H NMR analysis showed that there is no TMEDA in the so-obtained white solid, indicating that **1i** could completely exchange with TMEDA to afford a new iron complex. Moreover, both the *N*-heteroaryl-hydrogen (from δ 7.31 to δ 7.45) and the methyl-hydrogen (from δ 2.64 to δ 2.70) of **1i** shifted downfield (Figure 1), which was in accordance with the deshielding effect caused by the coordination of iron to nitrogen on the *N*-heteroaryl ring.

Secondly, competition experiments between 4,6-dimethylpyrimidin-2-yl sulfones **1i** and **1p** were per formed at different temperatures (Table 2). As monitored by ^{19}F NMR, the two sulfones of similar structure were consumed at the similar rate, despite the significant difference of their reduction potentials (**1i**, −1.67 V vs. Ag/AgCl; **1p**, −1.90 V vs. Ag/AgCl). These results demonstrate the generality of the reduction of 4,6-dimethylpyrimidin-2-yl sulfones by the in situ formed aryliron species. Furthermore, the ready reduction of sulfone **1p** supports the importance of N-Fe coordination in facilitating the single electron transfer from aryliron species to sulfones that are otherwise difficult to reduce.

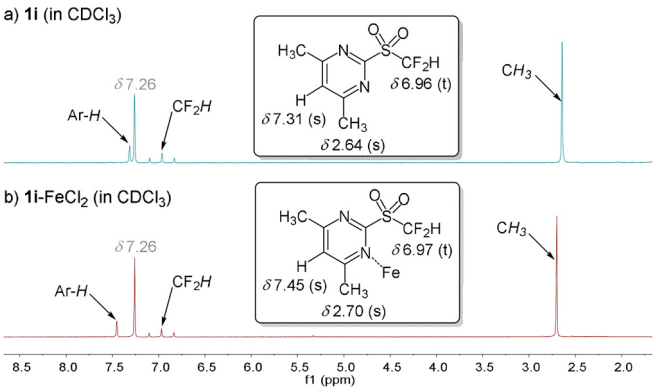
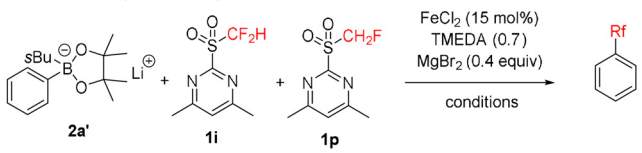


Figure 1. ^{1}H NMR study of **1i**-$FeCl_2$ complex. a) ^{1}H NMR of **1i**; b) ^{1}H NMR of **1i**-$FeCl_2$.

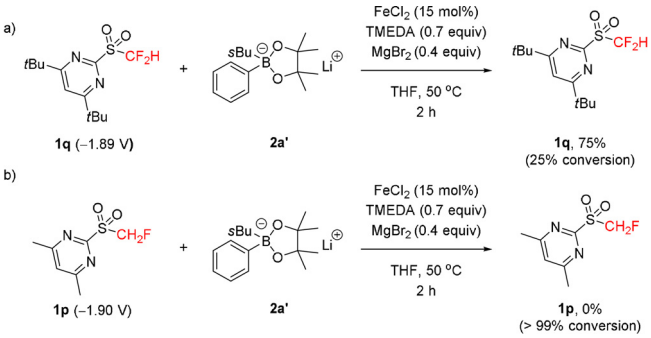
Table 2: Competition experiments with **1i** and **1p**.[a]



Entry	Conditions	1	*E* (V vs. Ag/AgCl)	Conversion of 1 [%][b]
1	50 °C, 2 h	**1i**	−1.67	60
		1p	−1.90	57
2	rt, 10 h	**1i**	−1.67	15
		1p	−1.90	16

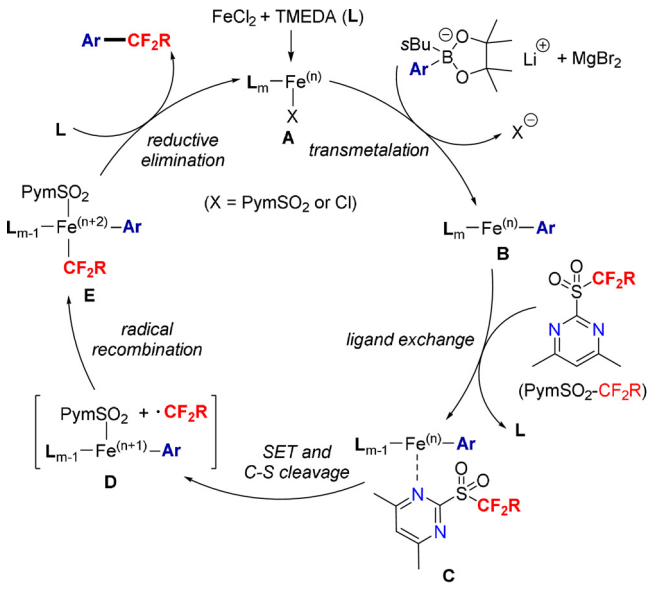
[a] Reaction conditions: **1i** (0.5 mmol, 1.0 equiv), **1p** (0.5 mmol, 1.0 equiv), **2a′** (1.0 mmol, 2.0 equiv), THF (10.0 mL). [b] Determined by ^{19}F NMR spectroscopy using trifluoromethoxybenzene as an internal standard.

Thirdly, sterically hindered difluoromethyl 4,6-di-*tert*-butylpyrimidin-2-yl sulfone (**1q**, −1.89 V vs. Ag/AgCl) was designed as a prober and its reduction by iron species was investigated (Scheme 3a). The reduction of less sterically demanding 4,6-dimethylpyrimidin-2-yl sulfone that is of similar reduction potential (**1p**, −1.90 V vs. Ag/AgCl) was performed separately under the same conditions (Scheme 3b). The observed much lower conversion rate of sulfone **1q** than that of **1p** suggests that the steric hindrance can inhibit the reduction of sulfone by blocking the N-Fe interaction.



Scheme 3. Effect of steric hindrance.

Based on the above-mentioned experimental results and previous investigations,[8] we propose the following reaction mechanism (Scheme 4). Initially, catalytically active low-valent iron species **A** is formed through the interaction between $FeCl_2$ and TMEDA in the presence of lithium arylborate. Then, a highly redox-active iron intermediate **C** is generated via N-Fe coordination between a sulfone reagent (such as 4,6-dimethylpyrimidin-2-yl sulfone) and aryliron species **B**. Subsequently, intramolecular single electron transfer (SET) from iron to sulfur (inner sphere electron transfer)[5] readily occurs to produce aryliron species **D** and an sp^3-carbon radical in very close proximity, the efficient recombination of which affords the high-valent iron intermediate **E**. Finally, TMEDA-promoted reductive elimination leads to the formation of the desired product and regeneration of the low-valent iron species **A**.



Scheme 4. Proposed reaction mechanism.

In summary, we have developed a novel iron-catalyzed alkylation of arylborates with sulfones. This method can use both difluoroalkyl and nonfluorinated alkyl *N*-heteroaryl sulfones as the sp^3-carbon radical sources to construct various alkylated aromatics. More importantly, we have shown that the coordination of low-valent iron to the nitrogen atom of *N*-heteroaryl sulfones can overcome the reduction potential limitation in intermolecular electron transfer process, thus enabling sulfones of low reduction potentials to efficiently participate in radical cross-coupling. Our work not only provides a useful protocol for organic synthesis, but it also gives new insights into single electron transfer chemistry. Further study in this direction is underway in our laboratory.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: arylborates · fluoroalkylation · iron catalysis · reduction potential · sulfones

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[16] Reaction conditions: difluoromethyl phenyl sulfone (0.5 mmol, 1.0 equiv), lithium arylborate (1.0 mmol, 2.0 equiv), $FeCl_2$ (0.1 mmol, 0.20 equiv), TMEDA (0.45 mmol, 0.9 equiv), $MgBr_2$ (0.2 mmol, 0.4 equiv), THF (10.0 mL), 50 °C, 2 h.
[17] For the measurement of reduction potentials, see the "Cyclic Voltammetry Study" part in the Supporting Information (SI).
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