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Iron-Catalyzed Halogen Exchange of Trifluoromethyl Arenes**

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Abstract: The facile production of $ArCF_2X$ and $ArCX_3$ from $ArCF_3$ using catalytic iron(III)halides is reported, which constitutes the first iron-catalyzed halogen exchange for non-aromatic C–F bonds. Theoretical calculations suggest direct activation of C–F bonds by iron coordination. $ArCX_3$ and $ArCF_2X$ products of the reaction are synthetically valuable due to their diversification potential. In particular, chloro- and bromodifluoromethyl arenes ($ArCF_2Cl$, $ArCF_2Br$ respectively) provide access to a myriad of difluoromethyl arene derivatives ($ArCF_2R$). To optimize for mono-halogen exchange, a statistical method called Design of Experiments was used. Optimized parameters were successfully applied to electron rich and electron deficient aromatic substrates, and to the late stage diversification of flufenoxuron, a commercial insecticide. These methods are highly practical, being run at convenient temperatures and using inexpensive common reagents.

C–F bonds impart desirable features to a molecule, such as chemical inertness and increased lipophilicity.[1] As such, fluorinated moieties continue to play a critical role in the modern pharmaceutical, agrochemical and materials chemistry fields, and are of longstanding synthetic interest to organic chemists.[2] A prominent example, the trifluoromethyl group (CF_3) is present in 24% of drugs globally approved in 2019.[3]

The selective conversion of C–F bonds to C–H or C–C bonds in polyfluorinated molecules has enjoyed increased focus as a strategy to access challenging fluorination patterns.[4] A related transformation is the conversion to higher halide C–X bonds (X = Cl, Br, I), through halogen-exchange (halex) reactions.[5,6] These larger halides are versatile synthetic handles, with heightened reactivity over the parent fluoride.

Halex reactions on fluorinated substrates are typically performed with stoichiometric early valent metal halides (TiX_4, $MoCl_5$), or p-block metalloid halides (BX_3, AlX_3, R_3SiX).[7] These halide reagents provide the necessary thermodynamic drive through formation of a strong fluoride bond (e.g. SiF_4 166 kcal mol^{-1}, BF_3 170 kcal mol^{-1})[8] However, additional catalysts are necessary to avoid high temperatures and long reaction times.

Iron, being a low-cost high abundance metal, has been surprisingly absent in catalytic defluorination development. The potential of iron catalysis in this field is nevertheless exemplified in enzymes such as horseradish peroxidase (Hrp), methane monooxygenase (Mmo) and cytochrome P450s (Cyp), all employing iron-based catalytic motifs, which perform catalytic defluorination along with oxygenation (Figure 1a).[9]

To our knowledge only one precedent exists for iron-catalyzed halogen exchange of C–F bonds: chlorination of perfluorinated benzenes (Figure 1b).[10]

The following work constitutes the first example of iron-catalyzed halogen exchange of non-aromatic C–F bonds, and to our knowledge the first halogen-exchange with mechanistic

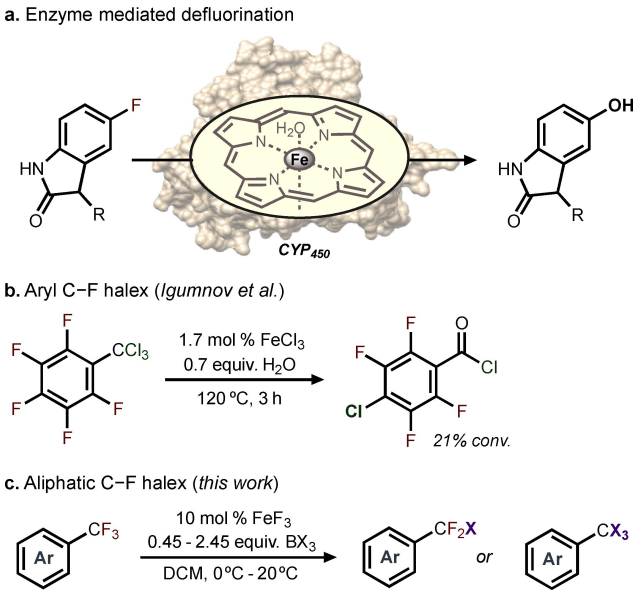

Figure 1. a) Cyp_{450}-catalyzed defluorination and concurrent hydroxylation.[9b] b) Prior iron-catalyzed aryl C–F halogen-exchange.[10] c) Iron-catalyzed benzylic C–F halogen-exchange described herein.

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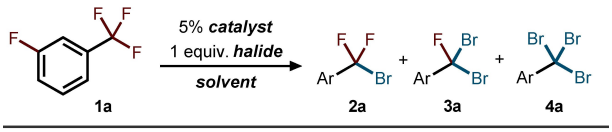
evidence for iron coordination and direct activation of a C–F bond. This method was applied and optimized for medicinally relevant $ArCF_3$ substrates (Figure 1c).

We explored a variety of halophilic Lewis acidic transition metal complexes in the presence of BBr_3 and trifluoromethyl (*m*-fluoro)benzene **1a**. In the absence of a catalyst, the known background reaction provides compound **2a** at 7% conversion (Table 1, entry 1).[6d] While silver(I), copper(I), iron(0) and iron(II) showed no improvements on C–F exchange efficiencies (entries 2–5), iron(III) and gallium(III) compounds accelerated the halex process (entries 6–10), generating tribrominated product **4a** at 83–91%. Interestingly, the identity of the halide on the iron(III) center did not affect the reaction significantly.

Ensuing investigations were performed with iron(III)fluoride. Solvent selection proved important (Table 1, entries 11–13), possibly due to the varying solubility of the iron(III)fluoride reagent. However, it should be noted that the iron complex showed a distinct increase in solubility upon boryl halide addition (see Figure S5, S15 in Supporting Information). Nitromethane coordination with BBr_3 was also observed in the ^{11}B NMR spectrum, and this interaction is suspected to mitigate reactivity.

Table 1. Screening Investigations.



entry	catalyst	halide	solvent	2a (%)	4a (%)	CF_{total} (%)[a]
1		BBr_3	DCM	7	*nd.*	7
2	AgBr	BBr_3	DCM	8	*nd.*	9
3	CuI	BBr_3	DCM	7	*nd.*	8
4	$Fe(CO)_5$	BBr_3	DCM	7	*nd.*	8
5	$FeCl_2$	BBr_3	DCM	6	*nd.*	7
6	$FeCl_3$	BBr_3	DCM	4	89	272
7	$FeBr_3$	BBr_3	DCM	5	83	256
8	FeF_3	BBr_3	DCM	5	83	255
9	$Fe(OTf)_3$	BBr_3	DCM	*tr.*	91	*273*
10	$Ga(OTf)_3$	BBr_3	DCM	*tr.*	83	*249*
11	FeF_3	BBr_3	heptane	*tr.*	*nd.*	*tr.*
12	FeF_3	BBr_3	PhCl	14	*tr.*	27
13	FeF_3	BBr_3	$MeNO_2$	*nd.*	*nd.*	*nd.*
14[b]	FeF_3	Me_2BBr	DCM	21	35	128
15[b]	FeF_3	(cat)BBr	DCM	*tr.*	*nd.*	*tr.*
16[c]	$FeCl_3$	BCl_3	DCM/NO_2Me	*tr.*	*75*	226
17[d]	FeF_3	BBr_3	DCM	*nd.*	*95*	284
18[e]	FeF_3	BBr_3	DCM	12	*nd.*	15

Reactions performed at 1.0 mmol scale, 0.2 M molarity, 20 °C, and 5 h. Conversions determined by ^{19}F NMR (relative to 4-fluorotoluene internal standard). **3a** was trace in all entries (< 3% conversion). *cat* = catechol. *nd.* = not detected. *tr.* = trace. [a] C–F_{total} refers to the molar fraction of C–F bonds converted to C–X bonds. [b] 3 equiv. R_2BBr used. [c] Chlorinated products formed ($ArCCl_3$ instead of **4a**). Conditions: DCM/NO_2Me (4:1), 0.6 equiv. $FeCl_3$, 4 equiv. BCl_3, 30 °C, 16 h. [d] Conditions: 10 mol% FeF_3, 1.5 equiv. BBr_3, 14 h. [e] Performed at −10 °C.

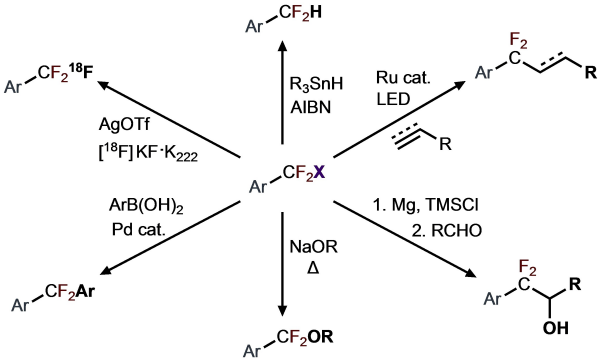


Figure 2. Transformations of $ArCF_2X$ (X = Br, Cl) reported in the literature.[12]

Different boryl halides were also competent in the halex reaction (entries 14–16), although these reactions were slow relative to those with BBr_3. When employing BCl_3, higher catalyst loadings enabled a high total C–F conversion and generation of the trichloromethyl arene as the sole product (entry 16). Tribromomethyl arene **4a** could also be obtained as a single product, using excess BBr_3 and an extended reaction time (entry 17).

Trihalomethyl arenes can be used in a number of synthetic applications, including conversion to carboxylic acids/esters, alkynes and alkenes, and to generate heterocycles.[11,6b] Accordingly, we envision this operationally-simple method to be quite useful, given the prevalence of trifluoromethyl groups in high-profile compounds.

However, there remained potential to optimize a single halogen-exchange, generating compound **2a**. In addition to unique intrinsic properties, such as increased capacity for halogen bonding, $ArCF_2X$ compounds are common intermediates for redox and cross-coupling reactions that generate a range of high value difluoro derivatives ($ArCF_2R$, Figure 2).[12,13]

Optimizing a single halogen exchange on a trifluoromethyl center is a challenge, as the C–F bond strength decreases with each fluorine removal.[14] Encouragingly, lowering of the reaction temperature increased conversion to $ArCF_2Br$ (**2a**) relative to $ArCBr_3$ (**4a**) (entry 18). This observation indicated that appropriate reaction tuning could provide synthetically viable amounts of $ArCF_2Br$.

The kinetic complexity of the mono-halex reaction led us to use the statistical method Design of Experiments (DOE) for optimization. DOE uses regression analysis to generate a mathematical model of a reaction outcome as a function of defined reaction parameters (variables).[15] The model developed is tailored to the reaction space defined by the chosen parameters. The relative importance of each parameter, as well as interaction effects between parameters is determined by analysis of variance (ANOVA).

We first performed a 5-variable fractional factorial DOE to evaluate main linear effects, followed by a response surface design, a more predictive model that accounts for non-linear effects. Evaluation of data normalcy, R^2 fit, $R^2_{predicted}$ (a leave-one-out cross-validation test for over-fitting), and analysis of error

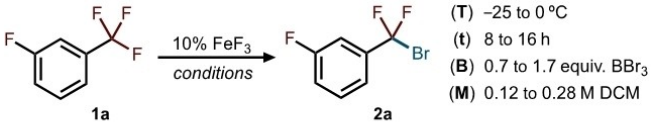
versus reaction order (test for systematic experimental error), indicated a well-fitted model for $ArCF_2Br$ conversion. Additional test points demonstrated experimental conversions comparable to those predicted by the model (see Table S6 in Supporting Information).

The significance of each variable in the DOE model is shown in the Pareto chart depicted in Figure 3. Such information can reflect mechanistic nuance. Temperature was found to have a strong correlation with $ArCF_2Br$ conversion, as well as a significant interaction effect with BBr_3. Figure 4 shows the parabolic shape of the temperature variable with a maximum at −3 °C.

Surprisingly, time was not a highly significant variable to the model, as shown by the shallow slope in Figure 4 and Pareto values in Figure 3 (see Supporting Information for other surface plots). These results suggest that optimal conversion is more complex than identifying a time point where a statistical mixture of products favors $ArCF_2Br$.

The DOE model predicted conditions for a maximum conversion to $ArCF_2Br$ **2a** of 25%. Experimentally, these conditions resulted in 27% conversion, slightly outperforming the model (Scheme 1, **2a**).

Given optimized reaction parameters for meta-fluoro substrate **1a**, we sought to apply conditions favoring $ArCF_2X$ formation to a selection of substrates (Scheme 1). The reaction was observed to progress more rapidly with electron-rich aromatic complexes, which was easily compensated for with shorter reaction times. Gratifyingly, similar conversions to the desired $ArCF_2Br$ could be obtained for most substrates examined. For compounds with Lewis basic functionalities, additional equivalents of BBr_3 were necessary (**2i**, **2j**, **2k**). Substitution at ortho, meta, and para positions,



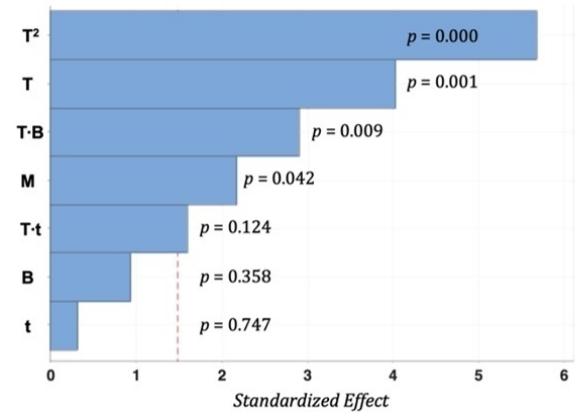


Figure 3. Pareto chart with *p*-values for a response surface model of **2a** conversion. The red dotted line is the standardized effect *t*-value determined by significance level $\alpha = 0.15$, where α is the probability of obtaining a false positive on a statistical test.

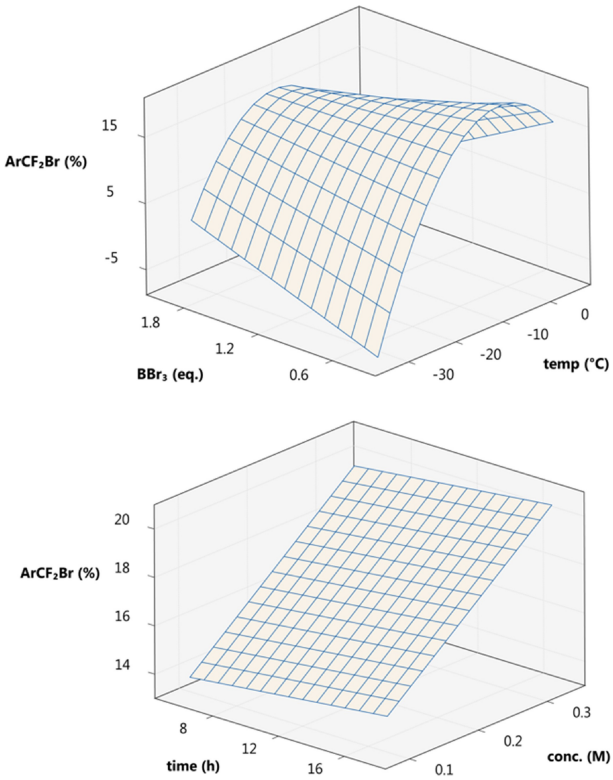
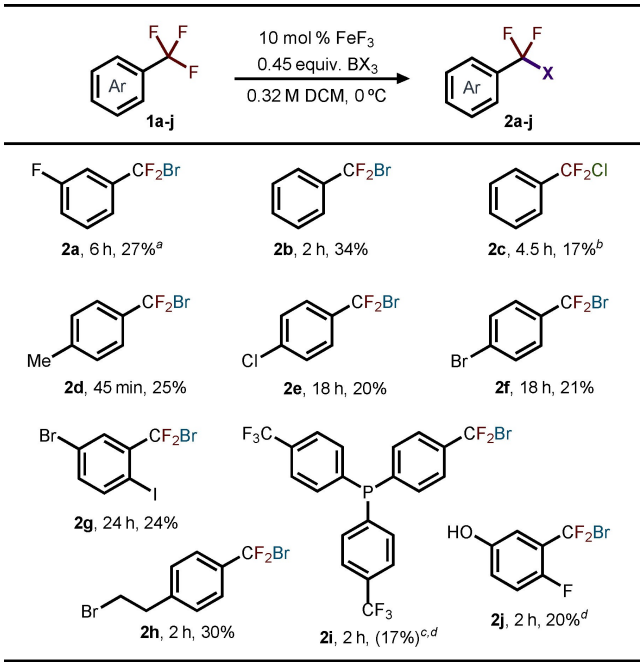


Figure 4. Surface plots from the DOE model. [Above] $ArCF_2Br$ conversion as a function of BBr_3 equivalents and temperature (constants: time = 12 h, concentration = 0.2 M). [Below] $ArCF_2Br$ conversion as a function of time and concentration (constants: BBr_3 = 1.2 equivalents, temperature = −12.5 °C).



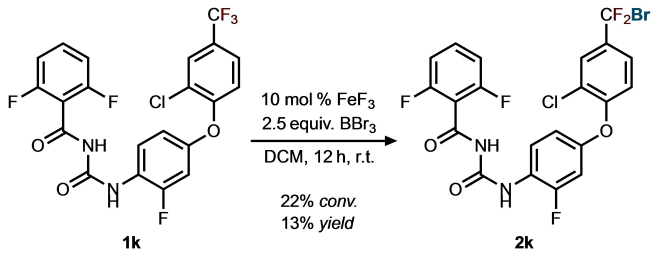
Scheme 1. Scope investigations for the mono-halex of trifluoromethyl arenes (0.40 mmol scale). Conversions determined by ^{19}F NMR (relative to 4-fluorotoluene), isolated yields in parentheses. [a] Performed at −3 °C. [b] Conditions: 0.20 M NO_2Me/DCM (2:1), 0.6 equiv. $FeCl_3$, 1.7 equiv. BCl_3, 10 °C. [c] $Fe(OTf)_3$ used (in place of FeF_3). [d] 1.45 equiv. BBr_3 used.

including halides, alkyl, and hydroxy groups were all well tolerated. Chlorination was also achieved using similar conditions (compound **2c**). Isolation of the $ArCF_2X$ products was performed using reverse-phase HPLC. Small molecule substrates (for which high volatility affected isolated yields) are reported as conversions, with additional characterization by GC-MS (see Supporting Information).

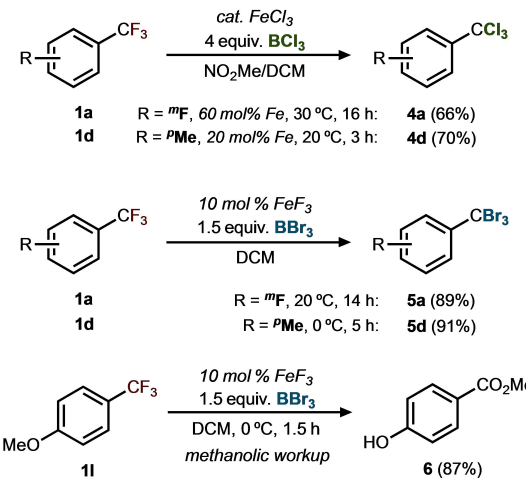
To our delight, phosphine **1i** was converted to desymmetrized mono-brominated compound **2i** in 17% isolated yield, despite 9 fluorines which can participate in the halex reaction. With substrate **1h**, no evidence of styrene derivatives or Friedel-Crafts alkylation arising from iron(III) activation of the alkyl bromide side chain was observed. Further, a commercial insecticide flufenoxuron (**1k**), was converted to mono-brominated derivative **2k** in 21% conversion and 13% yield (Scheme 2).

Under triple-halex conditions, both trichloro- (**4a**, **4d**) and tribromomethyl arenes (**5a**, **5d**), as well as compound **6**, were generated from substrates **1a**, **1d** and **1l**, respectively, with high isolated yields (66–91%; Scheme 3). Compound **6** results from rapid hydrolysis/methanolysis of the tribromomethyl group during workup procedures. These substrates demonstrate that electron-deficient and electron-rich arenes are similarly competent in triple halogen-exchange reactions.

At the outset of our mechanistic investigations, both heterogeneous and homogeneous catalysis appeared plausible in this system. Theoretical calculations were used to evaluate



Scheme 2. Halogen exchange with a commercial insecticide flufenoxuron.



Scheme 3. Isolated yields of trihalomethyl arenes produced via triple-halex.

the viability of a homogeneous process, given the high degree of solubilization of the iron complexes in the presence of the boron trihalide reagents. Further, should a homogeneous process appear reasonable, we wished to shed light on a potential role of the iron catalyst in the mechanism. Using unrestricted Kohn-Sham density functional theory B3LYP/6-31G**,[16] coordination energies between $PhCF_3$ **1b**, BBr_3, and FeF_3 were determined in dimeric and trimeric orientations. An analogous evaluation was performed with $PhCF_3$, BCl_3, and $FeCl_3$ for comparison (see Supporting Information).

The lowest dimeric coordination energy observed was between $PhCF_3$ and FeF_3 at $-7.62\ kcal\,mol^{-1}$ (Figure 5). This interaction is predicted to stretch the coordinated C–F bond by approximately 0.1 Å. In contrast, the binding energy of $PhCF_3$ and BBr_3 is predicted to be uphill by $7.01\ kcal\,mol^{-1}$. ^{19}F NMR experiments support these calculations and provide evidence for solution activation of the C–F bond. The fluorine signal in $PhCF_3$ is shifted downfield by 2.5 ppm in the presence of $FeCl_3$, whereas BCl_3 only elicits a downfield shift of 0.2 ppm (CD_2Cl_2).

The lowest energy trimers ($PhCF_3$, BBr_3 and FeF_3) have interactions dominated by $PhCF_3$ and FeF_3 binding, with the lowest energy trimer at $-0.78\ kcal\,mol^{-1}$ relative to the monomers. Therefore, while iron activation of the boron tribromide remains a valid mechanistic possibility, calculations and NMR experiments suggest direct interaction with $PhCF_3$ is energetically favorable and weakens the C–F bond.

Dimers of iron halides (Fe_2F_6 and Fe_2Cl_6) were also evaluated for their coordinating affinity for either the $PhCF_3$ substrate or the boron trihalide (BBr_3 and BCl_3, respectively, see Supporting Information).

Figure 6 shows plausible mechanisms based on these data. The nucleophilic bromide is likely delivered from a boron halide complex, as the identity of the boron halide reagent determines the major halex product. Subsequent transfer of the fluoride from the iron to the boron center is required for the process to be exergonic overall (1st Br exchange: $-25.74\ kcal\,mol^{-1}$ B3LYP/6-31G**),[17] and this is corroborated by the experimental observations of gas evolution (BF_3) and a disappearance of the ^{11}B NMR signal. This also highlights that ligand exchange between iron(III)fluoride and boron trihalides is facile under the reaction conditions, which is further supported by ^{19}F NMR experiments (see Supporting Information), so heteroleptic iron complexes likely play an important mechanistic role.

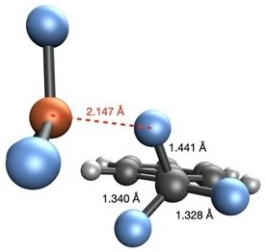


Figure 5. Computed geometries & bond lengths for FeF_3 coordination to $PhCF_3$.

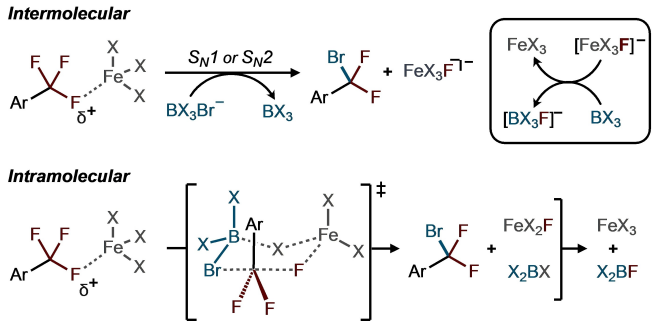


Figure 6. Plausible mechanisms for the halex reaction.

In conclusion, we have demonstrated that ferric halides catalyze halogen exchange between trifluoromethyl arenes and boron halides. While initially developed conditions favor full exchange of benzylic fluorides, providing $ArCX_3$ products, DOE analyses provided conditions that maximize mono-exchange to generate $ArCF_2X$ products in synthetically viable yields. Substrate scope investigations demonstrated successful application to electron-deficient and electron-rich arenes, with good functional group tolerance. The reaction is eminently practical, using inexpensive, readily available reagents and run at easily maintained temperatures.

Notably, mechanistic insight from computational analyses suggests that ferric halides may be direct activators of the C–F bond, which has important implications for future C–F activation methodology development.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: C–F activation · defluorination · halogen exchange · iron catalysis · late-stage modification

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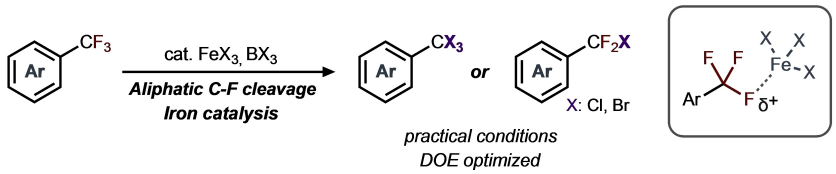

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The production of synthetically valuable $ArCF_2X$ and $ArCX_3$ compounds from $ArCF_3$ using catalytic iron(III)halides is described, which constitutes the first iron-catalyzed halogen exchange of non-aromatic C–F bonds. Theoretical calculations suggest direct activation of C–F bonds by iron coordination. To optimize for mono-exchange, a statistical analysis called Design of Experiments was used. Optimized parameters were successfully applied to both electron-rich and electron-deficient aromatic substrates, and to the late-stage diversification of flufenoxuron, a commercial insecticide.