Concise Report

pentafluoroethylation, arenediazonium salt, tetrafluoroethylene, copper, perfluoroalkylation, Sandmeyer-type reaction

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Pentafluoroethylation of Arenediazonium Tetrafluoroborates Using On-Site Generated Tetrafluoroethylene[†]

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Summary of main observation and conclusion Copper-mediated pentafluoroethylation of arenediazonium tetrafluoroborates with tetrafluoroethylene (TFE) on-site generated from $TMSCF_3$ has been developed as a new method to prepare pentafluoroethyl arenes. The active pentafluoroethylation reagent "CuC_2F_5" is pre-generated from CuSCN, TFE and CsF, and its generation and further reaction are strongly solvent-dependent. This pentafluoroethylation reaction represents the first example of Sandmeyer-type pentafluoroethylation, which exhibits good functional group tolerance and potential applications for the synthesis of complicated bioactive compounds.

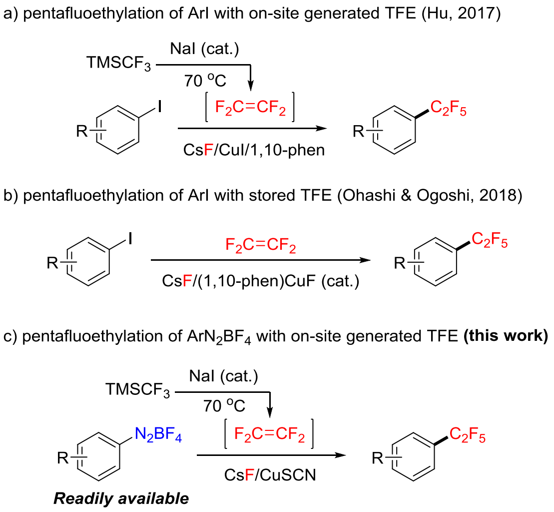
Background and Originality Content

Perfluoroalkylated compounds are of great interest in pharmaceutical, agrochemical and material research and industry.[1] In this context, numerous efforts have been devoted to developing novel methods for the introduction of trifluoromethyl group (CF_3) into organic aromatic compounds.[2] However, the similar pentafluoroethylation processes are still underexploited.[3-6] Currently available aromatic pentafluoroethylation methods mainly rely on transition-metal-mediated cross-coupling of aryl halides[3] or arylboron compounds,[4] and C—H functionalization of arenes.[5] In most cases, unreadily available or expensive C_2F_5 sources such as pentafluoroethylsilanes ($R_3SiC_2F_5$), pentafluoropropanoates ($C_2F_5CO_2M$), C_2F_5H and C_2F_5I are required.[3-6]

Tetrafluoroethylene (TFE) is a bulk fluorochemical for manufacturing poly(tetrafluoroethylene) and copolymers with other alkenes,[7] and recently has been used as a C2 building block[8] for pentafluoroethylation of aryl iodides in the presence of CsF by us[3m] and Ohashi, Ogoshi and coworkers,[3o] respectively (Schemes 1a and 1b). From a practical standpoint, TFE is an ideal C_2F_5 precursor for industrial production of pentafluoroethylated compounds. However, the use of stored TFE in academic laboratories is largely restricted due to the safety regulation on the storage and transport of this suspected carcinogenic and potentially explosive gas.[9] To address this problem, our group has developed a new method for the on-site preparation of TFE by dimerization of difluorocarbene *in-situ* generated from (trifluoromethyl)trimethylsilane ($TMSCF_3$) under mild conditions (Scheme 1a),[3m] which has paved the way for the development of new fluoroalkylation methods with TFE in academia.[10]

Arenediazonium salts are available from inexpensive aromatic amines on a large scale, and have been widely employed for various transformations,[11] including Sandmeyer-type fluoroalkylations.[12] However, to our knowledge, the Sandmeyer-type pentafluoroethylation is still unknown. According to our previous report on copper-mediated pentafluoroethylation of aryl iodides with on-site generated TFE and CsF, we were convinced that a similar strategy should also be applicable for the synthesis of pentafluoroethylarenes from arenediazonium salts (Scheme 1c).

Scheme 1 Aromatic pentafluoroethylation using TFE and CsF



Results and Discussion

Based on our previous experiments,[3m] we began our studies of pentafluoroethylation of benzenediazonium tetrafluoroborate (PhN_2BF_4) by choosing CuCl and 1,10-phenanthroline (1,10-phen) (1 : 1) as $C_2F_5^-$ stabilizer and cross-coupling promoter (Scheme 2). The active pentafluoroethylation reagent "CuC_2F_5" was pre-generated from $TMSCF_3$-derived TFE, CsF, CuCl, and 1,10-phen in DMF, and reacted with PhN_2BF_4, with PhN_2BF_4 and CuCl being the limiting reactants. We found that the existing form of the "CuC_2F_5" intermediate in DMF was dependent on the amounts of $TMSCF_3$ (to generate TFE) and CsF used. When 6.0 equiv of $TMSCF_3$ and 1.2 equiv of CsF were used, the "CuC_2F_5" intermediate existed as a mixture of a neutral species (1,10-phen)Cu(C_2F_5) and an ionic species $[Cu(C_2F_5)_2]^-$ (the total amount of $[C_2F_5^-]$ was around 0.8 equiv).[13] Increasing the equivalents of $TMSCF_3$ and CsF to 15.0 and 3.0 equiv, respectively, the ionic species $[Cu(C_2F_5)_2]^-$ was generated predominantly (the total amount of $[C_2F_5^-]$ was 1.3 equiv). However, in both cases, we got very low yields of the desired cou-

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[†] Dedicated to Professor Qing-Yun Chen on the occasion of his 90th birthday.

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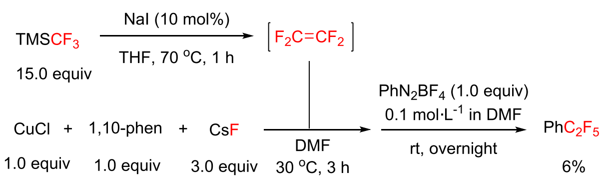
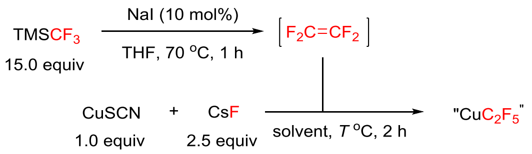
pling product (pentafluoroethyl)benzene (PhC_2F_5), which was significantly distinct from the cross-coupling with aryl iodides.[3m] GC-MS analysis of the reaction mixture showed that large amounts of chlorobenzene, biphenyl and diphenyldiazene were formed as the side products. This result suggested that: (1) the reduction of PhN_2BF_4 by (1,10-phen)Cu(I) complex to phenyl radical proceeds faster than the subsequent transfer of phenyl radical to Cu(II)-C_2F_5, and (2) the chlorination reaction proceeds faster than the pentafluoroethylation reaction. Thus, we envisioned that an efficient pentafluoroethylation protocol should not require the use of additional ligands and avoid the presence of strong nucleophilic counterions such as chloride ion.

Scheme 2 Initial attempt on the pentafluoroethylation



Inspired by Goossen's work on copper-mediated fluoroalkylation of arenediazonium salts with fluoroalkylsilanes ($R_3Si\text{-}R_f$),[12d-12f] we utilized copper thiocyanate (CuSCN) instead of CuCl for fluorocupration of TFE due to its relatively lower reactivity towards arenediazonium salts in the subsequent step (Table 1). An optimization of the preparation of "CuC_2F_5" (a mixture of $Cu(C_2F_5)$ and $[Cu(C_2F_5)_2]^-$) demonstrated that the fluorocupration of TFE with CuSCN and CsF could proceed smoothly at 70 °C in amide solvents such as NMP, DMAc and DMF in the absence of additional ligand 1,10-phen, with DMF being the superior solvent (Table 1, entries 3—5).[14] Additionally, the reaction temperature could significantly influence the fluorocupration process (Table 1, entries 6 and 7). However, only small amounts of $[C_2F_5^-]$ were produced when performed in DMSO and CH_3CN, respectively (Table 1, entries 1 and 2). Using DMF as the optimal solvent, an optimization of the other reaction parameters showed that reducing the amount of $TMSCF_3$ from 15 equiv to 12 equiv and shortening the fluorocupration time from 2 h to 1 h could afford $[C_2F_5^-]$ in the similar yield (Table 1, entries 8 and 9).

Table 1 Optimization of the preparation of "CuC_2F_5" from CuSCN and CsF[a]

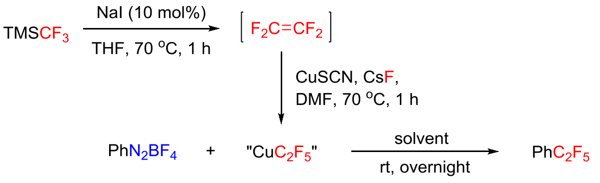


Entry	Solvent	T/°C	$[Cu(C_2F_5)_2]^-$ [b]/%	CuC_2F_5 [b]/%	$[C_2F_5^-]$ [b]/equiv
1	DMSO	70	< 5	< 5	< 0.15
2	MeCN	70	< 5	< 5	< 0.15
3	NMP	70	45	35	1.25
4	DMAc	70	32	26	0.90
5[c]	DMF	70	63	13	1.39
6	NMP	60	25	40	0.90
7	NMP	50	7	35	0.49
8[c,d]	DMF	70	62	12	1.36
9[c,d,e]	DMF	70	61	10	1.32

[a] Unless otherwise noted, reaction conditions are as follows: $TMSCF_3$ (3.0 mmol), NaI (0.3 mmol), THF (10 mL), CuSCN (0.2 mmol), CsF (0.5 mmol), and solvent (2 mL). [b] Yields and amounts were determined by ^{19}F NMR spectroscopy analysis using $PhCF_3$ as an internal standard (based on CuSCN). [c] Reaction conditions: $TMSCF_3$ (7.5 mmol), NaI (0.75 mmol), THF (10 mL), CuSCN (0.5 mmol), CsF (1.25 mmol), and solvent (5 mL). [d] $TMSCF_3$ (6.0 mmol) and NaI (0.6 mmol) were used. [e] Reaction time was 1 h.

We next tested the usefulness of "CuC_2F_5" prepared from CuSCN and on-site generated TFE in the pentafluoroethylation of arenediazonium salts by using PhN_2BF_4 as a model substrate (Table 2). The reaction was performed by adding a solution of PhN_2BF_4 (1.0 equiv) into the "CuC_2F_5" system in DMF. A screening of the solvents used to dissolve PhN_2BF_4 showed that the addition of MeCN was beneficial for the pentafluoroethylation process (Table 2, entries 1—3), which is consistent with most of the reported Sandmeyer-type fluoroalkylation procedures,[12] where MeCN was adopted as the solvent. However, the yield of PhC_2F_5 was only moderate (Table 2, entry 2). Although the coupling process was not sensitive to the reaction temperature (Table 2, entries 4—6), the use of an additional ligand 1,10-phen or the reverse addition of "CuC_2F_5" to PhN_2BF_4 could inhibit the desired reaction to some extent (Table 2, entry 7). To improve the yield of PhC_2F_5, DMF was removed from the system *in vacuo* at 50 °C after the formation of "CuC_2F_5" and was changed with MeCN before adding PhN_2BF_4.[14] In this case, PhC_2F_5 was obtained in 55% yield (Table 2, entry 10). Interestingly, we found that a substantial amount of neutral species CuC_2F_5 remained even after a long reaction time (overnight), implying that "CuC_2F_5" should be much more stable than PhN_2BF_4 in the current reaction system. In view

Table 2 Optimization of the pentafluoroethylation reaction[a]



Entry	Solvent	T/°C	Yield[b]/%
1	DMF	rt	20
2	MeCN	rt	40
3	DMSO	rt	22
4	MeCN	30	42
5	MeCN	40	37
6	MeCN	–5 to 0	37
7[c]	MeCN	rt	20
8[d]	MeCN	rt	39
9[d,e]	MeCN	rt	17
10[f]	MeCN	rt	55
11[g,h,i]	MeCN	rt	78

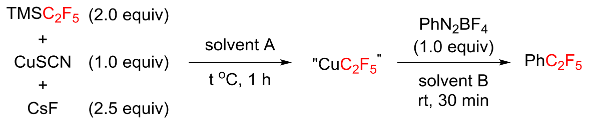
[a] Unless otherwise noted, "CuC_2F_5" was prepared from $TMSCF_3$ (3.0 mmol), NaI (0.3 mmol), THF (10 mL), CuSCN (0.2 mmol), CsF (0.5 mmol), and DMF (2 mL). The subsequent Sandmeyer-type pentafluoroethylation was performed with PhN_2BF_4 (0.2 mmol) and solvent (2 mL). [b] Yields were determined by ^{19}F NMR spectroscopy analysis using $PhCF_3$ as an internal standard. [c] 1,10-Phenantholine (1.0 equiv) was added. [d] Before use, the "CuC_2F_5" solution was filtered under N_2 atmosphere to remove the solid. [e] "CuC_2F_5" was added into PhN_2BF_4. [f] DMF was removed before the addition of MeCN (2 mL). [g] "CuC_2F_5" was prepared from $TMSCF_3$ (6.0 mmol), NaI (0.6 mmol), THF (10 mL), CuSCN (0.5 mmol), CsF (1.25 mmol), and DMF (5 mL). As an average of five parallel experiments, the so-prepared "CuC_2F_5" contains 0.585 mmol $[C_2F_5^-]$ after changing DMF with MeCN (2.5 mL). [h] $[C_2F_5^-]$ was used as the limiting reactant, and PhN_2BF_4 was used as the excess reactant (1.5 equiv). [i] The reaction time was 5 min.

of this, we calibrated the exact amount of $[C_2F_5^-]$ existed in MeCN before the addition of PhN_2BF_4 and used $[C_2F_5^-]$ as the limiting reactant (Table 2, entry 11). To our delight, a 78% yield of PhC_2F_5 was obtained when the amount of PhN_2BF_4 was increased to 1.5 equiv (relative to $[C_2F_5^-]$, not [Cu]). It is worthwhile to notice that "CuC_2F_5" was consumed completely within 5 min.

With the optimized conditions in hand (Table 2, entry 11), a survey of the substrate scope with regard to arenediazonium tetrafluoroborates was investigated. As shown in Scheme 3, substrates containing electron-donating groups such as alkyloxide (**2g**, **2k**), phenoxide (**2l**) and phenyl (**2d**) gave yields higher than 80%, while those bearing strong electron-withdrawing groups such as cyano (**2h**), nitro (**2j**) and sulfonyl (**2n**) delivered relatively lower yields (50%—60%). Substrates with carboxyl esters (**2a**, **2f**, **2o**) and carbonyls (**2e**, **2m**) were able to give moderate to good yields as well. Besides, this methodology displayed good functional group tolerance towards halides (**2i**, **2t**), pyridyl (**2s**), acidic protons (**2q**, **2x**) and trimethylsilyl protecting group (**2p**), which made the products ready to go through further functionalization. More structurally complicated diazonium tetrafluoroborates, such as dihydrobenzo[*b*][1,4]dioxine (**2k**), benzo[*d*]thiazole (**2r**), fluorene (**2v**), benzo[*d*][1,3]dioxol (**2u**), carbazole (**2w**), were also successfully pentafluoroethylated utilizing this strategy. Finally, derivative of tocopherol (**2y**) was synthesized to further demonstrate the application of this method.

Finally, to gain insights into this Sandmeyer-type pentafluoroethylation reaction, we prepared "CuC_2F_5" independently from $TMSC_2F_5$ and investigated its reaction with PhN_2BF_4. As shown in Table 3, the generation and reaction of "CuC_2F_5" were also solvent-dependent, which confirmed that there is a paradox in choosing solvents for Sandmeyer-type pentafluoroethylation. In the first step, although "CuC_2F_5" is relatively stable in MeCN, its generation prefers amide solvents such as DMF, which can accelerate the cupration of *in-situ* generated $C_2F_5^-$ (Table 3, entries 1—3). However, in the second step, the reaction of "CuC_2F_5" with arenediazonium salts must be conducted in MeCN, which can confine the aryl radical in a solvent cage,[12g] thus inhibiting the side reactions (Table 3, entries 1—2). Moreover, as compared with the trifluoromethylation conducted under similar conditions, the cross-coupling of "CuC_2F_5" with arenediazonium salts is more sensitive to the solvent system, which can be attributed to the lower reactivity of "CuC_2F_5" than "$CuCF_3$" (Table 3, entry 4).[3f,3k]

Table 3 Solvent effects in the pentafluoroethylation of PhN_2BF_4 with $TMSC_2F_5$[a]



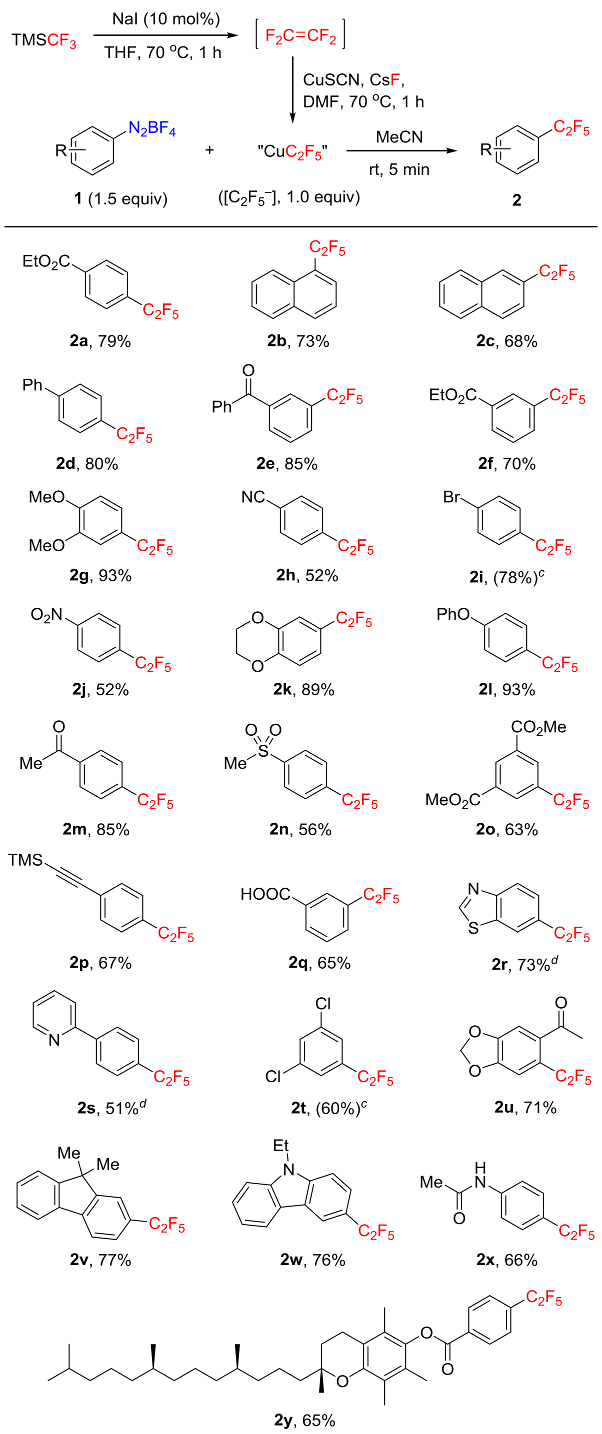
Entry	Solvent A	T/°C	Solvent B	PhC_2F_5/%
1	DMF	70	DMF	20
2[b]	DMF	70	MeCN	49
3[c]	MeCN	70	MeCN	—
4[d]	DMF	rt	MeCN	59[e]

[a] Yields were determined by ^{19}F NMR spectroscopy using benzotrifluoride as an internal standard. [b] DMF was evacuated *in vacuo* at 50 °C and substituted by MeCN before adding substrate into the mixture. [c] In the first step, only C_2F_5H was observed in ^{19}F NMR spectroscopy. [d] $TMSCF_3$ was used instead of $TMSC_2F_5$. [e] The yield of $PhCF_3$ was determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard.

Conclusions

In summary, we have developed a Sandmeyer-type pentafluoroethylation reaction utilizing on-site generated TFE as the C2 building block. This method exhibits great functional group tolerance and potential applications for synthesis of complicated bioactive compounds. In view of the low cost of TFE[15] and aromatic diazonium salts, this protocol is expected to find applications in the industrial production of pentafluoroethylated aromatics.

Scheme 3 Scope of pentafluoroethylation reaction[a,b]



[a] Reactions were performed with "CuC_2F_5" (containing *ca.* 0.585 mmol $[C_2F_5^-]$) prepared as per Table 2, entry 11. [b] Unless otherwise noted, yields given refer to the isolated yields of the analytically pure compounds. [c] The yield was determined by ^{19}F NMR spectroscopy analysis using $PhCF_3$ as an internal standard due to the volatility of the product. [d] 95% purity based on ^1H NMR spectroscopy analysis.

Experimental

Detailed experimental procedures, characterization data, and copies of ^{1}H NMR, ^{19}F NMR and ^{13}C NMR spectra of new compounds are provided in Supporting Information.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.201900268.

Acknowledgement

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[13] ^{19}F NMR data (in DMF, with PhCF$_3$ as an internal standard, δ –63.00): (1,10-phen)Cu(C$_2$F$_5$) [δ –84.42 (s, 3F), –111.71 (s, 2F)]; [Cu(C$_2$F$_5$)$_2$]$^-$ [δ

–84.36 (s, 3F), −117.58 (s, 2F)]. Our assignments are consistent to Grushin's report,[3f] but are contrary to Ogoshi and Hartwig's reports.[3o,4b]

[14] The ^{19}F NMR data of "Cu(C_2F_5)" prepared from CuSCN, TFE and CsF in various solvents are given in the Supporting Information.

[15] Our on-site protocol for TFE generation is for research in academic laboratories. For large-scale reactions, the industrially produced TFE (with much lower cost) should be used.

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