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This manuscript has been accepted and appears as an Accepted Article online.

This work may now be cited as: *Chin. J. Chem.* **2019**, *37*, 10.1002/cjoc.201900268.

The final Version of Record (VoR) of it with formal page numbers will soon be published online in Early View: <http://dx.doi.org/10.1002/cjoc.201900268>.

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

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Cite this paper: *Chin. J. Chem.* 2019, 37, XXX–XXX. DOI: 10.1002/cjoc.201900XXX

Copper-mediated pentafluoroethylation of arenediazonium tetrafluoroborates with tetrafluoroethylene (TFE) on-site generated from TMSCF₃ has been developed as a new method to prepare pentafluoroethyl arenes. The active pentafluoroethylation reagent “CuC₂F₅” 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 (CF₃) 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 halides³ or arylboron compounds,⁴ and C-H functionalization of arenes.⁵ In most cases, unreadily available or expensive C₂F₅ sources such as pentafluoroethylsilanes (R₃SiC₂F₅), pentafluoropropanoates (C₂F₅CO₂M), C₂F₅H and C₂F₅I are required.^{3–6}

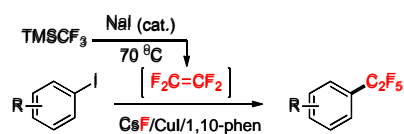
Tetrafluoroethylene (TFE) is a bulk fluorochemical for manufacturing poly(tetrafluoroethylene) and copolymers with other alkenes,⁷ and recently has been used as a C₂ building block⁸ for pentafluoroethylation of aryl iodides in the presence of CsF by *in situ* generation of TFE from (trifluoromethyl)trimethylsilane (TMSCF₃)^{3m} and Ohashi, Ogoshi and coworkers,³⁰ respectively (Scheme 1a and 1b). From a practical standpoint, TFE is an ideal C₂F₅ 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 (TMSCF₃) 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

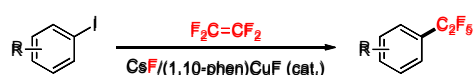
to our previous report on copper-mediated pentafluoroethylation of aryl iodides with on-site generated TFE and CsF, we were convinced that a similar strategy should also be applicable for the synthesis of pentafluoroethylarenes from arenediazonium salts (Scheme 1c).

Scheme 1 Aromatic pentafluoroethylation using TFE and CsF

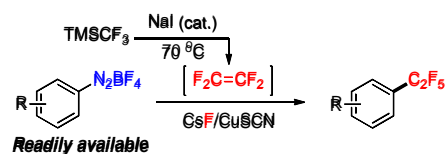
a) pentafluoroethylation of ArI with on-site generated TFE (Hu, 2017)



b) pentafluoroethylation of ArI with stored TFE (Ohashi & Ogoshi, 2018)



c) pentafluoroethylation of ArN₂BF₄ with on-site generated TFE (this work)



Results and Discussion

Based on our previous experiments,^{3m} we began our studies of pentafluoroethylation of benzenediazonium tetrafluoroborate (PhN₂BF₄) by choosing CuCl and 1,10-phenanthroline (1,10-phen) (1:1) as C₂F₅[−] stabilizer and cross-coupling promoter (Scheme 2). The active pentafluoroethylation reagent “CuC₂F₅” was pre-generated from TMSCF₃-derived TFE, CsF, CuCl, and 1,10-phen

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/cjoc.201900268

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 $(1,10\text{-phen})\text{Cu}(\text{C}_2\text{F}_5)$ and an ionic species $[\text{Cu}(\text{C}_2\text{F}_5)_2]^-$ (the total amount of $[\text{C}_2\text{F}_5^-]$ 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 $[\text{Cu}(\text{C}_2\text{F}_5)_2]^-$ was generated predominantly (the total amount of $[\text{C}_2\text{F}_5^-]$ was 1.3 equiv). However, in both cases, we got very low yields of the desired coupling 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 $(1,10\text{-phen})\text{Cu}(\text{I})$ complex to phenyl radical proceeds faster than the subsequent transfer of phenyl radical to $\text{Cu}(\text{II})\text{-C}_2\text{F}_5$, 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

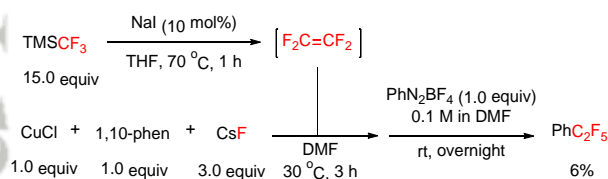


Table 1 Optimization of the preparation of " CuC_2F_5 " from CuSCN and CsF ^a

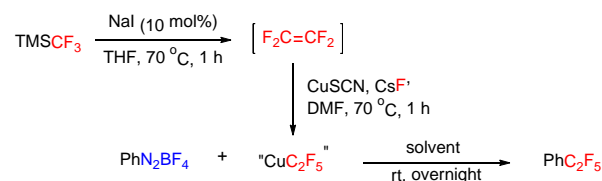
Entry	Solvent	T (°C)	$[\text{Cu}(\text{C}_2\text{F}_5)_2]^-$ (%) ^b	CuC_2F_5 (%) ^b	$[\text{C}_2\text{F}_5^-]$ (equiv) ^b
1	DMSO	70	< 5	< 5	< 0.15
2	MeCN	70	< 5	< 5	< 0.15
3	NMP	70	45	35	1.25
4	DMAc	70	32	26	0.90
5c	DMF	70	63	13	1.39
6	NMP	60	25	40	0.90
7	NMP	50	7	35	0.49

8 ^{c,d}	DMF	70	62	12	1.36
9 ^{c,d,e}	DMF	70	61	10	1.32

^aUnless otherwise noted, reaction conditions are as follows: TMSCF_3 (3.0 mmol), Nal (0.3 mmol), THF (10 mL), CuSCN (0.2 mmol), CsF (0.5 mmol), and solvent (2 mL). ^bYields and amounts were determined by ^{19}F NMR spectroscopy analysis using PhCF_3 as an internal standard (based on CuSCN). ^cReaction conditions: TMSCF_3 (7.5 mmol), Nal (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 Nal (0.6 mmol) were used. ^eReaction time was 1 h.

Inspired by Goossen's work on copper-mediated fluoroalkylation of arenediazonium salts with fluoroalkylsilanes ($\text{R}_3\text{Si-R}_f$),^{12d-f} 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 $\text{Cu}(\text{C}_2\text{F}_5)$ and $[\text{Cu}(\text{C}_2\text{F}_5)_2]^-$) 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 $[\text{C}_2\text{F}_5^-]$ 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 hours to 1 hour could afford $[\text{C}_2\text{F}_5^-]$ in the similar yield (Table 1, entries 8 and 9).

Table 2 Optimization of the pentafluoroethylation reaction^a

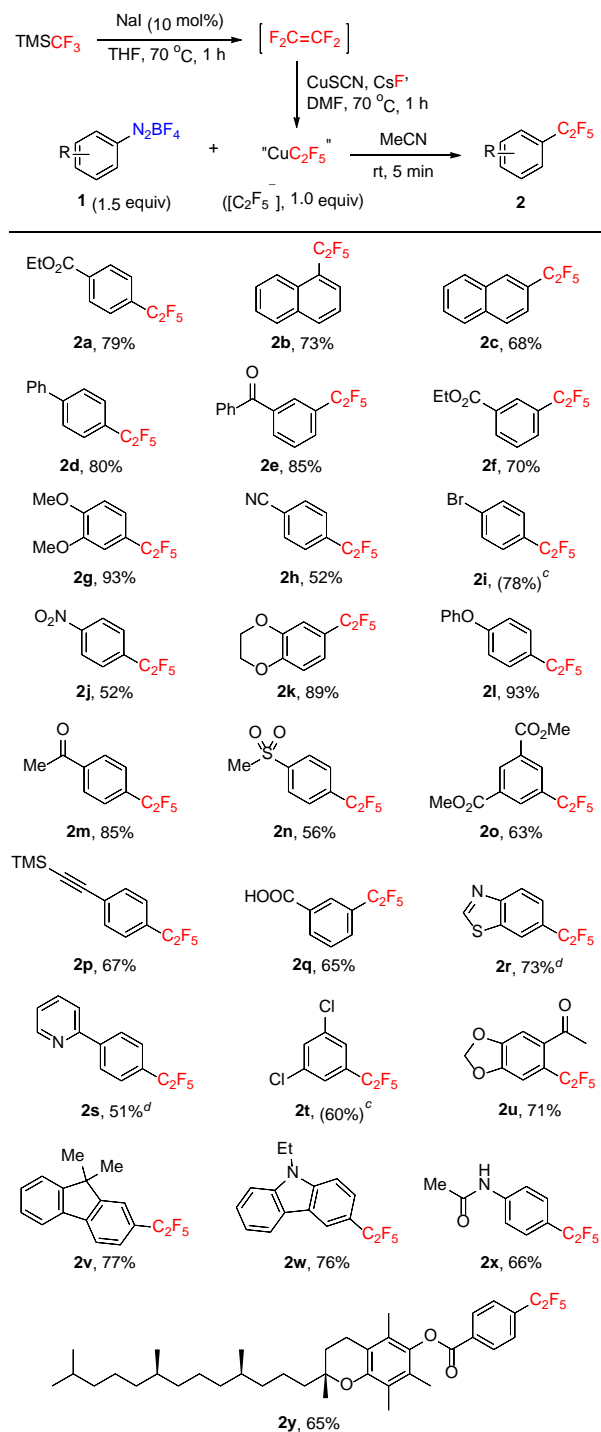


Entry	Solvent	T (°C)	Yield (%) ^b
1	DMF	rt	20
2	MeCN	rt	40
3	DMSO	rt	22
4	MeCN	30	42
5	MeCN	40	37
6	MeCN	-5 to 0	37
7 ^c	MeCN	rt	20
8 ^d	MeCN	rt	39
9 ^{d,e}	MeCN	rt	17
10 ^f	MeCN	rt	55

11 ^{g,h,i}	MeCN	rt	78
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^aUnless otherwise noted, "CuC₂F₅" was prepared from TMSCF₃ (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 PhN₂BF₄ (0.2 mmol) and solvent (2 mL). ^bYields were determined by ¹⁹F NMR spectroscopy analysis using PhCF₃ as an internal standard. ^c1,10-phenanthroline (1.0 equiv) was added. ^dBefore use, the "CuC₂F₅" solution was filtered under N₂ atmosphere to remove the solid. ^e"CuC₂F₅" was added into PhN₂BF₄. ^fDMF was removed before the addition of MeCN (2 mL). ^g"CuC₂F₅" was prepared from TMSCF₃ (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 "CuC₂F₅" contains 0.585 mmol [C₂F₅⁻] after changing DMF with MeCN (2.5 mL). ^h[C₂F₅⁻] was used as the limiting reactant, and PhN₂BF₄ was used as the excess reactant (1.5 equiv). ⁱThe reaction time was 5 min.

We next tested the usefulness of "CuC₂F₅" prepared from CuSCN and on-site generated TFE in the pentafluoroethylation of arenediazonium salts by using PhN₂BF₄ as a model substrate (Table 2). The reaction was performed by adding a solution of PhN₂BF₄ (1.0 equiv) into the "CuC₂F₅" system in DMF. A screening of the solvents used to dissolve PhN₂BF₄ 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 PhC₂F₅

Scheme 3 Scope of pentafluoroethylation reaction^{a,b}

^aReactions were performed with "CuC₂F₅" (containing ca. 0.585 mmol [C₂F₅⁻]) prepared as per Table 2, entry 11. ^bUnless otherwise noted, yields given refer to the isolated yields of the analytically pure compounds. ^cThe yield was determined by ¹⁹F NMR spectroscopy analysis using PhCF₃ as an

internal standard due to the volatility of the product. ^a95% purity based on ¹H NMR spectroscopy analysis.

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 "CuC₂F₅" to PhN₂BF₄ could inhibit the desired reaction to some extent (Table 2, entry 7). To improve the yield of PhC₂F₅, DMF was removed from the system *in vacuo* at 50 °C after the formation of "CuC₂F₅" and was changed with MeCN before adding PhN₂BF₄.¹⁴ In this case, PhC₂F₅ was obtained in 55% yield (Table 2, entry 10). Interestingly, we found that a substantial amount of neutral species CuC₂F₅ remained even after a long reaction time (overnight), implying that "CuC₂F₅" should be much more stable than PhN₂BF₄ in the current reaction system. In view of this, we calibrated the exact amount of [C₂F₅⁻] existed in MeCN before the addition of PhN₂BF₄ and used [C₂F₅⁻] as the limiting reactant (Table 2, entry 11). To our delight, a 78% yield of PhC₂F₅ was obtained when the amount of PhN₂BF₄ was increased to 1.5 equiv (relative to [C₂F₅⁻], not [Cu]). It is worthwhile to notice that "CuC₂F₅" 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 alkoxide (**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.

Table 3 Solvent effects in the pentafluoroethylation of PhN₂BF₄ with TMS-C₂F₅^a

Entry	Solvent A	T (°C)	Solvent B	PhC ₂ F ₅ (%)
1	DMF	70	DMF	20
2 ^b	DMF	70	MeCN	49
3 ^c	MeCN	70	MeCN	—
4 ^d	DMF	rt	MeCN	59 ^e

^aYields were determined by ¹⁹F NMR spectroscopy using benzotrifluoride

as an internal standard. ^bDMF was evacuated *in vacuo* at 50 °C and substituted by MeCN before adding substrate into the mixture. ^cIn the first step, only C₂F₅H was observed in ¹⁹F NMR spectroscopy. ^dTMSCF₃ was used instead of TMS-C₂F₅. ^eThe yield of PhCF₃ was determined by ¹⁹F NMR spectroscopy using PhOCF₃ as an internal standard.

Finally, to gain insights into this Sandmeyer-type pentafluoroethylation reaction, we prepared "CuC₂F₅" independently from TMS-C₂F₅ and investigated its reaction with PhN₂BF₄. As shown in Table 3, the generation and reaction of "CuC₂F₅" were also solvent-dependent, which confirmed that there is a paradox in choosing solvents for Sandmeyer-type pentafluoroethylation. In the first step, although "CuC₂F₅" is relatively stable in MeCN, its generation prefers amide solvents such as DMF, which can accelerate the cupration of in-situ generated C₂F₅⁻ (Table 3, entries 1-3). However, in the second step, the reaction of "CuC₂F₅" 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 "CuC₂F₅" with arenediazonium salts is more sensitive to the solvent system, which can be attributed to the lower reactivity of "CuC₂F₅" than "CuCF₃" (Table 3, entry 4).^{3f,3k}

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 TFE¹⁵ and aromatic diazonium salts, this protocol is expected to find applications in the industrial production of pentafluoroethylated aromatics.

Experimental

Detailed experimental procedures, characterization data, and copies of ¹H, ¹⁹F and ¹³C 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.2018xxxx>.

Acknowledgement

This work was supported by the National Basic Research Program of China (2015CB931900, 2012CB215500), the National Natural Science Foundation of China (21632009, 21421002), the Key Program of the Chinese Academy of Sciences (KGZD-EW-T08), the Key Research Program of Frontier Sciences of CAS (QYZDJ-SSWSLH049), and the Shanghai Rising-Star Program

(16QA1404600) for financial support.

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- [13] ^{19}F NMR data (in DMF, with PhCF_3 as an internal standard, δ –63.00 ppm): $(1,10\text{-phen})\text{Cu}(\text{C}_2\text{F}_5)$ [δ –84.42 (s, 3F), –111.71 (s, 2F)]; $[\text{Cu}(\text{C}_2\text{F}_5)_2]^-$ [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 " $\text{Cu}(\text{C}_2\text{F}_5)$ " 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.

(The following will be filled in by the editorial staff)

Manuscript received: XXXX, 2019

Manuscript revised: XXXX, 2019

Manuscript accepted: XXXX, 2019

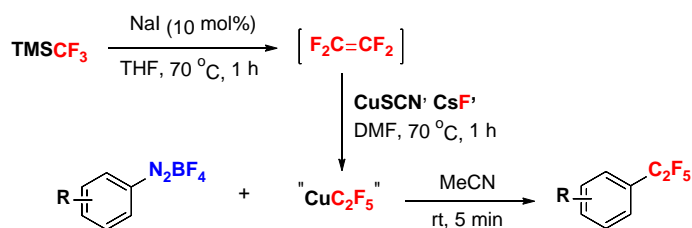
Accepted manuscript online: XXXX, 2019

Version of record online: XXXX, 2019

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Pentafluoroethylation of Arenediazonium
Tetrafluoroborates Using On-Site Generated
Tetrafluoroethylene



Max. Table height 6 cm

Copper-mediated pentafluoroethylation of arenediazonium tetrafluoroborates with Tetrafluoroethylene (on-site generated from TMSCF_3) has been developed as a new method to prepare pentafluoroethyl arenes.

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