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Perfluoroalkoxylation Reaction via Dual Concurrent Catalysis

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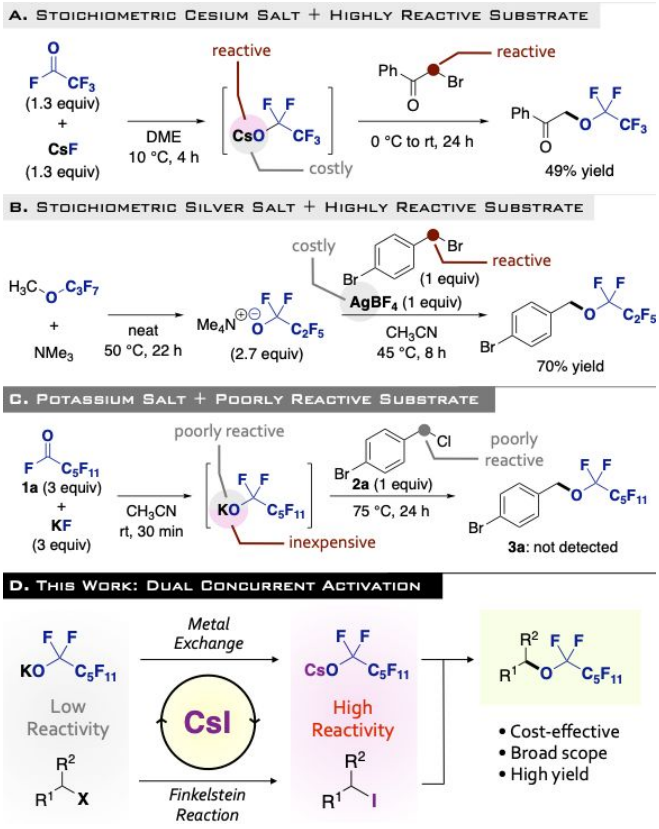
A catalytic amount of CsI enables dual concurrent activation of poorly reactive perfluoroalkoxide and alkyl halides, especially alkyl chlorides, leading to the formation of diverse perfluoroalkoxylated organic compounds. Installation of perfluoroalkoxy groups by this methodology is cost-effective, circumventing the need for over-stoichiometric cesium or silver salts. This methodology also provides high functional group compatibility and tolerance of sterically hindered substrates.

Introduction

Perfluoroalkylated compounds are important especially in materials science[1] and catalysis[2] due to the strongly electron-withdrawing character of the perfluoroalkyl (R_F) group. They have fascinating bulk properties, such as hydrophobic character leading to water repellency, high melting temperature, low electronic permittivity, and so on, arising from the interaction between R_F chains, which can be explained in terms of the stratified dipole array model.[3] Nevertheless, R_F groups are not widely utilized except for the minimum homologue, the CF_3 group,[4] largely due to the lack of synthetic methods. Moreover, recent advances in perfluoroalkylation reactions,[5] including our contributions,[6] have mainly focused on direct linkage between an R_F group and a carbon atom, and compounds possessing a heteroatom between these structural elements are still quite inaccessible. In other words, there is no synthetic method offering low cost, wide substrate scope, and sufficient scalability for industrial application for such classes of compounds, even though the expected drastic differences in properties, for instance between R_F and R_FO groups, would be potentially useful for the design of novel functional materials and drugs. These differences are exemplified by a comparison between CF_3 and CF_3O groups: electronegativity χ (3.5 vs 3.7),[7] inductive effect σ_I (0.39 vs 0.51), and lipophilicity Π (+0.88 vs +1.04).[8] A seminal report by Sokolenko on aliphatic perfluoroalkoxylation described nucleophilic substitution of α-bromoacetophenone with R_FOCs derived from perfluoroalkanoyl fluoride and CsF (Scheme 1A).[9] The successful C–O bond formation appears to be due to the use of Cs^+ to facilitate perfluoroalkoxide (R_FO^-) formation in the equilibrium.[10] Friesen elegantly prepared a series of tetraalkylammonium perfluoroalkoxides by the reaction of R_FOCH_3 with trialkyl amines, and these organic salts react with benzylic bromides[11] and alkyl iodides[12] with the aid of cationic silver salt (Scheme 1B). Although these pioneering works have had a significant impact, several issues remain. Specifically, the need for over-stoichiometric use of expensive metal reagents means that these reactions would not be cost-effective on an industrial scale,[13] and the substrates used for the synthesis of more diverse R_F-ethers are poorly reactive.[14] Here, we describe an efficient and user-friendly dual concurrent CsI-mediated catalytic activation[15] of inexpensive but poorly reactive R_FOK and poorly electrophilic substrates. Our strategy of employing a single alkali metal salt to simultaneously activate both the poorly reactive nucleophile and the electrophile provides ready access to a wide range of perfluoroalkoxylated compounds (Scheme 1C).



Scheme 1. Aliphatic Perfluoroalkoxylation Reactions.

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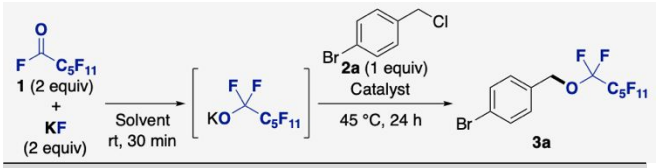
Results and discussion

Initially, we examined the reaction between 4-bromobenzyl chloride (**2a**) and R_FOK derived from $C_5F_{11}COF$ (**1**) and KF, which is a very inexpensive fluoride source, in CH_3CN, but found that the desired perfluoroalkoxylated product **3a** was not formed (entry 1, Table 1). Addition of a catalytic amount of KI to activate **2a** promoted the reaction, albeit the yield was very low (entry 2). Solvation of K^+ with glycol ethers is expected to favor the formation of R_FO^- species in the equilibrium, and the use of tetraglyme (TG) as a co-solvent increased the yield to 47% (entry 3). NaI and tetrabutylammonium iodide showed comparable reactivities to that in the case of KI (entries 4 and 5), whereas employment of CsI as a catalyst drastically improved the reaction efficiency (entry 6). It is noteworthy that RbI, an alkali metal iodide that is rarely used in organic synthesis, also showed similar activity to that of CsI (entry 7). The marked decrease of the yield of **3a** when CsBr was used emphasizes the importance of the synchronous action of I^- and Cs^+ in the catalysis (entry 8). The unique character of CsI was seen even more strikingly when 1 mol% catalyst was used; **3a** was still obtained in 42% yield under slightly harsher conditions (entry 9), whereas KI afforded only 18% yield (entry 10).

With the optimized conditions in hand (entry 6, Table 1), we examined the substrate scope of benzylic halides (Table 2). The reaction progress was little affected by the substitution pattern of the aromatic ring, and R_F-ethers with the synthetically useful Br substituent **3a**-**3c** were obtained in good yields. Electron-rich substrates are particularly suitable for this etherification (**3d** and **3e**), and a gram-scale reaction successfully afforded **3d** in high yield. Electron-neutral benzyl

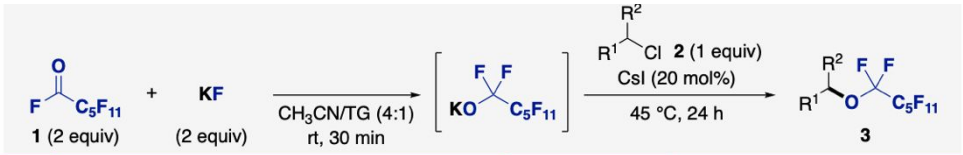
Table 1. Optimization of Reaction Conditions.

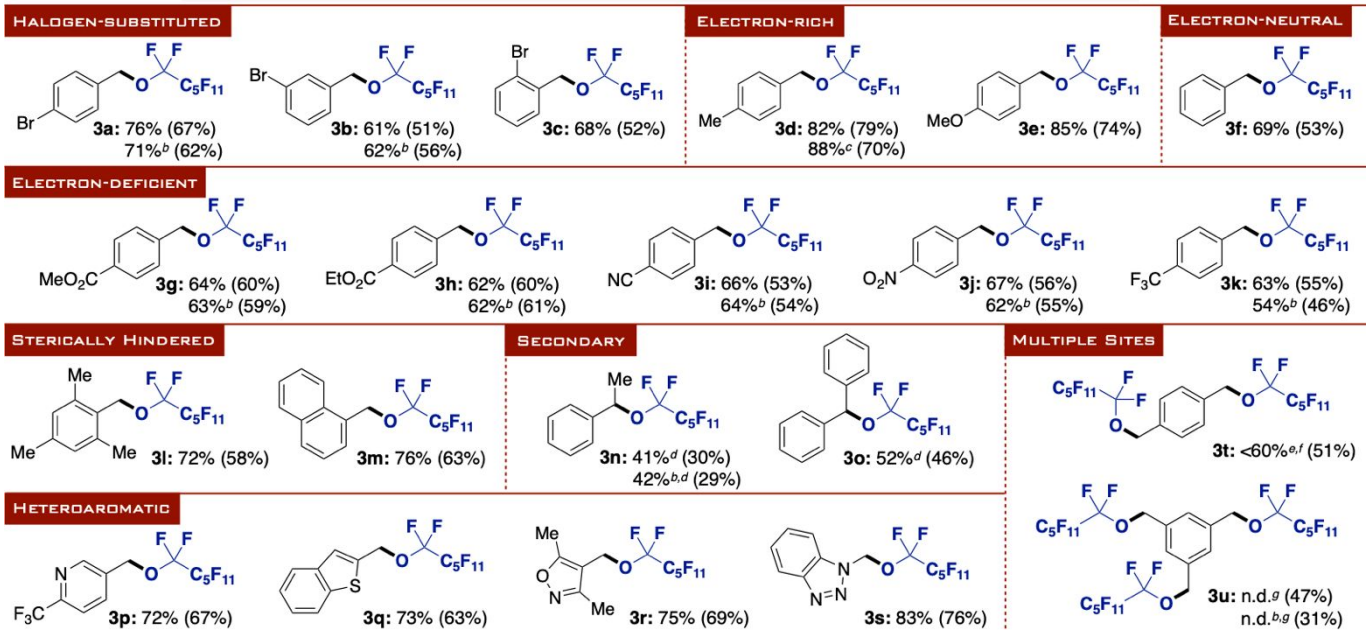


Entry	Cat. (mol%)	Solvent	Yield (%)[a]
1	None	CH_3CN	0
2	KI (20)	CH_3CN	7
3	KI (20)	CH_3CN/TG (4:1)	47
4	NaI (20)	CH_3CN/TG (4:1)	47
5	Me_4NI (20)	CH_3CN/TG (4:1)	45
6	CsI (20)	CH_3CN/TG (4:1)	76
7	RbI (20)	CH_3CN/TG (4:1)	71
8	CsBr (20)	CH_3CN/TG (4:1)	14
9[b]	CsI (1)	CH_3CN/TG (4:1)	42
10[b]	KI (1)	CH_3CN/TG (4:1)	18

[a] Determined by ^1H NMR using 1,4-bis(trifluoromethyl)benzene as an internal standard. [b] Run at 75 °C for 48 h. TG = tetraglyme.

Table 2. Scope of Benzylic Substrates.[a]





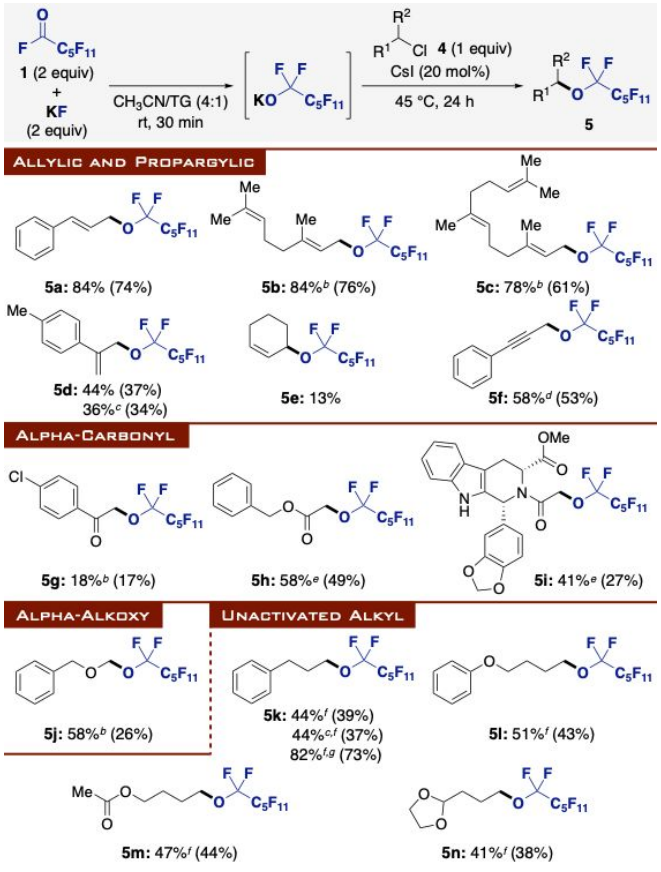
[a] Yields were determined by ^1H NMR using 1,4-bis(trifluoromethyl)benzene as an internal standard. Isolated yields are shown in parentheses. [b] Run with RbI (20 mol%) in lieu of CsI. [c] Run on 5.0 mmol scale. [d] Run with $C_5F_{11}COF$ (3 equiv), KF (3 equiv) at 75 °C. [e] Run with $C_5F_{11}COF$ (4 equiv), KF (4 equiv), and CsI (40 mol%). [f] The yield is approximate, because the NMR spectrum was complex due to the presence of the mono-substituted product and the starting material **2s**. [g] Amounts of all reagents were tripled except for CsI. Run with CsI (30 mol%) for 72 h.

chloride and a range of substrates with an electron-withdrawing substituent were well tolerated (**3f**-**3k**). Furthermore, sterically demanding substituents were not detrimental (**3l** and **3m**), and even secondary benzylic chlorides were available with this dual concurrent catalytic system (**3n** and **3o**). Both electron-deficient and electron-rich heteroaromatics were tolerated (**3p**-**3r**), and the 1*H*-benzo[*d*][1,2,3]triazolylated R_F-ether **3s** was also obtained in high yield. This methodology enables the formation of multiply perfluoroalkoxylated compounds by simply doubling or tripling the amounts of **1** and KF (**3t** and **3u**). It is worth noting that RbI also serves as an alternative catalyst to CsI for the formation of diverse benzylic R_F-ethers (**3b**, **3c**, **3g**-**3k**, **3n** and **3u**).

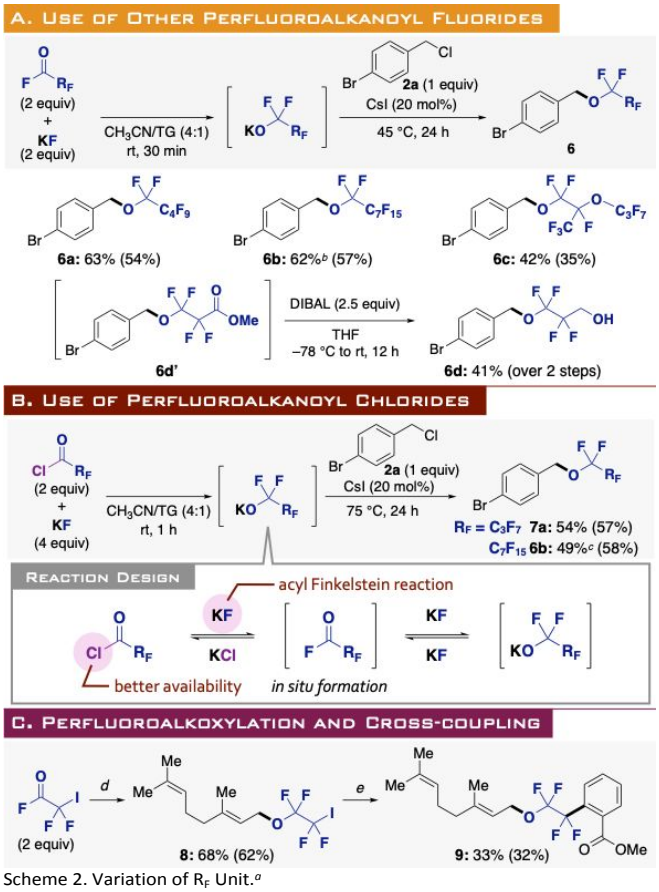
This protocol is not limited to benzylic chlorides, and diverse substrates are available (Table 3). Cinnamyl, geranyl, and farnesyl chlorides gave the corresponding products **5a**-**5c** in high yields. A substituent at the internal carbon of the C–C double bond of the allylic system slightly retarded the reaction, probably due to steric hindrance (**5d**). This catalytic system even promotes the reaction using the secondary allylic chloride (**5e**), and an R_FO group could also be installed at the propargylic position (**5f**). Clean conversion of α-chloroacetophenone was not achieved, although the desired product **5g** was formed. Use of α-chloroacetate provided facile access to the R_F-ether with the synthetically versatile ester moiety (**5h**). Chloropretadalafil (**4i**), the synthetic precursor of tadalafil (a PDE-5 inhibitor),[16] is also a suitable substrate for this transformation (**5i**). The unsymmetrically substituted acetal with benzyl and R_F groups is also accessible (**5j**). One of the highlights of this protocol is the transformation of unactivated alkyl chlorides in the presence of diverse functional groups such as ether, ester, and acetal (**5k**-**5n**), which suggests that this catalytic methodology might have great potential utility in organic synthesis. The present CsI catalysis was also effective for perfluoroalkoxylation of an unactivated alkyl bromide (**5k**).

Structural diversification of R_F-ethers focusing on the R_F unit was next investigated (Scheme 2). Besides the standard perfluoroalkanoyl fluoride **1** (C6), shorter (C5) and longer (C8) chain compounds were successfully employed (**6a** and **6b**), though the latter required slightly harsher conditions. An α-substituent of the perfluoroalkanoyl fluoride was not

Table 3. Additional Scope.[a]



[a] Yields were determined by ^{1}H NMR using 1,4-bis(trifluoromethyl)benzene as an internal standard. Isolated yields are shown in parentheses. [b] Run in the dark at rt. [c] Run with RbI (20 mol%) in lieu of CsI. [d] Run with $C_5F_{11}COF$ (3 equiv), KF (3 equiv) at 90 °C. [e] Run with $C_5F_{11}COF$ (3 equiv), KF (3 equiv) at 75 °C. [f] Run with $C_5F_{11}COF$ (3 equiv), KF (3 equiv), and CsI (30 mol%) at 90 °C for 48 h. [g] Run with the corresponding alkyl bromide.



Scheme 2. Variation of R_F Unit.[a]

[a] Yields were determined by ^{1}H NMR using 1,4-bis(trifluoromethyl)benzene as an internal standard. Isolated yields are shown in parentheses. [b] Run at 75 °C. [c] Run at 90 °C for 48 h. [d] Run with KF (2 equiv), CsI (20 mol%), geranyl chloride (1 equiv) in CH_3CN/TG (4:1) at 45 °C for 24 h. [e] Methyl 2-iodobenzoate (1 equiv), **8** (1.5 equiv), Et_2Zn (1.5 equiv), CuI (10 mol%), DMPU, 90 °C, 16 h.

detrimental (**6c**), and this result greatly expands the scope of the methodology. R_FO^- derived from methyl fluoroformyl 2,2-difluoroacetate was also available, though **6d** was isolated after reduction of the ester moiety of the primary product **6d'** due to facile decomposition of the latter upon exposure to silica gel. Perfluoroalkanoyl chlorides are potentially useful as surrogates for their fluoride counterparts in this transformation, since commercial availability of the fluorides is limited. We considered that the acyl Finkelstein reaction to convert chlorides to the corresponding fluorides *in situ* prior to R_FO^- formation might be a good solution for the installation of diverse R_FO groups at will (Scheme 2B).[17] Gratifyingly, the desired perfluoroalkylated ethers were obtained by employing two equivalents of perfluoroalkanoyl chloride and four equivalents of KF with respect to **2a** (**7a** and **6b**). The highlight of this methodology is the successive application of perfluoroalkoxylation and cross-coupling reaction for flexible decoration of R_F chains (Scheme 2C). Notably, iododifluoroacetyl fluoride provided compound **8** with a C–I bond at the terminus of the R_F chain, which would be a useful handle for diverse chemical transformations. For example, our zinc-mediated copper-catalyzed cross-coupling reaction with an aryl iodide led to the formation of the product **9**.[6a]

Conclusions

In summary, we report straightforward perfluoroalkoxylation methodology applicable to a diverse range of poorly reactive alkyl halides by means of a dual concurrent catalysis strategy in which a single alkali metal salt, CsI, is employed to simultaneously activate both the poorly reactive nucleophile with Cs^+ and the electrophile with I^-. Further studies to explore enantioselective perfluoroalkoxylation and aromatic perfluoroalkoxylation reactions are ongoing.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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