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Alkali Metal Fluorides in Fluorinated Alcohols: Fundamental Properties and Applications to Electrochemical Fluorination

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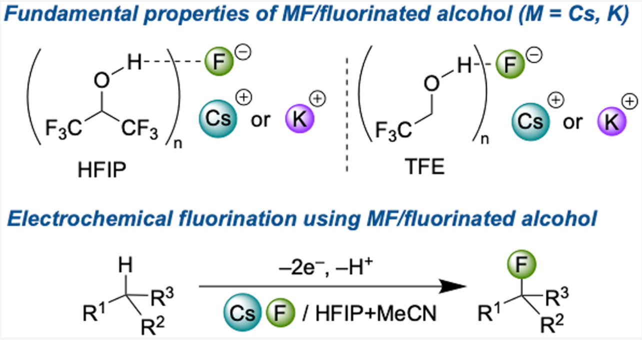
ABSTRACT: Fundamental properties of alkali metal fluorides (MF, M = Cs, K) dissolved in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) or in 3,3,3-trifluoroethanol (TFE) are investigated, including solubility, conductivity, and viscosity. Solid-state structures of single crystals obtained from CsF/HFIP and CsF/TFE are described for the first time, giving insights into the multiple interactions between fluorinated alcohols and CsF. Applications in electrochemical fluorination reactions are successfully demonstrated.



Fluorine-containing organic compounds play a central role in pharmaceuticals and agrochemicals.[1−3] Positron emission tomography (PET) accelerated the importance of developing efficient and reliable methodologies for the fluorination of organic compounds.[4] Fluorination of organic compounds is achieved by using fluorinating reagents.[5] Despite the matured chemistry of fluorinating reagents, their sensitivity to moisture and air hinders general usage.

In this context, alkali metal fluoride salts, MF (M represents alkali metals), as fluorine sources, are attractive targets due to their affordability, availability, and stability. To solubilize MF in an organic solvent to suppress the basicity of the fluoride anions, the use of hydrogen bond donors has been actively reported, inspired by the structure of a fluorinating enzyme.[6] Kim, Chi, Song, and co-workers reported on fluoride anions coordinated by aliphatic alcohols using tetrabutylammonium fluoride (TBAF) or CsF.[7−9] Gouverneur and co-workers reported the solid-state structure and reactivity of a variety of hydrogen-bonded TBAF complexes using a wide range of aliphatic alcohols,[10] and later expanded their chemistry to enantioselective fluorination with CsF as an F^- source by using urea-based phase transfer reagents.[11−13] Our group has previously reported electrochemical fluorination using CsF solubilized by poly(ethylene glycol) to achieve C−H fluorination of triphenylmethane derivatives.[14,15]

Although the fluoride anion hydrogen-bonded by aliphatic alcohols is a promising nucleophilic fluoride source, the nucleophilicity and oxidizable nature of aliphatic alcohols potentially impair the fluorination reaction. Thus, replacing aliphatic alcohols with weakly coordinating and oxidation-tolerant solvents can be an alternative strategy to compensate for such inherent limitations.

To this end, fluorinated alcohols, such as 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) or 2,2,2-trifluoroethanol (TFE), are an idealistic class of solvent. The strategy to dissolve alkali metal fluoride salts with fluorinated alcohols was reported by several groups. Doyle and co-workers reported copper-catalyzed C−F insertion of α-diazocarbonyl using KF solubilized by HFIP in 1,2-dichloroethane.[16] Hammond, Xu, and co-workers demonstrated the hydro(radio)fluorination of internal alkynes with KF dissolved in HFIP.[17] However, to the best of our knowledge, there is no precedent for an MF/fluorinated alcohol system in electrochemistry. In this context, we report herein the fundamental properties of MF/fluorinated alcohol (M = Cs, K) including conductance, viscosity, and solid-state structure. Application of the MF/fluorinated alcohol system to electrochemical fluorination is also demonstrated.

First, we examined the solubility of MF in TFE and HFIP. At room temperature, KF was soluble in TFE and HFIP at more than 1 M, whereas CsF was soluble in TFE and HFIP up to 3 and 2 M, respectively (Figure 1). Such a high concentration of the electrolyte is very attractive for various uses since the amount of solvent is very small. This entirely

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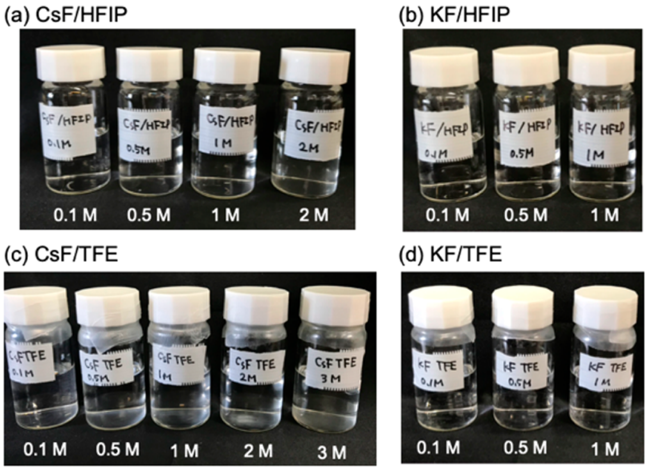

Figure 1. Photographs of MF/fluorinated alcohol solutions at various concentrations. (a) CsF/HFIP, (b) KF/HFIP, (c) CsF/TFE, (d) KF/TFE.

changes the solution chemistry compared to dilute electrolyte systems and is known in the field of superconcentrated electrolytes,[18] ionic liquids,[19] and deep eutectic solvents.[20]

Fluorinated alcohols were found to solubilize metal fluorides, well even in a mixed solvent system. We confirmed that up to 0.4 M of CsF is soluble in a MeCN/HFIP 8:2 (vol %) mixture. An even smaller amount (19 mM) of HFIP can solubilize 10 mM of CsF in MeCN, which is advantageous in terms of reducing the amount of HFIP for the reaction. In addition, the dissolution of CsF with a small amount (ca. 2 equiv) of HFIP in a relatively dilute solution indicates that there is a strong interaction between CsF and HFIP. It is noteworthy that our previous electrochemical system, where 0.3 M poly(ethylene glycol) (M_n ~ 200) in MeCN was used, solubilized CsF and KF up to 50 mM and 28 mM, respectively,[14] indicating the high potential of fluorinated alcohol as a solubilizing agent of metal fluorides.

We next investigated the conductivity and viscosity of a series of MF/fluorinated alcohol combinations (Figure 2). Both the conductivity and viscosity of HFIP-based electrolytes and TFE-based electrolytes were investigated in the temperature ranges of 298−328 K and 289−343 K, respectively.

As a general trend, the conductivity became higher at higher temperatures (Figure 2a). The HFIP-based electrolytes showed much lower conductivity than the TFE-based electrolytes. The KF-based electrolyte showed lower conductivity compared to the CsF-based electrolyte, presumably due to the higher lattice energy of KF than CsF. Conductivity plots as a function of the concentration at 303 K revealed that the conductivity increases with increasing molar concentration up to 1 M (Figure 2b). The conductivities of CsF/HFIP and CsF/TFE solutions were maximized at 1 and 2 M, respectively.

The viscosity of the electrolytes decreased at higher temperatures and increased with the increasing concentration of salts (Figure 2c,d). The viscosity of CsF/TFE was notably lower than that of the CsF/HFIP solution with the same concentration of CsF (Figure 2d), despite the fact that the viscosities of pure HFIP and pure TFE are similar.[21] The lower viscosity of CsF/TFE appears to contribute to the higher conductivity compared to CsF/HFIP, as well as the higher dielectric constant of TFE than that of HFIP.[20]

These data suggest that the conductivity was dominated by the concentration of charge carriers at <1 M range of concentration. The decrease in the conductivity of CsF/HFIP at 2 M and CsF/TFE at 3 M suggests that mass transfer was hindered due to the increase in viscosity.

Figures S1 and S2 show the potential windows for MF/HFIP and MF/TFE (M = Cs, K) electrolytes using a glassy carbon (GC) disk electrode or a platinum disk electrode, evaluated by linear sweep voltammetry (LSV). The measure-

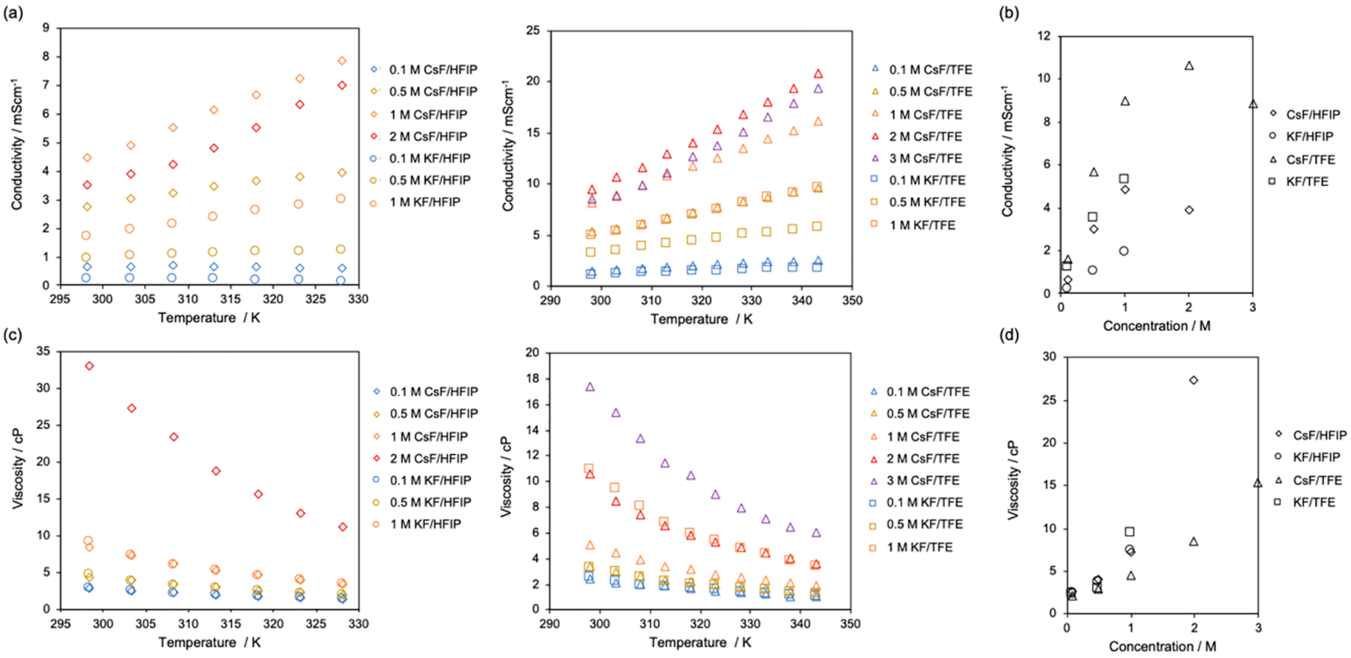

Figure 2. (a) Conductivity of MF/fluorinated alcohol as a function of temperature. (b) Conductivity MF/fluorinated alcohol as a function of the concentration of MF at 303 K. (c) Viscosity of MF/fluorinated alcohol as a function of temperature. (d) Viscosity of MF/fluorinated alcohol as a function of the concentration of MF at 303 K.

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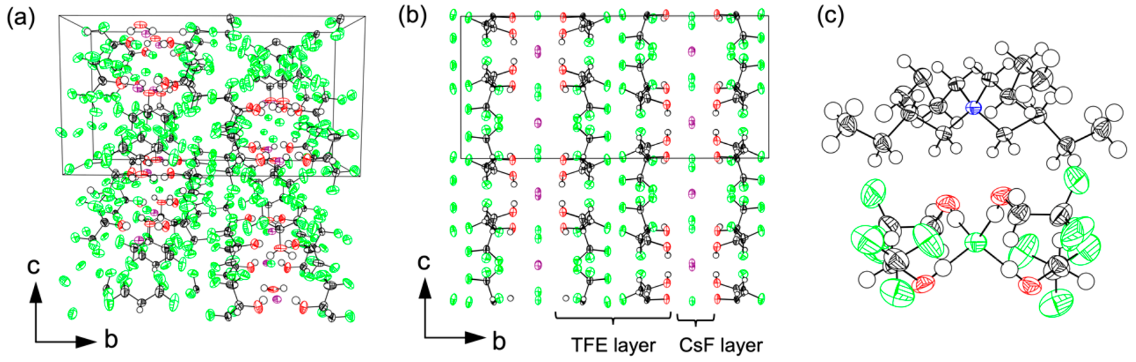


Figure 3. Packing diagram for (a) CsF/(HFIP)$_3$, (b) CsF/(TFE)$_2$, and the solid-state structure of (c) TBAF/(TFE)$_4$ with anisotropic displacement ellipsoids shown at the 50% probability level. Labeling of atoms is as follows: black, carbon; red, oxygen; green, fluorine; blue, nitrogen; purple, cesium; white, hydrogen.

ments were performed in the presence of molecular sieves. In HFIP-based electrolytes, an oxidation current appeared around 1.7 V vs SCE, while the oxidation onset appeared around 1.3 V in the case of TFE-based electrolytes. The anodic potential window for HFIP and TFE is expected to be wider, and thus these oxidation responses were attributed to adventitious water, although molecular sieves were used as an in situ drying agent. Interestingly, the Pt electrode showed a slightly wider oxidation potential window compared to GC. For TFE, oxidation waves appeared in all cases, presumably due to the contamination of water. Even so, the anodic window of 2 V vs SCE is sufficient for the oxidation of a wide range of organic compounds. We have also explored the potential window of 0.1 M CsF and KF in EtOH, where similar oxidation onset was observed compared to the HFIP and TFE system, presumably due to the presence of water (Figure S3). CsF and KF were not soluble in ^{i}PrOH, highlighting the unique solubility of these salts in HFIP.

Despite a number of precedents of solid-state structures of hydrogen-bonded fluoride ions using TBAF, the solid-state structures of hydrogen-bonded MF complexes remain relatively rare. Matsumoto and co-workers recently reported the solid-state structure of MF/aliphatic diol complexes (M = K, Cs, Rb).[22] Gouverneur and co-workers reported the solid-state structure of binaphthyl-based bisurea with CsF.[13] In this context, we were prompted to investigate the solid-state structures of MF/fluorinated alcohol complexes (M = Cs, K). Delightfully, we successfully prepared single crystals from oversaturated solutions of CsF/HFIP and CsF/TFE. These two crystals slowly melted while they were mounted at room temperature, preventing the collection of high-quality X-ray diffraction (XRD) data. Even so, we were able to obtain diffraction patterns to determine the geometry of each of the crystals. To the best of our knowledge, these are the first examples of the determination of the solid-state structure of complexes of MF/fluorinated alcohols. Single crystals were also prepared from an oversaturated solution of TBAF/TFE for comparison. Other MF/solvent combinations, such as KF/HFIP, KF/TFE, and TBAF/HFIP, did not form stable single crystals manipulable at room temperature.

Single crystals of the CsF/HFIP complex were obtained as colorless needles. A single-crystal XRD analysis revealed that the CsF/HFIP complex was composed of one CsF and three HFIP molecules, denoted as CsF/(HFIP)$_3$ (Figure 3a). Cesium ions and fluoride ions formed columnar structures surrounded by HFIP molecules. On the other hand, single crystals of CsF/TFE were found to be colorless plates. A single-crystal XRD analysis revealed that the complex was composed of one CsF and two TFE molecules, denoted as CsF/(TFE)$_2$ (Figure 3b). CsF/(TFE)$_2$ showed a layered packing structure. A single crystal of TBAF/TFE was composed of one CsF and four TFE molecules, denoted as TBAF/(TFE)$_4$ (Figure 3c). TBAF/(TFE)$_4$ showed similar structural features as the TBAF/aliphatic alcohol complexes, where the fluoride ion was coordinated to four hydroxy groups.[9,10]

The XRD analysis showed that CsF/(HFIP)$_3$ and CsF/(TFE)$_2$ have continuous layered structures of CsF. A similar continuous layered structure was reported for an aliphatic diol system.[22] Such continuous structures were obtained presumably due to the strong ionic bonding of cesium and fluoride ions, as supported by the distinct solid-state structure of TBAF/(TFE)$_4$.

In the solid-state structures of CsF/(HFIP)$_3$ and CsF/(TFE)$_2$, the oxygen atoms in HFIP and TFE interacted with cesium ions. The interaction of the hydrogen atoms of the OH groups with the fluoride ions also seems feasible based on the precedents.[7−9,13,22] Thus, the high solubility of MF in fluorinated alcohols is attributed to the multiple interactions of MF with OH groups.

We next investigated the electrochemical fluorination reaction using alkali metal fluorides dissolved in fluorinated alcohols. Triphenylmethane (**1**) was chosen as a model compound for fluorination. The electrolysis was performed using 0.3 M CsF dissolved in a MeCN/HFIP (8/2 in vol %) mixture as the electrolyte in the presence of 4 Å molecular sieves as a drying agent under an argon atmosphere. The desired fluorinated product, triphenylmethyl fluoride (**2**), was obtained in quantitative yield by passing 2.5 F/mol under a constant current condition (5 mA/cm^2) using an undivided cell equipped with a pair of platinum plates as an anode and a cathode (Table S2, entry 1). Note here that the conductivity of this electrolyte is much higher than 0.1−2 M CsF/HFIP, presumably due to the lower viscosity of MeCN compared to HFIP (Figure S4). Potential window analysis of 0.3 M CsF dissolved in a MeCN/HFIP (8:2 in vol %) mixture showed a similar feature to that of HFIP and TFE based systems (Figure S5). The use of MeCN as a cosolvent also increases the solubility of organic compounds, thus expanding the utility of this medium.

It is noteworthy that **2** was obtained in quantitative yield even in the presence of HFIP since it was reported that an additive amount of HFIP can activate the benzylic fluorine group via hydrogen bonding.[23−26] We attributed this to the hydrogen bonding interaction between the fluoride ion of CsF with HFIP, which decreased the interaction of HFIP with the benzylic fluoride.

The effect of experimental variables on the yield of the fluorinated product was also investigated (Table S2). KF was applicable in the reaction instead of CsF, which is desirable from an economic stand point (entry 2). Changing the charge to 2.0 F/mol slightly decreased the yield to 83% (entry 3). A lower concentration of CsF also reduced the product yield to 55% (Entry 4). Interestingly, the neat HFIP solution did not give the fluorinated product (entry 5). In this case, we observed the predominant formation of an ether product by gas chromatography−mass spectrometry (GC−MS), formed by nucleophilic attack of the alkoxide of HFIP. Although HFIP is an inherently weak nucleophile, the interaction with Cs ions may have increased the dissociation of the OH bonds, resulting in the generation of the alkoxide. The use of TFE instead of HFIP gave 65% yield of the product (entry 6). The reactions without molecular sieves 4A or under air resulted in lower yields, indicating that the reaction is moisture sensitive (entries 7 and 8). The use of GC as the anode instead of Pt significantly decreased the yield in this reaction, which is in agreement with the potential window analysis (entry 9). Lastly, a much smaller amount of HFIP, namely, 10 mL of MeCN with 600 μL of HFIP, was found to dissolve 0.3 M CsF and gave the desired product in good yield (entry 10).

With the optimized conditions in hand, we next investigated the scope of this reaction. This method was found to fluorinate various benzylic C−H bonds and C−H bonds adjacent to sulfides (Figure 4). Interestingly, some compounds were found to be formed more efficiently at a current density of 10 mA/cm^2 instead of 5 mA/cm^2. We attributed this to the aforementioned concomitant decomposition of benzylic fluorides by HFIP. In other words, the higher current density shortened the reaction time to increase the yield of the fluorinated products. The electrochemical fluorination of the C−S bond was also demonstrated with 2,2-diphenyl-1,3-dithiolane. The difluorinated product was obtained in 55% yield (Scheme 1).

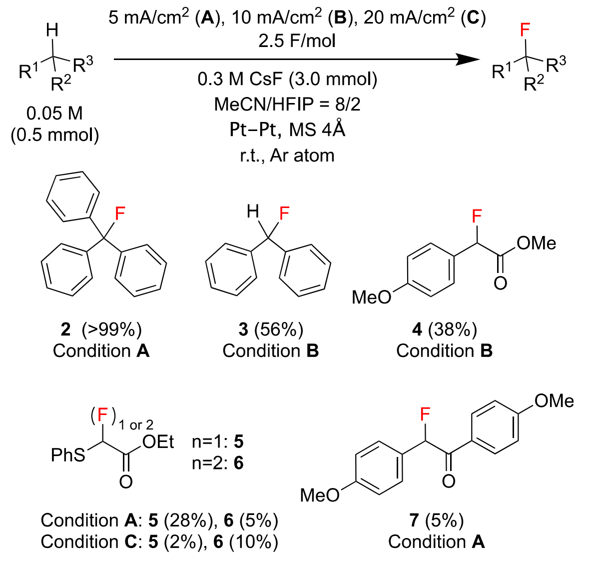
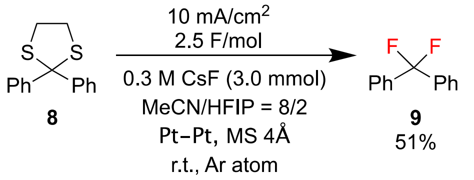


Figure 4. Electrochemical fluorination reactions using 0.3 M CsF in MeCN+HFIP (8:2 in vol %) solution as an electrolyte.

Scheme 1. Electrochemical Fluorination of 2,2-Diphenyl-1,3-dithiolane



In conclusion, we have reported fundamental properties of metal fluorides in fluorinated alcohols and demonstrated their application to electrochemical fluorination. We believe that this research will provide a new choice of reaction media for the synthesis of fluorinated compounds.

EXPERIMENTAL SECTION

General Considerations. Reagents and dehydrated solvents were obtained from commercial sources and used without further purification unless otherwise noted. CsF and KF were dried by heating under a vacuum overnight prior to use. ^{1}H and ^{19}F NMR spectra were recorded on a Bruker biospin AVANCE III 400A (^{1}H, 400.13 MHz; ^{19}F, 376.31 MHz) spectrometer using $CDCl_3$ or CD_3CN as a solvent. Monofluorobenzene was used as an internal standard for ^{19}F NMR measurements. The chemical shifts for ^{1}H and ^{19}F NMR spectra are given in δ (ppm) relative to internal TMS and monofluorobenzene, respectively. Multiplicities are abbreviated as singlet (s), doublet (d), triplet (t), quartet (q), sextet (sext), septet (sept), multiplet (m), and broad (br). The single-crystal X-ray analyses were carried out on a Rigaku XtaLAB Synergy-DW (with) hybrid photon counting (HPC) detector (Cu Kα radiation, λ = 1.54184 Å). An empirical absorption correction was carried out by the MULTI-SCAN method. The structures were solved by the SHELXT (SHELX2014) using OLEX2 or Yadokari-XG softwares.[27] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. Conductivity measurements were performed on a portable LAQUAact D-74 (HORIBA) equipped with a 3552−10D probe (cell constant: 1.026 cm^{-1}). Viscosity measurements were performed on a VM-10A (SEKONIC). Linear sweep voltammetry (LSV) measurements were performed using an ALS 6005C electrochemical analyzer. All CV measurements were carried out in the three-electrode system equipped with a glassy carbon (GC) disk (φ = 3 mm) or a platinum disk (φ = 3 mm) working electrode, a Pt plate counter electrode (10 mm × 10 mm), and a saturated calomel electrode (SCE) as a reference electrode at a scan rate of 100 mV s^{-1}. Electrochemical fluorination was performed using an HABF-501A (Hokutodenko). Gas chromatography−mass spectrometry was performed on a Shimadzu GSMS-QP2020 NX.

Single-Crystal X-ray Diffraction. *Preparation of Single Crystals.* Single crystals of $CsF/(HFIP)_3$, $CsF/(TFE)_2$, and $TBAF/(TFE)_4$ were obtained from the oversaturated solutions of the corresponding fluorinated alcohol. For the CsF-based crystals, oven-dried CsF was added into fluorinated alcohols at room temperature to give saturated solutions (ca. 2 M for HFIP, and ca. 3 M for TFE). The solution was heated to boiling under stirring conditions, and then CsF was added to reach oversaturation. The solutions were cooled to room temperature, where the formation of crystals was observed. The solutions were stored in a freezer to facilitate crystallization. Single crystals of $TBAF/(TFE)_4$ were obtained by the similar procedure described above using $TBAF/3H_2O$ salt as a starting material instead of CsF.

$CsF/(HFIP)_3$. ^{1}H NMR (400.13 MHz, CD_3CN, ppm): δ 7.51 (br), 4.59 (sep, $^3J_{H-F}$ = 6.6 Hz, 1H). ^{19}F NMR (376.31 MHz, CD_3CN, ppm): δ −74.89 (d, $^3J_{H-F}$ = 6.6 Hz), 143.17 (s).

CsF/(TFE)$_2$. ^{1}H NMR (400.13 MHz, CD_3CN, ppm): δ 6.78 (br), 3.85 (q, $^3J_{H-F}$ = 9.5 Hz, 2H). ^{19}F NMR (376.31 MHz, CD_3CN, ppm): δ −75.81 (t, $^3J_{H-F}$ = 9.5 Hz), 134.88 (s).

TBAF/(TFE)$_4$. ^{1}H NMR (400.13 MHz, CD_3CN, ppm): δ 3.82 (q, $^3J_{H-F}$ = 9.6 Hz), 3.21−2.88 (m), 1.67−1.49 (m), 1.35 (sext, $^3J_{H-H}$ = 7.4 Hz), 0.96 (t, $^3J_{H-H}$ = 7.4 Hz). ^{19}F NMR (376.31 MHz, CD_3CN, ppm): δ −74.89 (dt, $^3J_{H-F}$ = 9.6, J = 2.7 Hz), 136.45 (br).

General Procedure for the Electrochemical Fluorination. Electrochemical fluorination was performed according to the reported procedure with a slight modification.[14] Anodic oxidation of a substrate (0.5 mmol) was carried out in an undivided cell equipped with a platinum plate anode (20 mm × 20 mm) and a platinum cathode (20 mm × 20 mm) in a mixed solution of 10 mL of MeCN/HFIP (8:2 vol) containing CsF (3.0 mmol), grinded and oven-dried 4 Å molecular sieves (40 mg). Constant current electrolysis at 5.0 mA cm^{-2} was performed to pass up to 2.5 F/mol of charge at room temperature under an argon atmosphere. After the electrolysis, the electrolytic solution was passed through a short column filled with silica gel using EtOAc as an eluent to remove CsF. The formation of the fluorinated products **2**−**7** and **9** were confirmed by GC−MS, as well as ^{19}F NMR spectra of crude materials compared to the reported data.[14,16,28−32] The yield of the substrates in the eluent was estimated by ^{19}F NMR using monofluorobenzene as an internal standard.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00692.

> LSV data, conductivity measurements, crystallography data, optimization of electrochemical fluorination of **1**, ^{1}H and ^{19}F NMR data, and GC−MS data (PDF)

Accession Codes

CCDC 2067290−2067292 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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