

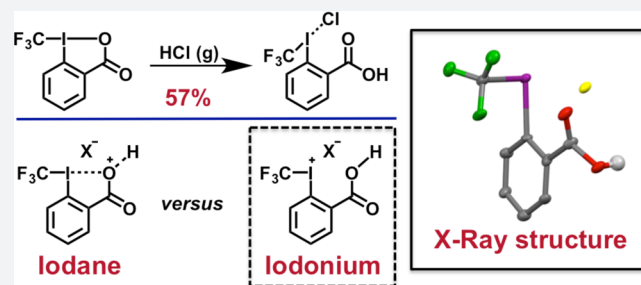
# Isolation and Reactivity of Trifluoromethyl Iodonium Salts

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## Supporting Information

**ABSTRACT:** The strategic incorporation of the trifluoromethyl (CF<sub>3</sub>) functionality within therapeutic or agrochemical agents is a proven strategy for altering their associated physicochemical properties (e.g., metabolic stability, lipophilicity, and bioavailability). Electrophilic trifluoromethylation has emerged as an important methodology for installing the CF<sub>3</sub> moiety onto an array of molecular architectures, and, in particular, CF<sub>3</sub> λ<sup>3</sup>-iodanes have garnered significant interest because of their unique reactivity and ease of handling. Trifluoromethylations mediated by these hypervalent iodine reagents often require activation through an exogenous Lewis or Brønsted acid; thus, putative intermediates invoked in these transformations are cationic CF<sub>3</sub> iodoniums. These iodoniums have, thus far, eluded isolation and investigation of their innate reactivity (which has encouraged speculation that such species cannot be accessed). A more complete understanding of the mechanistic relevance of CF<sub>3</sub> iodoniums is paramount for the development of new trifluoromethylative strategies involving λ<sup>3</sup>-iodanes. Here, we demonstrate that CF<sub>3</sub> iodonium salts are readily prepared from common λ<sup>3</sup>-iodane precursors and exhibit remarkable persistence under ambient conditions. These reagents are competent electrophiles for a variety of trifluoromethylation reactions, and their reactivity is reminiscent of that observed when CF<sub>3</sub> iodanes are activated using Lewis acids. As such, our results suggest the mechanistic relevance of CF<sub>3</sub> iodonium intermediates in trifluoromethylative processes mediated by λ<sup>3</sup>-iodanes. The isolation of CF<sub>3</sub> iodonium salts also presents the unique opportunity to employ them more generally as mechanistic probes.



## INTRODUCTION

Synthetic strategies for incorporating the trifluoromethyl (CF<sub>3</sub>) functionality into molecular scaffolds continue to garner extensive research interest, given that various therapeutic and agrochemical agents are decorated with this moiety (Figure 1).<sup>1–4</sup> Apart from serving as a metabolically stable analogue of CH<sub>3</sub>, the CF<sub>3</sub> group is also routinely harnessed as a Cl surrogate (given that the group electronegativity of CF<sub>3</sub> is commensurate with that of Cl).<sup>1–4</sup> The unique stereoelectronic properties of the CF<sub>3</sub> group render it a privileged motif for tailoring pharmacokinetics and pharmacodynamics, and the synthesis of fludelonone (a potent antimetabolic analogue of epothilone B) is a particularly salient example of how the introduction of a CF<sub>3</sub> substituent can enhance a drug's stability without sacrificing efficacy (Figure 1).<sup>5</sup> Of the available trifluoromethylative methodologies, those involving electrophilic reagents (which are typically easier to handle in the laboratory and can often be derived from inexpensive precursors) have risen to the forefront of the field.<sup>2</sup> Electrophilic trifluoromethylations involving λ<sup>3</sup>-iodanes<sup>6</sup> {e.g., 3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole [1]; 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one [2]; Figure 2}<sup>7–9</sup> have proven to be especially versatile methodologies, and the chemistry of these hypervalent iodine species has been extensively studied.<sup>10</sup> A variety of nucleophiles (including examples from groups 14–16) have been reported to undergo trifluoromethylation in the presence of 1 or 2;<sup>11–29</sup> however,

these transformations typically require the action of a Lewis or Brønsted acid in concert with the iodane. As such, CF<sub>3</sub> iodonium intermediates have long been speculated to play a critical role in the aforementioned reactions (Figure 2). Conclusively demonstrating the existence of a CF<sub>3</sub> iodonium and investigating its reactivity would be extremely valuable for elucidating mechanistic insights that can inform future reaction discovery and development.

Although spectroscopic evidence has suggested the transient existence of these species,<sup>30</sup> recent reports have rekindled the debate surrounding the relevance of CF<sub>3</sub> iodoniums. While exploring the Zn(NTf<sub>2</sub>)<sub>2</sub> [NTf<sub>2</sub> = bis(trifluoromethylsulfonyl)imide] mediated trifluoromethyl etherification of alcohols, Koller et al. isolated and characterized zinc complex 3 (Figure 2).<sup>12</sup> A salient feature of 3 is the lengthened I–O bond with respect to parent compound 2 [cf. 2.403(12) Å versus 2.283(2) Å],<sup>7</sup> which is suggestive of distortion toward a species with iodonium character. As such, the authors concluded that 3 was the reactive intermediate responsible for the observed etherifications. In a separate report, protonation of 1 with Brookhart's acid {[H(OEt)<sub>2</sub>][(3,5-CF<sub>3</sub>C<sub>6</sub>H<sub>3</sub>)<sub>4</sub>B]} was found to afford dimeric species 4 (Figure 2).<sup>31</sup> The solid-state structure of 4 exhibited elongated I–O bonds with respect to parent compound 1 [cf. 2.440(4) Å and 2.257(3) Å versus

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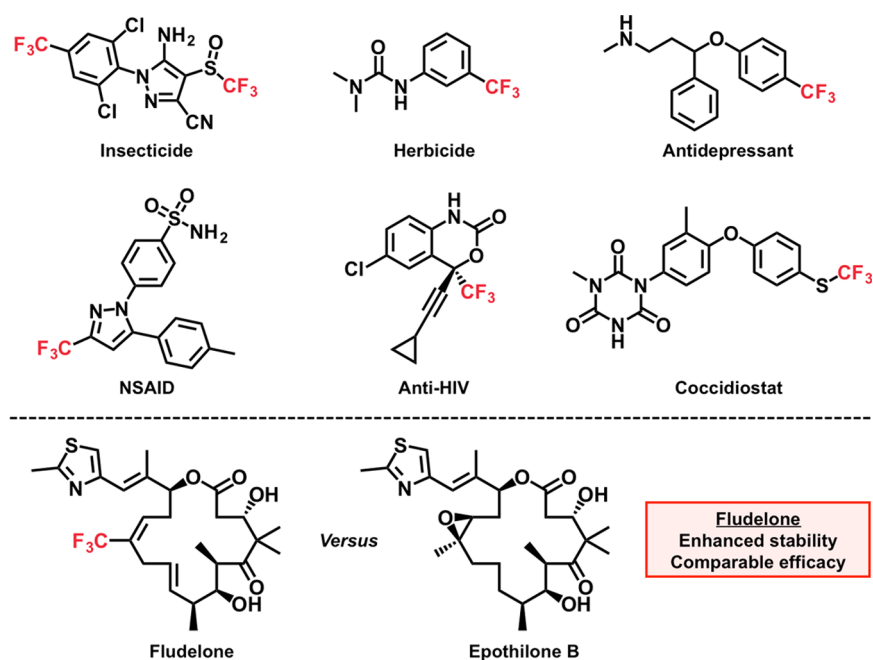


Figure 1. Representative  $\text{CF}_3$ -containing therapeutic and agrochemical compounds.

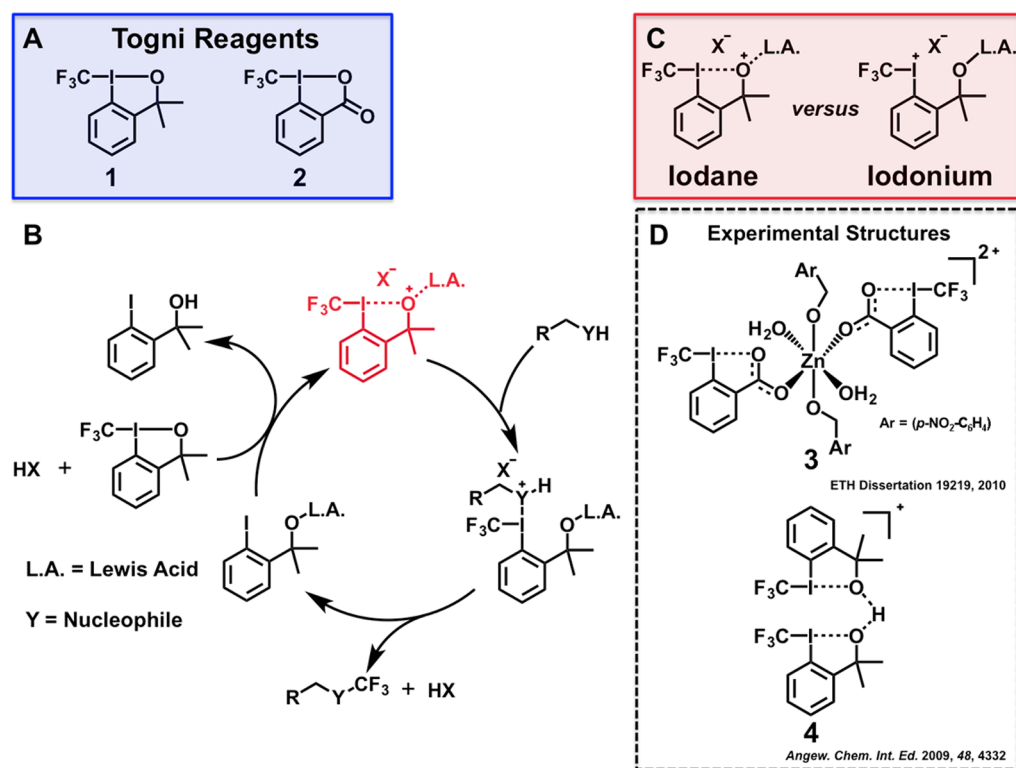
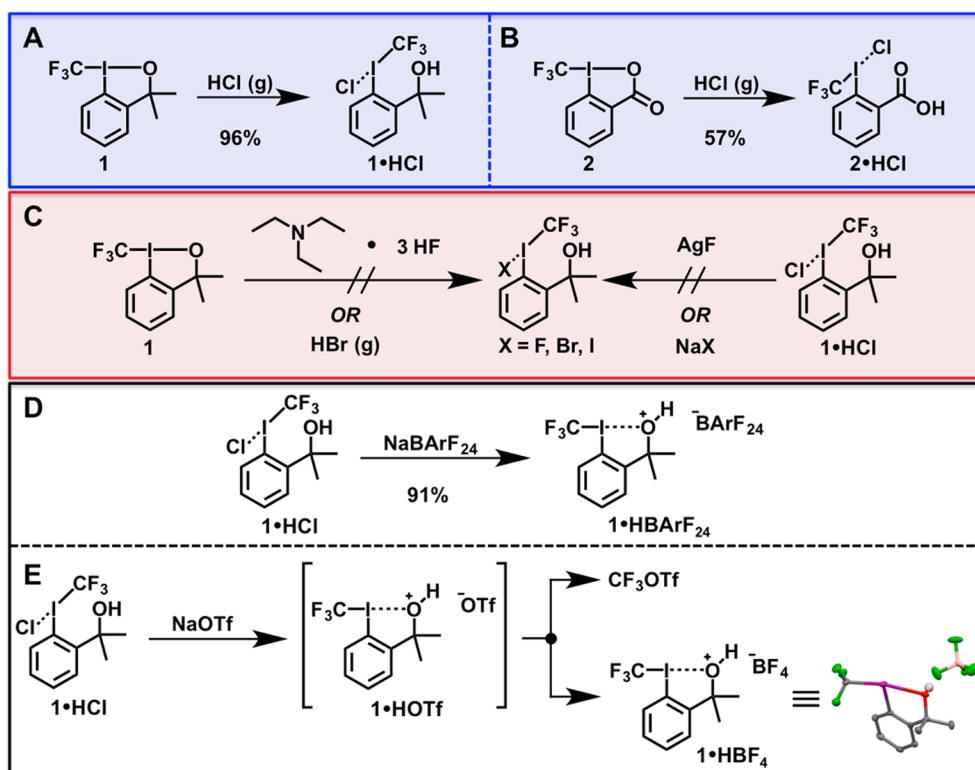
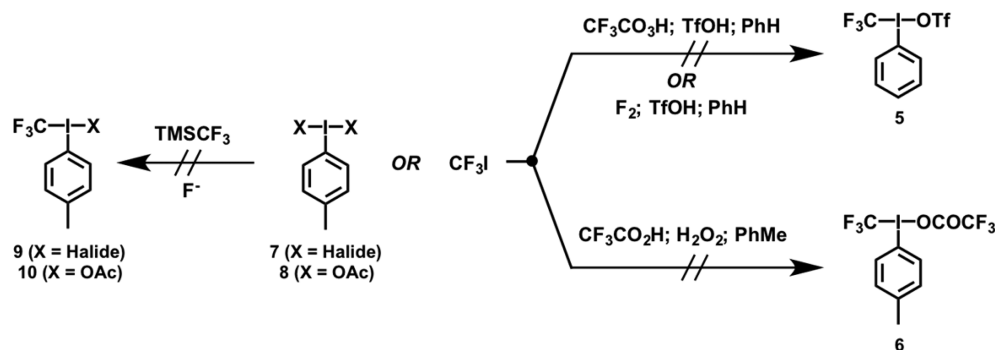


Figure 2. Trifluoromethylations involving hypervalent iodine reagents and proposed reactive intermediates. (A) Conventional  $\lambda^3$ -iodanes for electrophilic trifluoromethylation. (B) General mechanism for trifluoromethylation of a nucleophile under Lewis acid catalysis. The activated iodane is highlighted in red. (C) Structural distinctions between proposed intermediates in  $\lambda^3$ -iodane mediated trifluoromethylations. (D) Experimental evidence suggests the predominance of iodane character for 1 and 2 under Lewis or Brønsted acid activation.

2.118(2) Å],<sup>14</sup> again suggesting distortion toward a  $\text{CF}_3$  iodonium. However, interactions involving iodine(III) are known to exhibit weak covalent character, and bond lengths that exceed the sum of the covalent radii of I and O (2.06 Å) are not necessarily indicative of true iodonium character. The experimentally determined structures of 3 and 4 support the

hypothesis that activation of  $\text{CF}_3$  iodanes using Lewis or Brønsted acids does not afford the corresponding iodoniums.<sup>10</sup>

Despite decades of effort, the successful synthesis and isolation of a genuine  $\text{CF}_3$  iodonium has remained elusive (Scheme 1). Early efforts by Umemoto and Yagupolskii failed to prepare  $\text{CF}_3$  iodoniums using the respective protocols each laboratory had developed for the synthesis of perfluoroalkylio-

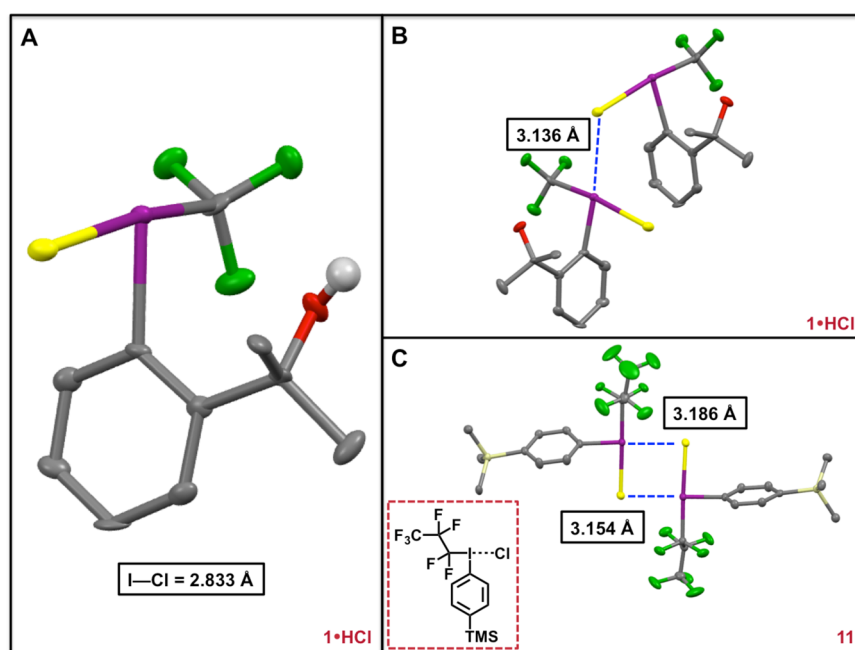
Scheme 1. Attempted Syntheses of CF<sub>3</sub> Iodoniums That Have Previously Been Reported

**Figure 3.** Synthesis of (A) 1·HCl and (B) 2·HCl by reacting their parent iodoniums with HCl (g). (C) The chloride counterion proved paramount for successful iodonium synthesis, as the remaining halide series proved ineffectual for stabilizing the nascent iodonium. (D) Anion metathesis of 1·HCl with NaBARF<sub>24</sub> afforded the corresponding salt, 1·HBARF<sub>24</sub>. (E) Anion metathesis of 1·HCl with NaOTf affords the unstable salt 1·HOTf, which subsequently decomposes via reductive elimination. One decomposition product was identified as 1·HBF<sub>4</sub>, and the X-ray structure of 1·HBF<sub>4</sub> (thermal ellipsoids at 50% probability) is shown [atom code: green (F); red (O); pink (B); violet (I)]. Only one of the two inequivalent molecules of 1·HBF<sub>4</sub> is shown. Hydrogen atoms other than the O–H atom have been omitted for clarity.

donium salts.<sup>32–34</sup> The Togni laboratory also attempted to react (dihalo)arenes and bis(acetoxy)iodoarenes with TMSCF<sub>3</sub> in the presence of CsF or tetrabutylammonium difluorotriphenylsilicate, but these synthetic efforts were ultimately unfruitful.<sup>7</sup> Given these failures, conventional wisdom has dictated that CF<sub>3</sub> iodoniums are inherently unstable and cannot be isolated. Wang and Liu more recently reported the *in situ* formation of a putative CF<sub>3</sub> iodonium (which was detected by mass spectrometry) from the reaction of TMSCF<sub>3</sub> with iodobenzene diacetate.<sup>30</sup> However, there is currently no direct evidence that CF<sub>3</sub> iodoniums are more than transient intermediates generated during ionization in a mass spectrometer.

We speculated that the inductive destabilization of the trifluoromethyl group should not necessarily preclude the

isolation of a CF<sub>3</sub> iodonium, at least from a thermodynamic perspective. Literature precedents for the isolation of C<sub>3</sub>F<sub>7</sub> iodonium salts were particularly encouraging, given that the group electronegativity of the C<sub>3</sub>F<sub>7</sub> fragment has been estimated to be similar to that of CF<sub>3</sub> (cf. ~3.3 versus 3.4, respectively, on the Pauling scale).<sup>35</sup> As such, we surmised that kinetic stabilization of the nascent ion pair would be paramount for accessing the desired iodoniums. The judicious selection of a mildly iodophilic anion seemed pertinent, given that strongly coordinating anions would generate a tight ion pair and subsequently undergo deleterious reductive eliminations. From a synthetic perspective, we decided to depart from traditional approaches to CF<sub>3</sub> iodoniums and discard (dihalo)arenes or bis(alcoxy)iodoarenes as potential precursors (given the established unsuitability of these moieties). Instead, our



**Figure 4.** (A) The solid-state structure of  $1 \cdot \text{HCl}$  (thermal ellipsoids at 50% probability). While the hydroxyl hydrogen atom is shown, all others have been removed for clarity. Atom code: green (F); red (O); violet (I); yellow (Cl). (B) Halide bridging interaction between one molecule of  $1 \cdot \text{HCl}$  in the asymmetric unit and a symmetry generated partner. (C) The solid-state structure of **11** (thermal ellipsoids at 50% probability). Hydrogen atoms have been removed for clarity. Atom code: green (F); violet (I); yellow (Cl); beige (Si).

attention focused on commercially available **1** and **2** as convenient scaffolds for transformation into the corresponding iodoniums. Cleavage of the I–O bond in **1** or **2** under the action of a Brønsted acid presented itself as a plausible route for accessing the target compounds, and we ultimately decided to employ mineral acids (which have not been investigated in this context) to ascertain whether or not halide salts of  $\text{CF}_3$  iodoniums would exhibit persistence.

## RESULTS AND DISCUSSION

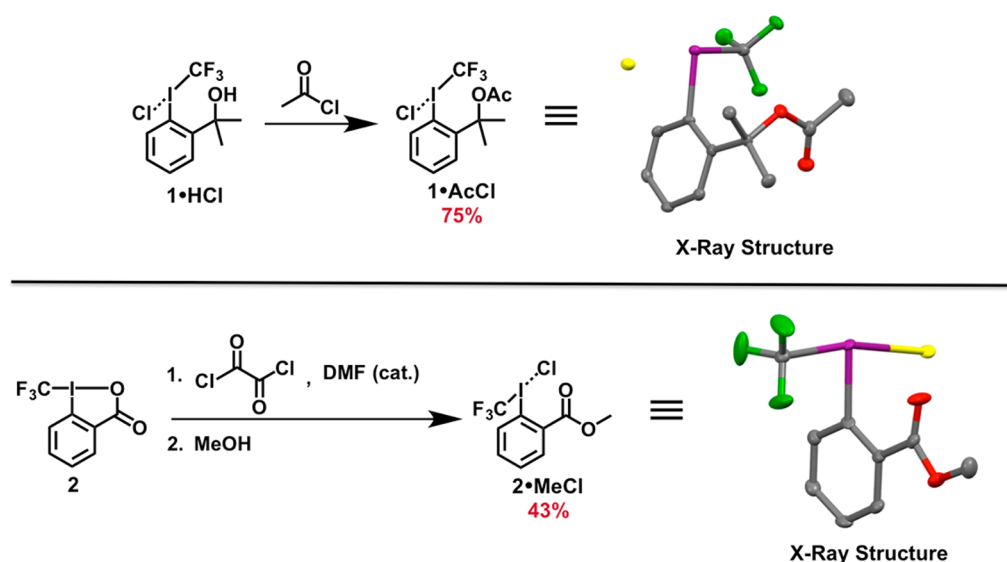
Dissolution of **1** in chloroform followed by sparging with HCl gas for approximately 5 min afforded a white, crystalline solid ( $1 \cdot \text{HCl}$ ; 96% yield) upon removal of volatiles (Figures 3 and 4). Analysis by  $^{19}\text{F}$  nuclear magnetic resonance (NMR) spectroscopy revealed a singlet that was shifted significantly downfield relative to **1** ( $\Delta\delta \approx 13$  ppm), which suggested the formation of a species with iodonium character.<sup>10</sup> The solubility properties of  $1 \cdot \text{HCl}$  were consistent with an ionic compound, as the salt exhibited poor solubility in low polarity solvents (e.g., aromatic, halogenated, or ethereal solvents). In contrast,  $1 \cdot \text{HCl}$  was readily dissolved in polar solvents (e.g., alcohols, acetone, acetonitrile). Single crystals of  $1 \cdot \text{HCl}$  spontaneously formed in a saturated  $\text{CDCl}_3$  solution and were analyzed by X-ray crystallography (Figure 4). The solid-state structure of  $1 \cdot \text{HCl}$  exhibited a distorted T-shape geometry, as evidenced by the  $173.37(16)^\circ$   $\text{C}_{\text{CF}_3}\text{--I--Cl}$  bond angle. Importantly, the I–O interatomic distance was found to be  $3.080(4)$  Å, which unambiguously indicates that there is no bonding interaction between the hypervalent iodine center and the pendent alcohol. The cleavage of the I–O bond occurs with concomitant shortening of the  $\text{C}_{\text{CF}_3}\text{--I}$  bond [cf.  $2.217(6)$  Å for  $1 \cdot \text{HCl}$  versus  $2.267(2)$  Å for **1**].

The chloride counterion interacts weakly with the iodine center [the I–Cl bond length is  $2.8331(14)$  Å], and,

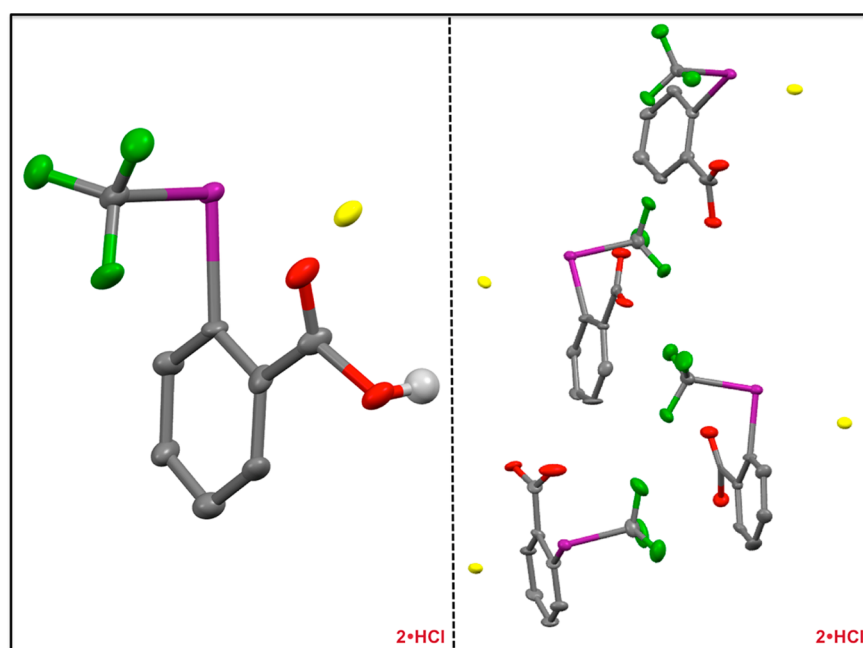
consequently, bridging chloride interactions are observed throughout the structure of  $1 \cdot \text{HCl}$  (Figure 4). Notably, the observed I–Cl bond length is significantly longer than the distances observed in  $\text{CF}_3\text{ICl}_2$  [ $2.478(2)$  Å and  $2.4572(2)$  Å]<sup>36</sup> and iodobenzene dichloride [ $2.45(15)$  Å].<sup>37</sup> Furthermore, the I–Cl length of  $1 \cdot \text{HCl}$  approaches the I–Cl<sub>bridging</sub> interactions observed in diphenyliodonium chloride [ $3.064(3)$  Å and  $3.105(3)$  Å].<sup>38</sup> We also note that the distorted T-shape geometry of  $1 \cdot \text{HCl}$  is consistent with that observed for diphenyliodonium chloride. Whereas the  $\text{CF}_3\text{--I--C}_{\text{aryl}}$  bond angle of  $1 \cdot \text{HCl}$  is  $90.5(2)^\circ$ , the  $\text{C}_{\text{aryl}}\text{--I--C}_{\text{aryl}}$  bond angle of diphenyliodonium chloride is  $92.6(3)^\circ$ .<sup>38</sup> Crystal packing forces can clearly enforce a coordination environment that favors the T-shape geometry; thus, distortion from a bent geometry (which one might anticipate for an iodonium salt) in the solid state does not necessarily preclude the existence of such a geometry in solution. We also prepared perfluoroalkyl iodonium chloride **11** for additional comparison, and a number of salient features regarding the crystal structure of **11** merit discussion [see the Supporting Information for additional details]. Figure 4 shows the two inequivalent molecules of **11** in the unit cell, which both exhibit similar distorted T-shape geometries (the  $\text{C}_{\text{alkyl}}\text{--I--Cl}$  bond angles are  $178.14(7)^\circ$  and  $178.78(7)^\circ$ , respectively). Moreover, the I–Cl bond lengths observed in **11** [ $2.7546(7)$  Å and  $2.7826(7)$  Å] are both significantly shorter than that of  $1 \cdot \text{HCl}$ . Taken together these data suggest that  $1 \cdot \text{HCl}$  exhibits significant iodonium character.

Consistent with our kinetic stabilization hypothesis (*vide supra*), the nature of the iodonium counteranion profoundly influenced the overall persistence of the salt (Figure 3). Treatment of **1** with triethylamine trihydrofluoride or salt metathesis of  $1 \cdot \text{HCl}$  with  $\text{AgF}$  did not afford  $1 \cdot \text{HF}$ . In both instances we only observed **1**, which suggests that the electronegativity of F precludes a sufficient enthalpic binding affinity to overcome the chelate effect from the pendent

Scheme 2. (Top) Synthesis of **1**·AcCl by Dissolution of **1**·HCl in Neat Acetyl Chloride at Room Temperature.<sup>a</sup> (Bottom) Synthesis of **2**·MeCl under Vilsmeier–Haack Conditions<sup>b</sup>



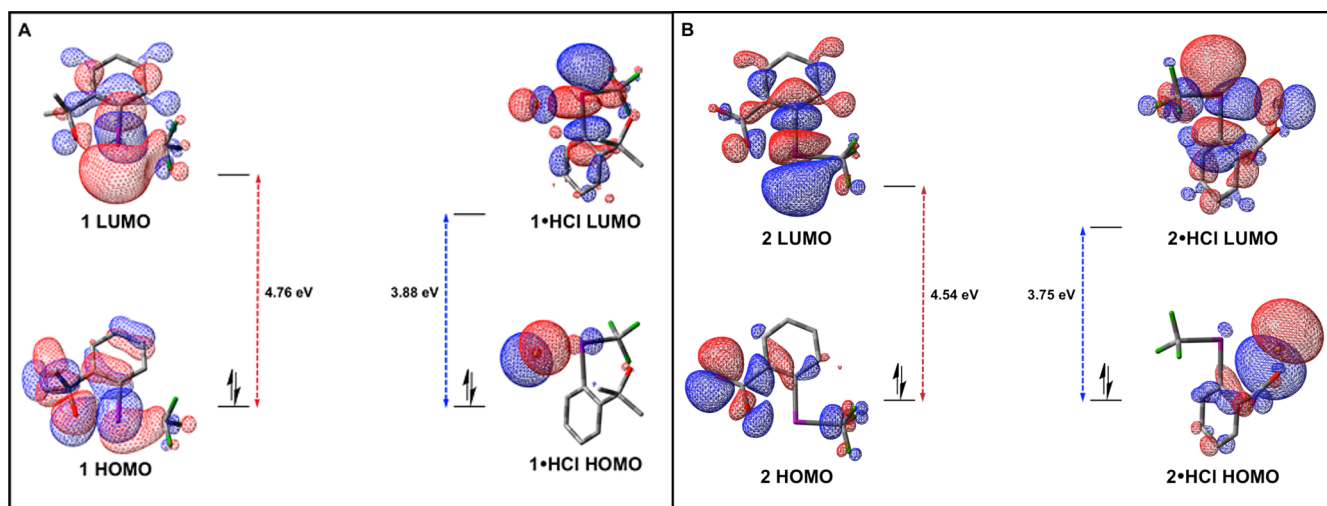
<sup>a</sup>The solid-state structure of **1**·AcCl is also shown (thermal ellipsoids at 50% probability). Hydrogen atoms are omitted for clarity. Atom code: green (F); red (O); violet (I); yellow (Cl). <sup>b</sup>Note: The acyl chloride intermediate is directly esterified without isolation. The solid-state structure of **2**·MeCl is also shown (thermal ellipsoids at 50% probability). Hydrogen atoms are omitted for clarity. Atom code: green (F); red (O); violet (I); yellow (Cl).



**Figure 5.** Solid-state structure of **2**·HCl. (Left) One of the four inequivalent molecules in the asymmetric unit (thermal ellipsoids at 50% probability). While the carboxylic acid hydrogen atom is shown, the remaining hydrogen atoms are omitted for clarity. Cocrystallized MeCN has also been omitted for clarity. Atom code: green (F); red (O); violet (I); yellow (Cl). (Right) The asymmetric unit observed for crystalline **2**·HCl (thermal ellipsoids at 50% probability). Hydrogen atoms and MeCN solvent molecules omitted for clarity.

oxygen. Although the reaction of **1** with HBr gas afforded a new compound exhibiting a <sup>19</sup>F NMR spectrum that was reminiscent of **1**·HCl, this species decomposed into a mixture of **1**, CF<sub>3</sub>Br, CF<sub>3</sub>I, and other minor byproducts after sitting at room temperature. Similarly, anion metathesis of **1**·HCl with NaBr led to the rapid formation of CF<sub>3</sub>I and CF<sub>3</sub>Br. Finally, salt metathesis of **1**·HCl was attempted with NaI, but only CF<sub>3</sub>I and small amounts of **1** were observed. These results indicate that bromide and iodide are both sufficiently reducing to

destabilize **1**·HBr and **1**·HI. Pseudohalide counteranions also proved deleterious, as **1**·HOTf (prepared from **1**·HCl using NaOTf) slowly decomposed in solution to afford primarily CF<sub>3</sub>OTf (Supporting Information). Interestingly, **1**·HBF<sub>4</sub> was generated during the decomposition of **1**·HOTf, as determined by X-ray crystallography (Figure 3). Presumably one of the decomposition products of **1**·HOTf abstracted boron from the borosilicate glass vessel in which the salt was generated. The I–O bond lengths observed in the solid state structure of **1**·HBF<sub>4</sub>



**Figure 6.** Electronic structure calculations showing the frontier molecular orbitals of (A) **1** and **1·HCl** and (B) **2** and **2·HCl** [DFT; B3LYP; 6-311+G(d,p)].

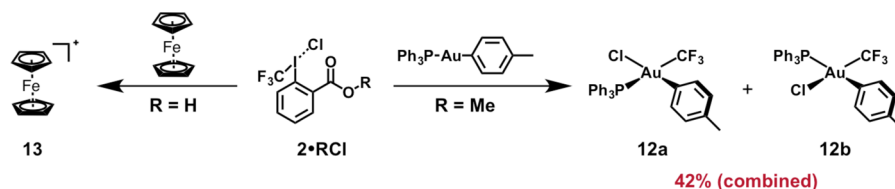
[2.514(4) Å and 2.504(3) Å] indicate that this species does not exhibit a meaningful degree of iodonium-like character, which is consistent with poor stabilization of the I(III) center by the  $\text{BF}_4$  anion. Inspired by this result, we attempted anion metathesis between **1·HCl** and other weakly coordinating counterions. For example, reaction of **1·HCl** with sodium tetrakis(3,5-trifluoromethyl)phenylborate ( $\text{NaBARF}_{24}$ ) generated **1·HBARF**<sub>24</sub> in excellent yield (91%; [Supporting Information](#)).

**1·HCl** is remarkably stable as a solid under ambient conditions (i.e., no decomposition was observed by  $^{19}\text{F}$  NMR after several months) and appears to be indefinitely stable at 4 °C. No precautions to exclude air or water are required when storing or handling **1·HCl**, and solutions of **1·HCl** may be heated to 80 °C without detectable decomposition. While we have not observed explosive decomposition of **1·HCl** while working with the reagent on larger scales (up to ~5.5 mmol), it should be noted that **1·HCl** decomposes violently when heated above 100 °C [as determined by differential scanning calorimetry (DSC); see [Supporting Information](#)]. Intriguingly, **1·HCl** may be further elaborated using routine transformations; for example, dissolution of the compound in neat acetyl chloride afforded **1·AcCl** in 75% yield ([Supporting Information](#); [Scheme 2](#)).

Our synthetic approach could also be extended to prepare  $\text{CF}_3$  iodoniums from **2** ([Figures 3](#) and [5](#)). Dissolution of **2** in dichloromethane followed by sparging with HCl gas for approximately 30 min induced the precipitation of **2·HCl** in 57% yield. As in the case of **1·HCl**, we found that **2·HCl** was only sparingly soluble in most organic solvents (with the exception of highly polar solvents). Slow crystallization of **2·HCl** from a saturated MeCN solution at  $-30$  °C afforded single crystals suitable for X-ray crystallographic analysis ([Figure 5](#)). The four inequivalent molecules of **2** in the asymmetric unit all exhibited the expected distorted T-shape geometries [ $\text{C}_{\text{CF}_3}$ –I–Cl bond angles of 177.4(2)°, 169.0(2)°, 174.6(2)°, and 172.0(2)°]. The I–O interatomic distances [3.058(6) Å, 2.956(6) Å, 2.963(7) Å, and 3.010(6) Å] are all consistent with the conclusion that no bonding interactions occur between the iodonium center and the ancillary carboxylic acids. As in the case of **1·HCl**, the long I–Cl bond lengths [2.996(2) Å, 2.942(2) Å, 3.001(2) Å, and 2.891(2) Å] result in bridging halide interactions within the solid state. The large fluctuation

in I–Cl bond lengths is a testament to the ionic nature of **2·HCl**, as one would not expect crystal packing forces to have such a pronounced influence on the length of significantly covalent interactions. Furthermore, the extremely long I–Cl bond lengths observed in the solid state (which are commensurate with those observed for diphenyliodonium chloride;<sup>38</sup> *vide supra*) unambiguously demonstrate the iodonium nature of **2·HCl**.<sup>39</sup> As with **1·HCl**, we could also prepare derivatives of **2·HCl**. For example, methyl ester **2·MeCl** could be prepared in 43% yield using a modified synthetic procedure ([Supporting Information](#); [Scheme 2](#)).

Having established synthetic routes to the targeted iodonium salts, we next turned our attention to evaluating their intrinsic reactivity. Electronic structure calculations were utilized to compare the frontier molecular orbitals of **1·HCl** and **2·HCl** to their parent iodonanes ([Supporting Information](#); [Figure 6](#)). All calculations were conducted using density functional theory,<sup>40</sup> with the B3LYP exchange-correlation energy functional,<sup>41</sup> the 6-311+G(d,p) basis set<sup>42</sup> for atoms other than I, and an effective core potential for I. To ensure that any qualitative trends were not basis set dependent, we also performed calculations using the aug-cc-PVTZ basis set for atoms other than I, and an effective core potential for I.<sup>10</sup> The lowest unoccupied molecular orbital (LUMO) of **1** is an antibonding orbital aligned along the  $\text{C}_{\text{aryl}}$ –I bond axis. In contrast, the LUMO of **1·HCl** exhibits antibonding character that is substantially polarized toward the  $\text{C}_{\text{CF}_3}$ –I bond (which suggests significant weakening of the associated 3c–4e interaction).<sup>10</sup> Moreover, the LUMO of **1·HCl** is substantially lowered with respect to that of **1**, which indicates that **1·HCl** should be a more potent oxidant. While the highest occupied molecular orbital (HOMO) of **1** exhibits antibonding character along the I–O bond, the HOMO of **1·HCl** is predominated by a  $\pi$ -antibonding I–Cl interaction. Qualitatively, the orbital characteristics for the HOMO and LUMO of **2·HCl** are analogous to that observed in **1·HCl** (the same is true for the HOMO/LUMO characteristics of **2** relative to **1**). The LUMO of **2·HCl** is significantly lowered with respect to the LUMO of **2**, consistent with the conclusion that **2·HCl** should exhibit enhanced electrophilicity. As a testament to the oxidizing capability of these iodonium species (which one would expect, given their low-lying LUMOs), we found that various transition

Scheme 3. Oxidation of Au(I) and Fe(II) Complexes by CF<sub>3</sub> Iodoniums<sup>a</sup>

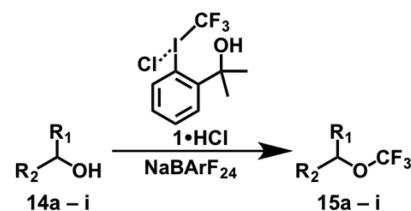
<sup>a</sup>General conditions: iodonium (1.0–3.0 equiv) and metal complex (1.0 equiv) were combined at room temperature and stirred (2–20 min). See the Supporting Information for complete details.

metals [e.g., Fe(II) and Au(I)] were susceptible to oxidation by a CF<sub>3</sub> iodonium (Scheme 3; Supporting Information; Figure S1).

The isolation of 1·HCl and 2·HCl presented the unique opportunity to also investigate the innate reactivity of CF<sub>3</sub> iodoniums experimentally. Within the purview of mechanistic considerations, comparing the reactivity profiles of 1·HCl and 2·HCl to those of Lewis activated 1 and 2 would undoubtedly be informative. For example, Zn activation has been shown to facilitate CF<sub>3</sub> ether formation from the reaction of alcohols with 2.<sup>12</sup> We found that both 1·HCl and 2·HCl were competent electrophiles for the direct trifluoromethylation of alcohols under solvolytic conditions (Supporting Information); however, the limited solubility of these reagents proved to be an impediment to further reaction optimization. To address this issue, we envisaged leveraging their ionic character under phase transfer conditions. NaBARF<sub>24</sub> was selected as a suitable phase transfer catalyst, as 1·HBARF<sub>24</sub> was found to have optimal solubility and kinetic persistence (*vide supra*). Gratifyingly, our strategy afforded CF<sub>3</sub> ethers from the corresponding alcohols under mild conditions (55 °C; 3.0 equiv of the alcohol; 10 mol % NaBARF<sub>24</sub>; 16 h) and in modest yields (Supporting Information; Table 1). Primary and secondary alcohols were suitable substrates, but aryl and tertiary alcohols proved ineffectual (for example, phenol gave poor yields of primarily ring substituted products). The direct use of 1·HBARF<sub>24</sub> in a control reaction afforded the desired CF<sub>3</sub> ether in modest yield, which supported the validity of the proposed phase transfer pathway (Supporting Information). We should stress that, since both the iodonium and the protonated iodane are competent reagents for alcohol trifluoromethylation (and interconversion between the two species under the reaction conditions cannot be excluded), the reactive intermediate responsible for alcohol trifluoromethylation could plausibly exhibit structural homology to either of these compounds.

Building on these results, we found that our phase transfer methodology could be extended to benzotriazole, affording a 19:1 mixture of N-trifluoromethylated isomers 17a and 17b in 59% combined yield (Scheme 4). This reactivity is commensurate with previous reports, wherein 17a could be prepared in 58% yield by reacting benzotriazole with 1 in CS<sub>2</sub> at 60 °C.<sup>19</sup> Benzimidazole could also be trifluoromethylated under phase transfer conditions to afford 19 in 41% yield (Scheme 4). The direct N-trifluoromethylation of benzimidazole is noteworthy, given that previous reports required *in situ* silylation of the azole to afford good yields (i.e., 71%).<sup>19,43</sup> Similar to reactivity observed under Cu activation,<sup>28,44</sup> 2·HCl was found to react directly with both carboxybenzyl protected skatole [furnishing 2-(trifluoromethyl) analogue 21 in 49% yield] and 1,1-diphenylethylene (furnishing vinyl product 23 in 37% yield) under relatively mild conditions (Scheme 4).

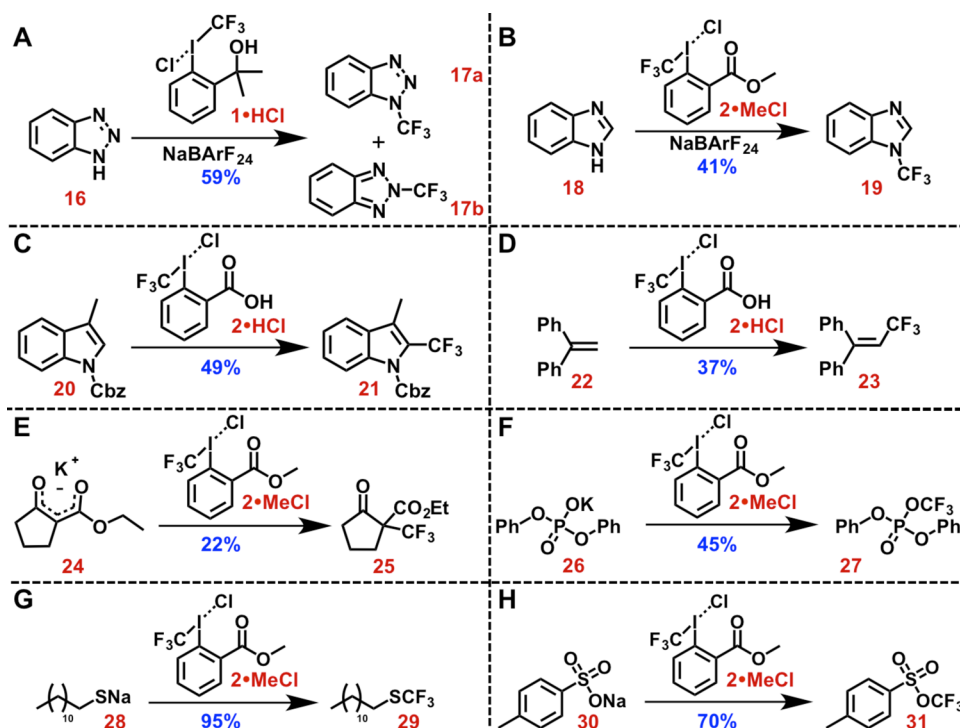
Table 1. Trifluoromethylation of Alcohols under Phase Transfer Catalysis<sup>a</sup>



Product	Yield (%) <sup>b</sup>
15a	55 (55)
15b	28 (28)
15c	30 (---)
15d	18 (12)
15e	35 (49)
15f	58 (98 <sup>c</sup> ); 88 <sup>d</sup>
15g	39 (27); 23 <sup>e</sup>
15h	39 (74 <sup>c</sup> ); 43 <sup>f</sup>
15i	23 (62 <sup>c</sup> ); 60 <sup>d</sup>

<sup>a</sup>Conditions: 1·HCl (1.0 equiv), alcohol (3.0 equiv), and NaBARF<sub>24</sub> (0.1 equiv) are added to MeCN in a conical tube ([1·HCl]<sub>0</sub> = 0.5 M) and heated at 55 °C for 16 h. <sup>b</sup>Determined by <sup>19</sup>F NMR spectroscopy using 4-fluorobiphenyl as an internal standard. Parenthetical yields are taken from ref 12 for comparison. <sup>c</sup>Yield from ref 12 using 75 equiv of alcohol. <sup>d</sup>NMR yield using 75 equiv of alcohol. <sup>e</sup>Isolated yield. <sup>f</sup>NMR yield using 10 equiv of alcohol.

Anionic carbon or heteroatom nucleophiles were also found to react with these iodonium reagents. For example, the potassium salt of 2-ethoxycarbonyl-1-cyclopentanone reacted with 2·MeCl to afford  $\alpha$ -trifluoromethylated product 25 in 22% yield

Scheme 4. Reactions of CF<sub>3</sub> Iodoniums with Azole (A, B), Indole (C), Olefinic (D), Enolate (E), Phosphate (F), Sulfide (G), and Sulfonate (H) Nucleophiles<sup>a</sup>

<sup>a</sup>General conditions: iodonium (1.0 equiv), substrate (1.0–3.0 equiv), and NaBARF<sub>24</sub> (0.0–0.1 equiv) were combined and stirred at an appropriate temperature (room temperature to 60 °C; 2–16 h). See the Supporting Information for complete details.

(Scheme 4). By comparison, related  $\beta$ -keto esters were found to react directly with Togni-type reagents in similar yields (40–67%).<sup>14</sup> The potassium salt of diphenylphosphate and sodium dodecyl sulfide reacted with 2·MeCl to afford the corresponding O- and S-trifluoromethylated products (27 and 29) in 45% and 95% yield, respectively. In contrast, diphenylphosphoric acid and dodecanethiol both gave poor yields of 27 and 29 (6% and 0%, respectively) under identical conditions. Previous work has established that Togni-type reagents react with phosphates<sup>45</sup> and sulfides<sup>14</sup> to afford congeners of 27 and 29 in similar yields (21–44% and 51%, respectively). The sodium salt of *p*-toluenesulfonic acid also reacted with 2·MeCl to afford O-trifluoromethyl sulfonate 31 in 70% yield (for comparison, *p*-toluenesulfonic acid reacted under identical conditions to afford 31 in 78% yield). Again, the reactivity observed here parallels previous reports, which found that 31 could be prepared from 2 in 90% yield.<sup>13</sup> In contrast, the salts of hard (i.e., less iodophilic) nucleophiles (such as potassium *tert*-butoxide, potassium benzotriazolide, potassium phthalimide, and sodium benzoate) failed to give any product upon salt metathesis. This suggests that harder nucleophiles react along a different pathway than the established reaction coordinate for sulfonates and phosphates. Previous kinetic studies regarding the reaction of sulfonic<sup>13</sup> and phosphoric acids<sup>45</sup> with Togni-type reagents have suggested an operative mechanism involving initial protonation and subsequent reductive elimination to form the trifluoromethylated product, which is consistent with our salt metathesis results. The failure of harder nucleophiles to exhibit analogous reactivity suggests that the mechanism for product formation in these cases is more complex. Regardless, these data show that CF<sub>3</sub> iodoniums could play a mechanistic role in reactions involving diverse nucleophiles.

In summary, the data reported here unambiguously demonstrate that CF<sub>3</sub> iodonium salts are observable species, and, in fact, they can be readily prepared from conventional  $\lambda^3$ -iodanes under the action of mineral acids. Chloride salts were found to exhibit optimal persistence, presumably the result of a subtle balance of iodophilicity and electronegativity. More weakly coordinating anions provided insufficient kinetic stabilization (resulting in the formation of species more accurately described as protonated iodanes), and strongly coordinating counterions induced decomposition through reductive elimination pathways. These iodonium salts were capable of trifluoromethylating an array of nucleophiles, suggesting that CF<sub>3</sub> iodoniums should not immediately be discarded as relevant intermediates when considering the mechanisms of reactions involving activated CF<sub>3</sub> iodanes. Indeed, in some cases the iodonium chloride itself was found to be a competent surrogate for iodane–Lewis acid systems (which suggests the broad potential use of isolated CF<sub>3</sub> iodoniums as mechanistic probes). The data presented here will undoubtedly inspire new synthetic strategies for trifluoromethylation, and future studies investigating the complete reactivity of CF<sub>3</sub> iodoniums will be reported in due course.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscentsci.6b00119.

- Crystallographic data for 1·HBF<sub>4</sub> (CIF)
- Crystallographic data for 1·HCl (CIF)
- Crystallographic data for 2·HCl (CIF)
- Crystallographic data for 2·MeCl (CIF)
- Crystallographic data for 11 (CIF)



Crystallographic data for 1-AcCl (CIF)

Experimental details including synthetic, oxidation, halide metathesis, and trifluoromethylation procedures, computational methods and data, UV profiles, NMR spectra, crystallographic, DSC, and TGA data, and cyclic voltammograms (PDF)

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### Notes

The authors declare no competing financial interest.

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