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Unexpected Reactivity of cyclic Perfluorinated Iodanes with Electrophiles

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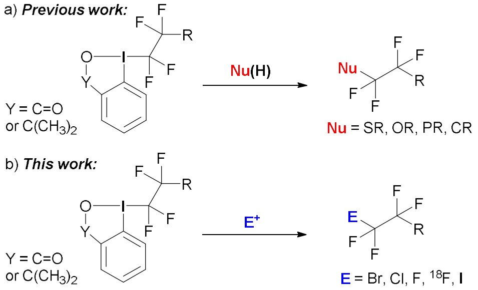
We have found that cyclic perfluorinated iodanes react with electrophiles (E^+ = Br, Cl, F, I) to afford perfluorinated E-R_F compounds. This reactivity is unexpected, since cyclic perfluorinated iodanes are considered as electrophilic reagents that normally react with nucleophiles (e.g. Nu^- = SR, OR) to afford Nu-R_F products. The utility of this new transformation is demonstrated for a $[^{18}F]CF_3CF_2$-containing compound which was prepared from $[^{18}F]XeF_2$ obtained from cyclotron produced $[^{18}F]$fluoride.

During the last decade hypervalent iodine compounds have enjoyed a very rich chemistry and therefore many novel reagents and reactions have been developed, including reagents for the introduction of fluorinated fragments.[1] In particular, the trifluoromethylating reagents developed by the group of Togni (3,3-dimethyl-1-(trifluoromethyl)-3H-1λ^3,2-benziodaoxole and 1-(trifluoromethyl)-3H-1λ^3,2-benziodaoxol-3-one) have attracted considerable interest and found practical applications in organofluorine chemistry and homogeneous catalysis.[2]

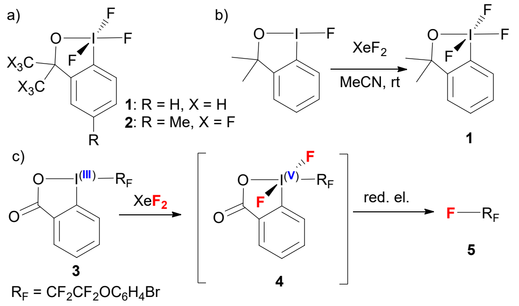


Scheme 1 Reactivity of perfluorinated hypervalent iodine reagents with: a) nucleophiles; b) electrophiles (*this work*).

Based on the successful utilization of these reagents the group of Togni has recently reported on the synthesis and application of cyclic hypervalent iodine compounds bearing perfluoroalkyl groups.[3] These novel reagents were used for the electrophilic perfluoroalkylation of various sulfur, oxygen, phosphorus and carbon nucleophiles (see Scheme 1a).

Herein, we describe the unexpected reactivity of perfluorinated iodanes with electrophiles (E^+ = Br, Cl, F, I) to afford perfluorinated E-R_F compounds. Furthermore, we demonstrate that this novel transformation can be used for the radiosynthesis of a $[^{18}F]CF_3CF_2$-Ar compound (see Scheme 1b).

The incentive to explore this chemistry came from the work of Martin on iodane(V) compounds almost 40 years ago, where he reported on the preparation and isolation of fluoro-iodane(V) compounds **1** and **2** (Scheme 2a).[4] Furthermore, a recent report demonstrated that compound **1** can be prepared by treating the corresponding fluoro-iodane(III) precursor with XeF_2 (Scheme 2b).[5] Based on these results we speculated that treatment of perfluorinated iodane(III) **3** with XeF_2 could afford the fluoro-iodane(V) intermediate **4** which potentially can undergo a reductive elimination to afford the pentafluorinated product **5** (Scheme 2c).



Scheme 2 a) Stable fluoro-iodanes(V) **1** and **2**.[4] b) Preparation of fluoro-iodane(V) **1** with XeF_2.[5] c) Desired transformation to afford the pentafluorinated product (F-R_F).

Initial experiments conducted in acetonitrile-d_3 in AR-glass vials between perfluorinated iodane **3** and XeF_2 at room temperature and 70 °C, respectively, revealed no formation of the desired pentafluorinated product **5**. However after 1 hour

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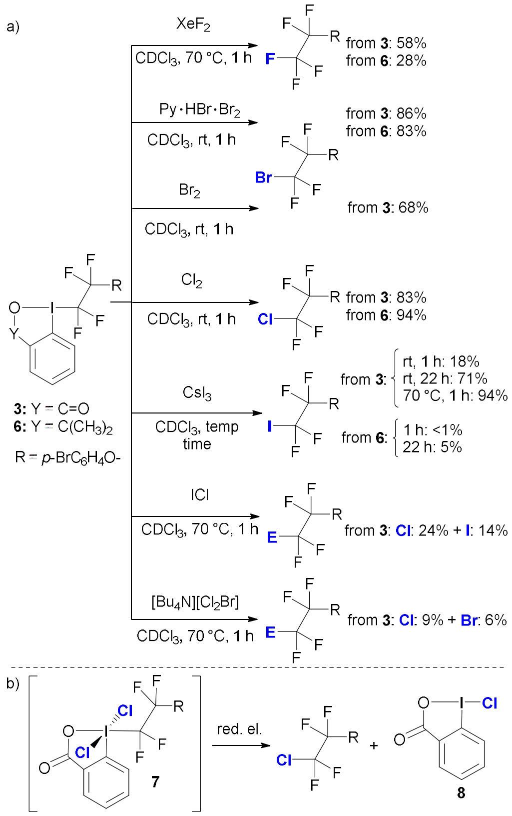
at 70 °C in chloroform-d_1 in a Reacti-Vial™ (made of borosilicate-glass[6]) the desired product was obtained in 58% yield (Scheme 3a).[7]



Scheme 3 a) Reaction of perfluorinated iodanes **3** and **6** with various electrophiles. Yields were determined with ^{19}F NMR using PhOCF$_3$ as internal standard. XeF$_2$: 1.5 equiv.; PyHBr$_3$: 1.5 equiv.; Br$_2$: 2.0 equiv.; Cl$_2$: excess gas; CsI$_3$: 1.5 equiv.; ICl: 2.0 equiv.; [Bu$_4$N][Cl$_2$Br]: 1.5 equiv. b) Reductive elimination from the postulated iodane(V) intermediate **7** should afford the desired product together with chloro-iodane by-product **8**.

In view of these results we were curious to known whether the reaction would be feasible with other electrophiles (E$^+$ = Br, Cl, I, see Scheme 3a). Performing the reaction in the presence of pyridinium tribromide or Br$_2$ at room temperature for one hour afforded p-Br-Ph-OCF$_2$CF$_2$Br in a yield of 86% and 68%, respectively as determined from NMR studies.[8] Furthermore, p-Br-Ph-OCF$_2$CF$_2$Cl could be obtained in 83% yield by reacting perfluorinated iodane **3** with chlorine gas at room.[9] Treatment of perfluorinated iodane **3** with CsI$_3$ for 1 hour at room temperature afforded the corresponding iodinated compound p-Br-Ph-OCF$_2$CF$_2$I in low NMR yield (18%).[8] However, performing the reaction for 22 hours or at elevated temperature (70 °C) afforded the product in 71% and 94% yield, respectively. A similar reactivity was observed when the corresponding alcohol-derived perfluorinated iodane **6** was treated with XeF$_2$, pyridinium tribromide and chlorine gas. Conversion to the desired F, Br and Cl-substituted products was observed in 28%, 83% and 94%, respectively. However, performing the reaction in the presence of CsI$_3$ afforded only traces of p-Br-Ph-OCF$_2$CF$_2$I, even after 22 hours (~5%).

Since we never observed any potential iodane(V) intermediates during our ^{19}F-NMR studies, we consequently performed the reaction with interhalogens to get a better understanding of the reaction. If the reaction proceeds via a penta-coordinated iodane(V) species the subsequent reductive elimination could lead to two different elimination products. Indeed, the reaction between ICl and perfluorinated iodane **3** at 70 °C[10] for one hour afforded a mixture of p-Br-Ph-OCF$_2$CF$_2$I (14%), p-Br-Ph-OCF$_2$CF$_2$Cl (24%) and remaining starting material **3** (62%).[11] Furthermore, treatment of perfluorinated iodane **3** with tetrabutylammonium dichlorobromide for one hour at 70 °C yielded p-Br-Ph-OCF$_2$CF$_2$Cl (9%), p-Br-Ph-OCF$_2$CF$_2$Br (6%) and remaining starting material **3** (85%). These experiments reveal that a reaction pathway via an iodane(V) intermediate could be plausible since two different halogenated products were observed. Based on this observation we then reinvestigated the reaction between perfluorinated iodane **3** with chlorine gas in detail to evaluate if the related chloro-iodane by-product **8** is present after reductive elimination from the postulated intermediate **7**. (Scheme 3b) Indeed, the ^{1}H NMR spectrum revealed the formation of the desired product p-Br-Ph-OCF$_2$CF$_2$Cl and chloro-iodane by-product **8** (see Figure S1 in the Supporting Information).

After exploring the reactivity of perfluorinated iodanes **3** and **6** with electrophiles, we next turned our attention to evaluate their reactivity with HCl.[12] Treatment of perfluorinated iodanes **3** and **6** with HCl afforded the corresponding chloride-derived compounds **9** and **10** in 93% and 92% yield, respectively (Figure 1a).

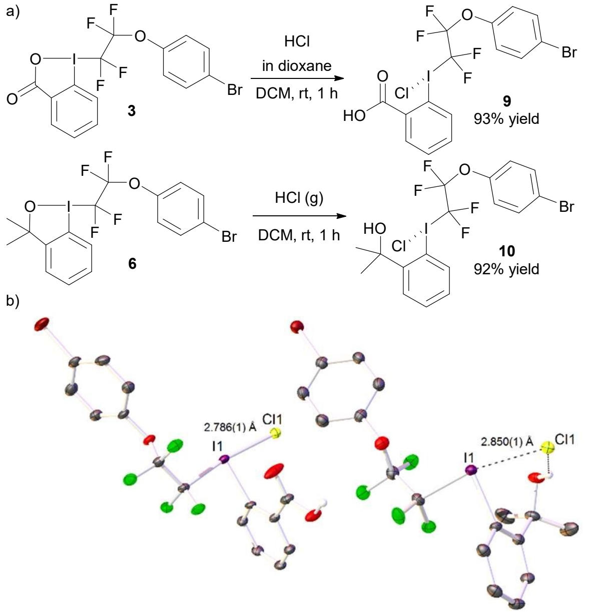


Fig. 1 a) Synthesis of chloride-derived perfluorinated iodanes **9** and **10**. b) Solid-state structure of **9** (left) and **10** (right).

The crystal structures of these compounds are shown in Figure 1b. The I1-Cl1 bond length of 2.786(1) Å in **9** is significantly longer than the iodine-chlorine bond of related cyclic chloro-iodanes (e.g. 2.461(1) Å for chloro-iodane **8**[13]). This indicates that the chloride ion is only weakly bond to the iodine atom, which is consistent with

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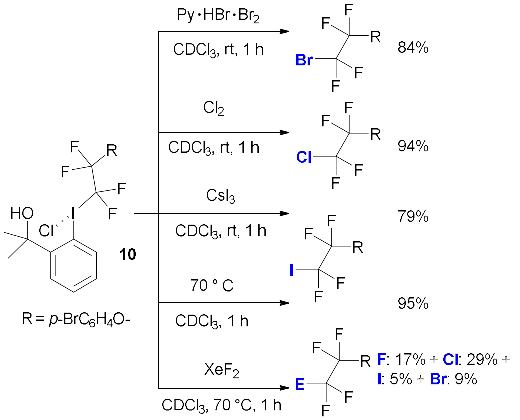
reported solid-state structures of CF_3-iodonium chlorides.[12a] The solid-state structure of **10** reveals an even weaker interaction between the iodine atom and chloride ion (I1-Cl1 bond length of 2.850(1) Å), however this distance is still shorter than the sum of the van der Waals radii (3.73 Å)[14].

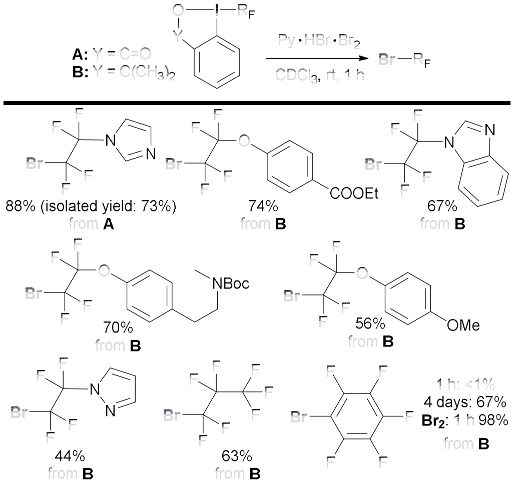
As a next step, we decided to investigate the reactivity of these chloro-iodanes with electrophiles, however the insolubility of iodane **9** in chloroform-d_1 precluded further reactivity studies. As shown in Scheme 4, the Br, Cl and I-substituted products were obtained in 84%, 94% and 79% yield, respectively. The formation of *p*-Br-Ph-OCF_2CF_2I in the presence of CsI_3 clearly reveals that iodane **10** exhibits a different reactivity profile than iodane **6**, which did not react in the presence of CsI_3 (see Scheme 3a). Interestingly, heating a solution of iodane **10** for one hour at 70 °C led to the formation of *p*-Br-Ph-OCF_2CF_2I in 95% yield. No formation of *p*-Br-Ph-OCF_2CF_2Cl was observed, which suggests that no Cl-R_F-reductive elimination from the iodane(III) species **10** occurred. Heating iodane **10** in the presence of XeF_2 afforded mainly the F and Cl-substituted products, but also minor quantities of *p*-Br-Ph-OCF_2CF_2I and *p*-Br-Ph-OCF_2CF_2Br[15] were observed.



Scheme 4 Reaction of perfluorinated iodane **10** with various electrophiles. Yields were determined with ^{19}F NMR using $PhOCF_3$ as internal standard. $PyHBr_3$: 1.5 equiv.; Cl_2: excess gas; CsI_3: 1.5 equiv.; XeF_2: 1.5 equiv.

To evaluate if such a reactivity is also possible with various other cyclic perfluorinated iodanes, reactions between pyridinium tribromide[16] and several R_F-iodanes (R_F = R-CF_2CF_2-) were investigated (Scheme 5). The desired Br-substituted products were obtained in NMR yields between 44 - 88% and a first experiment on a preparative scale (0.5 mmol of iodane) showed that imidazole-CF_2CF_2Br could be isolated in 73% yield.

Continuing, the reactivity between the non-perfluoroalkyl derived R_F-iodane **11**[12b] (R_F = F_5C_6-) was explored. In contrast to the perfluoroalkyl derived iodanes, the reaction was very slow and after four days at room temperature only 67% BrC_6F_5 was formed with pyridinium tribromide. However, performing the reaction in the presence of Br_2 afforded BrC_6F_5 in almost quantitative yield after 1 hour. These results led us to study these reactions by ^{19}F NMR spectroscopy. Interestingly, monitoring the reaction between **11** and Br_2 at -45 °C revealed the formation of a new species with five nonequivalent fluorides in addition to remaining **11** and BrC_6F_5. Upon warming this mixture to room temperature for 15 min full conversion to BrC_6F_5 was observed. Based on this observation it is tempting to speculate that this species is an iodine(V) intermediate which would also account for the lack of symmetry (see Supporting Information). On the other hand, the reaction between **11** and $PyHBr_3$ revealed the formation of a different fluorinated compound **12** after one hour at room temperature. Bromo-iodane **12** can also be prepared by treating iodane **11** with HBr in 90% yield and the crystal structure of **12** is shown in Figure 2.



Scheme 5 a) Reaction of various perfluorinated iodanes with pyridinium tribromide (1.5 equiv.). Yields were determined with ^{19}F NMR using $PhOCF_3$ as internal standard.

The solid-state structure reveals a distorted square-planar coordination of the iodine with a bond between the oxygen and iodine atoms. The bromine-iodine bond interaction is relatively weak with a bond length of 3.162(1) Å, which is still shorter than the sum of the van der Waals radii[14] (3.83 Å). Interestingly, heating a chloroform solution of iodane **12** for 18 hours at 70 °C led to the formation of C_6F_5I and 2-(2-bromophenyl)propan-2-ol in almost full conversion. This result demonstrates that reductive elimination from iodane(III) compound **12** (or nucleophilic aromatic substitution) affords the incorporation of the bromine in the electron-rich arene residue and not in the C_6F_5-fragment.

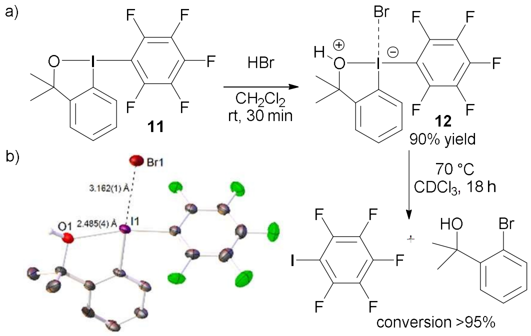


Fig. 2 a) Synthesis of bromo-derived perfluorinated iodane **12** and observed formation of C_6F_5I and 2-(2-bromophenyl)propan-2-ol after heating of **12**; b) Solid-state structure of **12**.

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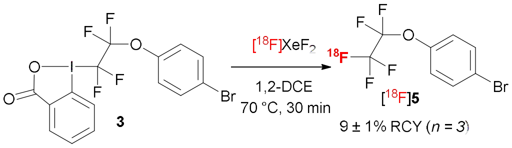
Our ongoing interest[17] in the development of new methods for fluorine-18 labelling prompted us to evaluate if the reaction is adaptable to radiofluorination. Today there is a pressing need to develop new methods for the radiolabeling of perfluorinated fragments with fluorine-18 for PET imaging applications, since the radiosynthesis of such motifs (e.g. $[^{18}F]CF_3CF_2$-) is scarcely described.[18] In a preliminary study, the one-pot reaction between $[^{18}F]XeF_2$[19] (produced in situ in 1,2-dichloroethane via $^{19}F/^{18}F$-exchange) and perfluorinated iodane **3** was investigated in a Reacti-Vial™at 70 °C (Scheme 6). To our delight this un-optimized protocol afforded $[^{18}F]$**5** in 9 ± 1% (*n* = *3*) radiochemical yield after 20 minutes and therefore opens up new options for the radiolabeling of CF_3CF_2-containing radiotracers from $[^{18}F]$fluoride.



Scheme 6 Preliminary study demonstrating the application of this reactivity to afford $[^{18}F]$**5**.

In conclusion, we have found an unexpected reactivity between cyclic perfluorinated iodanes with electrophiles (E^+ = Br, Cl, F, I) to afford perfluorinated $E-R_F$ compounds.[20] Several experiments have suggested that the reaction pathway proceeds presumably via an iodane(V) intermediate, which subsequently undergoes a reductive elimination to afford the perfluorinated products.[21] This novel transformation can be described as an umpolung reaction since it allows electrophiles to react with electrophilic reagents. The utility of this new transformation was demonstrated for a $[^{18}F]CF_3CF_2$-containing compound which was prepared from $[^{18}F]XeF_2$ obtained from cyclotron produced $[^{18}F]$fluoride. Further studies involving the application of this novel reactions are ongoing in our laboratory.

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Conflicts of interest

There are no conflicts to declare

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6 In an AR-glass vial only 18% product formation was observed. It is known from literature reports that different vessel materials can catalyze or hamper the reactivity of XeF_2 in solvents such as $CHCl_3$, CH_2Cl_2 and MeCN; see: C. A. Ramsden, *Arkivoc* 2014, 109.
7 The $^{19}F\{^1H\}$NMR spectrum showed a new triplet at -85.86 ppm and a quartet at -87.81 ppm with an integration of 3:2, which is in agreement with the CF_3CF_2-fragment of **5**. These ^{19}F-NMR data are consistent with values measured for a commercially obtained sample of *p*-Br-C_6H_4-OCF_2CF_3. Furthermore, the formation of product **5** could be confirmed by GC-MS (m/z = 289.9). Yields were determined by NMR, since the reactions were performed on a small scale (0.019 mmol of perfluorinated iodane) and due to the reason that only a limited amount of the perfluorinated iodanes were available. Furthermore, the perfluorinated products are relatively volatile, which makes product isolation on this reaction scale difficult. Currently a scale up of the process is under investigation in our laboratory to obtain adequate isolated yields. For a first example of an isolated yield see Scheme 5.
8 Product formation was confirmed by GC-MS and ^{19}F NMR data (see the Supporting Information for ^{19}F NMR chemical shifts).
9 *p*-Br-Ph-OCF_2CF_2Cl is a new compound and was fully characterized, see the Supporting Information.
10 No reaction was observed at rt.
11 However, due to the fact that the reaction was performed at elevated temperature, it cannot be excluded that *p*-Br-Ph-OCF_2CF_2I was formed from the decomposition of perfluorinated iodane **3**; see for example Scheme 4.
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21 The reaction between **6** and $PyHBr_3$ works also in the presence of radical-trapping reagents (see Figure S2 in the Supporting Information)

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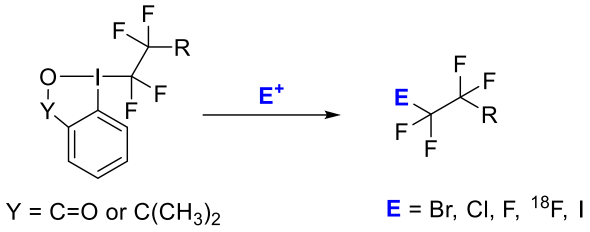
New concept of reactivtiy umpolung: Perfluorinated compounds can be prepared by reacting perfluorinated iodanes (considered as electrophilic reagents) with electrophiles.



- **Reactivtiy umpolung**
- **Adaptable to radiofluorination with [^{18}F]XeF$_2$**