JOC The Journal of Organic Chemistry

Article

Deconstructing the Catalytic, Vicinal Difluorination of Alkenes: HF-Free Synthesis and Structural Study of p-TolIF2

Jérôme C Sarie, Christian Thiehoff, Richard J Mudd, Constantin G. Daniliuc, Gerald Kehr, and Ryan Gilmour

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.7b01671 • Publication Date (Web): 28 Jul 2017

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Deconstructing the Catalytic, *Vicinal* Difluorination of Alkenes: HF-Free Synthesis and Structural Study of *p*-TolIF$_2$

Jérôme C. Sarie, Christian Thiehoff, Richard J. Mudd, Constantin G. Daniliuc,‡ Gerald Kehr, and Ryan Gilmour*

Institute of Organic Chemistry, Westfälische Wilhelms-Universität Münster, Corrensstrasse 40, 48149 Münster, Germany.

Supporting Information Placeholder

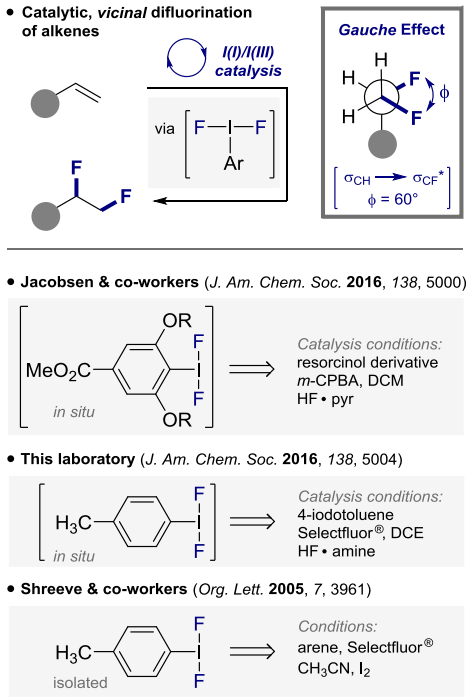
ABSTRACT: Recently, contemporaneous strategies to achieve the *vicinal* difluorination of alkenes via an I(I)/I(III) catalysis manifold were independently reported by this laboratory and by Jacobsen and co-workers. Both strategies proceed through a transient ArI(III)F$_2$ species generated by oxidation of the ArI catalyst. Herein, an efficient synthesis of *p*-TolIF$_2$ from *p*-TolI and Selectfluor® is presented, together with a crystallographic and spectroscopic study. To mitigate safety concerns and simplify reaction execution, an HF-free protocol was devised employing CsF as a substitute fluoride source. The study provides insight into the initial I(I) → I(III) oxidation stage of the catalytic protocol using Selectfluor®.

Introduction

The *vicinal* difluoroethylene unit is synonymous with the fluorine *gauche* effect; a reinforcing stereoelectronic phenomena that manifests itself in a characteristic *syn*-clinal conformation with respect to the F-C(sp^3)-C(sp^3)-F torsion angle ($\phi \approx 60°$).[1,2] The effectiveness of this motif in modulating structure and function has resulted in a rapid growth in the strategic installation of the *vicinal* difluoroethylene group in catalysts and biomolecules.[3] Despite this, efficient catalysis-based strategies to install this moiety from simple alkenes are rare; a problem that, although less pronounced, is common to the *vicinal* dihalogenation of olefins generally.[4] Whilst elegant strategies have been devised for olefin halogenation, many of which are stereospecific,[5] the deficiency of catalytic *vicinal* difluorination protocols is conspicuous.[6] The acuteness of the problem is further augmented by the preeminence of fluorine in pharmaceutical research and development.[7]

As part of a broader organo-fluorine program,[8] this laboratory recently reported a *vicinal* difluorination of alkenes catalyzed by *p*-TolI proceeding via a proposed I(I)/I(III) cycle with HF•amine as the fluoride source (Scheme 1).[9] Contemporaneously, Jacobsen and co-workers reported a similar transformation employing a resorcinol-based catalyst.[10] Common to both strategies is the *in situ* generation of an ArI(III)F$_2$ species from the corresponding aryl iodide, thereby constituting a catalytic variant of Hara and Yoneda's stoichiometric transformation.[11] These two catalytic advances are highly complementary, differing both in terms of substrate scope and mechanism.[8] Perhaps most notable are differences in the initial oxidation I(I) → I(III) and subsequent generation of the ArI(III)F$_2$ intermediate. In contrast to Jacobsen's procedure, whereby oxidation of the resorcinal catalyst by *m*-CPBA proceeds via an ArIO intermediate, our approach relied on Selectfluor® as the oxidant of choice.[12] Whilst highly effective, this oxidant raised a number of mechanistic questions regarding the formation of *p*-TolI(III)F$_2$, and the ultimate fate of the tetrafluoroborate counterion.

Scheme 1. Organocatalytic, *vicinal* difluorination of alkenes via a transient ArI(III)F$_2$ intermediate.



Mechanistic delineation was, however, hampered by difficulties in procuring this reagent from commercial sources. For the purposes of this study, an important consideration was that the commercial synthesis might not accurately resemble the conditions by which

the species is produced in the catalysis protocol. Consequently, an efficient synthetic route to *p*-TolI(III)F_2 from *p*-TolI and Selectfluor® was required to allow a structural study to be conducted. In addition to providing valuable insight into the initial phase of the catalytic process, this study would complement the existing data on *p*-TolI(III)F_2 and provide synthetic guidelines to prepare structurally related reagents.[13] It would also allow structural comparisons to be drawn between the title reagent and the popular 1-fluoro-3,3-dimethyl-1,3-dihydro-1-λ^3-benzo[*d*][1,2]iodoxole scaffold.[14]

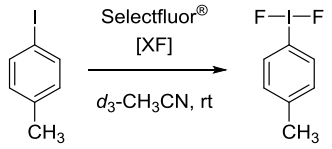
Since the discovery of ArI(III)F_2 reagents over a century ago,[15] a diverse arsenal of synthetic methods for their preparation have been reported. These vary in operational complexity, and range from direct fluorination with $F_{2(g)}$, through to multi-step sequences often involving potentially hazardous reagents (e.g. Cl_2/HF, HgO/HF, XeF_2, SF_4).[16] In 2005, Shreeve and co-workers reported an operationally simple route to iodine(III) reagents utilizing Selectfluor® (Scheme 1, lower).[17] In addition to the direct oxidation of iodoarenes, a convenient one-pot iodination/oxidation sequence was also disclosed starting from a suitably functionalized arene (*mono*-, 1,4-*di*, and 1,3,5-*tri*-alkylated), I_2 and Selectfluor®. Whilst combined yields are reported for the iodination/oxidation sequences, data for the direct oxidation of iodoarenes by Selectfluor® are not provided. This prompted us to streamline a general route to *p*-TolIF_2 with a view to investigating oxidation efficiency and reagent formation within the framework of the catalytic protocol.

Results and Discussion

As a logical starting point for this study, the effect of external fluoride additives was investigated to establish the ultimate source of both fluorine atoms in reagent **2** (Table 1). In the original protocol reported by Shreeve and co-workers, *p*-TolI (**1**) was treated with Selectfluor® in acetonitrile for 4 h at ambient temperature prior to the addition of Et_3N•3HF. As a control experiment, this reaction was repeated, this time in the absence of the HF source, and monitored by ^{1}H NMR spectroscopy (entry 1). After 4 h, 26% conversion was observed and two new aromatic species were clearly identifiable (300 MHz, 299 K, d_3-CH_3CN). One set of signals was attributed to *p*-TolIF_2 (**2**) (δ_H 7.92 ppm and 7.45 ppm), indicating that Selectfluor® can function as the source of both fluorine atoms. The second species showed broad signals in the ^{1}H NMR spectrum (δ_H 7.75 ppm and 7.24 ppm), indicative of a fluxional process.[18] Repeating the experiment and adding Et_3N•3HF (2 drops) after 4 h led to the complete disappearance of the second species (entry 2). For completeness, the order of HF addition was then investigated, and the reaction was performed with the rigorous exclusion of light and moisture. A significant increase in yield resulted when Et_3N•3HF (2 drops) was added at the beginning of the reaction (66%, entry 3). Again, the second fluxional species observed in entry 1 was notably absent. Exploring NFSI and *N*-fluoropyridinium tetrafluoroborate as oxidants proved to be detrimental to reaction efficiency (see SI for full details) and thus Selectfluor® was employed for the remainder of the study. Extending the reaction time did not enhance efficiency (59%, entry 4). Similarly, increasing the equivalents of Selectfluor® in the reaction mixture (2.6 to 5.0 eq.) did not significantly improve the outcome (66%, entry 5). However, augmenting these two parameters together led to an improved conversion of 80% (entry 6). It is important to note that when isolated, the resulting product *p*-TolIF_2 (**2**) decomposed at ambient temperature. However, it remained stable under the reaction conditions for 22 h. Modifying the number of equivalents of HF (entries 7-9) led to small variations in conversion. Collectively, parameter variation ultimately led to a set of conditions that allowed *p*-TolIF_2 to be isolated in 91% yield (entry 10).

Attention was then focused on mitigating the safety risks associated with handling HF reagents. Consequently, Et_3N•3HF was substituted by a variety of fluoride sources with the aim of identifying a safer alternative. Tetrabutylammonium fluoride proved unsuitable for this task, and decomposition of Selectfluor® was observed by ^{1}H NMR in this case (entry 11). In contrast, LiF gave an encouraging initial result and did not decompose the Selectfluor® (23%, entry 12). This was significantly improved when switching to the more soluble CsF (72%, entry 13).[19] Moreover, the reaction proceeded smoothly and cleanly, with side product formation completely suppressed. Further optimization with CsF allowed comparable isolated yields to be reached, thereby eliminating the need to use Et_3N•3HF for the preparation of *p*-TolIF_2 (**2**) (62% isolated yield, entry 14).

Table 1. Reaction optimization: Investigation of XF sources and the identification of an HF-free protocol.[a]



1 **2**

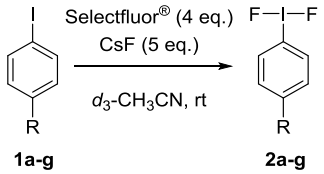
Entry	Selectfluor® (eq.)	XF source	F^- (eq.)	Time (h)	Conversion (%)
1	2.6	-	-	4	26
2	2.6	Et_3N•3HF	2 drops	4	56[b]
3	2.6	Et_3N•3HF	2 drops	4	66
4	2.6	Et_3N•3HF	2 drops	22	59
5	5.0	Et_3N•3HF	2 drops	4	66
6	5.0	Et_3N•3HF	2 drops	22	80
7	2.6	Et_3N•3HF	0.9	4	49
8	2.6	Et_3N•3HF	2.3	4	63
9	2.6	Et_3N•3HF	4.6	4	54
10	3.5	Et_3N•3HF	3.7	22	91[c]
11	2.6	TBAF•$3H_2O$	5.0	8	0
12	2.6	LiF	5.0	8	23
13	2.6	CsF	5.0	24	72
14	4.0	CsF	5.0	14	62[c]

[a] All reactions were performed in a borosilicate NMR tube with d_3-CH_3CN as solvent. Conversion determined by ^{1}H NMR, based on the consumption of *p*-TolI **1**; [b] Et_3N•3HF was added at the end of the reaction in accordance with the literature protocol;[17] [c] Yield (see SI).

These optimized conditions were then applied to a small collection of electronically modulated aryl iodides (Table 2). In contrast to the parent *p*-CH_3 system (62% isolated yield, 14 h), substrates bearing electron-withdrawing *para*-substituents required extended reaction times (48 h) and conversion was markedly reduced (entries 1-3; 13%, 14% and 51% for *p*-NO_2, *p*-CF_3 and *p*-CO_2Et, respectively). The *p*-chloro system was subjected to the optimized conditions and was smoothly oxidized to the corresponding $ArIF_2$

species (54% yield, entry 4). Gratifyingly, oxidation of electron rich systems proved to be more efficient, and comparable to the title compound (*p*-H, *p*-OBn and *p*-OMe; 80%, 75% and 89% conversion, respectively. Entries 5, 7 and 8). Unfortunately, this efficiency was offset by the intrinsic instability of the *p*-OBn and *p*-OMe analogues towards isolation.

Table 2. Exploring the effect of electronic modulation on the oxidation of *p*-substituted aryl iodides using Selectfluor® and CsF.



1a-g **2a-g**

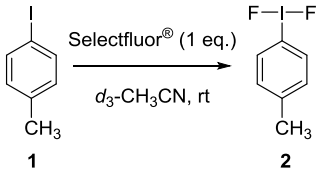
Entry	R	$ArIF_2$	Time (h)	Conversion (%)[a]
1	NO_2	**2a**	48	13
2	CF_3	**2b**	48	14
3	CO_2Et	**2c**	48	51
4	Cl	**2d**	24	54
5	H	**2e**	24	80
6	CH_3	**2**	24	74[b]
7	OBn	**2f**	6	75
8	OMe	**2g**	6	89[c]

[a] All reactions were performed in a borosilicate NMR tube with d_3-CH_3CN as solvent. Conversion determined by ^1H NMR, based on the consumption of ArI (**1a-g**); [b] Yield 62% (91% when using Et_3N•3HF for comparison); [c] Yield 76% when using Et_3N•3HF.

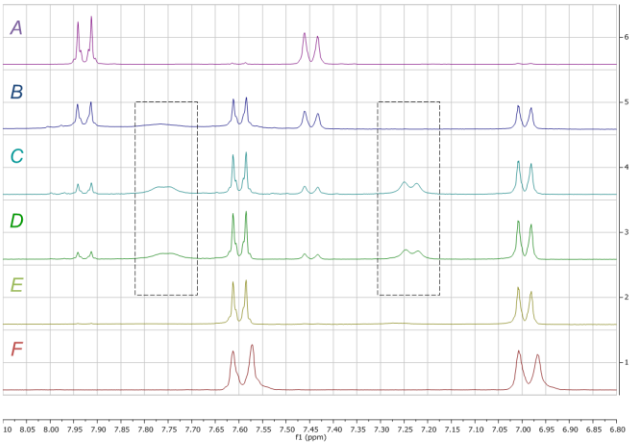
Solution phase NMR investigation: To gain further insights into the oxidation of *p*-TolI by Selectfluor®, the reaction was monitored by ^1H NMR spectroscopy over a period of 4 h in the absence of the fluoride source (XF). In contrast to the literature report,[17] disclosing the facile and quantitative generation of hypervalent aryl iodine difluorides from the reaction of 2.0 eq. of Selectfluor® with iodobenzene or iodotoluene, incomplete conversion after 4 h using 2.6 eq. Selectfluor® was noted (N.B. Figure 1 depicts the reaction with only 1.0 eq. Selectfluor®). Since our observation is at variance with the literature, careful analysis of the NMR time course was performed (Figure 1, Spectra A-F). As noted during the optimization process (Table 1), the generation of two new aromatic species was observed over this 4 h period. One can clearly be identified as *p*-$TolIF_2$ (**2**) [δ_H 7.93, 7.45 ppm, Figure 1, spectrum A], whilst the second has eluded isolation and unequivocal characterization [δ_H 7.75, 7.24 ppm, Figure 1, spectra C and D]. Since the formation of this unidentified species correlates with the consumption of Selectfluor®, and is converted to **2** upon addition of a fluoride source, it is tempting to implicate a transient, cationic complex of the type [*p*-$Tol\overset{+}{I}F\cdots R$], where R may be NR_3, CH_3CN or BF_4^- (Figure 1, spectra E to B).

In an attempt to provide substance to this conjecture, detailed ^1H NMR analyses were performed on the mixture to glean an insight into the solution phase behavior (Figures 1 and 2). To probe for the involvement of a transient [*p*-$Tol\overset{+}{I}F\cdots R$] complex, the reduced product generated from Selectfluor® (**3**) was prepared according to a literature procedure,[20] and its ^1H NMR spectrum recorded (Figure 2, spectrum E). As a reference, spectrum A is that of Selectfluor®.

Figure 1. Monitoring the oxidation of *p*-TolI by Selectfluor® in d_3-CH_3CN by ^1H NMR spectroscopy.[a]

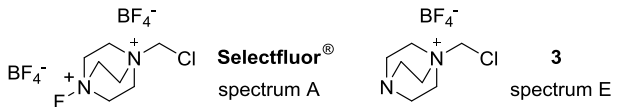


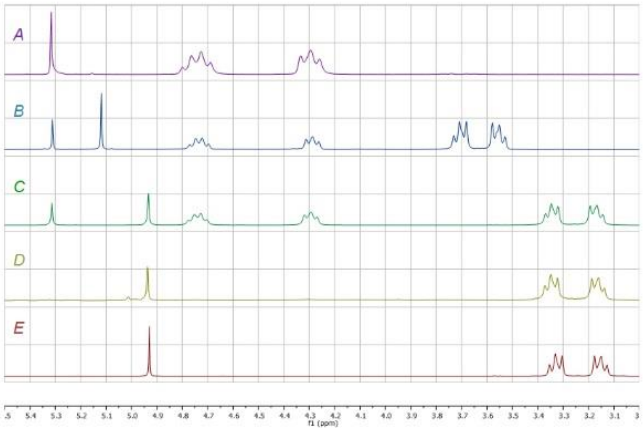
1 **2**



[a] All reactions were performed in a borosilicate NMR tube with d_3-CH_3CN as solvent (300 MHz, 299 K); 40 mM for compound **1**. A: Reference spectrum of *p*-$TolIF_2$ (**2**). B: Reaction mixture 240 min (after addition of 2 drops of Et_3N•3HF). C: Reaction mixture after 240 min (prior to addition of 2 drops of Et_3N•3HF). D: Reaction mixture after 130 min. E: Reaction mixture 26 min. F: Reference *p*-TolI (**1**) (200 MHz, 299 K).

Figure 2. Solution phase behavior of Selectfluor® and derivative 3 in d_3-CH_3CN by ^1H NMR spectroscopy.[a]





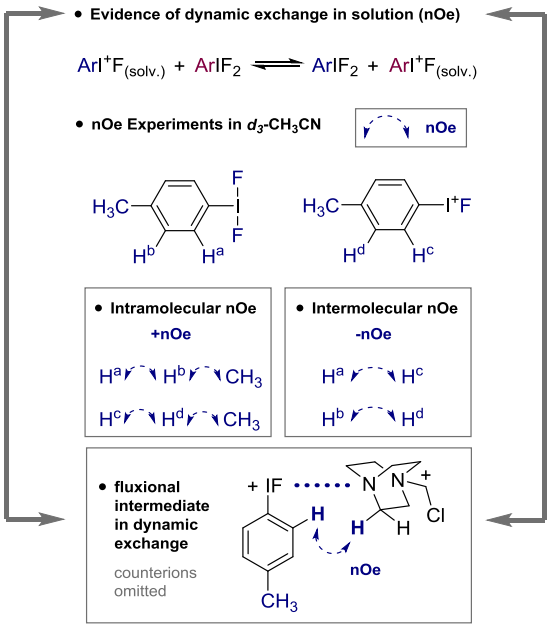
[a] All reactions were performed in a borosilicate NMR tube with d_3-CH_3CN as the solvent (300 MHz, 299 K). A: Spectrum of Selectfluor® (200 MHz, 299 K). B: Mixture of *p*-TolI (**1**) and Selectfluor® after 240 min. C: Mixture of amine **3** and Selectfluor® after 240 min. D: Mixture of *p*-TolI (**1**), Selectfluor® and CsF after 240 min. E: Spectrum of amine **3**.

When *p*-TolI (**1**) and Selectfluor® were mixed in a NMR tube, new signals at δ_H = 5.12, 3.70 and 3.56 ppm were observed (spectrum B). However, inspection of spectrum E indicates that these

are not simply attributable to **3**. Cognizant of an elegant study by Laali and co-workers, who reported that Selectfluor® and chloromethylated DABCO generate symmetric tricationic dimers upon mixing (80 °C),[20] a 1:1 mixture of Selectfluor® and **3** was prepared and investigated. However, at ambient temperature no changes in chemical shifts were observed (spectrum C). These observations are clearly at variance with the spectral signature of the reaction mixture as shown in spectrum B prior to XF addition. Although inconclusive, these experiments led us to gravitate towards the notion of a fluxional [ArI$^+$F$\cdots$R] complex,[21] as opposed to a dimeric, tricationic species. It was envisaged that preliminary validation for such a species could be obtained by simple addition of a non-protic fluoride source, such as CsF. Indeed, when *p*-TolI (**1**) and Selectfluor® were treated with CsF to produce *p*-TolIF$_2$ (**2**), amine **3** was clearly visible (spectrum D) [(*p*-TolI (**1**) + Selectfluor® + CsF → *p*-TolIF$_2$ (**2**) + **3** + $CsBF_4$)].

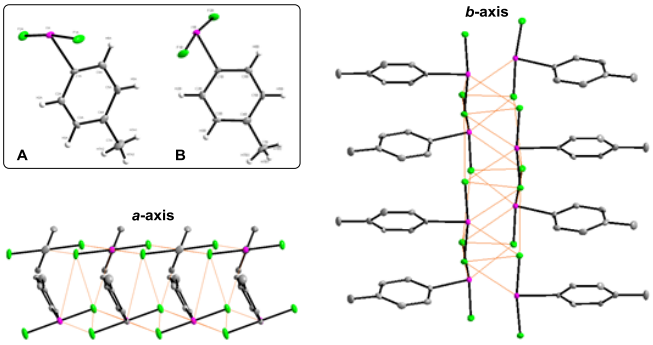
To describe the fluxional nature of the transient intermediate [TolI$^+$F$\cdots$R], a series of nOe experiments were conducted (200 mM for compound **1**) and are summarized in Scheme 2. Both positive and negative effects were observed, thereby providing evidence for dynamic exchange in solution (d_3-CH_3CN). The negative nOe effects observed between the *ortho*- and *meta*-tolyl hydrogens of TolIF$^+$ and TolIF$_2$, respectively, indicate a dynamic equilibrium between both species that is observable on the NMR time scale. This can be described as a simple fluoride exchange. The positive nOe effects between the *ortho*-hydrogens of the TolIF$^+$ species and the NC$\underline{H}_2$ of the chloromethylated DABCO donor confirm the proximity of these groups and support the transient [TolIF$^+\cdots$ DABCO] adduct depicted in Scheme 2 (lower).

Scheme 2. Solution phase analysis and evidence of dynamic exchange by nOe investigations.



Structural Characterization of *p*-TolIF$_2$ (2): Whilst efforts to isolate and characterize the postulated, cationic intermediate have been thus far unsuccessful, it was possible to prepare colorless needles of **2** that were suitable for X-ray analysis (CCDC 1555065, Figure 4).[22,23] Two symmetry independent conformers were found in the asymmetric unit cell, differing in the torsion angle between the F-I-F moiety and the π-system.

Figure 4. X-ray crystal structure of *p*-TolIF$_2$ (2) (CCDC1555065)[a]



[a] Two conformers (top-left, A and B) and extended structure viewed along the *a*-axis (bottom-left) and *b*-axis (right) of the unit cell. Ellipsoids are shown at the 50% probability level. Hydrogen atoms are omitted for clarity in the extended structure. Intramolecular interactions below 3.5 Å between iodine and fluorine are highlighted in orange.

A T-shape arrangement is observed, but distorted from the expected linear F-I-F geometry (conformer **A** = 170.8° and conformer **B** = 173.3°). The IF$_2$ unit is orientated neither parallel, nor perpendicular with respect to the aromatic ring (conformer **A** = -81.8° and conformer **B** = 61.5°): This is likely due to crystal packing effects between neighboring λ^3-iodane species as observed in the extended lattice. Short intermolecular F$\cdots$F contacts involving molecules of the same conformer (F1$\cdots$F2 2.793 Å for conformer **A** and F1$\cdots$F2 2.874 Å for conformer **B**) are present in the packing diagram. Consequently, the I-F distances show significant elongation (conformer **A** average = 2.012(3) Å; conformer **B** average = 2.015(3) Å).

Conclusions

Reaction deconstruction is an intuitive component of the method development process.[24] Theoretical and/or experimental interrogation of postulated reaction intermediates allows aspects of structure and reactivity to be systematically assessed, thereby informing rational design. Importantly, this process may provide rigorous, independent support for the involvement and competence of a postulated intermediate. In the context of our work on the catalytic, *vicinal* difluorination of alkenes, success was contingent on the formation of *p*-TolIF$_2$ generated by *in situ* oxidation of *p*-TolI using Selectfluor®. Although well-described in the literature,[15-17] this species was never detected nor isolated during the reaction development phase.[9] It was envisaged that insight into the I(I)→I(III) oxidation using Selectfluor®, and subsequent solution phase behavior, would facilitate future reaction development. An operationally simple route to *p*-TolIF$_2$ was thus been developed that substitutes potentially hazardous HF reagents by CsF, thereby mitigating safety concerns. Whilst observing the oxidation by NMR spectroscopy, a fluxional intermediate was determined that exists in a dynamic exchange with *p*-TolIF$_2$, prior to fluoride addition. Having discounted the possibility of bridged, dimeric, tricationic systems, it was observed that this species readily converts to *p*-TolIF$_2$ upon addition of a non-protic fluoride source. This is fully consistent with a mono-fluoride species [*p*-TolI$^+$F$\cdots$R], where R is likely the reduced form of Selectfluor® (i.e. **3**) and/or

acetonitirile. Assessing the impact of this solution phase behavior on catalysis is currently ongoing in our laboratories.

Experimental section

General information

All chemicals were reagent grade and used as supplied. Solvents for extractions and chromatography were technical grade and distilled prior to use. Analytical thin layer chromatography (TLC) was performed on pre-coated Merck silica gel 60 F_{254} aluminum sheets. Visualization was achieved using ultraviolet light (λ = 254 nm) or by dipping in potassium permanganate stain [$KMnO_4$ (10 g), K_2CO_3 (65 g), and aqueous NaOH solution (1 mol•L^{-1}, 15 mL) in water (1 L)] followed by heating. Column chromatography was carried out on VWR silica gel ZEOprep® 60 (230-400 mesh). Concentration *in vacuo* was performed at ≈10 mbar and 35 °C, drying at ≈10^{-2} mbar and ambient temperature unless stated otherwise. ^{1}H NMR, ^{19}F NMR and ^{13}C NMR spectra were recorded on Bruker AC 200 MHz or by the NMR service at the Institute of Organic Chemistry (WWU Münster) on a Bruker AV 300 MHz, a Bruker AV 400 MHz, Agilent VVMRS 500 MHz or an Agilent DD2 600 MHz spectrometer at ambient temperature. Chemical shifts δ are reported in ppm relative to the residual solvent. Coupling constants *J* are reported in Hz. The multiplicities are reported as: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet. ESI accurate masses were measured by the Mass Spectrometry department at the Institute of Organic Chemistry (WWU Münster) on a MicroTof (Bruker Daltronics, Bremen) with loop injection. Mass calibration was performed using sodium formate cluster ions immediately followed by the sample in a *quasi*-internal calibration. Mass spectra with direct inlet and electron ionization (EI) were measured on a Triplequad TSQ 7000 (Thermo-Finnigan-MAT, Bremen).

General Procedure 1: (Selectfluor® and CsF)

To a flame-dried Schlenk tube was added the iodoarene (1.0 mmol), Selectfluor® (1.41 g, 4.0 mmol, 4.0 eq.), CsF (760 mg, 5.0 mmol, 5.0 eq.) and dry acetonitrile (25 mL). The reaction mixture was flushed with argon three times, wrapped in aluminum foil to exclude light and stirred at room temperature for the indicated time. The reaction mixture was then evaporated to dryness. To this slurry was added a mixture of $CHCl_3$:*n*-hexane (1:1) to dissolve the product (4 mL). The organic material was transferred by syringe to a flame-dried Schlenk tube and the process was repeated 4 times. The solvent was evaporated to dryness at 0 °C (ice bath), flushed with argon and then stored in a freezer (-18 °C).

General Procedure 2: (Selectfluor® and Et_3N•3HF)

To a flame-dried Schlenk tube was added the iodoarene (1.0 mmol) and Selectfluor® (1.24 g, 3.5 mmol, 3.5 eq.) in dry acetonitrile (25 mL). The reaction mixture was flushed three times with argon and Et_3N•3HF (200 µL, 3.6 eq.) was added. The reaction mixture was wrapped in aluminum foil to exclude light and stirred at room temperature for the indicated time. The reaction mixture was then evaporated to dryness. To this slurry was added a mixture of $CHCl_3$:*n*-hexane (1:3) to dissolve the product (4 mL). The organic material was transferred by syringe to a flame-dried Schlenk tube and the process was repeated 4 times. The solvent was evaporated to dryness at 0 °C (ice bath), flushed with argon and then stored in a freezer (-25 °C).

Difluoro(*p*-tolyl)-λ^3-iodane (2)

Prepared according to General Procedure 1. Reaction time: 14 h. Yield = 160 mg, 62%.

Prepared according to General Procedure 2. Reaction time: 22 h. Yield = 232 mg, 91%.

Colorless needles crystallized from 4 mL of $CHCl_3$:*n*-hexane 1:3 at -18°C.

^{1}H NMR (300 MHz, d_3-CH_3CN) δ 7.92 (m, 2H), 7.44 (m, 2H), 2.45 (s, 3H). ^{19}F NMR (282 MHz, d_3-CH_3CN) δ -174.4. ^{13}C{^{1}H} NMR (75 MHz, d_3-CH_3CN) δ 143.9 (C), 132.9 (CH), 132.3 (CH, t, $^3J_{CF}$ = 2.5 Hz), 122.9 (C, t, $^2J_{CF}$ = 12.1 Hz), 21.3 (CH_3).

^{1}H NMR (300 MHz, *d*-$CHCl_3$) δ 7.84 (m, 2H), 7.39 (m, 2H), 2.47 (s, 3H). ^{19}F NMR (282 MHz, *d*-$CHCl_3$) δ -176.8. Data in agreement with literature.[17]

MS-EI-direct inlet: *m*/*z* (%) = 256.0 (32) $[M]^+$, 237.0 (4) $[M-F]^+$, 218.0 (98) $[M-F_2]^+$, 91.1 (100) $[M-IF_2]^+$.

Difluoro(4-methoxyphenyl)- λ^3-iodane (2g)

Prepared according to General Procedure 2. Reaction time: 4 h.

Yield = 207 mg, 76%.

Light yellow solid. Fast decomposition at ambient temperature, light sensitive.

^{1}H NMR (400 MHz, d_3-CH_3CN) δ 8.02 (m, 2H), 7.13 (m, 2H), 3.87 (s, 3H). ^{19}F NMR (282 MHz, d_3-CH_3CN) δ -170.2. ^{13}C{^{1}H} NMR (101 MHz, d_3-CH_3CN) δ 163.4 (C), 135.2 (CH, t, $^2J_{CF}$ = 1.7 Hz), 117.7 (CH), 117.1 (C, t, $^3J_{CF}$ = 13.7 Hz), 56.5 (CH_3).

MS-EI-direct inlet: *m*/*z* (%) = 272.0 (4) $[M]^+$, 234.0 (100) $[M-F_2]^+$, 107.0 (7) $[M-IF_2]^+$.

Characterization data for Table 2:

Difluoro(4-nitrophenyl)-λ^3-iodane (2a)[25]

^{1}H NMR (200 MHz, d_3-CH_3CN) δ 8.41 (m, 2H), 8.17 (m, 2H).

Difluoro(4-(trifluoromethyl)phenyl)-λ^3-iodane (2b)[26]

^{1}H NMR (600 MHz, d_3-CH_3CN) δ 8.14 (m, 2H), 7.93 (m, 2H). ^{19}F NMR (564 MHz, d_3-CH_3CN) δ -63.6, -177.0. ^{13}C{^{1}H} NMR (151 MHz, d_3-CH_3CN) δ 133.6 (C, q, J_{FC} = 33.0 Hz), 131.9 (CH, t, J_{FC} = 4.6 Hz), 129.0 (CH, q, J_{FC} = 3.8 Hz), 128.5 (C, tm, J_{FC} = 10.5 Hz), 124.5 (CF_3, q, J_{FC} = 271.9 Hz)

MS-EI-direct inlet: *m*/*z* (%) = 310.0 (8) $[M]^+$, 272.0 (100) $[M-F_2]^+$.

Ethyl 4-(difluoro-λ^3-iodanyl)benzoate (2c)

^{1}H NMR (400 MHz, d_3-CH_3CN) δ 8.20 (m, 2H), 8.06 (m, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (282 MHz, d_3-CH_3CN) δ -176.9. ^{13}C{^{1}H} NMR (101 MHz, d_3-CH_3CN) δ 165.8 (C), 134.4 (C), 132.7 (CH), 131.3 (CH, t, J_{FC} = 4.2 Hz), 129.2 (C, t, J_{FC} = 10.3 Hz), 62.5 (CH_2), 14.4 (CH_3).

MS-EI-direct inlet: *m*/*z* (%) = 314.0 (4) $[M]^+$, 231.0 (100) $[M-C_2H_5O]^+$.

Difluoro(4-chlorophenyl)-λ^3-iodane (2d)[25]

^{1}H NMR (200 MHz, d_3-CH_3CN) δ 7.97 (m, 2H), 7.64 (m, 2H).

MS-EI-direct inlet: *m*/*z* (%) = 275.9 (18) $[M]^+$, 238.0 (100) $[M-F_2]^+$.

Difluoro(phenyl)-λ³-iodane (2e)[17]

^{1}H NMR (200 MHz, d_3-CH_3CN) δ 8.03 (m, 2H), 7.63 (m, 3H).

Difluoro(4-(benzyloxy)phenyl)-λ³-iodane (2f)

Derived from reaction mixture (Table 2, entry 7): ^{1}H NMR (200 MHz, d_3-CH_3CN) δ 8.02 (m, 2H), 7.41 (m, 5H), 7.19 (m, 2H), 5.18 (s, 2H).

^{1}H NMR (600 MHz, *d*-$CHCl_3$) δ 7,91 (m, 2H), 7.40 (m, 5H), 7.14 (m, 2H), 5.15 (s, 2H). ^{19}F NMR (564 MHz, *d*-$CHCl_3$) δ -173.3.^{13}C{^{1}H} NMR (151 MHz, *d*-$CHCl_3$) δ 161.5 (C), 135.9 (CH), 132.9 (C), 129.9 (CH), 128.6 (CH), 127.6 (CH), 117.9 (CH), 115.0 (C, t, $^3J_{FC}$= 13.2 Hz), 70.6 (CH_2).

MS-EI-direct inlet: *m/z* (%) = 248.0 (2) $[M]^+$, 91.1 (100) $[M-C_6H_4F_2IO]^+$.

Synthesis of 1-chloromethyl-1,4-diazabicyclo[2.2.2]octan-1-ium chloride (4)[20]

A round-bottom flask was charged with 1,4-diazabicyclo[2.2.2]octane (1.0 g, 8.9 mmol, 1.0 eq.) dissolved in dichloromethane (3 mL), and the mixture heated at reflux for 16 h. The resulting white precipitate was filtered, washed with dichloromethane and placed under vacuum to afford 1-(chloromethyl)-1,4-diazabicyclo[2.2.2]octan-1-ium chloride as a white solid (1.6 g, 8.1 mmol, 91%).

^{1}H NMR (300 MHz, D_2O) δ 5.12 (s, 2H), 3.55 (m, 6H), 3.25 (m, 6H); ^{13}C{^{1}H} NMR (75 MHz, D_2O) δ 68.2 (CH_2), 51.2 (CH_2), 43.9 (CH_2).

HRMS (ESI-TOF) *m/z*: $[M-Cl]^+$ Calcd for $C_7H_{14}N_2Cl^+$ 161.0840; Found 161.0815.

Synthesis of 1-chloromethyl-1,4-diazabicyclo[2.2.2]octan-1-ium tetrafluoroborate (3)[20]

To a round-bottom flask was added 1-(chloromethyl)-1,4-diazabicyclo[2.2.2]octan-1-ium chloride (0.50 g, 2.5 mmol, 1.0 eq.), $NaBF_4$ (0.28 g, 2.5 mmol, 1.0 eq.) and water (5 mL). The reaction mixture was then stirred for 48 h at ambient temperature before being evaporated to dryness. Acetonitrile was added and the solid was filtered off and washed. The combined organic layers were evaporated under vacuum to afford 1-(chloromethyl)-1,4-diazabicyclo[2.2.2]octan-1-ium tetrafluoroborate (**3**) as a white solid (0.61 g, 2.46 mmol, 98%).

^{1}H NMR (400 MHz, D_2O) δ 5.15 (s, 2H), 3.59 (m, 6H), 3.30 (m, 6H); ^{13}C{^{1}H} NMR (75 MHz, D_2O) δ 68.2 (CH_2), 51.2 (CH_2), 43.9 (CH_2); ^{19}F NMR (282 MHz, D_2O) δ -150.41, -150.46 (BF_4^-).

HRMS (ESI-TOF) *m/z* (%): $[M-BF_4^-]^+$ Calcd for $C_7H_{14}N_2Cl^+$ 161.0840; Found 161.0814.

Synthesis of 1-benzyloxy-4-iodobenzene (5)

To a round-bottom flask was added 4-iodophenol (500 mg, 2.27 mmol, 1.0 eq.), benzyl bromide (297 µL, 2.50 mmol, 1.1 eq.), potassium carbonate (627 mg, 4.54 mmol, 2.0 eq.) and dimethylformamide (2 mL). The reaction mixture was stirred at ambient temperature for 20 h before being poured into a saturated solution of ammonium chloride (10 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed five times with water (2 mL) and once with brine (2 mL), dried over magnesium sulfate, filtered and evaporated under vacuum. The resulting material was purified by chromatography on silica gel (*n*-pentane:dichloromethane 9:1) to afford 1-benzyloxy-4-iodobenzene as a white solid (662 mg, 2.13 mmol, 94%). *Rf*: 0.2; ^{1}H NMR (300 MHz, *d*-$CHCl_3$) δ 7.55 (m, 2H), 7.39 (m, 5H), 6.76 (m, 2H), 5.04 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, *d*-$CHCl_3$) δ 158.8 (C), 138.4 (CH), 136.6 (C), 128.8 (CH), 128.2 (CH), 127.6 (CH), 117.4 (CH), 83.2 (C), 70.2 (CH_2). HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{13}H_{11}INaO^+$ 332.9753; Found 332.9751.
Analytical data in agreement with literature.[27]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental protocols, NMR spectra, crystallographic data (pdf file).

AUTHOR INFORMATION

Corresponding Author

ryan.gilmour@uni-muenster.de

Notes

The authors declare no competing financial interests.
‡ X-ray crystallographer
This manuscript is dedicated to Prof. Dr. Armido Studer on the occasion of his 50th birthday.

ACKNOWLEDGMENT

We acknowledge generous financial support from the WWU Münster, and the Deutsche Forschungsgemeinschaft (SFB 858, and Excellence Cluster EXC 1003 "*Cells in Motion – Cluster of Excellence*"). We are extremely grateful to Dr. Klaus Bergander (WWU Münster) for assistance with NMR spectroscopy.

REFERENCES

(1) (a) Wolfe, S. *Acc. Chem. Res*. **1972**, *5*, 102–111; (b) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308–319; (c) Thiehoff, C.; Rey, Y. P.; Gilmour, R. *Isr. J. Chem*. **2017**, *57*, 92–100.
(2) Akkerman, F.; Buschmann, J.; Lentz, D.; Luger, P.; Rödel, E. *J. Chem. Crystallogr*. **2003**, *33*, 969–975.
(3) (a) Zimmer, L. E.; Sparr, C.; Gilmour, R. *Angew. Chem. Int. Ed*. **2011**, *50*, 11860–11871; (b) Cahard, D.; Bizet, V. *Chem. Soc. Rev*. **2014**, *43*, 135–147.
(4) Cresswell, A. J.; Eey, S. T.-C.; Denmark, S. E. *Angew. Chem. Int. Ed*. **2015**, *54*, 15642–15682.
(5) Cresswell, A. J.; Eey, S. T.-C.; Denmark, S. E. *Nat. Chem*. **2015**, *7*, 146–152.
(6) Kohlhepp, S. V.; Gulder, T. *Chem. Soc. Rev.* **2016**, *45*, 6270–6288.
(7) (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev*. **2008**, *37*, 320–330; (b) Ojima, I. *J. Org. Chem.* **2013**, *78*, 6358–6383; (c) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem.* **2015**, *58*, 8315–8359.
(8) Molnár, I. G.; Thiehoff, C.; Holland, M. C.; Gilmour, R. *ACS Catal*. **2016**, *6*, 7167–7173.
(9) Molnár, I. G.; Gilmour, R. *J. Am. Chem. Soc*. **2016**, *138*, 5004–5007.
(10) Banik, S. M.; Medley, J. W.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2016**, *138*, 5000–5003.
(11) Hara, S.; Nakahigashi, J.; Ishi-I, K.; Sawaguchi, M.; Fukuhara, T.; Yoneda, N. *Synlett* **1998**, 495–496.
(12) For a recent example of I(I)/I(III) catalysis using Selectfluor® see Wöste, T. H.; Muñiz, K. *Synthesis* **2016**, *48*, 816–827.
(13) Arnold, A. M.; Ulmer, A.; Gulder, T. *Chem. Eur. J*. **2016**, *22*, 8728–8739.

(14) (a) Charpentier, J.; Früh, N.; Togni, A. *Chem. Rev.* **2015**, *115*, 650−682; (b) For the X-ray structure see Legault, C. Y.; Prévost, J. *Acta Crystallogr. E*. **2012**, *E68*, 01238.

(15) For the discovery of aryliodonium(III) difluorides see: Weinland, R. F.; Stille, W. *Ber. Dtsch. Chem. Ges*. **1901**, *34*, 2631−2633. Also see: Edmunds, J. J.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun*. **1989**, 881−883.

(16) (a) Stang, P. J.; Zhdankin, V. V. *Chem. Rev*. **1996**, *96*, 1123–1173; (b) Zhdankin, V. V. *ARKIVOC* **2009**, 1-62; Yoshimura, A.; Zhdankin, V. V. *Chem. Rev*. **2016**, *116*, 3328–3435.

(17) Ye, C.; Twamley, B.; Shreeve, J. *Org. Lett*. **2005**, *7*, 3961–3964.

(18) For mechanistic discussions see (a) Qin, L.; Hu, B.; Neumann, K. D.; Linstad, E. J.; McCauley, K.; Veness, J.; Kempinger, J. J.; DiMagno, S, *Eur. J. Org. Chem*. **2015**, 5919–5924; (b) Matoušek, V.; Václavík, J.; Hájek, P.; Charpentier, J.; Blastik, Z. E.; Pietrasiak, E.; Budinská, A.; Togni, A.; Beier, P. *Chem. Eur. J*. **2016**, *22*, 417–424; (c) Zhang, J.; Szabó, K. J.; Himo, F. *ACS Catal.* **2017**, *7*, 1093–1100.

(19) The solubility of XF salts is discussed in Wynn, D. A.; Roth, M. M.; Pollard, B. D. *Talanta*, **1984**, *31*, 11, 1036–1040.

(20) Laali, K.; Jamalian, A.; Zhao, C. *Tetrahedron Lett*. **2014**, *55*, 6643–6646.

(21) For a report on the synthesis of monofluoride iodane species stabilized by CH_3CN see: Frohn, H.-J.; Bailly, F.; Welting, D.; Bardin, V. V. *J. Fluorine Chem.* **2009**, *130*, 301–307.

(22) Crystallographic data: CCDC 1555065 contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. This is in line with the report by Shreeve.[17] For a structural study of aryl-λ^3-iodanes see Ochiai, M.; Sueda, T.; Miyamoto, K.; Kiprof, P.; Zhdankin, V. V. *Angew. Chem. Int. Ed*. **2006**, *45*, 8203–8206.

(23) For the first discussion of the X-ray structure of *p*-TolIF_2 see Wilkinson J. A. *Chem. Rev*. **1992**, *92*, 505-519; See reference [134]: Wilkinson, J. A. *Oxidation and Selective Fluorination of Organic Compounds using Organohypervalent Iodine Species*. Ph.D. Thesis, Imperial College: University of London, **1991**.

(24) Holland, M. C.; Gilmour, R. *Angew. Chem. Int. Ed*. **2015**, *54*, 3862–3871.

(25) Sawaguchi, M.; Ayuba, S.; Hara, S. *Synthesis*, **2002**, *13*, 1802-1803.

(26) Ochiai, M.; Yoshimura, A.; Mori, T.; Nishi, Y.; Hirobe, M. *J. Am. Chem. Soc.*, **2008**, *130*, 3742-3743.

(27) Uchiyama, M.; Furuyama, T.; Kobayashi, M.; Matsumoto, Y.; Tanaka, K. *J. Am. Chem. Soc.* **2006**, *128*, 8404–8405.

Graphical Abstract