Chemical Science

EDGE ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Sci.*, 2019, **10**, 7251

All publication charges for this article have been paid for by the Royal Society of Chemistry

Substituent-controlled, mild oxidative fluorination of iodoarenes: synthesis and structural study of aryl I(III)- and I(V)-fluorides†

Joel Häfliger,‡ Cody Ross Pitts,‡ Dustin Bornemann, Roland Käser, Nico Santschi, Julie Charpentier, Elisabeth Otth, Nils Trapp, René Verel, Hans Peter Lüthi and Antonio Togni*

Received 3rd May 2019
Accepted 23rd May 2019

DOI: 10.1039/c9sc02162k

rsc.li/chemical-science

We report a mild approach to the synthesis of difluoro(aryl)-λ^3-iodanes (aryl-IF_2 compounds) and tetrafluoro(aryl)-λ^5-iodanes (aryl-IF_4 compounds) using trichloroisocyanuric acid (TCICA) and potassium fluoride (KF). Under these reaction conditions, selective access to either the I(III)- or I(V)-derivatives is predictable based solely on the substitution pattern of the iodoarene starting material. Moreover, the discovery of this TCICA/KF approach prompted detailed dynamic NMR, kinetic, computational, and crystallographic studies on the relationship between the IF_2 group and the *ortho*-substituents on carefully designed probe molecules. It was during these experiments that the role of the *ortho*-substituent in inhibiting further oxidative fluorination of I(III)-compounds to I(V)-compounds during the reaction with TCICA and KF was revealed. Additionally, a notable exception to this empirical trend is discussed herein.

Oxidative fluorination chemistry has often stipulated the use of harsh reagents. Regarding the fluorination of aryl iodides, synthetic limitations arguably have had significant downstream effects on the ability to study structure and reactivity of difluoro(aryl)-λ^3-iodanes (aryl-IF_2 compounds) and, to an even greater extent, tetrafluoro(aryl)-λ^5-iodanes (aryl-IF_4 compounds) in the last several decades.[1] Aside from two important exceptions from the Shreeve[2] and Gilmour[3] laboratories (employing Selectfluor in the synthesis of electron-rich aryl-IF_2 compounds), the vast majority of methods for aryl-IF_2 synthesis rely on F_2, a source of HF, or a number of other notoriously hazardous reagents (*e.g.* SF_4, XeF_2, *etc.*).[1,4,5] Aryl-IF_4 synthesis is equally if not more challenging.[1,6]

As one possible solution to this accessibility problem, we present a mild, safe, and inexpensive oxidative fluorination of aryl iodides that requires only trichloroisocyanuric acid (TCICA) and potassium fluoride. Somewhat serendipitously, we found that the selectivity between aryl-IF_2 and aryl-IF_4 formation can be controlled reliably by the substitution pattern of the arene (Fig. 1). This discovery was made during an in-depth study on the relationship between the IF_2 group and *ortho*-substituents, whereby we conducted several variable-temperature NMR, computational, and crystallographic analyses, reported herein.

Reaction design and optimization

Originally, the reaction design was inspired by our recent foray into aryl-SF_4Cl compound synthesis, whereby we accomplished a mild, gas reagent-free oxidative fluorination of diaryl disulfides using TCICA, KF, and catalytic TFA.[7] Using a similar approach, we began screening with iodobenzotrifluoride isomers: this would potentially allow analysis of the material balance of the reaction mixtures by ^{19}F NMR. After stirring the reaction mixtures at rt in MeCN for 24 h using TCICA (1.0 equiv.), KF (3.0 equiv.), and TFA (10 mol%), we made two important observations: (1) when making the NMR samples in the fume hood (*i.e.* not under rigorously air- and moisture-free conditions), we noticed rapid formation of a precipitate in the

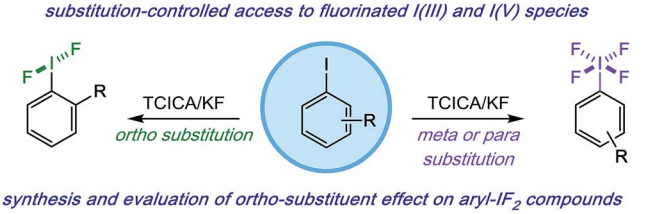


Fig. 1 Mild and predictable access to aryl-IF_2 and aryl-IF_4 compounds based on iodoarene substitution pattern.

Department of Chemistry and Applied Biosciences, ETH Zürich, Vladimir-Prelog-Weg 2, 8093 Zürich, Switzerland. E-mail: atogni@ethz.ch

† Electronic supplementary information (ESI) available. CCDC 1913138–1913140. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9sc02162k

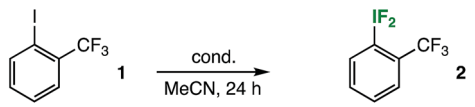
‡ These authors contributed equally.

filtered samples that employed the *meta*- and *para*-iodobenzotrifluoride isomers as substrates, but not in the *ortho*-isomer sample (specifically upon addition of an internal standard solution with slightly wet CD_3CN) and (2) although ^{19}F NMR analysis indeed showed formation of the corresponding difluoro(aryl)-λ^3-iodanes (*i.e.* aryl-IF_2 compounds) in all cases, the products were observed in only trace yields for the *meta*- and *para*-isomers and in about 20% for the *ortho*-isomer, the majority of the observable material balance being unreacted starting material.

At the time, we assumed the identity of the precipitate was the corresponding iodosoarene for each the *meta*- and *para*-iodobenzotrifluoride isomers. In this light, our observations suggested that the *ortho*-substituted aryl-IF_2 compound may be less susceptible to degradation, and thus easier to handle during the screening process. Accordingly, we continued to screen for optimized conditions using *ortho*-iodobenzotrifluoride **1** (Table 1) (notably, it was not until much later in the study that we determined the precipitate was not primarily a byproduct of aryl-IF_2 compound hydrolysis, but rather a byproduct of aryl-IF_4 compound hydrolysis, as discussed in more detail below. While our initial assumption was erroneous, the following series of experiments led us to this discovery of the effect of substitution on oxidative fluorination).

Immediately, we discovered that although an acid catalyst was beneficial for aryl-SF_4Cl formation in our previous work, it had no positive impact on aryl-IF_2 (**2**) product formation. Yet, we found that using TCICA and KF in slight excess had a considerable impact, bringing the yield up to 79% at room temperature in the absence of a catalyst. Next, we attempted the reaction at slightly elevated temperatures. To our surprise, the aryl-IF_2 product **2** not only survived heating the reaction mixture to 40 °C in a borosilicate vial for 24 h, but it formed in 94% yield by ^{19}F NMR (using 4.0 equiv. TCICA and 6.0 equiv. KF).

Table 1 Screening for optimal reaction conditions[a]



Entry	TCICA (equiv.)	KF (equiv.)	Additive	Temp. (°C)	Yield (%)
1	2.0	—	—	rt	—
2	2.0	5.0	—	rt	29
3	2.0	5.0	0.1 TFA	rt	27
4	4.0	5.0	—	rt	49
5	6.0	5.0	—	rt	79
6	6.0	7.0	—	rt	81
7	6.0	3.0	—	rt	75
8	2.0	3.0	—	50	61
9	4.0	5.0	—	50	62
10	**4.0**	**6.0**	**—**	**40**	**94**
11	6.0	5.0	—	40	26[b]

[a] Yields determined by ^{19}F NMR using fluorobenzene as an internal standard. [b] MeCN not dry.

We proceeded to screen with these optimized conditions. Additionally, we found that: (1) the reaction does not proceed in solvents such as DMF, DCM, EtOAc, and toluene, and the product yield is poor when the MeCN is not dry; (2) *N*-chlorosuccinimide and *N*-chlorophthalimide are not suitable replacements for TCICA under optimized conditions (*i.e.* no aryl-IF_2 product formation was observed in either case); (3) reaction times of less than 24 h (*e.g.* 16 h) may result in inferior product yields; and (4) the aryl-IF_2 product, over 2–3 days, decomposes more quickly when exposed to light in a filtered solution of the crude reaction mixture in CD_3CN at room temperature.

Substrate scope of difluoro(aryl)-λ^3-iodanes and the importance of *ortho*-substitution

The most remarkable aspect of the optimization process was the consistent absence of the expected decomposition product – 2-iodosobenzotrifluoride – as determined by ^{19}F NMR and lack of precipitate formation in the NMR tube. Suspecting that the substitution pattern plays an important role, we investigated the substrate scope by first holding the *ortho*-trifluoromethyl substituent constant (Table 2).

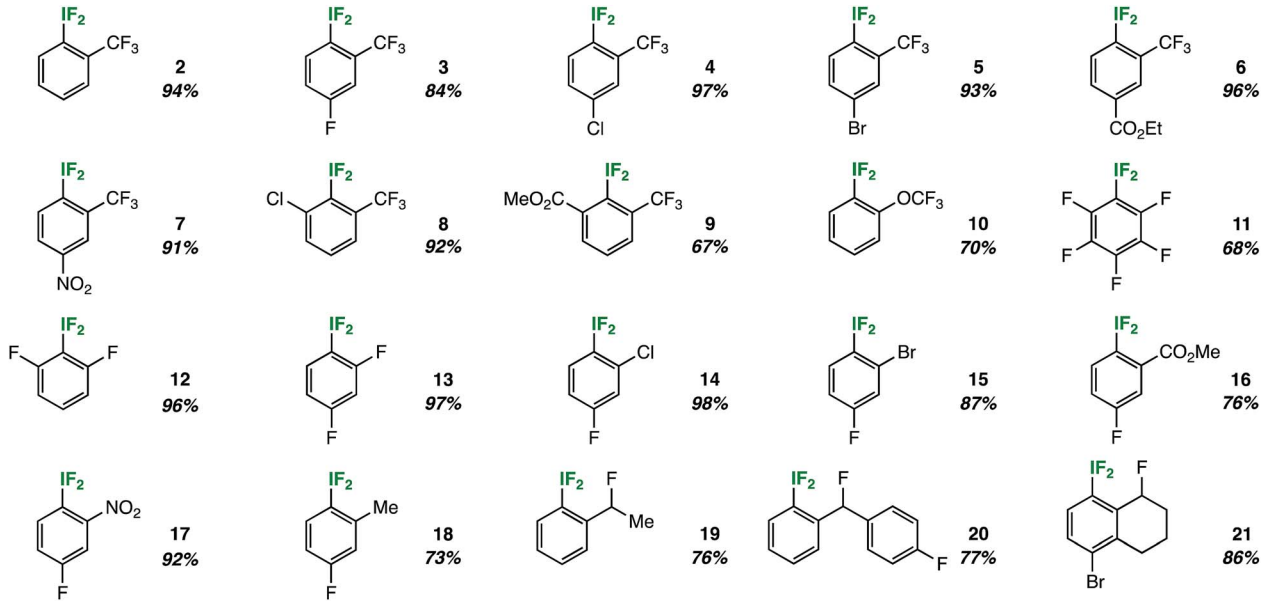
In doing so, we noted that the reaction tolerates substrates adorned with additional electron-withdrawing substituents, such as fluorine, chlorine, bromine, esters, and nitro groups (compounds **3–7**). Also, *ortho*-disubstitution does not inhibit aryl-IF_2 formation, as demonstrated by products **8** and **9**. This substrate class has been popularized recently as a privileged platform to access chiral aryl-IF_2 reagents.[8] On the other hand, the reaction does not tolerate strong electron-donating groups, as these substrates are prone to competitive ring and/or benzylic chlorination in the presence of TCICA.[9] Also, aryl-IF_2 product formation is not observed (or observed in very poor yield) in the presence of substituents with acidic protons, such as carboxylic acids or secondary amides.

Beyond *ortho*-trifluoromethyl substitution, we also discovered that aryl-IF_2 compounds containing other fluorinated substituents, such as *ortho*-trifluoromethoxy substituents (**10**) or *ortho*-difluoro substituents (**11** and **12**), may be synthesized in good yields under our conditions (Table 2).

Subsequently, we continued to vary systematically the *ortho*-substituent to electron-withdrawing groups of various sizes, such as halogens (compounds **13–15**), an ester (compound **16**), and a nitro group (compound **17**). The reaction performed well in all cases. Additionally, we found that mild donating groups (*e.g.* a methyl group) in the *ortho*-position are compatible under reaction conditions. That is, no notable background benzylic or ring chlorination was observed in the synthesis of compound **18**.

In nearly all cases, no decomposition or precipitation was observed upon analyzing the aryl-IF_2 products in Table 2, which is in stark contrast to the aforementioned *meta*- and *para*-substituted substrates. This prompted an important question:

Table 2 Substrate scope of *ortho*-substituted aryl-IF_2 compounds. Yields were determined by ^{19}F NMR using either fluorobenzene or benzotrifluoride as an internal standard and verified by analysis of the material balance



is *ortho*-substitution, in general, somehow important in relation to the hydrolytic stability of aryl-IF_2 compounds?

Probing an IF_2 interaction

Preliminary evidence for an interaction between the IF_2 group and the *ortho*-substituent stems from the observed *J*-coupling of 3.2 Hz between the IF_2 fluorine atoms and CF_3 fluorine atoms in the $^{19}F\{^1H\}$ NMR spectrum of compound **2**. Note that we also observed a *J*-coupling of 2.3 Hz between the IF_2 fluorine atoms and the *ortho*-fluorine atoms in compound **12**. Although initial attempts to clarify the results through ^{19}F–^{19}F NOESY experiments were unsuccessful, these *J*-values are likely attributed to a lone-pair interaction.

We examined the relationship between the IF_2 and CF_3 group in compound **2** further using DFT calculations. Geometry optimizations were performed using Gaussian[10] at the wB97xD/cc-pvdz level of theory,[11] using a cc-pvdz-PP basis set for the iodine atom,[12] on the *ortho*-, *meta*-, and *para*-trifluoromethyl aryl-IF_2 isomers **2**, **22**, and **23**. Interestingly, compound **2** is predicted to be the *least* thermodynamically stable by 9.8 kcal mol^{-1} (for **22** and **23**, $\Delta E \approx 0$), which rules out the possibility of a stabilizing interaction between the fluorine atoms on the CF_3 group and the iodine atom. A closer look at the structures reveals similar bond distances, angles, and natural charges predicted for all isomers, but one property is drastically different – the C_{ortho}–C_{ipso}–I–F dihedral angle (Table 3). In compounds **22** and **23**, the lowest energy conformations both have dihedral angles of virtually 0°, while the dihedral angle of compound **2** is 40° – forced out of plane with the ring. In this particular instance, the preferred angle of 0° in **22** and **23** calculated in the gas phase is likely attributed to a favorable interaction between the iodine lone pairs and the π-system, which the *ortho*-substituent in **2** seems to hinder. The calculated angles notably differ from the preferred orientation of the IF_2 group (and many related IX_2 groups) in a number of X-ray crystal structures.

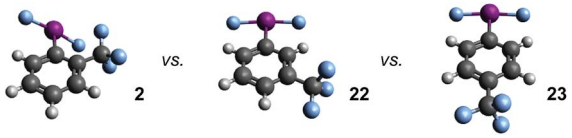
Overall, this provides little indication of what is going on in solution, but suggests that the CF_3 group may, in fact, have an influence on the preferred orientation of the IF_2 group. Specifically, in solution, this could affect the rotation about the C–I bond. One postulate could be that if the preferred IF_2 orientation is out of the plane of the ring, this would leave the iodine atom less susceptible to nucleophilic attack, thus offering one explanation for our observations thus far. An analogy may be drawn to the stabilizing effects of the *ortho*-methyl groups on the SF_3 moiety in Fluolead, for instance.[13]

Dynamic NMR probe

In order to examine the influence of the *ortho*-substituent on the conformation of the IF_2 group in solution, we designed probe molecules suitable for variable-temperature NMR (VT-NMR) studies. Initially, we synthesized compounds **19**[14] and **20**[14a,15] (Table 2), each with a stereogenic center and fluorine atom in the benzylic position, as possible probes. Theoretically, if the C–I bond in these molecules is not freely rotating, the fluorine atoms on the IF_2 moiety would become diastereotopic, thus leading to two spectroscopically distinct ^{19}F NMR signals.

In MeCN, no dynamic behavior was observed in the IF_2 signal by ^{19}F NMR down to approximately 233 K for compound **19**. However, this result may be complicated by free rotation about the C_{ortho}–$C_{benzylic}$ bond. In an attempt to limit this rotation, we replaced the methyl group in the benzylic position with a larger, aryl substituent (compound **20**); still, no dynamic behavior was observed down to 233 K.

Table 3 Comparing properties of isomers **2**, **22**, and **23** *via* DFT calculations[a]



2 **22** **23**

Subs.	d(C–I)	d(I–F)	q_C	q_I	q_F	θ_{C-I-F}	θ_{F-I-F}	$\phi_{C-C-I-F}$[b]
o-CF_3	2.13 Å	2.01 Å[c]	−0.248	1.419	−0.627[d]	86°[e]	172°	40°[f]
m-CF_3	2.13 Å	2.02 Å[g]	−0.251	1.409	−0.628	87°	174°	0°
p-CF_3	2.13 Å	2.03 Å[h]	−0.300	1.502	−0.649	87°	175°	0°

[a] Calculations peformed at wB97xD/cc-pvdz, with a cc-pvdz-PP basis set used for the iodine atom. C refers to *ipso* carbon atom and F refers to fluorine atom bound to iodine, unless otherwise specified. [b] Dihedral angle of C_{ortho}–C_{ipso}–I–F. [c] Average between 2.00 and 2.02 (not equal bond lengths). [d] Average between −0.621 and −0.633. [e] Average between 85° and 87°. [f] F atom proximal to substituent (dihedral angle is 38° for distal F). [g] Structure is nearly symmetric about F–I–F (mirror plane). [h] Structure is symmetric about F–I–F (mirror plane).

Assuming rotation about the C_{ortho}–$C_{benzylic}$ bond was, indeed, still complicating the picture, we synthesized a less-trivial tetrahydronaphthalene derivative **21** (Table 2) in order to eliminate this variable by locking the benzylic position into place with a more rigid ring structure (Fig. 2, top panel). This probe molecule **21** was made in 8 steps in 9% overall yield from commercially available 5,6,7,8-tetrahydro-1-naphthylamine **24** (see ESI† for details).[14,16] Not only was it designed to inhibit C_{ortho}–$C_{benzylic}$ bond rotation, but **21** was also adorned with an electron withdrawing group (*i.e.* a bromine atom) in the 4-position to deactivate the aromatic ring and benzylic position distal to the IF_2 moiety toward background chlorination from TCICA (Fig. 2, bottom panel).

To our satisfaction, we observed significant line broadening of the IF_2 signal in **21** upon cooling the sample and approached the coalescence temperature, which was likely just below 233 K. As this is near the freezing point of the solvent, we concentrated the reaction mixture and redissolved the residue in deuterated dichloromethane to access lower temperatures.

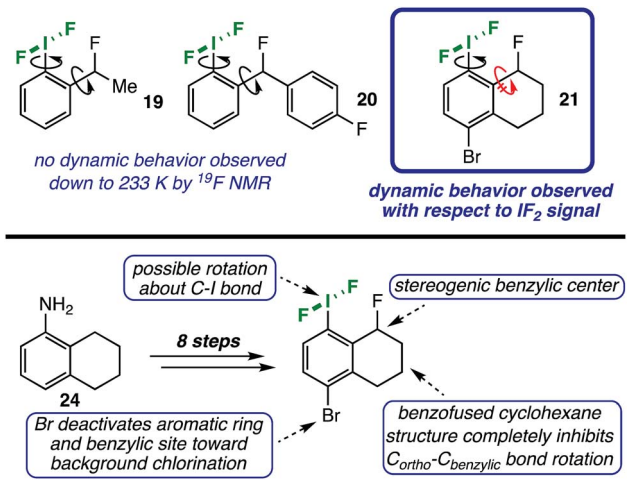


Fig. 2 (Top panel) Probe molecules used to investigate rotation of IF_2 moiety about C–I bond *via* VT-NMR. (Bottom panel) Highlighting design features of probe molecule **21**.

Upon cooling a solution of **21** in CD_2Cl_2, we determined a coalescence temperature (T_C) of 228 K and observed complete separation of the "IF_2" ^{19}F NMR signal into two distinct doublets with a clear roofing effect at temperatures below 202 K (Fig. 3).[17] Here, the fluorine atoms bound to iodine are seen as diastereotopic on the NMR time-scale with $^2J_{FF}$ = 98.3 Hz, and the distance between the two signals, *i.e.* $|(\nu_A - \nu_B)|$, is 1152 Hz. Note that no coupling constant between the benzylic fluorine atom and either of the iodine-bound fluorine atoms is observable at any temperature within our data set; however, as this coupling constant is expected to be small (*ca.* 2–3 Hz), it would likely be subsumed in the broader parent signals.

Additionally, it is important to state that we did not observe dynamic activity of either the benzylic fluorine or hydrogen atoms by either ^{19}F or ^1H NMR at any temperature down to 168 K, indicating that the benzo-fused cyclohexane ring-flipping dynamics have a negligible impact on the IF_2 dynamics.

At temperatures below 202 K, we also noted an apparent convergence of the two IF_2 ^{19}F signals down to 168 K, with $|(\nu_A - \nu_B)| = 989$ Hz. This is likely due to a more dramatic temperature-dependent shift of one of the fluorine signals over the other.[18] Although this phenomenon is not surprising, it complicates the accurate determination of rate constants (k), and thus activation energy (E_a), as the equations for the $T = T_C$ and $T > T_C$ temperature regimes both depend on the maximum chemical shift difference $|(\nu_A - \nu_B)|$ (see ESI† for details).[19] Accordingly, we have analyzed our data using two different assumptions: (1) $|(\nu_A - \nu_B)|$ = signal separation we observed at lowest measurable temperature (989 Hz) and (2) $|(\nu_A - \nu_B)|$ = largest signal separation we observed (1152 Hz) in our data set. Under these assumptions, we have determined activation energies from Arrhenius analyses, respectively, of 7.0 ± 0.9 and 7.4 ± 0.9 kcal mol^{-1}. We also note that respective enthalpies of activation ($\Delta H^{\ddagger}$) of 6.5 ± 0.9 and 6.9 ± 0.9 kcal mol^{-1} and entropies of activation ($\Delta S^{\ddagger}$) of −13 ± 4 and −11 ± 4 cal mol^{-1} K^{-1} were calculated for each assumption *via* Eyring plots. Considering there is a convergence of the $\Delta|(\nu_A - \nu_B)|$ that is exacerbated at lower temperatures, we believe that assumption (2) may be

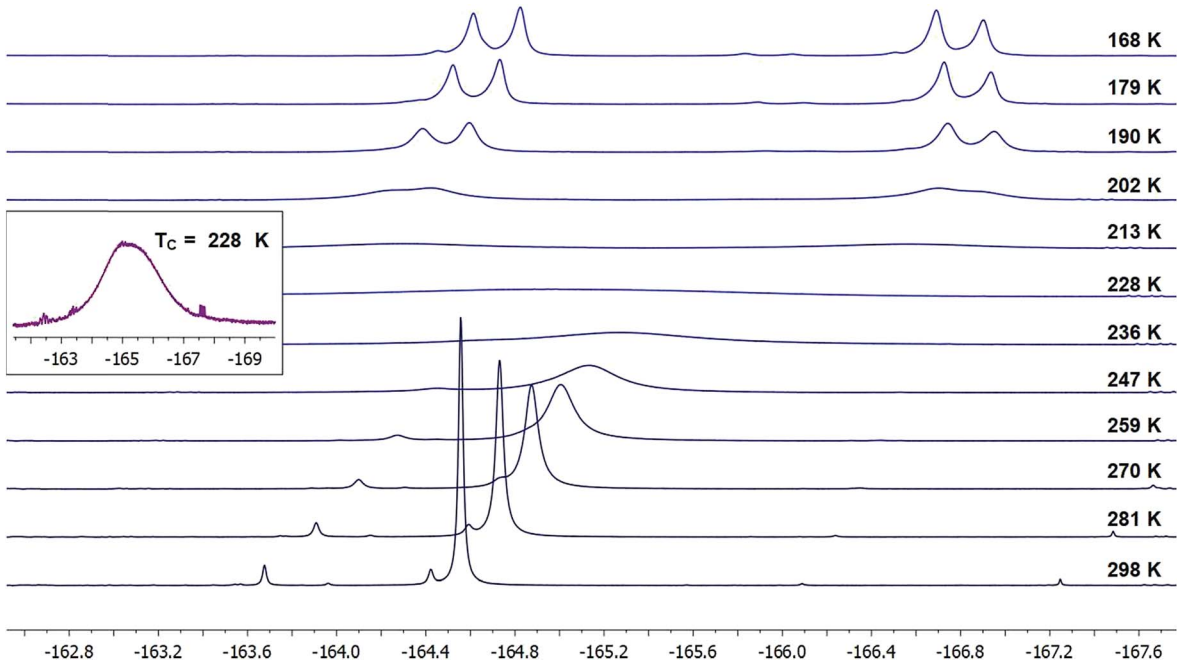


Fig. 3 Stacked ^{19}F NMR spectra of the IF_2 signal in probe molecule **21** over a range of temperatures from 298 K to 168 K. A zoomed-in spectrum is displayed for the coalescence temperature (T_C) at 228 K.

more appropriate, though both assumptions lead to values that are very close in agreement.

Although these thermodynamic parameters presumably describe rotation about the C–I bond, one must consider alternative mechanisms. For one, we ruled out the possibility of an intermolecular exchange mechanism by performing the VT-NMR studies at different concentrations (see ESI† for details).[20] A more challenging issue to address, however, is pseudorotation. Very few detailed dynamic NMR studies on I(III) compounds (and, notably, none on aryl-IF_2 compounds) have surfaced in the literature, but one can attribute the observed dynamic activity of diacetoxyaryl- and triaryl-substituted iodanes to pseudorotation in the works of Reich and Cooperman[21] and Ochiai and coworkers,[20] respectively. Their probe molecules are incomparable to compound **21** in terms of ligand substitution patterns, core skeletons, *etc.*; thus, there can be no straightforward comparison of our experimentally-determined thermodynamic values to the existing literature. In order to probe the likelihood of C–I rotation being the relevant mechanism over pseudorotation for our aryl-IF_2 model compound **21**, we turned to DFT calculations.

DFT analysis of rotational barrier

Compound **21** was optimized at the wB97xD/cc-pvdz level of theory (cc-pvdz-PP for the iodine atom), and then the IF_2 group was rotated 180° about the C–I bond in 12° increments. The structure was relaxed at each step of the rotation scan to determine the lowest energy conformations. From the plotted potential curve, we calculated an activation energy of 5.9 kcal mol^{-1} that comports well with our experimental value.

For the sake of comparison, we were able to find an alternative iodane structure on the potential energy surface (with a C_{ipso}–I–F three-centered bond) that represents a plausible pseudorotation intermediate (**21-*iso***);[22] it is 25 kcal mol^{-1} higher in energy than the optimized F–I–F three-centered bond structure (Fig. 4). This number serves as a lower-bound estimate of the barrier to pseudorotation, which would be prohibitively high in energy. Therefore, we can conclude that the observed dynamic activity more likely arises from C–I bond rotation.

Solid-state structure of 21

In addition to analyzing probe molecule **21** in solution, we obtained single crystals suitable for X-ray structure determination (Fig. 5). The typical, slightly distorted T-shape arrangement about the iodine atom was observed, with $\theta_{F-I-F} = 171.9°$, an average $\theta_{C-I-F} = 86.0°$, d(C–I) = 2.097 Å, and d(I–F) = 1.998 Å. The C_{ortho}–C_{ipso}–I–F torsion angle ($\phi_{C-C-I-F}$) is 82.9°, placing the IF_2 group out of plane with the arene, but not quite perpendicular to it.

Although it is plausible the *ortho*-substituent influences the orientation of the IF_2 group here, it is difficult to separate this

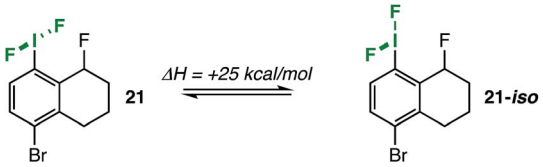


Fig. 4 Isodesmic relationship at wB97xD/cc-pvdz (cc-pvdz-PP for the iodine atom).

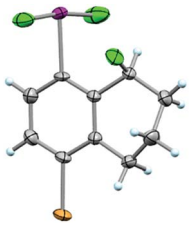


Fig. 5 Crystal structure of compound **21** determined from single-crystal X-ray diffraction (displacement ellipsoids depicted at 50% probability level).

phenomenon from packing effects. For instance, only a small number of aryl-IF_2 molecular structures have been reported in the CCDC to date, and there are no clear trends yet, for instance, in C_{ortho}–C_{ipso}–I–F torsion angles based on substitution patterns (*i.e.* presence *vs.* absence of *ortho*-substituents, considering *ortho*-substituents of various sizes, *etc.*).[23] Thus, in the solid state, the orientation of the IF_2 group is more likely governed by various interactions between the fluorine and iodine atoms of neighboring molecules in the extended lattice than arene substitution pattern (*e.g.* intermolecular C–I···F–I contacts of 2.888 Å and I–F···F–I contacts of 2.891 Å were observed in the packing motif of our probe molecule – note Σr_V[I,F] = 3.45 Å and Σr_V[F,F] = 2.94 Å – and others have reported similar short contacts in aryl-IF_2 structures). It is also worth mentioning that no short intermolecular contacts involving the Br substituent in **21** were observed.

An unexpected role of the *ortho*-substituent

Although it is clear that the *ortho*-substituent has an influence on the IF_2 group in solution (and potentially in the solid state) from the experiments outlined above, it is not completely understood whether the *ortho*-substituent actually influences the hydrolytic stability of aryl-IF_2 compounds. Thus, we performed a series of controlled hydrolysis experiments, whereby the NMR samples were prepared first under Ar and rigorously dry conditions, then flooded with water immediately prior to the measurements in an attempt to simulate pseudo-first order decays of the aryl-IF_2 compounds.[24]

Initially, we varied systematically the size and electronegativity of the *ortho*-substituents, performing the hydrolysis experiments on compounds **3**, **13**–**15**, and **17** and **18**. However, the precipitation of the byproducts seriously complicates the picture (even at lower concentrations), so it was not possible to obtain reliable, quantitative kinetic information or to establish definitive trends. Yet, qualitatively, we can at least note that the *ortho*-methyl-substituted compound **18** appears to decay at a similar rate to either the *ortho*-chloro- or *ortho*-bromo-substituted compounds **14** and **15** (see ESI† for details). This is an indication that, with respect to hydrolytic stability, the size of the *ortho*-substituent could play a more important role than electronegativity.

In addition, we varied the position of the trifluoromethyl substituent in the CF_3-substituted aryl-IF_2 compounds, *i.e.* investigating compounds **2**, **22**, and **23**. If our hypothesis that the presence of an *ortho*-substituent has a strong positive effect on hydrolytic stability is correct, then one would expect that compound **2** would decay at the slowest rate. Surprisingly, this is not the case. It appears the relative rates of decay based on substitution are: *meta*-CF_3 > *ortho*-CF_3 > *para*-CF_3 (with the *para*-CF_3 isomer being the most stable of the three). Based on a thermodynamic argument alone, one would expect the *ortho*-CF_3 isomer to decay the fastest, but this is also not the case. Thus, the *ortho*-substituent may, in fact, have a positive kinetic influence on hydrolytic stability, but it is not nearly as substantial as we anticipated at the outset of this study.

However, by analyzing the reaction mixtures under rigorously air- and moisture-free conditions during the hydrolysis experiments (prior to water addition), we unveiled an interesting and unexpected result when investigating the *meta*- and *para*-substituted substrates: formation of tetrafluoro(aryl)-λ^5-iodanes (aryl-IF_4 compounds). Aryl-IF_4 compounds are remarkably more sensitive toward hydrolysis than aryl-IF_2 compounds, so extremely careful preparation of the NMR samples was necessary in order to observe them (admittedly, that is how we had completely overlooked this finding earlier in this study). Thus, our initial assumption that the identity of the precipitate forming in the NMR samples prepared in air was strictly the iodosoarene (from hydrolysis of aryl-IF_2) was incorrect; the precipitate is actually made up of a more significant amount of iodylarene formation for samples employing *meta*- and *para*-substituted substrates.

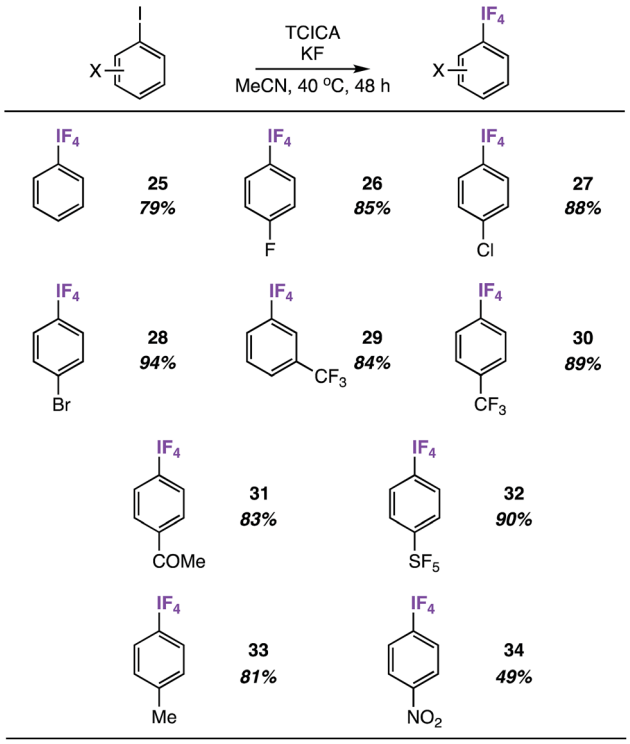
This key observation puts the role of the *ortho*-substituent into a new perspective. The hydrolysis experiments suggest that the *ortho*-substituent only has a minor positive influence on hydrolytic stability of aryl-IF_2 products once they are formed, but it plays a more noteworthy role *during the reaction with TCICA and KF* in inhibition of further oxidation of iodine(III) to iodine(V).

Substrate scope of tetrafluoro(aryl)-λ^5-iodanes

We discovered quickly that satisfactory yields of *meta*- and *para*-substituted aryl-IF_4 compounds can be obtained under nearly identical reaction conditions to those in Table 2 (*i.e.* 4.0 equiv. TCICA and 6.0 equiv. KF in MeCN at 40 °C) by simply letting the reactions stir for 48 h instead of 24 h.

Under these conditions, we synthesized a variety of aryl-IF_4 compounds in good yields (79–94%, Table 4). As anticipated, the functional group compatibility is similar to what we noted in Table 2: aryl-IF_4 formation from the unsubstituted iodobenzene (compound **25**) and iodoarenes substituted with either electron-withdrawing groups (*e.g.* halogens, ketones, trifluoromethyl, and pentafluorosulfanyl groups in compounds **26**–**32**) or mild electron-donating groups (*e.g.* a methyl group in compound **33**) proceeds smoothly. On the other hand, the

Table 4 Substrate scope of *meta*- and *para*-substituted aryl-IF_4 compounds[a]



[a] Yields determined by ^{19}F NMR using fluorobenzene or benzotrifluoride as an internal standard.

substrate with the most extreme electron-withdrawing group – a *para*-nitro group – only provided compound **34** in 49%.

Remarkably, only one *ortho*-fluorine substituent is enough to stifle aryl-IF_4 formation. For instance, letting 2,4-difluoroiodobenzene stir for 48 h under reaction conditions results in less than 10% of the corresponding aryl-IF_4 product by ^{19}F NMR (note the IF_4 signal was identified at −21.21 ppm in the $^{19}F\{^1H\}$ spectrum as a doublet with a *J*-coupling of 19.2 Hz to the *ortho*-fluorine atom). In nearly all other instances when the *ortho*-substituent is larger than a fluorine atom, the aryl-IF_2 product is formed exclusively.

We also discovered that these aryl-IF_4 compounds, although less hydrolytically stable than aryl-IF_2 compounds, may be more easily extracted from the reaction mixture by comparison (see ESI† for details). For instance, we extracted compound **26** from the reaction mixture under N_2 atmosphere in a glovebox using *n*-hexane and obtained a white solid in 77% isolated yield.

From this, single crystals were grown that proved suitable for X-ray structure determination (Fig. 6). As anticipated, a slightly distorted square pyramidal geometry was observed about the iodine atom with the arene in the apical position. In all, the structure displays similar features to the aryl-IF_4 compounds originally reported by Frohn[25] and Seppelt[26] (*e.g.* d(C–I) = 2.078 Å, average d(I–F) = 1.939 Å, average *trans* $\theta_{F-I-F} = 170.1°$, average *cis* $\theta_{F-I-F} = 89.6°$, average $\theta_{C-I-F} = 85.1°$, $\phi_{C-C-I-F} = 44.7°$, and short intermolecular I···F and F···F contacts can be observed in the packing motif).

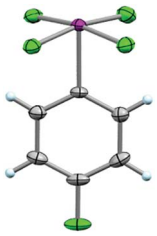


Fig. 6 Crystal structure of compound **26** determined from single-crystal X-ray diffraction (displacement ellipsoids depicted at 50% probability level).

Synthesis of another aryl-λ^5-iodane: an *ortho*-substituted exception

Inspired by the known reactivity of TCICA and KF in the synthesis of fluoroiodane **36** from alcohol **35** (Fig. 7),[27] we also wondered if **36** could be further oxidized to I(v) compound **37** under our reaction conditions. Compound **37** was originally synthesized by Amey and Martin from **35** using excess CF_3OF, and it was briefly explored as an oxidant.[28] More recently, it was synthesized in our laboratory using either XeF_2 or Cl_2/KF.[29] The TCICA/KF approach would make **37** significantly more accessible for future studies.

To our satisfaction, fluoroiodane **36** undergoes further oxidative fluorination under TCICA/KF conditions to provide **37** in 87% yield by ^{19}F NMR (Fig. 7). Moreover, under identical reaction conditions, alcohol **35** can also be converted into **37** directly in 69% yield. In all, our synthesis of **37** indicates that the TCICA/KF approach can be useful in the synthesis of fluorinated I(v)-compounds beyond aryl-IF_4, and it presents a notable "exception to the rule" that *ortho*-substituted iodoarenes show higher selectivity for the I(III) products over the I(v) products under these reaction conditions.

Solid-state structure of 37

Additionally, single crystals of **37** suitable for X-ray structure determination were analyzed that display some interesting features (Fig. 8) (note that there were two symmetry-

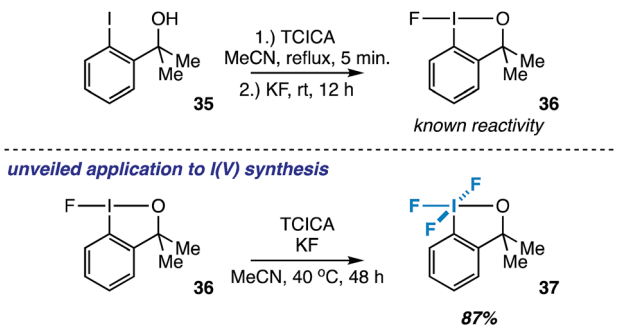


Fig. 7 Extended application to the synthesis of an *ortho*-substituted I(v) compound (**37**) as an exception to the rule. Yield determined by ^{19}F NMR.

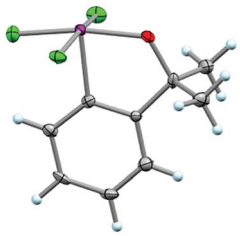


Fig. 8 Crystal structure of compound **37** determined from single-crystal X-ray diffraction (displacement ellipsoids depicted at 50% probability level, only one of two asymmetric moieties from asymmetric unit shown).

independent moieties in the asymmetric unit). Due to the participation of the oxygen atom on the *ortho*-substituent in a three-centered bonding interaction, the average C_{ortho}–C_{ipso}–I–F_{trans} torsion angle ($\phi_{C-C-I-F_t}$) is 171.9° and the average C_{ortho}–C_{ipso}–I–F_{cis} torsion angle ($\phi_{C-C-I-F_c}$) is 87.4°. This is a noteworthy deviation from the preferred orientation of the IF_4 moiety in aryl-IF_4 compounds such as **26**, whereby $\phi_{C-C-I-F} \approx 45°$.

Also, the average C–I bond distance (2.072 Å) is in close accord with aryl-IF_4 compound **26**, but the I–F bond distances in **37** are slightly longer, *i.e.* average $d(I–F_{cis}) = 1.963$ Å and average $d(I–F_{trans}) = 1.979$ Å (the latter bond conceivably elongated due to the greater trans effect of the oxygen atom; note that the average $d(O–I) = 1.924$ Å).[30] However, for another comparison, both the I–F_{trans} and O–I bonds in **37** are significantly shorter than those in the fluoroiodane precursor **36** (reported as 2.073 Å and 2.033 Å, respectively).[29]

We also noted that the bond angles across the three-centered bonds, on average (*trans* $\theta_{F–I–F} = 168.5°$ and *trans* $\theta_{O–I–F} = 167.9°$), deviate from linearity to a greater extent than aryl-IF_4 compound **26** (*trans* $\theta_{F–I–F} = 170.1°$), but slightly less than that of fluoroiodane **36** (*trans* $\theta_{O–I–F} = 167.9°$) (additional details about bond angle comparisons can be found in the ESI†). Lastly, it is important to mention that the crystal structure of **37** displayed short intermolecular I···F and F···F contacts in the packing motif and the tendency to form similar "chain" structures as Frohn,[25] Seppelt,[26] and we have observed (see ESI†).

Conclusions

Remarkably, this TCICA/KF approach to oxidative fluorination of iodoarenes can be employed to synthesize both aryl-IF_2 and aryl-IF_4 compounds. Under our reaction conditions, access to either the I(III)- or I(V)-derivatives is controlled primarily by the substitution pattern on the iodoarene substrate, *i.e.* an *ortho*-substituent inhibits further conversion of aryl-IF_2 to the corresponding aryl-IF_4 compound. An exception to this trend was also presented in the form of compound **37**, whereby the *ortho*-substituent participates in a three-centered bonding interaction with the iodine atom, thus making the I(V)-derivative accessible. Moreover, this method arguably presents the mildest synthesis of aryl-IF_4 compounds reported to date, as well as the mildest approach to electron-deficient aryl-IF_2 compounds, as a complement to the methods of Shreeve and Gilmour that can be used to access more electron-rich aryl-IF_2 compounds using Selectfluor.

Beyond the development of the TCICA/KF approach as an oxidative fluorination method, this study also raised several questions about the relationship between the IF_2 group and *ortho*-substituents on an arene. This resulted in a series of controlled hydrolysis experiments, computational studies, X-ray crystallographic analyses, and the synthesis of a probe molecule that allotted the first detailed dynamic NMR study on rotation about the C–I bond on substituted aryl-IF_2 compounds, from which, rotational barriers and thermodynamic parameters were reported herein.

In all, we hope that our easy access to and increased structural understanding of aryl-IF_2 and aryl-IF_4 compounds in both solution and the solid state will stimulate more research in this area. Future studies will be focused on studying the oxidative fluorination mechanism, as well as exploring applications of aryl-IF_2 and aryl-IF_4 compounds as possible reagents.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the ETH transfer office for support in filing a patent application on this work, in which C. R. P., N. S., and A. T. are listed as inventors. MoBiAS (ETH) is acknowledged for assistance with HRMS analyses. Financial support was provided by ETH Zürich and the ETH Postdoctoral Fellowship Program (C. R. P.).

Notes and references

1 V. V. Zhdankin, *Hypervalent Iodine Chemistry: Preparation, Structure and Synthetic Applications of Polyvalent Iodine Compounds*, John Wiley & Sons, West Sussex, UK, 2014.
2 C. Ye, B. Twamley and J. M. Shreeve, *Org. Lett.*, 2005, **7**, 3961.
3 J. C. Sarie, C. Thiehoff, R. J. Mudd, C. G. Daniliuc, G. Kehr and R. Gilmour, *J. Org. Chem.*, 2017, **82**, 11792.
4 For reviews, see: (*a*) P. J. Stang and V. V. Zhdankin, *Chem. Rev.*, 1996, **96**, 1123; (*b*) V. V. Zhdankin, *ARKIVOC*, 2009, 1; (*c*) A. Yoshimura and V. V. Zhdankin, *Chem. Rev.*, 2016, **116**, 3328.
5 For some examples, see: (*a*) M. Zupan and A. Pollak, *J. Fluorine Chem.*, 1976, **7**, 445; (*b*) I. Ruppert, *J. Fluorine Chem.*, 1980, **15**, 173; (*c*) D. Naumann and G. Rüther, *J. Fluorine Chem.*, 1980, **15**, 213; (*d*) K. Alam and A. F. Janzen, *J. Fluorine Chem.*, 1987, **36**, 179; (*e*) S. Hara, M. Yoshida, T. Fukuhara and N. Yoneda, *Chem. Commun.*, 1998, 965; (*f*) V. Padelidakis, W. Tyrra and D. Naumann, *J. Fluorine Chem.*, 1999, **99**, 9; (*g*) H. J. Frohn and V. V. Bardin, *J. Fluorine Chem.*, 2005, **126**, 1036; (*h*) C. Ye, B. Twamley and J. M. Shreeve, *Org. Lett.*, 2005, **7**, 3961; (*i*) S. Suzuki, T. Kamo, K. Fukushi, T. Hiramatsu, E. Tokunaga, T. Dohi, Y. Kita and N. Shibata, *Chem. Sci.*, 2014, **5**, 2754; (*j*) S. M. Banik, J. W. Medley and E. N. Jacobsen, *J. Am. Chem.*

Soc., 2016, **138**, 5000; (*k*) J. D. Haupt, M. Berger and S. R. Waldvogel, *Org. Lett.*, 2019, **21**, 242.

6 (*a*) L. M. Yagupol'skii, V. V. Lyalin, V. V. Orda and L. A. Alekseeva, *Zh. Obshch. Khim.*, 1968, **38**, 2813; (*b*) I. I. Maletina, V. V. Orda, N. N. Aleinikov, B. L. Korsunskii and L. M. Yagupol'skii, *Zh. Org. Khim.*, 1976, **12**, 1371; (*c*) H. J. Frohn, *Chem.-Ztg.*, 1984, **108**, 146.

7 C. R. Pitts, D. Bornemann, P. Liebing, N. Santschi and A. Togni, *Angew. Chem., Int. Ed.*, 2019, **58**, 1950.

8 S. Haubenreisser, T. H. Wöste, C. Martínez, K. Ishihara and K. Muñiz, *Angew. Chem., Int. Ed.*, 2016, **55**, 413.

9 U. Tilstam and H. Weinmann, *Org. Process Res. Dev.*, 2002, **6**, 384.

10 *Gaussian 09, Revision D.01*, Gaussian, Inc., Wallingford, CT, 2013.

11 J.-D. Chai and M. Head-Gordon, *Phys. Chem. Chem. Phys.*, 2008, **10**, 6615.

12 T. H. Dunning Jr, *J. Chem. Phys.*, 1989, **90**, 1007.

13 T. Umemoto, R. P. Singh, Y. Xu and N. Saito, *J. Am. Chem. Soc.*, 2010, **132**, 18199.

14 (*a*) A. L. Johnsen, *J. Org. Chem.*, 1982, **47**, 5220; (*b*) J. R. Wolstenhulme, J. Rosenqvist, O. Lozano, J. Ilupeju, N. Wurz, K. M. Engle, G. W. Pidgeon, P. R. Moore, G. Sandford and V. Gouverneur, *Angew. Chem., Int. Ed.*, 2013, **52**, 9796.

15 M. Wang, Q. Fan and X. Jiang, *Org. Lett.*, 2018, **20**, 216.

16 The synthesis of one of the tetralone intermediates required to make **21** is loosely based on a synthesis reported by Kutateladze and co-workers: W. C. Cronk, O. A. Mukhina and A. G. Kutateladze, *J. Org. Chem.*, 2014, **79**, 1235. Additional modifications were adapted from procedures in ref. 14, as well as: P. Nguyen, E. Corpuz, T. M. Heidelbaugh, K. Chow and M. E. Garst, *J. Org. Chem.*, 2003, **68**, 10195.

17 Note that a temperature calibration was performed prior to the following experiments using 4% MeOH in MeOH-d4 and a sample of pure MeOH-d4, see: A. L. Van Geet, *Anal. Chem.*, 1970, **42**, 679.

18 For an example of temperature-dependent shifts in ^{19}F NMR spectra, see: A. Dimitrov, U. Groß, S. Rüdiger, W. Storek and J. Burdon, *J. Fluorine Chem.*, 1996, **78**, 1.

19 (*a*) T. Drakenberg, K. Dahlqvist and S. Forsén, *Acta Chem. Scand.*, 1970, **24**, 694; (*b*) F. P. Gasparro and N. H. Kolodny, *J. Chem. Educ.*, 1977, **54**, 259; (*c*) F. A. Bovey, *Nuclear Magnetic Resonance Spectroscopy*, Academic Press, New York, 1988.

20 M. Ochiai, T. Yoshikazu and Y. Masaki, *J. Am. Chem. Soc.*, 1990, **112**, 5677.

21 H. J. Reich and C. S. Cooperman, *J. Am. Chem. Soc.*, 1973, **95**, 5077.

22 For a review on pseudorotation, see: H. L. Strauss, *Annu. Rev. Phys. Chem.*, 1983, **34**, 301.

23 C. R. Groom, I. J. Bruno, M. P. Lightfoot and S. C. Ward, *Acta Crystallogr., Sect. B: Struct. Sci., Cryst. Eng. Mater.*, 2016, **72**, 171. The CCDC search was conducted on May 3rd, 2019 using the online version, whereby a similarity search was performed on the core Ph-IF_2 structure. A total of 17 results were found (excluding our contributions), of which, only 8 represented aryl-IF_2 compounds (CCDC deposition numbers: 273254, 273255, 1555065, 139385, 938893, 760658, 760659, and 760660) and only 3 represented aryl-IF_4 compounds (CCDC deposition numbers: 216480, 1409048, and 1308449).

24 J. F. Corbett, *J. Chem. Educ.*, 1972, **49**, 663, and references cited therein.

25 H. J. Frohn, S. Görg, G. Henkel and M. Läge, *Z. Anorg. Allg. Chem.*, 1995, **621**, 1251.

26 S. Hoyer and K. Seppelt, *J. Fluorine Chem.*, 2004, **125**, 989.

27 (*a*) V. Matoušek, E. Pietrasiak, R. Schwenk and A. Togni, *J. Org. Chem.*, 2013, **78**, 6763; (*b*) J. Charpentier, N. Früh and A. Togni, *Chem. Rev.*, 2015, **115**, 650.

28 R. L. Amey and J. C. Martin, *J. Am. Chem. Soc.*, 1979, **101**, 5294.

29 J. Charpentier, PhD thesis no. 23352, ETH Zürich, 2016.

30 (*a*) J. V. Quagliano and L. Schubert, *Chem. Rev.*, 1952, **50**, 201; (*b*) M. Ochiai, T. Sueda, K. Miyamoto, P. Kiprof and V. V. Zhdankin, *Angew. Chem., Int. Ed.*, 2006, **118**, 8383.