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New hypervalent iodine reagents for electrophilic trifluoromethylation and their precursors: synthesis, structure, and reactivity

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ABSTRACT

Several new five- and a six-membered heterocyclic monochloroiodanes, including two cationic species, were synthesized. Three of which were used for the preparation of corresponding trifluoromethylation reagents. These compounds were characterized by X-ray crystallography for a comparative structural study. A reactivity study on the trifluoromethylation of *para*-toluenesulfonic acid has been conducted in order to compare initial rates. Compounds having a longer I–O bond display a higher reactivity.

1. Introduction

The first report of an organic hypervalent iodine compound by Willgerodt, (dichloro-λ^3-iodo)benzene,[1] inspired the synthesis of a plethora of new hypervalent iodine compounds. These compounds find widespread applications in organic synthesis such as in C–C, *C*-heteroatom, and heteroatom–heteroatom bond formation, oxidation, fragmentation, and rearrangement reactions.[2] In 2006, we published the syntheses of the new hypervalent iodine compounds **1a**–**c**[3] (Scheme 1) reagents for electrophilic trifluoromethylation, showing remarkable reactivity toward several nucleophiles such as thiols,[4] activated methylene compounds,[4] aromatic compounds,[5] sulfonic acids,[6] alcohols,[7] and phosphines.[8]

These compounds are synthesized in three steps: Oxidation of the appropriate 2-substituted iodobenzene to the cyclic iodine compounds **2a**–**c**, ligand exchange to the corresponding acetoxy compounds **3a**–**c** and in the last step an umpolung reaction using the nucleophilic Ruppert/Prakash reagent with a catalytic amount of fluoride to form the electrophilic trifluoromethylation reagents **1a**–**c**. Upon electrophilic trifluoromethylation of various substrates the reagents are converted to the respective starting materials **4a**–**c**, which may be isolated and reused as recyclable CF_3-carriers.

During our attempts to prepare hypervalent I-trifluoromethyl compounds we found that acyclic starting materials such as (difluoroiodo)toluene could not be transformed to the desired product, probably because the corresponding trifluoromethyl compounds are not stable, as indicated by the formation of CF_3I. This finding is consistent with the fact that cyclic iodanes have a considerably higher stability than their acyclic analogues.[9] This stabilization is usually explained by the bridging of an apical and an equatorial position by a five-membered ring and by better overlap of the lone pair electrons on the iodine atom with the aromatic system of the benzene ring.[10] There are several classes of heterocyclic iodane compounds known, the majority of which are derivatives of a five-membered ring benziodoxole **2c**. In Figure 1 some examples of heterocyclic five- or six-membered rings are represented by benziodazoles **5a**/**b**, benziodathiazoles **6**, benziodoxathioles **7**, cyclic phosphonates/phosphinate **8**, and a phosphate **9**.[11]

Monochloroiodanes such as **2a** and **2b** are useful intermediates for the synthesis of the electrophilic trifluoromethylation reagents **1a**–**c**. To the best of our knowledge the X-ray crystal structures of only four monochloroiodanes (**2b**,[12] **2c**,[12–14] **5a**,[14,15] and **5b**[16]) have been published so far. The synthesis of **2a** was published in 1979 by Martin.[17] However, no X-ray analysis was reported. Since we were interested in modifying our already existing trifluoromethylation reagents **1a**–**c** to enhance their reactivity and selectivity, we prepared and characterized a variety of new monochlorides, including six-membered heterocycles and cationic derivatives, as precursors for new trifluoromethylating reagents. Although it is possible to

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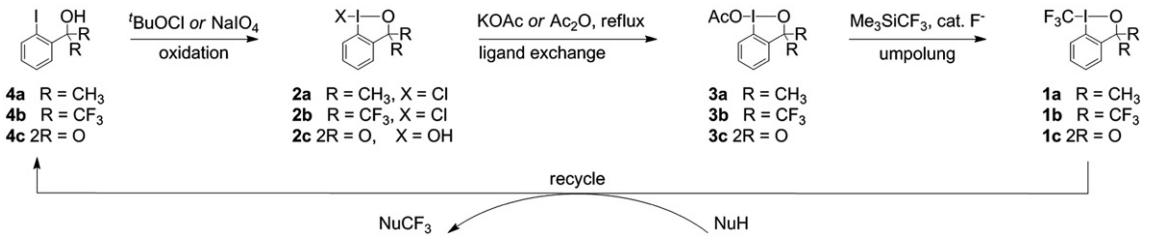


Scheme 1. Synthetic cycle of trifluoromethylation reagents **1a**–**b**.

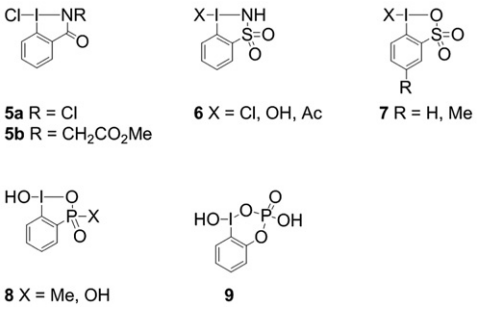


Figure 1. Examples of heterocyclic iodanes less common than benziodoxoles.

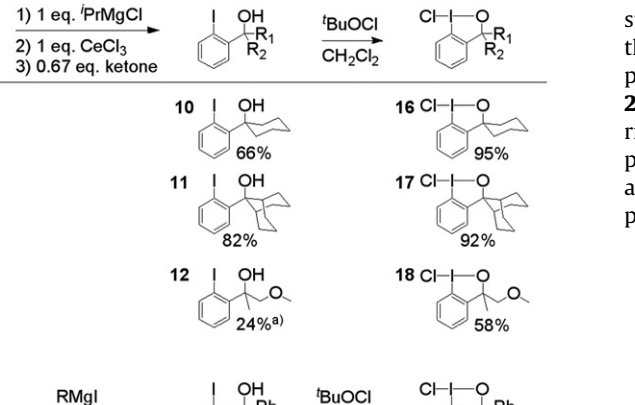
convert several neutral monochloroiodanes to the corresponding CF_3-compounds, including a six-membered heterocyclic derivative, following the synthetic procedure shown in Scheme 1, the attempted synthesis of corresponding cationic species was unsuccessful.

2. Synthesis

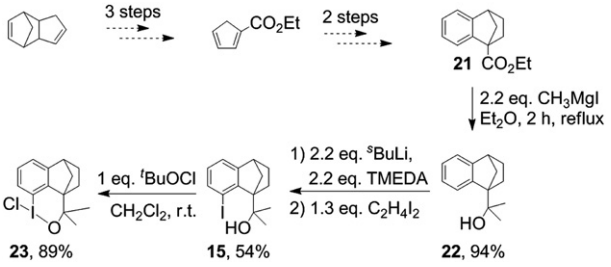
2.1. Synthesis of monochloroiodanes

Starting from alcohols **10**–**14** and **15** the corresponding neutral chlorides were prepared upon oxidation using ^{t}BuOCl (Scheme 2).

Recently, we reported a concise synthesis of 2-iodobenzyl alcohols via the addition of 2-iodophenyl Grignard reagents to ketones in the presence of $CeCl_3$.[20] This method was applied to the synthesis of alcohols **10** and **11**. However, under the same conditions alcohol **12** did not form and could only be obtained in the absence of $CeCl_3$ in low yield. Alcohol **13** was prepared according to a slightly modified procedure described by Yamataka,[18] and **14** was synthesized in a similar manner. Alcohols **10**–**14** were oxidized to the corresponding monochloroiodanes **16**–**20** under standard conditions using ^{t}BuOCl as oxidant in CH_2Cl_2. Alcohol **15** was synthesized in two steps from the known ester **21**, which was obtained by a five-step procedure as described by Tanida and Irie.[21] The conversion of ester **21** to alcohol **22** by twofold Grignard addition was achieved in good yield using a slight excess of methyl Grignard at reflux temperature. In the next step, alcohol **22** was iodinated by directed *ortho*-lithation with ^{s}BuLi/TMEDA in *n*-hexane at reflux temperature followed by the addition of 1,2-diiodoethane. Compound **15** was oxidized under similar conditions as described above to the six-membered cyclic monochloroidane **23** (Scheme 3).

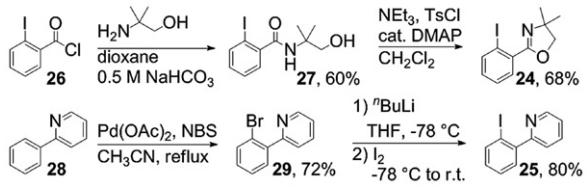


Scheme 2. Synthesis of neutral five-membered heterocyclic monochloroiodanes. (a) synthesized without the addition of $CeCl_3$; (b) synthesized according to a reported procedure;[18] (c) **14** was not isolated in pure form but directly converted to **20** in 44% yield over two steps; (d) synthesized according to a reported procedure.[19]



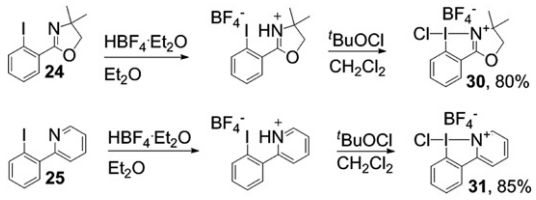
Scheme 3. Synthesis of six-membered cyclic iodane **23**.

Scheme 4 shows the synthesis of oxazolidine **24** and 2-(2-iodophenyl)pyridine (**25**). Oxazolidine **24** was synthesized in two steps from 2-iodobenzoic acid chloride (**26**) in 41% overall yield. In the first step acid chloride **26** was reacted with 2-amino-2-methylpropanol in a mixture of 1,4-dioxane and aq $NaHCO_3$ to form amide **27**, which was cyclized to form oxazolidine **24**. The pyridine derivative **25** was synthesized in 2 steps starting from 2-phenylpyridine (**28**) in 58% yield. Intermediate **29** was prepared by a slightly modified procedure published by Sanford et al.[22] Compound **25** was accessed by halide exchange.



Scheme 4. Synthesis of oxazoline **24** and 2-(iodophenyl)pyridine (**25**).

Precursors **24** and **25** were protonated using HBF_4 prior to oxidation with ^{t}BuOCl to yield the cationic 1-chloro-λ^3-iodanes **30** and **31** in good yields (Scheme 5).

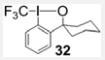


Scheme 5. Synthesis of cationic 1-chloro-λ^3-iodane **30** and **31**.

2.2. Synthesis of hypervalent trifluoromethyl compounds

As shown in Scheme 1, the trifluoromethylated compounds **1a**–**c** were obtained from the corresponding iodanes **2a**–**c** by a procedure involving two consecutive 'ligand exchange' processes. The acetoxy derivatives **3a**–**c** are formed as intermediates and react with $TMSCF_3$ as the nucleophilic CF_3-source in the presence of a catalytic amount of a fluoride to the trifluoromethylating reagents **1a**–**c**. The new CF_3-iodanes **32**, **33**, and **34** were thus prepared from the corresponding monochloroiodanes **16**, **19**, and **23** following this procedure. The yield of the crucial final step is highly dependent on the structure of the intermediate acetoxy derivative. Thus, compound **34**, the only six-membered iodacycle, could only be obtained in 14% yield (Table 1).

Table 1
Summary of synthetic results for new trifluoromethyl derivatives **32**–**34**[a]

Entry	Product Nr.	Acetate source	Yield [%]
1		AgOAc	37
2		KOAc	81
3		KOAc	14

[a] All syntheses were carried out without isolating the acetate intermediate in CH_3CN with an excess of $TMSCF_3$ and TBAT as catalytic fluoride source.

3. Solid-state structural analyses

3.1. The chloriodanes

Crystals suitable for X-ray measurements of compound **2a** were obtained by slow evaporation of a dichloromethane solution. Compounds **16**–**18**, **20**, and **23** were crystallized from CH_2Cl_2 by diffusion of pentane or Et_2O into a saturated solution. Under these conditions, **19** crystallizes in the space group *P*-1 incorporating a solvent molecule; using EtOAc instead of CH_2Cl_2 leads to crystallization in $P2_1/c$. Table 2 summarizes the important bond lengths, bond, and torsion angles for all oxygen-bonded monochloroiodanes (**2a**–**c**, **16**–**20**, and **23**). The crystal structures of all monochloroiodanes clearly show a distorted T-shaped geometry around iodine, typical for members of the hypervalent iodine(III) class. In all five-membered heterocycles the Cl–I–O angles are significantly smaller than 180° due to the repulsion of the two lone pairs at iodine as predicted by the VSEPR model. The O–I–C(1)–C(6) torsion angle of −17.17(15)° in compound **20** indicates that the five-membered heterocyclic unit displays an envelope-type conformation with the oxygen atom lying outside the plane defined by the phenyl ring. As summarized in Table 1 and illustrated in Figure 2, this angle flattens in the series **20**–**19**–**17**–**2a**–**16**–**18**–**2b**/**c**, such that compound **2c** shows almost perfect coplanarity with the adjacent phenyl ring (torsion angle 1.8°).

The Cl–I bond lengths lie between 2.438(2) and 2.5751(13) Å and increase in the series **2b**/**c**–**16**–**18**–**2a**/**19**–**17**–**20**, while the I–O bond length (2.110(5) to 2.0169(14) Å) decreases. These findings can mainly be ascribed to electronic effects derived from the substituents. The fine ordering is probably due to packing effects and remote intermolecular contacts in the solid state. In contrast to the I–Cl and I–O-bond lengths the I–C(1) bond lengths remain constant except for compound **18**, which may be explained by steric effects. The six-membered heterocyclic compound **23** shows an even longer I–C(1) bond-length and has a half-chair-type conformation with the two methyl groups in axial and equatorial position (similar to the corresponding trifluoromethyl compound **34** shown in Fig. 5, vide infra). An almost perfect T-shape geometry is observed around the iodine atom, as indicated by the Cl–I–O angle of 178.87(4)°. The oxygen atom deviates from the plane defined by the adjacent aryl ring to a similar extent as in compound **16**, (O–I–C(1)–C(6) torsion angles of 13.60(14)° and −12.4(3)°, respectively).

Table 2
Bond lengths, bond angles, and torsion angles of monochloroiodanes **2a**–**c**, **16**–**20**, and **2**

	2a	**2b**[12]	**2c**[12]	**16**	**17**[a]	**18**	**19**[b]	**20**	**23**
Bond lengths [Å]									
Cl–I	2.5491(8)	2.438(2)	2.461(1)	2.5135(9)	2.5751(13) 2.5741(13)	2.5201(7)	2.5406(7)	2.5805(6)	2.5703(6)
O–I	2.042(2)	2.110(5)	2.091(3)	2.049(2)	2.016(3) 2.005(3)	2.0511(18)	2.0437(2)	2.0169(14)	2.0220(15)
C(1)–I	2.102(3)	2.105(7)	2.100(4)	2.108(3)	2.104(5) 2.113(5)	2.117(2)	2.107(2)	2.108(2)	2.1259(19)
Bond angles [°]									
O–I–Cl	171.06(7)	172.0(1)	171.96(8)	170.17(7)	170.10(9) 170.94(10)	170.51(5)	169.86(5)	171.61(5)	178.87(4)
O–I–C(1)	80.57(10)	78.9(2)	79.5(1)	80.67(10)	79.68(15) 79.05(16)	80.20(9)	79.89(9)	80.5(7)	88.86(7)
C(1)–I–Cl	91.45(8)	93.2(2)	92.6(1)	90.77(9)	90.68(13) 92.23(14)	90.43(7)	91.15(7)	91.27(6)	92.02(5)
Torsion angles [°]									
O–I–C(1)–C(6)	10.8(2)	−6.4(6)	1.8(3)	10.0(2)	−12.4(3) 18.0(3)	8.36(18)	15.82(17)	17.17(15)	13.60(14)
Cl–I–C(1)–C(2)	6.0(3)	−4.7(5)	3.3(3)	2.9(3)	−11.4(4) 12.4(4)	3.9(2)	13.1(2)	15.18(18)	12.74(15)

[a] Asymmetric unit contains two independent molecules.
[b] Values given for $P2_1/n$ modification.

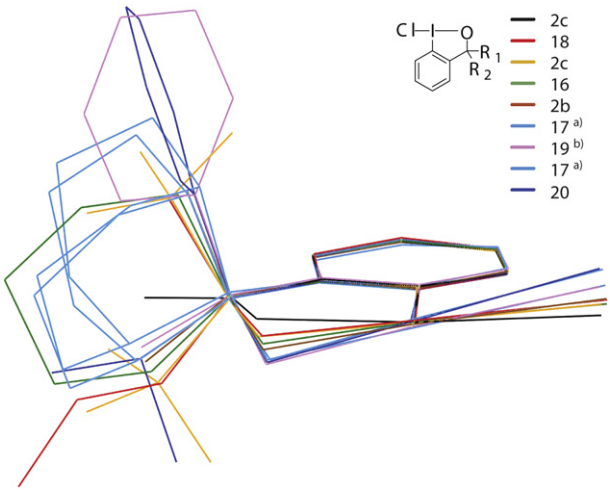


Figure 2. Structural overlap of compounds **2a**–**c** and **16**–**20** generated with the program MERCURY. (a) one of two independent molecules in the asymmetric unit; (b) structure given for the $P2_1/n$ modification.

X-ray-quality single crystals of the cationic compounds **30** and **31** were obtained by diffusion of Et_2O and CH_2Cl_2, respectively, into saturated acetonitrile solutions. The crystal structures of these highly hygroscopic materials are shown in Figure 3. Not surprisingly, the cationic species **30** and **31** show I–F contacts to the BF_4^- counter ions ranging between 3.028(3) and 3.173(1) Å. In compounds **30** and **31** the nitrogen atom is almost perfectly coplanar with the adjacent aryl ring (torsion angles of −1.1(2) and 1.01(10)°, respectively), similarly to compound **2b**/**c**. The Cl–I–bonds decrease in the series **5a**/**b**–**30**–**31** (2.563 to 2.4406(4) Å) and are comparable to the short Cl–I–bond of **2b**/**c** (2.438(2) and 2.461(1) Å, respectively). In the same series the N–I bond lengths increase from **5a** (2.06 Å), over **5b** (2.113 Å), to **30** (2.190(3) Å) and **31** (2.2273(12) Å) (Table 3).

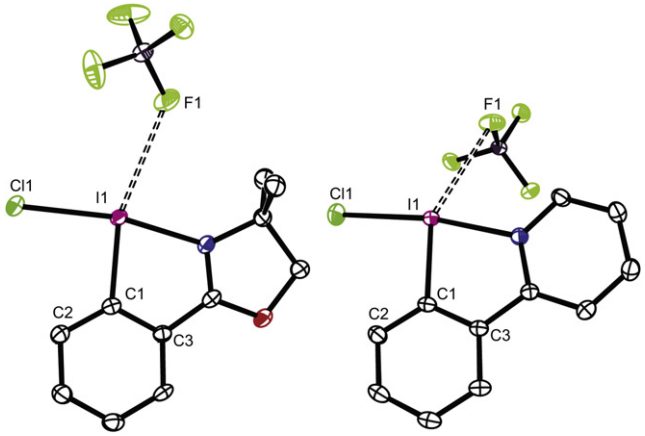


Figure 3. ORTEP drawing of compounds **30** (left) and **31** (right). Thermal ellipsoids are drawn at the 50% probability level, hydrogen atoms are omitted for clarity.

Table 3
Bond lengths, bond angles, and torsion angles of nitrogen-containing iodanes **5a**/**b** and **30**/**31**

	5a[a]	5b[b]	30	31
Bond lengths [Å]				
Cl–I	2.56[c]	2.563[c]	2.4612(9)	2.4406(4)
N–I	2.06[c]	2.113[c]	2.190(3)	2.2273(12)
C(1)–I	2.19[c]	2.101[c]	2.112(3)	2.1054(14)
Bond angles [°]				
N–I–Cl	171[c]	170.6[c]	169.15(7)	171.12(3)
C(1)–I–N	80[c]	79.0[c]	77.56(11)	77.36(5)
C(1)–I–Cl	90[c]	91.6[c]	91.65(9)	94.21(4)
Torsion angles [°]				
N–I–C(1)–C(6)		1.17[c]	−1.1(2)	−1.01(10)
Cl–I–C(1)–C(2)		1.96[c]	−1.8(3)	−4.27(12)

[a] Values taken from Ref. 15.
[b] Values taken from Ref. 16.
[c] Standard deviations not available.

3.2. Trifluoromethylating reagents

Single crystals for X-ray analysis for the new trifluoromethylated compound **32** were obtained by sublimation, while compounds **33** and **34** were crystallized by cooling a saturated pentane solution. Selected bond lengths, bond angles, and torsion angles are given in Table 4 and ORTEP representations of the structures are shown in Figure 4.

Table 4
Bond lengths, bond angles, and torsion angles of trifluoromethylating reagents

	1a[a]	1b[a]	32	33	34
Bond lengths [Å]					
F_3C–I	2.267(2)	2.229(2)	2.262(4)	2.2580(14)	2.304(2)
O–I	2.1176(14)	2.2014(15)	2.121(2)	2.1380(10)	2.0979(14)
C(1)–I	2.1211(19)	2.115(2)	2.123(3)	2.1153(12)	2.1314(18)
Bond angles [°]					
O–I–CF_3	169.77(8)	169.41(7)	169.69(13)	170.17(5)	177.90(6)
C(1)–I–O	78.72(6)	77.07(7)	78.15(11)	78.44(4)	87.23(6)
C(1)–I–CF_3	91.10(8)	92.37(8)	91.56(15)	91.75(5)	91.06(7)
Torsion angles [°]					
O–I–C(1)–C(6)	11.5(1)	−12.11(15)	−15.4(2)	−10.84(8)	14.94(14)
F_3C–I–C(1)–C(2)	13.2(2)	−11.7(2)	−14.7(3)	−14.45(11)	16.15(14)

[a] Values taken from Ref. 3.

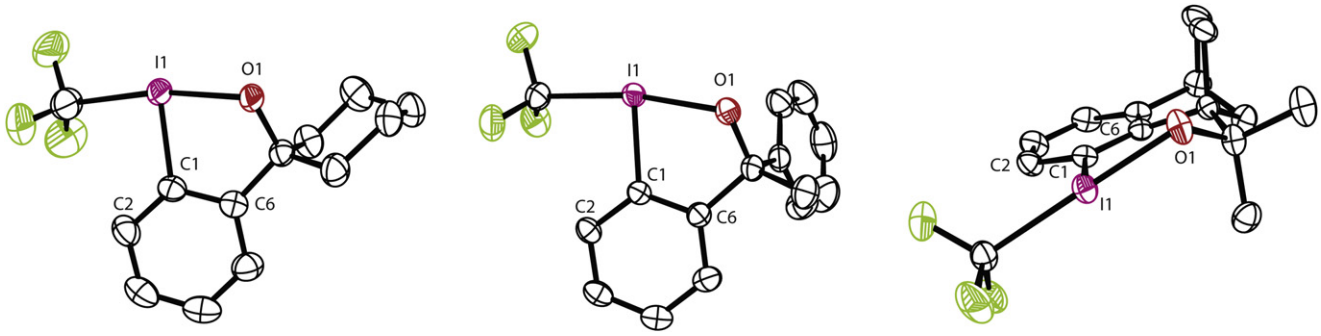


Figure 4. ORTEP drawing of compound **32**–**34** (left to right). Thermal ellipsoids drawn at the 50% probability level, hydrogen atoms are omitted for clarity reasons.

The same trends observed for the chloro compounds can be detected for the alcohol-derived trifluoromethyl compounds **1a**/**b** and **32**–**34** though in a less pronounced manner, as shown in Figure 5.

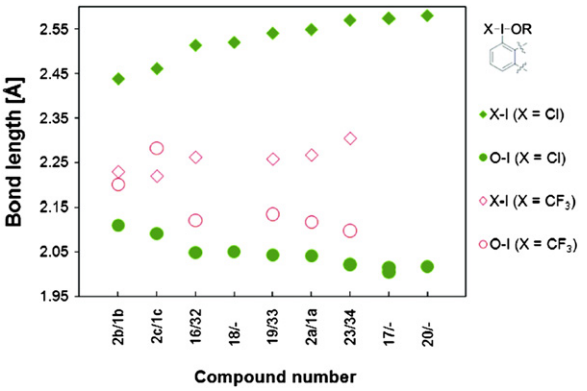


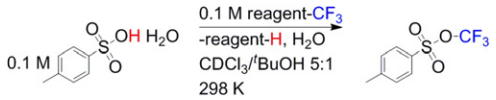
Figure 5. Correlation of bond lengths in chloro- and trifluoromethyliodanes.

Similar to the monochloroiodanes, a short I–O bond leads to an elongated F_3C–I bond. The I–O bonds in the CF_3-compounds are longer than in the corresponding chloro derivatives. The majority of the trifluoromethyl derivatives pack in a similar manner as their monochloro precursors and therefore show similar intermolecular contacts. If analogous packing is not observed, as in the case of compound **33**, bond length comparisons should be taken with care. However, our results show that the CF_3 derivatives of corresponding monochloroiodanes with long Cl–I bonds are likely to have long F_3C–I bonds as well.

4. Reactivity study

With the wealth of structural information available for 1-chloro- and 1-trifluoromethyl-1,2-benziodoxoles, studies were undertaken to correlate the structural features of the trifluoromethyl compounds to their relative reactivities toward a standard substrate. The primary goal of such studies is to identify structural features, which are potentially advantageous with regard to CF_3-group transfer that might be exploited to develop improved reagents. To this end, the initial rates of reaction (v_0) of compounds **1a**–**c** and **32**–**34** were measured for mixtures of 0.1 M trifluoromethylating agent and 0.1 M toluenesulfonic acid monohydrate in a 5:1 mixture of $CDCl_3$/*tert*-butanol at 298 K. As previously reported,[6] this reaction occurs smoothly at room temperature and displays a clean second order kinetics. The results of these studies are summarized in Table 5 and the experimental details of the investigations are included in the Experimental section.

Table 5
Initial rate constants of the trifluoromethylation of toluenesulfonic acid monohydrate with reagents **1a**–**c** and **32**–**34**



Entry	Reagent	v_0[mol/L s]
1	**1c**	2.3×10^{-5}
2	**33**	5.3×10^{-6}
3	**34**	9.4×10^{-7}
4	**1a**	5.7×10^{-7}
5	**32**	3.4×10^{-7}
6	**1b**	1.2×10^{-7}

Reaction conditions: 0.1 M trifluormethylating agent, 0.1 M toluenesulfonic acid monohydrate, solvent: 5:1 $CDCl_3$/^{t}BuOH, 298 K.

Unfortunately, no strongly convincing correlations between X-ray structural parameters and reactivity toward toluenesulfonic acid monohydrate were found. However, two vague, expected trends in observed bond lengths and reactivity behavior do appear to be present. Very generally, it seems that reagents with shorter CF_3–I bond distances and longer I–O distances tend to be slightly more reactive toward toluenesulfonic acid. This is in keeping with the previous observation that protonation of the reagent at oxygen (weakening of the I–O bond) is critical for the trifluoromethylation under acidic conditions.[6]

Part of the difficulty in assessing and comparing the structural and rate data seems to stem from packing effects, especially the strong intermolecular interactions between the alkoxide groups and iodine (III) centers of neighboring molecules in the crystal. It should also be noted that the initial rate runs were not repeated and therefore also incur a degree of unreliability. However, in this case, our experience strongly indicates that with sufficient care such experiments yield reproducible rate data within the standard deviations of the curve fitting routines.[23]

5. Conclusion

In conclusion, we synthesized and characterized several new five- and a six-membered heterocyclic monochloroiodanes, including two cationic species. The synthesis and the crystal structures of three new trifluoromethylating reagents are shown. These structures were compared with the X-ray structures of the monochloroiodanes and were tested in a reactivity study on the trifluoromethylation of *para*-toluenesulfonic acid. Although the data presented here should be taken as a qualitative guide and not as a rigorous quantitative study, it seems that the enhancement of reagent activity toward sulfonic acids is observed in structures containing a weakened I–O bond. Assessment of reagent performance relative to substrates other than those containing acidic hydroxyl groups remains a task for the future.

6. Experimental

6.1. General

All commercially available chemicals were of reagent grade and were used without further purification. Alcohol **13**,[18] monochloroiodanes **2a**,[17] **19**,[19] and ester **22**[21] were prepared according to known procedures. Et_2O, THF, and pentane were dried over Na/benzophenone, CH_2Cl_2, and CH_3CN were dried over CaH_2. All reactions were carried out using standard Schlenk techniques under an argon atmosphere. Flash column chromatography was carried out on silica gel 60 (230–400 mesh) from Fluka. TLC-plates were purchased from Merck (silica gel 60 F_{254}). NMR spectra were recorded on Bruker AC-200, DPX-250, DPX-300, DPX-400, DPX-500. Chemical shifts are given relative to tetramethylsilane for ^{1}H and ^{13}C NMR spectra. For ^{19}F NMR spectra, $CFCl_3$ was used as an external standard. The following abbreviations have been used to describe the signals: s for singlet; d for doublet; t for triplet; q for quadruplet; m for multiplet; u for unresolved and br for broad signals. High resolution mass-spectra were measured by the *MS-Service des Laboratoriums für Organische Chemie, ETH Zürich*. Elemental analyses were carried out by the *Mikroelementanalytisches Laboratorium der ETH Zürich*. Intensity data of single crystals glued to a glass capillary were collected at the given temperature (usually 100 K) on Bruker SMART APEIX platforms with CCD detector and graphite monochromated Mo K_α-radiation (λ=0.71073 Å). The program SMART served for data collection; integration was performed with the software SAINT.[24] The structure was solved by direct methods or Patterson methods, respectively, using the program SHELXS-97.[25] The refinement and

all further calculations were carried out using SHELXL-97.[26] All non-hydrogen atoms were refined anisotropically using weighted full-matrix least-squares on F^2. The hydrogen atoms were included in calculated positions and treated as riding atoms using SHELXL default parameters. In the end absorption correction was applied (SADABS)[27] and weights were optimized in the final refinement cycles. The absolute configuration of chiral compounds was determined on the basis of the Flack parameter.[28,29] CCDC 771236–771247 and 771565 contain the supplementary crystallographic data for compounds **2a**, **34**, **31**, **16**, **32**, **17**, **30**, **23**, **18**, **19** (in *P*-1), **33**, **20**, and **19** (in $P2_1/c$). These data can be obtained free of charge from the Cambridge Crystallographic Data Center via http://www.ccdc.cam.ac.uk/dada_request/cif.

*6.1.1. 1-(2-Iodophenyl)cyclohexanol (**10**).* Anhydrous $CeCl_3$ (713 mg, 2.89 mmol, 1.5 equiv) was suspended in dry THF (8 mL) and stirred for 12 h at room temperature. In a second Schlenk flask 1,2-diiodobenzene (955 mg, 2.89 mmol, 1.5 equiv) was dissolved in dry THF (10 mL) under argon. After cooling to −30 °C isopropylmagnesium chloride (1.45 mL, 2.0 M solution in THF, 2.89 mmol, 1.5 equiv) was added dropwise and the resulting orange colored mixture was warmed to −20 °C over a period of 20 min. The reaction was monitored by GC/MS. Both flasks were cooled to −78 °C and the freshly prepared Grignard reagent was added slowly to the $CeCl_3$ suspension by means of a syringe. The mixture was warmed to room temperature to ensure the complete formation of organocerium species by transmetallation. After cooling again to −78 °C cyclohexanone (0.2 mL, 1.92 mmol) was added and the mixture was allowed to warm up to rt overnight. After dilution with Et_2O (20 mL) the reaction mixture was hydrolyzed in an ice bath with satd aq NH_4Cl solution (20 mL), the layers were separated and the aqueous phase was extracted twice with Et_2O (20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated to dryness in vacuo. After purification of the crude product by flash chromatography (hexane/EtOAc 50:1 then 5:1) **10** (384 mg, 66%) was isolated as a white powder; δ_H(300 MHz, $CDCl_3$) 7.99 (1H, t, *J* 7.9 Hz, H_{arom}), 7.62 (1H, t, *J* 7.9 Hz, H_{arom}), 7.35 (1H, t, *J* 7.8 Hz, H_{arom}), 6.92 (1H, t, *J* 7.4 Hz, H_{arom}), 2.32 (1H, s, OH), 2.02–2.21 (4H, m, CH), 1.69–1.91 (5H, m, CH), 1.28–1.42 (1H, m, CH); δ_C (75 MHz, $CDCl_3$): 148.4, 143.0, 128.6, 128.2, 127.0, 93.5 (CI), 74.0 (COH), 36.0, 25.3, 22.0; HRMS (EI): M^+, found 302.0162, $C_{12}H_{15}IO$ requires 302.0168.

*6.1.2. 1-Chlorospiro[1λ^3,2-benziodaoxole-3.1′-cyclohexane] (**16**).* A round bottomed flask was charged with alcohol **10** (380 mg, 1.26 mmol) and CH_2Cl_2 (4 mL) and cooled to 0 °C. To the slightly yellow reaction mixture ^{t}BuOCl (148 μL, 1.27 mmol, 1.01 equiv) was added and the mixture was warmed to rt over night. The solution was concentrated and the crude product was recrystallized from CH_2Cl_2 to give compounds **16** as a yellow solid (403 mg, 95%). Single crystals for X-ray analysis were obtained by diffusion of pentane into a saturated CH_2Cl_2 solution; δ_H(300 MHz, $CDCl_3$) 8.04 (1H, d, *J* 7.5 Hz, H_{arom}), 7.50–7.59 (2H, m, H_{arom}), 7.18 (1H, d, *J* 6.9 Hz, H_{arom}), 1.90–1.94 (2H, m, CH), 1.58–1.82 (7H, m, CH), 1.22–1.36 (1H, m, CH); δ_C (75 MHz, $CDCl_3$) 149, 130.8, 130.5, 128.5, 126.1, 115.2 (*C*I), 86.4 (*C*OH), 37.2, 25.4, 22.1; HRMS (EI): M^+, found 335.9771, $C_{12}H_{14}ClIO$ requires 335.9778.

*6.1.3. 1-(Trifluoromethyl)spiro[1λ^3,2-benziodaoxole-3.1′-cyclohexane] (**32**).* Chlorobenziodaoxole **16** (1.2 g, 3.5 mmol) was dissolved in CH_3CN (25 mL) under argon and AgOAc (0.44 g, 3.7 mmol, 1.05 equiv) was added. The resulting suspension was stirred for 3 h, filtered, and concentrated to yield the corresponding acetate, which was used without further purification. It was dissolved in CH_3CN (30 mL) and $TMSCF_3$ (0.8 mL, 5.3 mmol, 1.5 equiv) was added, followed by a solution of TBAT (3.8 mg, 7 μmol, 0.2 mol %) in CH_3CN (2 mL) at −17 °C. The mixture was stirred at this temperature for 20 h. Then it was allowed to warm up to −12 °C, additonal $TMSCF_3$ (0.13 mL) was added and the stirring was continued for 24 h at ambient temperature. Pentane (20 mL) was added and the solution was filtered through cotton and concentrated. The crude product was purified by flash-chromatography (Alox, hexane/EtOAc=50:1) to give **32** as a white solid (0.48 g, 37%). X-ray quality crystals were obtained by sublimation under high vacuum (0.015 mbar, 60 °C); δ_H(300 MHz, $CDCl_3$) 7.52–7.56 (2H, m, H_{arom}), 7.40–7.45 (2H, m, H_{arom}), 1.90–1.94 (2H, m, CH), 1.63–1.78 (7H, m, CH), 1.25–1.29 (1H, m, CH); δ_C (75 MHz, $CDCl_3$) 149.5, 130.5, 129.5, 127.9 (q, *J* 2.7 Hz), 127.3, 111.3 (q, *J* 3 Hz, CI), 110.9 (q, *J* 397.0 Hz, CF_3), 78.1 (COH), 38.5, 25.7, 22.4; δ_F (188 MHz, $CDCl_3$) −40.3; HRMS (EI): M^+, found 370.0044, $C_{13}H_{14}F_3IO$ requires 370.0041.

*6.1.4. 9-(2-Iodophenyl)bicyclo[3.3.1]nonan-9-ol (**11**).* Starting from bicyclo[3.3.1]nonan-9-one (183 mg, 1.3 mmol), **11** was synthesized in analogy to compound **10**. Column chromatography (hexane/EtOAc 50:1 then 10:1) gave a white powder (363 mg, 82%); δ_H(300 MHz, $CDCl_3$) 8.03 (1H, t, *J* 7.7 Hz, H_{arom}), 7.62 (1H, t, *J* 7.5 Hz, H_{arom}), 7.35 (1H, t, *J* 7.5 Hz, H_{arom}), 6.91 (1H, t, *J* 6.9 Hz, H_{arom}), 3.03 (2H, s, CH), 2.40–2.51 (3H, m, CH), 1.57–2.03 (10H, m, CH), 1.41 (1H, m, CH); δ_C (75 MHz, $CDCl_3$) 145.4, 143.9, 129.4, 128.6, 127.6, 93.6 (CI), 76.1 (COH), 34.8, 29.9, 27.6, 20.8, 19.9; HRMS (EI): M^+, found 342.0477, $C_{15}H_{19}IO$ requires 342.0481.

*6.1.5. 1-Chlorospiro[1λ^3,2-benziodaoxole-3.9′-bicyclo[3.3.1]nonane] (**17**).* Starting from *ortho*-iodobenzyl alcohol **11** (356 mg, 1.04 mmol) **17** was synthesized in analogy to **16** to yield a yellow solid (360 mg, 92%). Single crystals for X-ray analysis were obtained by diffusion of pentane into a saturated CH_2Cl_2 solution; δ_H(300 MHz, $CDCl_3$) 8.16 (1H, d, *J* 6.0 Hz, H_{arom}), 7.81 (1H, d, *J* 6.0 Hz, H_{arom}), 7.51 (2H, m, H_{arom}), 1.52–2.35 (14H, m, 14H, CH); δ_C (75 MHz, $CDCl_3$) 147.7, 129.7, 129.5, 129.0, 128.9, 118.9 (CI), 88.6 (COH), 36.5, 28.8, 28.7, 20.1, 20.0; HRMS (EI): M^+, found 376.0086, $C_{15}H_{18}ClIO$ requires 376.0091.

*6.1.6. 2-(2-Iodophenyl)-1-methoxy-2-propanol (**12**).* 1,2-Diiodobenzene (0.2 mL, 1.5 mmol) was dissolved in THF (5 mL) and cooled to −30 °C. After the addition of ^{i}PrMgCl (1 mL, 2 M in THF, 2 mmol, 1.3 equiv) the solution was allowed to warm to −20 °C within 15 min and stirred at this temperature for 20 min. At −78 °C methoxyacetone (0.14 mL, 1.5 mmol, 1 equiv) in THF (2 mL) was added and the suspension was stirred at −78 °C during 4 h and in addition 3 h at rt. The resulting yellow solution was diluted with Et_2O (10 mL) and ice cooled NH_4Cl was added. The aqueous phase was extracted with Et_2O (3×10 mL) and the combined organic phases were washed with H_2O (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. After purification by flash chromatography (cyclohexane/EtOAc 6:1) compound **12** (0.105 g, 24%) was isolated as a colorless oil; R_f (cyclohexane/EtOAc 6:1) 0.24; δ_H (300 MHz, $CDCl_3$)7.98 (1H, d, *J* 7.8 Hz, H_{arom}), 7.77 (1H, dd, *J* 7.8 Hz, 1.2, H_{arom}),7.37 (1H, t, *J* 8.1 Hz, H_{arom}), 6.92(1H, dt, *J* 8.1, 1.2 Hz, H_{arom}), 3.95 (2H, dd, *J* 165, 9.5 Hz, CH_2), 3.39 (3H, s, OCH_3), 3.29 (1H, s, OH), 1.71 (3H, s, CH_3); δ_C (63 MHz; $CDCl_3$) 162.3, 146.2, 142.7, 128.8, 128.11, 128.06, 93.0, 77.5, 74.6, 59.3, 24.7; *m*/*z* (EI) 265 (M^+-CH_3O, 8), 246 ($M^+-C_2H_5O$, 100); 231 ($M^+-C_3H_8O$, 44), 203 ($M^+-C_4H_9O_2$, 11%); HRMS (EI): M^+, found 291.9953, $C_{10}H_{13}IO_2$ requires 291.9955.

*6.1.7. 1-Chloro-3-methoxymethyl-3-methyl-1H,3H-λ^3-dihydro-1,2-benziodoxole (**18**).* Starting from *ortho*-iodobenzyl alcohol **12** (105 mg, 0.34 mmol) **18** was synthesized in analogy to **16** to yield a yellow solid (63.4 mg, 58%); [Found: C, 36.61; H, 3.62; O, 9.81; Cl, 10.83; I, 38.73. $C_{10}H_{12}O_2ClI$ requires C, 36.78; H, 3.70; O, 9.80; Cl, 10.86; I, 38.86%]; δ_H (300 MHz, $CDCl_3$) 8.03 (1H, d, *J* 9.0 Hz, H_{arom}), 7.57

(2H, t, *J* 9.3 Hz, H_{arom}), 7.22 (1H, d, *J* 7.5, H_{arom}), 3.55 (2H, dd, *J* 25.7, 11.4 Hz, CH_2), 3.35 (3H, s, OCH_3), 1.55 (3H, s, CH_3); δ_C (63 MHz, $CDCl_3$) 146.4, 130.8, 130.7, 128.3, 127.1, 115.2, 86.1, 79.7, 59.8, 25.2; *m*/*z* (EI), 246 ($M^+-C_2H_5OCl$, 48), 231 ($M^+-C_3H_8OCl$, 82), 203 ($M^+-C_4H_8O_2Cl$, 20%); HRMS (EI): $M^{+\bullet}-C_2H_5O$, 280.9225; C_8H_7ClIO requires 280.9230.

*6.1.8. 1-Trifluoromethyl-3-methyl-3-phenyl-1H,3H-λ³-dihydro-1,2-benziodoxole (**33**).* A 100 mL Schlenk flask was charged with KOAc (1.43 g, 14.5 mmol, 1.65 equiv), which was dried under vacuum using a heat gun. In counter-flow, chloride **19** (3.16 g, 8.81 mmol, 1.0 equiv) was added. CH_3CN (25 mL) was added via syringe to give a yellow suspension. After stirring for 1 h at rt the now white suspension was filtered into a 100 mL Schlenk flask under argon. To the colorless solution further CH_3CN (20 mL) was added. After cooling to −19 °C, $TMSCF_3$ (2.1 mL, 14 mmol, 1.6 equiv) was added, followed by TBAT (5.4 mg, 0.088 mmol, 1 mol %) in CH_3CN (2 mL). The reaction mixture was stirred for 24 h at −16 °C, then warmed to −12 °C, at which temperature further $TMSCF_3$ (0.33 mL, 2.2 mmol, 0.25 equiv) was added. The reaction mixture was warmed to rt and the solvent was removed under vacuum. Dry pentane (40 mL) was added to the remaining brown solid, and the resulting mixture was filtered through a pad of dry Alox in a Young-filter. The clean, colorless solution was partially evaporated until a white solid precipitated. The suspension was cooled to −40 °C and the solvent was decanted. The white crystalline residue was dried under vacuum to yield **33** (2.80 g, 81%) as a white solid.

Enantiomerically pure **33** did not crystallize upon concentration and cooling, therefore the solution was concentrated under vacuo to give a colorless oil having identical spectroscopical properties as the racemate; [Found: C, 46.00; H, 3.10; F, 14.49. $C_{10}H_{12}O_2ClI$ requires C, 45.94; H, 3.08; F, 14.53%]; δ_H (300 MHz, $CDCl_3$) 7.63–7.52 (2H, m, H_{arom}), 7.49–7.39 (4H, m, H_{arom}), 7.36–7.21 (3H, m, H_{arom}), 1.86 (3H, s, CH_3); δ_F (282 MHz, $CDCl_3$) −39.74 (d, *J* 1.4 Hz, CF_3); δ_C (75 MHz, $CDCl_3$) 147.95, 147.51, 130.49, 130.08 (q, *J* 0.6 Hz), 129.36, 128.33, 128.11 (q, *J* 2.8 Hz), 127.10, 126.13, 112.08 (q, *J* 2.9 Hz), 110.65 (q, *J* 395.7 Hz, CF_3), 80.19, 30.83. *m*/*z* (MALDI) 393.0 (MH^+, 100%); HRMS (MALDI): MH^+, found 392.9958, $C_{15}H_{12}F_3IO$ requires 392.9957.

*6.1.9. 1-Chloro-3-isopropyl-3-phenyl-1H,3H-λ³-dihydro-1,2-benziodoxole (**20**).* A round bottom flask was charged with Mg turnings (675 mg, 27.8 mmol, 1.5 equiv) and Et_2O (10 mL). To this suspension was added 2-iodopropane (1.95 mL, 19.4 mmol, 1.05 equiv) at a rate to keep the suspension at reflux. After complete addition of 2-iodopropane the suspension was cooled to rt. In a second round bottom flask 2-iodobenzophenone (5.70 g, 18.5 mmol, 1.0 equiv) was dissolved in Et_2O (20 mL) and cooled to 0 °C. To this solution the Grignard reagent was added dropwise to give a dark orange suspension which was further stirred at 0 °C. After 2 h the suspension was warmed up to rt and quenched with satd NH_4Cl. The phases were separated and the aqueous phase was extracted with Et_2O. The combined organic phases were dried over $MgSO_4$ and concentrated to give a yellow oil (5.08 g). Purification proved to be cumbersome. Therefore, the crude reaction mixture was used for the next step without further purification. A round bottom flask was charged with the crude reaction mixture (500 mg, 1.42 mmol, 1.0 equiv) and CH_2Cl_2 (10 mL) and the solution was cooled to 0 °C. To the slight yellow reaction mixture ^{t}BuOCl (161 μL, 1.42 mmol, 1.0 equiv) was added, following by warming to rt over night. The solution was concentrated and redissolved in a minimum amount of CH_2Cl_2 and layered with Et_2O to give bright yellow crystals. The procedure was repeated two times and the combined crystals were recrystallized from CH_2Cl_2 and Et_2O to give bright yellow crystals (246 mg, 44% over two steps). [Found: C, 49.73; H, 4.22; O, 4.27; Cl, 9.25. $C_{16}H_{16}OClI$ requires C, 49.70; H, 4.17; O, 4.14; Cl, 9.17%]; δ_H (300 MHz, $CDCl_3$) 8.01 (1H, dd, *J* 1.3, 8.0 Hz, H_{arom}), 7.64–7.40 (5H, m, H_{arom}), 7.39–7.21 (3H, m, H_{arom}), 2.70 (1H, hept, *J* 6.7 Hz, C*H*$(CH_3)_2$), 0.93 (3H, d, *J* 6.7 Hz, CH(C*H*$_3$)$_2$), 0.84 (3H, d, *J* 6.8 Hz, CH(C*H*$_3$)$_2$); δ_C (75 MHz, $CDCl_3$) 147.11, 143.19, 130.50, 130.38, 128.53, 128.27, 128.07, 127.19, 125.64, 116.19, 92.44, 38.84, 17.49, 16.64.

*6.1.10. 2-(3,4-Dihydro-2H-1,4-methynonaphthalen-1-yl)-propan-2-ol (**22**).* In a two-neck round bottom flask (50 mL) with reflux condenser CH_3MgI (3.8 mL, 3 M in Et_2O, 11 mmol, 2.2 equiv) was diluted with Et_2O (20 mL). At 0 °C ethyl ester **21** (1.133 g, 5.2 mmol) dissolved in Et_2O (6 mL) was slowly added. The mixture was refluxed during 2 h, then cooled to 0 °C and satd aq NH_4Cl was slowly added. The mixture was extracted with Et_2O (3×15 mL), the organic phase dried over K_2CO_3, filtered, and the solvent was removed under reduced pressure. After purification by flash chromatography (hexane/EtOAc 5:1) compound **22** (0.982 g, 93%) was isolated as a colorless oil; [Found: C, 82.94; H, 8.98; O, 8.15. $C_{14}H_{18}O$ requires C, 83.12; H, 8.97; O, 7.91%]; R_f (hexane/EtOA 5:1) 0.4; δ_H (300 MHz, $CDCl_3$) 7.50–7.47 (1H, m, H_{arom}), 7.24–7.10 (3H, m, H_{arom}), 3.36 (1H, br s, C*H*), 2.31–2.01 (2H, m, CHH_{eq}CHH_{eq}), 1.74 (1H, dq, *J*8.6, 2.1 Hz, CHH_{endo}), 1.71 (1H, s, OH), 1.62 (1H, dd, *J* 6.9, 1.5 Hz, CH_{exo}H), 1.54 (3H, s, CH_3), 1.52 (3H, s, CH_3), 1.39–1.17 (2H, m, CH_{ax}HCH_{ax}H); δ_C (62.9 MHz, $CDCl_3$) 149.4, 146.8, 125.5, 125.3, 121.6, 120.8, 72.3, 62.8, 49.5, 42.9, 29.4, 27.7, 27.6, 27.5; *m*/*z* (EI) 202.14 (M^+, 42.7%), 116.1 (100%); HRMS (EI): M^+, found 202.1355, $C_{14}H_{18}O$ requires 202.1353.

*6.1.11. 2-(8-Iodo-3,4-dihydro-2H-1,4-methanonaphthalene-1-yl)-propan-2-ol (**15**).* In a two-neck round bottom flask with a reflux condenser, alcohol **22** (1.36 g, 6.7 mmol) was dissolved in *n*-hexane (27 mL) and TMEDA (2.2 mL, 14.6 mmol, 2.2 equiv) was added. The solution was cooled to −78 °C and ^{s}BuLi (11.4 mL, 1.3 M in hexane, 14.8 mmol, 2.2 equiv) was slowly added. The reaction mixture was heated to reflux for 20 h, afterward it was cooled to −78 °C and 1,2-diiodoethane (0.811 g, 2.9 mmol, 1.3 equiv) in THF (3 mL) was slowly added. The mixture was allowed to warm slowly to rt over night (16 h). Afterward satd aq $Na_2S_2O_3$ was added and the mixture was extracted with Et_2O. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and the solvent was removed under vacuum. The residue was purified by flash chromatography (hexane/EtOAc 10:1) to give compound **15** (1.18 g, 54%) as a colorless oil; [Found: C, 51.43; H, 5.26; O, 4.90; I, 38.78. $C_{14}H_{17}OI$ requires C, 51.24; H, 5.22; O, 4.88; I 38.67%]; R_f (hexane/EtOAc 10:1) 0.27; δ_H (300 MHz, $CDCl_3$)7.70 (1H, dd, *J* 7.9, 1.1 Hz, H_{arom}), 7.17 (1H, dd, *J* 7.0,1.0 Hz, H_{arom}), 6.77 (1H, dd, *J* 7.9,7.1 Hz, H_{arom}), 3.38 (1H, br s, 1OH), 3.32–3.30 (1H, s, C*H*), 2.16–1.98 (2H, m, CHH_{eq}CHH_{eq}), 1.71 (3H, s, CH_3), 1.67–1.58 (2H, m, CH_2), 1.38 (3H, s, CH_3), 1.34–1.21 (2H, m, CH_{ax}HCH_{ax}H); δ_C (62.9 MHz, $CDCl_3$) 154.0, 150.6, 139.2, 127.5, 120.8, 89.3, 71.7,66.5, 50.7, 43.1, 29.7, 29.5, 28.6, 26.8; *m*/*z* (EI) 328.0 (M^+, 37.9%), 270.0 (100%); HRMS (EI): M^+, found 328.0317, $C_{14}H_{17}IO$ requires 328.0319.

*6.1.12. 1-Chloro-3,3-dimethyl-3a,6-methano-3a,4,5,6,-tetrahydro-1H,3H-λ³-ioda-2-oxa-phenalene (**23**).* Starting from *ortho*-iodobenzyl alcohol **15** (1.12 g, 3.4 mmol) **23** was synthesized in analogy to **16** to yield colorless crystals (1.09 g, 88%). Single crystals for X-ray analysis were obtained by diffusion of pentane into a saturated CH_2Cl_2 solution; [Found: C, 46.44; H, 4.54; Cl, 10.07; I, 34.77; O, 4.51. $C_{14}H_{16}ClIO$ requires C, 46.37; H, 4.45; Cl, 9.78; I, 34.99; Cl, 9.78; I, 34.99; O, 4.41%]; δ_H (250 MHz, CD_2Cl_2) 8.25–8.18 (1H, m, H_{arom}), 7.37–7.30 (2H, m, H_{arom}), 3.41 (1H, u, C*H*), 2.14–2.01 (2H, m, CHH_{eq}CHH_{eq}), 1.61 (2H, s, CH_2), 1.55 (3H, s, CH_3), 1.44 (3H, s, CH_3), 1.26 (2H, d, *J* 7.5 Hz, CH_{ax}HCH_{ax}H); δ_C (63 MHz, CD_2Cl_2) 153.59, 144.73, 129.48, 125.28, 122.55, 106.66, 75.19, 57.20, 49.22, 42.12, 28.78, 28.50, 26.48, 24.02. *m*/*z*(EI) 347.0 (M^+-CH_3, 25%); HRMS (EI): M^+-CH_3, found 346.9695. $C_{14}H_{16}ClIO$ requires 346.9695.

*6.1.13. 1-Trifluoromethyl-3,3-dimethyl-3a,6-methano-3a,4,5,6-tetrahydro-1H,3H-λ³-ioda-2-oxa-phenalene (**34**).* Dry KOAc (0.337 g,

3.4 mmol, 1.7 equiv) and **23** (0.733 g, 2.0 mmol) were suspended in CH_3CN (5 mL). After 4 h the suspension was filtered, washed with CH_3CN (2×2.5 mL) and the filtrate was cooled to −40 °C. $TMSCF_3$ (0.45 mL, 3.0 mmol, 1.5 equiv) followed by TBAT (0.2 mL, 0.03 M in CH_3CN, 0.3 mol%) was added and the mixture was stirred over night (16 h). The mixture was allowed to warm to 0 °C (5 °C/1 h), after 2 h and 4 h $TMSCF_3$ (67 μL, 0.45 mmol, 0.22 equiv) was added, when the temperature reached 0 °C $TMSCF_3$ (0.15 mL, 1 mmol, 0.5 equiv) was added and the mixture was allowed to warm to rt where it was stirred for 3 h. The solvent was removed under reduced pressure and, after purification by flash chromatography (pentane/Et_2O 2:1), **34** (114 mg, 14%) was isolated as a microcrystalline solid; [Found: C, 45.47; H, 4.09; F, 14.34; I, 32.29. $C_{15}H_{16}OF_3I$ requires C, 45.47; H, 4.07; F, 14.39; I, 32.03%]; R_f (pentane/Et_2O 2:1) 0.25; δ_H (500 MHz, $CDCl_3$) 7.48 (1H, d, *J* 8.5 Hz, H_{arom}), 7.29 (1H, d, *J* 7.0 Hz, H_{arom}), 7.17 (1H, dd, *J* 8.5, 7.0 Hz, H_{arom}), 3.36 (1H, u, CH), 2.05 (2H, m, $CH\mathit{H}_{eq}CH\mathit{H}_{eq}$), 1.67 (1H, dq, *J* 9.0, 2.0 Hz, $CH_{2,\mathit{endo}}$), 1.54 (1H, dd, *J* 9.0, 1.3 Hz, $CH_{2,\mathit{exo}}$), 1.49 (3H, s, CH_3), 1.38 (3H, s, CH_3), 1.37–1.21 (2H, m, $C\mathit{H}_{ax}HC\mathit{H}_{ax}H$); δ_C (75.5 MHz, $CDCl_3$) 154.8, 149.9, 129.1, 125.3, 122.6, 116.6 (q, *J* 403 Hz, CF_3), 110.9 (q, $^3J_{C,F}$ 3.2 Hz, CI), 72.4, 58.9, 49.0, 42.6, 29.3, 28.7, 26.6 (2C); δ_F (188 MHz, $CDCl_3$) −44.2 (s, $^1J_{C,F}$ 403 Hz, CF_3); *m*/*z* (EI) 381.0 (M^+-CH_3, 43%), 43.0 (100%) HRMS (EI): M^+-CH_3 found 380.9962, $C_{14}H_{18}O$ requires 380.9958.

*6.1.14. N-(1-Hydroxy-2-methyl-2-propyl)-2-iodobenzenecarbamide (**27**).* In a two-neck round bottom flask 2-amino-2-methylpropanol (0.76 mL, 7.9 mmol, 1.1 equiv) was added to 1,4-dioxane (180 mL) and aq $NaHCO_3$-solution (0.5 M, 220 mL). Using an dropping funnel iodobenzoic acid chloride (**26**) (2.01 g, 7.5 mmol) dissolved in 1,4-dioxane (20 mL) was added during 5 min to the white suspension. In addition, the reaction was stirred at rt for 3 h. The mixture was extracted with EtOAc, and the combined org. phases were washed with HCl-solution (4 M, 100 mL), NaOH-solution (10 M, 100 mL) and brine (100 mL), dried over $MgSO_4$ and, after removal of the solvent, the product (1.430 g, 60%) was isolated as a white microcrystalline solid; [Found: C, 41.6; H, 4.5; N, 4.4; O, 10.0; I, 39.7. $C_{11}H_{14}NO_2I$ requires C, 41.4; H, 4.4; N, 4.4; O, 10.0; I, 39.8%]; δ_H (250 MHz, $CDCl_3$) 7.88 (1H, d, *J* 7.8 Hz, H_{arom}), 7.41 (1H, dd, *J* 4.3, 0.3 Hz, H_{arom}), 7.29–7.09 (1H, m, H_{arom}), 5.84 (1H, br s, NH), 4.32 (1H, t, *J* 9.0 Hz, OH), 3.75 (2H, d, *J* 6.3 Hz, CH_2), 1.45 (6H, s, 2×CH_3); δ_C (75.5 MHz, $CDCl_3$) 170.1, 142.4, 139.8, 131.2, 128.3, 128.2, 92.3, 70.3, 57.2, 24.6; *m*/*z* (EI) 287.99 (M^+-CH_3O, 100); HRMS (EI): M^+-CH_3O, found 287.9880, $C_{10}H_{11}NOI$ requires 287.9885.

*6.1.15. 2-(2-Iodophenyl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole (**24**).* Amide **27** (10.20 g, 32.0 mmol) and DMAP (587 mg, 4.8 mmol, 0.15 equiv) were dissolved in CH_2Cl_2 (200 mL) and Et_3N (20 mL 154 mmol, 4.8 equiv) was added. The white suspension was cooled to 0 °C and TsCl (7.41 g, 38.8 mmol, 1.2 equiv) was added. After complete addition the suspension was allowed to warm to rt and was stirred during 16 h. H_2O (100 mL) was then added and the resulting mixture was heated to reflux during 1 h. The mixture was extracted with CH_2Cl_2, the combined organic phases were washed with H_2O and brine and dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The yellow suspension was taken up in EtOAc and filtered over SiO_2. After the solvent was removed under reduced pressure, the residue was suspended in pentane, filtered and oxazoline **24** (6.534 g, 68%) was obtained as a colorless oil after the solvent was removed under reduced pressure; [Found: C, 44.16; H, 4.01; I, 41.87, N, 4.75; O, 5.33. $C_{11}H_{12}INO$ requires C, 43.88; H, 4.02; I, 42.14; N, 4.65; O, 5.31%]; δ_H (300 MHz; $CDCl_3$) 7.92 (1H, d, *J* 7.8, H_{arom}); 7.59 (1H, dd, *J* 7.8 and 1.5, H_{arom}); 7.38 (1H, t, *J* 7.5, H_{arom}); 7.12 (1H, dt, *J* 7.5 and 1.5, H_{arom}); 4.16 (2H, s, CH_2), 1.44 (6H, s, CH_3); δ_C (63 MHz; $CDCl_3$) 162.8, 140.1, 134.0, 131.5, 130.5, 127.8, 94.8, 79.4, 68.2, 28.3 (2C); *m*/*z* (EI) 301.0 (M^+, 98), 286 (M^+-CH_3, 100%); HRMS (EI) M^+ 300.9959 found $C_{11}H_{12}INO$ requires 300.9961.

*6.1.16. 7-Chloro-5,5-dimethyl-7λ³-ioda-3-oxa-6λ⁵-azatricyclo [6.4.0.0²,⁶]dodeca-1(8),2(6),9,11-tetraen-6-yliumtetrafluoroborate (**30**).* Oxazolidine **24** (485 mg, 1.61 mmol) was dissolved in Et_2O (6 mL). After the addition of $HBF_4\cdot Et_2O$ (0.7 mL, 51–57% in Et_2O, 2.41 mmol, 1.5 equiv) a white precipitate was formed, which was filtered off after 90 min, washed with Et_2O and dissolved in CH_2Cl_2 (14 mL). In the dark, ^{t}BuOCl (0.33 mL, 3.22 mmol, 2.0 equiv) was added dropwise. A white precipitate was formed immediately. After the suspension was stirred for additional 5 h, all volatile compounds were removed under reduced pressure. The white solid was washed with Et_2O and dried under HV to yield compound **30** (542 mg, 80%) as a white solid; X-ray quality, highly hygroscopic single crystals were obtained as plates by diffusion of a saturated acetonitrile solution into CH_2Cl_2; [Found: C, 31.11; H, 2.84; Cl, 3.28; $C_{11}H_{12}BClF_4INO$ requires C, 31.21; H, 2.86; Cl, 8.37; I, 29.97%]; δ_H (250 MHz, CD_3CN) 8.48 (1H, d, *J* 8.8, H_{arom}), 8.20 (2H, m, H_{arom}), 8.03 (1H, t, *J* 7.5 Hz, H_{arom}), 4.94 (2H, s, CH_2), 1.58 (6H, s, 2×CH_3); δ_C (62.9 MHz, CD_3CN) 171.2, 138.1, 132.6, 131.3, 129.4, 123.2, 122.0, 86.0, 69.0, 26.6; δ_F (188.3 MHz, CD_3CN) -151.3; *m*/*z* (MALDI) 335.7 ($M^{+\bullet}$, 8.2%), 302.0 (MH^+-Cl, 100%); HRMS (MALDI): $M^{+\bullet}$, found 335.9644, $C_{11}H_{12}ClINO$ requires 335.9647.

*6.1.17. 2-(2-Bromophenyl)pyridine (**29**).* $Pd(OAc)_2$ (72 mg, 0.32 mmol, 0.18 equiv), NBS (334.4 mg, 1.88 mmol, 1.1 equiv), and 2-phenylpyridine (**28**) (0.25 mL, 1.75 mmol) were dissolved in acetonitrile (10 mL). The solution was warmed to 100 °C and the flask was sealed with a Teflon cap. The mixture was refluxed for 48 h, then concentrated under reduced pressure. Chromatographic purification (EtOAc/hexane 1:20) yielded compound **28** as a colorless oil (295 mg, 72%); R_f (EtOAc/hexane 1:2) 0.45; δ_H ($CDCl_3$, 300 MHz) 8.73(1H, d, *J*4.4 Hz), 7.77 (1H, td, *J* 7.7, 1.6 Hz), 7.69 (1H, dd, *J* 8.0, 0.76 Hz), 7.61 (1H, d, *J* 7.9 Hz), 7.55 (1H, dd, *J* 7.6, 1.6 Hz), 7.41 (1H, td, *J* 7.5, 0.9 Hz), 7.34–7.23 (2H, m).

*6.1.18. 2-(2-Iodophenyl)pyridine (**25**).* 2-(2-Bromophenyl)pyridine (**29**) (295 mg, 1.26 mmol) was dissolved in 10 mL THF, then cooled to −78 °C and ^{n}BuLi (0.88 mL, 1.6 M in hexane 1.41 mmol, 1.1 equiv) was added. The lithiation was completed after 1 h and thereafter quenched with I_2-solution (5.4 mL, 1 M in THF, 5.4 mmol, 4.3 equiv). The reaction mixture was allowed to warm up to rt and was stirred for additional 12 h. An aqueous workup with satd NH_4Cl solution was then performed. Chromatographic purification (EtOAc/hexane 1:3) yielded **22** (284.8 mg,1.01 mmol, 80%) as a yellow oil; δ_H ($CDCl_3$, 300 MHz) 8.71(1H, d, *J* 4.3 Hz), 7.99 (1H, d, *J* 7.9 Hz), 7.83 (1H, td, *J* 7.7, 1.7 Hz), 7.52(1H, d, *J* 7.8 Hz,), 7.46 (2H, m), 7.35(1H, ddd, *J* 7.5, 5.0, 1.1 Hz), 7.12(1H, ddd, *J* 8.0, 5.1, 4.0 Hz); δ_C (CD_3CN, 75 MHz): 160.2, 148.5, 144.6, 139.6, 137.4, 130.3, 128.4, 124.8, 123.3, 117.3, 96.4.

*6.1.19. 8-Chloro-8λ³-ioda-7λ⁵-azatricyclo-[7.4.0.0²,⁷]trideca-1 (9),2,4,6,10,12-hexaen-7-ylium tetrafluoroborate (**31**).* 2-(2-Iodophenyl)pyridine (**25**) (205 mg, 0.73 mmol) was dissolved in Et_2O (2.5 mL). After dropwise addition of $HBF_4\cdot Et_2O$ (0.31 mL, 51–57% in Et_2O, 1.07 mmol, 1.5 equiv) a pale brown precipitate formed. The solvent was decanted after 90 min by syringe and the residual solid was washed once with Et_2O (2.5 mL), then dried under HV. CH_2Cl_2 (6.0 mL) was added yielding a clear solution. Dropwise addition of ^{t}BuOCl (0.16 mL, 0.15 mmol, 2.0 equiv) in the dark at rt yielded a white precipitate. The suspension was stirred for additional 12 h, then all volatiles were removed under HV. The residual solid was washed with CH_2Cl_2 and dried under HV to yield

compound **31** (257 mg, 0.64 mmol, 87%) as a pale yellow solid; X-ray quality, highly hygroscopic single crystals (platelets) were obtained by diffusion of CH_2Cl_2 into a saturated solution of the product in CH_3CN; [Found: C, 32.68; H, 2.11; N, 3.44. $C_{11}H_8NBF_4ClI$ requires C, 32.76; H, 2.00; N, 3.47%] δ_H (CD_3CN, 300 MHz) 9.04 (1H, d, *J* 5.9 Hz), 8.64–8.53 (3H, m), 8.40 (1H, d, *J* 7.9 Hz), 8.06–8.02 (2H, m), 7.90 (1H, td, *J* 6.6, 1.3 Hz); δ_C (CD_3CN, 75 MHz) 150.4, 144.3, 143.3, 135.6, 132.6, 132.3, 129.6, 129.1, 127.5, 123.7, 115.0; δ_F (CD_3CN, 188 MHz): −150.8; *m*/*z* (EI):315.9 (M^+, 9.6), 312.0 (100%); HRMS (EI): M^+, 315.9383 found 202.1351, $C_{11}H_8ClIN$ requires 315.9484.

6.2. General procedure for rate studies

All reactions were monitored by ^{19}F NMR spectroscopy using a Bruker AVANCE DPX 400 MHz NMR spectrometer operating at 376 MHz. Experimental temperatures (298 K) were maintained using a Bruker BVT3000 temperature control unit calibrated with a digital thermometer fit to a 5 mm NMR tube. Initially, the temperature in the spectrometer was equilibrated on a 'standard' sample containing reagent **1a** (600 μL, 0.1 M in $CDCl_3$/^{t}BuOH 5:1) and the internal standard ($PhCF_3$, 0.05 M) and the shim was optimized. A second tube charged with correct amount of the trifluoromethylating agent (300 μL, 0.2 M in $CDCl_3$/^{t}BuOH 5:1 containing 0.05 M $PhCF_3$) and the appropriate amount of *para*-toluenesulfonic acid monohydrate (300 μL, 0.2 M in $CDCl_3$/^{t}BuOH 5:1 containing 0.05 M $PhCF_3$) was added. The tube was shaken vigorously for 10–15 s after which it was exchanged with the standard in the spectrometer and the acquisition program was started.

6.2.1. Acquisition program. A pseudo 2D NMR experiment designed for kinetic measurements was utilized to monitor the reaction progress for all rate experiments. The time interval between individual acquisitions (d1), number of acquisitions averaged (one data point was obtained as the average of two individual acquisitions) and total number of data points could be varied to effect the frequency of acquisition, signal to noise ratio and experiment duration, respectively.

6.2.2. Data processing. For each data point, integrals corresponding to the ^{19}F NMR resonances of the trifluoromethyl group of the trifluoromethylating reagent, the trifluoromethyl group of the newly formed trifluoromethyl *para*-toluenesulfonate and $PhCF_3$ internal standard were extracted using Bruker's XWinNMR 3.5 software package. The resulting data were exported as tables of integral values for each signal over all data points measured. The ^{19}F NMR integration data were then imported into SigmaPlot10 and the data point numbers transformed into time values by multiplying by the correct acquisition duration and number of acquisitions averaged per data point. The time vs ^{19}F NMR integration data thus generated were fit to $[c]=\nu_0 t+b$ for a linear increase to a maximum of 10% conversion in order to extract initial rate values (ν_0).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.04.125. These data include MOL files and InChIKeys of the most important compounds described in this article.

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