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One-Pot Synthesis of Hypervalent Iodine Reagents for Electrophilic Trifluoromethylation

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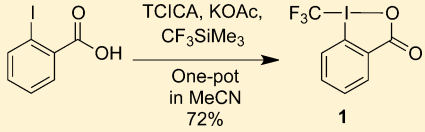
Supporting Information

ABSTRACT: Simplified syntheses suited for large scale preparations of the two hypervalent iodine reagents **1** and **2** for electrophilic trifluoromethylation are reported. In both cases, the stoichiometric oxidants sodium metaperiodate and *tert*-butyl hypochlorite have been replaced by trichloroisocyanuric acid. Reagent **1** is accessible in a one-pot procedure from 2-iodobenzoic acid in 72% yield. Reagent **2** was prepared via fluoroiodane **11** in a considerably shorter reaction time and with no need of an accurate temperature control.



In recent years, the arena of synthetic organic chemistry has witnessed a vigorous development of various synthetic methods for the introduction of polyfluorinated groups into a plethora of molecular targets.[1] The growing demand of such methods is intimately associated with the benefits derived from new molecules that have remarkable properties such as altered metabolic behavior, resistance toward chemical and enzymatic degradation, strong impact on acid–base equilibria,[2] and enhanced lipophilicity.[3] Consequently, fluoroalkylated compounds are highly desirable targets mostly in the context of medicinal, crop protection, and materials chemistry.

Several years ago, our research group reported a conceptually new family of formally electrophilic CF_3 transfer reagents based on a cyclic hypervalent iodine(III) core,[4] the most successful ones being the "acid reagent" **1** and the "alcohol reagent" **2** (Figure 1).[5]

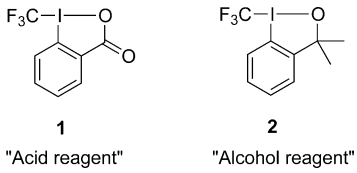


Figure 1. Hypervalent iodine reagents for electrophilic trifluoromethylation.

Recently, the substrate scope and general applicability of these reagents has been considerably expanded thanks to significant contributions from several research groups. The original notion that these reagents are primarily suited for trifluoromethylation of soft phosphorus-, sulfur-, and carbon-centered nucleophiles such as phosphines,[6] thiols, α-nitroesters, β-ketoesters,[7] phosphorothioates,[8] and aromatics[9] was soon overcome because even hard O-centered nucleophiles such as alcohols,[10] sulfonic acids,[11] and hydrogen phosphates[12] undergo trifluoromethylation under proper Lewis or Brønsted acid activation. The concept of Lewis acid activation of the CF_3 reagents analogously demonstrated its utility in the trifluoromethylation of nitrogen nucleophiles, such as in Ritter-type functionalizations of nitriles[13] and trifluoromethylations of trimethylsilylated azoles.[14] Transition metal-promoted transformations have provided a facile entry into selective trifluoromethylation of aromatic cores,[15] allylic trifluoromethylation of alkenes,[16] trifluoromethylation of terminal alkynes[17] and allylsilanes,[18] and oxidative functionalization of alkenes.[19] Substrates bearing enolizable carbon centers were shown to be good candidates for the stereoselective introduction of the CF_3 moiety, including α-trifluoromethylation of aldehydes cooperatively using Lewis acid activation and organocatalysis[20] or enantioselective trifluoromethylation of cyclic β-keto esters in the presence of chiral Cu complexes.[21] Finally, chiral enolates featuring the acyloxazolidinone motif were trifluoromethylated in a diastereoselective fashion.[22]

On the basis of this rapid progress, it is reasonable to assume that these hypervalent CF_3 iodine reagents might in the near future find further applications in the late steps of syntheses as well as in the production of valuable trifluoromethylated products on a multikilogram scale in the fine chemical industry.

We were therefore motivated to reexamine the current syntheses of **1** and **2** and subject them to careful redesign and optimization so they meet standards typical for larger scale preparations, such as scalability, reproducibility, a reduction of the manipulation steps, the use of less hazardous reagents, lower production of toxic aqueous streams, and a reduction in the amounts of costly reagents.

The original synthesis of **1** (Scheme 1) commences with the aqueous oxidation of 2-iodobenzoic acid **3** with 1.5 equiv of sodium metaperiodate at reflux overnight, which produces a suspension of hydroxyiodobenziodoxolone **4** in yields typically between 91 and 96% after additional acidification with dilute sulfuric acid. The dry **4** is then acetylated in hot, neat acetic anhydride. The progress of this acetylation can conveniently be visually monitored because the resulting acetoxyiodane **5** is very

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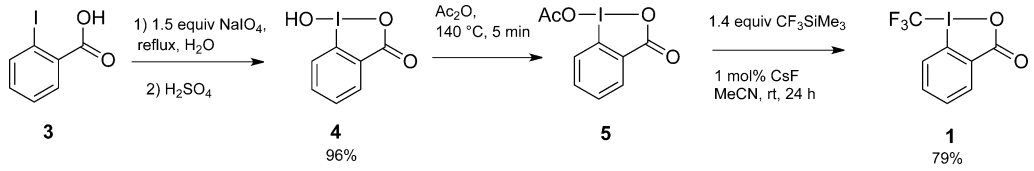
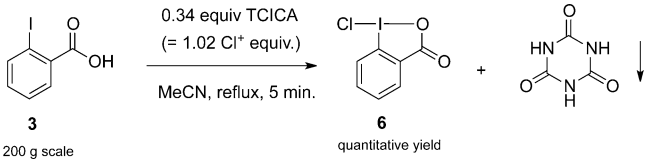
Scheme 1. Current Synthetic Sequence Leading to Reagent 1



soluble in the mixture of hot acetic anhydride/acetic acid, and finally a clear solution of **5** is obtained. Although we never experienced any accidents, the acetylation step has been always conducted behind a safety screen because of conceivable adventitious traces of iodine(V) impurities or traces of sodium iodate contaminating the starting material and possibly leading to violent decomposition processes.[23] Cooling the resulting solution to −20 °C brings about complete crystallization of **5**, from which the remaining mother liquor is decanted. For the final umpolung step, the crystalline **5** with acetic anhydride/acetic acid mixture has to be thoroughly dried. Although this procedure is acceptable for a small scale synthesis, the drying process becomes lengthy and is often incomplete as the batches exceed 30−40 g of material. The presence of acetic acid is detrimental to the last step, in which dry **5** is treated in acetonitrile suspension with 1.4 equiv of the Ruppert−Prakash reagent ($TMSCF_3$) and 1 mol % of cesium fluoride; in some cases, it was necessary to add cesium fluoride several times to initiate the umpolung reaction.

During our initial attempts to find an alternative cheap nonaqueous oxidant capable of selectively oxidizing 2-iodobenzoic acid to an appropriate iodine(III) intermediate, we were pleased to find that the stoichiometric use of 2,4,6-trichlorotriazin-1,3,5-trione, commonly termed as trichloroisocyanuric acid (TCICA),[24] gave a quantitative yield of the corresponding chloroiodane **6** with concomitant precipitation of insoluble isocyanuric acid. The resulting suspension was heated to reflux and filtered while hot over a pad of Celite; this gave a light yellow solution which, upon concentration, filtration, and washing with cold acetonitrile, provided free-flowing crystals of **6** in quantitative yield and with excellent purity (Scheme 2).

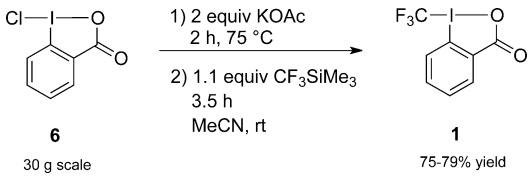
Scheme 2. Chlorination of 2-Iodobenzoic Acid 3 with Trichloroisocyanuric Acid



Subsequent treatment of **6** with 2 equiv of anhydrous KOAc in acetonitrile under reflux for 2 h provided a fine suspension of KCl and acetoxyiodane **5** which was then treated in situ with 1.1 equiv of $TMSCF_3$ at room temperature overnight. The resulting suspension was quickly heated to reflux and filtered over Celite to give a brownish solution which, after concentration and cooling, furnished crystals of **1** in 75−79% isolated yield (Scheme 3).

During the scale up of this procedure to 30 g, we encountered difficulties in reproducing yields, and the product was often contaminated with the intermediate acetoxyiodane **5**, indicating an incomplete umpolung step. We speculated that as

Scheme 3. Preparation of Reagent 1 from Chloroiodane Precursor 6

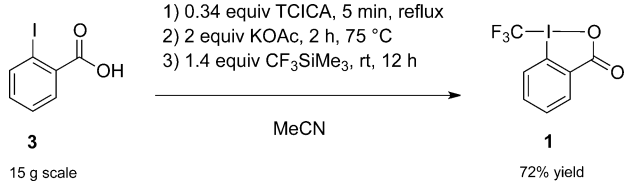


the scale of the reaction was increased, problems with efficient mass transfer in the reactor flask might have been responsible for the lower yields. Indeed, using more vigorous and turbulent stirring conditions restored the isolated yield. For larger scale work, the use of a mechanical propeller-shaped stirrer capable of achieving high Reynolds number (>10 000), optionally combined with installed baffles on the reactor walls, is highly recommended. Interestingly, the use of highly turbulent stirring on a 30 g scale considerably accelerated the umpolung step; the reaction was complete within 3.5 h, a significantly shorter time than previously observed.[25]

The first experiments to unite all steps (i.e., chlorination of 2-iodobenzoic acid, chloride/acetate exchange, and CF_3 umpolung) met with failure. 2-Iodobenzoic acid was mixed with dry KOAc in acetonitrile, and the rapid formation of a thick paste of potassium 2-iodobenzoate was observed. However, after the addition of trichloroisocyanuric acid, no chlorination took place. Changing the order of addition appeared to solve the problem—the chlorination of 2-iodobenzoic acid and subsequent addition of KOAc, followed by stirring at 75 °C for 2 h, gave a suspension of **5** accompanied by insoluble isocyanuric acid and KCl. $TMSCF_3$ (1.4 equiv) was added to this vigorously stirred suspension at room temperature, and the resulting mixture was vigorously stirred overnight. Subsequent quick heating to reflux, filtration over Celite, and crystallization provided reagent **1** in 72% isolated yield, demonstrating that all three steps can be conveniently united into a one-pot protocol (Scheme 4). The presence of practically insoluble isocyanuric acid seemed to somewhat decrease the rate of the CF_3 umpolung as compared to the rate of the previous variant starting from **6**.

The optimization of the synthesis of reagent **2**[26] started with a more cost-effective synthesis of methyl 2-iodobenzoate **8**. Instead of esterification of the relatively expensive 2-

Scheme 4. One-Pot Preparation of Reagent 1 from 2-Iodobenzoic Acid



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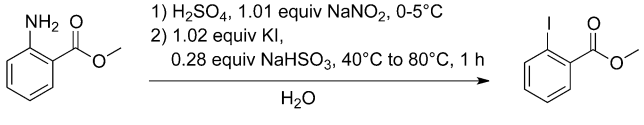
iodobenzoic acid, much cheaper methyl anthranilate was diazotized in aqueous diluted sulfuric acid, and the resulting cold solution of diazonium salt was slowly cannulated into an acidified solution of potassium iodide with 0.28 equiv of sodium hydrogen sulfite. The presence of hydrogen sulfite anion in substoichiometric amounts ensures that all iodine, which is a side product of radical decomposition of the diazonium salt, is reduced back to iodide, allowing us to use only a near-stoichiometric quantity of potassium iodide. The resulting methyl 2-iodobenzoate **8** can be readily separated from the aqueous phase without the need of extraction (Scheme 5).

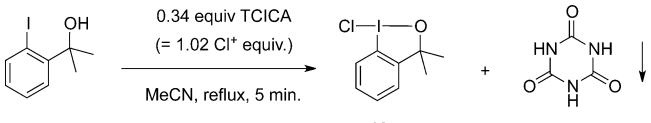
Scheme 5. Cost-Effective Synthesis of Methyl 2-Iodobenzoate



7 150 g scale — **8** 93% in 95% purity

The following addition of methylmagnesium iodide to methyl 2-iodobenzoate to form alcohol **9** was performed according to the literature procedure[26] with a minor modification of the quench step; that is, an inverse mode of quenching was preferred. With larger batches, this becomes especially convenient as compared to the original procedure where stirring problems were often encountered because the partially hydrolyzed magnesium salts hampered regular stirring and proper heat exchange. To transform the tertiary iodoalcohol **9** into the corresponding chloroiodane **10**, *tert*-butyl hypochlorite was used in the previous synthesis. However, the latter light-sensitive reagent has several disadvantages. It is a potent lachrymator, and its shelf life is short. Furthermore, it is linked to a history of documented violent decompositions,[27] and the commercial availability is restricted. To our delight, the same transformation could be effected in acetonitrile with stoichiometric amounts of trichloroisocyanuric acid in comparable yield (Scheme 6).

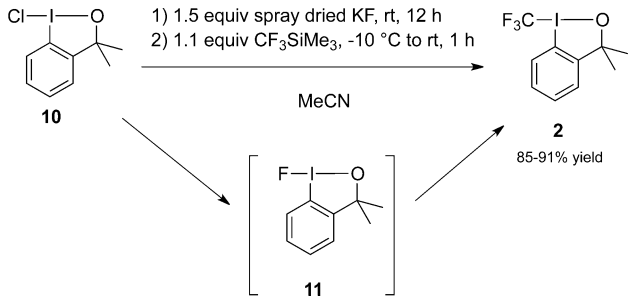
Scheme 6. Oxidation of Alcohol 9 with TCICA



9 190 g scale — **10** 89% yield

In the previous synthesis of **2**,[26] the final umpolung starting with 1-acetoxy-3,3-dimethyl-1,2-benziodoxole had to be performed using a carefully controlled temperature gradient and required more than 20 h in order to obtain high yields. We were therefore prompted to look for a more suitable hypervalent iodine precursor that does not necessitate such strict control of the reaction conditions. We were very pleased to find that the use of fluoroiodane intermediate **11** is a very good alternative to the corresponding acetate. The halogen exchange with 1.5 equiv of spray-dried KF reacts to completion overnight at rt, giving a clear white suspension of fluoroiodane **11**. The addition of 1.1 equiv of $TMSCF_3$ to this cooled suspension led to a smooth umpolung in 1 h, affording **2** in 85–91% isolated yield (Scheme 7).

Scheme 7. Fluoroiodane 11 as Intermediate in the Synthesis of Reagent 2



10 — **2** 85-91% yield — **11**

The intermediate fluoroiodane **11** could eventually be isolated in sufficiently pure form and excellent yield. X-ray quality crystals were grown by slowly cooling a corresponding solution in pentane/dichloromethane. The crystallographic analysis revealed, as already noted,[28] an I–O bond shortening in comparison to that of the related chloroiodane **10** due to an altered trans effect of the fluorine atom.[29] Studies directed toward the use of this relatively easily accessible fluoroiodane as an electrophilic fluorinating reagent are ongoing in our group.

In conclusion, both syntheses of the hypervalent iodine reagents **1** and **2** were subjected to a careful optimization. In the synthesis of reagent **1**, a one-pot protocol could be devised, whereas in the synthesis of reagent **2**, several important improvements could be made, particularly in terms of safety and operational simplicity. We hope this work will stimulate further interest from the organofluorine community in these already popular reagents.

EXPERIMENTAL SECTION

General Information. All experiments were carried out under an Ar atmosphere with oven-dried (140 °C) glassware and magnetic stirring if not otherwise stated. Acetonitrile (p.a.) and pentane (p.a.) were dried over activated 3 Å molecular sieves for at least 24 h prior to use. Potassium acetate (p.a.) was dried under a high vacuum (8×10^{-3} mbar) at 130 °C for 1–2 h prior to use (for one-pot synthesis of reagent **1**). 2-Iodobenzoic acid (98%) was supplied by TCI Chemicals, GmbH. Gray samples of 2-iodobenzoic acid obtained from some other suppliers gave inferior results. Other commercially available chemicals, including trichloroisocyanuric acid (TCICA, 97%) and spray-dried KF, were used as received. ^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded on a spectrometer operating at 300.1, 282, and 75.5 MHz, respectively. Because all compounds reported here are known, we do not describe corresponding NMR spectra. However, copies of NMR spectra are provided in the Supporting Information. Melting points are corrected.

Chlorination of 2-Iodobenzoic Acid (3) to 1-Chloro-1,2-benziodoxol-3(1*H*)-one (6). A 3 L three-necked, round-bottom flask equipped with a massive ellipsoidal magnetic stirring bar (6 cm diameter), Ar inlet, Dimroth condenser, and dropping funnel with pressure-equalizing side arm was charged under Ar with solid 2-iodobenzoic acid (200 g, 0.7902 mol, 1 equiv), and anhydrous MeCN (1.5 L) was added. The resulting stirred suspension was heated to 75 °C in an oil bath. The dropping funnel was charged with a solution of trichloroisocyanuric acid (63.7 g, 0.2660 mol, 1.02 Cl^+ equiv) in 300 mL of anhydrous MeCN. The solution of trichloroisocyanuric acid was dropped into the vigorously stirred reaction mixture within 5 min. During the addition of the trichloroisocyanuric acid solution, formation of insoluble isocyanuric acid became apparent. The dropping funnel was rinsed with further anhydrous MeCN (100 mL). After addition was complete, the reaction mixture was refluxed for an additional 5 min. The reaction mixture was vacuum-filtered over an oven-preheated, sintered-glass funnel with a tightly packed pad of Celite (1 cm thick), and the filter cake was rinsed with additional hot MeCN (100–200 mL). The combined filtrates were evaporated to

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near-dryness, and the resulting yellow solid was filtered over a sintered-glass funnel and washed with a small amount of cold MeCN. The mother liquor from filtration was partially concentrated on a rotavap, giving a second crop of crystals. The combined crops were dried for 2 h under high vacuum to give product **6** as free-flowing light yellow crystals in quantitative yield. Yield: 223 g. Mp: 178.5−180 °C (partial decomposition). ^{1}H NMR (300 MHz, $CDCl_3$, 23 °C): δ 7.79 (m, 1H), 7.99 (ddd, J = 8.6, 7.2, 1.6 Hz, 1H), 8.23 (ddd, J = 14.0, 8.0, 1.3 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$, 23 °C): δ 117.1, 126.9, 128.8, 131.9, 133.4, 136.6, 167.2. Anal. Calcd for $C_7H_4O_2ClI$: C, 29.77; H, 1.43. Found: C, 29.84; H, 1.60.

Preparation of Reagent 1 from 1-Chloro-1,2-benziodoxol-3(1*H*)-one (6). A 500 mL two-necked, round-bottom flask equipped with a massive ellipsoidal magnetic stirring bar (4 cm diameter), rubber septum, and Ar inlet was charged with potassium acetate (21 g, 0.212 mol, 2 equiv). This was heated with stirring under a high vacuum (8×10^{-3} mbar) for 5 min and then cooled to room temperature under Ar. 1-Chloro-1,2-benziodoxol-3(1*H*)-one (**6**, 30 g, 0.106 mol, 1 equiv) followed by anhydrous MeCN (300 mL) was added under a countercurrent flow of Ar. The resulting suspension was vigorously stirred under Ar at 75 °C for 2 h. The color went from slightly yellow to off-white. The suspension was cooled to room temperature, and trifluoromethyltrimethylsilane (17.3 mL, 16.57 g, 0.1166 mol, 1.1 equiv) was injected through the septum in one portion. The resulting suspension was vigorously stirred for 3.5 h, during which the mixture turned brown. ^{19}F NMR analysis on a sample of the reaction mixture revealed that trifluoromethyltrimethylsilane was almost completely consumed. Further anhydrous MeCN (100 mL) was added, and the reaction mixture was heated to 75 °C in an oil bath and filtered while hot over a Celite pad (1 cm thick). The Celite pad was rinsed with additional hot MeCN (100 mL). The brown filtrate was concentrated to approximately 80 mL end volume (where crystals of reagent **1** had already formed) and stirred at −20 °C to complete the crystallization. The crystals were filtered off, rinsed with cold MeCN (−20 °C, 30 mL), and dried under a vacuum. The mother liquor was again concentrated to approximately 25 mL end volume and cooled to −20 °C. The crystals were filtered off and washed with a little cold MeCN. Both crystalline fractions were dried under a high vacuum to give the product as a white solid (24.5 g first crop, 1.57 g second crop, combined yield 78%). Yields varied between 76 and 79%. Mp: 163 °C (decomposition). ^{1}H NMR (300 MHz, $CDCl_3$, 23 °C): δ 7.67−7.89 (m, 3H), 8.38−8.52 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$, 23 °C): δ 107.1 (q, J = 380.2 Hz), 114.8 (poorly resolved q, J = 1.1 Hz), 127.3 (q, J = 3.2 Hz), 131.9, 133.7, 135.7, 165.9. ^{19}F NMR (282 MHz, $CDCl_3$, 23 °C): δ −33.84. Anal. Calcd for $C_8H_4O_2F_3I$: C, 30.41; H, 1.28. Found: C, 30.40; H, 1.48.

One-Pot Preparation of Reagent 1 from 2-Iodobenzoic Acid (3). A 250 mL three-necked, round-bottom flask equipped with a massive ellipsoidal magnetic stirring bar (4 cm diameter), Dimroth condenser, dropping funnel with pressure-equalizing side arm, and Ar inlet was charged with 2-iodobenzoic acid (14.1 g, 55.7 mmol, 1 equiv) followed by dry MeCN (120 mL). The resulting stirred suspension was heated to 75 °C. Meanwhile, the dropping funnel was charged with a solution of trichloroisocyanuric acid (4.49 g, 18.75 mmol, 1.02 Cl^+ equiv) in MeCN (30 mL). The solution of trichloroisocyanuric acid was added within 5 min. After the addition was complete, the dropping funnel was rinsed with dry MeCN (10 mL). The reaction mixture was cooled to rt, dry potassium acetate (10.95 g, 114.4 mmol, 2 equiv) was added under a countercurrent flow of Ar, and the resulting suspension was again heated to 75 °C for 2 h and then cooled to rt. Trifluoromethyltrimethylsilane (11.5 mL, 11.1 g, 78 mmol, 1.4 equiv) was added at once, and the resulting mixture was vigorously stirred for 12 h. After this time, further dry MeCN (50 mL) was added, and the resulting suspension was brought to reflux and filtered over a pad of Celite (1 cm thick). The brown filtrate was concentrated in a rotavap to approximately one-third of its original volume and cooled to −20 °C while stirring. The formed crystals were filtered off and washed with a little cold MeCN. The mother liquor from filtration was further concentrated in a rotavap to one-third of the previous volume, cooled to −20 °C, and a second crop of crystals was isolated by filtration. Both crystal crops were dried under a high vacuum to give the product as a white to off-white solid (11.9 g first crop, 0.8 g second crop, combined yield 72%).

Synthesis of Methyl 2-Iodobenzoate (8) from Methyl Anthranilate (7).[30] A 2 L beaker equipped with an overhead mechanical stirrer was placed in a large plastic bowl and secured in position by symmetrically positioned pieces of elastic sponge placed between the external wall of the beaker and the internal wall of the plastic bowl. The mechanical stirring rod had small vanes (1 cm). The beaker, externally cooled with an ice−salt mixture, was subsequently charged with 300 g of ice, 100 mL of distilled water, and concentrated sulfuric acid (83 mL, 153 g), and the mixture was stirred. Methyl anthranilate (151 g, 1 mol, 1 equiv) was quickly poured into the beaker. Within a few seconds, full solidification of the reaction mixture to a white paste of the hydrogen sulfate salt occurred. The mixture was cooled to 0−5 °C and diluted with ice cold distilled water (100 mL). A solution of sodium nitrite (70 g, 1.01 mol, 1.01 equiv) in water (100 mL) was injected slowly under the surface of the stirred suspension to minimize losses of nitrite due to the decomposition to nitrous gases. During the addition of sodium nitrite, the temperature of the reaction mixture was held within the range 0−7 °C. Occasionally, addition of crushed precooled ice (liquid N_2 precooled) conveniently lowered the temperature of the reaction mixture. After all sodium nitrite had been added, the reaction mixture was stirred until it gave only a weak nitrite content as indicated by KI−starch paper. The diazonium salt solution, cooled to −5 °C, was then transferred over the course of 30 min via Teflon cannula into a well-stirred, warmed (40 °C) mixture of potassium iodide (170 g, 1.02 mol, 1.02 equiv), 300 mL of water, sodium hydrosulfite (75 g, 40% solution, 0.28 mol, 0.28 equiv), and sulfuric acid (36 mL of concentrated sulfuric acid diluted in 75 mL of distilled water). The mixture was placed in a well-stirred 3 L three-necked, round-bottom flask equipped with a massive magnetic stirring bar, Dimroth condenser, and vacuum-inlet. The addition was done in small portions in order to prevent excessive foaming during the decomposition. After the addition, the mixture was allowed to react at 40 °C for 5 min and then at 80 °C for 1 h. The dark brown reaction mixture was then cooled to rt, and the lower heavy organic phase was separated and washed subsequently with 20% diluted sulfuric acid (150 mL), diluted sodium hydrogen sulfite (150 mL), water (200 mL), and brine (200 mL). The organic phase was diluted with ethyl acetate (200 mL), dried over a mixture of anhydrous sodium sulfate and potassium carbonate, filtered, and concentrated to dryness to give orange methyl 2-iodobenzoate (**8**, 245 g, 93% yield in 95% purity, 88% yield corrected for purity). Analytically pure material can be obtained by vacuum distillation. ^{1}H NMR (300 MHz, $CDCl_3$, 23 °C): δ 3.91 (s, 3H), 7.12 (m, 1H), 7.37 (m, 1H), 7.77 (dd, J = 7.8, 1.7 Hz, 1H), 7.96 (dd, J = 7.9, 0.9 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$, 23 °C): δ 52.5, 94.1, 127.9, 131.0, 132.7, 135.2, 141.3, 167.0. Anal. Calcd for $C_8H_7O_2I$: C, 36.67; H, 2.69. Found: C, 37.09; H, 2.83.

Remarks for the Synthesis of 2-(2-Iodophenyl)propan-2-ol (9). The synthesis was performed as described in the literature,[26] but with minor modifications: (a) On a larger scale, the addition of methyl 2-iodobenzoate to the solution of methylmagnesium iodide in diethyl ether should be done with careful temperature control. Preferably, the solution of methylmagnesium iodide should be precooled to −30 °C. (b) Frequently, the reaction mixture does not have to be stirred overnight or refluxed. In most cases, the TLC reaction control revealed the reaction was complete within 6 h after the addition of methyl 2-iodobenzoate. Longer aging of the reaction mixture has been shown to lead to increased formation of byproducts. (c) On a larger scale, quenching of the reaction mixture is conveniently done in an inverse manner. The reaction mixture is allowed to run via a Teflon cannula onto a well stirred ice−slush−water mixture and then diluted with ethyl acetate. Insoluble magnesium salts are easily dissolved by addition of formic acid until a pH in the range of 4−6 is reached. In this way, possible thermal stress and stirring problems during the quench are eliminated.

Chlorination of 2-(2-Iodophenyl)propan-2-ol (9) to 1-Chloro-3,3-dimethyl-1,2-benziodoxole (10). A 2 L three-necked, round-bottom flask equipped with a massive ellipsoidal magnetic

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stirring bar (8 cm diameter), Ar inlet, Dimroth condenser, and dropping funnel with pressure-equalizing side arm was charged under Ar with crude 2-(2-iodophenyl)propan-2-ol (191 g of 90% purity, 0.656 mol, 1 equiv), and anhydrous MeCN (1.2 L) was added. The resulting suspension was stirred and heated to 75 °C in an oil bath. The dropping funnel was filled with a solution of trichloroisocyanuric acid (52.9 g, 0.2207 mol, 1.02 Cl^+ equiv) in anhydrous MeCN (200 mL). The solution of trichloroisocyanuric acid was added to the well-stirred solution of 2-(2-iodophenyl)propan-2-ol within 5 min. During the addition, formation of insoluble isocyanuric acid was observed. The resulting suspension was refluxed for further 5 min and then filtered hot over a preheated sintered-glass funnel covered with a tightly pressed pad of Celite (1 cm thick). The filter cake was then washed with boiling MeCN (100 mL). The yellow-to-brown filtrate was concentrated in a rotavap to 150 mL (end volume) and cooled to −20 °C, and the resulting yellow crystals were filtered off and washed with a little cold MeCN. Concentration of the mother liquor gave a further crop of crystals. The crystals were dried under a high vacuum. First crop 164 g, second crop 9 g, combined yield 89%. Mp: 145−147 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 23 °C): δ 1.55 (s, 6H), 7.12−7.21 (m, 1H), 7.46−7.62 (m, 2H), 7.95−8.09 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$, 23 °C): δ 29.2, 85.2, 114.7, 126.1, 128.5, 130.5, 131.0, 149.5. Anal. Calcd for $C_9H_{10}OClI$: C, 36.45; H, 3.40. Found: C, 36.57; H, 3.47.

Preparation of Reagent 2 from 1-Chloro-3,3-dimethyl-1,2-benziodoxole (10). A two-necked, 500 mL round-bottom flask equipped with a massive magnetic stirring bar was charged with anhydrous spray-dried potassium fluoride (8.71 g, 0.15 mol, 1.5 equiv) and flame-dried with vigorous stirring under a high vacuum (8×10^{-3} mbar) for 5 min. After the dried mixture was cooled to room temperature under Ar, solid 1-chloro-3,3-dimethyl-1,2-benziodoxole (**10**, 29.65 g, 0.1 mol, 1 equiv) followed by anhydrous MeCN (300 mL) was added. The resulting suspension was vigorously stirred for at least 8 h, preferably 12 h, during which the color changed from yellowish to white. (Alternatively, the cheaper ordinary-grade anhydrous KF can be employed, in which case at least 2 equiv of KF and stirring for 20 h is recommended to complete the halogen exchange.) After the halogen exchange is finished, the resulting suspension was cooled in an ice−salt bath to −10 °C, and trifluoromethyltrimethylsilane (16.3 mL, 15.6 g, 0.11 mmol, 1.1 equiv) was injected in one portion. The resulting suspension was stirred vigorously for 1 h, allowed to warm to rt, and filtered over a 1 cm thick pad of Celite (see Note 1), and the filter cake was washed with a little MeCN. The brown solution was concentrated to dryness in a rotavap. The crystalline crude residue was redissolved in dry pentane (400 mL) at rt, filtered over a pad of activated alumina (5 cm diameter, 1.5 cm thick, see Note 2), and covered by a protective compressed Celite layer into another two-necked round-bottom flask equipped with a magnetic stirring bar. The clear and almost colorless filtrate was slowly cooled with stirring under Ar to −78 °C, causing the full precipitation of reagent **2** (see Note 3). The residual mother liquor was removed by cannula with a filter, and the resulting white solid was dried under a high vacuum with stirring to give the target product (29.7 g, 90% yield). The yields varied between 85 and 91%.

Note 1. Alternatively, the crude reaction mixture can be concentrated to dryness without filtration. The resulting solid is then treated with pentane and processed as described above. No diminished yield was observed.

Note 2. Aluminum oxide of Brockmann Activity Grade I was heated with a heat gun in a 250 mL round-bottom flask under high vacuum (8×10^{-3} mbar) for 5−10 min and then allowed to cool to room temperature under Ar. During the filtration, aluminum oxide with a lower activity grade was shown to retain considerable amounts of reagent **2**; thus, it led to lower isolated yields.

Note 3. Recrystallization from cold pentane is the preferred purification method for a larger scale. Alternatively, sublimation leads to excessive thermal stress and gives lower recoveries and, in some cases, inferior purity than samples purified by recrystallization. In view of the recent reports of its potential exothermic decomposition,[23b] such a practice should be discouraged.

Preparation of 1-Fluoro-3,3-dimethyl-1,2-benziodoxole (11) from 1-Chloro-3,3-dimethyl-1,2-benziodoxole (10). 1-Fluoro-3,3-dimethyl-1,2-benziodoxole **11** was prepared following the previous procedure with only one modification; just one-tenth of the original scale was used. The reaction mixture was filtered by cannula under Ar into another Schlenk flask and then concentrated to dryness with an external cold trap. White crystalline material was obtained in 94% isolated yield and 92% purity. X-ray quality crystals were obtained by slow cooling of the saturated solution of the title compound in a pentane/dichloromethane solvent mixture. Alternatively, the crude product can be recrystallized from boiling diisopropyl ether. ^{1}H NMR (300 MHz, $CDCl_3$, 23 °C): δ 1.51 (d, J = 1.1 Hz, 6H), 7.16 (m, 1H), 7.42−7.59 (m, 2H), 7.77 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, 23 °C): δ 29.05 (d, J = 3.2 Hz), 85.20 (d, J = 2.6 Hz), 115.95 (d, J = 8.0 Hz), 125.93 (s), 128.58 (d, J = 8.5 Hz), 130.20 (s), 130.54 (s), 148.50 (d, J = 1.8 Hz). ^{19}F NMR (282 MHz, $CDCl_3$, 23 °C): δ −142.93. HRMS (EI, EBE-triSector) calcd for $C_9H_{10}FIO$ 279.9755 [M^+], 264.9521 [$M^+ - CH_3$]; found 279.9731 [M^+, 0.7%], 264.9522 [$M^+ - CH_3$, 100%]. Anal. Calcd for $C_9H_{10}FIO$: C, 38.60; H, 3.60. Found: C, 38.68; H, 3.69.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of NMR spectra of the reported compounds and a cif file for compound **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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