Note

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One-Pot Synthesis of Hypervalent Iodine Reagents for Electrophilic Trifluoromethylation

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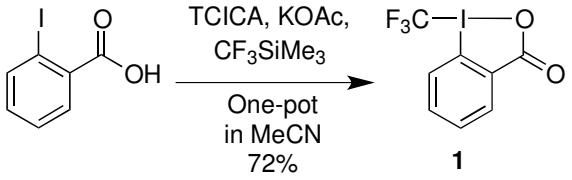
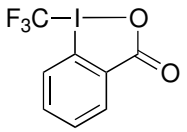


Abstract: Simplified syntheses suited for large scale preparations of the two hypervalent iodine reagents **1** and **2** for electrophilic trifluoromethylation are reported. In both cases the stoichiometric oxidants sodium metaperiodate and *t*-butyl hypochlorite, respectively, have been replaced by trichloroisocyanuric acid.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

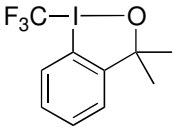
In recent years, the arena of synthetic organic chemistry has witnessed a vigorous development of various synthetic methods for the introduction of polyfluorinated groups into a plethora of molecular targets.[1] The growing demand of such methods is intimately associated with the benefits deriving from new molecules having remarkable properties such as altered metabolic behavior, resistance towards 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]



1
"Acid reagent"



2
"Alcohol reagent"

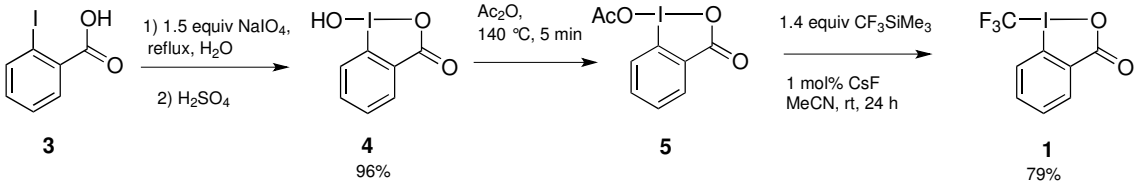
Figure 1. Hypervalent iodine reagents for electrophilic trifluoromethylation.

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 to be overcome since 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 trifluromethylations 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] 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 using cooperatively 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]

Based on this rapid progress, it is reasonable to assume that these hypervalent CF_3 iodine reagents might find in the near future further applications in 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 a careful redesign and optimization for them to meet standards typical for larger scale preparations, such as scalability, reproducibility, reduction of manipulation steps, use of less hazardous reagents, lower production of toxic aqueous streams and finally reduction of the amounts of costly reagents.

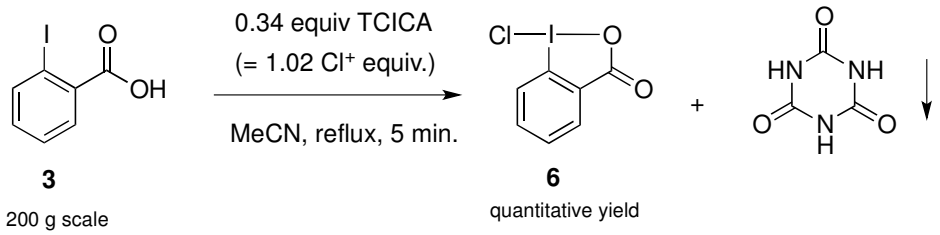


Scheme 1. Current synthetic sequence leading to reagent **1**.

The original synthesis of **1** (Scheme 1) commences with the aqueous oxidation of 2-iodobenzoic acid **3** with 1.5 equivalents of sodium metaperiodate at reflux overnight producing a suspension of hydroxyiodobenziodoxolone **4** in typical yields between 91-96% after additional acidification with dilute sulfuric acid. The dry **4** is then acetylated in hot neat acetic anhydride. The progress of this acetylation can be conveniently visually monitored as the resulting acetoxy iodane **5** is well soluble in the mixture of hot acetic anhydride/acetic

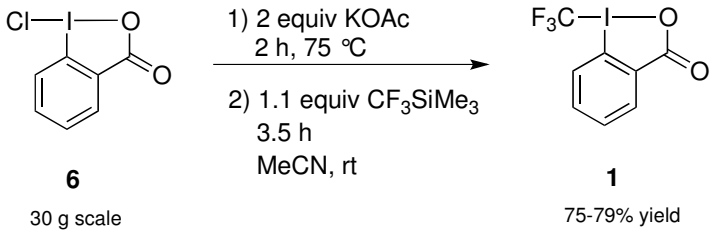
acid and finally a clear solution of **5** is obtained. Although we never experienced any accident, the acetylation step has been always conducted behind a safety screen because of conceivable adventitious traces of iodine(V) impurities or traces of sodium iodate contaminating the starting material and possibly leading to violent decomposition processes.[23] Cooling the resulting solution to -20 °C brings about complete crystallization of **5** which is decanted from the remaining mother liquor. 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 rather lengthy and 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 non-aqueous oxidant capable of selectively oxidizing 2-iodobenzoic acid to an appropriate iodine(III) intermediate, we were pleased to find out that the use of stoichiometric 2,4,6-trichloro-triazin-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. Heating the resulting suspension to reflux and filtration over a pad of Celite® while hot gave a light yellow solution which upon concentration, filtration and washing with cold acetonitrile provided free-flowing crystals of **6** in quantitative yield and excellent purity (Scheme 2).



Scheme 2. Chlorination of 2-iodobenzoic acid **3** with trichloroisocyanuric acid.

Subsequent treatment of **6** with 2 equivalents of anhydrous KOAc in acetonitrile under reflux for 2 h provided a fine suspension of KCl and acetoxyiodane **5** which was in situ treated 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).

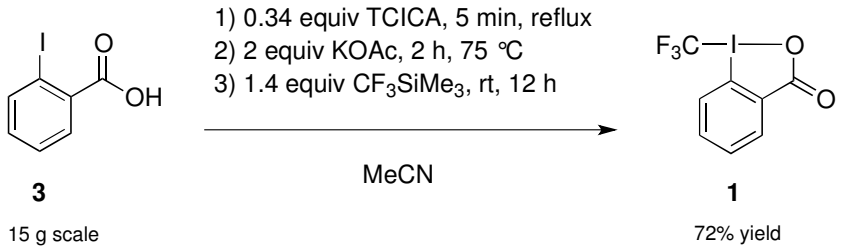


Scheme 3. Preparation of reagent **1** from chloroiodane precursor **6**.

During the scale up of this procedure to 30 g we have 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 the scale of the reaction was increased, problems of 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 (> 10000), optionally combined with installed baffles on the reactor walls is therefore highly recommended. Interestingly, the use of highly turbulent

stirring on a 30 g scale considerably accelerated the umpolung step, since the reaction was complete within 3.5 hours, a significantly shorter time than previously observed.[25]

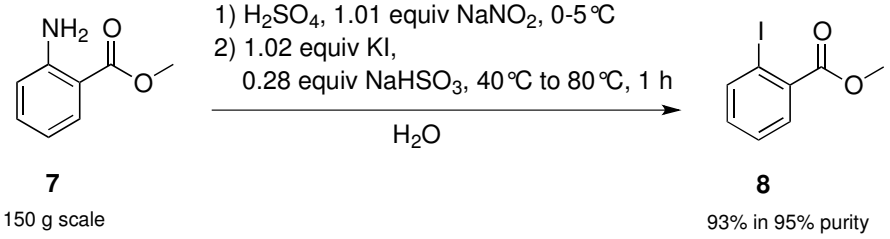
First experiments to unite all steps, i.e. chlorination of 2-iodobenzoic acid, chloride/acetate exchange and CF_3 umpolung met with failure. Upon mixing 2-iodobenzoic acid with dry KOAc in acetonitrile, the rapid formation of a thick paste of potassium 2-iodobenzoate was observed. However, after addition of trichloroisocyanuric acid, no chlorination took place. Changing the order of addition appeared to solve the problem - chlorination of 2-iodobenzoic acid and subsequent addition of KOAc followed by stirring at 75 °C for 2 hours gave a suspension of **5** accompanied by insoluble isocyanuric acid and KCl. To this vigorously stirred suspension was added at room temperature 1.4 equiv. of $TMSCF_3$ 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 previous variant starting from **6**.



Scheme 4. One-pot preparation of reagent **1** from 2-iodobenzoic acid.

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 relatively expensive 2-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 equivalents of sodium hydrogensulfite. The presence of hydrogensulfite 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 to use only 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).

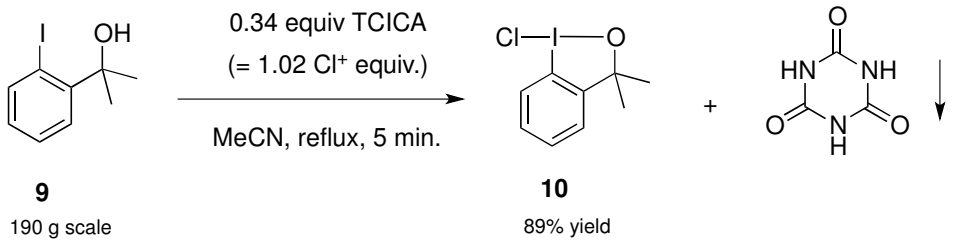


7
150 g scale

8
93% in 95% purity

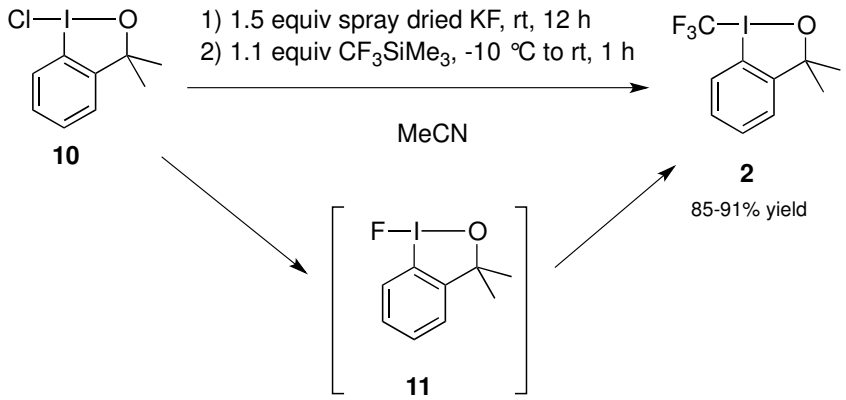
Scheme 5. Cost-effective synthesis of methyl 2-iodobenzoate.

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, i.e. 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**, *t*-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.

In the previous synthesis of **2**,[26] the final umpolung starting from 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 a strict control of 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 goes to completion overnight at room temperature, 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 one hour affording **2** in 85-91% isolated yield (Scheme 7).



Scheme 7. Fluoroiodane **11** as intermediate in the synthesis of reagent **2**.

The intermediate fluoroiodane **11** could be eventually 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] a I-O bond shortening in comparison to the related chloroiodane **10** due to an altered trans effect of the fluorine atom.[29] Studies directed towards 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, while 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. 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.) was dried for at least 24 h prior to use over activated 3Å molecular sieves. Potassium acetate (p.a.) was dried under 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. Grey 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 MHz, 282 MHz, and 75.5 MHz, respectively. Since 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(1H)-one (6). A 3-liter 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 anhydrous MeCN. The solution of trichloroisocyanuric acid was dropped into the vigorously stirred reaction mixture within 5 minutes. During the addition of trichloroisocyanuric acid, 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 further 5 minutes. 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 near dryness, the resulting yellow solid was filtered over a sintered-glass funnel and washed with little 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 hours under high vacuum to give product **6** as free flowing light yellow crystals in quantitative yield. (223 g): mp 178.5-180 °C (partial dec.); δ_H (300 MHz, $CDCl_3$, 23°C) 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); δ_C (75.5 MHz, $CDCl_3$, 23°C) 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(1H)-one (6). A 500 mL two-necked round-bottom flask equipped with a massive ellipsoidal-shaped 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 high vacuum ($8 \cdot 10^{-3}$ mbar) for 5 minutes, then cooled down to room temperature under Ar. 1-Chloro-1,2-benziodoxol-3(1H)-one (**6**, 30 g, 0.106 mol, 1 equiv) was added in counter-current flow of Ar followed by anhydrous MeCN (300 mL). The resulting suspension was vigorously stirred under Ar at 75°C for 2 hours. The color went from slightly yellowish 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 and the resulting suspension was vigorously stirred for 3.5 h during which the mixture turned brownish. A sample of the reaction mixture revealed by ^{19}F NMR analysis that

trifluoromethyltrimethylsilane was almost completely consumed. Further anhydrous MeCN (100 mL) was added, the reaction mixture was heated to 75°C in an oil bath and filtered 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 approx. 80 mL end volume (whereby crystals of reagent **1** already formed) and stirred at -20 °C to complete crystallization. The crystals were filtered off, rinsed with cold MeCN (-20 °C, 30 mL) and dried under vacuum. The mother liquor was again concentrated to ca. 25 mL end volume, cooled to -20°C, the crystals were filtered off and washed with little cold MeCN. Both crystalline fractions were dried under 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 (dec.); δ_H (300 MHz, $CDCl_3$, 23°C) δ 7.67 – 7.89 (m, 3H), 8.38 – 8.52 (m, 1H); δ_C (75.5 MHz, $CDCl_3$, 23° C) 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; δ_F (282 MHz, $CDCl_3$, 23 °C) -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-shaped 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 minutes. After the addition was complete, the dropping funnel was rinsed with dry MeCN (10 mL). The reaction mixture was cooled to r. t., dry potassium acetate (10.95 g, 114.4 mmol, 2 equiv) was added under a counter-current flow of Ar and the resulting suspension was again heated to 75 °C for 2 h and then cooled to r. t. 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, the resulting suspension brought to reflux and filtered over a pad of Celite® (1 cm thick). The brown filtrate was concentrated in a rotavap to ca. 1/3 of its original volume and cooled to -20 °C under stirring. The formed crystals were filtered off and washed with little cold MeCN. The mother liquor from filtration was further

concentrated in a rotavap to 1/3, cooled to -20 °C, and a second crop of crystals was isolated by filtration. Both crystal crops were dried under high vacuum to give the product as 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-liter beaker equipped with an overhead mechanical stirrer was placed in a larger 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 should preferably have rather smaller vanes (1 cm). The beaker, externally cooled with ice-salt mixture, was subsequently charged with 300 g ice, 100 mL 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 few seconds, full solidification of the reaction mixture to a white paste of the hydrogensulfate 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 decomposition to nitrous gases. During the addition of sodium nitrite, temperature of the reaction mixture should be held within the range 0-7 °C. Occasionally, addition of crushed precooled ice (liquid N_2-precooled) conveniently lowers the temperature of the reaction mixture. After all sodium nitrite has 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 during 30 minutes via Teflon cannula into a well-stirred, warmed (40 °C) mixture of potassium iodide (170 g, 1.02 mol, 1.02 equiv), 300 mL water, 40% solution of 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 distilled water) placed in a well-stirred 3-liter three-necked round-bottom flask equipped with massive magnetic stirring bar, Dimroth condenser and vacuum-inlet. The addition should be done preferably 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 minutes and then at 80 °C for 1 hour. The dark brown reaction mixture was then cooled to r. t., the lower heavy organic phase was separated and washed subsequently with 20% diluted sulfuric acid (150 mL), diluted sodium hydrogensulfite (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-colored 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. δ_H (300 MHz, $CDCl_3$, 23°C) 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); δ_C (75.5 MHz, $CDCl_3$, 23°C) 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] however with minor modifications: a) On a larger scale, addition of methyl 2-iodobenzoate to the solution of methylmagnesium iodide in diethylether 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 be stirred overnight or refluxed. In most cases TLC reaction control revealed the reaction to be complete within 6 hours after addition of methyl 2-iodobenzoate. Longer ageing 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 pH= 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-liter three-necked round-bottom flask equipped with a massive ellipsoidal magnetic 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 stirred suspension was 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 minutes. During addition, formation of insoluble isocyanuric acid was observed. The resulting suspension was refluxed for further 5 minutes 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, 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 high vacuum. (first crop 164 g, second crop 9 g, combined yield 89%). mp 145-147 °C; δ_H (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); δ_C (75.5 MHz, $CDCl_3$, 23°C) 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 2-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 high vacuum ($8 \cdot 10^{-3}$ mbar) for 5 minutes. After cooling down to room temperature under Ar, solid 1-chloro-3,3-dimethyl-1,2-benziodoxole (**10**, 29.65 g, 0.1 mol, 1 equiv) was added, followed by anhydrous MeCN (300 mL). The resulting suspension was vigorously stirred for at least 8 h, preferably 12 h during which the color changed from yellowish to white. (Alternatively, cheaper ordinary grade anhydrous KF can also be employed, in which case at least 2 equiv 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 vigorously stirred for 1 h allowing to warm up to r. t., filtered over a pad of Celite® (1 cm thick) *(Note 1)*, and the filter cake was washed with little MeCN. The brown solution was concentrated to dryness in a rotavap. The crystalline crude residue was redissolved in dry pentane (400 mL) at room temperature and filtered over a pad of activated alumina *(Note 2)* (5 cm diameter,1.5 cm thick), covered by a protective compressed Celite® layer into another 2-necked round bottom flask equipped with magnetic stirring bar. The clear almost colorless filtrate was slowly cooled under Ar with stirring

to -78°C causing full precipitation of reagent **2** *(Note 3)*. The residual mother liquor was removed by cannula with filter and the resulting white solid was dried in high vacuum with stirring to give the target product (29.7 g, 90% yield). The yields varied between 85-91%.

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 I was heated with a heat gun in a 250 mL round bottom flask under high vacuum ($8 \cdot 10^{-3}$ mbar) for 5-10 minutes and then allowed to cool to room temperature under Ar. During the filtration, aluminum oxide with lower activation grade was shown to retain considerable amounts of reagent **2** and thus led to lower isolated yields.

Note 3: Recrystallization from cold pentane is the preferred purification method for larger scale. As opposed to that, 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 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 the only modification that just 1/10 of the original scale was used. The reaction mixture is filtered by cannula under Ar into another Schlenk flask and then concentrated to dryness with an external cold trap. White crystalline material is 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 diisopropylether. δ_H (300 MHz, $CDCl_3$, 23°C) 1.51 (d, J = 1.1 Hz, 6H), 7.16 (m, 1H), 7.42 – 7.59 (m, 2H), 7.77 (m, 1H); δ_C (75 MHz, $CDCl_3$, 23 °C) 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); δ_F (282 MHz, $CDCl_3$, 23°C) -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.

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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.

References and Notes

(1) For recent reviews and monographs, see: (a) Isanbor, C.; O'Hagan, D. *J. Fluorine Chem.* **2006**, *127*, 303. (b) Müller K.; Faeh, C.; Diederich, F. *Science* **2007**, 317, 1881. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev*. **2008**, 37, 320. (d) Furuya, T., Kamlet, A.S.; Ritter, T. *Nature* **2011**, *473*, 470. (e) Tomashenko, O.A.; Grushin, V.V. *Chem. Rev.* **2011**, *8*, 4475. (f) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, Wiley-VCH, Weinheim, **2004**. (g) Uneyama, K. *Organofluorine Chemistry*, Blackwell Publishing, Oxford, **2006**. (h) Shibata, N.; Matsnev, A.; Cahard, D. *Beilstein J. Org. Chem.* **2010**, *6*, 65. (i) Ma, J.A.; Cahard, D. *Chem. Rev*. **2008**, *108*, 9, PR1-PR43. (j) Mac, Y., Magnier, E. *Eur. J. Org. Chem.* **2012**, 2479.

(2) Leroux, F.R.; Manteau,B.; Vors, J.P. Pazenok, S.; *Beilstein J. Org. Chem*. **2008**, *4*, 13.

(3) Lintvedt, R.L.; Holtzclaw, H.F. *J. Am. Chem. Soc.* **1966**, *88*, 2713.

(4) Eisenberger, P.; Gischig, S.; Togni, A. *Chem. Eur. J*. **2006**, *12*, 2579.

(5) „Acid reagent" and „alcohol reagent" are the denominations routinely used in our laboratory and stem from the starting materials used for the corresponding syntheses, an acid and an alcohol, respectively. We are aware of the fact that they are often referred to

in the literature as *Togni's reagents*. The senior author, though, refrains from actively attaching his name to these chemicals.

(6) Eisenberger, P.; Kieltsch, I.; Armanino, N.; Togni, A. *Chem. Commun.* **2008**, 1575.

(7) Kieltsch, I.; Eisenberger, P.; Togni, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 754.

(8) Santschi, N.; Togni, A. *J. Org. Chem.* **2011**, *76*, 4189.

(9) Wiehn, M.S.; Vinogradova, E.V.; Togni A. *J. Fluor. Chem.* **2010**, *131*, 951.

(10) Koller, R.; Stanek, K.; Stolz, D.; Aardoom, R.; Niedermann, K.; Togni, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 4332.

(11) Koller, R.; Huchet,Q.; Battaglia, P.; Welch, J.M.; Togni, A. *Chem. Commun.* **2009**, 5993.

(12) Santschi, N.; Geissbühler, P.; Togni, A. *J. Fluorine Chem*. **2012**, *135*, 83.

(13) Niedermann, K.; Früh, N.; Vinogradova, E.; Wiehn, M.S, Moreno, A.; Togni, A. *Angew. Chem. Int. Ed*. **2011**, *50*, 1059.

(14) Niedermann, K.; Früh, N.; Senn, R.; Czarniecki, B.; Verel, R.; Togni, A. *Angew. Chem. Int. Ed.* **2012**, *51*, 6511.

(15) Liu T.; Shen, Q. *Org Lett*. **2011**, *13*, 2342.

(16) a) Xu, J.; Fu,Y.;Luo, D.F.; Jiang, Y.Y.;Xiao, B.; Liu, Z.J. ;Gong, T.J.; Liu,L. *J. Am. Chem. Soc.* **2011**, *133*, 15300. b) Wang, X.;Ye,Y.; Zhang, S.; Feng, J.; Xu,Y.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 16410.

(17) Weng, Z.; Li, H.; He, W.; Yao, L.F.; Tan, J.; Yuan, Y.; Huang, K.W. *Tetrahedron* **2012**, *68*, 2527.

(18) Shimizu, R.; Egami, H.; Hamashima, Y.; Sodeoka, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 4577.

(19) a) Janson, P.G.; Ghoneim, I.; Ilchenko, N.O.; Szabó, K.J. *Org Lett.* **2012**, *14*, 2882. b) Zhu, R.; Buchwald, S. *J. Am. Chem. Soc.* **2012**, *134*, 12462 c) Egami, H.; Shimizu, R.; Kawamura, S.; Sodeoka, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 4000.

(20) Allen, A.E.; MacMillan, D.W.C. *J. Am. Chem. Soc.* **2010**, *132*, 4986.

(21) Deng, Q.-H.; Wadepohl, H.; Gade, L. *J. Am. Chem. Soc.* **2012**, *134*, 10769.

(22) Matoušek, V.; Togni, A.; Bizet, V.; Cahard, D. *Org. Lett.* **2011**, *13,* 5762.

(23) (a) Plumb, J. B.; Harper, D. *J. Chem. Eng. News* **1990**, *68*, 3. (b) Very recently, a report about the potential explosive properties of reagent **1**, still prepared via the acetoxy route, has appeared. See: Fiederling, N.; Haller, J.; Schramm, H. *Org. Process Res. Dev.* **2013**, *17*, 318.

(24) For a review about the use of TCICA, see : Tilstam, U.; Weinmann, H. *Org. Process Res. Dev*. **2002**, *6*, 384.

(25) Stanek, K.; Koller, R.; Togni, A. *J. Org. Chem.* **2008**, *73*, 7678.

(26) Eisenberger, P.; Kieltsch, I.; Koller, R.; Stanek, K.; Togni, A. *Org. Synth.* **2011**, *88*, 68.

(27) Bradshaw, C.P.C.; Nechvatal, A. *Proc. Chem. Soc.* **1963**, 213.

(28) The crystal structure of **11** has been recently reported, see: Legault, C.Y.; Prévost, J. *Acta Cryst.* **2012**, *E68*, o1238.

(29) Ochiai, M.; Sueda, T.; Miyamoto, K.; Kiprof, P.; Zhdankin, V.V. *Angew. Chem. Int. Ed.* **2006**, *45*, 8203.

(30) Urbach, H. (BASF, Aktiengesellschaft, Germany), US4007221, A, February 8, 1977.