Reactivity of a 10-I-3 Hypervalent Iodine Trifluoromethylation Reagent With Phenols

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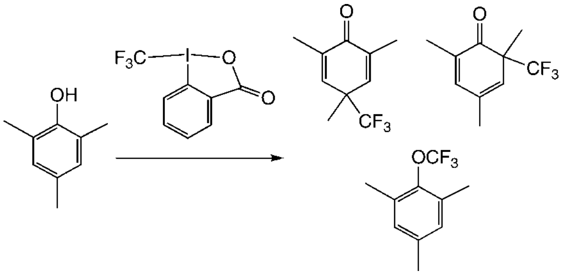

The reaction of the 10-I-3 hypervalent iodine electrophilic trifluoromethylation reagent 1-trifluoromethyl-1,2-benziodoxol-3-(1*H*)-one (**2**) with 2,4,6-trimethylphenol, after deprotonation with NaH and in the presence of 18-crown-6 in a polar, nonprotic solvent, affords 1,3,5-trimethyl-2-(trifluoromethoxy)benzene (**4**) only as a byproduct. Trifluoromethylation occurs preferentially at the *ortho*- and *para*-positions of the aromatic core, giving the corresponding trifluoromethylcyclohexadienones **5** and **6**. In case the *ortho*- and/or *para*-positions are not substituted, the corresponding products of an aromatic, electrophilic substitution are obtained in moderate yield, for example, 2-trifluoromethyl-4-*tert*-butylphenol (**10a**) from 4-*tert*-butylphenol (**10**).

Introduction

Fluoroorganic molecules are eminently important for the pharmaceutical industry such that about 15% of all newly marketed pharmaceuticals contain one or more fluorine atoms. Besides single fluorine atoms, very often at aromatic positions the trifluoromethyl substituent also plays a very important role.[1] The same is very much true for crop protection agents, in which case the share of fluorinated molecules is much higher. However, examples of *trifluoromethoxy* derivatives[2] as medicines are still quite rare.[3] Examples among these are Riluzole,[4] the first approved drug for the treatment of neurological diseases such as amyotrophic lateral sclerosis, Celikalim,[5] a potent potassium channel opener in human airway smooth muscles, and CP-122,721,[6] a potent antagonist of neurokinin-1 receptor, with potential indication for a variety of disorders, from depression and pain to inflammatory diseases. Finally, the trifluoromethoxy group is essential for the effect of pesticides such as Triflumuron,[7] a chitin synthesis inhibitor, or Indoxacarb,[8] a sodium channel blocking insecticide. For all these biologically active compounds, the increased lipophilicity due to the trifluo-

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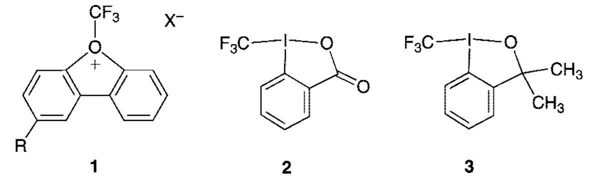
10.1021/jo8014825 CCC: $40.75



1 2 3

R = H, *t*-Bu, OMe, F
X = SbF_6, PF_6, BF_4, Sb_2F_{11}

FIGURE 1. Electrophilic trifluoromethylation reagents.

romethoxy group seems to play a crucial role influencing bioavailability and activity.[9]

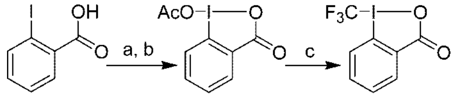
In the synthesis of complex trifluoromethoxy compounds, the chemical industry is still strongly dependent on the availability of corresponding building blocks. Simple trifluoromethoxy aryls are indeed commercial compounds, and in these cases, the fluorine atoms have been introduced by hazardous and harsh reaction conditions using, for example, CCl_4/HF, COF_2, SF_4, or SbF_5.[10] Obviously, simple, late stage and functional group tolerant methods for the trifluoromethylation of phenols is needed, has been eagerly sought for decades, and continues to be so at present.[11]

Electrophilic trifluoromethylation reagents have been introduced by the Yagupol'skii research group[12] and further developed by Umemoto and co-workers.[13] They are based on S-, Se-, and Te-(trifluoromethyl)dibenzothio-, seleno-, and tellurophenium salts and are suitable for the trifluoromethylation of metal enolates, silyl enolates, thiolates, enamines, and electron-rich aromatics in moderate to good yields. However, no direct O-trifluoromethylation is observed with these reagents.

Very recently, again Umemoto and co-workers reported a first solution to the problem of the direct, electrophilic O- or N-trifluoromethylation of both aliphatic and aromatic alcohols and amines, respectively.[14] They introduced a new series of *O*-(trifluoromethyl)dibenzofuranium salts of type **1** (Figure 1), which are more reactive toward hard nucleophiles, giving the corresponding trifluoromethylated products in good yields. The drawbacks one could mention are the in situ preparation at −90 °C, the lack of recyclability, and the fact that they need in the starting material an OCF_3 group, which needs to be constructed in the first place.

Our research group contributed to the growing family of electrophilic trifluoromethylation reagents with a new type of 10-I-3 hypervalent trifluoromethyliodine derivatives. Compounds **2** and **3** (Figure 1) are derived from 2-iodobenzoic acid, and they can be handled in air, are stable in a freezer over years, and give good to excellent yields in the trifluoromethylation of thiols and primary as well as secondary phosphines.[15] Their easy handling and synthesis and their possible recyclability make **2** and **3** attractive, possibly even for industrial applications. Therefore, as part of a general assessment of the reactivity of our reagents, it was an obvious step to examine their trifluoromethylation ability toward hard oxygen nucleophiles, especially phenols. Herein we present our findings and describe experiments carried out with a series of model systems.

SCHEME 1. Improved Synthesis of Reagent 2



a; $NaIO_4$, H_2O, reflux.
b; Ac_2O, reflux.
c; $TMSCF_3$ (1.4 equiv.), CsF (1%), MeCN, rt.
76% overall yield

2

Results and Discussion

With respect to the originally reported synthesis of reagent **2**, we were able to simplify and improve its preparation such that it is now available on a multigram scale in 76% overall yield starting from 2-iodobenzoic acid (Scheme 1). This reagent may be purified by column chromatography or sublimation and is air as well as moisture stable over months at room temperature.

Trifluoromethylation of 2,4,6-Trimethylphenol. First experiments with the most simple substrate, such as phenol, gave products of aromatic electrophilic substitution only, in a 9:4 ratio by ^{19}F NMR spectroscopy of the *para* and *ortho* regioisomers, accompanied by traces of the *meta* isomer. We therefore decided to carry out reactions of compound **2** with 2,4,6-trimethylphenol, thus speculating that the "occupied" *ortho* and *para* positions could favor reaction at the oxygen atom. Since reagent **2** has no incorporated alcoholate functionality acting as a sufficiently strong base as in the case of **3**, the phenol has been deprotonated with NaH in a polar nonprotic solvent such as DMF prior to the addition of reagent **2**. Furthermore, in order to ensure solubility of the corresponding sodium phenolate and avoid the possible formation of oligomeric aggregates,[16] reactions have been carried out in the presence of 1 equiv of the crown ether 18-crown-6. It is known that crown ethers are able to stabilize iodonium salts by weak iodine−oxygen interactions and that such complexes may be isolated in crystalline form.[17] However, it is not clear whether or not this type of interaction plays any significant role in the reactions reported here.

Thus, the desired 1,3,5-trimethyl-2-(trifluoromethoxy)benzene (**4**) could indeed be detected but only as a minor product. The cyclohexadienones **5**, **6**, and **7** arising from the oxidation/trifluoromethylation of the starting phenol constituted the major products (Scheme 2). Oxidation/methoxylation reactions of

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(8) Indoxacarb is (*S*)-methyl 7-chloro-2,5-dihydro-2-[[(methoxycarbonyl)[4-(trifluoromethoxy)phenyl]amino]carbonyl]indeno[1,2-*e*][1,3,4]oxadiazine-4a(3*H*)carboxylate. See: McCann, S. F. ; Cordova, D. ; Andaloro, J. T. ; Lahm, G. P. In *Modern Crop Protection Compounds*; Krämer, W., Schirmer, U., Eds.; Wiley-VCH: Weinheim, Germany, 2007; Vol. 3, pp 1031−1048.

(9) For substituent effects on lipophilicity as expressed by log *P*, see: Fujita, T.; Iwasa, J.; Hansch, C. *J. Am. Chem. Soc.* **1964**, *86*, 5175–5180.

(10) For a review, see: (a) Langlois, B.; Desbois, M. *Ann. Chim. Fr.* **1984**, *9*, 729–741. For specific examples, see: (b) Feiring, A. E. *J. Org. Chem.* **1979**, *44*, 2907–2910. (c) Salomé, J.; Mauger, C.; Brunet, S.; Schanen, V. *J. Fluorine Chem.* **2004**, *125*, 1947–1950. (d) Yagupol'skii, L. M. *Dokl. Akad. Nauk SSSR* **1955**, *105*, 100–102. (e) Yarovenko, N. N.; Vasil'eva, A. S. *Zh. Obshch. Khim.* **1958**, *28*, 2502–2504. (f) Yagupol'skii, L. M.; Orda, V. V. *Zh. Obshch. Khim.* **1961**, *31*, 915–924.

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(16) See, for example: (a) Kunert, M.; Dinjus, E.; Nauck, M.; Sieler, J. *Chem. Ber./Recueil* **1997**, *130*, 1461–1465. (b) Czado, W.; Müller, U. *Z. Kristallogr. NCS* **1999**, *214*, 63–64.

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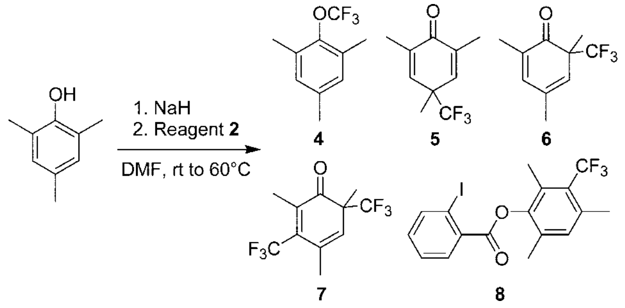
SCHEME 2. Products Observed in the Reaction of 2 with 2,4,6-Trimethylphenol



phenols have already been described by Kita as well as Pelter using $PhI(OCOCF_3)_2$ and/or $PhI(OAc)_2$ in MeOH acting as an external nucleophile giving corresponding ketones.[18] Also, in Friedel−Crafts-type reactions on substituted phenols, similar cyclohexadienones had been observed as early as in 1906.[19] On the other hand, rare examples of compounds containing the structural elements of a geminal alkyl/trifluoromethyl disubstitution pattern adjacent or in vinylogous position to the carbonyl group in a cyclohexanone system are known in the literature, and they have been prepared by a variety of methods from already trifluoromethylated starting materials.[20] The access to such structures by a direct trifluoromethylation process, as it is here the case, is new.

In an attempt to influence the selectivity of the reaction, either toward the trifluoromethoxy derivative **4** or to the not less interesting cyclohexadienones **5** and **6**, we carried out a series of experiments, thereby varying several reaction parameters, such as temperature, solvent, substrate/reagent ratio, and additives. The results are collected in Table 1.

These reactivity studies put forward several interesting aspects. When reagent **2** was used in excess, 97% of trimethylphenol was consumed within 2 days (run 8, conversion monitored by ^{1}H NMR; see Supporting Information), but only a total of 29% of trifluoromethylated products could be detected. HCF_3 and DCF_3 were also observed (the reaction was carried out in deuterated DMF), approximately accounting for the missing 71% of the CF_3 unit by ^{19}F NMR spectroscopy. Thus, a major decomposition pathway of reagent **2** seems to involve hydrogen abstraction from the solvent. Moreover, the reaction did also work in other aprotic, polar solvents such as DMSO, DMA, sulfolane, and NMP but not in CH_2Cl_2, CCl_4, or H_2O. For the case of excess reagent **2**, elevated temperatures were needed to complete the reaction. Higher temperatures favor the formation of the desired product **4** but concomitantly also trigger the decomposition of **2** to HCF_3. Higher excess of **2** unexpectedly lowered the total yield of fluorinated products (run 4). This prompted us to use trimethylphenol in excess instead (runs 9−13). This change of reaction conditions drastically increased the yields of cyclohexadienones **5** and **6**, based on reagent **2**, especially at lower temperatures and shortened the reaction time from about 24 h (runs 2−8) to 50 min at −50 °C. Although the total yield of trifluoromethylated products increased to ca. 70%, the drawback was the lowered yield of **4**.

TABLE 1. Trifluoromethylation of 2,4,6-Trimethylphenolate

run	ratio substrate/**2**	solvent	*T* (°C)	additive	yield[a] (%) **4**	**5**	**6**	**7**	**8**
1[b]	1/1.2	DMF	−20 to rt	18-crown-6	4	8	3	2	1
2	1/1.2	DMF	rt to 75	18-crown-6	12	17	7	2	−
3	1/1.6	DMF	rt to 60	18-crown-6	11	16	2	2	−
4	1/2.5	DMF	rt to 75	18-crown-6	9	13	3	4	−
5	1/1.2	DMA	rt to 75	−	11	17	8	2	−
6	1/1.2	DMSO	rt to 75	18-crown-6	14	16	7	3	−
7	1/1.6	sulfolane	rt to 60	18-crown-6	15	10	2	5	2
8	1/1.6	DMF-d_7	rt to 60	CsCl	8	11	1	6	3
9	2.5/1	DMF	rt	18-crown-6	12	24	20	−	3
10	2.5/1	DMF	55	18-crown-6	10	20	20	−	4
11	2.5/1	DMF	− 40 to rt	18-crown-6	7	33	25	−	3
12	2.5/1	DMF-d_7	−60 to −40	−	7	29	22	−	3
13	2.5/1	DMF	−40 to rt	18-crown-6 and Phenyl *N-tert*-butylnitrone	13	32	26	−	−

[a] Yields were determined by ^{19}F NMR with $C_6H_5CF_3$ as internal standard and calculated based on the compound in deficit. [b] Run 1 did not go to completion within 6 days.

Since it proved very difficult to obtain the desired product (**4**) with high selectivity and useful yields, we also investigated the possible catalytic effect of various metal salts and complexes. However, $FeCl_3$, $FeCl_2$, $MnCl_2$, $CoCl_2$, $Pb(OAc)_4$, $AlCl_3$, or $RuCl_2(PPh_3)_3$ just favored the formation of side products **7** and **8** along with other unidentified products. Furthermore, addition of a base is crucial for the reaction to occur, but when Hünig's base was used instead of NaH, compound **8** was formed predominatly as part of a complex mixture of unidentified products.

Other Substituted Phenols. The possibility to oxidize and trifluoromethylate 2,4,6-trimethylphenol encouraged us to extend this type of reacivity to various other substituted phenols.

The results collected in Table 2 clearly demonstrate that the oxidized products are only accessible when both the *ortho* and *para* positions of the phenol are already substituted (blocked). If not, trifluoromethylation exclusively takes place at these positions in moderate yields. Furthermore, bistrifluoromethylation is possible despite the decreased nucleophilicity of the monotrifluoromethylated intermediate. This is apparent in the cases of 4-*tert*-butyl phenol **10** and 5-indanol **12**. The 2,6-bis(trifluoromethyl) substitution pattern of product **12b** has been verified by a ^{1}H/^{19}F HOESY NMR experiment (see Supporting Information). In the case of estradiol **13**, the ^{19}F NMR spectrum of the reaction mixture showed, besides the main product **13a**, another monosubstituted derivative (at −60.5 ppm) along with a disubstituted product (at −52.1 and −61.7 ppm), accounting for 12 and 8% yield, respectively. Unfortunately, we were not able to isolate these two derivatives in pure form, but we assume that the observed product mixture reflects an analogous *ortho* substitution pattern as for indanol **12**. A substrate such as *β*-estradiol (**13**) could have given access, in case of a quaternization of the *para* position, to a hitherto unknown derivative of testosterone in which the methyl group at the A/B ring junction of the steroid system has been replaced by a CF_3 group.

Finally, a remarkable result was obtained when 2,4,6-trimethylphenol was reacted with reagent **3**. Trifluoromethylation took place at the benzylic position and products **4**, **5**, and **6** were only detected in traces (<5%). This benzylic trifluorom-

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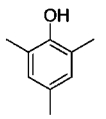
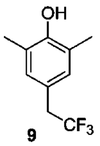
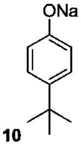
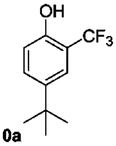
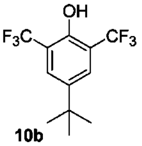
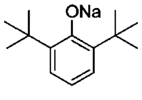
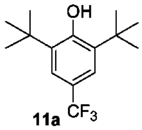
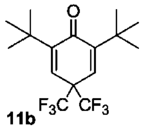
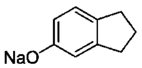
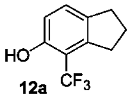
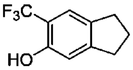
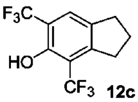
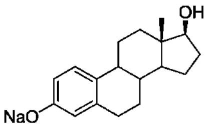
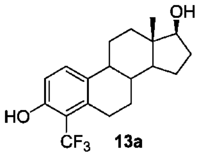
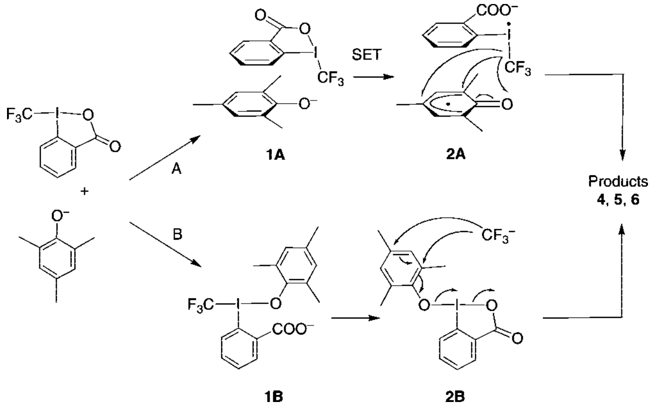
TABLE 2. Trifluoromethylation of Various Phenols

Entry	Substrate	Products	Yields (%)
1[a]		 9	**9** = 49 (35)
2[b]	 10	 10a  10b	**10a** = 49 **10b** = 10
3[b]	 11	 11a  11b	**11a** = 23 **11b** = 18
4[b]	 12	 12a  12b  12c	**12a** = 28 (5) **12b** = 19 (5) **12c** = 7 (5)
5[b]	 13	 13a	**13a** = 33 (13)

[a] The phenol was reacted with 1.2 equiv of reagent **3** in CH_2Cl_2 at rt. [b] Sodium phenolate (2.5 equiv) was reacted with reagent **2** (1 equiv) in DMF with 18-crown-6 as additive at −60 °C to rt. Yields were calculated on the basis of **2** by ^{19}F NMR spectroscopy of the reaction mixture using $C_6H_5CF_3$ as standard; isolated yields are given in brackets.

SCHEME 3. Possible Mechanistic Descriptions for the Reaction of 2 with 2,4,6-Trimethylphenol



ethylation could not be observed under the same conditions for electron-poor substrates such as 4-nitrotoluene. This is indicative of different mechanistic characteristics for the two reagents.

Mechanistic Aspects. Two limiting mechanistic descriptions, as shown in Scheme 3, are conceivable. Path A involves the formation of a charge-transfer complex between reagent **2** and the phenolate anion (**1A**), followed by a single electron transfer (SET). This leads to a cyclohexadienone radical still associated with and antiferromagnetically coupled with the one-electron-reduced form of the reagent (i.e., **2A** is a singlet diradical). This description is reminiscent of the situation occurring in the Ti-catalyzed electrophilic fluorination of β-keto esters, as indicated by computational chemistry studies.[21] Product formation would then occur by the transfer of a CF_3 radical, that is, by a radical recombination. A comparable SET pathway has been suggested by Kita and co-workers for the oxidative coupling of arenes using hypervalent iodine oxidants.[22] Path B initially invokes a nucleophilic ligand exchange at iodine(III), with the phenolate replacing the carboxylate (**1B**). Such an exchange seems realistic due to the stronger *trans* influence of the CF_3 group and the resulting weakening of the I−O bond in the 4e-3c hypervalent interaction in reagent **2**.[23] Intermediate **1B** may be viewed as an adduct between an iodonium cation and the phenolate anion. Liberation of the CF_3 anion leads to a system having, attached to the phenol oxygen, a phenyliodonium leaving group which is generally known for its extreme nucleofugality.[24] This means that the phenol fragment is an equivalent of a phenoxonium cation and is therefore susceptible to nucleophilic attack by CF_3^-. Kita[18a,b] and, independently, Pelter[18c] discussed similar ionic pathways in their work about phenol oxidation/methoxylation. Moreover, Ozanne-Beaudenon and Quideau reported a phenylation reaction of phenols by chlorodiphenyl-λ^3-iodane for

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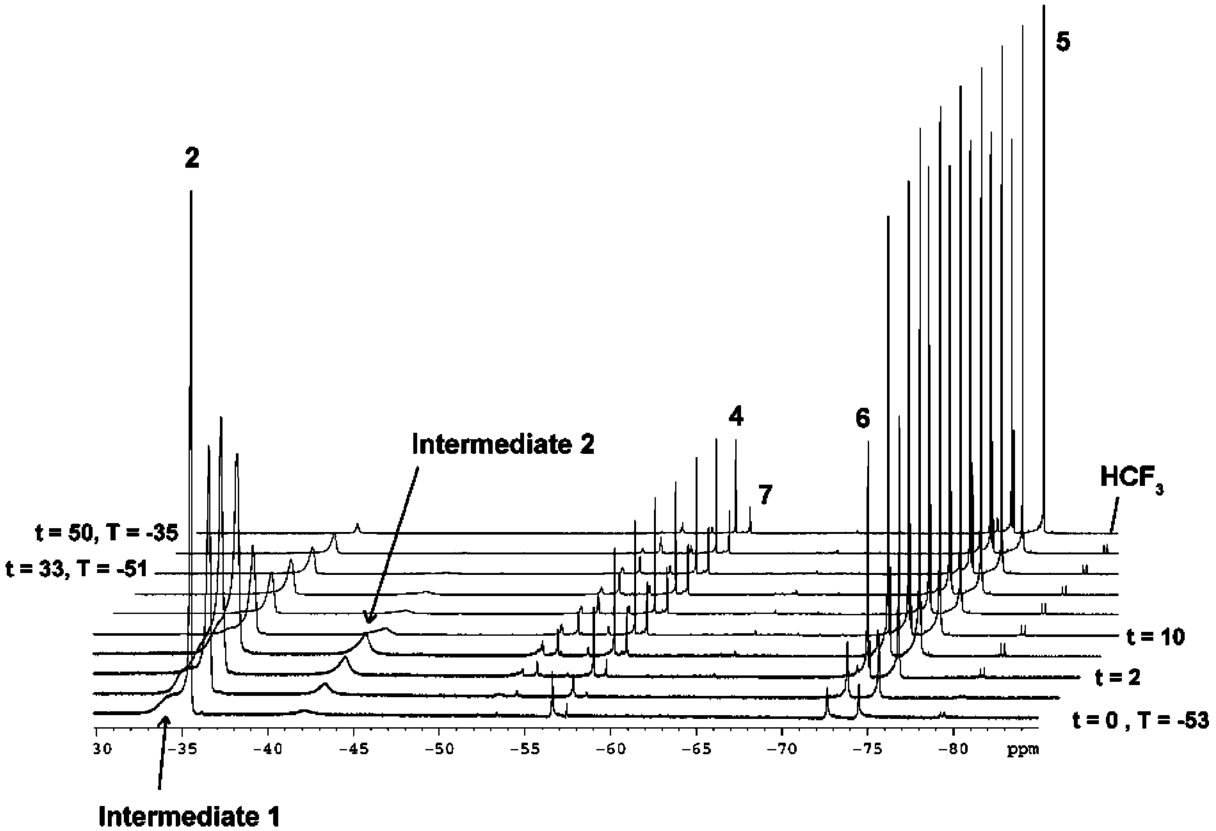

FIGURE 2. ^{19}F NMR series of the trifluoromethylation of trimethylphenol. Time (*t*) is given in minutes, temperature (*T*) in °C.

which they envisaged a ligand exchange followed by a ligand coupling at iodine.[25] Most recent investigations by Kita using chiral iodine(III) reagents in enantioselective dearomatization reactions of phenols strongly support the formation of stable phenoxy-λ^3-iodane intermediates.[26]

For the reaction corresponding to run 12 in Table 1, a sample of trimethylphenolate and reagent **2** in DMF-d_7 was prepared at −100 °C (MeOH/N$_2$(l)). After carefully warming the frozen sample to −55 °C, a series of ^{19}F NMR spectra were recorded as a function of time and are illustrated in Figure 2. This monitoring shows the rapid consumption of reagent **2** and the formation of products **4**−**7**, accompanied by traces of trifluoromethane. Interestingly, there are two broad signals, at ca. −34 and −42 ppm, respectively, initially increasing in intensity and then disappearing from the spectrum at later stages of the reaction. We tentatively assign these two signals to possible reaction intermediates. Although no structural information is available, these two species could coincide with intermediates of type **1A** and/or **1B** (Scheme 3). Since pathway B would imply the involvement of the trifluoromethyl anion, one could imagine this ion to be temporarily trapped by DMF as the corresponding aminoalcoholate, which is known to be stable for hours at temperatures below −20 °C.[27] However, the corresponding signal (−78 ppm, $J = 7.6$ Hz) could not be detected.

The same reacting mixture was also examined by EPR spectroscopy. The frozen sample was warmed to −55 °C, held at that temperature for a specified time, cooled again to −93 °C, at which temperature spectra were recorded (see Supporting Information). These spectra show two singlet radical species accumulating with time, the concentration of the major one reaching ca. 2.9×10^{-9} mol/mL after 10 min at rt. This is very low, as compared to the initial concentration of 1.8×10^{-4} mol/mL for the reagent. We interpret this as being indicative of minor iodo-radical byproducts, not directly involved with the main transformation. That the reaction does not generate free radicals was also corroborated by the fact that the addition of the radical scavanger phenyl *N*-*tert*-butylnitrone (run 13, Table 1) did not affect the reaction to any significant extent, both in terms of rate and product yield.

Stavber and co-workers[28] showed that the fluorination of 4-*tert*-butyl anisole with F-TEDA proceeds via SET, whereby the resulting radical cation eliminates the stable *tert*-butyl cation and radical recombination leads to *para*-fluoroanisole. A similar mechanism is conceivable in the case of electrophilic trifluoromethylation, and *para*-trifluoromethyl anisole would be the expected product. Surprisingly, the corresponding experiment produced a completely different result. When reagent **2** was exposed to either 1 equiv or a catalytic amount (10 mol %) of 4-*tert*-butyl anisole (**14**), we observed its decomposition to 2-iodobenzoic acid fluoride (**15**, Scheme 4) as the main isolable product. The missing "OCF$_2$" unit could not be identified in form of any byproduct by ^{19}F NMR spectroscopy.

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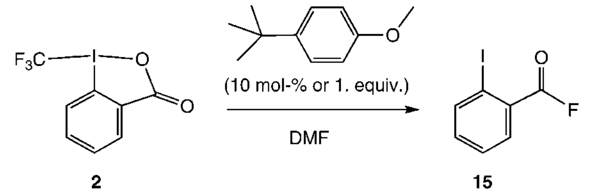
SCHEME 4. Decomposition of 2 with 4-*tert*-Butyl Anisole



Conclusions

Our reactivity studies of reagent **2** with phenols have shown that it is possible to generate the corresponding trifluoromethylether, however, only in the case of 2,4,6-trimethylphenol and up to an extent of only ca. 15%. The main products observed are generated by carbon functionalization. As noted recently by Umemoto,[14] the trifluoromethylation ability of a reagent toward hard nucleophiles, such as the oxygen atom of a phenolate, strongly depends on the hardness of the atom initially bearing the CF_3 unit. Reagent **2** is therefore to be described as a soft reagent with a particular affinity for soft nucleophiles such as, for example, thiols[15b] and primary or secondary phosphines.[15c] From a mechanistic point of view, our observations are still inconclusive as to the exact course of the trifluoromethyl transfer from reagent **2** to phenols. The intermediate formation of phenoxy-λ^3-iodane species that would undergo nucleophilic attack by a transient trifluoromethyl anion is probable and would reflect the general reactivity pattern of a number of known hypervalent iodine compounds. Equally, an SET pathway not involving free radicals cannot be excluded. However, for both scenarios, solid experimental evidence is still lacking.

Experimental Section

1-Trifluoromethyl-1,2-benziodoxol-3-(1*H*)-one (2). 1-Hydroxy-1,2-benziodoxol-3-(1*H*)-one (6.00 g, 21.1 mmol) was refluxed in Ac_2O for a few minutes until a clear solution was obtained. Upon cooling, white crystals began to separate and cooling was continued to −20 °C for 4 h. The solution was decanted, and the crystals were dried under vacuum for 24 h under stirring. The resulting white powder was identified as 1-acetoxy-1,2-benziodoxol-3-(1*H*)-one. This was dissolved in dry MeCN (50 mL) under Ar. $TMSCF_3$ (4.5 mL, 30.4 mmol) followed by dry CsF (0.05 g, 0.33 mmol) was added, and the suspension was vigorously stirred at rt for 22 h. The solvent was evaporated under reduced pressure, and the brown residue was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH = 15/1) giving the title compound in 5.65 g (79% yield over 2 steps, 76% from 2-iodobenzoic acid). Purification is also possible by sublimation (HV, 40 °C). NMR data are in agreement with the reported data.[15a] Anal. Calcd for $C_8H_4O_2F_3I$: C, 30.41; H, 1.28. Found: C, 30.56; H, 1.11.

Standard Method for the Trifluoromethylation of 2,4,6-Trimethylphenol. In a representative experiment, 2,4,6-trimethylphenol (100 mg, 0.734 mmol) was dissolved in dry DMF (2 mL) and deprotonated with NaH (18.5 mg, 0.771 mmol, previously washed with hexane). After ca. 15 min, the reaction temperature was set and reagent **2** (0.4−2.5 equiv) was added in one portion. The reaction was monitored by TLC or ^{19}F NMR. After no more reagent **2** was detectable, BTF (10 μL) as internal standard and C_6D_6 were added. The yields were calculated from the ^{19}F NMR integrals.

To isolate the products, the mixture was poured into water (ca. 10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure (>200 mbar due to the volatility of some products). Purification by flash column chromatography (SiO_2, pentane/Et_2O = 20/1 to 15/1) gave three different fractions: Fraction one contained the OCF_3 products; a second highly UV-active fraction contained a mixture of the oxidized products, and a third fraction contained starting phenol. The individual products could be further separated and purified by additional steps as described below.

1-(Trifluoromethoxy)-2,4,6-trimethylbenzene (4). This compound was purified by flash column chromatography (SiO_2, pentane/Et_2O = 20/1 to 15/1) where the product and disubstituted impurities were in the very first fractions, showing very poor UV activity and could not be stained. A second chromatography (SiO_2, pentane) afforded reasonably clean volatile oil. It is also possible to extract the product with pentane directly from the DMF reaction mixture, although in lower yields: ^{1}H NMR ($CDCl_3$, 400.13 MHz) δ 6.87 (s, 2H), 2.27 (s, 9H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 136.8, 132.1, 130.1, 121.7 (q, J = 256 Hz, CF_3), 21.1, 17.0; ^{19}F NMR ($CDCl_3$, 188.3 MHz) δ −56.7; GC−MS (EI, *m/z*) calcd for $C_{10}H_{11}F_3O$ 204.08 (M^+, 100%), 205.08 (11.1%), found 204.07 (100%), 205.09 (11%).

4-(Trifluoromethyl)-2,4,6-trimethylcyclohexa-2,5-dienone (5). This compound could be separated by an additional flash column chromatography with pure toluene: R_f (toluene, $KMnO_4$ stain) = 0.4; ^{1}H NMR ($CDCl_3$, 300.1 MHz) δ 6.60 (s, 2H), 1.95 (s, 6H), 1.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 186.1, 139.9 (q, J = 16 Hz), 138.4, 126.3 (q, J = 283 Hz, CF_3), 45.6 (q, J = 27 Hz), 20.8 (q, J = 2 Hz), 16.7; ^{19}F NMR ($CDCl_3$, 188.3 MHz) δ −74.6; MS (HR-EI, *m/z*) calcd for $C_{10}H_{11}F_3O$ 204.0762 (M^+, 100%), found 204.0746 (100%).

2,4,6-Trimethyl-6-(trifluoromethyl)cyclohexa-2,4-dienone (6). This compound was part of the UV-active fraction of the first column chromatography (SiO_2, pentane/Et_2O = 20/1 to 15/1) and could be fully characterized by 1D and 2D NMR techniques and GC−MS: ^{1}H NMR ($CDCl_3$, 300.1 MHz) δ 6.70 (m, 1H), 5.85 (br s, 1H), 1.96 (s, 6H), 1.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 196.6 (q, J = 0.8 Hz), 141.9, 139.5, 125.0 (q, J = 284 Hz), 52.9 (q, J = 24.3 Hz), 21.5, 19.7 (q, J = 2 Hz), 15.3; ^{19}F NMR ($CDCl_3$, 188.3 MHz) δ −72.6; GC−MS (EI, *m/z*) calcd for $C_{10}H_{11}F_3O$ 204.08 (M^+, 100%), 205.08 (11.1%), found 204.05 (100%), 205.13.

2,4,6-Trimethyl-3,6-bis(trifluoromethyl)cyclohexa-2,4-dienone (7). This compound was part of the UV-active fraction of the first column chromatography (SiO_2, pentane/Et_2O = 20/1 to 15/1) and could be fully characterized by 1D and 2D NMR techniques and GC−MS: ^{1}H NMR ($CDCl_3$, 400.13 MHz) δ 6.0 (br s, 1 H), 2.16 (q, J = 4.3 Hz, 3H), 2.12 (m, 3H), 1.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 197.4, 137.2, 135.4, 131.0, 130.0, 124.9 (q, J = 281 Hz, *o*-CF_3), 53.1 (q, J = 65 Hz), 21.4, 19.5, 12.6; ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ −57.3 (qqd, J = 4.3, 2.9, 1.2 Hz,), −72.6; GC−MS (EI, *m/z*) calcd for $C_{11}H_{10}F_6O$ 272.06 (M^+, 100%), 273.07 (12.2%), found 272.03 (100%), 273.06 (12%).

1-(Trifluoromethoxy)-3-(trifluoromethyl)-2,4,6-trimethylbenzene. This compound was an impurity of the first fraction of the first column chromatography (SiO_2, pentane/Et_2O = 20/1 to 15/1) and could be fully characterized by 1D and 2D NMR techniques: ^{1}H NMR ($CDCl_3$, 400.13 MHz) δ 7.01 (br s, 1H), 2.47 (q, J = 3.7 Hz, 3H), 2.43 (m, 3H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 145.8, 136.0, 135.7, 133.4, 132.8, 127.5, 21.8, 17.1, 14.0; ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ −53.9 (m, Ar-CF_3), −56.4 (s, OCF_3).

2-Iodobenzoic Acid 3-(Trifluoromethyl)-2,4,6-trimethylphenyl ester (8). This compound was part of the UV-active fraction of the first column chromatography (SiO_2, pentane/Et_2O = 20/1 to 15/1) and could be further purified by a second chromatography (SiO_2, pentane/Et_2O = 20/1 to 15/1) and a third chromatography (SiO_2, hexane/toluene = 3/1 to 1/1): ^{1}H NMR ($CDCl_3$, 400.13 MHz) δ 8.16 (d, J = 7.8 Hz, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.52 (dd, J = 7.8, 7.4 Hz, 1H), 7.26 (dd, J = 8.0, 7.4 Hz, 1H), 7.02 (br s, 1H), 2.47 (q, J = 3.8 Hz, 3H), 2.33 (q, J = 2.9 Hz, 3H), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 163.8, 146.8, 142.1 135.0 (q, J = 2 Hz), 133.6, 133.2, 132.6, 131.5, 130.3 (q, J = 2 Hz), 128.2, 125.5 (q, J = 277 Hz, CF_3), 95.1, 21.5 (q, J = 4.5 Hz), 16.9, 13.6 (q, J = 4.2 Hz); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ −53.9 (qqd, J = 3.8, 2.9, 0.9 Hz); MS (HR-EI, *m/z*) calcd for $C_{17}H_{14}F_3IO_2$ 433.9991 (M^+, 100%), 435.0024 (18.9%), found 433.9987 (100%), 435.0025 (18.7%).

2,6-Dimethyl-4-(2,2,2-trifluoroethyl)phenol (9). 2,4,6-Trimethylphenol (50 mg, 0.367 mmol) was dissolved in 1 mL of CH_2Cl_2 and cooled to −20 °C. Reagent **3** (145 mg, 0.441 mmol) was added portionwise, and the mixture was slowly warmed to rt. After 4 days, the reagent could no longer be detected in the reaction mixture by ^{19}F NMR spectroscopy. Twenty microliters of BTF as internal standard was added, and the yield was calculated to be 49%. The mixture was concentrated and purified by flash column chromatography (SiO_2, pentane/Et_2O = 9:1 to 5:1) to give the title compound as colorless needles in 35% yield (27 mg). Further purification was possible by sublimation (16 mbar, 40 °C): R_f (hexane/EtOAc = 9/1) = 0.27; mp = 81−82 °C; ^1H NMR ($CDCl_3$, 300.13 MHz) δ 6.91 (s, 2H), 4.66 (s, 1H), 3.23 (q, *J* = 10.8 Hz, 2H), 2.25 (s, 6H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 152.5, 130.7, 126.4 (q, *J* = 276.6 Hz, CF_3), 123.7, 122.0 (q, *J* = 3.4 Hz), 39.8 (q, *J* = 29.5 Hz), 16.2; ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ −66.3 (t, *J* = 10.8 Hz); MS (HR-EI, *m/z*) calcd 204.0762 (M^+, 100%), 205.0796 (11.1%), found 204.0755 (100%), 205.0789 (11.6%). Anal. Calcd for $C_{10}H_{11}OF_3$: C, 58.82; H, 5.43. Found: C, 58.86; H, 5.61.

4-*tert*-Butyl-2-trifluoromethylphenol (10a). 4-*tert*-Butylphenol (119 mg, 0.791 mmol) was dissolved in DMF (2 mL) and deprotonated with NaH (19 mg, 0.791 mmol), and 18-crown-6 (209 mg, 0.791 mmol) was added. The mixture was cooled to −60 °C, and reagent **2** (100 mg, 0.316 mmol) was added in one portion. The reaction was heated slowly to rt overnight. DMF was evaporated, and the residue was extracted with hexane, which gave mainly 18-crown-6. The residue was therefore purified by flash column chromatography (SiO_2, hexane/Et_2O = 3:1) to give a mixture of starting phenol and compound **10a**. The two products could be separated by preparative HPLC (OD-H, hexane/isopropanol = 98:2): ^1H NMR ($CDCl_3$, 400.1 MHz) δ 7.48 (m, 1H), 7.44 (m, 1H), 6.89 (d, *J* = 8.6 Hz, 1H), 5.28 (br s, 1H), 1.31 (s, 9H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 144.0, 131.0, 123.5, 34.5, 31.7; ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ −60.5; MS (HR-EI, *m/z*) calcd for $C_{11}H_{13}F_3O$ 218.0918 (M^+, 100%), 219.0952 (12.2%), found 218.0915 (100%), 219.0946 (12.3%). NMR data are in agreement with the literature.[29]

2,6-Bis(trifluoromethyl)-4-*tert*-butylphenol (10b). This compound was obtained in the same reaction as **10a** but could not be isolated in pure form. It was idientified in the crude mixture by GC−MS (EI, *m/z*), calcd for $C_{12}H_{12}F_6O$ 286.08, found 286.09. NMR data are in agreement with the literature.[29]

2,6-Di-*tert*-butyl-4-trifluoromethylphenol (11a). 2,6-Di-*tert*-butylphenol (75 mg, 0.364 mmol) was dissolved in DMA and deprotonated with NaH (9.6 mg, 0.40 mmol), and 18-crown-6 (106 mg, 0.40 mmol) followed by reagent **2** (138 mg, 0.436 mmol) was added at rt. The mixture was heated to 60 °C for 24 h and then poured into diluted brine. The aqueous layer was extracted with Et_2O (3 × 10 mL), and the combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, pentane/Et_2O = 1:0 to 10:1) gave a 1:1 mixture of mono- and ditrifluoromethylated products in 15% yield (17 mg): ^1H NMR ($CDCl_3$, 300.1 MHz) δ 7.41 (s, 2H), 5.55 (s, 1H), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 156.5 (q, *J* = 1.4 Hz, C-OH), 136.2, 125.0 (q, *J* = 271 Hz, CF_3), 122.2 (q, *J* = 3.8 Hz), 121.5 (q, *J* = 32 Hz), 34.4, 30.1; ^{19}F NMR ($CDCl_3$, 282.4 MHz) δ −61.1; MS (HR-EI, *m/z*) calcd for $C_{15}H_{21}F_3O$ 274.1544 (M^+, 100%), 275.1578 (16.7%), found 274.1539 (100%), 275.1585 (18.8%).

4,4-Bis(trifluoromethyl)-2,6-di-*tert*-butylcyclohexa-2,5-dienone (11b). This compound was obtained in the same way as the monotrifluoromethylated di-*tert*-butylphenol, but the two products could not be separated by standard chromatography techniques: ^1H NMR ($CDCl_3$, 300.1 MHz) δ 6.53 (s, 2H), 1.27 (s, 18H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 184.1, 155.5, 124.9 (hept, *J* = 1.6 Hz), 52.7 (hept, *J* = 27 Hz), 35.8, 29.1; ^{19}F NMR ($CDCl_3$, 282.4 MHz) δ −69.7 (s, 6F); MS (HR-EI, *m/z*) calcd for $C_{16}H_{20}F_6O$ 342.1418 (M^+, 100%), found 342.1398 (100%).

4-Trifluoromethylindan-5-ol (12a). Indan-5-ol (106 mg, 0.791 mmol) was deprotonated using NaH (19 mg, 0.791 mmol) in 2 mL of DMF. 18-Crown-6 (209 mg, 0.791 mmol) was added, and the mixture was cooled to −60 °C. Reagent **2** (100 mg, 0.316 mmol) was added in one portion, and the mixture was slowly warmed to rt overnight. The yields were calculated from ^{19}F NMR using 10 μL of $C_6H_5CF_3$ as internal standard. The mixture was poured into water and extracted with EtOAc, and the combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated. Purification by column chromatography (SiO_2, hexane/EtOAc = 9:1) gave a mixture of starting phenol and the two monosubstituted products in one fraction. The two products could be separated by preparative HPLC (OD-H, hexane/isopropanol = 98.5:1.5) giving the title compound as colorless needles in 3.5 mg (5%) yield: ^1H NMR ($CDCl_3$, 400.1 MHz) δ 7.25 (d, *J* = 8.3 Hz, 1H), 6.77 (d, *J* = 8.3 Hz, 1H), 5.53 (s, 1H), 3.08 (m, 2H), 2.86 (t, *J* = 7.5 Hz, 2H), 2.11 (quint, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 152.8 (m), 144.0, 138.0, 129.0, 116.5, 33.3 (q, *J* = 2.6 Hz), 32.0, 25.7; ^{19}F NMR ($CDCl_3$, 282.4 MHz) δ −55.9; MS (HR-EI, *m/z*) calcd for $C_{10}H_9F_3O$ 202.0605 (M^+, 100%), 203.0639 (11.1%), found 202.0596 (100%), 203.0631 (14.1%).

6-Trifluoromethylindan-5-ol (12b). This compound was obtained in the same way as **12a** in 5% yield (3 mg) as colorless needles: ^1H NMR ($CDCl_3$, 400.1 MHz) δ 7.35 (s, 1H), 6.83 (s, 1H), 5.29 (s, 1H), 2.91 (t, *J* = 7.5 Hz, 2H), 2.88 (t, *J* = 7.5 Hz, 2H), 2.12 (quint, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 151.7 (q, *J* = 165 Hz), 151.2, 136.8, 122.3 (q, *J* = 5 Hz), 114.1, 33.5, 32.2, 26.0; ^{19}F NMR ($CDCl_3$, 282.4 MHz) δ −60.2; MS (HR-EI, *m/z*) calcd for $C_{10}H_9F_3O$ 202.0605 (M^+, 100%), 203.0639 (11.1%), found 202.0599 (100%), 203.0638 (10.6%).

4,6-Bis(trifluoromethyl)indan-5-ol (12c). Indan-5-ol (76 mg, 0.566 mmol) was dissolved in DMF (1 mL); NaH (14.9 mg, 0.623 mmol) and CsCl (105 mg, 0.623 mmol) were added, and the mixture was stirred for 15 min. Reagent **2** (215 mg, 0.68 mmol) was added in one portion at rt, and the reaction mixture was warmed to 50 °C and kept at this temperature for 24 h. The mixture was poured into water and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. Compound **12c** could be isolated by column chromatography (SiO_2, pentane/Et_2O = 20:1 to 4:1), the first fraction containing pure ditrifluoromethylated product in 5% yield (7.5 mg): ^1H NMR ($CDCl_3$, 400.1 MHz) δ 7.54 (s, 1H), 6.09 (q, *J* = 4 Hz, 1H), 3.11 (t, *J* = 7.5 Hz, 2H), 2.89 (t, *J* = 7.5 Hz, 2H), 2.13 (quint, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 151.3 (m), 148.8, 138.0, 126.2 (m), 125.1 (q, *J* = 275 Hz), 124.0 (q, *J* = 273 Hz), 117.4, 114.7, 33.7 (q, *J* = 3 Hz), 31.1, 25.5; ^{19}F NMR ($CDCl_3$, 282.4 MHz) δ −56.1 (m), −61.4 (s); MS (HR-EI, *m/z*) calcd for $C_{11}H_8F_6O$ 270.0479 (M^+, 100%), found 270.0474.

4-Trifluoromethyl-estra-1,3,5(10)-triene-3,17*β*-diol (13a). *β*-Estradiol (70 mg, 0.257 mmol) was suspended in DMF (1 mL) and deprotonated with NaH (6.8 mg, 0.283 mmol) giving a yellowish solution. 18-Crown-6 (75 mg, 0.283 mmol) followed by reagent **2** (98 mg, 0.308 mmol) was added at rt. The mixture was kept at rt for 4 h, then heated to 50 °C for 1 day and kept for additional 3 days at 60 °C, after which it was poured into water and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. Purification by column chromatography (SiO_2, hexane/EtOAc = 4/1 to 1/1 and a second hexane/Et_2O = 1/2) gave pure product in 13% yield (11 mg): ^1H NMR ($CDCl_3$, 300.1 MHz) δ 7.36 (d, *J* = 8.8 Hz, 1H), 6.79 (d, *J* = 8.8 Hz, 1H), 6.06 (q, *J* = 7.4 Hz, 1H), 3.74 (t, *J* = 8.4 Hz, 1H), 2.96 (m, 2H), 2.32−1.13 (m, 20H), 0.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 152.5 (q,

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J = 2.2 Hz), 137.3 (q, J = 1.4 Hz), 134.0, 130.5, 126.3 (q, J = 275.6 Hz, CF_3), 116.1, 113.1 (q, J = 26.4 Hz), 81.8, 50.0, 44.3, 43.2, 37.7, 36.7, 30.7, 26.8, 26.7, 23.0, 11.1; ^{19}F NMR ($CDCl_3$, 188.3 MHz) δ −52.6 (br s); MS (HR-EI, *m/z*) calcd 340.1650 (M^+, 100%), 341.1684 (21.1%), found 340.1645 (100%), 341.1688 (20.6%). Anal. Calcd for $C_{19}H_{23}O_2F_3$: C, 67.04; H, 6.81. Found: C, 66.77; H, 6.97.

2-Iodobenzoyl Fluoride (15). Reagent **2** (67 mg, 0.212 mmol) was dissolved in DMF-d_7, and 4-*tert*-butyl anisole (31.6 mg, 0.192 mmol) was added in one portion. After 1 h at rt, the mixture was heated to 60 °C for 1.5 h. The ^{19}F NMR spectrum of the crude reaction mixture showed quantitative decomposition of reagent **2** to 2-iodobenzoyl fluoride. This decomposition takes place also with catalytic (0.1 equiv) amounts of anisole. After aqueous workup and column chromatography (SiO_2, pentane/Et2O = 1/0 to 20/1), compound **15** could be isolated in 13% yield: ^{1}H NMR (DMF-d_7, 300.1 MHz) δ 8.44 (td, J = 7.9, 1.3 Hz, 1H), 8.30 (dd, J = 7.9, 1.7 Hz, 1H), 7.87 (dt, J = 7.9, 1.2 Hz, 1H), 7.69 (dt, J = 7.9, 1.7 Hz, 1H); ^{13}C NMR (DMF-d_7, 75 MHz) δ 155.7 (d, J = 345 Hz, COF), 142.9 (d, J = 3.8 Hz), 136.0, 133.7 (d, J = 1.9 Hz), 129.1, 128.6 (d, J = 60.9 Hz), 97.3 (d, J = 5.7 Hz); ^{19}F NMR (DMF-d_7, 282.4 MHz) δ 29.0; MS (HR-EI, *m/z*) calcd for C_7H_4FOI 249.9291 (M^+, 100%), 250.9324 (7.8%), found 249.9291 (100%), 250.9316 (7.4%).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds described in the Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

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