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On the Effect of Backbone Modifications in 3,3-Dimethyl-1-(trifluoromethyl)-3H-1 λ^3 ,2-benziodaoxole

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We report on the effect of small side-chain modifications to the structure of 3,3-dimethyl-1-(trifluoromethyl)-3*H*-1 λ ³,2benziodaoxole (**1b**) on its reactivity, as expressed by the initial rate v_0 in a model reaction, and show how the latter can be successfully correlated to an easily determined physical parameter *p*, a ¹³C NMR chemical shift. The relationship v₀ ~ *p* is already present in the simplest starting material devoid of the hypervalent bond and the iodine core and, therefore, presents an interesting approach towards the future scaffold-optimization of this class of reagents.

Introduction

Hypervalent iodine compounds have become increasingly popular in the synthetic community, as they provide a stable scaffold for several electrophilic-group transfer reactions. For example, recent years have seen the rise of electrophilic trifluoromethylating,^[1] alkynylating,^[2] and azidetransfer agents^[3] and their widespread applications in synthesis. To further establish this chemistry, fundamental information relating the reactivity of the reagent to the structure of the scaffold is desirable. In 2010, the first attempts were undertaken in this direction by comparison of the data derived from solid-state structures (bond lengths) and the initial rates (v_0) determined in the model reaction of *para*-toluenesulfonic acid (*p*TsOH) with a variety of structurally diverse electrophilic trifluoromethylating reagents (Scheme 1).^[4]

Although vague trends could be elucidated, no simple descriptor correlating with the reactivity v_0 was found that would allow for a directed optimization of the scaffold. For example, the I–Cl bond lengths in the precursor chloro-iodinanes **1a–6a** are loosely associated with the I–CF₃ bond lengths in the final reagents **1b–6b**. More recently, a reexamination of the original data suggested that the difference in the I–X (X = Cl or CF₃) and I–O bond lengths, $\Delta_{I-X/I-O}$, is a suitable measure of the reactivity as it reflects the bonding

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CF_3 sources (X = CF_3)



Model reaction

pTsOH CF_3 source pTsOCF₃

Scheme 1. Hypervalent iodine trifluoromethylating agents **1b–6b** and model reaction for the assessment of their reactivity.

situation in the hypervalent motif.^[1b] In particular, when comparing two reagents, a larger $\Delta_{I-X/I-O}$ value corresponds to lower p character of the I–X bond and, thereby, leads to a more-labile reagent. Unfortunately, however, the previously reported reagents **1b–6b** are structurally too diverse to be described by a tabulated classical physicochemical parameter.

Therefore, an additional small library was required with modifications to the backbone minimal such that the Taft inductive parameters σ^* could be used to adequately describe these new structures and uncover a relationship of the form $\sigma^* \sim p.^{[5]}$ Therein, *p* is an easily determined, structure-related parameter, for example, a specific chemical shift, that accurately describes the electronic features of the reagent. Ideally, *p* should be solution-phase-based to circumvent the problems associated with crystal-structure-

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based reactivity analysis such as errors caused by packing effects (vide infra). Consequently, by determining p for all available reagents, including **1b–6b**, and comparing p versus the initial rates v_0 observed in the model trifluoromethylation of pTsOH, a structure–reactivity relationship should result and unveil the impact of backbone modifications.

Results and Discussion

Synthesis of Reagents 7d-10d

The key iodinated alcohols 7b–11b were accessed by a slightly modified Seebach ortho-lithiation protocol starting from the tertiary alcohols 7a-11a (Scheme 2).^[6] Hence, bromobenzene was lithiated with *n*BuLi in tetrahydrofuran (THF) at -78 °C and quenched with the appropriate ketone to afford the desired alcohols in good-to-excellent yields (Table 1). Subsequently, 7a-11a were treated with nBuLi and tetramethylethylenediamine (TMEDA) overnight. After the further addition of *n*BuLi and stirring at room temperature, the reactions were quenched with solid iodine. Whereas the polarities of alcohols 7a-11a and the corresponding iodine-functionalized compounds 7b-11b are almost identical and, therefore, render chromatographic purification tedious, the differences in the boiling points by ca. 50 °C render the products amenable to purification by distillation. Consequently, column chromatography was only applied for smaller-scale experiments (<2 g of starting material) and fractional high-vacuum distillation was employed for larger-scale experiments (ca. 10 g of starting material). Thus, iodoalcohols **7b–11b** were obtained in 11–38% yield (Table 1).



Scheme 2. Synthesis of reagents 7d-10d.

Table 1. Yields for the syntheses of 7d-10d and 11c.

$\overline{\mathbb{R}^1}$	a [%] ^[a]	b [%]	c [%]	d [%]	Overall [%]
Et (7)	87	28	75	61	11
<i>n</i> Pr (8)	78	36	86	35	8
<i>i</i> Bu (9)	85	29	80	55	11
<i>i</i> Pr (10)	90	38	70	58	14
Cv (11)	90	11	73	_	7 ^[b]

[a] The descriptors **a**, **b**, **c**, and **d** refer to the explicit structures of 7–11, for example, 7**a**, 7**b**, and so on. [b] Overall yield over three steps to 11**c**.

The oxidations of **7b–11b** to the corresponding 1-chloro- $1\lambda^3$,2-benziodaoxoles (7c–11c) with tBuOCl in dichloromethane (DCM) at 0 °C again proceeded smoothly in 73-86% yield (Table 1).^[1a] Finally, the introduction of the CF₃ moiety was achieved through in situ preparation of the corresponding 1-fluoro- $1\lambda^3$,2-benziodaoxoles by treatment of 7c-10c with a large excess of anhydrous KF in dry MeCN overnight, followed by the addition of Ruppert-Prakash reagent [trifluoromethyltrimethylsilane (TMSCF₃)] at 0 °C.^[7] Then, the crude reagents 7d–10d were purified by high-vacuum sublimation followed by recrystallization from pentane at low temperature to afford the pure products in 35–61% yield (Table 1). 1-Chloro- $1\lambda^3$,2-benziodaoxole **11c** was not further converted into the corresponding reagent, as only small amounts were available owing to the poor yield of the ortho-iodination (11%). Thus, four new reagents (7d-10d) were accessed with overall yields of 8-14% over four steps. The ortho-iodination was found to be a limiting factor but still outperformed strategies relying either on Grignard additions to 2'-iodoacetophenone or metalation of 1,2-diiodobenzene followed by quenching with appropriate ketones. Overall, the reagents 7d-10d were accessed in gram amounts, sufficient for additional kinetic studies.

X-ray Analysis of Chlorides 7c-11c

Compounds **7c–11c** were subjected to solid-state analysis by X-ray crystallography, as the bond length difference $\Delta_{I-CI/I-O}$ was previously proposed as a rough measure of reactivity.^[1b] Gratifyingly, suitable crystals were readily grown by the vapor diffusion of pentane into saturated solutions of the chlorides in diethyl ether. The important bond lengths I–Cl and I–O, $\Delta_{I-CI/I-O}$, and the O–I–Cl bond angle are given in Table 2, and ORTEP representations are shown in Figure 1.

Table 2. Bond lengths, bond length differences, and angles of 7c-11c.

R^1	I–O [Å]	I–Cl [Å]	$\Delta_{I-C1/I-O}$ [Å]	0–I–Cl [°]
Et (7c) ^[a]	2.043(5)	2.5343(17)	0.491	170.41(15)
	2.043(4)	2.544(16)	0.501	171.80(14)
<i>n</i> Pr (8c)	2.046(5)	2.5350(19)	0.489	171.51(16)
<i>i</i> Bu (9c) ^[a]	2.043(6)	2.533(2)	0.490	171.39(18)
	2.031(6)	2.543(2)	0.512	172.12(18)
<i>i</i> Pr (10c)	2.0433(16)	2.527(17)	0.484	171.87(5)
Cy (11c) ^[a]	2.047(2)	2.5422(10)	0.495	171.29(7)
	2.057(2)	2.5131(10)	0.456	172.01(8)

[a] Asymmetric unit contains two independent molecules.

A comparison of the bond lengths and $\Delta_{I-CI/I-O}$ values presented in Table 2 with those of the standard reagent **1a** [I–O 2.042(2) Å, I–Cl 2.5491(8) Å, $\Delta_{I-CI/I-O} = 0.507$ Å] reveals no special deviations. Indeed, whereas the reported $\Delta_{I-CI/I-O}$ descriptors for structures **3a–6a** range from 0.328 Date: 12-02-15 13:22:46

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Figure 1. ORTEP representations of 7c-11c. Hydrogen atoms are omitted for clarity, and thermal ellipsoids are set to 50% probability.

to 0.548 Å, the corresponding values for **7c–11c** display a narrower distribution around (0.490 ± 0.016) Å. Moreover, neither the electronic nature of the substituent R¹ (Et/nPr/*i*Bu vs. *i*Pr/Cy) nor its steric bulk (Et/nPr<*i*Pr/Cy<*i*Bu) seem to affect these values or the O–I–Cl angles significantly. On the basis of this qualitative comparison, the reagents **7d–10d** are expected to be as reactive as the standard reagent **1b** in the electrophilic trifluoromethylation of *para*-toluenesulfonic acid (Scheme 1).

Interestingly, **7c**, **9c**, and **11c** have two independent molecules in their asymmetric units. Short van der Waals contacts between I^1 – O^2 and I^2 – O^1 of 2.88/2.84, 2.79/2.76, and 2.92/2.87 Å, respectively, suggest that the iodine cores are stabilized through the coordination of an additional oxygen ligand to yield four-coordinate hypervalent iodine(III) species (Figure 2). In addition, the two molecules in the asymmetric unit of **11c** form a homodimer (*S/S* or *R/R*) with the cyclohexyl rings oriented in a parallel fashion. This may grant further stabilization by van der Waals contacts (Figure 2). However, as these packing effects cannot be directly quantified, the errors that affect reactivity predictions derived from solid-state structural parameters are unknown and, consequently, small differences in reactivity may be obscured.



Figure 2. ORTEP representation of the asymmetric unit of **11c**. Hydrogen atoms are omitted for clarity, and thermal ellipsoids are set to 50% probability. Short van der Waals contacts of 2.92 and 2.87 Å are found between I^1 – O^2 and I^2 – O^1 , respectively. The parallel orientation of the cyclohexyl rings suggests that there is further van der Waals stabilization.

Parameter p

In search for a solution-phase parameter, p, to correlate to the reactivity of the reagents **1b**, **3b–6b**, and **7d–10d**, we turned to ¹³C NMR spectroscopic data. Although structural diversity is present, two carbon atoms in proximity to the reactive center can be identified as a common element in all structures: the aryl carbon atom (C_{ipso}) attached to the iodine core and the quaternary carbon atom (C_{meso}) of the alkoxide ligand (Figure 3). Although " C_{meso} " in **6b** is a homobenzylic position, it will be referred to as the *meso* position for simplicity and consistency.



Figure 3. The common carbon atoms found in all reagents are labeled C_{ipso} and C_{meso} .

Thus, we first investigated whether the ¹³C NMR shifts for C_{ipso} and C_{meso} in **1b** and **7d–10d** can be described as a function of the reported Taft inductive parameter (σ^*) and the Taft steric parameter (E_S) of R^{1.[5a]} If applicable, this would allow the description of all available structures by an readily determined quantity. However, the initial consideration of the C_{ipso} data dismissed this carbon atom as a valid descriptor as, irrespective of R¹, roughly the same chemical shift was found [$\delta = 110.6-111.2$ ppm, maximal $\Delta \delta_{inso}$ (CF₃)

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= 0.6 ppm]. Thus, we concentrated on C_{meso} as a more promising candidate with a maximal $\Delta \delta_{meso}$ (CF₃) = 4.8 ppm between R¹ = *i*Pr and R¹ = Me. In Table 3, a summary of all relevant ¹³C NMR spectroscopic data is presented, and δ_{meso} (X) refers to the chemical shift of the *meso*-carbon atom in the (trifluoromethyl)iodinanes (X = CF₃, e.g., 7d), chloroiodinanes (X = Cl, e.g., 7c), iodoalcohols (X = I, e.g., 7b), or parent noniodinated benzyl alcohols (X = H, e.g., 7a).

Multidimensional regression analysis according to $\delta_{meso}(CF_3) = \delta_1 \cdot \sigma^* + \delta_2 \cdot E_S + \delta_3$ for the data set consisting of **1b** and **7d–10d** delivered the row vector $(\delta_1, \delta_2, \delta_2) = (-26.2, -0.1, 76.5)$ with $R^2 = 0.98$; this analysis implies that δ_2 (sterics) has a less-pronounced effect on the prediction than δ_1 (electronics; Figure 4, A). In addition, a simpler linear model including only the electronic term, $\delta_{meso}(CF_3) = \delta_1 \cdot \sigma^* + \delta_2$, produced $(\delta_1, \delta_2) = (-24.7, 76.5)$ with $R^2 = 0.94$ for the same data set. Therefore, both models suggest a direct relationship between the Taft parameter and the ¹³C NMR chemical shift of C_{meso} in (trifluoromethyl)iodinanes; hence, $\delta_{meso}(CF_3)$ may be utilized as a measure *p* for the electronic and steric environments in all reagents examined (**1b**, **3b–6b**, **7d–10d**). Importantly, a comparison of the bond length differences $\Delta_{I-CI/I-O}$ in **7c–10c** with the correspond-

Table 3. Compilation of ${}^{13}C_{meso}$ NMR spectroscopic data for compound series 1 and 7–11.

	1b	7d	8d	9d	10d	11d
$\delta_{ipso}(CF_3)$ [ppm] $\delta_{meso}(CF_3)$ [ppm]	110.6 76.5	111.2 79.2	111.0 79.1	110.8 79.6	111.0 81.3	_
	1a	7c	8c	9c	10c	11c
δ_{meso} (Cl) [ppm]	85.2	87.8	87.7	88.2	88.8	89.8
	12 ^[a]	7b	8b	9b	10b	11b
$\delta_{meso}(I)$ [ppm]	73.6	76.2	76.0	76.4	78.0	77.9
	13 ^[b]	7a	8a	9a	10a	11a
$\delta_{\text{max}}(\text{H})$ [ppm]	72.4[8]	75.1	74.8	75.4	76.9	76.8

[a] Compound **12** is 2-(2-iodophenyl)propan-2-ol. [b] Compound **13** is 2-phenylpropan-2-ol.

ing values for **1b** did not reveal any impact of the electronic or steric nature of \mathbb{R}^1 (vide supra). However, ¹³C NMR spectroscopic analysis clearly distinguishes between the individual side chains and is, therefore, considered a more accurate methodology. Moreover, the data presented in Table 3 also suggests that the relationship $\delta_{meso}(X) \sim \sigma^* + E_S$ is already present in the simple alcohol precursors **7a**– **11a** (X = H).



Figure 4. Graphic representation of the data listed in Table 3. The data were correlated to the Taft electronic (σ^*) and steric (E_s) parameters according to $\delta_{meso}(X) = \delta_1 \cdot \sigma^* + \delta_2 \cdot E_s + \delta_3$, and the results presented in row vector form as (δ_1 , δ_2 , δ_2). The dashed lines are projections to the $\sigma^* - \delta_{meso}(X)$ plane ($\delta_2 = 0$).



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A graphical depiction of these findings is given in Figure 4, in which projections onto the $\delta_{meso}(X)$ versus σ^* plane are presented by choosing $\delta_2 = 0$. The full row vectors $(\delta_1, \delta_2, \delta_2)$ for the two-dimensional fits and the R² values are presented in the lower left corners, and the general compound structures are given in the upper right corners of Figure 4 (A–D). Irrespective of the specific structure of the compounds analyzed, good correlations between the ¹³C NMR spectroscopic data and the Taft parameters were found. Most intriguingly, on the basis of these results, the hypothesis that the $\delta_{meso}(H)$ values of starting alcohols **7a–11a** can be used to describe the reactivity v_0 of the final reagents can be formulated.

The Correlation $\delta_{meso}(\mathbf{X}) \sim v_0$

As suggested by the analysis presented above, the ¹³C NMR chemical shift $\delta_{meso}(X)$ may be a suitable solutionphase parameter to describe the reactivity of reagents 1b, **3b–6b**, and **7d–10d**. Thus, to further test this hypothesis, the initial rates v_0 for 7d–10d for the electrophilic trifluoromethylation of para-toluenesulfonic acid were obtained (Scheme 1, further details concerning the experimental setup and data processing can be found in the Supporting Information).^[4] Each set of experiments was repeated at least three times to ensure reproducibility and allow for error estimation. Hence, the v_0 values for 1b and 7d–10d were obtained with relative uncertainties of 5.5 to 10.5%. A summary of the initial rates for 1b, 3b-6b, and 7d-10d, standard deviations (σ) if available, and the ¹³C NMR chemical shift $\delta_{meso}(H)$ for the noniodinated parent alcohols, such as 7a-11a, is provided in Table 4.

Table 4. Compilation of ¹³C NMR shifts $\delta_{meso}(H)$ of noniodinated parent alcohols, initial rates v_0 , standard deviations, and predicted initial rates v'_0 .

$\begin{array}{c c c c c c c c c c c c c c c c c c c $					
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	Reagent	$\delta_{meso}(H)$ [ppm]	$v_0 [{ m M s}^{-1}]$	σ [M s ⁻¹]	$v'_0 [{ m M}{ m s}^{-1}]^{[a]}$
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	1b	72.4 ^[8]	4.69×10^{-7}	4.92×10^{-8}	3.96×10^{-7} (0.84)
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	3b	78.8	$1.2 \times 10^{-7[4a]}$	_	$1.09 \times 10^{-7} (0.91)$
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	4b	73.1 ^[9]	$3.4 \times 10^{-7[4a]}$	_	3.44×10^{-7} (1.01)
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	5b	76.4 ^[10]	$5.3 \times 10^{-6[4a]}$	_	$1.76 \times 10^{-7} (0.03)$
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	6b	72.3	$9.4 \times 10^{-7[4a]}$	_	4.05×10^{-7} (0.43)
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	7d	75.1	2.17×10^{-7}	1.87×10^{-8}	2.30×10^{-7} (1.06)
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	8d	74.8	1.99×10^{-7}	1.97×10^{-8}	2.44×10^{-7} (1.23)
10d 76.9 1.65×10^{-7} 9.05×10^{-9} 1.59×10^{-7} (0.96)	9d	75.4	2.21×10^{-7}	1.47×10^{-8}	2.16×10^{-7} (0.98)
	10d	76.9	1.65×10^{-7}	9.05×10^{-9}	1.59×10^{-7} (0.96)

[a] The v'_0/v_0 ratio is given in parentheses.

An inspection of v_0 for **7d–10d** reveals that, contrary to the initial prediction based on $\Delta_{I-Cl/I-O}$ for **7c–10c** (Table 2), there is a clear order of reactivity: **1b** (R¹ = Me) > **7d** (R¹ = Et)/**8d** (R¹ = *n*Pr)/**9d** (R¹ = *i*Bu) > **10d** (R¹ = *i*Pr). Further analysis of the subset **7d–9d** also suggests that the steric demand of R¹ has a negligible effect on the reactivity (σ^* : Et $\approx n$ Pr $\approx i$ Bu, E_S : Et $\approx n$ Pr >> *i*Bu). Finally, a plot of v_0 versus δ_{meso} (H) delivers Figure 5 (A). As ¹³C_{meso} in **5b** is a double-benzylic position and ¹³C_{meso} in **6b** is a tertiary alkyl position, both data points constitute structural outliers and will be neglected in the following analyses. The reduced data set consisting of 1b, 3b-4b, and 7d-10d suggests that there is a nonlinear relationship between the reactivity and the chemical shift of the meso-carbon atom (Figure 5, B). The curvature is understood on the basis of the relationship $\delta_{meso}(X) \sim \sigma^*$ with the small steric contribution neglected (vide supra). Therefore, the Taft equation $\log(k/k_0) = \rho^* \cdot \sigma^*$ with $\delta = 0$ can be rewritten to $\log(v_0/M s^{-1}) \sim \rho^* \cdot \delta_{meso}(X)/\delta$ ppm and an exponential fit to the data proposed (dashed line). Indeed, a plot of $\log(v_0/M s^{-1})$ versus δ_{meso} (H)/ppm and a fit according to a linear model delivered $\log(v_0/M s^{-1}) =$ $-(8.79 \pm 1.04) \times 10^{-2} \cdot \delta_{meso}$ (H)/ppm $- (3.78 \pm 77.9) \times 10^{-2}$ with $R^2 = 0.94$. Furthermore, analysis of the differences between the predicted and actual values (residuals) further corroborated the goodness of fit, and there was no clear relationship between $\delta_{meso}(H)$ and the residuals. The deviations of the predicted initial rates v'_0 from the measured v_0 values, as measured by the ratio v'_0/v_0 , are in the range 0.84 to 1.23 for 1b, 3b-6b, and 7d-10d (Table 4). As expected, however, the reactivities of reagents 5b and 6b are underestimated by factors of 0.43 and 0.03. A likely explanation for the reactivity of **6b** is found in its solid-state structure, in which the alkoxide ligand at the iodine atom is part of a six-membered ring that adopts an energetically unfavorable half-chair conformation.^[4a]



Figure 5. The chemical shifts $\delta_{meso}(H)$ and the reactivities v_0 correlate exponentially (B) if the initial data set (A) is reduced by removing outliers **5b** and **6b**.

Therefore, the initial hypothesis that the $\delta_{meso}(H)$ values of the parent alcohols devoid of iodine may serve as a solution-phase descriptor *p* for the reactivity (v_0) of hypervalent-iodine-based trifluoromethylating agents was verified, although some restrictions apply. An additional phenyl group should not be attached to the *meso*-carbon atom, and the I–O bond of the hypervalent interaction should be part of a five-membered ring, as in the original reagent **1b**, to allow for an accurate prediction.

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Considering the electronic nature of the individual substituents, one identifies the general trend that reagents featuring a more-electron-donating substituent are less reactive and feature lower initial rates v_0 in the model reaction (Figure 5, B). For example, the standard reagent **1b** (R¹ = Me, $\sigma^* = 0$) reacts 2.8 times faster than the slightly electronricher reagent **10d** (R¹ = *i*Pr, $\sigma^* = -0.19$). Moreover, the introduction of the strongly electron-withdrawing NO₂ group ($\sigma^* = 4.66$) *para* to the iodine atom in reagent **2b** leads to increased labilization of the hypervalent bond under acidic conditions.^[11] This further substantiates that electron-releasing substituents are generally expected to lead to diminished reactivity.

On first sight, however, on the understanding that the trifluoromethyl group is strongly electron-withdrawing (σ^* = 2.00-3.00), the bis-trifluoromethyl derivative **3b** does not satisfy this criterion as it reacts 3.9 times slower than 1b. However, in 1967, Pople and Gordon noted that fluorine does not display a standard halogen-inductive effect, as shown in Figure 6 (A), that is, it does not lead to a decreasing positive polarization (black) along an alkyl chain.^[12] Instead, alternating charges along the chain are found such that the β and δ carbons feature a partial negative charge (grey), contrarily to the intuitively expected positive one (Figure 6, B). Holmes et al. also observed this effect experimentally for the CF₃ moiety in (trifluoromethyl)benzene model systems (Figure 6, C).^[13] Indeed, a consideration of the structure of **3b** reveals that C_{meso} is at the β position relative to the fluorine substituents. Hence, on the basis of these considerations, Cmeso would feature a (small) negative partial charge owing to the six electron-donors and, therefore, further corroborate the overall observed trend.



Figure 6. Fluorine displays a nonintuitive inductive effect such that an alkyl chain is polarized alternatively (B) rather than linearly (A). Therefore, reagent **3b** features a comparably electron-rich C_{meso} atom, which accounts for its low reactivity.

Conclusions

Four new electrophilic trifluoromethylating agents (7d– 10d) were accessed through the formal replacement of a methyl group in 3,3-dimethyl-1-(trifluoromethyl)-3*H*-1 λ^3 ,2benziodaoxole (1b) by different alkyl chains. Subsequently, by relating the ¹³C NMR chemical shifts to the Taft inductive parameter σ^* , $\delta_{meso}(X)$ was identified as a suitable solution-phase parameter *p* to adequately describe the reactivity of a reagent in a model trifluoromethylation reaction, as measured by the initial rate v_0 . In stark contrast to predictions derived from solid-state structures, this method allowed the reactivities of 1b and 7d–10d to be distinguished clearly. Furthermore, the predicted reactivities v'_0 for reagents 1b, 3b–4b, and 7d–10d were in excellent agreement with the experimentally determined ones. For two reagents, 5b and 6b, v'_0 was underestimated by factors of 0.43 and 0.03, respectively; this underestimation is attributable to significant variations in the molecular structures of these reagents compared with that of reference compound 1b. Most intriguingly, however, the correlation $\delta_{meso}(X) \sim v_0$ already exists at the earliest stage of the synthesis (X = H) and, thereby, allows for future optimization studies of the scaffold before the actual reagents are accessed. On the basis of these findings, endeavors towards the synthesis of morereactive structures are ongoing and will be reported in due course.

Experimental Section

General: Reactions with moisture-sensitive chemicals were conducted under an atmosphere of argon by using Schlenk techniques. High-vacuum (HV) refers to a pressure of less than 0.01 mbar. Dry solvents refer to solvents distilled before use either from CaH₂ (MeCN) or from Na/benzophenone (THF). All commercially available chemicals were used without further purification. Chromatographic purification was performed with silica gel 60 (230-400 mesh) from Fluka or MP Alumina B, Act. I from MP Biomedicals Germany GmbH. TLC plates were obtained from Merck (silica gel 60 F₂₅₄). The NMR spectra were recorded with Bruker DPX 300, DPX 400, Avance III HD Nanobay-300, and Avance III HD Nanobay-400 spectrometers. The ¹H and ¹³C NMR chemical shifts are referenced to residual solvent signals. The ¹⁹F NMR chemical shifts are referenced to external CFCl₃. Mass spectra (EI, ESI, MALDI) were recorded by the MS service of the Laboratory of Organic Chemistry (ETH Zurich). Elemental analyses were performed by the Laboratory of Microelemental Analysis (ETH Zürich). Melting points were determined with a Büchi Melting Point B-540 apparatus.

CCDC-1031953 (for 7c), -1031954 (for 8c), -1031955 (for 9c), -1031956 (for 10c), and -1031957 (for 11c) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

2-Phenylbutan-2-ol (7a): A heat-gun-dried 500 mL three-necked round-bottomed flask equipped with a magnetic stirring bar, an argon inlet, a pressure-equalized dropping funnel, and a rubber septum was charged with bromobenzene (16 mL, 0.15 mol, 1 equiv.) and THF (300 mL, pro Analysis). The solution was cooled to -78 °C (dry ice/acetone), and nBuLi (100 mL, 1.6 M, 0.15 mol, 1.05 equiv.) was slowly added by cannula transfer to yield a pale vellow solution, which was stirred at -78 °C for an additional 2 h. Then, butan-2-one (16.4 mL, 0.18 mol, 1.2 equiv.) in THF (20 mL, pro Analysis) was added dropwise over 15 min, and the mixture was warmed to ambient temperature overnight (16 h). The reaction mixture was diluted with diethyl ether (200 mL) and washed with distilled water (500 mL). The aqueous layer was back-extracted twice with diethyl ether (2 \times 500 mL), and the combined organic layers were concentrated under reduced pressure. The crude product was then purified by high-vacuum distillation (75 °C bath temperature, 40-50 °C vapor temperature, 0.05 mbar) to afford the product (19.9 g, 87%) as a viscous colorless oil. The spectroscopic data agree with those previously reported.^[10] ¹H NMR (400 MHz, CDCl₃): δ = 7.48–7.45 (m, 2 H), 7.39–7.35 (m, 2 H), 7.29–7.25 (m,

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1 H), 1.93–1.82 (m, 2 H), 1.81 (s, 1 H), 1.58 (s, 3 H), 0.83 (t, J = 7.4 Hz, 3 H) ppm. ¹³C NMR (101 MHz, CDCl₃): $\delta =$ 147.9, 128.2, 126.6, 125.0, 75.1, 36.8, 29.7, 8.4 ppm.

2-(2-Iodophenyl)butan-2-ol (7b): A heat-gun-dried 500 mL threenecked round-bottomed flask equipped with a magnetic stirring bar, an argon inlet, a pressure-equalized dropping funnel, and a rubber septum was charged with nBuLi (200 mL, 1.6 M, 0.32 mol, 2.5 equiv.) and TMEDA (4.8 mL, 32 mmol, 0.25 equiv.). The resulting solution was stirred for 45 min at ambient temperature to afford an off-white suspension that was subsequently cooled to 0 °C (ice bath). Then, 7a (19.2 g, 0.13 mol, 1 equiv.) in hexane (60 mL, pro Analysis) was added over the course of 60 min, and the mixture was slowly warmed to ambient temperature (16 h). Additional nBuLi (100 mL, 1.6 M, 0.16 mol, 1.25 equiv.) was added, and stirring was continued for 24 h. Finally, the orange solution was cooled to 0 °C (ice bath), and solid iodine (100 g, 0.39 mol, 3.1 equiv.) was added under vigorous stirring. Then, the mixture was warmed to ambient temperature over the course of 60 h. The resulting brown mixture was washed with aqueous sodium thiosulfate (50 wt.-%, 500 mL), and the aqueous layer was backextracted with diethyl ether (2×500 mL). The combined organic layers were concentrated under reduced pressure. Two subsequent fractional high-vacuum distillations (170 °C bath temperature, 80-95 °C vapor temperature, 0.02 mbar) afforded the product (9.8 g, 28%) as a viscous yellow oil. ¹H NMR (400 MHz, CDCl₃): δ = 7.97 (d, J = 7.47 Hz, 1 H), 7.64 (dd, J = 8.0, 1.2 Hz, 1 H), 7.34– 7.30 (m, 1 H), 6.90–6.86 (m, 1 H), 2.33 (dq, J = 14.5, 7.3 Hz, 1 H), 2.04 (s, 1 H), 2.00 (dq, J = 14.5, 7.3 Hz, 1 H), 1.72 (s, 3 H), 0.80 (t, J = 7.4 Hz, 3 H) ppm. ¹³C NMR (101 MHz, CDCl₃): $\delta = 147.9$, 142.9, 128.6, 128.1, 128.0, 93.1, 76.2, 33.7, 27.95, 8.5 ppm. HRMS (EI): calcd. for C₁₀H₁₃IO [M]⁺ 276.0006; found 276.0009.

1-Chloro-3-ethyl-3-methyl-3H-1³,2-benziodaoxole (7c): Compound 7b (9.8 g, 35 mmol, 1 equiv.) was dissolved in DCM (80 mL, pro Analysis) in a round-bottomed flask wrapped in aluminum foil. The resulting solution was cooled to 0 °C (ice bath), tBuOCl (4.1 mL, 36.4 mmol, 1.04 equiv.) was added in one portion, and the mixture was slowly warmed to ambient temperature overnight (16 h). The neon-yellow solution was concentrated under reduced pressure, and the resulting residue was washed with pentane to afford the product (8.3 g, 75%) as a yellow solid. X-ray quality crystals were obtained by the vapor diffusion of pentane into a saturated ethyl acetate solution at 4 °C; m.p. 100-102 °C. ¹H NMR (400 MHz, CDCl₃): δ = 8.03 (dd, J = 8.0, 0.7 Hz, 1 H), 7.57 (td, J = 7.6, 1.5 Hz, 1 H), 7.52 (td, J = 7.3, 0.8 Hz, 1 H), 7.10 (dd, J =7.3, 1.5 Hz, 1 H), 1.93 (dq, J = 14.4, 7.3 Hz, 1 H), 1.80 (dq, J = 14.4, 7.2 Hz, 1 H), 1.49 (s, 3 H), 0.88 (t, J = 7.4 Hz, 3 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 148.8, 130.9, 130.6, 128.6, 126.8, 115.1, 87.8, 35.2, 27.8, 8.3 ppm. HRMS (EI): calcd. for C₉H₉ClIO $[M - CH_3]^+$ 294.9382; found 294.9383. $C_{10}H_{12}CIIO$ (310.56): calcd. C 38.68, H 3.89; found C 38.42, H 3.93.

3-Ethyl-3-methyl-1-(trifluoromethyl)-3H-1\lambda^3,2-benziodaoxole (7d): Potassium fluoride (2.2 g, 37.9 mmol, 2.9 equiv.) was added to a Schlenk flask and flame-dried under high-vacuum. Then, 7c (4 g, 12.9 mmol, 1 equiv.) was added under an argon counterflow, and the solids were suspended in dry MeCN (72 mL) and stirred vigorously for 62 h at ambient temperature. The resulting white suspension was cooled to 0 °C (ice bath), and Ruppert–Prakash reagent (TMSCF₃, 4.2 mL, 28.4 mmol, 2.2 equiv.) was added in one portion. Stirring was continued for 1 h at 0 °C, and then the brown

mixture was vacuum-filtered through a densely packed Celite pad. The latter was washed with additional MeCN, and the combined organic phases were concentrated under reduced pressure. The brown residue was dissolved in pentane (pro Analysis) and vacuum-filtered through neutral alumina, and the resulting solution was concentrated to dryness. The solid obtained was then subjected to high-vacuum sublimation (30 °C, 0.02 mbar) and finally recrystallized from pentane at -17 °C to afford the product (2.7 g, 61%) as colorless crystals; m.p. 77-78 °C. ¹H NMR (300 MHz, CDCl₃): $\delta = 7.55 - 7.50 \text{ (m, 2 H)}, 7.45 - 7.39 \text{ (m, 1 H)}, 7.33 - 7.30 \text{ (m, 1 H)},$ 1.85 (dq, J = 14.8, 7.4 Hz, 1 H), 1.74 (dq, J = 14.0, 7.4 Hz, 1 H), 1.43 (s, 3 H), 0.80 (t, J = 7.4 Hz, 3 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 148.1, 130.6, 130.0, 128.0, 127.9 (q, $J_{C,F}$ = 2.8 Hz), 111.2 (q, $J_{C,F} = 3.1 \text{ Hz}$), 110.5 (q, $J_{C,F} = 395.9 \text{ Hz}$), 79.2, 36.6, 29.8, 8.4 ppm. ¹⁹F NMR (282 MHz, CDCl₃): δ = -40.1 ppm. HRMS (EI): calcd. for $C_9H_7F_3IO [M - C_2H_5]^+$ 314.9489; found 314.9485. C11H12F3IO (344.11): calcd. C 38.39, H 3.51; found C 38.47, H 3.52.

Supporting Information (see footnote on the first page of this article): full experimental data including copies of NMR spectra of all new compounds.

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FULL PAPER

The reactivity of hypervalent-iodine-based trifluoromethylating agents, as expressed by the initial rate v_0 in a model reaction, correlates to an easily determined physical parameter *p*, a ¹³C NMR chemical shift.



Reactivity Patterns

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On the Effect of Backbone Modifications in 3,3-Dimethyl-1-(trifluoromethyl)-3*H*- $1\lambda^3$,2-benziodaoxole

Keywords: Hypervalent compounds / Kinetics / Reactivity predictions / Electrophilic addition / Iodine / Trifluoromethylation

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