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Reactivity of Electrophilic Trifluoromethylating Reagents

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Kinetics of the reactions of colored carbanions (reference nucleophiles) with *S*-(trifluoromethyl)dibenzothiophenium ions (Umemoto's reagents) and hypervalent trifluoromethyl-substituted iodine compounds (Togni's reagents) have been determined photometrically using stopped-flow techniques. The second-order rate constants k_2(20 °C) for the reactions of Umemoto's sulfonium ions (generation I and II) with the reference nucleophiles in DMSO follow the correlation $\lg k_2(20\,°C) = s_N(N+E)$ and can be used to determine the electrophilicity parameters *E* of these trifluoromethylating reagents. It is shown that the conditions reported for the reactions of Umemoto's generation I reagents with a variety of C-nucleophiles are in line with the electrophilicity parameter $E \approx -13$ determined for these reagents. Though Togni's hypervalent iodine-based trifluoromethylation reagents do not follow this linear free energy relationship, the kinetics of their reactions with carbanions indicate that they cover the same reactivity range as Umemoto's generation I and II reagents.

Introduction

Electrophilic trifluoromethylation is a powerful tool for introducing the trifluoromethyl (CF_3) group into organic molecules, which has found numerous applications in synthetic and pharmaceutical chemistry.[1,2] Following Yagupolskii's pioneering work on the synthesis and application of diaryl(trifluoromethyl)sulfonium ions,[3] Umemoto and coworkers reported that the electrophilic reactivities of the diaryl(trifluoromethyl)sulfonium ions can significantly be enhanced by integrating the diaryl sulfide units in a five-membered heterocycle.[4] The resulting *S*-(trifluoromethyl)dibenzothiophenium triflate (**1 a**) and tetrafluoroborate (**1 b**) became known as Umemoto's reagents type I (Figure 1).[4a]

Subsequently, a large variety of further electrophilic trifluoromethylating reagents have been developed, as summarized in Figure 1 of ref. [5], among which **1 a** and **1 b** as well as Togni's hypervalent iodine compounds **1 d** and **1 e**[6] became most popular. Despite the wide use of **1 a** and **1 b** in synthesis, there were some drawbacks. Their preparation requires many steps, and large amounts of dibenzothiophene are left as waste after trifluoromethylation. For that reason, Umemoto and associates developed 2,8-difluoro-substituted trifluoromethylating reagents (e.g., **1 c**) in 2017, which are thermally more stable, one-pot-producible, and recyclable.[5] One can, therefore, expect that Umemoto's reagents generation II (such as **1 c**), which are commercially available like the other trifluoromethylating agents in Figure 1 will find broad applications in synthesis.

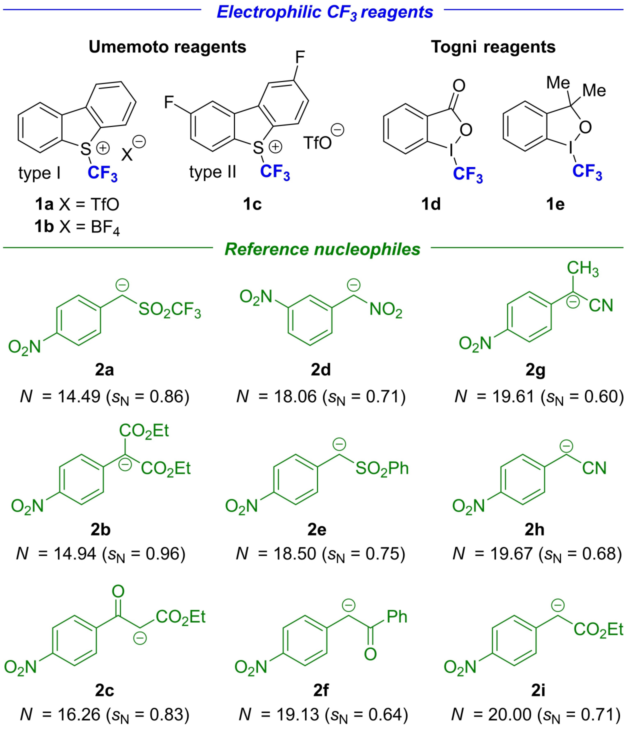

Figure 1. Electrophilic trifluoromethylating reagents **1 a**–**1 e** and reference nucleophiles **2 a**–**2 i** used in this work (*N* and s_N parameters refer to reactivity in DMSO solution, data from refs. [7,8]).

The question arises which reagents to use for certain trifluoromethylations. Umemoto and coworkers have derived the relative trifluoromethylating power of trifluoromethylchalcogenium salts from the relative rates of their S_EAr reactions with aniline.[2a,4b] Xue, Cheng and coworkers developed an energetic guide for estimating trifluoromethyl cation donor abilities of electrophilic trifluoromethylating reagents, which is

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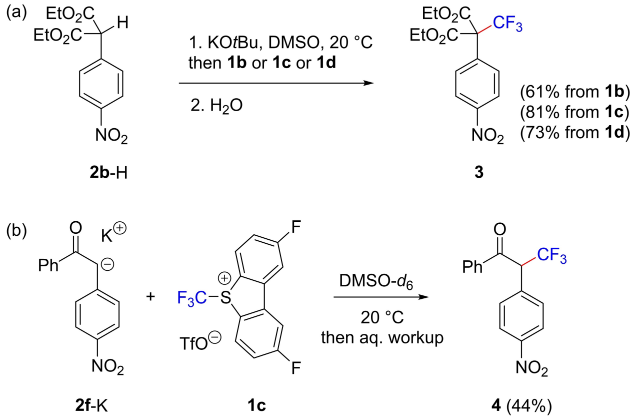
based on quantum-chemically calculated heterolytic X–CF_3 bond dissociation enthalpies (X = O, S, Se, Te, and I).[9]

Since previous work in our laboratory has shown that the linear free energy relationship (1) can be used to predict second-order rate constants k_2 for the reactions of electrophiles with nucleophiles from the solvent-dependent nucleophile-specific parameters N and s_N and the electrophilicity parameter E,[10] we have now examined whether Equation (1) can also be used to describe the synthetic potential of the most popular electrophilic trifluoromethylating reagents **1 a**–**1 e**.

$$\lg k_2(20\,^\circ\mathrm{C}) = s_\mathrm{N}(N + E) \tag{1}$$

For that reason, we have investigated the kinetics of the reactions of compounds **1 a**–**1 e** with carbanions **2 a**–**2 i** (reference nucleophiles), whose N and s_N parameters are listed in Figure 1.



Scheme 1. Reactions of trifluoromethylating reagents **1 b**, **1 c**, and **1 d** with nucleophiles (a) **2 b** and (b) **2 f** in DMSO.

Results and Discussion

Product Studies

To establish the course of the reactions, which we intended to investigate kinetically, we studied the products of some representative trifluoromethylation reactions in DMSO. The diethyl 2-aryl-malonate anion **2 b** which was either generated from **2 b**-H by treatment with KO*t*Bu in DMSO solution or used as preformed **2 b**-K, reacted with the Umemoto reagents I (**1 b**) and II (**1 c**) as well as with the Togni reagent **1 d** to afford the diethyl 2-(trifluoromethyl)malonate **3** (Scheme 1a). The trifluoromethylated product **3** was isolated in moderate yields after purification by column chromatography and characterized by NMR spectroscopy and HRMS.

The *p*-nitro deoxybenzoin-derived anion **2 f** (isolated as **2 f**-K from the reaction of the corresponding CH acid with 1.05 equivalents of KO*t*Bu) reacted with the sulfonium triflate **1 c** in DMSO to give 44 % of the α-trifluoromethylated ketone **4** after aqueous workup and purification by column chromatography (silica gel, pentane/ethyl acetate).

Kinetic Studies

The kinetics of the reactions of carbanions **2** (reference nucleophiles listed in Figure 1, counterion: K^+) with the electrophilic trifluoromethylating reagents **1** were studied at 20 °C in DMSO solution using the stopped-flow technique described previously.[11] The carbanions **2** were used as preformed potassium salts or were prepared in solution by deprotonation of the corresponding CH acids (**2**-H) with 1.05 equiv. of KO*t*Bu in DMSO. The progress of the reaction was monitored photometrically by following the disappearance of the absorbances of the colored carbanions **2** at or close to their UV/vis absorption maxima as depicted exemplarily for the reaction of carbanion **2 c** with the Umemoto reagent **1 c** in Figure 2a.

In order to simplify the evaluation of the kinetic experiments, the electrophilic CF_3-reagents **1** were used in large excess over the colored nucleophiles **2** ($[\mathbf{1}]_0 \gg [\mathbf{2}]_0$) to keep the

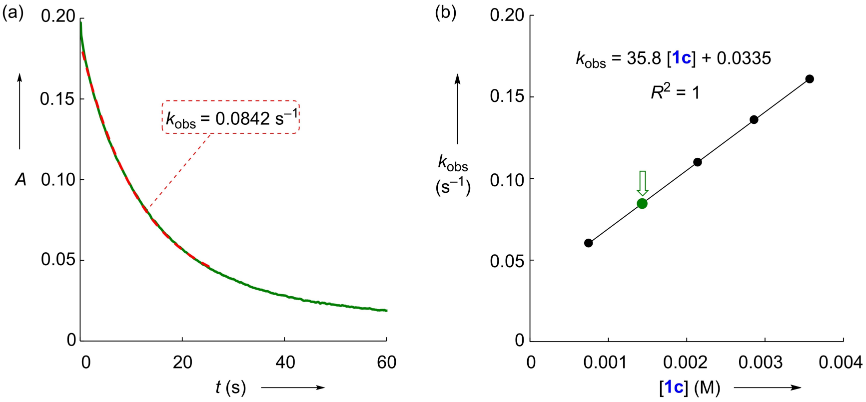


Figure 2. (a) Exponential decay of the absorbance of carbanion **2 c** ($c_0 = 6.32\times10^{-5}$ M) at 450 nm during its reaction with the trifluoromethylating reagent **1 c** ($c_0 = 1.43\times10^{-3}$ M). (b) Correlation of the rate constants k_obs with [**1 c**] in DMSO at 20 °C. The tagged data point refers to the depicted absorption-time trace.

concentration of electrophiles almost constant throughout the reactions, accomplishing pseudo-first-order conditions [Equation (2)].

$$-\mathrm{d}[\mathbf{2}]/\mathrm{d}t = k_{\mathrm{obs}}[\mathbf{2}], \text{ with } k_{\mathrm{obs}} = k_2[\mathbf{1}]_0 \quad (2)$$

From the resulting mono-exponential decays of the absorbances of carbanions **2**, the pseudo-first-order rate constants k_{obs} (s^{-1}) were obtained by least-squares fitting of the function $A_t = A_0 \exp(-k_{\mathrm{obs}}t) + C$ to the time-dependent absorbances (Figure 2a). As exemplified by Figure 2b for the reaction of carbanion **2c** with the Umemoto reagent **1c**, the plots of k_{obs} versus the concentrations of electrophiles were linear with small intercepts, as required by the relation $k_{\mathrm{obs}} = k_2[\mathbf{1}]_0$. The slopes of these linear plots gave the second-order rate constants k_2^{exp} (in $\mathrm{M}^{-1}\,\mathrm{s}^{-1}$), which are summarized in Table 1 (see Supporting Information for the individual correlations of all investigated reactions).

In earlier work, we have already demonstrated that ion-pairing of the potassium salts of stabilized carbanions in dilute DMSO solution (< 0.005 M) does not affect the kinetics.[12,13] Accordingly, we now found that addition of 1.05 equiv. of 18-crown-6 ether to DMSO solutions of **2c**-K had almost no effect on the carbanion's reactivity towards **1c** (increase of k_2 by 7 %) and **1d** (k_2 lowered by 7 %), and we assign these slight changes in k_2 to experimental inaccuracies.

Furthermore, we found that Umemoto's sulfonium tetrafluoroborate **1b** reacted 1.1 to 2.0 times slower with carbanions **2** than the corresponding sulfonium triflate **1a** (Table 1), indicating that ion-pairing also plays little role in the electrophilic reactivities of Umemoto's generation I reagents.

Kinetic studies of the reaction of carbanion **2i** with the non-fluorinated *S*-methyldibenzothiophenium ion gave a second-order rate constant $k_2 = 2.4\times10^4\ \mathrm{M}^{-1}\,\mathrm{s}^{-1}$ (DMSO, 20 °C) which is five times lower than k_2 for the reaction of **2i** with the *S*-(trifluoromethyl)-substituted ion **1a**. Reactions of several other carbanions with the non-fluorinated *S*-methyl salt did not follow clear second-order kinetics and were not investigated in detail.

Table 1. Second-order rate constants k_2 for the reactions of trifluoromethylation reagents **1** with reference nucleophiles **2** in DMSO at 20 °C.

Electrophiles	Electrophilicity *E*	Nucleophiles	k_2^{exp} ($\mathrm{M}^{-1}\,\mathrm{s}^{-1}$)	$k_2^{\mathrm{Eq1[a]}}$ ($\mathrm{M}^{-1}\,\mathrm{s}^{-1}$)	$k_2^{\mathrm{exp}}/k_2^{\mathrm{Eq1}}$
1a	−13.08	**2b**	4.61×10^1	6.10×10^1	0.76
		2c	1.79×10^2	4.35×10^2	0.41
		2f	1.09×10^4	7.44×10^3	1.5
		2h	6.16×10^4	3.03×10^4	2.0
		2i	1.21×10^5	8.18×10^4	1.5
1b	−13.39	**2b**	2.99×10^1	3.11×10^1	0.96
		2c	1.19×10^2	2.43×10^2	0.49
		2f	1.01×10^4	4.75×10^3	2.1
		2i	6.12×10^4	4.97×10^4	1.2
1c	−12.80	**2a**	2.48×10^1	2.84×10^1	0.87
		2b	1.69×10^2	1.13×10^2	1.5
		2c	3.58×10^1 (3.82×10^1)[b]	7.44×10^2	0.05
		2e	9.77×10^3	1.88×10^4	0.52
		2f	3.51×10^4	1.13×10^4	3.1
		2h	1.91×10^5	4.70×10^4	4.1
		2i	5.78×10^5	1.29×10^5	4.5
1d	[c]	**2b**	4.28×10^2		
		2c	7.59×10^1 (7.02×10^1)[b]		
		2d	7.40×10^1		
		2f	2.21×10^2		
		2h	3.17×10^3		
		2i	6.22×10^3		
1e	[c]	**2g**	1.24×10^3		
		2h	2.22×10^4		
		2i	2.72×10^3		

[a] Rate constants k_2^{Eq1} are calculated by Equation (1) from the *E* parameters in this table and *N* (and s_{N}) from Scheme 1. [b] In the presence of 18-crown-6 ether (1.05 equiv. with respect to carbanion **2**). [c] Equation (1) not applicable.

Correlation Analysis

Figure 3 shows that plots of (lg k_2)/s_N vs N are linear for the reactions of Umemoto's reagents **1 a** and **1 c** with carbanions **2**. A similar plot is shown for the analogous reactions of **1 b** in Figure S2 (Supporting Information). Since the slopes of these correlations are close to 1, Equation (1) is applicable and the electrophilicity parameters E for **1 a**–**1 c** (given in Table 1) were determined by least squares minimization of $\Sigma\Delta^2 = \Sigma(\lg k_2^{exp} - s_N(N+E))^2$.[10b] The mechanisms of CF_3 transfer reactions from Umemoto's reagents are still under debate, and various types of mechanisms (via radicals, side-on attack or backside attack of nucleophiles) have been derived from experimental and quantum-chemical investigations.[2a,14] A general picture has not yet evolved and the mechanism of CF_3 transfer reactions may indeed be to some degree nucleophile-dependent as stated by Umemoto.[2a] The fact that Equation (1) holds for these reactions is in line with quantum chemical calculations showing that the reactions of Umemoto's reagents with carbanions (as well as with hetarenes) proceed via polar mechanisms and not via SET processes,[14b] in analogy to the reactions used for parametrizing Equation (1).

The closely similar E parameters of **1 a** and **1 c** as well as comparison of the individual rate constants for reactions of both electrophiles with carbanions in Table 1 show that the fluorine substituents in **1 c** have only little influence on reactivity, as expected from the Hammett substituent constant $\sigma_p(F) = +0.06$,[15] close to zero. Strong electron acceptors, such as NO_2 ($\sigma_m = +0.71$[15]) or OCF_3 ($\sigma_p = +0.35$[15]), lead to a significant increase of electrophilicity of dibenzothiophenium ions, however, as qualitatively shown by Umemoto.[16,17]

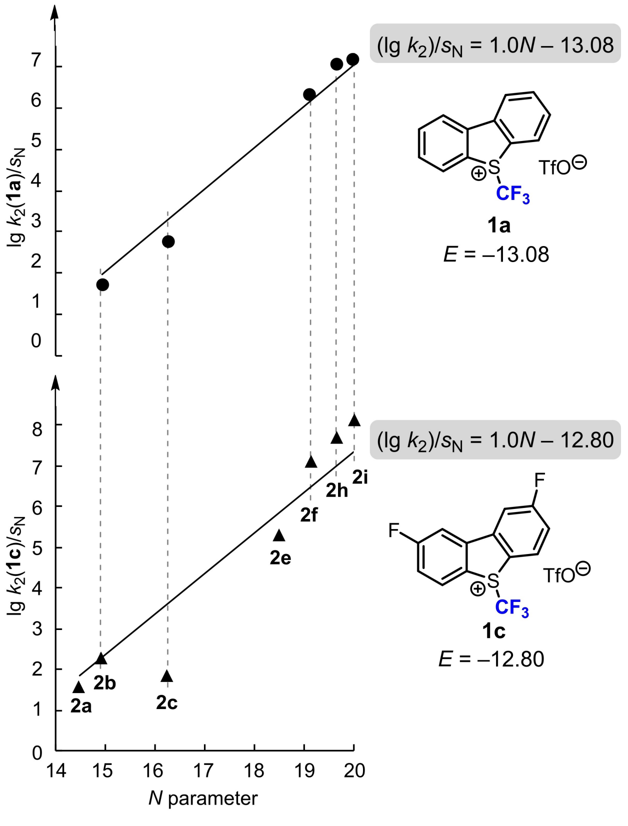


Figure 3. Correlations of (lg k_2)/s_N for the reactions of trifluomethylating reagents **1 a** and **1 c** with the carbanions **2** against the nucleophilicity parameters N of **2** (DMSO, 20 °C). For both correlations, a slope of 1.0 was enforced, as required by Equation (1).

In contrast to the fair correlations shown for the reactions of Umemoto's reagents in Figure 3, the rate constants for the analogous reactions of Togni's reagents **1 d** and **1 e** with the carbanions **2** did not follow Equation (1), as illustrated in Figures S4 and S5 (Supporting Information). Possibly, radical mechanisms are involved, as suggested for the reactions of Togni's reagents with hetarenes.[18] Thus, electrophilicity parameters E of the hypervalent iodine compounds **1 d** and **1 e** cannot be derived and used for predicting potential nucleophilic reaction partners.

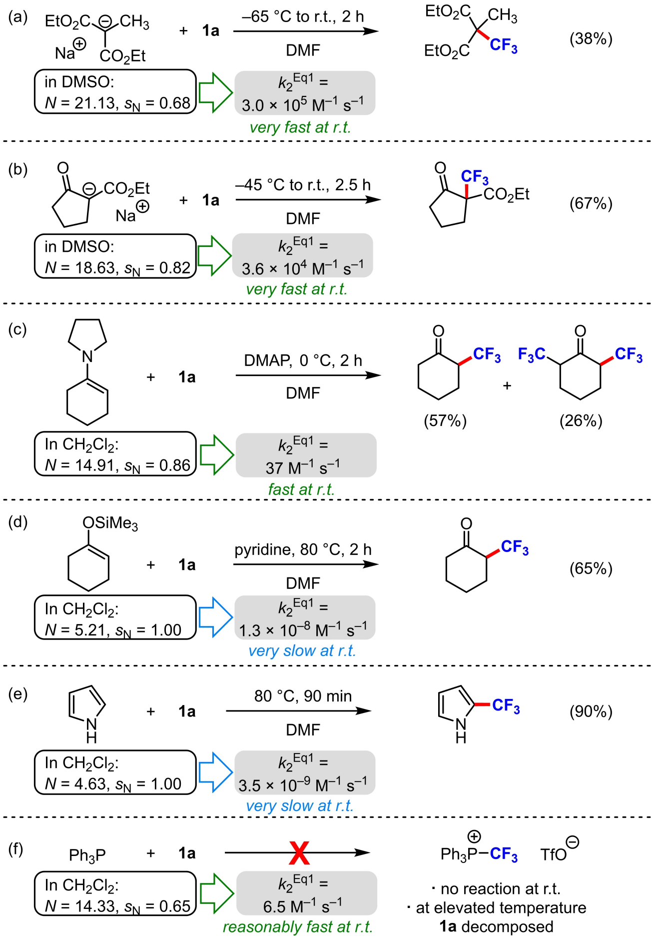
Direct comparison of the individual rate constants for the reactions of Umemoto's reagent **1 a** and Togni's reagent **1 d** with five different carbanions shows **1 a**/**1 d** ratios varying from 0.11 to 49 indicating that different mechanisms are operating. One can see, however, that the relative reactivities of all trifluoromethylating agents **1 a**–**1 e** toward any carbanion in Table 1 differ by less than two orders of magnitude. The huge differences of the thermodynamic driving forces, **1 a** ≫ **1 d** ≫ **1 e**, as expressed by the comprehensive "trifluoromethyl cation donating ability scale",[9] thus, are not reflected by the kinetics.

Can the electrophilicity parameters of Umemoto's reagents **1 a**–**1 c** be used to predict the scope of potential nucleophilic reaction partners? In earlier work on electrophilic fluorination agents, we have shown that plots, as depicted in Figure 3, show separate correlation lines for reactions with carbanions and neutral nucleophiles (enamines).[11a] For that reason, the predictive power of the electrophilicity parameters for **1 a**–**1 c** for reactions with neutral nucleophiles may be limited.

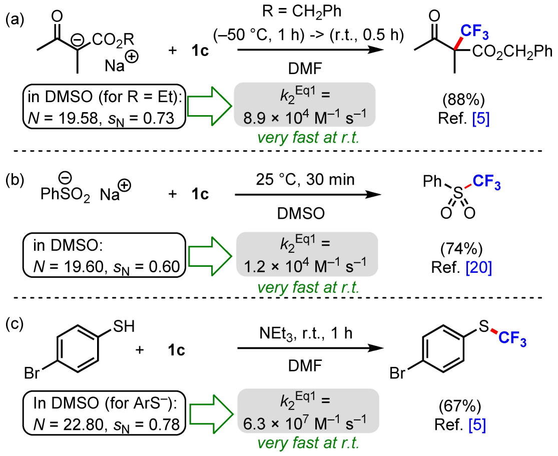
Despite these limitations, comparison of the rate constants calculated by Equation (1), k_2^{Eq1}, with the results of reported trifluoromethylation reactions (Schemes 2 and 3) show how the kinetic data presented in this work can be used for synthesis planning using Umemoto's generation I and II reagents.

The large second-order rate constants k_2^{Eq1} calculated for the reactions of the carbanions (Scheme 2, entries a and b) imply that these reactions will proceed on the millisecond time scale at room temperature, in accord with the fact that these reactions were carried out at low temperature. Probably the reported warming up to room temperature would not have been needed. The calculated rate constant for the reaction of **1 a** with the enamine, which predicts a reaction time of seconds at 20 °C (depending on concentrations), is in line with the fact that this reaction was carried out at 0 °C (Scheme 2, entry c).

Very low rates are calculated for the reactions of **1 a** with 1-(trimethylsiloxy)cyclohexene or pyrrole at 20 °C, and in line with these predictions, elevated temperatures were used to achieve these trifluoromethylations (Scheme 2, entries d and e). It should be noted, however, that TBDMS enol ethers have been reported to react via radical pathways.[14a] In contrast to the prediction of a fast reaction with triphenylphosphine by Equation (1), Umemoto and Ishihara reported that Ph_3P did not react with **1 a** at room temperature (Scheme 2, entry f).[4b]



Scheme 2. Influence of nucleophile reactivities on trifluoromethylations of (a, b) carbanions, (c) enamines, (d) trimethylsilyl enol ethers, (e) pyrrole, and (f) triphenylphosphine by the Umemoto reagent I **1 a**. – Reaction conditions and yields from ref. [4b], reactivity parameters N and s_N were taken from ref. [7], second-order rate constants k_2^{Eq1} (at 20 °C) were calculated by using Equation (1) and the reactivity parameters E(**1 a**), N, and s_N.



Scheme 3. Nucleophiles that have been reported in refs. [5, 20] to undergo trifluoromethylations with the Umemoto reagent II (**1 c**): (a) carbanions, (b) phenylsulfinate, and (c) 4-bromo-thiophenolate. – Reaction conditions and yields from refs. [5, 20], reactivity parameters N and s_N were taken from ref. [7], second-order rate constants k_2^{Eq1} (at 20 °C) were calculated by using Equation (1) and the reactivity parameters E(**1 c**), N, and s_N.

Raising the temperature led to decomposition of **1 a**, but smooth trifluoromethylation of Ph_3P was achieved with a 3,7-dinitro-substituted analogue of **1 a**, which furnished (trifluoromethyl)triphenylphosphonium triflate in a yield of 78 % (in MeCN, 5 h, r.t.).[4b] Since DFT calculations at the SMD(MeCN)/PWPB95-D4/def2-TZVPP//SMD(MeCN)/r^{2}SCAN-3c level of theory[19] show that the trifluoromethylation of Ph_3P with **1 a** is highly exergonic ($\triangle G^0 \approx -168$ kJ mol^{-1}), thermodynamics cannot account for the failure of **1 a** to react with Ph_3P, and we can presently not explain this discrepancy.

Only highly reactive *C*- and *S*-centered nucleophiles were used in uncatalyzed reactions with the Umemoto reagent II **1 c** (Scheme 3).[5,20] Further reactions with significantly less nucleophilic π-systems have been reported but generally required metal catalysis or irradiation with light or both to become effective.[2f] Such reactions follow different mechanisms and cannot be predicted by using Equation (1). The trifluoromethylation of reference nucleophile **2 b** ($N = 14.94$, $s_N = 0.96$) in a yield of 79 % (Scheme 1) proposes, however, that the scope of the Umemoto reagent II (**1 c**) in uncatalyzed reactions is wider than indicated by the examples in Scheme 3.

Conclusions

The agreement between calculated rate constants for the trifluoromethylations with Umemoto's generation I and II reagents **1 a**–**1 c** and the reported synthetic transformations suggests that one can expect reactions of **1 a**–**1 c** with carbon nucleophiles of $N > 5$ at elevated temperature and with nucleophiles of $N > 8$ at room temperature.

The reactivities of the electrophilic hypervalent iodine compounds **1 d** and **1 e** (Togni reagents) cannot be described by Equation (1). Our kinetic data show, however, that the scope of nucleophilic reaction partners does not differ significantly from that of Umemoto's reagents **1 a**–**1 c**.

In summary, we anticipate that the quantification of the electrophilic reactivities of the most commonly used trifluoromethylating reagents by carbon-carbon bond-forming reactions with reference nucleophiles will be of use for designing novel synthetic transformations. The work-flow in our study provides a blue-print for analogous studies on CF_3-transfer reagents that are continuously being developed.[17,21]

Supporting Information

The authors have cited additional references within the Supporting Information (Ref. [22–29]).

Acknowledgements

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: carbanions · hypervalent iodine compounds · kinetics · sulfonium ions · trifluoromethylations

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