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The Influence of Perfluorinated Substituents on the Nucleophilic Reactivities of Silyl Enol Ethers

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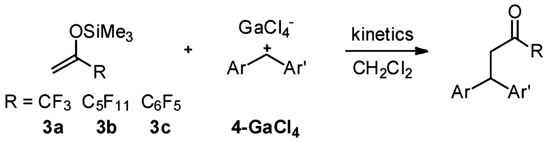
ABSTRACT



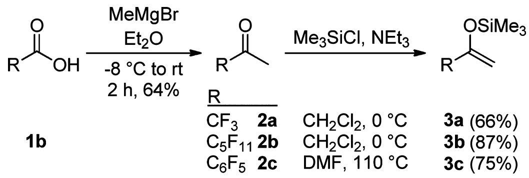
The fluorinated trimethylsilyl enol ethers 3a−c were synthesized, and the kinetics of their reactions with the benzhydrylium ions 4 was studied by UV−vis spectroscopy in dichloromethane. Comparison with nonfluorinated analogues shows that replacement of CH_3 by CF_3 reduces the nucleophilic reactivity by 8 orders of magnitude, while the exchange of C_6H_5 by C_6F_5 retards the reactions by 4.5 orders of magnitude.

Owing to its high electronegativity and lipophilicity, the introduction of fluorine into organic molecules significantly changes chemical, physical, and biological properties.[1] Approximately 20% of all presently used pharmaceuticals and 30% of agrochemicals contain one or more fluorine atoms. Due to this importance we started an investigation of silyl enol ethers bearing perfluoroalkyl substituents that should be interesting building blocks for the synthesis of many fluorinated products, including donor−acceptor-substituted cyclopropanes.[2]

Although silyl enol ethers are widely used in synthetic chemistry,[3] studies on the preparation and reactivity of fluoroalkyl substituted silyl enol ethers are very limited.[4,5]

In order to investigate the effect of fluorine substitution on the nucleophilic reactivity of CC-double bonds, we prepared three different silyl enol ethers: **3a** with a trifluoromethyl group, **3b** bearing the longer perfluoropentyl substituent, and the pentafluorophenyl substituted compound **3c** (Scheme 1).

Scheme 1. Synthesis of Fluorinated Silyl Enol Ethers **3**



Trifluoroacetone (**2a**) and pentafluoroacetophenone (**2c**) were obtained from commercial sources, and **2b**[6] was prepared in analogy to other methyl perfluoroalkyl ketones by treatment of the corresponding carboxylic acid **1b** with MeMgBr.[7] The moderate yield of **2b** (64%) results from the formation of a tertiary alcohol by addition of MeMgBr to the ketone. The enol ethers **3a**−**c** where synthesized by treatment of the methyl ketones **2a**−**c** with triethylamine and trimethylsilyl chloride. Due to the strong electron-withdrawing effect of the perfluoroalkyl groups,

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the conversions of **2a** and **2b** into **3a** and **3b**, respectively, proceeded already at 0 °C, while elevated temperatures were necessary for the preparation of the perfluorophenyl substituted product **3c**.[8] Enol ethers **3b** and **3c** were isolated in yields of 87% and 75%, respectively. We attribute the lower yield of 66% for **3a** to its higher volatility.

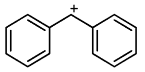
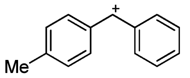
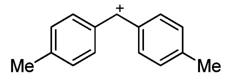
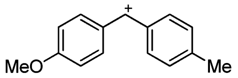
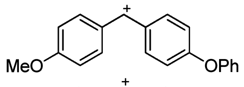
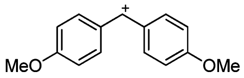
In order to quantify the influence of the electron-withdrawing substituents on the nucleophilic reactivities of the corresponding trimethylsilyl enol ethers **3a**–**c**, the benzhydrylium method[9] was employed, which allowed us to compare the data with those of previously investigated silyl enol ethers.[9a,b,10]

Benzhydrylium ions with variable *p*- and *m*-substituents, which cover a broad range of reactivity while the steric shielding of the reaction center is kept constant, have been used as reference electrophiles for the construction of a comprehensive nucleophilicity scale based on eq 1, where electrophiles are characterized by one parameter (E) and nucleophiles are characterized by the solvent-dependent parameters s_N (slope) and N (nucleophilicity).[9a]

$$\log k(20°\mathrm{C}) = s_N(N + E) \qquad (1)$$

The benzhydrylium ions **4a**–**f** (Table 1) with electrophilicity parameters E ranging from 0 to +5.47 reacted with the silyl enol ethers **3a**–**c** with conveniently measurable rates.

Table 1. Reference Electrophiles Utilized for Quantifying the Nucleophilicities of **3a**–**c**

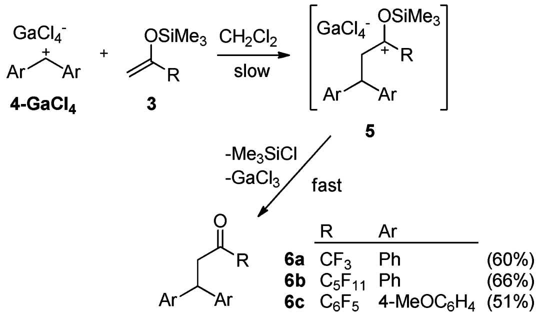
	reference electrophile	E^a
4a		5.47[b]
4b		4.43[b]
4c		3.63
4d		1.48
4e		0.61
4f		0.00

[a] Empirical electrophilicities E from ref 9a. [b] The electrophilicities of **4a** and **4b** in ref 9a have been revised in ref 11.

The fluorinated enol ethers **3a**–**c** gave analogous reaction products as previously investigated silylated enol ethers,[10] as demonstrated by the formation of **6a** and **6b** from **4a-GaCl$_4$** and **3a** or **3b**, respectively, and of **6c** from **4f-GaCl$_4$** and **3c** (Scheme 2).

As the intermediates **5** and the products **6** are colorless, the nucleophilic attack at the electrophilic center was followed spectrophotometrically. Addition of at least 8 equiv of the trimethylsilyl enol ethers **3** to solutions of the colored benzhydrylium tetrachlorogallates **4-GaCl$_4$** in CH_2Cl_2 led to monoexponential decays of the absorbances of the benzhydrylium ions (Figure 1). As previous studies have shown that the rates of the reactions are only slightly affected by the counterion and the desilylations to products **6** are fast,[10] the measured reaction rates correspond to the formation of the C–C bonds.

Scheme 2. Reactions of **3** with the Benzhydrylium Salts **4-GaCl$_4$**



The reactions with the highly electrophilic benzhydrylium ions **4a**–**d** were studied between −70 and −10 °C.

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(5) For examples with special substitution patterns (in particular with additional electron-withdrawing groups), see: (a) Jullien, J.; Pechine, J. M.; Perez, F.; Piade, J. J. *Tetrahedron* **1982**, *38*, 1413–1416. (b) Seifert, F. U.; Röschenthaler, G.-V. *J. Fluorine Chem.* **1994**, *68*, 169–174. (c) Neumayer, D. A.; Belot, J. A.; Feezel, R. L.; Reedy, C.; Stern, C. L.; Marks, T. J.; Liable-Sands, L. M.; Rheingold, A. L. *Inorg. Chem.* **1998**, *37*, 5625–5633. (d) Kruchok, I. S.; Gerus, I. I.; Kukhar, V. P. *Tetrahedron* **2000**, *56*, 6533–6539. (e) Dilman, A. D.; Belyakov, P. A.; Korlyukov, A. A.; Tartakovsky, V. A. *Tetrahedron Lett.* **2004**, *45*, 3741–3744. (f) Chung, W. J.; Ngo, S. C.; Higashiya, S.; Welch, J. T. *Tetrahedron Lett.* **2004**, *45*, 5403–5406. (g) Levin, V. V.; Dilman, A. D.; Belyakov, P. A.; Korlyukov, A. A.; Struchkova, M. I.; Tartakovsky, V. A. *Eur. J. Org. Chem.* **2004**, 5141–5148. (h) Chizhov, D. L.; Röschenthaler, G.-V. *J. Fluorine Chem.* **2006**, *127*, 235–239. (i) Büttner, S.; Riahi, A.; Hussain, I.; Yawer, M. A.; Lubbe, M.; Villinger, A.; Reinke, H.; Fischer, C.; Langer, P. *Tetrahedron* **2009**, *65*, 2124–2135. (j) Metz, S.; Burschka, C.; Tacke, R. *Organometallics* **2009**, *28*, 2311–2317. (k) Büttner, S.; Bendrath, F.; Langer, P. *Tetrahedron Lett.* **2010**, *51*, 5106–5108.

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(7) (a) Kondo, A.; Iwatsuki, S. *J. Fluorine Chem.* **1984**, *26*, 59–67. (b) Croxtall, B.; Fawcett, J.; Hope, E. G.; Stuart, A. M. *J. Fluorine Chem.* **2003**, *119*, 65–73.

(8) Gostevskii, B. A.; Vyazankina, O. A.; Vyazankin, N. S. *Zh. Obshch. Khim.* **1984**, *54*, 2613–2617; *J. Gen. Chem. USSR* **1985**, *54*, 2334–2337.

(9) (a) Mayr, H.; Bug, T.; Gotta, M. F.; Hering, N.; Irrgang, B.; Janker, B.; Kempf, B.; Loos, R.; Ofial, A. R.; Remennikov, G.; Schimmel, H. *J. Am. Chem. Soc.* **2001**, *123*, 9500–9512. (b) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66–77. (c) Mayr, H.; Ofial, A. R. In *Carbocation Chemistry*; Olah, G. A., Prakash, G. K. S., Eds.; Wiley: Hoboken, NJ, 2004; Chapter 13, pp 331–358. (d) Mayr, H.; Ofial, A. R. *Pure Appl. Chem.* **2005**, *77*, 1807–1821. (e) Mayr, H.; Ofial, A. R. *J. Phys. Org. Chem.* **2008**, *21*, 584–595. (f) For a comprehensive database of reactivity parameters, see http://www.cup.uni-muenchen.de/oc/mayr/DBintro.html.

(10) (a) Burfeindt, J.; Patz, M.; Müller, M.; Mayr, H. *J. Am. Chem. Soc.* **1998**, *120*, 3629–3634. (b) Tokuyasu, T.; Mayr, H. *Eur. J. Org. Chem.* **2004**, 2791–2796. (c) Dilman, A. D.; Mayr, H. *Eur. J. Org. Chem.* **2005**, 1760–1764. (d) Laub, H. A.; Yamamoto, H.; Mayr, H. *Org. Lett.* **2010**, *12*, 5206–5209.

For electrophiles **4a**,**b** a shift of the absorption maximum (−14 nm for **4a** and −5 nm for **4b**) was observed at conversions above 80%. As the origin of this shift is not clear, the corresponding measurements were evaluated until this shift occurred (when evaluating over the whole time period, k_{obs} changes by up to 10%). The resulting first-order rate constants k_{obs} were divided by the corresponding mean nucleophile concentrations $[\mathbf{3}]_{av} = [\mathbf{3}]_0 - 0.5[\mathbf{4\text{-}GaCl_4}]_0$ to give the second-order rate constants k_2 at the specific temperature. The values of k_2 at 20 °C (given in Table 2) were calculated from the linear Eyring plot of $\ln(k_2/T)$ versus $1/T$ (Figure 1).

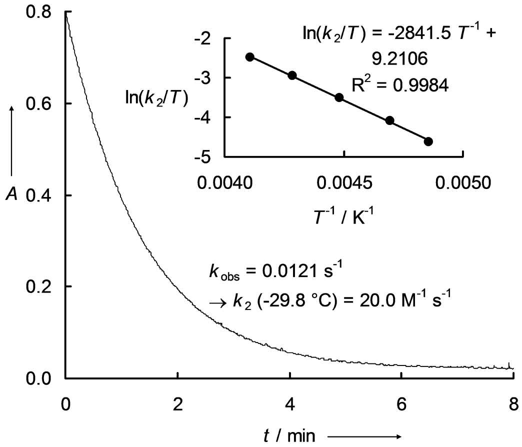
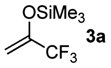
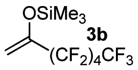
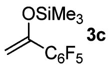


Figure 1. Exponential decay of the absorbance at 452 nm during the reaction of **3b** (c = 6.27 × 10^{-4} M) with **4a-GaCl$_4$** (c = 4.69 × 10^{-5} M) at −29.8 °C in CH_2Cl_2. Insert: Correlation of $\ln(k_2/T)$ vs $1/T$ allows the computation of the second-order rate constant k_2 (20 °C) = 181 M^{-1} s^{-1} by using the Eyring equation.

Table 2. Second-Order Rate Constants k_2 and Eyring Activation Parameters for the Reactions of the Enol Ethers **3** with the Benzhydrylium Ions **4**

nucleophiles **3**	**4**	k_2 (20 °C) / M^{-1} s^{-1}	$\Delta H^{\neq}$ / kJ mol^{-1}	$\Delta S^{\neq}$ / J mol^{-1} K^{-1}
 **3a**	**4a**	634	27.5	-97.2
	4b	47.6	30.6	-108.5
	4c	5.73	36.9	-104.3
 **3b**	**4a**	181	23.6	-121.0
	4b	13.2	29.3	-123.5
	4c	1.25	33.4	-128.9
 **3c**	**4d**	427	21.9	-119.6
	4e	63.1	–	–
	4f	21.2	–	–

The reactions of the benzhydrylium ions **4e** and **4f** with **3c** were studied at 20 °C. As the resulting first-order rate constants k_{obs} correlated linearly with the concentrations of **3c** (Supporting Information, p S16 f), the second-order rate constants given in Table 2 could be derived from the slopes of these linear correlations.

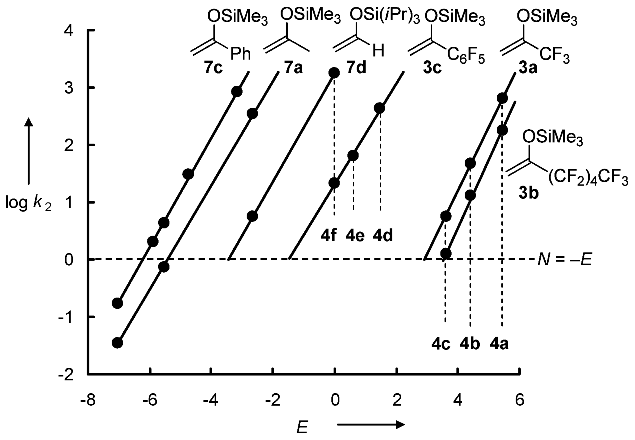
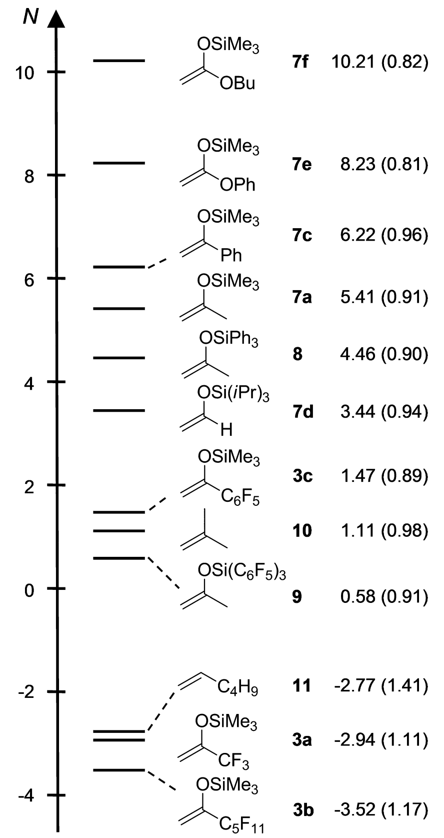


Figure 2. Plots of log k_2 for the reactions of the silyl enol ethers **3** and **7a**,**c**,**d** (from ref 9a) with benzhydrylium ions in CH_2Cl_2 at 20 °C versus the electrophilicity parameters E of the benzhydrylium ions used as reference electrophiles.

Scheme 3. Nucleophilicities N of Fluorinated Silyl Enol Ethers **3** Compared to Those of Other π-Nucleophiles[9f] (s_N Values Given in Parentheses)



Plots of log k_2 for the reactions of the fluorinated silyl enol ethers **3** with the reference electrophiles **4** versus their

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(11) Ammer, J.; Nolte, C.; Mayr, H. Submitted.

empirical electrophilicity parameters E gave linear correlations (Figure 2) and allowed us to calculate the N and s_N parameters for compounds **3** according to eq 1.

Scheme 3 compares the reactivities of **3a**–**c** with those of other π-systems[9f] and shows that substitution of the methyl group of **7a** attached to the developing carbenium center by a trifluoromethyl group (compound **3a**) reduces the nucleophilic reactivity by more than 8 orders of magnitude.

As the activating effects of triisopropylsiloxy and trimethylsiloxy have been shown to be comparable,[10a] the comparison of **3a** with triisopropylsiloxyethylene (**7d**) demonstrates a deactivation of more than 6 orders of magnitude by the trifluoromethyl group relative to hydrogen. Elongation of the perfluorinated alkyl chain to undecafluoropentyl (compound **3b**) results in a further decrease in nucleophilicity by a factor of 3–4 (Table 2, Scheme 3).

Comparison of compounds **7c** and **3c** demonstrates that replacement of the phenyl group by a pentafluorophenyl substituent reduces the reactivity by approximately 4.5 orders of magnitude, showing that perfluorination of the phenyl group has a slightly smaller deactivating effect than perfluorination of an alkyl group. A comparable deactivation was observed when the three phenyl groups in **8** were perfluorinated (→**9**, Scheme 3).[10c]

In summary, Scheme 3 demonstrates that the nucleophilic reactivities of silyl enol ethers are so strongly reduced by the introduction of perfluorinated alkyl and phenyl groups that compounds **3a**–**c** show nucleophilicities comparable to those of alkyl substituted ethylenes (e.g., isobutylene (**10**)[9a] or hex-1-ene (**11**)[9a,11]). With N-parameters around -3, the perfluoroalkyl substituted enol ethers **3a,b** can be expected only to react with electrophiles of $E > -2$; i.e., they should be accessible to Mukaiyama-type aldol reactions (for E-parameters for carbonyl Lewis acid complexes, see ref 12) but not to iminium activated reactions (for E-parameters for iminium ions, see ref 13).

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Supporting Information Available. Details of product synthesis and characterization and the kinetic experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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