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Article

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Nucleophilicity parameters of arylsulfonyl substituted halomethyl anions

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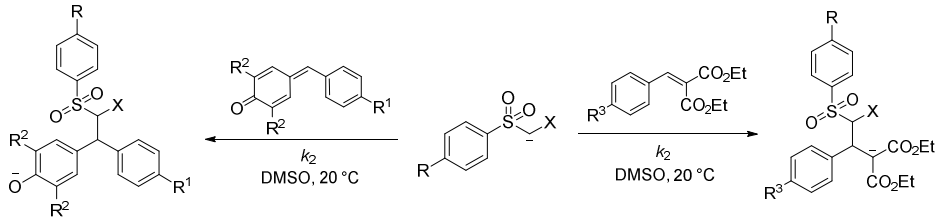
Abstract



The rates of the reactions of the arylsulfonyl substituted carbanions carrying α-chloro and α-bromo substituents **1a−e** with quinone methides **2a−g** and benzylidenemalonates **2h−i** in DMSO were determined photometrically at 20 °C. The reactions were carried out under pseudo-first-order conditions, and the second-order rate constants were obtained as the slopes of the plots of the pseudo-first-order rate constants versus the concentrations of the reactants used in excess. The second-order rate constants correlate linearly with the parameters *E* of the reference electrophiles according to the linear free-energy relationship log k_2(20 °C) = $s_N(N + E)$, which allowed to derive the nucleophile-specific parameters *N* and s_N of the carbanions **1a−e**. The resulting nucleophilicity parameters in the range 23 < *N* < 29 reveals the title compounds to be among the most reactive nucleophiles, so far integrated in our comprehensive nucleophilicity scale.

Introduction

Carbanions bearing leaving groups at the α-position are useful reagents in organic synthesis. They are widely used in Darzens condensations,[1] cyclopropanations,[2] and vicarious nucleophilic substitutions.[3] Knowledge of the nucleophilic reactivities of these carbanions would be a valuable tool for designing their use in synthesis. In numerous previous investigations, we had found that the rates of the reactions of nucleophiles with carbocations and acceptor-substituted ethylenes can be predicted by eq 1, which characterizes electrophiles by one parameter, the electrophilicity *E*, and nucleophiles by two solvent-dependent parameters, the nucleophilicity parameter *N* and the susceptibility parameter s_N.[4]

$$\log k_2(20\ ^\circ\mathrm{C}) = s_N(N + E) \quad (1)$$

More than 1000 nucleophiles and 270 electrophiles have so far been characterized on the basis of this linear free-energy relationship.[5] We now report on the application of this method to characterize the nucleophilicities of arylsulfonyl substituted carbanions carrying α-chloro and α-bromo substituents **1a−e** (Scheme 1). Quinone methides **2a−g** and benzylidenemalonates **2h−i** (Table 1) were used as reference electrophiles for these investigations.

SCHEME 1. Cl-Stabilized Carbanions 1a−d, and Br-Stabilized Carbanion 1e

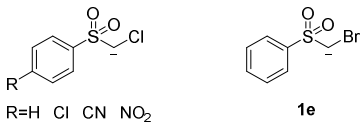
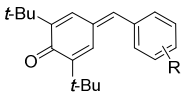
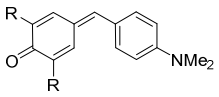
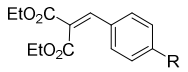
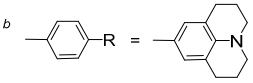


TABLE 1. Quinone Methides 2a−g and Diethyl Benzylidenemalonates 2h−i.

Electrophile		R	E^a
	**2a**	3-F	-15.03
	2b	4-Me	-15.83
	2c	4-OMe	-16.11
	2d	4-NMe_2	-17.29
	2e	jul[b]	-17.90
	**2f**	Me	-16.36
	2g	OMe	-17.18
	**2h**	NMe_2	-23.10
	2i	jul[b]	-23.80

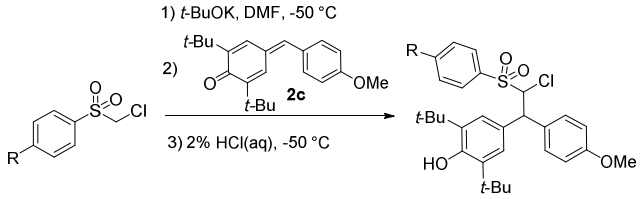
[a] Electrophilicity parameters *E* of **2a, 2f,** and **2g** were taken from ref 6a, of **2b**–**e** from ref 6b, of **2h**–**i** from ref 6c.

[b] 

Results and Discussion

Product studies. As representative examples for the reactions of carbanions **1** with quinone methides **2a−g**, we have investigated the corresponding reactions with **2c**. Treatment of **1a**-H with 1 equivalent of *t*-BuOK in DMF at -50 °C and subsequent addition of 0.5 equivalent of **2c** gave a phenolate which was treated with 2% aqueous HCl after 5 min at -50 °C to yield 75% of **3a**-H as a mixture of two diastereomers. The reaction of **1d** with **2c** proceeded analogously (Scheme 2).

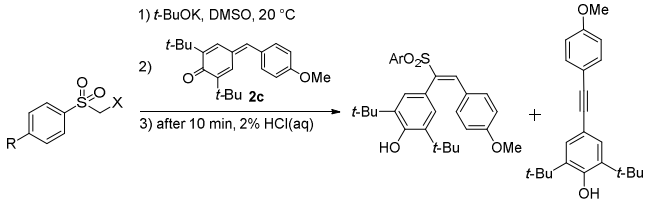
SCHEME 2. Synthesis of Michael Adducts 3-H by the Reactions of Carbanions 1 with Quinone Methide 2c at -50 °C



[a] Diastereomeric ratios (dr) correspond to isolated products.

When the reactions of **1a−c** and of **1e** with **2c** were carried out in DMSO at 20 °C and quenched with 2% aqueous HCl after 10 min, mixtures of **4**-H and **5a**-H were obtained, while **1d** gave a complex mixture of products (Scheme 3). Because of the high melting point of DMSO, low temperature studies were not possible as in DMF (see above).

SCHEME 3. Reaction of Carbanion 1 with Quinone Methide 2c at 20 °C



1a-H	**4a**-H (70%)	**5a**-H (10%)
1b-H	**4b**-H (61%)	**5a**-H (30%)
1c-H	**4c**-H (44%)	**5a**-H (45%)
1d-H	decomposition	none
1e-H	**4a**-H(70%)	**5a**-H(10%)

The structure of **4a**-H was confirmed by single crystal X-ray crystallography (Figure 1). Treatment of isolated **4a**-H with *t*-BuOK led to formation of **5a**-H (Scheme 4). In order to investigate whether the weaker Brønsted base **1a**-K which may be the effective base under the conditions of Scheme 3 can also affect this elimination, **4a**-H was also treated with **1a**-K. As shown in Scheme 4, this reaction proceeded slowly, and after 10 min a similar amount of **5a**-H was obtained as in the reaction of **1a** with **2c** described in Scheme 3.

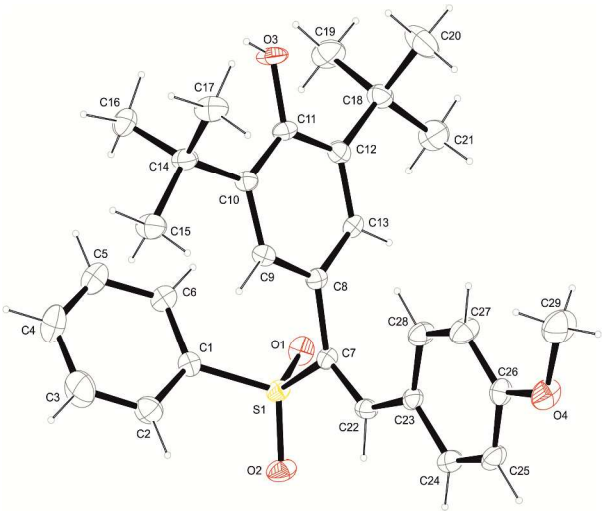
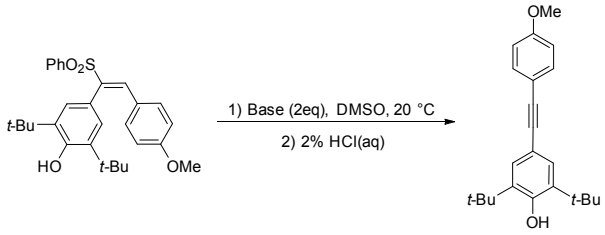


FIGURE 1. ORTEP-drawing of the crystal structure of **4a**-H. (The ellipsoid probability level is 50%)

SCHEME 4. Transformation of 4a-H into 5a-H.



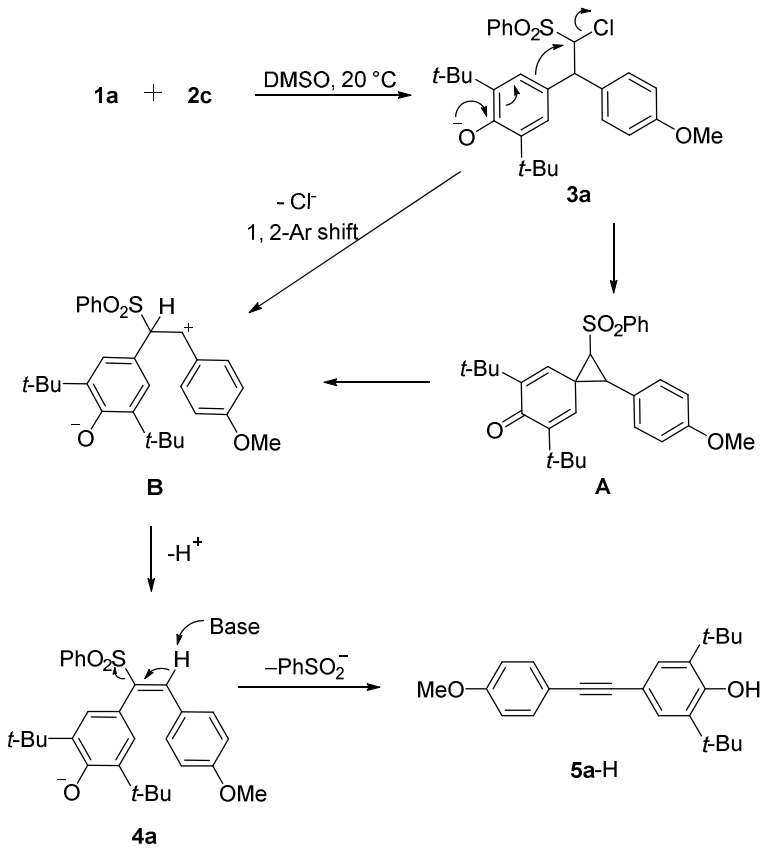
4a-H	Base	**5a**-H[a]	
	t-BuOK	10 min	10%
		30 h	90%
	1a-K	10 min	6%
		60 h	90%

[a] Yield of isolated product.

These observations suggest the reaction mechanism described in Scheme 5. Michael addition of the carbanion **1a** to the electrophilic double bond of the quinone methide **2c** yields the phenolate anion **3a**. This intermediate was trapped by protonation with 2% aqueous HCl, when the reaction was carried out in DMF at -50 °C (Scheme 2). At 20 °C, intramolecular cyclization may lead to the formation of spirodienone **A**, which undergoes spontaneous ring opening with formation of the mesomerically stabilized zwitterion **B.** As an alternative to this mechanism suggested by Groszek,[7] phenoxide-migration with substitution of Cl^- gives **B** directly through a transition state resembling **A**. Deprotonation yields the phenolate **4a** (**4a**-H was isolated, Scheme 3 and Figure 1), which is selectively formed as the (*E*)-diastereomer, probably because of attractive intramolecular π-π interaction of the two aryl rings in the intermediate zwitterion B, as previously suggested by Groszek.[7] Slow

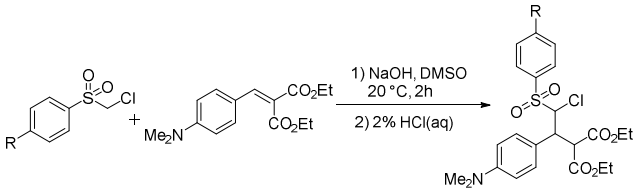
elimination of $PhSO_2^-$ from **4a** yields the alkynyl substituted phenol **5a**-H. The formation of Michael adducts of type **3**-H and of the rearranged elimination products **4**-H from the reaction of tolylsulfonyl chloromethyl anion **1** (R = Me) with quinone methides has previously been reported by Groszek and coworkers.[7]

SCHEME 5. Plausible Mechanism for the Reaction of 1a with 2c



The NaOH induced reaction of **1a**-H with benzylidenemalonate **2h** in DMSO gave the Michael adduct **6a**-H, as previously reported for the corresponding reaction in DMF.[8] The reaction of **1b**-H with **2h** proceeded analogously (Scheme 6).

SCHEME 6. Reaction of Benzylidenemalonate 2h with Carbanions 1



[a] Diastereomeric ratios dr correspond to crude products.

Kinetic investigations. All kinetic investigations were performed in DMSO solution at 20°C and monitored photometrically by following the disappearance of the colored quinone methides or benzylidenemalonates. Generally a high excess of the carbanions over the electrophiles was used to achieve first-order kinetics. As reported earlier,[9] the carbanions **1a−e** disproportionate slowly at room temperature. For that reason, the double-mixing mode of stopped flow UV-Vis spectrometers was used to generate solutions of the carbanions **1a−e** by mixing the CH acids (**1a−e**)-H with *t*BuOK. After a user-defined delay period (1 − 30s), the solutions of carbanions were combined with the electrophiles **2a−i**.

Figure 2 illustrates the decay of the absorption of **2c** (λ_{max} = 393 nm) in DMSO at 20 °C after addition of 20 equivalents of **1a** (pseudo-first-order conditions). The absorbance decreases to about 15% of its initial value within 50 ms and then shows a very slow increase. Separate UV-Vis measurements showed that the residual absorbance after 50 ms is due to the generation of **4a**, which has an absorption maximum at 504 nm. The subsequent slow increase (insert of Figure 2) is due to the formation of **5a** by elimination of $PhSO_2H$ from **4a**. Depending on the excess of base used for these experiments, the alkyne is either formed as the anion **5a** or its conjugate acid **5a**-H. While an analogous behavior was observed for all other reactions of **1** with the quinone methides **2a−g**, the corresponding reactions with the benzylidenemalonates **2h**,**i** showed only the fast decay of the absorption band of **2h**,**i**.

The first-order rate constants k_{obs} were obtained by least-squares fitting of the exponential function $A = A_0 \exp(-k_{obs}t) + C$ to the observed time-dependent absorbances A of the quinone methides **2a−g** (in the initial period) and of the benzylidenemalonates **2h**,**i**. According to eq 2 and eq 3, the pseudo-first-order rate constant k_{obs} should be proportional to the concentration of the carbanions **1**. As shown for the reaction of **1a** with **2c** in Figure 3, k_{obs} correlates linearly with the concentrations of the carbanions **1**, and the negative intercept may be due to partial decomposition of the carbanions **1**. Though the intercept is small and negligible in most of these correlations (SI), in few cases even small positive intercepts were observed. The second-order rate constants k_2 listed in Table 2 correspond to the slopes of the k_{obs} versus [**1**] correlations. The experimental second-order rate constant k_2 for the reaction of **1a** with **2h** (149 M^{-1} s^{-1}) is close to that (200 M^{-1} s^{-1}) extrapolated for this reaction in DMF at 20 °C from the measured rate constant at -40 °C.[8]

$$-d[\mathbf{2}]/dt = k_2[\mathbf{1}][\mathbf{2}] \qquad (2)$$

for $[\mathbf{1}]_0 >> [\mathbf{2}]_0 \Rightarrow k_{obs} = k_2[\mathbf{1}]_0$ (3)

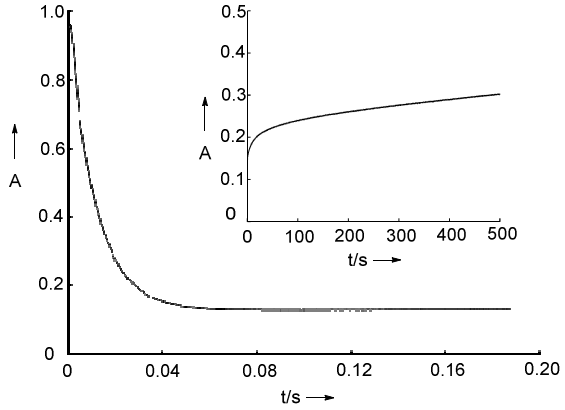


FIGURE 2. Monoexponential decay of the absorbance A (at 393 nm) during the first 200 ms of the reaction of **1a** (1.00×10^{-3} mol L^{-1}) with **2c** (5.00×10^{-5} mol L^{-1}) in DMSO at 20 °C. Inset: slow increase of the absorbance at 393 nm at 20 °C between 0.05 and 500 s.

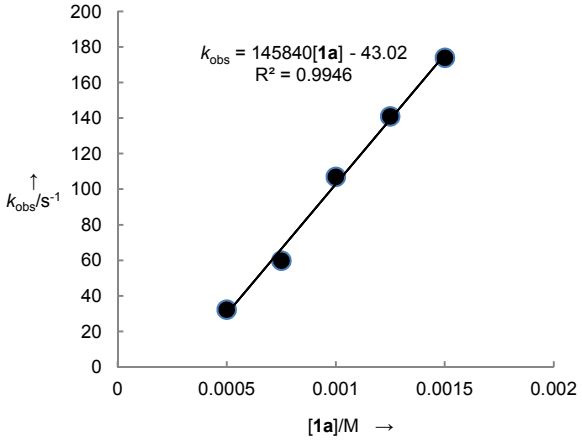


FIGURE 3. Correlation of k_{obs} for reaction of **1a** with **2c** versus the concentration of **1a**.

In order to determine the nucleophile-specific parameters N and s_N of the carbanions **1a−e** according to eq 1, the second-order rate constants (log k_2) of their reactions with electrophiles **2** (see Table 2) were plotted against the previously reported electrophilicity parameters E of **2a−i** (Table 1). Figure 4 and Figure S1 (SI) show that log k_2 for these reactions correlate linearly with E as required by eq 1 and thus allow the calculation of the nucleophile-specific parameters N and s_N listed in Table 2. The similarities of the slopes of the correlations for the carbanions **1b−d** (Figure 4 and Figure S1), which are numerically expressed by the s_N parameters in Table 2, imply that the relative nucleophilicities of the carbanions **1b−d** depend only slightly on the electrophilicities of the reaction partners. The Hammett correlation for the

reactions of carbanions **1a−d** with benzylidenemalonate **2h** is of moderate quality and gives rise to the Hammett reaction constant ρ = -1.50 (Figure 5). Since the substituted aryl ring is separated from the nucleophilic reaction center by the sulfonyl group, the Hammett reaction constant ρ has a small negative value.

TABLE 2. Second-Order Rate Constants (k_2) for the Reactions of Carbanions 1a-e with Quinone Methides 2a−g and Benzylidenemalonates 2h−i in DMSO at 20°C

Carbanion	Electrophile	k_2 (M^{-1} S^{-1})	N, s_N[a]
1a	**2c**	1.46×10^5	28.27, 0.42
	2d	3.35×10^4	
	2e	2.65×10^4	
	2g	3.92×10^4	
	2h	1.49×10^2	
1b	**2b**	1.08×10^5	26.90, 0.45
	2c	8.87×10^4	
	2d	2.01×10^4	
	2h	4.90×10^1	
	2i	2.85×10^1	
1c	**2d**	1.77×10^4	25.59, 0.51
	2e	9.19×10^3	
	2f	5.65×10^4	
	2g	2.21×10^4	
1d	**2a**	6.89×10^4	24.88, 0.49
	2b	2.90×10^4	
	2c	2.00×10^4	
1e	**2a**	2.78×10^5	23.90, 0.62
	2c	7.11×10^4	
	2d	1.17×10^4	
	2e	4.90×10^3	

[a] The nucleophile-specific parameters N and s_N were derived from the intercepts (on the abscissa) and the slopes of the correlations between log k_2 (this table) and the electrophilicity parameters E from Table 1. For details see text.

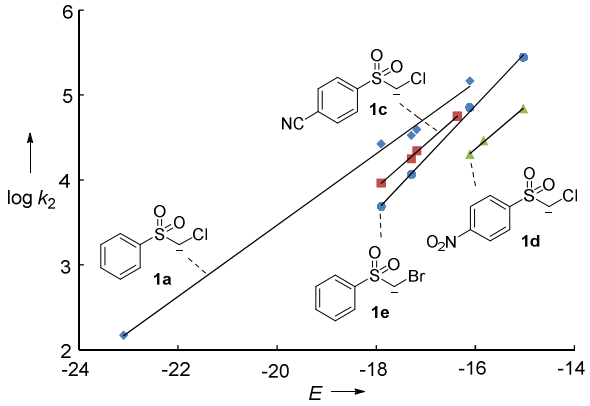


FIGURE 4. Correlation of log k_2 for the reactions of the carbanions **1a** and **1c−e** with the quinone methides **2a−g** and benzylidenemalonates **2h−i** versus the electrophilicity parameters E of the corresponding electrophiles. For the sake of clarity, the correlation line for **1b** is only shown in the SI.

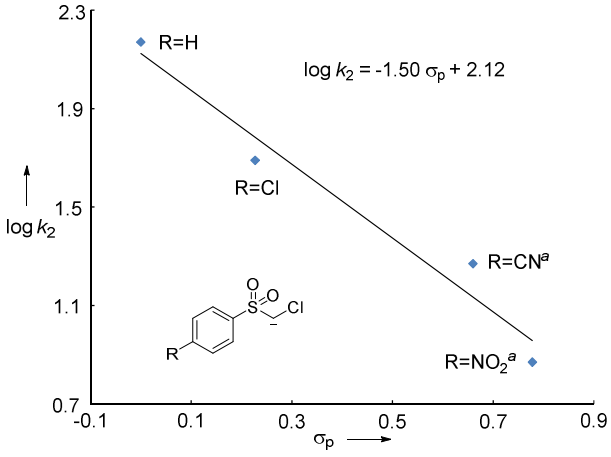


FIGURE 5. Correlation of log k_2 of the reactions of carbanions **1a−d** with benzylidenemalonate **2h** versus the Hammett σ_p values for R. [a] log k_2 calculated by eq 1 with E from Table 1.

Figure 6 compares the reactivities of **1a−e** with that of the previously characterized phenylsulfonyl substituted benzyl anion **1f**. As the s_N values for these carbanions differ slightly, their relative nucleophilic reactivities depend somewhat on the electrophilicity of the reaction partner. The reactivities of the arylsulfonyl substituted halomethyl anions **1a−e** towards **2c** differ by less than a factor of 7. The chloro-substituted carbanion **1a** is two times more reactive than the corresponding bromo-derivative **1e**. The similar nucleophilic reactivities of the phenylsulfonyl substituted carbanions **1a** and **1f** show that α-chloro and α-phenyl substitution has a similar effect on nucleophilic reactivities as on the corresponding basicities in DMSO (**1a**-H : pK_a = 23.8,[10] **1f**-H: pK_a = 23.43[11]).

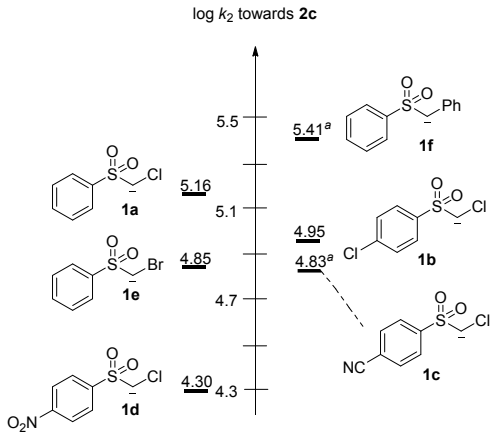


FIGURE 6. Comparison of log k_2 for the reactions of carbanions **1a-f** with electrophile **2c** in DMSO at 20 °C. [a] log k_2 (**2c**) calculated by eq 1 with E from Table 1. N and s_N values of **1f** from ref 12d.

Conclusion

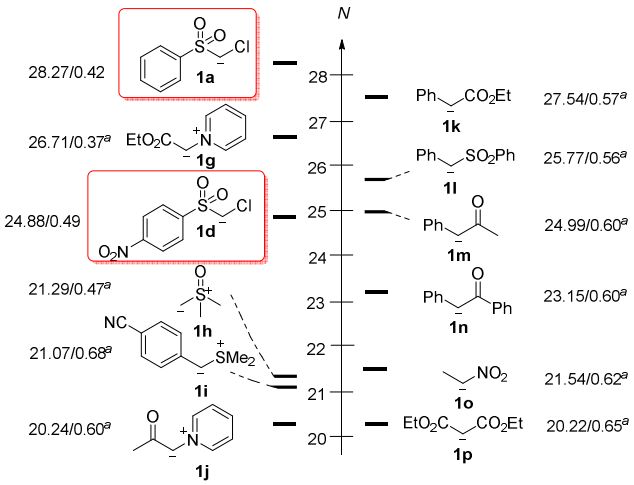


FIGURE 7. Comparison of nucleophilicity parameters N (in DMSO at 20 °C) of **1a** and **1d** with other classes of nucleophiles. [a] N and s_N values of **1g** and **1j** were taken from ref 12a, of **1h** and **1i** from ref 12b, of **1k** from ref 12c, of **1l**, **1m** and **1n** from ref 12d, of **1o** from ref 12e, of **1p** from ref 4b.

The rate constants for the reactions of the Cl-, Br-substituted carbanions **1a−e** with the selected reference electrophiles (quinone methides and diethyl benzylidenemalonates) in DMSO follow the linear free-energy relationship eq 1. For that reason, it is possible to include these compounds in our comprehensive nucleophilicity scale and to compare their reactivities with those of other nucleophiles (Figure 7). As they contain halogens in α-position, which can be nucleophilically substituted, carbanions **1** show carbenoid character and yield epoxides[1], aziridines[1c,13] and cyclopropanes[2] by reaction with carbonyl compounds, imines, and Michael acceptors, respectively. In this aspect they

resemble the behavior of sulfur and nitrogen ylides, some representatives of which are also shown on the left side of Figure 7. Though the relative reactivities of these nucleophiles depend somewhat on the electrophilicity of the reaction partner due to the different values of s_N, the ranking based on *N* in Figure 7 gives a rough orientation. Thus, one can see that the arylsulfonyl substituted chloromethyl anions are stronger nucleophiles than semistabilized sulfur ylides, and therefore, can be used for the synthesis of epoxides from non-activated ketones. The high nucleophilic reactivities of **1a−e** combined with the high nucleofugality of chloride and bromide, also explains their versatile applications in vicarious nucleophilic substitutions.[3]

Experimental Section

Chloromethyl aryl sulfones (1a−d)-H and bromomethyl phenyl sulfone 1e-H. Chloromethyl phenyl sulfone **1a**-H (>97%) and bromomethyl phenyl sulfone **1e**-H (98%) are commercially available compounds. Compounds (**1b−d**)-H were prepared by chlorination of the corresponding 4-substituted thioanisoles[14], and subsequent *m*-CPBA oxidation[15] following literature procedures.[14,15] **1b**-H is a known compound fully characterized already.[16] For the reason of simplicity, the ^{1}H NMR signals of AA'BB'-spin systems of *p*-disubstituted aromatic rings of all compounds described below were treated as doublets. NMR signal assignments were based on additional 2D-NMR experiments (COSY, HSQC, HMBC).

Chloromethyl 4-nitrophenyl sulfone (1d-H) (General procedure 1). 4-Nitrothioanisole (3.50 g, 20.7 mmol) was treated with *N*-chlorosuccinimide (3.18 g, 23.8 mmol) in dry carbon tetrachloride (21 mL) at 35 °C for 24 h. Succinimide precipitated and was removed by filtration. After evaporation of the solvent the residue was dissolved in 65 mL of DCM, cooled in an ice-water bath with stirring, and 77% *m*-chloroperoxybenzoic acid (11.0 g, 49.1 mmol) was added in portions within 5 min. The mixture was stirred at 0 °C for 40 min and 5 h at room temperature. After addition of ether, the solution was washed with water, 10% aqueous NaOH, an aqueous solution of $Na_2S_2O_3$-NaI-NaOH, and a saturated aqueous solution of NaCl. The organic extract was dried over $MgSO_4$, and the solvent was removed using a rotary evaporator. The residue was recrystallized from EtOAc and pentane to give a yellow solid **1d**-H (3.42 g, 14.5 mmol, 70%), mp 138−143 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (d, *J* = 8.8 Hz, 2 H, H-3 and H-5), 8.23 (d, *J* = 8.9 Hz, 2 H, H-2 and H-6), 5.50 (s, 2 H, H-1). ^{13}C NMR (101 MHz, DMSO-d_6) δ 151.1 (C-4), 141.2 (C-7), 130.6 (C-2 and C-6), 124.6 (C-3 and C-5), 57.1 (C-1). HRMS (EI) m/z: [$M^{+\cdot}$] calcd

for $C_7H_6ClNO_4S$ 234.9701, found 234.9702. IR (ATR) ***v*** (cm^{-1}) **=** 2942, 1607, 1531, 1475, 1401, 1334, 1236, 1209, 1155, 1131, 1083, 1011, 873, 854, 796, 755, 723, 679.

Chloromethyl 4-cyanophenyl sulfone (1c-H). General procedure 1 was applied to 4-cyanothioanisole (1.49 g, 10.0 mmol), *N*-chlorosuccinimide (1.40 g, 10.5 mmol) and 77% *m*-chloroperoxybenzoic acid (5.31 g, 23.7 mmol). **1c**-H was obtained as a white solid (1.62 g, 7.53 mmol, 75%) mp 133−138 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (d, *J* = 8.7 Hz, 2 H, H-2 and H-7), 8.13 (d, *J* = 8.7 Hz, 2 H, H-3 and H-6), 5.46 (s, 2 H, H-1). ^{13}C NMR (101 MHz, DMSO-d_6) δ 139.9 (C-8), 133.5 (C-2 and C-7), 129.6 (C-3 and C-6), 117.4 (C-5), 117.1 (C-4), 57.0 (C-1). HRMS (EI) m/z: [$M^{+\cdot}$] calcd for $C_8H_6ClNO_2S$ 214.9802, found 214.9796. IR (ATR) ***v*** (cm^{-1}) **=** 3019, 2240, 1387, 1327, 1293, 1146, 1081, 1015, 850, 841, 794, 778, 732, 693.

Reaction of carbanion 1a with quinone methide 2c in DMF at -50 °C (General procedure 2). To a solution of *t*-BuOK (112 mg, 1.00 mmol) in anhydrous DMF (5 mL) at -50 °C was added a solution of **1a**-H (190 mg, 1.00 mmol) in anhydrous DMF (5 mL) and successively a solution of **2c** (162 mg, 0.500 mmol) in anhydrous DMF (5 mL). After 5 min, 100 mL of 2% aqueous HCl was added and the mixture was extracted with $CHCl_3$. The organic phase was washed by water three times to remove remaining DMF, dried with anhydrous $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography to give a pale yellow liquid: 2,6-Di-tert-butyl-4-(2-chloro-1-(4-methoxyphenyl)-2-(phenylsulfonyl)ethyl)phenol (**3a**-H), ~ 1.3:1 mixture of diastereomers. (193 mg, 0.375 mmol, 75%). Diastereomer A: ^{1}H NMR (599 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.6 Hz, 2 H, H-15 x 2), 7.57 (t, *J* = 7.3 Hz, 1 H, H-17), 7.43 (dd, *J* = 7.2, 7.2 Hz, 2 H, H-16 x 2), 7.33 (d, *J* = 8.2 Hz, 2 H, H-4 x 2), 7.12 (s, 2 H, H-8 x 2), 6.81 (d, *J* = 8.0 Hz, 2 H, H-5 x 2), 5.41 – 5.38 (m, 1 H, H-1, overlap with B), 5.14 (s, 1 H, OH), 5.06 (d, *J* = 4.7 Hz, 1 H, H-2), 3.78 (s, 3 H, H-7 x 3), 1.39 (s, 18 H, H-11 x 18). ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.8 (C-6), 153.0 (C-12), 137.1 (C-14), 136.0 (C-9 x 2), 134.0 (C-17), 131.0 (C-3), 130.9 (C-13), 130.8 (C-4 x 2), 129.7 (C-15 x 2), 128.8 (C-16 x 2), 125.0 (C-8 x 2), 113.6 (C-5 x 2), 79.4 (C-1), 55.3 (C-7), 50.6 (C-2), 34.4 (C-10 x 2), 30.3 (C-11 x 6). Diastereomer B: ^{1}H NMR (599 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.5 Hz, 2 H, H-15 x 2), 7.54 (t, *J* = 7.1 Hz, 1 H, H-17), 7.38 (dd, *J* = 7.4, 7.4 Hz, 2 H, H-16 x 2), 7.25 (d, *J* = 9.3 Hz, 2 H, H-4 x 2), 7.15 (s, 2 H, H-8 x 2), 6.81 (d, *J* = 8.0 Hz, 2 H, H-5 x 2), 5.41 – 5.38 (m, 1 H, H-1, overlap with A), 5.12 (s, 1 H, OH), 4.97 (d, *J* = 5.3 Hz, 1 H, H-2), 3.77 (s, 3 H, H-7 x 3), 1.38 (s, 18 H, H-11 x 18). ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.7 (C-6), 153.1 (C-12), 136.6 (C-14), 135.5

(C-9 x 2), 133.9 (C-17), 132.4 (C-3), 130.0 (C-15 x 2), 129.4 (C-4 x 2), 128.8 (C-13), 128.5 (C-16 x 2), 126.4 (C-8 x 2), 114.1 (C-5 x 2), 79.8 (C-1), 55.3 (C-7), 51.2 (C-2), 34.4 (C-10 x 2), 30.4 (C-11 x 6). HRMS (EI) m/z: [$M^{+\cdot}$] calcd for $C_{29}H_{35}ClO_4S$ 514.1939, found 514.1948. IR (ATR) ***v*** (cm^{-1}) **=** 3634, 2956, 1610, 1511, 1435, 1361, 1322, 1309, 1250, 1212, 1179, 1150, 1135, 1081, 1032, 887, 836, 810, 685, 667.

(*E*)-2,6-Di-tert-butyl-4-(2-(4-methoxyphenyl)-1-((4-nitrophenyl)sulfonyl)vinyl)phenol (3d-H): General procedure 2 was applied to **1d**-H (235 mg, 1.00 mmol), **2c** (162 mg, 0.500 mmol) and *t*-BuOK (112 mg, 1.00 mmol). **3d**-H was obtained as a pale yellow liquid and a mixture of diastereomers. (199 mg, 0.355 mmol, 71%, dr ~ 1.1:1). Diastereomer A: ^{1}H NMR (599 MHz, $CDCl_3$) δ 8.20 (d, *J* = 9.0 Hz, 2 H, H-16 x 2), 7.84 (d, *J* = 9.0 Hz, 2 H, H-15 x 2), 7.29 (d, *J* = 8.8 Hz, 2 H, H-4 x 2), 7.08 (s, 2 H, H-8 x 2), 6.78 (d, *J* = 8.9 Hz, 2 H, H-5 x 2), 5.42 (d, *J* = 5.5 Hz, 1 H, H-1), 5.16 (s, 1 H, OH), 5.01 (d, *J* = 5.5 Hz, 1 H, H-2), 3.77 (s, 3 H, H-7 x 3), 1.37 (s, 18 H, H-11 x 18). ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.19 (C-6), 153.35 (C-12), 150.77 (C-17), 142.55 (C-14), 136.28 (C-9 x 2), 131.16 (C-15 x 2), 130.80 (C-4 x 2), 130.42 (C-3), 130.07 (C-13), 125.06 (C-8 x 2), 123.67 (C-16 x 2), 113.83 (C-5 x 2), 79.77 (C-1), 55.38 (C-7), 50.92 (C-2), 34.51 (C-10 x 2), 30.39 (C-11 x 6). Diastereomer B: ^{1}H NMR (599 MHz, $CDCl_3$) δ 8.14 (d, *J* = 9.1 Hz, 2 H, H-16 x 2), 7.75 (d, *J* = 9.0 Hz, 2 H, H-15 x 2), 7.20 (d, *J* = 8.9, 2 H, H-4 x 2), 7.12 (s, 2 H, H-8 x 2), 6.79 (d, *J* = 8.8 Hz, 2 H, H-5 x 2), 5.45 (d, *J* = 6.0 Hz, 1 H, H-1), 5.15 (s, 1 H, OH), 4.93 (d, *J* = 5.9 Hz, 1 H, H-2), 3.75 (s, 3 H, H-7 x 3), 1.34 (s, 18 H, H-11 x 18). ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.06 (C-6), 153.55 (C-12), 150.67 (C-17), 142.15 (C-14), 135.88 (C-9 x 2), 131.53 (C-15 x 2), 131.48 (C-3), 129.45 (C-4 x 2), 128.19 (C-13), 126.45 (C-8 x 2), 123.39 (C-16 x 2), 114.28 (C-5 x 2), 80.29 (C-1), 55.34 (C-7), 51.38 (C-2), 34.41 (C-10 x 2), 30.32 (C-11 x 6). HRMS (EI) m/z: [$M^{+\cdot}$] calcd for $C_{29}H_{34}ClNO_6S$ 559.1790, found 559.1795. IR (ATR) ***v*** (cm^{-1}) **=** 3631, 2956, 1608, 1531, 1511, 1434, 1346, 1309, 1251, 1179, 1150, 1080, 1032, 908, 853, 752, 681.

Reaction of carbanion 1a with quinone methide 2c in DMSO at 20 °C (General procedure 3). To a solution of **1a** (190 mg, 1.00 mmol) in anhydrous DMSO (5 mL) was added a solution of *t*-BuOK (112 mg, 1.00 mmol) in anhydrous DMSO (5 mL) at room temperature. After 2 min, a solution of **2c** (162 mg, 0.500 mmol) in anhydrous DMSO (10 mL) was added to the resulting solution. The completion of the reaction was checked by TLC and quenched by 100 mL 2% aqueous HCl followed with $CHCl_3$ extraction. The organic extract was washed by water three times to remove remaining DMSO, dried with anhydrous $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography to obtain white solid **4a**-H (167 mg, 0.351 mmol, 70%) and byproduct colorless

liquid **5a**-H (16.8 mg, 0.0499 mmol, 10%).

(*E*)-2,6-Di-tert-butyl-4-(2-(4-methoxyphenyl)-1-(phenylsulfonyl)vinyl)phenol (4a-H): white solid, mp 147−152 °C. ^{1}H NMR (599 MHz, $CDCl_3$) δ 7.84 (s, 1 H, H-1), 7.66 – 7.57 (m, 2 H, H-15 x 2), 7.50 (t, *J* = 7.4 Hz, 1 H, H-17), 7.37 (dd, *J* = 8.5, 7.1 Hz, 2 H, H-16 x 2), 7.05 (d, *J* = 8.9 Hz, 2 H, H-3 x 2), 6.71 (s, 2 H, H-9 x 2), 6.69 (d, *J* = 9.0 Hz, 2 H, H-4 x 2), 5.31 (s, 1 H, OH), 3.75 (s, 3 H, H-6 x 3), 1.28 (s, 18 H, H-13 x 18). ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.03 (C-5), 154.60 (C-11), 139.54 (C-14), 139.47 (C-7), 136.62 (C-1), 136.55 (C-10 x 2), 132.83 (C-17), 132.35 (C-3 X 2), 128.83 (C-15 x 2), 128.58 (C-16 x 2), 127.71 (C-9 x 2), 125.96 (C-2), 122.10 (C-8), 113.96 (C-4 x 2), 55.41 (C-6), 34.39 (C-12 x 2), 30.33 (C-13 x 6). HRMS (EI) m/z: [$M^{+\cdot}$] calcd for $C_{29}H_{34}O_4S$ 478.2172, found 478.2172. IR (ATR) ***v*** (cm^{-1}) **=** 3552, 2949, 1606, 1513, 1444, 1419, 1376, 1305, 1282, 1256, 1236, 1177, 1147, 1110, 1036, 1023, 981, 895, 840, 804, 765, 751, 714, 689, 666.

2,6-Di-tert-butyl-4-((4-methoxyphenyl)ethynyl)phenol (5a-H): colorless liquid. ^{1}H NMR (599 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.7 Hz, 2 H, H-4 x 2), 7.34 (s, 2 H, H-9 x 2), 6.86 (d, *J* = 8.7 Hz, 2 H, H-3 x 2), 5.35 (s, 1 H, OH), 3.82 (s, 3 H, H-1 x 3), 1.45 (s, 18 H, H-12 x 18). ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.4 (C-2), 154.3 (C-13), 136.2 (C-10 x 2), 133.0 (C-4 x 2), 128.6 (C-9 x 2), 116.1 (C-5), 114.5 (C-8), 114.1 (C-3 x 2), 89.3 (C-7), 87.0 (C-6), 55.4 (C-1), 34.5 (C-11 x 2), 30.4 (C-12 x 6). HRMS (EI) m/z: [$M^{+\cdot}$] calcd for $C_{23}H_{28}O_2$ 336.2084, found 336.2081. IR (ATR) ***v*** (cm^{-1}) **=** 3625, 2956, 1606, 1509, 1433, 1287, 1174,1152，1119, 1105, 1031, 885, 830, 806, 774, 757.

(*E*)-2,6-Di-tert-butyl-4-(1-((4-chlorophenyl)sulfonyl)-2-(4-methoxyphenyl)vinyl)phenol (4b-H). General procedure 3 was applied to **1b**-H (225 mg, 1.00 mmol), **2c** (162 mg, 0.500 mmol) and *t*-BuOK (112 mg, 1.00 mmol). **4b**-H was obtained as a pale yellow liquid (156 mg, 0.305 mmol, 61%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1 H, H-1), 7.52 (d, *J* = 8.6 Hz, 2 H, H-15 x 2), 7.34 (d, *J* = 8.5 Hz, 2 H, H-16 x 2), 7.06 (d, *J* = 8.8 Hz, 2 H, H-3 x 2), 6.72 (s, 2 H, H-9 x 2), 6.70 (d, *J* = 8.8 Hz, 2 H, H-4 x 2), 5.34 (s, 1 H, OH), 3.76 (s, 3 H, H-6 x 3), 1.30 (s, 18 H, H-13 x 18). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.19 (C-5), 154.72 (C-11), 139.52 (C-17), 139.21 (C-7), 138.03 (C-14), 136.82 (C-1), 136.76 (C-10 x 2), 132.42 (C-3 x 2), 130.29 (C-15 x 2), 128.80 (C-16 x 2), 127.76 (C-9 x 2), 125.78 (C-2), 121.88 (C-8), 114.02 (C-4 x 2), 55.43 (C-6), 34.42 (C-12 x 2), 30.33 (C-13 x 6). HRMS (EI) m/z: [$M^{+\cdot}$] calcd for $C_{29}H_{33}ClO_4S$ 512.1783, found 512.1792. IR (ATR) ***v*** (cm^{-1}) **=** 3628, 2955, 1601, 1510, 1474, 1436, 1375, 1303, 1253, 1176, 1145, 1029, 982, 828, 765, 706, 669.

(*E*)-2,6-Di-tert-butyl-4-(1-((4-cyanophenyl)sulfonyl)-2-(4-methoxyphenyl)vinyl)phenol (4c-H): General procedure 3 was applied to

1c-H (215 mg, 1.00 mmol), **2c** (162 mg, 0.500 mmol) and *t*-BuOK (112 mg, 1.00 mmol). **4c**-H was obtained as a yellow solid (111 mg, 0.220 mmol, 44%) mp 135−140 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1 H, H-1)), 7.71 (d, *J* = 8.1 Hz, 2 H, H-15 x 2), 7.66 (d, *J* = 8.2 Hz, 2 H, H-16 x 2), 7.06 (d, *J* = 8.4 Hz, 2 H, H-3 x 2), 6.74 (s, 2 H, H-9 x 2), 6.71 (d, *J* = 8.4 Hz, 2 H, H-4 x 2), 5.38 (s, 1 H, OH), 3.77 (s, 3 H, H-6 x 3), 1.30 (s, 18 H, H-13 x 18). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.5 (C-5), 154.9 (C-11), 144.1 (C-14), 138.2 (C-1 and C-7), 137.0 (C-10 x 2), 132.6 (C-3 x 2), 132.2 (C-16 x 2), 129.4 (C-15 x 2), 127.8 (C-9 x 2), 125.5 (C-2), 121.4 (C-8), 117.4 (C-18), 116.4 (C-17), 114.1 (C-4 x 2), 55.5 (C-6), 34.4 (C-12 x 2), 30.4 (C-13 x 6). HRMS (EI) m/z: [$M^{+\cdot}$] calcd for $C_{30}H_{33}NO_4S$ 503.2125, found 503.2124. IR (ATR) ***v*** (cm^{-1}) **=** 3598, 2956, 2232, 1664, 1603, 1511, 1436, 1422, 1358, 1310, 1174, 1120, 1081, 1033, 978, 892, 826, 755, 670.

Reaction of carbanion 1 with benzylidenemalonate 2h (General procedure 4). To a solution of **1a** (98.0 mg, 0.516 mmol) and **2h** (100 mg, 0.344 mmol) in anhydrous DMSO (5 mL) was added anhydrous NaOH (20.6 mg, 0.515 mmol). The resulting solution was stirred for 2h at room temperature and then quenched by saturated NH_4Cl solution followed with $CHCl_3$ extraction. The organic extract was washed by water three times to remove remaining DMSO, dried with anhydrous $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography to obtain yellow liquid diethyl 2-(2-chloro-1-(4-(dimethylamino)phenyl)-2-(phenylsulfonyl)ethyl)malonate (**6a**-H) (119 mg, 0.248 mmol, 72%, dr ~ 5:1). The major diastereomer could be isolated in pure form and its full characterization is as same as literature reported.[7]

Diethyl 2-(2-chloro-2-((4-chlorophenyl)sulfonyl)-1-(4-(dimethylamino)phenyl)ethyl)malonate (6b-H). General procedure 4 was applied to **1b**-H (117 mg, 0.520 mmol), **2h** (100 mg, 0.344 mmol) and NaOH (20.6 mg, 0.515 mmol). **6b**-H was obtained as a pale yellow liquid (123 mg, 0.238 mmol, 70%, dr ~ 2:1), minor diastereomer decomposed during purification. Major diastereomer:^{1}H NMR (599 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.7 Hz, 2 H, H-16 x 2), 7.36 (d, *J* = 8.6 Hz, 2 H, H-17 x 2), 7.16 (d, *J* = 8.8 Hz, 2 H, H-11 x 2), 6.49 (d, *J* = 8.3 Hz, 2 H, H-12 x 2), 5.66 (d, *J* = 7.3 Hz, 1 H, H-1), 4.44 (d, *J* = 8.6 Hz, 1 H, H-3), 4.18 – 4.09 (m, 3 H, H-2 and H-8 x 2), 4.01 (q, *J* = 7.1 Hz, 2 H, H-5 x 2), 2.91 (s, 6 H, H-14 x 6), 1.21 (t, *J* = 7.2 Hz, 3 H, H-9 x 3), 1.08 (t, *J* = 7.1 Hz, 3 H, H-6 x 3). ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.0 (C-7), 167.6 (C-4), 150.4 (C-13), 140.5 (C-18), 136.4 (C-15), 131.1 (C-11 x 2), 130.6 (C-16 x 2), 129.3 (C-17 x 2), 121.5 (C-10), 112.0 (C-12 x 2), 76.5 (C-1), 62.0 (C-8), 61.7 (C-5), 55.4 (C-3), 47.4 (C-2), 40.5 (C-14 x 2), 14.1 (C-9), 13.9 (C-6). HRMS (EI) m/z: [$M^{+\cdot}$] calcd for $C_{23}H_{27}Cl_2NO_6S$ 515.0931, found

515.0925. IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 2981, 2929, 1728, 1613, 1523, 1475, 1445, 1394, 1332, 1279, 1256, 1089, 1012, 947, 819, 751, 666.

Associated Content

Supporting Information

Details of the kinetic experiments, correlation line (log k_2 against E) for **1b**, NMR spectra of all characterized compounds, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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