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Quantification of the Electrophilic Reactivities of Aldehydes, Imines, and Enones

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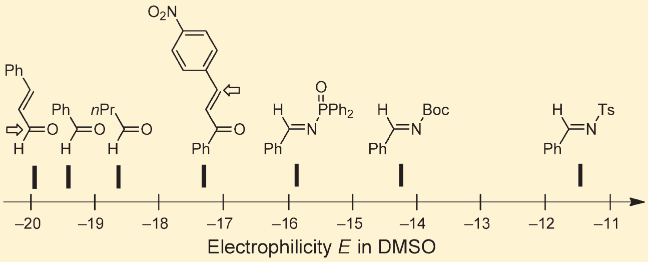
Supporting Information



ABSTRACT: The rates of the epoxidation reactions of aldehydes, of the aziridination reactions of aldimines, and of the cyclopropanation reactions of α,β-unsaturated ketones with aryl-stabilized dimethylsulfonium ylides have been determined photometrically in dimethyl sulfoxide (DMSO). All of these sulfur ylide-mediated cyclization reactions as well as the addition reactions of stabilized carbanions to *N*-tosyl-activated aldimines have been shown to follow a second-order rate law, where the rate constants reflect the (initial) CC bond formation between nucleophile and electrophile. The derived second-order rate constants (log k_2) have been combined with the known nucleophilicity parameters (N, s_N) of the aryl-stabilized sulfur ylides **4a**,**b** and of the acceptor-substituted carbanions **4c**–**h** to calculate the electrophilicity parameters E of aromatic and aliphatic aldehydes (**1a**–**i**), *N*-acceptor-substituted aromatic aldimines (**2a**–**e**), and α,β-unsaturated ketones (**3a**–**f**) according to the linear free-energy relationship $\log k_2 = s_N(N + E)$ as defined in *J. Am. Chem. Soc.* **2001**, *123*, 9500–9512. The data reported in this work provide the first quantitative comparison of the electrophilic reactivities of aldehydes, imines, and simple Michael acceptors in DMSO with carbocations and cationic metal–π complexes within our comprehensive electrophilicity scale.

INTRODUCTION

The majority of reactions used in organic synthesis can be considered as combinations of electrophiles with nucleophiles. In recent years, we have developed an ordering system, which uses eq 1 to predict rates and selectivities for these reactions:[1]

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

Equation 1 calculates the second-order rate constants $k_{20°\mathrm{C}}$ (L mol^{-1}s^{-1}) from two solvent-dependent parameters for nucleophiles [sensitivity s_N (previously termed s) and nucleophilicity N] and one parameter E for electrophiles, which has usually been treated as solvent independent. Using a series of benzhydrylium ions and structurally related quinone methides as reference electrophiles,[2] we have been able to generate a comprehensive nucleophilicity scale covering more than 30 orders of magnitude.[3] Vice versa, the reactivity parameters E for electrophiles have been derived from the rate constants of their reactions with carbon-centered nucleophiles of known N and s_N.[3]

The fact that linear log $k_{20°\mathrm{C}}$ vs E plots were obtained with the same set of E parameters for benzhydrylium ions and quinone methides in solvents as different as dichloromethane, acetonitrile, DMSO, and water does not mean that the degree of solvation is the same for all electrophiles. It implies, however, that the solvation of the reference electrophiles changes linearly with the electrophilicities E. Variable solvation of these electrophiles is thus shifted into the solvent-dependent nucleophile-specific parameters N and s_N.[4] This procedure allowed us to construct an undivided nucleophilicity scale including aliphatic and aromatic π-systems, hydride donors, and n-nucleophiles, such as alkoxides and amines.[3]

Whereas the use of solvent-independent electrophilicity parameters E also appears to work well for other types of carbocations and a variety of Michael acceptors,[1b,c] solvation of the electrophiles has to be considered explicitly in the treatment of S$_N$2 reactions.[5] From the fact that additions of nucleophiles to carbonyl groups usually require hydrogen-bond-donating solvents or catalysts or Lewis-acidic metal cations, e.g., Li$^+$ or Mg^{2+},[6] which coordinate to the developing alkoxide ions, one can conclude that the electrophilicities of carbonyl compounds are also strongly affected by the nature of the solvents.

While kinetics of the additions of nucleophiles to carbonyl groups in aqueous and alcoholic solution have previously been reported,[7] it was the goal of this work to investigate the electrophilic reactivities of nonactivated carbonyl groups in an aprotic polar solvent and to compare them with the electrophilicities of imines and α,β-unsaturated ketones. Inclusion of these synthetically important electrophiles into our comprehensive reactivity scales will significantly improve the value of these scales for designing organic syntheses.

Attempts to determine E parameters of aldehydes in DMSO by their reactions with acceptor-stabilized carbanions (e.g., the highly nucleophilic *p*-nitrophenylacetonitrile anion)[3] failed, because no significant conversion of the carbanions was observed when they were combined with an excess of ordinary aldehydes

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Scheme 1. Mechanism of Sulfur Ylide-Mediated Epoxidations, Aziridinations, and Cyclopropanations (Corey−Chaykovsky Reaction)[9−11]

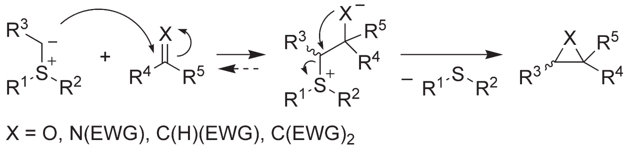
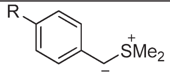
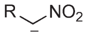
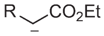
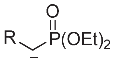


Table 1. Sulfur Ylides 4a,b and Carbanions 4c−h and Their Nucleophilicity Parameters N and s_N in DMSO

Nucleophile		R	N (s_N)[a]
	**4a**	CN	21.07 (0.68)
	4b	NO_2	18.42 (0.65)
	**4c**	Me	21.54 (0.62)
	4d	H	20.71 (0.60)
	**4e**	S(O)Me	20.61 (0.64)
	4f	CO_2Et	20.22 (0.65)
	**4g**	CO_2Et	19.23 (0.65)
	4h	CN	18.57 (0.66)

[a] Nucleophilicity parameters N and s_N for **4a,b** were taken from ref 12b, for **4c,d** from ref 13, for **4e** from ref 14, for **4f** from ref 2b, and for **4g,h** from ref 15.

(e.g., PhCHO) in DMSO. Obviously, the low thermodynamic stability of the developing alkoxides (pK_a = 29.0 for MeOH in DMSO)[8b,c] makes these reactions highly reversible in the aprotic polar solvent DMSO, while they proceed readily in protic solvents, where alkoxide ions are much better stabilized (pK_a = 15.5 for MeOH in H_2O).[8a]

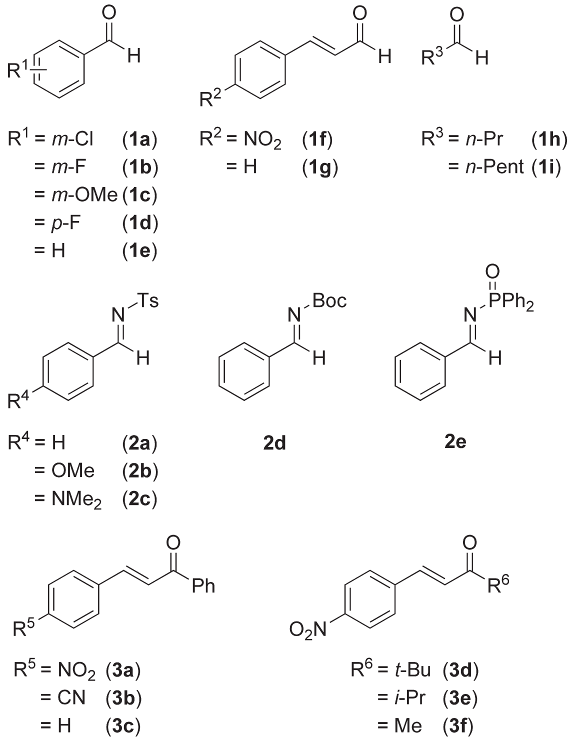
A possibility to achieve irreversible additions of carbon nucleophiles to carbonyl groups in DMSO is the rapid trapping of the intermediate alkoxide anion by an internal electrophile, which is encountered in the reactions of sulfur ylides with carbonyl compounds (Scheme 1). Detailed investigations revealed a common mechanistic course of these epoxidation reactions[9] and of the analogous aziridination[10] and cyclopropanation reactions.[9b,11] In all cases, the sulfur ylide initially attacks at an electrophilic carbon center to form a betaine intermediate, which then undergoes an intramolecular nucleophilic displacement to yield an epoxide, an aziridine, or a cyclopropane, respectively (Scheme 1).

As the formation of the betaine intermediate is often nonreversible and rate determining (dependent on ylide stability and electrophile),[9e,h,n,10a,10c,10d,11b,11e,12] the kinetics of the reactions of the sulfur ylides **4a,b** (Table 1) with the aldehydes **1a−i**, the N-activated imines **2a−e**, and the α,β-unsaturated ketones **3a−f** (Scheme 2) will now be employed to determine the electrophilicity parameters E for these synthetically important compounds in DMSO.

RESULTS

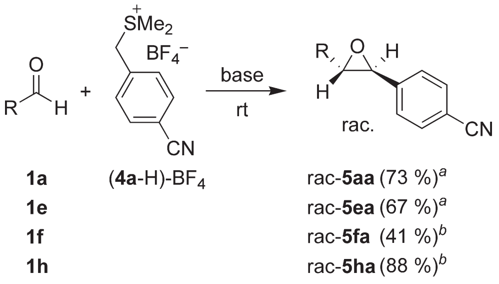
Product Studies. In line with earlier investigations,[9e,h,n] the semistabilized sulfur ylide **4a** was found to give *trans*-epoxides **5** with the benzaldehydes **1a** and **1e** as well as with *p*-nitrocinnamaldehyde (**1f**) and butanal (**1h**) (Scheme 3).

Scheme 2. Aldehydes 1a−i, Imines 2a−e, and Enones 3a−f Investigated in this Work[a]



[a] Ts = *p*-methylbenzenesulfonyl, and Boc = *t*-butoxycarbonyl.

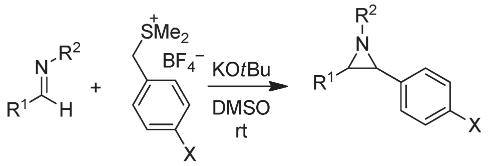
Scheme 3. Reactions of Sulfur Ylide 4a with the Aldehydes 1a,e,f,h



[a] KO*t*Bu, DMSO. [b] K_2CO_3 (aq), $CHCl_3$.

The reactions of the sulfur ylides **4a,b** with all imines **2** examined yielded the aziridines **6** (Scheme 4). While the N-tosyl-substituted aziridines **6ab**, **6ba**, and **6bb** were formed as mixtures of *cis*- and *trans*-isomers, exclusively *trans*-isomers were isolated from the N-*tert*-butoxycarbonyl-substituted imine **2d.** NMR studies of the crude products obtained from the N-diphenylphosphinoyl-substituted imine **2e** showed the formation of **6ea** (cis/trans 1:3) and **6eb** (cis/trans 1:6) as mixtures of diastereomers, which were separated by column chromatography. The corresponding trans products were isolated and characterized, while the cis products could not be obtained in pure form. Detailed descriptions of the experimental procedures and the characterizations of the isolated compounds are given in the Supporting Information.

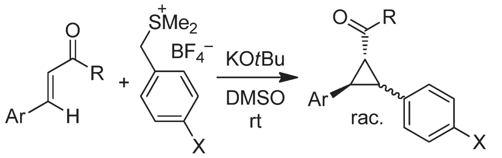
Scheme 4. Reactions of the Sulfur Ylides 4a,b with the Imines 2a,b,d,e



2a	(**4b**-H)-BF$_4$	**6ab** (88 %, *cis*/*trans* ~ 1 : 1.6)[a]
2b	(**4a**-H)-BF$_4$	**6ba** (58 %, *cis*/*trans* ~ 1 : 1.0)[a]
2b	(**4b**-H)-BF$_4$	**6bb** (71 %, *cis*/*trans* ~ 1 : 1.6)[a]
2d	(**4a**-H)-BF$_4$	**6da** (50 %, only *trans*)[a]
2d	(**4b**-H)-BF$_4$	**6db** (41 %, only *trans*)[a]
2e	(**4a**-H)-BF$_4$	**6ea** (58 %, *cis*/*trans* ~ 1 : 3)[b]
2e	(**4b**-H)-BF$_4$	**6eb** (71 %, *cis*/*trans* ~ 1 : 6)[b]

[a] *Cis*/*trans*-ratio corresponds to the isolated products. [b] Yield isolated refers to *trans*-isomer; *cis*/*trans*-ratio corresponds to the crude product.

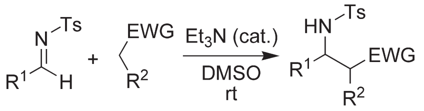
Scheme 5. Reactions of the Sulfur Ylides 4a,b with the Michael Acceptors 3a−f[a]



3a	(**4b**-H)-BF$_4$	rac-**7ab** (65 %, *dr* ~ 1 : 1.5)[b]
3b	(**4a**-H)-BF$_4$	rac-**7ba** (93 %, *dr* ~ 1 : 3)[b]
3c	(**4a**-H)-BF$_4$	rac-**7ca** (51 %, *dr* ~ 1 : 3)[c]
3d	(**4a**-H)-BF$_4$	rac-**7da** (63 %, *dr* ~ 1 : 3)[c]
3e	(**4a**-H)-BF$_4$	rac-**7ea** (84 %, *dr* ~ 1 : 5)
3f	(**4a**-H)-BF$_4$	rac-**7fa** (85 %, *dr* ~ 1 : 3)

[a] Diastereomeric ratios *dr* correspond to the isolated products. [b] Minor diastereomer is a meso compound. [c] Yield isolated refers to major diastereomer; *dr* corresponds to the crude product.

Scheme 6. Reactions of the Carbanions 4c,d,f with the Imines 2a−c



2a	**4d**-H	**8ad** (65 %)
2b	**4c**-H	**8bc** (52 %)[a]
2b	**4d**-H	**8bd** (58 %)
2b	**4f**-H	**8bf** (83 %)[b]
2c	**4d**-H	**8cd** (18 %)

[a] Only the major diastereomer was isolated and characterized (*dr* ∼ 1:3 for the crude product). [b] Reaction conditions: KO*t*Bu, THF, −80 to −40 °C.

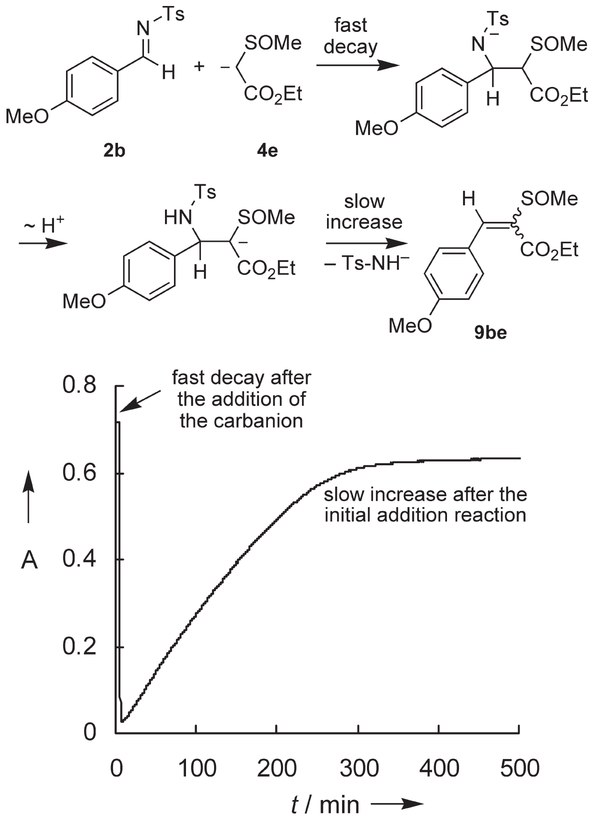


Figure 1. UV−vis spectroscopic monitoring at 318 nm of the reaction of imine **2b** (4.73×10^{-5} mol L^{-1}) with the methylsulfinyl-stabilized carbanion **4e** (8.03×10^{-5} mol L^{-1}) in DMSO at 20 °C.

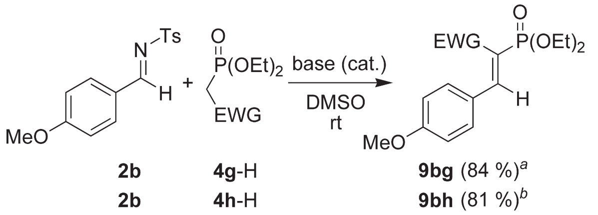
In line with previous reports on the reactions of cinnamaldehyde with aryl-stabilized sulfur ylides,[16] Scheme 3 shows that *p*-nitrocinnamaldehyde (**1f**) reacts exclusively at the carbonyl group with **4a**. In contrast, the α,β-unsaturated ketones **3a**−**f** reacted selectively at the C=C double bond to yield the cyclopropanes **7** as mixtures of diastereomers (Scheme 5). The diastereomers of the cyclopropanes **7ca** and **7da** were separated, and the major isomers were isolated and characterized. The relative configurations of the cyclopropanes **7** have been defined by the characteristic coupling constants of the corresponding cyclopropane protons in the ^{1}H NMR spectra. Detailed descriptions of the experimental procedures and the characterizations of the isolated compounds are given in the Supporting Information.

In contrast to the *N*-Boc- and *N*-diphenylphoshinoyl-substituted imines **2d** and **2e**, which reacted only with the sulfur ylides **4a**,**b** (see Scheme 4), the *N*-tosyl-substituted imines **2a**−**c** also reacted with the carbanions **4c**−**h** in DMSO. As depicted in Scheme 6, the addition products **8** were obtained from the reactions of the *N*-tosyl-activated imines **2a**−**c** with the nitronates **4c**,**d** and the diethyl malonate anion (**4f**).

The methylsulfinyl-stabilized carbanion **4e** and the phosphonate-stabilized carbanions **4g**,**h** did not yield simple addition products with the imine **2b**. Instead, Knoevenagel-type condensation reactions took place with the formation of the olefins **9** (Figure 1 and Scheme 7), as previously described for the reactions of **4g** and **4h** with *N*-tosyl-substituted imines.[17] UV−vis spectroscopic monitoring of these reactions showed that the fast additions of the carbanions to the imine **2b** are followed by slow eliminations of the tosylamide group to give the Knoevenagel products **9** (Figure 1 and Supporting Information, Tables S18, S21, and S23).

In all investigated Knoevenagel-type condensation reactions, only one stereoisomer was obtained. In the case of compound **9be** (Figure 1) the configuration of the double bond was not determined. However, the *E*-configurations of the olefins **9bg** and **9bh** (Scheme 7) were derived from the characteristic coupling constant

Scheme 7. Condensation Products from the Phosphoryl-Stabilized Carbanions 4g,h and Imine 2b



[a] KOtBu (18 mol %). [b] Et_3N (18 mol %).

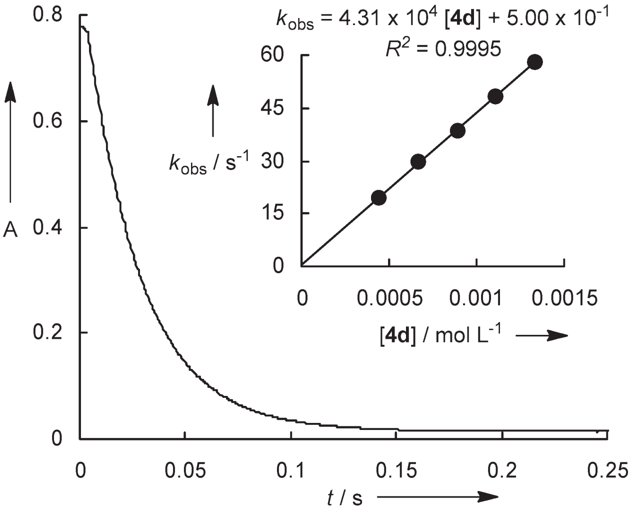


Figure 2. UV–vis spectroscopic monitoring of the reaction of the nitromethyl anion (**4d**, 4.44×10^{-4} mol L^{-1}) with the imine **2b** (3.77×10^{-5} mol L^{-1}) at 330 nm in DMSO at 20 °C. Insert: Determination of the second-order rate constant $k_2 = 4.31 \times 10^4$ L mol^{-1} s^{-1} from the dependence of the first-order rate constant k_{obs} on the concentration of **4d**.

of the olefinic proton with the phosphorus nucleus (J_{HP} = 24 and 21 Hz, respectively).[17,18] Detailed reaction conditions for the preparation of the compounds **9be**, **9bg**; and **9bh** are given in the Supporting Information.

Kinetic Investigations. All kinetic investigations were performed in DMSO solution at 20 °C. As reported earlier,[12b] the aryl-stabilized sulfur ylides **4a**,**b** decompose slowly at room temperature and were, therefore, prepared by deprotonation of the corresponding CH acids (**4a**,**b**-H)-BF_4 with 1.00–1.05 equiv of KOtBu in dry THF at ≤−50 °C. Small amounts of these solutions were dissolved in DMSO at room temperature directly before each kinetic experiment. Stock solutions of the carbanions **4c**–**h** were prepared by deprotonation of the corresponding CH acids (**4c**–**h**)-H with 1.00–1.05 equiv of KOtBu in DMSO. All kinetic investigations were monitored photometrically, either by following the disappearance of the colored imines **2a**–**c** or of the colored aryl-stabilized sulfur ylides **4a**,**b** at or close to their absorption maxima. The kinetic investigations of the reactions of the carbanions **4c**–**h** with the imines **2a**–**c** (also prepared as stock solutions in DMSO) were performed with a high excess of the carbanions over the imines to achieve first-order kinetics. Vice versa, first-order kinetics for the reactions of the aryl-stabilized ylides **4a**,**b** with the electrophiles **1**–**3** were realized by using at least 10 equiv of the electrophiles **1**–**3**. As the absolute concentration of the minor component is not crucial for the determination of the pseudo-first-order rate constants k_{obs} (eqs 2a and 2b) when the rate of decomposition is much slower than the reaction under consideration, we have thus circumvented the problem that the absolute concentrations of the semistabilized ylides **4a**,**b** cannot precisely be determined due to their low stability.

From the exponential decays of the UV–vis absorbances of the imines **2a**–**c** (Figure 2) or of the sulfur ylides **4a**,**b**, the first-order rate constants k_{obs} were obtained. Plots of k_{obs} (s^{-1}) against the concentrations of the reaction partners used in excess were linear with negligible intercepts, as required by the relation $k_{obs} = k_2[\mathrm{Nu}]_0$ (eq 2a and Figure 2) or $k_{obs} = k_2[\mathrm{E}]_0$ (eq 2b), respectively. Only in the reactions of the carbanions **4f**–**h** with **2b** incomplete consumption of the imine **2b** as well as the positive intercepts of plots of k_{obs} vs [**4**] were observed due to the high reversibility of the additions; because of slow subsequent reactions a reliable determination of the equilibrium constants was not possible. However, in all cases the second-order rate constants could be derived from the slopes of the linear correlations of k_{obs} versus $[\mathrm{Nu}]_0$ or $[\mathrm{E}]_0$, respectively (Table 2):

$$-\,\mathrm{d}[\mathrm{E}]/\mathrm{d}t = k_2[\mathrm{Nu}][\mathrm{E}] \qquad (2)$$

$$\text{for } [\mathrm{Nu}]_0 \gg [\mathrm{E}]_0 \Rightarrow k_{obs} = k_2[\mathrm{Nu}]_0 \qquad (2a)$$

$$\text{for } [\mathrm{E}]_0 \gg [\mathrm{Nu}]_0 \Rightarrow k_{obs} = k_2[\mathrm{E}]_0 \qquad (2b)$$

■ DISCUSSION

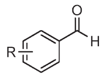
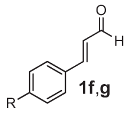
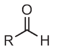
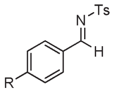
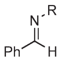
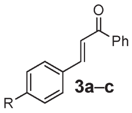
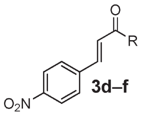
Epoxidation Reactions. Elegant crossover experiments by Aggarwal and co-workers[9e] have shown that the independently generated *anti*-betaine **10** underwent fast cyclization with exclusive formation of *trans*-stilbene oxide (Scheme 8). The analogous generation of the *syn*-betaine **11** led to retro-addition, however, and the regenerated sulfur ylide could be trapped by the more electrophilic *p*-nitrobenzaldehyde.

Analogous crossover experiments showed that also in acetonitrile the *anti*-betaine does not cleave to sulfur ylide and aldehyde but gives the *trans*-stilbene oxide selectively.[9n]

As a consequence, the selective formation of *trans*-epoxide from benzaldehyde and semistabilized sulfur ylides (Scheme 8) must either be due to selective formation of the *anti*-betaine **10** ($k_{anti} \gg k_{syn}$) or to the parallel formation of both betaines ($k_{anti} \approx k_{syn}$), followed by cyclization of the *anti*-betaine **10** and retro-addition of the *syn*-betaine **11**. The second mechanism is only compatible with the observed second-order kinetics if the retro-addition of the *syn*-betaine (k_{-syn}) is very fast. If significant equilibrium concentrations of the *syn*-betaine would build up during the reaction, then deviations from the second-order rate law would be expected, as the UV–vis spectroscopically monitored sulfur ylide **4a** would continuously be regenerated from the reservoir of the *syn*-betaine. No matter whether the *syn*-betaine is formed as a short-lived intermediate or not, the rate constants listed in Table 2 reflect the rate-determining formation of the *anti*-betaine (k_{anti}) as exemplified in Scheme 8.[19]

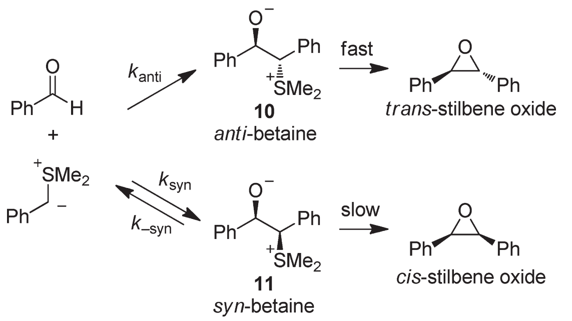
As shown in Table 2, the rates of the reactions of the sulfur ylide **4a** with the aldehydes **1a**–**e** increase with the increasing electron-withdrawing properties of the groups bound to the *meta*- or *para*-positions of the benzaldehydes **1a**–**e**. From the fair correlation of log k_2 versus Hammett's substituent constants

Table 2. Experimental and Calculated Second-Order Rate Constants (L mol^{-1}s^{-1}) for the Reactions of the Sulfur Ylides **4a,b** and the Carbanions **4c–h** with the Aldehydes **1**, the Imines **2**, and the Michael Acceptors **3** in DMSO at 20°C

Electrophile		E[a]	Nucleophile	Identified Product	k_2^{exp}	k_2^{calcd}[b]
 **1a–e**	**1a** (R = *m*-Cl)	−18.03[c]	**4a**	**5aa**	1.17×10^{2}	identical[c]
	1b (R = *m*-F)	−18.27[c]	**4a**		8.06×10^{1}	identical[c]
	1c (R = *m*-OMe)	−19.32[c]	**4a**		1.54×10^{1}	identical[c]
	1d (R = *p*-F)	−19.42[c]	**4a**		1.32×10^{1}	identical[c]
	1e (R = H)	−19.52[c]	**4a**	**5ea**	1.13×10^{1}	identical[c]
 **1f,g**	**1f** (R = NO$_2$)	−18.19[c]	**4a**	**5fa**	9.04×10^{1}	identical[c]
	1g (R = H)	−19.92[c]	**4a**		6.03	identical[c]
 **1h,i**	**1h** (R = *n*-Pr)	−18.72[c]	**4a**	**5ha**	3.98×10^{1}	identical[c]
	1i (R = *n*-Pent)	−18.76[c]	**4a**		3.72×10^{1}	identical[c]
 **2a–c**	**2a** (R = H)	−11.50	**4b**	**6ab**	4.15×10^{4}	3.15×10^{4}
			4d	**8ad**	2.50×10^{5}	3.36×10^{5}
	2b (R = OMe)	−13.05	**4a**	**6ba**	3.21×10^{5}	2.84×10^{5}
			4b	**6bb**	6.19×10^{3}	3.09×10^{3}
			4c	**8bc**	2.62×10^{5}	1.84×10^{5}
			4d	**8bd**	4.31×10^{4}	3.94×10^{4}
			4e	**9be**	1.33×10^{5}	6.89×10^{4}
			4f	**8bf**	7.65×10^{3}[d]	4.58×10^{4}
			4g	**9bg**	2.35×10^{3}[d]	1.04×10^{4}
			4h	**9bh**	1.63×10^{4}[d]	4.40×10^{3}
	2c (R = NMe$_2$)	−15.09	**4c**		1.03×10^{4}	9.98×10^{3}
			4d	**8cd**	1.58×10^{3}	2.36×10^{3}
			4e		4.79×10^{3}	3.41×10^{3}
 **2d,e**	**2d** (R= Boc)	−14.22	**4a**	**6da**	3.97×10^{4}	4.55×10^{4}
			4b	**6db**	6.17×10^{2}	5.37×10^{2}
	2e (R= POPh$_2$)	−15.89	**4a**	**6ea**	4.46×10^{3}	3.33×10^{3}
			4b	**6eb**	3.21×10^{1}	4.41×10^{1}
 **3a–c**	**3a** (R = NO$_2$)	−17.33	**4a**		3.46×10^{2}	3.49×10^{2}
			4b	**7ab**	5.22	5.11
	3b (R = CN)	−17.64	**4a**	**7ba**	2.41×10^{2}	2.15×10^{2}
			4b		2.89	3.21
	3c (R = H)	−18.82[c]	**4a**	**7ca**	3.41×10^{1}	identical[c]
 **3d–f**	**3d** (R = *t*-Bu)	−19.15[c]	**4a**	**7da**	2.02×10^{1}	identical[c]
	3e (R = *i*-Pr)	−19.17[c]	**4a**	**7ea**	1.97×10^{1}	identical[c]
	3f (R = Me)	−19.36[c]	**4a**	**7fa**	1.45×10^{1}	identical[c]

[a] Determined by least-squares minimization of $\Delta^2 = \Sigma(\log k_2^{\mathrm{exp}} - s_N(N + E))^2$ using the second-order rate constants k_2^{exp} given in this table and the N and s_N parameters of the nucleophiles **4a–h** from Table 1. For details, see Tables S10, S27, S32, S38, S42 and Figures S1–S3 of the Supporting Information. [b] Calculated by eq 1 with the N and s_N parameters for the nucleophiles **4** (Table 1) and the optimized electrophilicity parameters E for the imines **2a–e** and the enones **3a,b** determined in this work. [c] Only one k_2^{exp} value was used for the determination of E. [d] Incomplete consumption of the electrophile was observed indicating an equilibrium situation.

Scheme 8. Mechanism Accounting for the High Trans Selectivity in the Epoxidation Reaction of Benzaldehyde with Semistabilized Sulfur Ylides[9e,h]



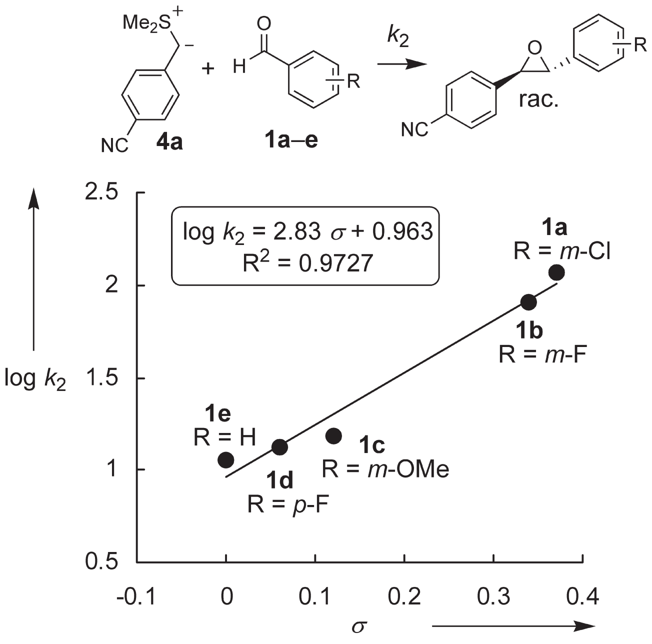


Figure 3. Correlation of the second-order rate constants k_2 for the reactions of the sulfur ylide **4a** with the benzaldehydes **1a**−**e** in DMSO at 20 °C versus Hammett's σ (taken from ref 20).

σ shown in Figure 3, one can derive a reaction constant of $\rho = 2.8$ in line with a rate-determining nucleophilic addition of sulfur ylide **4a** to the aldehydes **1a**−**e**. A similar reaction constant of $\rho = 2.5$ was reported for the epoxidations of various benzaldehydes with dimethylsulfonium benzylide in CD_3CN.[9n]

As the second-order rate constants (Table 2) for the reactions of sulfur ylide **4a** with the aldehydes **1a**−**i** reflect the rate of attack of a carbon nucleophile at a carbonyl group with formation of an alkoxide anion, they can be used for a quantitative comparison of the electrophilic reactivities of the aldehydes **1a**−**i**. Figure 4 shows that the reactivities of the aldehydes **1a**−**i** cover only 1.5 orders of magnitude. The least reactive compound in this series is the unsubstituted cinnamaldehyde (**1g**), which is approximately half as reactive as benzaldehyde (**1e**). The aliphatic aldehydes **1h** and **1i** are three times more electrophilic than benzaldehyde. Equation 1 was used to calculate the electrophilicity parameters E of **1a**−**i** (Table 2) from the rate constants listed in Table 2 and the N and s_N parameters of the sulfur ylide **4a** (Table 1).

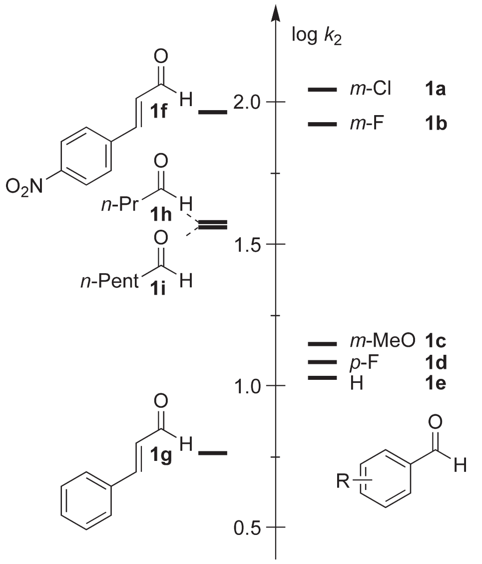


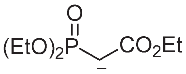
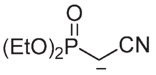
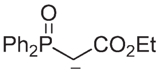
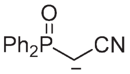
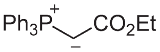
Figure 4. Comparison of the rate constants (log k_2) for the reactions of the aldehydes **1a**−**i** with sulfur ylide **4a** in DMSO at 20 °C.

In previous work we have determined rate constants for the olefination reactions of aromatic aldehydes with phosphoryl-stabilized carbanions and with phosphorus ylides.[15] Table 3 compares the experimental rate constants with those calculated by eq 1 from the E values of the aldehydes in Table 2 and the previously reported N and s_N parameters[15] for phosphorus ylides and phosphoryl-substituted carbanions.

In view of the generally accepted model for salt-free Wittig reactions, which involves concerted oxaphosphetane formation,[22,23] the similarity of k_2^{exp} and k_2^{calcd} in Table 3 is unexpected and remarkable: All rate constants calculated by using eq 1 for the reactions of the phosphoryl-stabilized carbanions **4g**−**j** and the phosphorus ylide **4k** listed in Table 3 with the benzaldehydes **1a,d,e** deviate by less than a factor of 66 from the corresponding experimental values. As the confidence limit of eq 1, which uses only three parameters to predict absolute rate constants in a reactivity range of 40 orders of magnitude, is a factor of 10−100, one cannot unambiguously assign the origin of these deviations. In any case, the small $k_2^{\text{exp}}/k_2^{\text{calcd}}$ ratios in Table 3 prove that the oxaphosphetanes must be generated by highly asynchronous processes from **4g**−**k** and **1a,d,e** via transition states which are not significantly stabilized by the formation of the new PO bonds. Though the similarity between k_2^{exp} and k_2^{calcd} in Table 3 suggests that eq 1 may generally be applicable for defining scope and limitations of the olefination reactions with Wittig and Horner−Wadsworth−Emmons reagents, it is presently not clear whether this approximation also holds for reactions with other types of phosphoryl-stabilized carbanions and phosphorus ylides.

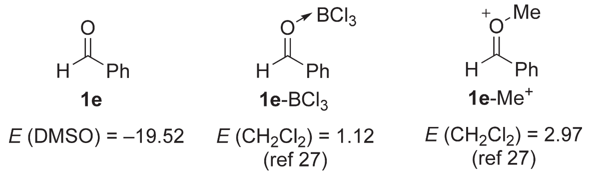
While the electrophilicity parameters for aldehydes (Table 2) reflect the intrinsic reactivities of aldehydes in DMSO, Scheme 9 demonstrates the striking increase of the electrophilic reactivity of benzaldehyde (**1e**), when its carbonyl group is activated by a Lewis acid or by O-methylation.[24] Accordingly, the boron trichloride complex **1e**-BCl_3 is more than 20 orders and the carboxonium ion **1e**-Me^+ is more than 22 orders of magnitude more reactive than benzaldehyde (**1e**). The mild conditions for many Knoevenagel[25] and Henry[26] reactions indicate, however, that the electrophilicities of aldehydes increase significantly in aqueous or alcoholic solvents.

Table 3. Comparison of the Experimental and Calculated Second-Order Rate Constants (L mol^{-1} s^{-1}) for the Olefination Reactions of the Benzaldehydes **1a,d,e** with Phosphoryl-Stabilized Carbanions **4g**−**j** and Phosphorus Ylide **4k** in DMSO at 20°C [a,b]

Nucleophile (N / s_N)		**1a** (*m*-Cl)	**1d** (*p*-F)	**1e** (H)
	k_2^{exp}	5.73×10^1	4.05	2.02
	k_2^{calcd}	6.03	7.52×10^{-1}	6.48×10^{-1}
4g (19.23 / 0.65)	$k^{\text{exp}}/k^{\text{calcd}}$	9.5	5.4	3.1
	k^{exp}	1.48×10^2	1.17×10^1	7.16
	k^{calcd}	2.27	2.75×10^{-1}	2.36×10^{-1}
4h (18.57 / 0.66)	$k_2^{\text{exp}}/k_2^{\text{calcd}}$	65	43	30
	k_2^{exp}	1.58		
	k_2^{calcd}	6.42		
4i (19.20 / 0.69)	$k_2^{\text{exp}}/k_2^{\text{calcd}}$	0.25		
	k_2^{exp}	6.67	7.08×10^{-1}	5.52×10^{-1}
	k_2^{calcd}	2.99	2.98×10^{-1}	2.53×10^{-1}
4j (18.69 / 0.72)	$k_2^{\text{exp}}/k_2^{\text{calcd}}$	2.2	2.4	2.2
	k_2^{exp}			1.44×10^{-3} [c]
4k (12.21 / 0.62)	k_2^{calcd}			2.94×10^{-5}
	$k_2^{\text{exp}}/k_2^{\text{calcd}}$			49

[a] N and s_N parameters and rate constants k_2^{exp} (DMSO, 20 °C) taken from ref 15 if not indicated otherwise. [b] Rate constants k_2^{calcd} were calculated by using eq 1, the N and s_N parameters for the nucleophiles (column 1 of this table), and the electrophilicity parameters E for **1a,d,e** (Table 2). [c] Taken from ref 21.

Scheme 9. Comparison of the Electrophilic Reactivity E of Benzaldehyde **1e** in DMSO with Those of the Boron Trichloride Complex **1e**-BCl$_3$ and the Carboxonium Ion **1e**-Me$^+$ in CH$_2$Cl$_2$



Reactions with Imines. Previous mechanistic studies revealed that the aziridination reactions of *N*-tosyl-substituted aldimines (e.g., imines **2a**−**c**) with aryl-stabilized sulfur ylides (e.g., **4a**,**b**) proceed in a stepwise manner via initial irreversible nucleophilic attack.[10a,c,d] Thus, a single C—C bond is generated in the rate-determining step of these aziridination reactions, like in the addition reactions of the carbanions **4c**−**h** to the imines **2a**−**c**. As a consequence, eq 1 should be applicable to both types of reactions. Therefore, we have calculated the electrophilicity parameters E for **2a**−**c** by least-squares minimization of $\Delta^2 = \Sigma(\log k_2^{\text{exp}} - s_N(N + E))^2$ using the corresponding second-order rate constants k_2^{exp} given in Table 2 and the N and s_N parameters of **4a**−**h** from Table 1. The optimized E parameters for **2a**−**c** listed in Table 2 and the N and s_N parameters of **4a**−**h** listed in Table 1 have been substituted into eq 1 to give the k_2^{calcd} values listed in the last column of Table 2. Though the nucleophile-specific parameters N and s_N of the sulfur ylides **4a**,**b** and of the carbanions **4c**−**h** have been derived from the rates of their reactions with benzhydrylium ions and Michael acceptors, the similarity between k_2^{calcd} and k_2^{exp} in Table 2 shows that they can be combined with the electrophilicity parameters of the *N*-tosyl-substituted benzaldimines **2a**−**c** to calculate the rate constants for the aziridination reactions as well as for the addition reactions of the carbanions to the C═N double bond. In 5 of 8 cases, the agreement between calculated and experimental reactivities of **2b** is better than factor 2.1 and in all other cases better than a factor of 6.

A graphical illustration for this agreement is presented in Figure 5. The correlation lines drawn in this figure are derived from the previously reported reactivities of the sulfur ylides **4a**,**b** and the nitromethyl anion (**4d**) toward reference electrophiles (e.g., benzhydrylium ions, quinone methides, and diethyl benzylidenemalonates)[12b,13] without considering the rate constants determined in this work. The good matching of the rate constants for the reactions of the aryl-stabilized sulfur ylides **4a**,**b** and the carbanion **4d** with the imines **2a**−**e** to these correlation lines illustrates the applicability of the previously reported N and s_N parameters of these nucleophiles to their reactions with imines. Figure 5 furthermore emphasizes the mechanistic analogy between the rate-determining step of the aziridination reactions and the nucleophilic attack of carbanions to imines.

Figure 5 illustrates the fact that the electrophilic reactivities of the *N*-tosyl-activated imines **2a**−**c** increase with decreasing electron-donating effects of the *p*-substituents. A correlation of the rate constants for the reactions of **2a**−**c** with **4d** vs Hammett's σ_p is shown on page S42 of the Supporting Information. The resulting Hammett reaction constant of $\rho = 2.6$ is similar to that obtained for the reactions of the benzaldehydes **1a**−**e** with the sulfur ylide **4a** ($\rho = 2.8$, see above). When the tosyl group of the imine **2a** is replaced by less electron-withdrawing substituents, i.e., the *tert*-butoxycarbonyl group in case of **2d** or the diphenylphosphinoyl group in case of **2e**, the electrophilic reactivity toward **4b** decreases by a factor of 67 and 1290, respectively.

Cyclopropanation Reactions. As shown in previous work[12b] and illustrated in Figure 6, we have observed that the rate constants of the cyclopropanation reactions of Michael acceptors (e.g., diethyl benzylidenemalonates) with sulfur ylides fit the same correlations of log k_2 vs electrophilicity E as the corresponding reactions of sulfur ylides with benzhydrylium ions. A stepwise formation of the cyclopropanes with rate-determining formation of the intermediate zwitterions was thus indicated. In analogy to Figure 5, the depicted correlation lines in Figure 6 have been derived from the previously reported reactivities of the sulfur

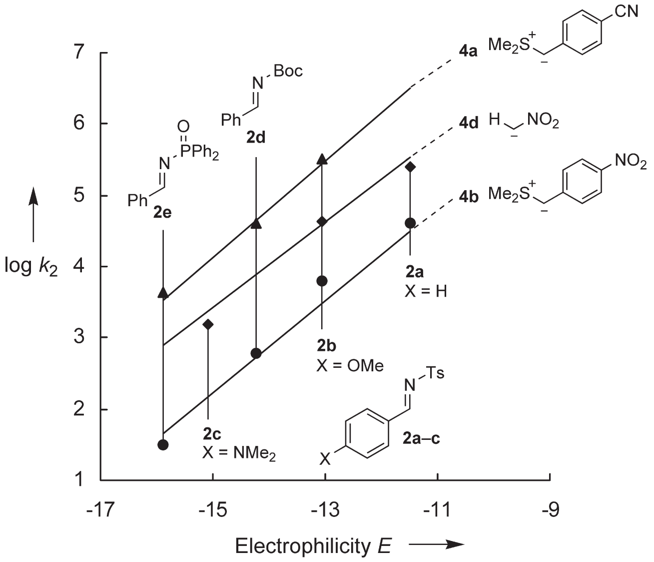


Figure 5. Matching of the rate constants for the reactions of the aryl-stabilized sulfur ylides **4a**,**b** and the carbanion **4d** with the imines **2a**−**e** to the previously derived correlation lines for the reactions of **4a**,**b**,**d** with reference electrophiles (e.g., benzhydrylium ions, quinone methides, and diethyl benzylidenemalonates) in DMSO at 20 °C.[12b,13]

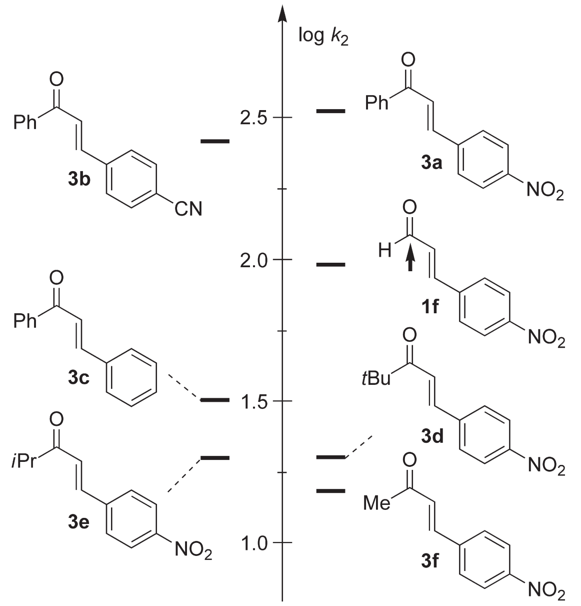


Figure 7. Comparison of the rate constants (log k_2) for the reactions of the enones **3a**−**f** and *p*-nitrocinnamaldehyde (**1f**) with the sulfur ylide **4a** in DMSO at 20 °C.

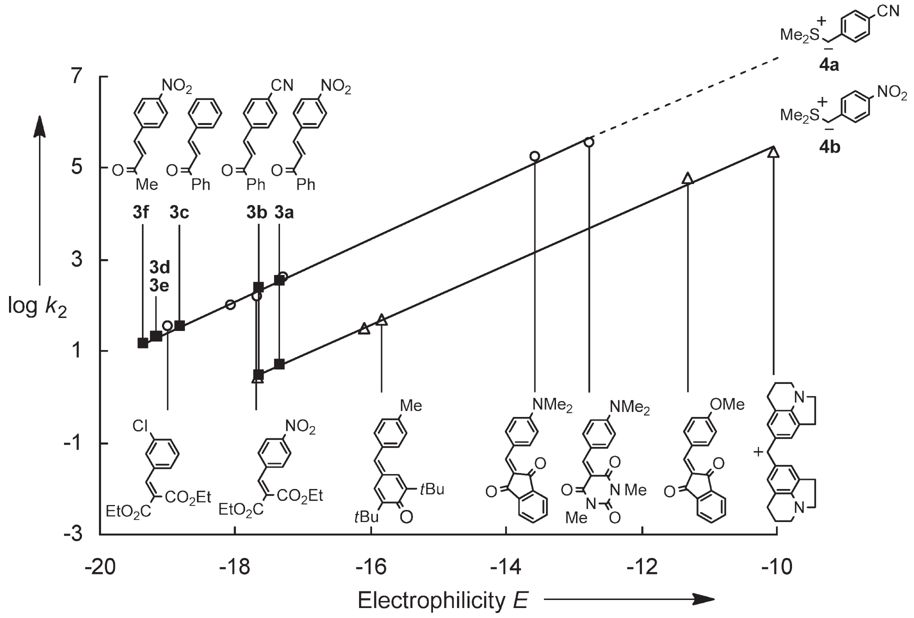


Figure 6. Matching of the rate constants for the reactions of the semistabilized sulfur ylides **4a**,**b** with the enones **3a**−**f** to the previously derived correlation lines for the reactions of **4a**,**b** with reference electrophiles (e.g., benzhydrylium ions, quinone methides, and diethyl benzylidenemalonates) in DMSO at 20 °C.[12b] Nonidentified points refer to reference electrophiles which are specified in Figure S4 of the Supporting Information.

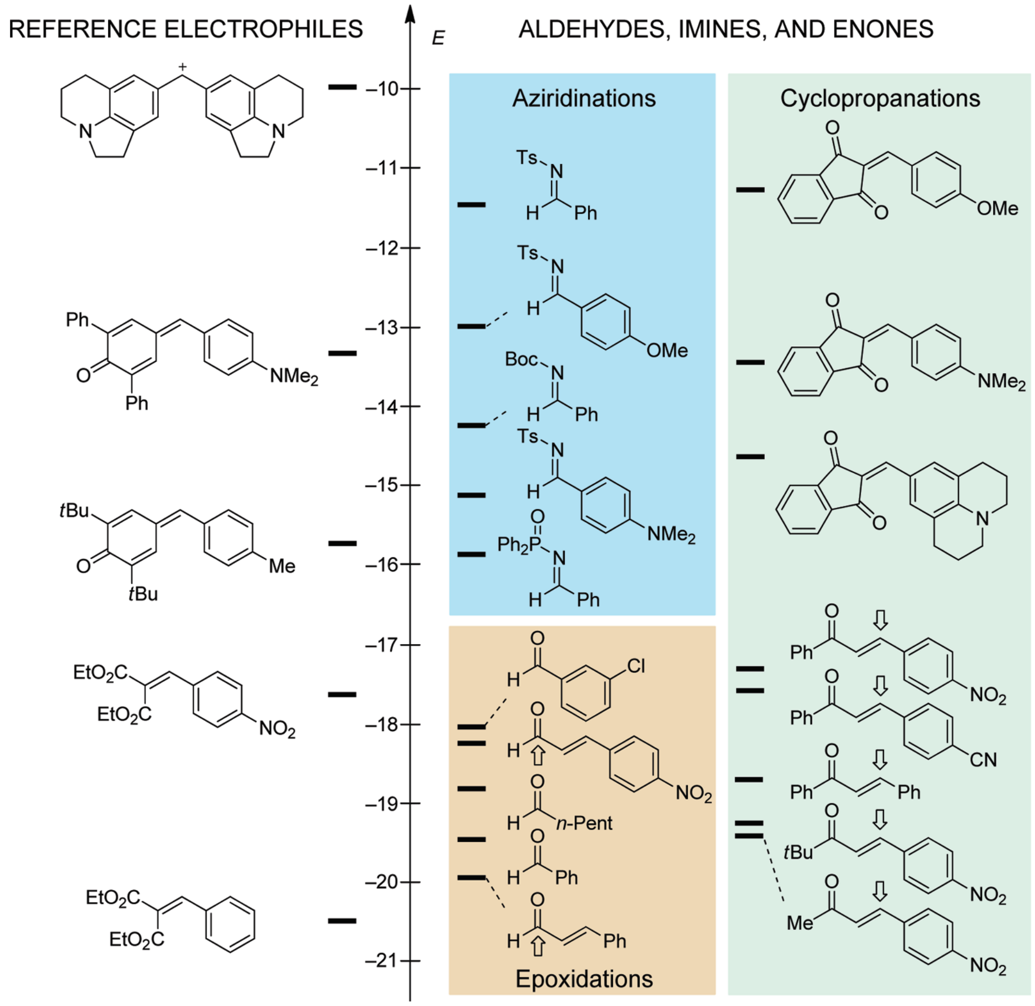


Figure 8. Comparison of the electrophilicity parameters E of aldehydes, imines, and enones with different Michael acceptors in DMSO.

ylides **4a**,**b** toward reference electrophiles (e.g., benzhydrylium ions, quinone methides, and diethyl benzylidenemalonates)[12b] without considering the rate constants determined in this work. The good match of the rate constants for the reactions of the aryl-stabilized sulfur ylides **4a**,**b** with the enones **3a**,**b** to these correlation lines shows that the relative reactivities of the sulfur ylides **4a** and **4b** toward **3a** and **3b** are identical to those previously observed for their reactions with reference electrophiles.[12b] Analogous reaction mechanisms are thus again indicated.

From the Hammett correlation on page S48 of the Supporting Information one derives a reaction constant of ρ = 1.3 for the reactions of the enones **3a**−**c** with the sulfur ylide **4a**, indicating a moderate increase of reactivity by electron-withdrawing substituents. As illustrated in Figure 7, the reactivities of the α,β-unsaturated ketones **3a**−**f** differ by less than a factor of 25. While variation of the alkyl group in the ketones **3d**−**f** has almost no effect on the reactivities of the C═C double bond, the corresponding phenyl compound **3a** is 24 times more reactive than **3f**, despite the opposite ordering of the Hammett substituent constants [σ_p(COMe) = 0.50 and σ_p(COPh) = 0.43].[20]

Product analysis of the reaction of p-nitrocinnamaldehyde (**1f**) with the sulfur ylide **4a** (Scheme 3) as well as several literature reports on reactions of semistabilized sulfur ylides with α,β-unsaturated aldehydes[16] show that epoxide formation is generally preferred over the cyclopropane formation when α,β-unsaturated aldehydes are used as reactants. The attack at the carbonyl group of **1f** (i.e., epoxidation) is kinetically preferred over the attack to the conjugate position (i.e., cyclopropanation). This selectivity indicates that the C═C double bond of **1f** is less reactive than that of **3d** and **3f**, though the formyl group has a similar Hammett σ_p value [σ_p(CHO) = 0.42][20] as the acetyl and benzoyl group.

CONCLUSION

Epoxidation, aziridination, and cyclopropanation reactions of aldehydes, imines, and Michael acceptors with sulfur ylides, which proceed by a stepwise mechanism with rate-determining formation of an intermediate zwitterion (Scheme 1), have been investigated kinetically. As the first step of these reactions is mechanistically related to the electrophile−nucleophile combinations which have been employed to derive eq 1,[1,2] the resulting second-order rate constants (log k_2) could be combined with the previously published N and s_N parameters of sulfur ylides[12b] to calculate the corresponding reactivity parameters E of these electrophiles.

Figure 8 shows that N-tosyl-, N-*tert*-butoxycarbonyl-, and N-phosphinoyl-substituted benzaldimines are significantly more electrophilic in DMSO than the corresponding benzaldehydes. While the reactions of most aldehydes and imines with stabilized carbanions are highly reversible and cannot be investigated in aprotic solvents, the strong electron-withdrawing effect of the *N*-tosyl group in the benzaldimines **2a**−**c** allowed us also to measure the rate constants of their reactions with ordinary carbanions. In line with the stepwise mechanism for the aziridinations, the rates of the reactions of sulfur ylides and carbanions with imines were found to match with the correlation lines, which were previously derived from the rate constants of the reactions of these nucleophiles with benzhydrylium ions and structurally related reference electrophiles (Figure 5).

Though rate constants for the reactions of phosphorus ylides and phosphoryl-substituted carbanions with aldehydes have already been published previously,[15] we had been reluctant to use these data for determining electrophilicity parameters of aldehydes, because of the evidence for the concerted formation of the oxaphosphetanes.[15,22,23] We were, therefore, surprised that the rate constants for the Wittig and Horner−Wadsworth−Emmons reactions listed in Table 3 can properly be derived from the electrophilicity parameters *E* of aldehydes in Table 2 and the *N* and s_N parameters of the phosphorus-stabilized nucleophiles **4g**−**k**, which have previously been derived from their one-bond-forming reactions with benzhydrylium ions and quinone methides.[15] From the agreement between calculated and experimental rate constants of these olefination reactions, we can conclude that the oxaphosphetane formation for the reactions in Table 3 proceeds via a transition state which is only weakly stabilized by the formation of the new PO bond. The concertedness of the oxaphosphetane formations as well as the rate-limiting steps of Wittig and the related olefination reactions may significantly change, however, when other types of phosphorus ylides and phosphoryl-substituted carbanions are employed.

In previous work we had shown that the electrophilicity parameters *E* of our reference electrophiles (benzhydrylium ions and quinone methides), which were derived from reactions in dichloromethane or DMSO, can also be employed for reactions in other solvents, e. g., acetonitrile, methanol, and water.[1−4] We, therefore, concluded that these reference electrophiles do not experience differential solvation, i.e., that the changes of their solvation energies in different solvents are linearly correlated with *E*. By using solvent-independent electrophilicity parameters *E* for the reference electrophiles, solvent effects have been shifted into the solvent-dependent nucleophile-specific parameters *N* and s_N of eq 1, which allowed us to develop a comprehensive nucleophilicity scale.[4]

Absence of differential solvation cannot generally be expected for ordinary carbonyl compounds and imines, because strong interactions of the polar C═O or C═N double bonds with protic solvents may increase the corresponding electrophilicity parameters *E* in Figure 8,[28] which restricts use of the *E* parameters for these compounds to DMSO solution. Unlike the electrophilicity parameters *E* of carbocations and Michael acceptors, which can be employed for reactions with all types of nucleophiles (e.g., C-, N-, O-, or P-centered), the *E* parameters for aldehydes and imines may be restricted to their reactions with carbon nucleophiles. In reactions with oxygen- or nitrogen-centered nucleophiles, the well-known anomeric stabilization[29] of the resulting products may already affect the transition states. As anomeric effects are not included in the reactivity parameters *N*, s_N, and *E*, amines and alkoxides can be expected to react faster with aldehydes and imines than predicted by eq 1.

The α,*β*-unsaturated ketones depicted in Figure 8 show reactivities comparable to those of diethyl benzylidenemalonates, indicating that a single benzoyl group has a similar activating effect on the electrophilicity of a C═C double bond as two ethoxycarbonyl groups. Obviously, the electrophilicities of these Michael acceptors are not closely correlated with the pK_{aH} values of the resulting carbanions, demonstrating the need for a systematic investigation of their electrophilicities.[30]

EXPERIMENTAL SECTION

Materials and Product Analysis. The sulfonium tetrafluoroborates (**4a**,**b**-H)-BF_4 were prepared as reported earlier.[12b] Ethyl 2-(methylsulfinyl)acetate (**4e**)-H,[31] *p*-nitrocinnamaldehyde (**1f**),[32] enone **3b**,[33] and imines **2a**−**e**[34] were prepared as reported in the literature. The enones **3e**,**f** were prepared in analogy to the procedure as for *p*-nitrocinnamaldehyde (**1f**). The syntheses of the enones **3a**,**d** were achieved according to the same procedure as for **3b**. All other chemicals were purchased from commercial sources and (if necessary) purified by recrystallization or distillation prior to use. A detailed description for the preparation and characterization of the epoxides **5**, the aziridines **6**, the cyclopropanes **7**, the addition products **8**, and the condensation products **9** is given in the Supporting Information.

Kinetics. The rates of all reactions were determined photometrically in dry DMSO (H_2O content <50 ppm). The temperature was kept constant (20.0 ± 0.1 °C) by using a circulating bath thermostat. All reactions were performed under first-order conditions by using conventional diode array and stopped flow UV−vis spectrometers. A detailed description of the procedure is given in the Supporting Information.

ASSOCIATED CONTENT

Supporting Information. Details of the kinetic experiments, synthetic procedures, and NMR spectra of all characterized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(2) (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) Lucius, R.; Loos, R.; Mayr, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 91–95.

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