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Nucleophilicity Parameters of Pyridinium Ylides and Their Use in Mechanistic Analyses

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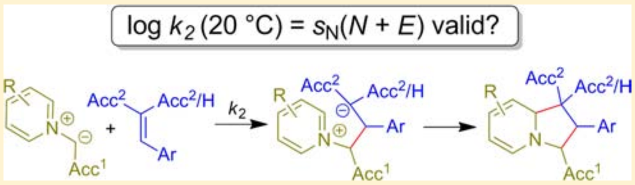
Supporting Information



ABSTRACT: Kinetics of the reactions of pyridinium, isoquinolinium, and quinolinium ylides with diarylcarbenium ions, quinone methides, and arylidene malonates (reference electrophiles) have been studied in dimethylsulfoxide solution by UV–vis spectroscopy. The second-order rate constants (log k_2) were found to correlate linearly with the electrophilicities E of the reference electrophiles, as required by the linear free-energy relationship log $k_{20°C} = s_N(N + E)$ (*J. Am. Chem. Soc.* **2001**, *123*, 9500), which allowed us to derive the nucleophile-specific parameters N and s_N for these ylides. Pyridinium substitution is found to have a similar effect on the reactivity of carbanionic reaction centers as alkoxycarbonyl substitution. Agreement between the rate constants measured for the 1,3-dipolar cycloadditions of pyridinium, isoquinolinium, and quinolinium ylides with acceptor substituted dipolarophiles (arylidenemalononitrile and substituted chalcone) and those calculated from E, N, and s_N shows that the above correlation can also be employed for predicting absolute rate constants of stepwise or highly unsymmetrical concerted cycloadditions. Deviations between calculated and experimental rate constants by a factor of 10^6 were demonstrated to indicate a change of reaction mechanism.

INTRODUCTION

Pyridinium ylides are readily accessible nucleophiles and their chemistry has been studied intensively.[1−6] They undergo various reactions, e. g., 1,3-dipolar cycloadditions[7−9] Michael additions,[10] or cyclopropanations[11] depending on the nature of the employed electrophile. The nucleophilic reactivities of pyridinium ylides have mostly been rationalized by the pK_a values of the corresponding pyridinium ions,[2a,c] although it is known that pK_a values are not a reliable gauge of relative reactivities of nucleophiles,[12] even when the reaction center is kept constant.[13] While some kinetic studies on the formation[3] and reactions[4] of pyridinium ylides have been performed, their reactivities have, to our knowledge, not been analyzed in relationship with other nucleophiles, such as carbanions.

In previous work we have shown that the rates of the reactions of carbocations and Michael acceptors with n-, π-, and σ-nucleophiles, including various ylides,[14] can be described by eq 1, where $k_{20°C}$ is the second-order rate constant in M^{-1} s^{-1}, s_N is a nucleophile-specific sensitivity parameter, N is a nucleophilicity parameter, and E is an electrophilicity parameter.[15,16] The reactivity parameters N and E were used to develop comprehensive reactivity scales, which provide direct comparisons of many different classes of nucleophiles and electrophiles.

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

We recently reported that the [3 + 2]-cycloaddition reactions of pyridinium ylides with benzylidene malonates proceed stepwise.[9] This observation encouraged us to analyze the kinetics of reactions of pyridinium ylides with various electrophiles, including electron-deficient ethylenes, by eq 1, in order to include the ylides **1** (Table 1) into our comprehensive nucleophilicity scale. We now report on the kinetics of the reactions of the pyridinium ylides **1a–g**, the isoquinolinium ylide **1h**, and the quinolinium ylide **1i** with the benzhydrylium ions **2**, the quinone methides **3**, and the benzylidene malonates **4**, which were commonly used as reference electrophiles (Chart 1).[14−16] Subsequently we investigated the kinetics of the reactions of pyridinium ylides with benzylidene malononitrile **5a** and chalcone **5b** to examine whether the N and s_N parameters for pyridinium ylides derived from the reactions of **1a–i** with reference electrophiles can also be employed for predicting the rates of the reactions of pyridinium ylides with other types of Michael acceptors, which undergo diverse subsequent reactions after a common initial rate-determining C–C bond-forming step.

RESULTS AND DISCUSSION

Products. The pyridinium (**1(a–g)**H^+X^-), the isoquinolinium (**1h**H^+Br^-), and the quinolinium salts (**1i**H^+Br^-) were obtained by nucleophilic substitution from the corresponding pyridines, isoquinoline, or quinoline in tetrahydrofuran (THF) as described previously (Table 1).[9] As most ylides (**1a–i**) are unstable compounds, we made no attempts to isolate them but generated them in solution by treating their conjugate acids **1**H^+X^- (X^- = Cl^-, Br^-) with a base.

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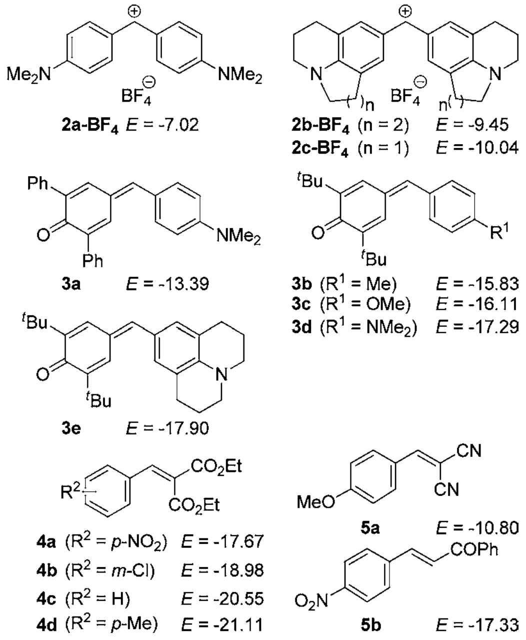
Table 1. Synthesis and pK_a Values of the Pyridinium Salts $1H^+X^-$ Employed as Precursors for the Pyridinium Ylides 1 and Visible Absorption Maxima of the Ylides 1

Pyr	EWG	X	Salt	Yield/%	pK_a(DMSO)	Ylide	λ_{max}(DMSO)[a]/nm
Pyridine	CO_2Et	Br	**1aH⁺Br⁻**	82[b]	14.1[c]	**1a**	425
Pyridine	$CONEt_2$	Br	**1bH⁺Br⁻**	83[b]	~20[d]	**1b**	425
Pyridine	CN	Br	**1cH⁺Br⁻**	quant[b]	16.5[c]	**1c**	433
Pyridine	COMe	Cl	**1dH⁺Cl⁻**	45[b]	11.8[c]	**1d**	425
Pyridine	COPh	Br	**1eH⁺Br⁻**	94[b]	10.7[c]	**1e**	443
4-Me_2N-Pyridine	COPh	Br	**1fH⁺Br⁻**	98	13.2[e]	**1f**	425
3-Cl-Pyridine	COPh	Br	**1gH⁺Br⁻**	88	-	**1g**	453
Isoquinoline	COPh	Br	**1hH⁺Br⁻**	93[b]	~10[f]	**1h**	479
Quinoline	COPh	Br	**1iH⁺Br⁻**	85	-	**1i**	516

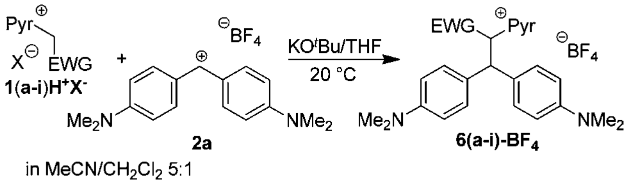
[a] Absorption maximum in the visible range; full UV−vis spectra are given in the Supporting Information. [b] From ref 9. [c] From ref 2c. [d] Estimated from the average difference of $\Delta pK_a \sim 4.5$ between pyridinium and analogously substituted trimethylammonium salts.[2c] [e] In H_2O; from ref 2d. [f] Estimated from the difference of $\Delta pK_a \sim 3$ between the pK_a (**1eH⁺Br⁻**) and pK_a (**1aH⁺Br⁻**) and pK_a of the analogously substituted isoquinolinium salt isoquin$^+CH_2CO_2Et\ Br^-$ (pK_a = 13.5 in DMSO).[2c]

Chart 1. Electrophiles Employed in This Work[a]



[a] Electrophilicities E from refs 15b, c, and 16.

Table 2. Reactions of the Ylides 1 with the Benzhydrylium Tetrafluoroborate $2a\text{-}BF_4$



salt	Pyr	EWG	product	yield, %[a]
1aH⁺Br⁻	pyridine	CO_2Et	**6a-BF₄**	39
1bH⁺Br⁻	pyridine	$CONEt_2$	**6b-BF₄**	98
1cH⁺Br⁻	pyridine	CN	**6c-BF₄**	88
1dH⁺Cl⁻	pyridine	COMe	**6d-BF₄**	69
1eH⁺Br⁻	pyridine	COPh	**6e-BF₄**	quant.[b]
1fH⁺Br⁻	4-NMe_2-pyridine	COPh	**6f-BF₄**	quant.
1gH⁺Br⁻	3-Cl-pyridine	COPh	**6g-BF₄**	quant.[c]
1hH⁺Br⁻	isoquinoline	COPh	**6h-BF₄**	57
1iH⁺Br⁻	quinoline	COPh	**6i-BF₄**	63

[a] After recrystallization from Et_2O/acetonitrile (MeCN) or MeCN. [b] **1eH⁺Br⁻** was dissolved in aq KOH (0.1 M), and the resulting ylide **1e** was extracted with $CHCl_3$. The benzhydrylium tetrafluoroborate **2a-BF₄** (1 equiv) in CH_2Cl_2 was added to the $CHCl_3$ solution of **1e** at room temperature. [c] Yield of the crude product; purification by crystallization from Et_2O/MeCN failed due to decomposition of **6g-BF₄**.

The benzhydrylium tetrafluoroborate **2a-BF₄** was chosen as representative to study the products of the reactions of the ylides **1** with the benzhydrylium ions **2**. Slow addition of a solution of potassium *tert*-butoxide (KOᵗBu) in THF to a suspension of equimolar amounts of benzhydrylium tetrafluoroborate **2a-BF₄** and **1(a−i)H⁺X⁻** in acetonitrile/dichloromethane (5:1) at room temperature gave rise to the formation of the pyridinium salts **6(a−i)-BF₄**, which were purified by crystallization and isolated in 39% to quantitative yields (Table 2). The structures of the products were identified by NMR spectroscopy (^1H and ^{13}C) and HRMS as well as by the crystal structure of **6e-BF₄** (Figure 1).

Electrophile **3b** was chosen as a representative example for investigating the course of the reactions of the ylides **1** with the quinone methides **3**. The salts **1(a−i)H⁺X⁻** and quinone methide **3b** were suspended in acetonitrile at room temperature and treated with triethylamine (2.2 equiv). This procedure afforded the Michael adducts **7a−h** in excellent yields and modest diastereoselectivities (Table 3). The quinolinium derivative **7i** could not be isolated from the reaction of ylide **1i** with quinone methide **3b**, and only decomposition was observed.

As already mentioned above, we recently reported on the reactions of the ylides **1** with benzylidene malonates **4** (Scheme 1).[9] We observed that in polar solvents, such as dimethylsulfoxide (DMSO), addition of ylide **1a** to benzylidene malonate **4d** gave the Michael adduct **9a** via the intermediate betaine **8a**.[9]

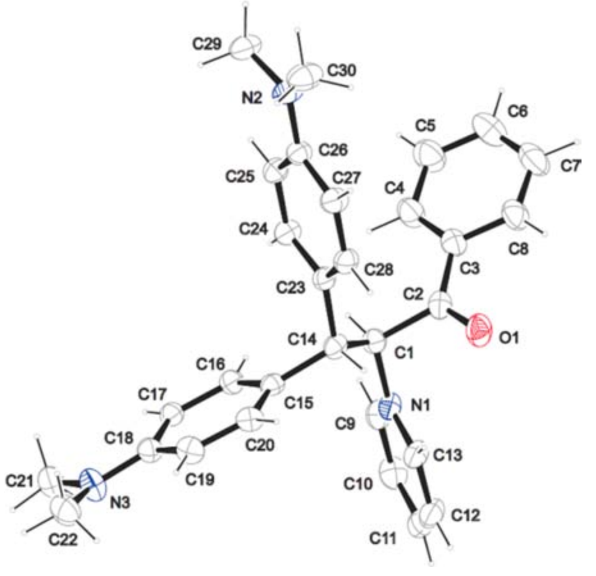
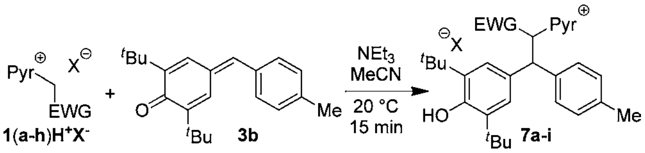


Figure 1. ORTEP-drawing of the crystal structure of **6e-BF$_4$**.

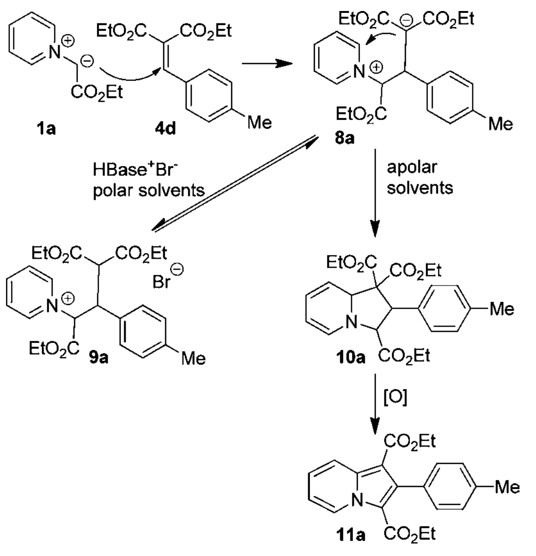
Table 3. Synthesis of the Michael Adducts 7a−h



salt	Pyr	EWG	product	yield, %	dr[a]
$\mathbf{1aH^+Br^-}$	pyridine	CO_2Et	**7a**	94	1:2
$\mathbf{1bH^+Br^-}$	pyridine	$CONEt_2$	**7b**	quant.	1:2
$\mathbf{1cH^+Br^-}$	pyridine	CN	**7c**	quant.	1:2
$\mathbf{1dH^+Cl^-}$	pyridine	COMe	**7d**	quant.	2:3
$\mathbf{1eH^+Br^-}$	pyridine	COPh	**7e**	quant.	1:7
$\mathbf{1fH^+Br^-}$	4-NMe_2-pyridine	COPh	**7f**	quant.	1:5
$\mathbf{1gH^+Br^-}$	3-Cl-pyridine	COPh	**7g**	quant.	1:5
$\mathbf{1hH^+Br^-}$	isoquinoline	COPh	**7h**	quant.	1:3
$\mathbf{1iH^+Br^-}$	quinoline	COPh	**7i**	0	−

[a] Determined by ^1H NMR of the isolated product.

Scheme 1. Solvent Dependence of the Reaction of the Ylide 1a with Benzylidene Malonate 4d[9]



Carrying out the reaction of **1a** with **4d** in a nonpolar solvent, such as CH_2Cl_2, led to the formation of the [3 + 2]-cycloadduct **10a**,[9] which was subsequently oxidized to the indolizine **11a**. The scope of this indolizine formation was tested for a broad variety of differently substituted pyridinium ylides (including **1a**−**e**) and Michael acceptors (including **4a**−**d**).[9] The reaction of isoquinolinium ylide **1h** with benzylidene malonate **4a** did not give a Michael adduct in DMSO but the [3 + 2]-cycloadduct, which was isolated in 75% yield.[9]

Kinetic Investigations. The kinetics of the reactions of the ylides **1** with the electrophiles **2**−**4** in DMSO at 20 °C were monitored photometrically by following the disappearance of one of the two reagents at or close to their absorption maxima (see Supporting Information, SI). Because of the low stabilities of the ylides **1**, they were generated in solution by combining freshly prepared solutions of the salts $\mathbf{1(a{-}i)H^+X^-}$ and KO^{t}Bu (typically 1.05 equiv) in DMSO directly before the kinetic experiments. The formation of the ylides **1a**−**i** was confirmed by their UV−vis spectra (see Table 1 and SI). In order to ensure that the pyridinium ions $\mathbf{1(a{-}i)H^+}$ were quantitatively deprotonated, the pyridinium ion with the highest pK_a value in the series ($\mathbf{1bH^+}$, Table 1) was titrated with a solution of KO^{t}Bu in DMSO, while the absorbance of the ylide **1b** was monitored by UV−vis spectroscopy at 425 nm. After the addition of 1 equiv of KO^{t}Bu, addition of further portions of KO^{t}Bu did not lead to an increase of the absorbance of ylide **1b**, indicating the complete deprotonation of $\mathbf{1bH^+}$ by 1 equiv of KO^{t}Bu (see SI). To simplify the kinetics, one of the two components, nucleophile or electrophile, was used in high excess (≥10 equiv), which resulted in monoexponential decays of the UV−vis absorbances of the minor component. From the decays of the UV−vis absorbances, the first-order rate constants k_{obs} (s^{-1}) were derived by least-squares fitting of the exponential function $A_t = A_0 \exp(-k_{obs}t)$ to the time-dependent absorbances A_t of the minor component (Figure 2). Plots of k_{obs} against the concentrations of the excess compound were linear, mostly with negligible intercepts (Figure 2, insert). From the slopes of these plots, the second-order rate constants k_2 for the reactions of the ylides **1** with the reference electrophiles **2**−**4** could be derived as listed in Table 4. Errors given refer to

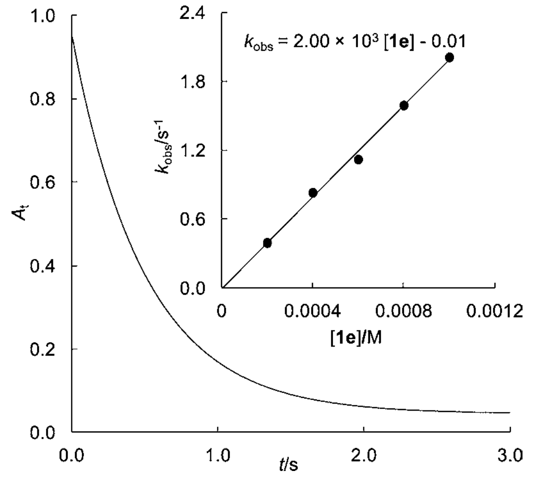


Figure 2. Decay of the absorbance of **3a** (2.00×10^{-5} M) at 533 nm during its reaction with **1e** (1.00×10^{-3} M) in DMSO at 20 °C. Insert: linear correlation of k_{obs} with the concentration of **1e**.

standard deviations of the correlations k_{obs} vs concentration of the compounds used in excess.

Plots of log k_2 for the reactions of the pyridinium ylides **1a,b** and **1d,e** with the reference electrophiles **2**–**4** against the corresponding electrophilicity parameters *E* are linear, as depicted for some representative examples in Figure 3 (for ylides **1c,f**–**i** see SI). From the linearity of these correlations one can deduce that the additions of pyridinium ylides to benzhydrylium ions **2**, quinone methides **3**, and benzylidene malonates **4** in DMSO have analogous rate-limiting steps despite leading to different reaction products. Since the *E* parameters for **2**–**4** were derived from reactions of benzhydrylium ions with π_{C-C}-nucleophiles and from reactions of quinone methides and benzylidene malonates with carbanions, i.e., reactions in which *one* new C–C-bond is formed in the rate-determining step, we conclude that the rate constants listed in Table 4 also correspond to the formation of one C–C-bond by attack of the ylides **1** at one carbon of the benzhydrylium ions **2** or the Michael acceptors **3**,**4**. From the slopes of the linear correlations, the nucleophile-specific slope parameters s_N can be derived, and the negative intercepts on the abscissa give the nucleophilicity parameter *N* of the pyridinium ylides **1** (Figure 3; Table 4).

The different sensitivities s_N of the various ylides **1a**–**i** imply that their relative reactivities are significantly affected by the nature of the electrophilic reaction partner. As shown in Figure 4 for **3a** as reference electrophile, the reactivities of the ylides **1a**–**i** toward the quinone methide **3a** differ by almost a factor of 500. While the pyridinium ylides **1a**–**c** with CO_2Et, $CONEt_2$, and CN substituents are the most reactive nucleophiles, the acetyl and benzoyl substituted ylides **1d,e** are 1 to 2 orders of magnitude less reactive. Comparison of the benzoyl substituted ylides **1e**, **1h**, and **1i** shows that variation of the heterocyclic ring has little influence on the nucleophilicity. Nevertheless, one can see that the isoquinolinium ylide **1h** is more reactive than the pyridinium ylide **1e** and the quinolinium ylide **1i**. An interpretation of this ranking will not be attempted because of the small differences in reactivity that can even be inverted when other electrophiles are used as references.

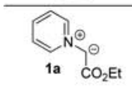
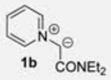
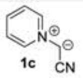
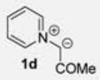
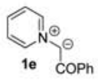
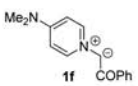
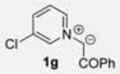
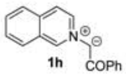
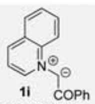
Applications to Mechanistic Analyses. To investigate the applicability of the *N* and s_N parameters in Table 4 to reactions with other types of electrophiles, the kinetics of the reactions of the ylides **1** with the benzylidene malononitrile **5a** and chalcone **5b** were studied.

*Benzylidene Malononitrile **5a**.* Table 5 lists the experimental (k_{exp}) and calculated (k_{calcd} by eq 1) second-order rate constants for the reactions of the ylides **1d**–**i** with **5a**, which were determined by following the consumption of the ylides in DMSO at 20 °C. While the experimental and calculated second-order rate constants for the reactions of ylides **1d,f,h,i** with **5a** agree within a factor of 7 (i.e., within the confidence limit of eq 1), **1e** and **1g** react 10^6 times more slowly than calculated (Table 5). This behavior prompted us to investigate the reactions of pyridinium ylides **1a**–**i** with the benzylidene malononitrile **5a** more closely.

The reactions of the ylides **1** with benzylidene malononitrile **5a** may either give the betaines **12**, the cyclopropanes **13**, or the tetrahydroindolizines **14**, as summarized in Scheme 2.

When an equimolar solution of the 4-dimethylamino-substituted pyridinium salt **1fH$^+$Br$^-$** and benzylidene malononitrile **5a** in DMSO-d_6 was treated with 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) as base, quantitative formation of the betaine **12f** was observed with moderate diastereoselectivity

Table 4. Second-Order Rate Constants k_2 for the Reactions of the Ylides 1 with the Reference Electrophiles 2(b–c)-BF_4, 3, and 4 in DMSO at 20 °C

Nucleophile N/s_N	Electrophile	Excess of	λ/nm[a]	k_2(20 °C)/M^{-1} s^{-1}
 **1a** 26.71/0.37	**3a**	**1a**	533	$(9.00 \pm 0.30) \times 10^4$
	3b	**1a**	371	$(9.68 \pm 0.37) \times 10^3$
	3e	**1a**	521	$(1.09 \pm 0.04) \times 10^3$
	4a	**1a**	302	$(1.37 \pm 0.09) \times 10^3$
	4b	**4b**	445	$(1.08 \pm 0.02) \times 10^3$
	4c	**4c**	445	$(1.97 \pm 0.03) \times 10^2$
	4d	**4d**	445	$(1.13 \pm 0.01) \times 10^2$
 **1b** 27.45/0.38	**3a**	**1b**	533	$(2.99 \pm 0.26) \times 10^{5}$[b]
	3b	**1b**	371	$(3.21 \pm 0.23) \times 10^{4}$[b]
	3d	**1b**	486	$(7.94 \pm 0.64) \times 10^{3}$[b]
	3e	**1b**	521	$(3.79 \pm 0.26) \times 10^{3}$[b]
	4a	**4a**	425	$(4.23 \pm 0.30) \times 10^3$
	4c	**4c**	425	$(6.10 \pm 0.50) \times 10^2$
 **1c** 25.94/0.42	**3a**	**1c**	533	$(2.34 \pm 0.10) \times 10^5$
	3b	**1c**	371	$(2.03 \pm 0.11) \times 10^4$
	3d	**1c**	486	$(2.67 \pm 0.09) \times 10^3$
	3e	**1c**	521	$(2.13 \pm 0.12) \times 10^3$
	4a	**1c**	302	$(2.08 \pm 0.11) \times 10^3$
	4b	**1c**	277	$(6.26 \pm 0.49) \times 10^2$
	4c	**1c**	283	$(1.77 \pm 0.14) \times 10^2$
	4d	**1c**	295	$(1.77 \pm 0.05) \times 10^2$
 **1d** 20.24/0.60	**3a**	**1d**	533	$(1.09 \pm 0.07) \times 10^4$
	3a	**1d**	533	$(1.07 \pm 0.08) \times 10^{4}$[c]
	3b	**1d**	371	$(5.02 \pm 0.30) \times 10^2$
	3c	**1d**	393	$(4.13 \pm 0.22) \times 10^2$
	3d	**1d**	486	$(7.18 \pm 0.51) \times 10^1$
	4a	**4a**	425	$(2.26 \pm 0.01) \times 10^1$
 **1e** 19.46/0.58	**2b-BF$_4$**	**1e**	635	$(7.08 \pm 0.31) \times 10^5$
	2c-BF$_4$	**1e**	630	$(3.85 \pm 0.14) \times 10^5$
	3a	**1e**	533	$(2.00 \pm 0.08) \times 10^3$
	3b	**1e**	371	$(1.29 \pm 0.10) \times 10^2$
	3e	**1e**	521	$(1.03 \pm 0.03) \times 10^1$
 **1f** 21.61/0.58	**3a**	**1f**	533	$(5.51 \pm 0.32) \times 10^4$
	4a	**4a**	425	$(1.77 \pm 0.09) \times 10^2$
	4b	**4b**	425	$(3.39 \pm 0.24) \times 10^1$
 **1g** 17.98/0.63	**2b-BF$_4$**	**1g**	630	$(2.49 \pm 0.13) \times 10^5$
	3a	**1g**	533	$(5.73 \pm 0.31) \times 10^2$
	4a	**4a**	476	1.78 ± 0.16
 **1h** 20.08/0.57	**2b-BF$_4$**	**1h**	630	$(1.51 \pm 0.11) \times 10^6$
	3a	**1h**	533	$(3.88 \pm 0.28) \times 10^3$
	4a	**4a**	482	$(3.05 \pm 0.12) \times 10^1$
 **1i** 19.38/0.50	**2b-BF$_4$**	**1i**	630	$(1.17 \pm 0.08) \times 10^5$
	3a	**1i**	533	$(7.54 \pm 0.31) \times 10^2$
	4a	**4a**	530	8.48 ± 0.43

[a] Monitored wavelength. [b] Excess of pyridinium salt, i.e., **1bH$^+$Cl$^-$**:KO^{t}Bu = 1.9:1.0. [c] Reproduction with excess of pyridinium salt (**1dH$^+$Cl$^-$**:KO^{t}Bu = 1.9:1.0).

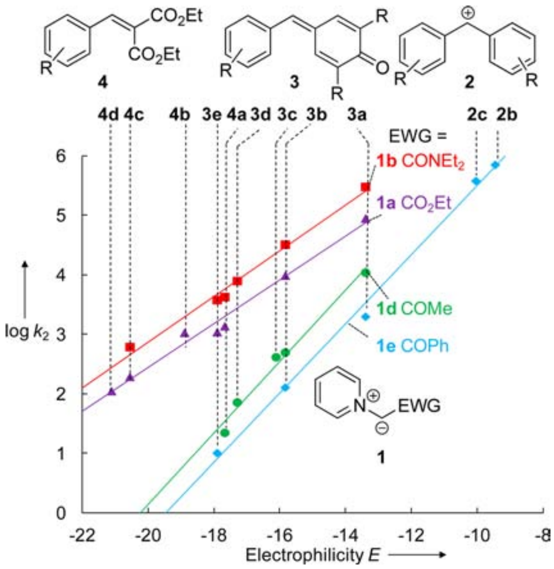


Figure 3. Plots of log k_2 (DMSO, 20 °C) for the reactions of the pyridinium ylides **1a**,**b**,**d**,**e** with the reference electrophiles **2**–**4** versus their electrophilicity parameters E. For the sake of clarity, the correlation lines for **1c** and **1f**–**i** are not shown (see SI).

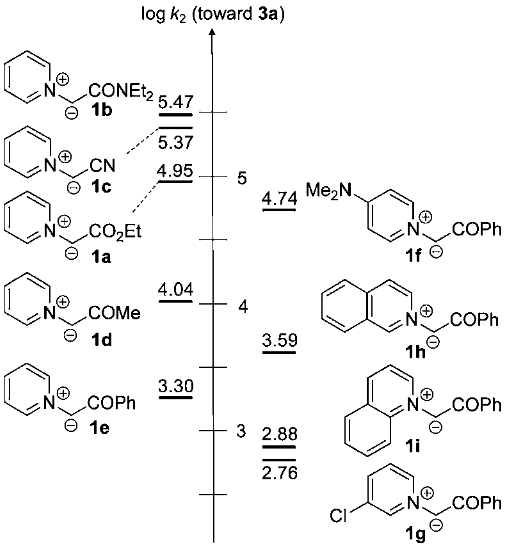


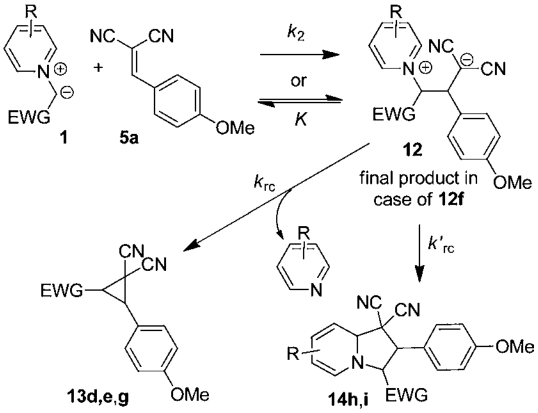
Figure 4. Reactivities (log k_2 toward **3a**) for the reactions of ylides **1a**–**i** with the quinone methide **3a** in DMSO at 20 °C.

Table 5. Experimentally Determined (k_{exp}) and Calculated (k_{calcd}) Second-Order Rate Constants for the Reactions of the Ylides 1d–i with the Electrophile 5a in DMSO at 20 °C

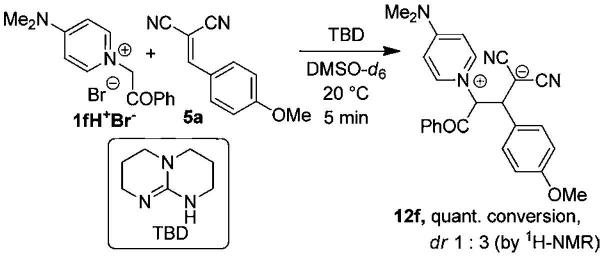
ylide	k_{exp}, M^{-1} s^{-1}	k_{calcd}, M^{-1} s^{-1}[a]	k_{exp}/k_{calcd}	k_{exp} =
1d	$(2.14 \pm 0.07) \times 10^5$	4.86×10^5	0.44	k_2
1e	$(2.19 \pm 0.15) \times 10^{-1}$	1.05×10^5	2.09×10^{-6}	Kk_{rc}
1f	$(4.27 \pm 0.25) \times 10^5$	1.70×10^6	0.25	k_2
1g	$(2.02 \pm 0.08) \times 10^{-1}$	3.11×10^4	6.50×10^{-6}	Kk_{rc}
1h	$(2.95 \pm 0.06) \times 10^4$	1.96×10^5	0.15	k_2
1i	$(5.73 \pm 0.13) \times 10^3$	2.07×10^4	0.28	k_2

[a] Calculated by eq 1 from E (Chart 1) and N, s_N from Table 4.

Scheme 2. Reactions of Ylides 1 with Benzylidene Malonate 5a in DMSO



Scheme 3. Reaction of the Ylide 1f with Benzylidene Malononitrile 5a in DMSO-d_6

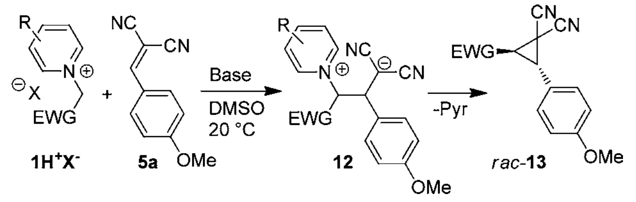


(Scheme 3). The structure of betaine **12f** could be assigned by 2D-NMR, but attempts to isolate **12f** failed. The ^{13}C NMR signal at δ = 16.0 ppm was assigned to a carbanionic center, in agreement with published data for betaines derived from carboxamido-substituted pyridinium ylides and benzylidene malononitriles.[11a] As the pyridinium ring is stabilized by the dimethylamino group in 4-position, **12f** does not undergo subsequent cyclizations, and the measured rate constant corresponds to k_2.

As expected from the large rate constant for the reaction of **1d** with **5a** reported in Table 5, complete consumption of the reactants was observed in the ^1H NMR spectrum taken immediately after mixing **1dH**$^+$**Cl**$^-$ with benzylidene malononitrile **5a** and KO^{t}Bu in DMSO-d_6 at ambient temperature. ^1H NMR spectra taken after 5, 30, and 60 min showed 40/60, 21/79, and 0/100 mixtures of betaine **12d** and cyclopropane **13d**, respectively, indicating that the fast formation of the betaine **12d** is followed by a slow cyclization step. The cyclopropane **13d** was isolated in 53% yield when the mixture obtained from **1dH**$^+$**Cl**$^-$, **5a**, and KO^{t}Bu was worked up after a reaction time of 60 min (Table 6). The exclusive formation of *trans*-**13d** was derived from a NOESY experiment.[17]

A different behavior was observed for the ylides **1e**,**g**. When the reaction of **1eH**$^+$**Br**$^-$ with **5a** and 1.8 equiv triethylamine was monitored by ^1H NMR spectroscopy in DMSO-d_6, the intermediate betaine **12e** was not observable, and the reaction mixture showed signals of the reactants **1eH**$^+$**Br**$^-$ and **5a**, the ylide **1e**, and the cyclopropane **13e**, the yield of which increased from 41% after 5 min to 81% after 30 min. Combination of **1eH**$^+$**Br**$^-$ with benzylidene malononitrile **5a** and triethylamine in DMSO at ambient temperature yielded cyclopropane **13e** with complete *trans*-selectivity within 30 min (Table 6), as confirmed by the crystal structure of **13e** (Figure 5). Analogously, combination of the 3-chloro-substituted ylide **1g** with **5a** afforded cyclopropane **13g** (= **13e**) with complete *trans*-selectivity within 30 min.

Table 6. Formation of the Cyclopropanes 13 in DMSO



salt	R	EWG	base	betaine	cyclopropane	yield, %
1dH$^+$Cl$^-$	H	COMe	KO^{t}Bu	**12d**	**13d**	53[a]
1eH$^+$Br$^-$	H	COPh	NEt$_3$	**12e**	**13e**	67[b]
1gH$^+$Br$^-$	3-Cl	COPh	NEt$_3$	**12g**	**13g** (= **13e**)	95[b]

[a] After column chromatography over silica (*n*-pentane:EtOAc ≅ 5:1). [b] After recrystallization from EtOH.

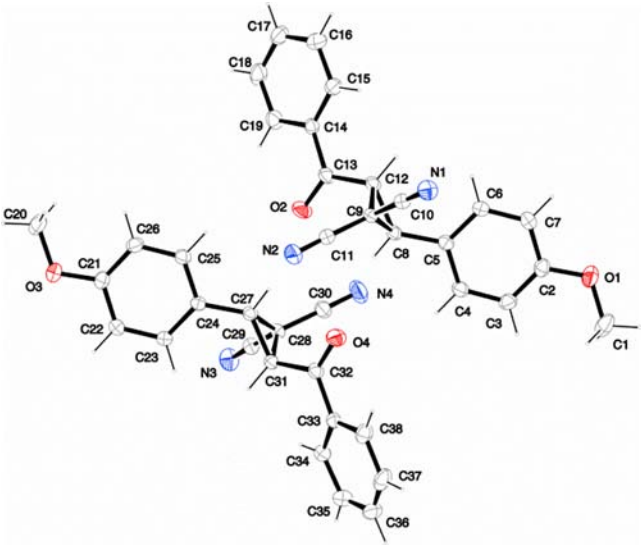
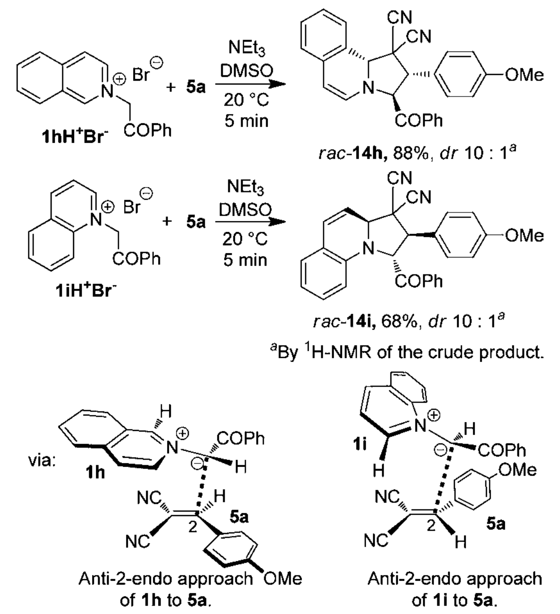


Figure 5. ORTEP-drawing of the crystal structure of **13e**. The asymmetric unit contains two formula units.

Scheme 4. Formation of the Tetrahydroindolizines 14h,i in DMSO



[a] By ^{1}H-NMR of the crude product.

The non-observance of the intermediate betaines **12e**,**g** in the reactions of **1e**,**g** with **5a** implies that in the reactions of these less Lewis-basic ylides (pK_a in Table 1), the equilibrium depicted on top of Scheme 2 is completely shifted to the left side, with the consequence that the experimentally determined rate constants k_{exp} correspond to Kk_{rc}, which explains the large deviation of k_{exp} from k_{calcd} for these two combinations in Table 5.

The reactions of the ylides **1h**,**i** with benzylidene malononitrile **5a** in DMSO yielded 88% and 68% of the [3 + 2]-cycloadducts **14h**,**i**, respectively (Scheme 4). The stereochemistry of **14h**,**i** was assigned on the basis of NOESY correlations between the protons and the substituents of the pyrrolidine rings. From the stereochemistry of the [3 + 2]-cycloadducts one can deduce that the depicted major diastereoisomers of **14h**,**i** were formed via an endo approach of electrophiles to the anti ylides (Scheme 4), in agreement with literature reports for similar [3 + 2]-cycloadducts obtained from isoquinolinium ylides and benzylidene malononitriles.[7b,c] The stereochemistry of the minor diastereoisomers could not be assigned unambiguously.

The formation of the [3 + 2]-cycloadducts **14h**,**i** from isoquinolinium and quinolinium ylides, instead of betaines or cyclopropanes as obtained with pyridinium ylides (see above), can be explained by the lower aromaticity of the heterocyclic ring of the bicyclic reactants **1h**,**i**, which facilitates the cyclization of the intermediate betaine.[5b]

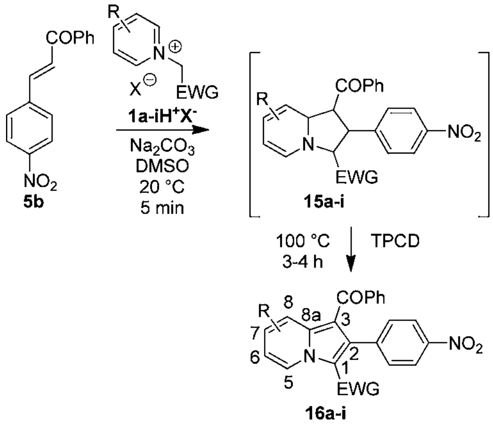
In line with quantum chemical calculations by Matsumura, which indicated a barrier of only 2.9 kJ/mol for the cyclization of a betaine generated from an isoquinolinium ylide and 1,1-dicyanoethylene,[5b] one can conclude that the betaines formed from **5a** and **1h**,**i** undergo fast subsequent ring closures with formation of the [3 + 2]-adducts **14h**,**i** (Scheme 4), with the consequence that in these cases k_{exp} corresponds to k_2. The observation $k_{exp} \approx k_{calcd}$ also excludes concerted 1,3-dipolar cycloadditions **5a** + **1h**,**i** with a high energy of concert, because in this case k_{exp} should be considerably larger than k_{calcd}.[18]

*Chalcone **5b**.* All ylides **1** underwent [3 + 2]-cycloadditions with **5b**,[19] as evidenced by the isolation of the indolizines **16a**–**i**, obtained by oxidation of the initially generated tetrahydroindolizines **15a**–**i** with tetrakispyridinocobalto(II)-dichromate (TPCD; Table 7).

Because of the low stabilities of the initially formed tetrahydroindolizines **15a**–**i**, which were already reported in the literature,[7b] their isolation was generally not attempted. Only the tetrahydroindolizine **15i** was obtained in low yield by the reaction of ylide **1i** with chalcone **5b**, analyzed by ^{1}H NMR spectroscopy, and identified as a 5:27:68 mixture of diastereoisomers. The stereochemistry of the depicted major diastereoisomer of **15i** (Scheme 5) was derived from the NOESY correlations between the protons and the substituents at the pyrrolidine ring. Its formation can be explained by the 1-endo-2-exo approach of the electrophile **5b** to the anti configuration of ylide **1i**, in agreement with Tsuge's interpretation of the stereoselectivities of the reactions of isoquinolinium ylides with several different chalcones.[7b] The stereochemistry of the other diastereoisomers could not be assigned unambiguously. The purification of the [3 + 2]-cycloadduct **15i** failed due to its decomposition during workup, which may also explain the low yield.

For the [3 + 2]-cycloadditions of the ylides **1** with the chalcone **5b**, concerted or stepwise mechanisms have to be considered (Scheme 6). In case of a stepwise mechanism with rate-determining formation of the intermediate betaine **18**, the

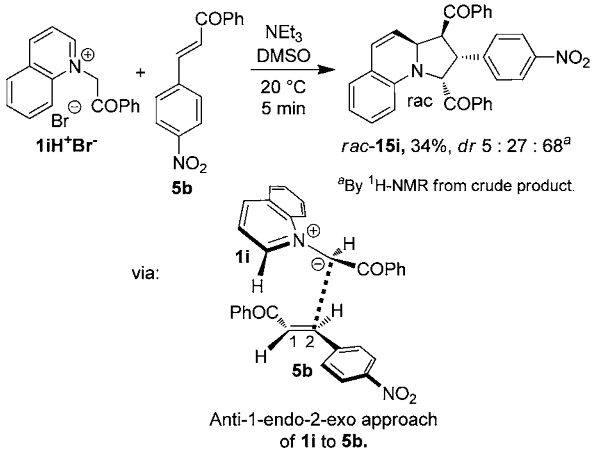
Table 7. Synthesis of the Indolizines 16



salt	R	EWG	product	yield, %
1aH$^+$Br$^-$	H	CO_2Et	**16a**	54
1bH$^+$Br$^-$	H	$CONEt_2$	**16b**	63[a]
1cH$^+$Br$^-$	H	CN	**16c**	95
1dH$^+$Cl$^-$	H	COMe	**16d**	50
1eH$^+$Br$^-$	H	COPh	**16e**	93
1gH$^+$Br$^-$	3-Cl	COPh	**16g**	85[b]
1hH$^+$Br$^-$	isoquinoline	COPh	**16h**	91
1iH$^+$Br$^-$	quinoline	COPh	**16i**	77[a]

[a] CH_2Cl_2 aq NaOH (32%), 20 °C; chloranil (2 equiv), CH_2Cl_2, 20 °C. [b] Mixture of isomers; **16g-(8-Cl)**:**16g-(6-Cl)** = 4:1.

Scheme 5. Reaction of Salt 1iH$^+$Br$^-$ with Chalcone 5b in DMSO



Scheme 6. Concerted and Stepwise 1,3-Dipolar Cycloaddition of Ylides 1 with Chalcone 5b

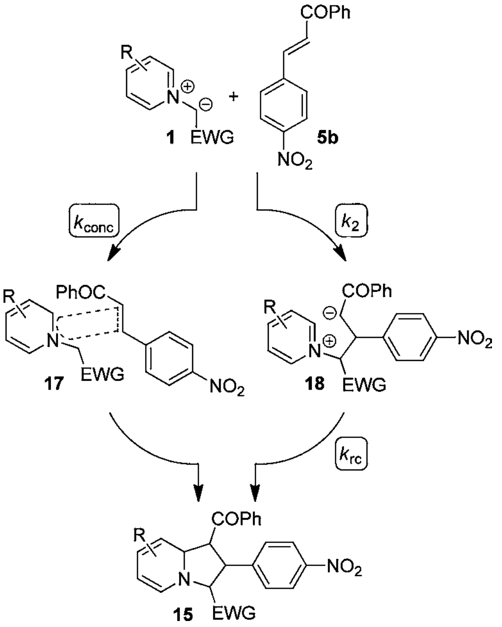


Table 8. Experimentally Determined (k_{exp}) and Calculated (k_{calcd}) Second-Order Rate Constants for the [3 + 2]-Cycloadditions of the Ylides 1a–i with the *p*-NO_2 Chalcone 5b in DMSO at 20 °C

ylide	k_{exp}, M^{-1} s^{-1}	k_{calcd}, M^{-1} s^{-1}[a]	k_{exp}/k_{calcd}
1a	$(4.82 \pm 0.10) \times 10^3$	2.68×10^3	1.80
1b	$(6.12 \pm 0.28) \times 10^3$	7.80×10^3	0.78
1c	$(7.92 \pm 0.37) \times 10^3$	4.13×10^3	1.92
1d	$(2.55 \pm 0.09) \times 10^1$	5.61×10^1	0.45
1e	$(8.54 \pm 0.45) \times 10^{-1}$	1.72×10^1	0.05
1g	3.67 ± 0.12	2.56	1.43
1h	$(3.56 \pm 0.22) \times 10^1$	3.70×10^1	0.96
1i	$(1.64 \pm 0.05) \times 10^1$	1.08×10^1	1.52

[a] Calculated by eq 1 from *E* (Chart 1) and *N*, s_N from Table 4.

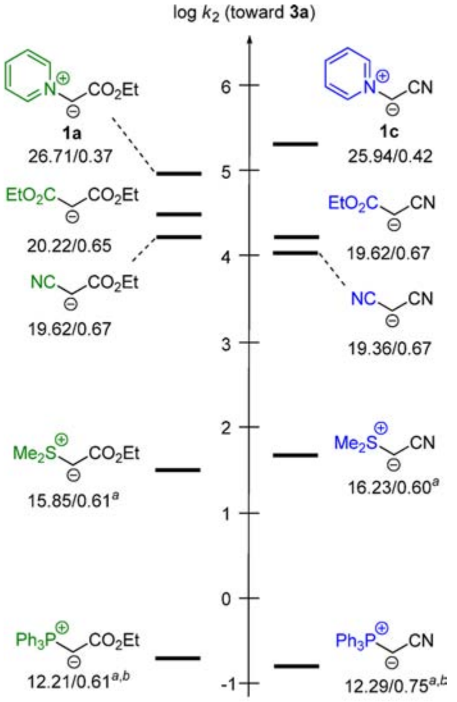
experimentally determined rate constant k_{exp} should correspond to k_2 and agree with the calculated rate constant k_{calcd} within the general confidence limit of eq 1 (1−2 orders of magnitude).[15a,b]

The kinetics of the reactions of the ylides **1** with chalcone **5b** were studied by monitoring the consumption of the ylides **1a**–**i**. Table 8 lists the experimental (k_{exp}) and calculated second-order rate (k_{calcd} by eq 1) for these reactions in DMSO at 20 °C. For 7 of the 8 reactions of the ylides **1** with chalcone **5b** experimental and calculated second-order rate constants agree within a factor of 2.5, indicating a stepwise mechanism with rate-determining formation of the betaine **18** (Table 8). Only the reaction of ylide **1e** with chalcone **5b** proceeds 20 times more slowly than calculated by eq 1. This deviation might be due to a partial reversibility of the betaine formation followed by rate-determining cyclization, but since the deviation is within the confidence limit of eq 1, we do not want to speculate.

In case of concerted cycloadditions k_{exp}/k_{calcd} should be >1, depending on the degree of concertedness.[18] Because of the large error limits of eq 1, the kinetic data do not allow us to differentiate stepwise cycloadditions from concerted processes with highly unsymmetrical transition states and a small energy of concert. As none of the experimental rate constants k_{exp} in Table 8 is considerably faster than k_{calcd}, we conclude that none of these cycloadditions proceeds with a high energy of concert, which implies that eq 1, which has been derived for one-bond-forming reactions of electrophiles with nucleophiles, can also be employed for predicting absolute rate constants for stepwise cycloadditions or concerted cycloadditions with highly unsymmetrical transition states. As the *E* parameters used for these calculations have previously been derived from the rate constants of carbanion additions (*E* for **5a**)[16a] or from stepwise cyclopropanations with sulfonium ylides (*E* for **5b**),[16c] the general power of this approach has thus been corroborated.

■ CONCLUSION

The rates of the reactions of the pyridinium ylides **1** with benzhydrylium ions **2**, quinone methides **3**, and arylidenemalonates **4** follow the linear free-energy relationship (eq 1), which allows us to characterize the synthetically important pyridinium ylides by the reactivity parameters *N* and s_N and to include them in our comprehensive nucleophilicity scale.[15h] Figure 6 compares the reactivities of the ethoxycarbonyl-substituted pyridinium ylide **1a** (left) and the cyano-substituted pyridinium ylide **1c** (right) with those of analogously substituted carbanions as well as with those of phosphorus and sulfur ylides. Both columns show that pyridinium ylides are approximately a million times more reactive than analogously substituted triphenylphosphonium ylides and about thousand times more reactive than the corresponding dimethylsulfonium ylides. The close similarity of the reactivities of the pyridinium ylides and of diethyl malonate and ethyl cyanoacetate anions shows that pyridinium substitution affects the reactivities of nucleophilic reaction centers to a similar extent as ethoxycarbonyl and cyano substitution. Because of the smaller sensitivities s_N of the pyridinium ylides compared to the other C-nucleophiles, the relative reactivities of the pyridinium ylides with respect to the other nucleophiles of Figure 6 will depend on the nature of the electrophilic reaction partner. Pyridinium ylides will show a lower relative reactivity toward reaction partners which are more electrophilic than **3a** ($E > -13$), while they will show an even higher relative reactivity toward less reactive electrophiles ($E < -13$).



^{a}Log k_2 (**3a**) calculated by eq 1 with *E* from Chart 1.
^{b}In CH_2Cl_2.

Figure 6. Comparison of the log k_2-values (toward **3a**) of analogously substituted ylides[14a,c] and carbanions[15c] toward electrophile **3a**. *N* and s_N-values are given below each nucleophile (reactivities refer to DMSO as solvent).

As correlation eq 1 allows one to calculate the rate constants for the formation of the zwitterions (betaines) from pyridinium ylides **1** and Michael acceptors, it can be employed for the analysis of reaction mechanisms. From the agreement between calculated (eq 1) and experimental rate constants for the 1,3-dipolar cycloadditions of the isoquinolinium (**1h**) and quinolinium ylide (**1i**) with the benzylidenemalononitrile **5a** and of all investigated ylides **1** with the chalcone **5b**, we have concluded that these cycloadditions proceed stepwise or in a concerted way with negligible energy of concert.

In two cases, i.e., in the reactions of the benzylidenemalononitrile **5a** with the pyridinium ylides **1e**,**g**, the experimental rate constants were found to be a million times smaller than calculated by eq 1. NMR spectroscopic monitoring of these reactions showed that they proceed with reversible formation of the intermediate betaines, which undergo subsequent slow, rate-determining ring-closure with formation of cyclopropanes. The large deviation between experimental and calculated rate constants thus was indicative of a change of the reaction mechanism, illustrating the value of eq 1 for mechanistic analyses.

The differentiation of concerted and stepwise 1,3-dipolar cycloadditions[20] has been a challenge for mechanistic chemistry for many decades.[21] While mechanistic investigations indicate a concerted pathway for most 1,3-dipolar cycloadditions,[22] stepwise processes via zwitterionic intermediates have been observed in reactions of thiocarbonyl ylides (electron-rich 1,3-dipoles) with electron-deficient dipolarophiles.[23]

Our observation that eq 1 allows one to predict absolute rate constants for 1,3-dipolar cycloadditions of pyridinium, isoquinolinium, and quinolinium ylides with the electron-poor dipolarophiles **4a**−**d** and **5a**,**b** implies a remarkable extension of the validity range of eq 1. It now appears feasible that eq 1 can generally be employed for predicting absolute rate constants of cycloadditions of highly nucleophilic 1,3-dipoles with highly electrophilic dipolarophiles as well as of electrophilic 1,3-dipoles with electron-rich dipolarophiles. In view of the great recent interest in the mechanisms of 1,3-dipolar cycloadditions using the distortion/interaction energy model[24] or activation strain model,[25] we expect that these data will significantly broaden the experimental basis of these models and assist the further development of this theoretical approach.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, product characterization, kinetic experiments, copies of all NMR spectra 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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