

Nucleophilicity Parameters for Phosphoryl-Stabilized Carbanions and Phosphorus Ylides: Implications for Wittig and Related Olefination Reactions

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Abstract: The kinetics of the reactions of four phosphoryl-stabilized carbanions **1a–d** and four phosphorus ylides **1e–h** with benzhydrylium ions **2a–h** and structurally related quinone methides **2i–m** have been determined by UV–vis spectroscopy. The second-order rate constants (*k*) correlated linearly with the electrophilicity parameters *E* of **2a–m**, as required by the correlation $\log k = s(N + E)$ (*J. Am. Chem. Soc.* **2001**, *123*, 9500–9521), allowing us to calculate the nucleophile-specific parameters *N* and *s* for phosphoryl-substituted carbanions and phosphorus ylides. In this way, a direct comparison of the nucleophilic reactivities of Horner–Wadsworth–Emmons carbanions and Wittig ylides became possible. Ph₂PO- and (EtO)₂PO-substituted carbanions are found to show similar reactivities toward Michael acceptors, which are 10⁴–10⁵ times higher than those of analogously substituted phosphorus ylides. The relative reactivities of these nucleophiles toward benzaldehydes differ significantly from those toward carbocations and Michael acceptors, in accordance with a concerted [2 + 2] cycloaddition being the initial step of these olefinations reactions. Effects of the counterion (K⁺, Na⁺, or Li⁺) on the nucleophilicities of the phosphoryl-stabilized carbanions in DMSO have been studied. Whereas the effects of K⁺ and Na⁺ are almost negligible for all types of carbanions investigated, Li⁺ coordination reduces the reactivities of phosphonate-substituted acetic ester anions (**1a**) by a factor of 10² while the reactivities of phosphonate-substituted acetonitrile anions (**1b**) remain almost unaffected.

Introduction

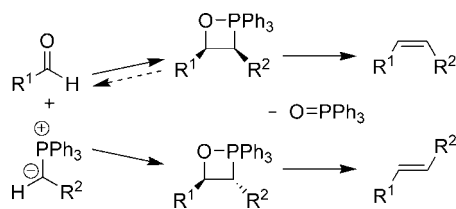
The Wittig reaction¹ as well as the related Wittig–Horner² and Horner–Wadsworth–Emmons³ reactions are among the most important methods for synthesizing C=C double bonds. These olefinations provide access to a wide structural variety

and can be carried out with high stereoselectivity.⁴ Detailed mechanistic investigations by Vedejs and co-workers^{4e,5} and Maryanoff, Reitz, and co-workers⁶ as well as quantum-chemical approaches by Yamataka and co-workers,^{7a,b} Aggarwal, Harvey, and co-workers,^{7c,d} and other authors⁸ led to the generally accepted model of salt-free Wittig reactions (Scheme 1). In the first step, an oxaphosphetane is formed via a concerted asynchronous [2 + 2] cycloaddition with a transition state in which the C–C bond formation is more advanced than the P–O bond formation. The resulting oxaphosphetane decomposes into

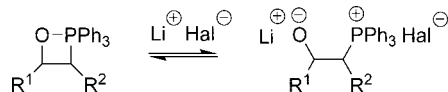
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Scheme 1. Mechanism of the Salt-Free Wittig Reaction



Scheme 2. Betaine Intermediates in the Presence of Lithium Halides



the olefin and phosphine oxide. NMR studies showed that the initial oxaphosphetane formation is in general a nonreversible step,^{4a,e,5g,6a,9} although some exceptions have also been reported.^{4a,e,5d,g,10}

In the presence of lithium halides, the oxaphosphetane intermediates can be transformed into betaine intermediates^{5b,11} (Scheme 2), which may be isomerized by additional base before they cyclize, forming the thermodynamically more stable *trans*-oxaphosphetanes, which finally yield the *trans*-olefins selectively.^{4b,e,5g,12} Recently, alternative ionic intermediates have been suggested to account for the stereochemical drift.¹³

The mechanistic course of the Horner–Wadsworth–Emmons reactions is closely related to that of the Wittig reaction,^{4b,i,k,l} although it is still controversial whether the initial attack of the carbanion at the carbonyl group and the oxaphosphetane ring closure proceed in a concerted or stepwise manner and which step is rate-determining in the latter case.¹⁴ Systematic kinetic investigations of this reaction in ethanol solution by Larsen and Aksnes¹⁵ led to the conclusion that the oxaphosphetane intermediate is formed in a concerted manner in the rate-determining step.

It is well-known that phosphoryl-substituted carbanions are generally more reactive than phosphorus ylides. A quantitative comparison of these two classes of compounds has, to our knowledge, not been performed to date.

In recent years, we have developed the most comprehensive nucleophilicity scale presently available.¹⁶ By defining a series of structurally related benzhydrylium ions and quinone methides

Table 1. Benzhydrylium Ions **2a–h** and Quinone Methides **2i–m** Employed in This Work

			E^a	
2a	X	NPh ₂	-4.72	
2b		N(Ph)(Me)	-5.89	
2c		NMe ₂	-7.02	
2d		N(CH ₂) ₄	-7.69	
2e ($n = 2$)			-8.22	
2f ($n = 1$)			-8.76	
2g ($n = 2$)			-9.45	
2h ($n = 1$)			-10.04	
			E^a	
2i	Y	Ph	OMe	-12.18
2j		<i>t</i> Bu	Me	-15.83
2k		<i>t</i> Bu	OMe	-16.11
2l		<i>t</i> Bu	NMe ₂	-17.29
2m		<i>t</i> Bu		-17.90

^a E values for **2a–h** were taken from ref 16b and those for **2i–m** from ref 16c.

(some of them are depicted in Table 1) having widely varying reactivities, we have been able to directly compare nucleophiles that differ largely in reactivity.^{16b–f} In this way, we have circumvented the problem that a single reference electrophile does not allow one to compare a large variety of nucleophiles because (1) second-order rate constants $k_2 < 10^{-6} \text{ M}^{-1} \text{ s}^{-1}$ cannot easily be determined and (2) the upper limit for the rates of bimolecular reactions is given by diffusion control ($k_2 = 10^9\text{--}10^{10} \text{ M}^{-1} \text{ s}^{-1}$ in typical solvents). It has been demonstrated that the nucleophile-specific parameters N and s (defined by eq 1), which are derived from the second-order rate constants of a particular nucleophile with a series of benzhydrylium ions and/or quinone methides, correctly predict the reactivity of this

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nucleophile toward other types of carbocations and Michael acceptors of known electrophilicity $E_{16b-f,17}$

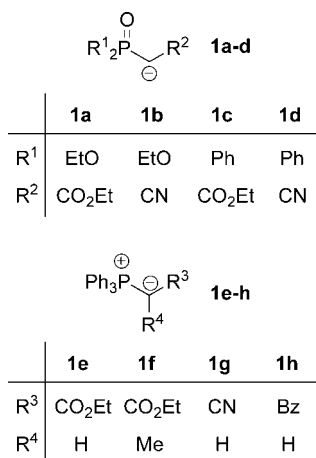
$$\log k_{20^\circ\text{C}} = s(N+E) \quad (1)$$

In this work, we have employed this method for characterizing the nucleophilicities of four phosphorus ylides and four phosphoryl-stabilized carbanions (Scheme 3), and we will discuss the impact of these results on carbonyl olefinations. In order to achieve conveniently measurable reactions, the carbanions **1a–d** were predominantly characterized by their reactions with quinone methides **2i–m** and the least electrophilic benzhydrylium ion **2h**, while the much less nucleophilic phosphorus ylides **1e–h** were almost exclusively characterized through their reactivities toward benzhydrylium ions **2a–h**.

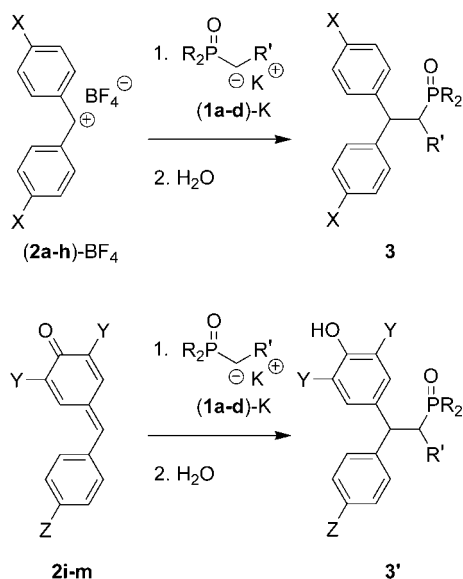
Results

Product Studies. As shown in Scheme 4, the phosphoryl-stabilized carbanions **1a–d** react with the reference electrophiles **2** to give the addition products **3** or **3'**. Solutions of the carbanions **1a–d** were generated either by deprotonating the corresponding CH-acids in DMSO with KO*t*Bu or by isolating

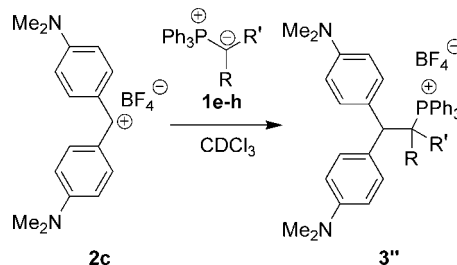
Scheme 3. Phosphoryl-Stabilized Carbanions **1a–d** and Phosphorus Ylides **1e–h** Investigated in This Work



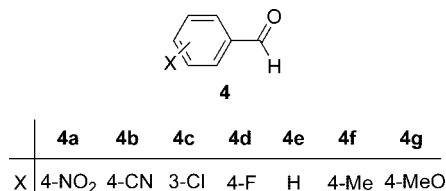
Scheme 4. Reactions of the Phosphoryl-Stabilized Carbanions **1a–d** with the Reference Electrophiles **2**



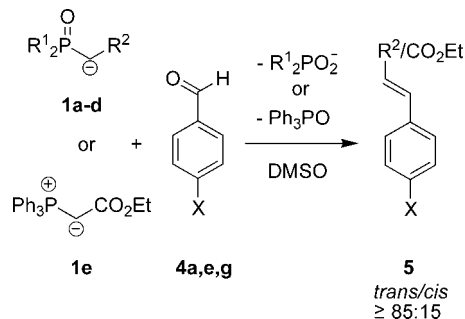
Scheme 5. Reactions of the Phosphorus Ylides **1e–h** with the Reference Electrophile **2c**



Scheme 6. Substituted Benzaldehydes **4** Employed in This Work



Scheme 7. Reactions of the Phosphoryl-Stabilized Carbanions **1a–d** and the Phosphorus Ylide **1e** with the Benzaldehydes **4a**, **4e**, and **4g**



the potassium salts (**1a–d**)–K and dissolving them in DMSO or CH₃CN. The particular electrophile, in DMSO or CH₂Cl₂ solution or in a mixture of the two solvents, was then added. Detailed procedures and characterizations of the isolated products **3** or **3'** are reported in the Supporting Information.

The bis(*p*-dimethylamino)benzhydrylium ion **2c** was the only electrophile used for product studies with the phosphorus ylides **1e–h** (Scheme 5). One can assume that variation of the remote aryl substituent of the electrophile does not affect the types of products. The formation of **3'** from **1e–h** and **2c** was studied in CDCl₃ solution by NMR, and the procedure as well as the characterizations of the addition products are described in the Supporting Information.

The olefination reactions with the nucleophiles **1a–e** were studied with the series of substituted benzaldehydes **4** (Scheme 6). Representative combinations of the nucleophiles **1a–e** with the benzaldehydes **4a**, **4e**, and **4g** in DMSO showed the expected *trans* selectivity (Scheme 7). The *cis/trans* ratio of the olefins **5** was determined by GC/MS. In order to exclude the possibility that the observed *cis/trans* ratio was changed during workup or purification, samples were taken from the reaction mixtures after different reaction times and analyzed after dilution with acetone. Details are given in the Supporting Information.

Kinetic Investigations. For the kinetic measurements, solutions of the carbanions **1a–d** were generated either by deprotonation of the corresponding CH-acids with 1.00–1.05 equiv of KO*t*Bu in DMSO solution or by isolating the potassium salts

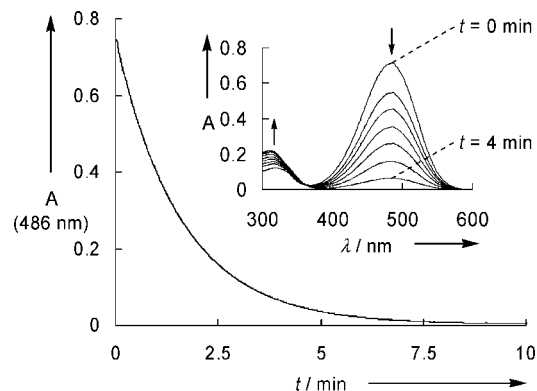


Figure 1. UV-vis spectroscopic monitoring of the reaction of the phosphoryl-stabilized carbanion **1a** ($7.57 \times 10^{-4} \text{ mol L}^{-1}$) with the quinone methide **2l** ($3.52 \times 10^{-5} \text{ mol L}^{-1}$) at 486 nm in DMSO at 20 °C.

(**1a–d**)–K and then dissolving them in DMSO. The reactions of the nucleophiles **1a–h** with the reference electrophiles **2a–m** in DMSO or CH_2Cl_2 at 20 °C were monitored by UV-vis

Table 2. Second-Order Rate Constants for the Reactions of the Phosphoryl-Stabilized Carbanions **1a–d** and 0–1.3 equiv of 18-Crown-6 with the Reference Electrophiles **2h–m** in DMSO at 20 °C

Nucleophile	Counter Ion	Electrophile	$k_2 / \text{L mol}^{-1} \text{s}^{-1}$	
<i>N / s^a</i>				
 1a	$\text{K}^+ / 18\text{-crown-6}$	2h	5.82×10^5	
	$\text{K}^+ / 18\text{-crown-6}$	2i	6.06×10^4	
	K^+	2j	1.99×10^2	
	19.23 / 0.65	$\text{K}^+ / 18\text{-crown-6}$	2k	1.28×10^2
		$\text{K}^+ / 18\text{-crown-6}$	2l	1.38×10^1
	$\text{K}^+ / 18\text{-crown-6}$	2m	6.02	
 1b	$\text{K}^+ / 18\text{-crown-6}$	2h	3.66×10^5 ^b	
	$\text{K}^+ / 18\text{-crown-6}$	2i	2.23×10^4 ^b	
	$\text{K}^+ / 18\text{-crown-6}$	2j	6.71×10^1	
	18.57 / 0.66	$\text{K}^+ / 18\text{-crown-6}$	2k	4.38×10^1 ^b
		$\text{K}^+ / 18\text{-crown-6}$	2l	6.47 ^b
	K^+	2m	2.80 ^b	
 1c	$\text{K}^+ / 18\text{-crown-6}$	2h	1.85×10^6 ^b	
	$\text{K}^+ / 18\text{-crown-6}$	2i	8.99×10^4 ^b	
	$\text{K}^+ / 18\text{-crown-6}$	2j	2.32×10^2 ^b	
	19.20 / 0.69	$\text{K}^+ / 18\text{-crown-6}$	2k	1.28×10^2 ^b
		$\text{K}^+ / 18\text{-crown-6}$	2l	1.41×10^1 ^b
	$\text{K}^+ / 18\text{-crown-6}$	2m	1.05×10^1	
 1d	$\text{K}^+ / 18\text{-crown-6}$	2h	1.98×10^6 ^b	
	$\text{K}^+ / 18\text{-crown-6}$	2i	4.12×10^4 ^b	
	$\text{K}^+ / 18\text{-crown-6}$	2j	1.21×10^2 ^b	
	18.69 / 0.72	$\text{K}^+ / 18\text{-crown-6}$	2k	6.75×10^1 ^b
		$\text{K}^+ / 18\text{-crown-6}$	2l	1.10×10^1 ^b

^a Values of the nucleophilicity parameters *N* and *s* were derived using eq 1, as described in the Discussion. ^b Reaction occurred in the presence of the corresponding conjugate CH-acid (**1b–d**)–H.

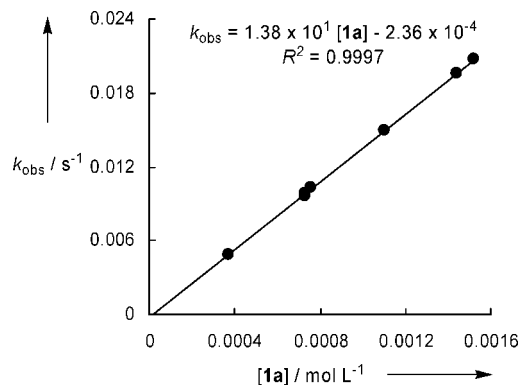


Figure 2. Determination of the second-order rate constant $k_2 = 1.38 \times 10^1 \text{ L mol}^{-1} \text{ s}^{-1}$ for the reaction of the phosphoryl-stabilized carbanion **1a** with the quinone methide **2l** in DMSO at 20 °C.

spectroscopy at or close to the absorption maxima of the electrophiles. In all of the cases examined, complete consumption of the electrophiles **2** was observed when their solutions were combined with an excess of the carbanions **1a–d**, as shown in Figure 1.

Because the nucleophiles **1a–h** were employed in large excess over the electrophiles **2a–m**, their concentrations can be considered almost constant throughout the reactions, resulting in first-order kinetics with an exponential decay of the concentrations of **2** (eq 2):

$$-\frac{d[\mathbf{2}]}{dt} = k_{\text{obs}}[\mathbf{2}] \quad (2)$$

The first-order rate constants k_{obs} were obtained by least-squares fitting of the single-exponential $A_t = A_0 \exp(-k_{\text{obs}}t) + C$ to the time-dependent absorbances *A* of the electrophiles. Second-order rate constants then were obtained as the slopes of plots of k_{obs} versus the concentration of the nucleophile (Figure 2).

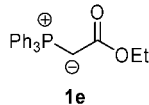
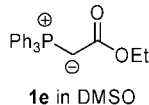
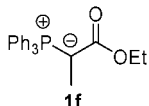
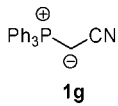
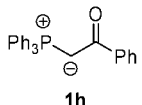
The rate constants listed in Table 2 refer to the reactivities of the free carbanions **1a–d**. Though most of the reactions of (**1a–d**)–K were performed in the presence of 18-crown-6, this additive was not really necessary. In a control experiment, it was found that the rate of the reaction of **1b–K** with **2k** remained constant in the absence of crown ether even when large amounts of KBF_4 (up to $1.6 \times 10^{-2} \text{ mol L}^{-1}$) were added (see Table S88 in the Supporting Information). However, as discussed below, counterion effects were observed when sodium or lithium salts were employed.

Analogously, the reactions of the phosphorus ylides **1e–h** with the electrophiles **2** generally proceeded with full conversion of the electrophile. In only a few cases, which are marked in Table 3, was the consumption of the electrophiles **2** not complete, indicating equilibrium situations.

The kinetics of the reactions of the nucleophiles **1a–e** with the substituted benzaldehydes **4a–g** were investigated in DMSO at 20 °C using large excesses of the nucleophiles. The first-order rate constants k_{obs} were usually derived from the single-exponential increase of the absorbances of the resulting styrenes **5**. As shown in Figure 3 for the reaction of *p*-methoxybenzaldehyde **4g** with the phosphoryl-stabilized carbanion **1b**, the rate of consumption of *p*-methoxybenzaldehyde (monitored at 270 nm) was equal to the rate of formation of *p*-methoxycinnamionitrile (monitored at 310 nm), excluding the formation of a long-lived intermediate during the reaction.

Second-order rate constants (Table 4) were again obtained as the slopes of plots of k_{obs} versus the concentration of the nucleophile (Figure 4).

Table 3. Second-Order Rate Constants for the Reactions of the Phosphorus Ylides **1e–h** with the Reference Electrophiles **2a–i** in CH₂Cl₂ at 20 °C

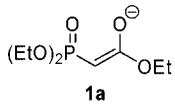
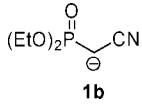
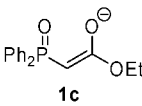
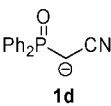
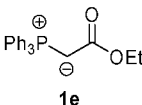
Nucleophile	Electrophile	$k_2 / \text{L mol}^{-1} \text{s}^{-1}$
N / s^a		
 1e	2c	2.65×10^4
	2e	3.69×10^3
	2f	1.26×10^3
	2h	1.28×10^2
12.79 / 0.77		
 1e in DMSO	2c	1.86×10^3
	2d	6.80×10^2
	2f	1.05×10^2
	2h	2.51×10^1
12.21 / 0.62		
 1f	2b	2.03×10^5
	2c	2.34×10^4
	2e	3.90×10^3
	2g	4.64×10^2 ^b
	13.09 / 0.73	
 1g	2a	4.35×10^5
	2c	1.21×10^4
	2e	1.21×10^3
	2h	4.33×10^1 ^b
12.29 / 0.75		
 1h	2b	3.37×10^3
	2c	2.73×10^2 ^b
9.54 / 0.97		

^a Values of the nucleophilicity parameters N and s were derived using eq 1, as described in the Discussion. ^b Incomplete consumption of the electrophile was observed, indicating an equilibrium situation.

Counterion Effects. In order to gain more insight into the role of the counterions in the reactions of the carbanions **1** with the reference electrophiles **2** as well as with the aldehydes **4**, additional studies in the presence of different alkali cations were performed. For this purpose, the CH-acids **1a–H** and **1b–H** were deprotonated with 1.00–1.05 equiv of NaOtBu or LiOtBu in DMSO solution to generate the corresponding sodium or lithium salts **1a–Na** and **1b–Na** or **1a–Li** and **1b–Li**, respectively. Their reactions with the reference electrophiles **2j–m** and the aldehydes **4a**, **4e**, and **4g** were then investigated kinetically using the same method as described above.

All of the reactions, which are listed in Table 5, followed first-order kinetics regardless of the counterion (K⁺, Na⁺, or Li⁺) when the carbanions **1a** and **1b** were used in large excess over the electrophiles **2** or **4**. Except for the reactions of **1a–Li**, second-order rate laws were followed, as derived from the linear increase of k_{obs} with the concentrations of **1a** and **1b** (Figures 2 and 4; for details, see Tables S70–S76, S89–S97, and S99–S103 in the Supporting Information). In contrast, the plots of k_{obs} versus [**1a–Li**] were curved (Figure 5 and Tables S78

Table 4. Second-Order Rate Constants for the Reactions of the Phosphoryl-Stabilized Carbanions **1a–d** (with K⁺/18-Crown-6 as the Counterion) and the Phosphorus Ylide **1e** with the Aldehydes **4a–g** in DMSO at 20 °C

Nucleophile	Electrophile	$k_2 / \text{L mol}^{-1} \text{s}^{-1}$
 1a	4a	1.20×10^3
	4b	4.78×10^2
	4c	5.73×10^1
	4d	4.05
	4e	2.02
	4f	4.64×10^{-1}
 1b	4a	2.45×10^3
	4b	1.05×10^3
	4c	1.48×10^2
	4d	1.17×10^1
	4e	7.16
	4f	1.73
	4g	3.64×10^{-1}
 1c	4a	2.51×10^1
	4b	1.11×10^1
	4c	1.58
 1d	4a	9.32×10^1
	4b	4.46×10^1
	4c	6.67
	4d	7.08×10^{-1}
	4e	5.52×10^{-1}
 1e	4a	3.07×10^{-1}
	4e	1.44×10^{-3} ^a

^a From ref 23d.

and S85 in the Supporting Information), and it was not possible to determine second-order rate constants for the reactions of **1a–Li** with the electrophiles.

In order to obtain more information about the effect of Li⁺ on the reactivity of **1a**, further kinetic studies of the reactions of **1a** with different electrophiles were performed at various concentrations of Li⁺. For that purpose, the carbanion concentration [**1a**] (obtained by deprotonation of the corresponding CH-acid **1a–H** with 1.00–1.05 equiv of LiOtBu) was kept constant while the Li⁺ concentration was modulated by adding various amounts of LiBF₄. As depicted in Figure 6, the first-order rate constants k_{obs} for the reactions of the quinone methide **2k** with **1a** decreased dramatically as the Li⁺ concentration was increased.

Li⁺ effects on k_{obs} , as depicted in Figure 6, were also observed for the reactions of **1a** with the benzhydrylium ion **2h** (see Tables S83 and S84 in the Supporting Information) and the

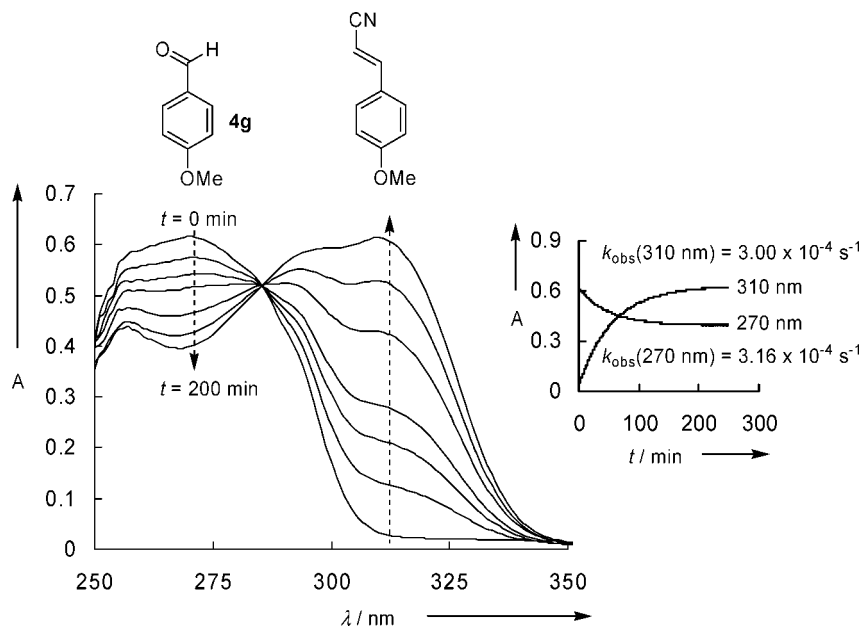


Figure 3. Reaction of *p*-methoxybenzaldehyde **4g** ($5.58 \times 10^{-5} \text{ mol L}^{-1}$) with the phosphoryl-stabilized carbanion **1b** ($7.99 \times 10^{-4} \text{ mol L}^{-1}$) in DMSO at 20°C (the UV absorption of **1b** at $\lambda_{\text{max}} = 257 \text{ nm}$ is partially superimposed by the aldehyde). The inset shows the time traces along with the corresponding k_{obs} values for the single-exponential increase of the reaction product *p*-methoxycinnamionitrile and the single-exponential decrease of the aldehyde **4g**.

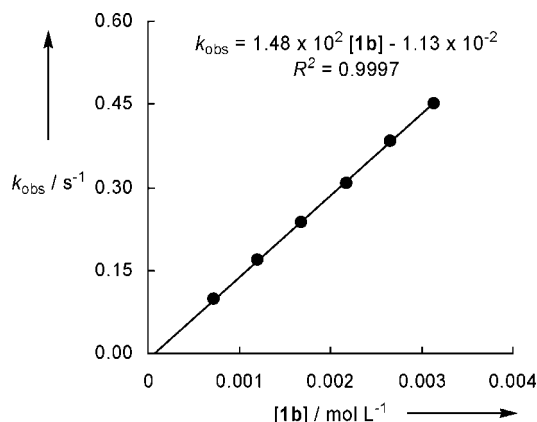


Figure 4. Determination of the second-order rate constant $k_2 = 1.48 \times 10^2 \text{ L mol}^{-1} \text{ s}^{-1}$ for the reaction of the phosphoryl-stabilized carbanion **1b** with *m*-chlorobenzaldehyde **4c** in DMSO at 20°C .

aldehyde **4a** (see Tables S86 and S87 in the Supporting Information). In contrast, the addition of LiBF_4 had only small effects on the rates of the reactions of the carbanion **1b** with electrophiles. Thus, the reaction of **1b** with the quinone methide **2k** was only 2.3 times slower than the corresponding reaction of the free carbanion **1b** at a high concentration of Li^+ ($[\text{Li}^+] = 1.19 \times 10^{-2} \text{ mol L}^{-1}$ and $[\mathbf{1b}] = 8.02 \times 10^{-4} \text{ mol L}^{-1}$; see Table S98 in the Supporting Information). The rates of the reactions of the phosphorus ylide **1e** with the benzhydrylium ion **2h** as well as with the aldehyde **4a** were not at all affected by the addition of variable amounts of LiBF_4 (see Tables S104–S106 in the Supporting Information).

Discussion

Counterion Studies. Variation of the counterion of the cyano-stabilized phosphonate **1b** from K^+ via Na^+ to Li^+ revealed (within the error limits of our experiments) no change in the reactivity toward the quinone methides **2j–m** (Table 5, entries 12–15). Consequently, the nucleophilic reactivity of this

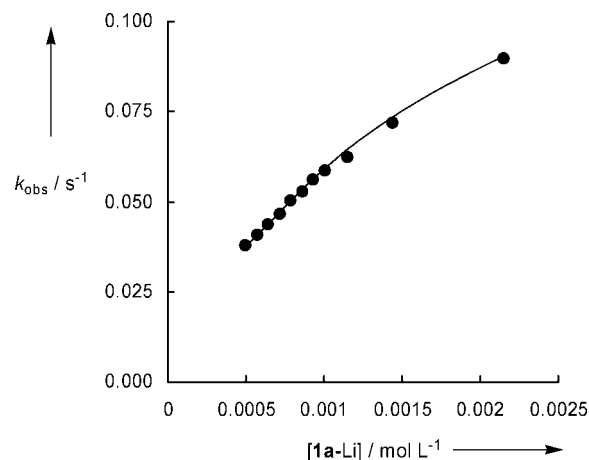
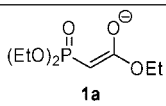
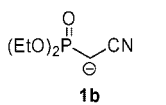


Figure 5. Nonlinear dependence of k_{obs} on the concentration of the nucleophile for the reaction of **1a** with the reference electrophile **2j** in the presence of Li^+ in DMSO at 20°C .

carbanion, in which the negative charge is mainly localized on the nucleophilic carbon center,¹⁸ is not affected by the positively charged alkali ions. Even when a 15-fold excess of Li^+ ($[\text{Li}^+] = 1.19 \times 10^{-2} \text{ mol L}^{-1}$) over the carbanion **1b** was employed, the reactivity of **1b** toward **2k** decreased by a factor of only 2.3 (see Table S98 in the Supporting Information). The reactions of **1b** with the aldehydes **4a**, **4e**, and **4g** were even 9–34% faster in the presence of Na^+ and Li^+ counterions (Table 5, entries 16–18) than in the presence of K^+ /18-crown-6. A slight stabilizing coordination of Na^+ and Li^+ with the partial negative

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Table 5. Second-Order Rate Constants for the Reactions of the Phosphoryl-Stabilized Carbanions **1a** and **1b** with the Reference Electrophiles **2h–m** and the Aldehydes **4a**, **4e**, and **4g** in the Presence of Different Counterions in DMSO at 20 °C

Nucleophile	Entry	Electrophile	$k_2 / \text{L mol}^{-1} \text{s}^{-1}$		
			$\text{K}^+/\text{18-crown-6}^a$	Na^+	Li^+
 1a	1	2h	5.82×10^5	-	$(1.85 \times 10^5)^b$
	2				$(1.44 \times 10^4)^c$
	3	2j	1.99×10^2	1.47×10^2	$(5.79 \times 10^1)^b$
	4	2k	1.28×10^2	9.56×10^1	$(3.57 \times 10^1)^b$
	5				$(2.49)^c$
	6	2l	1.38×10^1	1.02×10^1	-
	7	2m	6.02	4.43	-
	8	4a	1.20×10^3	1.11×10^3	$(3.25 \times 10^2)^b$
	9	4a			$(4.70 \times 10^1)^c$
	10	4e	2.02	2.53	-
	11	4g	9.31×10^{-2}	1.59×10^{-1}	-
 1b	12	2j	6.71×10^1	6.81×10^1	6.92×10^1
	13	2k	4.38×10^1	4.35×10^1	4.48×10^1
	14	2l	6.47	6.78	6.84
	15	2m	2.80	2.78	2.81
	16	4a	2.45×10^3	2.72×10^3	2.70×10^3
	17	4e	7.16	8.30	8.35
	18	4g	3.64×10^{-1}	4.88×10^{-1}	4.44×10^{-1}

^a Reactions used 0–1.3 equiv of 18-crown-6; data from Tables 2 and 4. ^b No second-order kinetics; $k = k_{\text{obs}}/[\mathbf{1a}]$ at $[\mathbf{1a}] = [\text{Li}^+] = 1 \times 10^{-3} \text{ mol L}^{-1}$. ^c No second-order kinetics; $k = k_{\text{obs}}/[\mathbf{1a}]$ at $[\mathbf{1a}] = 1 \times 10^{-3} \text{ mol L}^{-1}$ and $[\text{Li}^+] = 9 \times 10^{-3} \text{ mol L}^{-1}$.

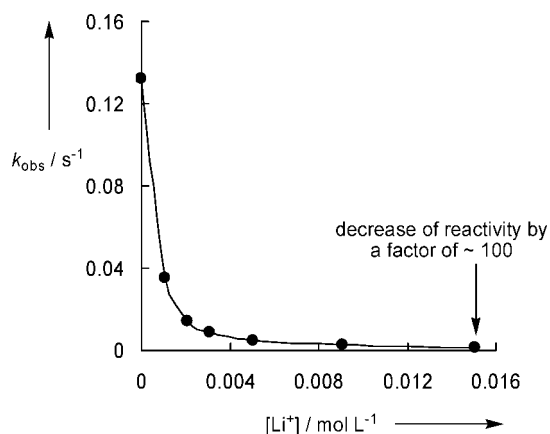


Figure 6. Dependence of k_{obs} on the absolute concentration of Li^+ for the reaction of **1a** ($1 \times 10^{-3} \text{ mol L}^{-1}$) with the quinone methide **2k** ($3 \times 10^{-5} \text{ mol L}^{-1}$) in DMSO at 20 °C. (The second-order rate constant $k_2 = 128 \text{ L mol}^{-1} \text{ s}^{-1}$ for the reaction of **1a**– $\text{K}/18\text{-crown-6}$ with **2k** in DMSO at 20 °C (see Table 2) was used to calculate the k_{obs} value for $[\text{Li}^+] = 0 \text{ mol L}^{-1}$).

charge of the carbonyl oxygen of the aldehyde in the transition state of the olefination reaction may account for this observation.

The situation is different for the ethoxycarbonyl-stabilized carbanion **1a**. In this case, even the Na^+ counterion has a slight decelerating effect (by a factor of 1.35) on the reactions of **1a** with the quinone methides **2j–m** (Table 5, entries 3, 4, 6, and 7). In the olefination reactions, the slight reduction of the nucleophilicity of **1a** by Na^+ is overcompensated by the activation of the aldehydes by Na^+ , and **1a**– Na reacts 1.3 and

1.7 times faster with the aldehydes **4e** and **4g** than the free carbanion (Table 5, entries 10 and 11). As shown in the Supporting Information (e.g., Table S51), K^+ also has a slight activating effect (by a factor of 1.1–1.3) on the olefination reactions of aldehydes when high concentrations of the potassium salts ($[(\mathbf{1a-d})\text{-K}] > 1.30 \times 10^{-3} \text{ mol L}^{-1}$) were employed without crown ether. Below this concentration, the addition of 18-crown-6 did not affect reactivity.

With Li^+ as the counterion, the reactions of **1a** become considerably slower and do not follow simple second-order kinetics (Table 5, entries 1–5, 8, and 9). These findings can be explained by the high charge delocalization in this carbanion, with most of the negative charge residing on the oxygen atom of the carbonyl group (enolate structure). The higher affinity of the (charged) oxygen for the lithium counterion results in the formation of less reactive contact ion pairs even in DMSO (dielectric constant $\epsilon_r = 46.45$). Because the degree of ion-pairing increases with increasing concentration, the nonlinear correlation in Figure 5 can be rationalized. The strong decrease of k_{obs} at constant $[\mathbf{1a}]$ with increasing $[\text{Li}^+]$ (Figure 6) can also be explained by the increasing degree of ion-pairing.

According to Table 5, at $[\text{Li}^+] = 1 \times 10^{-3} \text{ mol L}^{-1}$, **1a**– Li reacts 3.1–3.7 times more slowly than the free carbanion **1a** with **2h–k** and **4a** (Table 5, entries 1, 3, 4, and 8). At a higher concentration of Li^+ ($[\text{Li}^+] = 9 \times 10^{-3} \text{ mol L}^{-1}$), **1a**– Li reacts 25–51 times more slowly than the free carbanion with the benzhydrylium ion **2h**, the quinone methide **2k**, and the aldehyde **4a** (Table 5, entries 2, 5, and 9). Because the magnitude of the Li^+ effect depends only slightly on the nature of the electrophile, we have to conclude that under these conditions, the activation

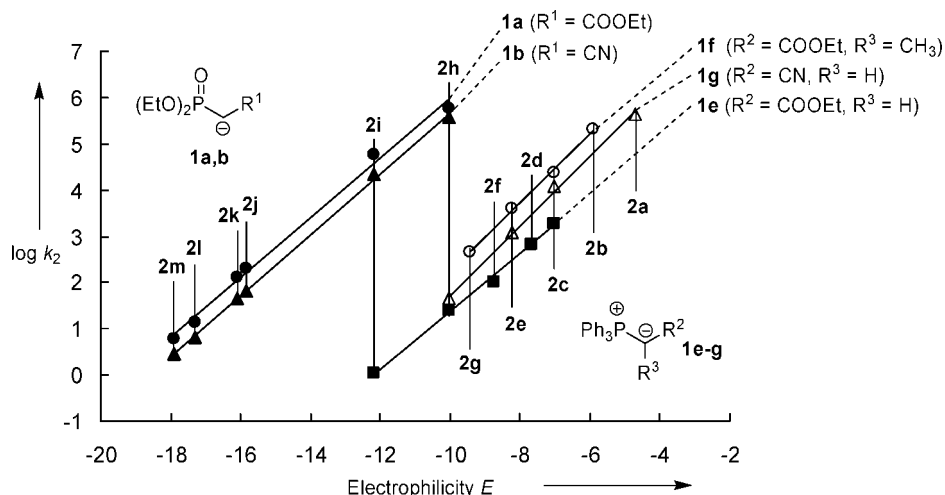


Figure 7. Plots of $\log k_2$ for the reactions of the phosphoryl-stabilized carbanions **1a** and **1b** and the phosphorus ylides **1e–g** with the reference electrophiles **2a–m** at 20 °C (filled symbols denote reaction in DMSO, open symbols reaction in CH_2Cl_2) versus the electrophilicity parameters E of **2a–m**.

of the electrophiles by Li^+ is much less important than the deactivation of the carbanion **1a** by Li^+ coordination.

The reactivity of phosphorus ylide **1e** is not affected by Li^+ ions at all in either the reaction with benzhydrylium ion **2h** or the olefination reaction with *p*-nitrobenzaldehyde **4a** (see Tables S104–S106 in the Supporting Information).

Nucleophilicity Parameters. As previously shown for many nucleophile–electrophile combinations,^{16,17,19} the second-order rate constants given in Tables 2 and 3 correlate well with the electrophilicity parameters E of the benzhydrylium ions **2a–h** and quinone methides **2i–m**. In Figure 7 these correlations are shown exemplarily for the nucleophiles **1a**, **1b**, and **1e–g**. The correlations for the other nucleophiles used in this work (**1c**, **1d**, and **1h**) are of similar quality and allow the calculation of the values of the nucleophile-specific parameters N and s , which are listed in Tables 2 and 3.

The similarities of the slopes for the correlations of the nucleophiles **1a–e** in DMSO and for the nucleophiles **1e–g** in CH_2Cl_2 (Figure 7), which are numerically expressed by the s parameters in Tables 2 and 3, imply that the relative nucleophilicities of **1a–e** in DMSO and **1e–g** in CH_2Cl_2 depend only slightly on the electrophilicity of the reaction partner. Consequently, the N parameters can be used to compare the relative reactivities of these compounds (Figure 8).

Figure 8 shows that phosphonate-stabilized (**1a**, **1b**) and phosphine oxide-stabilized carbanions (**1c**, **1d**) do not differ much in reactivity. This indicates that ethoxy substituents on the phosphorus center have a similar effect on the nucleophilicity of the carbanionic center as phenyl substituents. In analogy to the behavior of other carbanions bearing CN and CO_2R groups,^{16c} the ethoxycarbonyl-substituted carbanions **1a** and **1c** show slightly higher reactivities than the cyano-stabilized carbanions **1b** and **1d**.

A comparison of the substituent effects on the reactivity (given by the N parameters for their reactivities in CH_2Cl_2) of the phosphorus ylides **1e–h** also shows that the ethoxycarbonyl-

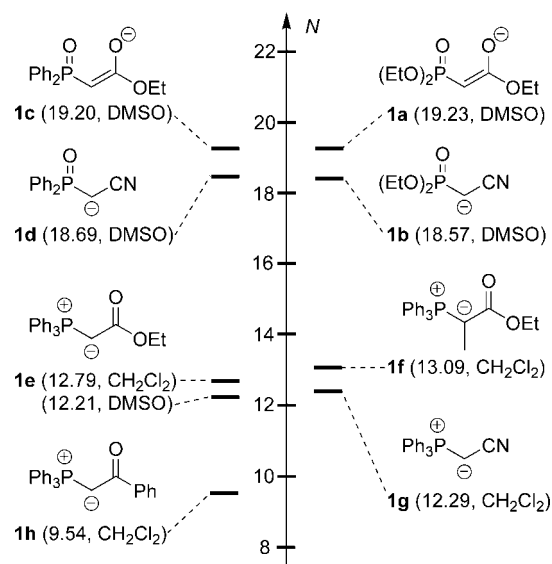


Figure 8. Comparison of the nucleophilicity parameters N (in DMSO or CH_2Cl_2) of the phosphorus ylides **1e–h**, the phosphonate-stabilized carbanions **1a** and **1b**, and the phosphine oxide-stabilized carbanions **1c** and **1d**.

stabilized ylide **1e** is slightly more reactive than the cyano-stabilized ylide **1g**. Substitution of an α -H atom of **1e** by a methyl group has almost no effect on the nucleophilic reactivity (cf. **1f** vs **1e**). The benzoyl-substituted ylide **1h** is $\sim 10^2$ times less reactive than the structurally analogous phosphorus ylides **1e** and **1f**. Because **1h** could only be investigated with two different reference electrophiles, the atypically high s value of 0.96 is not reliable and shall not be discussed in detail.

It has long been known that the phosphoryl-stabilized carbanions react faster with carbonyl compounds than the Wittig ylides.^{3,20} The N (and s) values for the phosphoryl-stabilized carbanions **1a–d** and the ylides **1e–h** in Figure 8 now provide a quantitative comparison of the reactivities of phosphoryl-stabilized carbanions and phosphorus ylides. A problem in this

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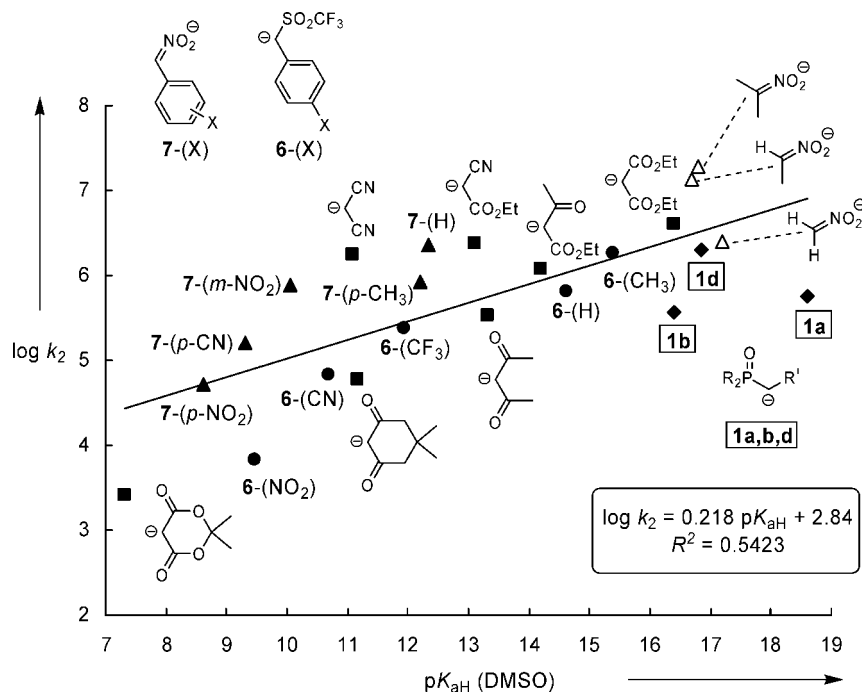


Figure 9. Plot of $\log k_2$ for the reactions of the phosphoryl-stabilized carbanions **1a**, **1b**, and **1d** and other classes of carbanions with the benzhydrylium ion **2h** (DMSO, 20 °C) versus the corresponding pK_{aH} values of the carbanions (DMSO, 25 °C). The second-order rate constants k_2 (filled symbols) were taken from refs 16c, 17a, 19a, and 19c. Second-order rate constants k_2 for the alkyl nitronates (open symbols) were calculated using eq 1. The pK_{aH} values were taken from ref 21.

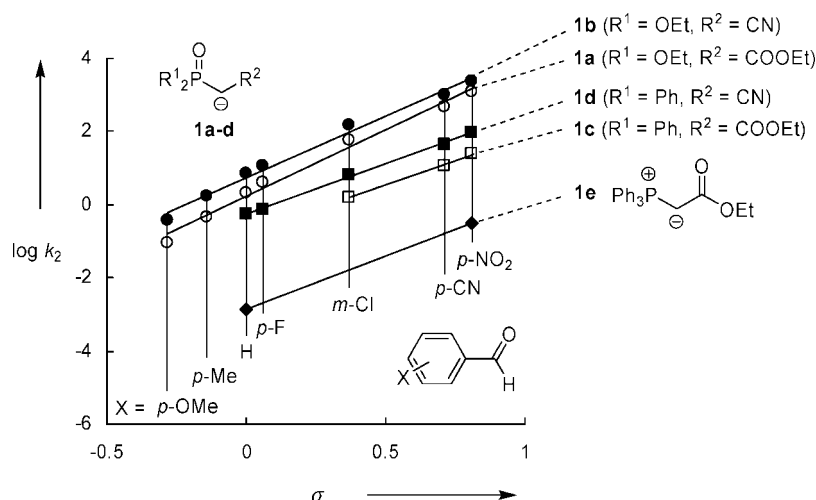


Figure 10. Correlation of the second-order rate constants k_2 for the reactions of the phosphoryl-stabilized carbanions **1a–d** and the phosphorus ylide **1e** with the benzaldehydes **4** in DMSO at 20 °C versus Hammett's σ_p or σ_m values for the substituents of the benzaldehydes: (●) $\log k_2 = 3.38\sigma + 0.734$, $R^2 = 0.9887$, $n = 7$; (○) $\log k_2 = 3.64\sigma + 0.214$, $R^2 = 0.9894$, $n = 7$; (■) $\log k_2 = 2.76\sigma - 0.268$, $R^2 = 0.9978$, $n = 5$; (□) $\log k_2 = 2.67\sigma - 0.800$, $R^2 = 0.9953$, $n = 3$; (◆) $\log k_2 = 2.87\sigma - 2.84$, $R^2 = 1$, $n = 2$. The data point for the reaction of **1e** with benzaldehyde (**4e**) was taken from ref 23d.

comparison is the different solvents used for the two classes of compounds. While the carbanions **1a–d** were investigated in DMSO solution, the kinetic investigations of the phosphorus ylides **1e–h** were performed in CH_2Cl_2 . However, the ylide **1e** was investigated in both solvents, showing that the reactivity is less than 1 order of magnitude higher in CH_2Cl_2 than in DMSO. Comparison of the nucleophilicities of the Wittig ylide **1e** and the two structurally analogous phosphoryl-stabilized carbanions **1a** and **1c** reveals a difference of nucleophilic reactivity of $\Delta N \approx 7$ (for N in DMSO). For an averaged s value of 0.65, this difference implies that the ylide **1e** is 10^4 – 10^5 times less reactive than the carbanions **1a** and **1c**. A similar reactivity ratio can be derived for the comparison of the cyano-substituted

carbanions **1b** and **1d** with the cyano-substituted phosphorus ylide **1g**, if one assumes that the change from CH_2Cl_2 to DMSO solution has an effect on the reactivity of **1g** similar to that on **1e**.

Figure 9 shows a rather poor relationship between the rates of the reactions of the benzhydrylium ion **2h** with carbanions^{16c,17a,19a,c} and the carbanion pK_{aH} values in DMSO.²¹ One can see that the phosphoryl-stabilized carbanions **1a**, **1b**, and **1d** are located in the lower part of this “correlation corridor”. The phosphonate-substituted carbanions **1a** and **1b** are even less reactive than several of the phenyl-substituted nitronates **7–(X)** and the malononitrile anion $(\text{NC})_2\text{CH}^-$, even though the basicities of **1a** and **1b** are 4–8 units higher. It is probably the stabilization

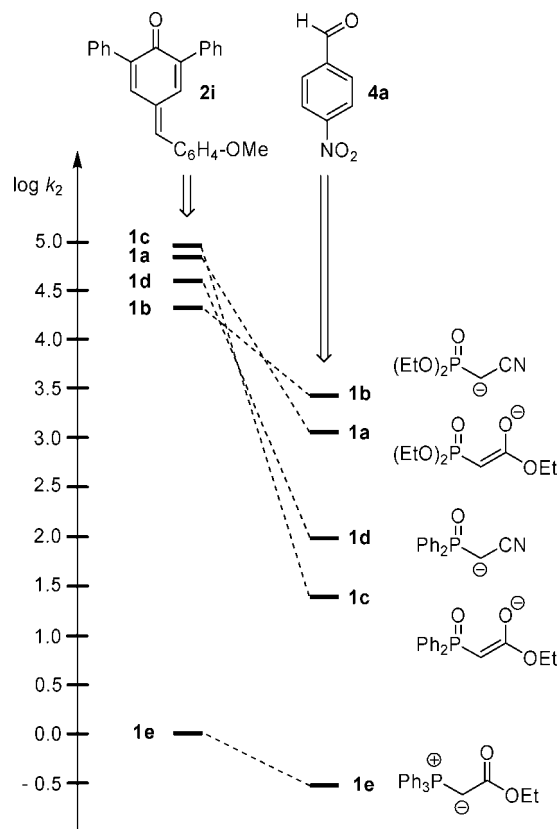
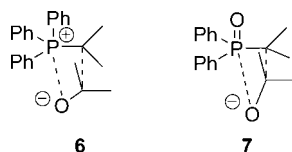


Figure 11. Comparison of the second-order rate constants k_2 for the reactions of the nucleophiles **1a–e** with the quinone methide **2i** (on the left) and *p*-nitrobenzaldehyde **4a** (on the right) in DMSO at 20 °C.

Scheme 8. Schematic Transition States for the Reactions of Phosphorus Ylides and Phosphoryl-Substituted Carbanions with Carbonyl Groups



of the phosphoryl-stabilized carbanions **1** through dipole–dipole interactions in DMSO that is responsible for the unusually high intrinsic barriers²² of their reactions with electrophiles. Because of the low quality of this correlation, we refrain from interpreting the slope.

Olefination Reactions. The kinetic studies on the reactions of the nucleophiles **1a–e** with the benzaldehydes **4** in DMSO

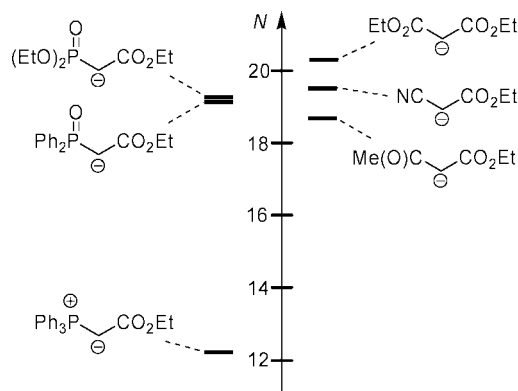


Figure 12. Comparison of the nucleophilicities of different ethoxycarbonyl-stabilized carbanions in DMSO.

(Table 4) showed that in all cases, electron-withdrawing groups at the 3- or 4-position of the benzaldehydes **4** increase the reaction rate whereas electron-donating substituents decelerate the reaction (Figure 10).

Plots of $\log k_2$ versus the Hammett substituent constants σ are linear (Figure 10) and yield $\rho = 3.4–3.6$ for the olefination reactions of the phosphonate-stabilized carbanions **1a** and **1b**, $\rho = 2.7–2.8$ for the reactions of the phosphine-oxide stabilized carbanions **1c** and **1d**, and $\rho = 2.9$ for the reactions of the ylide **1e**. Because the correlations with **1c** and **1e** are based on only 3 and 2 data points, respectively, the resulting ρ values for these compounds should be treated with caution. Similar reaction constants ρ have been reported for the Wittig reactions of ester-stabilized triphenylphosphonium ylides with substituted benzaldehydes in benzene at 25 °C ($\rho = 2.7$)^{23c} and in acetonitrile at 20 °C ($\rho = 2.9$)^{23d} as well as for the Wittig reaction of benzyliidenetriphenylphosphorane with substituted benzaldehydes in THF at 0 °C ($\rho = 2.77$).^{23e} The substituent effects are in line with a concerted [2 + 2] cycloaddition in which the formation of the C–C bond is more advanced in the transition state than the formation of the P–O bond.²³ In the calculations by Aggarwal, Harvey, and co-workers,^{7c,d} the bond lengths in the transition state for the reaction of benzaldehyde with $\text{Ph}_3\text{PCHCO}_2\text{Me}$ are reported to be 1.86 Å for the C–C bond and 2.76 Å for the P–O bond.

Whereas the change from ethoxy to phenyl substituents on the phosphorus center of phosphoryl-stabilized carbanions revealed no significant change in reactivity toward the reference electrophiles **2** (Table 2 and Figure 8), the phosphine oxide-stabilized carbanions **1c** and **1d** react considerably more slowly with aldehydes than the corresponding phosphonates **1a** and **1b** (Table 4 and Figure 10).

Figure 11 illustrates significant differences in the relative reactivities toward the Michael acceptor **2i** and the benzaldehyde **4a**. Whereas the phosphine oxide-substituted carbanions **1c** and **1d** react with **2i** slightly faster (by factors of 1.5 and 1.8, respectively) than the analogous phosphonate-substituted carbanions **1a** and **1b**, **1a** and **1b** are more reactive toward **4a** (by factors of 47 and 26, respectively) than the corresponding phosphine oxide-substituted carbanions **1c** and **1d**. Steric effects may account for this inversion of reactivity. Because in the Horner–Wadsworth–Emmons (HWE) reaction, C–C bond formation is accompanied by the formation of the P–O bond to yield the oxaphosphetane, the more bulky phenyl groups of the phosphine oxides **1c** and **1d** in comparison with the smaller ethoxy groups of the phosphonates **1a** and **1b** may explain the lower reactivities of **1c** and **1d** in the [2 + 2] cycloaddition

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with **4a**. Analogously, the smaller size of CN compared with CO₂Et may account for the finding that the cyano-stabilized carbanions **1b** and **1d** are more reactive in the HWE reaction than the corresponding ethoxycarbonyl-substituted systems **1a** and **1c**, even though their relative reactivities toward the Michael acceptor **2i** are the other way around.

A major difference can be seen in the relative reactivities of the ethoxycarbonyl-substituted carbanions **1a** and **1c** on one side and the ethoxycarbonyl-substituted phosphorus ylide **1e** on the other side. Whereas the carbanions **1a** and **1c** are almost 10⁵ times more reactive than **1e** in the Michael additions (Figure 11, left), the reactivity ratio shrinks to a factor of 100–4000 in the HWE reaction (Figure 11, right). Obviously, the cycloaddition of the phosphorus ylide **1e** profits more from concertedness than the cycloadditions of the carbanions **1a** and **1c**, because the energy gain by forming the P–O bond in the transition state **6** is much higher than in transition state **7** (Scheme 8).

Conclusions

By using benzhydrylium ions and structurally related quinone methides as reference electrophiles, we have been able to directly compare the nucleophilic reactivities of phosphoryl-stabilized carbanions and stabilized phosphorus ylides. Because the same reference electrophiles have previously been employed for quantifying the reactivities of a large variety of π , n , and σ nucleophiles,^{16,19} we can now integrate the synthetically important phosphorus-substituted nucleophiles **1a–h** into the comprehensive nucleophilicity scale based on eq 1.

Figure 12 compares the effects of (EtO)₂PO, Ph₂PO, and Ph₃P⁺ groups on the nucleophilicities of ethoxycarbonyl-substituted carbanions and illustrates that the effect of the phosphoryl group is comparable to that of an acetyl or cyano group.^{16c}

Since the pK_a values of the conjugate acids of **1a–d** are much higher than those of ethyl acetoacetate and ethyl cyanoacetate,²¹ we must conclude that the intrinsic barriers for the reactions of the phosphoryl-substituted carbanions are considerably higher than those for the reactions of carbanions stabilized by ester, cyano, and carbonyl groups.

Significant differences between the relative reactivities of the phosphoryl-substituted nucleophiles toward carbocations and Michael acceptors on one side and benzaldehydes on the other side are in line with concerted asynchronous oxaphosphetane formation in the rate-determining step of the olefination reactions.

Experimental Section

Materials. Dimethyl sulfoxide (DMSO) with a H₂O content of <50 ppm and dry CH₂Cl₂ (freshly distilled over CaH₂) were used for the kinetic experiments. The phosphine oxides **1c–H** and **1d–H** were synthesized according to a literature procedure,²⁴ as was the phosphorus ylide **1g**.²⁵ The potassium salts of **1a–d** were prepared as described in the Supporting Information. Benzhydrylium

tetrafluoroborates^{16b} (**2a–h**)–BF₄ and quinone methides²⁶ **2i–m** were prepared as described previously. All of the other chemicals were purchased from commercial sources and (if necessary) purified by recrystallization or distillation prior to use.

Kinetics. The rates of all of the investigated reactions were determined photometrically. The temperature of the solutions during all of the kinetic studies was kept constant (20.0 ± 0.1 °C) using a circulating bath thermostat. The reactions with the carbanions in DMSO were carried out either with stock solutions of the potassium salts of the CH-acids or by deprotonation of the CH-acids with 1.00–1.05 eq of KO^tBu, NaO^tBu, or LiO^tBu in DMSO. The reactions with the ylides in DMSO or CH₂Cl₂ were carried out with solutions of the ylides in the corresponding solvent. The electrophiles were also prepared in stock solutions of the particular solvent and were always employed as the minor component in the reactions with the nucleophiles, resulting in first-order kinetics.

The rates of slow reactions ($\tau_{1/2} > 10$ s) were determined using a J&M TIDAS diode array spectrophotometer controlled by Labcontrol Spectacle software and connected to a Hellma 661.502-QX quartz Suprasil immersion probe (5 mm light path) via fiber-optic cables and standard SMA connectors. For the evaluation of fast kinetics ($\tau_{1/2} < 10$ s), a Hi-Tech SF-61DX2 stopped-flow spectrophotometer system or Applied Photophysics SX.18MV-R stopped-flow reaction analyzer was used.

Rate constants k_{obs} (s⁻¹) were obtained by fitting the single-exponential functions $A_t = A_0 \exp(-k_{\text{obs}}t) + C$ (exponential decrease) or $A_t = A_0[1 - \exp(-k_{\text{obs}}t)] + C$ (exponential increase) to the observed time-dependent absorbance (averaged from at least four kinetic runs for each nucleophile concentration in the case of applying the stopped-flow method).

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

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