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Ambident Reactivity of Acetyl- and Formyl-Stabilized Phosphonium Ylides

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Abstract

The kinetics and mechanism of the reactions of formyl-stabilized ylide $Ph_3P=CHCHO$ (**1**) and acetyl-stabilized ylide $Ph_3P=CHCOMe$ (**2**) with benzhydrylium ions (Ar_2CH^+, **3**) were investigated by UV-Vis and NMR spectroscopy. As ambident nucleophiles, ylides **1** and **2** can react at oxygen as well as at the α-carbon. For some reactions, it was possible to determine the second-order rate constant for O-attack as well as for C-attack and to derive the nucleophile-specific parameters N and s_N according to the correlation $\lg k$ (20 °C) = $s_N(E + N)$ for both nucleophilic sites. Generally, O-attack of benzhydrylium ions is faster than C-attack. However, the initially formed benzhydryloxyvinylphosphonium ions can only be observed by NMR spectroscopy when benzhydryl cations with high Lewis acidity are employed. In other cases, rearrangement to the thermodynamically more stable products arising from C-attack occurs. The results derived from our investigations are employed to rationalize the behavior of ambident nucleophiles **1** and **2** in reactions with carbon-centered electrophiles in general. It is shown that the principle of hard and soft acids and bases (HSAB) and the related Klopman-Salem concept of charge and orbital control lead to incorrect predictions of regioselectivity. We also show that the rate of the Wittig reaction of ylide **2** with aldehyde **14** is significantly faster than the rate of either C- or O-attack calculated using $\lg k$ (20 °C) = $s_N(E + N)$, thus indicating that the oxaphosphetane is formed by a concerted [2 + 2] cycloaddition.

Introduction

Phosphonium ylides are one of the most widely used classes of compound in synthetic organic chemistry, not least because of their involvement in Wittig reactions[1] and related variants. Numerous publications on various aspects of Wittig chemistry have appeared in the recent chemical literature. Included amongst these are regio- and stereoselective olefinations of keto-sugars,[2] mechanistic and computational studies,[1b,3] new methods for phosphonium salt and ylide generation,[4] syntheses of metal-containing analogues of Wittig intermediates,[5,6] Wittig-type reactions of N-sulfonyl imines,[7] new methods for byproduct separation,[8] and syntheses of macrocycles,[9] modified nucleosides,[10] vinyl isocyanides,[11] and novel Michael acceptors.[12] Transition metal catalysis of Wittig reactions has become popular, with catalyzed production of ylide from a stoichiometric phosphorus source,[13,14] or of carbonyl reactant from a stoichiometric amount of alcohol.[15] Most exciting of all is the development of several ingenious methods for Wittig and aza-Wittig reactions that are catalytic in phosphorus.[16,17,18] Recent studies on other aspects of phosphonium ylide chemistry have focused on organocatalytic CO_2 activation by stabilized ylides to form cyclic carbamates and carbonates,[19] on ylide hydrolysis and alcoholysis,[20] and on computational quantification of the thermodynamic stability of ylides.[21] In particular, carbonyl-stabilized ylides are playing an increasingly important role in modern synthesis – they are crucial constituents of many of the newly developed catalytic Wittig reactions[16b-d,17] and other processes[2,8c,13,14] described in the publications cited above.

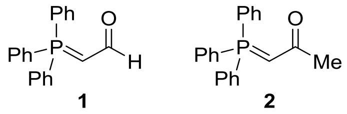
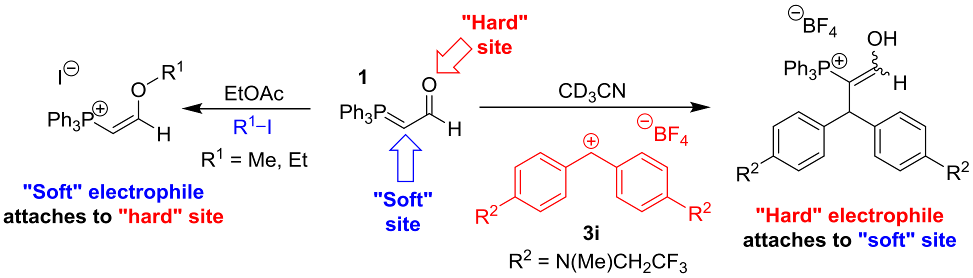


Chart 1. Carbonyl-stabilized ylides.

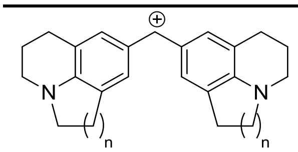
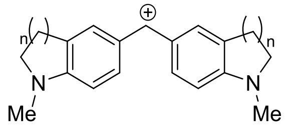
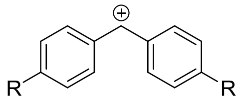
Carbonyl-stabilized phosphonium ylides (e.g. formyl-stabilized ylide **1** and acetyl-stabilized ylide **2** in Chart 1) are ambident nucleophiles – that is, they may attack an electrophile through oxygen or through the α-carbon.[22] In recent years, the most popular means of rationalizing the outcomes of reactions of ambident organic nucleophiles have been the hard-soft acid-base (HSAB) principle (originally proposed by Pearson to apply in inorganic reactivity)[23a-f] and the related concept of charge vs. orbital control.[23g,h] According to the HSAB rationale, the reaction of a carbonyl-stabilized ylide with “soft” electrophiles such as MeI, EtI, or EtBr should result in the alkyl group of the electrophile being appended to the “soft” α-carbon nucleophilic site of the ylide, while reactions with “hard” electrophiles such as carbocations should result in attachment of the electrophile to the “hard”, partially negatively charged ylide oxygen.



Scheme 1. Reactions of ylide **1** with alkyl iodides and benzhydrylium ion **3i**.

It has repeatedly been observed that carbonyl-stabilized ylides such as **1** and **2** undergo alkylation exclusively at the ylide oxygen in their reactions at room temperature with alkyl iodides and bromides – i.e., archetypal “soft” covalent electrophiles attach irreversibly to the “hard” site of the ylide.[24,25,26] We recently observed that the reaction of ylide **1** with benzhydrylium ion **3i** (Table 1) gives a C-alkylated product (see Scheme 1) – i.e., the carbocation, commonly considered a “hard” electrophile, attaches to the “soft” site of the ylide. In light of this discrepancy, we considered a systematic study on the nucleophilicity of such ylides to be of great relevance for our understanding of the behavior of enolates and enolate equivalents, and in a wider sense to the field of ambident organic reactivity. Furthermore, given the frequency with which carbonyl-stabilized ylides appear in modern synthetic methods,[2,8c,13,14,16b-d,17,19] it is clear that quantification of their reactivity is particularly apposite at present.

Table 1. Benzhydrylium ions **3** used as reference electrophiles in this study.

Reference Electrophile	Compound number	Electrophilicity E [a]
	**3a** (n = 1)	-10.04
	3b (n = 2)	-9.45
	**3c** (n = 1)	-8.76
	3d (n = 2)	-8.22
	**3e** R = *N*-pyrrolidino	-7.69
	3f R = NMe_2	-7.02
	3g R = N(Me)Ph	-5.89
	3h R = *N*-morpholino	-5.53
	3i R = $N(Me)CH_2CF_3$	-3.85
	3j R = OMe	0.00
	3k R = Me	3.63

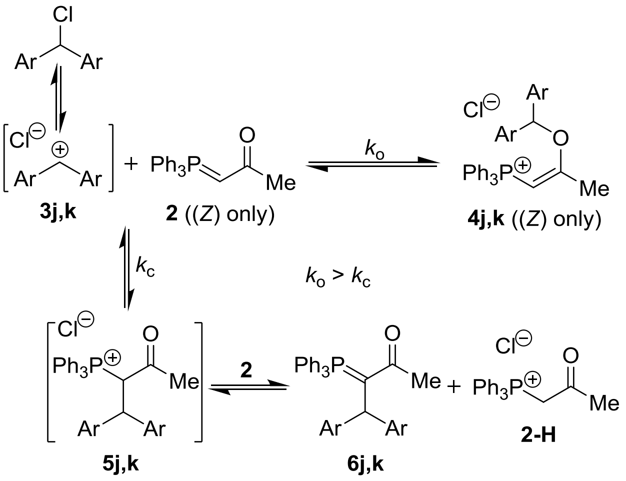
[a] Values of E are taken from ref. 27b.

In numerous articles we have shown that the second-order rate constant k for the bimolecular reaction of an electrophile with a nucleophile at 20 °C may be calculated using equation 1,

$$\lg k = s_N (E + N) \tag{1}$$

where E characterizes the electrophilicity of the electrophile, while N represents the nucleophilicity of the nucleophile, and s_N is a nucleophile-specific susceptibility parameter.[27] By treating E as a solvent-independent parameter, all solvent effects are shifted into the nucleophile-specific parameters N and s_N. A linear correlation between lg k and E has been shown to exist for a hugely diverse range of reactions,[28] and on this basis the most comprehensive organic reactivity scale presently available has been developed.[29] Values of s_N and N for four representative cyano-, keto- and ester-stabilized phosphonium ylides (nucleophilic attack through the ylide α-carbon) have already been determined in the course of the development of this reactivity scale.[30]

Product Characterization



Ar =	Time	Conversion[a]	**4:6**
j *p*-$MeOC_6H_4$	15 min	Quant.	68:32
	1 h	Quant.	35:65
	4 h	Quant.	5:95
k *p*-MeC_6H_4	1 d	28%	84:16
	3 d	52%	85:15
	5 d	70%	86:14

[a] Consumption of Ar_2CHCl

Scheme 2. Products formed in the reactions of ylide **2** with benzhydryl chlorides **3j-Cl** and **3k-Cl** in CD_3CN at 25 °C. The ratios **4j**:**6j** and **4k:6k** were determined by ^1H NMR.

The reaction of **3j** (generated in situ by uncatalyzed ionization of covalent **3j-Cl**) with ylide **2** (2 equivalents) in CD_3CN at 25 °C initially gives mainly β-benzhydryloxyvinylphosphonium salt **4j-**Cl (see Scheme 2 and bottom NMR spectrum of Figure 1) accompanied by 32% of **6j**, which arises from C-alkylation of **2** to give **5j** and subsequent deprotonation.[31] The amount of the C-alkylated adduct (**6j**) increased with time at the expense of the O-alkylated adduct (see Scheme 2 and Figure 1, middle and top spectra), until no **4j** remained. The ultimate product, **6j**, was isolated by extraction of the crude product with ethyl acetate and crystallized from ethyl acetate/cyclohexane.[32] The residue from the extraction contained mainly **2-H** (the parent phosphonium chloride salt of ylide **2**) as a mixture of keto and enol tautomers.[33,34,35]

The reaction of **2** with **3k-Cl** in CD_3CN gave an 86:14 mixture of **4k** and **6k**, which did not change with time (Scheme 2).[36] Crystalline **4k-OTf** was obtained when this reaction was carried out in MeCN in the presence of NaOTf. The exclusive formation of the (Z)-isomer of **4k** (indicated by X-ray diffraction[37] and 1D-NOESY experiments) is consistent with the stereospecific formation of the (Z)-alkoxyvinylphosphonium salts in the alkylation of **2** with $[Et_3O]BF_4$,[38] EtBr,[24g] and MeOTf.[39]

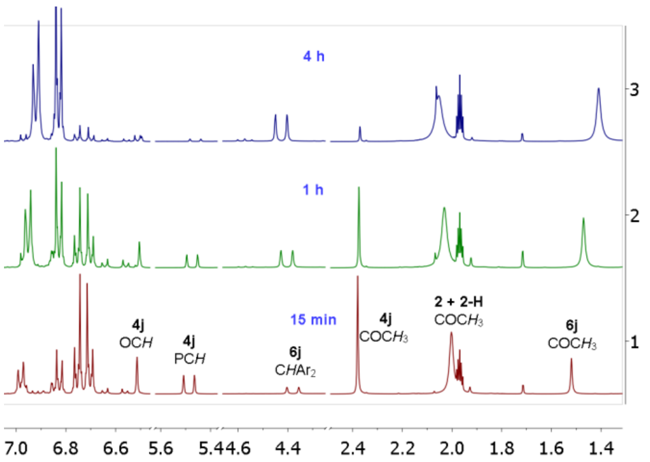
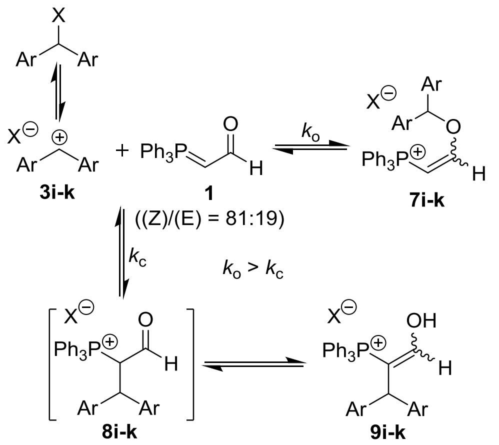


Figure 1. Stacked ^{1}H NMR spectra for the reaction of **2** (2 equivalents) with **3j**. The chemical shift of the signals of **6j** is discussed on p. S5-S7 of the Supporting Information.

In the reaction of ylide **1** with an equimolar amount of **3i-BF$_4$** in CD$_3$CN, quantitative conversion to a mixture of (Z) and (*E*)-isomers of **9i** was observed by NMR analysis straight after mixing the reactants, while **7i** was not detectable. The benzhydrylium ion **3i** obviously attacks **1** at the α-carbon to give **8i**, which tautomerizes to the hydroxyvinyl phosphonium ion **9i** (see Scheme 3). This result is consistent with previous observations of tautomerization of β-phosphoryl[40,41] and β-phosphonium[33] substituted aldehydes to their enol forms. When the ylide **1** is employed in excess over **3**, as in our kinetic experiments (*vide infra*), partial deprotonation of **9i** by **1** is highly likely.



3-X	Time^a	% **7** ((Z)/(E))	% **9** ((Z)/(E))
i (F$_3$CCH$_2$(Me)N-C$_6$H$_4$)$_2$CH$^+$ BF$_4^-$	2 min	- ^{b}	Quant. (80:20)
j (*p*-MeOC$_6$H$_4$)$_2$CHCl	15 min	Quant. (41:59)	- ^{b}
	16 h	55 (36:64)^c	- ^{c}
	44 h	21 (33:67)^c	- ^{c}
k (*p*-MeC$_6$H$_4$)$_2$CHBr	2 d	96 (58:42)	4

[a] Consumption of **3i-k** was quantitative in all cases.

[b] Not detected by ^{1}H, ^{13}C or ^{31}P NMR.

[c] **7j** decomposed without formation of **8j** or **9j; %7** based on integration vs. C*H*D$_2$CN signal in ^{1}H NMR.

Scheme 3. Products formed in the reactions of ylide **1** with benzhydrylium salt **3i-BF$_4$**, and with benzhydryl halides **3j-Cl** and **3k-Br** in CD$_3$CN. The (*Z*)/(*E*) ratios of **7j**, **7k**, and **9i** were determined by ^{1}H and ^{31}P NMR.

In contrast, the reaction of ylide **1** with **3j-Cl** in CD_3CN yielded the O-alkylation product **7j** ((*Z*)/(*E*) = 41:59; see Scheme 3). **7j** underwent decomposition in solution over *ca.* 2 days, but the formation of adducts arising from C-alkylation (**8j**, **9j**) was not observable by ^1H and ^{31}P NMR spectroscopy.

The reaction of ylide **1** with **3k-Br** in CD_3CN at 25 °C afforded β-benzhydryloxyvinylphosphonium salt **7k** ((*Z*)/(*E*) = 58:42; Scheme 3) within 2 days, accompanied by a small amount of C-alkylation product (**9k**, 4%).[42] Crystalline **7k-OTf** was obtained when this reaction was carried out in MeCN in the presence of NaOTf. Recrystallization from CH_2Cl_2 / Et_2O gave (*Z*)-**7k-OTf**, which was characterized by X-ray crystal structure analysis (Figure 2).[43]

Isolated (*Z*)-**7k-OTf** does not undergo isomerization in CD_3CN by reversal to starting materials or by C=C bond rotation. Since, in addition, the (*Z*)/(*E*) ratio of **7k** in the reaction mixture is invariant with time, we conclude that **7k** is formed irreversibly. The (*Z*)/(*E*) ratio of the crude product **7k** differs from that of the ylide **1** in CD_3CN. The (Z)-**7k**/(E)-**7k** ratio reported in Scheme 3 is the result of kinetic control. As it differs from the (*Z*)/(*E*) ratio of the ylide **1** (81:19), we assume that the interconversion of the ylide conformers[44,45,46] is faster than their reaction with **3k-Cl** (via benzhydrylium ion **3k**), and that (*E*)-**1** is more reactive than (*Z*)-**1**. Similar observations have been made in studies of the O-alkylation reactions of **1** with MeOTf in CD_3CN ((*Z*)/(*E*) = 60:40),[47] with MeI in $CDCl_3$,[25] and with EtI in $CDCl_3$.[26,48]

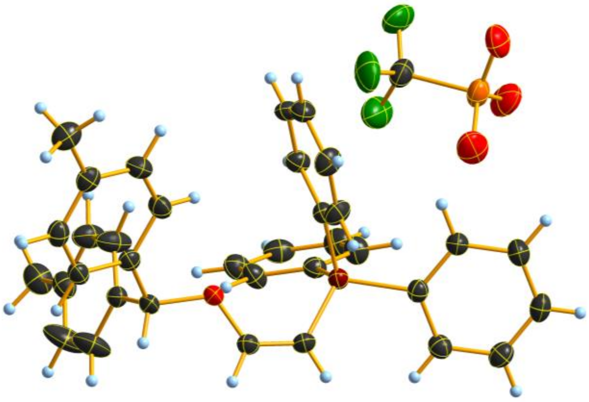


Figure 2. X-ray crystal structure of alkoxyvinylphosphonium salt (*Z*)-**7k-OTf**.

The experimental data shown in Schemes 2 and 3 indicate that O-attack at **1** and **2** by benzhydrylium ions is generally faster than C-attack. However, O-attack is thermodynamically disfavored and readily reversible for benzhydrylium ions with $E \leq 0$, which explains the observed rearrangement of **4j** to **6j**, and the exclusive formation of **9i** in the reaction of amino-substituted benzhydrylium ion **3i** with **1** (Scheme 3).

Reaction Rates

The rates of the reactions of ylides **1** and **2** with benzhydrylium ions **3a-f** in MeCN were measured by following the decay of the benzhydrylium ions by UV-Vis spectroscopy. Pseudo first-order rate constants k_{obs} for each of the reactions of **1** and **2** with selected benzhydrylium ions from **3a-f** (at different initial ylide concentration, $[\mathbf{1}]_0$ or $[\mathbf{2}]_0 >> [\mathbf{3}]_0$) were obtained by fitting of the single-exponential function $A_t = A_0 e^{-k_{\text{obs}}t} + C$ (A_0 and A_t are the absorbances at time 0 and time t, respectively, and C is the value of the constant final absorbance) to the experimental decay curves (see main images in Figures 3a,b and 5 below). The second-order rate constant k for the reaction of the ylide with a given benzhydrylium ion was then obtained from linear plots of the k_{obs} values vs. ylide concentration (see inset images in Figures 3a,b and 5 below).

Based on the results of our product studies (*vida supra*), two separate processes might be observed (each with its own rate constant) in the reactions of ylide **1** with benzhydrylium ions **3**. The reversible formation of **7**, the product of O-attack, does not proceed quantitatively. However, carrying out the reaction at high concentrations of **1** should favor the formation of **7** in the equilibrium and thus facilitate the determination of the rate constant for O-attack. Conversely, carrying out the reaction at relatively low ylide concentrations (while still maintaining pseudo-first-order conditions) should result in reduced or even negligible formation of **7**, enabling us to measure the rate of the slower, thermodynamically favored C-alkylation reaction.

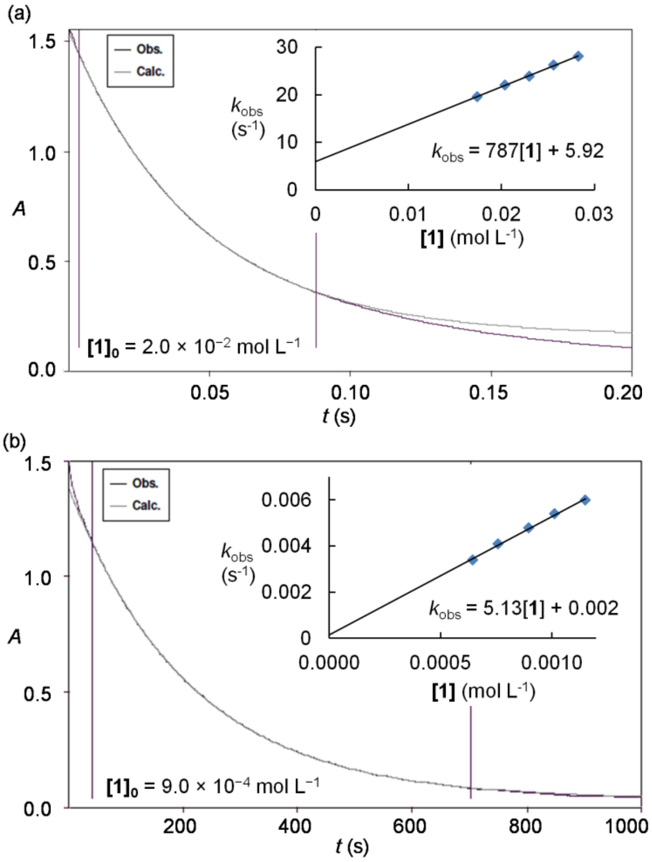
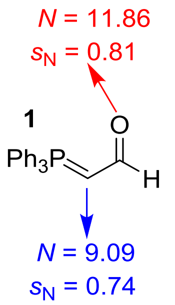
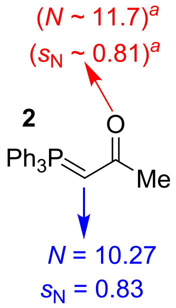


Figure 3. Absorbance (A at 620 nm) vs. time (t) plots for the decay of **3d-BF₄** (2×10^{-5} mol L^{-1}) in its reactions with **1**. The experimental decay, calculated fitting curves, and fitting limits (indicated by vertical lines) are shown. (a) Fast reaction carried out at high concentration of **1**, giving O-attack. Inset: Linear plot of k_{obs} vs. [**1**] (slope = k_{O}); (b) Slower reaction carried out at low concentration of **1**, giving C-attack. Inset: Linear plot of k_{obs} vs. [**1**] (slope = k_{C}).

Photometric monitoring of the reactions of **1** with benzhydrylium ions **3b-e** at high concentrations of **1** (> 1.7×10^{-2} mol L^{-1}) yielded mono-exponential decay curves (see Figure 3a). Plots of k_{obs} vs. $[\mathbf{1}]_0$ yielded the second order rate constants for O-attack which are shown in Table 2.

In the experimental decay curves from similar measurements on the reactions of **1** with **3a-3f** using relatively low concentrations of **1** ($\leq 1 \times 10^{-3}$ mol L^{-1}) mono-exponential decay of the benzhydrylium ion occurred due to C-attack of **1** (see Figure 3b for an example).[49] Each value of k_{obs} for the reaction of a given benzhydrylium ion with **1** (different concentration employed in each reaction) was determined by fitting of the mono-exponential decay curve of the slow process, and the second-order rate constants k for the C-alkylation reactions, listed in Table 2, were then obtained from the slopes of plots of k_{obs} vs. $[\mathbf{1}]_0$. The decay of the absorbance in the C-alkylation reactions of benzhydrylium ions **3e** and **3f** slowed down as the reactions neared completion (> 80% conversion). We discuss this phenomenon and its origin on p. S34-S36 of the Supporting Information.

Table 2. Second-order rate constants k for the reactions of **1** and **2** with benzhydrylium ions **3** in MeCN at 20 °C, and the derived values of N and s_N for the two nucleophilic sites of ylides **1** and **2**.[a]

Ylide		Ar_2CH^+	k (L mol^{-1} s^{-1})
1 	O-attack	**3b**	81
		3c	371
		3d	787
		3e	2.40×10^3
	C-attack	**3a**	0.18
		3b	0.53
		3d	5.13
		3e	12.1
		3f	28.1
2 	O-attack	**3g**	5.38×10^4
	C-attack	**3a**	1.54
		3b	5.82
		3c	17.8

[a] An approximate value of N was determined for the O-nucleophilic site of **2** based on the assumption that the s_N value of the O-site of **2** is 0.81, i.e. it is the same as that of the O-site of **1**.

As shown in Table 2, separate rate constants for O- and C-attack were determined for the reactions of **1** with each of the benzhydrylium ions **3b**, **3d**, and **3e**. Additional rate constants for the reactions of **1** with **3c** (O-attack; high ylide concentration) and with **3a** and **3f** (C-attack; low ylide concentration) were also measured.

Plots of lg k vs. E for C-attack and O-attack (Figure 4) in the reactions of **1** with **3a-f** showed excellent linear correlations, from which values of $N = 9.09$ and $s_N = 0.74$ (C-attack) and $N = 11.86$

and s_N = 0.81 (O-attack) were calculated using equation 1 for the respective nucleophilic sites of **1** (see Table 2). It is not possible at present to differentiate the reactivities of the two ylide conformers (*vide supra*).[25,26,33] Since the experimental decay curves are generally mono-exponential, we report a single set of values of the nucleophilicity parameters in Table 2.

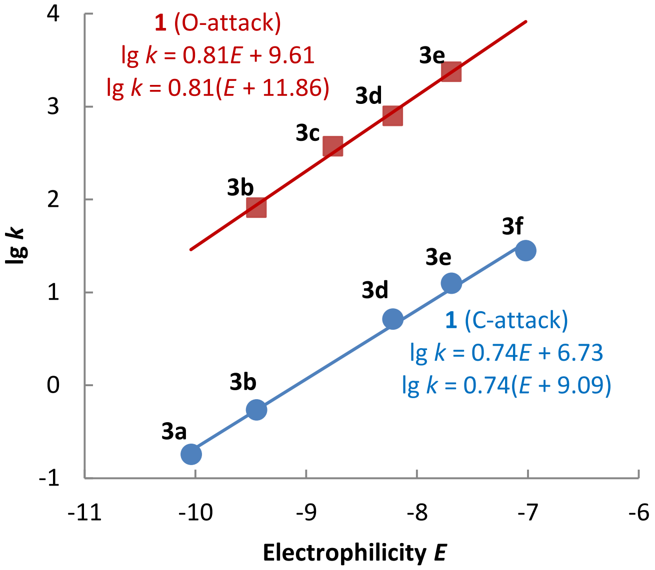


Figure 4. Plot of lg k (20 °C) vs. E for reactions of benzhydrylium ions **3** with ylide **1** (C-attack blue circles; O attack red squares).

Using a similar procedure to that described above, rate constants for the slow C-alkylation of **2** by **3a-c** in MeCN were determined using low concentrations of **2** (see Table 2 for rate constants, and Figure 5 for an example of a decay curve).

Increasing the concentration of **2** to the limit of its solubility in MeCN[50] led to the observation of complex decay curves for **3a-c**, caused by the superposition of fast O-alkylation and slower C-alkylation processes. Reliable rate constants for O-attack could not be extracted from these data. Similarly complex decay curves were observed for all reactions of **2** with **3e** and **3f**, regardless of the concentration of **2** employed.[51] Hence, neither the rate of O-alkylation nor of C-alkylation of **2** with these electrophiles could be established. Therefore, only the rate constants derived from the reactions of **2** with **3a-c** were used in a plot of lg k vs. E to derive values of the nucleophilicity parameters N = 10.27 and s_N = 0.83 for the α-carbon nucleophilic site of ylide **2** (see Table 2 and Figure S7 on pg. S37 of the Supporting Information).

In the reaction of **2** with the more Lewis acidic benzhydrylium ion **3g**, the rapid O-alkylation was dominant even at low concentrations of **2**, and the resulting rate constant (lg k_O) lies far above the correlation line for C-attack (Figure S7), as expected from the behavior of **1** (Figure 4).

As the reactions of **2** with the more reactive benzhydrylium ions **3h** and **3i** proved to be too rapid to be followed using a stopped-flow spectrophotometer, the characterization of the nucleophilicity of the O-site of **2** had to be based on only one rate constant. An approximate value of $N \approx 11.7$ was derived for the oxygen nucleophilic site of **2** (see Figure S7 and Table 2) by assuming that the O-terminus of ylide **2** has a similar value of s_N (≈ 0.81) to that of ylide **1**.

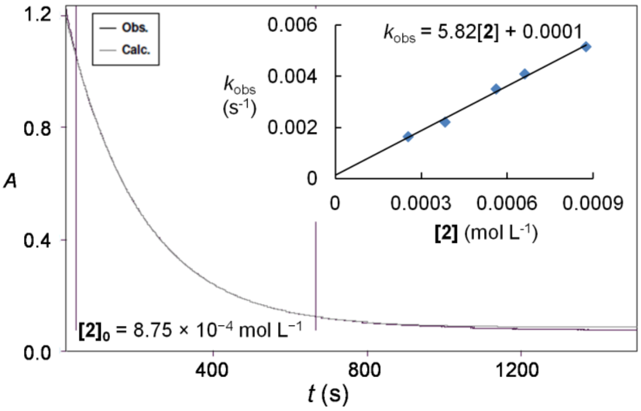


Figure 5. Main image: Absorbance (*A* at 635 nm) vs. time (*t*) plot for the decay of **3b** in its reaction with **2** (C-attack). The experimental decay and the calculated fitting curve (fitting limit indicated by vertical line at 700 s) are shown. Inset: Linear plot of k_{obs} vs. [**2**] (slope = k_C).

Discussion

Product studies and kinetic experiments thus indicate that in all reactions of **1** and **2**, O-attack by benzhydrylium ions is generally preferred kinetically, but is highly reversible for benzhydrylium ions of $E \leq 0$, enabling the measurement of the slower C-attack at low concentrations of the ylides. Let us now compare the reactivities of the carbonyl-stabilized ylides **1** and **2** with those of other types of ylides.

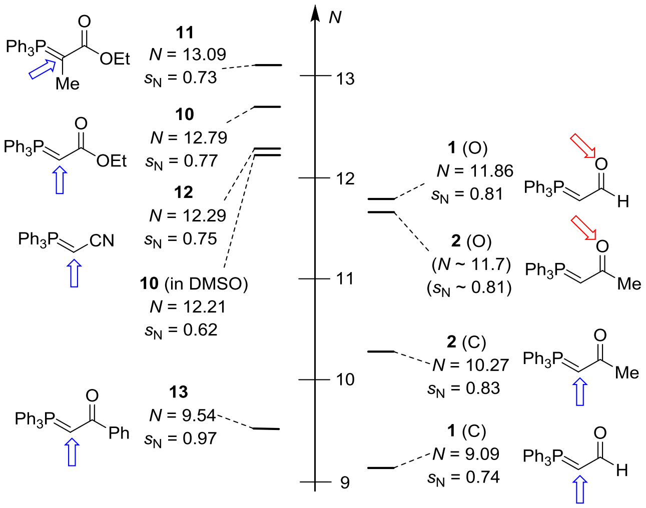


Figure 6. Comparison of the values of *N* and s_N for the α-carbon of ylides **10-13** (in CH_2Cl_2 unless otherwise indicated; one value in DMSO is also given)[30] and for the α-carbon and oxygen sites of ylides **1** and **2** (in MeCN; this work).

Values of *N* and s_N for the α-carbon of phosphonium ylides **10-13** have previously been determined in DMSO and/or CH_2Cl_2 solution in a similar way (Figure 6).[30] Since the reactivity of **10** in DMSO was found to differ only slightly from that in CH_2Cl_2, and since the s_N values for **10-13** in CH_2Cl_2 were similar to those of **10** and other phosphoryl-stabilized anions in DMSO (Figure 6), one can conclude that the nucleophilicities of **10-13** depend only slightly on the nature of the solvent. Thus, comparison of the *N* values of the α-carbon sites of **1** and **2** (determined in MeCN) with those of **10-13** (determined in CH_2Cl_2 or DMSO) is warranted (Figure 6).

The C-nucleophilicities of **1** and **2** in MeCN ($N = 9.09$ and 10.27, respectively) are similar to that of benzoyl-stabilized ylide **13** ($N = 9.54$ in CH_2Cl_2). They are significantly less nucleophilic at the ylide α-carbon than the ester and nitrile-stabilized ylides **10-12**, i.e. the keto and formyl substituents reduce the nucleophilic reactivity of the α-carbon of phosphonium ylides more than ester or nitrile groups.

The oxygen nucleophilicities of **1** ($N = 11.86$) and **2** ($N \approx 11.7$) are significantly higher than the corresponding carbon nucleophilicities. Since only mono-exponential decays were observed (due to C-alkylation) in reactions of ester-stabilized ylides **10** and **11** with weakly Lewis acidic benzhydrylium ions, O-attack for these ylides seems to be highly reversible (further discussion below).[52]

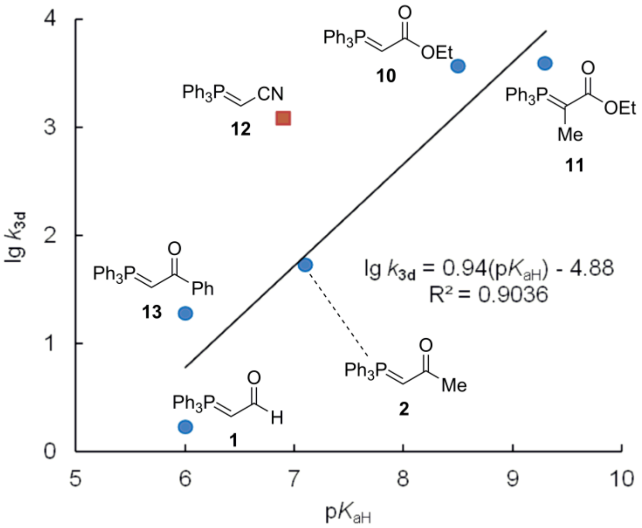
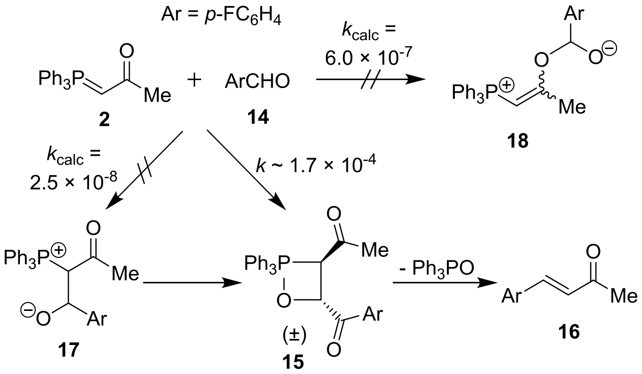


Figure 7. Brønsted plot (lg k_{3d} vs. pK_{aH} in DMSO) for ylides **1**, **2**, and **10-13**. Nitrile-stabilized ylide **12** is excluded from the correlation. The rate constants for the reactions of **3d** with **10-12** were taken from reference 30, and that for **1** + **3d** was taken from Table 2. Rate constants for **2** and **13** were calculated using equation 1.

Figure 7 shows that lg *k* values for the reactions of ylides **1**, **2**, **10**, **11**, and **13** with benzhydrylium ion **3d** correlate moderately with the corresponding Brønsted basicities (pK_{aH} in DMSO).[53] Cyano-stabilized ylide **12** deviates significantly from the correlation line in Figure 7, in line with previous observations that cyano-stabilized carbanions react over lower intrinsic barriers and, therefore, are more nucleophilic than ester- and carbonyl-stabilized carbanions with similar pK_{aH} values.[28c,54,55]

In order to examine the relevance of these observations for Wittig reactions, we have also measured the rate of the reaction of ylide **2** with 4-fluorobenzaldehyde (**14**) in CD_3CN at 23 °C by following the growth of the ^1H NMR signal of the methyl group of the olefination product **16**. The observed second-order rate constant of 1.7×10^{-4} L mol^{-1} s^{-1} is 6800 times greater than that calculated (2.5×10^{-8} L mol^{-1} s^{-1}) by eq. (1) for the formation of betaine **17** in acetonitrile at 20 °C (from $E = -19.42$ for the aldehyde **14**[28d] and the reactivity parameters for **2** shown in Table 2 and

Figure 6). If one neglects the difference in temperature, one may conclude that the oxaphosphetane **15** is formed by a process which has a Gibbs activation energy 22 kJ mol^{-1} lower than that expected for the formation of betaine **17**. This observation is consistent with the operation of a concerted [2 + 2] cycloaddition mechanism. Although this value should be treated with caution because of the uncertainty of the extrapolations using eq. (1), the relatively small difference between calculated and experimental activation energy unequivocally shows that oxaphosphetane formation profits only slightly from the interaction between P and O in the transition state.



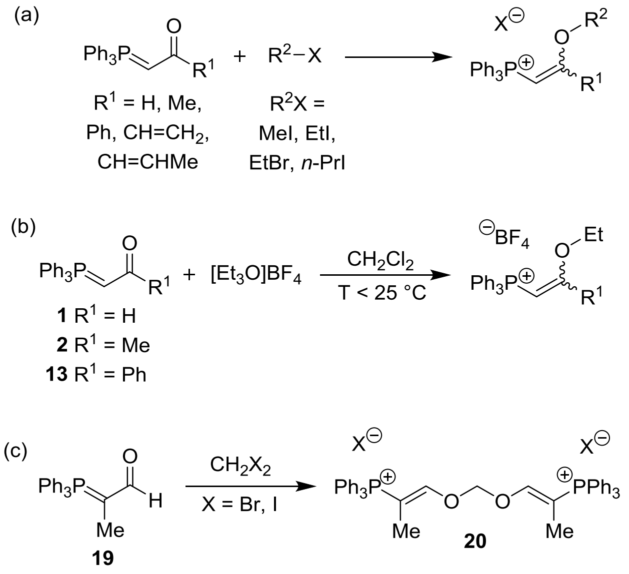
Scheme 4. Concerted Wittig reaction and putative 1-bond forming reactions of ylide **2** with 4-fluorobenzaldehyde (**14**) in CD_3CN at 23 °C. Rate constants all have units of L mol^{-1} s^{-1}.

Since the measured rate constant for the Wittig reaction of **2** with 4-fluorobenzaldehyde **14** is even greater than that calculated for O-attack (6.0×10^{-7} L mol^{-1} s^{-1}; formation of **18** in Scheme 4) by eq. (1), it is unlikely that the actual Wittig reaction, i.e. cycloaddition of the ylide with the aldehyde, is preceded by reversible attachment of the aldehyde to the oxygen of **2**.

Alkylations and Acylations of Acceptor-Substituted Phosphonium Ylides

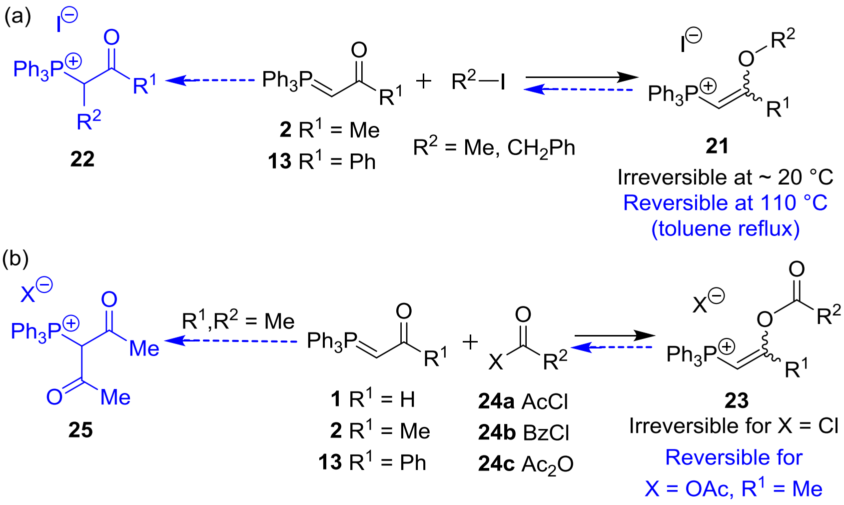
With the assumption of kinetically controlled O-attack in the reactions of carbonyl-stabilized ylides with carbon-centered electrophiles and thermodynamically controlled C-attack, we can now use the reactivity parameters derived from reactions with benzhydrylium ions (Figure 6) to rationalize literature reports on the ambident reactivities of carbonyl- and ester-substituted phosphonium ylides.

Reactions of carbonyl-stabilized ylides (including **1**, **2**, and **13**) with alkyl halides (Scheme 5a),[24,25,26,56,57] and $[Et_3O]BF_4$ (Scheme 5b),[38] have been reported to result in irreversible attachment of the alkyl group to the ylide oxygen. The reaction of ylide **19** with CH_2Br_2 or CH_2I_2 yielded the bis-O-alkylated phosphonium salts **20** (Scheme 5c).[25] Furthermore, treatment of ylide **2** with $[Ph_2I]BF_4$ resulted in exclusive phenylation of oxygen.[58]



Scheme 5. Irreversible O-alkylations of carbonyl-stabilized ylides with (a) alkyl halides,[24,25,26,56,57] (b) $[Et_3O]BF_4$,[38] (c) dihalomethanes.[25]

The alkylations of **2** and **13** with MeI and $PhCH_2I$ (Scheme 6a) were found to occur on oxygen at room temperature, while C-alkylated products were obtained at elevated temperature. This behavior can be rationalized by reversibility of O-alkylation at higher temperature.[56] The isolated O-methylated adduct **21** ($R^1 = R^2 =$ Me) was shown independently to revert to the starting keto-ylide **2** (by S_N2 attack of iodide on the OMe group), which subsequently formed **22** ($R^1 = R^2 =$ Me) upon heating in toluene in a sealed vessel (Scheme 6a). O-Alkylations of **2** and **13** with EtI or *n*-PrI under the same conditions were found to be irreversible even at high temperature (Scheme 5a).[56]

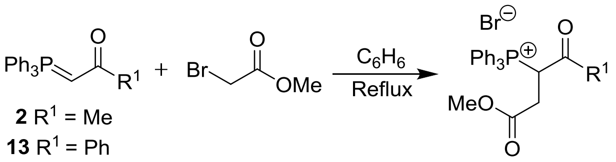


Scheme 6. Reactions of carbonyl-stabilized ylides: (a) O-methylation and benzylation occurs under conditions of kinetic control, whereas C-methylation and benzylation takes place under conditions of thermodynamic control;[56] (b) O-acylation is kinetically controlled with acyl chlorides,[59,60] but thermodynamically controlled with Ac_2O.

O-Acylated products **23** were formed irreversibly from the reactions of ylides **1**, **2**, and **13** with acyl chlorides **24a** and **24b** (Scheme 6b).[59,60] In the presence of $[(n\text{-Bu})_4N]OAc$ in hot $CHCl_3$, the isolated O-acylated product **23** ($R^1 = R^2 =$ Me; Scheme 6b) rearranged to C-acylated product **25**, which was formed exclusively when the acylation of **2** was carried out with Ac_2O (**24c**).[59]

The regioselectivities observed in the reactions in Schemes 5 and 6 confirm that O-attack occurs under conditions of kinetic control, independent of the hardness or softness of the electrophile, and that C-attack is observed only under conditions of thermodynamic control, mirroring exactly the behavior observed in reactions of carbonyl-stabilized ylides with benzhydrylium ions.

In some cases, alkylations of keto-stabilized ylides have been reported to lead only to products of C-attack. Thus, the reactions of a series of keto-stabilized ylides (including **2** and **13**) with $BrCH_2CO_2Me$ in refluxing benzene led to C-alkylated products (Scheme 7),[61] as did the reactions of bis-ylide $(Ph_3P{=}CH)_2CO$ with various dihaloalkanes in toluene (the reaction temperature was not reported).[62] We cannot definitively rule out kinetically controlled C-alkylation in these reactions. However, it seems likely, by analogy with the reactions in Schemes 5 and 6, that also in these reactions O-attack is kinetically favored, and that C-alkylation results from the operation of thermodynamic control.



Scheme 7. C-Alkylations with $BrCH_2CO_2Me$ in refluxing benzene.[61]

By analogy with the behavior of **1** and **2**, one might also expect O-attack to be kinetically favored in the reactions of ester-stabilized ylides with carbon electrophiles. Indeed, although the products of C-attack are formed from ester-stabilized ylides and alkyl halides (in refluxing EtOAc, benzene, or $CHCl_3$)[63] or $[Me_3O]BF_4$ (in CH_2Cl_2 at 0 °C),[38] irreversible O-alkylation was reported for the reactions of ester-stabilized ylides with $[Et_3O]BF_4$ at −78 °C.[38,64] In addition, while C-acylation of ester-stabilized ylides occurs with acyl halides at room temperature,[60,65] low temperature monitoring of the reactions of various acyl chlorides with ylide **11** by NMR has shown that O-attack is kinetically favored.[66] Although the available evidence is not definitive, it seems reasonable to conclude that O-attack at ester-stabilized ylides is faster, but is highly reversible at ambient temperature, and hence products arising from C-attack are generally observed in reactions of ester-stabilized ylides with carbon electrophiles.

Reactions of ester-stabilized ylides **10** and **11** with benzhydrylium ions at 20 °C were reported to give the products of C-alkylation exclusively.[30] Since in all cases mono-exponential decays were observed during kinetic monitoring of these reactions, one can conclude that products of O-attack never accumulated and were always below detectable concentrations. As only benzhydrylium ions with low Lewis acidities (i.e. highly stabilized benzhydrylium ions) were employed, this behavior is consistent with the above interpretation.

Conclusions

Kinetic investigations by UV-Vis spectroscopy and product studies by NMR spectroscopy and X-ray crystallography demonstrated that all of the reactions of ylides **1** and **2** with benzhydrylium ions result in initial (kinetically favored) addition of the electrophile to the ylide oxygen atom. Irreversible O-alkylation of **1** and **2** with the most Lewis acidic benzhydrylium ion of this series, **3k**, gives stable adducts **7k** and **4k**, respectively. For benzhydrylium ions with $E \leq 0$, O-attack is reversible, and as a consequence the thermodynamically more favorable products arising from C-attack are formed. Using the reactivity parameters N and s_N derived for ylides **1** and **2**, we were able also to rationalize numerous literature reports on the reactions of acceptor-substituted phosphonium ylides with C-centered electrophiles.

Previous work by our group has shown that the application of the HSAB principle of Pearson[23a-f,67] and of the Klopman-Salem concept of charge vs. orbital control[23g,h] does not satisfactorily predict the regioselectivities of reactions of ambident nucleophiles.[68]

Thus, we have demonstrated that thiocyanate anions are preferentially attacked at sulfur by soft and hard C-electrophiles (kinetic control) and that isothiocyanates, the products arising from N-attack, are the result of thermodynamic control.[68a] Free cyanide ions are generally attacked at carbon by all alkylating and acylating agents, and isonitriles are formed when the attack at the cyanide carbon is blocked by coordination, e.g., with silver ions.[68b] Kornblum had already reported that nitroalkanes, and not alkyl nitrites, are the major products formed from primary alkyl halides and silver nitrite.[69,68c] In view of these results, Fleming concluded that "other factors are at work, and this pattern (*HSAB*) is unreliable".[70] After demonstrating the failure of the HSAB rationalization in many other cases,[68] we have suggested the use of Marcus theory,[71] which derives the Gibbs activation energy $\Delta G^{\neq}$ from the Gibbs reaction energy ΔG^0 and the intrinsic barrier $\Delta G_0^{\neq}$, for rationalizing the behavior of ambident organic reactants.[72] An important consequence of Marcus theory is that the formation of a contra-thermodynamic product is possible only if it is formed via the lower intrinsic barrier.

According to the Hoz-rule,[73] the magnitudes of the intrinsic barriers in nucleophilic substitution reactions depend on the nature of the central element of the nucleophile, decreasing from left to right across the periodic table (i.e., C > N > O > F). Our results are thus consistent with intrinsically controlled O-attack for the reactions of **1**, **2**, and **13** with C-electrophiles. Similar observations have been made for reactions of other enolates.[74] Although carbon electrophiles commonly prefer to attack the intrinsically preferred oxygen center of free enolate ions under conditions of kinetic control,[72,74] C-attack often becomes kinetically dominant when O-attack is blocked by strong coordination of the enolate to a counter-ion, especially Li^+,[72,75] or when C-attack is accelerated by other factors, e.g., if a concerted mechanism operates, as in the Wittig reactions mentioned above.

We are now in a position to rationalize the observations presented in Scheme 1. As discussed above, kinetically controlled reactions of carbon electrophiles with ylides **1** and **2** generally lead to the formation of products of O-attack. If the O-alkylation reaction is reversible (as it is with benzhydrylium ion **3i**), the thermodynamically more stable products of C-attack are isolated. These observations are directly at odds with the outcomes predicted on the basis of the HSAB principle. There are no preferential "soft-soft" (orbital-controlled) interactions or "hard-hard"(charge-controlled) interactions dictating the outcomes of the reactions of **1** and **2**. Hence, the behavior of phosphonium ylides **1** and **2** neatly encapsulates the problems inherent in using HSAB theory to rationalize ambident reactivity.

Supporting Information

Experimental procedures and characterization of compounds **4j**, **4k**, **6j**, **7j**, **7k** and **9i**; details of kinetic experiments; plot of lg *k* vs. *E* for reactions of ylide **2** with benzhydrylium ions; details of single crystal X-ray diffraction experiments; copies of NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI:_

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32 Formation of transylidation product in ylide alkylation has previously been observed in the reaction of ester-stabilized ylide **10** with [Me$_3$O]BF$_4$.[38]

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34 See pg. S7-8 of the Supporting Information for characterization details.

35 See pg. S6-7 of the Supporting Information for a discussion of the equilibrium that exists in the reaction mixture involving ylide and keto and enol tautomers of the phosphonium salt(s).

36 Ionization of **3k-Cl** in MeCN is comparatively slow, and hence this reaction required two days for completion.

37 See pg. S39-40 and S45-48 the Supporting Information for details of the crystal structure determination.

38 Kayser, M. M.; Hatt, K. L.; Hooper, D. L. *Can. J. Chem.* **1991**, *69*, 1929.

39 See pg. S19 of the Supporting Information.

40 Formation of β-hydroxyvinylphosphonates: (a) Aboujaouade, E. E.; Collignon, N.; Savignac, P. *Tetrahedron* **1985**, *41*, 427; (b) Yoffe, S. T.; Petrovsky, P. V.; Goryunov, Y. I.; Yershova, T. V.; Kabachnik, M. I. *Tetrahedron* **1972**, *28*, 2783.

41 Formation of β-hydroxyvinylphosphine oxides: Regitz, M.; Anschütz, W. *Chem. Ber.* **1969**, *102*, 2216.

42 The identity of the C-alkylated adduct is assigned by analogy with the formation of product **9i** in the reaction of **1** with **3i**; the quantity of C-alkylated adduct in this reaction is too small to distinguish between β-hydroxyvinylphosphonium salt **9k** and an ylide product analogous to **6k**.

43 See pg. S39-44 of the Supporting Information for details of the crystal structure determination.

44 Interconversion of isomers of formyl-stabilized[25,26,45] and ester-stabilized[46] ylides through their respective parent phosphonium salts has been shown by NMR to occur readily at room temperature if a suitable acid catalyst (such as the parent phosphonium salt, even in trace amounts) is present.

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47 See pg. S19 of the Supporting Information.

48 Ethylation of **1** with $[Et_3O]BF_4$ in CH_2Cl_2 at 0 °C is reported to give ethoxyvinylphosphonium salt with a (*Z*)/(*E*) ratio matching exactly that of the starting ylide ((*Z*)/(*E*) = 3:2).[38] However, the same reaction conducted at room temperature was reported to give a slightly different product (*Z*)/(*E*) ratio of 2:1.

49 An almost negligible fast decay of the absorbance can be seen at the very start of the decay curves in each of these reactions due to reversible O-attack (see Figure 3b). To account for this, the initial portion of the curve was excluded from the fitting procedure to obtain k_{obs}, as shown in Figure 3b.

50 MeCN solutions of **2** at 20 °C become saturated at a concentration of approximately 6.3×10^{-2} mol L^{-1}.

51 The final portions of the decay curves (> 80% conversion) for the reactions of **2** with **3c**-**3f** indicated a slowing of the consumption of the benzhydrylium ion. This effect is almost negligible for **3c** but becomes increasingly pronounced as the Lewis acidity of the benzhydrylium ion increases (i.e. it is greatest for **3f**). We discuss this phenomenon and its origin on pg. S33-S34 of the Supporting Information.

52 Reactions of ylide **13** were conducted using relatively low concentrations of the ylide ([**13**] < 1.5×10^{-3} mol L^{-1}),[30] i.e. under conditions where the observation of exclusive C-alkylation is likely.

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