Distinction between Polar and Electron-Transfer Routes. A Mechanistic Study on the Wittig Reactions of Nonstabilized Ylides

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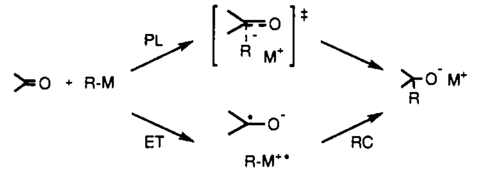
Abstract: The Wittig reaction of nonstabilized ylides with benzaldehyde and benzophenone was investigated in detail by means of carbonyl-^{14}C kinetic isotope effects, substituent effects, and isotope-scrambling and probe experiments. The reaction with benzophenone gave the carbon isotope effects and the Hammett ρ values of considerable magnitude both in Li salt-free and salt-present conditions. In contrast, they are quite small for the reaction with benzaldehyde. Enone-isomerization and dehalogenation probe experiments indicated that the nonstabilized ylide has enough ability to transfer an electron to benzaldehyde and benzophenone. These results were interpreted in a self-consistent manner by the mechanism that the Wittig reaction of nonstabilized ylides proceeds via initial electron transfer from the ylide to the carbonyl compounds. The electron-transfer step is rate-determining for benzaldehyde, while radical coupling following the electron-transfer step is rate determining for benzophenone. From the probe experiments together with the isotope effects and the substituent effects reported previously, the reaction of semistabilized ylides was concluded to proceed through a polar nucleophilic addition mechanism.

Introduction

Nucleophilic addition to carbonyl functions is one of the most basic reactions in organic synthesis, but the mechanism of this fundamental transformation is not fully understood. There are two possible reaction routes, the polar addition (PL) mechanism and the electron-transfer (ET)–radical coupling (RC) sequence, eq 1, and the mechanism is highly nucleophile dependent. The



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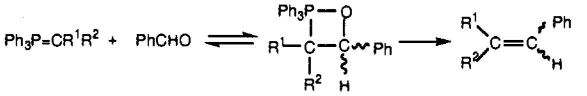
current reaction design for synthetic purposes of additions of common nucleophiles to aldehydes and ketones is mostly based on the polar mechanism, but apparently the ET process is involved in some reactions of, for example, Grignard and organolithium reagents.[1,2]

In general, the distinction between PL and ET mechanisms is not straightforward. Various experimental methods have been used so far to demonstrate the ET process; these include spectroscopic detection of radical intermediates,[1c,d,2b,3] detection of products indicative of radical intermediates,[2b,4] and measurement of secondary deuterium kinetic isotope effects (KIEs).[5] However, none of the methods is conclusive enought by itself. We have been using the combination of several experimental methods, including KIEs, substituent effects, and probe experiments, in order to distinguish the ET process from the PL process for the addition reactions of Grignard,[1a,6a–d] organolithium,[2c,d,6c] and other organometallic reagents.[6e] We report in this paper the results on the Wittig reaction of nonstabilized ylides and discuss the mechanistic difference between nonstabilized and semistabilized ylides.[7]

Recent studies on the Wittig reaction have shown that the reaction proceeds through the oxaphosphatene intermediate (eq 2) and the decomposition of oxaphosphetane to the product alkene



(2)

is stereospecific.[8] The mechanistic problem that remains unsolved is how the oxaphosphetane intermediate is formed especially for

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Table I. First-Order Rate Constants for Decomposition of Oxaphosphetane Derived from Substituted Benzaldehyde and Isopropylidene Ylide[a]

substituent	k_X[b]	substituent	k_X[b]
H	$7.99 \pm 0.84 \times 10^{-5}$	*m*-Cl	$6.52 \pm 0.26 \times 10^{-5}$
o-Me	$1.88 \pm 0.09 \times 10^{-3}$	*p*-Cl	$7.61 \pm 0.14 \times 10^{-5}$
m-Me	$8.52 \pm 0.03 \times 10^{-5}$	*m*-CF_3	$6.70 \pm 0.16 \times 10^{-5}$
p-Me	$8.35 \pm 0.46 \times 10^{-5}$	*m*-F	$7.00 \pm 0.12 \times 10^{-5}$
o-Cl	$2.64 \pm 0.42 \times 10^{-4}$		

[a] In THF at 0 °C under Li salt-free conditions. [b] Average of two runs.

Table II. Substituent Effects and Carbonyl-^{14}C KIEs of the Wittig Reactions in THF

substrate	ylide	conditions, °C	$^{12}k/^{14}k$	ρ values
PhCHO	$Ph_3P{=}CMe_2$	Li salt free, 0	1.003 ± 0.002	0.59 ± 0.04
		Li salt present, 0	0.971 ± 0.004	0.20 ± 0.02
	$Ph_3P{=}CHPr$	Li salt free, 0	0.998 ± 0.002	0.20 ± 0.03
		Li salt present, 0	0.995 ± 0.003	0.18 ± 0.02
		Li salt free, −78	0.993 ± 0.003	-0.25 ± 0.77
$Ph_2C{=}O$	$Ph_3P{=}CMe_2$	Li salt free, 0[a]	1.053 ± 0.002	1.40 ± 0.17
		Li salt present, 0[b]	1.041 ± 0.010	1.19 ± 0.14
PhCHO	$Ph_3P{=}CHPh$	Li salt free, 0[c]	1.060 ± 0.003	2.77 ± 0.15
		Li salt present, 0[c]	1.015 ± 0.004	1.38 ± 0.12

[a] Data taken from ref 10. [b] In Et_2O. [c] Data taken from ref 9.

Table III. Percent Scrambling between Benzaldehyde and Nonstabilized Ylides[a]

ylide	reaction conditions	% scrambling
$Ph_3P{=}CMe_2$	Li salt free	13.1 ± 1.5
	Li salt present	59.7 ± 4.7
$Ph_3P{=}CHPr$	Li salt free	19.2 ± 3.1
	Li salt present	44.1 ± 7.6

[a] At 0 °C. Errors are the standard deviations.

Chart I[a]

rate-determining step	carbonyl-^{14}C KIE	Hammett ρ value	enone-isomerization	dehalogenation probe
PL	large	large	no	no
RC	large	large	yes	yes
ET	small	small	yes*	yes*

[a] Asterisk denotes a possible "no" in cases where the RC step is fast compared to isomerization or dehalogenation.

nonstabilized ylides. A polar cycloaddition mechanism with a variable transition state has been proposed to account for the variable cis/trans selectivity of the different classes of ylides. Thus, the transition state is reactantlike with a nonstabilized ylide that yields a cis alkene preferentially, while it is productlike with a stabilized ylide that affords a trans alkene as the major product.[8a] Our present experimental results suggest that the mechanism is qualitatively different for nonstabilized and semistabilized ylides. The reaction of the latter class of ylides proceeds via the polar mechanism, but the reaction of nonstabilized ylides may be considered to proceed via the ET route.

Results

Benzaldehyde reacts with nonstabilized ylides quickly even at −78 °C to form oxaphosphetane, which then decomposes slowly at 0 °C to alkene and phosphine oxide. This suggests the possibility that KIEs and substituent effects can be determined for both the initial oxaphosphetane-formation step and the oxaphosphetane-deomposition step separately under suitably selected conditions. In the present study, we have measured substituent effects under two different conditions. First, a pair of differently substituted benzaldehydes was treated with a deficient amount of ylide at 0 °C for 10 s; this procedure allows determination of the substituent effects for the oxaphosphetane-formation step with minimal contribution from oxaphosphetane decomposition. The extent of the oxaphosphetane reversal to aldehyde and ylide under the reaction conditions was estimated by isotope-scrambling experiments shown below. Second, substituted benzaldehyde was allowed to react with excess ylide to form oxaphosphetane, and the rate of the oxaphosphetane decomposition was determined by monitoring the product alkene formation by GC. The decrease of oxaphosphetene concentration (or the increase of alkene concentration) obeyed the first-order rate law nicely, from which the decomposition rate constant was calculated. The first-order rate constants obtained are listed in Table I. These substituent effects are plotted against the Hammett σ values and are shown in Figure 1. Here, the closed circles denote the reactivity of ortho-substituted benzaldehydes and the open circles refer to that of meta- or para-substituted derivatives.

Carbonyl-^{14}C KIEs for the oxaphosphetane-formation step were measured as reported previously[9] and are shown in Table II together with a list of the Hammett ρ values. Measurement of the KIE in the oxaphosphetane-decomposition step could not be performed because of the experimental difficulty in measuring the radioactivity of alkene and oxaphosphetane in required accuracy. In contrast to the cases of benzaldehydes, oxaphosphetane is not a stable intermediate for the reaction of benzophenone with nonstabilized ylides, and therefore, substituent effects and KIEs can be determined only for the overall reaction in the benzophenone case. They were measured under the Li salt-present conditions in the same manner as reported before.[10]

The isotope-scrambling experiment was carried out to measure the extent of oxaphosphetane reversal. In method 1, unlabeled oxaphosphetane was prepared from benzaldehyde (0.40 M, 0.60 mmol, referred to as A) and excess ylide (0.30 M, 1.20 mmol). At this stage, most of the benzaldehyde was converted to oxaphosphetane and only a small amount (x%) of benzaldehyde remained. ^{14}C-Labeled benzaldehyde (0.40 M, 1.20 mmol, referred to as B) was added to the reaction mixture, and after 10 s, benzaldehyde was recovered and its molar radioactivity was measured. If no oxaphosphetane reversal occurred, then the observed radioactivity (R_0) would be given by eq 3, while on the other hand, if there was complete scrambling, then the radioactivity (R_{100}) should be given by eq 4. Then, the extent of scrambling (% scrambling) is given by eq 5.[11] Here, R and R_{obs}

$$R_0 = BR/(B + Ax) \tag{3}$$

$$R_{100} = BR/(B + A) \tag{4}$$

$$\% \text{ scrambling} = (R_{obs} - R_0)/(R_{100} - R_0) \tag{5}$$

refer to the radioactivity of the benzaldehyde added and recovered, respectively. A similar experiment was repeated by starting with labeled aldehyde, and unlabeled aldehyde was added later (method 2). Duplicate experiments were carried out for each method, and the results agreed within 2%. Table III lists the scrambling values, which are the averages of the results obtained by methods 1 and 2, under various reaction conditions.

Discussion

Mechanistic Criteria. Chart I summarizes the mechanistic criteria that we used in the present study. The size of heavy-atom KIEs is usually considered to be positive (larger than unity) when the total bonding at the labeled atom is decreasing in the transition state (TS) and negative (less than unity) when the

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(11) In most cases, a small amount (2–5%) of benzaldehyde remained when benzaldehyde was mixed with the ylide, while as much as 28% of benzaldehyde remained when $Ph_3P{=}CMe_2$ was used under Li salt-present conditions.

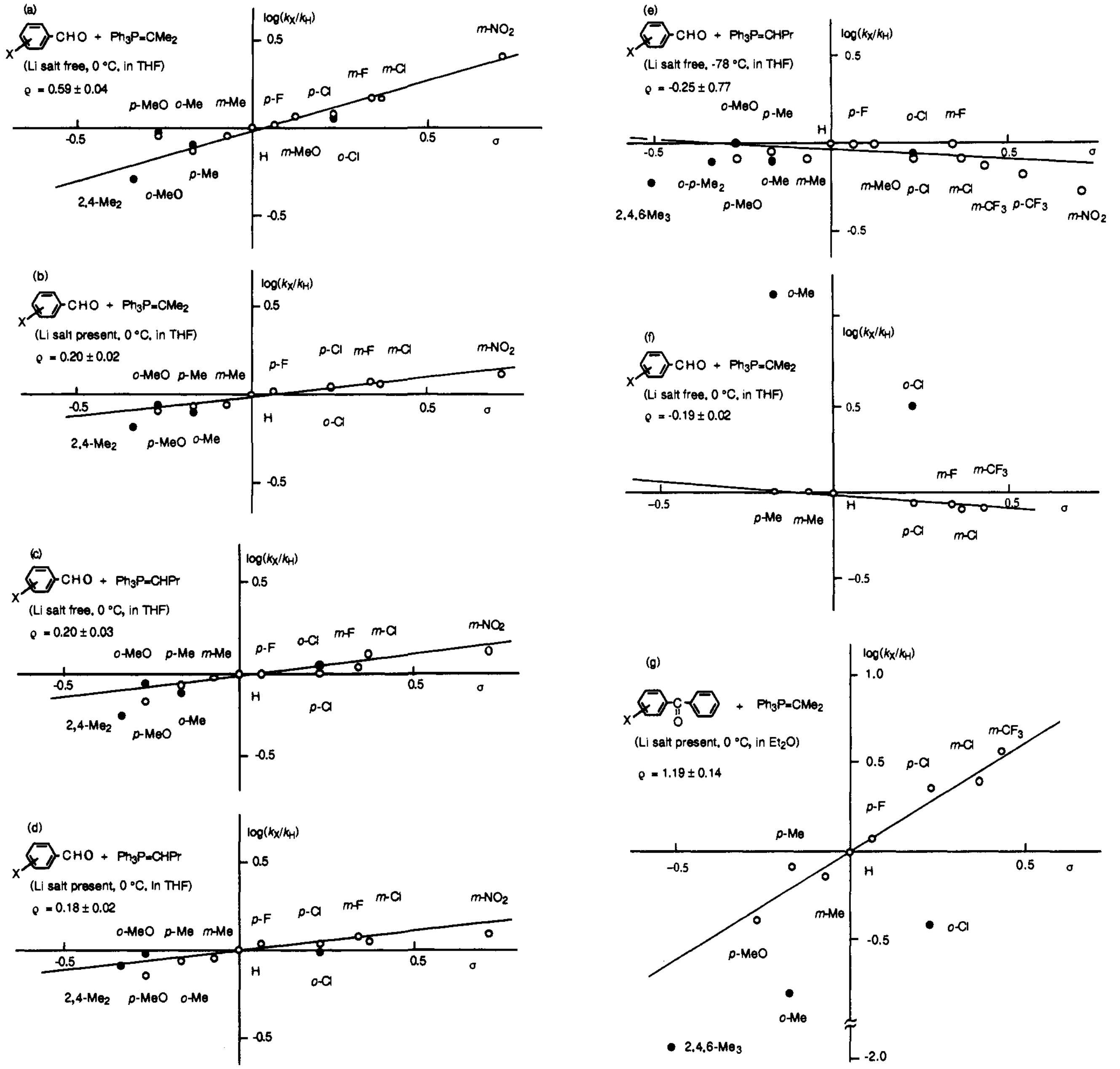

Figure 1. Variations of reactivity with σ values for the oxaphosphetane formation of substituted benzaldehydes with (a) isopropylidene ylide at 0 °C under Li salt-free conditions in THF, (b) isopropylidene ylide at 0 °C under Li salt-present conditions in THF, (c) butylidene ylide at 0 °C under Li salt-free conditions in THF, (d) butylidene ylide at 0 °C under Li salt-present conditions in THF, and (e) butylidene ylide at −78 °C under Li salt-free conditions in THF; (f) variations of reactivity with σ values for the decomposition of oxaphosphetane derived from substituted benzaldehydes with isopropylidene ylide at 0 °C under Li salt-free conditions in THF; and (g) variations of reactivity with σ values for the overall reactions of substituted benzophenones with isopropylidene ylide at 0 °C under Li salt-present conditions in ether.

bonding is increasing. This is truly an important factor to the KIE, but an equally or even more important factor that determines the size of a primary KIE is the dynamic character of the TS;[12] the KIE is larger if the labeled atom is involved to a greater extent in the reaction-coordinate motion. The importance of the reaction-coordinate contribution has been throughly demonstrated by model calculations of primary carbon KIEs.[13] Thus, the carbonyl-carbon KIE is expected to be of considerable magnitude if the reaction proceeds via the polar mechanism or if the rate-determining step is the RC step in the ET–RC route since the motion of the labeled carbon is directly involved in the reaction coordinate in these cases. In contrast, the KIE would be much smaller for the rate-determining ET mechanism since there is no contribution from the reaction-coordinate motion.

A large substituent effect is reasonably expected for the polar mechanism. It would also be large for the rate-determining RC mechanism because this mechanism involves ET preequilibrium, for which the Hammett ρ value is quite large.[14] Thus, the PL and the rate-determining RC mechanisms would show similar kinetic behavior. On the other hand, the magnitude of the ρ value for the rate-determining ET mechanism is not easily predictable; however, previous results suggested that the ρ value

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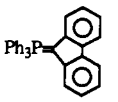
Table IV. *E–Z* Isomerization during the Reaction of *Z*-Enone with Various Ylides in THF at 0 °C[a]

ylide	time, min	recovered enone *Z*:*E*
$Ph_3P{=}CMe_2$ (**1**)	15	86.1:13.9
	60	33.2:66.8
$Ph_3P{=}CHPh$ (**2**)	15	98.2:1.8
	60	96.7:3.3
 (3)	15	97.1:2.9
	60	98.4:1.6
blank	60	98.5:1.5

[a] Wittig products were not detected. *E*:*Z* ratio was normalized; 100% = *E* + *Z*.

can be rather small,[1a,2c,d] which was rationalized in terms of the predominant contribution of solvent reorganization in the activation process of the ET step.[2c]

Enone-isomerization[15] and dehalogenation[6d,16] experiments are the probes that measure whether a reagent has enough ability to transfer an electron to enone and halobenzophenone, respectively, and therefore, if these two probes were positive, then there would be a good possibility that the reaction proceeds via the ET–RC sequence. Thus, the combined use of the four criteria would give us an insight for the reaction pathway of the addition reactions.

Reaction of Benzophenone. The carbonyl-^{14}C KIE and the Hammett ρ value are both positive for the reaction of benzophenone with isopropylidene ylide in ether under Li salt-present conditions (Table II, Figure 1g). These values are qualitatively the same as those reported previously for the reaction in THF under Li salt-free conditions[10] and suggest that the reaction proceeds via either the polar route or the electron-transfer route with the RC step as rate-determining.

The enone-isomerization probe was previously used by House and Ashby for RLi and RMgX.[15] Here, isomerization of the starting cis enone to the trans enone upon mixing with a reagent is taken as an indication of the occurrence of ET from the reagent to the enone. Since the reduction potential of (Z)-2,2,6,6-tetramethylhept-4-en-3-one is more negative (−2.28 V vs SCE) than those of benzaldehyde (−1.84 V) and benzophenone (−1.82 V),[17] a positive result of the enone-isomerization experiment then indicates the possible occurrence of ET to the aromatic aldehyde and ketone. The results of the probe experiment with various classes of Wittig reagents are summarized in Table IV. It is clear in Table IV that nonstabilized ylide **1** shows the positive response whereas semistabilized and stabilized ylides **2** and **3** are negative.

The dehalogenation experiment, recently introduced by us, measures the occurrence of ET from a reagent to halobenzophenone.[6d] As indicated by Saveant[18] and Tanner,[19] the halobenzophenone radical anion undergoes dehalogenation with rate constants ranging from 10^2 to 10^6 when the halogen is Br or I, and this reaction may be competitive with the RC step if a radical ion-pair intermediate was formed by ET. Although for the actual reaction intermediate the dehalogenation rate would be much slower than that reported because of strong interaction between the ketyl and the counter radical cation of the nucleophile, there would be good possibility for dehalogenation to occur if one uses *o*-halobenzophenones, for which the RC step is slowed down by the ortho steric effect.[1a,20] The results of the radical anion probe for the Wittig reactions are listed in Table V. Clearly, the nonstabilized ylide shows different reactivity than the semistabilized and stabilized ylides.

The two probe experiments above indicate that only the nonstabilized ylide can transfer an electron to the aromatic ketone. It is concluded that the reaction of benzophenone with isopropylidene ylide proceeds via initial ET followed by rate-determining RC to give the oxaphosphetane intermediate.

Reaction of Benzaldehyde. Reactivity Study. Substituent effects on the oxaphosphetane-formation step between substituted benzaldehydes and nonstabilized ylides are small (ρ = −0.25–0.59) at 0 and −78 °C in THF (Figures 1a–e), in sharp contrast to those observed for the reactions of benzophenone. The carbonyl-^{14}C KIEs are also very small for the former reactions. The results clearly indicate the mechanistic difference between the aldehyde and the ketone. These small substituent effects and KIEs, coupled with the probe experiments of the nonstabilized ylide, suggest that the oxaphosphetane-formation reaction of benzaldehyde with nonstabilized ylides proceeds via the rate-determining ET mechanism.

The small Hammett ρ value alone can be interpreted in different ways. First, the reaction proceeds through a polar four-centered transition state, in which the extents of the C–C and P–O bond formation are balanced with each other. Accidental balancing of this kind was previously observed for the BH_3 reduction of substituted benzophenone, in which the Hammett ρ value was near zero.[20] Second, the TS lies very early along the reaction coordinate of the rapid polar addition.

The first possibility can be eliminated by comparing the Hammett ρ values for the nonstabilized and semistabilized ylide (benzylidene ylide). The carbanion center of the semistabilized ylide should have less nucleophilicity than that of the nonstabilized ylide due to conjugative stabilization by the phenyl ring, while the electrophilicity of the phosphorus center is less influenced. Therefore, if the reaction of the nonstabilized ylide goes though a well-balanced TS, then the C–C bond formation should be less advanced than the P–O bond formation in the TS for the semistabilized ylide and the reaction of the semistabilized ylide should give a negative Hammett ρ value, which is contrary to the experimental results. Molecular orbital calculations in the literature also indicate that the C–C bond is much stronger than the P–O bond in a four-centered TS of simple Wittig reactions.[21]

The importance of the reaction-coordinate contribution in governing the magnitude of carbon isotope effects is well recognized as described above. Thus, the observed near-unity KIEs in the present reactions indicate that the bonding change is not occurring in the TS and clearly eliminate the first possibility raised above (a balanced four-centered TS). In the same sense, the experimental results are also inconsistent with the second possibility (an early TS) because even in an early TS, there should be some bonding change at the carbonyl carbon in the TS, which should give some positive KIE. Such a case was indeed observed previously for the $LiAlH_4$ reduction of benzophenone, where, due to its early TS, the Hammett ρ value was as small as 0.45 but the carbonyl-^{14}C KIE of 1.024 was detected.[20,22]

Oxaphosphetane Decomposition. We have focused so far on the oxaphosphetane-formation step because it is mechanistically the most controversial step in the overall Wittig reaction. However, kinetic investigation on the oxaphosphetane-decomposition step is also important, since, in most other cases than the

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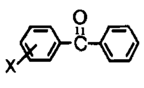
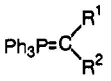
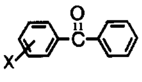
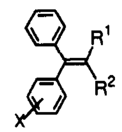
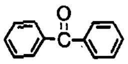
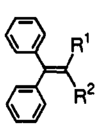
Table V. Recovered Materials in the Reactions of Halobenzophenones with Various Ylides[a]

entry						
1[b]	X = *o*-Br	$R^1 = R^2$ = Me (**1**)	76.1 ± 1.4	*c*	7.7 ± 0.6	0.8 ± 0.2
2	*m*-Br	**1**	37.8 ± 4.9	56.7 ± 6.2	*c*	*c*
3	*p*-Br	**1**	22.4 ± 2.3	77.8 ± 0.4	*c*	*c*
4	*o*-I	**1**	78.7 ± 2.9	*c*	14.8 ± 2.4	0.9 ± 0.3
5	*m*-I	**1**	37.4 ± 5.2	54.1 ± 4.2	4.7 ± 0.8	0.4 ± 0.1
6	*p*-I	**1**	45.0 ± 1.5	43.0 ± 0.5	6.5 ± 0.4	0.3 ± 0.1
7	*o*-Br	R^1 = H, R^2 = Ph (**2**)	97.8 ± 0.4	*c*	0.8 ± 0.2	*c*
8	*m*-Br	**2**	99.1 ± 0.3	*c*	*c*	*c*
9	*p*-Br	**2**	96.5 ± 0.3	*c*	*c*	*c*
10	*o*-I	**2**	96.8 ± 1.4	*c*	3.2 ± 0.4	*c*
11	*m*-I	**2**	100.0 ± 0.2	*c*	*c*	*c*
12	*p*-I	**2**	102.2 ± 0.2	*c*	1.9 ± 0.1	*c*
13	*o*-Br	R^1,R^2 = 2,2′-biphenyldiyl (**3**)	99.3 ± 1.1	*c*	*c*	*c*
14	*o*-I	**3**	100.1 ± 1.9	*c*	*c*	*c*

[a] In THF at 0 °C, 2 h. Figures are average GC yields (%) from 2 to 3 runs. Errors are standard deviations. [b] *o*-Bromobenzhydrol was also detected in 0.8 ± 0.2% yield. [c] Not detected.

reactions of aldehydes with nonstabilized ylides, oxaphosphetane is not stable enough to allow kinetic investigation on its formation and decomposition separately and only information of the overall process can be obtained. A separate experiment on the oxaphosphetane-decomposition step is thus necessary to calibrate the results of the overall reaction.

The decomposition rates of oxaphosphetanes derived from substituted benzaldehydes and isopropylidene ylide to phosphine oxides + alkenes were found to be in the order of 10^{-5}–10^{-4} s^{-1} at 0 °C. Maryanoff et al. recorded the time dependence of ^{31}P NMR for the reaction of benzaldehyde with butylidene ylide and estimated the oxaphosphetane-decomposition rate for the first time.[23] The reported rate constants for the cis oxaphosphetane at −30 °C under LiBr-present conditions are (6.77–7.90) × 10^{-5} s^{-1}. These values are judged to be in good agreement if one takes the differences in temperature, reaction conditions (presence or absence of LiBr), and ylide structure into consideration. The important features we can see in the Hammett plots in Figure 1f are the large rate acceleration effect of ortho substituents and the small ρ value. The steric acceleration indicates that the decomposition transition state is sterically less crowded than the oxaphosphetane. The small ρ value suggests that the transition state is nonpolar in the decomposition step. The comparison of the small electronic effect observed in the oxaphosphetane-decomposition step with the large substituent effect in the overall reaction of benzophenone with isopropylidene ylide supports the previous conclusion that the substituent effect in the latter reaction principally reflects the oxaphosphetane-formation step.[10]

Oxaphosphetane Reversal. The occurrence of oxaphosphetane reversal and the possibility of stereochemical isomerization through it have been a matter of recent mechanistic interest. A variety of experiments including a ^{31}P-NMR measurement,[8c,23] a crossover experiment,[8b,c,23,24] and an independent generation of oxaphosphetane[8b,c,25] have been carried out, and it was concluded that there is no proof for the Wittig reversal in the reactions of salt-free nonstabilized ylides with unbranched aliphatic aldehydes under typical Wittig conditions and that these reactions are kinetic controlled regardless of the product olefin geometry. In contrast, aromatic aldehydes behave differently.[23,24a–c] The crossover experiments indicated the occurrence of reversal even at low temperature.

In order to obtain information on the extent of the reversal under our reaction conditions, namely at 0 °C for 10 s, we have carried out a crossover experiment for benzaldehyde + nonstabilized ylide by using ^{14}C as a label. As Table III shows, a significant amount of scrambling occurs even at very short period of time during which oxaphosphetane decomposition does not occur. The large % scrambling value of 60 for the Li salt-present reaction suggests that nearly complete scrambling would be expected for reaction conditions under which the products alkenes form from the oxaphosphetane. Although the scrambling of the label does not directly relate to stereoisomerization of oxaphosphetane, the larger extent of scrambling for the Li salt-present reactions compared to that of the Li salt-free counterparts is consistent with the well-known feature of the more facile stereochemical drift for the former reactions.

The occurrence of the oxaphosphetane reversal may have significant inlfuence on the kinetic observations. Especially, the observed values for the Li salt-present reaction of isopropylidene ylide should have a significant contribution from the reversal. Baddenbaum and Shiner indicated in their fractionation factor treatment that the magnitude of equilibrium carbon isotope effects primarily depends on the number and nature of the atom attached directly to the isotopically labeled carbon.[26] For example, the ^{13}C equilibrium isotope effect between $CH_2{=}CH_2/{*}CH_2{=}CH_2$ and $CH_3{-}CH_2{-}CH_3/CH_3{-}{*}CH_2{-}CH_3$ was calculated to be 0.988. Here, the isotope effect is inverse (smaller than unity) because the number of bonds to the labeled carbon atom increases from 3 to 4 on the product side. Transformation from aldehyde to oxaphosphetane is analogous to the equilibrium cited above in the sense that a new C–C bond is formed in place of the change of the original double bond to a single bond. Therefore, the ^{14}C equilibrium isotope effect for the oxaphosphetane-formation step is expected to be inverse. The observed inverse KIE for the Li salt-present reaction of benzaldehyde with isopropylidene ylide is considered to result from the contribution of the equilibrium isotope effect.

The influence of the equilibrium on the Hammett ρ values is not obvious, although the ρ value for the oxaphosphetane-formation equilibrium may be estimated to be positive on the

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basis of other carbonyl addition equilibria[27] and, therefore, the contribution from the equilibrium should make the ρ value larger. The apparent absence of the contribution from the reversal is probably attributable to intrinsically different magnitudes of the ρ values between the Li salt-present and Li salt-free reactions.

Nonstabilized and Semistabilized Ylides. The Hammett ρ values and the carbonyl-^{14}C KIEs are of considerable magnitudes for the semistabilized ylide and quite different from those for the nonstabilized ylide (Table II). As shown by the probe experiments, the two classes of ylides have different electron-transfer abilities in reacting with aromatic carbonyl compounds. Thus, all these data are consistent with two different reaction mechanisms, the ET route for the nonstabilized ylide and the PL route for the semistabilized ylides. Although it has not clearly been shown whether the rate-determining step of the overall Wittig reaction of the semistabilized ylide is the oxaphosphetane-formation step, it would be safe to assume on the basis of the available experimental data, such as stereochemical results in the decomposition of oxaphosphetane generated via non-Wittig routes[8b,25b,28] and crossover experiments,[28b,29] that oxaphosphetane formation is rate-determining. The magnitudes of the Hammett ρ values, which are similar to typical nucleophilic addition reactions to aromatic carbonyl compounds, e.g., cyanohydrin formation (ρ = 2.33) and $NaBH_4$ (ρ = 2.45), also suggest that the Wittig reaction with the semistabilized ylide goes through a polar mechanism of strong nucleophilic addition character.[20,30]

ET Mechanism and Cis Selectivity. The origin of preferential cis selectivity in the reaction of aldehyde with nonstabilized ylide has been a central issue in the Wittig mechanism. Through extensive investigation, Vedejs has concluded that oxaphosphetane decomposition to an alkene is stereospecific and that the observed cis selectivity is directly related to the oxaphosphetane-formation step.[8] Several reaction models that account for the stereoselective oxaphosphetane formation have been presented; they include a puckered four-centered transition-state model,[24a] a planar four-centered model (leeward approach),[31] an anti-approach model,[21c,f] and an SET model.[17] The first three models assume the C–C bond formation in the transition states and thus require a significant carbonyl-^{14}C isotope effect. The SET model is different from these proposals in that it considers an initial formation of a radical ion-pair intermediate as the rate-determining step and that the subsequent reaction of the intermediate determines the stereochemistry of oxaphosphetane. Two modes are conceivable for the formation of oxaphosphetane from the intermediate: direct cyclization of the radical ion pair and two-step cyclization through a transient zwitterionic intermediate.

Suppose that oxaphosphetane is formed via the direct cycloaddition of the radical ion pair. The interacting orbitals at the [2 + 2] transition state are SOMOs and LUMOs of the radical ions, whose energy levels calculated by the ab initio method at the HF/6-31+G* level are shown in Figure 2 together with the geometries of the ylide radical cation and the aldehyde radical anion.[32] It can be seen that the interactions occur between orbitals that were originally HOMO of the ylide and LUMO of the aldehyde. The transition state should thus have a criss-crossed geometry as in the [2s + 2a] reaction of neutral species and therefore would preferably give the cis adduct. In the alternative mechanism, a betaine intermediate is formed on the way to oxaphosphetane. The selectivity is attained by the predominant formation of the antiperiplanar conformer, which upon C–C rotation leads to a cis oxaphosphetane. The betaine intermediate is reactive and can escape from detection by NMR. Vedejs excluded the intermediacy of betaine on the main path of the Wittig reaction on the basis of their independent-betaine-formation experiment.[33] However, betaine generated from the base treatment of β-hydroxyphosphonium salt and that formed by the collapse of a radical ion pair can be different in the solvation shell structure and may behave in different manners.

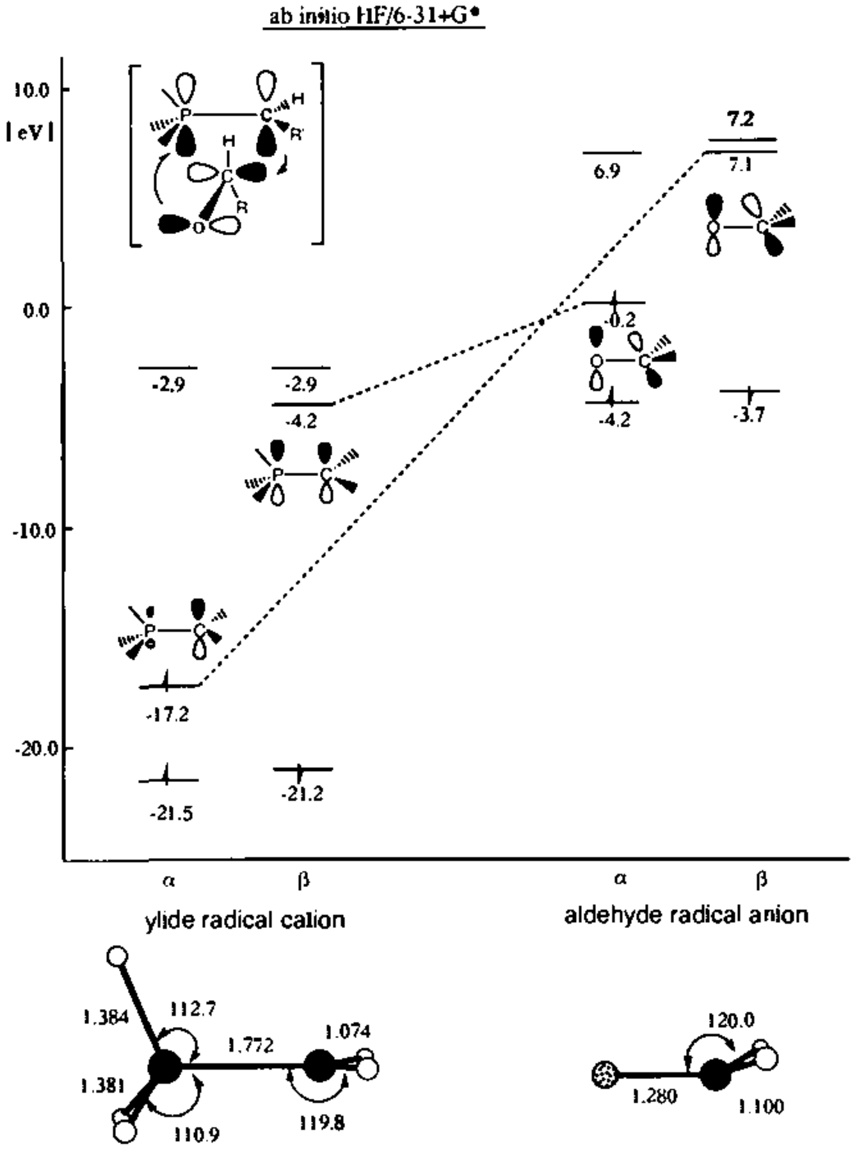

Figure 2. Optimized geometries and frontier molecular orbital levels of the radical ion pair at HF/6-31+G*.

One may argue that reaction of the highly reactive radical ion pair would not show high selectivity as observed.[7c] The idea is based on the reactivity–selectivity principle, which has become controversial in recent years. The argument does not hold especially if one looks at the reaction of a reactive intermediate to another reactive intermediate and if the two possible structures of the second intermediate are different in energy as in the betaine intermediate scheme discussed here. We do not claim that the ET mechanism is the only possible answer for the question on the origin of stereoselectivity of the Wittig reaction, but we would like to point out that the mechanism proposed in this paper is one of the possible answers to the mechanistic questions of the Wittig reaction and is to be taken into consideration for further investigation.

Experimental Section

Materials. THF was dried over sodium/benzophenone and distilled immediately before use. All substituted benzaldehydes were commercially available and purified by either distillation or recrystallization. Substituted benzophenones were obtained as described in the literature.[10] Benzaldehyde-*carbonyl*-^{14}*C* was synthesized by tributyltin hydride reduction[34] of benzoyl-7-^{14}*C* chloride that was obtained by chlorination of benzoic-

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[27] For example, see: Stewart, R.; Van Dyke, J. D. *Can. J. Chem.* **1970**, *48*, 3961. Anderson, B. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1960**, *82*, 1773.

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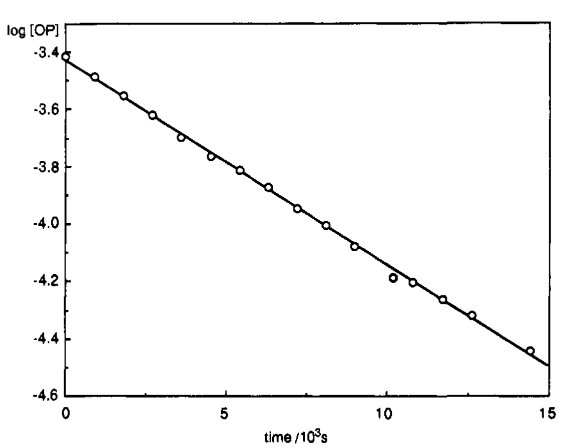

Figure 3. First-order rate plot for the decomposition of oxaphosphetane derived from PhCHO and $Ph_3P{=}CMe_2$.

7-^{14}C acid (NEN) with thionyl chloride. Benzophenone-*carbonyl-^{14}C* was prepared by the Friedel–Crafts benzoylation of benzene with benzoyl-*7-^{14}C* chloride. Isopropyltriphenylphosphonium iodide was obtained by heating a mixture of triphenylphosphine (7.87 g, 30 mmol) and isopropyl iodide (5.61 g, 33 mmol) at 90 °C for 20 h. The resulting crude solid was collected and recrystallized from EtOH/Et_2O. Butyltriphenylphosphonium bromide was prepared in a similar manner. (*Z*)-2,2,6,6-Tetramethylhept-4-en-3-one was synthesized as described in the literature.[35]

Reactions. All reactions were carried out under dry nitrogen using the Schlenk tube technique.[36] Ylide solutions were prepared by adding an equimolar amount of sodium hexamethyldisilazide (NaHMDS, 1.0 M Aldrich), LiHMDS (1.0 M, Aldrich), or PhLi (2.0 M, Aldrich) to a suspension of the appropriate alkyltriphenylphosphonium halide in THF or ether at 0 °C. The Wittig reactions were followed by GC, ^{31}P NMR, or ^{1}H NMR. Typically, ^{1}H-NMR measurement of the reaction between benzaldehyde and isopropylidene ylide was carried out as follows. In an NMR tube (5.0 mm i.d.) was placed an ylide solution (THF, 0.75 mL, 0.1 M), and the solution was cooled under a dry nitrogen atmosphere in a dry ice/acetone bath. To this was added a 0.25-mL THF solution of benzaldehyde (0.3 M) and mesitylene (0.11 M). The NMR tube was sealed and the mixture allowed to react at 0 °C. At appropriate time intervals, the solution was cooled down and the spectrum was measured at –60 °C. The relative intensities of benzaldehyde (CHO, δ 10.09), oxaphosphetane (PhCH, δ 5.09), and alkene (PhCH=, δ 6.35) were measured against mesitylene (aromatic proton, δ 6.84) as reference. Immediately after the mixing of ylide and aldehyde, the aldehyde signal disappeared and the signals of oxaphosphetane emerged. The formation of oxaphosphetane was quantitative (102% based on the starting aldehyde). After 15 min at room temperature, the concentration of oxaphosphetane decreased to 34.8% while the product alkene formed in 64.9%, and thus, the material balance was excellent. Each Wittig reaction gave the expected alkene(s), and no other product was detected except those derived from the ylide. The products were isolated from the reaction mixture and characterized by NMR and GC.

Scrambling Experiment. Method 1. To a THF solution of PhCHO (1.5 mL, 0.60 mmol) was added a nonstabilized ylide solution (4.0 mL, 1.2 mmol) under nitrogen at 0 °C. After 1 min, a THF solution of Ph*CHO (3 mL, 1.2 mmol, molar radioactivity was 0.3240 ± 0.0003 mCi/mol) was added to the solution, which was then allowed to react for 10 s. The reaction mixture was worked up with dilute HCl, and extracted with ether. The organic layer was dried over $MgSO_4$ and treated with excess PhLi, which converts the remaining benzaldehyde to Ph_2CHOH.[9] 1,1-Diphenylethanol was recovered by TLC and purified by repeated recrystallization, and its radioactivity was measured by liquid scintillation.[13b] In a control experiment, benzaldehyde was allowed to react with an excess amount of ylide (2 equiv) and worked up as usual. The treatment of the organic layer with PhLi gave essentially no 1,1-diphenylethanol, confirming that Ph_2CHOH comes from the benzaldehyde present in the reaction mixture. **Method 2.** The method is the same as method 1 except that PhCHO was allowed to react first and then Ph*CHO was added.

Competition Experiment. The relative reactivity of substituted benzophenones against isopropylidene ylide under Li salt-present conditions was measured as described before.[10] The relative reactivity of substituted benzaldehydes in the oxaphosphetane-formation step was determined by the similar method reported previously.[9]

Rate Constant Measurement for Oxaphosphetane Decomposition. In a test tube were placed a trace amount of dibenzyl ether (internal standard for GC), substituted benzaldehyde in THF (0.50 mL, 0.050 mmol), and a THF solution of ylide (1.0 mL, 0.10 mmol) under nitrogen at 0.0 ± 0.1 °C. The resultant oxaphosphetane was then allowed to react at that temperature for a preset time, and the amount of product alkene was quantified after the usual workup by GC. Since the material balance of the reaction was confirmed excellent, the measured GC response factor of substituted benzaldehydes and alkenes allowed us to calculate the amount of oxaphosphetane at each reaction time from the GC results. The first-order rate constants were obtained from a log[OP] vs *t* plot. A typical first-order rate plot is shown in Figure 3.

^{14}C KIE Measurements. Carbonyl-^{14}C KIEs for the reactions of nonstabilized ylides with benzophenone[10] and benzaldehyde[9] were determined as reported previously.

Enone-Isomerization Experiment. To a THF solution of ylide (1.0 mL, 0.1 mmol) was added a solution of (*Z*)-2,2,6,6-tetramethylhept-4-en-3-one (0.5 mL, 0.05 mmol) containing diphenyl ether (internal standard for GC). After appropriate reaction time, the solution was treated with dilute HCl, extracted with hexane, and dried by using a short $MgSO_4$ column, and the extent of cis–trans isomerization was determined by GC (OV1, 2 m)

Ketyl Radical Probe Experiment. A THF solution of halobenzophenone (1.0 mL, 0.15 mmol, containing dibenzyl ether as an internal standard for GC) was added to 2 equiv of a THF solution of an ylide (1.0 mL, 0.3 mmol) and allowed to react at 0.0 ± 0.1 °C for 2 h. After the usual workup, all products were characterized by NMR and their amounts were measured by GC by calibrating the response factors.

Acknowledgment. We thank the Ministry of Education, Science and Culture, Japan, for financial support and the Material Analysis Center of ISIR, Osaka University, for NMR measurements.

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