Relative Reactivity and Stereoselectivity in the Wittig Reactions of Substituted Benzaldehydes with Benzylidenetriphenylphosphorane

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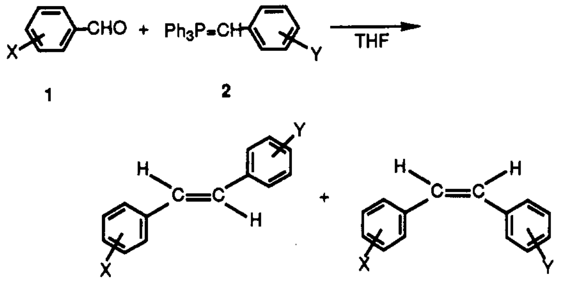
Carbonyl carbon-14 kinetic isotope effects and substituent effects on the relative reactivity and on the cis–trans product ratio were determined in the Wittig reaction of XC_6H_4CHO with $Ph_3P{=}CHC_6H_4Y$ in THF at 0 °C. The isotope effect and the Hammett ρ value were positive under both Li salt-free ($^{12}k/^{14}k = 1.060 \pm 0.003$ and $\rho_X = 2.77 \pm 0.15$) and Li salt-present ($^{12}k/^{14}k = 1.015 \pm 0.004$ and $\rho_X = 1.38 \pm 0.12$) conditions, although they were much larger in the former case. These, together with the absence of enone isomerization for the benzylidene ylide reported previously, suggested that the reactions proceed via a polar cycloaddition transition state of considerable nucleophilic character. The cis–trans ratio of the product stilbene was essentially unchanged (40:60 in the Li salt-free and 60:40 in the Li salt-present reaction) by the change in concentration, the mode of addition, and the molar ratio of aldehyde and ylide, and it was varied only slightly for most substituents X and Y. However, the ratio was significantly varied when *o*-MeO or *o*-Cl was introduced as X. The results could be rationalized by assuming a chelating interaction between the lone pair of the ortho substituents and the phosphorus of the ylide.

Introduction

The Wittig reaction is one of the most important reactions in organic chemistry and has attracted much attention from both mechanistic and synthetic points of view.[1] Stereochemistry of the product alkene is primarily governed by the nature of the ylide used; nonstabilized ylides and stabilized ylides predominantly yield cis and trans alkene, respectively, while semistabilized ylides give a mixture of cis and trans alkene. The origin of this stereochemical diversity has been extensively investigated in connection with the mode of formation of oxaphosphetane as the stereochemistry-determining step.[2] There are many other factors which may affect the product stereochemistry such as the presence or absence of the Li cation, the structure of aldehyde, reaction temperature, concentration, and so on.

We now report the results of our study on the carbonyl carbon kinetic isotope effect (KIE) and substituent effects on the relative reactivity and stereoselectivity of the Wittig reaction of benzaldehydes (1) with benzylidenetriphenylphosphoranes (2) in THF (eq 1). The reaction system was chosen because it gives a nearly 50:50 mixture of the cis–trans isomers and also because of ease of introduction of substituents to both reactants.



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Results and Discussion

Kinetic Isotope Effects. Table I shows the carbonyl carbon-14 KIEs for the present reactions with a semistabilized ylide together with the one observed previously for the reaction with a nonstabilized ylide.[3] It can be seen that the magnitude of the KIEs is very much dependent on the ylide used. Obviously, the reaction mechanism is different for the two types of ylides. The normal (larger than unity) KIEs observed in the present study for the semistabilized ylide indicate that the bonding to the carbonyl carbon is changing in the rate-determining transition state, which is consistent with the nucleophilic character of the transition state inferred from the substituent effect discussed below.

Table I. Carbonyl Carbon-14 Kinetic Isotope Effects in Reactions of Benzaldehyde with $Ph_3P{=}CHPh$ and $Ph_3P{=}CHMe_2$[a]

ylide	base[b]	$^{12}k/^{14}k$
$Ph_3P{=}CHPh$	NaHMDS	1.060 ± 0.003
$Ph_3P{=}CHPh$	LiHMDS	1.015 ± 0.004
$Ph_3P{=}CMe_2$	NaHMDS	1.003 ± 0.002[c]

[a] In THF at 0 °C. [b] Base used to prepare ylides from the corresponding phosphonium bromides. [c] Data taken from ref 3.

Reactivity. Relative reactivities in the reactions of substituted benzaldehydes with 2 (Y = H) were determined in THF at 0.0 ± 0.1 and −72.0 ± 0.5 °C by the competition experiments as described previously.[4] The reactivity data obtained are listed as supplementary material. Figures 1–3 show the log (k_X/k_H) vs σ plots for the Li salt-free and the Li salt-present reactions. Here, the closed circles denote the reactivity of ortho-substituted benzaldehydes and the open circles refer to those of meta- or para-substituted derivatives. In each reaction, a reasonably good straight line was obtained for the meta- and the para-substituted compounds except the methoxy derivatives. The downward deviations for the methoxy derivatives are not unexpected because such deviations have been commonly observed for similar addition reactions to substituted benzaldehydes and benzophenones carried out in ethereal solvents.[4,5] The observed fairly large ρ values (2.77, Li salt free, 0 °C; 2.59, Li salt free, −72 °C; 1.38, Li salt present, 0 °C) are in qualitative agreement with those reported in the literature (ρ = 1.8–2.7) for related reactions of substituted benzaldehydes with semistabilized ylides.[6] These

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[1] Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* 1989, *89*, 863.

[2] Among others, see, for example: (a) Vedejs, E.; Marth, C. F. *J. Am. Chem. Soc.* 1988, *110*, 3948. (b) Vedejs, E.; Fleck, T. J. *Ibid.* 1989, *111*, 5861. (c) Vedejs, E.; Marth, C. F.; Ruggerri, R. *Ibid.* 1988, *110*, 3940.

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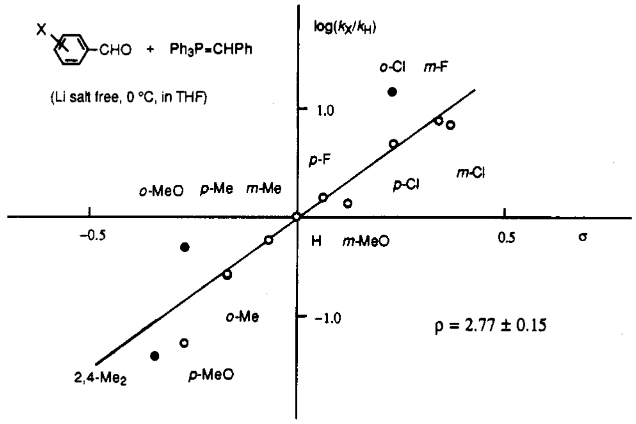

Figure 1. Variations of reactivity with the σ values for the reactions of substituted benzaldehydes with the benzylidene ylide at 0 °C under the Li salt-free conditions.

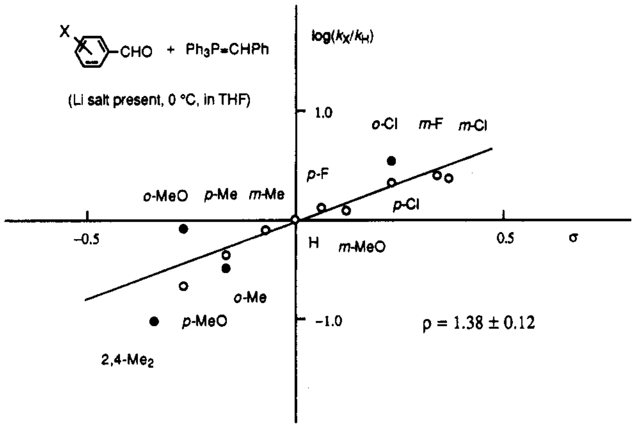

Figure 2. Variations of reactivity with the σ values for the reactions of substituted benzaldehydes with the benzylidene ylide at 0 °C under the Li salt-present conditions.

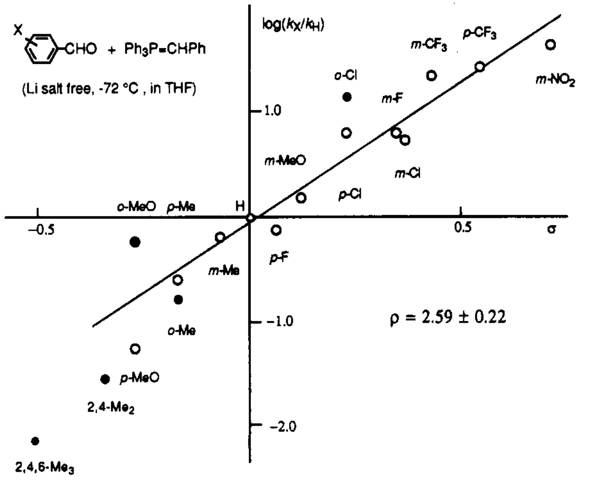

Figure 3. Variations of reactivity with the σ values for the reactions of substituted benzaldehydes with the benzylidene ylide at -72 °C under the Li salt-free conditions.

Table II. Effect of Concentration and the Mode of Addition on the Cis-Trans Product Ratio for the Reaction of Benzaldehyde with Benzylidenetriphenylphosphorane at 0 °C in THF[a]

concn[b]		mode of	% cis	
ylide	aldehyde	addition[c]	Li salt free[d]	Li salt present[e]
0.50	0.50	normal	43.3 ± 0.1	61.5 ± 0.1
		inverse	42.9 ± 0.1	61.9 ± 0.1
0.10	0.10	normal	42.5 ± 0.1	61.2 ± 0.1
		inverse	42.2 ± 0.1	61.2 ± 0.2
0.01	0.01	normal	41.3 ± 0.1	57.8 ± 0.1
		inverse	41.3 ± 0.1	57.6 ± 0.1

[a] The figures are averages of at least two independent runs, and the errors are standard deviations. [b] The figures refer to concentration in mol/L before mixing the two solutions. [c] Normal addition refers to the addition of a ylide solution to an aldehyde solution. [d] NaHMDS was used as a base. [e] LiHMDS was used as a base.

Table III. Effect of Reaction Temperature on the Cis-Trans Product Ratio for the Reaction of Benzaldehyde with Benzylidenetriphenylphosphorane in THF

	% cis	
temp (°C)	Li salt free[a]	Li salt present[b]
25	38.3	58.6 ± 0.1
0	41.7	61.3 ± 0.1
-25	46.2	64.2 ± 0.4
-50	53.4	68.3 ± 0.4

[a] NaHMDS was used as a base. [b] LiHMDS was used as a base.

positive ρ values indicate that the Wittig reaction is nucleophilic in nature.

It was shown that the Wittig reaction of a semistabilized ylide, like a nonstabilized ylide, proceeds through oxaphosphetane as an intermediate, and oxaphosphetane once formed retains its stereochemistry under the salt-free conditions and affords alkene stereospecifically.[2c,7] It then appears reasonable to assume that the rate-determining step of the overall Wittig reaction is involved in the oxaphosphetane formation process. If we accept the idea that oxaphosphetane is formed by a cycloaddition mechanism via a four-centered transition state, we may conclude on the basis of the present finding that the C-C bond formation is much advanced of the P-O bond formation at the transition state. The magnitude of the Hammett ρ value and carbonyl carbon KIE are larger for the Li salt-free reaction than for the Li salt-present counterpart. The reason for this is not clear at present, but these results may be explained by assuming that the Li salt-free reaction has a later transition state compared to the reaction under the Li salt-present conditions, since the ρ value and the carbonyl-carbon KIE are expected to be larger for a later transition state.[8]

Figures 1-3 show that the o-Cl- and the o-MeO-substituted benzaldehydes react much faster than the corresponding para-substituted counterparts. Such an ortho effect was observed only for the heteroatom substituents; the o-Me-substituted benzaldehyde showed no acceleration effect. Similar findings have recently been reported in the allyltributyltin-benzaldehyde condensation; here, o-chlorobenzaldehyde reacted ca. 3 times faster than the p-Cl derivative.[9] The ortho-halogen acceleration was ascribed to a chelating interaction between the halogen atom and the tin reagent in the transition state. It seems reasonable to assume a similar chelating interaction between the ortho heteroatom and the ylide phosphorus in the Wittig reaction. If such an interaction is present in the transition state, it would also affect the cis-trans ratio of the product

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Table IV. Effects of Substituents on the Cis–Trans Product Ratio for Reactions of Substituted Benzaldehydes with Benzylidenetriphenylphosphorane at 0 and −72 °C in THF[a]

	% cis		
subst	Li salt free[b,d]	Li salt present[c,d]	Li salt free[b,e]
2,4-Me_2	34.0 ± 0.1	55.0 ± 0.3	62 ± 8
p-MeO	38.7 ± 0.1	61.3 ± 0.1	60 ± 7
o-MeO	83.7 ± 0.2	68.4 ± 0.1	94 ± 1
m-MeO	46.3 ± 0.7	55.8 ± 0.1	71 ± 1
p-Me	38.6 ± 0.1	62.6 ± 0.2	63 ± 1
o-Me	37.4 ± 0.3	55.4 ± 0.1	57 ± 1
m-Me	38.0 ± 0.2	58.6 ± 0.1	62 ± 1
H	42.9 ± 0.5	61.3 ± 0.1	64 ± 3
p-Cl	43.6 ± 0.1	55.9 ± 0.1	63 ± 1
o-Cl	86.3 ± 0.1	63.6 ± 0.1	92 ± 5
m-Cl	43.9 ± 0.2	56.9 ± 0.3	64 ± 1
m-F	45.3 ± 0.2	58.5 ± 0.1	61 ± 5
m-CF_3	44.6 ± 0.1	56.1 ± 0.2	63 ± 1

[a] The figures are averages of at least two independent runs, and the errors are standard deviations. [b] NaHMDS was used as a base. [c] LiHMDS was used as a base. [d] 0 °C. [e] −72 °C.

Table V. Effect of Substituent on the Cis–Trans Product Ratio for Reactions of Benzaldehyde with Substituted Benzylidenetriphenylphosphorane at 0 °C in THF[a]

	% cis	
substituent	Li salt free[b]	Li salt present[c]
p-MeO	54.0 ± 0.7	60.3 ± 0.1
o-MeO	33.6 ± 0.1	41.4 ± 0.2
p-Me	44.6 ± 0.5	57.0 ± 0.5
o-Me	30.9 ± 1.2	44.0 ± 2.0
H	42.9 ± 0.5	61.3 ± 0.1
p-Cl	57.4 ± 0.1	67.1 ± 0.2
o-Cl	43.8 ± 0.3	64.2 ± 0.6

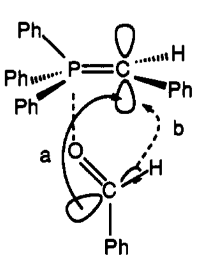
[a] The figures are averages of at least two independent runs, and the errors are standard deviations. [b] NaHMDS was used as a base. [c] LiHMDS was used as a base.

stilbene, and this was indeed observed (vide infra). Interestingly, the related reactions of a nonstabilized ylide with benzaldehyde and with benzophenone did not show any acceleration by the ortho halogen or methoxy substituent, again suggesting the different mechanisms for the different ylides.[3,10]

Product Ratio. The cis–trans ratio of the product stilbene was thoroughly determined under various conditions, and the results were summarized in Tables II–V. There is a large amount of literature which reports the variation in the cis–trans ratio with the change of substituents and the reaction conditions in the benzaldehyde–benzylidene ylide reaction.[11,12] The present results are in agreement with the earlier reports when the comparison can be made.

First of all, the effects of concentration and of the mode of addition were briefly investigated. As Table II shows the product ratio (% cis) was unaffected by these changes. Furthermore, when the reactions were carried out with different ylide–aldehyde molar ratio and for different reaction time, the % cis value did not change at all (data not listed). On the other hand, the % cis value was found to depend on the reaction temperature as shown in Table III. The lower the temperature, the more *cis*-stilbene was formed, consistent with the earlier reports.[11a] The effects of the substituent of benzaldehyde on the cis–trans ratio were summarized in Table IV. For the meta and para series in the Li salt-free reaction at 0 °C, benzaldehyde with a more electron-withdrawing substituent seems to give slightly more *cis*-stilbene; thus a more reactive benzaldehyde gives more cis product. The same trend could be seen in the data reported by Ward and McEwen.[11b]

Chart I



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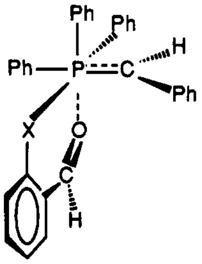

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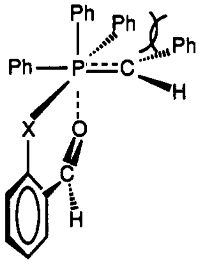

4b

In discussing the origin of the experimentally observed cis selectivity of a nonstabilized ylide, Vedejs argued that the reaction of a nonstabilized ylide has an early transition state while the reaction of a stabilized ylide goes through a late transition state.[2a] We believe that the available experimental data including those reported here argue that the reaction of benzaldehyde with the benzylidene ylide goes through the concerted cycloaddition transition state. If it is possible to generalize the Vedejs proposal into the substituent effects in the present reaction, the Leffler–Hammond principle[13] would predict that benzaldehyde with a more electron-withdrawing substituent should react via an earlier transition state (due to its higher reactivity) and then should yield more cis oxaphosphetane and consequently more *cis*-stilbene. This prediction is consistent with the present and Ward–McEwen's observation, although the variation in the % cis value may not be large enough to allow intensive discussion. Larger % cis values in the Li salt-present reaction, observed in the present study and in the literature,[11b,12a] can be explained by assuming that the transition state for the Li salt-present reaction is more reactant-like as mentioned above.

Compared to the effects of the meta and para substituents, the ortho substituent effect in the Li salt-free reaction is unusual; the *o*-Cl- and the *o*-MeO-substituted benzaldehydes afforded much larger % cis values compared to their meta and para counterparts. Interestingly, no such effect was observed for the methyl substituent. As mentioned above, these ortho effects are accompanied by a large enhancement in the reactivity (Figure 1). Sim-

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[10] Yamataka, H.; Nagareda, K.; Takai, Y.; Sawada, M.; Hanafusa, T. *J. Org. Chem.* **1988**, *53*, 3877.

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ilar ortho-substituent effects on the reactivity and the cis selectivity were also detected in the Li salt-present reaction but to a much less extent.

The observed enhanced cis selectivity may be rationalized as follows. In the initial step of the Wittig reaction, aldehyde and ylide are likely to form a σ complex by a weak interaction between the carbonyl oxygen and the electron-deficient phosphorus atom of the ylide. Such a complex was illustrated in Chart I. In case of the parent system **3**, the aldehyde phenyl group should point down away from the ylide to avoid steric repulsion. The C–P–O–C dihedral angle can be varied relatively freely and then the carbonyl carbon may lie on the same side with or on the opposite side of the benzylidene phenyl group. If it is assumed that the stereochemistry of the oxaphosphetane primarily depends on the way of approach of the two reactants on going to the transition state, the complex would give a nearly 1:1 mixture of *cis*- and *trans*-oxaphosphetane by the approach either a or b in **3**. If the MeO or Cl substituent is introduced to the ortho position of benzaldehyde, the σ complex may adopt a different conformation; the phosphorus atom takes a hypervalent octahedral structure and accepts two electron-donating atoms, the carbonyl oxygen, and the heteroatom of the ortho substituent, as illustrated in **4**. The phenyl group of the benzylidene moiety prefers the same side with the phenyl group of the benzaldehyde to avoid steric repulsion from the equatorial phenyl ligands on P, (**4a** over **4b**); the conformation **4a** is favorable for the *cis*-oxaphosphetane formation. Since such chelating stabilization should be present partly in the oxaphosphetane-formation transition state, benzaldehyde with the *o*-MeO or *o*-Cl substituent is likely to afford more cis product compared to the para-substituted counterpart for which the chelating effect is absent. Kayser postulated a similar chelating interaction between a neighboring methoxy group and the ylide phosphorus at the transition state in order to account for the observed regioselectivity in the reactions of maleic anhydrides with a carbomethoxy-stabilized ylide.[14]

Table V shows the effect of substituents of the benzylidene ylide on the product cis–trans ratio. Here again the ortho substituents influence the product ratio but in a different manner from substitution on benzaldehyde. The % cis value decreased rather than increased for the *o*-MeO-, *o*-Me-, and *o*-Cl-substituted ylides. Since the *o*-MeO and *o*-Me substituents behave similarly, the ortho effects are considered steric in origin. In a closely related system of benzylidene ylides with substituted benzaldehydes in benzene under Li salt-present conditions, Takakis et al. found that the reactions of *O*-(methoxymethyl)salicylaldehyde with benzylidenetriphenylphosphorane gave more cis product (54%) than the reaction of benzaldehyde with [*o*-(methoxymethoxy)benzylidene]triphenylphosphorane (45%).[12e] Although the change in the cis selectivity is small, the trend is the same with the present results.

Semistabilized vs Nonstabilized Ylides. Benzylidenetriphenylphosphorane reacts with benzaldehyde very rapidly at 0 °C while it does not react with benzophenone even for a prolonged reaction time at the same temperature. Such higher reactivity with aldehyde compared to that with ketone reflects steric effects and is known to be a typical characteristic of nucleophilic additions to carbonyl compounds. In contrast to this, isopropylidenetriphenylphosphorane (nonstabilized ylide) reacts with both benzaldehyde and benzophenone, and the reaction with benzophenone is slower than with benzaldehyde. This is consistent with the electron transfer (ET)–oxaphosphetane formation sequence of the reaction, in which the ET step is rate determining with benzaldehyde while the latter step is rate determining with benzophenone.[3,10] The ET rate is likely to be similar for both substrates, but the subsequent C–C bond formation may suffer from steric hindrance and therefore the oxaphosphetane formation becomes the slower rate-determining step for the ketone. The basic mechanistic difference is in line with the ^{14}C KIE as well as the earlier enone-isomerization experiment which showed that a nonstabilized ylide has much higher electron-donating ability than a semistabilized ylide.[3] The mechanism for nonstabilized ylides will be discussed in detail in the forthcoming full article.

Experimental Section

Materials. THF was dried over sodium/benzophenone and distilled immediately before use. All substituted benzaldehydes were commercially available and purified either by distillation or recrystallization. Benzaldehyde-*carbonyl*-^{14}C was synthesized by tributyltin hydride reduction[15] of benzoyl-7-^{14}C chloride which was obtained by chlorination of benzoic-7-^{14}C acid (NEN) with thionyl chloride. *p*-Methoxy-, *p*-chloro-, *p*-methyl-, *o*-methyl-, and *o*-chloro-substituted benzyl chlorides and the parent benzyl bromide were purchased and purified by distillation or recrystallization. *o*-Methoxybenzyl chloride was prepared by $LiAlH_4$ reduction of *o*-anisaldehyde, followed by chlorination with thionyl chloride. Benzyltriphenylphosphonium bromide was obtained by heating the mixture of 7.87 g (30.0 mmol) of triphenyl phosphine and benzyl bromide 5.64 g (33.0 mmol) at 90 °C for 2 h. The resulting crude solid was collected and recrystallized from $EtOH/Et_2O$. Substituted benzyltriphenylphosphonium halides were prepared from the corresponding substituted benzyl halides and triphenyl phosphine in a manner similar to that for the unsubstituted compound except that the reactions were carried out at xylene reflux. Melting points for these phosphonium halides are (uncorrected): substituent, mp; H, 298.7–300.2 °C (lit.[16] mp 279–281 °C); *p*-MeO, 247.0–247.8 °C (lit.[17] mp 241–243 °C); *o*-MeO, 261.5–262.5 °C; *p*-Cl, 299.0–300.0 °C; *o*-Cl, 252.5–253.5 °C; *p*-Me, 269.5–270.0 °C (lit.[18] mp 240–241 °C); *o*-Me, 281.3–282.9 °C.

Reactions. All reactions were carried out under dry nitrogen using the Schlenk tube technique.[19] Ylide solutions were prepared by adding an equimolar amount of sodium hexamethyldisilazide (NaHMDS) or LiHMDS (1.0 M, Aldrich) to a suspension of benzyltriphenylphosphonium halide in THF at 0 °C. Each Wittig reaction gave a mixture of *cis*- and *trans*-stilbenes, and no other products were detected except those derived from the ylide. Products were isolated and characterized by ^{1}H NMR (Bruker-360, $CDCl_3$). The chemical shifts are listed as supplementary material.

Relative Reactivity Measurement. A pair of benzaldehydes (normally the parent and a substituted one, 0.2 mmol each) and diphenyl ether (ca. 0.1 mmol, internal standard) were placed in a flame-dried, serum-capped test tube and dissolved in 4 mL of dry THF. The solution was divided to four parts; thus, each test tube contained two kinds of benzaldehydes, 0.05 mmol each. To three test tubes out of the four was added 0.5 mL of an ylide solution (0.1 M in THF, 0.05 mmol) at 0 or −72 °C by means of hypodermic syringe. The solution was then allowed to react for 10 s under stirring. The reaction mixture was treated with dilute HCl, extracted with hexane, dried over $MgSO_4$, and subjected to GC analysis (2-m glass column packed with 3% PEG-HT). The relative intensity of each reactant to that of the internal standard was compared to the corresponding relative intensity from the

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solution (one test tube out of the four) to which the ylide solution was not added. The fractions of reaction were calculated for both reactants, and the reactivity ratio was computed according to the equation

$$k_A/k_B = \log (1 - f_A)/\log (1 - f_B)$$

Carbon-14 KIE Measurement. A THF solution of benzaldehyde-*carbonyl*-^{14}C (0.60 M, 25 mL) containing diphenyl ether (internal standard) was divided into six parts and transferred with a stainless steel needle into flame-dried test tubes capped with rubber septa. To these solutions were added preset amounts of benzylidenetriphenylphosphorane solution (0.3 M, THF) at 0 °C under stirring; the molar ratio of the ylide to the aldehyde was in the range 0.0–0.8. The solutions were stirred vigorously at 0 °C for 10 s and were then worked up in a usual manner and subjected to GC analysis to determine the fractions of reaction. Since we had encountered trouble in determining molar radioactivity of ^{14}C-labeled benzaldehyde in desired accuracy probably due to the difficulty in purifying, weighing, and transferring the liquid sample to a counting vial, we treated the recovered benzaldehyde with an excess amount of PhLi. The reaction of benzaldehyde with PhLi was known to give benzhydrol quantitatively with the carbonyl-^{14}C KIE of unity,[20] and therefore this procedure would have no influence on the radioactivity of the sample. The resulting benzhydrol was easy to handle and readily purified by recrystallization from hexane. The molar radioactivities were measured by a liquid scintillation counter (Beckman LS-9000) as reported previously,[21] and KIE was calculated by the least-squares method according to the equation[22]

$$\log R_r = \log R_0 - [1 - (^{14}k/^{12}k)] \log (1 - f)$$

Radioactivity data are listed in the supplementary material.

Cis–Trans Ratio. In a standard procedure, 1.0 mL of THF solution (1.0 M) of ylide was added at 0.0 ± 0.1 °C to a 1.0-mL of THF solution (1.0 M) of benzaldehyde, and the solution was allowed to react for 10 s under stirring. The reaction mixture was worked up in a usual manner and subjected to GC analysis to determine the product ratio. Similar experiments were carried out under a variety of conditions. Variables include reaction temperature, concentration, the mode of addition, and reaction time. Specific conditions were shown in Tables II–V.

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Supplementary Material Available: Tables of relative reactivities, molar radioactivities, and a list of ^1H NMR chemical shifts of substituted stilbenes (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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Spectroscopic Evidence for a Spirooxirane Intermediate in the Synthesis of 4-(Hydroxymethyl)-2-[(dimethylamino)methyl]thiazole

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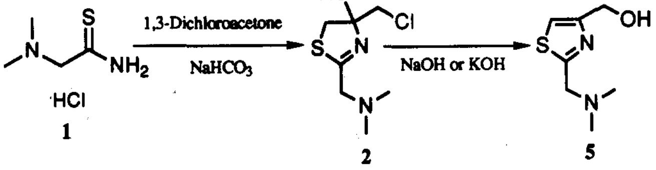
The synthesis of 4-(hydroxymethyl)thiazole derivatives from the corresponding 4-(chloromethyl)-4-hydroxythiazole derivatives have been speculated to proceed through spirooxirane intermediates. NMR spectroscopy was used to provide evidence for the existence of such an intermediate in the synthesis of 4-(hydroxymethyl)-2-[(dimethylamino)methyl]thiazole. Experimental conditions for the optimum formation and stabilization of a suspect intermediate were determined and spectral data obtained to support the speculated structure. Comparisons were made between couplings constants predicted in molecular models and the experimental data.

Scheme I



During our investigations of different synthetic routes toward functionalized thiazole ring systems,[1] methods to generate 4-(hydroxymethyl)-2-[(dimethylamino)methyl]thiazole (**5**) became of interest. This compound is presently produced by the synthetic route shown in Scheme I. (Dimethylamino)thioacetamide hydrochloride (**1**) is treated with 1,3-dichloroacetone in the presence of $NaHCO_3$ to afford the thiazole derivative **2**. Compound **2** is then treated with either aqueous NaOH or KOH to afford **5**. Two possible mechanisms on comparable substrates have been proposed.[2] The mechanisms, using the substrate of primary interest, are shown in Scheme II. One mechanism starts with dehydration of **2** to the corresponding 4-(chloromethyl)thiazole **3** followed by chloride displacement to produce **5**. The other mechanism starts with abstraction of the hydroxyl proton from **2** followed by chloride displacement to afford the spirooxirane **4**. Subsequent proton abstraction from the thiazoline ring of **4** followed by rearrangement would result in the alkoxide of **5**.

Yield claims of 92% by Brown and Newberry[2] for the conversion of a thioamide to the corresponding 4-(hydroxymethyl)thiazole prompted our interest in the evalu-

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