The Reaction of Stable Phosphorus Ylides with Elemental Sulfur. Formation of Olefins; cis-trans Selectivity

Kentaro Okuma,* Tomoko Ishida, Shinya Morita, Hiroshi Ohta, and Tohru Inoue

Department of Chemistry, Faculty of Science, Fukuoka University, Jonan-ku, Fukuoka 814-01, Japan

Received 6 October 1994

ABSTRACT

Metal and temperature effects on thio-Wittig reactions have been studied. Stabilized phosphorus ylides, such as carbomethoxymethylenetriphenylphosphorane, reacted with sulfur to afford dimethyl maleate and dimethyl fumarate in a 1:4 ratio. As in the case of conventional Wittig reactions with semistabilized ylides, it has been shown that the stereochemistry (E:Z ratio) of alkene formation is determined at the point that a new carbon–carbon bond has been formed to give a thiaphosphetane intermediate. The temperature dependence of this reaction is also discussed.

INTRODUCTION

The chemistry of thiocarbonyl compounds is of current interest [1]. It is well known that the *cis-trans* selectivity of the Wittig reaction is dependent on the presence of metal ions [2]. Ward and McEwen reported that the reactions of semistabilized phosphorus ylides (1) with aldehydes afforded *cis* and *trans* olefins in good yields and that the product ratios were changed by adding lithium or sodium salts [3]. However, there is no report on the *cis-trans* selectivity of thio-Wittig reactions. Recently, we have reported that the reaction of

phosphorus ylides, 1, with elemental sulfur or selenium afforded the corresponding symmetrical olefins via thio- or selenoaldehyde intermediates [4]. We report herein a reasonable rationalization about the mechanism of the reaction of stabilized ylides, 1, with elemental sulfur.

RESULTS AND DISCUSSION

We have already reported that the reaction of stable phosphorus ylides with elemental sulfur gives symmetrical olefins. The intermediacy of a thioaldehyde (2) is confirmed by the result of a control reaction involving a cycloaddition with cyclopentadiene [4]. (Recently, Kirby et al. reported on the alkylation of Diels–Alder cycloadducts of thioaldehydes [5].) Olefins were also formed by the reactions of a sulfenyl halide with triethylamine, followed by the addition of phosphorus ylides. Thus, the formation of thioaldehydes from phosphorus ylides and sulfur appears to be a good system for the investigation of metal ion effects on thio-Wittig reactions (Scheme 1).

For this reason, we have carried out a study of salt effects on thio-Wittig reactions of phosphorus ylides, 1, with elemental sulfur.

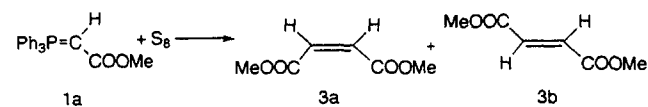### METAL ION EFFECTS IN THE REACTION OF STABILIZED OR SEMISTABILIZED PHOSPHORUS YLIDES WITH SULFUR

We first carried out the reaction of carbomethoxymethylentriphenylphosphorane (1a) with elemental sulfur under a variety of conditions. The solvents used in this reaction were toluene and tet-
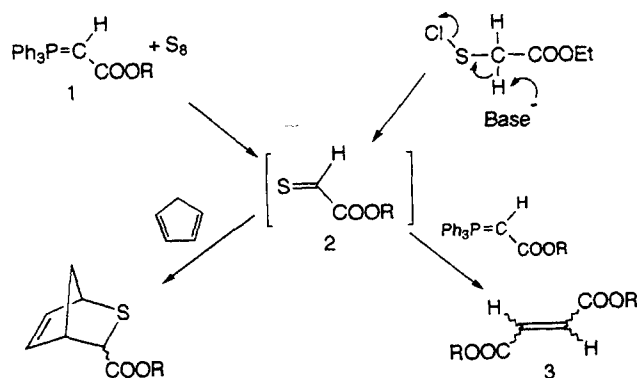
SCHEME 1

SCHEME 2

rahydrofuran (THF). Stable ylide **1a** was allowed to react with elemental sulfur in the presence of several different metal ions to afford dimethyl maleate (**3a**) and dimethyl fumarate (**3b**) in moderate yields (Scheme 2). The results are shown in Table 1.

By use of toluene as a solvent, the *cis/trans* ratio was not changed significantly by the presence of LiI, NaI, or KI. It was noted, however, that a higher *cis* selectivity was observed by using THF as a solvent. This result might be due to the low affinity between sulfur and alkali metal ions and to the low solubility of metal halides (in the case of KBr or KI) even in refluxing toluene. Then, we carried out the reaction of benzyltriphenylphosphonium bromide with several different bases, followed by the addition of elemental sulfur.

Benzyltriphenylphosphonium bromide was converted to the semistabilized ylide, benzylidenetriphenylphosphorane **1b**, by the reaction with

TABLE 1 Metal Ion Effects in the Reaction of **1a** with Elemental Sulfur

Salts	Solvent	Temperature (°C)	Yields of 3 (%)[a]	cis/trans
None	toluene	reflux	54	19/81
LiI	toluene	reflux	57	17/83
NaI	toluene	reflux	52	19/81
KI	toluene	reflux	55	20/80
None	THF	reflux	48	49/51
KI	THF	reflux	44	35/65
KBr	THF	reflux	52	49/51
NaCl	THF	reflux	54	48/52

[a]Small amounts of unidentified products were obtained in every case.

TABLE 2 The Reaction of Benzyltriphenylphosphonium Bromide with Several Kinds of Bases followed by the Addition of Elemental Sulfur

Base Used	Solvent	Temperature (°C)	Time (h)	Yield of 3 (%)	cis/trans
BuLi	toluene	reflux	2	65	17/83
NaH	toluene	reflux	2	45	12/88
NaH	DMSO	100	2	66	13/87
t-BuOK	toluene	reflux	2	55	19/81
t-BuOK	DMSO	100	2	65	18/82

an appropriate base, under anhydrous conditions, and under an inert atmosphere. The solvents used throughout this study were anhydrous toluene or dimethyl sulfoxide (DMSO). The bases used for generation of the ylide were butyllithium, sodium hydride, or potassium *tert*-butoxide. The orange yellow ylide solution was allowed to react with elemental sulfur, and the results are displayed in Table 2. Generally, *trans* stilbene (Scheme 3) (**3c**) is the preferred alkene product of this reaction.

The use of sodium hydride as a base produced the lowest ratio of *cis/trans* stilbene. These results were quite different from those of the Wittig reaction with ordinary aldehydes. Maryanoff et al. reported that the cation present in the Wittig reaction mixture affects the *E* selectivity [6]. Ward and McEwen [3] reported that *E* selectivity was observed in the presence of lithium ions, while, when sodium or potassium ions are present, the Z-isomer predominated. Differences in the selectivity might be attributable to the metal ion affinity for oxygen as against sulfur.

TEMPERATURE DEPENDENCE IN THE REACTION OF A STABLE PHOSPHORUS YLIDE WITH ELEMENTAL SULFUR

When THF was used as a solvent, the relative amount of *trans* isomer formed in the reaction of **1a** with S_8 was decreased, as shown in Table 1. We first thought that the polarity of the solvent might be of importance in this regard. However, when the reaction was carried out at 60°C in toluene, a tendency similar to that found by the use of THF as the solvent was observed. Thus, the reaction temperature is also an important consideration in this reaction. Therefore, we decided to investigate the temperature dependence of the *cis/trans* ratio of
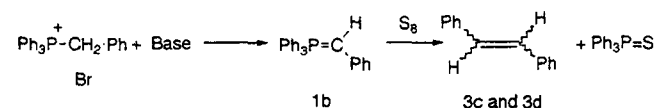
SCHEME 3

TABLE 3 The Reaction of Carbomethoxymethylenetriphenylphosphorane, **1a** with Elemental Sulfur in Toluene at Various Temperature

Temperature (°C)	Time (h)	Olefin, 3a and 3b (Yield %)	cis/trans
20	28	36	61/39
40	24	40	54/46
60	6	50	35/65
80	2	51	35/65
100	2	52	38/62
110	2	54	18/82

alkenes produced in the reaction of stable ylides with elemental sulfur. When carbomethoxymethylentriphenylphosphorane was used as the starting ylide and the reaction was carried out in refluxing toluene, dimethyl maleate and dimethyl fumarate were obtained in a 1:5 ratio; thus, the *trans* form was predominant in this case. When this reaction was carried out at room temperature, however, the ratio was changed to 61/39. The results of several experiments carried out at various temperatures are shown in Table 3.

MECHANISTIC CONSIDERATIONS OF THE STEREOCHEMISTRY OF THE THIO–WITTIG REACTION

On the basis of the experimental findings obtained in the present study, we will discuss the mechanism of thio-Wittig reaction, stressing the stereochemistry of the olefin products. The present study revealed two important facts concerning this problem: one is that no important effect of metal ions is observed in the thio-Wittig reaction, and the other is a remarkable temperature dependence of the stereochemistry of olefin formation.

In previous papers [4], we have demonstrated that the formation of olefin by the reaction of carbomethoxymethylenetriphenylphosphorane with elemental sulfur proceeds via a thioaldehyde as an intermediate (see Scheme 1). As shown in Scheme 4, the stereochemistry of olefin formation by this type of thio-Wittig reaction should be determined by the structure of the thiaphosphetane, which is formed by the attack of the ylide on the thioaldehyde. For usual Wittig reactions of semistabilized phosphorus ylides, it has been reported by Ward and McEwen that two distinct mechanisms are operative in the reaction step in which the oxaphosphetane intermediate is formed from the ylide and aldehyde [3]: one is an ionic mechanism, and the other is a spin-paired biradical mechanism. When the reaction proceeds through the ionic mechanism, the stereochemistry of the products is expected to exhibit a strong salt dependence. Since

there is no salt effect in the present reaction (see Table 1), the ionic mechanism may be excluded for the thio-Wittig reaction.
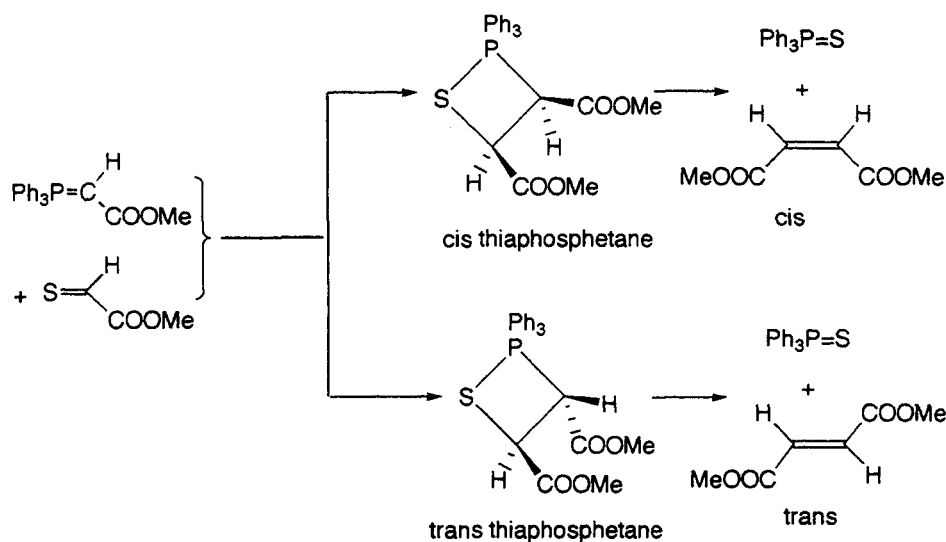
Ward and McEwen suggested the formation of spin-paired biradical intermediates in the reaction of semistabilized phosphorus ylides with aldehydes under the appropriate conditions [3]. In the case of the thio-Wittig reaction, corresponding transition spin-paired biradical intermediates are expected to be more stable and thus more readily formed than those in the usual Wittig reaction. Additionally, the present experiments were carried out at temperatures higher than those for usual Wittig reactions, which may also facilitate spin-paired biradical formation. Thus, it is plausible that the reaction of an ylide with a thioaldehyde in the thio-Wittig reaction proceeds via spin-paired biradical intermediates (Scheme 4).

Vedejs et al. have proposed a model for the geometry of the transition state, i.e., the unstable intermediate, in the reaction between an ylide and an aldehyde [7]. This model may also be applicable to explain the thio-Wittig reaction. In analogy with the Vedejs model, the most favorable steric arrangements for the spin-paired biradical intermediates are considered to be those illustrated in Scheme 5. Unstable intermediate A, in which the thioaldehyde is approaching the ylide orthogonally and the COOR group is placed away from the ylide's COOR group, is the least sterically hindered arrangement. According to the Vedejs geometry, this unstable biradical leads to the *cis* thiaphosphetane, which in turn results in the formation of the *cis* olefin. Another unstable intermediate, B, would be formed by thioaldehyde approaching the ylide in a parallel arrangement, in which the two COOR groups are in a skewed arrangement so as to minimize the repulsive interaction caused by steric hindrance. In this case, the *trans* thiaphosphetane is derived, which then undergoes pseudorotation and ring opening, leading to the formation of the *trans* product (Scheme 5).
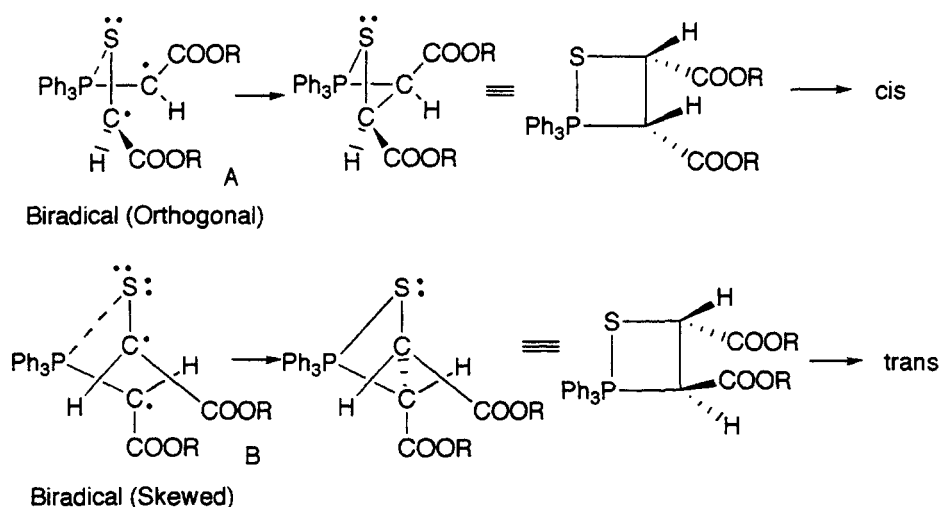
The postulation of the previous two biradical species as unstable intermediates for the thio-Wittig reaction is consistent with the results concerning the temperature dependence of the stereochemistry of olefin products, as described below.

As seen in Table 3, the *cis-to-trans* ratio of the olefin produced by this reaction varies with temperature. At low temperature, the *cis* form is preferred, while the *trans* isomer becomes predominant at high temperature. It may be reasonable to assume that the *cis-to-trans* ratio in the reaction products is determined by the rate of formation of each species, because no conversion between the two isomers occurs at the temperature range maintained in the present experiments. As mentioned earlier, the rate of olefin formation is determined by the reaction rate of the thioaldehyde

SCHEME 4

cis thiaphosphetane

trans thiaphosphetane

SCHEME 5

Biradical (Orthogonal)

Biradical (Skewed)

with the ylide. Then, the formation rates of the olefin isomers are expressed by

$$v_{cis} = k_{cis} \text{ [ylide] [thioaldehyde]}$$

$$v_{trans} = k_{trans} \text{ [ylide] [thioaldehyde]}$$

where k represents the rate constant. Thus, the cis-to-trans ratio, r, of the olefin will be given by

$$r = \frac{cis}{trans} = \frac{v_{cis}}{v_{trans}} = \frac{k_{cis}}{k_{trans}} \qquad (1)$$

According to the transition state theory of reaction rate, the rate constant is related to the activation parameters by the following expression:

$$k = \frac{k_B T}{h} e^{-\Delta G^{\ddagger}/RT} = \frac{K_B T}{h} e^{-\Delta S^{\ddagger}/RT} \qquad (2)$$

where $\Delta G^{\ddagger}$, $\Delta S^{\ddagger}$, and $\Delta H^{\ddagger}$ are the molar free energy,

entropy, and enthalpy of activation, respectively, and k_B represents the Boltzmann constant, h is the Planck constant, R is the gas constant, and T is the absolute temperature. By combining Equations 1 and 2, one can obtain

$$r = \frac{cis}{trans} = e^{-\Delta\Delta G^{\ddagger}/RT} \qquad (3)$$

In the above expression, $\Delta\Delta G^{\ddagger}$ corresponds to the difference in the activation free energies between cis and trans isomer formation, being defined by

$$\Delta\Delta G^{\ddagger} = \Delta G^{\ddagger}_{cis} - \Delta G^{\ddagger}_{trans}$$

Equation 3 means that the cis-to-trans ratio of the olefin is determined by the free energy difference between the activated complexes, or unstable intermediates, leading to the corresponding isomers. By expressing the free energy in terms of the en-
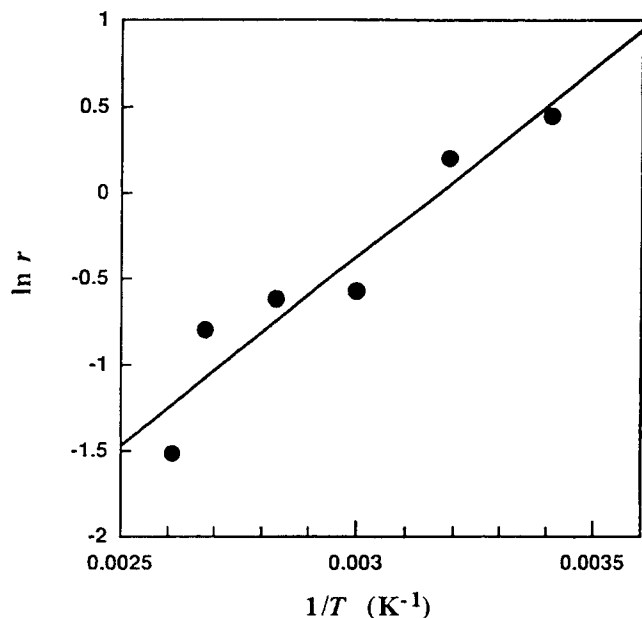
FIGURE 1   Plot of ln *r* vs. 1/*T*.

thalpy and entropy, the following relation is derived from Equation 3:

$$\ln r = \frac{\Delta\Delta S^{\ddagger}}{R} - \frac{\Delta\Delta H^{\ddagger}}{RT} \qquad (4)$$

Equation 4 predicts a linear relationship between ln *r* and 1/*T*. In addition, from the slope and intercept of the straight line of ln *r* vs. 1/*T* plot, one can estimate the differences in the activation enthalpy and entropy between *cis* and *trans* isomer formation.

Figure 1 shows the plot of ln *r* against 1/*T* for the data listed in Table 3. As seen in this figure, the plot is almost linear, although some scatter is observed in the data points. The slope and intercept of the straight line provided $\Delta\Delta H^{\ddagger} = -4.4 \pm 0.7$ kcal mol^{-1} and $\Delta\Delta S^{\ddagger} = -14 \pm 2$ cal K^{-1} mol^{-1}. These values of differences in activation parameters indicate that both the activation enthalpy and entropy are larger for the *trans* olefin than for the *cis* olefin formation. This result is consistent with the assignment of transition states for *cis* and *trans* olefins as unstable biradical intermediates, A and B, respectively. In biradical B, the two COOR groups are located on two parallel planes with skewed configuration, and accordingly, much more space is needed between ylide and thioaldehyde compared with biradical A, in which the two COOR groups are located far the away from each other. Thus, the P–S "bond" length in biradical B should be larger than that in biradical A, which means that the P–S "bond" for biradical B is much looser than that for A. This would bring about higher val-

ues of enthalpy and entropy for biradical B compared with biradical A, and results in higher activation enthalpy and entropy for the formation of the *trans* olefin as compared with the *cis* olefin.

In summary, the salt effect and the temperature effect on the thio-Wittig reaction have been studied. No significant salt effect was observed on the stereochemistry of olefin formation, but the *cis*-to-*trans* ratio of olefin was strongly affected by variation of reaction temperature; the formation of the *trans* olefin is preferred at the higher temperature. Both the salt effect and temperature effect on the stereochemistry of the thio-Wittig reaction coincide well with the spin-paired biradical mechanism.

EXPERIMENTAL

General. Melting points are uncorrected. ^{1}H NMR spectra were measured on a JEOL GSX-400 spectrometer. Chemical shifts are given in δ units downfield from tetramethylsilane. Thin-layer chromatography analyses were performed using Merck Silica gel 60 F254 aluminum plates.

Material. Carbomethoxymethylenetriphenylphosphorane and benzyltriphenylphosphonium bromide were purchased from Waco, Osaka, Japan. The cycloadduct shown in Scheme 1 was prepared by the method described in the literature. Authentic dimethyl fumarate, dimethyl maleate, *trans* stilbene, and *cis* stilbene were purchased from Aldrich, Milwaukee, WI.

Reaction of Carbomethoxymethylentriphenylphosphorane with Elemental Sulfur in the Presence of Lithium Iodide

To a solution of carbomethoxymethylenetriphenylphosphorane (0.67 g, 2 mmol) in toluene (25 mL) was added elemental sulfur (0.065 g, 2 mmol) and lithium iodide (0.13 g, 1 mmol) portionwise. After having been refluxed for 2 hours, the reaction mixture was evaporated to give pale brown crystals. The resulting mixture was extracted with pentane (10 mL × 3) to give a crude mixture of dimethyl fumarate and dimethyl maleate (0.21 g, 1.46 mmol) in 73% combined yield. ^{1}H NMR analysis indicated that the *cis/trans* ratio was 17/83. Further purification was performed by silica gel chromatography, elution being effected with hexane: dichloromethane (1:1). A mixture of dimethyl maleate and dimethyl fumarate was obtained in 57% combined yield (0.16 g, 1.14 mmol). Other reactions were carried out in a similar manner.

Reaction of Benzyltriphenylphosphonium Bromide with Butyllithium followed by the Addition of Elemental Sulfur

To a solution of benzyltriphenylphosphonium bromide (0.87 g, 2 mmol) in toluene (25 mL) was added

a solution of butyllithium (1.6 M in hexane, 1.6 mL, 2.2 mmol) at 0°C. After the mixture had been stirred for 15 minutes, elemental sulfur was added to this solution, and the new mixture was refluxed for 2 hours. The reaction mixture was washed with water (30 mL), dried over magnesium sulfate, filtered, and evaporated to give pale yellow crystals. The ^{1}H NMR spectrum of the mixture indicated that cis and trans stilbene had been obtained in a 17:83 ratio. The resulting mixture was chromatographed on silica gel with elution by hexane to give a mixture of cis and trans stilbene (0.23 g, 1.3 mmol) in 65% yield. Triphenylphosphine sulfide was obtained by elution with dichloromethane-hexane (0.46 g, 1.56 mmol, 78%). Other reactions were carried out in a similar manner.

Temperature Dependence of the Thio-Wittig Reaction

To a solution of carbomethoxymethylenetriphenylphosphorane (0.33 g, 1 mmol) in toluene (20 mL) was added elemental sulfur (0.032 g, 1 mmol) in one portion. After having been stirred for 28 hours at room temperature, the reaction mixture was evaporated to give pale yellow oily crystals, which were subjected to ^{1}H NMR analysis. The resulting crystals were extracted with hexane (10 mL × 3). Unreacted carbomethoxytriphenylphosphorane was recovered in 38% yield (0.12 g, 0.38 mmol). The combined hexane extract was evaporated and chromatographed on silica gel with elution by hexane-dichlorometane (1:1) to afford a mixture of dimethyl maleate and dimethyl fumarate (0.051 g, 0.036 mmol). The dichloromethane eluant gave triphenylphosphine sulfide (0.13 g, 0.44 mmol) in 44% yield. Other reactions were carried out in a similar manner.

REFERENCES

[1] D. C. Smith, S. W. Lee, P. L. Fuchs, *J. Organomet. Chem.*, *59*, 1994, 348; R. Hock, S. Hillenbrand, G. Erker, C. Kruger, S. Werner, *Chem. Ber.*, *126*, 1993, 1895; G. Pfisterguillouzo, F. Gracian, A. Senio, F. Bourdon, Y. Vallee, J. L. Ripoll, *J. Am. Chem. Soc.*, *115*, 1993, 324; N. Tokitoh, T. Matsumoto, K. Manmaru, R. Okazaki, *J. Am. Chem. Soc.*, *115*, 1993, 8855; S. S. M. Choi, G. W. Kirby, M. P. Mahajan, *J. Chem. Soc.*, *Perkin Trans.*, *1*, 1992, 191; I. L. Pinto, D. R. Buckle, H. K. Rami, D. G. Smith, *Tetrahedron Lett.*, *33*, 1992, 7597; S. S. M. Choi, G. W. Kirby, *J. Chem. Soc.*, *Perkin Trans.*, *1*, 1991, 3225; Y. Vallee, J. L. Ripoll, *Phosphorus, Sulfur and Silicon*, *59*, 1991, 415.

[2] M. Schlosser, F. K. Christmann, A. Piskala, D. Coffinet, *Synthesis*, 1971, 29; also see J. I. G. Cadogan: in I. Gosney, A. G. Rowley (eds): *Organophosphorus Reagents in Organic Synthesis*, Academic Press, London pp. 26–89 (1979).

[3] W. J. Ward, Jr., W. E. McEwen, *J. Org. Chem.*, *55*, 1990, 493.

[4] K. Okuma, J. Sakata, Y. Tachibana, T. Honda, H. Ohta, *Tetrahedron Lett.*, *28*, 1987, 6649; K. Okuma, Y. Tachibana, J. Sakata, T. Komiya, I. Kaneko, Y. Komiya, S. Yamamoto, H. Ohta, *Bull. Chem. Soc. Jpn.*, *61*, 1988, 4323.

[5] G. W. Kirby, M. P. Mahajan, M. S. Rahman, *J. Chem. Soc.*, *Perkin*, *1*, 1991, 2033.

[6] B. E. Maryanoff, A. B. Reitz, B. A. Duhl-Emswiler, *J. Am. Chem. Soc.*, *107*, 1985, 217.

[7] E. Vedejs, C. F. Marth, R. J. Ruggeri, *J. Am. Chem. Soc.*, *110*, 1988, 3940; E. Vedejs, C. F. Marth, *J. Am. Chem. Soc.*, *110*, 1988, 3948.