

Reactivity and Selectivity in the Wittig Reaction: A Computational Study

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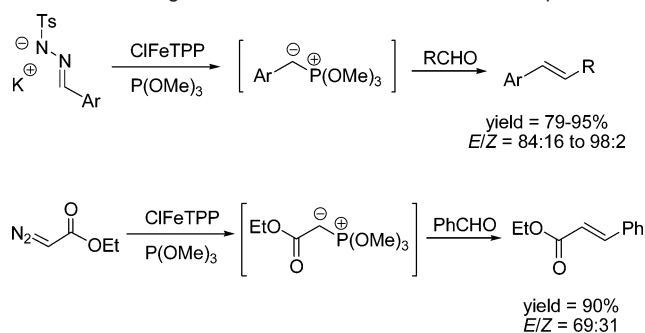
Abstract: The salt-free Wittig reaction of non-, semi-, and stabilized ylides has been investigated on realistic systems using density functional theory (DFT) calculations, including continuum solvation. Our results provide unequivocal support for the generally accepted mechanism and are in very good agreement with experimental selectivities. This study shows that *E/Z* selectivity of non- and semi-stabilized ylides cannot be fully understood without considering the energy of the elimination TS. The influence of ylide stabilization and the nature of phosphorus substituents on reversibility of oxaphosphetane formation is clarified. Unexpectedly, the puckering ability of addition TSs is shown not to depend on ylide stabilization, but the geometry of the TS is decided by an interplay of 1,2; 1,3; and C–H···O interactions in the case of non- and semi-stabilized ylides, whereas a dipole–dipole interaction governs the addition TS structures for stabilized ylides. The well-known influence of ylide stabilization on selectivity of PPh₃ derivatives is explained as follows: in non- and semi-stabilized ylides reactions, *cis* and *trans* addition TSs have, respectively, puckered and planar geometries, and selectivity is governed by an interplay of 1,2 and 1,3 interactions. For stabilized ylides, the high *E* selectivity is due to a strong dipole–dipole interaction at the addition TS. The influence of the nature of phosphorus substituents on selectivity is also detailed, the different behavior of (MeO)₃PCHCO₂Me ylides being explained by their lower dipole. This novel picture of the factors determining TS structures and selectivity provides a sound basis for the design of new ylides.

Introduction

The Wittig reaction generates a double bond, usually with a high level of geometrical control.^{1,2} Using triphenylphosphonium ylides (Ph₃PCHR), the Wittig reaction yields preferentially *Z* alkenes for non-stabilized ylides (R = alkyl), mixtures of *Z* and *E* alkenes for semi-stabilized ylides (R = aryl), and *E* alkenes for stabilized ylides (R = CO₂R' or CN). This *E/Z* selectivity has also been found to depend on the substituents bonded to the phosphorus atom; replacing the phenyl groups with alkyl groups usually increases the *E* selectivity. The experimental conditions, such as the presence of salts (especially lithium salts), or the nature of the solvent are also known to noticeably influence the selectivity of the reaction.

Recently, we have applied the carbene transfer strategy to the synthesis of a new class of ylides bearing alkoxy substituents

Scheme 1. Wittig Reaction of Ylides Derived from Phosphites



on the phosphorus atom ((R'O)₃PCHR) (Scheme 1).³ These ylides have not been readily available previously, as alkylation of phosphites leads to phosphonate esters through the Arbuzov reaction. These ylides were observed to lead to significantly different *E/Z* selectivities as compared to more common triphenylphosphonium derivatives: the *E* selectivity is enhanced in the semi-stabilized case (R = Ph) but is decreased with ester-stabilized ylides (R = CO₂R'). This observation led us to try to gain a better understanding of the factors that control selectivity in the Wittig reaction and, in particular, of the reasons for these differences in selectivity with ylides derived from phosphites.

- (1) For reviews, see: (a) Abell, A. D.; Edmonds, M. K. In *Organophosphorus Reagents*; Murphy, P. J., Ed.; Oxford University Press: Oxford, U.K., 2004; pp 99–127. (b) Edmonds, M.; Abell, A. In *Modern Carbonyl Olefination*; Takeda, T., Ed.; Wiley-VCH: Weinheim, Germany, 2004; Chapter 1. (c) Kolodiazny, O. I. *Phosphorus Ylides: Chemistry and Applications in Organic Chemistry*; Wiley-VCH: New York, 1999. (d) Nicolaou, K. C.; Harter, M. W.; Gunzner, J. L.; Nadin, A. *Liebigs Ann.* **1997**, 7, 1283–1301. (e) Lawrence, N. J. *Preparation of Alkenes: A Practical Approach*; Williams, J. M. J., Ed.; Oxford University Press: Oxford, U.K., 1995. (f) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, 89, 863–927. (g) Bestmann, H. J.; Vostrowsky, O. *Top. Curr. Chem.* **1983**, 109, 85–163.
- (2) For leading mechanistic and selectivity reviews, see: (a) Vedejs, E.; Peterson, M. J. *Top. Stereochem.* **1994**, 21, 1–157. (b) Vedejs, E.; Peterson, M. J. In *Advances in Carbanion Chemistry*; Snieckus, V., Ed.; Jai Press: Greenwich, CN, 1996; Vol. 2.

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Extensive efforts have been devoted to elucidate the reaction mechanism of the Wittig reaction.² It is generally accepted that the main steps involved in the mechanism are formal [2+2] cycloaddition to form an oxaphosphetane, pseudorotation at phosphorus, and decomposition of the cyclic intermediate to yield the olefin and phosphine oxide. This sequence of steps has been firmly supported by the detection of oxaphosphetanes by low-temperature ³¹P NMR during reactions of non- and semi-stabilized ylides.^{4,5} With stabilized ylides R₃PCHCO₂R', the oxaphosphetanes are less stable and decompose rapidly into alkene and phosphine oxide and, therefore, have not yet been observed. The nature of the pathway leading to the initial formation of the oxaphosphetane has, however, been the topic of debate. Perhaps due to early mechanistic suggestions by Wittig, a stepwise process involving initial C–C bond formation leading to a betaine intermediate has received widespread attention,^{2b} but most experiments suggest instead that the formal cycloaddition occurs directly through a four-center transition state.⁶ The evidence for the stepwise route is indirect, as despite many attempts, the postulated betaine intermediates have never been observed spectroscopically under salt-free Wittig reaction conditions. In fact, involvement of betaines under salt-free conditions has proven to be inconsistent with numerous experimental results.² In some cases, experimental work has even been able to prove conclusively that betaines are not involved under such conditions.⁷ The situation is slightly different in the presence of strongly coordinating ions such as lithium, when betaine intermediates may sometimes be formed, and selectivities are different. In the remainder of this work, we will focus on salt-free reactions.

³¹P NMR monitoring of the Wittig reaction has shown that oxaphosphetane formation is usually nonreversible.^{2,4c,d} This has been confirmed by experiments involving the independent generation of these intermediates in the presence of reactive aldehydes. No crossover products, which would have been formed in the case of competing equilibration to regenerate the starting ylides, were detected.^{2,4d,5,8} There are, however, some exceptions to this rule, with significant reversal of the initial cycloaddition found to occur along the pathway to formation of *Z* alkenes from non-stabilized (alkyl)₃P=CH(alkyl) and in some cases from Ph₃P=CH(alkyl) ylides.^{2,4d,8b} In general, however, oxaphosphetane formation step is nonreversible and should thereby determine reactivity as well as the *E/Z* selectivity of the products.

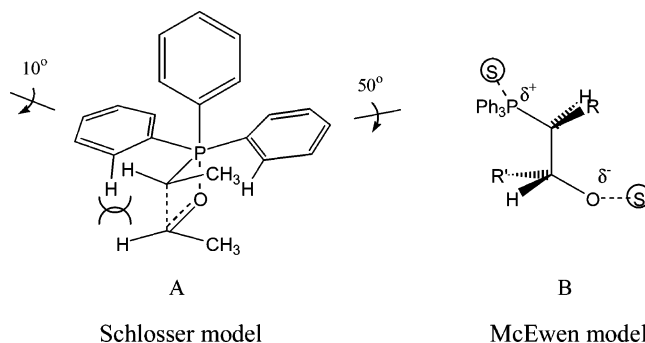


Figure 1. TS structure models.

As mentioned above, the selectivity can be very different when starting with different types of ylides (Y₃PCHR) and can also depend on the nature of the co-reactant carbonyl compound (R'R''C=O).⁹ Considerable effort has been put into developing rational models to explain the observed product ratios. Schlosser proposed one of the first models of the key initial cycloaddition transition state, and suggested that interaction of the ylide substituent with a phenyl substituent on phosphorus leads to a preference for a planar four-center transition structure shown as structure A in Figure 1.¹⁰ In this model, the steric repulsion between an *o*-hydrogen atom of a phenyl group and the substituent of the aldehyde is an important factor that makes the *cis* transition state more stable than the *trans* and, hence, explains the *Z* selectivity for reactions of non-stabilized ylides. However, this model does not account for the high *E* selectivity observed with stabilized ylides.

More recently, McEwen et al. studied the first step of the reaction using MNDO–PM3 methods.^{11g,h} The transition states obtained at this level of theory involve a syn approach of the reactants and show significant C–C bonding, with only a small amount of P–O bonding. The low amount of P–O bonding corresponds to a very betaine-like electronic structure at the TS. The authors therefore suggest that the preference for syn approach is an artifact of the gas-phase environment used in the calculations, whereas in the presence of solvent, the anti geometry would be better solvated and hence favored. The authors also suggest that the anti addition TS could lead directly to the oxaphosphetane by rotation around the C–C bond without formation of a discrete betaine intermediate. In the anti transition state (structure B; Figure 1), they suggested that the erythro form would be favored due to 1,2 interactions, thereby leading

- (4) (a) Vedejs, E.; Snoble, K. A. *J. Am. Chem. Soc.* **1973**, *95*, 8778–8780. (b) Vedejs, E.; Meier, G. P.; Snoble, K. A. *J. Am. Chem. Soc.* **1981**, *103*, 2823–2831. (c) Reitz, A. B.; Mutter, M. S.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1984**, *106*, 1873–1875. (d) Maryanoff, B. E.; Reitz, A. B.; Mutter, M. S.; Inners, R. R.; Almond, H. R.; Whittle, R. R.; Olofson, R. A. *J. Am. Chem. Soc.* **1986**, *108*, 7664–7678. (e) Vedejs, E.; Marth, C. F. *J. Am. Chem. Soc.* **1989**, *111*, 1519–1520. (f) Bangerter, F.; Karpf, M.; Meier, L. A.; Rys, P.; Skabal, P. *J. Am. Chem. Soc.* **1998**, *120*, 10653–10659. (g) Appel, M.; Blaurock, S.; Berger, S. *Eur. J. Org. Chem.* **2002**, *7*, 1143–1148.
- (5) Vedejs, E.; Fleck, T. *J. Am. Chem. Soc.* **1989**, *111*, 5861–5871.
- (6) It has been suggested as well that the Wittig reaction of non-stabilized ylides proceeds via initial electron transfer from the ylide to the carbonyl group (see Olah, G. A.; Krishnamurthy, V. V. *J. Am. Chem. Soc.* **1982**, *104*, 3987–3990 and Yamataka, H.; Nagareda, K.; Takatsuka, T.; Ando, K.; Hanafusa, T.; Nagase, S. *J. Am. Chem. Soc.* **1993**, *115*, 8570–8576). However, because of the lack of evidence collected to support it and its inconsistency with some experimental observations (see ref 1f, 2b), this suggestion has been refuted.
- (7) Vedejs, E.; Marth, C. F. *J. Am. Chem. Soc.* **1990**, *112*, 3905–3909.
- (8) (a) Vedejs, E.; Fleck, T.; Hara, S. *J. Org. Chem.* **1987**, *52*, 4637–4639. (b) Vedejs, E.; Marth, C. F.; Ruggeri, R. *J. Am. Chem. Soc.* **1988**, *110*, 3940–3948.

- (9) The reaction almost always involves singly substituted ylides (i.e., only one R group on the phosphorus-bearing carbon, which we will refer to as the “ylidic substituent”). Common R groups include alkyl (non-stabilized ylides), aryl (semi-stabilized ylides), and ester or cyano (stabilized ylides). We refer to Y as the “phosphorus substituent” and consider cases where Y = alkyl, phenyl, and alkoxy. Finally, most Wittig reactions involve aldehyde co-reactants (i.e., R'' = H), and we refer to R' as the aldehydic substituent, which usually has less effect on selectivity.
- (10) Schlosser, M.; Schaub, B. *J. Am. Chem. Soc.* **1982**, *104*, 5821–5823.
- (11) (a) Trindle, C.; Hwang, J.-T.; Carey, F. A. *J. Org. Chem.* **1973**, *38*, 2664–2669. (b) Höler, R.; Lischka, H. *J. Am. Chem. Soc.* **1980**, *102*, 4632–4635. (c) Rose, I. A. *J. Am. Chem. Soc.* **1984**, *106*, 6117–6119. (d) Volatron, F.; Eisenstein, O. *J. Am. Chem. Soc.* **1984**, *106*, 6117–6119. (e) Volatron, F.; Eisenstein, O. *J. Am. Chem. Soc.* **1987**, *109*, 1–14. (f) Rzepa, H. S. *J. Chem. Soc. Perkin Trans 2* **1989**, *12*, 2115–2119. (g) Mari, F.; Lahti, P. K.; McEwen, W. E. *Heteroat. Chem.* **1991**, *2*, 265–276. (h) Mari, F.; Lahti, P. K.; McEwen, W. E. *J. Am. Chem. Soc.* **1992**, *114*, 813–821. (i) Naito, T.; Nagase, S.; Yamataka, H.; *J. Am. Chem. Soc.* **1994**, *116*, 10080–10088. (j) Restrepo-Cossio, A. A.; Cano, H.; Mari, F.; Gonzalez, C. A. *Heteroat. Chem.* **1997**, *8*, 557–569. (k) Restrepo-Cossio, A. A.; Gonzalez, C. A.; Mari, F. *J. Phys. Chem. A* **1998**, *102*, 6993–7000. (l) Lu, W. C.; Wong, N. B.; Zhang, R. Q. *Theor. Chem. Acc.* **2002**, *107*, 206–210. (m) Seth, M.; Senn, H. M.; Ziegler, T. *J. Phys. Chem. A* **2005**, *109*, 5136–5143.

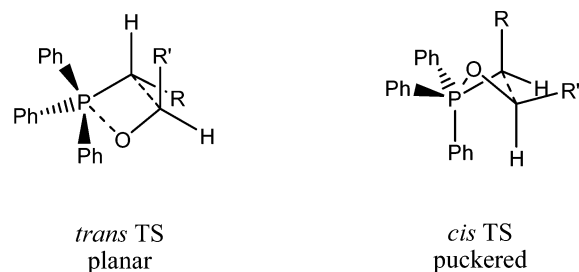


Figure 2. TS structure for the reaction of non-stabilized ylides according to the Vedejs model.

to preferential formation of a *cis* oxaphosphetane and *Z* alkenes. Given the lack of practical methods to include solvent effects in calculations at the time of this work, it was not possible for the authors to provide strong evidence in favor of this hypothesis.

The model which best accounts for the range of experimental observations was developed by Vedejs et al.^{2,5,8a,12} on the basis of extensive experimental investigations. In this model, selectivity is explained by an interplay of 1,2 and 1,3 steric interactions in the four-center transition state. Non-stabilized ylides add to aldehydes through an early and, hence, fairly flexible transition state. Relief of steric interactions between the ylide substituent and the aldehyde substituent (1,2 interaction) and between the aldehyde substituent and the phosphorus substituents (1,3 interaction) leads to a preferred geometry for the *cis* TS, which is puckered (Figure 2). In the *trans* TS, puckering to relieve 1,3 interactions (clockwise motion of the aldehyde in Figure 2) would lead to increased 1,2 interactions, so the preferred geometry is planar. The balance of the steric effects favors the *cis* TS, and hence, the reaction leads preferentially to *Z* alkenes. For stabilized ylides, it is generally accepted that the transition state must be later (more oxaphosphetane-like) and hence less flexible, so that it is constrained to be closer to planar, which leads to unfavorable 1,2 interactions in the *cis* TS, whereas the *trans* TS is less hindered.^{1c,f,2,12} As a result, the *trans* TS is favored, and this explains the overall *E* selectivity in reactions of stabilized ylides.

Alongside the experimental work, computation has been used to characterize the transition states involved and to attempt to rationalize observed *E/Z* selectivities. Until recently, calculations have been carried out on simple models (e.g., PH_3 or PMe_3 ylides) and/or using low levels of theory.¹¹ Such work is intrinsically unable to provide a full picture, as it is known experimentally that substituents on the ylide phosphorus atom play an important role in determining the geometry of the TS and the product stereochemistry.^{2,8b,11k,12} Accordingly, the early computations were able to provide support for the accepted mechanism involving oxaphosphetane formation and cleavage, but they were not very informative on the origin of selectivity. More recently, the first study using a realistic model (PPh_3 ylides) together with density functional theory (DFT, B3LYP/6-31G*) was published by Yamataka and Nagase.¹³ These authors investigated the Wittig reaction of non- and semi-stabilized ylides (surprisingly, stabilized ones were not considered) and focused on the first step, thereby precluding conclusions concerning the reversibility of oxaphosphetane formation. They found that the transition states for the addition of Ph_3 -

Table 1. Reactions Studied in This Manuscript and Corresponding Experimental Selectivities

	reaction	experimental selectivity
Non-Stabilized Ylides		
(1)	$\text{Me}_3\text{PCHMe} + \text{MeCHO}$	<i>trans</i>
(2)	$\text{Ph}_3\text{PCHMe} + \text{MeCHO}$	highly <i>cis</i>
Semi-Stabilized Ylides		
(3)	$\text{Me}_3\text{PCHPh} + \text{PhCHO}$	highly <i>trans</i>
(4)	$\text{Ph}_3\text{PCHPh} + \text{PhCHO}$	<i>cis/trans</i> mixture
(5)	$(\text{MeO})_3\text{PCHPh} + \text{PhCHO}$	highly <i>trans</i>
Stabilized Ylides		
(6)	$\text{Me}_3\text{PCHCO}_2\text{Me} + \text{PhCHO}$	highly <i>trans</i>
(7)	$\text{Ph}_3\text{PCHCO}_2\text{Me} + \text{PhCHO}$	highly <i>trans</i>
(8)	$(\text{MeO})_3\text{PCHCO}_2\text{Me} + \text{PhCHO}$	low <i>trans</i>

PCH(alkyl) and Ph_3PCHPh ylides to benzaldehyde are preferentially planar in the *trans* cases and puckered in the *cis* ones, as predicted by the Vedejs model. Furthermore, with the (non-stabilized) Ph_3PPCHMe ylide, the *cis* puckered TS was found to be 1.4 kcal/mol more stable than the *trans* planar one, whereas for the semi-stabilized ylide (Ph_3PCHPh), the reverse was observed, with the *trans* TS 2.1 kcal/mol lower than the *cis* one. These results are in partial agreement with experiment: they correctly predict *Z* selectivity for the non-stabilized ylides but incorrectly suggest high *E* selectivity for semi-stabilized ylides, which in fact give ca. 50/50 mixtures of the two isomers.

It should be noted that almost all the work so far has been carried out using gas-phase models. However, in this as in other reactions involving polar reactants and intermediates, solvent effects are expected to be significant and should be included, at least with a continuum treatment,¹⁴ if accurate results are to be obtained. For example, the mechanism of the Horner–Wadsworth–Emmons reaction can only be rationalized by including solvation effects,¹⁵ and all the computational studies of the reactivity and diastereoselectivity of onium ylide reactions needed to be carried out using continuum solvent as the gas-phase potential energy surface is not at all meaningful.^{16,17}

In summary, despite the long history and enormous practical importance of the Wittig reaction, a detailed atomistic account of its mechanism and selectivity is still lacking. Particularly unclear issues concern the cause of the different level of reversibility with different substituents (this aspect has never been examined computationally on realistic models), solvent effects, and the origin of selectivity in non-stabilized, semi-stabilized and stabilized ylides. From our own point of view, the unexpected selectivity with the phosphite-based ylides raises questions as to the effect of the phosphorus substituent on selectivity. The present work addresses these issues, focusing on the salt-free Wittig reaction of non-, semi-, and stabilized ylides using realistic model systems with DFT and a continuum description of solvation. Given our interest in the influence of the phosphorus substituent, we have examined PMe_3 , PPh_3 , and P(OMe)_3 ylides. Table 1 shows the principal reactions considered in this manuscript together with the corresponding experi-

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(17) (a) Silva, M. A.; Bellenie, B. R.; Goodman, J. M. *Org. Lett.* **2004**, *6*, 2559–2562. (b) Lindvall, M. K.; Koskinen, A. M. P. *J. Org. Chem.* **1999**, *64*, 4596–4606.

mental selectivities. To validate our chosen methodology, and for purposes of comparison with previous work, we have also studied the model reaction between formaldehyde and CH_2PMe_3 at a variety of different levels of theory.¹⁸

Computational Details

The bulk of the computations has been carried out using the Jaguar 4.0 pseudospectral program package.¹⁹ All species have been fully geometry optimized, and the Cartesian coordinates are supplied in the Supporting Information. In the case of transition states, the “loose” geometry convergence parameters within Jaguar (which correspond to rms gradients below 0.0015 hartree/au) have been used. Test calculations using the standard convergence criteria led to insignificant changes in structure but were much more time-consuming. Geometry optimization was carried out using the well-established B3LYP hybrid density functional as implemented in Jaguar (optimization using a more demanding *ab initio* method, MP2, did not lead to significant structure changes for the model reaction). The standard split-valence polarized 6-31G* basis set was used. Single point calculations at the gas-phase B3LYP/6-31G* geometries were carried out for every structure using the polarizable continuum-Poisson method as incorporated in Jaguar.²⁰ Single point calculations of the relative energies of *cis* and *trans* addition TSs were also carried out using a larger basis (B3LYP/6-311+G**-(THF) level), and results are reported in the Supporting Information. These calculations do not lead to significant changes in the relative energy of the two diastereomeric addition TSs; thus, our discussion focuses, for reasons of simplicity, on the smaller basis set results. The structure of reactants and the addition TSs leading to the oxaphosphetanes was reoptimized in the presence of continuum solvent. The results are not expected to depend strongly on the parameters used for the continuum solvent, so we have used a single set of parameters, i.e., a dielectric constant of 7.4 and a solvent probe radius of 2.52 Å, that is suitable for tetrahydrofuran (THF), one of the most common solvents used in Wittig reactions. All given energies are obtained after corresponding single point calculations using the fine grid and high accuracy parameters within Jaguar.

Frequency calculations for all gas-phase transition states have been carried out using Jaguar 5.0²¹ to check for the presence of a single imaginary frequency; the corresponding eigenvector was carefully inspected to check that it corresponded to the expected reaction coordinate. For reasons of computational expense due to the large size of some of the systems, frequency calculations have not been carried out on minima; thus, the results do not include zero-point energy corrections—these are expected to be fairly small and to be near identical for isomeric pathways leading to *E* and *Z* products. Entropic effects, which could also be derived from frequency calculations, are also neglected here. However, these too should be very similar for *cis* and *trans* species.

For the model reaction $\text{CH}_2\text{PMe}_3 + \text{CH}_2\text{O}$, gas-phase stationary points have been located at the B3LYP and MP2 levels using standard 6-31G*, 6-31+G*, and 6-311+G** basis sets. Single point energies at the B3LYP/6-31G* and MP2/6-31G* geometries have then been evaluated at several levels of theory: B3LYP/6-311+G**, MP2/6-311+G**, and QCISD(T)/6-31G*. G3(MP2)//B3LYP/6-31G* single point energies²² have also been calculated. Solvent effects have been treated both using single point calculations at the B3LYP/6-31G* and B3LYP/6-311+G** levels of theory using B3LYP/6-31G* gas-phase

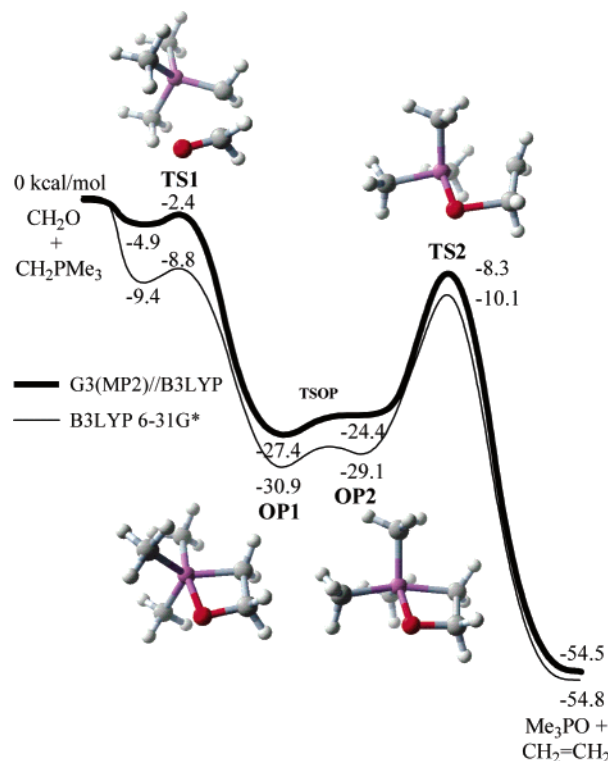


Figure 3. Calculated gas-phase potential energy surface (kcal/mol) for the model reaction $\text{CH}_2\text{O} + \text{CH}_2\text{PMe}_3$ at the B3LYP/6-31G* and G3(MP2)//B3LYP levels of theory.

structures and by geometry optimization in the presence of continuum solvent at the B3LYP/6-31G* level. MP2 calculations were performed using the Gaussian 03 program package,²³ with the QCISD(T) single-point calculations obtained using the MOLPRO program package.²⁴

For the large reaction systems, there are usually several local minima or saddle points corresponding to each intermediate or transition state. This is due to the possibility of multiple conformations of substituents positioned on phosphorus or the ylidic carbon. In some cases, different transition states varying by their degree of puckering have also been found. We have systematically varied the relevant dihedral angles and optimized several different local minima and saddle points (up to 10 different calculations for each species). The data presented refer to the lowest-energy form unless mentioned otherwise (see Supporting Information for a full list of geometries).

The transition state for pseudorotation in the oxaphosphetane has been located for the model reaction and for many of the other systems. In all cases, this point was found to lie very close in structure and energy to the less-stable isomer of the oxaphosphetane, i.e., the one with the ylidic carbon in an apical position. Given its low energy, this transition state clearly does not play an important role in defining reactivity (or selectivity), and we therefore do not discuss its structure and energy in the text.

Results

1. Model Reaction. Our results for the model reaction ($\text{CH}_2\text{O} + \text{CH}_2\text{PMe}_3$) are, on the whole, very similar to those reported in the literature,^{11f,k,l} and we will restrict the discussion to the main points, with the full results presented in the Supporting Information. The most representative results are those obtained at the B3LYP/6-31G* and G3(MP2)//B3LYP/6-31G* levels of theory, and these are shown in Figure 3.

(18) It has already been shown that the simplest CH_2PH_3 ylide model is not adequate to describe the general reaction (see refs 11k,l and 13).

(19) *Jaguar 4.0*; Schrödinger, Inc.: Portland, OR, 1991–2000.

(20) (a) Tannor, D. J.; Marten, B.; Murphy, R.; Friesner, R. A.; Sitkoff, D.; Nicholls, A.; Ringnalda, M.; Goddard, W. A., III; Honing, B. *J. Am. Chem. Soc.* **1994**, *116*, 11875–11882. (b) Marten, B.; Kim, K.; Cortis, C.; Friesner, R. A.; Murphy, R. B.; Ringnalda, M. N.; Sitkoff, D.; Honing, B. *J. Phys. Chem.* **1996**, *100*, 11775–11788.

(21) *Jaguar 5.0*; Schrödinger, L.L.C.: Portland, OR, 1991–2003.

(22) Badoul, A. G.; Curtiss, L. A.; Redfern, P. C.; Raghavachari, K. *J. Chem. Phys.* **1999**, *110*, 7650–7657.

(23) Frisch, M. J. et al. *Gaussian 03*, revision B.04; Gaussian, Inc., Pittsburgh, 2003.

(24) Werner H.-J. et al. *MOLPRO*, version 2002.3.

The first stationary point on the potential energy surface is a weakly bound encounter complex. This complex, already mentioned in previous work,^{11g,i-k,13} is unimportant in solution reactions and so will not be discussed further. Addition of the phosphorus ylide to formaldehyde then leads to the formation of an oxaphosphetane. This could, in principle, occur either via a two-center nucleophilic addition (anti approach; see McEwen model) or a four-center pathway (syn or quasi-syn approach; see Schlosser and Vedejs models). In the gas phase, a low-lying TS involving a syn approach of the reactants was located, while every attempt to obtain a TS corresponding to an anti approach or a betaine led to reactants.

As in previous computational studies,^{11,13} the obtained four-center transition state has a very planar structure with a large asynchronous character: the forming C–C and P–O bond lengths are 2.05 and 3.08 Å, respectively (compared to 1.53 and 1.85 Å, respectively, in OP1). This observation is consistent with the bond order analysis carried out by McEwen using a semiempirical method, which showed that the new C–C bond is about 40% formed in the TS, while the P–O bond order is still insignificant at that stage.^{11g,h} The oxaphosphetane formation step is thereby perhaps best described as a concerted, asynchronous, double nucleophilic addition of C to C then O to P, in which C–C bond formation is well advanced at the TS, while the P–O interaction is still mainly electrostatic, with P–O bond formation occurring after the TS.

Upon including continuum solvent, syn and anti approach of the reactants lead directly to an oxaphosphetane (OP1) and an anti betaine respectively without an energy barrier.²⁵ A betaine intermediate can now be localized. This latter lies, however, 12.50 kcal/mol higher in energy than OP1, suggesting that it does not play an important role. Recent calculations using a small model system and a continuum model of a more polar solvent, DMSO, find a betaine intermediate with the oxaphosphetane lying higher in energy.^{11m} The difference with respect to our calculations may be due to the different solvent model or the use of a different DFT functional. In any case, the simplicity of model systems such as the one used here prevents one from drawing firm conclusions about whether betaines are involved as transient or stable intermediates in more typical Wittig reactions.

In the initially formed OP1 intermediate, the coordination geometry around phosphorus is roughly a trigonal bipyramid, with the oxygen derived from the aldehyde group in an apical position. This then undergoes pseudorotation over a low barrier to yield an isomer OP2 with the ylidic carbon in apical position (OP2), which is the formal precursor to the C–P bond cleavage step leading to ethylene and trimethylphosphine oxide. The TS for this last step is somewhat asynchronous, with significant C–P bond cleavage ($d_{C-P} = 2.516$ Å) as compared to the C–O bond ($d_{C-O} = 1.790$ Å).

The energy profile of the reaction has been obtained at a variety of levels of theory (see Supporting Information for details). The geometries obtained do not vary significantly according to the method used. The relative energies, however, are somewhat more spread out. The most important discrepancy concerns the relative energy of TS1 and TS2. Taking the

accurate G3(MP2)/B3LYP energies as a reference, we find that all other methods underestimate the height of TS1 relative to TS2, thereby falsely suggesting that the overall process should demonstrate significant reversibility of the initial addition step. Within the DFT framework, this effect was even found to increase upon using larger basis sets,²⁶ which also lead to an underestimate of the stability of the oxaphosphetanes. The best compromise between cost and accuracy is therefore the B3LYP/6-31G* method, and we have therefore used this in all further work. Even at this level, however, the gas-phase stability of TS1 is exaggerated by about 4 kcal/mol as compared to that of TS2 and of the reactants. It is to be noted that a major part of this work is aimed at understanding selectivity, and this is determined by the relative energies of TSs leading to *E* and *Z* products. In such cases, favorable error cancellation can be expected so that relative errors should be smaller than the absolute errors discussed here.

2. Non-Stabilized Ylides. In this section, we consider the reaction of non-stabilized ylides with acetaldehyde (reactions 1 and 2), with relative energies at the B3LYP/6-31G* level of theory shown in Table 2 and the reaction profile for reaction 2 depicted in Figure 4.

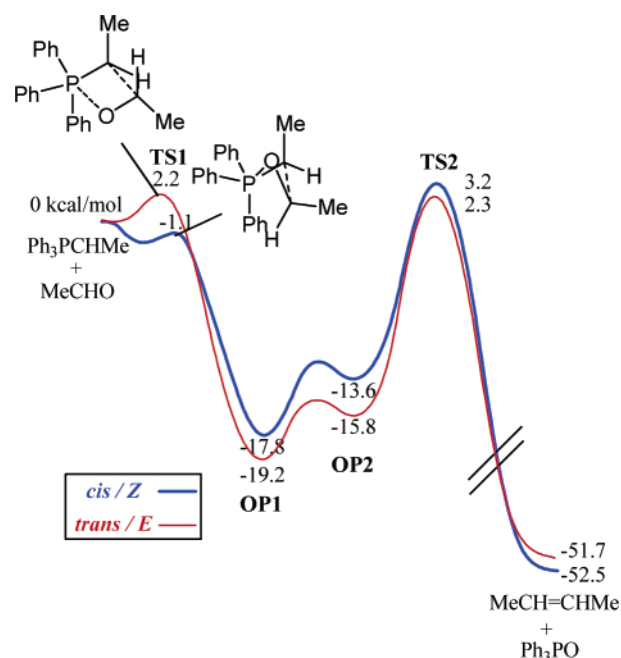


Figure 4. Calculated potential energy surface (kcal/mol) for reaction 2, $\text{Ph}_3\text{PCHMe} + \text{MeCHO}$, at the B3LYP/6-31G*(THF)//B3LYP/6-31G* level of theory.

The first step, oxaphosphetane formation, is slightly less exothermic than in the model reaction, especially in the case of phenyl substitution on the phosphorus atom. This can be readily understood by the destabilizing steric interaction between substituents in the oxaphosphetane. As for the model reaction, the addition step is very facile, involving an early TS at low

(25) A set of constrained geometry optimization at successively smaller values of the C–C distance was carried out to check that the interaction between reactants is indeed uniformly attractive in solution.

(26) This suggests that significant error cancellation occurs at the B3LYP/6-31G* level, between the error due to the basis and that due to the method. Although these errors cannot be expected to cancel in all cases, we note that a similar decrease in accuracy upon using larger basis sets with B3LYP has been observed previously for Diels–Alder reaction and dimerization of carbene; see respectively (a) Koch, W.; Holthausen, M. C. *A Chemist's Guide to Density Functional Theory (Second Edition)*; Wiley-VCH: New York, 2000. (b) Alder, R. W.; Blake, M. E.; Chaker, L.; Harvey, J. N.; Paolini, F.; Schuetz, J. *Angew. Chem., Int Ed.* **2004**, *43*, 5896–5911.

Table 2. Calculated Relative Energies (kcal/mol) and Selected Structural Parameters^a for the Reaction between Non-stabilized Ylides and Acetaldehyde

method		TS1	OP1	OP2	TS2	products	structure of TS1		experimental selectivity ^b
							C–C	PCCO	
(1) Me₃PCHMe + MeCHO → Butene + P(O)Me₃									
B3LYP/6-31G*	<i>cis</i>	-2.29 ^c	-26.41	- ^d	-3.18	-51.56	2.104	25.0	<i>trans</i>
	<i>trans</i>	-4.23	-27.92	- ^d	-4.09	-50.72	2.112	-14.5	
B3LYP/6-31G*(THF)//B3LYP/6-31G*	<i>cis</i>	-3.25 ^e	-22.41	- ^d	0.84	-54.27			
	<i>trans</i>	-4.96	-23.81	- ^d	0.13	-53.50			
B3LYP/6-31G*(THF)	<i>cis</i>	-1.47 ^f	-22.29	- ^d	1.09	-54.12	3.012	-2.4	
	<i>trans</i>	-1.48	-23.61	- ^d	0.54	-53.35	2.904	3.1	
(2) Ph₃PCHMe + MeCHO → Butene + P(O)Ph₃									
B3LYP/6-31G*	<i>cis</i>	2.39 ^g	-20.93	-18.84	-1.28	-51.74	1.991	92.9	highly <i>cis</i>
	<i>trans</i>	1.94	-23.07	-20.76	-2.31	-50.90	2.107	-19.4	
B3LYP/6-31G*(THF)//B3LYP/6-31G*	<i>cis</i>	-1.12	-17.85	-13.60	3.25	-52.51			
	<i>trans</i>	2.20	-19.24	-15.78	2.34	-51.73			
B3LYP/6-31G*(THF)	<i>cis</i>	-0.23 ^h	-17.87	-13.56	3.42	-52.57	2.950	81.8	
	<i>trans</i>	1.96 ⁱ	-19.65	- ^d	2.54	-51.82	2.471	-15.9	

^a C–C corresponds to the forming carbon(aldehyde)–carbon(ylide) bond and PCCO denotes the dihedral angle as defined in Figure 5. Bond lengths are given in Å and angles in degrees. ^b Those reactions are known to undergo stereochemical equilibration. ^c Other TSs at -2.01 (C–C = 2.056; PCCO = 4.5) and -1.19 (C–C = 2.030; PCCO = 68.5). ^d Attempts to optimize this structure led to OP1. ^e Other TSs at -3.39 (C–C = 2.056; PCCO = 4.5) and -4.75 (C–C = 2.030; PCCO = 68.5). ^f Other TS at -0.54 (C–C = 2.647; PCCO = 89.5). ^g Other TS at 4.91 (C–C = 2.051; PCCO = 40.4). ^h Other TSs at 0.46 (C–C = 2.499; PCCO = 99.7) and 2.86 (C–C = 2.269; PCCO = 165.4). ⁱ Other TS at +2.07 (C–C = 2.270; PCCO = -25.3).

energy. Upon including solvent effects, the relative stability of the oxaphosphetane is decreased further due to the higher solvation energy of the more polar reactants. Unlike in the model system, where the inclusion of solvent effects led to the disappearance of the barrier to addition, TS1 can still be located. The potential energy surface is, however, rather flat, as shown by the much earlier character of TS1 upon optimization with THF continuum. However, the degree of puckering is rather similar in the gas phase and in the continuum model.

The existence of a barrier to oxaphosphetane formation means that it is possible to examine whether anti addition leading to a betaine is able to compete. With Me₃PCHMe, a betaine intermediate lying at -7.69 kcal/mol (14.6 kcal/mol higher than the corresponding OP1) was found at the B3LYP/6-31G*(THF) level of theory, but it was impossible to locate an anti addition TS, with every attempt leading to the puckered syn TS. In the case of the Ph₃PCHMe reactant, it was possible to locate a transition state for the anti addition at the B3LYP/6-31G*(THF) level of theory (Table 2). This TS is, however, 3 kcal/mol higher in energy than the corresponding puckered four-center TS, with the betaine lying at -1.59 kcal/mol (16.2 kcal/mol above the corresponding OP1). This seems to be due to unfavorable steric interactions between the aldehydic substituent and the phenyl groups on the phosphorus atom during anti approach. Overall, betaine formation does seem to be possible in some cases at least, but the corresponding pathways lie higher in energy than those leading directly to the oxaphosphetane; thus, we will not consider this type of mechanism further.²⁷

Using the Me₃PCHMe ylide (reaction 1), the structure of the key addition TS1 is found to be quite similar to that of the model reaction for both the *cis* and *trans* pathways; that is, it is planar. The *cis* TS is slightly higher in energy given the unfavorable 1,2 interaction between the aldehydic and ylidic methyl substituents. However, upon optimization in THF, which yields

(27) The increase in bulkiness of the aldehydic substituent (R' = Ph) in the following reactions is likely to disfavor even more the betaine pathway. Preliminary calculations reveal moreover that there is no trend towards greater stabilization of such TSs and intermediates with increasing ylide stabilization; attempts to optimize the geometry of a betaine for reaction 6 gave high energies during the initial phases of the optimization, followed by splitting into reactants.

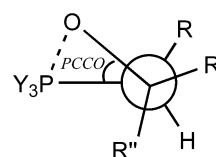


Figure 5. Definition of the PCCO dihedral angle.

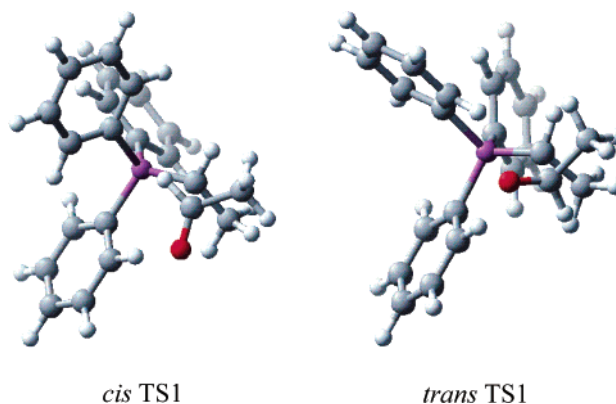


Figure 6. B3LYP/6-31G*(THF) diastereoisomeric transition states for addition of Ph₃PCHMe to MeCHO.

earlier TS structures with longer bond lengths for the forming carbon–carbon bond, this difference in energy disappears.

For reaction 2 (Ph₃PCHMe ylide), the larger phenyl substituents on the phosphorus atom lead to greater 1,3 steric interactions with the aldehydic substituent. Combined with the 1,2 interaction between the aldehydic and ylidic methyl groups, this leads to a significant puckering of TS1 (i.e., to a large PCCO dihedral angle; see Figure 5) in the *cis* case, as predicted by the Vedejs model (see Figure 6). Along the pathway leading to the *trans* oxaphosphetane, as also predicted in that model, the absence of 1,2 interactions leads to a planar structure.²⁸

An important structural feature of TSs involving a syn or quasi-syn approach of the reactants is the presence of C–H···O hydrogen bonds²⁹ between the oxygen atom of the approaching aldehyde and hydrogen atoms situated on one (or two) of the groups bonded to phosphorus (see Figure 6 for Ph₃PCHMe ylide). The short H···O distances (2.29–2.44 Å) and the C–H·

$\cdots\text{O}$ angles ($140\text{--}172^\circ$) observed in the TS1 structures are indicative of stabilizing hydrogen bonds.³⁰ Similar hydrogen bonding has also been suggested to play a crucial role in defining the stereoselectivity in the Horner-Wadsworth-Emmons reaction.¹⁵

Due to 1,2 steric interactions between the aldehydic and ylidic methyl substituents, the *cis* oxaphosphetanes intermediates are less stable than their *trans* isomers for the reactions of both the PMe_3 and PPh_3 ylides. Likewise, the cleavage TS2 leading to *Z* alkenes is significantly higher in energy than the *E* isomer in both cases. This is significant because the TS2 transition state is close in energy to the initial addition barrier TS1. Even when taking into account the fact that the energy of TS1 is likely to be underestimated relative to that of TS2 at the B3LYP/6-31G* level (as in the model reaction), this means that formation of *cis* oxaphosphetane should be somewhat reversible for both reaction 1 and 2. In contrast, given the lower energy of TS2 in the reaction leading to *trans* alkenes, formation of *trans* oxaphosphetane should be much less reversible in reactions of Me_3PCHMe and not at all so with Ph_3PCHMe .

These observations are in good agreement with the stereochemical equilibration studies of Maryanoff^{4d} and Vedejs^{8b} using $\text{Bu}_3\text{PCH(alkyl)}$ ylides. In these ^{31}P NMR experiments at low temperature, the proportion of *cis* oxaphosphetane intermediate observed throughout the reaction was found to be higher than that of *Z* alkene in the products, consistent with the reversible formation of the oxaphosphetane. With $\text{Ph}_3\text{PCH(alkyl)}$ ylides, on the other hand,^{4d} both the oxaphosphetane and alkene were formed with a high ($>96/4$) *cis/trans* (*Z/E*) selectivity. No change in product stereochemistry was observed upon treatment of independently generated *cis* and *trans* β -hydroxyphosphonium salts with base.^{4d,8b} Deprotonation should lead initially to a betaine, which can then either split into reactants or cyclize to the oxaphosphetane. Deprotonation of the *cis* β -hydroxyphosphonium salts in the presence of *m*-chlorobenzaldehyde did lead to some crossover products, suggesting that either the betaine or the oxaphosphetane could revert to reactants in this case. Based on our results, these observations can be explained if *trans* oxaphosphetane formation is completely nonreversible, whereas the *cis* oxaphosphetane can undergo some reversion to reactants, but with the corresponding addition TS1 and decomposition TS2 lying lower in energy than the addition TS1 leading to *trans* oxaphosphetane. It is also possible that the crossover products are formed from decomposition of the *cis* betaine into reactants.

Due to the reversibility of the first step, the *E/Z* selectivity in the reaction of Me_3PCHMe must be governed by the relative energy of the *cis* and *trans* TS2s, which, as mentioned above, favor the *trans* isomer by 0.55 kcal/mol (B3LYP/6-31G*(THF)). This energy difference is in good agreement with the 67/33 *E/Z*

selectivity obtained experimentally for the reaction of $\text{Et}_3\text{PCHMe} + (\text{alkyl})\text{CHO}$ at -78°C (see page 57 in ref 2a). In the case of Ph_3PCHMe , reversibility does not affect selectivity, since *cis* TS2 is lower in energy than *trans* TS1 (provided one takes into account the fact that the B3LYP/6-31G* level underestimates the energy of TS1 compared to TS2). Despite the reversibility of the initial step, formation of the *Z* olefin should be favored over the competing reaction leading to the *E* isomer. This, too, is in good agreement with experiment, which gives a ratio of 6/94 or lower of *E* and *Z* products in the reactions of Ph_3PCHMe with $(\text{alkyl})\text{CHO}$ (see page 59 in ref 2a).

From these first results on realistic models, one can observe that, as expected, it is essential to include a description of solvation effects to account correctly for selectivity. Continuum solvation affects the relative energies of transition states and intermediates significantly: gas-phase calculations of the relative energy of *cis* and *trans* TS1s do not reproduce the observed preference for *Z* alkenes. Only upon including a continuum model of solvent, whether using single point calculations or including geometry optimization, do the relative energies agree with experiment. This can be understood based on the higher polarity of the highly puckered *cis* TSs (due to the greater spatial separation between the two charged groups, the positive phosphorus and the negative oxygen), which will therefore be better stabilized by solvent than the less polar *trans* TS1.

Because solvation does not affect the structure of TSs and intermediates in a significant way (except in some cases for TS1s) and given the large number of atoms and hence computational expense involved in the reactions treated in the following sections, only TS1 has been optimized in the presence of the continuum model of THF in the remainder of this study. Solvent effects for the other species on the energy profiles have been estimated using single point calculations at the gas-phase geometries. In any case, the second step has progressively less importance for defining selectivity with increasing ylide stabilization.

3. Semi-Stabilized Ylides. We have investigated in this part the reaction of benzaldehyde with phenyl-stabilized ylides with methyl, phenyl, and methoxy substituents on the phosphorus atom (reactions 3, 4, and 5, respectively). The results are summarized in Table 3; the energy profile for reaction 4 is depicted in Figure 7.

Because of the partial stabilization of the ylide and the increased steric bulk of the substituents on both reactants, oxaphosphetane formation from the Me_3P and Ph_3P ylides is less exothermic here than for non-stabilized ylides. Oxaphosphetane formation from the $(\text{MeO})_3\text{PCHPh}$ ylide is, however, surprisingly exothermic (>10 kcal/mol) given the high stabilization of the ylide.³¹ This suggests that the methoxy groups stabilize the oxaphosphetanes much more than the reactants. In line with the lower exothermicity of oxaphosphetane formation from Me_3P and Ph_3P ylides, the first barrier is increased in these reactions. Despite the higher exothermicity for $(\text{MeO})_3\text{PCHPh}$, the barrier is still fairly high, suggesting that the stabilizing effect of the methoxy groups present in the oxaphosphetanes is not

(28) In ref 13, Yamataka and Nagase have also optimized the transition state for the addition of Ph_3PCHMe onto MeCHO at the B3LYP/6-31G* level. We were able to locate a TS with the same structure as found by these authors, and this has a relative energy of 3.3 kcal/mol. However, careful examination of the potential energy surface shows that this is not the lowest TS; we found another one which is more stable by 1.36 kcal/mol. The conformation of the phosphorus-bound phenyl groups differs between the two TSs.

(29) (a) Desiraju, G. R. *Acc. Chem. Res.* **1996**, *29*, 441–449. (b) Grabowski, S. J. *J. Phys. Org. Chem.* **2004**, *17*, 18–31.

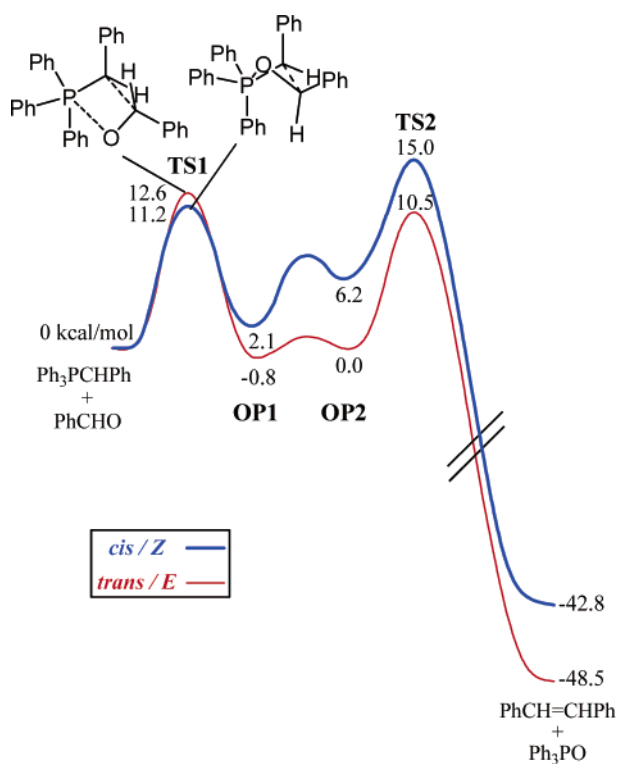
(30) C–H \cdots O hydrogen bonding is generally held to be present for H \cdots O distances between 2.0 and 2.8 Å, C–H \cdots O angles of 110 to 180° , and C=O \cdots H angles of 120 to 140° (see ref 29 and references therein). All C–H \cdots O hydrogen bonds considered in this study fall within these ranges.

(31) The increasing electron-withdrawing character of substituents on phosphorus can be expected to exacerbate stabilization of a negative charge in α of the phosphorus group. Relative stabilization can be estimated by the energy of the following isodesmic reactions $\text{CH}_3^- + \text{PhCH}_2\text{PY}_3^+ \rightarrow \text{CH}_4 + \text{PhCHPY}_3$. The calculated (B3LYP/6-31G*(THF)) energy of this reaction is -68.2 , -72.7 , and -82.0 kcal/mol, respectively, for Y = Me, Ph, and OMe.

Table 3. Relative Energies (in kcal/mol) Compared to Reactants and Relevant Geometrical Parameters^a for TS1 for the Reaction of Semi-stabilized Ylides with Benzaldehyde

method		TS1	OP1	OP2	TS2	products	structure of TS1		experimental selectivity
							C–C	PCCO	
(3) Me₃PCHPh + PhCHO → Stilbene + P(O)Me₃									
B3LYP/6-31G*	<i>cis</i>	6.26	-11.15	-8.46	4.17	-41.36	1.966	35.7	highly <i>trans</i>
	<i>trans</i>	3.36	-13.85	-13.81	0.58	-46.48	1.877	-28.8	
B3LYP/6-31G*(THF)//B3LYP/6-31G*	<i>cis</i>	9.50	-2.30	1.70	11.99	-42.65			
	<i>trans</i>	5.91	-5.37	-1.67	8.52	-48.40			
B3LYP/6-31G*(THF)	<i>cis</i>	7.68					2.279	39.6	
	<i>trans</i>	5.05					2.045	-24.7	
(4) Ph₃PCHPh + PhCHO → Stilbene + P(O)Ph₃									
B3LYP/6-31G*	<i>cis</i>	11.44	-4.63	-2.42	7.72	-41.68	1.803	76.8	<i>cis/trans</i> mixture
	<i>trans</i>	10.04	-8.10	-7.36	4.27	-46.80	1.967	-26.0	
B3LYP/6-31G*(THF)//B3LYP/6-31G*	<i>cis</i>	11.19	2.14	6.21	14.97	-42.80			
	<i>trans</i>	12.59	-0.77	0.03	10.53	-48.54			
B3LYP/6-31G*(THF)	<i>cis</i>	11.98					2.033	66.4	
	<i>trans</i>	12.39					2.024	-34.3	
(5) (MeO)₃PCHPh + PhCHO → Stilbene + P(O)(OMe)₃									
B3LYP/6-31G*	<i>cis</i>	14.49	-18.33	-16.91	12.27	-44.09	2.003	49.2	highly <i>trans</i>
	<i>trans</i>	10.86	-22.07	-19.72	8.55	-49.22	1.954	-39.3	
B3LYP/6-31G*(THF)//B3LYP/6-31G*	<i>cis</i>	18.26	-10.92	-9.01	19.67	-44.82			
	<i>trans</i>	15.51	-14.92	-11.66	15.70	-50.57			
B3LYP/6-31G*(THF)	<i>cis</i>	16.31					2.093	53.5	
	<i>trans</i>	13.26					1.978	-42.6	

^a C–C corresponds to the forming carbon(aldehyde)–carbon(ylide) bond, and PCCO denotes the dihedral angle as defined in Figure 5. Bond lengths are given in Å and angles in degrees.

**Figure 7.** Calculated potential energy surface (kcal/mol) for reaction 7, Ph₃PCHPh + PhCHO, at the B3LYP/6-31G*(THF)//B3LYP/6-31G* level of theory.

yet present in the addition transition state. The lower exothermicity of the addition also has an impact on TS structures: addition TSs have a later character, with the distance between the carbon atoms of the forming C–C bond being shorter than in the reactions of non-stabilized ylides.

In terms of puckering, the optimized TS1 structures are somewhat similar to those obtained with non-stabilized ylides. The *cis* and *trans* addition TS are both slightly puckered in the

case of the trimethyl substituted ylide, whereas the corresponding non-stabilized TSs were both almost planar. This can be attributed to the larger size of the aldehydic substituent and subsequently of its 1,3 interactions with the groups bonded to the phosphorus atom. In the case of the triphenyl substituted ylide, the *cis* TS is somewhat less puckered than its non-stabilized analogue (which has a PCCO angle of 81.8°). This could be due to increased 1,3 interactions which become important for puckering angles higher than 60°. It is also possible that dipole–dipole interactions similar but of reduced magnitude to those involved in the stabilized ylide reaction (see below) play some role.

Hydrogen bonding is also changed at the addition TS. The later character of the TSs (shorter C–C forming bond) allows closer C–H···O interactions (H···O distances = 2.0–2.4 Å), although with reduced and, hence, less favorable C–H···O angles (142–156°).³² Interestingly, hydrogen bonding is also observed with methoxy substituents on phosphorus, with both the *cis* and *trans* TS1 structures for reaction 5 showing close C–H···O contacts between the aldehydic oxygen atom and C–H bonds on two of the methoxy groups. These stabilizing interactions probably explain why TS1 is slightly puckered with this type of ylide (see Discussion).

The barriers to decomposition of the oxaphosphetanes derived from semi-stabilized ylides are lower than for those derived from non-stabilized ylides. This is in agreement with the fact that semi-stabilized oxaphosphetanes are more difficult to observe experimentally. Accordingly, the first step is less inclined to reversibility than in the corresponding non-stabilized ylide reaction. Under some conditions, formation of the *cis* oxaphosphetane could, however, be partly reversible, especially in the case of methyl- and methoxy-substituted ylides.

(32) There is a general consensus that linear bonds are structurally more significant because of the dipole–monopole and dipole–dipole contribution to the electrostatic energy, which is maximum at C–H···O angle = 180° (see ref 29).

Table 4. Computed Energies (kcal/mol) Relative to Reactants for Reactions of Stabilized Ylides with Benzaldehyde, and Optimized Geometrical Parameters^a for TS1

method		TS1	OP1	OP2	TS2	products	structure of TS1		experimental selectivity
							C–C	PCCO	
(6) Me₃PCHCO₂Me + PhCHO → PhC=CHCO₂Me + P(O)Me₃									
B3LYP/6-31G*	<i>cis</i>	14.52	1.99	2.90	8.10	-27.07	1.865	-12.2	highly <i>trans</i>
	<i>trans</i>	11.58	-0.24	-1.78	3.58	-31.45	1.782	-34.2	
B3LYP/6-31G*(THF)/B3LYP/6-31G*	<i>cis</i>	18.89	10.71	11.76	13.62	-26.14			
	<i>trans</i>	14.48	8.23	7.15	8.39	-31.68			
B3LYP/6-31G*(THF)	<i>cis</i>	14.95					1.838	32.5	
	<i>trans</i>	12.29					1.845	-37.0	
(7) Ph₃PCHCO₂Me + PhCHO → PhC=CHCO₂Me + P(O)Ph₃									
B3LYP/6-31G*	<i>cis</i>	24.09	6.91	6.33	9.50	-29.77	2.085	24.3	highly <i>trans</i>
	<i>trans</i>	20.25	4.23	0.94	4.62	-34.15	1.913	-36.0	
B3LYP/6-31G*(THF)/B3LYP/6-31G*	<i>cis</i>	29.57	14.01	14.71	15.82	-27.82			
	<i>trans</i>	24.82	12.15	9.17	10.16	-33.36			
B3LYP/6-31G*(THF)	<i>cis</i>	23.76					1.887	26.1	
	<i>trans</i>	21.30					1.860	-40.1	
(8) (MeO)₃PCHCO₂Me + PhCHO → PhC=CHCO₂Me + P(O)(OMe)₃									
B3LYP/6-31G*	<i>cis</i>	18.45	-9.59	-7.24	10.81	-33.99	1.920	37.4	low <i>trans</i>
	<i>trans</i>	18.86	-12.33	-11.88	10.08	-38.36	1.888	-41.5	
B3LYP/6-31G*(THF)/B3LYP/6-31G*	<i>cis</i>	22.91	-2.59	-0.43	16.52	-32.88			
	<i>trans</i>	21.52	-5.68	-5.03	13.29	-38.42			
B3LYP/6-31G*(THF)	<i>cis</i>	21.26					1.933	33.8	
	<i>trans</i>	19.77					1.854	-43.8	

^a C–C corresponds to the forming carbon(aldehyde)–carbon(ylide) bond, and PCCO denotes the dihedral angle as defined in Figure 5. Bond lengths are given in Å and angles in degrees.

Given the near-planar structure of both *cis* and *trans* TS1s in the reaction of Me₃PCHPh ylide, the discrimination between the two isomers is governed by the 1,2 interaction between the aldehyde and the ylidic substituents. This steric effect is larger than in the case of non-stabilized ylides due to the later character of the TS and the increased size of the ylidic substituent. This leads to a high selectivity for the formation of the *trans* oxaphosphetane. As *cis* oxaphosphetane formation is also expected to be reversible in this case, the calculations predict a high overall *E* selectivity. This is in good agreement with the 91/9 *E/Z* selectivity obtained experimentally for the reaction of Bu₃PCHPh with benzaldehyde at room temperature (see page 66 in ref 2a).

In reaction 4 (with Ph₃PCHPh ylide), the *trans* TS1 is nearly planar and thereby has smaller 1,2 interactions between the ylidic and aldehyde phenyl groups than its *cis* isomer, but on the other hand has slightly larger 1,3 interactions with the phosphine phenyl groups. This conflicting effect of the 1,2 and 1,3 interactions leads to an overall energy difference between the two barriers that is slightly in favor of the *trans* isomer in the gas phase. In solution, however, the more polar, puckered *cis* TS is slightly better solvated, leading to a very low energy difference. The energy of the *cis* TS2 is close to that of the two TS1 barriers; thus, some reversibility in the formation of *cis* oxaphosphetane can be expected under some conditions (salt effects, uncontrolled temperature effects, etc). This prediction is in good agreement with experiments, which lead to ratios of *E/Z* stilbene ranging from 25/75 to 75/25, depending on the conditions, in the reaction of Ph₃PCHPh with benzaldehyde (see pages 62 and 63 in ref 2a).

In the case of the (MeO)₃PCHPh ylide (reaction 5), C–H···O interactions make both isomers of TS1 slightly puckered so that selectivity is governed by the 1,2 interactions, which favor the *trans* isomer. The calculated energy difference between the two competing TS1s suggests that products should be formed with high *E* selectivity. Here too, TS2 for *cis* oxaphosphetane

cleavage is in an energy range such that some reversibility of the initial addition is possible, which would lead to even higher *E* selectivity. Experimentally, the ratio of stilbenes formed at 40 °C varies from 84/16 to 97/3 *E/Z* in (MeO)₃PCHAr + ArCHO reactions,³ in good agreement with our predictions.

4. Stabilized Ylides. Our results on the reaction of benzaldehyde with ester-stabilized phosphorus ylides with methyl, phenyl, and methoxy substituents on the phosphorus atom (reactions 6, 7, and 8, respectively) are summarized in Table 4, with the energy profile of reaction 7 depicted in Figure 8.³³

Given the high stabilization of the ylides, oxaphosphetane formation is now endothermic in the case of the Me₃PCHCO₂Me and Ph₃PCHCO₂Me ylides. For the phosphite-derived ylide, the stabilization effect of the methoxy groups on the oxaphosphetane already noted with the semi-stabilized ylides is present again, and the first step is thereby somewhat exothermic.

Due to the high endothermicity (or lower exothermicity) of the oxaphosphetane formation, the addition barrier is higher than in the previous cases for all the reactions. The highest barrier is obtained with the triphenylphosphonium ylide (reaction 7), with the trimethylphosphonium addition involving a significantly lower barrier, perhaps due to less steric hindrance. The activation energy with the triphenylphosphonium ylide is very slightly higher than that for the phosphite-derived ylide, which is unexpected given that the latter is more stabilized. Indeed, competition experiments³ show that (MeO)₃PCHCO₂Et is less reactive than Ph₃PCHCO₂Me. This discrepancy may be due to errors in the computational method, which is plausible given the difference in electronic structure between the two types of ylide. It may also be due to solvent effects, as discussed below.

In terms of structures, the later character of the addition TS is also apparent, with the distance between the carbon atoms of

(33) Reactions 7 and 8 have been the subject of a preliminary communication on the origin of the high *E* selectivity in the Wittig reaction of stabilized ylides: Robiette, R.; Richardson, J.; Aggarwal, V. K.; Harvey, J. N. *J. Am. Chem. Soc.* **2005**, *127*, 13468–13469.

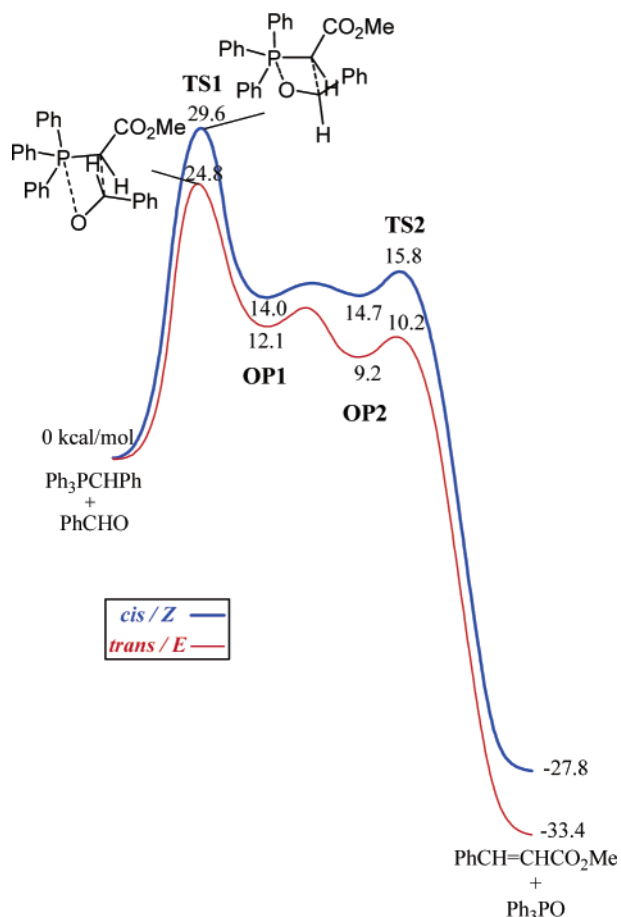


Figure 8. Calculated potential energy surface (kcal/mol) for reaction 7, $\text{Ph}_3\text{PCHCO}_2\text{Me} + \text{PhCHO}$, at the B3LYP/6-31G*(THF)//B3LYP/6-31G* level of theory.

the forming C—C bond being shorter than in the other reactions. In this series, the *cis* addition TSs are found to be less puckered than in the reactions of non- and semi-stabilized ylides, whereas the *trans* TSs are on the contrary, and somewhat surprisingly at first sight, *more* puckered. In previous work, it has been assumed that the late TSs associated with reactions of stabilized ylides will prevent puckering.² The unexpected structural trends can be explained by the emergence of a dipole–dipole interaction between the two reactants at the transition state.^{33,34,35} There is, of course, a strong dipole associated with the C=O bond of the aldehyde. Most of the phosphorus ylides discussed here are fairly polar, due to the formal negative charge on carbon and positive charge on the phosphorus group. In the non-stabilized ylides, the dipole moment is relatively small (2.75 D for Ph_3PCHMe ³⁶), oriented along the C—P bond, and does not affect selectivity. In the stabilized ylides, however, the dipole is relatively large (5.32 D for $\text{Ph}_3\text{PCHCO}_2\text{Me}$ ³⁶) and has a significant component along the C(ylide)—C(ester) bond, due to delocalization of the negative charge into the ylidic ester group. The semi-stabilized ylides are intermediate in this

(34) For a review discussing the influence of electrostatic effects on selectivities, see: Mehta, G.; Chandrasekhar, J. *Chem. Rev.* **1999**, *99*, 1437–1467.

(35) A similar dipole–dipole interaction is also used by Heathcock and Denmark to rationalize stereoselectivity in aldol reaction occurring via an open transition states (for a recent example, see Denmark, S. E.; Beutner, G. L.; Wynn, T.; Eastgate, M. D. *J. Am. Chem. Soc.* **2005**, *127*, 3774–3789, and for a review, see Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095–1120).

(36) Calculated dipoles for Ph_3PCHMe , $\text{Ph}_3\text{PCHCO}_2\text{Me}$, and $(\text{MeO})_3\text{PCHCO}_2\text{Me}$ are 2.75, 5.32, and 2.12 D, respectively. See Supporting Information for a detailed description of respective dipoles.

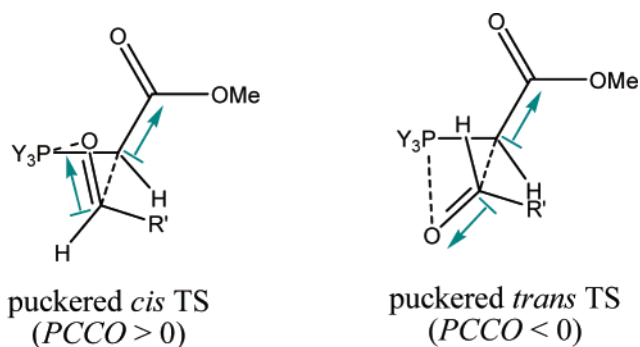


Figure 9. Dipole–dipole interaction in TS1s of stabilized ylides reactions.

respect.³⁶ The electrostatic interaction between the two dipoles in the stabilized ylide reactions is destabilizing in geometries with a puckering angle PCCO larger than 0, where both dipoles are parallel, and stabilizing for values of the puckering angle smaller than 0, i.e., when the dipoles are antiparallel. The unfavorable orientation of the dipoles occurs whenever a *cis* TS undergoes puckering to relieve 1,2 and 1,3 steric strain (Figure 9). This explains the much more planar geometry found for the *cis* TS1 here. In contrast, puckering of the *trans* TS leads to the favorable relative orientation of dipoles (Figure 9), so although it also leads to some 1,2 steric strain, it can be understood why the *trans* TS structures optimized here are less planar than those we found for the reactions of the other types of ylide. In the case of the $\text{Me}_3\text{PCHCO}_2\text{Me}$ ylide, where the 1,3 interactions are low, the *cis* TS1 optimized in the gas phase is, in fact, puckered the opposite way than usual (i.e., with $\text{PCCO} < 0$), which also leads to a somewhat favorable relative orientation of the dipoles.

The second barrier, decomposition of the oxaphosphetane, is very low for stabilized ylides. This is consistent with the fact that oxaphosphetanes derived from representative stabilized ylides have escaped detection so far. The examination of geometries of TS2s (gas phase) reveals a very asynchronous character of the transition structures, with a C—P bond between 2.55 and 2.78 Å, and the C—O bond is close to 1.59 Å. This suggests that the lowering of the barrier is due to the ability of the electron withdrawing group (CO_2Me) to stabilize a developing negative charge on the ylidic carbon at the transition state. For $(\text{MeO})_3\text{PCHCO}_2\text{Me}$ ylide, however, the high stabilization of the oxaphosphetanes makes the barrier higher than for phosphine-derived ylides.

The very low second barrier together with the high energy of the TS1s renders the reaction of stabilized ylides completely nonreversible. The *E/Z* selectivity is thus determined exclusively by the relative energy of *cis* and *trans* TS1s, which is mainly governed by the dipole–dipole interaction. In addition, the low puckering and the late character of TS1s makes the 1,2 interaction also an important factor in determining the energetic discrimination between the two isomers. Consequently, a systematic high *E* selectivity is computed. This is in good agreement with experiment where >96/4 and 95/5 *E/Z* selectivities for the reaction of benzaldehyde with, respectively, $\text{Ph}_3\text{PCHCO}_2\text{Et}$ and $\text{Bu}_3\text{PCHCO}_2\text{Et}$ are observed (see page 78–79 in ref 2a).

The case of the $(\text{MeO})_3\text{PCHCO}_2\text{Me}$ ylide is less straightforward. The difference in energy between *cis* and *trans* TS1 is much lower than for the trialkyl and triphenyl phosphonium

ylides. This can be explained by the smaller effect of the dipole–dipole interaction between the two reactants in this system, due to the smaller dipole present in the ylide derived from trimethyl phosphite (see Discussion).³⁶ This lesser discrimination between the formation of the two isomers with methoxy substituent in the case of stabilized ylides is in good agreement with experiment, which gives low *E/Z* selectivity (69/31) for salt-free reaction of ylides derived from phosphite.³

Discussion

1. Mechanism. Like previous studies on simple models,^{11b,d–f,j} our calculations on realistic systems using a computational method including solvent effects provide unequivocal support for the generally accepted mechanism for the salt-free Wittig reaction. There are two important steps along each of the diastereoisomeric pathways leading to *cis* and *trans* olefins. The first one is addition of the ylide to the aldehyde to form an oxaphosphetane. This step can be best described as a concerted, asynchronous, double nucleophilic addition occurring via a four-center transition state in which the C–C bond formation is well advanced, whereas the P–O interaction is mainly electrostatic, the P–O bond formation occurring after the TS. Although it is also possible in some cases to find a transition state leading to a betaine, such barriers lie higher in energy than the corresponding four-center transition state and are unlikely to play an important role in the mechanism.

In the oxaphosphetane formed by addition of the ylide onto the aldehyde (OP1), the aldehydic oxygen adopts an apical position in the phosphorus coordination sphere. In formal terms, before the second key step can occur, this oxaphosphetane needs to undergo a pseudorotation around the pentacoordinated (trigonal bipyramidal) phosphorus atom to give an oxaphosphetane with the ylidic carbon in apical position (OP2). This latter conformer lies slightly higher in energy (1–4 kcal/mol) than OP1, and the barrier for the interconversion is very low.

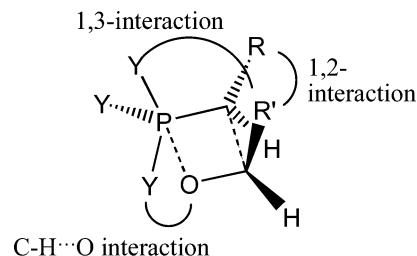
Our calculations show that the last barrier, for decomposition of the oxaphosphetane into products, decreases in energy upon going from non-stabilized to stabilized ylides, which explains why oxaphosphetanes derived from representative stabilized ylides have not yet been observed experimentally. For ylides derived from phosphites, however, a high stabilization of oxaphosphetanes, relative to reactants and transition states, has been found in all cases; this leads to a large barrier for their decomposition.

The relative energy of the barrier to the initial addition varies in the opposite direction to that for oxaphosphetane decomposition; that is, it increases with increasing stabilization of the ylide. This too leads to a decrease in reversibility of the first step upon going from non-stabilized to stabilized ylides. This observation is in good agreement with experiment, which demonstrates that lithium-free Wittig reactions proceed without reversal, except for the reaction of (alkyl)₃P ylides or, in some cases, the reaction of Ph₃PCH(alkyl) with aliphatic aldehydes.^{2,4d,8b} Our calculations confirm moreover a consistent tendency for more reversibility in the formation of *cis* oxaphosphetanes than in that of *trans* ones, because of a higher energy for *cis* TS2s compared to the *trans* isomers. The increase in reversibility with alkyl groups on phosphorus (instead of phenyls) is reproduced as well by our calculations; the propensity to reversal follows the order Me₃P > (MeO)₃P > Ph₃P ylides. This trend can perhaps be

explained by the relative bulkiness of those substituents and the more sterically demanding character of the first step over the second one.

In the case of the stabilized ylides, competition experiments show that the phosphite-derived ylides are less reactive than triphenylphosphonium ylides (i.e., reaction 7 is faster than reaction 8). This is the trend that is expected, given that the trialkoxyphosphonium group stabilizes the ylidic negative charge better than triphenylphosphonium.³¹ Our calculations (Table 4) find a slightly lower barrier for the addition step with the phosphite-derived stabilized ylide, which does not agree at first sight with the experimental observations. This may be due to computational error: a change of 3 kcal/mol in the relative energies of the addition transition states in the phosphite and triphenylphosphine cases would be enough to agree with experiment. An error of this magnitude is certainly possible despite the expected error cancellation. However, it should be pointed out that entropy is known to play a large role in activation free energies for ester-stabilized ylide Wittig reactions,² as the highly polar ylide needs to be mostly desolvated before addition takes place. As the triphenylphosphonium ylide is so much more polar than the phosphite-derived one,³⁶ it is possible that such effects, too subtle to be captured by the continuum solvent model, play an important role in determining the relative reactivity.

2. Structure of TS1. The degree of puckering of TS1 has been found to depend strongly on steric and electronic interactions involving the substituents on the aldehyde and the ylide. These interactions are:



1,2 Interaction. In the case of the *cis* isomer, a parallel approach (planar structure) of the two reactants induces a steric interaction between the aldehyde substituent (R') and the ylide substituent (R); puckering enables a decrease of this interaction. In the case of *trans* TSs, it is, on the contrary, a planar geometry which minimizes this destabilizing interaction. This effect is thereby the main cause of the difference in degree of puckering between *cis* and *trans* TS1s in non- and semi-stabilized ylide reactions.

1,3 Interaction. In the case of a planar transition structure, the substituent on the aldehyde (R') can interact with the groups bonded to the phosphorus atom (Y). The puckering of the transition structures always occurs in such a way as to decrease this destabilizing interaction (except for the *cis* TS in the case of reaction 6; vide supra). The influence of this interaction on the degree of puckering can be directly observed by looking at the transition states for the addition of Me₃PCH₂ to aldehydes with different substituents (R') (entries 1–3 in Table 5): the degree of puckering increases with the bulkiness of the aldehydic substituents. It should be pointed out that this interaction

Table 5. Geometrical Parameters for Transition Structure of Addition of Y_3PCHR Onto $R'CHO$ (B3LYP/6-31G*)

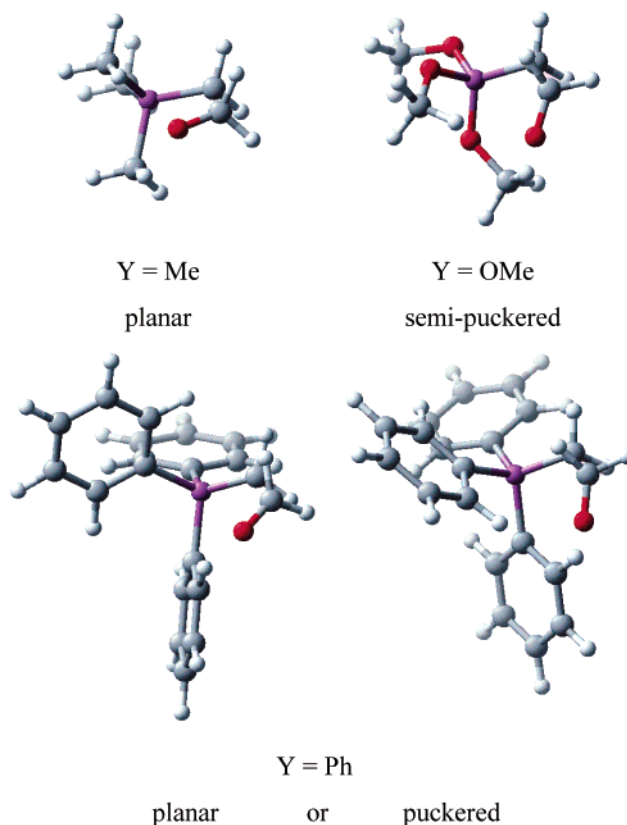
entry	Y	R	R'	PCCO (deg)	$d_{H\cdots O}$ (Å)	$CH\cdots O$ (deg)
1	Me	H	H	1.0	2.16	134
					2.17	134
2	Me	H	Me	17.0	2.12	134
					2.19	132
3	Me	H	Ph	24.6	2.13	133
					2.21	131
4	Ph	H	H	51.8 ^a	1.96	158
					2.20	142
5	OMe	H	H	45.1 ^b	2.01	156
					2.07	155
6	Me	Me	H	14.8 ^c	2.21	134
					2.23	134
7	Me	Ph	H	-35.5	2.20	130
					2.20	131
8	Me	CO ₂ Me	H	-31.2	2.14	122
					2.27	119

^a Another TS, 0.41 kcal/mol higher, has also been found with a PCCO angle of 15.7° and having one C–H⋯O interaction. ^b Other TSs, varying by the conformation of the methoxy groups, have been found. Only the more stable is reported in this table. ^c Another TS with a PCCO angle of -16.7° and lying 0.54 kcal/mol higher in energy was also found.

decreases with increasing puckering until the puckering angle reaches 60°, after which the interaction increases with further puckering.

C–H⋯O Interaction. The syn approach of the reactants enables C–H⋯O hydrogen bonding to occur in the transition state structure.³⁷ The strength of this type of interaction in other systems has been reported to range from 0.5 to 4 kcal/mol, depending on the acidity of the hydrogen and the topology of the bond.^{29b} The ensuing stabilization in Wittig reaction addition TSs therefore depends strongly on the nature of the substituents on phosphorus and on the geometry of the transition state. This is one of the main reasons why the degree of puckering at the TS varies depending on the substituent at phosphorus (Figure 10). The structures of the transition states for the reaction of Y_3PCH_2 with CH_2O , in which 1,2 and 1,3 interactions are absent, show how important this effect is (see entries 1, 4, and 5 in Table 5). The PMe_3 ylide reacts via a planar transition structure in which there is hydrogen bonding between the aldehydic oxygen and two of the methyl groups on phosphorus. Careful examination of other PMe_3 ylide transition state structures obtained in this study shows that slight puckering (<30°) of the TS does not significantly disrupt these C–H⋯O interactions. In the case of triphenyl substitution, the situation is different: two different transition states are obtained for the addition of Ph_3PCH_2 onto formaldehyde (entry 4 in Table 5), one of which is strongly puckered while the other is nearly planar. Both geometries allow a favorable topology for the C–H⋯O interactions. In the case of $P(OMe)_3$ ylide, however, to obtain two hydrogen bonds with a good topology, the aldehyde and ylide need to approach each other with an angle of 40–50°. This explains why TS1 is always semi-puckered in these cases (see entry 5 in Table 5, Figure 10, and TS1s of reactions 5 and 8).

Dipole–Dipole Interaction. In the case of stabilized ylide systems, in addition to the interactions mentioned above, a dipole–dipole interaction between the two reactants influences

**Figure 10.** Influence of phosphorus substituents (Y) on the geometry of TS1.

the degree of puckering. Stabilized ylides have a large dipole moment, with a large component oriented in the direction of the C–CO₂Me bond (see Figure 9): the magnitude of the dipole is of 4.60, 2.12, and 5.32 D for the stabilized ylides with Y = Me, OMe, and Ph, respectively. For a comparison, the non-stabilized Ph_3PCHMe ylide has a dipole of 2.75 D pointing roughly along the direction of the C–PMe₃ bond. As mentioned above, puckering of *trans* TS1s induces an antiparallel, and hence stabilizing, arrangement between the ylide and aldehydic C=O dipoles, whereas in the case of *cis* TSs, puckering produces an unfavorable (parallel) orientation (see Figure 9). To estimate the energetic impact of this dipole–dipole interaction, we consider the addition of Me_3PCHCO_2Me onto formaldehyde, in which steric effects are absent. The optimized geometry of the transition state is similar to that of the *trans* addition TS to benzaldehyde, with a PCCO puckering angle of -31.2° (Table 5, entry 8). Upon reoptimizing the geometry with the PCCO dihedral angle fixed to +30°, i.e., a value close to that observed in the *cis* TS, an energy 2.8 kcal/mol higher is obtained. Similar values are expected for stabilized PPh_3 ylides. However, the much smaller dipole observed for the phosphite-derived ylides means that this interaction is of much reduced impact in that case. The semi-stabilized ylides also have fairly large dipoles, which have however a small component along the C(ylide)–C(aryl) bond (it is largely orientated along the P–C(ylide) bond). As discussed above, however, the decreased puckering of the *cis* addition TS in this case may be a result of dipole–dipole interactions analogous but of smaller magnitude to those involved in the reactions of stabilized ylides.

Puckering Effects: Summary. In ref 13, Yamataka and Nagase examined the energetic impact of puckering for TS1

(37) A similar interaction has already been suggested by Brandt et al. in their rational of selectivity in Horner–Wadsworth–Emmons reaction (see ref 15a).

by carrying out calculations on the addition of Ph_3PCH_2 onto benzaldehyde. The authors found two transition structures: one which was nearly planar, and one which was highly puckered; the latter was also more stable (by 2.5 kcal/mol). Since steric repulsion between the ylidic hydrogens and the aldehyde moiety (1,2 interaction) is expected to be small in this reaction system (one has to notice however that 1,3 interactions are not expected to be negligible!), the authors concluded that the puckered conformation of the TS was inherently more stable in reactions of non-stabilized ylides. Our results on the model reaction and on the addition of Me_3PCHMe to formaldehyde (Table 5, entry 6) and MeCHO (reaction 1), where 1,2 and 1,3 interactions can be neglected (vide supra), are not in agreement with this suggestion, as we find the planar structure to be favored in the absence of significant steric effects. However, the computed energy differences between the planar and puckered transition structures in reaction 1 (in THF) as well as in the $\text{Ph}_3\text{PCH}_2 + \text{CH}_2\text{O}$ reaction (Table 5, entry 4) are found to be low (<0.9 kcal/mol), so that although puckering is not found to be inherently favored, it does not appear to be highly destabilizing.³⁸ On the other hand, our results on reactions of Y_3PCH_2 ylides (see entries 1–6 in Table 5) indicate that the geometry of the transition states for reactions of non- and semi-stabilized ylides is to a large degree dictated by $\text{C}-\text{H}\cdots\text{O}$ and 1,3 interactions and, hence, by the nature of the substituents bonded to phosphorus. The presence of methyl groups on phosphorus leads to planar structures, whereas transition states for PPh_3 ylides can be either planar or puckered, and the ylides derived from phosphites induce a semi-puckering of TSs in all cases. The 1,2 interactions, which are present only in the *cis* TSs and decrease upon puckering, also have a large influence on the geometry of transition states, accounting for the fact that *cis* addition always involves greater puckering for non- and semi-stabilized systems.

For stabilized ylides, it has previously been generally assumed that the transition state must be later (more oxaphosphetane-like) and, hence, less flexible, so that it is constrained to be closer to planar.^{1c,f,2,12} Our results do reveal a later character of TS1 upon increasing ylide stabilization (see respective C–C bond lengths in Tables 3–5). However, this does not correlate with more planar geometries, suggesting that the addition TS for all Wittig reactions can undergo puckering relatively easily.³⁸ Thus, in the case of the *cis* TS1s, a decrease in puckering is observed (PCCO = 81.8°, 66.4°, and 26.1° for non-, semi-, and stabilizing PPh_3 ylides, respectively), but a clear *increase* in puckering of *trans* TS1 is obtained (PCCO = –15.9°, –34.3°, and –40.1° for PPh_3 ylides bearing a Me, Ph, and CO_2Me substituent, respectively). To further probe this effect, we also determined the geometry of the addition TS for of the reaction of PMe_3 ylides bearing a methyl, phenyl, and ester substituent (i.e., respectively, non-, semi-, and stabilizing ylides) with formaldehyde, in which no influence of 1,2 or 1,3 interactions on the structure is expected (Table 5, entries 6–8). This series of transition state geometries confirms that there is no intrinsic

preference for planar addition TSs upon increased ylide stabilization; in fact, there is even an *increase* in puckering with ylide stabilization!³⁹

This last unexpected observation can be explained by the importance of dipole–dipole interactions in determining the geometry of TS1 in stabilized ylide reactions.³³ As mentioned above, this electrostatic interaction is destabilizing in the case of puckered *cis* TS, which explains the decrease in puckering of this isomer with ylide stabilization. Puckering of the *trans* isomer is conversely favorable, which explains the unexpected increase in puckering in this latter case. This effect is important for the most common types of ylide, namely those with alkyl and aryl groups on phosphorus, but much less so in the case of alkoxy substituents (phosphite-derived ylides). Our calculations show that the dipole on the ylide is in the latter case much reduced (vide supra), which makes the dipole–dipole interaction less important. The geometry of TS1 in reactions of $(\text{MeO})_3\text{P}-\text{HCO}_2\text{Me}$ ylide is instead governed, like for the semi-stabilized ylide $(\text{MeO})_3\text{PCHPh}$, by hydrogen-bonding $\text{C}-\text{H}\cdots\text{O}$ interactions.

3. Selectivity. The experimentally observed *E/Z* selectivities for all studied reactions are nicely reproduced by our calculations with a continuum description of solvation. The chosen set of reactions highlights the way in which these selectivities depend strongly on ylide stabilization and on the nature of the substituents Y bonded to phosphorus. For clarity, we will first discuss the influence of ylide stabilization on the *E/Z* selectivity in reactions of the most common PPh_3 ylides and then comment on the influence of the nature of Y groups.

In the case of non- and semi-stabilized PPh_3 ylides (reactions 2 and 4), as predicted by the Vedejs model,^{2,5,8a,12} there is a large difference in geometry between *cis* and *trans* addition transition states, so that 1,2 steric interactions are weak in both cases and cannot explain observed selectivities on their own. Yamataka et al. suggested¹³ that the puckered geometry is inherently favorable in the reaction of non-stabilized ylides. As this is the geometry adopted by the *cis* addition TS, this would explain the observed *Z* selectivity. The *trans* addition is much less puckered, which in this interpretation is an unfavorable response to steric strain. For semi-stabilized ylides, the same authors suggested that the lower nucleophilic character of the ylidic carbon favored a planar geometry for the addition TS and, hence, the *trans* isomer. However, we have shown (vide supra) that, in reactions of non- and semi-stabilized ylides, there is no significant intrinsic preference (or strong disadvantage) for a puckered geometry and that the TS geometry is mainly governed by the nature of the substituents on phosphorus. The difference in selectivity between non- and semi-stabilized ylides can thus not be explained by an intrinsic higher propensity to puckering of transition states in non-stabilized ylides reactions.

Our calculations suggest that factors governing selectivity of the first step must be a balance between 1,2 and 1,3 interactions. In non-stabilized reactions, as predicted by the Vedejs model,^{2,5,8a,12} the high puckering of *cis* TS1 minimizes both 1,2 and 1,3 interactions, making it more stable than its planar *trans* isomer (Figure 11). This is in agreement with the general trend for *Z* selectivity in reactions of non-stabilized triphenylphosphonium ylides.^{1,2} For semi-stabilized ylides, *cis* TS is less

(38) We note that the addition of sulfur ylides to aldehydes is calculated (see ref 16) to go through rather similar near-cyclic addition TSs but, unlike in the present case, leads to betaines in which there is no S–O bonding. The preference for a *syn* approach of the reactants in that case is due purely to favorable Coulombic interactions between the positively charged sulfur and negatively charged oxygen. In the present case, if P–O Coulombic interactions, which vary smoothly with increasing distance, dominate over more steeply varying covalent interactions in the region of the addition TS, this would explain the high flexibility towards puckering.

(39) Mari has observed the same trend comparing methyl-, propargyl-, and cyano-substituted ylides (see ref 11j).

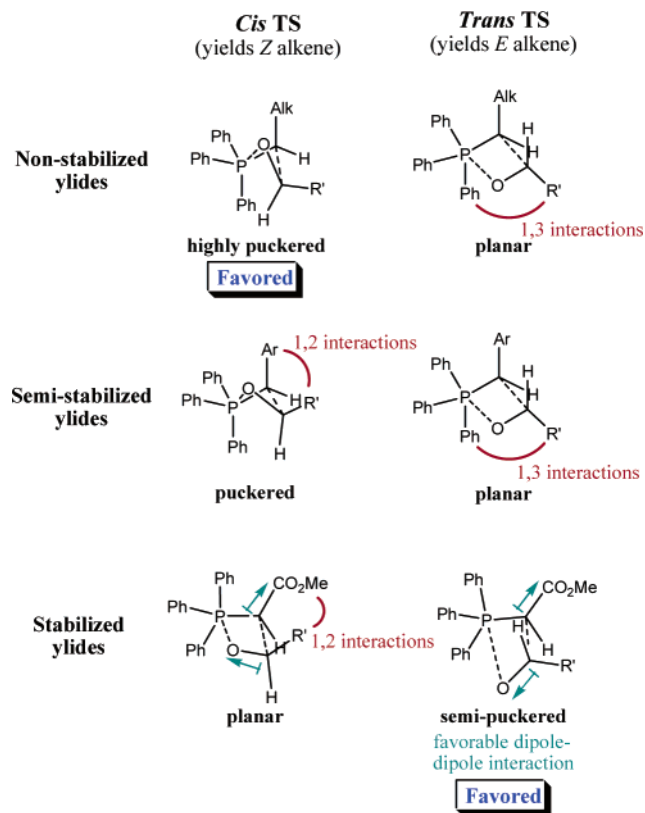


Figure 11. TS structure model and rationale of selectivity for triphenylphosphonium ylides.

puckered, and the role of 1,2 interactions in *cis/trans* discrimination is thereby increased. The *cis* isomer is more favorable in terms of the 1,3 interactions but less favorable in terms of the 1,2 interactions. Dipole–dipole interactions may also play some role in stabilizing the *trans* TS, as in the reactions of stabilized ylides. The net effect is a very low preference for the *cis* oxaphosphetane formation for semi-stabilized ylides, which is in agreement with observed low *E/Z* selectivity in reactions of this type of ylide.^{1,2}

The discussion above assumes that selectivity is determined at the initial addition step. Previous computational work has not located the transition states for alkene formation for realistic systems (e.g., with triphenyl phosphonium ylides) but has found that these TSs lie quite close in energy for model systems.^{11j} In fact, we find that B3LYP calculations predict TS2 to lie close to or even higher than TS1 (Tables 1 and 2). This would suggest considerable reversibility for the initial step. High-level G3 energies for the model reaction, however, show that B3LYP underestimates the energy of TS1 relative to TS2, and taking this bias into account, our calculations predict that reversal should not be of great importance in reactions of semi-stabilized ylides. In the non-stabilized ylide case (reaction 2), our results show on the contrary that *cis* oxaphosphetane formation might in some cases occur reversibly, which is consistent with experiment.^{2,4d,8b} This would not, however, prevent high selectivity for the *Z* alkene, because the *cis* elimination TS is lower in energy than the *trans* addition TS.

In the case of the triphenylphosphonium stabilized ylide (reaction 7), TS2 is very low in energy, showing that reversal cannot occur in these reactions, which is in agreement with experiment^{2,5,8a} but unlike previous suggestions.⁴⁰ *E/Z* selectivity

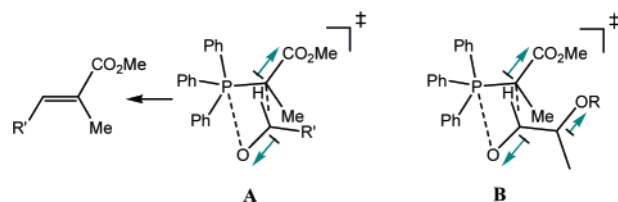


Figure 12. (A) Rationale for the high *trans* selectivity in reaction of disubstituted stabilized ylides and (B) low selectivity in α -alkoxy aldehydes reactions with stabilized ylides.

is thereby determined solely by the relative energy of *cis* and *trans* TS1s. These energies, as well as the geometry of the respective TS1s, are strongly affected by a dipole–dipole interaction between the two reactants. This interaction prevents the large puckering of the *cis* transition states, which minimizes the role of 1,2 interactions in the reactions of non- and semi-stabilized ylides. It also leads to an additional stabilization of the *trans* TS1 and destabilization of the *cis* isomer. The outcome for stabilized ylides is thus a high *E* selectivity.⁴¹

Interestingly, the inclusion of dipole–dipole interactions allows a rationalization for the surprising consistent high *trans* selectivity observed in reactions of disubstituted stabilized ylides ($\text{Ph}_3\text{PCRCO}_2\text{Et}$) (see A in Figure 12).² In this case, discrimination by steric effects is decreased, as compared to the $\text{Ph}_3\text{CHCO}_2\text{Et}$ ylide, but dipole–dipole interactions are not affected by the second substitution and still favor the *trans* TS (over the *cis* one). Also, the sometimes quite-low *E* selectivity (or even preferential formation of *Z* product)^{1f,2} observed in reactions of α -alkoxy aldehydes may be explained by interactions between the ylide, $\text{C}=\text{O}$, and $\alpha(\text{C}-\text{O})$ dipoles, e.g., B in Figure 12.

In related work, Vedejs et al. have determined the activation parameters for *E* and *Z* alkene formation in reactions of $\text{Ph}_3\text{PCHCO}_2\text{Et}$ with $\text{PhCH}_2\text{CH}_2\text{CHO}$ in several solvents. The measured *E/Z* ratio was observed not to vary across the temperature range studied, which suggests an entropic origin for *E* selectivity. At first sight, this is contradictory with our calculations which predict a difference in enthalpy between the two TSs. However, the inconsistency is not as great as it first seems for two reasons. First, the range of temperatures considered in the experiments (20 °C⁴²) and the accuracy of the measurements are not large enough to exclude some enthalpic component to the selectivity. For example, a change in the relative yield of the minor *Z* product from 5.0 to 5.5% between 60 and 80 °C corresponds to a difference in activation enthalpy of more than 1 kcal/mol—of the same order of magnitude as the differences calculated here. Next, our calculations including the continuum solvent model incorporate some entropic contributions, because they include a term corresponding to solvation free energy.²⁰ The discussion above of the solvent effect on *E/Z* selectivity suggests that the *cis* addition TS would undergo enthalpically favorable but entropically unfavorable enhanced solvation compared to the *trans* TS1, due

(40) (a) House, H. O.; Rasmusson, G. H. *J. Org. Chem.* **1961**, *26*, 4278–4281. (b) Bestmann, H. J.; Kratzer, O. *Chem. Ber.* **1962**, *95*, 1894. (c) Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry*; Oxford University Press: New York, 2000.

(41) This interpretation suggests an explanation for the observed solvent effect on *E/Z* selectivity in reactions of stabilized ylides. Polar protic solvents give much lower *E* selectivity, presumably because hydrogen bonding to the aldehyde oxygen alleviates the unfavorable dipole–dipole interaction. However, the similar effect expected for polar aprotic solvents is not observed, showing that this effect is complicated (see ref 2).

(42) Vedejs, E., personal communication.

to the need to compensate for the dipole–dipole repulsion. These enthalpic and entropic contributions could cancel out in the solvent model. The continuum solvent model is not detailed enough to be able to address this question quantitatively, but it is clear that our calculations are consistent with the experimental observations.

Turning to the reactions of trimethylphosphonium ylides Me_3PCHR (reactions 1, 3, and 6), given the near-planar character of all TS1 structures, the relative energies between the two diastereoisomeric TS1s is mainly governed by 1,2 interactions, which explains the general observation of higher *E* selectivity in trialkyl-substituted ylides reactions (compared to their PPh_3 analogues). Moreover, in the reaction of non- and semi-stabilized ylides, the overall selectivity can be influenced in some cases, if not totally governed, by reversibility, which would exacerbate further the *E* selectivity.

In the case of ylides derived from phosphites (P(OMe)_3 ylides), experiment has shown that the *E* selectivity is enhanced in the semi-stabilized case⁴³ but is actually decreased with ester-stabilized ylides, as compared to PPh_3 derivatives.³ Our calculations reproduce these counter-intuitive effects, and a detailed analysis of the structures and electronic properties of the addition TSs also enable us to understand the trends. In the case of semi-stabilized ylides (reaction 5), the strong $\text{C-H}\cdots\text{O}$ interactions lead to a preference for semi-puckered addition TSs, and this in turn increases the 1,2 interaction in *cis* TS1 while allowing a decrease of the 1,3 interactions in the *trans* isomer, as compared to the analogous triphenylphosphonium structures. Both effects lead to a decrease in the relative energy of the *trans* TS1 over the *cis* one and, hence, increase the *E* selectivity. In the case of the stabilized ylide (reaction 8), the unexpected decrease in *E* selectivity can be explained by the low dipole present in the ylide as compared to the triphenylphosphonium-stabilized ylide, leading to a much decreased effect of dipole–dipole interactions on the structure and relative energy of the two addition TSs. Both isomeric TS1s are semi-puckered, and their relative energy is consequently mainly governed by the extent of 1,2 interaction.

Conclusions

In this study, we have first shown that it is necessary to use computational methods including solvent effects to provide a consistent description of the potential energy surfaces for the Wittig reaction and that one needs to use realistic large-scale systems to capture all the steric, electronic, and stereochemical effects involved. We have shown moreover the importance of including the two key steps of the process in the analysis for understanding selectivity. It is also necessary to use a high level of theory, in our case B3LYP density functional theory validated (and in part corrected) by the use of G3 calculations on a model system. Our study has been the first to meet all these criteria throughout and yields insight on a number of important mechanistic questions relating to the selectivity of Wittig reactions.

First, our calculations provide unequivocal support for the generally accepted oxaphosphetane mechanism for the salt-free Wittig reaction and ruled out the intervention of betaine in the

mechanism. Next, our calculations on the reactions with non- and semi-stabilized ylides show that both the initial addition step and the subsequent elimination step can play a role in selectivity. Reactions of stabilized ylides, in contrast, are shown to involve no reversal in all cases. The origin of the influence of ylide stabilization and nature of groups bonded to phosphorus on the reversibility of the process has been clarified.

Our calculated potential energy surfaces are in excellent agreement with experimental observations concerning *E/Z* selectivity in all cases and give detailed insight into the origin of this selectivity. As previously suggested, puckering around the PCCO dihedral angle in the addition TS is shown to play a crucial role. However, we have shown that the degree of puckering is not determined by the extent of ylide stabilization and, hence, by the early or late nature of the addition TS. Instead, it is determined by a combination of factors such as $\text{C-H}\cdots\text{O}$ hydrogen bonding, steric 1,2 and 1,3 interactions, and dipole–dipole interactions between the ylide and the aldehyde. The magnitude of all of these interactions (except the 1,2 steric strain) depends on the nature of the phosphorus substituents Y, leading to different trends in selectivity between trialkyl, triaryl, and trialkoxy phosphonium ylides. It should be pointed out that although $\text{C-H}\cdots\text{O}$ interactions play an important role in determining the geometry of the TSs, because they are present in both diastereomeric TSs, they do not directly influence the stereochemical outcome of the reaction.

In the case of the non- and semi-stabilized ylide reactions, methyl and methoxy groups on phosphorus are respectively found to favor planar and semi-puckered structures for the addition TS, which in turn leads to the 1,2 steric interactions playing a leading role in determining selectivity, usually in favor of the *trans* addition TS and the *E* alkene. With the more common triphenylphosphonium ylides, both planar and puckered geometries are possible for the addition TS, and the selectivity is determined by a complex interplay of 1,2 and 1,3 interactions. In the non-stabilized case, ylides add to aldehydes via *trans* planar and *cis* puckered TSs. Lower 1,3 interactions and better solvation of the latter make it more stable. In this case, the *cis* elimination TS is fairly low in energy, so that reversibility does not play an important role and *Z* alkenes are favored. In the case of semi-stabilized ylides, puckering is reduced, so that 1,2 interactions play an increased role in *cis/trans* discrimination. The relative energy of the two isomeric TS1s is determined by a balance between 1,2 and 1,3 interactions, which leads to a low selectivity.

For stabilized ylides, our calculations reveal that the main effect on TS1 structure and energetics is a dipole–dipole interaction between the reactants. Previous suggestions whereby selectivity was mainly due to steric interactions in late, highly planar addition TSs is incorrect. In fact, *trans* TSs show a considerable degree of puckering, and the well-known *E* selectivity is instead due to a strong dipole–dipole interaction at the TS. The electrostatic effect is stabilizing in the case of the *trans* TS and destabilizing for the *cis* isomer. The fact that *E* selectivity is electrostatic in origin rather than steric helps to explain why it is so widely observed. The consistent very high *E* selectivity observed with disubstituted stabilized ylides ($\text{Ph}_3\text{-CRCO}_2\text{Me}$), for instance, cannot be rationalized by steric interactions but is easily accounted for by dipole–dipole interactions. Finally, the observation of low *E* selectivity for

(43) A similar increase in *E* selectivity (compared to PPh_3 analogues) has also been observed with triamino-substituted semi-stabilized ylides; see Wang, Z.; Zhang, G.; Guzei, I.; Varkade, J. G. *J. Org. Chem.* **2001**, *66*, 3521–3524.

stabilized ylides derived from trialkoxyphosphites is explained by the fact that these ylides have much lower dipole moments than the triphenylphosphonium species.

Our analysis of factors governing selectivity should assist in the design of new ylides for highly *E/Z* selective synthesis of alkenes as well as for the development of asymmetric Wittig reactions.

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Supporting Information Available: Tables with optimized Cartesian coordinates for all species discussed in the text, together with corresponding total energies at the different levels of theory. Complete ref 23 and 24. Full results on model reaction. Computed dipoles of ylides (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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