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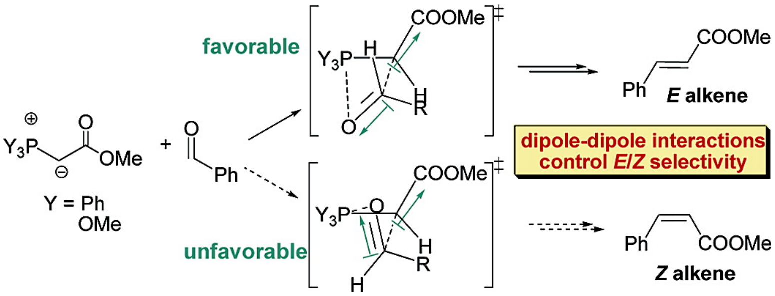
J. Am. Chem. Soc., **2005**, 127 (39), 13468-13469• DOI: 10.1021/ja0539589 • Publication Date (Web): 08 September 2005



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On the Origin of High *E* Selectivity in the Wittig Reaction of Stabilized Ylides: Importance of Dipole−Dipole Interactions

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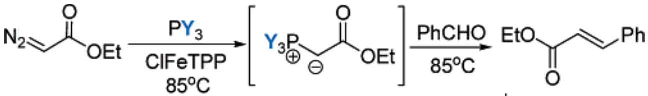
The Wittig reaction occupies a central role in organic synthesis as it generates a double bond with high levels of stereocontrol: nonstabilized ylides (Ph_3PCHR, R = alkyl) give high *Z* selectivity, whereas stabilized ylides (**1**, R = EWG) furnish high *E* selectivity.[1] The first step of the process, oxaphosphetane formation,[2] is recognized as determining the selectivity in most cases, and the different behavior of nonstabilized and stabilized ylides is best accounted for by the transition state models developed by Vedejs.[3,4] However, these models were developed for triphenylphosphonium ylides only and, therefore, cannot be used directly to analyze our recent observation[5] that, unlike ylides **1**, stabilized ylides **2** derived from phosphites give low *E* selectivity in Wittig reactions (Scheme 1). We use computation to gain insight into the factors controlling these surprising selectivity trends in the reaction of stabilized ylides and find that they are largely due to the hitherto unrecognized yet important role of dipole−dipole interactions.

Scheme 1. Wittig Reaction of PPh_3 and $P(OMe)_3$ Stabilized Ylides



Y		yield	*E/Z*
Y = Ph	(**1**)	85	96:4
OMe	(**2**)	90	69:31

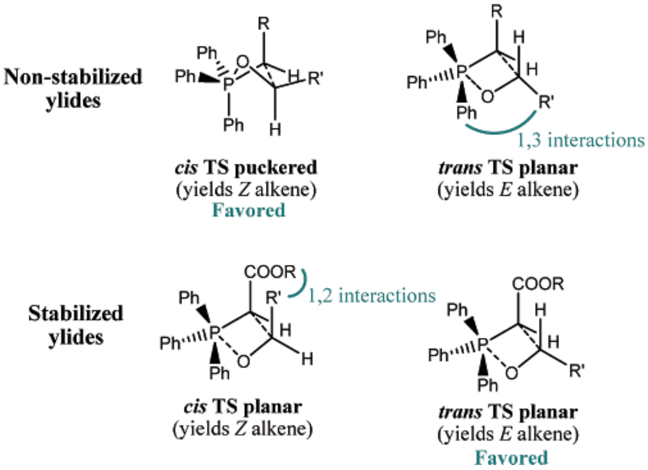


Figure 1. TS models commonly used to account for *E/Z* selectivity in Wittig reactions.[1,3,4]

In the Vedejs model, nonstabilized ylides preferentially add to aldehydes through an early puckered *cis* TS, which minimizes 1,2 and 1,3 steric interactions (Figure 1). The *trans* TS is more planar despite unfavorable 1,3 interactions, as puckering would lead to increased 1,2 interactions. The balance of steric effects thereby favors *cis* TS (*Z* alkenes). For stabilized ylides, the later character of the transition state (more oxaphosphetane-like) favors more planar TS geometries. This leads to a preference for the *trans* TS and hence *E* products, as 1,3 interactions are roughly the same in both TSs, but 1,2 steric hindrance is present only in the *cis* TS. If one attempts to extend the Vedejs model to the stabilized phosphite ylide **2**, the predicted *E* selectivity should be similar or even greater than that for traditional stabilized ylides. They are more stabilized[6] and would therefore be expected to react via even later transition states, which should lead to higher—not lower—*E* selectivity.

In our calculations[7−9] on the reaction of benzaldehyde with ylides **1** and **2**, we find significant barriers to formation of the oxaphosphetane, followed by much lower barriers to cleavage of the latter (see Supporting Information). This confirms that initial cycloaddition is nonreversible.[3a,c] The relative energies of the *cis* and *trans* TSs (shown in Figure 2) thereby determine *E/Z* selectivity.

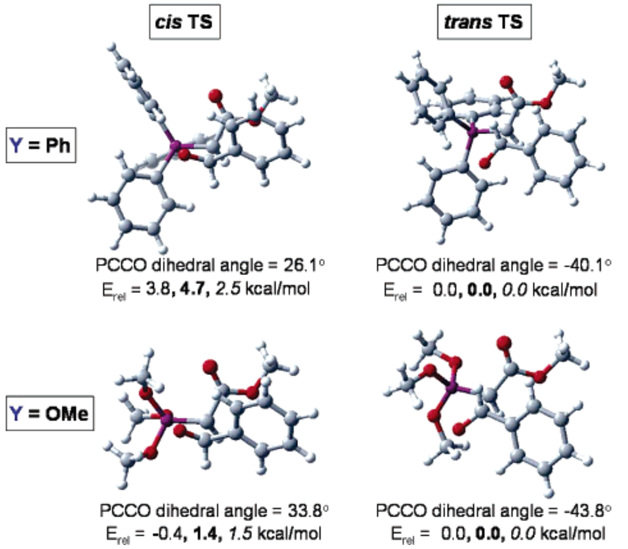


Figure 2. Structure and relative energy[7] of *cis* and *trans* TSs for the addition of ylides **1** and **2** to benzaldehyde (roman font: gas phase; bold: single point energies with continuum THF; italics: optimized in THF).

In the case of Ph_3PCHCO_2Me **1**, the TS for formation of *trans* oxaphosphetane is substantially lower than that leading to the *cis* isomer, consistent with the high experimental *E* selectivity. In contrast, the two isomeric TSs for the addition of $(MeO)_3PCHCO_2Me$ **2** to benzaldehyde are much closer in energy, with the *trans* TS lying slightly lower in energy when continuum solvent effects are included. This is consistent with the observed low *E/Z* selectivity with this type of ylide.[5] All the addition TSs lie at a similar position along the reaction coordinate, with a forming C−C bond length between 1.85 and 1.93 Å. Moreover, the trend in dihedral angles around the C−C bond (PCCO) is actually *opposite* to that expected: the *cis* TSs are close to planar, whereas the *trans* TSs are both significantly puckered.[10]

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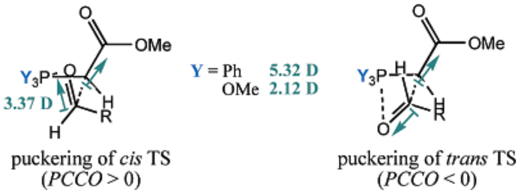

Figure 3. Computed[7] dipoles of ylides **1** and **2**, and their interaction with the dipole of the aldehyde in puckered *cis* and *trans* TSs.

Given the similar geometries and hence steric effects for the addition TSs of the two classes of stabilized ylides, how can one account for the difference in energetics and selectivity? One factor not discussed previously in this context is the role of dipole−dipole interactions at the TS.[11] The aldehyde has a strong dipole oriented along the C═O bond (3.37 D), and ylide **1** has a strong dipole pointing along the C(ylide)−C(ester) bond (5.32 D; Figure 3).[12] The latter dipole is due to delocalization of the ylidic negative charge onto the carbonyl group of the ester. The interaction energy between these two dipoles will be quite large and very dependent on their relative orientation.[13] Puckering of the *cis* TS to relieve 1,2 and 1,3 steric strain (PCCO > 0) will lead to an unfavorable configuration in which the two dipoles are nearly parallel (Figure 3). The near-planarity of the *cis* addition TSs is needed to avoid this unfavorable interaction. In contrast, puckering of the *trans* TS not only decreases 1,3 interactions but also leads to a favorable antiparallel orientation of the dipoles. Bearing in mind that deviation too far from planarity leads to 1,2 steric strain, this explains the significant puckering of the *trans* TS structures. Note that switching the aldehydic H atom and R group in the *trans* TS gives a *cis* TS with more favorable dipole−dipole interactions. This structure, however, has significant 1,2 and 1,3 steric repulsion. Any attempts to localize such a TS led to the TS shown in Figure 2, which is the lowest-lying *cis* conformer found in our calculations.

The smaller difference in energy between the *cis* and *trans* addition TSs in the case of ylide **2** is explained by the much smaller dipole (2.12 D; Figure 3) of the latter, due to competition between delocalization of the ylidic carbon lone pair into the ester carbonyl and σ^*_{PO} of the trialkoxyphosphonium groups. In the absence of significant dipole−dipole interactions, the difference in energy between the *cis* and *trans* addition TSs is much smaller, and consequently, selectivity is lost.

The reactant dipoles and their relative orientation at the TS suggest an explanation for solvent effects on *E/Z* selectivity in reactions of **1**: stronger solvation of the *cis* TS in highly polar solvents could alleviate the unfavorable dipole−dipole interaction effect, and hence lower the *E/Z* selectivity.[14] Indeed, protic solvents (but not polar aprotic solvents, suggesting that this is a complex effect) give lower *E* selectivities.[4]

In summary, we have shown that TS structures and *E*/*Z* selectivity in triphenylphosphonium-derived stabilized ylides **1** are controlled by a dipole−dipole interaction as well as the well-known 1,2 and 1,3 steric interactions. The existing models accounting for selectivity in reactions of stabilized ylides therefore need to be extended to include these polar interactions, which help to explain why *E* selectivity is such a consistent outcome with stabilized ylides. Also, the assumption that addition TSs for stabilized ylides are late and hence near-planar is incorrect: the *trans* TSs show considerable puckering due to the dipolar interactions. The observation of low *E* selectivity for stabilized ylides derived from trialkoxyphosphites, such as **2**, is explained by the fact that these ylides have much lower dipole moments than the triphenylphosphonium species. Including dipole−dipole interactions now allows us to rationalize the key experimental observations relating to Wittig reactions of stabilized ylides under salt-free conditions.

Acknowledgment. The authors thank E. Vedejs for helpful comments, the Université catholique de Louvain for a F.S.R. grant to R.R., Merck and Pfizer for unrestricted grants, and the EPSRC (Advanced Research Fellowship for J.N.H.).

Supporting Information Available: Full computational details, tables with optimized Cartesian coordinates, and corresponding energies for all species discussed in the text (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) 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: $CH_3^- + PhCH_2PY_3^+ \rightarrow CH_4 + PhCHPY_3$. Energy of this reaction is −68.15, −72.67, and −82.01 kcal/mol, respectively, for Y = Me, Ph, and OMe.

(7) Calculations were carried out at the B3LYP/6-31G* level of theory using the Jaguar 4.0 program package (*Jaguar 4.0*, Schrödinger, Inc.: Portland, OR, 1991−2000). Relative energies correspond to electronic energies calculated in the gas phase or using a PCM continuum model of THF solvent. See Supporting Information for full computational details.

(8) A complete investigation of *E*/*Z* selectivity in Wittig reactions, including non- and semi-stabilized ylides, will be reported in due course.

(9) For previous DFT studies on the Wittig reaction, see: (a) Yamataka, H.; Nagase, S. *J. Am. Chem. Soc.* **1998**, *120*, 7530−7536. (b) Restrepo-Cossio, A. A.; Gonzalez, C. A.; Mari, F. *J. Phys. Chem. A* **1998**, *102*, 6993−7000. (c) Restrepo-Cossio, A. A.; Cano, H.; Mari, F.; Gonzalez, C. A. *Heteroatom Chem.* **1997**, *8*, 557−569.

(10) This trend is also opposite to the situation in reactions of non- and semi-stabilized ylides in which the *cis* TSs, as suggested in Vedejs model (see ref 4) and confirmed by computational studies (see refs 8 and 9a), are significantly more puckered than the corresponding *trans* one; the reason for this being the release of 1,2 steric interactions.

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

(12) Dipoles were computed using *Jaguar 5.0* (Schrödinger, L.L.C.: Portland, OR, 1991−2003).

(13) The dipole−dipole interaction is quite strong; as a rough estimate, the difference in interaction energy between gas-phase dipoles of 3 and 5 D lying in parallel and antiparallel arrangements similar to those of the *cis* and *trans* TSs of Figure 3 is 54 kcal/mol. This number is an exaggeration of the effect encountered in the ylide addition TSs, in which the dipoles are partly neutralized and are not interacting in a vacuum, but nevertheless indicates the importance of dipole repulsions.

(14) Kinetic studies (see ref 4) find *E* selectivity for reaction of **1** to be due to entropic effects, not energetic or enthalpic, as suggested here. However, the accuracy of the kinetic analysis is not sufficient to exclude some enthalpic contribution. Also, enthalpically favorable but entropically unfavorable enhanced solvent ordering around the *cis* addition TS acting to shield the two dipoles from each other is conceivable, based on our calculations. Our calculations are thereby consistent with experimental observations.

JA0539589