

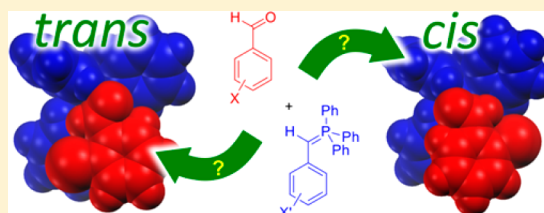
Anomalous Stereoselectivity in the Wittig Reaction: The Role of Steric Interactions

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S Supporting Information

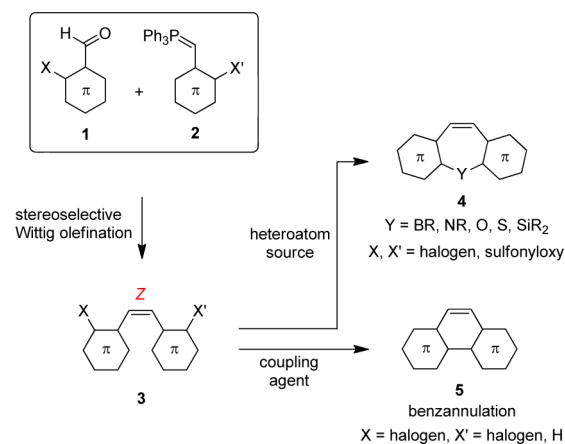
ABSTRACT: Density functional theory calculations combined with a distortion/interaction energy analysis show that the anomalous *Z* selectivity observed in Wittig reactions of *ortho*-substituted benzaldehydes is not caused by phosphorus–heteroatom interactions in the addition transition state, as assumed in earlier work, but is predominantly steric in nature. The calculations reproduced correctly the stereoselectivity preferences for a wide range of reactant pairs as well as relative reactivities for different substituent types, providing deeper structural insight into the mechanism of Wittig olefination.



The Wittig olefination reaction^{1–3} between aryl aldehydes **1** and (arylmethylene)triphenylphosphoranes **2** (Scheme 1) provides a well-established route to stilbene derivatives (**3**).⁴ Wittig reactions involving semistabilized ylides, such as **2**, typically show poor stereoselectivity, yielding mixtures of *Z* and *E* isomers.^{2,3} Interestingly, for many *ortho*-substituted arylaldehydes (**1**, $X \neq H$), Wittig olefinations with arylmethylene ylides are highly *Z*-selective, and the effect is cooperatively enhanced by the presence of another *ortho* substituent on the ylidic aryl group (X').^{3,5–8} This increase of stereoselectivity is preparatively useful when the *X* and X' groups are halogens because the resulting (*Z*)-stilbenes are valuable precursors to various heterocyclic systems, including fused azepines,^{9,10} oxepines,¹¹ borepines,^{12–15} and silepines¹⁶ (Scheme 1). Furthermore, direct couplings of mono- and di-halo-(*Z*)-stilbenes provide a regioselective alternative to photochemical benzannulations.^{17–19} We have recently explored the utility of the latter strategy in our ongoing work on the synthesis of distorted π -aromatics^{20,21} and have become interested in the mechanistic aspects of the Wittig reaction.

A generally accepted explanation^{5,7,8,22,3} for the enhancement of *Z* selectivity described above involves the influence of phosphorus–heteroatom bonding,^{23–25} which was proposed to occur between the *ortho* substituent and the ylidic P center in the cycloaddition transition state. It has been suggested that this interaction preferentially stabilizes the *Z*-selective TS and that it strongly affects the interaction geometry between the ylide and the aldehyde.⁸ However, this interesting postulate relies on indirect arguments, and the existence of $P \cdots X$ bonding has not been demonstrated in either experimental or theoretical studies. Herein is presented computational evidence that the anomalous *Z* selectivity does not result from ancillary bonding interactions in the transition state but is principally a steric effect. The present model, which is based on a straightforward application of DFT methods, is in excellent agreement with experimental data and might be useful for routine predictions of reactivity.

Scheme 1. Synthetic Applications of the Wittig Reaction between Aryl Aldehydes **1 and (Arylmethylene)triphenyl phosphoranes **2** (Reactants Are Shown as “Anti” Conformers)**

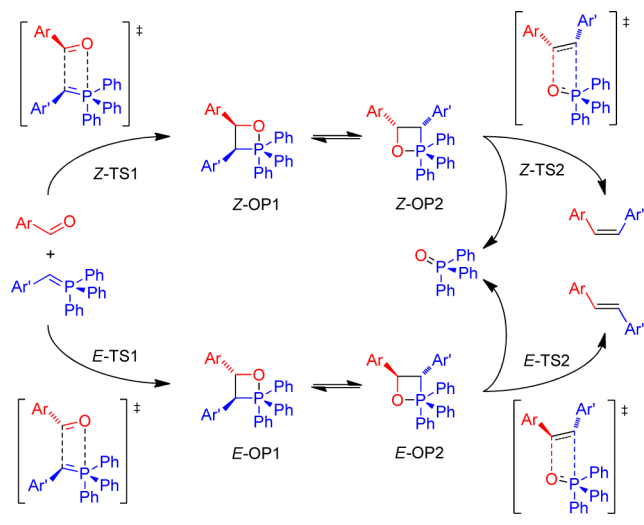


In the currently accepted mechanism (Scheme 2), proposed on the basis of combined experimental and theoretical data,³ the Wittig reaction between aryl-substituted ylides and aryl-substituted aldehydes, carried out under salt-free conditions, proceeds via an asynchronous transition state (TS1) leading to the four-membered oxaphosphetane intermediate (OP1). This cycloaddition is nonreversible and determines the stereoselectivity of the entire process. The OP1 structure undergoes pseudorotation, which brings the former ylidic P–C bond into an apical position, and the resulting oxaphosphetane OP2 undergoes cleavage to give the alkene and phosphine oxide via transition state TS2. This reaction pathway was successfully modeled for the reaction between benzaldehyde (**6-H**) and

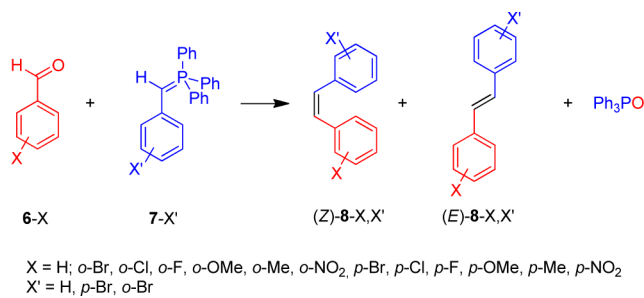
Received: July 30, 2013

Published: August 28, 2013

Scheme 2. The Currently Accepted Mechanism of the Wittig Olefination, Shown for the Reaction between an Aryl Aldehyde and an (Arylmethylene)triphenylphosphorane



Scheme 3. Scope of the Wittig Reaction between Benzaldehydes (6-X) and (Benzylidene)triphenylphosphoranes (7-X') Explored in This Work (for Brevity, Reactions Are Labeled as X/X', e.g., *o*-Br/H or H/H)



benzylidene-triphenylphosphorane (7-H) (Scheme 3) by the groups of Aggarwal and Harvey, who showed that the selectivities of many types of Wittig reactions could be satisfactorily reproduced by standard DFT techniques.^{26–28} In the present work, the B3LYP/6-31G**(DCM) level of theory was chosen as the principal computational method, where DCM stands for dichloromethane solvation modeled with the IEF PCM method (a detailed discussion of the methods used is given in the Supporting Information).

The initial analysis was focused on the synthetically relevant reaction between 2-bromobenzaldehyde (6-*o*-Br) and (2-bromobenzylidene)triphenylphosphorane (7-*o*-Br) (Scheme 3), which is known to afford 2,2'-dibromostilbene [8-*o*-Br]₂ with high *Z* selectivity (experimental *Z*:*E* ratio of 95:5⁷). As a consequence of ortho substitution, the potential energy surface of the *o*-Br/*o*-Br reaction becomes more complex than with unsubstituted reactants (i.e., 6-H + 7-H, denoted as H/H), necessitating more extensive conformational searches at all stages of the reaction (for further details, see the Supporting Information). Importantly, each ortho-substituted reactant has two accessible conformations, labeled anti and syn, characterized by different orientations of the reactive group relative to the C–Br bond. The anti conformers of 6-*o*-Br and 7-*o*-Br are defined respectively by OCCC(Br) and PCCC(Br) torsional angles of 180° (cf. structures 1 and 2 in Scheme 1). The anti

conformers are predicted to be more stable, with calculated syn – anti energy differences of 1.81 and 2.54 kcal/mol for 6-*o*-Br and 7-*o*-Br, respectively. Furthermore, it was found that the lowest-energy geometry of the *Z*-selective TS1 (Z-TS1, 5.95 kcal/mol) corresponds to the addition between anti-6-*o*-Br and anti-7-*o*-Br (*aa* addition). In the case of *E*-TS1, the *aa* addition and the *syn*-aldehyde, anti-ylide (*sa*) addition yield almost identical energies (8.56 and 8.42 kcal/mol, respectively). In view of the higher expected population of the anti-6-*o*-Br conformer, it can be assumed that both *Z*- and *E*-selective TS1 will preferentially occur through *aa* addition. The predicted stereoselectivity can be described in terms of $\Delta\Delta E^\ddagger = \Delta E^\ddagger(\text{Z-TS1}) - \Delta E^\ddagger(\text{E-TS1})$. The *o*-Br/*o*-Br reaction yields $\Delta\Delta E^\ddagger = -2.61$ kcal/mol, consistent with the experimentally observed *Z* selectivity. In contrast, a $\Delta\Delta E^\ddagger$ value of only 0.05 kcal/mol was obtained for the non-stereoselective H/H reaction.

The *aa* addition geometries optimized for the *o*-Br/*o*-Br reaction retain basic structural features of *Z*- and *E*-selective TS1 revealed in earlier work²⁷ (Figure 1). The addition is

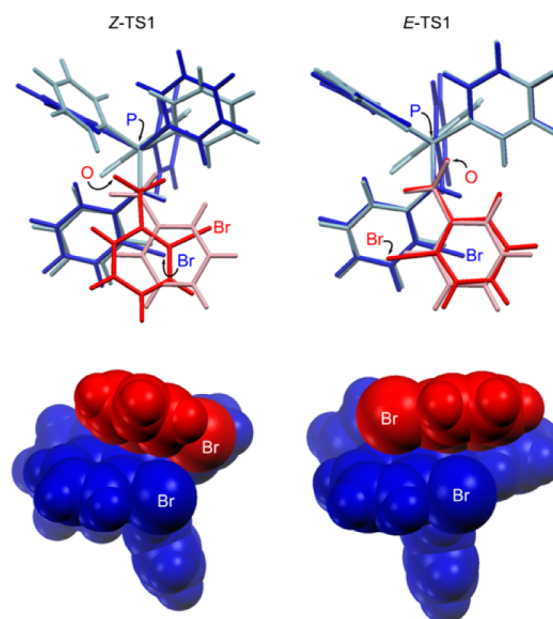


Figure 1. B3LYP/6-31G**(DCM) geometries of *Z*- and *E*-selective TS1 optimized for the *aa* addition between 6-*o*-Br (red) and 7-*o*-Br (blue). Top: view along the nascent C^a–C^y bond overlaid with the corresponding TS geometries for the H/H reaction (pink and light blue). Bottom: side view showing the relative orientations of the *o*-bromo substituents.

asynchronous (with late formation of the P–O bond), and in both Z-TS1 and E-TS1 the aldehyde oxygen is involved in a CH⋯O interaction with one of the P–Ph substituents. The E-TS1 geometries obtained for the *o*-Br/*o*-Br and H/H reactions are nearly superimposable and are characterized by relatively small puckering (PCCO torsion angles of –29° and –28°, respectively). In the case of the Z-TS1 structure, the effect of ortho-substitution is more significant: the aldehyde molecule is rotated around the axis of the nascent C^a–C^y bond, apparently minimizing steric interactions between the *o*-Br substituent and the P–Ph groups. As a consequence, the Z-TS1 structure becomes less puckered in the presence of ortho substituents (PCCO torsion angles of 72° and 86° for *o*-Br/*o*-Br and H/H, respectively). Importantly, in the Z-TS1 structure obtained for the *o*-Br/*o*-Br addition, no interaction between the ylidic

phosphorus and the aldehydic *o*-Br substituent is observed, in contrast to previously proposed interaction models.^{3,5,7,8,22} In fact, the shortest P...Br distances observed in the optimized TS1 conformations (see the Supporting Information) were those involving the ylidic *o*-Br group, and they were in the range expected for a van der Waals contact ($r_p + r_{Br} = 3.65 \text{ \AA}$).

Even though the anomalous *Z* selectivity of the *o*-Br/*o*-Br reaction is clearly demonstrated by the calculations described above, it is not immediately apparent how ortho-substitution affects the energetics of the reaction. To get a deeper understanding of these mechanistic aspects and separate possible steric and electronic effects, a detailed analysis of substitution effects was deemed necessary. To this end, the *Z*-TS1 and *E*-TS1 geometries were optimized for a number of differently substituted reactant pairs (Scheme 3; see the Supporting Information for complete data). The aldehyde substitution included both ortho and para derivatives and was varied over a large range of Hammett σ constants (from $-\text{OMe}$ to $-\text{NO}_2$). To probe the cooperative effect of ylide substitution, three derivatives, 7-H, 7-*o*-Br, and 7-*p*-Br, were included in the calculations. For consistency, it was assumed that the *aa* addition is operative in all cases, so the full potential energy surface was not investigated.

The resulting selectivity predictions, expressed in terms of $\Delta\Delta E^\ddagger$, are presented in Figure 2. Consistent with the

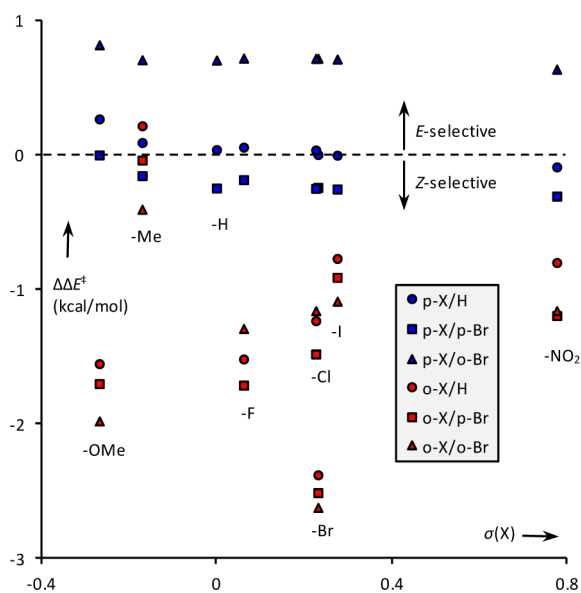


Figure 2. Differences between *Z*- and *E*-TS1 energy barriers ($\Delta\Delta E^\ddagger$) calculated for various combinations of substituents on aldehyde 6-*X* and ylide 7-*X'*. Negative $\Delta\Delta E^\ddagger$ values correspond to *Z* selectivity.

experimentally observed lack of *Z*/*E*-selectivity, the reactions between para-substituted benzaldehydes and ylides 7-H and 7-*o*-Br yield small absolute $\Delta\Delta E^\ddagger$ values (less than 0.5 kcal/mol), which are effectively independent of the $\sigma(X)$ parameter. Inclusion of an *o*-Br substituent on the ylide (*p*-*X*/*o*-*Br* series) is predicted to result in increased *E* selectivity, in agreement with literature data.⁷ The $\Delta\Delta E^\ddagger$ values obtained for reactions with ortho-substituted benzaldehydes are highly variable; however, moderate to high *Z* selectivity is predicted for all of the *o*-halogen substituents and the *o*-OMe group, in line with experimental observations,^{5–8} and for the *o*-NO₂ group, for which no systematic stereoselectivity analysis has been performed. Remarkably, the singular behavior of aldehyde 6-

o-Me, which does not induce the anomalous *Z* selectivity,^{5–7} is also reproduced by the calculations, indicating a smaller steric demand of the *o*-Me substituent. Cooperative selectivity enhancement via ylide ortho substitution is observed for some members of the *o*-*X*/*o*-*Br* series, but the effect is not systematic.

The present calculations correctly predict that electron-withdrawing groups on the benzaldehyde should accelerate the reaction.^{29,30} The opposite effect is consistently observed when an electron-withdrawing group (Br) is placed on the ylide. For reactions involving para-substituted aldehydes 6-*p*-*X*, the calculated *Z*- and *E*-TS1 energy barriers showed excellent linear correlations with substituent $\sigma(X)$ constants for all variants of ylide substitution (Figure S2 in the Supporting Information). The estimated reaction constants ρ are in the range 4.6–4.9, indicating somewhat larger sensitivity to aldehyde substitution than observed experimentally ($\rho \approx 2.8$ in tetrahydrofuran, 293 K⁵). Linear relationships between $\sigma(X)$ and ΔE^\ddagger are not observed for reactions involving ortho-substituted aldehydes. Importantly, however, the calculations predict 6-*o*-Cl and 6-*o*-OMe to react with 7-H faster than their para isomers and 6-*o*-Me to react slower than 6-*p*-Me, in agreement with available experimental data.⁵

A distortion/interaction ($\Delta E_d^\ddagger/\Delta E_i^\ddagger$) energy analysis^{31–35} performed on the optimized TS1 structures revealed that the anomalous *Z* selectivity observed with 6-*o*-*X* aldehydes originates from uncompensated variations of the distortion component ΔE_d^\ddagger . The latter quantity is defined as the sum of the energy contributions necessary to distort each isolated reactant molecule (aldehyde and ylide) into its transition state geometry, whereas $\Delta E_i^\ddagger = \Delta E^\ddagger - \Delta E_d^\ddagger$. Both ΔE_d^\ddagger and ΔE_i^\ddagger show a significant dependence on the electron-donating character of the *X* substituent. With decreasing $\sigma(X)$ values, the TS moves later along the reaction coordinate, resulting in an increase of the distortion component.³⁶ Consequently, there is a strong correlation between ΔE_d^\ddagger and the C^a–C^y distance that is particularly noticeable for *p*-*X*/*X'* reactions (Figure S6). In the case of para-substituted aldehydes, ΔE_d^\ddagger strongly favors *E* addition, but this energetic preference is balanced by the opposite influence of ΔE_i^\ddagger . This effect is illustrated in Figure 3, which shows how reactant substitution affects the distortion and interaction components of $\Delta\Delta E^\ddagger$, defined respectively as $\Delta\Delta E_d^\ddagger = \Delta E_d^\ddagger(\text{Z-TS1}) - \Delta E_d^\ddagger(\text{E-TS1})$ and $\Delta\Delta E_i^\ddagger = \Delta E_i^\ddagger(\text{Z-TS1}) - \Delta E_i^\ddagger(\text{E-TS1})$.

The introduction of an ortho substituent on the aldehyde (other than *o*-Me) causes a decrease in $\Delta\Delta E_d^\ddagger$ that is not fully compensated by an increase in $\Delta\Delta E_i^\ddagger$, resulting in enhanced *Z* selectivity. Because inductive and resonance effects are similar for corresponding *Z*- and *E*-TS1 structures, the $\Delta\Delta E^\ddagger$, $\Delta\Delta E_d^\ddagger$, and $\Delta\Delta E_i^\ddagger$ values should mainly reflect the differences in steric and field contributions to the energy barriers. While the realignment of C–X bond dipoles associated with changes in the PCCO angles can influence ΔE^\ddagger to some extent,^{26,27} the large $\Delta\Delta E_d^\ddagger$ values exhibited by the majority of *o*-*X*/*X'* reactions indicate that a steric effect is operative.^{36,37} Inspection of the optimized geometries suggests that the major steric contribution might come from the 1,2-interaction between the ylidic and aldehydic substituents, which is instrumental in determining the stereoselectivity of many types of Wittig reactions.²⁷ In the *E*-selective TS1, the aldehydic ortho substituent is eclipsed by the ylidic aryl group, resulting in an increased steric repulsion (Figure 1). In the puckered *Z*-TS1 structures, the *o*-*X* group is tilted away from the ylidic aryl, and

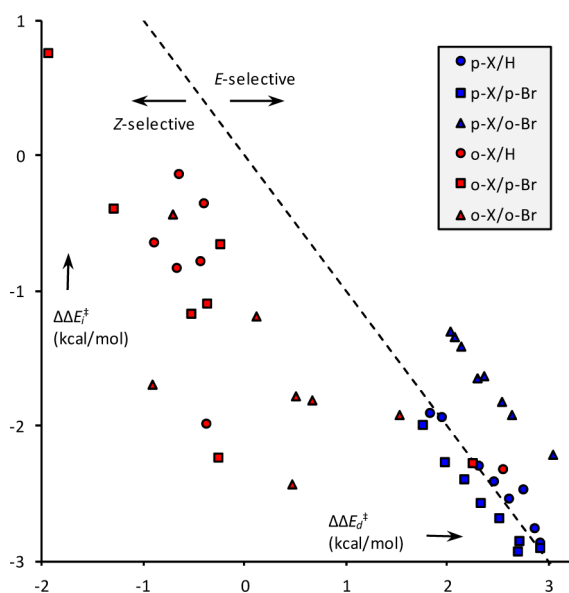


Figure 3. Differential distortion/interaction energy analysis for the reactions listed in Scheme 3. $\Delta\Delta E^\ddagger = \Delta\Delta E_d^\ddagger + \Delta\Delta E_i^\ddagger$. The dashed line corresponds to $\Delta\Delta E^\ddagger = 0$ kcal/mol.

the structure is sufficiently flexible to avoid 1,3-interactions with P–Ph groups by reduction of the puckering angle PCCO, which takes values in the 60–79° range.

The present results demonstrate that in the Wittig synthesis of *o*-substituted stilbenes, TS1 geometries are more conservative than previously assumed⁸ and a common structural model is applicable to a wide range of reactants. The anomalous stereoselectivity observed in this reaction is governed by steric effects and should not be explained in terms of ancillary phosphorus–heteroatom interactions. The latter hypothesis, while elegant, was in fact inconsistent with some experimental observations. For instance, it did not explain why reactions with 2,6-dichlorobenzaldehyde (6-2,6-Cl₂) are markedly *E*-selective⁷ rather than *Z*-selective, even though this aldehyde should be similar to 6-*o*-Cl in its P⋯Cl bonding capability. The behavior of 6-2,6-Cl₂ is, however, correctly reproduced by the present approach, which yields a $\Delta\Delta E^\ddagger$ value of +1.71 kcal/mol for the reaction between 6-2,6-Cl₂ and 7-H. This result further indicates that reliable predictions of selectivity in Wittig reactions can be made on the basis of cost-effective DFT calculations as long as an accurate reactivity model is available. Such calculations, which can be rapidly performed even for large systems, can be used to predict the outcome of nontrivial reactions and provide assistance in the design of new olefination reagents.

■ ASSOCIATED CONTENT

● Supporting Information

Computational details, data tables, and additional figures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the National Science Center (Grant N N204 199340) is kindly acknowledged. Quantum-chemical calculations were performed in the Wrocław Center for Networking and Supercomputing.

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