Theoretical Rationale for Regioselection in Phosphine-Catalyzed Allenoate Additions to Acrylates, Imines, and Aldehydes
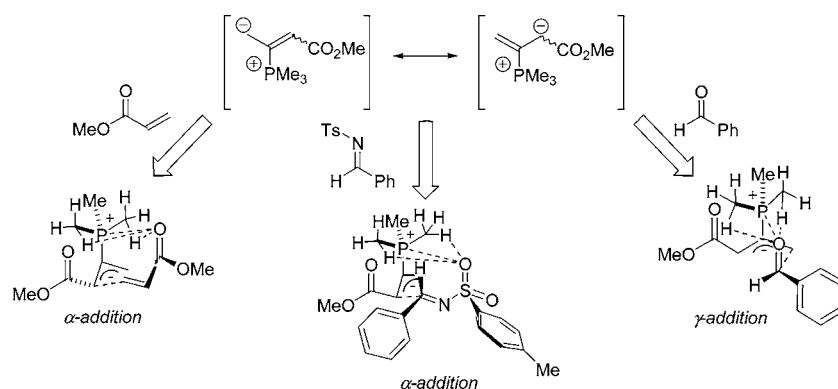
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ABSTRACT

A rationale for regioselection in phosphine-promoted annulations of acrylates, imines, and aldehydes with allenoates has been developed using computation at the B3LYP/6-31G(d) level of theory. The computed transition states revealed that Lewis acid activation, strong hydrogen bonding (H-bonding), and minimization of unfavorable van der Waals contacts are the guiding factors responsible for regioselection. An excellent level of correlation between the calculated regioselectivities and experiment was observed.

The past decade has witnessed the introduction of numerous phosphine-mediated annulation methodologies for the preparation of biologically and medicinally useful carbo- and heterocyclic products.[1] In this regard extensive investigation has provided effective synthetic methodology for the [3 + 2] annulations of activated allenic esters with electron-deficient imine and acrylate acceptors. It is now well established that acrylate **5** and imine **8** undergo predominant α-addition to zwitterionic intermediate **1**↔**2** (Scheme 1,

pathways A and B).[2,3,4] More recently a γ-selective [2 + 2 + 2] annulation of aldehyde **11** has been reported to afford

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(1) For recent reviews, see: (a) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035−1050. (b) X. Lu, C. Zhang, Z. Xu, *Acc. Chem. Res.* **2001**, *34*, 535−544 and references therein.

(2) Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 2906−2908. To facilitate computation, methyl 2,3-butadienoate and trimethylphosphine were substituted for reagents ethyl 2,3-butadienoate and tributylphosphine used experimentally.
(3) Xu, Z.; Lu, X. *J. Org. Chem.* **1998**, *63*, 5031−5041. For reasons of computational efficiency trimethylphosphine was used instead of tributylphosphine for the calculation of imine regioselectivity.
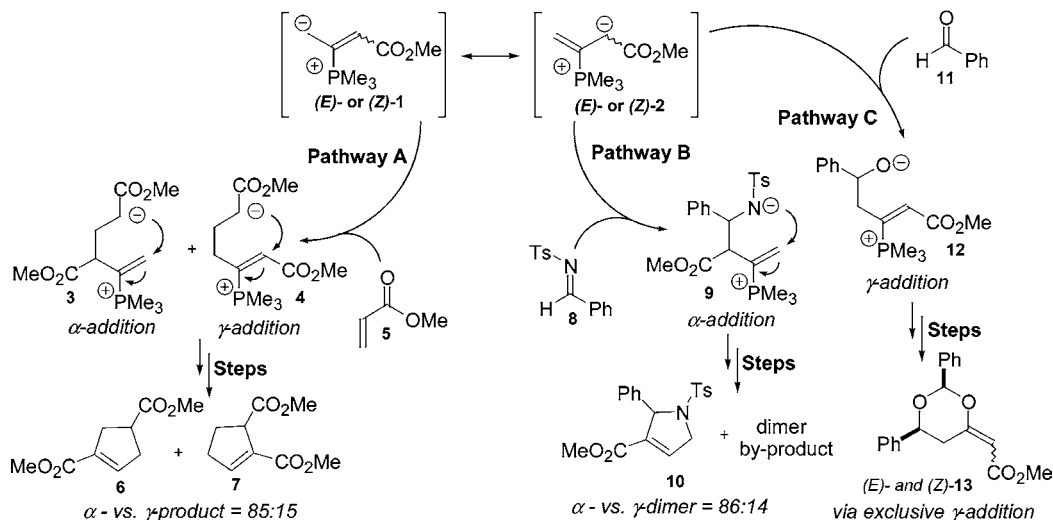(4) Recently one of our groups has reported a variant of these reactions that affords exclusively six-membered tetrahydropyridines of γ-addition; see: Zhu, X.-F.; Lan, J.; Kwon, O. *J. Am. Chem. Soc.* **2003**, *125*, 4716−4717. Expanding upon this earlier work, Wurz and Fu have developed a catalytic enantioselective methodology for the preparation of chiral piperidine derivatives; see: Wurz, R. P.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 12234−12235.

dioxanylidene (*E*)-**13** and (*Z*)-**13** (*E:Z* > 8:1) with exclusive *cis*-diastereoselectivity (Scheme 1, pathway C).[5]

Intrigued by these differences in acrylate, imine, and aldehyde regioselectivity, we have investigated the regioselective addition steps of these reactions using Density-Functional Theory (DFT) at the B3LYP[6]/6-31G(d)[7] level as implemented in the Gaussian 98 and 03 series of programs.[8] Reported herein is a rationale for regioselection in phosphine-promoted annulations of allenoates.[9]

Initial examination of the regiodetermining transition states for acrylate addition α-**TS1** and γ-**TS1** revealed that both structures possess distorted six-membered chair conformations (Figure 1, colored blue).[10] In each case the direct products **3** and **4** of α-**TS1** and γ-**TS1** were zwitterionic intermediates of stepwise additions, Scheme 1. To further confirm the stepwise nature of these additions, subsequent transition states for ring closure were computed, and the activation barriers were found to be less endergonic than α-**TS1** and γ-**TS1** by 14.3 and 16.4 kcal/mol, respectively.[11] It is also noted that repeated attempts to locate unconstrained transition state geometries for concerted [3 + 2] cyclization

proved unsuccessful. With specific reference to the preferred α-addition mode α-**TS1**, a C···C bond forming distance of 2.00 Å was measured, and the approaching acrylate resided in a gauche orientation (dihedral$_{(C1-C2-C3-C4)}$ = 44.4°) relative to zwitterionic enolate **1↔2**.[12] The decisive factors responsible for the greater stability of α-**TS1** are attributed to formation of a stabilizing $P^+ \cdots O^{\delta-}$ interaction (3.31 Å),
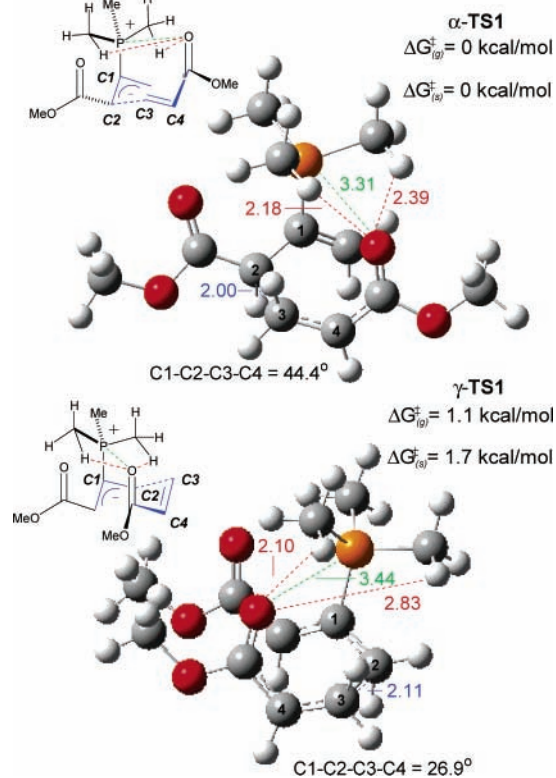

Figure 1. Favored regioselective transition states α-**TS1** and γ-**TS1** for acrylate addition.

(5) To our knowledge this is the first reported example of a phosphine-catalyzed addition of allenoates to aldehydes; see: Zhu, X.-F. Henry, C. E.; Wang, J.; Dudding, T.; Kwon, O. *Org. Lett.* **2005**, *7*, 1387−1390.

(6) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652. (b) Stephens, P. J.; Devlin, F. J.; Chabalowski, G. C.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623−11627. (c) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1987**, *37*, 785−789.

(7) (a) Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P. v. R. *J. Comput. Chem.* **1983**, *4*, 294−301. (b) Frisch, M. J.; Pople, J. A.; Binkley, J. S. *J. Chem. Phys.* **1984**, *80*, 3265−3269.

(8) See Supporting Information for a complete list of authors of these programs.

(9) To further validate experiment, we are currently investigating the regiochemical outcome of these additions when triphenylphosphine is used in place of trimethylphosphine. In addition a full disclosure of the reaction pathways of phosphine-mediated [2 + 2 + 2] aldehyde and [3 + 2] imine/acrylates additions will be reported by our groups shortly.

(10) Low energy transition state structures for acrylate, imine, and aldehyde additions were located through potential energy surface (PES) scans.

(11) For ring closure transition states α-**TS4** and γ-**TS4**, see Supporting Information.

strong bifurcated H-bonds[13] (colored red) with measured distances of 2.18 and 2.39 Å, and minimization of unfavorable van der Waals contacts resulting from the 1,4-diequatorial arrangement of the enolate ester and methoxy portion of the acrylate ester. In contrast the 26.9° dihedral$_{(C1-C2-C3-C4)}$ angle in γ-**TS1** results in a repulsive steric interaction between the acrylate and enolate esters.

Structural manifestation of this effect surfaces in elongation of the forming C···C bond by 0.11 Å, lengthening of the P$^+$···O$^-$ distance (3.44 Å) and a noticeably longer H-bond which is elongated by 0.44 Å with respect to the corresponding distance found in α-**TS1**. Based on the calculated difference in $\Delta G^{\ddagger}$ values of 1.1 kcal/mol in vacuo and 1.7 kcal/mol in benzene ($\epsilon = 2.27$) for α- versus γ-addition, a 95:5 product ratio is predicted, which is consistent with experiment (α- versus γ-addition 85:15).[14]

As for imine additions, the distinct preference for a distorted five-membered envelope transition state assembly (colored blue) in low energy α-**TS2** results from favorable Lewis acid activation and minimization of unfavorable van der Waals interactions (Figure 2).[15] Similarly, in a fashion analogous to acrylate addition, only stepwise reaction pathways could be located and the activation barriers for addition structures α-**TS2** and γ-**TS2** were more energetically demanding than those for ring closure via α-**TS5** and γ-**TS5** by 8.93 and 7.72 kcal/mol.[16] In the context of Lewis acid activation, increased electron density at the oxygen proximal to phosphorus due to anomeric donation of the imine nitrogen lone pair into the S–O* anti-bond ($n_N \rightarrow \sigma_{S-O}$*)[17] leads to enhanced P$^+$···O$^{\delta-}$ (3.35 Å) coordination.[18] In addition the *trans* relationship of the imine phenyl substituent and enolate ester in α-**TS2** (dihedral$_{(C1-C2-C3-N)}$ = 57.8°) appears optimal for minimizing steric repulsion. With specific reference to the regiochemical outcome of this reaction set, α-addition is favored by 0.5 kcal/mol in vacuo and 1.2 kcal/mol in benzene. It is noted that the calculated (86:14) preference for α-addition is consistent with experiment.[19]
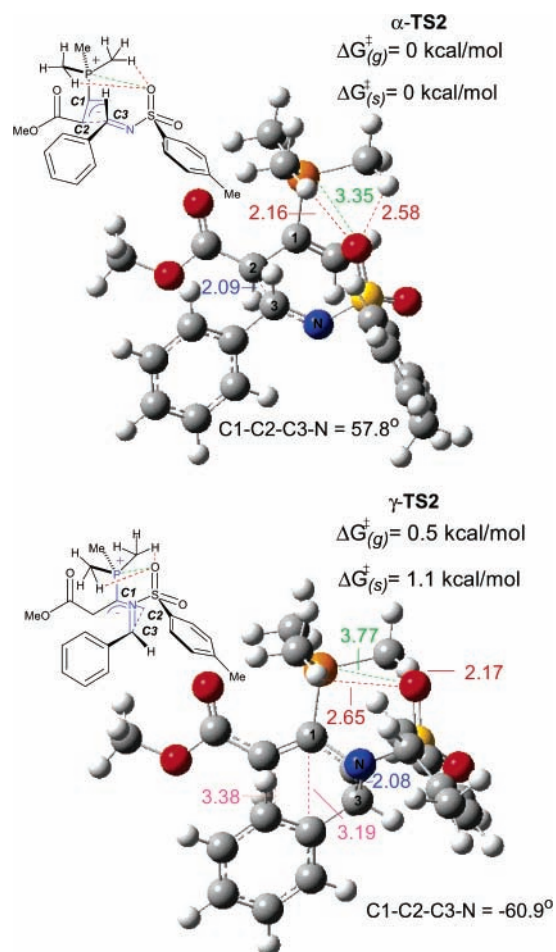

Figure 2. Favored regioselective transition states α-**TS2** and γ-**TS2** for imine addition.

An exhaustive survey of the potential energy surface (PES) for aldehyde addition located low energy α- and γ-transition states γ-**TS3** and α-**TS3** (Figure 3). Detailed examination of energetically preferred γ-**TS3** revealed that the transition state is relatively late on the reaction coordinate with a C···C bond forming distance of 1.86 Å. Of specific interest is the close approach of aldehyde and enolate components in a five-membered envelope arrangement (colored blue) that reinforces the need for minimizing steric strain. Importantly, the *anti*-arrangement between the aldehyde aryl substituent and methoxy carbonyl group of the approaching enolate accommodates this requirement (dihedral$_{(C1-C2-C3-O)}$ = 62.2°). Further stabilization of γ-**TS3** is provided through polarized H-bond contacts between the phosphonium α-hydrogens and negatively charged aldehyde oxygen (2.05 and 2.24 Å, colored red). Of additional benefit is a P$^+$···O$^{\delta-}$ bond (3.11 Å), which is measurably shorter than comparable contacts found within low energy imine α-**TS2** (3.35 Å) and acrylate α-**TS1** (3.31 Å).

(12) Ground-state optimization of the possible enolate geometries revealed that the (Z)-isomeric configuration between the ester and phosphonium groups is energetically preferred; see Supporting Information. For a discussion on the divergent reactivity of the (E)- and (Z)-configurations of zwitterionic intermediate **1↔2**, see: Zhu, X.-F.; Schaffner, A.-P.; Li, R. C.; Kwon, O. *Org. Lett.* **2005**, *7*, 2977–2980.

(13) For a recent discussion regarding the strength of R$_3$N$^+$–C–H··· O=C hydrogen bond interactions, see: Cannizzaro, C. E.; Houk, K. N. *J. Am. Chem. Soc.* **2002**, *124*, 7163–7169.

(14) Calculated using the CPCM solvation model. (a) Barone, B.; Cossi, M. *J. Phys. Chem.* **1998**, *102*, 1995–2001. (b) Barone, B.; Cossi, M.; Tomasi, J. *J. Comput. Chem.* **1998**, *19*, 404–417.

(15) An extensive conformation search evaluating both *re*- and *si*-imine facial selectivity identified α-**TS2** and γ-**TS2** as the lowest energy transition state structures for α- and γ-addition.

(16) Thermochemical data and coodinates for zwitterionic intermediates **9** and **14** as well as ring closure transition states α-**TS5** and γ-**TS5** can be found in Supporting Information.

(17) Redistribution of charge density from nitrogen (Mulliken charge = −0.55) to the sulfone oxygen closest to phosphorous (Mulliken charge = −0.63) via n $\rightarrow \sigma_{S-O}$* donation has a second-order perturbation energy of mixing 9.37 kcal/mol based on NBO analysis.

(18) For previous theoretical discussions of anomeric sulfonamide nitrogen lone pair donation into the S–O* bond, see: Lee, P. S.; Du, W.; Boger, D. L.; Jorgensen, W. L. *J. Org. Chem.* **2004**, *69*, 5448–5453 and references therein.
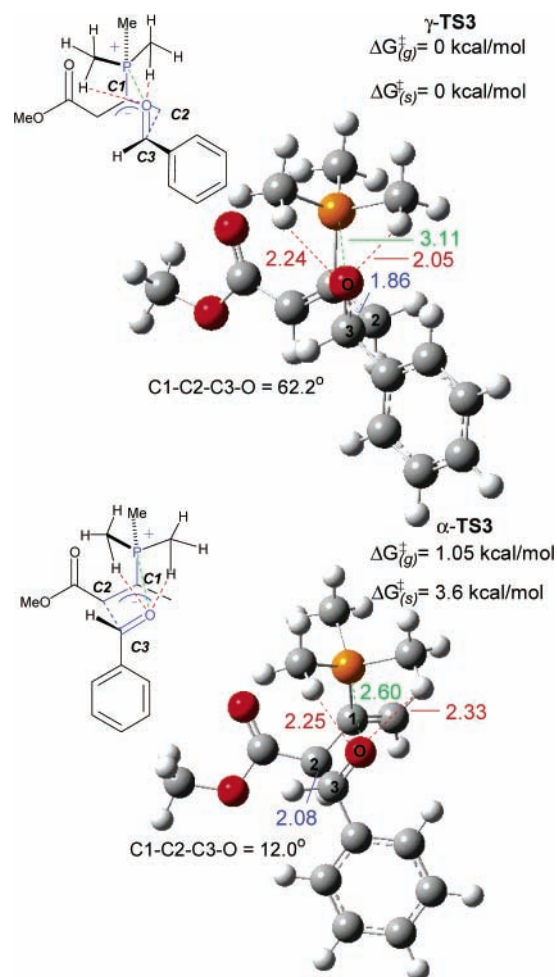
(19) Experimentally an 83% yield of the α-addition product and 13% yield of a three-component adduct resulting from initial γ-addition is isolated. This product distribution corresponds to a ratio of 84:16.

Figure 3. Favored regioselective transition states α-**TS3** and γ-**TS3** for aldehyde addition.

For the α-mode of addition, repulsive steric contacts dominate. An eclipsing conformation between the approach-

ing aldehyde carbonyl and enolate C—C bond contained within the five-membered transition state (dihedral$_{(C1-C2-C3-O)}$ = 12.0°) forms the basis of repulsive van der Waals contacts in α-**TS3** and results in a lengthened C···C of 2.08 Å. The short P$^+$···O$^{\delta-}$ distance of 2.60 Å is indicative of strong Lewis acid coordination and provides stabilization to α-**TS3**. A counterintuitive finding considering the short P$^+$···O$^{\delta-}$ distance in α-**TS3** is the presence of longer H-bond distances (colored red) of 2.25 and 2.33 Å. Ultimately the imbalanced steric demand placed upon C···C bond formation in γ-**TS3** leads to γ-addition being favored by 3.6 kcal/mol in CHCl$_3$ and 1.1 kcal/mol in vacuo, providing a calculated product ratio of 99.8:0.2 in solution, which is in accord with experiment.[5]

To summarize, application of hybrid density functional theory at the B3LYP/6-31G(d) level of theory has provided a rationale for regioselection in phosphine-promoted annulations of acrylates, imines and aldehydes. The theoretical models derived have identified three factors, (1) Lewis acid activation, (2) strong H-bonding, and (3) minimization of unfavorable van der Waals contacts, as key for determining regioselection. Of particular interest is the identification of anomeric $n_N \rightarrow \sigma_{S-O}^*$ donation which contributes to stabilization of α-**TS2** in imine additions. Noteworthy is the observation that the mechanistic rationale offered for regioselective acrylate, imine, and aldehyde additions is consistent with experiment.

Supporting Information Available: Full Gaussian references, Cartesian coordinates, and energies of reported structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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