Phosphine triggered [3+2] allenoate–acrylate annulation: a mechanistic enlightenment

Evan Mercier,[a] Branden Fonovic,[a] Chris Henry,[a,b] Ohyun Kwon[b,*] and Travis Dudding[a,*]

[a]*Department of Chemistry, Brock University, St. Catharines, Ont., Canada LS2 3A1*
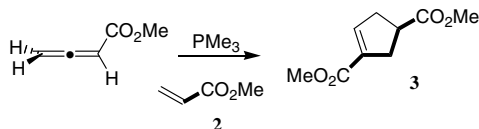[b]*Department of Chemistry and Biochemistry, University of California, Los Angeles, CA 90095-1569, United States*

Abstract—A mechanistic study of phosphine-mediated [3+2] annulation of allenoate and acrylate is presented. The insight gained has identified that (1) [3+2] cycloaddition proceeds through a stepwise mechanism and (2) the involvement of a molecule of water, which services as a proton-shuttle, is essential for annulated product formation.
© 2007 Elsevier Ltd. All rights reserved.

Since its inception by Lu and co-workers in 1995 phosphine-mediated [3+2] allenoate–acrylate annulation has served as a powerful resource for the construction of functionalized carbocycles.[1,2] As testimonal to the versitility of this [3+2] construct in modern chemical synthesis Lu, Krische and Pyne have utilized this methodology in natural product syntheses.[3] Integrated within the timeline of this evolving subset of chemical ingenuity Zhang[4] and Fu[5] have also developed enantioselective variants of this reaction.

To further complement this productive area of synthesis targeting biologically and medicinally important carbo- and heterocyclic templates, we have recently engaged in a combined experimental and theoretical program to rationalize the mechanistic events governing phosphine catalyzed allenoate additions.[6] Positioned within this directed program of research we present herein a mechanistic study of phosphine-mediated [3+2] allenoate–acrylate annulation computed at the B3LYP[7]/6-31G(d)[8,9] level (Scheme 1). Single point solvation calcu-

lations were performed on all stationary points using the implicit CPCM solvation model[10] with cavities containing explicit spheres around hydrogen atoms. The highlighted work suggest phosphine triggered [3+2] cycloadditions of acrylates and allenoates proceed by way of stepwise mechanisms and require the involvement of molecular water.

Simply, the reaction initiates with addition to (*s-cis*)-**1** and (*s-trans*)-**1** to generate isomeric enolates **5$_a$** and **5$_b$** via transition states **TS1$_a$** ($\Delta G^{\neq} = 17.4$ kcal/mol) and **TS1$_b$** ($\Delta G^{\neq} = 17.5$ kcal/mol) possessing P$\cdots$C bond forming distances of 2.24 and 2.12 Å, respectively (Scheme 2). It is briefly noted that although the formation of at least four geometrically distinct local minima **5$_a$**, **5$_b$**, **5$_c$**, and **5$_d$** having relative free-energies of 0, 7.07, 6.77, and 9.36 kcal/mol, are conceivable only **5$_a$** and **5$_b$** are observed upon optimization of **TS1$_a$** and **TS1$_b$** to products. Within the context of a weighted Boltzmann distribution of states enolate **5$_a$** represents >99.99% of the population. A set of IRC[11] calculations were conducted starting from transition states **TS1$_a$** and **TS1$_b$** the results of which confirmed that zwitterions **5$_a$** and **5$_b$** were indeed the direct products of phosphine addition.[12] The origin of tourquoselective formation of **5$_a$**[13] appears assignable to transition state stabilization resulting from P$^+$–(CH$_2$)–H$\cdots^{-\delta}$OH-bonding between the phosphonium α-hydrogens and ester carbonyl oxygen.[14]

The next step of the reaction mechanism traverses regioselective rate determining C–C bond forming transition state **TS2** ($\Delta G^{\neq} = 17.9$ kcal/mol).[15] Structurally, **TS2** is
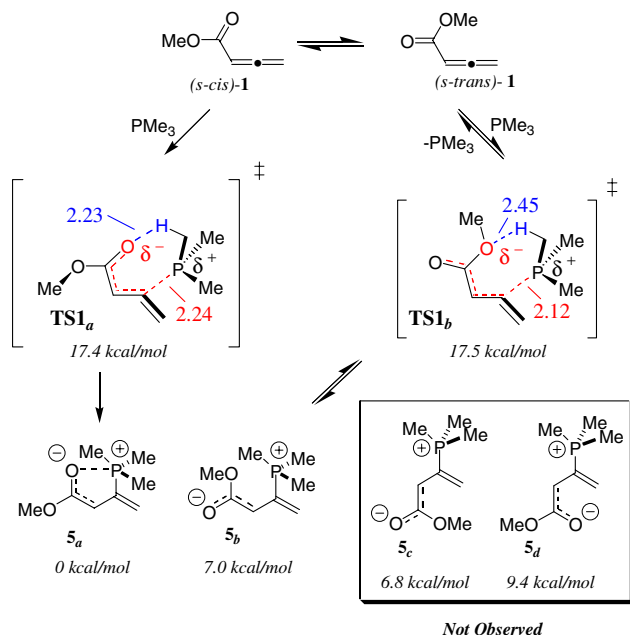
Scheme 1. Trimethylphosphine catalyzed annulation of allenoate and acrylate.

* Corresponding authors. Tel.: +1 908 688 5550 (T.D.); e-mail: tdudding@brocku.ca

Scheme 2. Selective formation of enolate 2_a. Distances in angstroms (Å) and relative energies in kcal/mol.

best defined as a distorted six-membered chair conformation possessing a C···C bond forming distances of 2.00 Å. Aside from the highlighted metrics and of greater significance with respect to fundamental chemical understanding is the observed stepwise nature of this cycloaddition process as optimization of **TS3** afforded zwitterionic minimum **6**.

Following this initial mechanistic insight we were intrigued as to if a concerted [3+2] cycloaddition transition state was energetically feasible. To this end transition state geometries for concerted addition were sought after. Despite successful optimization of a transition state using constrained C···C bond forming distances, repeated attempts to locate an unconstrained first-order saddle point proved unsuccessful. The latter is of particular interest as current mechanistic dogma has interpreted this reaction as being [3+2] concerted in nature.[16]

Subsequent ring closing of charge-separated intermediate **6** (Mulliken charges on carbon atoms involved in bond formation: −0.359, +0.613) proceeds through an early[17] low barrier ($\Delta G^{\neq} = 2.14$ kcal/mol) transition state **TS3**, which showcases a noticeably elongated C···C bond forming distance of 2.56 Å. The direct resultant of **TS3**, intermediate **7**, resides 17.5 kcal/mol lower in energy on the potential energy surface (PES) and deserves of additional comment. Of particular interest was the question arrived at after a brief detailing of assignable metrics, 'Was the canonical form of intermediate **7** best described as a hypervalent phosphorus species ($R_3P{=}C$) or a charge-separated phosphonium ylide ($R_3P^{+}{-}C^{-}$)?' Resolution to this uncertainty was secured in the framework of computed Wiberg bond indices from which it was concluded that **7** more closely resembles a charge-separated zwitterion ($C^{-}···^{+}P$, 1.71 Å, Wiberg bond index 1.21).[18]

At this stage in the reaction mechanism it was initially envisioned that regeneration of catalytic phosphine from α-anion **7** involved a thermal, formally symmetry-forbidden,[19] concerted 1,2-proton shift resulting in the formation of β-anion **9** followed by a *syn*-periplaner $E1_{cb}$-elimination of trimethyl phosphine. However, upon location of transition state **TS4** corresponding to suprafacial $[_{\sigma}2_s + _{\omega}2_s]$ proton migration the likelihood of such a process was judged unlikely based on the demanding endergonicity of this process ($\Delta G^{\neq} = 37.58$ kcal/mol).[20] Reasoned as well, was the involvement of an intermolecular exchange sequence involving two molecules of α-anion **7**. However, this conceptual possibility was ruled improbable as a transition state structure suitably positioning a matched pair of α-anions toward coupled proton transfer to yield a set of β-anion intermediates could not be located despite repeated attempts.

Drawn from the above insight an alternative mechanistic route, namely, a stepwise proton-shuttle relay sequence facilitated by a molecule of water, was investigated.[21] It was hypothesized that adventitious water would provide the necessary reagent compliment for the conversion of α-anion **7** to β-anion **9** (Fig. 1).

Following this line of reasoning the calculated pathway for 1,2-proton migration from the phosphonium C_{α}- to C_{β}-(sp^3)-methine carbon centers commences with water mediated protonation of α-anion **7** by way of **TS5** ($\Delta G^{\neq} = 8.3$ kcal/mol) generating intimate-ion complex **8** (Fig. 2). A detailed inspection of **TS5** revealed that the major factors contributing to transition state stabilization were assignable to the presence of two favorable equidistant $P^{+}{-}CH_2{-}H···^{-}OH$ (2.06 Å) H-bond contacts lying between a pair of methyl phosphonium α-hydrogens and the short-lived hydroxide species. To further probe this mechanistic step, a series of experimental studies involving the addition of water were undertaken. In this regard, phosphine catalyzed annulations of ethyl allenoate with methyl acrylate were carried out with and without the addition of one equivalent of water. Based upon this variable reaction set no rate enhancement was observed. It is noteworthy that these results are consistent with calculated findings which suggest that C–C bond formation is rate determining and product formation is necessarily mediated by molecular water.

To gain a more enriched understanding of the electronic effects governing this process coupled with an interest in having a numerical measure of stabilization assignable to $P^{+}{-}CH_2{-}H···^{-}OH$ bonding in **TS5**, a natural bond orbital (NBO)[22] analysis was conducted, which concluded that the stability gained from these interactions equated to 10.69 and 8.3 kcal/mol, respectively. With regard to the pertinent geometric features of intermediate **8**, the hydroxide ion sits positioned within a network of four stabilizing H-bonding contacts comprised of two bridging $C{-}H···^{-}OH$ interactions between the C_{α}- and C_{β}-(sp^3)-methine hydrogens (distances = 2.02, 2.1 Å) and a pair of $P^{+}{-}CH_2{-}H···^{-}OH$ contacts (distances = 1.90, 2.04 Å). Subsequent drifting of the hydroxide toward the C_{α}-(sp^3)-methine hydrogen leads to deproto-
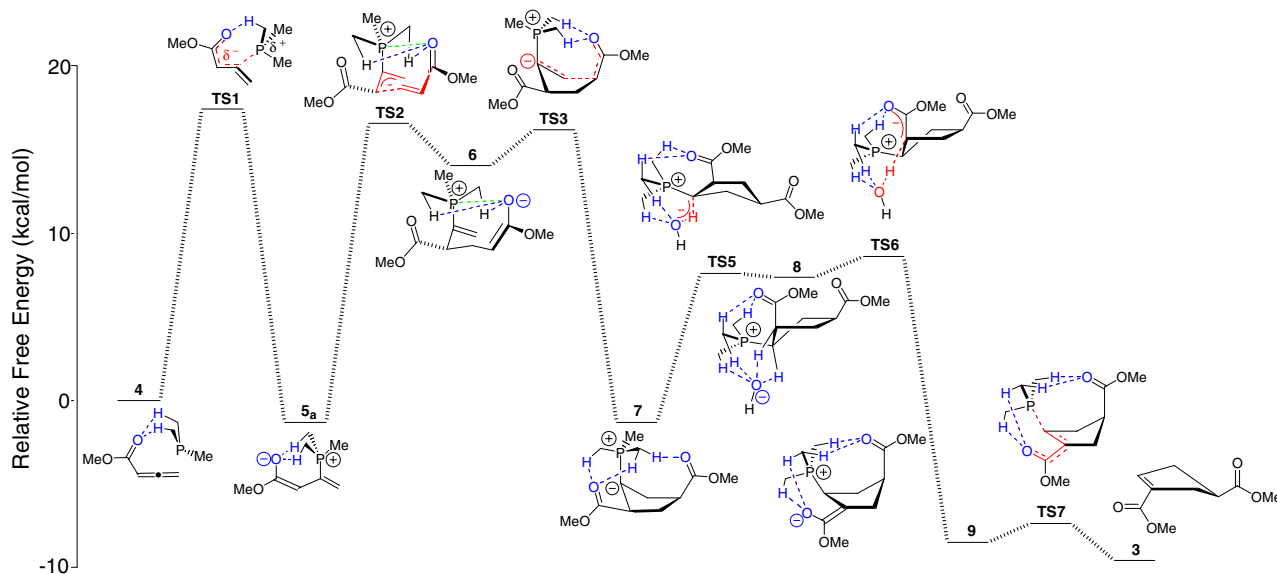
Figure 1. Mechanistic free-energy profile of trimethylphosphine triggered [3+2] allenoate–acrylate annulation. Bond making/breaking events are colored red and hydrogen bond interactions are colored blue.
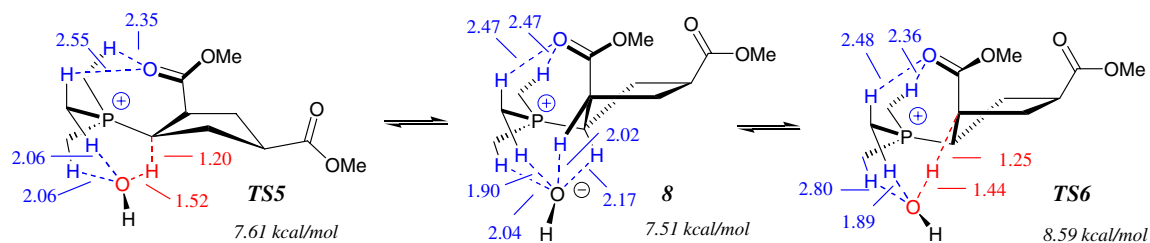

Figure 2. Geometries of stepwise, water assisted proton transfer. Bond making/breaking events are colored red and hydrogen bond interactions blue. Selected distances are in angstroms (Å).

nation transition state **TS6** ($\Delta G^{\neq} = 1.08$ kcal/mol), having measured $C^{\delta-} \cdots H^{+} \cdots {}^{-\delta}OH$ bond making/breaking distances of 1.44 and 1.25 Å. The direct product of proton transfer is a hydrated complex which, after dissociation of molecular water, affords zwitterion **9** in what reduces to an overall exergonic process worth 17.06 kcal/mol.

Regarding zwitterion **9**, the deprotonated phosphonium β-carbon has undergone a ($sp^3 \rightarrow sp^2$)-rehybridization leading to delocalization of the resultant anion into the adjacent ester group. Associated with this transformation, the ester and phosphonium substituents align in manner allowing for the formation of a stabilizing $P^{+} \cdots {}^{-\delta}O$ interaction in what visually appears to be a distorted five-membered-envelope geometry. Intrigued as to the origin of the preferred linear orientation of the $P^{+} \cdots {}^{-\delta}O$ dipoles the respective bond paths defined by the electron density ρ (rho) in zwitterion **9** were examined within the framework of Bader's atoms-in-molecules theory.[23] Two bond critical points attributed to electrostatic $P^{+} \cdots {}^{-\delta}O$ interactions ($\nabla^2\rho(r_c) > 0$) and four critical points corresponding to covalent ($\nabla^2\rho(r_c) < 0$) P^{+}–C bonds were identified as the contributing factors leading to stabilization in **9**.

The end game of the highlighted [3+2] annulation sequence appears driven by donation of electron density from the resonance stabilized β-anion **9** into the σ^*_{P-C} bond leading to P–C bond scission (Fig. 3). Phosphine elimination occurs through transition state **TS7** possessing an 8.44 kcal/mol activation barrier. This geometry is characterized by a noticeably elongated P···C distance of 2.05 versus 1.91 Å in **9** reflective of phosphine elimination and contraction of the C_α–C_β bond distance from 1.49 to 1.45 Å, which is indicative of increasing C=C bond character. Ultimately, the formation of annulated
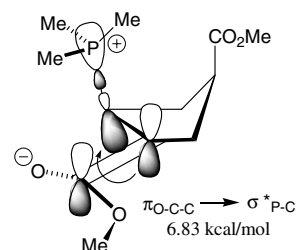

Figure 3. NBO donations in zwitterion **9** promoting phosphine elimination.

product **3** results in a reaction profile that in sum total is exergonic by 9.6 kcal/mol.

The theoretical study presented suggests, contrary to popular opinion, that phosphine triggered allenoate–acrylate annulations proceed by stepwise rather than concerted mechanisms to form a cyclic zwitterionic ylide intermediate such as **7**. More fundamentally, it has been realized that a molecule of water is required for the final conversion of cyclic ylide **7** to β-phosphonium α-enolate **9**. It is noted that the involvement of catalytic water in the proton transfer process has broad implications in the interpretation of reaction mechanisms and development of new phosphine-catalyzed reactions of allenes, as most mechanistic proposals of phosphine-mediated [3+2] allenoate–acrylate cycloadditions involve proton transfer processes.[24]

Acknowledgments

Supplementary data

Supplementary data (full Gaussian references, Cartesian coordinates and energies of reported structures) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.03.030.

References and notes

1. Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 2906–2908.
2. For reviews on phospine-catalyzed reactions of allenoates see: (a) Lu, X.; Du, Y.; Lu, C. *Pure Appl. Chem.* **2005**, *77*, 1985–1990; (b) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035–1050; (c) Lu, X.; Zhang, C.; Zu, Z. *Acc. Chem. Res.* **2001**, *34*, 535–544.
3. For highlighted explains of [3+2] phosphine-mediated allenoate–acrylate annulations in natural product synthesis, see: (a) Du, Y.; Lu, X. *J. Org. Chem.* **2003**, *68*, 6463–6465; (b) Wang, J.-C.; Krische, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5855–5857; (c) Pham, T. Q.; Pyne, S. G.; Skelton, B. W.; White, A. H. *J. Org. Chem.* **2005**, *70*, 6369–6377.
4. Zhu, G.; Chen, Z.; Jiang, Q.; Xiao, D.; Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 3836–3837.
5. Wilson, J. E.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1426–1429.
6. (a) Dudding, T.; Kwon, O.; Mercier, E. *Org. Lett.* **2006**, *8*, 3643–3646; (b) Zhu, X.-F.; Henry, C. E.; Wang, J.; Dudding, T.; Kwon, O. *Org. Lett.* **2005**, *7*, 1387–1390; (c) Zhu, X.-F.; Schaffner, A.-P.; Li, R. C.; Kwon, O. *Org. Lett.* **2005**, *7*, 2977–2980; (d) Tran, Y. S.; Kwon, O. *Org. Lett.* **2005**, *7*, 4289–4291; (e) Zhu, X.-F.; Henry, C. E.; Kwon, O. *Tetrahedron* **2005**, *61*, 6276–6282; (f) Zhu, X.-F.; Lan, J.; Kwon, O. *J. Am. Chem. Soc.* **2003**, *125*, 4716–4717.
7. (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.
8. (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. S. *J. Chem. Phys.* **1984**, *80*, 3265–3269.
9. Calculations were performed using the GAUSSIAN 03 suite of programs. See Supplementary data for a complete list of authors of these programs.
10. (a) Barone, V.; Cossi, M. *J. Phys. Chem. A* **1998**, *102*, 1995–2001; (b) Cossi, M.; Rega, N.; Scalmani, G.; Barone, V. *J. Comp. Chem.* **2003**, *24*, 669–681.
11. (a) Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154–2161; (b) Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523–5527.
12. The barrier for **TS1$_a$**↔**TS1$_b$** interconversion via ester rotation is calculated to be 19.5 kcal/mol while reversion of enolate **TS1$_b$** back to starting reagents requires only 13.1 kcal/mol.
13. Kirmse, W.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 1991–7989.
14. Preferential stabilization of **TS1$_a$** and **TS1$_b$** appears reducible to a favorable P^+–C–H$\cdots O^{\delta-}$ as corroborated by NBO second-order perturbation theory, which determined that this interaction imparts 4.6 kcal/mol of stabilization to **TS1$_a$** while **TS1$_b$** benefits from a mere 1.1 kcal/mol of stability. (NBO Version 3.1, Glendening, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F.)
15. In a previous Letter addressing regioselection in phosphine catalyzed allenoate additions we have reported that α-**TS1** is 1.7 kcal/mol more stable then γ-**TS1** in benzene ($\varepsilon = 2.27$). As it is of direct relevance the calculated 1.7 kcal/mol preference for α- versus γ-addition equates to a predicted product ratio of 95:5, which is a figure consistent with experiment (α- versus γ-addition 85:15), see Ref. 6a.
16. Zhu, G.; Chen, Z.; Jiang, Q.; Xiao, D.; Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 3836–3837.
17. Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334–338.
18. Wiberg, K. B. *Tetrahedron* **1968**, *24*, 1083–1096.
19. Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *87*, 395–397.
20. See Supplementary data for computed structure and thermochemical data.
21. Interestingly, an electrostatic potential map of intermediate **7**, reveals that the surface charges are well positioned to interact with a hydrogen bond donor/acceptor regions of a water molecule: see Supplementary data.
22. NBO Version 3.1, Glendening, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F.
23. Bader, R. F. W. *Atoms in Molecules: a Quantum Theory*; Oxford University Press: Oxford, England, 1990.
24. (a) Refs. 2c and 6c; (b) Kuroda, H.; Tomita, I.; Endo, T. *Org. Lett.* **2003**, *5*, 129–131; (c) Jung, C.-K.; Wang, J.-C.; Krische, M. *J. Am. Chem. Soc.* **2004**, *126*, 4118–4119; (d) Fan, R.-H.; Hou, X.-L.; Dai, L.-X. *J. Org. Chem.* **2004**, *69*, 689–694; (e) Kamijo, S.; Kanazawa, C.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 9260–9266.