

## An Unexpected Role of a Trace Amount of Water in Catalyzing Proton Transfer in Phosphine-Catalyzed (3 + 2) Cycloaddition of Allenates and Alkenes

Yuanzhi Xia,<sup>†,‡</sup> Yong Liang,<sup>†</sup> Yuanyuan Chen,<sup>†</sup> Ming Wang,<sup>†</sup> Lei Jiao,<sup>†</sup> Feng Huang,<sup>†</sup> Song Liu,<sup>†</sup> Yahong Li,<sup>‡,§</sup> and Zhi-Xiang Yu<sup>\*,†</sup>

Beijing National Laboratory for Molecular Sciences (BNLMS), Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Peking University, Beijing 100871, China, Qinghai Institute of Salt Lakes, Chinese Academy of Sciences, Xining 810008, China, and Key Laboratory of Organic Synthesis of Jiangsu Province, Department of Chemistry and Chemical Engineering, Suzhou University, Suzhou 215006, China

Received November 16, 2006; E-mail: yuzx@pku.edu.cn

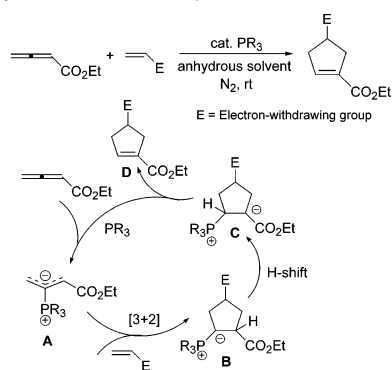
The Lu phosphine catalyzed (3 + 2) cycloaddition between allenates and activated alkenes,<sup>1,2</sup> as exemplified by the reaction shown in Scheme 1, provides an efficient approach for the synthesis of five-membered carbocycles, which are prevalent in many natural products and compounds of pharmaceutical significance. The proposed mechanism for the Lu reaction (shown in Scheme 1) starts from the formation of a zwitterionic intermediate **A** between allenate and phosphine.<sup>1,2a</sup> Intermediate **A** acts as a 1,3-dipole and undergoes a (3 + 2) cycloaddition with an electron-deficient olefin to give a phosphorous ylide **B**. Then an intramolecular [1,2] proton transfer is speculated to convert the phosphorous ylide **B** to another zwitterionic intermediate **C**, which, upon loss of the phosphine catalyst, gives rise to the final cycloadduct **D**. The Lu (3 + 2) cycloaddition is also efficient for the synthesis of five-membered heterocycles if imines are used as dipolarophiles.<sup>3</sup> Through elegant work in the groups of Zhang and Fu,<sup>4</sup> asymmetric versions of the Lu (3 + 2) cycloaddition have been developed. Applications of the Lu (3 + 2) cycloaddition to the total synthesis of natural products have also been documented by Lu, Krische, and Pyne, respectively.<sup>5</sup> Further elegant developments and extensions of the chemistry of allene-PR<sub>3</sub> have been widely pursued by many other groups as well.<sup>6</sup>

However, to date, the detailed mechanism of the Lu reaction has not been investigated either experimentally or theoretically.<sup>7</sup> In-depth understanding of the potential energy surface, structures of the intermediates and transition states, and regio- and stereochemistry in the Lu reaction would be useful. Mechanistic information concerning the Lu reaction may help to guide future design of new organocatalytic reactions.<sup>8</sup>

Here we wish to communicate our theoretical and experimental study of the Lu (3 + 2) reaction, with emphasis on the details of the [1,2] proton-transfer step. Although the typical Lu reaction condition is supposed to be anhydrous, our study shows that a trace amount of water existing in the reaction system plays a critical role in assisting the process of [1,2] proton shift.

DFT calculations<sup>9</sup> using the B3LYP/6-31+G(d) method have been applied to understand the Lu reaction, and the computed potential-energy surfaces for the model reaction of 2,3-butadienoate **1**, acrylate **2**, and PMe<sub>3</sub> are given in Figure 1. Calculations show that the formation of 1,3-dipole **3** from **1** and PMe<sub>3</sub> is slightly exothermic by 1.0 kcal/mol in terms of  $\Delta E_0$  in the gas phase. The free energies of this complex are +11.5 and +9.7 kcal/mol

**Scheme 1.** The Lu (3 + 2) Reaction and Its Proposed Mechanism (Only the Major Product Is Given).



compared to reactants in the gas phase and benzene solution, respectively. Calculations indicated that the subsequent (3 + 2) cycloaddition process between **3** and **2** is stepwise, starting from a Michael addition to generate a zwitterionic intermediate **IN1**, which then converts to **IN2** via a ring-closure reaction. These two transition structures in the stepwise (3 + 2) cycloaddition process are very close in energy in both the gas phase and solution. The overall process transforming the reactants and the catalyst to **IN2** requires activation free energies of 31.3 and 28.3 kcal/mol in the gas phase and benzene solution, respectively. The formation of **IN2** is exothermic by 13.9 kcal/mol; however, this (3 + 2) process is endergonic by 12.2 and 11.0 kcal/mol in the gas phase and benzene solution, respectively, suggesting that the formation of **IN2** is not favorable thermodynamically. Therefore, the stepwise (3 + 2) steps must be followed by some exergonic reactions to drive the reaction to completion.

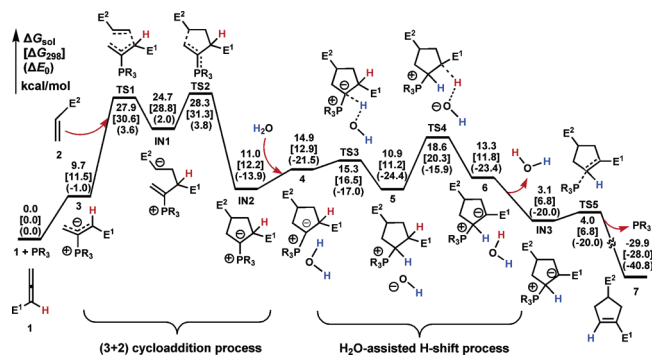
The originally proposed [1,2] proton transfer converting **IN2** to **IN3** is exergonic by about 8.0 kcal/mol, implying that formation of **IN3** can drive the above stepwise (3 + 2) cycloaddition to occur. However, the computed activation free energy of the [1,2] proton transfer from **IN2** to **IN3** is 39.3 and 39.6 kcal/mol in the gas phase and in benzene solution,<sup>10</sup> indicating that this step is not possible kinetically, considering the fact that the Lu (3 + 2) cycloadditions are usually conducted at room temperature.

To obtain more information about the Lu reaction, we conducted a PPh<sub>3</sub> catalyzed (3 + 2) cycloaddition of deuterium labeled 2,3-butadienoate **8** (2-D incorporation level is about 95%) and fumarate **9** (**I**, Scheme 2) in anhydrous benzene (refluxed with Na and freshly distilled prior to use) according to Lu's procedure.<sup>1</sup> It was found that 4-D and 4-H substituted products **10** and **11** were both obtained

<sup>†</sup> Peking University.

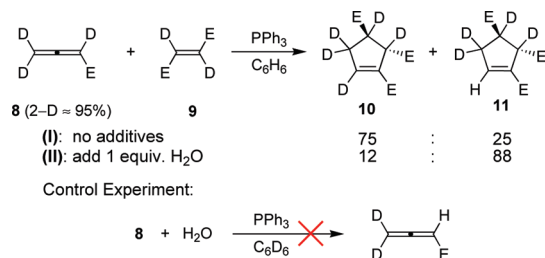
<sup>‡</sup> Qinghai Institute of Salt Lakes.

<sup>§</sup> Suzhou University.



**Figure 1.** The DFT computed energy surfaces of the Lu (3 + 2) reaction ( $E^1 = E^2 = \text{CO}_2\text{Me}$ ,  $R = \text{CH}_3$ ).<sup>9</sup>

**Scheme 2.** Isotopic Labeling Experiments ( $E = \text{CO}_2\text{Me}$ ).<sup>11</sup>



with a ratio of 75:25. This indicates that the [1,2] proton transfer from **IN2** to **IN3** is not a simple intramolecular process. We speculated that the formation of **11** was due to the presence of a trace amount of water in the reaction system. Therefore, we computed a possible  $\text{H}_2\text{O}$  assisted [1,2] proton shift process, which is also given in Figure 1. Calculations showed that **IN2** can form a complex with water, and this complexation step is exothermic by 7.6 kcal/mol and endergonic by 3.9 kcal/mol in benzene. Then a proton transfer from water to the carbon atom connected with the phosphorus atom requires only 0.4 kcal/mol activation free energy in benzene. This step leads to the formation of another complex **5**, in which there is a strong attraction between the hydroxyl anion and the  $\text{PMe}_3$  moiety. The subsequent step is the abstraction of proton by hydroxyl anion with an activation free energy of 7.7 kcal/mol in benzene, giving rise to another complex **6**. Loss of water from complex **6** gives **IN3**, which can then easily furnish final (3 + 2) cycloadduct **7** and  $\text{PMe}_3$  with an activation free energy of 0.9 kcal/mol in benzene. The water assisted H-shift process converting **IN2** to the final product and  $\text{PR}_3$  requires only 7.7 kcal/mol activation free energy and is exergonic by 40.9 kcal/mol.

We also ran the reaction between **8** and **9** in the presence of 1 equiv of  $\text{H}_2\text{O}$  (II, Scheme 2). It was found that the ratio of 4-H substituted product **11** was remarkably increased (from 25% to 88%). To rule out the possibility that the introduction of hydrogen takes place between 1,3-dipole **3** and  $\text{H}_2\text{O}$ , we conducted a control experiment (Scheme 2).  $^1\text{H}$  NMR indicated that no deuterium and hydrogen exchange between allenolate and water occurred, proving that the hydrogen exchange happens after the formation of **IN2** (Figure 1).<sup>11</sup> These results further confirm that the intramolecular [1,2] H-shift is impossible and a trace amount of water does play a catalytic role in assisting the [1,2] proton transfer.

In conclusion, the Lu (3 + 2) cycloaddition has been investigated with joint forces of computation and experiment. The formation of a 1,3-dipole is slightly exothermic, and the subsequent (3 + 2) cycloaddition is a stepwise process with an activation free energy

of 28.3 kcal/mol. The generally accepted intramolecular [1,2] proton shift in the Lu reaction is not possible owing to the very high activation barrier of 39.6 kcal/mol required for this process.<sup>10</sup> Calculations and experiments revealed that water assists this process with an activation free energy of 7.7 kcal/mol. The discovery of the catalytic role of a trace amount of water in the Lu reaction suggests that a trace amount of water could also act as a catalyst in some other “anhydrous” reactions involving [1,2] or [1,*n*] proton shifts.<sup>12</sup> The present study could have implications for other organocatalytic reactions.<sup>8,13,14</sup> Further mechanistic investigations on allene chemistry and other organocatalytic reactions are in progress.

**Acknowledgment.** We are indebted to generous financial support from Peking University and the Natural Science Foundation of China (Grants 9800445, 0240203, and 20672005).

**Supporting Information Available:** Computational and experimental details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

**References**

- Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 2906.
- For reviews on phosphine catalyzed reactions, see: (a) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535. (b) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035.
- (a) Xu, Z.; Lu, X. *Tetrahedron Lett.* **1997**, *38*, 3461. (b) Xu, Z.; Lu, X. *J. Org. Chem.* **1998**, *63*, 5031. (c) Xu, Z.; Lu, X. *Tetrahedron Lett.* **1999**, *40*, 549. (d) Zhu, X.-F.; Henry, C. E.; Kwon, O. *Tetrahedron* **2005**, *61*, 6276.
- (a) Zhu, G.; Chen, Z.; Jiang, Q.; Xiao, D.; Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 3836. (b) Wilson, J. E.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1426.
- (a) Du, Y.; Lu, X. *J. Org. Chem.* **2003**, *68*, 6463. (b) Wang, J.-C.; Krische, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5855. (c) Pham, T. Q.; Pyne, S. G.; Skelton, B. W.; White, A. H. *J. Org. Chem.* **2005**, *70*, 6369.
- (a) Zhu, X.-F.; Lan, J.; Kwon, O. *J. Am. Chem. Soc.* **2003**, *125*, 4716. (b) Tran, Y. S.; Kwon, O. *Org. Lett.* **2005**, *7*, 4289. (c) Wurz, R. P.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 12234. (d) Evans, C. A.; Miller, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 12394. (e) Wang, L.-C.; Luis, A. L.; Agapiou, K.; Jang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 2402. (f) Frank, S. A.; Mergott, A. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 2404.
- Only a few computational studies have been done to rationalize the regiochemistry in the (3 + 2) cycloaddition step shown in Scheme 1, see: (a) Pham, T. Q.; Pyne, S. G.; Skelton, B. W.; White, A. H. *Tetrahedron Lett.* **2002**, *43*, 5953. (b) Ung, A. T.; Schafer, K.; Lindsay, K. B.; Pyne, S. G.; Amornraksa, K.; Wouters, R.; Linden, I. V.; Biesmans, I.; Lesage, J. A. S.; Skelton, B. W.; White, A. H. *J. Org. Chem.* **2002**, *67*, 227. (c) Dudding, T.; Kwon, O.; Mercier, E. *Org. Lett.* **2006**, *8*, 3643.
- For a recent thematic issue on organocatalysis, see: Houk, K. N.; List, B. *Acc. Chem. Rev.* **2004**, *137*, 487 and references therein.
- Computational details and references are given in the Supporting Information. The reported relative energies are free energies in benzene ( $\Delta G_{\text{sol}}$ ), and free energies ( $\Delta G_{298}$ ) and the zero-point energies corrected electronic energies ( $\Delta E_0$ ), both in the gas phase, respectively. Even though for a bi- or trimolecular process, the computed  $\Delta G_{\text{sol}}$  values are somehow overestimated (owing to the overestimation of the entropy contributions in solution), the main purpose of such calculations is to appreciate how solvent influences a reaction (such as on its reaction rate, regio- and stereochemistry). A discussion of regiochemistry is given in the Supporting Information.
- Calculations showed that tunneling effect for this step is negligible.<sup>9</sup>
- There is no deuterium and hydrogen exchange between the deuterated (3 + 2) cycloadduct **10** and  $\text{H}_2\text{O}$  in the presence of  $\text{PPh}_3$ . For details of these and other experiments, see the Supporting Information.
- [1,2] or [1,3] proton shift is proposed in many phosphine catalyzed reactions: (a) Jung, C.-K.; Wang, J.-C.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 4118. (b) Kamijo, S.; Kanazawa, C.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 9260. (c) Kuroda, H.; Tomita, I.; Endo, T. *Org. Lett.* **2003**, *5*, 129. (d) Zhu, X.-F.; Schaffner, A.-P.; Li, R. C.; Kwon, O. *Org. Lett.* **2005**, *7*, 2977. (e) Virieux, D.; Guillouze, A.-F.; Cristau, H.-J. *Tetrahedron* **2006**, *62*, 3710. (f) Fan, R.-H.; Hou, X.-L.; Dai, L.-X. *J. Org. Chem.* **2004**, *69*, 689.
- Such water-assisted proton shifts have been found in many enzymatic reactions, for a recent review, see: Blomberg, M. R. A.; Siegbahn, P. E. M. *Biochim. Biophys. Acta* **2006**, *1757*, 969 and references therein.
- (a) Brogan, A. P.; Dickerson, T. J.; Janda, K. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 8100. (b) Hayashi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 8103 and references therein.

JA068215H