

# Thieme Chemistry Journal Awardees – Where are They Now?

## Phosphine- and Water-Cocatalyzed [3+2] Cycloaddition Reactions of 2-Methyl-2,3-butadienoate with Fumarates: A Computational and Experimental Study

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**Abstract:** With the aid of computation and experiment, the phosphine- and water-cocatalyzed [3+2] cycloaddition reactions of 2-methyl-2,3-butadienoate with fumarates have been developed. In this reaction, 2-methyl-2,3-butadienoate is used as a three-carbon synthon generated through a water-catalyzed [1,4]-proton-shift process. The DFT calculations and isotopic labeling experiment have been done to explore how this [3+2] reaction occurs.

**Key words:** phosphine, water, organocatalysis, density functional calculations, reaction mechanisms

The Lu phosphine-catalyzed [3+2] cycloaddition reactions of 2,3-butadienoates or 2-butynoates with unsaturated electrophiles are very efficient for the construction of five-membered carbocycles and heterocycles,<sup>1–3</sup> which exist as the backbones of many natural products and other compounds of pharmaceutical significance. Recently, we reported a computational and experimental investigation into the detailed mechanisms of these [3+2] reactions.<sup>4</sup> One of the most important findings from these mechanistic studies is that the widely accepted intramolecular [1,2]-proton shift should be corrected to a water-catalyzed [1,2]-proton shift (Scheme 1), since the intramolecular [1,2]-proton shift is a 4-electron-2-orbital interaction process with an insurmountable energy barrier. Here we wish to report another discovery that water is also critical for the [3+2] cycloaddition of 2-methyl-2,3-butadienoate and fumarate, where 2-methyl-2,3-butadienoate acts as a three-carbon synthon generated through a water-catalyzed [1,4]-proton-shift process.

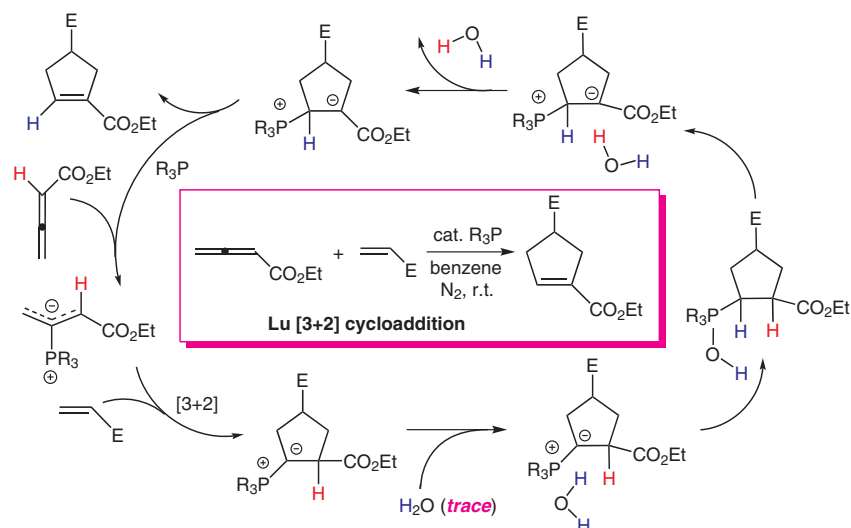
Based on the mechanistic insights into the Lu [3+2] reaction, we hypothesized that, if 2-methyl-2,3-butadienoate instead of 2,3-butadienoate was used under the cocatalysis of phosphine and water, the Lu [3+2] reaction was not expected to occur since the required hydrogen in the [1,2]-proton-shift step was replaced by a methyl group. We tested this hypothesis experimentally by carrying out the reaction of methyl 2-methyl-2,3-butadienoate (**1**) and dimethyl fumarate (**2**) with stoichiometric amounts of triphenylphosphine and water at 80 °C for 12 hours in



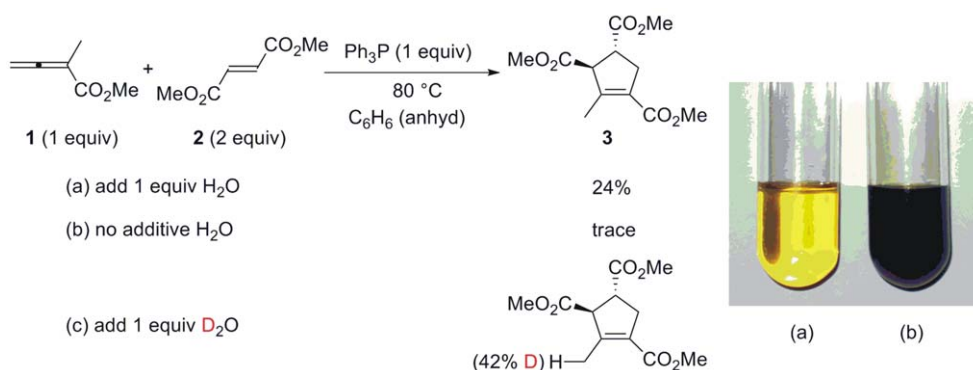
**Zhi-Xiang Yu** was born in Hubei province, P. R. of China in 1969. He obtained his BSc (Wuhan University, 1991), MSc (synthetic organic chemistry, Peking University, 1997), PhD (computational and theoretic organic chemistry, the Hong Kong University of Science & Technology, 2001). After a three-year postdoctoral study (University of California, Los Angeles, USA), he joined Peking University as an associate professor in 2004 and was promoted to a full professor in 2008. His main research interests are to apply computational organic chemistry and synthetic organic chemistry to study reaction mechanisms, develop new reactions and catalysts, and synthesize natural and non-natural products. In 2008, he received the Thieme Synlett/Synthesis Journal Award, the Young Chemist Award from the Chinese Chemical Society & the Royal Society of Chemistry, and the Asian Core Program Lectureship Award of the Asian Cutting-Edge Organic Chemistry programs. Recently, he won the National Science Fund for Distinguished Young Scholars of China in 2008.

benzene (Scheme 2). To our surprise, a new [3+2] cycloadduct **3** was obtained in 24% yield. However, when a control experiment without water was run, only a trace amount of **3** was detected (Scheme 2), suggesting that water played an important catalytic role in this new [3+2] reaction. To obtain more information about the mechanism of this [3+2] reaction, an isotopic labeling experiment was also conducted. It was found that, when one equivalent of D<sub>2</sub>O was added to the reaction system, 3-CH<sub>2</sub>D-substituted [3+2] product was generated with a ratio of 42% (Scheme 2).<sup>5</sup> The success of this [3+2] reaction indicates that 2-methylallenoate can be used as a three-carbon synthon. This is the first report of 2-methylallenoate as a three-carbon synthon. Previously 2-methylallenoate was used as either a two-carbon synthon or a four-carbon synthon.<sup>6,7</sup>

How does 2-methylallenoate act as a three-carbon synthon? We thought that water-catalyzed [1,4]-proton-shift process was responsible for this and proposed a mecha-



**Scheme 1** Phosphine-catalyzed [3+2] reaction of allenates and electron-deficient alkenes (only the major regioisomer is given; E = electron-withdrawing group)

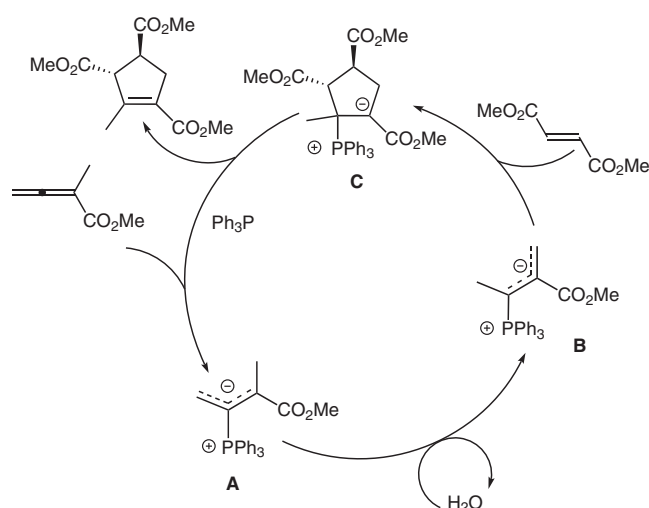


**Scheme 2** Initial study of phosphine- and water-cocatalyzed [3+2] reaction (reaction a: the reaction system turns light yellow after 12 h), control experiment (reaction b: the reaction system turns dark brown after 12 h), and isotopic labeling experiment (reaction c)

nism of phosphine- and water-cocatalyzed [3+2] reaction of 2-methylallenoate and fumarate (Scheme 3). The catalytic cycle starts with the formation of a zwitterionic intermediate **A**, generated from 2-methylallenoate and the phosphine catalyst. Then a water-catalyzed [1,4]-proton shift converts **A** into another zwitterionic intermediate **B**, which reacts with fumarate to form five-membered intermediate **C**. Finally, the [3+2] product is generated from **C** through the elimination of the phosphine catalyst.

The above mechanism, especially the detailed process of water-catalyzed [1,4]-proton shift, was further supported by the density functional theory (DFT) calculations.<sup>8</sup> Structural optimization and single-point energy calculations were obtained at the B3LYP/6-31+G(d) level,<sup>9,10</sup> and solvent effects were computed using the CPCM model.<sup>11</sup> The computed energy surface is given in Figure 1, and the optimized structures are shown in Figure 2. All discussed energies below are enthalpies in benzene unless specified.

We chose the addition of trimethylphosphine (**8**) to methyl 2-methyl-2,3-butadienoate (**1**) with a cocatalyst water as the model for the DFT investigation. Calculations indi-



**Scheme 3** Proposed mechanism for phosphine- and water-cocatalyzed [3+2] reaction of 2-methylallenoate and fumarate

cate that the formation of the zwitterionic 1,3-dipole **9** is exothermic by 2.3 kcal mol<sup>-1</sup> in terms of enthalpy, but is endergonic by 11.7 kcal mol<sup>-1</sup> owing to entropy loss in

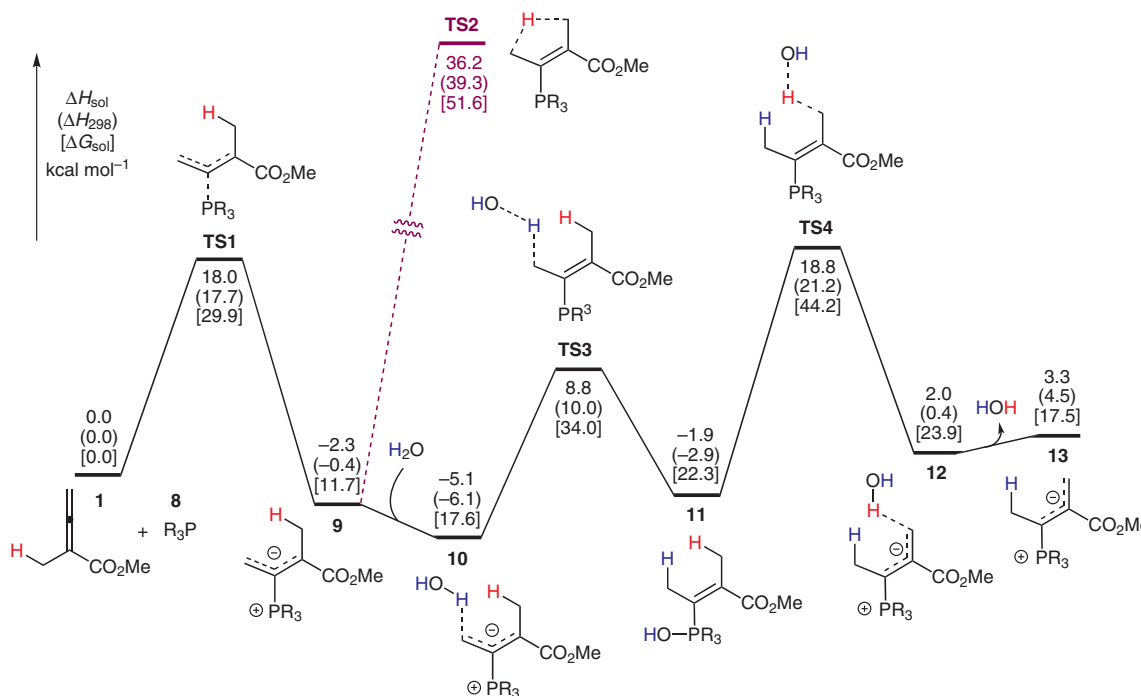
this process. The activation enthalpy for this nucleophilic addition is  $18.0 \text{ kcal mol}^{-1}$  and its activation free energy is  $29.9 \text{ kcal mol}^{-1}$ . The forming P–C bond distance in the addition transition-state structure **TS1** is  $2.42 \text{ \AA}$ , and the formed P–C bond length in **9** is  $1.83 \text{ \AA}$  (Figure 2).

Through a [1,4]-proton-shift step, 1,3-dipole **9** can be transformed to a new zwitterion **13** (Figure 1). The intramolecular concerted [1,4]-proton-shift process is highly energy demanding with an activation enthalpy of  $38.5 \text{ kcal mol}^{-1}$ . In contrast, a water-catalyzed [1,4]-proton shift is much easier. This water-catalyzed process starts with the formation of complex **10** between **9** and water, with a reaction enthalpy of  $-2.8 \text{ kcal mol}^{-1}$ . The conversion of **10** into **11** via proton-transfer transition state **TS3** requires  $13.9 \text{ kcal mol}^{-1}$  of activation enthalpy. In **TS3**, the breaking O–H and the forming C–H distances are  $1.52$  and  $1.21 \text{ \AA}$ , respectively (Figure 2). In intermediate **11**, the in situ generated hydroxide anion coordinates to the phosphorus atom. Through another proton-transfer transition state **TS4**, in which the breaking C–H distance is  $1.24 \text{ \AA}$  and the forming O–H distance is  $1.50 \text{ \AA}$  (Figure 2), complex **12** is generated from **11**. This step requires an activation enthalpy of  $20.7 \text{ kcal mol}^{-1}$ . Dissociation of water from **12** leads to the formation of zwitterion **13**, which is exergonic by  $6.4 \text{ kcal mol}^{-1}$  in terms of free energy in benzene.<sup>12</sup> The zwitterion **13** can then undergo the [3+2] reaction shown in Scheme 3 to give the final cycloadduct **3**.

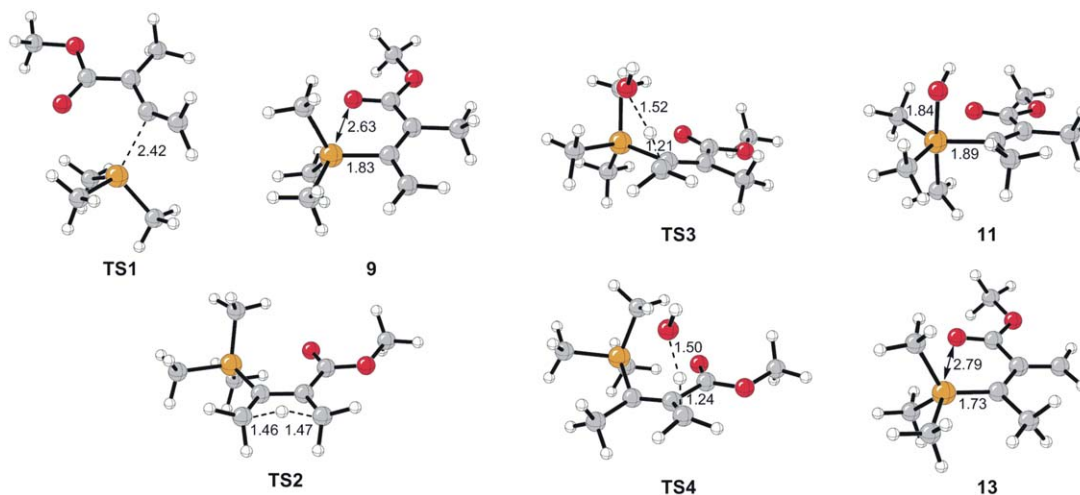
The above computational studies reveal a reasonable reaction pathway for the generation of zwitterionic intermediate **13** from methyl 2-methyl-2,3-butadienoate (**1**) in the presence of phosphine and water. The computed activa-

tion enthalpy in benzene of the whole process is  $23.9 \text{ kcal mol}^{-1}$  (from the most stable intermediate **10** to the highest transition state **TS4**, Figure 1). **TS4** is the rate-determining transition state of the present [3+2] reaction. In terms of activation free energy, the whole process requires an activation free energy of  $44.2 \text{ kcal mol}^{-1}$ , which is much overestimated due to the overestimation of the entropy loss for the multicomponent reaction.<sup>13</sup> According to our previous kinetic studies on the phosphine-catalyzed Lu [3+2] reaction, the entropic contribution in solution is about 60% of the computed gas-phase value for a trimolecular process.<sup>4b</sup> Thus, we assume that the entropic contribution in solution is also about 60% of the computed gas phase value for this process. Therefore, the estimated activation free energy in benzene of this reaction could be about  $36 \text{ kcal mol}^{-1}$ . This energy barrier well explained why the present [3+2] reaction had to be conducted at a relatively high temperature, with a high catalyst loading, and for a long reaction time.

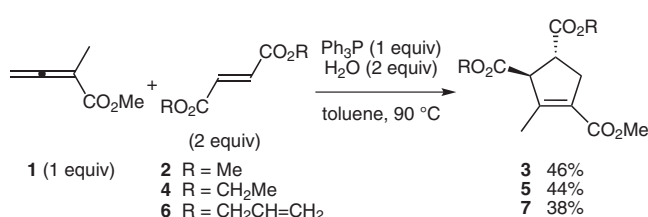
After optimization of the reaction conditions, the yield of product **3** was improved to 46% when the reaction was run at  $90 \text{ }^\circ\text{C}$  in toluene for 12 hours under the cocatalysis of 1 equivalent of  $\text{Ph}_3\text{P}$  and 2 equivalents of  $\text{H}_2\text{O}$  (Scheme 4). When other fumarates were used, the corresponding [3+2] products were also obtained in moderate yields (Scheme 4). Unfortunately, extensive experimental screening to expand this [3+2] reaction revealed that other electron-deficient alkenes, such as acrylate, vinyl ketone, and maleate, were not suitable for this [3+2] reaction. The failure to expand this reaction could be due to the fact that many unknown side reactions are very competitive in the reaction system.



**Figure 1** DFT-computed energy surface for the formation of **9** and its conversion into **13** ( $R = \text{Me}$ ;  $\Delta H_{\text{sol}}$  and  $\Delta G_{\text{sol}}$  are the computed relative enthalpies and free energies in benzene solution, while  $\Delta H_{298}$  is the computed relative enthalpies in the gas phase)



**Figure 2** Structures of key intermediates and transition states (carbon, gray; hydrogen, white; oxygen, red; phosphorus, yellow; distances are given in Å)



**Scheme 4** Phosphine- and water-cocatalyzed [3+2] reaction of 2-methylallenoate and fumarates.<sup>14</sup>

In conclusion, we have reported the first example for the [3+2] cycloaddition reaction between 2-methylallenoate and fumarate. Through the joint forces of computation and experiment, it is discovered that 2-methylallenoate can be used as the three-carbon synthon under the cocatalysis of triphenylphosphine and water. Furthermore, the detailed mechanism of water-catalyzed [1,4]-proton shift has been verified by both DFT calculations and the isotopic labeling experiment. Further investigations on other phosphine-catalyzed reactions or water-catalyzed reactions are ongoing in our laboratory.

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- (14) **General Procedure for the Ph<sub>3</sub>P- and H<sub>2</sub>O-Cocatalyzed [3+2] Reaction**  
To a mixture of the fumarate (1 mmol), Ph<sub>3</sub>P (0.5 mmol), and H<sub>2</sub>O (1 mmol) in toluene (5 mL) was added via syringe under nitrogen methyl 2-methylallenoate (0.5 mmol). After stirring at 90 °C for 12 h, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography on SiO<sub>2</sub> to yield the product.
- trans-Trimethyl 3-Methylcyclopent-3-ene-1,2,4-tricarboxylate (3)**  
Colorless oil; *R<sub>f</sub>* = 0.27 (PE-EtOAc, 6:1). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 2.13 (m, 3 H), 2.90 (ddm, *J* = 16.5, 6.6 Hz, 1 H), 3.08 (ddm, *J* = 16.5, 9.6 Hz, 1 H), 3.50 (dt, *J* = 9.6, 6.6 Hz, 1 H), 3.72 (s, 3 H), 3.74 (s, 3 H), 3.77 (s, 3 H), 3.96 (dm, *J* = 6.6 Hz, 1 H). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>): δ = 14.8, 36.0, 43.4, 51.3, 52.3, 52.4, 59.1, 128.2, 149.7, 165.3, 172.3, 174.0. IR: ν = 1717, 1735 cm<sup>-1</sup>. MS (EI): *m/z* (%) = 256 (5) [M<sup>+</sup>], 224 (63), 196 (76), 164 (100). HRMS: *m/z* calcd for C<sub>12</sub>H<sub>16</sub>O<sub>6</sub>: 256.0947; found: 256.0950.
- trans-1,2-Diethyl-4-methyl 3-Methylcyclopent-3-ene-1,2,4-tricarboxylate (5)**  
Colorless oil; *R<sub>f</sub>* = 0.37 (PE-EtOAc, 6:1). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 1.27 (t, *J* = 7.2 Hz, 3 H), 1.30 (t, *J* = 7.2 Hz, 3 H), 2.14 (m, 3 H), 2.88 (ddm, *J* = 16.5, 6.6 Hz, 1 H), 3.08 (ddm, *J* = 16.5, 9.6 Hz, 1 H), 3.48 (dt, *J* = 9.6, 6.6 Hz, 1 H), 3.74 (s, 3 H), 3.93 (dm, *J* = 6.6 Hz, 1 H), 4.14–4.27 (m, 4 H). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>): δ = 14.09, 14.15, 14.8, 35.9, 43.5, 51.2, 59.3, 61.0, 61.3, 128.1, 149.9, 165.4, 171.8, 173.6. IR: ν = 1717, 1732 cm<sup>-1</sup>. MS (EI): *m/z* (%) = 284 (6) [M<sup>+</sup>], 252 (13), 238 (53), 210 (100). HRMS: *m/z* calcd for C<sub>14</sub>H<sub>20</sub>O<sub>6</sub>: 284.1260; found: 284.1257.
- trans-1,2-Diallyl-4-methyl 3-Methylcyclopent-3-ene-1,2,4-tricarboxylate (7)**  
Colorless oil; *R<sub>f</sub>* = 0.36 (PE-EtOAc, 6:1). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 2.14 (m, 3 H), 2.91 (ddm, *J* = 16.5, 6.6 Hz, 1 H), 3.10 (ddm, *J* = 16.5, 9.6 Hz, 1 H), 3.54 (dt, *J* = 9.6, 6.6 Hz, 1 H), 3.74 (s, 3 H), 3.99 (dm, *J* = 6.6 Hz, 1 H), 4.60–4.67 (m, 4 H), 5.23–5.39 (m, 4 H), 5.85–6.00 (m, 2 H). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>): δ = 14.8, 35.9, 43.5, 51.3, 59.2, 65.6, 65.9, 118.4, 118.8, 128.2, 131.5, 131.7, 149.7, 165.3, 171.4, 173.2. IR: ν = 1717, 1733 cm<sup>-1</sup>. MS (EI): *m/z* (%) = 308 (3) [M<sup>+</sup>], 276 (5), 250 (20), 222 (18), 41 (100). HRMS: *m/z* calcd for C<sub>16</sub>H<sub>20</sub>O<sub>6</sub>: 308.1260; found: 308.1252.