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2-(Acetoxymethyl)buta-2,3-dienoate, a Versatile 1,4-Biselectrophile for Phosphine-Catalyzed (4 + *n*) Annulations with 1,*n*-Bisnucleophiles (*n* = 1, 2)

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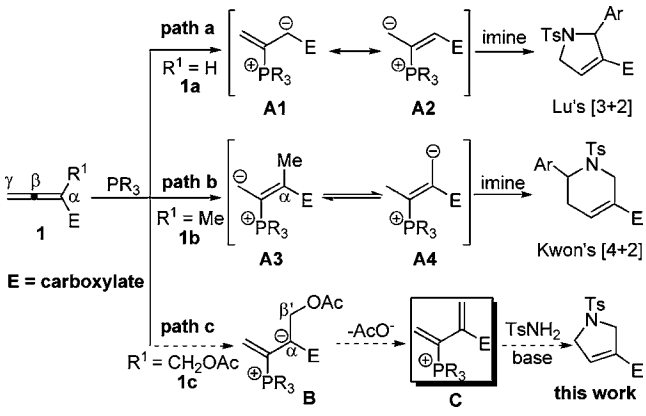
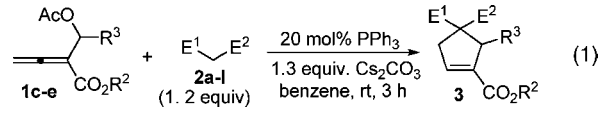
Since the Diels−Alder reaction was reported in 1928,[1] cycloaddition reactions have evolved into one of the most fascinating fields in organic chemistry because of their powerful applications in convergent synthesis of cyclic compounds from simpler starting materials. In this context, nucleophilic phosphine catalysis has played a significant role in the development of cycloaddition chemistry, which regio- and stereoselectively generates carbo- and heterocyclic motifs, which occur frequently in many natural products and biologically active molecules.[2,3] In particular, Lu's phosphine-catalyzed [3 + 2] cycloadditions of 2,3-butadienoates **1a** with imines or alkenes have been well-established (Scheme 1, path a)[4] and demonstrate[5] great potential for the syntheses of natural products. Recently, Kwon's group employed a novel strategy using 2-substituted allenoates **1b** as substrates to realize [4 + 2] and [3 + 3] annulations (Scheme 1, path b).[6] It was thought that these transformations rely on the formation of dipolar-type intermediates such as **A1**−**4** derived from the addition of phosphine to allenoates (Scheme 1, paths a and b).[2] Furthermore, these transformations have also strongly demonstrated that the dipolar intermediates **A1**−**4**, under mechanistic consideration, might serve as nucleophiles to react with diverse electrophiles.[2−6]

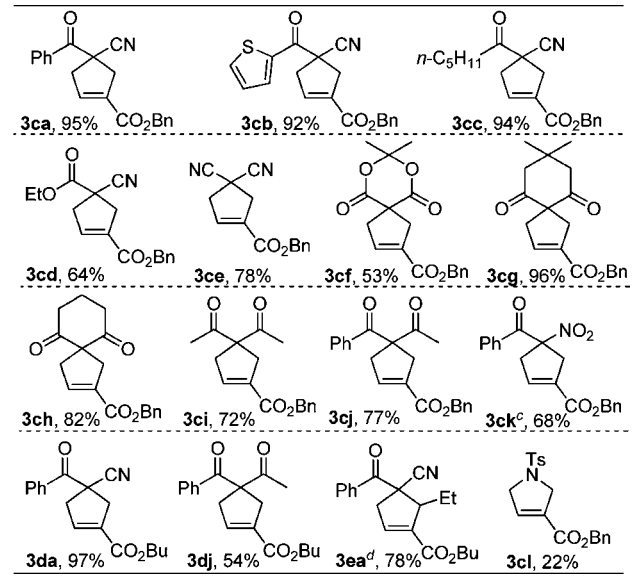
Scheme 1. Reactivity of the 2,3-Butadienoate Derivatives in the Presence of Phosphine Catalyst



We envisioned that introducing an acetate group β' to the 2,3-butadienoate would create an alternative to the normal reaction modes (Scheme 1, path c). Such a substrate, e.g., benzyl 2-(acetoxymethyl)buta-2,3-dienoate (**1c**), would, in the presence of phosphine catalyst, generate intermediate **B**, which in turn would undergo 1,2-elimination of the acetate group to yield intermediate **C**. It should be emphasized that a similar strategy has been employed for 2-(acetoxymethyl)alkenoates by Lu's group.[7] However, the putative intermediate **C** would possess different electronics from that of intermediates **A1**−**4**, exhibiting electrophilicity due to the electron-withdrawing effect of the phosphonium and carboxylate groups. Herein, we report the phosphine-catalyzed (4 + 1) annulations[8] of allenolates **1c**−**e** with 1,1-bisnucleophiles **2**, in which **1c**−**e** work as 1,4-biselectrophiles and four-atom units (eq 1, Table 1).

Table 1. Scope of the PPh_3-Catalyzed (4 + 1) Annulations[a,b]





[a] See the Supporting Information for experimental details. [b] Isolated yield. [c] $NaHCO_3$ was used as the base. [d] Reaction time 12 h.

To test our hypothesis, we started our investigation with the model reaction between **1c** and 3-oxo-3-phenylpropanenitrile (**2a**) in the presence of 20 mol % PPh_3. Exploratory studies showed that the combination of benzene as the solvent and cesium carbonate (1.3 equiv) as the base gave the best results at room temperature (Table S1 in the Supporting Information). Under the optimized conditions (Table S1, entry 3), the (4 + 1) annulations proceeded smoothly with a range of bisnucleophiles **2** to afford diverse cyclopentene derivatives **3** in good to excellent yields (Table 1). Interestingly, tosyl amide **2l** was also a competent nucleophile, so 2,5-dihydropyrrole **3cl** could be obtained, albeit in lower yield.

Upon the success of the (4 + 1) annulations, we extended our research to the (4 + 2) annulations with compound **4** as the two-atom unit and discovered that the corresponding tetrahydropyridazine derivative **5** could be readily obtained in 81% yield (eq 2).

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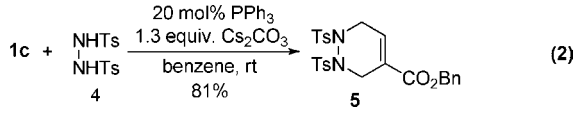
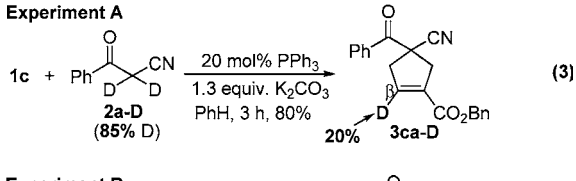
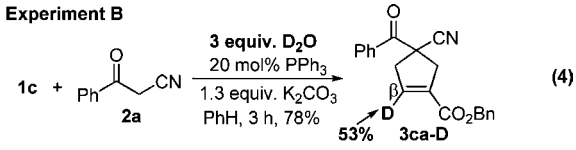


(2)

In order to investigate the mechanism of the reaction, two control experiments were conducted.[9] In experiment A (eq 3), deuterium-labeled substrate **2a-D** (85% D) was subjected to the reaction conditions, and only 20% of the deuterium was transferred to product **3ca-D** at the β carbon atom. These results indicated that the intermediate with the carbanion located at the β carbon center would be formed. The erosion of deuterium content was probably due to the presence[6d] of adventitious H_2O and intermolecular proton transfer.[10] To support these conclusions, the reaction of **2a** was conducted under the same conditions except for the introduction of an additional 3.0 equiv of D_2O (experiment B, eq 4). The reaction also performed well, affording the product in 78% yield, and 53% of the deuterium was incorporated into the β carbon atom of **3ca-D**.



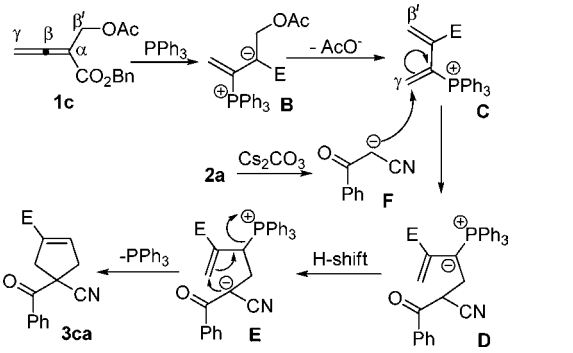
(3)



(4)

On the basis of the above observations, our proposed mechanism is depicted in Scheme 2. The reaction is triggered by addition of PPh_3 to 2,3-butadienoate **1c** to form intermediate **B**, which undergoes 1,2-elimination of the acetate group to generate intermediate **C**. In previous phosphine-catalyzed reactions of 2,3-butadienoate derivatives, nucleophilic phosphine can increase the electron density of the 2,3-butadienoate via an addition reaction. In our case, departure of the newly introduced acetate group would completely remove electrons from intermediate **B**, thus forming electrophilic intermediate **C**.[11] Carbanion **F** attacks the γ carbon[12] of intermediate **C** to form intermediate **D**. It has to be mentioned that an alternative pathway involving addition of carbanion **F** to the β' carbon cannot be excluded completely at this stage. Next, an intramolecular H shift in intermediate **D** results in the formation of **E**, which undergoes conjugate addition and elimination of PPh_3 to generate product **3ca** and regenerate the catalyst.

Scheme 2. Plausible Reaction Mechanism (E = CO_2Bn)



In summary, we have developed novel PPh_3-catalyzed (4 + 1) and (4 + 2) annulations of **1c**−**e** that efficiently provide facile access to cyclopentene and tetrahydropyridazine derivatives, respectively. Introduction of an acetate group β' to the 2,3-butadienoate plays a crucial role in inverting the normal phosphine-catalyzed reaction modes of 2,3-butadienoates. Thus, 2-(acetoxymethyl)-buta-2,3-dienoates **1c**−**e** serve as versatile 1,4-biselectrophiles and participate in (4 + *n*) annulations with 1,*n*-bisnucleophiles. Further studies of the reaction mechanism and asymmetric catalysis are ongoing in our laboratories and will be reported in due course.

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Supporting Information Available: Preparative methods and spectral and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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