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Phosphine-Catalyzed [4 + 2] Annulation of γ-Substituent Allenoates: Facile Access to Functionalized Spirocyclic Skeletons

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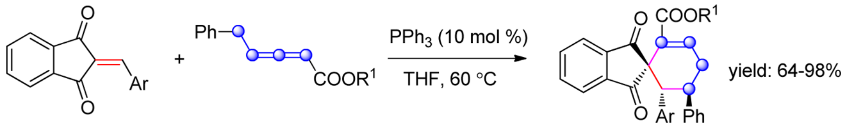
ABSTRACT



The first phosphine-catalyzed [4 + 2] annulation of γ-substituted allenoates with 2-arylidene-1*H*-indene-1,3(2*H*)-diones is disclosed. In the reaction, the γ-substituted allenoate serves as a new type of 1,4-dipolar synthon; this broadens the application of γ-substituted allenoates. This method also offers a powerful approach to the construction of highly substituted spiro[4.5]dec-6-ene skeletons in excellent yields, and with complete regioselectivity and high diastereoselectivity.

Spirocyclic skeletons are the structural centerpieces of a wide variety of natural and synthetic compounds that exhibit diverse biological activities. Consequently, approaches to the efficient synthesis of these molecules have received considerable attention.[1]

Various methods such as organocatalysis[2] and transition-metal catalysis[3] have previously been described in the literature. However, drawbacks such as unsatisfactory yields, tedious purification processes, and poor chemo- and/or diastereoselectivities have restricted the application of these approaches. The development of novel, straightforward, and flexible methods for the preparation of spirocyclic compounds is therefore highly desirable.

Recently, because of their comparatively strong and readily tunable nucleophilicities, phosphines have been used as efficient catalysts in organic synthesis.[4,5] A series

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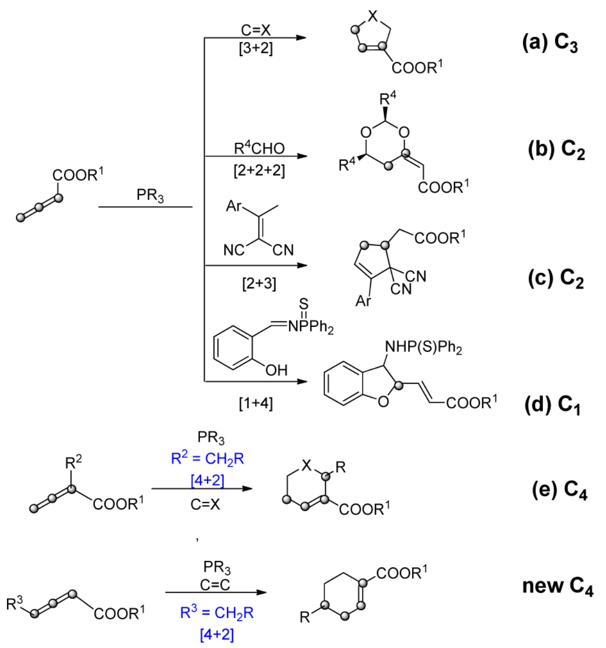
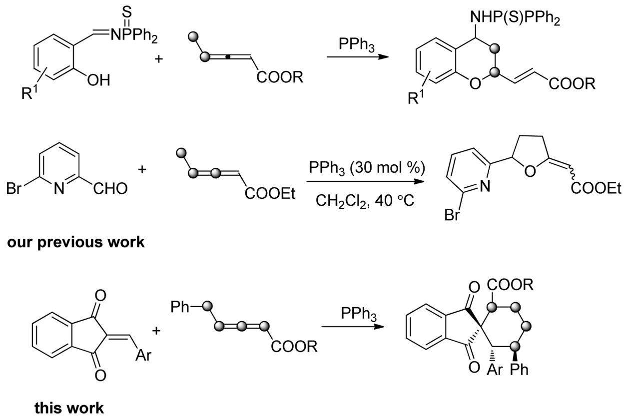
of named reactions, such as the Rauhut–Currier and Morita–Baylis–Hillman reactions, have been developed. Among these significant studies, Lu first reported the phosphine-catalyzed [3 + 2] cycloaddition of activated olefins with 2,3-butadienoate for the construction of various five-membered carbocyclic compounds and heterocyclic compounds [Scheme 1, (a)].[6] In further investigations, Kwon and Lu independently reported new [2 + 2 + 2] and [2 + 3] annulations catalyzed by phosphines [Scheme 1, (b) and (c)].[7] At the same time, our group first reported a novel [1 + 4] annulation of allenoates and salicyl-*N*-thiophosphinylimines using a new bifunctional phosphine catalyst, (2′-hydroxybiphenyl-2-yl)diethylphosphane (LBBA-1), in which allenoates served as one-carbon units participating in a domino process [Scheme 1, (d)].[8] Based on these pioneering studies, Kwon et al. developed a phosphine-catalyzed [4 + 2] cycloaddition of α-substituted allenoates with imides,[9] and subsequent research has shown that the [4 + 2] cycloaddition of α-substituted allenoates with activated olefins or ketones is also feasible [Scheme 1, (e)].[10] Kwon et al. used this method in the synthesis of natural products and bioactive compounds, further proving its synthetic efficiency.[11] However, compared with the significant progress made with allenoates and α-substituted allenoates, phosphine-catalyzed domino reactions involving γ-substituted allenoates are rare.[12] In 2009, our group reported the first example of γ-substituted allenoates acting as C_2 and C_3 synthons in phosphine-catalyzed [4 + 2] and [3 + 2] annulations.[12a] Recently, Shi et al. and Nair et al. reported novel phosphine-catalyzed reactions of γ-substituted allenoates.[13] However, to the best of our knowledge, γ-substituted allenoates acting as a new type of 1,4-dipolar synthon have not been reported. In this letter, we disclose the first case of a phosphine-catalyzed [4 + 2] annulation of γ-substituted allenoates and activated olefins under mild conditions (Scheme 1).

Scheme 1. Various Pathways for Phosphine-Catalyzed Annulations



Scheme 2. Phosphine-Catalyzed Annulations of γ-Substituent Allenoates



In view of our previous study of phosphine-catalyzed domino reactions of allenoates,[14] we initially used 2- benzylidene-1*H*-indene-1,3(2*H*)-dione (**1a**) (0.3 mmol) and methyl 5-phenyl-2,3-pentadienoate (**2a**) (0.6 mmol) as the model substrates and a catalytic amount of PPh_3 (30 mol %) as the catalyst at 40 °C in CH_2Cl_2 to test the reaction procedure (Scheme 2).[12a] Unfortunately, this

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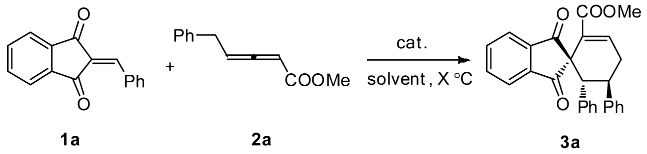
Table 1. Optimization of [4 + 2] Annulation of γ-Substituent of the Allenoate with 2-Benzylidene-1*H*-indene-1,3(2*H*)-dione[a]



entry	cat. (mol %)	solvent	*t* (h)	yield (%)[b]
1	PPh_3 (30)	CH_2Cl_2	6	trace
2	PPh_3 (50)	toluene	9	80
3	PPh_3 (50)	CH_3CN	9	53
4	PPh_3 (50)	THF	5	97
5	PPh_3 (50)	CH_2ClCH_2Cl	1.5	47
6	PPh_3 (50)	$CHCl_3$	12	63
7	$(4\text{-}ClC_6H_4)_3P$ (20)	THF	14	91
8	$(4\text{-}MeOC_6H_4)_3P$ (20)	THF	36	74
9	PPh_3 (20)	THF	9	96
10	PPh_3 (10)	THF	9	95
11[c]	PPh_3 (10)	THF	20	89
12[d]	PPh_3 (20)	THF	24	trace

[a] Unless otherwise specified, all reactions were carried out using **1a** (0.3 mmol) and **2a** (0.6 mmol) at 60 °C. [b] Yield of isolated products. [c] **1a** (0.3 mmol) and **2a** (0.45 mmol) were used. [d] The reaction was carried out at room temperature.

reaction did not show any activity, and no product was obtained. In toluene, with a temperature of 60 °C and an increased catalyst loading, the reaction proceeded smoothly to give the corresponding [4 + 2] cycloaddition adduct in 80% yield (Table 1, entry 2). It should be noted that the [4 + 2] cycloaddition reaction is completely regioselective and highly diastereoselective (only one isomer was detected in all reactions). Various solvents were tested, and THF was found to be the best, affording **3a** in 97% yield (Table 1, entries 1−6). Subsequent catalyst screening demonstrated that PPh_3 was the best choice (Table 1, entries 6−8). On decreasing the amount of catalyst to 20 and 10 mol %, similar results were obtained (Table 1, entries 9 and 10). However, changing the ratio of **1a** to **2a** resulted in a slight decrease in the yield (Table 1, entry 11). Furthermore, it was found that no reaction occurred in the presence of PPh_3 (20 mol %) at room temperature (Table 1, entry 12). Based on these experimental results, the best reaction conditions were confirmed to be PPh_3 (10−20 mol %), at 60 °C in THF. The structure and stereochemistry of **3** were determined using a combination of NMR and HRMS spectroscopies and single-crystal X-ray analysis (**3a**) (Figure 1).

With the optimized conditions in hand, we next explored the substrate scope of the new phosphine-catalyzed [4 + 2] cycloaddition; the results are listed in Table 2. The position of the substituent on the aromatic ring of substrate **2** had no significant influence on the yields and diastereoselectivities. Phenyl groups with electron-withdrawing or -donating groups worked well as substituents (Table 2, entries 1−9). When the substituents were phenyl groups with strong electron-withdrawing or -donating groups, a slightly higher catalyst loading (20 mol % PPh_3) was needed (Table 2, entries 10−12). When the substituent on the benzene ring was 4-nitro, 3-bromo, 3-methyl, or 4-methoxy, high yields and diastereoselectivities were still obtained, but a significantly longer reaction time was required (Table 2, entries 6, 7, 10, and 11). 2-Arylidene-1*H*-indene-1,3(2*H*)-dione **2** containing 2-naphthyl or heteroaryl groups could also be used in the reaction (Table 2, entries 13 and 14). The steric properties of the esters had

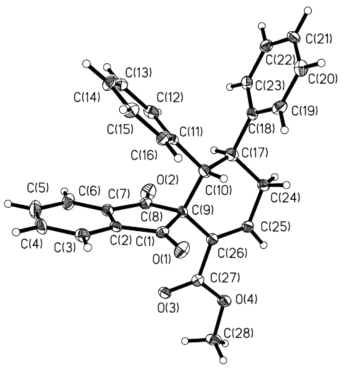
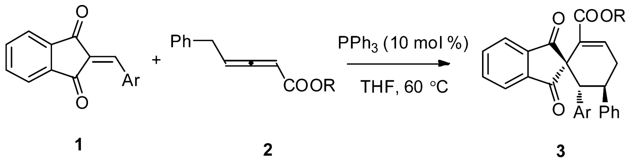


Figure 1. X-ray crystal structure of **3a**.

Table 2. Scopes of the Phosphine-Catalyzed [4 + 2] Annulation of γ-Substituent Allenoates in the Presence of PPh_3[a]



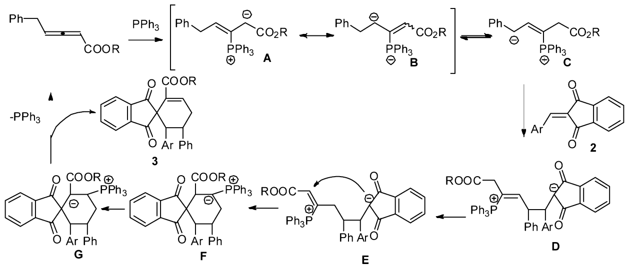
entry	Ar	R	*t* (h)	yield (%)[b]
1	C_6H_5	Me	9	95 (**3a**)
2	$4\text{-}MeC_6H_5$	Me	10	92 (**3b**)
3	$4\text{-}BrC_6H_5$	Me	10	98 (**3c**)
4	$4\text{-}ClC_6H_5$	Me	16	86 (**3d**)
5	$4\text{-}FC_6H_5$	Me	16	88 (**3e**)
6	$3\text{-}BrC_6H_5$	Me	36	88 (**3f**)
7	$3\text{-}MeC_6H_5$	Me	36	89 (**3g**)
8	$2\text{-}BrC_6H_5$	Me	12	96 (**3h**)
9	$2\text{-}MeC_6H_5$	Me	12	89 (**3i**)
10[c]	$4\text{-}NO_2C_6H_5$	Me	16	82 (**3j**)
11[c]	$4\text{-}MeOC_6H_5$	Me	16	96 (**3k**)
12[c]	$2.4\text{-}Cl_2C_6H_3$	Me	10	92 (**3l**)
13[c]	2-thienyl	Me	36	64 (**3m**)
14[c]	1-naphthyl	Me	36	88 (**3n**)
15	C_6H_5	Et	9	98 (**3o**)
16	C_6H_5	t-Bu	9	98 (**3p**)
17	C_6H_5	Bn	9	92 (**3q**)

[a] Unless otherwise noted, all reactions were carried out with **1** (0.3 mmol) and **2** (0.6 mmol) in THF (3.0 mL) at 60 °C. [b] Yield of isolated product. [c] The reactions were carried out with **1** (0.3 mmol) and **2** (0.6 mmol) in the presence of PPh_3 (20 mol %) in THF (3.0 mL) at 60 °C.

only a slight influence on the yield (Table 2, entries 1, 15−17).

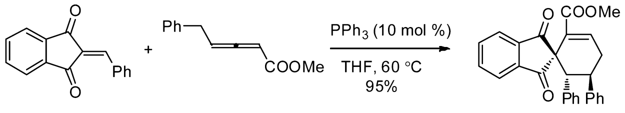
Based on our experimental results and previous studies,[15] we proposed a possible mechanism for the formation of spiro[4.5]dec-6-ene and the stereochemistry of this domino reaction (Scheme 3). Conceivably, the first step is nucleophilic addition of triarylphosphine to the allene ester, giving 1,3-dipolar zwitterion **A** or **B**. Intermediate **A** or **B** undergoes a reversible equilibrium overall proton shift, giving intermediate **C**. The allylic carbanion **C** then undergoes a Michael addition with **2**, enabling the formation of intermediate **D**; in this step, the steric effect of the large substituent on substrates will enable good product diastereoselectivity. Then, **D** followed by an isomerization to give intermediate **E**, an umpolung addition, and a proton shift forms intermediate **G**. Finally, elimination of the phosphine catalyst gives **3** and completes the catalytic cycle.

Scheme 3. Possible Mechanism for the Formation of **3**



In order to demonstrate the practicality of the strategy, we performed the phosphine-catalyzed [4 + 2] annulation reaction at large scale (×10). The reaction of 2-benzylidene-1*H*-indene-1,3(2*H*)-dione (**1a**) and methyl 5-phenyl-2,3- pentadienoate (**2a**) was carried out under the optimal conditions; the domino reaction proceeded smoothly and afforded the desired adduct **3a** at the gram scale, without loss of reactivity and diastereoselectivity (Scheme 4).

Scheme 4. Large Scale [4 + 2] Annulation between **1a** and **2a**



1a (3 mmol) **2a** (6 mmol) **3a** 1.24 g

In conclusion, we have developed a novel method for the synthesis of spiro[4.5]dec-6-ene through a phosphine-catalyzed [4 + 2] annulation, with excellent yields and high diastereoselectivities. More importantly, we have disclosed the first example of γ-benzyl allenoates acting as a new type of C_4 synthon and participating in a phosphine-catalyzed domino reaction. Further investigations will focus on designing new domino reactions using these new 1,4-dipolar synthons and on performing asymmetric versions of the annulation.

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Supporting Information Available. Detailed experimental procedures, spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.