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Phosphine-Catalyzed Sequential [2 +3] and [3 + 2] Annulation Domino Reaction of γ-Benzyl-Substituted Allenoates with α,β-Unsaturated Ketimines To Construct aza-Bicyclo[3,3,0]octane Derivatives

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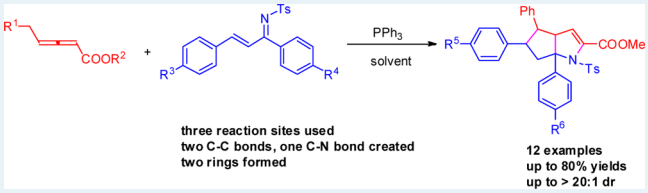
Supporting Information

ABSTRACT: A novel phosphine-catalyzed sequential [2 + 3] and [3 + 2] annulation domino reaction of γ-benzyl-substituted allenoates has been developed. The reaction can proceed smoothly to produce the corresponding aza-bicyclo-[3,3,0]octane derivatives in good yields and excellent diastereoselectivity (only one isomer).



KEYWORDS: *phosphine, sequential annulation, domino reaction, ketimine, γ-substituent allenoates*

Aza-bicyclo[3,3,0]octane derivatives are important structural motifs present in numerous biologically active natural products,[1] for example, the alkaloid nakadomarin A,[2] the topoisomerase II inhibitor S36888,[3] the melodinus alkaloids isolated from either *Apocynaceae* or *Kopsia* species, meloscine.[4] Therefore, the development of efficient synthetic methods for accessing these useful aza-bicyclo compounds has been an attractive field for organic chemists (Figure 1).

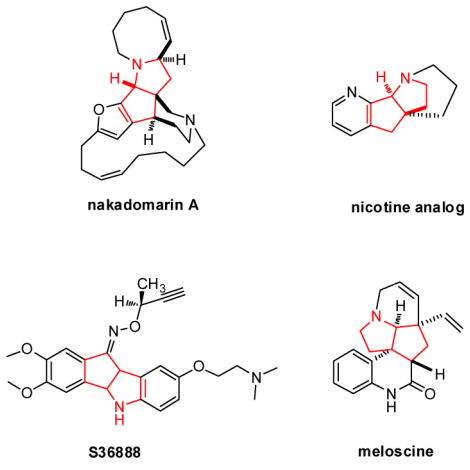
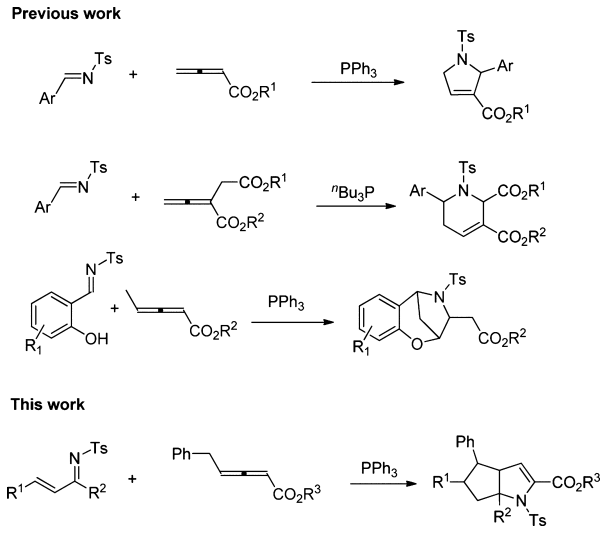


Figure 1. Representative biologically active natural products.

Domino reactions have received considerable interest, since they achieve rapid access to architecturally complex molecules under extremely convenient reaction conditions.[5] In particular, a phosphine-catalyzed domino reaction has been established as a reliable platform for the efficient assembly of a wide array of cyclic products from simple building blocks.[6] In 1995, Lu et al. reported first a phosphine-catalyzed [3 + 2] annulation reaction to construct monocyclopentene derivatives by using 2,3-butadienoates with electron-deficient olefins.[7] Consequently, Lu's [3 + 2] annulation was applied to construct dihydropyrrole compounds.[8] Furthermore, Kwon et al. applied this method in the synthesis of natural products and bioactive compounds, which further proved its synthetic efficiency (Scheme 1).[9]

Scheme 1. Phosphine-Catalyzed Cycloaddition Reactions of Allenoates



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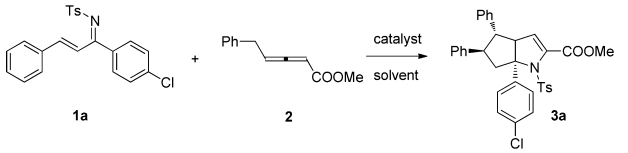
With the explosive development of organophosphine-catalyzed domino reactions, substituted allenoates have been also used as substrates in many domino reactions. In 2003, Kwon et al. reported first a phosphine-catalyzed [4 + 2] annulation reaction of α-substituted allenoates.[10] Recently, our group developed a novel phosphine-catalyzed [4 + 2] annulation reaction of γ-substituted allenoates,[11] although only one ring was formed in these reactions. Step economy to produce bicyclo compounds remained challenging. More recently, we reported an interesting domino sequential annulation reaction of γ-substituent allenoates with salicyl N-tosylimines in 2013 (Scheme 1),[12] in which, under the catalysis of phosphine, γ-substituted allenoates acted as a C3 synthon to produce benzoxiazepine derivatives. At the same time, Ma reported a bisphosphine-triggered sequential [3 + 2]/[3 + 2] annulations reaction of allenoates with cyclic ketimines. In this reaction, the bicyclo products were formed in a stepwise [3 + 2] annulations manner.[13] Herein, we report the results of our studies on the one-pot synthesis of aza-bicyclo compounds by a phosphine-catalyzed sequential [2 + 3] and [3 + 2] cycloaddition reaction of (*E*)-(1,3-diarylallylidene)-4-methyl-benzenesulfonamide with γ-benzyl-substituted allenoates. The domino reaction can proceed smoothly to produce the desired bicyclo compounds in moderate to good yields.

Initially, we selected ((*E*)-1-(4-chlorophenyl)-3-phenylallylidene)-4-methylbenzenesulfonamide **1a** and methyl γ-benzyl-substituted allenoates **2** in toluene in the presence of 20 mol % PPh_3 as the catalyst. The reaction proceeded smoothly to produce the desired product **3a** in 57% yield (Table 1, entry 1).

Table 1. Optimization of Reaction Conditions[a]



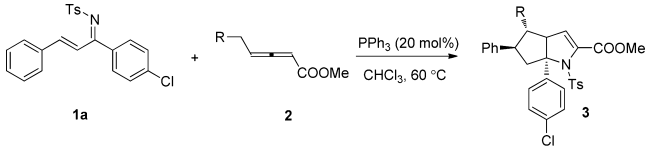
entry	cat. (%)	solvent	temp (°C)	*T* (h)	yield (%)[b]
1	PPh_3(20)	toluene	60	5	57
2	PPh_3(20)	CH_2Cl_2	60	5	69
3	PPh_3(20)	CH_3CN	60	5	44
4	PPh_3(20)	THF	60	3	42
5	**PPh_3(20)**	**$CHCl_3$**	**60**	**5**	**80**
6[c]	Ar_3P(20)	$CHCl_3$	60	24	36
7	$EtPh_2P$(20)	$CHCl_3$	60	10	42
8	PBu_3(20)	$CHCl_3$	60	10	
9[d]	PPh_3(20)	$CHCl_3$	40	5	66
10	PPh_3(20)	$CHCl_3$	60	5	55
11	PPh_3(30)	$CHCl_3$	60	5	56
12	PPh_3(50)	$CHCl_3$	60	0.5	69
13	PPh_3(10)	$CHCl_3$	60	20	48
14[e]	PPh_3(30)	$CHCl_3$	60	2	49
15[e]	PPh_3(20)	$CHCl_3$	60	5	46
16[f]	PPh_3(20)	$CHCl_3$	60	5	71
17[g]	PPh_3(20)	$CHCl_3$	60	2	68
18[h]	PPh_3(20)	$CHCl_3$	60	2	62
19[i]	PPh_3(20)	$CHCl_3$	60	2	63

[a]Unless otherwise noted, all reactions were carried out with **1a** (0.2 mmol), **2** (0.4 mmol), in solvent (2 mL). [b]Isolated yields. [c]Ar = 4-ClC_6H_4. [d]4 Å MS was used. [e]5 mL $CHCl_3$ was used [f]**1a**:**2** = 1:1.5. [g]$PhCO_2H$ (20 mol %) was used. [h]CH_3CO_2H (20 mol %) was used. [i]*p*-Benzenediol (20 mol %) was used.

It should be noted that the successive [2 + 3] and [3 + 2] cycloaddition reaction is highly diastereoselective, and only one isomer was detected in all reactions. The screen of several different solvents revealed that $CHCl_3$ was more suitable for this reaction, with 80% yield (Table 1, entries 1−5). Then we systematically examined the influence of different catalysts and found that PPh_3 was the best choice (Table 1, entries 5−8). When PBu_3 was used, a complex and intractable mixture of products was obtained. Subsequently, a 4 Å molecular sieve was used, and no better yield was received (Table 1, entry 9). Further studies suggested the amount of catalyst has a certain influence on the reaction (Table 1, entries 10−13). By decreasing the ratio of **1a** and **2** or increasing the amount of solvent to 5 mL, lower yields were obtained (Table 1, entries 14−16). When some additives (such as $PhCO_2H$, CH_3CO_2H, and *p*-benzenediol) were added, no positive results were obtained (Table 1, entries 17−19). Thus, we finally established the optimal reaction conditions for this reaction: using 20% PPh_3 as a catalyst and $CHCl_3$ as solvent to perform the reaction at the 60 °C.

To further improve the yield of **3a**, different γ-substituents of allenoates **2** were examined; the results are shown in Table 2.

Table 2. The Reaction of 1a and 2[a]



entry	R	*T* (h)	Yield (%)[b]
1	H	5	0
2	Me	5	0
3	*n*-Pr	5	0
4	Ph	5	80

[a]Unless otherwise noted, all reactions were carried out with **1a** (0.2 mmol) and **2** (0.4 mmol) in solvent (2 mL). [b]Isolated yields.

No reaction occurred when γ-substituents of allenoates were replaced from Ph to H, Me, and Et. This was because the activity of allenoates has a significant decline in the presence of a γ-substituted group (such as Me, Et, *n*-Bu), although the phenyl could activate the methylene of γ-benzyl-substituted allenoates by π-conjugative effect. Thus, only γ-benzyl-substituted allenoates were effective in the successive [2 + 3] and [3 + 2] cycloaddition reaction. The results suggest that phenyl has the key role in the domino reaction.

With the above optimized reaction conditions, we then surveyed the substrate scope and limitations of the phosphine-catalyzed successive [2 + 3] and [3 + 2] cycloaddition reaction with different (*E*)-1,3-diarylallylidene)-4-methyl-benzenesulfonamide **1** with γ-benzyl-substituted allenoates **2**, and the results are shown in Table 3. For the ketimine, aryl units containing electron-donating or electron-withdrawing substitutents were readily tolerated, thus giving preferentially the corresponding aza-bicyclic[3,3,0]octane derivatives in moderate to good yields (Table 3, 3a−l). First, the electronic properties of the substituent on **2** have a certain influence on this domino reaction, and strong electron-withdrawing substituents resulted in low yields (Table 3: 3c, 3d vs 3a, 3b, 3e). When the same substituent of R1 and R2 was used, 71% yield was obtained (Table 3: 3f). It is noteworthy that the position of the substituent on the phenyl group has a remarkable influence on

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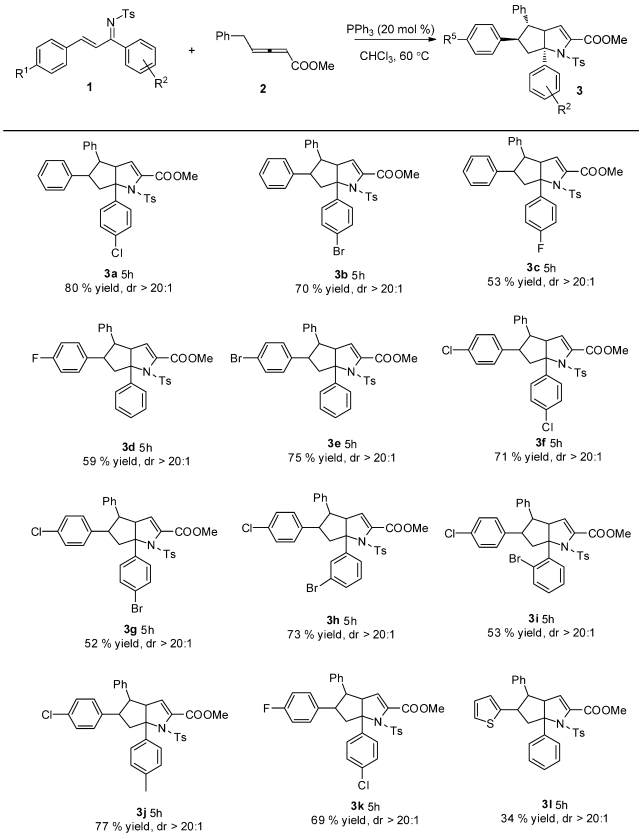
Table 3. The Reaction of 1 and 2.[a,b]



[a]Reaction conditions: catalyst PPh_3 (20 mol %)), **1** (0.2 mmol), **2** (0.4 mmol), $CHCl_3$ (2.0 mL), 60 °C, 5 h. [b]Isolated yields.

this reaction. We found that the best level of yields was obtained for the ketimine with a meta substituent (Table 3: 3g, 3h, 3i). When a different substituent of R1 and R2 was used, similar results were received (Table 3: 3j, 3k vs 3f). We were delighted to find that the ketimine bearing 2-thienyl groups underwent smooth successive annulations with **2**, readily affording the corresponding aza-bicyclo[3,3,0]octane derivatives, albeit with a low yield (Table 3: 3l). The structure and stereochemistry of **3** was characterized by combination of NMR, HRMS spectra, and single-crystal X-ray analysis (**3a**) (Figure 2) (see the Supporting Information).

According to our experimental results and related studies,[14,15] we propose a possible mechanism for this domino reaction (Scheme 2). Nucleophilic addition of phosphine to the γ-benzyl-substituted allenoates **2** gives intermediate **A**, which

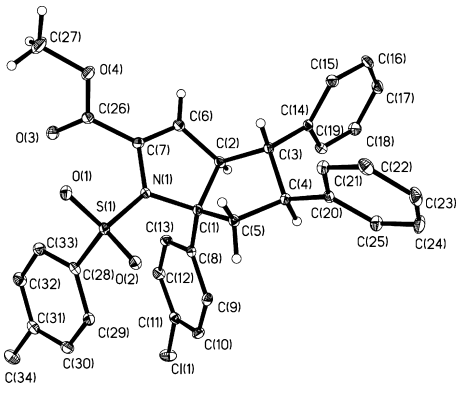
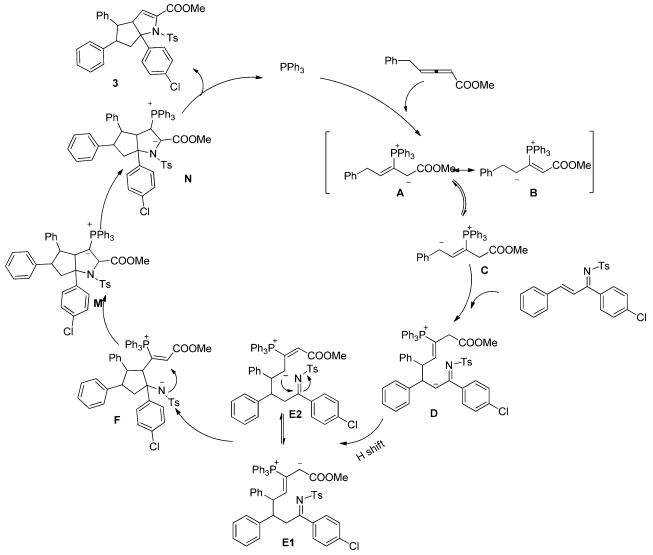


Figure 2. X-ray Crystal Structure of **3a**.

Scheme 2. Mechanism for the Phosphine-Catalyzed Successive [2 + 3] and [3 + 2] Cycloadditions of the Ketimine 1 and γ-Benzyl-Substituted Allenoate 2



can isomerize to intermediate **B**. The crucial event is the formation of the zwitterionic intermediate **C**, which undergoes a sterically favored δ-carbanion addition to the ketimine, producing the intermediate **D**, followed by a hydrogen shift to get the intermediate **E1** and **E2** by a reverse equilibrium. which undergoes another nucleophilic addition to give intermediate **M**. Proton transfer and subsequent β-elimination of the catalyst phosphine leads to the formation of the corresponding adducts.

In conclusion, we have developed a novel phosphine-catalyzed sequential [2 + 3] and [3 + 2] annulation reaction of (*E*)-(1,3-diarylallylidene)-4-methyl-benzenesulfonamide with γ-benzyl-substituted allenoates. This protocol provides a simple and practical strategy for the synthesis of bicyclo compounds. Following this methodology, a series of aza-bicyclo[3,3,0]-octanes were obtained in moderate to good yields. Further mechanistic investigations and applications to the synthesis of bi- or polycyclic compounds are currently underway in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Details of condition optimization, experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org..

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Notes

The authors declare no competing financial interest.

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