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A Phosphine-Catalyzed [3+6] Annulation Reaction of Modified Allylic Compounds and Tropone

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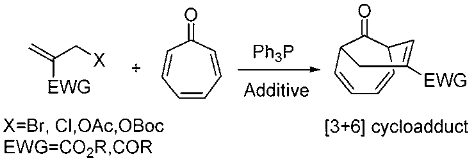
ABSTRACT



A novel phosphine-catalyzed reaction of modified allylic compounds, including acetates, bromides, chlorides, or *tert*-butyl carbonates derived from the Morita–Baylis–Hillman (MBH) reaction with tropone to yield [3+6] annulation products in excellent yields was developed. It offers a simple and convenient method for constructing bridged nine-membered carbocycles.

Ylide reactions are among the most powerful tools for constructing olefins[1] and cyclopropanes.[2] Catalytic olefinations, epoxidations, aziridinations, and cyclopropanations of tellurium or sulfur ylides are well developed.[2,3] Recently Gaunt's group reported the catalytic cyclopropanation through nitrogen ylides.[4] To our knowledge, the catalytic version of the carbon−phosphorus ylide reaction is rarely reported. As a part of our continuing study on the development of tertiary phosphine-catalyzed annulation reactions,[5,6] recently we developed a phosphine-catalyzed [3+2] annulation of carbon−phosphorus ylides with electron-deficient olefins.[7]

The discovery of this novel phosphine-catalyzed reaction of carbon−phosphorus ylides, generated in situ from Morita−Baylis−Hillman (MBH) reaction products including acetates, bromides, or *tert*-butyl carbonates, stimulated us to explore its new reaction with other kinds of dipolarophiles.

Tropone is a molecule with interesting electronic properties. From Frontier Molecular Orbital theory, it was suggested that nucleophilic attack on tropone should occur preferentially at C(2) and C(7).[8] Indeed, in cycloadditions of dienes with tropone, a [4+6] pathway may compete with the [4+2] reaction.[9] On the other hand, tropone has been reported to yield [2+8] cycloadducts on reaction with tetracarbethoxy-

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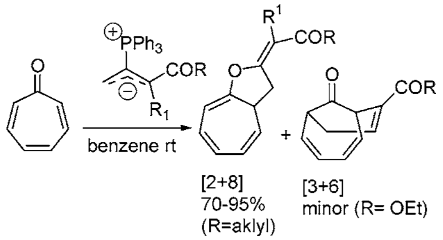
Scheme 1

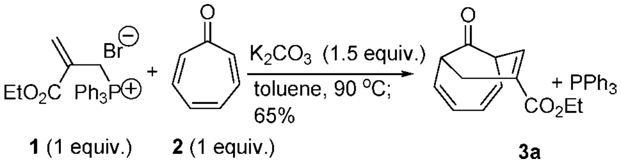


allene and phenylsulfonylallene in refluxing benzene.[10] Trost reported a [3+6] cycloaddition of 2-[(trimethylsilyl)methyl]-allyl carboxylates with tropone using a Pd(0) catalyst.[11] When tropone reacted with an allenic ketone/ester under the catalysis of Ph_3P, [2+8] cycloadducts are obtained in high yields and the [3+6] cycloadduct has been isolated only in the case of allenic ester as a minor product (Scheme 1).[12] In some cases, the reaction of tropone with a variety of ethyl 2,3-dienoates yielded a number of [2+4] cycloadducts in low yield.[13]

Herein, we wish to report our recent results which demonstrate that the allylic−phosphorus ylide cannot only form five-membered rings with electron-deficient alkenes but also undergoes exclusively the formation of bridged nine-membered carbocycles by [3+6] annulation with tropone under the catalysis of Ph_3P.

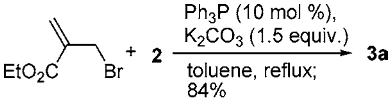
To initiate our study, phosphonium salt **1**, tropone **2**, and potassium carbonate in toluene were stirred at 90 °C, affording a [3+6] adduct **3a** in 65% yield and Ph_3P. Formation of any [3+2] or [2+8] addition product was not observed (Scheme 2).

Scheme 2



Compound **3a** was characterized by spectroscopic analysis (IR, ^1H NMR, ^{13}C NMR, $^1H-^1H$ COSY spectra, mass spectra, and high-resolution mass spectra).[14] Since phosphonium salt **1** was prepared from ethyl 2-bromomethyl-2-propenoate (**4a**) and Ph_3P, it was expected that the above reaction might occur starting from **4a** by utilizing a catalytic amount of Ph_3P. Accordingly, adding the solution of the C3 component (**4a**, 1.2 equiv) and the C6 component (tropone **2**, 1.0 equiv) in toluene dropwise with a syringe pump to a mixture of Ph_3P (10 mol %) and K_2CO_3 (1.5 equiv) in refluxing toluene, product **3a** was isolated in 84% yield after chromatography (Scheme 3). In the absence of Ph_3P, no reaction occurred.

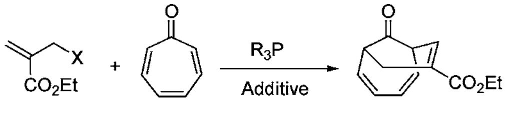
Scheme 3



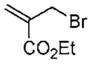
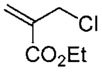
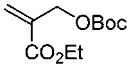
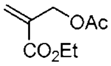
4a

To test the feasibility of these processes, chloride and acetate analogues of **4a** were reacted with **2**, using Ph_3P as

Table 1. Phosphine-Catalyzed [3+6] Annulation of Compound **4** and Tropone[a]



4a-d **3a**

entry	C3 component	R3P	T(°C)	t (h)	yield (%)[b]
1	 4a	Ph_3P	reflux	3	84
2	4a	Ph_3P	rt	24	Trace
3	 4b	Ph_3P	reflux	3	68
4[c]	 4c	Ph_3P	reflux	3	87
5[c]	4c	Ph_3P	rt	5	65
6	 4d	Ph_3P	reflux	3	92
7[d]	4d	Ph_3P	reflux	5	57
8	4d	$EtPh_2P$	reflux	3	78
9	4d	$(Tol)_3P$	reflux	3	88

[a] General reaction conditions: Under Ar, a solution of C3 components (0.60 mmol) and tropone (0.50 mmol) in toluene (2 mL) was added over the indicated time with a syringe pump to a mixture of phosphine (0.05 mmol) and K_2CO_3 (0.75 mmol) in toluene (0.5 mL) at the indicated temperature and the reaction mixture was stirred further for 3 h. [b] Isolated yield. [c] The reaction conditions were similar to those in footnote a, except that the reaction was performed without the addition of K_2CO_3. [d] The reaction conditions were similar to those in footnote a, except that the reaction was performed without slow addition.

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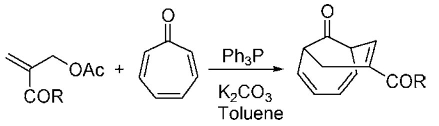
(14) Characterization data for **3a** as well as $^1H-^1H$ COSY specra are available in the Supporting Information.

Table 2. Triphenylphosphine-Catalyzed [3+6] Annulation of Tropone and Allylic Acetates with Different Substituents[a]



4e-j **3b-g**

entry	R	t (h)	product	yield (%)[b]
1	OMe (**4e**)	3	**3b**	90
2	Ph (**4f**)	1	**3c**	85
3	4-Me-C_6H_4- (**4g**)	1	**3d**	89
4	4-Cl-C_6H_4- (**4h**)	1	**3c**	93
5	4-Br-C_6H_4- (**4i**)	1	**3f**	95
6	4-MeO-C_6H_4- (**4j**)	1	**3g**	91

[a] General reaction condition: Under Ar, a solution of C3 components (0.60 mmol) and tropone (0.50 mmol) in toluene (2 mL) was added over the indicated time with a syringe pump to a mixture of Ph_3P (0.05 mmol) and K_2CO_3 (0.75 mmol) in refluxing toluene (0.5 mL) and the reaction mixture was stirred further for an hour. [b] Isolated yield.

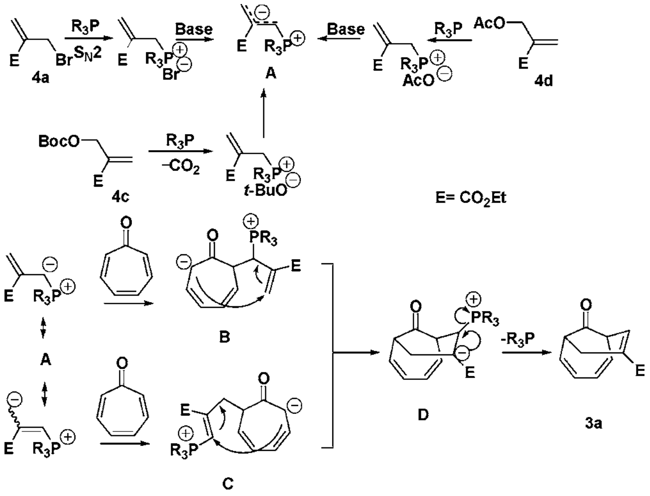
the catalyst and K_2CO_3 as the base (Table 1, entries 1, 3, 6, and 7). Among them, the acetate derivative **4d** is the most efficacious C3 component. As for the *tert*-butyl carbonate derivative, the reaction can be carried out in the absence of a base because the in situ generated *tert*-butoxide anion can act as a base (Table 1, entries 4 and 5). While room temperature retarded the reaction of the bromide derivative (**4a**) (Table 1, entry 2), the *tert*-butyl carbonate **4c** can still react albeit with a little lower yield at room temperature (Table 1, entry 5). A screen of alternative catalysts led to our optimal selection of Ph_3P (Table 1, entries 8 and 9).

The results of modified allylic acetates are listed in Table 2 in which the [3+6] cycloadducts were detected in all cases exclusively with good to excellent yield.

Not only the ester, but also different kinds of carbonyl substituted allylic acetates perform well in this reaction (Table 2). Thus, this novel reaction potentially provides a new approach to the preparation of multifunctionalized bridged nine-membered rings.

A plausible mechanism for this phosphine-catalyzed [3+6] annulation reaction of the substituted allylic compounds and tropone is proposed (Scheme 4).

Scheme 4



The reaction might be initiated by the formation of the phosphonium salt via S_N2 or the addition−elimination mechanism,[7,15] which was deprotonated by potassium carbonate or by the in situ generated *tert*-butoxide anion affording an ylide **A**. As exemplified by the case of annulation reaction of tropone and **4a**, subsequent nucleophilic α- or γ-addition of the ylide **A** to the electron-deficient olefin (tropone) yielded zwitterionic intermediates **B** or **C**, followed by cyclization via intramolecular conjugate addition affording the same betaine **D**. Finally, elimination of the phosphine completed the catalytic cycle. As shown in Scheme 4, either α- or γ-attack of the ylide **A** to tropone can lead to the formation of **3a**.

In summary, a catalytic [3+6] annulation reation is realized by reaction of electron-deficient allylic compounds with tropone. In contrast to the reported modes of reactions of dienes and allene with tropone,[9,11] the reaction of allylic phosphorus−ylide with tropone proceeds only via the [3+6] mode. The appealing features of this process involve the ready availability of the starting materials (e.g., C3 components including bromides, chloride, acetates, or *tert*-butyl carbonates could be easily obtained by further transformation of the adduct of the Morita−Baylis−Hillman reaction).

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Supporting Information Available: Typical experimental procedures and characterization data for new compounds (**3a**−**g**, **4g**−**j**), ^{1}H and ^{13}C NMR spectra of **3a** and **3b**, and COSY spectra of **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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