



Phosphine-catalyzed [3+3] annulation reaction of modified *tert*-butyl allylic carbonates and substituted alkylidenemalononitriles

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ABSTRACT

A phosphine-catalyzed [3+3] annulation reaction of modified *tert*-butyl allylic carbonates with various alkylidenemalononitriles to form cyclohexenes was developed. The use of protic solvent is crucial in this reaction. When non-polar solvent, toluene or xylene, was used, only non-cyclized product was obtained.

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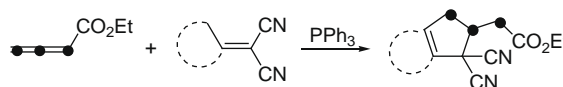
Recently, reports of phosphines as nucleophilic catalysts have grown significantly.^{1,2} For example, phosphine-catalyzed reaction of allenates and butynoates has proven to be efficient for the synthesis of polyfunctionalized structures,² especially the cyclopentene derivatives. Recently we reported an unexpected phosphine-catalyzed [3+2] reaction of allenates with substituted alkylidenemalononitriles in which the allenates acted as the two-carbon unit in the formed cyclopentenes instead of the three-carbon unit in general.^{2a} This is due to the acidity of the hydrogen atom of the substituted methyl group in alkylidenemalononitriles (Scheme 1).

On the other hand, we also developed the phosphine-catalyzed [3+2] and [3+6] annulation reactions of carbon-phosphorus ylides with electron-deficient olefins³ and imines.⁴ In these reactions, simple allylic compounds, which can be easily obtained by one-step transformation of the product of Morita–Baylis–Hillman reaction, can be used as three-carbon unit instead of the complex alkyneates or allenates.^{3–5} On detailed study, we found that the reaction of allylic compounds has some different results as compared with the allenates,^{3,4} which stimulated us to study the reaction of the modified *tert*-butyl allylic carbonates and substituted alkylidenemalononitriles.

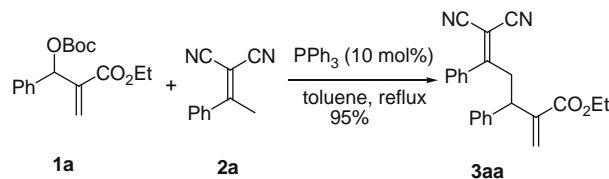
Compared with [3+2] and [4+2] annulation reactions, relatively little was known about the [3+3] cycloaddition.⁶ No [3+3] annulation in phosphine-catalyzed reaction was reported.⁷ Herein, we wish to report our recent results on the [3+3] annulation of modi-

fied allylic compounds with 3-substituted 1,1-dicyanoalkenes via a catalytic carbon–phosphorus ylide reaction to form substituted cyclohexenes.

In our initial study, we examined the reaction of the *tert*-butyl allylic carbonate (**1a**) and 2-(1'-phenylethylidene)malononitrile (**2a**) with PPh₃ (10 mol %) in toluene under reflux. Unfortunately, a non-cyclized product **3aa** was obtained (Scheme 2). From the structure of **3aa**, it is clear that the basicity of the phosphine was insufficient to promote the intramolecular conjugate addition to complete the cyclization. Then the reaction was carried out in different solvents. In non-polar solvents, for example, toluene and

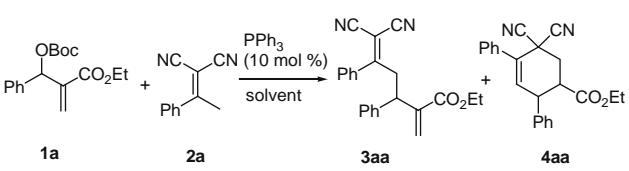


Scheme 1. Phosphine-catalyzed [3+2] reaction of allenates and substituted alkylidenemalononitriles.



Scheme 2.

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Table 1Effect of solvents on the formation of **3aa** and **4aa** from phosphine-catalyzed reaction of **1a** and **2a**^a


Entry	Solvent	Temp.	3aa ^b (%)	4aa ^b (%) (trans:cis) ^c
1	Toluene	Reflux	95	Trace
2	Xylene	Reflux	79	Trace
3	ClCH ₂ CH ₂ Cl	Reflux	42	52 (2.7:1)
4	Dioxane	Reflux	51	28 (1.6:1)
5	CH ₃ CN	Reflux	48	42 (3.4:1)
6	EtOH	Reflux	17	44 (5.2:1)
7	<i>i</i> -PrOH	Reflux	16	75 (4.8:1)
8	<i>t</i> -BuOH	Reflux	39	56 (5:1)
9	PEG (200–300)	90 °C	—	45 (4.8:1)

^a Reaction conditions: Under Ar, a mixture of **1a** (73 mg, 0.24 mmol), **2a** (33.6 mg, 0.2 mmol), and PPh₃ (5.3 mg, 0.02 mmol) in solvents (2 mL) was stirred at the temperature indicated.

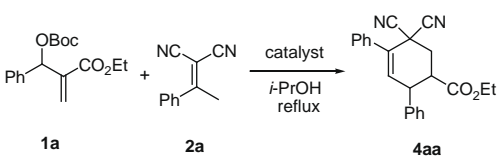
^b Isolated yields.

^c Diastereoisomeric ratio was determined by ¹H NMR.

xylene, **3aa** was the only product (Table 1, entries 1 and 2). In polar solvents, both products **3aa** and **4aa** were obtained (Table 1, entries 3–9). Encouragingly, the [3+3] addition product **4aa** was obtained as mixture of a 4.8:1 (trans:cis) stereoisomers in 75% yield with 16% of product **3aa** when 2-propanol was used as solvent (Table 1, entry 7).⁸ The assignment of the trans stereochemistry of the major isomer **4aa** was confirmed by ¹H NMR spectra and X-ray crystallography.⁹ On further reaction of **3aa** and PPh₃ in 2-propanol, **4aa** could also be produced. Thus, 2-propanol was selected as the optimal solvent in this reaction. The use of 2-propanol as solvent to promote the intramolecular conjugate addition in phosphine-catalyzed reaction has been reported recently.¹⁰

Many phosphines could be used as catalyst in this reaction (Table 2). Using 20 mol % of triphenylphosphine provided optimal reactivity, giving the cyclization product **4aa** as 5:1 mixture of diastereoisomers in 89% yield (Table 2, entry 2). No product was obtained when the strong nucleophilic phosphine PBu₃ was used (Table 2, entry 5).

Under these optimized conditions, the scope of the phosphine-catalyzed [3+3] cycloaddition was studied (Table 3). The reaction was general and was found to occur with **2a** and different substituted *tert*-butyl allylic carbonates. Good yields were obtained for

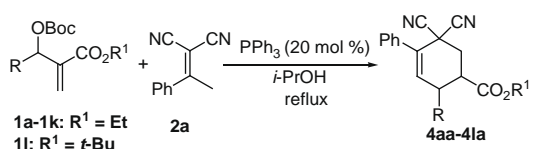
Table 2Formation of **4aa** from **1a** and **2a** using different catalysts^a


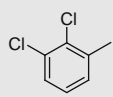

Entry	Catalyst	Yield ^b (%)	trans:cis ^c
1	PPh ₃ (10 mol %)	75	4.8:1
2	PPh ₃ (20 mol %)	89	5.2:1
3	PPh ₂ Et (20 mol %)	76	5.9:1
4	PPhEt ₂ (20 mol %)	76	4.5:1
5	PBu ₃ (20 mol %)	—	—

^a Reaction conditions: Under Ar, a mixture of **1a** (73 mg, 0.24 mmol), **2a** (33.6 mg, 0.2 mmol), and catalyst in 2-propanol (2 mL) was stirred at reflux.

^b Isolated yields.

^c Diastereoisomeric ratio was determined by ¹H NMR.

Table 3Reaction of **2a** and **1** with different substituents^a


Entry	R	Product	Yield ^b (%)	trans:cis ^c
1	Ph	4aa	89	5.1:1
2	<i>p</i> -MeC ₆ H ₄	4ba	88	3.9:1
3	<i>p</i> -MeOC ₆ H ₄	4ca	84	4:1
4	<i>p</i> -ClC ₆ H ₄	4da	91	5.5:1
5		4ea	70	5.8:1
6	<i>p</i> -NO ₂ C ₆ H ₄	4fa	74	>10:1
7		4ga	61	4:1
8	CH ₃	4ha	87	>10:1
9	<i>n</i> -Pr	4ia	84	>10:1
10	<i>i</i> -Pr	4ja	37	>10:1
11	<i>i</i> -Bu	4ka	54	>10:1
12	Ph (R ¹ = <i>t</i> -Bu)	4la	87	5:1

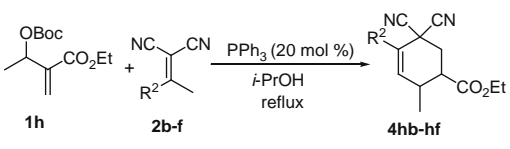
^a Reaction conditions: Under Ar, a mixture of **1a** (73 mg, 0.24 mmol), **2a** (33.6 mg, 0.2 mmol), and PPh₃ (11.6 mg, 0.04 mmol) in 2-propanol (2 mL) was stirred at reflux.

^b Isolated yields.

^c Diastereoisomeric ratio was determined by ¹H NMR.

the aryl substituted substrates with both electron-donating and electron-withdrawing groups. When the aryl group was changed to alkyl, the yield was high (Table 3, entries 8 and 9) and the diastereoselectivities were improved (Table 3, entries 8–11). The yields were decreased as the substituents became bulky (Table 3, entries 10 and 11). When a bulky *t*-butyl ester was used, similar yield was obtained (Table 3, entry 12).

To further establish the scope of the reaction, the reaction of substrates **2** with different substituents in aryl group with **1h** was also tried. Electronic effect was found to be very important. The compounds with electron-withdrawing group gave better yields

Table 4Reaction of **1h** and **2** with different substituents^a


Entry	R ²	Product	Yield ^b (%)	trans:cis ^c
1 ^d	<i>p</i> -MeC ₆ H ₄	4hb	59	>10:1
2 ^e	<i>p</i> -MeOC ₆ H ₄	4hc	58	>10:1
3	<i>p</i> -BrC ₆ H ₄	4hd	100	>10:1
4	<i>p</i> -NO ₂ C ₆ H ₄	4he	67	>10:1
5	<i>t</i> -Bu	4hf	75	>10:1

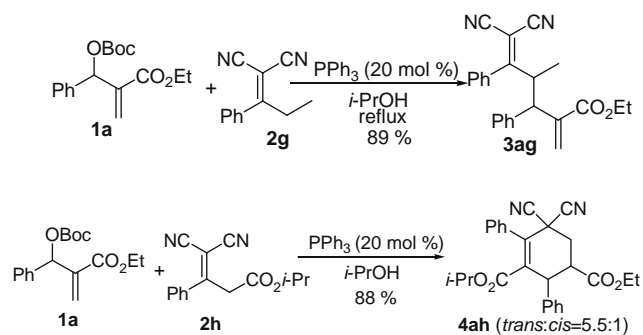
^a Reaction conditions: Under Ar, a mixture of **1a** (73 mg, 0.24 mmol), **2a** (33.6 mg, 0.2 mmol), and PPh₃ (11.6 mg, 0.04 mmol) in 2-propanol (2 mL) was stirred in reflux.

^b Isolated yields.

^c Diastereoisomeric ratio was determined by ¹H NMR.

^d Non-cyclized product **3hb** was isolated in 29% yield.

^e Non-cyclized product **3hc** was isolated in 25% yield.



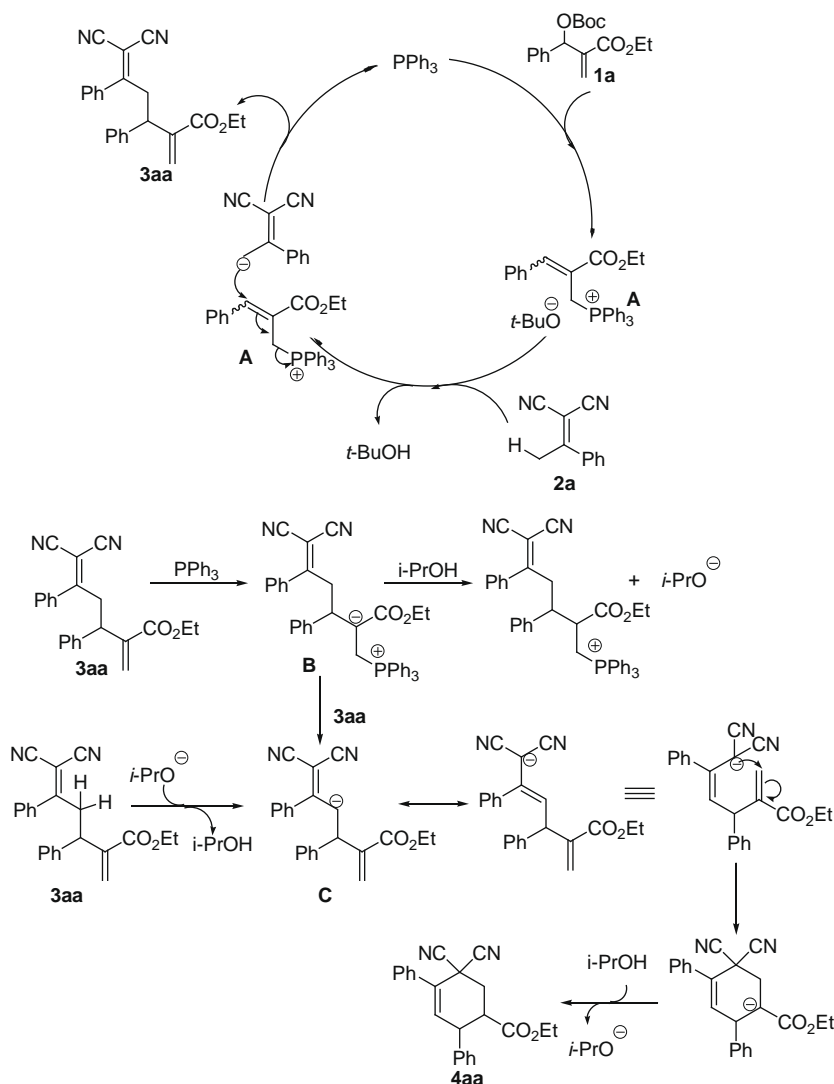
Scheme 3.

(Table 4, entries 3 and 4). For the compounds with electron-donating group, the non-cyclized products **3** could also be obtained (Table 4, entries 1 and 2). When the aryl group was changed to *tert*-butyl group, the reaction can still occur with similar yield. When the methyl group of substrate **2** was changed to ethyl (substrate **2g**), the cyclization could not proceed and only non-cyclized product **3ag** was obtained (Scheme 3), which might be due to the lower acidity of the ethyl group. This can be supported by the fact

that a high yield of **4ah** occurred when a carboxylate group was introduced into the ethyl group (substrate **2h**) (Scheme 3).

The possible mechanism of this [3+3] cyclization reaction was shown in Scheme 4. As elucidated in our previous paper, the phosphonium salt **A** was formed from PPh₃ and the allylic substrate first.^{5,6} The methyl group of **2** was believed to be deprotonated by the *tert*-butoxy anion generated in situ because of its acidic property. The formed carbanion could attack the intermediate **A** and PPh₃ was eliminated giving the non-cyclized product **3aa**. Conjugate addition of the phosphine to **3aa** generated a phosphonium-substituted carbanion **B**. This carbanion may serve as the base for the intramolecular conjugate addition.¹¹ The intermediate **B** is possible to attract the proton from **3aa** to form **C** making the intramolecular cyclization possible. In the presence of 2-propanol, protonation of **B** may occur easily to form the alkoxide ion which can serve as the base in the intramolecular cyclization of **3aa** to improve the reaction yield.¹⁰

In conclusion, we developed a novel phosphine-catalyzed [3+3] annulation reaction of modified allylic *tert*-butyl carbonates and substituted alkylidenemalononitriles yielding functionalized cyclohexene derivatives in moderate to excellent yield with moderate to good diastereoselectivity. The use of protic solvent is crucial in this reaction. Detailed study of the mechanism is underway.



Scheme 4. Possible mechanism of the [3+3] annulation reaction.

Acknowledgments

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Supplementary data

Supplementary data (Experimental procedure, characterization data, and copies of ^1H and ^{13}C NMR spectra for new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.05.085.

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- Control experiment showed that no transesterification was found between **1** and 2-propanol.
- The structure of the product **4aa** was confirmed by X-ray crystallography. Deposit number of compound **4aa** from Crystallographic Data Centre: CCDC 234945. Copies of the data can be obtained free of charge on application to CCDC, 12, Union Road, Cambridge CB21EZ, UK; fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk.
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