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Phosphine-Catalyzed [4 + 3] Annulation for the Synthesis of Highly Functionalized Bicyclo[3.2.2]nonadienes

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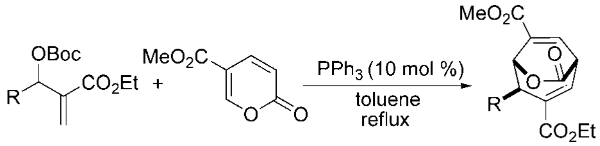
ABSTRACT



A phosphine-catalyzed [4 + 3] annulation of modified allylic carbonates with methyl coumalate was developed. This strategy offered a powerful method for the construction of bicyclo[3.2.2]nonadiene skeleton with high stereoselectivity.

The [4 + 3] cycloaddition reaction affords a convenient way to prepare relatively complex seven-membered rings from simple starting materials.[1,2] It is always used to synthesize target molecules such as natural products and drugs containing seven-membered rings.

Recently, phosphine catalysis as a growing area of synthetic organic chemistry is attracting more and more attention.[3,4] In particular, phosphine-catalyzed annulations have been proven to be very useful methods to provide various carbo- and heterocycles. As to the [4 + 3] annulations, Ishar's group reported a phosphine-catalyzed [4 + 3] annulation reaction between allenes and 3-(*N*-aryliminomethyl)chromones to afford *N*-aryl-2,3-dihydro-4-ethoxycarbonylchromano[2,3-b]azepine-6-ones.[5] Herein we report a

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(1) Recent reviews of [4 + 3] cycloaddition, see: (a) Harmata, M. *Adv. Synth. Catal.* **2006**, *348*, 2297. (b) Harmata, M. *Acc. Chem. Res.* **2001**, *34*, 595.

(2) Recent reports of [4 + 3] cycloaddition, see: (a) Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 9244. (b) Olson, J. P.; Davies, H. M. L. *Org. Lett.* **2008**, *10*, 573. (c) Hsu, Y.-C.; Datta, S.; Ting, C.-M.; Liu, R.-S. *Org. Lett.* **2008**, *10*, 521. (d) Manning, J. R.; Davies, H. M. L. *Tetrahedron* **2008**, *64*, 6901. (e) Shintani, R.; Murakami, M.; Hayashi, T. *Pure Appl. Chem.* **2008**, *80*, 1135. (f) Antoline, J. E.; Hsung, R. P. *Synlett* **2008**, 739. (g) Montana, A. M.; Barcia, J. A.; Kociok-Kohn, G.; Font-Bardia, M.; Solans, X. *Helv. Chim. Acta* **2008**, *91*, 187. (h) Ivanova, O. A.; Budynina, E. M.; Grishin, Y. K.; Trushkov, I. V.; Verteletskii, P. V. *Angew. Chem., Int. Ed.* **2008**, *47*, 1107. (i) Shintani, R.; Murakami, M.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12356. (j) Gulias, M.; Duran, J.; Lopez, F.; Castedo, L.; Mascarenas, J. *J. Am. Chem. Soc.* **2007**, *129*, 11026. (k) MaGee, D. I.; Godineau, E.; Thornton, P. D.; Walters, M. A.; Sponholtz, D. J. *Eur. J. Org. Chem.* **2007**, 2203. (l) Saito, S.; Takeuchi, K. *Tetrahedron Lett.* **2007**, *48*, 595. (m) Dai, X.; Davies, H. M. L. *Adv. Synth. Catal.* **2006**, *348*, 2449.

(3) For reviews on phosphine-catalyzed reactions, see: (a) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535. (b) Valentine, D. H., Jr.; Hillhouse, J. H. *Synthesis* **2003**, 317. (c) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035. (d) Lu, X.; Du, Y.; Lu, C. *Pure Appl. Chem.* **2005**, *77*, 1985. (e) Nair, V.; Menon, R. S.; Sreekanth, A. R.; Abhilash, N.; Biju, A. T. *Acc. Chem. Res.* **2006**, *39*, 520. (f) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560. (g) Ye, L.-W.; Zhou, J.; Tang, Y. *Chem. Soc. Rev.* **2008**, *37*, 1140.

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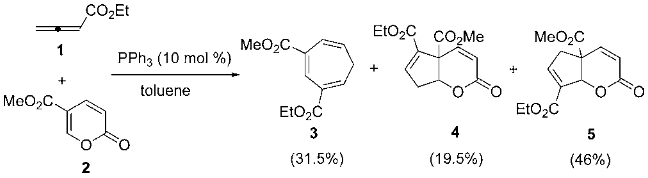
phosphine-catalyzed highly diastereoselective synthesis of bicyclo[3.2.2]nonadienes by [4 + 3] cycloaddtion.

Methyl coumalate is a very useful synthon in organic synthesis. It can be served as diene or dienophile depending on their reaction partners in **D**−**A** reaction.[6] However, it is rarely used in [4 + 3] cycloaddition. Only one example is the [4 + 3] cycloaddition of 2-[(trimethylsilyl)methyl]allyl carboxylates with methyl coumalate using a Pd(0) catalyst reported by Trost.[7] No phosphine-catalyzed reaction using methyl coumalate was reported.

In our earlier work, ethyl allenoate **1**, methyl coumalate **2**, and a catalytic amount of PPh_3 were stirred in toluene at room temperature to afford three products. Besides the seven-membered [4 + 3] adduct **3**, two [3 + 2] annulation products, **4** and **5**, were also produced (Scheme 1). It is worth noting that carbon dioxide was eliminated in the [4 + 3] adduct **3**. Changing the solvents and catalysts, the selectivity was not improved.

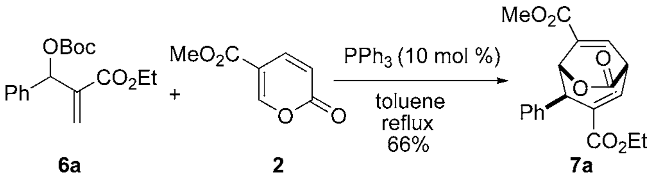
Scheme 1. PPh_3-Catalyzed Reaction of Methyl Coumalate and Ethyl Allenoate



Recently, our group developed a series of phosphine-catalyzed reactions of carbon−phosphorus ylides with electron-deficient olefins or imines.[8] In these reactions, the modified allylic compounds were used as the three carbon unit. After detailed study, it was found that the reaction behavior of allylic compounds exhibit some different results compared with the allenoates.[8] These discoveries stimulated us to explore the reaction of the modified allylic compounds with methyl coumalate **2**.

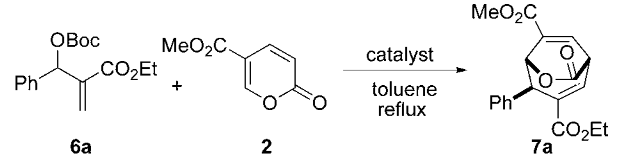
When *tert*-butyl allylic carbonate **6a** was used to react with methyl coumalate **2** in toluene at reflux under 10 mol % of PPh_3, the reaction went smoothly providing the main [4 + 3] adduct **7a** in 66% yield with a small amount of unidentified byproducts (Scheme 2). The structure of **7a** was established by X-ray crystallography of the analogous product **7c** with a *p*-methoxy group on the benzene ring.[9] To our surprise, carbon dioxide was not eliminated in this new reaction (Scheme 2).

Scheme 2. PPh_3-Catalyzed Reaction of Methyl Coumalate and Modified Allylic Carbonate



To improve the yield of **7a**, the ratio of two substrates, the solvents and other phosphines were tested (Table 1).

Table 1. Formation of **7a** from **6a** and **2** under the Catalysis of Different Phosphines[a]



entry	catalyst (10 mol %)	**6a**:**2**	temp. (°C)	time (h)	yield (%)[b]
1[c]	PPh_3	1.2:1	reflux	6	66
2	PPh_3	1:1.2	reflux	6	87
3[d]	PPh_3	1:1.2	reflux	6	78
4	PPh_2Et	1:1.2	rt	15	83
5	$PPhEt_2$	1:1.2	rt	2	80
6	$(^n\mathrm{Bu})_3$	1:1.2	rt	96	26

[a] Reaction conditions: Under Ar, a mixture of **6a** (61 mg, 0.2 mmol), **2** (37 mg, 0.24 mmol) and catalyst (0.02 mmol) in toluene (2 mL) was stirred at reflux. [b] Isolated yields. [c] Under Ar, a mixture of **6a** (73 mg, 0.24 mmol), **2** (31 mg, 0.2 mmol) and PPh_3 (5.3 mg, 0.02 mmol) in toluene (1 mL) was stirred at reflux. [d] One milliliter of toluene was used.

Changing PPh_3 to the more nucleophilic phosphines PPh_2Et or $PPhEt_2$, similar yields were obtained (Table 1, entries 4 and 5). The strong nucleophilic phosphine PBu_3 displays a very poor reactivity giving a very low yield (Table 1, entry 6). In the tested phosphines, PPh_3 gave the best result. This reaction is sensitive to temperature. The time of reaction became longer and the yield decreased at lower temperature.

The reactions in different solvents were also studied (Table 2). Low yield of products could be isolated in solvents with low boiling point (e.g., ethyl ether and CH_2Cl_2, Table 2, entries 3−6). The yields were also very poor in polar solvents. Toluene was chosen as the best solvent.

Under these optimized conditions, the scope of the phosphine-catalyzed [4 + 3] cycloaddition was explored

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(6) Recent reports using methyl coumalate as diene, see: (a) Delaney, P. M.; Browne, D. L.; Adams, H.; Plant, A.; Harrity, J. P. A. *Tetrahedron* **2008**, *64*, 866. (b) Delaney, P. M.; Moore, J. E.; Harrity, J. P. A. *Chem. Commun.* **2006**, 3323. (c) Chen, C. H.; Liao, C. C. *Org. Lett.* **2000**, *2*, 2049. (d) Kitamura, T.; Wasai, K.; Todaka, M.; Fujiwara, Y. *Synlett* **1999**, 731. (e) Obata, T.; Shimo, T.; Suishu, T.; Somekawa, K. *J. Heterocycl. Chem.* **1998**, *35*, 1361. (f) Jung, M. E.; Street, L. J.; Usui, Y. *J. Am. Chem. Soc.* **1986**, *108*, 6810. Recent reports using methyl coumalate as dienophile, see: (g) Shimo, T.; Yamasaki, S.; Date, K.; Uemura, H.; Somekawa, K. *J. Heterocycl. Chem.* **1993**, *30*, 419. (h) Colvin, E. W.; Thom, I. G. *Tetrahedron* **1986**, *42*, 3137. (i) Kraus, G. A.; Frazier, K. *J. Org. Chem.* **1980**, *45*, 4820. (j) Matsui, T.; Kitajima, S.; Nakayama, M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 316. (k) Brown, B. A.; Colvin, E. W. *J. Chem. Soc., Chem. Commun.* **1984**, 1514.

(7) Trost, B. M.; Schneider, S. *Angew. Chem., Int. Ed.* **1989**, *28*, 213.

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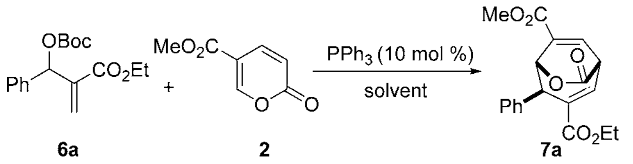
(9) Please see the CIF file in the Supporting Information.

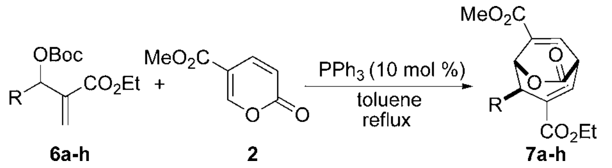
Table 2. Formation of **7a** from **6a** and **2** in Different Solvents[a]



entry	solvent	temp.	time (h)	yield (%)[b]
1	toluene	reflux	6	87
2	*n*-hexane	reflux	13	50
3	CH_2Cl_2	rt	17	N.R.
4	CH_2Cl_2	reflux	12	20
5	diethyl ether	rt	16	N.R.
6	diethyl ether	reflux	11	6
7	THF	reflux	30	24
8	dioxane	reflux	35	38
9	*t*-BuOH	reflux	13	18
10	CH_3CN	reflux	11	N.R.

[a] Reaction conditions: Under Ar, a mixture of **6a** (61 mg, 0.2 mmol), **2** (37 mg, 0.24 mmol) and PPh_3 (5.3 mg, 0.02 mmol) in toluene (2 mL) was stirred at reflux. [b] Isolated yields.

Table 3. Synthesis of **7** from Different Allylic Compounds[a]

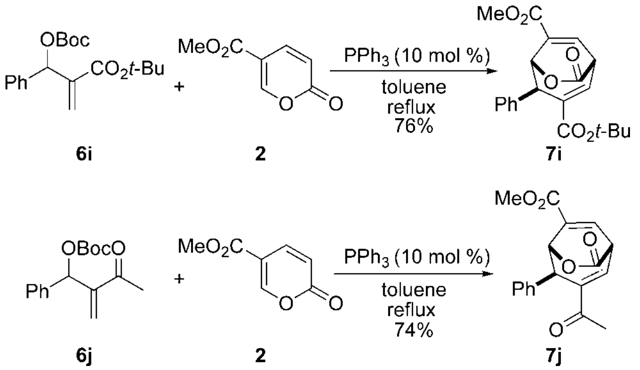


entry	R	product	time (h)	yield (%)[b]
1	Ph	**7a**	6	87
2	*p*-MeC_6H_4	**7b**	4	77
3	*p*-$MeOC_6H_4$	**7c**	4	86
4	*p*-ClC_6H_4	**7d**	3	77
5	*o*-Cl(*m*-Cl)C_6H_3	**7e**	3	57
6	*p*-$NO_2C_6H_4$	**7f**	5.5	62
7	CH_3	**7g**	11	54
8	*i*-Pr	**7h**	28	58

[a] Reaction conditions: Under Ar, a mixture of **6** (0.2 mmol), **2** (37 mg, 0.24 mmol) and PPh_3 (5.3 mg, 0.02 mmol) in toluene (2 mL) was stirred at reflux. [b] Isolated yields.

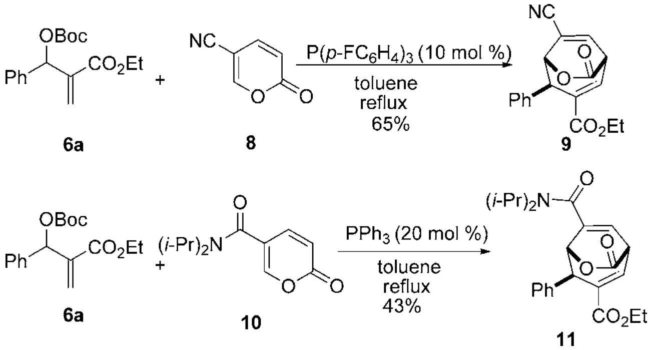
(Table 3). The reaction was general and could occur with different substituted *tert*-butyl allylic carbonates providing products in moderate to good yields no mater with the electron-donating or electron-withdrawing group in aryl group. When the aryl group was changed to alkyl, the reaction also provided moderate yields of products. Increasing the steric bulkiness of the ester group of *tert*-butyl allylic carbonates (**6i** in Scheme 3), a little lower yield was obtained. When the ester group of *tert*-butyl allylic carbonates was changed to carbonyl (**6j** in Scheme 3), the reaction can still occur.

Scheme 3. PPh_3-Catalyzed Reactions of Methyl Coumalate and Allylic Carbonates **6i** and **6j**



To further examine the scope of the reaction, the reactions of other pyrones with *tert*-butyl allyl carbonate (**6a**) were studied. Using the nitrile or amide substituted pyrones (**8** or **10**), the reactions can still occur with little change of the conditions (Scheme 4).

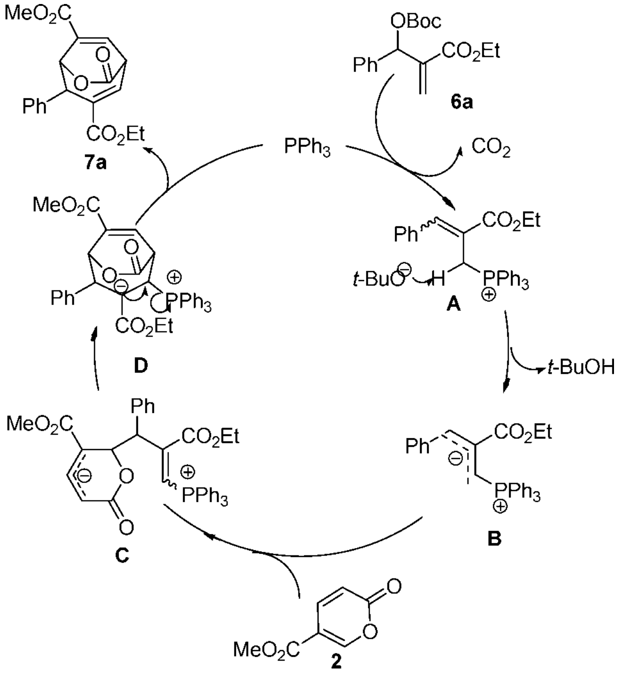
Scheme 4. Phosphine-Catalyzed Reactions of Allylic Carbonate **6a** and Pyrones



Although the mechanism of this cyclization reaction has not been unequivocally established, a possible mechanism for this phosphine-catalyzed [4 + 3] cycloaddition is proposed (Scheme 5). The reaction might be initiated by the formation of the phosphonium salt **A** via the addition−elimination mechanism,[8] followed by deprontonation by the in situ generated *tert*-butoxide anion affording a ylide **B**. Subsequent nucleophilic addition of intermediate **B** to methyl coumalate **2** yields the intermediate **C**. **C** adds intramolecularly to the electron-deficient olefin and gives the intermediate **D** which will eliminate phosphine affording [4 + 3] adduct. The high selectivity of this reaction might be explained by the steric hindrance of the bulky phosphine and the substituents on coumalate in reaction of intermediate **B** or **C** as shown in Figure 1. Of course, another possibility that the reaction is under thermodynamic control cannot be excluded.

Comparing the two [4 + 3] reactions of allenoates or *tert*-butyl allylic carbonates with methyl coumalate (Schemes 1 and 2), it is worth mentioning that there is a big difference in the elimination of carbon dioxide. According to the similar

Scheme 5. Proposed Mechanism for [4 + 3] Cycloaddition of *tert*-Butyl Allylic Carbonates with Methyl Coumalate



mechanism, the reaction of allenoates with methyl coumalate will generate the intermediate **E** in which carbon dioxide is easily eliminated by β-elimination, but the similar elimination of carbon dioxide cannot occur in the intermediate **D** from the reaction of *tert*-butyl allylic carbonates and methyl coumalate as shown in Scheme 6.

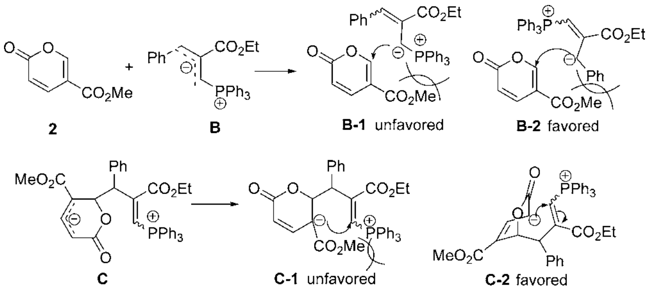
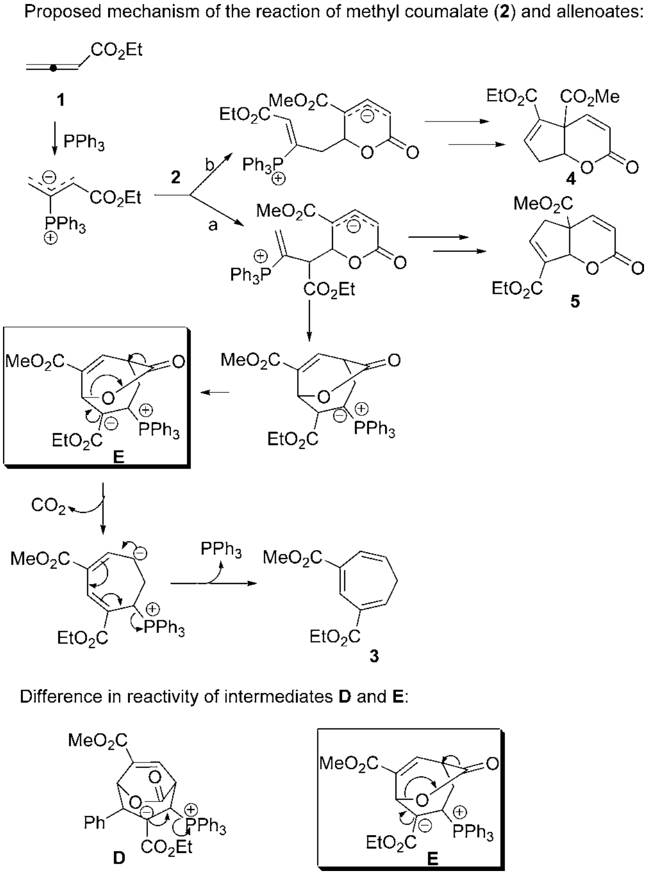


Figure 1. Steric hindrance of the bulky phosphine and the substituents on coumalates in the reaction.

Scheme 6. Difference in Reactivity of Reactions of Methyl Coumalate with Allenoates or Modified Allylic Carbonates



In summary, a novel phosphine-catalyzed [4 + 3] reaction of *tert*-butyl allylic carbonates with methyl coumalate was developed. This strategy offered a powerful method for the construction of bicyclo[3.2.2]nonadiene skeleton with high stereoselectivity.

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Supporting Information Available: Experimental procedures, characterization data and copies of ^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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