ORGANIC LETTERS

2011
Vol. 13, No. 4
580–583

Phosphine-Catalyzed Cascade [3 + 2] Cyclization−Allylic Alkylation, [2 + 2 + 1] Annulation, and [3 + 2] Cyclization Reactions between Allylic Carbonates and Enones

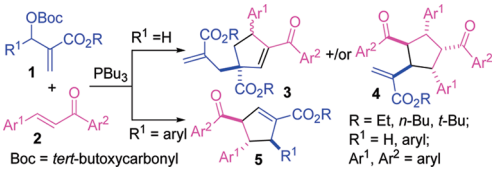
Rong Zhou, Jianfang Wang, Haibin Song, and Zhengjie He*

The State Key Laboratory of Elemento-Organic Chemistry and Department of Chemistry, Nankai University, 94 Weijin Road, Tianjin 300071, P.R. China

zhengjiehe@nankai.edu.cn

Received November 12, 2010

ABSTRACT



The phosphine-catalyzed annulations between Morita−Baylis−Hillman adduct carbonates and enones are reported. Under the catalysis of PBu_3 (20 mol %), cascade [3 + 2] cyclization−allylic alkylation, [2 + 2 + 1] annulation, and [3 + 2] cyclization reactions chemoselectively occur depending on the substituent variation of both the carbonate and enone. These reactions provide efficient syntheses of highly functionalized cyclopentenes and cyclopentanes.

Over the past decade, nucleophilic phosphine catalysis has attracted much research effort.[1] As a result, a number of highly efficient synthetic reactions including many new annulations to form carbocycles and heterocycles have been developed.[2] In those reactions, the most popular substrates are electron-deficient allenes and alkynoates. Recently, a new class of so-called modified allylic derivatives such as halides, acetates, and *tert*-butyl carbonates, which could be conveniently prepared from Morita−Baylis−Hillman adducts,[3] has emerged as complementary and versatile substrates in nucleophilic phosphine catalysis.[4] The pioneering and extensive work by Lu and colleagues has disclosed that the modified allylic derivatives could be

(1) For leading reviews on nucleophilic phosphine catalysis, see: (a) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535. (b) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035. (c) Marinetti, A.; Voituriez, A. *Synlett* **2010**, 174. (d) Xu, S.; He, Z. *Sci. Sinica Chim.* **2010**, *40*, 856.

(2) For important reviews, see: (a) Ye, L.-W.; Zhou, J.; Tang, Y. *Chem. Soc. Rev.* **2008**, *37*, 1140. (b) Cowen, B. J.; Miller, S. J. *Chem. Soc. Rev.* **2009**, *38*, 3102. For representative examples, see:(c) Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 2906. (d) Xu, Z.; Lu, X. *Tetrahedron Lett.* **1997**, *38*, 3461. (e) Cowen, B. J.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 10988. (f) Zhu, X.-F.; Lan, J.; Kwon, O. *J. Am. Chem. Soc.* **2003**, *125*, 4716. (g) Tran, Y. S.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 12632. (h) Wurz, R. P.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 12234. (i) Xu, S.; Zhou, L.; Ma, R.; Song, H.; He, Z. *Chem.—Eur. J.* **2009**, *15*, 8698. (j) Wang, T.; Ye, S. *Org. Lett.* **2010**, *12*, 4168.

(3) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811.

(4) (a) Du, Y.; Lu, X.; Zhang, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 1035. (b) Du, Y.; Feng, J.; Lu, X. *Org. Lett.* **2005**, *7*, 1987. (c) Feng, J.; Lu, X.; Kong, A.; Han, X. *Tetrahedron* **2007**, *63*, 6035. (d) Zheng, S.; Lu, X. *Org. Lett.* **2008**, *10*, 4481. (e) Zheng, S.; Lu, X. *Tetrahedron Lett.* **2009**, *50*, 4532. (f) Zheng, S.; Lu, X. *Org. Lett.* **2009**, *11*, 3978. (g) Ye, L.-W.; Sun, X.-L.; Wang, Q.-G.; Tang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 5951. (h) Chen, Z.; Zhang, J. *Chem.—Asian J.* **2010**, *5*, 1542. (i) Xie, P.; Huang, Y.; Chen, R. *Org. Lett.* **2010**, *12*, 3768. (j) Cho, C.-W.; Kong, J.-R.; Krische, M. J. *Org. Lett.* **2004**, *6*, 1337. (k) Cho, C.-W.; Krische, M. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 6689. (l) Park, H.; Cho, C.-W.; Krische, M. J. *J. Org. Chem.* **2006**, *71*, 7892. (m) Jiang, Y.-Q.; Shi, Y.-L.; Shi, M. *J. Am. Chem. Soc.* **2008**, *130*, 7202.

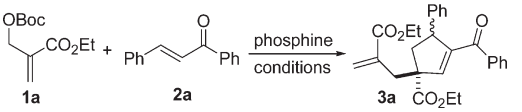
10.1021/ol102738b
Published on Web 01/14/2011

readily used as a C_3 synthon in a series of intra- and intermolecular phosphine-catalyzed [3 + *n*] annulations (*n* = 2, 3, 4, 6).[4a−g] Very recently, Zhang and Huang respectively reported that the allylic carbonates underwent [4 + 1] annulations as a C_1 component.[4h,i] Apart from their use in the annulation reactions, the allylic derivatives like acetates were also proven by Krische[4j−l] and Shi[4m] to be effective allylic alkylating agents under nucleophilic phosphine catalysis.[5] As to their diverse reactivity patterns and potential applications in organic synthesis, although the above encouraging results have been achieved, the modified allylic derivatives remain much less explored, especially by comparison with electron-poor allenes. Further effort in this area is still in demand.

As part of our continuous efforts on exploring phosphine-mediated carbon−carbon bond forming reactions particularly involving *in situ* generated phosphorus ylide intermediates,[6] the allylic carbonates have also attracted our attention as a clean and readily available source of *in situ* formed allylic phosphorus ylide upon treatment with tertiary phosphines.[6d] Although a few phosphine-catalyzed annulations of modified allylic compounds like allylic carbonates with enones were previously reported, the scope of the enones involved was, however, very limited.[4a,b,g,h] Considering the successes in the phosphine-catalyzed [3 + 2] cycloadditions of allenoates and enones,[7] and the similarities in the reactivity between allenoates and modified allylic compounds,[4a−g] we intended to further investigate the phosphine-mediated reactivity of the modified allylic compounds with enones. Herein, we wish to report the results from such investigations.

Since the choice of allylic carbonates as the substrate could allow the reaction to be run in a clean and homogeneous media, we started our study with the allylic carbonate **1a** and chalcone **2a** (Table 1). To our delight, a new product **3a** was initially isolated from the model reaction of **1a** (1.0 mmol) and **2a** (1.0 mmol) under the catalysis of PPh_3 (20 mol %), albeit in only 8% yield (Table 1, entry 1). Structural determination of **3a** implied that a three-component cascade/tandem [3 + 2] cyclization−allylic alkylation reaction[8] occurred between two molecules of the carbonate **1a** and one molecule of chalcone **2a**. This reaction represents a new reactivity pattern of the allylic carbonates with enones, while providing a facile protocol to construct highly functionalized cyclopentenes bearing one all-carbon quaternary stereogenic center.[9]

Table 1. Optimization of Conditions on the Model Reaction[a]



entry	phosphine	solvent	time (d)	yield of **3a** (%)[b]	*syn*/*anti*[c]
1	PPh_3	CH_2Cl_2	5	8	11:1
2	$P(4\text{-}ClPh)_3$	CH_2Cl_2	4	trace	/
3[d]	$P(4\text{-}CF_3Ph)_3$	CH_2Cl_2	4	trace	/
4	Ph_2PMe	CH_2Cl_2	3	40	8:1
5	$PhPMe_2$	CH_2Cl_2	3	50	10:1
6	PBu_3	CH_2Cl_2	2	64	3:1
7	PBu_3	CH_2Cl_2	2	81	3:1
8	PBu_3	$CHCl_3$	2	89	9:1
9	PBu_3	THF	2	66	11:1
10	PBu_3	toluene	4	30	10:1
11	PBu_3	CH_3CN	3	60	4:1
12	PBu_3	DMF	2	24	7:1
13	PBu_3	ethanol	2	/	/

[a] Typical conditions: under a N_2 atmosphere, a mixture of **1a** (for entries 2−6, 1.0 mmol; for entries 7−13, 1.5 mmol), **2a** (0.5 mmol), and phosphine (0.1 mmol) in solvent (2.0 mL) was stirred at rt for a specified time. [b] Isolated yield. [c] Determined by ^1H NMR of the isolated **3a**. [d] A [3 + 2] cyclization product was isolated in low yield (see ref 10).

Optimization of the conditions on the model reaction was conducted (Table 1). A couple of common tertiary phosphines were screened in the model reaction with the adjusted molar ratio of **1a**/**2a** (Table 1, entries 2−7). Electron-rich PBu_3 gave the best yield of **3a** but in lowered diastereoselectivity (entry 7). With PBu_3 as the catalyst, several common solvents other than CH_2Cl_2 were further surveyed (entries 8−13). $CHCl_3$ emerged as the best in respect to the yield and diastereoselectivity of **3a** (entry 8). The reaction run in protic solvent ethanol was completely inhibited (entry 13).

The scopes of both allylic carbonates **1** and enones **2** were examined under the optimized conditions (Table 2). With the allylic carbonate **1a**, the cascade/tandem [3 + 2] cyclization−allylic alkylations of a wide array of substituted chalcones **2** readily proceeded, giving the corresponding cyclopentenes **3** in modest to excellent yields and good to high diastereoselectivity (entries 1−12). The chalcones bearing electron-donating substituents apparently were less effective, suffering inferior yields of **3** (entries 2, 7). 2-Furyl-substituted enone **2m** and phenyl-substituted dienone **2n** were also suitable substrates in the PBu_3-catalyzed cascade/tandem [3 + 2] cyclization−allylic alkylation with **1a** (Scheme 1).

n-Butyl (**1ab**) and *tert*-butyl (**1ac**) analogues of the allylic carbonate **1a** were also explored (Table 2). With the chosen

(5) A series of asymmetric allylic alkylations catalyzed by chiral amines have been developed by Chen and coworkers with allylic carbonates. Peng, J.; Huang, X.; Cui, H.-L.; Chen, Y.-C. *Org. Lett.* **2010**, *12*, 4260 and references cited therein.

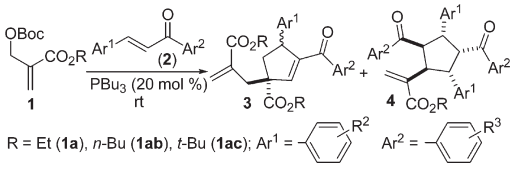
(6) (a) Xu, S.; Zhou, L.; Zeng, S.; Ma, R.; Wang, Z.; He, Z. *Org. Lett.* **2009**, *11*, 3498. (b) Xu, S.; Zhou, L.; Ma, R.; Song, H.; He, Z. *Org. Lett.* **2010**, *12*, 544. (c) Xu, S.; Zou, W.; Wu, G.; Song, H.; He, Z. *Org. Lett.* **2010**, *12*, 3556. (d) Zhou, R.; Wang, C.; Song, H.; He, Z. *Org. Lett.* **2010**, *12*, 976.

(7) (a) Wilson, J. E.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1426. (b) Cowen, B. J.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 10988. (c) Voituriez, A.; Panossian, A.; Fleury-Bregeot, N.; Retailleau, P.; Marinetti, A. *J. Am. Chem. Soc.* **2008**, *130*, 14030. (d) Pinto, N.; Neel, M.; Panossian, A.; Retailleau, P.; Frison, G.; Voituriez, A.; Marinetti, A. *Chem.—Eur. J.* **2010**, *16*, 1033.

(8) For most recent examples of phosphine-catalyzed multicomponent cascade/tandem annulations, see: (a) Liu, H.; Zhang, Q.; Wang, L.; Tong, X. *Chem. Commun.* **2010**, *46*, 312. (b) Cai, L.; Zhang, B.; Wu, G.; Song, H.; He, Z. *Chem. Commun.* **2011**, *47*, 1045.

(9) For reviews on the construction of quaternary carbon center, see: (a) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363. (b) Bella, M.; Gasperi, T. *Synthesis* **2009**, 1583.

Table 2. PBu_3-Catalyzed Cascade [3 + 2] Cyclization−Allylic Alkylation and [2 + 2 + 1] Annulation of **1** and **2**[a]



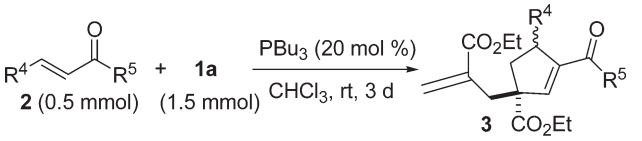
entry	1	R^2 in Ar^1	R^3 in Ar^2	time (d)	3 (%)[b], dr[c]	4 (%)[b]
1	**1a**	H	H (**2a**)	2	**3a**, 89, 9:1	/
2	**1a**	4-MeO	H (**2b**)	2	**3b**, 49, 11:1	/
3	**1a**	4-F	H (**2c**)	1	**3c**, 80, 10:1	/
4	**1a**	4-Cl	H (**2d**)	2	**3d**, 91, 7:1	/
5	**1a**	3-NO_2	H (**2e**)	3	**3e**, 83, 7:1	/
6	**1a**	4-NO_2	H (**2f**)	2	**3f**, 76, 10:1	/
7	**1a**	4-Me	4-MeO (**2g**)	2	**3g**, 29, 7:1	/
8	**1a**	H	4-Cl (**2h**)	3	**3h**, 81, 7:1	/
9	**1a**	4-CF_3	4-Cl (**2i**)	3	**3i**, 68, 7:1	/
10	**1a**	H	4-Br (**2j**)	1	**3j**, 77, 7:1	/
11	**1a**	4-F	4-Br (**2k**)	3	**3k**, 62, 8:1	/
12	**1a**	4-Cl	4-Br (**2l**)	3	**3l**, 77, 7:1	/
13	**1ab**	H	H (**2a**)	2	**3o**, 80, 8:1	/
14	**1ab**	4-Cl	H (**2d**)	3	**3p**, 94, 7:1	/
15	**1ac**	4-F	H (**2c**)	4	**3q**, 70, 20:1	**4a**, 5
16	**1ac**	4-Cl	H (**2d**)	3	**3r**, 64, 14:1	**4b**, 11
17	**1a**	H	4-NO_2 (**2o**)	2	**3s**, 15, 20:1	**4c**, 74
18	**1a**	4-Cl	4-NO_2 (**2p**)	2	**3t**, 12, 14:1	**4d**, 65
19[d]	**1ab**	H	4-NO_2 (**2o**)	3	/	**4e**, 60
20[d]	**1ab**	4-Cl	4-NO_2 (**2p**)	2	/	**4f**, 62
21[d]	**1ac**	H	4-NO_2 (**2o**)	3	/	**4g**, 71
22[d]	**1ac**	4-Cl	4-NO_2 (**2p**)	3	/	**4h**, 56

[a] For entries 1−16, the molar ratio of **1**/**2** was 3:1; for entries 17−22, the molar ratio of **1**/**2** was 1:1; for more experimental detail, see Supporting Information. [b] Isolated yield based on **2**. [c] Referring to *syn*-/*anti*-**3**, determined by ^1H NMR of isolated **3**. [d] Other unidentified stereoisomers of **4** were isolated in 3−10% yields.

chalcones (**2a**, **2c**, or **2d**) employed, the allylic carbonates **1ab** (R = *n*-Bu) and **1ac** (R = *t*-Bu) readily gave the corresponding cyclopentenes **3o**−**r** in good yields and stereoselectivity (entries 13−16). In cases of **1ac**, however, a minor product **4a** or **4b** was isolated in low yield as a single diastereomer (entries 15, 16). **4a** and **4b** were identified as the [2 + 2 + 1] annulation products which were generated from two molecules of the chalcone **2** and one molecule of the allylic carbonate **1ac**. Further survey unveiled that, under accordingly optimized conditions (**1**/**2** molar ratio 1:1; 20 mol % of PBu_3 relative to **2**), the electron-deficient chalcones (**2o**, **2p**) bearing a 4-nitrophenyl at the carbonyl all gave the [2 + 2 + 1] annulation products **4** as the major in medium yields in the reactions with the allylic carbonates **1a**, **1ab**, or **1ac** (entries 17−22). Thus, this PBu_3-catalyzed [2 + 2 +1] annulation reaction between allylic carbonates **1** and electron-poor chalcones **2** represents a facile synthesis for highly functionalized cyclopentanes **4**.

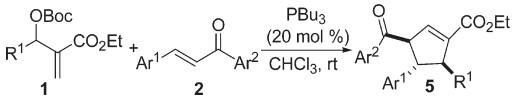
The substituted allylic carbonates **1** were further tested in the reactions with representative chalcones **2** under the

Scheme 1. Cascade [3 + 2] Cyclization−Allylic Alkylation between **1a** and Other Enones



R^4	R^5	2	3	yield	*syn/anti*
2-furyl	Ph	**2m**	**3m**	77%	5:1
Ph	*E*-styryl	**2n**	**3n**	50%	8:1

Table 3. PBu_3-Catalyzed [3 + 2] Cyclization of **1** and **2**[a]



entry	R^1 in **1**	Ar^1 in **2**	Ar^2 in **2**	time (d)	5 (%)[b]
1	Ph (**1b**)	Ph	Ph (**2a**)	1	**5b**, 68
2	Ph (**1b**)	4-CF_3Ph	Ph (**2q**)	1	**5c**, 89
3	Ph (**1b**)	4-ClPh	4-NO_2Ph (**2p**)	1	**5d**, 84
4	4-MeO-Ph (**1c**)	4-ClPh	Ph (**2d**)	1	**5e**, 59
5	4-ClPh (**1d**)	4-CF_3Ph	Ph (**2q**)	1	**5f**, 65
6	2-furyl (**1e**)	4-ClPh	Ph (**2d**)	2	**5g**, 78

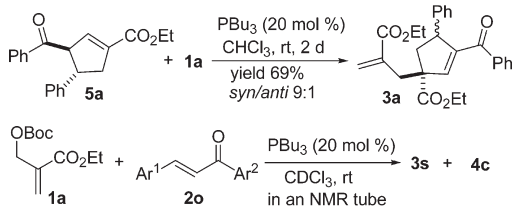
[a] Reaction conditions: a mixture of allylic carbonates **1** (0.6 mmol), chalcones **2** (0.5 mmol), and PBu_3 (0.1 mmol) in $CHCl_3$ (2 mL) was stirred at rt. [b] Isolated yield based on **2**.

reoptimized conditions (Table 3). It was found that, under the catalysis of PBu_3 (20 mol %), the aryl-substituted allylic carbonates **1** readily gave the [3 + 2] cyclization products **5** as a single diastereomer in satisfactory yields (entries 1−6). This result definitely broadens the substrate scope for the phosphine-catalyzed [3 + 2] cyclization reactions between the allylic derivatives and enones.[4a,b,g,h] It also provides an efficient synthesis for differently substituted cyclopentenes which could not be accessed by the phosphine-catalyzed [3 + 2] cycloaddition of allenoates and enones.[7] However, an alkyl such as methyl and *n*-propyl-substituted allylic carbonates **1** (R^1 = Me, *n*-Pr) were not suitable substrates; under the same conditions, their reactions with the chalcone **2a** all resulted in a complex mixture.

The structures of compounds **3**, **4**, and **5** were identified by ^1H, ^{13}C NMR and HRMS-ESI measurements. Representative compounds were further confirmed by a combination of HMBC, HMQC, NOESY, and X-ray crystallographic analyses (for detail, see Supporting Information).

To better understand the PBu_3-catalyzed annulations in this study, the following experiments were deliberately conducted (Scheme 2). The isolated [3 + 2] cyclization product **5a** from the allylic carbonate **1a** and chalcone

Scheme 2. Experiments for Mechanistic Investigations



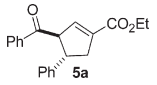
Ar^1 = Ph; Ar^2 = 4-NO_2-Ph; the sample was scanned at 1, 8, 24 h.

1a	2o	ratio of 1a/2o	ratio of 3s/4c
0.1 mmol	0.1 mmol	1:1	1:5
0.05 mmol	0.1 mmol	1:2	1:5

2a[10] was treated with **1a** under the same conditions as those shown in Table 2, and the allylic alkylation product **3a** was readily collected in 69% yield and a 9:1 *syn*/*anti* ratio. This result implies that the cyclopentenes **3** from the allylic carbonates **1** and enones **2** are most likely generated in a [3 + 2] cyclization−allylic alkylation sequence. To evaluate the competition relationship between the formation of **3** and **4** in the PBu_3-catalyzed reaction of the allylic carbonates **1** and enones **2**, the reactions of **1a** and **2o** with different **1a**/**2o** ratios were run in $CDCl_3$ and monitored by ^1H NMR (Scheme 2). Results indicated that the ratio between the corresponding products **3s** and **4c** nearly remained constant in the course of the monitored processes. This fact implies that, under the given conditions, the ratio between **3** and **4** solely depends on the reactivity of the substrates **1** and **2**.

On the basis of the experimental results in this work, a proposed mechanism to account for the formation of **3**, **4**, and **5** is depicted in Scheme 3. Initially, upon treatment with PBu_3, the allylic carbonate **1** gives the allylic phosphorus ylide intermediate **6** via an addition−elimination−deprotonation process.[11] Subsequent γ-addition of the ylide **6** to the enone **2** generates the enolate **7**. When R^1 is an aryl group in **7**, the enolate **7** is prone to a ring-closure via an intramolecular Michael addition, followed by an elimination of PBu_3 to produce the [3 + 2] cyclization product **5**. On the other hand, when R^1 is hydrogen in **7**, consequently the intramolecular ring-closure of **7** to generate the intermediate **9** (path A) will compete with the Michael addition of **7** to the enone **2** leading to the formation of the intermediate **11** (path B). When the enone **2** is relatively less electron-deficient, the intermediate **9** is predominantly formed. **9** then undertakes a direct addition−elimination (an S_N2' process)[12] with the carbonate **1**, followed by the release of the catalyst PBu_3 under the aid

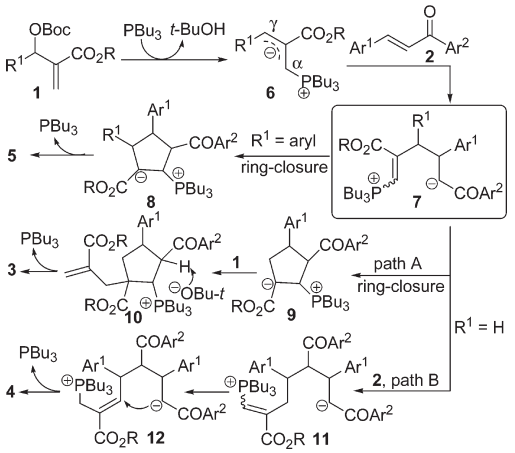
(10) A [3 + 2] cycloaddition product **5a** was obtained in 6% yield in the P(4-CF_3Ph)$_3$-catalyzed model reaction (Table 1, entry 3).



(11) Reference 6d and references cited therein.

(12) Ramachandran, P. V; Madhi, S.; Bland-Berry, L.; Reddy, M. V. R.; O'Donnell, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 13450 and references cited therein.

Scheme 3. Proposed Mechanism for Formation of **3**, **4**, and **5**



of the *in situ* generated *tert*-butoxide anion to accomplish the formation of the cascade [3 + 2] cyclization−allylic alkylation product **3**.[13] When the enone **2** is more electron-deficient, particularly attached with a 4-nitrophenyl group at its carbonyl, the conversion of **7** into **11** via path B is favored. The intermediate **11** subsequently undergoes a double-bond migration, followed by an intramolecular Michael addition and elimination of PBu_3 to furnish the cascade [2 + 2 + 1] annulation product **4** (Scheme 3).

In conclusion, the PBu_3-catalyzed cascade [3 + 2] cyclization−allylic alkylation, [2 + 2 + 1] annulation, and [3 + 2] cyclization reactions between allylic carbonates and enones have been demonstrated, which provide efficient accesses to highly functionalized cyclopentenes and cyclopentanes. Together with the previous reports,[4a,b,g,h] this work offers a clear profile about the phosphine-mediated diverse reactivity of the modified allylic derivatives with a broad array of enones. Future efforts in our laboratory will be directed toward further expanding the scope and developing asymmetric versions of these annulations.

Acknowledgment. Financial support from National Natural Science Foundation of China (Grant Nos. 20872063, 21072100) is gratefully acknowledged.

Supporting Information Available. Experimental details; characterization data; ^1H and ^{13}C NMR spectra for **3**, **4**, and **5**; NOESY, HMBC, and HMQC spectra for representative compounds; X-ray crystallographic data (CIF files) and ORTEP drawings for **3r** and **4c**. This material is available free of charge via the Internet at http://pubs.acs.org.

(13) Although a stepwise synthesis of **3a** was realized from the [3 + 2] addition product **5a** and **1a** (Scheme 2), it is believed that the stepwise synthesis of **3a** probably proceeds via the same intermediate **9** (Scheme 3) which can be generated from the nucleophilic attack of PBu_3 to **5a**. Hence, the formation of **3** is most likely via a cascade sequence, although a tandem one (see Supporting Information) could not be completely ruled out. For the definition of a cascade/tandem reaction, see: Chapman, C. J.; Frost, C. G. *Synthesis* **2007**, 1.