

Phosphine-Catalyzed [4 + 2] Annulation of γ -Substituent Allenates: Facile Access to Functionalized Spirocyclic Skeletons

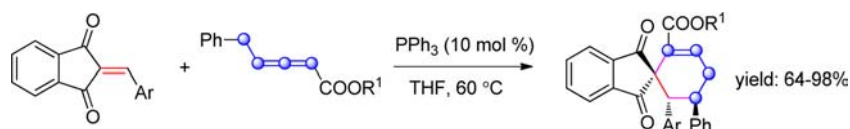
Erqing Li, You Huang,* Ling Liang, and Peizhong Xie

State Key Laboratory and Institute of Elemento-Organic Chemistry, Nankai University,
Tianjin 300071, China

hyou@nankai.edu.cn

Received May 15, 2013

ABSTRACT



The first phosphine-catalyzed [4 + 2] annulation of γ -substituted allenates with 2-arylidene-1*H*-indene-1,3(2*H*)-diones is disclosed. In the reaction, the γ -substituted allenate serves as a new type of 1,4-dipolar synthon; this broadens the application of γ -substituted allenates. This method also offers a powerful approach to the construction of highly substituted spiro[4.5]dec-6-ene skeletons in excellent yields, and with complete regioselectivity and high diastereoselectivity.

Spirocyclic skeletons are the structural centerpieces of a wide variety of natural and synthetic compounds that

exhibit diverse biological activities. Consequently, approaches to the efficient synthesis of these molecules have received considerable attention.¹

Various methods such as organocatalysis² and transition-metal catalysis³ have previously been described in the literature. However, drawbacks such as unsatisfactory yields, tedious purification processes, and poor chemo- and/or diastereoselectivities have restricted the application of these approaches. The development of novel, straightforward, and flexible methods for the preparation of spirocyclic compounds is therefore highly desirable.

Recently, because of their comparatively strong and readily tunable nucleophilicities, phosphines have been used as efficient catalysts in organic synthesis.^{4,5} A series

(1) (a) Ma, S.; Han, X. Q.; Krishnan, S.; Virgil, S. C.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 8037. (b) Shangary, S. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 3933. (c) Schulz, V.; Davoust, M.; Lemarie, M.; Lohier, J.-F.; Santos, J. S. O.; Metzner, P.; Briere, J.-F. *Org. Lett.* **2007**, *9*, 1745. (d) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. (e) Franz, A. K.; Dreyfuss, P. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 1020. (f) Ding, K. *J. Am. Chem. Soc.* **2005**, *127*, 10130. (g) Chen, C.; Li, X.; Neumann, C. S.; Lo, M. M. C.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 2249. (h) Lo, M. M. C.; Neumann, C. S.; Nagayama, S.; Perlstein, E. O.; Schreiber, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 16077. (i) Lin, H.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 36. (j) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209.

(2) (a) Tan, B.; Candeias, N. R.; Barbas, C. F., III. *Nat. Chem.* **2011**, *3*, 473. (b) Tan, B.; Candeias, N. R.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2011**, *133*, 4672. (c) Tan, B.; Hernandez-Torres, G.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2011**, *133*, 12354. (d) Cao, Y.; Jiang, X.; Liu, L.; Shen, F.; Zhang, F.; Wang, R. *Angew. Chem., Int. Ed.* **2011**, *50*, 9124. (e) Zhong, F.; Han, X.; Wang, Y.; Lu, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 7837. (f) Jiang, X.; Cao, Y.; Wang, Y.; Liu, L.; Shen, F.; Wang, R. *J. Am. Chem. Soc.* **2010**, *132*, 15328. (g) Bencivenni, G.; Wu, L.-Y.; Mazzanti, A.; Giannichi, B.; Pesciaoli, F.; Song, M.-P.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7200.

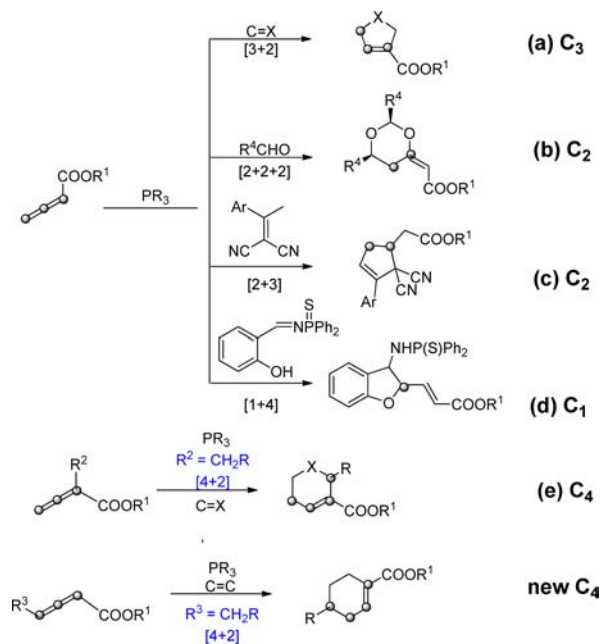
(3) (a) Hanhan, N. V.; Ball-Jones, N. R.; Tran, N. T.; Franz, A. K. *Angew. Chem., Int. Ed.* **2011**, *50*, 1. (b) Badillo, J. J.; Arevalo, G. E.; Fetting, J. C.; Franz, A. K. *Org. Lett.* **2011**, *13*, 418. (c) Hojo, D.; Noguchi, K.; Tanaka, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 8129. (d) Tanaka, K.; Otake, Y.; Sagae, H.; Noguchi, K.; Hirano, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 1312. (e) Trost, B. M.; Cramer, N.; Silverman, S. M. *J. Am. Chem. Soc.* **2007**, *129*, 12396. (c) Basavaiah, D.; Reddy, K. R. *Org. Lett.* **2007**, *9*, 57.

(4) For reviews, see: (a) Cowen, B. J.; Miller, S. J. *Chem. Soc. Rev.* **2009**, *38*, 3102. (b) Ye, L.-W.; Zhou, J.; Tang, Y. *Chem. Soc. Rev.* **2008**, *37*, 1140. (c) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560. (d) Nair, V.; Menon, R. S.; Sreekanth, A. R.; Abhilash, N.; Biju, A. T. *Acc. Chem. Res.* **2006**, *39*, 520. (e) Lu, X.; Du, Y.; Lu, C. *Pure Appl. Chem.* **2005**, *77*, 1985. (f) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035. (g) Valentine, D. H.; Hillhouse, J. H. *Synthesis* **2003**, 317. (h) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535.

(5) Some example on Domino reactions, see: (a) Yao, C.; Xiao, Z.; Liu, R.; Li, T.; Jiao, W.; Yu, C. *Chem.—Eur. J.* **2013**, *19*, 456. (b) Ma, C.; Jia, Z.; Liu, J.; Zhou, Q.; Dong, L.; Chen, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 948. (c) Zhou, S.-L.; Li, J.-L.; Dong, L.; Chen, Y.-C. *Org. Lett.* **2011**, *13*, 5874.

of named reactions, such as the Rauhut–Currier and Morita–Baylis–Hillman reactions, have been developed. Among these significant studies, Lu first reported the phosphine-catalyzed [3 + 2] cycloaddition of activated olefins with 2,3-butadienoate for the construction of various five-membered carbocyclic compounds and heterocyclic compounds [Scheme 1, (a)].⁶ In further investigations, Kwon and Lu independently reported new [2 + 2 + 2] and [2 + 3] annulations catalyzed by phosphines [Scheme 1, (b) and (c)].⁷ At the same time, our group first reported a novel [1 + 4] annulation of allenates and salicyl-*N*-thiophosphinylimines using a new bifunctional phosphine catalyst, (2'-hydroxybiphenyl-2-yl)diethylphosphane (LBBA-1), in which allenates served as one-carbon units participating in a domino process [Scheme 1, (d)].⁸ Based on these pioneering studies, Kwon et al. developed a phosphine-catalyzed [4 + 2] cycloaddition of

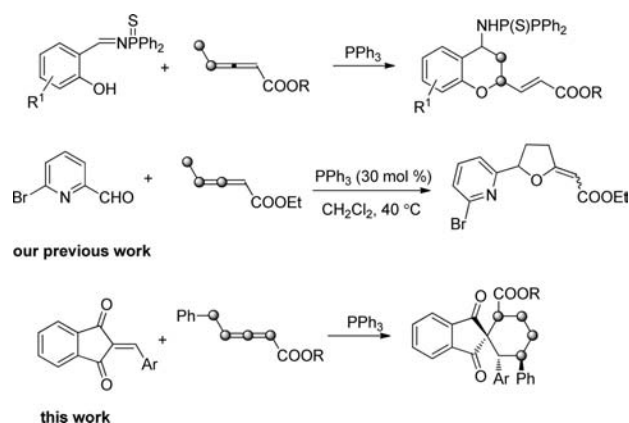
Scheme 1. Various Pathways for Phosphine-Catalyzed Annulations



α -substituted allenates with imides,⁹ and subsequent research has shown that the [4 + 2] cycloaddition of α -substituted allenates with activated olefins or ketones is also feasible [Scheme 1, (e)].¹⁰ Kwon et al. used this method in the synthesis of natural products and bioactive

compounds, further proving its synthetic efficiency.¹¹ However, compared with the significant progress made with allenates and α -substituted allenates, phosphine-catalyzed domino reactions involving γ -substituted allenates are rare.¹² In 2009, our group reported the first example of γ -substituted allenates acting as C₂ and C₃ synthons in phosphine-catalyzed [4 + 2] and [3 + 2] annulations.^{12a} Recently, Shi et al. and Nair et al. reported novel phosphine-catalyzed reactions of γ -substituted allenates.¹³ However, to the best of our knowledge, γ -substituted allenates acting as a new type of 1,4-dipolar synthon have not been reported. In this letter, we disclose the first case of a phosphine-catalyzed [4 + 2] annulation of γ -substituted allenates and activated olefins under mild conditions (Scheme 1).

Scheme 2. Phosphine-Catalyzed Annulations of γ -Substituent Allenates

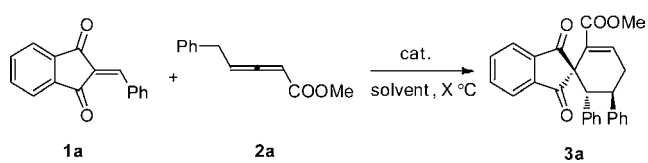


In view of our previous study of phosphine-catalyzed domino reactions of allenates,¹⁴ we initially used 2-benzylidene-1*H*-indene-1,3(2*H*)-dione (**1a**) (0.3 mmol) and methyl 5-phenyl-2,3-pentadienoate (**2a**) (0.6 mmol) as the model substrates and a catalytic amount of PPh₃ (30 mol %) as the catalyst at 40 °C in CH₂Cl₂ to test the reaction procedure (Scheme 2).^{12a} Unfortunately, this

- (6) Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 2906.
 (7) (a) Zhu, X.-F.; Henry, C. E.; Wang, J.; Dudding, T.; Kwon, O. *Org. Lett.* **2005**, *7*, 1387. (b) Lu, Z.; Zheng, S.; Zhang, X.; Lu, X. *Org. Lett.* **2008**, *10*, 3267.
 (8) Meng, X.; Huang, Y.; Chen, R. *Org. Lett.* **2009**, *11*, 137.
 (9) Zhu, X.-F.; Lan, J.; Kwon, O. *J. Am. Chem. Soc.* **2003**, *125*, 4716.
 (10) (a) Tran, Y. S.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 12632. (b) Castellano, S.; Fijji, H. D. G.; Kinderman, S. S.; Watanabe, M.; de Leon, P.; Tamanoi, F.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 5843. (c) Zh, X.-F.; Schaffner, A.-P.; Li, R. C.; Kwon, O. *Org. Lett.* **2005**, *7*, 2977. (d) Wurz, R. P.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 12234. (e) Wang, T.; Ye, S. *Org. Lett.* **2010**, *12*, 4168.

- (11) (a) Andrews, I. P.; Kwon, O. *Chem. Sci.* **2012**, *3*, 2510. (b) Villa, R. A.; Xu, Q. H.; Kwon, O. *Org. Lett.* **2012**, *14*, 4634. (c) Jones, R. A.; Krische, M. J. *Org. Lett.* **2009**, *11*, 1849. (d) Tran, Y. S.; Kwon, O. *Org. Lett.* **2005**, *7*, 4289. (e) Wang, J. C.; Krische, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5855.
 (12) (a) Meng, X.; Huang, Y.; Zhao, H.; Xie, P.; Ma, J.; Chen, R. *Org. Lett.* **2009**, *11*, 911. (b) Ma, R.; Xu, S.; Tang, X.; Wu, G.; He, Z. *Tetrahedron* **2011**, *67*, 1053. (c) Xu, S.; Zhou, L.; Ma, R.; Song, H.; He, Z. *Chem.—Eur. J.* **2009**, *15*, 8698.
 (13) (a) Zhang, X.-C.; Cao, S.-H.; Wei, Y.; Shi, M. *Chem. Commun.* **2011**, *47*, 1548. (b) Jose, A.; Lakshmi, K. C. S.; Suresh, E.; Nair, V. *Org. Lett.* **2013**, *15*, 1858.
 (14) (a) Xie, P.; Li, E.; Zheng, J.; Li, X.; Huang, Y.; Chen, R. *Adv. Synth. Catal.* **2013**, *355*, 161. (b) Yang, L.; Xie, P.; Li, E.; Li, X.; Huang, Y.; Chen, R. *Org. Biomol. Chem.* **2012**, *10*, 7628. (c) Hu, C.; Geng, Z.; Ma, J.; Huang, Y.; Chen, R. *Chem.—Asian J.* **2012**, *7*, 2032. (d) Xie, P.; Lai, W.; Geng, Z.; Huang, Y.; Chen, R. *Chem.—Asian J.* **2012**, *7*, 1533. (e) Xie, P.; Huang, Y.; Chen, R. *Chem.—Eur. J.* **2012**, *18*, 7362. (f) Xie, P.; Huang, Y.; Lai, W.; Meng, X.; Chen, R. *Org. Biomol. Chem.* **2011**, *9*, 6707. (g) Ma, J.; Xie, P.; Hu, C.; Huang, Y.; Chen, R. *Chem.—Eur. J.* **2011**, *17*, 7418. (h) Xie, P.; Huang, Y.; Chen, R. *Org. Lett.* **2010**, *12*, 3768. (i) Meng, X.; Huang, Y.; Chen, R. *Chem.—Eur. J.* **2008**, *14*, 6852.

Table 1. Optimization of [4 + 2] Annulation of γ -Substituent of the Allenolate with 2-Benzylidene-1*H*-indene-1,3(2*H*)-dione^a



entry	cat. (mol %)	solvent	<i>t</i> (h)	yield (%) ^b
1	PPh ₃ (30)	CH ₂ Cl ₂	6	trace
2	PPh ₃ (50)	toluene	9	80
3	PPh ₃ (50)	CH ₃ CN	9	53
4	PPh ₃ (50)	THF	5	97
5	PPh ₃ (50)	CH ₂ ClCH ₂ Cl	1.5	47
6	PPh ₃ (50)	CHCl ₃	12	63
7	(4-ClC ₆ H ₄) ₃ P (20)	THF	14	91
8	(4-MeOC ₆ H ₄) ₃ P (20)	THF	36	74
9	PPh ₃ (20)	THF	9	96
10	PPh ₃ (10)	THF	9	95
11 ^c	PPh ₃ (10)	THF	20	89
12 ^d	PPh ₃ (20)	THF	24	trace

^a Unless otherwise specified, all reactions were carried out using **1a** (0.3 mmol) and **2a** (0.6 mmol) at 60 °C. ^b Yield of isolated products. ^c **1a** (0.3 mmol) and **2a** (0.45 mmol) were used. ^d The reaction was carried out at room temperature.

reaction did not show any activity, and no product was obtained. In toluene, with a temperature of 60 °C and an increased catalyst loading, the reaction proceeded smoothly to give the corresponding [4 + 2] cycloaddition adduct in 80% yield (Table 1, entry 2). It should be noted that the [4 + 2] cycloaddition reaction is completely regioselective and highly diastereoselective (only one isomer was detected in all reactions). Various solvents were tested, and THF was found to be the best, affording **3a** in 97% yield (Table 1, entries 1–6). Subsequent catalyst screening demonstrated that PPh₃ was the best choice (Table 1, entries 6–8). On decreasing the amount of catalyst to 20 and 10 mol %, similar results were obtained (Table 1, entries 9 and 10). However, changing the ratio of **1a** to **2a** resulted in a slight decrease in the yield (Table 1, entry 11). Furthermore, it was found that no reaction occurred in the presence of PPh₃ (20 mol %) at room temperature (Table 1, entry 12). Based on these experimental results, the best reaction conditions were confirmed to be PPh₃ (10–20 mol %), at 60 °C in THF. The structure and stereochemistry of **3** were determined using a combination of NMR and HRMS spectroscopies and single-crystal X-ray analysis (**3a**) (Figure 1).

With the optimized conditions in hand, we next explored the substrate scope of the new phosphine-catalyzed [4 + 2] cycloaddition; the results are listed in Table 2. The position of the substituent on the aromatic ring of substrate **2** had no significant influence on the yields and diastereoselectivities. Phenyl groups with electron-withdrawing or -donating groups worked well as substituents (Table 2, entries 1–9). When the substituents were phenyl groups

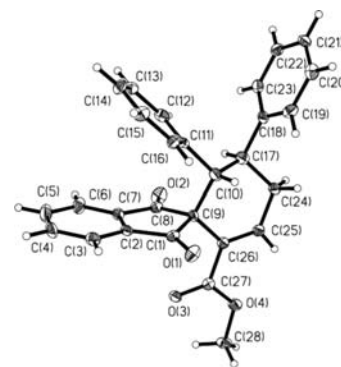
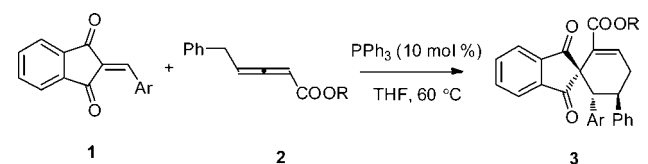


Figure 1. X-ray crystal structure of **3a**.

with strong electron-withdrawing or -donating groups, a slightly higher catalyst loading (20 mol % PPh₃) was needed (Table 2, entries 10–12). When the substituent on the benzene ring was 4-nitro, 3-bromo, 3-methyl, or 4-methoxy, high yields and diastereoselectivities were still obtained, but a significantly longer reaction time was required (Table 2, entries 6, 7, 10, and 11). 2-Arylidene-1*H*-indene-1,3(2*H*)-dione **2** containing 2-naphthyl or heteroaryl groups could also be used in the reaction (Table 2, entries 13 and 14). The steric properties of the esters had

Table 2. Scopes of the Phosphine-Catalyzed [4 + 2] Annulation of γ -Substituent Allenolates in the Presence of PPh₃^a



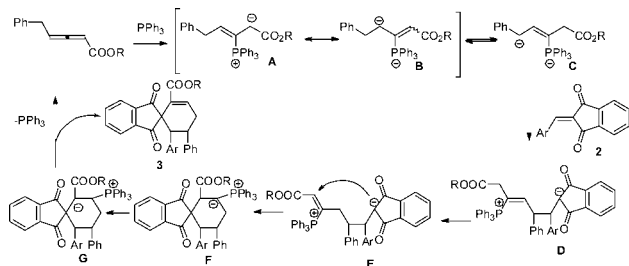
entry	Ar	R	<i>t</i> (h)	yield (%) ^b
1	C ₆ H ₅	Me	9	95 (3a)
2	4-MeC ₆ H ₅	Me	10	92 (3b)
3	4-BrC ₆ H ₅	Me	10	98 (3c)
4	4-ClC ₆ H ₅	Me	16	86 (3d)
5	4-FC ₆ H ₅	Me	16	88 (3e)
6	3-BrC ₆ H ₅	Me	36	88 (3f)
7	3-MeC ₆ H ₅	Me	36	89 (3g)
8	2-BrC ₆ H ₅	Me	12	96 (3h)
9	2-MeC ₆ H ₅	Me	12	89 (3i)
10 ^c	4-NO ₂ C ₆ H ₅	Me	16	82 (3j)
11 ^c	4-MeOC ₆ H ₅	Me	16	96 (3k)
12 ^c	2,4-Cl ₂ C ₆ H ₃	Me	10	92 (3l)
13 ^c	2-thienyl	Me	36	64 (3m)
14 ^c	1-naphthyl	Me	36	88 (3n)
15	C ₆ H ₅	Et	9	98 (3o)
16	C ₆ H ₅	<i>t</i> -Bu	9	98 (3p)
17	C ₆ H ₅	Bn	9	92 (3q)

^a Unless otherwise noted, all reactions were carried out with **1** (0.3 mmol) and **2** (0.6 mmol) in THF (3.0 mL) at 60 °C. ^b Yield of isolated product. ^c The reactions were carried out with **1** (0.3 mmol) and **2** (0.6 mmol) in the presence of PPh₃ (20 mol %) in THF (3.0 mL) at 60 °C.

only a slight influence on the yield (Table 2, entries 1, 15–17).

Based on our experimental results and previous studies,¹⁵ we proposed a possible mechanism for the formation of spiro[4.5]dec-6-ene and the stereochemistry of this domino reaction (Scheme 3). Conceivably, the first step is nucleophilic addition of triarylphosphine to the allene ester, giving 1,3-dipolar zwitterion **A** or **B**. Intermediate **A** or **B** undergoes a reversible equilibrium overall proton shift, giving intermediate **C**. The allylic carbanion **C** then undergoes a Michael addition with **2**, enabling the formation of intermediate **D**; in this step, the steric effect of the large substituent on substrates will enable good product diastereoselectivity. Then, **D** followed by an isomerization to give intermediate **E**, an umpolung addition, and a proton shift forms intermediate **G**. Finally, elimination of the phosphine catalyst gives **3** and completes the catalytic cycle.

Scheme 3. Possible Mechanism for the Formation of **3**

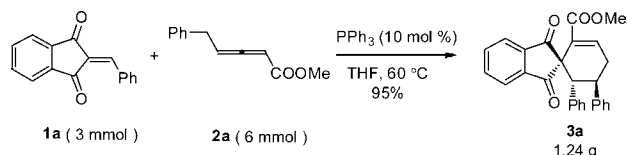


In order to demonstrate the practicality of the strategy, we performed the phosphine-catalyzed [4 + 2] annulation

(15) For mechanistic studies of the phosphine-catalyzed cycloaddition reaction, see: (a) Liang, Y.; Liu, S.; Xia, Y.; Li, Y.; Yu, Z.-X. *Chem.—Eur. J.* **2008**, *14*, 4361. (b) Mercier, E.; Fonovic, B.; Henry, C.; Kwon, O.; Dudding, T. *Tetrahedron Lett.* **2007**, *48*, 3617. (c) Xia, Y.; Liang, Y.; Chen, Y.; Wang, M.; Jiao, L.; Huang, F.; Liu, S.; Li, Y.; Yu, Z.-X. *J. Am. Chem. Soc.* **2007**, *129*, 3470. (d) Dudding, T.; Kwon, O.; Mercier, E. *Org. Lett.* **2006**, *8*, 3643. (e) Zhu, X.-F.; Henry, C. E.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 6722.

reaction at large scale ($\times 10$). The reaction of 2-benzylidene-1*H*-indene-1,3(2*H*)-dione (**1a**) and methyl 5-phenyl-2,3-pentadienoate (**2a**) was carried out under the optimal conditions; the domino reaction proceeded smoothly and afforded the desired adduct **3a** at the gram scale, without loss of reactivity and diastereoselectivity (Scheme 4).

Scheme 4. Large Scale [4 + 2] Annulation between **1a** and **2a**



In conclusion, we have developed a novel method for the synthesis of spiro[4.5]dec-6-ene through a phosphine-catalyzed [4 + 2] annulation, with excellent yields and high diastereoselectivities. More importantly, we have disclosed the first example of γ -benzyl allenoates acting as a new type of C₄ synthon and participating in a phosphine-catalyzed domino reaction. Further investigations will focus on designing new domino reactions using these new 1,4-dipolar synthons and on performing asymmetric versions of the annulation.

Acknowledgment. This work was supported financially by the National Natural Science Foundation of China (21172115, 20972076) and the Natural Science Foundation of Tianjin (10JCYBJC04000).

Supporting Information Available. Detailed experimental procedures, spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.