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Phosphine-Catalyzed Domino Reaction: Highly Stereoselective Synthesis of *trans*-2,3-Dihydrobenzofurans from Salicyl *N*-Thiophosphinyl Imines and Allylic Carbonates

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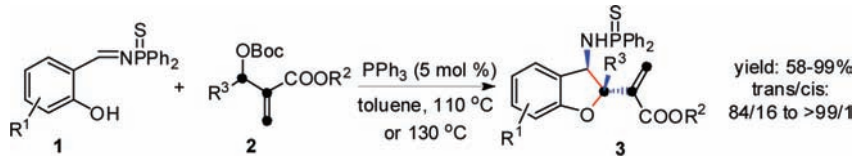
ABSTRACT



A novel phosphine-catalyzed domino reaction of salicyl *N*-thiophosphinyl imines and allylic carbonates was developed. The allylic carbonate, in this reaction, serves as a new kind of 1,1-dipolar synthon. This method offered a powerful approach to the construction of a highly substituted *trans*-2,3-dihydrobenzofuran skeleton with high diastereoselectivity.

The 2,3-dihydrobenzofuran (DHB) ring system constitutes the core skeletons of an increasing number of biologically active compounds,[1] such as pterocarpans, neolignans, as well as synthetic drugs used in the treatment of pulmonary hypertension, atherosclerotic peripheral arterial disease, and central nervous system trauma and ischemia.[2] These biological properties have attracted chemists in developing an efficient synthesis of these DHBs. To date, various approaches have been described in the literature: radical cyclization, electrocyclizations,[3] Lewis acid promoted reactions,[4] biomimetic couplings and cycloadditions,[5] anionic cyclizations,[6] transition-metal-catalyzed processes,[1a,7] and so on.[8] However, impeding the wide application of these methods are certain drawbacks including unsatisfactory yields, poor chemo- and/or diastereoselectivities, tedious processes for purification, and precious reaction conditions. Hence, the development of simple, convenient, highly chemo- and diastereoselective methodologies for the synthesis of 2,3-dihydrobenzofuran have been, and continue to be, a challenging endeavor at the forefront of synthetic chemistry.

Phosphine-mediated domino reactions have become a powerful tool in generating carbo- and heterocycles.[9] In particular, phosphine-catalyzed [3 + 2] and [4 + 2] cy-

(1) (a) Coy, E. D.; Jovanovic, L.; Sefkow, M. *Org. Lett.* **2010**, *12*, 1976. (b) Bertolini, F.; Pineschi, M. *Org. Prep. Proced. Int.* **2009**, *41*, 385. (c) Sefkow, M. *Synthesis* **2003**, 2595.

(2) Leticia, J.-G.; Sergio, G.-M.; Miriam, Á.-C.; Manuel, M.-D.; Ignacio, R.-G. *Chem.—Eur. J.* **2007**, *13*, 557.

(3) (a) Meijs, G. F.; Beckwith, A. L. J. *J. Am. Chem. Soc.* **1986**, *108*, 5890. (b) Boisvert, G.; Giasson, R. *Tetrahedron Lett.* **1992**, *33*, 6587. (c) Clive, D. L. J.; Etkin, N.; Joseph, T.; Lown, J. M. *J. Org. Chem.* **1993**, *58*, 2442. (d) Rai, R.; Collum, D. B. *Tetrahedron Lett.* **1994**, *35*, 6221. (e) Itoh, T.; Ohara, H.; Emoto, S. *Tetrahedron Lett.* **1995**, *36*, 3531. (f) Snider, B. B.; Han, L.; Xie, C. *J. Org. Chem.* **1997**, *62*, 6978. (g) Terstiege, I.; Maleczka, R. E. *J. Org. Chem.* **1999**, *64*, 342. (h) Vailard, S. E.; Postigo, A.; Rossi, R. A. *J. Org. Chem.* **2002**, *67*, 8500. (i) Kurono, N.; Honda, E.; Komatsu, F.; Orito, K.; Tokuda, M. *Tetrahedron* **2004**, *60*, 1791. (j) Lin, H.; Schall, A.; Reiser, O. *Synlett* **2005**, 2603. (k) Park, D. Y.; Gowrisankar, S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1440.

(4) (a) Kokubo, K.; Harada, K.; Mochizuki, E.; Oshima, T. *Tetrahedron Lett.* **2010**, *51*, 955. (b) Engler, T. A.; Iyengar, R. *J. Org. Chem.* **1998**, *63*, 1929. (c) Rupprecht, K. M.; Boger, J.; Koogsteen, K.; Nachbar, R. B.; Springer, J. P. *J. Org. Chem.* **1991**, *56*, 6180.

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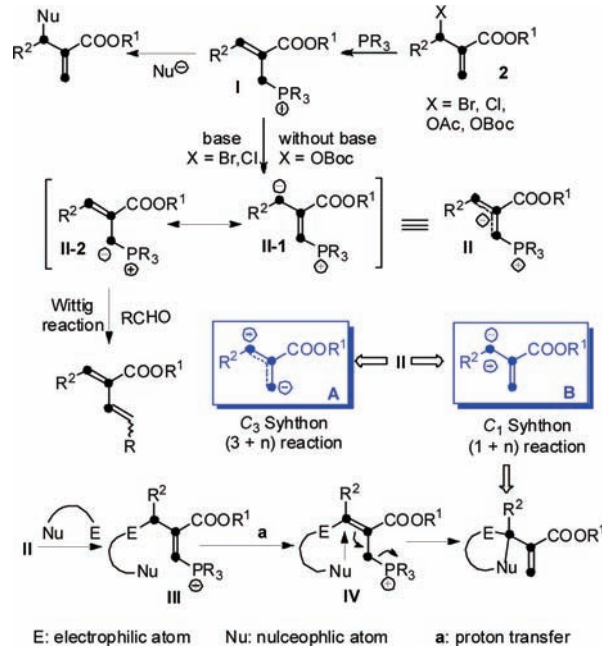
cloadditions[10] from allenoates and imine/alkenes have been applied in the synthesis of several natural products.[11] These remarkable works also re-emphasize the advantage of domino reactions. Intrigued by those elegent studies and our phosphine-mediated novel selective aza-MBH domino reaction,[12] we have reported the phosphine-catalyzed domino reaction constructing *cis*-dihydrobenzofuran[13] and chroman[14] skeletons from allenoates and salicyl *N*-thiophosphinyl imines.

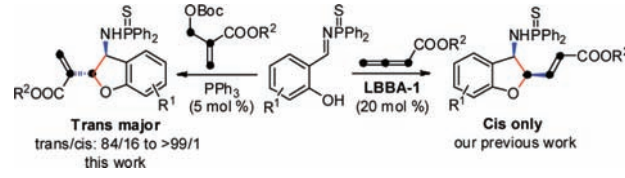
Recently, Lu and Tang reported the [3 + 2], [3 + 3], [3 + 6], and [3 + 4] annulations,[15] in which a class of modified allyic derivatives **2** were used as versatile C_3 synthons (**A** in Scheme 1). Kim, Aggarwal, and He discoverd the Wittig reactions[16] generating the 1,3-diene compounds. In those reactions, phosphine converts modified allyic derivatives **2** into allylic phosphorus ylides **II** by a S_N2 or addition−elimination (**2-I**) and

Scheme 1. Various Phosphine-Catalyzed Reaction Types of Allylic Carbonates



deprotonation process (**I**−**II**).[15a] Krisher developed the first phosphine-catalyzed allylation reaction through tandem S_N2'−S_N2' substitution.[17] Upon the basis of those studies and our work concerning the phosphine-catalyzed domino annulations, we envision that the allylic phosphorus ylide first reacts with imines/alkenes via γ-carbon addition (**II**−**III**), then, if the proton transfer occurs (**III**−**IV**), it might serve as a 1,1-dipolar (**B** in Scheme 1) reacting with salicyl *N*-thiophosphinyl imines to form *trans*-2,3-dihydrobenzofurans (Scheme 2) through a

Scheme 2. Phosphine-Catalyzed Domino Reactions: Selectively Constructing *cis*- and *trans*-2,3-Dihydrobenzofurans[a]



[a] LBBA-1: 2′-(diethylphosphino)-[1,1′-biphenyl]-2-ol.

domino process. During our preparation of this manuscript, Zhang and co-workers reported the case where modified allyic derivatives **2** serve as C_1 synthons.[18]

(5) (a) Lomberget, T.; Baragona, F.; Fenet, B.; Barret, R. *Org. Lett.* **2006**, *8*, 3919. (b) Kuethe, J. T.; Wong, A.; Journet, M.; Davies, I. W. *J. Org. Chem.* **2005**, *70*, 3727. (c) Nair, V.; Rajesh, C.; Dhanya, R.; Rath, N. P. *Org. Lett.* **2002**, *4*, 953. (d) Apers, S.; Paper, D.; Bürgermeister, J.; Baranikova, S.; Dick, S. V.; Lemière, G.; Vlietinck, A.; Pieters, L. *J. Nat. Prod.* **2002**, *65*, 718. (e) Benbow, J. W.; Katoch-Rouse, R. *J. Org. Chem.* **2001**, *66*, 4965. (f) Engler, T. A.; Letavic, M. A.; Iyengar, R.; LaTessa, K. O.; Reddy, J. P. *J. Org. Chem.* **1999**, *64*, 2391. (g) Engler, T. A.; Chai, W.; LaTessa, K. O. *J. Org. Chem.* **1996**, *61*, 9297. (h) Engler, T. A.; Combrink, K. D.; Ray, G. E. *J. Am. Chem. Soc.* **1988**, *110*, 7931.

(6) (a) Barlugenga, J.; Fananas, F. J.; Sanz, R.; Marcis, C. *Chem.—Eur. J.* **2005**, *11*, 5397. (b) Kneisel, F. F.; Monguchi, Y.; Knapp, K. M.; Zipse, H.; Knochel, P. *Tetrahedron Lett.* **2002**, *43*, 4875. (c) Plotkin, M.; Chen, S.; Spoors, P. G. *Tetrahedron Lett.* **2000**, *41*, 2269. (d) Nakao, J.; Inoue, R.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1997**, *62*, 1910.

(7) For recent transation-metal-catalyzed processes, see: (a) René, O.; Lapointe, D.; Fagnou, K. *Org. Lett.* **2009**, *11*, 4560. (b) Natori, Y.; Tsutsui, H.; Sato, N.; Nakamura, S.; Nambu, H.; Shiro, M.; Hsshimoto, S. *J. Org. Chem.* **2009**, *74*, 4418. (c) Szlosek-Pinaud, M.; Diza, P.; Martinez, J.; Lamaty, F. *Tetrahedron* **2007**, *63*, 3340. (d) Pelly, S. C.; Govender, S.; Fernandes, M. A.; Schmalz, H.-G.; Koning, C. B. *J. Org. Chem.* **2007**, *72*, 2857. (e) Grant, V. H.; Liu, B. *Tetrahedron Lett.* **2005**, *46*, 1237. (f) Pan, C.; Ma, Z.; Yu, J.; Zhang, Z.; Hui, A.; Wang, Z. *Synlett* **2005**, 1922. (g) Zhang, H.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 6144. (h) Kurosawa, W.; Kobayashi, H.; Kan, T.; Fukuyama, T. *Tetrahedron* **2004**, *60*, 9615. (i) Trost, B. M.; Thiel, O. R.; Tsui, H.-C. *J. Am. Chem. Soc.* **2003**, *125*, 13155. (j) Cheung, W.-H.; Zheng, S.-L.; Yu, W. Y.; Zhou, G.-C.; Che, C.-M. *Org. Lett.* **2003**, *5*, 2535. (k) Zheng, S. L.; Yu, W. Y.; Xu, M. X.; Che, C. M. *Tetrahedron Lett.* **2003**, *44*, 1445. (l) Kurosawa, W.; Kan, T.; Fukuyama, T. *Synlett* **2003**, 1028. (m) Saito, H.; Oishi, H.; Kitagaki, S.; Nakamura, S.; Anada, M.; Hashimoto, S. *Org. Lett.* **2002**, *4*, 3887. (n) Kuwabe, S.-I.; Torraca, K. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 12202. (o) Davies, H. M. L.; Grazini, M. V. A.; Aouad, E. *Org. Lett.* **2001**, *3*, 1475.

(8) Such as synthesis via benzyne, intramolecular substitutions without metal catalysts, miscellaneous methods, see selected examples: (a) Shen, Z.; Dong, V. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 784. (b) Beltrán-Rodil, S.; Peña, D.; Guitán, E. *Synlett* **2007**, 1308. (c) Fousteris, M.; Chevrin, C.; Le Bras, J.; Muzart, J. *Green Chem.* **2006**, *8*, 522. (d) Liu, G.; Lu, X. *J. Am. Chem. Soc.* **2006**, *128*, 16504.

(9) For reviews, 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) Lu, X.; Du, Y.; Lu, C. *Pure Appl. Chem.* **2005**, *77*, 1985. (d) Nair, V.; Menon, R. S.; Sreekanth, A. R.; Abhilash, N.; Biji, A. T. *Acc. Chem. Res.* **2006**, *39*, 520. (e) Ye, L.-W.; Zhou, J.; Tang, Y. *Chem. Soc. Rev.* **2008**, *37*, 1140. (f) Marinetti, A.; Voituriez, A. *Synlett* **2010**, 174.

(10) For reviews, see: Cowen, B. J.; Miller, S. J. *Chem. Soc. Rev.* **2009**, *38*, 3102 and the references cited therein.

(11) Tran, Y. S.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 12632.

(12) Meng, X.; Huang, Y.; Chen, R. *Chem.—Eur. J.* **2008**, *14*, 6852.

(13) Meng, X.; Zhao, H.; Huang, Y.; Xie, P.; Ma, J.; Chen, R. *Org. Lett.* **2009**, *11*, 991.

(14) Meng, X.; Huang, Y.; Chen, R. *Org. Lett.* **2009**, *11*, 137.

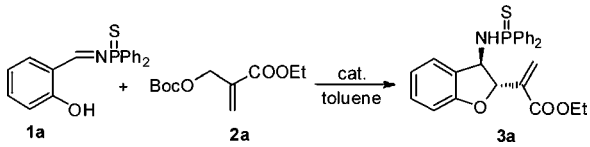
(15) (a) Du, Y.; Lu, X.; Zhang, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 1035. (b) Du, Y.; Feng, J.; Lu, X. *Org. Lett.* **2005**, *7*, 1987. (c) Ye, L.-W.; Sun, X.-L.; Wang, Q.-G.; Tang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 5951. (d) Feng, J.; Lu, X.; Kong, A. *Tetrahedron* **2007**, *63*, 6035. (e) Ye, L.-W.; Han, X.; Sun, X.-L.; Tang, Y. *Tetrahedron* **2008**, *64*, 1487. (f) Zheng, S.; Lu, X. *Org. Lett.* **2008**, *10*, 4481. (g) Zheng, S.; Lu, X. *Tetrahedron Lett.* **2009**, *50*, 4532. (h) Zheng, S.; Lu, X. *Org. Lett.* **2009**, *11*, 3978.

(16) (a) Lee, C. G.; Lee, K. Y.; Kim, S. J.; Kim, J. N. *Bull. Korean Chem. Soc.* **2007**, *28*, 719. (b) Palmelund, A.; Myers, E. L.; Tai, L. R.; Tisserand, S.; Butts, C. P.; Aggarwal, V. K. *Chem. Commun.* **2007**, 4128. (c) Zhou, R.; Zhang, C.; Song, H.; He, Z. *Org. Lett.* **2010**, *12*, 976. (d) Singh, V.; Batra, S. *Tetrahedron* **2008**, *64*, 4511.

(17) For phosphine-catalyzed allylation, see: (a) Cho, C.-W.; Kong, J.-R.; Krische, M. J. *Org. Lett.* **2004**, *6*, 1337. (b) Cho, C.-W.; Krische, M. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 6689. (c) Jiang, Y.-Q.; Shi, Y.-L.; Shi, M. *J. Am. Chem. Soc.* **2008**, *130*, 7202.

We initiated our investigation by subjecting carbonate **2a** (1.2 equiv) to salicyl *N*-thiophosphinyl imines **1a** in the presence of PPh_3 (10 mol %) in toluene at 110 °C. To our delight, **3a** was isolated as stereoisomers in 48% yield with diastereomeric ratio of 60/40 (trans/cis) (entry 1, Table 1).

Table 1. Screening Catalysts and Condition for the Domino Reactions[a]



1a 2a 3a

entry	cat. (%)	**1a/2a**	*t* (h)	trans/cis[b]	yield (%)[c]
1	PPh_3 (10)	1/1.2	48	60/40	48
2	PPh_3 (10)	1/1.5	48	69/31	63
3	PPh_3 (10)	1/2	5	93/7	71
4	PPh_3 (10)	1/3	45 min	97/3	83
5	PPh_3 (20)	1/2	4.5	69/31	85
6	PPh_3 (20)	1/3	50 min	83/17	81
7	PPh_3 (50)	1/3	30 min	84/16	85
8	PPh_2Et (10)	1/3	15 min	72/28	56
9	$PPhEt_2$ (10)	1/3	15 min	76/24	79
10	PBu_3 (10)	1/3	–	–	–
11	PPh_3 (5)	1/3	50 min	97/3	99
12	PPh_3 (5)	1/2.5	55 min	97/3	99
13[d]	PR_3 (5)	1/2.5	2	>99/1	83
14[e]	PPh_3 (5)	1/2.5	48	–	–
15[f]	PPh_3 (5)	1/2.5	5	97/3	83

[a] The reaction was carried out in 1/3 mmol scale in solvent (2.5 mL) at 110 °C. [b] Determined by ^{31}P NMR of the crude reaction mixture. [c] Isolated yields. [d] $PR_3 = P(p\text{-}ClC_6H_4)_3$. [e] The reaction temperature is 25 °C. [f] The reaction was carried out at 80 °C.

The ratio of **1a**/**2a** has a great effect on this reaction. Screening of the ratio of **1a/2a** revealed that 1/2.5 (**1a/2a**) gave the best result with respect to the reaction time, yield, as well as diastereoselectivity (entries 1−4, 12). The more nucleophilic phosphine PPh_2Et or $PPhEt_2$ led to lower yield and stereoselectivity (entries 8 and 9), and strong nucleophilic PBu_3 delivered no product at all (entry 10). Although a better diastereoselectivity was obtained when $P(p\text{-}ClC_6H_4)_3$ was used (entry 13), prolonged reaction time was required, and the yield of product decreased. Increasing the amounts of PPh_3 resulted in a substantial decrease in the diastereoselectivity and efficiency (entries 5−7), while decreasing the amounts of catalyst to 0.05 equiv did not affect the yield as well as the diastereoselectivity (entry 12). At room temperature, no reaction occurred (entry 14). When the temperature decreased to 80 °C, longer reaction time was needed (entry 15). Thus, we established the optimal reaction conditions for this reaction: using 5% PPh_3 as the catalyst and toluene as the solvent to perform the reaction at 110 °C. The structure and stereochemistry of **3** was characterized by combination of NMR, HRMS spectra, and single-crystal X-ray analysis (**3b**, Figure 1) (see Supporting Information).

(18) Chen, Z.; Zhang, J. *Chem. Asian J.* **2010**, *5*, 1542.

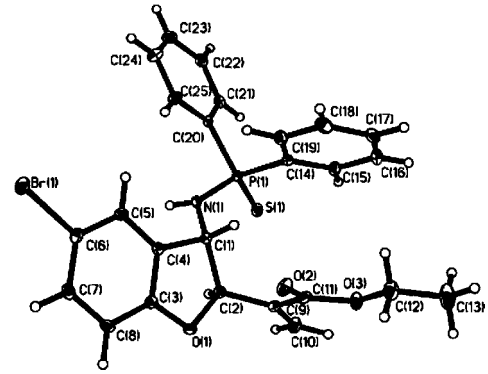
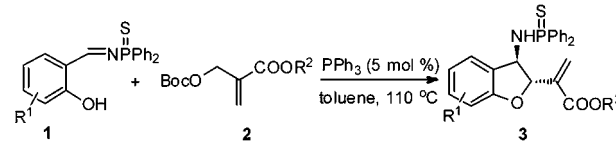


Figure 1. X-ray crystal structure of **3b**.

Under the optimized reaction conditions, a variety of salicyl *N*-thiophosphinyl imines were examined (Table 2).

Table 2. Scope of the Domino Reactions in the Presence of Phosphine[a]



1 2 3

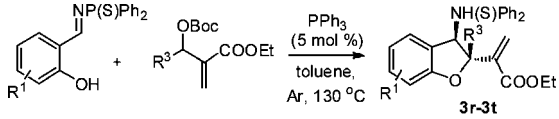
entry	R^1	R^2	*t* (min)	trans/cis[b]	yield (%)[c]
1	H	Et	45	97/3	99 (**3a**)
2	5-Br	Et	40(150)[d]	84/16(94/6)[d]	88 (83)[d] (**3b**)
3	3,5-*t*Bu	Et	90	>99/1	83 (**3c**)
4	5-*t*Bu	Et	85	>99/1	74 (**3d**)
5	5-NO_2	Et	30 (150)	76/24(84/16)	88 (84) (**3e**)
6	5-Cl	Et	30 (150)	86/14 (94/6)	86 (82) (**3f**)
7	5-OMe	Et	60	>99/1	72 (**3g**)
8	5-Me	Et	65	97/3	72 (**3h**)
9	3-Me	Et	77	98/2	86 (**3i**)
10	3-Cl	Et	30 (150)	73/27(86/14)	89 (88) (**3j**)
11	3-Ph	Et	45	95/5	90 (**3k**)
12	3-Ph	Me	45	94/6	95 (**3l**)
13	5-*t*Bu	Me	35	94/6	83 (**3m**)
14	5-Br	Me	30 (120)	87/13 (92/8)	92 (90) (**3n**)
15	H	Me	50	97/3	91 (**3o**)
16	3-Ph	Bu	35	92/8	98 (**3p**)
17	5-Br	Bu	30 (120)	85/15 (96/4)	82 (99) (**3q**)

[a] Unless otherwise noted, the reaction we carried out in 1/3 mmol scale in solvent (2.5 mL). The ratio of **1**/**2** is 1.0/2.5. [b] Determined by ^{31}P NMR of the crude reaction mixture. [c] Isolated yields. [d] Values in parentheses are the result catalyzed by $P(p\text{-}ClC_6H_4)_3$ (0.05 equiv).

Basically, the reaction, even with a sterically hindered substrate, proceeded smoothly to give the desired products in high yields. The diastereoselectivity was to some degree sensitive to electronic property of the substituent on the phenyl ring and benefitted from the electronic donating feature (entries 2, 5, 6, 10, 14, and 17). The lower diastereoselectivity for imines with the electronic-drawing feature could be overcome by using a less nucleophilic

phosphine P(*p*-ClC_6H_4)$_3$. As shown in Table 2, a high diastereoselectivity and parallel yield can be obtained in this way (values in parentheses of entries 2, 5, 6, 10, 14, and 17). Moreover, the size of the ester substituent of **2** had a minor effect on the domino process (entries 12−17). For substituted allylic compound **2**, a prolonged reaction time and higher temperature were needed, while there was no effect on the diastereoselectivity, albeit with a slight lower yield (Scheme 3). It was very difficult to analyze the

Scheme 3. Domino Reaction of Substituted Allylic Carbonates **2** with Sailcyl *N*-Thiphosphinyl Imine[a]



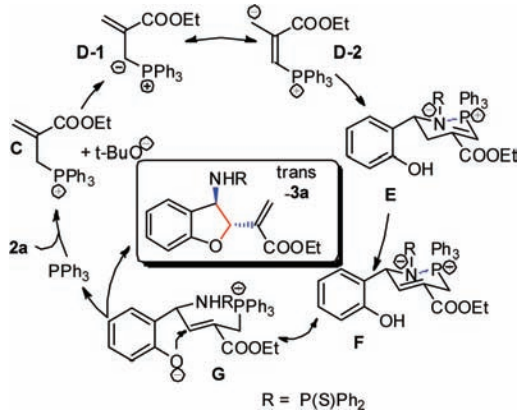
3r: R^1 = 5-Br, R^3 = C_6H_5, trans/cis: 94/6, yield: 73%
3s: R^1 = 5-Br, R^3 = 4-Cl-C_6H_4, trans/cis: 92/8, yield: 58%
3t: R^1 = 3-C_6H_5, R^3 = 4-CH_3-C_6H_4, trans/cis: >99/1, yield: 76%

[a] For experimental details, see Supporting Information.

stereochemistry of the trisubstituted products **3r**−**3t** by NMR and HRMS spectra. Furthermore, the structure and stereochemistry of **3r** were confirmed by single-crystal X-ray analysis.

The detailed mechanism of the domino reaction above has not been clarified. According to our experimental results (Scheme 3) and some related literature,[15d] we proposed a mechanism for this domino reaction as follows (Scheme 4).

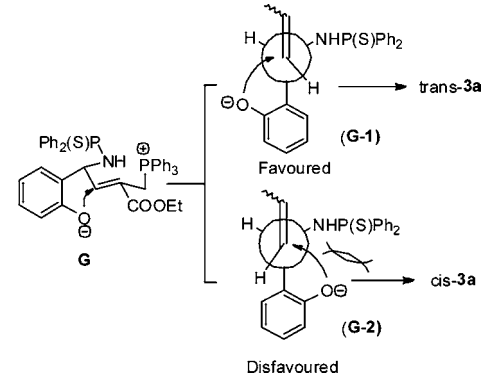
Scheme 4. Possible Mechanism for the Formation of **3**



The reaction might be initiated by the formation of the phosphonium salt **C** via an addition−elimination process, which was deprotonated by the in situ generated *tert*-butyloxide anion to form the ylide **D** (**D-1** or **D-2**).[15d] Subsequent nucleophilic addition of the ylide **D-2** to the electron-deficient imine **1a** yielded the intermediate **E** via γ-carbon addition. Intermediate **E** would isomerize into intermediate **G** under proton transfers (**E**−**F**−**G**), Intramolecular annulation involving the oxygen anion addition to the olefinic double bond gave the *trans*-2,3-disubstituted dihydrobenzofran **3a** with the regeneration of PPh_3 to complete the catalytic cycle.

As shown in Newman projections **G-1** and **G-2**, the steric repulsion between the oxygen anion and two phenyl groups on the phosphorus atom suggests that intermediate **G-1** is the favored one (Scheme 5). Therefore, intermediate **G-1**

Scheme 5. Stereoselectively Favored Reaction Path



undergoes facile addition to produce the 2,3- dihydrobenzofurans with *trans*-enriched configuration.

In summary, we have developed a simple, convenient, highly stereoselective phosphine-catalyzed domino reaction between salicyl *N*-thiophosphinyl imines and allylic carbonates. Significantly, the allylic carbonate was used as a 1,1-dipolar synthon and thus provides a new method for the construction of *trans*-2,3-dihydrobenzofurans in excellent yields. Further efforts on the application of this new 1,1-dipolar synthon in organic synthesis and the asymmetric version of the reaction are in progress.

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

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