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Bifunctional Phosphine-Catalyzed Domino Reaction: Highly Stereoselective Synthesis of *cis*-2,3-Dihydrobenzofurans from Salicyl *N*-Thiophosphinyl Imines and Allenes

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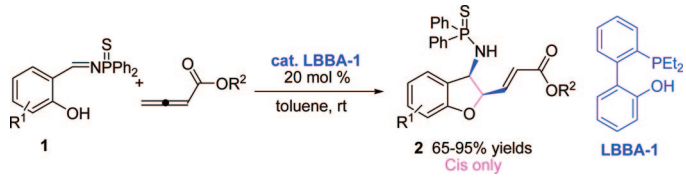
ABSTRACT



A new bifunctional phosphine catalyst, (2′-hydroxy-biphenyl-2-yl)-diethylphosphane (LBBA-1), was developed for the highly stereoselective synthesis of *cis*-2,3-dihydrobenzofurans via an aza-Morita−Baylis−Hillman/umpolung addition domino reaction of salicyl *N*-thiophosphinyl imines with electron-deficient allenes. Dual activation of both nucleophile and electrophile by the bifunctional catalyst accounts for the observed high reactivity and stereoselectivity.

During the past few years, domino reactions catalyzed by organocatalysts have emerged as a powerful tool in organic synthesis.[1] These reactions can rapidly form complex molecules from readily available substrates in a single operation without isolation of intermediates. Therefore, considerable efforts have been made to develop catalytic domino transformations by an organocatalyst.[2] Most successful classes of organocatalysts used for this purpose are usually secondary amines, especially the prolinol derivatives.[3] Other classes of organocatalysts for this purpose are few.[4−6] Thus, the development of a new catalyst with high activity and stereoselectivity is the key issue and remains a great challenge. Meanwhile, for the purpose of designing a new organocatalyst, the concept of activating and binding both reacting partners for a catalytic transformation has been widely reported using synthetic small molecules.[7] Recently, there has been considerable interest in the unique reactivity of phosphine catalysts,[8] and combining the reactive phosphine group with a hydrogen bonding motif in one molecule is a new direction in designing new bifunctional catalysts. For example, Shi, Sasai, and Ito reported a series of chiral phosphine bifunctional catalysts which can efficiently catalyze the asymmetric aza-Morita−Baylis−Hillman (aza-MBH) reactions.[9] Jacobsen developed an efficient phosphinothiourea catalyst for imine−allene [3 + 2] cycloadditions.[10] Miller reported an α-amino acid type phosphine catalyst for enantioselective [3 + 2] cycloaddition.[11]

The reaction of imines with allenic esters catalyzed by phosphine usually gives [3 + 2][12] or [4 + 2][12a,13] cycloadducts. As outlined in Scheme 1, the reaction of salicylic

(1) For reviews on domino reactions, see: (a) Tietze, L. F.; Brasche, G.; Gericke, K.; *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006. (b) Guo, H.-C.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2006**, *45*, 354. (c) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed.* **1993**, *32*, 131. (d) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.

(2) For recent reviews on organocatalytic domino reactions, see: Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570.

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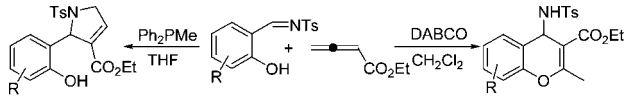
Scheme 1. Reaction of Ethyl 2,3-Butadienoate with Salicyl *N*-Tosylimine



imines with allenic esters catalyzed by DABCO (1,4-diazabicyclo[2.2.2]octane) or phosphine gives highly functionalized chromenes or [3 + 2] cycloadducts, respectively.[14] We have reported a bifunctional phosphine organocatalyst (**LBBA-2**) for the novel selective aza-MBH domino reaction and aza-MBH reaction of N-sulfonated imines with acrolein.[6] On the basis of the information on our bifunctional phosphine as catalyst of the aza-MBH reaction, and the knowledge of the phosphine as the catalyst of umpolung addition of allenes and 2-alkynoates,[15] we envisioned that the bifunctional phosphine catalysts may catalyze the salicyl *N*-thiophosphinyl imines and allenes to form the 2,3-disubstituted dihydrobenzofurans through an aza-MBH/umpolung addition domino reaction. Herein, we wish to report such a novel domino reaction catalyzed by a new easily synthesized Lewis base and Brϕnsted acid (**LBBA-1**) bifunctional catalyst (Figure 1) and its application to the highly stereoselective synthesis of a wide range of *cis*-2,3-disubstituted dihydrobenzofurans.

Functionalized 2,3-dihydrobenzofurans are common sub-

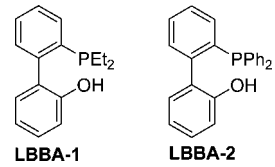


Figure 1. Structures of the catalysts.

structures existing in natural products and have been identified to possess a range of biological activities.[16] Various procedures for synthesis of the 2,3-dihydrobenzofurans have been developed during the past few years.[17] However, a new method is still needed to rapidly synthesize the highly functionalized 2,3-dihydrobenzofurans, such as the *cis*-2,3-disubstituted dihydrobenzofurans. Up to now, only a few methods are suitable for the stereoselective synthesis of the

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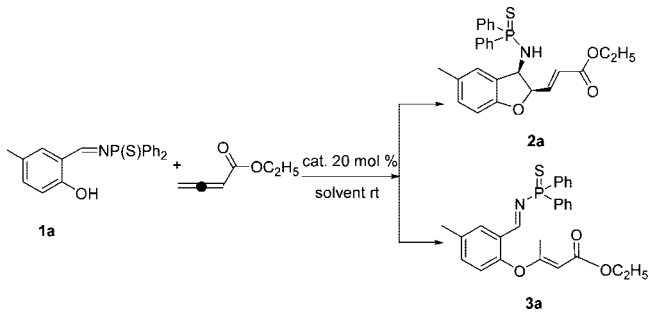
Table 1. Screening Catalysts and Solvents for the Domino Reactions[a]



				yield (%)	
entry	catalyst	solvent	time (h)	**2a**	**3a**
1	LBBA-2	toluene	6	0	0
2	LBBA-1	CH_3CN	6	60	0
3	LBBA-1	CH_2Cl_2	6	65	0
4	LBBA-1	THF	6	83	0
5	LBBA-1	toluene	6	88	0
6[b]	LBBA-1	toluene	4	90	0
7[c]	LBBA-1	toluene	1	89	0
8	PPh_3	toluene	24	0	0
9[d]	$^nBu_3P$	toluene	6	51	0
10[e]	DABCO	toluene	6	0	95
11[e]	DBU	toluene	24	0	10

[a] The reaction was carried out in 0.5 mmol scale in solvent (2 mL). The ratio of the **1a**/allene is 1/1.5. [b] 30 mol % catalyst was used. [c] The reaction temperature is 50 °C. [d] *cis*- and *trans*-isomers were determined by ^{31}P NMR spectroscopic analysis. C/T = 1:1. [e] oxa-Michael addition product **3a**.

cis-2,3-disubstituted dihydrobenzofurans by the intramolecular cyclization reaction.[18]

The reaction of salicyl *N*-thiophosphinyl imines **1a** (see Supporting Information) and ethyl 2,3-butadienoate with **LBBA-2** as catalyst was first tested (entry 1), but no desired product was obtained. However, with **LBBA-1**, the analogue of **LBBA-2**, as the catalyst, the reaction proceeded smoothly and gave exlcusively the *cis*-2,3-disubstituted dihydrobenzofuran **2a** in different solvent systems (Table 1, entries 2−5). This domino reaction with toluene as solvent gave the best result (88% yield, entry 5). Reaction temperature and catalyst amount were also examined as shown in Table 1 (entries 6 and 7). The optimal reaction condition is with 20 mol % of **LBBA-1** as catalyst in toluene at room temperature. Other phosphine catalysts, such as PPh_3, were not effective for this domino reaction (entry 8). The reaction under $^nBu_3P$ led to the target molecule as a mixture of *cis*- and *trans*-isomers without stereoselectivity (entry 9). Employing DABCO (entry 10) and DBU (entry 11) as the catalysts did not give the desired product; instead, an umpolung addition product **3a** was obtained. The structure

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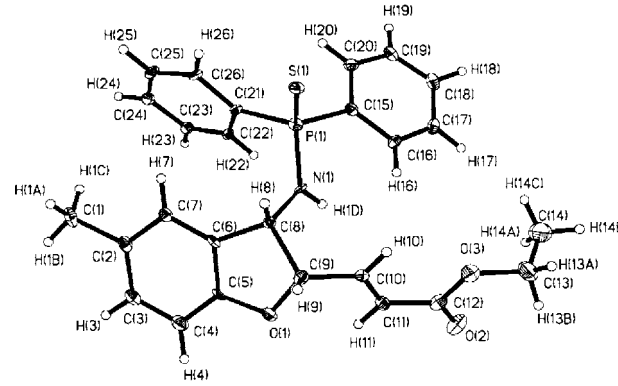
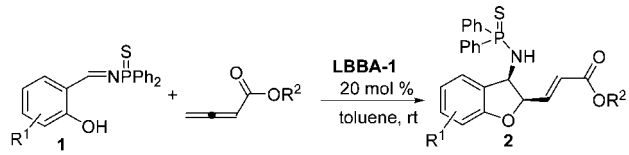


Figure 2. ORTEP representation of **2a**.

Table 2. Scope of the Aza-MBH/oxa-Michael Domino Reaction[a]



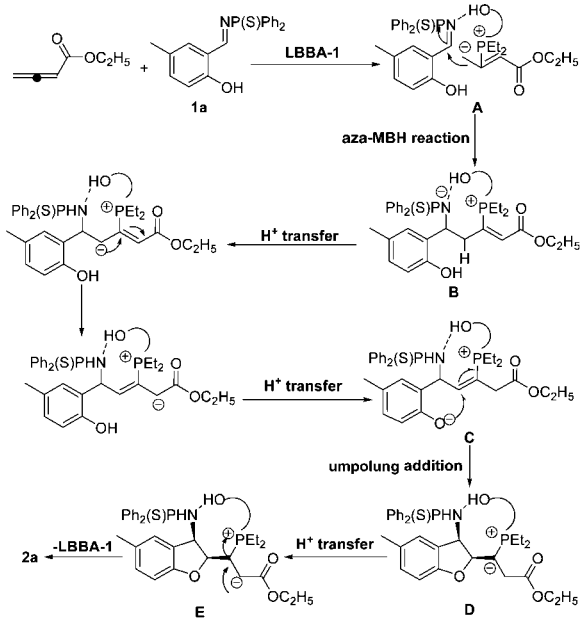
entry	R^1	R^2	time (h)	yield (%)
1	5-CH_3	C_2H_5	6	88 (**2a**)
2	5-^{t}Bu	C_2H_5	6	88 (**2b**)
3[b]	5-Br	C_2H_5	12	72 (**2c**)
4	3-CH_3	C_2H_5	6	92 (**2d**)
5	4-CH_3	C_2H_5	6	90 (**2e**)
6[b]	3-Cl	C_2H_5	12	65 (**2f**)
7	5-CH_3O	C_2H_5	1	75 (**2g**)
8	3,5-^{t}Bu	C_2H_5	1	95 (**2h**)
9	H	C_2H_5	6	90 (**2i**)
10	3-CH_3	^{t}Bu	8	83 (**2j**)
11	5-CH_3	^{t}Bu	8	85 (**2k**)
12	5-^{t}Bu	^{t}Bu	8	87 (**2l**)
13[b]	5-Cl	^{t}Bu	18	70 (**2m**)
14[b]	5-Br	^{t}Bu	18	68 (**2n**)

[a] The reaction was carried out in 0.5 mmol scale in solvent (2 mL). The ratio of the **1a**/allene is 1/1.5. [b] The reaction temperature is 50 °C. [c] All of the products are cis isomer only.

and configuration of the product **2a** were unequivocally confirmed by single-crystal X-ray analysis. The ORTEP diagram is shown in Figure 2.

With the optimal reaction conditions in hand, we next explored the scope of this domino reaction using a variety of salicyl *N*-thiophosphinyl imines and ethyl 2,3-butadienoate (Table 2). The corresponding *cis*-2,3-dihydrobenzofurans were obtained in good to excellent yields. For imines with electron-withdrawing groups on the phenyl rings, a prolonged reaction time and higher temperature were needed, and the yields were slightly low (entries 3, 6, 13, and 14). The reason is that the electron-withdrawing groups decrease the nucleophilicity of the oxygen atom. In contrast, for imines with electron-donating groups on the phenyl rings, the reaction was completed in a short time to give the corresponding

Scheme 2. Possible Catalytic Cycle



product with excellent yields (entries 1, 2, 4, 5, 7−12,). Surprisingly, when a sterically hindered substrate (**1h**) was used (entry 8), the reaction proceeded smoothly to give the corresponding product in good yield with a short reaction time. Similarly, *tert*-butyl 2,3-butadienoate can also react with various salicyl *N*-thiophosphinyl imines under identical conditions to give the desired *cis*-2,3-disubstituted dihydrobenzofurans in good yields.

The detailed mechanism of the above domino reaction has not been clarified. According to these experimental results and some literature for the bifunctional phosphine-catalyzed reactions,[6,9a] we proposed a possible mechanism for this novel aza-MBH domino reaction as follows (Scheme 2). The bifunctional phosphine catalyst **LBBA-1** first reacts with the allene[19] and meanwhile activates the imine by the hydrogen bond to form **A**. The subsequent aza-MBH reaction was carried out by a γ addition to **1a** affording intermediate **B**,[12f,20] which forms intermediate **C** via two proton transfers.[12f] The hydrogen bonding interaction between the OH group of the bifunctional phosphine catalyst and the substrate $RNHP(S)Ph_2$ group fixes the conformation of intermediate **C** and thus ensures generation of the *cis*-isomer. Then an intramolecular umpolung addition of the oxygen anion to the γ carbon in **C** from the backside of the $RNHP(S)Ph_2$ group leads to the cyclized cis intermediate **D**,[15a] followed by another proton transfer to afford **E**.[12f] Finally, the reaction gives the *cis*-2,3-disubstituted dihydrobenzofuran **2a** with the regeneration of **LBBA-1** to complete the catalytic cycle.

In summary, we have developed a novel bifunctional phosphine-catalyzed aza-MBH/umpolung addition domino reaction to generate the *cis*-2,3-dihydrobenzofurans from salicyl *N*-thiophosphinyl imines and allenic esters with high stereoselectivity. Our future efforts will focus on an asymmetric version of this reaction and applying this new method to the construction of natural products.

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Supporting Information Available: Detailed experimental procedures, spectral data for all new compounds, and X-ray crystal structure CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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