Annulations

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Phosphine-Catalyzed β,γ-Umpolung Domino Reaction of Allenic Esters: Facile Synthesis of Tetrahydrobenzofuranones Bearing a Chiral Tetrasubstituted Stereogenic Carbon Center

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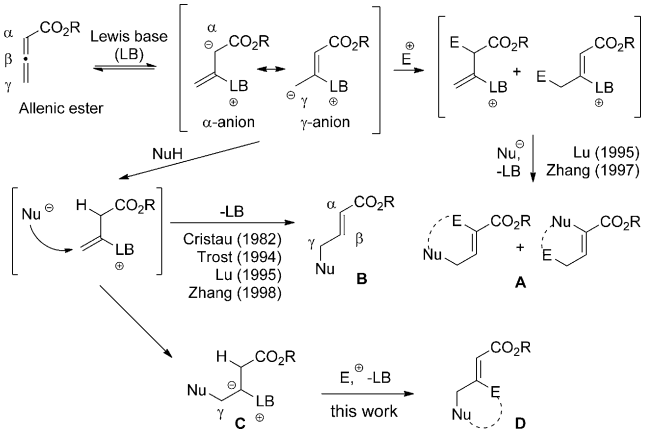
Abstract: *An enantio-, diastereo-, regio-, and chemoselective phosphine-catalyzed β,γ-umpolung domino reaction of allenic esters with dienones has been developed for the first time. The designed sequence, involving oxy-Michael and Rauhut–Currier reactions, produced highly functionalized tetrahydrobenzofuranones, bearing a chiral tetrasubstituted stereogenic center, in up to 96 % ee.*

A Lewis base (LB) catalyzed reactions of allenic esters with electrophiles and/or nucleophiles have been extensively investigated as a powerful tool for the preparation of structurally divergent molecules.[1] In 1995, Zhang and Lu presented phosphine-catalyzed [3+2] annulations between allenic esters and either enones or imines (Scheme 1) via either α- or γ-zwitterionic intermediates.[2a] With further contributions, such as the enantioselective annulation developed by Zhang and co-workers,[2b] $[n+2]$ annulations were widely explored for the synthesis of carbocyclic and heterocyclic compounds.[1,3] Within this related field, γ-umpolung addition of nucleophiles to electron-deficient alkynes and allenes allows the formation of γ-substituted α,β-unsaturated carbonyl compounds (Scheme 1). Since the pioneering works of the groups of Cristau[4a] (stoichiometric reaction), Trost[4b] (catalytic reaction for alkynes), Lu[4c] (catalytic reaction for allenes), and Zhang[4d] (catalytic and enantioselective reaction), there has been increasing interest in γ-umpolung additions of various nucleophiles to electron-deficient alkynes and allenes.[5] As part of our effort in the exploration of chiral LB catalysis,[6] we were interested in designing novel domino reactions to access important structural motifs by



Scheme 1. A Lewis base (LB) catalyzed reactions of allenic esters with electrophiles and/or nucleophiles.

nucleophilic attack on the γ-position of allenic esters. We assumed that the zwitterionic intermediate **C** (Scheme 1) could react with electrophiles before elimination of the LB catalyst, thus leading to a formal dual umpolung coupling. To the best of our knowledge, there is no report on an enantioselective domino process initiated by the nucleophilic attack at the γ-position of allenic esters.

To explore the possibility of the proposed domino process, we designed the LB-mediated desymmetrization of the prochiral dienones **2** with allenic esters **1** (Scheme 2). Addition of a LB to **1** generates the zwitterionic intermediate **I**, which could work as a Brønsted base for **2**, thus leading to the formation of the key intermediate **II** and alkoxide **III**. The γ-addition[4] of **III** to **II** would give the intermediate **IV**, and form an allylic ether **4** after elimination of the catalyst.[5] Alternatively, the tether ylide **IV** could react intramolecularly with a dienone through a β-addition process, thus resulting in the formation of **V** and leading to the chiral tetrahydrobenzofuranone **3** by proton transfer and elimination of the catalyst. Tetrahydrobenzofuranones are common to a vast number of natural products, such as loukacinol A, sorbicillactone A, and cryptocaryone, and they exhibit various biological activities (e.g., anticancer, anti-HIV, and glucose transport inhibitor; Figure 1).[7] The present domino process would be a straightforward and atom-economical way to prepare a chiral tetrahydrobenzofuranone skeleton.

As the first step in the development of our domino reaction, achiral LB catalysts were evaluated using **1a** and **2a**

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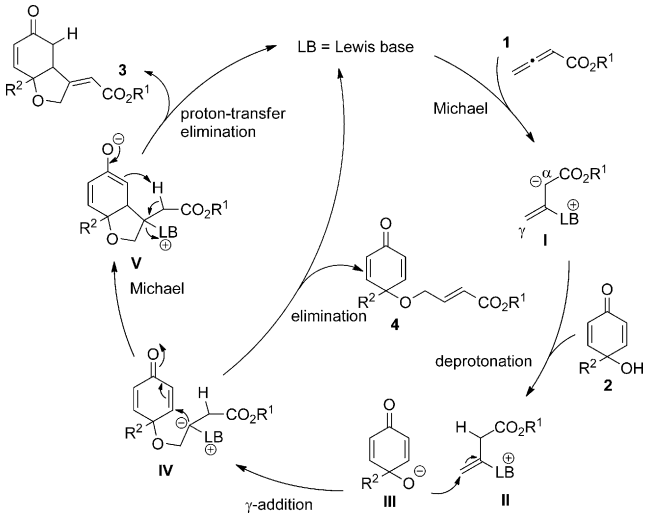


Scheme 2. An enantio-, diastereo-, regio-, and chemoselective β,γ-umpolung domino reaction mediated by a LB organocatalyst.

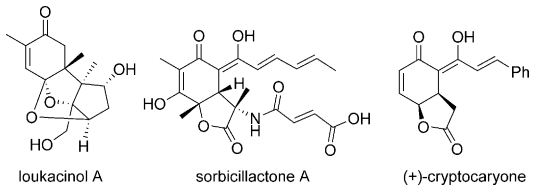
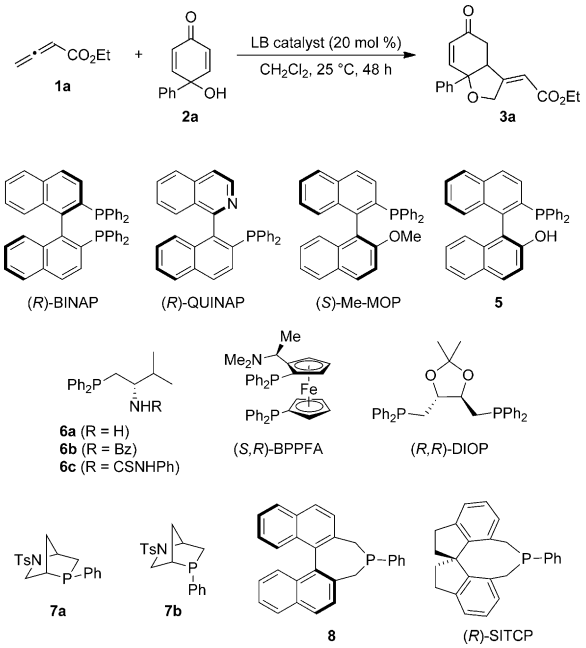


Figure 1. Examples of tetrahydrobenzofuranones isolated from natural sources.

as prototypical substrates in dichloromethane at 25 °C (Table 1, entries 1 and 2). To our delight, PPh_3 was found to promote the desired reaction efficiently and product **3a** was obtained as an *E*/*Z* mixture (1:1) in 72 % yield (entry 1),[8] albeit with self-condensation of **1a**, and the formation of the allylic ether **4a** (R^1 = Et, R^2 = Ph), as shown in Scheme 2, which is difficult to purify from the crude reaction mixture. In contrast, an amine catalyst such as DMAP, DBU, or DABCO (entry 2) rarely catalyzed the annulation reaction, thus affording only trace amounts of **3a**. Next, various chiral phosphine catalysts were tested (entries 3–12). The initial experiments revealed that axially chiral, bulky triaryl phosphines, BINAP, QUINAP, and Me-MOP are inactive in this transformation (entry 3). The bifunctional chiral organocatalysts **5** (Shi's catalyst)[9] and **6**,[10] some of which are known to mediate the enantioselective Morita–Baylis–Hillman and Rauhut–Currier (RC) processes, gave the product but in low yields with low or no selectivities (entries 4–7). The other phosphine catalysts such as (*S*,*R*)-BPPFA, (*R*,*R*)-DIOP, and **7** (Kwon's catalyst)[3p] also exhibited low or no catalytic activities (entries 8–10). During this screening process, the C_2-symmetrical chiral organocatalysts **8**[11] and (*R*)-SITCP,[12] possessing a highly nucleophilic monoaryl phosphine unit, gave promising outcomes (entries 11 and 12). In particular, the reaction of **1a** and **2a** with (*R*)-SITCP for 0.5 hours afforded **3a** in 57 % yield with 84 % *ee*.

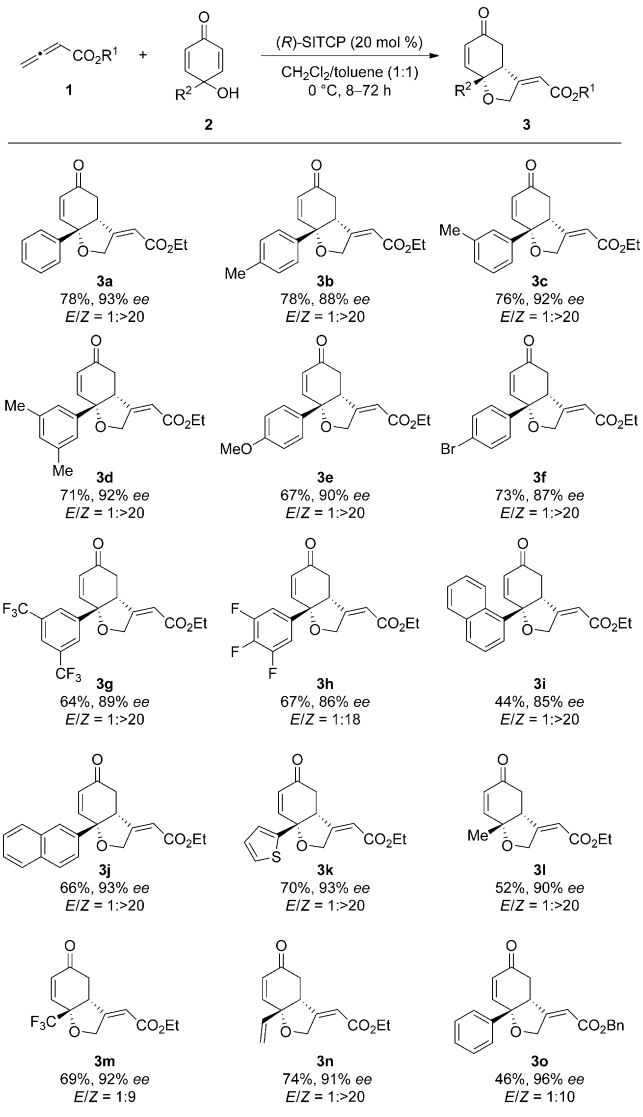
Table 1: Catalyst screening of the β,γ-umpolung domino reaction.[a]



Entry	LB catalyst	*E*/*Z*	Yield [%][b]	*ee* [%][c]
1	PPh_3	1:1	72 (16[d])	–
2	DMAP, DBU, or DABCO	–	trace	–
3	(*R*)-BINAP, (*R*)-QUINAP, or (*S*)-Me-MOP	–	trace	–
4	**5**	1:5	9	15
5	**6a**	1:4	15	31
6	**6b**	1:2	30	25
7	**6c**	1:2	25	0
8	(*S*,*R*)-BPPFA	1:6	8	5
9	(*R*,*R*)-DIOP	1:3	13	5
10	**7a** or **7b**	–	n.r.	–
11	**8**	1:6	40	34
12[e]	(*R*)-SITCP	1:10	57	84

[a] Reaction conditions: **1a** (3.0 equiv), **2a**, and catalyst (20 mol %) in CH_2Cl_2 at 25 °C for 48 h. [b] Determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [c] Determined by HPLC analysis using a chiral stationary phase. [d] In the presence of *t*BuOK (20 mol %). [e] For 0.5 h. n.r. = no reaction. Bz = benzoyl, Ts = 4-toluenesulfonyl.

After the optimization of other reaction conditions (solvents, temperature, and ratio of **1a** and **2a**; see the Supporting Information), the best result (**3a**: *E*/*Z* = 1:>20, 78 % yield, 93 % *ee*) was obtained when the reaction of **1a** (1.5 equiv) and **2a** with (*R*)-SITCP (20 mol %) was performed in a mixed solvent system consisting of CH_2Cl_2/toluene (1:1) at 0 °C (Scheme 3). Under the optimal reaction conditions, highly *Z*-selective tetrahydrobenzofuranones (**3**) were obtained in good yields (44–78 %) with high enantioselectivities (85–96 % *ee*) irrespective of the electronic nature of R^2 in **2** including aryl and vinyl groups. When R^2 is alkyl, such as methyl (**2l**) and trifluoromethyl (**2m**), the cyclic products **3l** (90 % *ee*) and **3m** (92 % *ee*), respectively, were isolated. The reaction of benzyl allenoate (**1b**: R^1 = Bn) with **2a** resulted in the formation of the corresponding **3o** in 96 % *ee*.[13] Finally,



Scheme 3. Substrate scope. Yields are those of isolated **3**. The *ee* value of **3** was determined by HPLC on a chiral stationary phase. Reaction conditions: **1** (1.5 equiv), **2**, and (*R*)-SITCP (20 mol%) in CH_2Cl_2/toluene (1:1) at 0°C for 48 h (**3a–f**, and **3i–n**), for 8 h (**3g**), for 24 h (**3h**), and for 72 h (**3o**).

the absolute and regio configurations of the cyclized product **3k** were determined, by the crystalline sponge method,[14] to be *R,R* and a *Z* configuration for olefin moiety (Figure 2; and see the Supporting Information).[15]

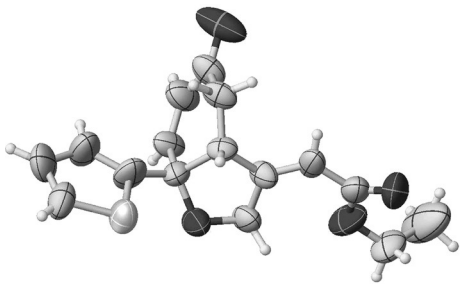
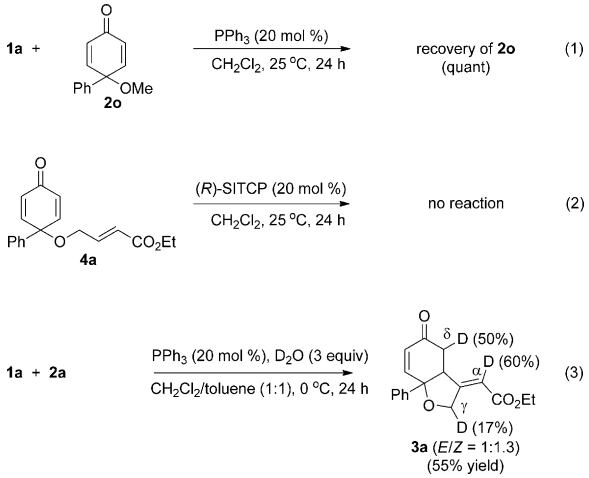
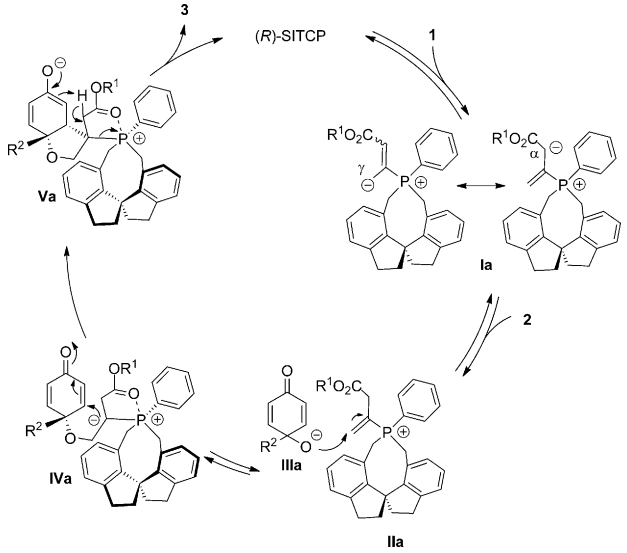


Figure 2. X-ray structure of **3k**. ORTEP drawing with thermal ellipsoids at 30% probability level.

When either the methyl-capped **2o** or allylic ether **4a** was used in the reaction, no conversion was observed [Eqs. (1) and (2)]. The free hydroxy group in **2** would be pivotal for initiating the γ-addition, and the allylic ether **4** is not a reaction intermediate on the way to give **3**. The reaction of **1a** and **2a** in the presence of D_2O (3 equiv) gave the partially deuterated product **3a** [D content (%) α: 60, γ: 17, δ: 50] [Eq. (3)], thus indicating that anionic species were formed at α-, γ-, and δ-positions on the reaction sequence.



These results are in agreement with a mechanism of a β,γ-umpolung domino reaction as shown in Scheme 4. The reaction is initiated by the nucleophilic attack of the phosphine catalyst (*R*)-SITCP to the β-position of the allenic ester **1**, thus affording the resonance-stabilized betaine **Ia** with anionic character at the carbon atom in the α- and γ-positions. Subsequent protonation of the α-position from the hydroxy group on the dienone **2** establishes the electrophilic nature of the intermediate **IIa**, thus enabling a nucleophilic γ-addition of **IIIa** to **IIa**. Thereby, the ylide **IVa** is formed and can then



Scheme 4. Proposed reaction mechanism.

undergo an enantioselective intramolecular Michael addition to one of the enone moieties. To avoid steric interactions between the R^2 substituent of **2** and the indane aromatic part in the catalyst, the reaction using (*R*)-SITCP would favor the generation of the *R,R*-configured product. Finally, the tetrahydrobenzofuranone **3** would be provided in the fragmentation of **Va** with a stabilizing $P^{+}\cdots O^{\delta-}$ interaction[16] between a less hindered monoarylphosphine group in (*R*)-SITCP and the carbonyl group in CO_2R^1, thus leading to the *Z* form with concurrent regeneration of the catalyst. Since an intermolecular oxy-Michael reaction involves reversibility of the alcohol addition under basic conditions,[17] these results suggest that the intramolecular Michael reaction from **IVa** to **Va** could be the rate-controlling step for the present domino reaction.

In summary, we have developed a highly stereoselective phosphine-catalyzed oxy-Michael/RC sequence. The present transformation is the first example of an enantio-, diastereo-, regio-, and chemoselective domino reaction initiated by the nucleophilic attack to the γ-position of allenic esters.[18,19] Further investigation into the reaction mechanism and scope as well as its application to the enantioselective synthesis of biologically active compounds is currently underway.

Experimental Section

General procedure: Under an atmosphere of nitrogen, the allenic ester **1** (0.15 mmol) was added to a solution of the hydroxy dienone **2** (0.1 mmol) and (*R*)-SITCP (20 mol%) in CH_2Cl_2/toluene (1:1, 0.1M) at 0°C and stirred for 8–72 h at the same temperature. The crude reaction mixture was purified by preparative TLC (hexanes/EtOAc 7:3) to obtain the desired product **3** as a colorless oil or solid.

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